Epidemiology and treatment effects in Chronic Obstructive Pulmonary Disease

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Epidemiology and treatment effects in Chronic Obstructive Pulmonary Disease

Epidemiologie en de effecten van de behandeling bij chronische obstructief longlijden

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"The greatness of a nation and its moral progress
can be judged by the way its animals are treated"
Mahatma Gandhi

Para ti…

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CHAPTER 1
General introduction

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a major health epidemic, which has important consequences for patients and community, and still receives insufficient attention from the health care professionals and scientists [1, 2]. COPD is a leading cause of chronic morbidity (affects 210 million people) and mortality (causes 3 million deaths per year) worldwide [3, 4], and according to the World Health Organization (WHO), it is the fifth most common cause of death and the 10th most burdensome disease [5].

Definition

The first definition of chronic obstructive pulmonary disease (COPD) can be found in the 60's and incorporates both terms "emphysema" and "chronic bronchitis" [6].

According to the Global Initiative for obstructive lung diseases (GOLD) [3], COPD is defined as a "preventable and treatable disease with some significant extra-pulmonary effects that may contribute to the severity in individual patients. The pulmonary component is characterized by airflow limitation, which is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases, such as cigarette smoke" [7]. COPD is clinically characterized by symptoms like cough, sputum production, and/or dyspnea. The diagnosis is confirmed by spirometry and accordingly has four stages, from mild (GOLD stage I) to very severe (GOLD stage IV) [3]. Patients with COPD typically have a decrease in both FEV_1 and a FEV_1/FVC ratio of less than 0.7. Using this ratio as cut-off point for all patients is currently questioned as it may underestimate COPD in the young and overestimate COPD in older populations [8, 9].

The GOLD definition has become globally accepted for the diagnosis of COPD and some crucial components of this definition have been incorporated by the European Respiratory Society (ERS) and by the American Thoracic Society (ATS) [10].

Epidemiology of COPD

Worldwide, the prevalence of COPD in the general population is estimated to be above 1% for all ages, and to be 8-10% in individuals 40 years or older [11, 12]. In Europe, COPD prevalence rates range from 4-10% in the adult population [13]. A meta-analysis of population-based studies on the prevalence of COPD (based on spirometry) reported a pooled prevalence of 9.2% [13]. However, there are large differences in prevalence depending on the population being studied, the definition being used and the availability of spirometry data. Estimates based on physician diagnosis from medical record databases, lack sensitivity as mild to moderate disease is often undiagnosed and thus the COPD prevalence will be underestimated [14, 15]. Overall, the prevalence tends to be higher in countries where smoking levels are high. In addition, prevalence estimates increase with age, and are higher in men than in women [16].

Although numerous data on the prevalence of COPD are available, very few population-based studies investigated the incidence of COPD. Among the studies that have been conducted, a wide range of incidence rates can be observed, varying between 2-16/1,000PY depending on the COPD definition being used and the population being studied [9, 17-24].

COPD is one of the few chronic diseases that caused an increase in mortality in recent years [25]. In 1990, the WHO estimated the European standardized mortality rate of COPD to be 50/100,000 in men and 20/100,000 in women [26, 27]. Data provided by the WHO in 1997, showed that COPD was the cause of death in 4.7% men and 2.4% women [26, 27] in Europe, and the World Health Report of 1998 stated that 2.9 million adults die each year of this disease [27, 28], By 2020, it is expected that COPD will be the third-leading cause of death worldwide [29, 30], but a more recent WHO projection predicts COPD to become the fourth commonest cause of death by 2030 [31].

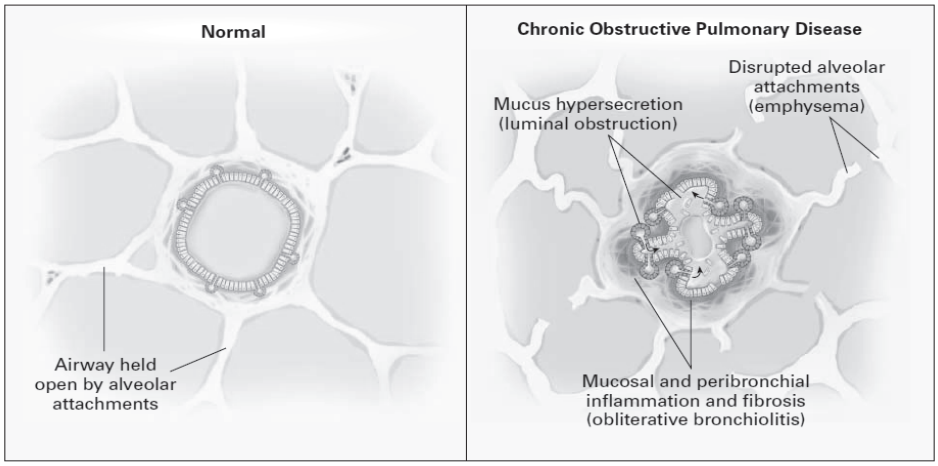
Pathophysiology

The pathophysiology of COPD includes chronic obstructive bronchiolitis with fibrosis and obstruction of the small airways, and emphysema with destruction of the lung parenchyma, loss of lung elasticity, closure of the small airways and enlargement of airspaces (figure 1) [32-34].

COPD and effect of smoking on lung function

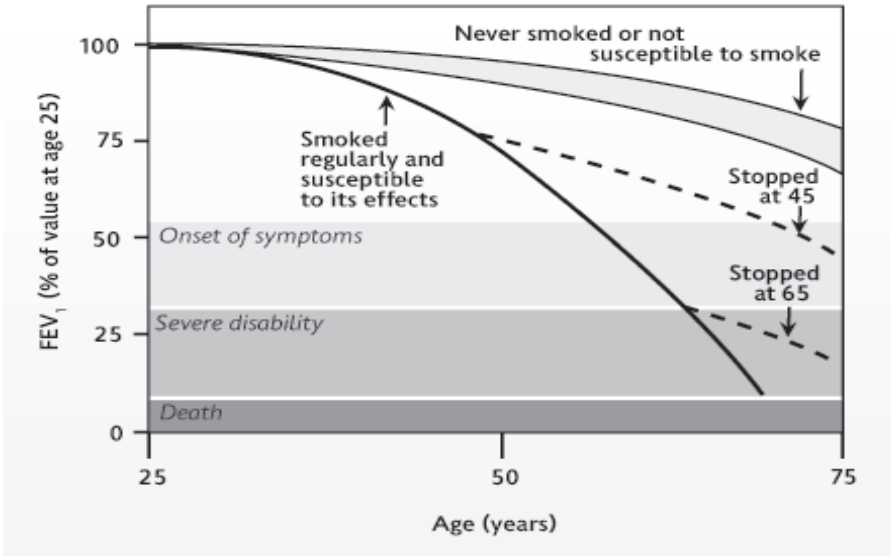
In humans, at the age of 15 to 25 years, the lung function reaches its peak, and this remains relatively constant for a decade ("plateau" phase). With aging, the lung function starts to decline, and in non-smoking subjects, the speed decline is of forced expiratory volume in one second (FEV1) approximately 25 to 30 mL/year [13, 35]. At present, the exact mechanism

Figure 1 Mechanisms of airflow limitation in COPD



(Adapted from NEJM, [Barnes P. Chronic obstructive pulmonary disease. *NEJM*, 2000:343(4); 269-280][33])

Figure 2 Old "paradigm" of COPD: Fletcher-Peto curve illustrating the effect of smoking on FEV_1



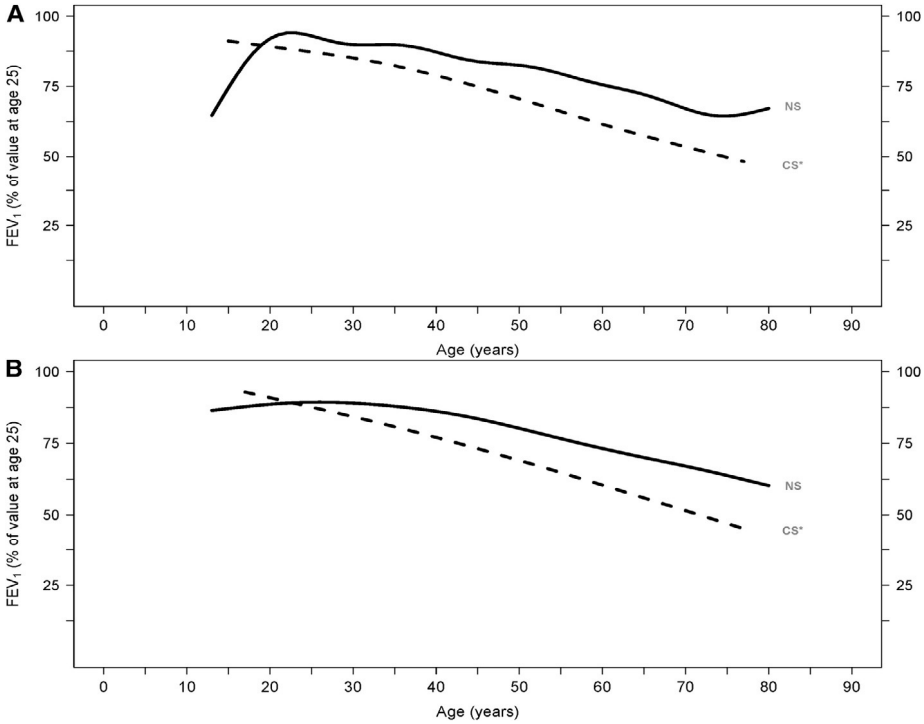
(Adapted from BMJ, [Fletcher C, Peto R. The natural history of COPD. *BMJ*, 1977:1; 1645-1648][37])

for this loss of post-bronchodilator FEV_1 with increasing age is not well understood [36]. In susceptible smokers, the decline rate of expiratory airflow is often twice more pronounced than the rate associated with normal aging. In addition, smoking, including passive smoking, may reduce the maximal FEV_1 attained and shorten the "plateau" phase or even eradicate it [21,37]. This effect can be observed in figure 2. In a population study of 792 London working men, Fletcher *et al*. demonstrated an accelerated decline in lung function over time due to smoking [37].

This study was criticized because 1) the length of the study period was considered too short for a chronic disease such as COPD, 2) because, it did not take into account inter-individual variations in the rate of lung function being lost [38, 39], 3) because the study did not include women nor elderly, and 4) finally spirometry examination was not standardized. More recently, Kohansal *et al.* performed a similar study overcoming the limitations of the previous study, and they demonstrated that lung function development differs between sexes in nearly every age category, but smoking has a similar deleterious role in both men and women (figure 3) [38].

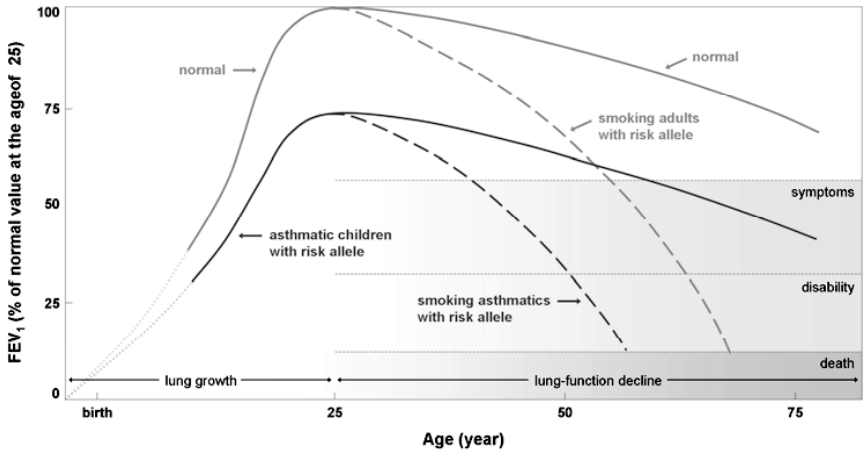
More recently, Brusselle described a paradigm shift in COPD (figure 4). The new paradigm of COPD accounted for the fact that interactions between multiple environmental exposures and genetic factors determine lung function and COPD risk. Moreover, both impaired lung function growth in early life and/ or accelerated decline in lung function in adulthood are known to be involved in the pathogenesis of COPD [40].

Figure 3 Mean FEV_1 values (expressed as percent of its value at age 25), by age for never-smokers (NS) and continuous smokers (CS). Data for men (A) and women (B)



(Adapted from AJRCCM, [Kohansal R et al. The natural history of chronic airflow obstruction revisited. *AJRCCM*, 2009:180(1); 3-10][38])

Figure 4 New "paradigm" of COPD: impaired lung function growth and/ or decline in lung function.



(Adapted from N Engl J Med, [Brusselle G. Matrix metalloproteinase 12, asthma, and COPD. N Engl J Med, 2009:361; 2664-65] [40])

Risk factors

Over the last decade, several risk factors for the development of COPD have been described, and among those, cigarette smoking is by far the strongest one [41, 42]. Other risk factors include environmental tobacco smoke, indoor and outdoor pollution, such as biomass fuel [16], and occupational dusts and chemicals [43]. The last factors are more important in developing countries [44]. Additional risk factors include poor socioeconomic status [45], adulthood infections (including a history of pulmonary tuberculosis [46]), as well as chronic asthma and airway responsiveness, the two last ones being more controversial [47].

Symptoms

Cough is frequently the first symptom of COPD, and may be intermittent, accompanied by sputum production, or can also be unproductive. Other complaints include wheezing, and chest tightness. Dyspnea is typically progressive, persistent and worsens with increase in exercise, and is known to have a weak relationship with FEV_1 [48]. Other conditions associated with COPD are cor pulmonale caused by secondary pulmonary hypertension, anxiety, depression, fatigue, anorexia and weight loss [32].

Growing evidence suggest that there are differences in the characteristics of COPD between men and women [49], including in the prevalence and experience of COPD symptoms. It is recognized that women with COPD are more likely to have dyspnea and depression, anxiety and fatigue, and less frequently report phlegm production [50, 51]. In addition, women often report lower exercise capacity, more airway hyperresponsiveness [52] and a general worse health related quality of life [53].

COPD disease course

The disease is often complicated by frequent and recurrent exacerbations that arise with increasing severity [54] and contribute to declining lung function [55]. Acute exacerbations of COPD are important events in the clinical course of the disease. An exacerbation of COPD is generally defined as an event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough, and/ or sputum that is beyond normal daily variations, is acute in onset and may warrant a change in regular medication [3]. The most common causes of exacerbations include lower airway infection and airway pollution, but in one third of severe exacerbations, the cause is unknown [3]. The severity of an exacerbation can vary from no more than a troublesome increase in respiratory symptoms to life-threatening respiratory failure [55].

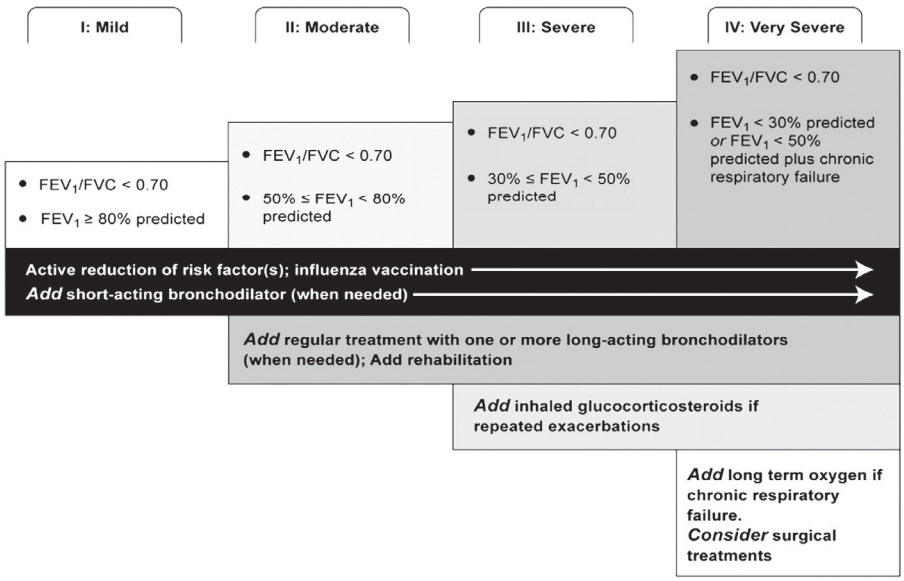
Each exacerbation may have a large and sustained effect on health status. Although the initial recovery can be short, the period for full recovery may be long (several months) with consequent deterioration of lung function [55], and not all patients fully recover to baseline condition [57, 58].

COPD treatment

None of the existing medications (see below) have been proven to change the long-term decline in lung function. Therefore, COPD pharmacotherapy is mainly used to decrease symptoms and to prevent exacerbations of disease. According to the GOLD guidelines, bronchodilators are the mainstay for symptomatic management of COPD [7]. Bronchodilator treatments include β_2-agonists, anticholinergics (AC), and methylxanthines, used alone or in combination. Long-acting bronchodilators are found to be more effective and convenient than the short-acting agents [59].

Figure 5 describes the GOLD guidelines for the treatment of COPD. In patients with mild COPD, short-acting bronchodilators are given on an as needed basis. In patients with moderate COPD, regular treatment with one or more long-acting bronchodilators is added. In patients with severe COPD, in case of repeated exacerbations, inhaled glucocorticoids are added to the treatment with long-acting bronchodilators. Finally, in patients with very sevexre COPD, oxygen therapy is added to the previously described treatment regimen [3]. Long-acting bronchodilators are known to be more effective and convenient than the short-acting ones [59]; and consist of long-acting β_2-agonists (LABA) (salmeterol, formoterol, and the recently released ultra-long LABA namely indacaterol), and the long-acting AC drug (tiotropium) [7].

Figure 5 Therapy according to severity of COPD



(Adapted from AJRCCM, [Rabe K et al. Global strategy for the diagnosis, management, and prevention of COPD. *AJRCCM*, 2007:176(6); 532-555] [7])

Most of the efficacy and safety data on respiratory drugs is generated from RCTs. These RCTs use stringent inclusion and exclusion criteria, which jeopardizes the extrapolation of the study findings to the general population, and often have a short duration of follow-up. The efficacy and safety of tiotropium have been demonstrated in several randomized placebo-controlled trials [60-68], in one randomized placebo-controlled trial [69], and in a pooled clinical trial analysis of tiotropium safety and efficacy [70], with imprecise reductions observed for mortality and a significantly lower risk observed for COPD exacerbations [62]. Compared to LABA, tiotropium shows a decrease of 48% in the incidence of COPD exacerbations [71]. Only few RCTs compared lung function and health outcomes between users of tiotropium and salmeterol, in patients with moderate to severe COPD [64, 72-74].

As most of the COPD patients need chronic treatment with respiratory drugs and concomitantly use other drugs for the treatment of co-existing comorbidities, the safety of respiratory drugs under real life circumstances is crucial. Real life observational studies allow studying the safety but also the effectiveness or respiratory drugs.

Aims and outline of this thesis

COPD is a leading and still-increasing cause of chronic morbidity and mortality worldwide. As a result of its burden and the impact on health care, we aimed to study the epidemiology of COPD (chapter 2), to explore the effectiveness (chapter 3) and the safety (chapter 4) of drugs given for the treatment of COPD under real life conditions.

For these studies, we used data from the Integrated Primary Care Information (IPCI) database. IPCI is a longitudinal observational database (dynamic cohort) that contains data from computer based patient records of GPs throughout the Netherlands. Within this database we defined 3 COPD or COPD drug user cohorts, which were the basis for all studies. 1) One cohort of COPD patients, included data from 1996 to 2006, and COPD was identified on the basis of COPD diagnosis codes without further validation. The disease severity was defined by the algorithm of Ernst *el al.* [75] (chapter 4.2). 2) A second cohort of COPD patients, contained data from 2000 to 2007, and all COPD cases were reviewed/validated by a medical doctor, and the doubtful ones reviewed by a specialist. COPD disease severity was determined using spirometry values, when available, or by previously published algorithms for COPD severity assessment [76-78] (chapters 2, 3, 4.3, 4.4 and 4.5). 3) A third cohort was created on the basis of COPD drug (tiotropium) users, using data between 2000 and 2010. The presence of COPD, diagnosed through COPD diagnosis codes or free text, was considered a separate covariate in the analysis. COPD severity was assessed based on the number of prescriptions of systemic corticosteroids and the number of antibiotics (chapter 4.1) in the one year prior to tiotropium use.

The COPD cohort allowed us to study the incidence, prevalence, mortality and lifetime risk of COPD. In addition, we compared mortality rates, both in the general population and in the COPD cohort (chapter 2).

Furthermore, we studied the effectiveness and safety of respiratory drugs. We investigated the association between the use of inhaled respiratory drugs and the risk of hospitalization for COPD exacerbation, where we compared the effectiveness of tiotropium with LABAs (chapter 3).

As safety studies, we explored the use of tiotropium, administered either via Respimat® SMI or HandiHaler®, and the risk of all-cause mortality (chapter 4.1). In addition, we studied the association between the use of inhaled AC drugs and the risk of urinary retention (chapter 4.2), and renal failure (chapter 4.3).

As tiotropium continues to be used in a wider population, and in order to further assess safety risks in clinical practice, we studied the cardiovascular safety and risk of death during use of inhaled AC drugs. This research was driven by the safety warning issued by the FDA in 2008, on a small excess risk of stroke in patients treated with tiotropium compared to placebo (chapter 4.4).

At last, we analyzed the risk of severe COPD exacerbations in patients with COPD, when being exposed to β-blockers (chapter 4.5).

The meaning and limitations of the studies are discussed in chapter 5 of this thesis and recommendations are made for future research.

CHAPTER 2
Epidemiology

2.1

COPD in the general population: incidence, prevalence and survival

Summary

Worldwide, COPD is a leading cause of chronic morbidity and mortality. Although its prevalence is already well documented, very few studies have measured its incidence. We therefore investigated the prevalence, incidence and lifetime risk of COPD in the general population.

In a population-based study including subjects ≥ 40, with 12 months of history available in the Dutch IPCI database, we identified COPD cases by a two-step validation algorithm.

Among 185,325 participants with 601,283 years of follow-up, 7,308 subjects with COPD were identified, and 1,713 had incident COPD. The overall IR of COPD was 2.92/1,000PY (95%CI 2.78-3.06). The incidence of COPD was higher in men (3.54; 95%CI 3.33-3.77) than in women (2.34; 95%CI 2.17-2.52), and the overall baseline prevalence of COPD was 3.02% (95%CI 2.94-3.10). For people who had entered the study free of COPD at the age of 40, the risk of developing COPD within the next 40 years was 12.7% for men and 8.3% for women. In patients with very severe COPD, 26% died after 1 year of follow-up, whereas 2.8% died among the non-COPD subjects.

In the general population in the Netherlands, three on 1,000 subjects developed COPD per year. The incidence increased rapidly with age and was higher in men than in women. One in eight men and one in 12 women, being COPD free at the age of 40 will develop COPD during their further life. Mortality rates differed substantially between COPD patients and non-COPD subjects of the same age, underlining the burden of this disease.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by a largely irreversible obstruction of the airways, and encompasses both emphysema and chronic bronchitis [2]. The obstruction of the airways is usually both progressive, and often associated with an abnormal inflammatory response of the lungs to harmful particles or gases such as tobacco smoke. COPD is a leading and still-increasing cause of chronic morbidity and mortality worldwide [79], and according to the World Health Organization (WHO), it is the fifth most common cause of death and the 10th most burdensome disease [5]. Chapman et al [80] and Mannino et al [15] projected that between 1990 and 2020, COPD will become the third most common cause of death worldwide. A Dutch study predicts that an increase of 76% in the prevalence of COPD can be expected within approximately twenty years [81].

Although the prevalence of COPD has been well studied [17, 35, 82-84], few population-based studies [9, 17-22, 85] have investigated its incidence. Among the studies that have been conducted, a wide range in incidence rates can be observed varying between 2-16/1,000 PY depending on the COPD definition being used and the population being studied [9, 17-24]. Little is known about trends in COPD prevalence, incidence and all-cause mortality [24].

COPD is one of the few chronic diseases that caused an increase in mortality in recent years [25]. In 1990, the WHO estimated the European standardized mortality rate of COPD to be 50 per 100,000 in males and 20 per 100,000 in females [26, 27]. Data provided by the WHO in 1997, showed that COPD was the cause of death in 4.7% of men and 2.4% of women [26, 27] in Europe, and the World Health Report of 1998 stated that 2.9 million adults die each year of this disease [27, 28]. Death rates in patients with COPD are usually lower among women than among men in all countries. At present, there are very few observational studies reporting mortality rates in COPD patients [28].

The objectives of our study were to investigate the prevalence, incidence, mortality and lifetime risk of COPD as a function of age and sex in the general population.

Methods

Setting

The study was conducted within the Integrated Primary Care Information (IPCI) database, a longitudinal observational database (dynamic cohort), that started in 1992 and contains data from computer based medical records of general practitioners (GPs) throughout the Netherlands [86]. The database covers data from more than 400 GPs who currently capture data on more than 1 million patients [86]. In the Dutch health care system, patients are registered with a single GP who acts as a gatekeeper for and receiver of information from secondary care [87]. The GPs' electronic medical records contain coded and anonymous data on patient

demographics, narratives, patient reported symptoms, signs, GP and specialist diagnoses (using the International Classification of Primary Care (ICPC) codes and free-text [88]), as well as prescriptions, physical findings, laboratory values, and summaries of specialist letters [86, 88]. Downloads are made periodically and the information is sent to the gatekeeper who de-identifies all information before further access is provided.

Prescription data encompass product name, quantity dispensed, dosage regimens, 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 [89-91]. The system complies with European Union guidelines on the use of medical research and has been proven valid for pharmaco-epidemiological research [91]. All observational research using IPCI data is conducted according to good pharmaco-epidemiological guidelines [92].

Source population

The source population comprised 185,325 men and women aged 40 or older, with at least one year of valid database history meaning 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 guarantee sufficient medical history prior to study entry. The study started on 1 January 2000 or the date at which one year of valid history was obtained. All patients were followed from study entry until the date of diagnosis of (incident) COPD, death or 1 July 2007, whichever occurred first.

COPD cohort

A broad automated search was conducted on ICPC COPD disease codes and narratives to identify all potential COPD patients. The medical records of all potential cases were reviewed by a medical doctor and classified as: *definite COPD* - diagnosis by a specialist or a GP diagnosis confirmed by spirometry (GOLD definition of FEV1/FVC<70%); *probable COPD* - COPD diagnosed by the GP with at least two records of COPD within one year of the first record of COPD. Doubtful COPD patients were further reviewed and classified by a pulmonologist (GB).

All COPD patients were further categorized into prevalent or incident COPD. Patients with a COPD diagnosis prior to study entry were classified as prevalent (pre-existing) COPD. If patients were disease free (no respiratory symptoms) at cohort entry and later developed COPD, they were considered as having incident (newly onset) COPD.

COPD severity was assessed at the time of cohort entry and changes in COPD severity were captured during follow-up. If spirometry was available, severity of COPD was determined according to the GOLD guidelines and not based on the true lower limit of normal (LLN) of FEV1 as information on height and race was not consistently reported in the database [93]. In all other patients, previously published algorithms for COPD severity assessment were

used [76-78]. In summary, patients were considered to have mild COPD at the time of their first symptoms of COPD, moderate COPD if patients were on regular bronchodilating treatment (defined as at least 2 prescriptions of the same drug class within 6 months of the first prescription), and severe COPD if they were hospitalized for COPD, received a third courses of antibiotics for the treatment of lower respiratory tract infections in one year time, or received their second systemic corticosteroid course for the treatment of COPD exacerbations in one year time. Finally, patients were considered to have very severe COPD when they were prescribed oxygen therapy for chronic use or were scheduled for lung transplantation.

Statistical analysis

To compare the baseline characteristics of the COPD cases with the characteristics of the total population (without COPD) at study entry the Mann-Whitney U test was applied for continuous variables, and the Chi-square test for categorical variables. Age and gender-specific (in 5-year age categories) incidence rates of COPD (IRs) per 1,000 person-years (PY) were calculated by dividing the number of incident COPD cases by the total number of PY accumulated by the study population, and censoring the patients with COPD at baseline (prevalent cases). Relative risks were calculated by dividing two different incidence rates of COPD. Weighted (3 year mean) annual incidence rates by sex were also calculated by dividing the number of incident cases in a given year by the total number of individuals at risk for COPD in PY. The 95% confidence intervals (CI) were calculated according to a Poisson distribution (Episheet, Rothman). Cumulative prevalence of COPD by age and sex was calculated by dividing the number of people with prevalent COPD by the number of subjects present in the study with the same age and sex. For this analysis, all study participants were used, and 95% CI were calculated with the Wilson score method for a binominal distribution (Episheet, Rothman). The cumulative incidence and the lifetime risk of COPD was calculated on the basis of a Cox regression model adjusted for competing risk of death, as described by Rosthoj et al [94]. This model was used to calculate the age specific 10, 20, 30 and 40 years risks of COPD, adjusted for the competing risk of dying, in men and women being disease free at study entry.

To compare the mortality rates in subjects with or without COPD, 4 controls were sampled from the source population for each COPD patient, matched on age, sex, smoking status and calendar year (year of entry into the cohort). Mortality rates were calculated by dividing the number of deaths by the person years attributed, and stratified by sex. Survival analyses were conducted using Kaplan-Maier analysis [95]. To compare our incidence rates to the IRs as published in literature, we standardized our IR to the age distribution presented in the different studies (table 4). All statistical analyses were conducted with SPSS/PC 15.0 (SPSS Inc, Chicago, Ill).

Results

Baseline characteristics

In the source population of 185,325 patients with at least one-year of valid history (601,283 years of follow-up time), 18,643 COPD potential cases were identified (figure 1). The mean follow-up time was 3.4 years (standard deviation (SD), ± 3.2 years). After manual validation of the complete medical record, 7,308 patients were identified as having COPD of which almost half were male. Table 1 shows the baseline characteristics of the total source population at study entry (n=185,325) and the patients with COPD (n=7,308), both incident and prevalent. COPD patients were older, more frequently male, and had more co-morbidity than non-COPD patients at study entry (table 1).

Figure 1 Flow-chart

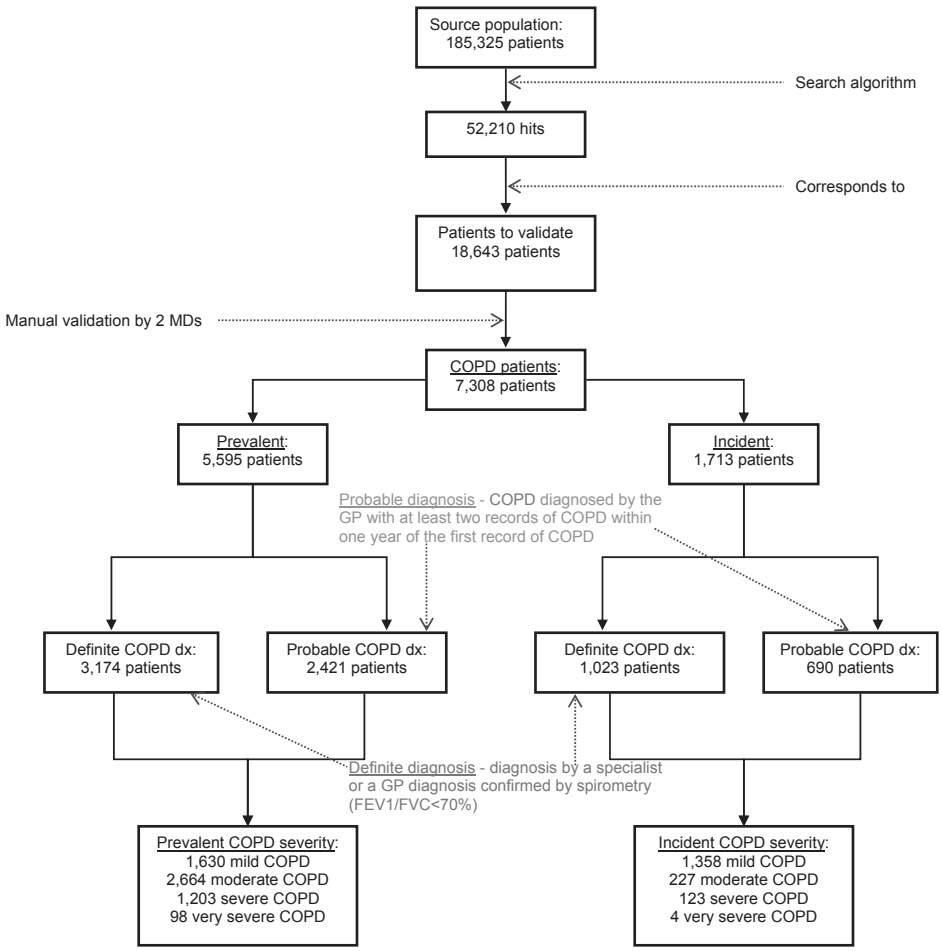


Table 1 Description of source population and COPD cohort - Demographics

Characteristics	Source population n=185,325		Overall COPD		Incident COPD		Prevalent COPD	
	No.	%	No.	%	No.	%	No.	%
Number of COPD patients	7,308	3.9	7,308	100.0	1,713	23.4	5,595	76.6
♂	89,697	48.4	4,153	57.3	995	58.1	3,158	56.4
♀	95,628	51.6	3,155	42.7	718	41.9	2,437	43.6
Age (years)								
40-59	119,798	64.6	1,982	26.5	501	29.2	1,481	26.5
60-69	30,930	16.7	1,872	25.6	473	27.6	1,399	25.0
>= 70	34,597	18.7	3,454	47.9	739	43.1	2,715	48.5
Mean age (±SD)	56.5	±13.3	67.8	±12.1	64.7	±11.8	67.8	±12.3
Smoking history[1]	39,625	21.4						
never smoked			475	7.7	125	7.3	350	6.3
current smoking			2,821	40.3	810	47.3	2,011	35.9
past smoking			433	6.1	165	9.6	268	4.8
smoking not specified			3,573	45.7	611	35.7	2,962	52.9
Severity at cohort entry[1]								
Severity by spirometry								
Mild (GOLD stage I)			639	9.0	243	14.2	393	7.0
Moderate (GOLD stage II)			923	13.3	187	10.9	736	13.2
Severe (GOLD stage III)			558	8.1	73	4.3	485	8.7
Very Severe (GOLD stage IV)			21	0.3	3	0.2	18	0.3
Severity by proxy								
Mild			2,352	30.7	1,115	65.1	1,237	22.1
Moderate			1,968	26.7	40	2.3	1,928	34.5
Severe			768	10.8	50	2.9	718	12.8
Very Severe			81	1.2	1	0.1	80	1.4
Mean time since first diagnosis (years) (±SD)					0	0	3.16	±4.47
Co-morbidity at cohort entry[1]								
History of asthma	1,384	0.7	1,042	15.3	251	14.7	881	15.7
History of myocardial infarction	2,286	1.2	457	6.7	136	7.9	344	6.1
Angina pectoris	5,454	2.9	994	14.6	241	14.1	808	14.4
History of ischemic heart disease	1,783	1.0	188	2.8	47	2.7	154	2.8
History of stroke or TIA	3,471	1.9	391	5.8	97	5.7	319	5.7
Peripheral arterial disease	4,047	2.2	441	6.5	131	7.6	339	6.1
Heart failure	2,708	1.5	793	11.7	179	10.5	697	12.4
Ventricular arrhythmia	3,492	1.9	28	0.4	7	0.4	22	0.4
Hypertension	20,499	11.1	1,422	20.9	369	21.5	990	17.7
Lipid disorder	7,694	4.2	1,769	26.1	533	31.1	1,296	23.2
Diabetes	8,023	4.3	767	11.3	195	11.4	651	11.6
Renal insufficiency	1,371	0.7	184	2.7	54	3.2	174	3.1
History of malignancy	8,423	4.5	673	9.9	159	9.3	544	9.7
Pneumonia (year prior)	3,241	1.7	571	8.4	131	7.6	483	8.6
Parkinsonism	436	0.2	21	0.3	7	0.4	16	0.3
History of depressive disorders	9,449	5.1	540	8.0	172	10.0	416	7.4
Dementia diagnosis	436	0.2	23	0.3	4	0.2	22	0.4

[1] At baseline for prevalent COPD patients or at the date of diagnosis for incident COPD patients

A total of 5,595 patients (77%) in the COPD cohort had prevalent COPD at baseline and 1,713 (23%) were incident COPD patients. Incident COPD patients were slightly younger than the prevalent ones (mean age 64.7, SD ± 11.8, versus 67.8, SD ± 12.3), and more often smoked or had smoked in the past (table 1). The mean and median age at first diagnosis did not change over time (data not shown). The majority of incident COPD patients had mild COPD at the time of first diagnosis.

Co-morbidity was similar between incident and prevalent COPD patients apart from a history of heart failure, which was more often recorded in prevalent COPD patients (12.3% versus 9.8%), and hypertension, lipid disorders and a history of depressive disorders, which were more common in incident COPD patients (table 1).

Incidence, prevalence, risk and mortality

The overall incidence of COPD in persons 40 years and older was 2.92/1,000PY (95%CI, 2.78-3.06) (table 2). The incidence of COPD was higher in men than in women (with a relative risk (RR) of 1.5-fold higher in men). The incidence increased almost 10 fold from 0.78/1,000 PY at age 40-44 to 6.82/1,000PY at age 75-79 (figure 2).

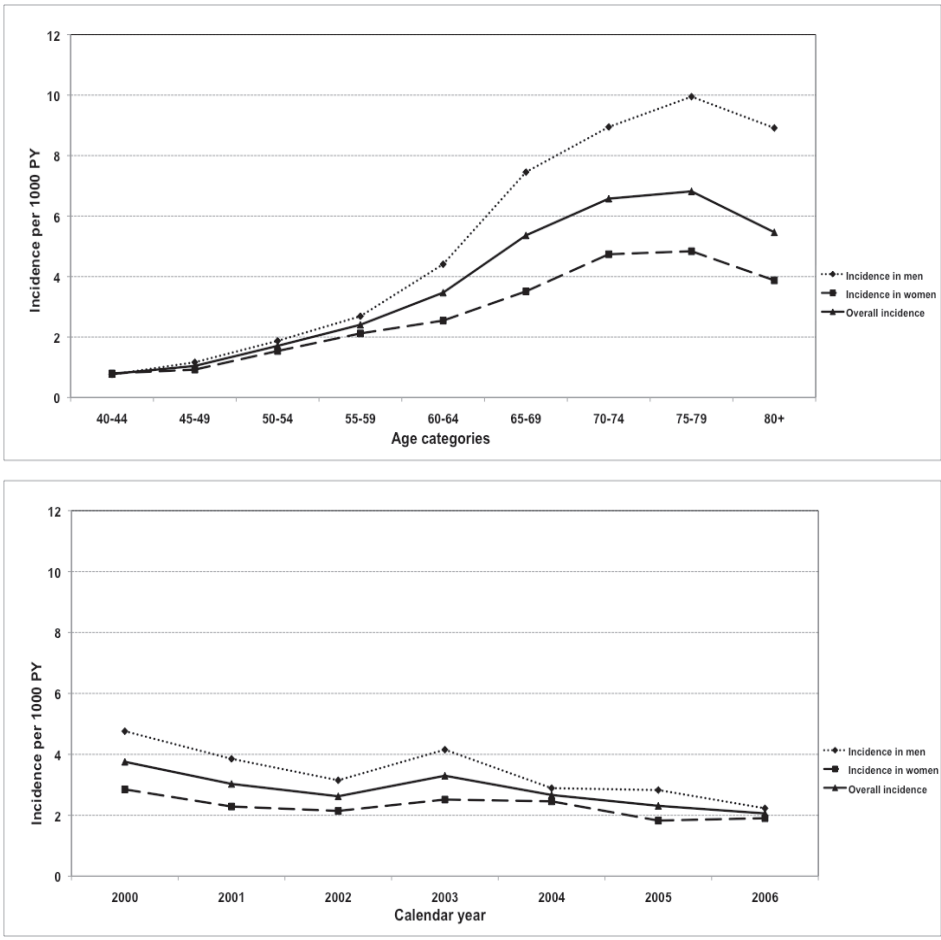
The prevalence of COPD at cohort entry was 3.02%, 95%CI (2.94-3.10). The age-specific cumulative prevalence of COPD is shown in figure 4. As can be observed from this graph, the prevalence increased with age until the age of 81 years in men and 83 years in women. After this age, the prevalence did no longer increase and even gradually declined, especially in men. The prevalence of COPD was, for all age categories, higher in men than in women (figure 4).

For a man free of COPD at the age of 40, the risk to develop COPD was 0.8% (10 years), 2.8% (20 years), 7.2% (30 years) and 12.7% (40 years) respectively. For a woman of the same age, the risks were 0.8%, 2.3%, 5.0% and 8.3% (figure 5).

Table 2 Incidence of diagnosed COPD

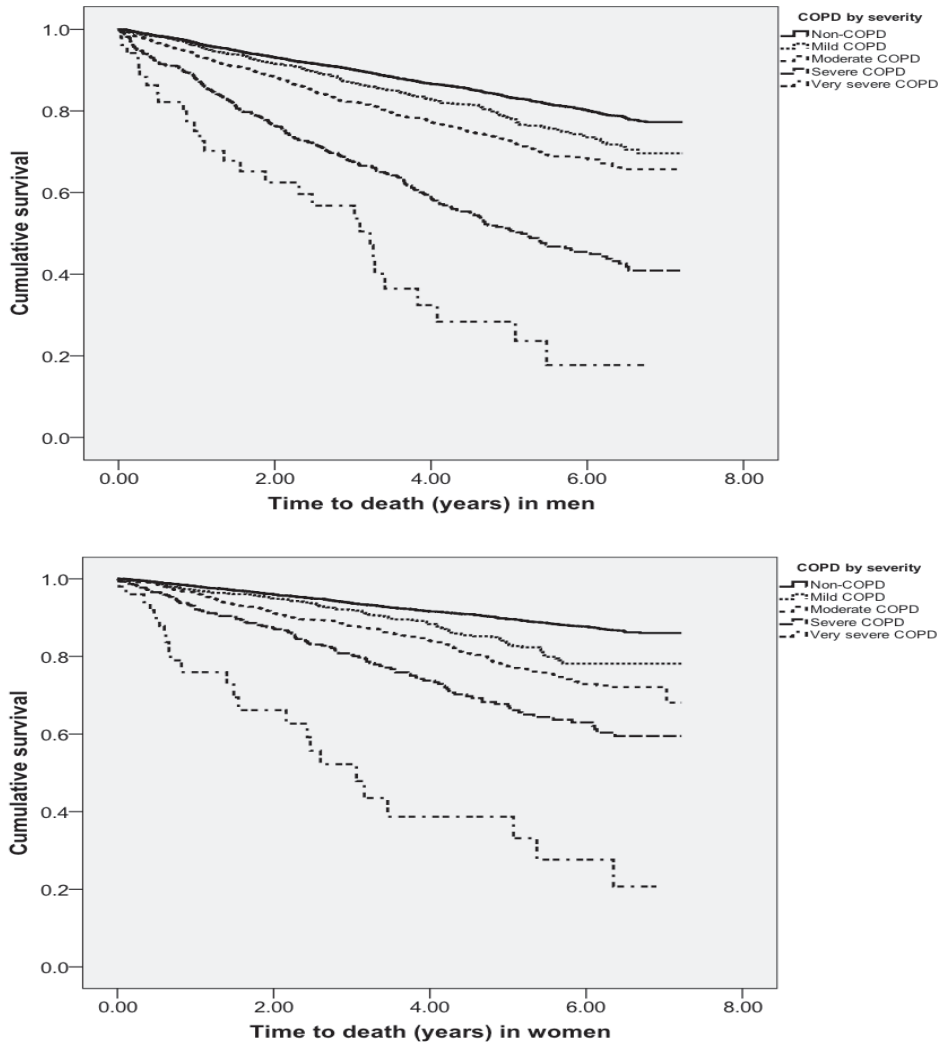
Age groups, years	Overall		Men		Women	
	IR	95%CI	IR	95%CI	IR	95%CI
40-44	0.78	0.62-0.97	0.76	0.54-1.04	0.80	0.57-1.09
45-49	1.04	0.85-1.26	1.16	0.89-1.50	0.92	0.68-1.23
50-54	1.71	1.46-1.99	1.87	1.51-2.29	1.54	1.21-1.93
55-59	2.40	2.08-2.76	2.69	2.22-3.23	2.12	1.70-2.61
60-64	3.47	3.02-3.96	4.41	3.70-5.20	2.54	2.02-3.16
65-69	5.36	4.74-6.04	7.45	6.40-8.64	3.51	2.84-4.29
70-74	6.57	5.83-7.39	8.94	7.65-10.39	4.74	3.92-5.68
75-79	6.82	5.98-7.74	9.95	8.35-11.77	4.84	3.96-5.86
80+	5.46	4.76-6.24	8.91	7.34-10.72	3.87	3.17-4.69
All age categories	2.92	2.78-3.06	3.54	3.33-3.77	2.34	2.17-2.52

Figure 2 Age- and gender specific incidence rates of diagnosed COPD (/1,000 PY) (top) and weighted (3 year mean) calendar year-specific incidence of COPD (bottom)



Mortality rates were 2.0-fold higher for COPD patients than for the age and sex matched reference population. Mortality rates increased with COPD severity from 48.1/1,000PY (95%CI, 42.5-54.3/1,000PY) in mild to 262/1,000PY (95%CI, 179-371/1,000PY) in very severe COPD patients (table 3). Survival is lower in COPD patients than non-COPD subjects and is highly influenced by COPD severity (figure 3). The one-year risk of dying was 26% (95%CI 18.4-35.4%) in the very severe COPD patients while the risk in the sex and age matched reference group was nearly ten times lower namely 2.8% (95%CI 0.92-8.17%).

Figure 3 Survival among (top) men and (bottom) women diagnosed with COPD by severity status and reference population (controls are COPD free)



Discussion

In this large population based cohort study of the general Dutch population of 40 years and older, the overall incidence rate of diagnosed COPD was 2.92/1,000PY. The incidence increased with age, and was higher in men than in women. Based on these data the risk to be diagnosed with COPD in the coming 40 years was 12.7% for a 40-year-old male and 8.3% for a 40-year-old female. Mortality was high; especially in very severe COPD patients with one-year mortality risks nearly 10-fold that of non-COPD subjects of the same age.

Figure 4 Age-specific cumulative prevalence of COPD in men (grey) and women (black)

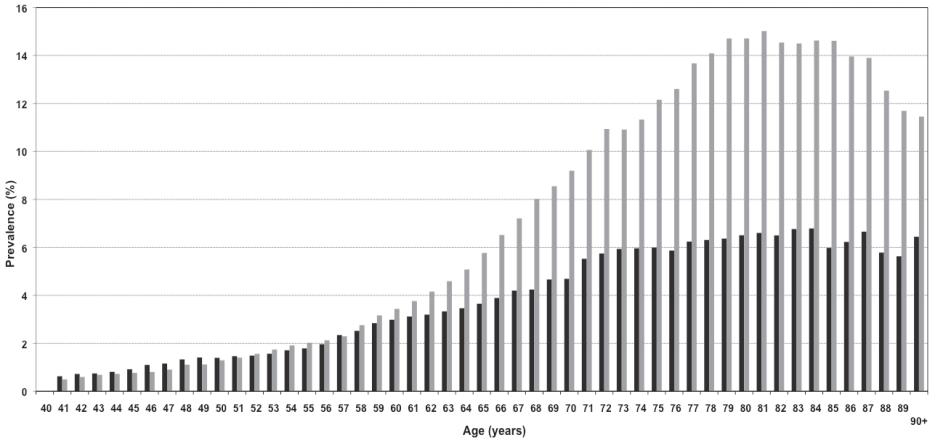


Table 3 Number of deaths and mortality rates (/1,000PY) in patients with and without COPD

	COPD					Non-COPD
	All	Mild	Moderate	Severe	Very severe	
Total number patients, n (%)	7,308	2,989 (40.9)	2,891 (39.6)	1,326 (18.1)	102 (1.4)	24,722
Number of deaths	1,371	393	523	402	53	2,750
♂	897 (65.4)	259 (65.9)	329 (62.9)	280 (69.6)	29 (54.7)	1,886 (68.6)
♀	474 (34.6)	134 (34.1)	194 (37.1)	122 (30.3)	24 (45.3)	864 (31.4)
Mean (SD) age at death	78.2 (±9.3)	78.2 (±9.8)	78.9 (±8.8)	77.7 (±9.2)	73.6 (±9.7)	79.7 (±8.6)
Age at death, n (%)						
40-59	53 (3.9)	18 (4.6)	15 (2.9)	15 (3.7)	5 (9.5)	89 (3.3)
60-69	195 (14.2)	54 (13.7)	64 (12.2)	64 (16.0)	13 (24.5)	261 (9.5)
>= 70	1,123 (81.9)	321 (81.7)	444 (84.9)	323 (80.3)	35 (66.0)	2,400 (98.2)
Mortality rate (/1,000PY), 95%CI						
♂	70.4 (65.9-75.1)	48.1 (42.5-54.3)	63.9 (57.3-71.1)	133.4 (118.5-149.8)	262.0 (179.1-370.9)	36.3 (34.7-38.0)
♀	48.5 (44.3-53.0)	33.5 (28.2-39.6)	47.5 (41.1-54.5)	76.8 (64.0-91.3)	236.7 (195.5-404.9)	21.7 (20.3-23.2)
All	60.9 (57.7-64.2)	41.9 (37.9-46.2)	56.6 (51.9-61.6)	109.0 (98.7-120.1)	249.9 (189.2-324.2)	30.0 (28.9-31.1)

*Matched for age, sex, smoking status and calendar year (year of entry in the cohort); 4 controls were sampled from the source population for each COPD patient

Previous studies mainly focused on the prevalence of COPD as they often applied a cross sectional spirometry based approach to obtain the true prevalence of COPD (see table 4). Very few spirometry based incidence studies have been reported [9, 17-21]. Studies reporting diagnosed COPD, based on health care databases, were conducted in the UK and in Canada (table 4) [22-24]. The most recent incidence study, published in 2010, is a Canadian study investigating trends in incidence, prevalence and mortality of COPD over time [24]. For this

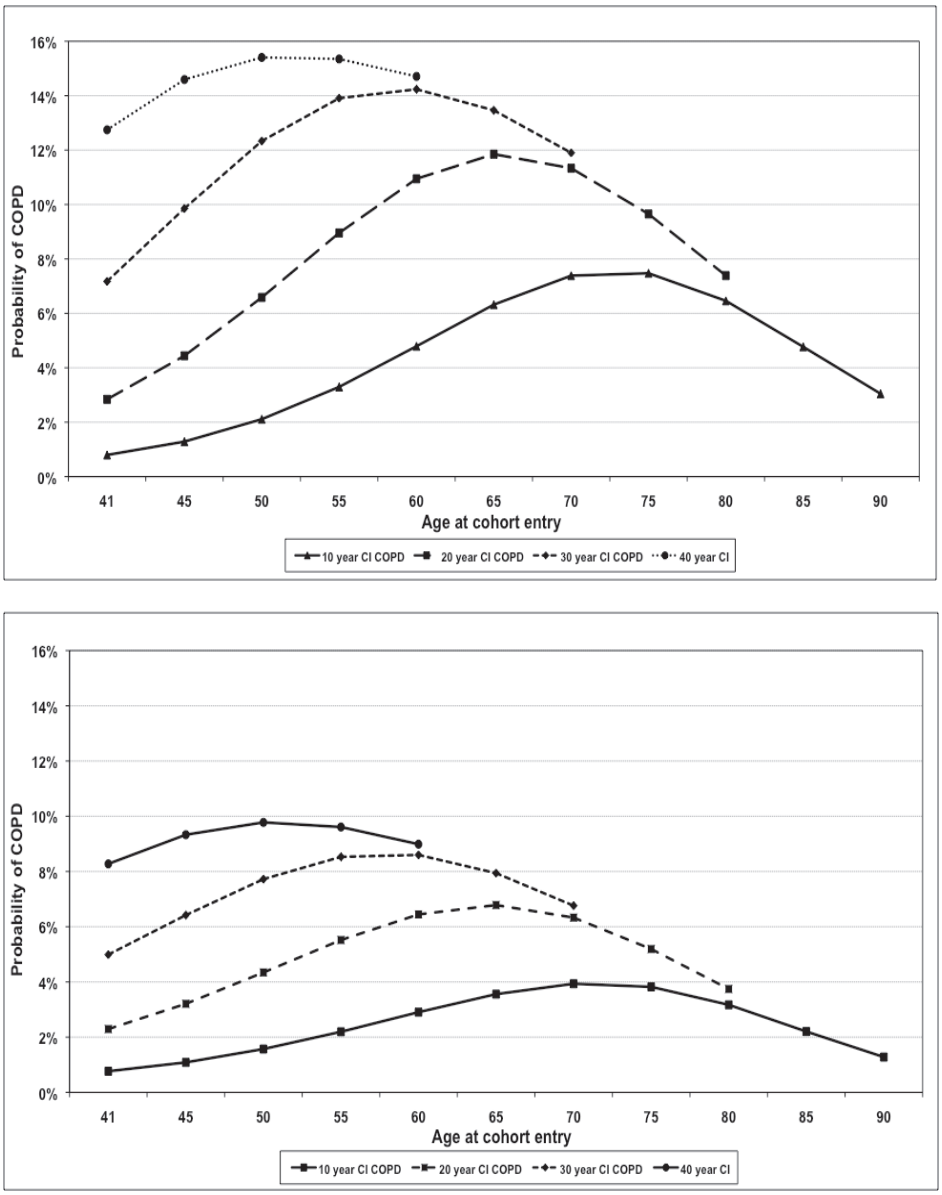
Table 4 Overview of studies that have investigated the incidence of COPD (Overall rate of diagnosed COPD in our study 2.9/1,000PY)

Author	Source population	Country	COPD definition	Year of study	Cohort size	Follow-up time	# incident COPD in cohort	Age in years	IR COPD
Spirometry based studies									
van Durme et al [17] Chest 2009	Population based	the Netherlands (Rotterdam)	Spirometry/ discharge letters	1990-2004	7,983	11 yrs	648	>= 55	9.2/1,000PY
Krzyzanowski M et al [18] Am R Res Dis 1986	Longitudinal data, random sample; older persons and those with chest complaints performed lung function tests	Poland (Cracow)	Spirometry	1968-1981	4,612	13 yrs	1,864	19-70	5.0/1,000PY
Huhti E et al [19] Eur J Res Dis 1980	Non-selected population and standard questionnaire on respiratory symptoms filled in for each subject	Finland (Harjavalta)	Spirometry	1961-1971	1,476	10 yrs	1,163	40-64	2.0/1,000PY and 10.0/1,000PY smokers
de Marco R et al [21] AJRCCM 2007	ECRHS on random sample of young adults. Participants were invited by questionnaire. Of the responders, a random sample of 20% were invited for lung function examination	Belgium, Denmark, Estonia, France, Germany, Iceland, Italy, the Netherlands, Norway, Spain, Sweden, Switzerland, UK	Spirometry (FEV1/FVC < 70%)	ECRHS I: 1991-1993 ECRHS II: 1999-2002	5,002	8.9 yrs	123	20-44	2.8 /1,000PY 10 yrs CI 2.8%
Lindberg A, et al [20] Chest 2006	Participants selected via postal questionnaire and a random sample was invited to a structured interview and spirometry in 1996 and 2003	Sweden (Noorbotten)	Spirometry (GOLD)	85% (1,009) participated in 1996 and 2003	963	7 yrs	45 (Gold II and more) 91 (Gold I and more)	46-77	6.7/1,000PY Gold II (CI 4.9%), 13.5/1,000PY Gold I and more (CI 11.0%)
Vestbo J et al [9]	General population sample without COPD at study entry, selected at random after age stratification; participants were invited	Denmark (Copenhagen)	Spirometry	1976-1778 1981-1983 1992-1994	14,223 (maximal)	9 yrs	?	>= 20 years	19/1,000PY (5 yrs) and 9/1,000PY (15 yrs), 5 yrs CI 9.7% and 15 yrs CI 13.2%
Diagnosis based studies									
Garcia Rodriguez et al [22]	Population based – GPRD	UK	OXMIS and Read Codes	1996-	808,513	?	1,927	40-89	2.6/1,000PY
Huerta C et al [23]	Population based – GPRD	UK	Presence of recorded diagnosis	1993-1998	5,000	6 yrs	206	60-85	7.2/1,000PY
Gershon et al [24]	Population based – Claims database	Canada	ICD codes	1996-2007	5-6.4 million	12 yrs	61,998-55,903	>=35	11.8-8.5/1,000PY

* BTS criteria: FEV1/FVC ratio, <0.70; and FEV1, <80% predicted; GOLD criteria: FEV1/FVC ratio, <0.70

**GOLD: GOLD stage I to IV with FEV1/FVC ratio of <0.70; GOLDII: GOLD II and higher with FEV1/FVC ratio if <0.70 and FEV1<80% predicted

Figure 5 Age-related risk for COPD to develop over the coming 10, 20, 30, and 40 years in men (top) and women (bottom). CI= cumulative



study, the Ontario Health Insurance Plan database was used and COPD was defined based on visits and hospitalization with ICD-9 or ICD-10 codes for COPD [24]. The incidence of COPD was high: 11.8/1,000 in 1996 and 8.5/1,000 in 2007 [24]. The rates of incidence and prevalence were much higher than observed in our study (even after standardization), but the study was very inclusive and did not validate COPD. Codes included terms such as chronic bronchitis

and asthmatic bronchitis which not necessarily are synonyms of COPD [24]. Our COPD definition was much stricter requiring specialist diagnosed COPD or COPD diagnosed by GP in case of spirometry and/or at least 2 records of COPD within one year explaining our lower IRs.

Van Durme et al also studied the incidence of COPD in a prospective cohort of elderly in the Netherlands. , COPD was defined based on specialists/GPs (similar to ours) diagnosis as well as on tri-annual spirometry assessments. Our age standardized rate was 35% lower showing the level of underdiagnosis [17]. Using the indirect age standardization, the calculated standardized incidence rate was 0.49 (95%CI 0.46-0.52), which means that there is a difference in the two populations in weight, and in our population we expect 50% less patients with a COPD diagnosis. Our IR is probably much lower than in the study from Van Durme et al, as in the latter; spirometry was conducted on 44% of the study population whereas in our setting, spirometry was only conducted in case of respiratory complaints. Our IRs are more in line with the results of a recent population based cohort study, using similar data and similar methodology, from the UK GPRD database [22]. The incidence rate of diagnosed COPD in 40-89 year-olds was 2.6/1,000 PY which is almost identical to the incidence rate we found (2.9/1,000 PY) [22]. In summary, there is a large heterogeneity between reported prevalence and incidence rates of the different studies, which can be explained by the method of assessing and validating COPD and age differences.

In our study, all-cause mortality rates were higher in COPD patients than in patients without COPD of similar age and sex. Our mortality rates are much in line with the data from Soriano et al [28] and Gershon et al [24], who also studied mortality in COPD patients. In their study, Gershon et al describe mortality rates that vary between 5.7% in 1996 to 4.3% in 2007 [24], which is in line with the mortality rate of 6.1% that we found in our COPD patients. Soriano et al reported an overall death rate of 8.5% per year [28]. Furthermore, in comparison with data of patients with COPD followed by GPs [96], Lundback et al refer to a better survival among the subjects with COPD identified by an epidemiological population study, with a 5-year risk of dying of approximately 7% in subjects without either chronic bronchitis and asthma-like phenotype, and approximately 15% in subjects with chronic bronchitis [97]. Our 5-year risk of dying was somehow higher with 14% in non-COPD patients and 27% in COPD patients, probably not only because Lundback et all include younger patients in the beginning of their study, but also their definition of chronic bronchitis may differ from our COPD definition, and direct to a slightly different inclusion of patients in both studies.

Similar to previous literature [24, 28] we also found that mortality in patients with COPD is still higher in men than in women. A partial explanation could be that, on average, women with COPD have still less severe disease than men, because women used to smoke less or were not inhaling tobacco as frequently as men.

As for all observational studies, our study has strengths and weaknesses. The strength of this study is the population-based design; its large cohort size and the detailed information that is available on underlying co-morbidity. Furthermore, the large population in this study

is representative of the general population, which eliminates selection bias. To avoid inclusion of false positive cases we followed a rigorous validation algorithm and used data from spirometry and specialist referral letters if available. In addition, we assessed COPD severity according to spirometry data or according to an algorithm already successfully used by other research groups [76-78]. Unfortunately, as this is a population-based study, we did not have spirometry data on all subjects. For this reason we believe that we probably underestimated the true incidence rate of COPD in the general population. This is one of the reasons why our COPD incidence rate is lower than in those studies where COPD was assessed mainly by spirometry. In our study, patients diagnosed to have COPD are mainly the ones presenting themselves with respiratory symptoms. Probably a considerable proportion of patients with respiratory symptoms get accustomed to these complaints and never consult their GP [98]. Another limitation is the fact that the GOLD definition of COPD (FEV1/FVC<70%) for patients with spirometry data instead of the use of LLN values for FEV1/FVC. However, it is known that this ratio declines with age, and so the true lower limit of normal (LLN) for FEV1/FVC also declines. This may result in misclassification of disease, with an overdiagnosis in the elderly and underdiagnosis in the young age categories [99]. The sex differences in the incidence may also be influenced by this reasoning since the cross over point for a plot of the fixed ratio FEV1/FVC and the true LLN against age is at a later age in women [93]. We are aware of this limitation, but as information on height and race is not systematically reported in the database, we were not able to calculate the LLN and had to use the fixed ratio of FEV1/FVC [100].

In conclusion, in the Netherlands around 3 on 1,000 subjects are newly diagnosed with COPD per year, however, the true incidence of COPD, based on spirometry criteria, may be 30-40% higher. The lifetime risk that COPD would be diagnosed over the coming 40 years, if diagnostic criteria and processes remain the same, was 12.7% for a 40 year-old-man still free of COPD and 8.3% for a woman. If ascertainment increases this is likely to be higher. Mortality rates are substantially higher in patients with COPD than in the general population, which emphasizes the need for better primary and secondary prevention in patients with COPD.

CHAPTER 3

Effectiveness of long-acting bronchodilators in COPD

3.1

Comparative effectiveness of tiotropium and long-acting β_2-agonists in preventing severe COPD exacerbations

Abstract

Aim: To compare the risk of chronic obstructive pulmonary disease (COPD) exacerbations requiring hospitalization, between COPD patients treated with tiotropium and those treated with long-acting β_2-agonists (LABA).

Methods: A nested case-control study was conducted in a cohort of COPD patients using data from the Dutch IPCI database from 2000 to 2007. Cases were all COPD patients diagnosed with a first COPD exacerbation requiring hospitalization. To each case, all eligible controls were matched on age, sex and index-date. COPD severity was assessed either via spirometry or proxy. The odds of hospitalization for COPD exacerbation during use of tiotropium was compared to the odds during use of LABA. Conditional logistic regression analysis was used to calculate adjusted odds ratios (OR_{adj}) with 95% confidence intervals (CIs).

Results: Within the cohort of 6,788 COPD patients, 619 had at least one COPD exacerbation requiring hospitalization during follow-up. The one-year risk of exacerbations requiring hospitalization was 2.2% (95%CI 1.8%-2.6%) in mild/moderate and 10% (95%CI 8.2-11.8%) in severe/very severe COPD patients. The risk of hospitalizations for COPD exacerbations was lower during use of tiotropium compared to use of LABA (OR_{adj} 0.69, 95%CI 0.40-1.19) although not statistically significant.

Conclusion: In this primary care-based study of COPD patients, there was a statistically non-significant reduced risk for COPD hospitalizations with tiotropium compared to LABA.

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of chronic morbidity and mortality worldwide. The disease is often complicated by exacerbations that ensue with increasing severity [54] and contribute to declining lung function and health status [55]. Hurst et al recently concluded that although exacerbations become more frequent and more severe as COPD progresses, the rate at which they occur appears to reflect an independent susceptibility phenotype [101]. An exacerbation of COPD is defined as "an event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough, and/or sputum and beyond normal day-to-day variations, that is acute in onset and may warrant a change in regular medication in a patient with underlying COPD" [102, 103]. Exacerbations contribute considerably to the morbidity associated with COPD [104]. Moreover, exacerbations lead to an increase in health care costs, disability, and result in premature death. As a consequence, exacerbations are currently considered to be one of the most relevant outcome parameters in randomized controlled trials in patients with COPD [103].

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, bronchodilators are the mainstay for symptomatic management of COPD [105]. Bronchodilator treatments include short-acting and long-acting β_2-agonists (LABA), short-acting and long-acting anticholinergics (LAAC), and methylxanthines. Long-acting bronchodilators are found to be more effective and convenient than the short-acting agents [59]. Tiotropium is currently the only EMA/FDA approved long-acting inhaled anticholinergic bronchodilator, which should be used once daily for long-term maintenance treatment of COPD. The efficacy and safety of tiotropium have been demonstrated in several randomized placebo-controlled trials [60-68], in one ipratropium-controlled trial [69], and in a pooled clinical trial analysis of tiotropium safety [70]. Compared to placebo, inhaled LABA (salmeterol or formoterol) reduced the risk of severe COPD exacerbations requiring withdrawal or hospitalization, and compared with LABA, tiotropium resulted in a decrease of 48% in the incidence of COPD exacerbations [71].

Only few RCTs compared lung function and health outcomes between users of tiotropium and salmeterol, in patients with moderate to severe COPD [64, 72-74]. However, these trials (total of 2,483 patients only and 1,079 patient years) focused mainly on lung function as primary endpoint and were possibly not powered to study equivalence or differences between the two drugs regarding less common hard clinical endpoints such as COPD exacerbations leading to hospitalization. No RCTs comparing tiotropium and formoterol in patients with COPD focusing on hospitalisation due to COPD exacerbation are available; however, a RCT has been designed to investigate the comparative efficacy of two long-acting bronchodilators tiotropium 18 µg daily and salmeterol 50 µg twice daily on exacerbations, but results have not been published yet [104]. In modern health care it is important not only to demonstrate the efficacy of drugs against placebo, but also to compare effectiveness between

treatment alternatives in clinical practice. The need to conduct comparative effectiveness studies is clear from the increasing resources that are made available for this research [106].

The objective of this nested case control study, in a large cohort of 6,788 COPD patients with 23,930 person-years of follow-up, was to compare the effectiveness of tiotropium and LABA in the prevention of hospitalizations for COPD exacerbations in clinical practice.

Methods

Setting

A nested case-control study was conducted in a cohort of COPD patients from the Integrated Primary Care Information Project (IPCI) database. IPCI is a population-based longitudinal database that contains the complete computer-based medical records of currently more than 400 General Practitioners (GPs) throughout the Netherlands [86]. 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 and therefore the medical records do not only capture GP diagnoses and symptoms but also the results and summaries of specialist care. At present, the IPCI database contains information on more than 1 million patients. This database contains anonymized patient identification information (age, sex, patient identification number, and GP registration information), narratives, symptoms, signs, GP and specialist diagnoses, prescriptions, laboratory values, and summaries of specialist letters [86, 88]. The 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 studies [91]. All observational research on the IPCI database is being conducted according to good pharmaco-epidemiological guidelines [92].

The source population consisted of all patients in the IPCI database who were 40 years of age or older, and with at least one year of valid history available in the database. The study period started in January 2000 and ended in May 2007.

COPD cohort

The study population consisted of all patients present during the study period, with at least one year of medical history, diagnosed with COPD and a minimum age of 40 years at time of study entry. COPD patients were identified from diagnoses and narratives. The medical records of all potential cases were reviewed by a medical doctor and classified as: definite COPD - diagnosis by a specialist or a GP diagnosis confirmed by spirometry (FEV1/FVC<70%); probable COPD - COPD diagnosed by the GP with at least two records of COPD within one year of the first record of COPD. All doubtful COPD patients were further reviewed and classified by a pulmonologist (GB). All COPD patients were further categorized into prevalent or incident COPD. Patients with a COPD diagnosis prior to entry into the source population

(e.g. COPD diagnosed in 1995) were defined as having prevalent (existing) COPD. Start date for these patients in the COPD cohort was the start of follow-up for the source population. If patients were disease free at time of start in the source population, and later developed COPD, they were considered as having incident (newly onset) COPD. Start date for these patients in the COPD cohort was the date of incident COPD.

COPD severity was assessed at the time of cohort entry and changes in COPD severity were captured during follow-up, which meant that we allowed severity to change over time. If spirometry was available, severity of COPD was determined according to the GOLD guidelines; in all other patients, previously published algorithms for COPD severity assessment were used [76-78]. In summary, patients were considered to have mild COPD at the time of their first symptoms of COPD, moderate COPD if patients were on regular bronchodilatory treatment (defined as at least 2 prescriptions of the same drug class within 6 months of the first prescription), and severe COPD if they were hospitalized for COPD, or at the time they had their third course of antibiotics for the treatment of respiratory infections in one year time, or at the time they had their second systemic corticosteroid course for the treatment of COPD exacerbations. Finally, patients were considered to have very severe COPD when they were prescribed oxygen therapy or were scheduled for lung transplantation because of COPD.

All COPD patients were followed from cohort entry until the first COPD exacerbation requiring hospitalization, death or end of follow-up, whichever came first.

Cases and controls

All COPD exacerbations were identified in the electronic medical records and adjudicated by two medical doctors, a third doctor arbitrated in case of discrepancies. For this study we only considered COPD exacerbations that resulted in hospitalization. The index date was the date of the first COPD exacerbation leading to hospitalization after study entry.

To each case, all available controls were matched from the COPD cohort on index date, gender and year of birth. Due to this sampling approach, controls could be re-sampled at different moments in time and their contribution should be considered in person-time (moments) rather than subjects (32). This also means that the number of controls per case varies and the proportions may be slightly different.

Exposure

Exposure was categorized by type of drug, timing, duration and dose. All information was obtained from the prescription records. The following types of bronchodilating and anti-inflammatory drugs were considered as study drugs: tiotropium as long-acting anticholinergic agent (LAAC), short-acting anticholinergic agents (SAAC), single-ingredient short-acting β_2-agonists (SABA), single-ingredient long-acting β_2-agonists (LABA, such as salmeterol and formoterol), inhaled corticosteroids (ICS), xanthines and fixed combination therapies (ICS and LABA). Drugs were grouped to look at class effects. The ACs as a class consisted of LAAC

and SAAC, and the class of β_2-agonists comprised of SABA and LABA. ICS was either classified separately or adjusted for depending on the analysis (patients with fixed combinations of ICS and LABA counted in the respective bronchodilator class). Drug exposure was further categorized by timing of use in current use (last prescription covered the index date or ended less than 30 days prior to the index date), past use (last prescription ended more that 30 days prior to the index date), or no use. The primary analysis compared the effect on hospitalized COPD exacerbations between current use of tiotropium and LABA.

Covariates

As potential confounders we considered the severity of COPD as well as various co-morbidities and concomitant drug use. For the primary analysis we used the COPD severity status one year prior to the index date, since severity could be an intermediate factor between the exposure and hospitalization for COPD exacerbation. In addition, we conducted a sensitivity analysis in which we adjusted for severity just prior to the index date.

Other covariates included were smoking history, use of concomitant medication (at least use in the month prior to the index date) and concomitant diseases such as heart failure, ischemic heart diseases, diabetes mellitus, lipid disorders, malignancies and diseases affecting the central nervous system. Finally, resource use, by means of the number of GP office and home visits as well as a home bound life style (two or more home visits in the last month prior to the index date) were taken into account.

Analysis

The risk of hospitalization for a COPD exacerbation was calculated for the COPD cohort while stratifying by COPD severity using Kaplan-Meyer survival analysis. To study potential differences in co-morbidity between patients being prescribed LABA, tiotropium, or LABA and tiotropium together (same prescription dates), we compared patient characteristics between the three groups at the time of the first prescription of any of these drugs after cohort entry. Patients could only appear in tiotropium group and in LABA group if with different dates, or in the tiotropium plus LABA group when those were prescribed in the same date, not being possible to appear in the tiotropium alone or LABA alone a posteriori. Differences in co-morbidity and use of concomitant medication were tested using a non-parametric, Mann-Whitney U test for continuous variables and the Chi-square test for categorical variables.

Conditional logistic regression analysis was used to estimate the matched unadjusted and adjusted risk estimates and 95% CI for the comparison between tiotropium and LABA. Patients currently using both tiotropium and LABA at the same time for more than 15 days were classified separately. In a sensitivity analysis we considered these combined users as either all tiotropium or LABA to look at the robustness of our estimates. All models were adjusted for at least COPD severity, duration of COPD, and smoking. In addition we adjusted

for all factors that were univariately associated with the outcome ($p<0.10$), and also changed the effect estimate of tiotropium by more than 5%.

Stratified analyses were conducted by gender, calendar year, severity of COPD (mild/moderate versus severe/very severe) and, incident or prevalent COPD at study entry. We tested effect modification by adding an interaction term in the conditional logistic regression model (multiplicative interaction). Only if the interaction term based on the effect modifier of interest and current use of tiotropium turned out to be statistically significant ($p<0.05$) in the adjusted model, effect measure modification was considered to be present. All statistical analyses were conducted with the statistical software packages SPSS/PC 15.0 (SPSS Inc, Chicago, Ill).

Results

COPD Cohort

From the source population of 185,325 participants 40 years and older, 6,788 patients were diagnosed with COPD of which 23% were newly diagnosed during the study period (incident COPD). The median follow-up time per COPD patient was 3.5 years, with a total follow-up time of 23.930 person-years. Baseline characteristics of the COPD cohort (at time of cohort entry and at time of first prescriptins) are described in table 1. For 30% of COPD patients the severity was based on FEV1 according to GOLD (spirometry). In the remaining 70%, the

Table 1 Patient characteristics at time of cohort entry and at time of first prescriptions for LABA or tiotropium or tiotropium plus LABA during FU

Time	**At cohort entry**	**At start of first prescription during follow-up**		
Characteristics	**COPD cohort No.(%)**	**Tiotropium No.(%)*†**	**LABA No.(%)***	**Tiotropium plus LABA No.(%)*†‡**
Number of patients	6,788	1,048	3,214	153
Gender				
♂	3,889 (57.3)	639 (61.0)	1,829 (56.9)	84 (54.9)
♀	2,899 (42.7)	409 (39.0)	1,385 (43.1)	69 (45.1)
Age (mean, SD)	67.3 (±12.2)	69.1 (±11.0)	67.6 (±11.9)	67.3 (±11.0)
40-59 (No.,%)	1,797 (26.5)	**225 (21.5)**	863 (26.9)	39 (25.5)
60-69 (No.,%)	1,739 (25.6)	**278 (26.5)**	828 (25.8)	43 (28.1)
70+ (No.,%)	3,252 (47.9)	**545 (52.0)**	1,523 (47.3)	71 (46.4)
Smoking history				
No smoking	525 (7.7)	**82 (7.8)**	265 (8.2)	**6 (3.9)**
Current smoking	2,737 (40.3)	**520 (49.6)**	1,413 (44.0)	**66 (43.1)**
Past smoking	417 (6.1)	**105 (10.0)**	202 (6.3)	**11 (7.2)**
Smoking unknown	3,101 (45.7)	**340 (32.4)**	1,334 (41.5)	**70 (45.8)**

Table 1 (continued)

Time	At cohort entry	At start of first prescription during follow-up		
Characteristics	**COPD cohort No.(%)**	**Tiotropium No.(%)*†**	**LABA No.(%)***	**Tiotropium plus LABA No.(%)*†1**
Severity at cohort entry				
Mild	2,694 (39.7)	237 (22.6)	763 (23.8)	**29 (19.0)**
Moderate	2,713 (40.0)	489 (46.7)	1,508 (46.9)	**70 (45.8)**
Severe	1,280 (18.9)	301 (28.7)	874 (27.2)	**50 (32.7)**
Very Severe	101 (1.5)	21 (2.0)	69 (2.1)	**4 (2.5)**
Mean time since first diagnosis	**2.4 (±4.1)**	**2.1 (±1.7)**	**0.9 (±1.2)**	**1.1 (±1.5)**
Co-morbidity (history) at cohort entry or at time of first prescription				
Asthma	1,042 (15.4)	176 (16.8)	625 (19.4)	17 (11.1)
Myocardial infarction	457 (6.7)	80 (7.6)	231 (7.2)	13 (8.5)
Angina pectoris	994 (14.6)	166 (15.8)	518 (16.1)	26 (17.0)
Ischemic heart disease	188 (2.8)	**46 (4.4)**	98 (3.0)	5 (3.3)
History of stroke or TIA	391 (5.8)	69 (6.6)	193 (6.0)	7 (4.6)
Peripheral arterial disease	441 (6.5)	**107 (10.2)**	233 (7.2)	**20 (13.1)**
Heart failure	793 (11.7)	136 (13.0)	395 (12.3)	17 (11.1)
Ventricular arrhythmia	335 (6.3)	9 (0.9)	15 (0.5)	0
Hypertension	1,422 (21.0)	**266 (25.4)**	334 (10.4)	**22 (14.4)**
Hyperlipidemia	1,769 (26.1)	**387 (36.9)**	937 (29.2)	**58 (37.9)**
Diabetes mellitus	767 (11.3)	151 (14.4)	382 (11.9)	22 (14.4)
Renal insufficiency	184 (2.7)	37 (3.5)	85 (2.6)	4 (2.6)
Tumors	673 (10.0)	**147 (14.0)**	389 (12.1)	**22 (14.4)**
Pneumonia	571 (8.4)	**149 (14.2)**	353 (11.0)	**18 (11.8)**
Depressive disorders	540 (8.0)	105 (10.0)	305 (9.5)	24 (15.7)
Number GP visits (mean, SD)	5.7 (±5.0)	6.2 (±4.8)	6.2 (±5.1)	5.9 (±5.2)
Home bound lifestyle	58 (1.1)	**9 (0.9)**	7 (0.2)	1 (0.7)
Previous use of drugs				
Ipratropium	1,393 (20.5)	**438 (41.8)**	1,117 (34.8)	**39 (25.5)**
SABA	1,427 (21.0)	394 (37.6)	1,190 (37.0)	**49 (32.0)**
ICS	1,919 (28.3)	**543 (51.8)**	2,290 (71.3)	**114 (74.5)**
Xanthines	182 (2.7)	48 (4.6)	127 (4.0)	**5 (3.3)**
Oral steroids	579 (8.5)	**561 (44.0)**	990 (30.8)	**52 (34.0)**

The values in bold were statistic significant in Chi-square test comparing tiotropium, or TIO+LABA against LABA. *First prescription of tiotropium in tiotropium group or LABA in LABA group. †LABA is the reference category. †1 First prescription of tiotropium and LABA at the same date. Patients can only appear in TIO and in LABA group if with different dates, but not in the TIO+LABA group and then TIO alone or LABA alone (this category corresponds to the first prescription of both drugs at the same date). Abbreviations: ICS (inhaled corticosteroids), GP (general practitioner), LABA (long-acting β_2-agonists), SABA (short-acting β_2-agonists), TIA (transient ischemic attack), SD (standard deviation).

severity of COPD was determined using a proxy as previously described [76-78]. Up to 80% of patients had mild or moderate COPD at cohort entry.

Since COPD has lately been recognized as a systemic disease, we thoroughly characterized extra-pulmonary co-morbidities in the COPD cohort. The most frequent co-morbidities were angina pectoris, hypertension, heart failure, hyperlipidemia, diabetes mellitus and tumors (table 1).

Table 1 also describes the characteristics of cohort members starting with LABA, tiotropium or tiotropium & LABA (same prescription dates), during follow-up. Almost half of the COPD patients had moderate COPD at the time of first prescription of any of these drugs (table 1). In general, patients receiving tiotropium were slightly older and had more co-morbidities than patients starting on LABA. Age, smoking history, and some comorbidities differed significantly between persons starting on LABA or tiotropium (table 1). The small group (n=153) of patients receiving both tiotropium and LABA as first prescription during follow-up tended to have more severe COPD compared to the LABA and tiotropium users.

Hospitalization due to COPD exacerbations

Within the cohort, 619 patients were hospitalized for a COPD exacerbation of which 351 (56.7%) were male (table 2). The mean age of the cases was 72.2 (SD=±10.2) years. COPD severity (severe/very severe) was strongly related to hospitalization for COPD. The one-year risk of at least one exacerbation requiring hospitalization was 2.2% (95%CI 1.8%-2.6%) for mild/moderate COPD patients and 9.7% (95%CI 8.2%-11.8%) for severe/very severe COPD patients (figure 1).

Table 2 Characteristics of cases and controls and crude OR for a COPD exacerbation leading to hospitalization

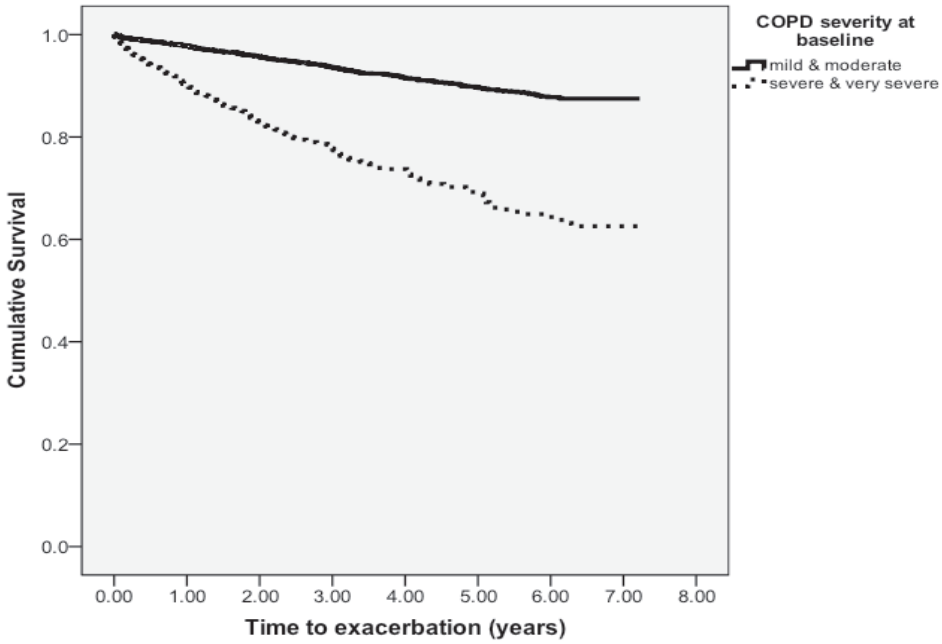
Characteristics	Cases N=619 (%)	Control moments N=24,820 (%)	Matched OR* (95% CI)
Age (mean, SD)	72 (10.2)	72.7 (7.9)	
Male	351 (56.7)	17,055 (68.7)	
Smoking			
Never	43 (6.9)	2,510 (10.1)	Reference
Current	260 (42.0)	9,361 (37.7)	1.59 (1.14-2.21)
Past	27 (4.4)	1,896 (7.6)	0.89 (0.54-1.45)
Missing	289 (46.7)	11,033 (44.5)	1.46 (1.05-2.03)
COPD severity			
Mild	67 (10.8)	5,648 (22.8)	Reference
Moderate	155 (25.0)	12,503 (50.4)	1.03 (0.77-1.34)
Severe	344 (55.6)	6,305 (25.4)	4.75 (3.64-6.21)
Very severe	53 (8.6)	358 (1.4)	12.2 (8.33-18.0)
Number of GP visits (mean, SD)	7.8 (6.3)	5.7 (4.7)	1.07 (1.06-1.08)
Home bound lifestyle	26 (4.2)	221 (0.9)	4.83 (3.15-7.4)

Table 2 (continued)

Characteristics	Cases N=619 (%)	Control moments N=24,820 (%)	Matched OR* (95% CI)
Co-morbidity (history of events)			
Myocardial infarction	60 (9.7)	2,346 (9.5)	1.17 (0.89-1.54)
Angina pectoris	134 (21.6)	4,444 (17.9)	1.33 (1.09-1.63)
Other ischemic heart disease	24 (3.9)	1,044 (4.2)	1.01 (0.67-1.54)
Peripheral arterial disease	71 (11.5)	2,175 (8.8)	1.36 (1.05-1.75)
Stroke	52 (8.4)	2,140 (8.6)	0.98 (0.73-1.32)
Arrhythmia (atrial fibrillation, other)	57 (9.2)	2,559 (10.3)	0.88 (0.67-1.17)
Hypertension	145 (23.4)	6,319 (25.5)	0.88 (0.73-1.06)
Heart failure	181 (29.2)	3,759 (15.1)	2.56 (2.11-3.09)
Hyperlipidemia	174 (28.1)	8,584 (34.6)	0.78 (0.65-0.94)
Diabetes mellitus (type I, type II)	103 (16.6)	3,595 (14.5)	1.22 (0.98-1.51)
Renal disease	34 (5.5)	1,029 (4.1)	1.46 (1.02-2.10)
Pneumonia	152 (24.6)	3,053 (12.3)	2.29 (1.89-2.77)
Depressive disorders	71 (11.5)	2,004 (8.1)	1.31 (1.02-1.69)
Tumors (non-cerebral)	109 (17.6)	3,633 (14.6)	1.27 (1.03-1.58)
Concomitant medication (current versus non use)			
Central nervous system drugs			
Hypnotics and sedatives	96 (15.5)	2,524 (10.2)	1.54 (1.23-1.94)
Anxiolytics	83 (13.4)	2,206 (8.9)	1.49 (1.18-1.90)
Antidepressants (SSRI)	31 (5.0)	755 (3.0)	1.51 (1.04-2.19)
Anticholinergic drugs (except respiratory)	19 (3.1)	608 (2.4)	1.25 (0.78-1.99)
Drugs affecting cerebrovascular and cardiovascular disease			
Nitrates	52 (8.4)	1,481 (6.0)	1.43 (1.06-1.92)
Platelet inhibitors	118 (19.1)	4,749 (19.1)	1.08 (0.88-1.33)
Anti-hypertensives	275 (44.4)	10,158 (40.9)	1.20 (1.00-1.40)
Corticosteroids (systemic)	207 (33.4)	2,044 (8.2)	5.93 (4.97-7.09)
Antibiotics	147 (23.7)	2,030 (8.2)	3.50 (2.89-4.25)
NSAIDs	35 (5.7)	1,834 (7.4)	0.73 (0.52-1.03)
Vitamin K antagonists	56 (9.0)	2,013 (8.1)	1.20 (0.90-1.59)
Lipid lowering drugs	60 (9.7)	2,862 (11.5)	0.87 (0.66-1.15)
Other respiratory drugs			
Mucolytics	105 (17.0)	1,454 (5.9)	3.52 (2.82-4.39)
Short-acting anticholinergics	245 (39.6)	6,389 (25.7)	2.87 (2.32-3.55)
Short-acting β_2 agonists	257 (41.5)	5,106 (20.6)	4.55 (3.49-5.92)
Inhaled corticosteroids	273 (44.1)	8,699 (35.0)	2.18 (1.73-2.74)
Xanthines	44 (7.1)	635 (2.6)	3.60 (2.61-4.97)

ORs are not displayed if fewer than 5 subjects exposed to comparison of interest (NA= not applicable as fewer than 5 exposed subjects). Proportions seem to be different because we do not always have the same number of controls per each case. *Matched on age, gender and index date.

Figure 1 Risk of hospitalization for COPD exacerbation over time (years)



Underlying co-morbidities that significantly increased the risk of hospitalization were angina pectoris, peripheral arterial disease, heart failure, renal insufficiency, pneumonia, depression and cancer. Current smoking and use of concomitant medication (as proxy for underlying co-morbidities) such as opioids, hypnotics & sedatives, anxiolytics, and antidepressants were also related to the outcome (table 2). Current use of oral steroids and antibiotics was strongly associated with an increased risk of hospitalisation due to COPD exacerbation but this is explained by protopathic bias where these drugs are initiated for the first symptoms of the COPD exacerbation.

Comparative effectiveness of tiotropium versus LABA

In this primary care-based study, we observed a non-statistically significant reduced risk of COPD exacerbations leading to hospitalization for tiotropium as compared to LABA (OR_{adj} 0.69; 95%CI 0.40-1.19). In patients who used both tiotropium and LABA concomitantly, the probability of exacerbations was increased (OR_{adj} 1.27, 95%CI 0.78-2.07) as compared to LABA alone. Assignment of the combined users group to either tiotropium or LABA (reference) showed that the estimate for tiotropium remained below 1 with either choice. Within the LABA group, the risk of exacerbations requiring hospitalizations did not differ between formoterol and salmeterol (OR_{adj} 1.07; 95%CI 0.79-1.45). Restricting the analysis to patients who used their long-acting bronchodilator for at least 30 days at the index date (to avoid protopathic bias) did not change the effect materially (OR_{adj} 0.76; 95%CI 0.44-1.33) (table 3).

Table 3 Association between use of tiotropium (LABA as reference category) and hospitalizations for COPD exacerbations

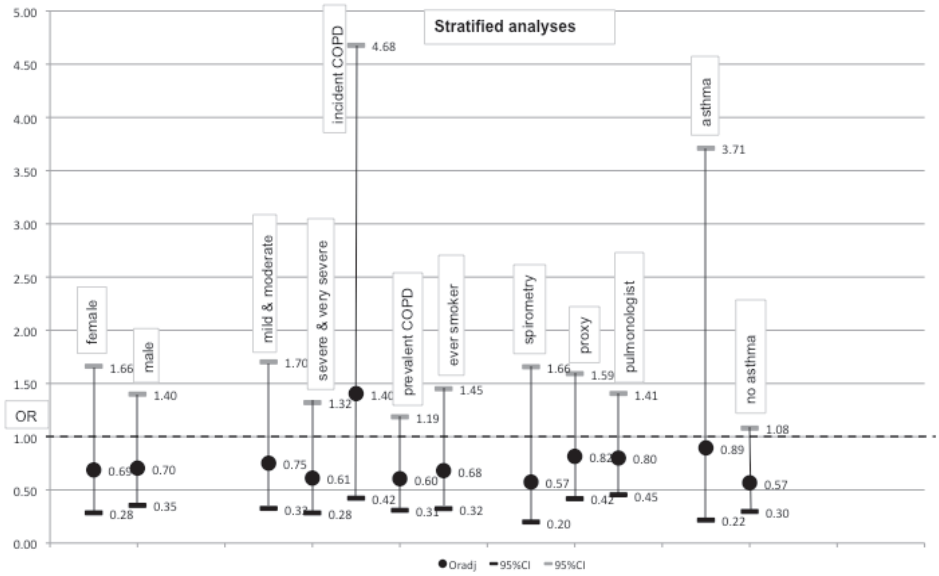
Drugs class	Cases N=619 (%)	Control moments N=24,820 (%)	Matched OR (95%CI)*	Adjusted OR (95%CI) Model 1	Adjusted OR (95%CI) Model 2
Current use of LABA or tiotropium alone or in combination					
Main drug effect					
LABA no tiotropium	196 (31.7)	5,582 (22.5)	Reference	Reference[1]	Reference[1]
Tiotropium no LABA	18 (2.9)	756 (3.0)	0.60 (0.36-1.00)	0.69 (0.40-1.19)	0.69 (0.40-1.19)
Tiotropium + LABA[†]	22 (3.6)	445 (1.8)	1.42 (0.89-2.26)	1.21 (0.74-1.98)	1.27 (0.78-2.07)
Duration of use					
LABA <30 days	10 (1.6)	205 (0.8)	Reference	Reference	Reference
Tiotropium <30 days	1 (0.2)	86 (0.3)	NA	NA	NA
LABA ≥30 days	186 (30.0)	5,377 (21.7)	Reference	Reference	Reference
Tiotropium ≥30 days	17 (2.7)	670 (2.7)	0.65 (0.38-1.10)	0.77 (0.44-1.34)	0.76 (0.44-1.33)
Type of LABA					
Salmeterol	111 (17.9)	3,379 (13.6)	Reference	Reference	Reference
Formoterol	85 (13.7)	2,203 (8.9)	1.21 (0.90-1.61)	1.05 (0.77-1.42)	1.07 (0.79-1.45)

Reference category is "LABA" (NA= not applicable as fewer than 5 exposed subjects). Tiotropium HandiHaler® use.
* Matched on age, gender and index date
Model 1: adjusted for severity of COPD at index date, duration of COPD and smoking
Model 2: adjusted for severity of COPD one year prior to the index date, duration of COPD and smoking (final model in the analysis)
1: Additionally adjusted for number systemic corticosteroids, mucolytics and ICS, SABA, and xanthines.
[†] Use of both drugs started at least 2 weeks prior to index date

Stratified analysis were conducted to inspect effect modification, however no major heterogeneity in effect estimates of tiotropium against LABA was seen across gender, calendar time, and smoking (figure 2). A slightly stronger effect was observed in severe and very severe COPD patients with an OR_{adj} 0.62 (95%CI 0.28-1.34) when compared to mild and moderate COPD patients with an OR_{adj} 0.74 (95%CI 0.33-1.68). Sensitivity analyses addressing some assumptions and biases also showed no major impact on the effect estimates. When stratifying for patients visiting pulmonologist yes or no, no major differences in risk estimates could be observed. In patients with severity assessment by spirometry the protective effect for tiotropium was stronger than in patients for whom COPD severity was assessed by proxy OR_{adj} 0.57 (95%CI 0.20-1.66), versus OR_{adj} of 0.82 (95%CI 0.42-1.59).

In patients without a history of asthma, the protective effect seemed to be stronger (OR_{adj} 0.57, 95% CI 0.30-1.00) compared to patients with a history of asthma (OR_{adj} 0.89; 95% CI 0.22-3.71).

Figure 2 Stratified analyses on association between tiotropium use and the association with hospitalizations due to COPD exacerbation



Adjusted OR (95%CI) for current use of tiotropium versus LABA (might include use of ICS and/or SABA)
* Adjusted for COPD severity 1 year prior to index date, duration of COPD, smoking. Additionally adjusted for number systemic corticosteroids, mucolytics and ICS, SABA, and xanthines.
Notes: Stratified for gender, year of COPD, severity of COPD, incident vs. prevalent COPD, smoking, COPD assessment, and pulmonologist visit and asthma history. Results not shown for <2002 as tiotropium was registered from 2002 on; never smoker and no pulmonologist visit not shown due to low numbers.

Discussion

This COPD cohort study showed several important findings. First, tiotropium reduced the risk of COPD exacerbations leading to hospitalizations in COPD patients in real life as compared to LABA, although this was not statistically significant. This effect was not modified by sex and was strongest in patients whose COPD severity could be assessed by spirometry and in patients without a medical history of asthma. Second, the effect of formoterol and salmeterol on COPD exacerbations leading to hospitalization did not differ. To our knowledge, our data are one of the first to compare the effectiveness of tiotropium and LABA (salmeterol and formoterol) in clinical practice, by means of an observational study.

Third, we demonstrated that several underlying co-morbidities such as angina pectoris, peripheral arterial disease, heart failure, renal insufficiency, pneumonia, depressive disorders and cancer are risk factors for a COPD exacerbation leading to hospital admission.

The efficacy of tiotropium and LABA on the reduction of COPD exacerbations leading to hospitalization has mainly been studied in placebo controlled RCTs. In summary, these RCTs

Table 4 Stratified analyses by COPD severity on association between respiratory drug use and hospitalizations due to COPD exacerbation

Drugs class Mild & Moderate COPD	Cases N=222 (%)	Control moments N=18,157 (%)	Matched OR (95%CI)*	Adjusted OR (95%CI) Model 1	Adjusted OR (95%CI) Model 2
Current use of LABA or tiotropium alone or in combination					
Main drug effect					
LABA no tiotropium	60 (27.0)	3,615 (19.9)	Reference	Reference[1]	Reference[1]
Tiotropium no LABA	8 (3.6)	542 (3.0)	0.84 (0.39-1.81)	0.75 (0.33-1.71)	0.75 (0.33-1.70)
Tiotropium + LABA[†]	8 (3.6)	275 (1.5)	1.85 (0.84-4.08)	2.22 (0.96-5.15)	2.20 (0.95-5.10)
Duration of use					
LABA ≥30 days	55 (24.8)	3,463 (19.1)	Reference	Reference	Reference
Tiotropium ≥30 days	7 (3.2)	476 (2.6)	0.83 (0.37-1.89)	0.75 (0.31-1.78)	0.73 (0.31-1.74)
Type of LABA					
Salmeterol	111 (17.9)	2,320 (12.8)	Reference	Reference	Reference
Formoterol	85 (13.7)	1,295 (7.1)	1.10 (0.64-1.88)	1.10 (0.62-1.94)	1.11 (0.63-1.96)
Drugs class Severe & Very severe COPD	Cases N=397 (%)	Control moments N=6,663 (%)	Matched OR (95%CI)*	Adjusted OR (95%CI) Model 1	Adjusted OR (95%CI) Model 2
Current use of LABA or tiotropium alone or in combination					
Main drug effect					
LABA no tiotropium	136 (34.3)	1,967 (29.5)	Reference	Reference[1]	Reference[1]
Tiotropium no LABA	10 (2.5)	214 (3.2)	0.56 (0.27-1.16)	0.63 (0.29-1.37)	0.61 (0.28-1.32)
Tiotropium + LABA[†]	14 (3.5)	170 (2.6)	1.31 (0.70-2.46)	1.08 (0.56-2.07)	1.07 (0.56-2.05)
Duration of use					
LABA ≥30 days	131 (33.0)	1,914 (28.7)	Reference	Reference	Reference
Tiotropium ≥30 days	10 (2.5)	194 (2.9)	0.61 (0.30-1.27)	0.72 (0.33-1.57)	0.69 (0.32-1.52)
Type of LABA					
Salmeterol	73 (18.4)	1,059 (15.9)	Reference	Reference	Reference
Formoterol	63 (15.9)	908 (13.6)	0.97 (0.67-1.40)	0.92 (0.63-1.35)	0.93 (0.64-1.37)

Reference category is "LABA" (NA= not applicable as fewer than 5 exposed subjects). Tiotropium HandiHaler® use.
* Matched on age, gender and index date
Model 1: adjusted for severity of COPD at index date, duration of COPD and smoking
Model 2: adjusted for severity of COPD one year prior to the index date, duration of COPD and smoking (final model in the analysis)
1: Additionally adjusted for number systemic corticosteroids, mucolytics and ICS, SABA, and xanthines.
[†] Use of both drugs started at least 2 weeks prior to index date

have shown that both LABA and tiotropium were efficacious in reducing the risk of hospitalization related to COPD in comparison to placebo with risk estimates around 0.70, both for tiotropium and LABA [62, 68, 70, 71, 107].

Some RCTs have compared the effect of tiotropium and LABA on the risk of surrogate endpoints and hospitalization for COPD exacerbations. Rodrigo et al [71] conducted a sys-

tematic review with meta-analysis of 27 RCTs (with more than one month in duration), using data of 20,527 patients with COPD, GOLD II or III. They concluded that compared with LABA, tiotropium resulted in a decrease of severe COPD exacerbations (RR 0.52; 95% CI 0.31-0.86) [71]. In their meta-analysis of nine RCTs and 8,002 patients included, Barr et al [62] found similar reductions in hospitalizations for COPD exacerbations when comparing tiotropium with ipratropium or salmeterol, but neither of these differences was statistically significant. Briggs et al [73] and Brusasco et al [72] also reported a reduced risk of hospitalisation for COPD exacerbation in patients treated with tiotropium compared to salmeterol. In their 12-week RCT of 653 COPD patients, when comparing tiotropium with salmeterol, Briggs et al [73] reported an OR 0.43 (95%CI, 0.13-1.42), and Brusasco et al [72] an OR 0.59 (95%CI, 0.29-1.23), in their RCT of 1,207 patients with COPD; however, these short-term studies were possibly underpowered to discern significant differences in COPD related hospitalizations. In their network meta-analysis of exacerbations, Baker et al report for tiotropium versus LABA an OR 0.82 (95%CI 0.72-0.93) for the mixed-treatment comparison meta-analysis of 43 RCTs using and a total of 31,020 patients [108]. To resume, most of the published studies report a better performance of tiotropium when compared to LABA with regard to the prevention of COPD exacerbations.

Although we have data from RCTs on the efficacy of tiotropium, compared to LABA, on the risk reduction of severe COPD exacerbation, data from RCTs cannot always be extrapolated to the general population as RCTs use stringent inclusion and exclusion criteria, and severity differed, as in some of the RCTs, patients had to have moderate-to-severe COPD to be included in the study. For this reason, it is important to study the effectiveness of tiotropium on the risk of COPD exacerbation requiring hospitalization under real life circumstances.

As for all observational studies, our study has strengths, but also limitations. The main strengths are the size and quality of our data. Great emphasis was put on the assessment of the disease severity and endpoints that were all manually validated by at least 2 medically trained persons. The external validity of our data can be deducted by the fact that our risk estimates and incidence rates are in line with published data. Being observational, the study is sensitive to bias and confounding. We tried to limit misclassification of the outcome by manually reviewing the electronic medical records of all cases by two medically trained researchers who were blinded to drug exposure. Only the definite cases of exacerbations requiring hospitalization were included in our analysis.

Misclassification of exposure might be an issue in our study as exposure was assessed based on the prescription data, rather than dispensing data or actual patient intake, and could thus underestimate or overestimate patient exposure. In addition, in a chronic disease such as COPD, prescriptions initiated by the specialist may have been missed. To study the potential of exposure bias, a sensitivity analysis was conducted by stratifying on patients not seen by a pulmonologist and patients who consulted a pulmonologist. For the group of patients not seen by a pulmonologist, by definition, all prescriptions for respiratory drugs are

available in the database. The results for this group of patients were similar to the results of the overall dataset suggesting that bias due to misclassification of exposure is minimal.

To limit confounding by indication, we decided to use current use of LABA as reference category assuming that patients being treated with LABA are more similar to patients being treated with tiotropium regarding COPD severity and underlying co-morbidity. Baseline characteristics of tiotropium and LABA users at the time of first prescription showed indeed that COPD severity was very similar in tiotropium and LABA users whereas the underlying comorbidity was higher in the tiotropium-exposed group compared to the LABA exposed group, implying that our effect estimate for tiotropium versus LABA is a conservative estimate and that the actual risk might in reality be lower. Significant efforts were put into adjusting for COPD severity, by assessing COPD severity longitudinally, which allowed for flexibility in the timing for adjustment, which is an improvement over regular practice in pharmacoepidemiological studies in the area of COPD. However, we were aware that spirometry was only available for 30% of subjects meaning that residual confounding by severity cannot be excluded. When stratifying by spirometry versus proxy, the trend remained, which indicates that the proxy measure used was quite accurate. Residual confounding by severity may explain why the risk of exacerbations was higher in patients using both tiotropium and LABA together as compared to LABA alone. Furthermore, protopathic bias may play a role but was dealt with in the study. One could well hypothesize that general practitioners initiate the use of inhaled bronchodilators as treatment for the first worsening of symptoms of these endpoints. Conducting a sensitivity analysis only including those patients who used the drugs for more than 30 days controlled for this bias.

Finally, we demonstrated that the reduced risk of COPD exacerbation was mainly observed in COPD patients without a medical history of asthma compared to patients with a medical history of asthma. This finding is important as tiotropium; is currently under investigation as add-on treatment in adults with persistent asthma [109].

In conclusion, in a nested case-control study in a primary care based COPD cohort, we demonstrated a statistically non-significant trend towards a reduced risk for COPD hospitalizations with tiotropium compared to LABA.

CHAPTER 4
Safety

4.1

Use of tiotropium Respimat® Soft Mist Inhaler vs. tiotropium HandiHaler® and mortality in patients with COPD

Abstract

Background: Tiotropium is a long-acting once daily-inhaled anticholinergic that can be delivered via HandiHaler®, a dry powder inhaler or via Respimat® Soft Mist Inhaler (SMI), a novel, propellant-free inhaler which has been developed and proposed as an alternative delivery device. Data from RCTs suggest that use of tiotropium Respimat® is associated with an increased risk of mortality.

Objectives: To explore the risk of mortality in a cohort of users of tiotropium administered via Respimat® SMI versus HandiHaler®.

Methods: Within the Dutch primary care IPCI database, we first defined a source population of patients being 40 years or older with at least 1 year of follow-up. The study period ran from 2000 to 2010. All patients were followed from start of study until the patient died or end of follow-up. From this source population, we defined a cohort of tiotropium users, either being prescribed Respimat® SMI or HandiHaler®. Based on tiotropium prescription data, we defined episodes of tiotropium use (Respimat® SMI or HandiHaler®) taking gaps and overlap of prescriptions into account. The risk of mortality, within these episodes of drug use, was calculated using a Cox proportional hazard regression analysis. Crude and adjusted hazard ratios (HR) were calculated with corresponding 95% confidence intervals (CI).

Results: Within the total source population of 501,474 patients we defined a tiotropium cohort of 11,753 users, 272 patients died while being exposed to either tiotropium HandiHaler® or tiotropium Respimat® SMI. Use of tiotropium Respimat® SMI, compared to use of tiotropium HandiHaler®, was associated with a 50% increased risk of dying (crude HR 1.51, 95% CI 1.09 - 2.09), but this effect attenuated upon adjustment for baseline differences (HR_{adj} 1.21, 95% CI 0.85 – 1.73). No dose response relationship could be observed. No association with cardiovascular and cerebrovascular death could be observed.

Conclusions: Use of tiotropium Respimat® SMI versus tiotropium HandiHaler®, is not associated with an statistically increased risk of dying. We can exclude an excess risk of more than 73%.

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 [110]. COPD is characterized by a progressive decline in lung function, which cannot be reversed by treatment. In 2004, the Food and drug administration (FDA) approved the use of tiotropium in the USA, delivered by the HandiHaler® device, a single-dose dry powder inhaler (DPI) [111], and the first long-acting anticholinergic bronchodilator for the treatment of COPD [112], but in the Netherlands it was marketed in 2002. Tiotropium exerts his action via a prolonged (24-hour) blockade of the muscarinic M_3-receptors [113].

Tiotropium HandiHaler® (Spiriva®) is known to be a potent long-acting bronchodilator whose clinical benefits have been established in several clinical studies [62, 66-68]. The lung function improvements and the safety associated with tiotropium HandiHaler® have been well established in clinical trials of COPD patients [64, 67, 69, 72, 114, 115], 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.

A new generation, propellant-free inhaler, known as the Respimat® Soft Mist Inhaler (SMI), has been developed and proposed as an alternative device for use with tiotropium [116]. 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 DPIs of MDIs [113, 117].

In 2008, concerns were raised on the cardiovascular and cerebrovascular safety of tiotropium. 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 case-control study reporting an increased risk for mortality and/or cardiovascular events in patients who received inhaled anticholinergics (ipratropium or tiotropium). [112, 118, 119] In their initial report to the FDA, Boehringer Ingelheim also reported an increased risk of mortality with tiotropium Respimat® SMI device (not yet approved in the US) 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 data from 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 [120].

As the UPLIFT study only included a treatment regimen of tiotropium HandiHaler® versus placebo, evidence about the risk of mortality in patients treated with tiotropium Respimat® SMI is still limited. We therefore conducted a cohort study to compare the risk of mortality in patients treated with tiotropium Respimat® SMI using treatment with tiotropium HandiHaler® as reference category.

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 [86]. 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 [88]. 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 [90]. 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 [91]. Guidelines on good pharmaco-epidemiological research are rigorously followed by all researchers working on the IPCI database [92].

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. 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 comorbidity. The study period lasted from 01.01.2000 up to 30.09.2010.

Tiotropium cohort

All patients who received a prescription for tiotropium (either Respimat® SMI or HandiHaler®), 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 (inception cohort) or start of follow-up for prevalent users.

From the tiotropium prescriptions, episodes of use were delineated taking into account potential overlap and gaps. If the subsequent prescription overlapped the previous prescription, with more than 20%, the two prescriptions were combined into one episode and the stop date of that episode was the date of the second prescription. In case the prescriptions overlapped for less than 20%, the prescriptions were combined into one episode and the stop date of the episode was the stop date of the second prescription extended by the number of days of overlap. In case of a gap between two prescriptions, these prescriptions were only combined into one episode if the duration of the gap was less than 20% of the duration of the first prescription. Subsequent prescriptions were only combined into 1 episode of use in case of equal formulation (either Respimat® SMI or HandiHaler®). A patient was considered as being a switcher when switching from Respimat® SMI to HandiHaler® or vice-versa.

COPD covariate

For reasons of power, we considered all prescriptions of tiotropium, irrespective of indication of use. Co-existing COPD was considered as a separate variable in the analysis. A patient was classified as having 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".

COPD severity was assessed at the start date of each treatment episode, and was based on the number of prescriptions of systemic corticosteroids or the number of antibiotics for the treatment of lower respiratory tract infections, all measured in the one year prior to the episode start. In addition, we took previous hospitalizations for COPD exacerbations and the number of GP visits in the one-year prior to treatment episode start into account.

Follow-up

Subjects were followed from episode start of tiotropium use (either Respimat® SMI or HandiHaler®) until the stop date of the episode of use, the end of follow-up or death whichever occurred first.

Death

All deaths occurring in the tiotropium cohort were identified by a broad search in the database on ICPC code "A96" (death) and death as reason for end of follow-up in the IPCI database. The cause of death was classified into respiratory death, cardio and cerebrovascular death, death related to lung cancer, death related to cancer (excluding lung cancer), other causes or cause unknown. This classification allowed us to conduct subanalysis by cause of death.

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. Concomitant drug use included central nervous system drugs, drugs affecting the cerebrovascular and cardiovascular system, and drugs affecting the respiratory system.

Statistical analysis

To compare the baseline characteristics of the patients using tiotropium Respimat® SMI or tiotropium HandiHaler®, at time of start of treatment episode, the 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 of all cause death associated with the use of tiotropium Respimat® SMI versus HandiHaler®. The final model was built upon adjustment for smoking, COPD severity (by proxy), previous use of tiotropium and adjusting on all factors that changed the crude HR with more than 5%.

Subanalyses were done on cause of death, and diagnosis of COPD. Sensitivity analysis were done excluding episodes of switching. All statistical analyses were conducted with the statistical software packages SPSS/PC 15.0 (SPSS Inc, Chicago, III).

Results

Cohort of tiotropium users

Within the total source population of 501,474 patients we identified 11,753 tiotropium users, having a total of 30,217 episodes of tiotropium use (either HandiHaler® or Respimat® SMI). The mean (SD) age of the patients at the start of the first tiotropium treatment episode was 67.9 (11.7) years and 52.5% of patients were male. 5,337 out of the 11,753 patients (45.4%) were already prescribed a treatment with tiotropium (either HandiHaler® or Respimat® SMI) at cohort entry and thus could be considered as being prevalent users. The mean duration of tiotropium use was 114 days per treatment episode (SD 208 days). Baseline characteristics of patients at start of first prescription of either tiotropium HandiHaler® or tiotropium Respimat® SMI are described in table 1. COPD severity (measured by proxy) and cardiovascular co-morbidity (angina pectoris, peripheral artery disease, myocardial infarction, stroke or transient ischemic attack (TIA), heart failure, ventricular arrhythmia, hypertension, dyslipidemia), cancer 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, anticholinergic drugs, nitrates, systemic corticosteroids, antibiotics, lipid lowering drugs, antiplatelets, diuretics, calcium channel blockers (CCB), anti-arrhythmic drugs, leukotriene receptor antagonists (LTRA), short-acting anticholinergics (SAAC), short-acting β-agonists

(SABA), long-acting β-agonists (LABA), also differed significantly between persons prescribed tiotropium HandiHaler® versus patients being prescribed tiotropium Respimat® SMI (table 1).

All cause mortality

During a total tiotropium exposure of 9,433 treatment years, 272 patients died. The incidence rate of dying was 42.6 per 1,000 person-years (PY) during tiotropium Respimat® SMI exposure and 27.1 per 1,000PY during tiotropium HandiHaler® exposure.

Table 2 describes the crude and adjusted hazard ratio of risk of dying in patients receiving tiotropium Respimat® SMI versus tiotropium HandiHaler®. From the 272 patients who died, 227 (83.4%) were receiving tiotropium HandiHaler® while 45 were receiving tiotropium Respimat® SMI (16.5%). In the crude analysis, use of tiotropium Respimat®, compared to use

Table 1 Patient characteristics at start of first treatment episode during FU

Characteristics	Tiotropium Handihaler Nº.(%)	Tiotropium Respimat* Nº.(%)
Number of patients	10,290	2,064
Age (mean, SD)	67.9 (11.6)	68.0 (11.7)
Gender		
♂	5,391 (52.4)	1,088 (52.7)
♀	4,899 (47.6)	976 (47.3)
Smoking history	**7,133 (69.3)**	**1,487 (72)**
COPD	9,062 (88.1)	1,829 (88.6)
COPD severity		
Number of antibiotics in 1 year prior (mean, SD)	1.5 (0.9)	1.5 (0.7)
Number of systemic corticosteroids in 1 year prior (mean, SD)	**2.2 (2.0)**	**2.8 (2.7)**
Number of GP visits in the 1 year prior (mean, SD)	**7.5 (6.7)**	**9.8 (7.8)**
Hospitalization for COPD exacerbation in 1 year prior	**169 (1.6)**	**83 (4.0)**
Co-morbidity (medical history of any of the conditions)		
Asthma	3,063 (29.8)	639 (31.0)
Angina pectoris	1,269 (12.3)	282 (13.7)
Ischemic heart disease	713 (6.9)	155 (7.5)
Peripheral arterial disease	**1,230 (12.0)**	**300 (14.5)**
Myocardial infarction	**654 (6.4)**	**180 (8.7)**
Stroke or TIA	**779 (7.6)**	**204 (9.9)**
Heart failure	**1,001 (9.7)**	**258 (12.5)**
Ventricular arrhythmia	887 (8.6)	205 (9.9)
Hypertension	**3,803 (37.0)**	**849 (41.1)**
Dyslipidemia (lipid disorders)	**1,572 (15.3)**	**382 (18.5)**
Cancer	**1,420 (13.8)**	**370 (17.9)**
Pneumonia (1 year before)	**563 (5.5)**	**171 (8.3)**
Parkinsonism	80 (0.8)	20 (1.0)

Table 1 (continued)

Characteristics	Tiotropium Handihaler Nº.(%)	Tiotropium Respimat* Nº.(%)
Depression	1,324 (12.9)	266 (12.9)
Dementia	146 (1.4)	27 (1.3)
Diabetes mellitus	**1,716 (16.7)**	**392 (19.0)**
Renal failure	**609 (5.9)**	**169 (8.2)**
Use of concomitant medication at start of prescription		
Central nervous system drugs		
Opioids	498 (4.8)	121 (5.9)
Hypnotic and sedatives	1,032 (10.0)	218 (10.6)
Anxiolytics	1,043 (10.1)	197 (9.5)
Antidepressants (SSRI)	468 (4.5)	110 (5.3)
Antipsychotics	141 (1.4)	22 (1.1)
Anti-Parkins drugs	61 (0.6)	18 (0.9)
Anticholinergics	**343 (3.3)**	**92 (4.5)**
Antihistaminics	512 (5.0)	107 (5.2)
Drugs affecting cerebrovascular and cardiovascular disease		
Nitrates	594 (5.8)	140 (6.8)
Vitamin K antagonists	812 (7.9)	187 (9.1)
Lipid lowering drugs	**2,459 (23.9)**	**577 (28.0)**
Antiplatelets	**2,204 (21.4)**	**535 (25.9)**
Diuretics	**2,109 (20.5)**	**479 (23.2)**
β-blockers	**2,080 (20.2)**	**462 (22.4)**
CCB	**1,239 (12.0)**	**301 (14.6)**
ACE inhibitors	**2,781 (27.0)**	**640 (31.0)**
Anti-arrhythmic drugs	164 (1.6)	34 (1.6)
Other drugs		
Corticosteroids	**1,010 (9.8)**	**318 (15.4)**
Antibiotics	**2,055 (20.0)**	**512 (24.8)**
NSAIDs	820 (8.0)	155 (7.5)
Respiratory drugs		
Mucolytics	**491 (4.8)**	**155 (7.5)**
LTRA	**178 (1.7)**	**59 (2.9)**
SAAC (Ipratropium)	**699 (6.8)**	**224 (10.9)**
SABA	**1,569 (15.2)**	**430 (20.8)**
LABA	**3,129 (30.4)**	**679 (32.9)**
ICS	**3,505 (34.1)**	**763 (37.0)**
Xanthines	119 (1.2)	28 (1.4)

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

Table 2 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**
Variable	HR (95% CI)	HR (95% CI)	HR (95% CI)
Unadjusted (crude)	**1.51 (1.09 - 2.09)**	**2.14 (1.22 – 3.76)**	1.35 (0.92 – 1.96)
Covariates included in the Cox model to calculate adjusted HRs			
Age	**1.54 (1.11 - 2.13)**	**1.83 (1.04 – 3.22)**	**1.45 (0.99 – 2.10)**
+ Gender	**1.53 (1.10 - 2.12)**	**1.87 (1.07 – 3.28)**	**1.43 (0.98 – 2.08)**
+ smoking	**1.54 (1.11 - 2.12)**	**1.87 (1.06 – 3.28)**	**1.43 (0.98 – 2.08)**
+ use of corticosteroids in 1 year prior to episode start	**1.40 (1.01 – 1.94)**	1.53 (0.87 – 2.71)	1.36 (0.93 – 1.97)
+ number of GP visits in 1 year prior to episode start	1.26 (0.91 – 1.75)	1.36 (0.76 – 2.40)	1.23 (0.84 – 1.79)
+ hospitalization for COPD in 1 year prior to episode start	1.22 (0.88 - 1.70)	1.32 (0.74 – 2.34)	1.18 (0.81 – 1.73)
+ use of Antibiotics for treatment of LRTI in 1 year prior to episode start	1.22 (0.87 - 1.70)	1.32 (0.74 – 2.34)	1.18 (0.81 – 1.73)
+ adjustment for use of mucolytics and diuretics*	1.15 (0.82 – 1.60)	1.18 (0.66 – 2.10)	1.13 (0.77 – 1.66)
+ number of previous episodes of tiotropium Respimat® and/or HandiHaler® use	1.15 (0.82 – 1.60)	1.18 (0.66 – 2.10)	1.13 (0.77 – 1.66)
+ calendar time (year of start date treatment episode)	1.21 (0.85 – 1.73)	1.23 (0.68 – 2.22)	1.20 (0.81 – 1.80)

* variables that changed the crude HR with more than 5%

of tiotropium HandiHaler®, was associated with a 50% increased risk of dying (crude HR 1.51, 95%CI 1.09-2.09) (table 2). This effect attenuated upon adjustment for age, gender, COPD severity, use of diuretics or mucolytics, previous episodes of tiotropium use, and calendar time (HR_{adj} 1.21, 95%CI 0.85-1.73) (table 2). No dose response relationship could be observed: the risk of dying in users of tiotropium Respimat® SMI 2.5 µg daily was similar to the one of tiotropium Respimat® SMI 5 µg daily.

Subanalyses

Cause of death was cardiovascular or cerebrovascular in 66 patients (24.3%), respiratory in 43 patients (15.8%), cardiovascular and respiratory in 15 patients (5.5%), lung cancer in 46 patients (16.9%), other cancers in 31 patients (11.4%), death due to other causes in 24 patients (8.8%) and for 47 patients (17.3%), the cause of death could not be defined based on the information in the medical record.

The risk of cardio-and cerebrovascular death was not increased (HR_{adj} 0.97, 95%CI 0.46-2.04) (table 3). It should be noted however; that the power for cause of death analyses was due to low numbers.

In the majority of users of tiotropium, (87.8%), the indication for tiotropium use was COPD. In patients with COPD, the adjusted risk of dying for patients treated with tiotropium Respimat® SMI was 1.22 (95%CI 0.84-1.77) whereas it was 0.88 (95%CI 0.24-3.27) in patients without COPD (table 4).

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

Cardiovascular and cerebrovascular mortality (n= 66)	
Variable	HR (95% CI)
Unadjusted (crude)	1.17 (0.58 – 2.37)
Covariates included in the Cox model to calculate adjusted HRs	
Age	1.19 (0.59 – 2.42)
+ Gender	1.19 (0.59 – 2.41)
+ smoking	1.19 (0.59 – 2.42)
+ use of corticosteroids in 1 year prior to episode start	1.16 (0.57 – 2.31)
+ number of GP visits in 1 year prior to episode start	1.07 (0.52 – 2.19)
+ hospitalization for COPD in 1 year prior to episode start	1.06 (0.51 – 2.16)
+ use of Antibiotics for treatment of LRTI in 1 year prior to episode start	1.06 (0.52 – 2.17)
+ adjustment for use of mucolytics and diuretics*	1.01 (0.49 – 2.07)
+ nº. of previous episodes of tiotropium Respimat® and/or HandiHaler® use	0.98 (0.48 – 2.02)
+ calendar time (year of start date treatment episode)	0.97 (0.46 – 2.04)

*- variables that changed the crude HR with more than 5%

Table 4 Sensitivity analysis: Crude and adjusted Hazard Ratios (HRs) for all-cause mortality in users of tiotropium Respimat® versus users of tiotropium HandiHaler®

Mortality in patients with COPD (n= 245)	
Variable	HR (95% CI)
Unadjusted (crude)	**1.56 (1.11 – 2.19)**
Fully adjusted model*	1.22 (0.84 – 1.77)
Mortality in patients without COPD (n= 27)	
Variable	HR (95% CI)
Unadjusted (crude)	0.91 (0.27 – 3.06)
Fully adjusted model*	0.88 (0.24 – 3.27)
Mortality in patients excluding switchers (n=268)	
Variable	HR (95% CI)
Unadjusted (crude)	**1.57 (1.12 – 2.20)**
Fully adjusted model*	1.29 (0.90 – 1.86)

*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, diuretics, mucolytics, previous episodes of tiotropium use and calendar time.

Sensitivity analyses

A sensitivity analysis was conducted excluding treatment episodes that consisted of switching of tiotropium formulation. Upon exclusion of these episodes, the risk of dying (HR_{adj} 1.29, 95%CI 0.90-1.86), related to the use of tiotropium Respimat® SMI did not differ substantially from the risk estimated for the complete dataset (HR_{adj} 1.21, 95%CI 0.85-1.73).

Discussion

In this observational cohort study in the general Dutch population of patients being 40 years or older, we found that the risk of dying was higher in patients being exposed to tiotropium Respimat® SMI compared to tiotropium HandiHaler®, but this effect disappeared almost entirely upon adjustment. Stratification by type of death showed that the risk of cardiovascular death in tiotropium Respimat® SMI vs. tiotropium HandiHaler® was not increased. In the past, concerns were raised on the cardiovascular safety and mortality in patients treated with tiotropium HandiHaler® [118, 119]. The current available data do not longer support this potential association and the FDA reported that tiotropium HandiHaler® can be used in patients with COPD as long as the instructions, as mentioned in the drug label, are respected [121]. In their initial report to the FDA, Boehringer Ingelheim reported a potential increase of death from any cause in association with tiotropium Respimat®. These data were derived from three, one-year, placebo-controlled trials reporting an imbalance in mortality favoring placebo. In the combined trials, the risk of dying was 70 % higher in tiotropium Respimat® treated patients compared to placebo (RR 1.7, 95%CI 1.1-2.8) [120]. Boehringer Ingelheim is currently conducting a large safety study to elucidate the risk of dying in patients treated with tiotropium Respimat® SMI, using tiotropium HandiHaler® as reference category.

Data on the safety of tiotropium in Respimat® SMI mainly result from randomized clinical trials (RCTs), using placebo as reference and with a short duration of follow-up. 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 [116]. 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®. In this study as well, no difference in safety and efficacy of both formulations could be observed [111].

Similar to the data from these clinical trials, we could not observe an increased all-cause mortality or cardiovascular mortality in patients treated with tiotropium Respimat® SMI compared to tiotropium HandiHaler®. In the past, safety concerns on the use of tiotropium mainly related to cardiovascular safety, which cannot be confirmed by the UPLIFT study or by our data. Stratification between patients with or without diagnosis of COPD did not show major differences apart from a somewhat lower risk in patients without COPD diagnosis. This is of importance, especially since the recent publication of the TALC (Tiotropium bromide as an Alternative to increased inhaled glucocorticoid in asthma patients inadequately controlled on a Lower dose of inhaled Corticosteroid) study, demonstrating that – when added to ICS– tiotropium improved symptoms and lung function in patients with inadequately controlled

asthma [122]. The publication of this study will certainly increase the off-label prescription and use of tiotropium in patients with asthma, and information of the safety of these drugs in patients with asthma is important.

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, the source population being used is representative from the general population, which eliminates selection bias. Being observational, the study is sensitive to bias and confounding. To adjust for COPD severity, we used an algorithm already successfully used by other research groups [76-78]. Despite these measures, remaining confounding by indication, including 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.

In conclusion, we did not observe a higher risk of mortality in patients treated with tiotropium Respimat® compared to tiotropium HandiHaler® in the adjusted analyses.

4.2

Inhaled anticholinergic drugs and the risk of acute urinary retention

Abstract

Objective: Acute urinary retention (AUR) has been associated with the use of inhaled anticholinergic drugs, which are used as first-line treatment of chronic obstructive pulmonary disease (COPD). This association has not yet been investigated and quantified under real life circumstances.

Materials and methods: We conducted a nested case-control study within a cohort of COPD patients from the Integrated Primary Care Information (IPCI) database. The cohort consisted of all COPD patients ≥ 45 years, registered between 1996 and 2006, with at least 12 months of valid history. Cases were patients with a first diagnosis of AUR. To each case, controls were selected matched on age, gender and index date. Multivariate conditional logistic regression analysis was used to calculate adjusted odds ratios (OR_{adj}) with 95% confidence intervals (95%CI).

Results: Within the cohort of 22,579 COPD patients, 209 cases were identified. Current use of inhaled anticholinergic drugs was associated with a 40% increase in risk for AUR (OR_{adj} 1.40; 95%CI 0.99-1.98) compared to non-users. Among current users, the risk was highest for the recent starters (OR_{adj} 3.11; 95%CI: 1.21-7.98). The risk of long-acting anticholinergic drug tiotropium was not substantially different from that of the short-acting anticholinergic ipratropium. The association was not dose-dependent, but changed by mode of administration, with nebulizers having the highest risk (OR_{adj} 2.92; 95%CI, 1.17-7.31). Especially in male COPD patients with benign prostatic hyperplasia the association was strongest (OR_{adj} 4.67; 95%CI, 1.56-14.0).

Conclusion: Current use of inhaled anticholinergic drugs increases the risk of AUR especially in patients with benign prostatic hyperplasia or if administered via nebulizer.

Introduction

Chronic obstructive pulmonary disease (COPD) is a disease characterized by a largely irreversible obstruction of the airways, and encompasses both emphysema and chronic bronchitis. COPD is a leading cause of chronic morbidity and mortality worldwide [2]. The primary goal of COPD treatment is to reduce the symptoms of breathlessness and to improve quality of life. Bronchodilator medications are central to the symptomatic management of COPD and encompass inhaled β_2-agonists and anticholinergics. For both types of inhaled bronchodilators, short-acting (multiple administrations per day) and long-acting (once daily) drugs are available. The long-acting β_2-agonists (salmeterol, formoterol) and the long-acting anticholinergic drug (tiotropium) are recommended as maintenance treatment in patients with moderate to very severe COPD [7]. However, systemic use of anticholinergic drugs has been associated with acute urinary retention (AUR) [123], which causes significant morbidity and mortality [124]. Both COPD and AUR are highly prevalent diseases in elderly males [125].

Anticholinergic drugs bind to muscarinic receptors and thereby inhibit the parasympathetic chain which causes bronchodilation and reduces mucous secretion [126], but also impairs contraction of the detrusor muscle which could lead to urinary retention [125]. The association between systemic use of anticholinergics and AUR has been demonstrated before, but little is known about the effects of inhaled anticholinergics on AUR [127]. In addition short-acting (ipratropium and oxitropium) and long-acting (tiotropium) anticholinergic drugs may have different effects [128]. Although the systemic effect of inhaled anticholinergics is expected to be low, as absorption via the gastro-intestinal tract and the lungs is limited, adverse effects from inhaled anticholinergic products have been described [123]. In addition, case reports, case series and clinical trials reported the occurrence of urinary retention or urinary outflow obstruction in association with short- and long-acting inhaled anticholinergic drugs [129-131]. Recently published, the UPLIFT study reported an increase of AUR in patients being treated with tiotropium compared to placebo (0.34 vs. 0.21 case per 100 patient-years at risk; Relative Risk (RR) 1.65, 95% confidence interval (CI) 0.92-2.93) [132]. To our knowledge, the association between the use of inhaled anticholinergics and the occurrence of AUR has never been quantified in real life by means of observational studies, where users may differ substantially from selected patients participating in clinical trials. For this reason, we conducted a case control study nested in a cohort of COPD patients.

Materials and methods

Database setting

The study was conducted within the Integrated Primary Care Information (IPCI) database, a longitudinal observational database (dynamic cohort) that started in 1992, and contains

data from computer based patient records of general practitioners (GPs) throughout the Netherlands [133]. The database covers data from more than 500 GPs and encompasses approximately 1 million patients [134].

In the Dutch health care system, patients are registered with a single GP who acts as a gatekeeper of medical care. The electronic medical records from the GP contain coded and anonymous data on patient demographics, symptoms and diagnoses (using the International Classification of Primary Care (ICPC) and free text), clinical findings, referrals, laboratory findings and hospitalizations [133, 135]. Summaries of the hospital discharge letters and information from specialists are entered in a free text format, and hard copies can be provided upon request. The database as well holds all GP prescriptions with details on brand name, quantity, formulation, strength, indication, prescribed daily dose, the Anatomical Therapeutic Chemical (ATC) classification code, and the physician-linked indication [89, 136]. To maximize completeness of the data, GPs are not allowed to use paper-based records [125].

Source population

The source population for this study comprised 191,085 men and women 45 years or older, with at least 12 months of valid database history (i.e. the practice had been contributing data to the IPCI database for at least 12 months and the patient had been registered with the GP for at least 12 months). A one year pre-enrollment period was required in order to be able to characterize the patients. Follow-up started on January 1st, 1996, or the date at which 12 months of valid history was obtained, whichever date was latest.

Study design

To guarantee high exposure prevalence, we conducted a case-control study within a cohort of COPD patients (both incident and prevalent COPD). A patient was considered to have COPD if there was a coded diagnosis for COPD (ICPC R95 or R91), a diagnosis of COPD in the narratives (free text search) or the use of at least 2 bronchodilating drugs during follow-up [137].

Within the COPD cohort, all subjects were followed from cohort entry (start date of follow-up for prevalent COPD patients or date of diagnosis of COPD for incident COPD patients) until the first episode of AUR, the end of the study period (30th September 2006), the time of transferring out of the practice, or death, whichever event occurred first. Patients with a history of AUR prior to the study entry were excluded.

Cases and controls

AUR was defined as the sudden inability to pass any urine, requiring catheterization.

Within the COPD cohort, all potential cases of AUR were selected by searching on diagnosis codes (ICPC U05.2) and narratives including "urinary", "retention" and "urinary catheterization" as terms. All potential cases of AUR were manually reviewed by 2 medical doctors and

categorized into 3 groups (definite, possible or no AUR). Reviewers were blinded to drug exposure throughout the entire validation process. The date of first symptoms of AUR was considered as the index date. Only the definite cases of AUR were used in the main analysis; a sensitivity analysis was performed using both definite and possible cases. For each case, we used as controls all individuals who had the same age and sex as the case and were in the cohort and AUR free at the index date. Controls were repeatedly sampled according to the incidence density sampling approach and therefore represent control moments rather than persons.

Exposure to anticholinergic drugs

All prescriptions for the inhaled anticholinergic drugs were retrieved from the prescription database. Exposure to these agents was classified as current (last prescription covered the index date or <30 days prior to it), a recent past (last prescription ended ≥30 days and <180 days prior to the index date), distant past (last prescription ended ≥180 days prior to the index date) or never use. For current users of anticholinergic drugs, the effect of daily dose, frequency of use, time since first use and mode of administration was investigated. Daily dose was expressed in defined daily doses (DDD); 1DDD is the average dose of a drug for an adult for the main indication, as defined by the WHO [89].

To study the effect of time since first use, we categorized current users of inhaled anticholinergic drugs into recent starters (patients who received their prescription for an inhaled anticholinergic drug within 2 weeks prior to the index date while not having used anticholinergic drugs in the past 2 years) and chronic users (patients currently using inhaled anticholinergic drugs for more than 2 weeks). To study the mode of administration, we categorized current use of inhaled AC drugs into use via metered-dose (MDI), dry powder inhaler or nebulizer. To study the frequency of use, we categorized current use of inhaled anticholinergic drugs into three categories (=<1, >1 and <4, or >=4 times per day).

Covariates

Data on the presence of different risk factors for AUR - including benign prostatic hyperplasia (BPH) - were extracted from the computerized patient records in the IPCI database through a computerized search on the respective ICPC (for concomitant diseases) or ATC (for concomitant medication) codes. BPH was defined as ICPC code "Y85 = benign prostatic hyperplasia". Only risk factors prior to the index date were taken into account and this was equally done for both cases and controls [138]. Risk factors included current use of concomitant drugs known to cause AUR (other drugs with anticholinergic effects [antihistaminics, antipsychotics and tricyclic antidepressants (TCA's)], analgesic narcotics, benzodiazepines and diuretics), other respiratory drugs (inhaled β_2-mimetics, inhaled corticosteroids, xanthines and oral corticosteroids). In addition, we checked for a medical history of BPH, prostate cancer, urinary incontinence, diabetes mellitus, cardiac diseases (heart failure and myocardial infarction),

cancer, and stroke prior to the index date and a recent (within 30 days prior to the index date) history of urinary tract infection, constipation and immobility [139]. The severity of COPD was quantified in line with the paper from Ernst et al, taking into account the number of dispensed prescriptions of respiratory medications (β_2-mimetics, inhaled corticosteroids, and xanthines, excluding the study drugs), the number of prescriptions for oral corticosteroids, and/or the presence of hospitalization with a primary diagnosis of COPD, all measured in the year before the index date [140].

Statistical analysis

All statistical analyses were conducted with SPSS/PC 12.0 (SPSS Inc, Chicago, Ill). The association between inhaled anticholinergic drugs and AUR was studied by means of a conditional logistic regression analysis. To check for confounders, we first included, together with the exposure of interest (anticholinergics), all covariates that were univariately associated with the outcome. Each risk factor that changed the OR for the anticholinergic drugs with more than 10% was included into the fully adjusted model [141]. In the final model, we also adjusted for COPD severity as well as for those factors that changed the odds ratio (OR) for current exposure of anticholinergic drugs with more than 10%. Effect modification was investigated for presence of BPH and gender. Finally, we included both definite and probable AUR cases to check whether the estimate would decrease as expected.

Results

Patient characteristics

Within the cohort of 22,579 COPD patients 45 years or older, we identified 209 definite and 27 possible cases of AUR. The 209 definite AUR cases that were included in the primary analysis were matched to 16,164 controls. Mean age in the cases was 77.2 (SD= ± 9.4) years and 73.9 (SD= ± 8.1) years in controls.

Compared to controls, the AUR cases were more likely to suffer from immobility and to be affected by prostate cancer, BPH, a recent urinary tract infection or constipation (Table 1). Use of systemic drugs with anticholinergic effects (such as antihistamines and TCAs), inhaled β_2-mimetics, inhaled corticosteroids, analgesic narcotics, benzodiazepines, diuretics and systemic corticosteroids were risk factors for AUR in this COPD cohort (Table 2).

Association of acute urinary retention (AUR) with inhaled anticholinergic drugs

Current use of any inhaled anticholinergic drug was associated with a 50% increase in risk for AUR (OR_{adj} 1.51; 95%CI, 1.08-2.12). After adjusting for COPD severity the risk of AUR associated with inhaled anticholinergic drugs decreased (OR_{adj} 1.40; 95%CI, 0.99-1.98) (Table 3). Past use of inhaled anticholinergic drugs, either recent or distant past, was not associated with an in-

Table 1 Patient characteristics and the association with AUR

Characteristic	Cases (n=209) (%)	Controls (n=16,164) (%)	[a]ORmatched* (95% CI)
Age			
<50	2 (1.0)	127 (0.8)	
50-65	23 (11.0)	2,348 (14.5)	
>65	184 (88.0)	13,689 (84.7)	
Gender			
Male	178 (85.2)	13,918 (86.1)	
Female	31 (14.8)	2,246 (13.9)	
Comorbidity			
Benign prostatic hyperplasia[b]	31 (14.8)	1,143 (7.1)	**1.94 (1.29-2.91)**
Prostate cancer[b]	11 (5.3)	273 (1.7)	**2.56 (1.35-4.85)**
Urinary tract infection	16 (7.7)	79 (0.5)	**16.28 (9.19-28.8)**
Urinary incontinence	10 (4.8)	574 (3.6)	1.05 (0.55-2.04)
Constipation	24 (11.5)	488 (3.0)	**3.28 (2.09-5.15)**
Diabetes mellitus	31 (14.8)	1,933 (12.0)	1.31 (0.89-1.93)
Cardiac diseases	87 (41.6)	6,843 (42.3)	0.96 (0.73-1.27)
Stroke	20 (9.6)	1,229 (7.6)	1.12 (0.69-1.79)
Dementia	2 (1.0)	85 (0.5)	N.A.
Neurological disorders	2 (1.0)	100 (0.6)	N.A.
Cancer	20 (9.6)	1,125 (7.0)	1.37 (0.86-2.19)
Immobility	96 (45.6)	1,800 (11.1)	**5.80 (4.29-7.85)**

Abbreviations: AUR (acute urinary retention); CI (confidence interval); N.A. (non-accessible); OR (odds ratio)

[a] OR for current use vs. no use; [b] only for males

* Matched by age, gender and index date

creased risk of AUR. Among current users of inhaled anticholinergic drugs, the risk – adjusted for COPD severity – was highest for recent starters (prescription started less than 2 weeks prior to the index date), with an OR_{adj} of 3.11 (95%CI, 1.21-7.98), whereas the risk for chronic users (current use for more than 2 weeks) was 1.33 (95%CI, 0.94-1.90) (Table 3).

We did not observe differences in the risk of AUR between long-acting and short-acting anticholinergic drugs: OR_{adj} for tiotropium was 1.55; 95% CI, 0.80-3.00, whereas it was 1.37; 95% CI, 0.96-1.98 for ipratropium (Table 3); this "comparability in risk" remained in all subgroup analyses. The association between the use of inhaled anticholinergic drugs and AUR did not show a clear dose-response effect and no association with frequency of inhalation could be observed (Table 3).

Administration of AC drugs through nebulizers was associated with the strongest risk of AUR (OR_{adj} 2.92; 95%CI, 1.17-7.31), whereas other modes of administration did not significantly increase the risk of AUR (Table 3).

Table 2 Medication use and AUR

Concomitant medication	Cases (n=209) (%)	Controls (n=16,164) (%)	ORmatched [a]* (95% CI)
Inhaled β_2 mimetics	62 (29.7)	3,485 (21.6)	**1.63 (1.17-2.26)**
LABA	19 (9.1)	1,426 (8.8)	1.25 (0.76-2.06)
SABA	37 (17.7)	1,780 (11.0)	**1.84 (1.25-2.71)**
Combination LABA-SABA	6 (2.9)	279 (1.7)	2.18 (0.94-5.04)
Inhaled Corticosteroids	66 (31.6)	4,213 (26.1)	**1.59 (1.14-2.20)**
Antihistaminics	10 (4.8)	421 (2.6)	**2.07 (1.08-3.96)**
Cough suppressants/expectorants	18 (8.6)	957 (5.9)	1.45 (0.88-2.40)
Xanthines	5 (2.4)	335 (2.1)	1.11 (0.45-2.74)
ACE inhibitors	40 (19.1)	3,181 (19.7)	1.04 (0.73-1.49)
Narcotic analgesics	22 (10.5)	514 (3.2)	**3.67 (2.30-5.88)**
5-α-reductase inhibitors (G04CB)[1]	5 (2.4)	150 (0.9)	1.92 (0.70-5.32)
α-blockers (C02CA,G04CA)[1]	35 (16.7)	885 (5.5)	**3.68 (2.49-5.44)**
Antipsychotics	4 (1.9)	126 (0.8)	2.07 (0.74-5.73)
Antidepressants	16 (7.7)	652 (4.0)	**2.42 (1.43-4.10)**
TCA	7 (3.3)	162 (1.0)	**3.93 (1.80-8.55)**
SSRI	7 (3.3)	376 (2.3)	1.66 (0.77-3.58)
Other	2 (1.0)	120 (0.7)	1.63 (0.40-6.68)
Benzodiazepines	42 (20.1)	2,368 (14.6)	**1.50 (1.05-2.15)**
β-blockers	28 (13.4)	2,120 (13.1)	1.04 (0.69-1.57)
Calcium channel blockers	26 (12.4)	1,878 (11.6)	1.03 (0.68-1.57)
Class Ia antiarrhytmics	31 (14.8)	1,656 (10.2)	1.33 (0.90-1.97)
Diuretics	65 (31.1)	3,037 (18.8)	**1.82 (1.32-2.51)**
NSAIDs	15 (7.2)	765 (4.7)	1.61 (0.93-2.79)
Systemic corticosteroids	25 (12.0)	857 (5.3)	**2.62 (1.68-4.07)**
Urinary antispasmodics (G04BD)[2]	6 (2.9)	144 (0.9)	**2.82 (1.22-6.54)**

Abbreviations: AUR (acute urinary retention); β (beta); CI (confidence interval); LABA (long-acting beta agonist); NSAIDs (nonsteroidal anti-inflammatory drugs); N.A. (non-accessible); NSAIDs (non-steroidal anti-inflammatory drugs); OR (odds ratio); SABA (short-acting beta agonist); SSRI (selective serotonin reuptake inhibitor); TCA (tricyclic antidepressants)

[a] OR for current use vs. no use

* Matched by age, gender and index date

[1] Medication used for BPH.

[2] Medication used for overactive bladder.

Effect modification by gender and benign prostatic hyperplasia (BPH) and sensitivity analysis

To study effect modification by gender and underlying comorbidity, we stratified cases and controls by gender and the presence of BPH. The association between inhaled anticholinergic drugs and AUR was much stronger in males than in females (OR_{adj} 1.73; 95%CI, 1.20-2.51 and

Table 3 Use of inhaled anticholinergics and the risk of AUR

	Cases (n = 209) (%)	Controls (n = 16,164) (%)	ORmatched* (95% CI)	ORadj†1/†2/†3 (95% CI)	ORadj‡ COPD severity (95%CI)
Anticholinergics Use				†1	
No use	91 (43.5)	8,676 (53.7)	reference	Reference	reference
Current use	69 (33.0)	3,463 (21.4)	**1.85 (1.34-2.56)**	**1.51 (1.08-2.12)**	1.40 (0.99-1.98)
Type AC				†1	
Tiotropium	12 (5.7)	625 (3.9)	1.75 (0.92-3.31)	1.64 (0.85-3.15)	1.55 (0.80-3.00)
Ipratropium	57 (27.3)	2,838 (17.6)	**1.88 (1.33-2.64)**	**1.49 (1.04-2.13)**	1.37 (0.96-1.98)
Recency current use				†2	
< 2 weeks	5 (2.4)	123 (0.8)	**4.12 (1.64-10.4)**	**3.28 (1.29-8.38)**	**3.11 (1.21-7.98)**
≥ 2 weeks	64 (30.6)	3,340(20.7)	**1.77 (1.28-2.47)**	**1.53 (1.10-2.14)**	1.33 (0.94-1.90)
Dosage				†3	
Tiotropium					
PDD = 1**	12 (5.7)	625 (3.9)	1.75 (0.92-3.32)	1.62 (0.84-3.13)	1.55 (0.80-3.00)
Ipratropium					
PDD < 1	24 (11.5)	1,070 (6.6)	**2.01 (1.27-3-19)**	1.50 (0.92-2.44)	1.47 (0.91-2.37)
PDD ≥ 1	33 (15.8)	1,768 (10.9)	**1.79 (1.19-2.70)**	1.37 (0.89-2.12)	1.31 (0.85-2.02)
Frequency				†1	
≤ 1	11 (5.3)	665 (4.1)	1.54 (0.80-2.97)	1.41 (0.72-2.76)	1.34 (0.68-2.63)
> 1 and < 4	29 (13.9)	1,462 (9.0)	**1.82 (1.19-2.80)**	1.52 (0.98-2.37)	1.44 (0.92-2.24)
≥ 4	29 (13.9)	1,336 (8.3)	**2.05 (1.33-3.15)**	1.54 (0.98-2.42)	1.39 (0.88-2.21)
Type administration				†2	
MDI[a]	27 (12.9)	1,134 (7.0)	**2.07 (1.33-3.22)**	**1.60 (1.02-2.50)**	1.37 (0.85-2.18)
Dry powder	36 (17.2)	2,239 (13.9)	**1.54 (1.04-2.29)**	1.46 (0.98-2.18)	1.35 (0.90-2.03)
Tiotropium			1.86 (0.99-3.49)	1.82 (0.96-3.46)	1.66 (0.86-3.21)
Ipratropium			1.42 (0.91-2.23)	1.34 (0.86-2.11)	1.24 (0.78-1.98)
Nebulizer[a]	6 (2.9)	90 (0.6)	**7.40 (3.13-17.5)**	**4.09 (1.69-9.92)**	**2.92 (1.17-7.31)**
Recent past use	20 (9.6)	1,276 (7.9)	1.46 (0.89-2.38)	1.22 (0.73-2.02)	1.15 (0.70-1.91)
Distant past use	29 (13.9)	2,749 (17.0)	1.00 (0.65-1.53)	0.94 (0.60-1.46)	0.96 (0.62-1.48)

Abbreviations: AC (anticholinergic); adj (adjusted); AUR (acute urinary retention); CI (confidence interval); COPD (chronic obstructive pulmonary disease); MDI (metered dose inhaler); OR (odds ratio); PDD (prescribed daily dosage)

[a] Only Ipratropium

* Matched by age, gender and index date

** Given dosage for tiotropium (PDD=1)

†1 Adjusted for immobility, systemic corticosteroids

†2 Adjusted for immobility

†3 Adjusted for immobility, *β2 mimetics*, systemic corticosteroids

‡ Adjusted for immobility and for COPD severity

The column at the right gives the OR for the final model (always adjusting for COPD severity)

OR_{adj} 0.28; 95%CI, 0.08-1.00 respectively), although the number of female cases was very low (Table 4). The risk of AUR was the highest in patients with BPH (OR_{adj} 4.67; 95%CI, 1.56-14.0) (Table 4).

Table 4 Use of inhaled anticholinergics and the risk of AUR: stratifications (BPH, gender)

Stratification according to BPH	**Cases (n = 31) (%)**	**Controls (n = 1,143) (%)**	**ORmatched* (95% CI)**	**ORadj†1 (95% CI)**	**ORadj‡ COPD severity (95%CI)**
BPH					
Anticholinergics Use					
No use	10 (32.3)	593 (51.9)	Reference	Reference	reference
Current use	14 (45.2)	235 (20.6)	**5.77 (2.04-16.8)**	**5.35 (1.83-15.6)**	**4.67 (1.56-14.0)**
Type AC					
Tiotropium	3 (9.7)	60 (5.2)	**5.69 (1.02-31.8)**	5.57 (0.94-33.1)	4.02 (0.66-24.6)
Ipratropium	11 (35.5)	175 (15.3)	**5.77 (1.98-16.9)**	**5.30 (1.74-16.1)**	**4.73 (1.53-14.6)**
Recent past use	1 (3.2)	88 (7.7)	N.A.	N.A.	N.A.
Distant past use	6 (19.4)	227 (19.9)	1.74 (0.48-6.24)	1.94 (0.54-6.97)	1.96 (0.53-7.26)
Stratification according to gender	**Cases (n = 209) (%)**	**Controls (n = 16,164) (%)**	**ORmatched* (95% CI)**	**ORadj†1 (95% CI)**	**ORadj‡ COPD severity (95%CI)**
Males	178	13,918			
Anticholinergics Use					
No use	69 (38.8)	7,304 (52.5)	Reference	Reference	reference
Current use	66 (37.1)	3,117 (22.4)	**2.21 (1.56-3.13)**	**1.93 (1.36-2.75)**	**1.73 (1.20-2.51)**
Type AC					
Tiotropium	10 (5.6)	545 (3.9)	1.84 (0.91-3.72)	1.81 (0.88-3.72)	1.65 (0.80-3.42)
Ipratropium	56 (31.5)	2,572 (18.5)	**2.30 (1.60-3.31)**	**1.96 (1.35-2.82)**	**1.75 (1.19-2.57)**
Recent past use	19 (10.7)	1,139 (8.2)	**1.71 (1.02-2.86)**	1.50 (0.89-2.55)	1.39 (0.82-2.37)
Distant past use	24 (13.5)	2,358 (16.9)	1.06 (0.66-1.70)	1.04 (0.64-1.68)	1.01 (0.63-1.64)
Females	31	2,246			
Anticholinergics Use					
No use	22 (71.0)	1,372 (61.1)	Reference	Reference	reference
Current use	3 (9.7)	346 (15.4)	0.46 (0.14-1.56)	0.37 (0.11-1.28)	0.28 (0.08-1.00)
Type AC					
Tiotropium	2 (6.5)	80 (3.6)	N.A.	N.A.	N.A.
Ipratropium	1 (3.2)	266 (11.8)	N.A.	N.A.	N.A.
Recent past use	1 (3.2)	137 (6.1)	N.A.	N.A.	N.A.
Distant past use	5 (16.1)	391 (17.4)	0.81 (0.30-2.20)	0.87 (0.32-2.36)	0.78 (0.28-2.15)

Abbreviations: AC (anticholinergic); adj (adjusted); AUR (acute urinary retention); BPH (benign prostatic hyperplasia); CI (confidence interval); COPD (chronic obstructive pulmonary disease); MDI (metered dose inhaler); OR (odds ratio); N.A. (non-accessible)

* Matched for age, gender and index date

†1 Adjusted for immobility

‡ Adjusted for immobility and for COPD severity

The column at the right gives the OR for the final model (always adjusting for COPD severity)

Sensitivity analysis including both definite and possible cases of AUR reduced the association between AC drugs and AUR (OR_{adj} 1.32; 95%CI, 0.95-1.83, for current users of inhaled anticholinergic drugs, and OR_{adj} 2.62; 95%CI, 1.02-6.72, for recent starters) (data not shown).

Discussion

This study shows that inhaled anticholinergic drugs increase the risk of AUR in COPD patients, especially in men with BPH and when using nebulizers. To our knowledge, this is the first study quantifying the association between the use of inhaled anticholinergic drugs and the risk of AUR under real life circumstances.

The association between the use of inhaled anticholinergic drugs and AUR has been described in case reports and randomized clinical trials. Pras and Lozewicz reported four cases of urinary retention associated with ipratropium bromide. All these male patients were approximately 70 years old, had a medical history of BPH and used ipratropium via nebulizer [129, 130]. Our estimate is lower than the estimates recently reported in a pooled clinical trial analysis and a meta-analysis. The pooled analysis of 19 randomized, double-blinded, placebo-controlled trials with tiotropium in patients with obstructive lung disease showed a RR of 10.9, 95% CI, 1.26-94.88 in patients using tiotropium against placebo, but the confidence intervals were wide due to low numbers [142]. A recent meta-analysis by Barr et al showed a non-significant association between the use of tiotropium and the risk of AUR (OR 2.5, 95% CI 0.5-14) [131]. The UPLIFT study reported a non-significant relative risk of 1.65 (95%CI, 0.92-2.93) in patients using tiotropium against placebo, this estimate is in line with our findings[132].

The risk of AUR in our study was the highest in patients who recently started their inhaled anticholinergic treatment. This might be explained by the fact that chronic users tolerate their treatment better compared to recent starters. Several studies have indeed demonstrated that most of the anticholinergic side effects occur early upon initiating a drug [129, 130]. Martin-Merino et al. recently published the results of their case control study on the association between the use of oral anticholinergic drugs and AUR and also found that the risk of AUR was the highest during early treatment with no clear dose-response relationship [127].

In our nested case control study, we did not observe different risks between tiotropium and ipratropium. The meta-analysis of Barr et al demonstrated that the risk of dry mouth was higher in tiotropium users compared to placebo or ipratropium (OR 4.6, 95%CI 3.0-7.1 vs. OR 2.1, 95%CI 1.05-4.2) [131].

As we could not observe a difference in risk of AUR for tiotropium compared to ipratropium, we hypothesize that dry mouth might be more due to a local buccal effect than a systemic effect [143]. Indeed, it is known that the magnitude of systemic effects of long-acting anticholinergic drugs are similar to those of short acting anticholinergic drugs [69, 123].

The association between inhaled anticholinergic drugs and AUR was strongest for nebulizer therapy. Systemic effects might be higher for nebulized therapy compared to drugs administered via metered dose inhaler or dry powder inhaler [144-146], probably because higher doses are administered during a longer time of inhalation [147]. However, the higher risk of AUR in patients treated with nebulized anticholinergic drugs could as well be explained by confounding by COPD severity. Patients with severe to more severe COPD are less mobile, which by itself is one of the major risk factors for AUR. In addition, patients with severe to very severe COPD experience more difficulties in using dry powder aerosol or MDI and also have more frequent COPD exacerbations justifying the need for nebulizer therapy. As confounding by severity could be an issue, we adjusted for immobility and COPD severity defined by the algorithm of Ernst et al [140]. Upon adjustment, the association between the use of inhaled anticholinergic drugs and AUR remained.

The association between the use of inhaled anticholinergic drugs and AUR was the highest in male patients with BPH, although recent systematic reviews and meta-analyses have shown that the risk of urinary retention in patients being treated with antimuscarinic drugs (oxybutynin, tolterodine, etc.) for the treatment of overactive bladder - a condition that in males is often associated with BPH - is low [148-150]. These randomized controlled trials (RCTs) however use stringent inclusion and exclusion criteria, often have a short duration of follow-up and monitor patients closely by means of repeated uroflowmetry [149]. We believe that the risk of urinary retention in patients using these drugs is probably higher in a real life non-controlled setting, which is in line with our observations of a (non-adjusted) risk estimate of AUR of 2.82 in patients being treated with oral antimuscarinic drugs. As BPH and COPD are prevalent diseases in elderly males, it might be advisable, prior to initiation of inhaled anticholinergic drugs, to check if voiding dysfunctions are present and if present, to closely monitor the patient by means of regular uroflow measurements.

RCTs have shown that, in patients with BPH, 5ARIs especially in combination with an α-blocker, reduce the risk of AUR and BPH surgery [151-153]. We did not observe a protective effect of current use of 5ARIs, alone or in combination, on the risk of AUR. It should be emphasized however that our case-control study was not designed to study the effectiveness of 5 ARIs and α-blockers for the treatment of BPH. This type of research would better be conducted by means of a cohort study taking severity of BPH into account.

As for all observational research, our data need to be interpreted with caution. First, the exposure was assessed based on GP prescriptions, rather than dispensing data or actual patient intake, and could thus under- or overestimate patient exposure. It is likely however that this exposure misclassification was non-differential (evenly distributed between cases and controls), and thus did not influence the association between the use of inhaled anticholinergic drugs and AUR. To avoid information bias by misclassification of the outcome, all cases were manually reviewed by medically trained researchers who were blinded to drug exposure, and only the definite cases of AUR were included in our analysis. Indeed, when we

conducted a sensitivity analysis, including both definite and possible cases of AUR, we found that the association between anticholinergic drugs and AUR became less strong, but still significant in recent starters and in male with BPH. Finally, selection bias was unlikely since cases and controls were obtained from the same source population of COPD patients, using prospectively collected medical records.

In conclusion, our study shows that the risk of AUR is increased in COPD patients recently starting inhaled anticholinergics (irrespective of duration of action) and most particularly in males with BPH. This latter observation is important since both BPH and COPD are highly prevalent diseases in elderly males. It might be advisable to consider alternatives for anticholinergic drugs (e.g. inhaled long-acting β_2-mimetics) in COPD patients with BPH.

4.3

Inhaled anticholinergic drugs and the risk of renal failure

Abstract

Background: Data from a pooled clinical trial analysis on the safety of tiotropium reported the occurrence of renal failure during use of tiotropium. In addition, several cases of renal failure, both for ipratropium bromide and tiotropium, were reported to the adverse drug reaction database-"Vigisearch" from the WHO. To our knowledge, the association between inhaled anticholinergic drugs and the occurrence of renal failure has never been studied in clinical practice.

Objectives: To compare the risk of renal failure, in COPD patients treated with inhaled anticholinergic drugs.

Methods: We conducted a nested case-control study in a cohort of COPD patients using data from the Dutch Integrated Primary Care Information (IPCI) medical record database. The study period ran from 2000 to 2007. Cases were all COPD patients who, during follow-up, were diagnosed with renal failure (acute or chronic). To each case, all eligible controls were matched on age, sex and indexdate. COPD severity was assessed either via spirometry or via proxy. Exposure was assessed using prescription records. The odds of renal failure during use of inhaled anticholinergic drugs (ipratropium bromide or tiotropium) was compared to the odds during no use or use of inhaled β_2-agonists. Conditional logistic regression analysis was used to calculate adjusted odds ratios (OR_{adj}) with 95%CI.

Results: Within the cohort of 6,788 COPD patients, 83 new cases of renal failure were identified. Current use of anticholinergic drugs overall (ipratropium or tiotropium) was not associated with an increased risk of renal failure as compared to no use (OR_{adj} 0.78, 95% CI 0.43-1.42) or current use of β_2-agonists (OR_{adj} 1.42, 95%CI 0.57-3.54).

Conclusion: Current use of anticholinergic drugs was not associated with an increased risk of renal failure as compared to no use or use of β_2-agonists.

Introduction

Chronic obstructive pulmonary disease (COPD) is the seventh most frequent chronic disease and is expected to rank fourth by 2020 [105]. This makes COPD a leading cause of chronic morbidity and mortality worldwide [2]. It is characterized by a largely irreversible obstruction of the airways, and encompasses both emphysema and chronic bronchitis. The primary goal of COPD treatment is to reduce the symptoms of breathlessness and to improve the quality of life. Bronchodilator medications are central to the symptomatic management of COPD and encompass inhaled β_2-agonists and anticholinergics. For both types of inhaled bronchodilators, short-acting (multiple administrations per day) and long-acting (once daily) drugs are available. The long-acting β_2-agonists (salmeterol, formoterol) and the long-acting anticholinergic drug (tiotropium which bind to M3 subtype muscarinic receptors) are recommended as maintenance treatment in patients with moderate to very severe COPD [105].

Kesten et al. recently studied the safety of tiotropium, a long acting inhaled anticholinergic drug used for the symptomatic treatment of chronic obstructive pulmonary disease (COPD), by pooling safety data from 26 randomized clinical trials (RCTs) on tiotropium against placebo. They found that renal failure, as adverse event, was somewhat less frequently reported for tiotropium compared to placebo (risk difference (RD) -0.02, 95%CI -0.20-0.16)). In contrast, renal failure, as serious adverse event, was more often reported for tiotropium, but this difference was not statistically significant (RD 0.07, 95%CI -0.14-0.28) [154]. In addition, using data from the WHO adverse drug reaction database (Vigisearch), several reports on renal failure during use of tiotropium or ipratropium bromide were reported between 2000 and 2010 [155].

Renal failure is defined as a deterioration of kidney function that results in the retention of waste products, and can broadly be divided into two categories: acute renal failure (ARF) and chronic kidney disease (CKD) [156]. ARF is, as the name implies, a rapidly progressive loss of renal function [157], and the level of renal impairment varies from moderate to severe requiring renal replacement therapy [158]. CKD usually develops slowly and shows few initial symptoms; it is a gradually loss of renal function over a period of time. CKD might be the long-term result of irreversible acute disease or be part of a disease progression of underlying diabetic nephropathy, hypertension or glomerular nephritis [157]. The prevalence of CKD increases with age and in elderly patients, CKD is often unrecognized, as it is likely to coincide with other chronic diseases including chronic obstructive pulmonary disease (COPD) [159, 160].

Animal and human studies have shown that acetylcholine is important to preserve renal blood flow through a relaxation of the interlobular arteries as well as the glomerular arterioles. It is unknown whether use of anticholinergic drugs, and in particular inhaled anticholinergic drugs; increase the risk of renal failure.

We conducted a nested case-control study in a large cohort of 6,788 COPD patients with 23,930 person-years of follow-up in the Netherlands, to compare the risk of renal failure, in COPD patients treated with inhaled anticholinergic drugs compared to no use or use of inhaled β_2-agonists.

Methods

Setting

A nested case-control was conducted in a cohort of COPD patients from the Integrated Primary Care Information Project (IPCI) database. IPCI is a population-based longitudinal database that contains the complete computer-based medical records of currently more than 400 General Practitioners (GPs) throughout the Netherlands, who voluntarily chose to supply data to the database [86]. 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 and therefore the medical records do not only capture GP diagnoses and symptoms but also the results and summaries of specialist care [161]. At present, the IPCI database contains information on more than 1 million patients. This database contains anonymized patient identification information (age, sex, patient identification, and GP registration information), narratives, patient reported symptoms, signs, GP and specialist diagnoses, prescriptions, physical findings, laboratory values, and summaries of specialist letters [86, 88]. The International Classification of Primary Care (ICPC) is the coding system for patient complaints and diagnoses, but these can as well be entered as free text [162]. Prescription data encompass product name, quantity dispensed, dosage regimens, 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 [90]. The system complies with European Union guidelines on the use of medical data for medical research and has been proven valid for pharmaco-epidemiological studies [91]. All observational research on the IPCI database is being conducted according to good pharmaco-epidemiological guidelines [92].

The source population consisted of all patients in the IPCI database who were 40 years of age or older, and with at least one year of valid history available in the database. The study period started in January 2000 and ended in May 2007.

COPD cohort

COPD patients were identified from diagnoses and narratives. The medical records of all potential cases were reviewed by a medical doctor and classified as: definite COPD - diagnosis by a specialist or a GP diagnosis confirmed by spirometry (FEV1/FVC<70%); probable COPD

- COPD diagnosed by the GP with at least two records of COPD within one year of the first record of COPD. All doubtful COPD patients were further classified by a pulmonologist (GB). Patients with a COPD diagnosis prior to study entry were classified as prevalent (existing) COPD. If patients were disease free at cohort entry and later developed COPD, they were considered as having incident (newly onset) COPD.

COPD severity was assessed at the time of cohort entry and changes in COPD severity were captured during follow-up. If spirometry was available, severity of COPD was determined according to the GOLD guidelines; in all other patients, previously published algorithms for COPD severity assessment were used [76-78]. In summary, patients were considered to have mild COPD at the time of their first symptoms of COPD; moderate COPD if patients were on regular bronchodilatory treatment (defined as at least 2 prescriptions of the same drug class within 6 months of the first prescription), and severe COPD if they were hospitalized for COPD, or at the moment they had their third courses of antibiotics for the treatment of lower respiratory tract infections in one year time, or at the time they had their second systemic corticosteroid course for the treatment of COPD exacerbations. Finally, patients were considered to have very severe COPD when they were prescribed oxygen therapy or were scheduled for lung transplantation because of COPD.

All COPD patients were followed from cohort entry until a first diagnosis of renal failure (either acute or chronic), death or end of follow-up, whichever came first.

Cases and controls

All renal failure cases were identified in the electronic medical records and adjudicated by two medical doctors who were blinded to the exposure, and a third doctor arbitrated in case of discrepancies. As acute renal failure is an event requiring hospitalization, only acute renal failure confirmed by the specialist was considered as a case. Chronic kidney disease (CKD) was defined as patients requiring dialysis (end stage renal failure), CKD confirmed by the specialist or renal failure based on age adjusted clearance formulas (using 4v-MDRD formula) for at least 3 months apart [163]. Patients with a diagnosis of renal failure prior to cohort entry were censored for this outcome, and also excluded for being a control. A case was considered as being a patient newly diagnosed with acute or chronic kidney disease. The index date was the date of the first diagnosis of renal failure (either acute or chronic) after study entry.

To each case, all available controls were matched from the COPD cohort on index date, gender and year of birth. Due to this sampling approach [164], controls could be re-sampled at different moments in time and their contribution should be considered in person-time (moments) rather than subjects.

Exposure

Exposure was categorized by type of drug, timing, duration and dose. All information was obtained from the prescription records. The following types of bronchodilating and anti-in-

flammatory drugs were considered as study drugs: tiotropium as long-acting anticholinergic agent (LAAC), short-acting anticholinergic agents (SAAC), single-ingredient long-acting β_2-agonists (LABA), single-ingredient short-acting β_2-agonists (SABA), inhaled corticosteroids (ICS) and xanthines. Drugs were grouped to look at class effects. The anticholinergics as a class consisted of LAAC and SAAC, and the class of β_2-agonists comprised of SABA and LABA. In an attempt to separate out the effects of the individual bronchodilating drugs while recognizing that COPD treatment is often a multidrug regimen we created the following mutually exclusive categories: only inhaled anticholinergic drugs, only β_2-agonists or only xanthines. Patients who used multiple bronchodilating products were classified as users of a multiple drug combination. Drug exposures were further categorized by timing of use in current use (last prescription covers the index date or ends less than 30 days prior to the index date), past use (last prescription ended more that 30 days), or no use. The main analysis compared the effect on renal failure between current use of anticholinergics and current use of β_2-agonists.

Covariates

As potential confounders we considered the severity of COPD as well as various co-morbidities and concomitant drug use. For the primary analysis we used the COPD severity status one year prior to the index date, since severity could be an intermediate factor between the exposure and renal failure. In addition, we conducted sensitivity analyses in which we adjusted for severity just prior to the index date.

Other covariates included were smoking history, use of concomitant medication (at least one month prior to the index date) and diseases including heart diseases, diabetes mellitus, lipid disorders, malignancies and. Finally, resource use, by means of the number of GP office and home visits as well as a home bound life style (two or more home visits in the last month prior to the index date) were taken into account.

Analysis

Conditional logistic regression analysis was used to estimate the matched unadjusted and adjusted risk estimates for the comparison between current use of anticholinergics and non-use (allowing use of other COPD drugs) or current use of β_2-agonists. All models were adjusted for at least COPD severity (either at index date or one year prior to it), duration of COPD, and smoking. In addition, we adjusted for the factors that were univariately associated with the outcome ($p<0.10$), and also changed the effect estimate of current use of anticholinergics by more than 5%. Risk estimates were only calculated in case the exposure category included at least 5 exposed cases. Stratified analysis was conducted by type of renal failure, namely acute or CKD. All statistical analyses were conducted with the statistical software packages SPSS/PC 15.0 (SPSS Inc, Chicago, Ill).

Results

COPD Cohort and case-control set

From the source population of 185,325 participants 40 years and older, 6,788 patients were diagnosed with COPD of which 23% were newly diagnosed during the study period (incident COPD). The median follow-up time per COPD patient was 3.5 years, with a total follow-up time of 23,930 person-years. Baseline characteristics of this COPD cohort are described in table 1. For 30% we could estimate the severity based on FEV1 (spirometry). In the remaining 70%, a proxy, as described in the methods sections, measured the severity of COPD. Up to 80% of patients had mild or moderate COPD at cohort entry. The most frequent co-morbidities were angina pectoris, hypertension, heart failure, hyperlipidemia, diabetes mellitus, and tumors (table 1).

Within the COPD cohort, 83 new cases of renal failure were identified, of which 73 were chronic and 10 acute cases. Of the cases, 64 (77.1%) were male and the mean age of the cases was 73.8 (SD=±8.6) years. Underlying co-morbidities that increased the risk of renal failure were a medical history of angina pectoris, heart failure, hypertension, hyperlipidemia and diabetes mellitus. Use of concomitant medication (as proxy for underlying co-morbidities) such as anti-hypertensives, vitamin K antagonists and lipid lowering drugs were also related to the outcome (table 1).

Compared to no use, current use of inhaled anticholinergic drugs (ipratropium and tiotropium) was not associated with an increased risk of renal failure (OR_{adj} 0.78, 95%CI 0.43-1.42) (table 2). Current use of ipratropium was not associated with an increased risk of renal failure and no dose relation or a relation by type of formulation could be observed (table 2). Due to low numbers (N=4), the association between current use of tiotropium and renal failure could not be investigated.

Current use of other respiratory drugs was not associated with an increased risk of renal failure and a trend for a decreased risk of renal failure was observed for LABA (OR_{adj} 0.61, 95%CI 0.31-1.20) (data not shown).

When using current use of β_2-agonists as reference category, current use of inhaled anticholinergic drugs slightly increased the risk of renal failure but this association was not statistically significant (OR_{adj} 1.42, 95%CI 0.57-3.54). Due to low exposure numbers, the effect of current use of ipratropium and tiotropium separately could not be quantified (table 2).

Stratified analysis

The main analyses were repeated stratifying between acute and CKD. Using CKD as outcome, current use of inhaled anticholinergics, as compared to no-use, was not associated with an increased risk (OR_{adj} 0.74, 95% CI 0.39-1.42). A slightly increased risk (OR_{adj} 1.77, 95%CI 0.67-4.66), but not statistically significant, was observed for inhaled anticholinergic drugs compared to current use of inhaled β_2-agonists (table 3). Using acute renal failure as outcome,

Table 1(a) Patient characteristics at time of cohort entry and characteristics for cases (renal failure) and controls

Characteristics	COPD cohort N=6,788 (%)	Cases N=83 (%)	Control moments N=3,975 (%)	Matched OR* (95% CI)
Gender				
Male	3,889 (57.3)	64 (77.1)	3,420 (86.0)	
Age (mean, SD)	67.3 (±12.2)	75.5 (±8.49)	75.1 (±5.98)	
40-59 (No.,%)	1,797 (26.5)	5 (6.0)	124 (3.1)	
60-69 (No.,%)	1,739 (25.6)	20 (24.1)	1,059 (26.6)	
70+ (No.,%)	3,252 (47.9)	58 (69.9)	2,792 (70.2)	
Smoking history				
Never	525 (7.7)	12 (14.5)	418 (10.5)	Reference
Current	2,737 (40.3)	27 (32.5)	1,397 (35.1)	0.71 (0.35-1.43)
Past	417 (6.1)	5 (6.0)	340 (8.6)	0.60 (0.21-1.75)
Missing	3,101 (45.7)	39 (47.0)	1,816 (45.7)	0.73 (0.37-1.44)
Severity at cohort entry				
Mild	2,694 (39.7)	19 (22.9)	842 (21.2)	Reference
Moderate	2,713 (40.0)	40 (48.2)	1,850 (46.5)	0.87 (0.50-1.53)
Severe	1,280 (18.9)	21 (25.3)	1,225 (30.8)	0.74 (0.39-1.39)
Very severe	101 (1.5)	3 (3.6)	56 (1.4)	NA
Mean time since first diagnosis	2.4 (±4.1)	2.6 (±4.2)	2.8 (±4.3)	0.99 (0.99-1.00)
Co-morbidity (history of events)				
History of asthma	1,042 (15.4)	5 (6.0)	479 (12.1)	0.44 (0.17-1.12)
History of myocardial infarction	457 (6.7)	11 (13.3)	494 (12.4)	1.18 (0.62-2.24)
Angina pectoris	994 (14.6)	26 (31.3)	739 (18.6)	**1.91 (1.18-3.10)**
Ischemic heart disease	188 (2.8)	4 (4.8)	160 (4.0)	NA
History of stroke or TIA	441 (6.5)	10 (12.0)	412 (10.4)	1.20 (0.61-2.37)
Peripheral arterial disease	391 (5.8)	10 (12.0)	330 (8.3)	1.52 (0.77-2.99)
Heart failure	793 (11.7)	32 (38.6)	702 (17.7)	**2.96 (1.85-4.75)**
Ventricular arrhythmia	335 (6.3)	8 (9.6)	448 (11.3)	0.85 (0.41-1.79)
Hypertension	1,422 (21.0)	28 (33.7)	917 (23.1)	**1.73 (1.09-2.77)**
Lipid disorder	1,769 (26.1)	38 (45.8)	1,231 (31.0)	**2.27 (1.43-3.61)**
Diabetes mellitus (type I, type II)	767 (11.3)	23 (27.7)	590 (14.8)	**2.32 (1.41-3.81)**
Migraine	95 (1.4)	0 (0)	25 (0.6)	NA
History of malignancy	673 (10.0)	8 (9.6)	610 (15.3)	0.58 (0.28-1.22)
Concussion and head injury	26 (0.4)	0 (0)	15 (0.4)	NA
Pneumonia	571 (8.4)	11 (13.3)	542 (13.6)	0.97 (0.51-1.86)
Parkinsonism	21 (0.3)	0 (0)	18 (0.5)	NA
Depressive disorders	540 (8.0)	7 (8.4)	259 (6.5)	1.22 (0.55-2.71)
Dementia	23 (0.3)	0 (0)	23 (0.6)	NA
Number of GP visits (mean, SD)	5.7 (±5.0)	6.9 (±4.7)	5.7 (±4.8)	**1.04 (1.00-1.08)**
Home bound lifestyle	58 (1.1)	3 (1.9)	42 (1.0)	3.32 (0.97-11.4)

Table 1(b) Patient characteristics at time of cohort entry and characteristics for cases (renal failure) and controls

Characteristics	COPD cohort N=6,788 (%)	Cases N=83 (%)	Control moments N=3,975 (%)	Matched OR (95% CI)*
Concomitant medication (current vs. non use)				
Central nervous system drugs				
Opioids	122 (2.3)	4 (4.8)	92 (2.3)	NA
Hypnotics and sedatives	519 (9.8)	8 (9.6)	393 (9.9)	0.95 (0.45-2.00)
Anxiolytics	504 (9.5)	8 (9.6)	316 (7.9)	1.24 (0.59-2.59)
Antipsychotics (typical, atypical)	49 (0.9)	0 (0)	41 (1.0)	NA
Antidepressants (SSRI)	189 (3.6)	3 (3.6)	100 (2.5)	NA
Antiepileptic drugs	65 (1.2)	2 (2.4)	58 (1.5)	NA
Anticholinergic drugs (except respiratory)	155 (2.3)	5 (6.0)	103 (2.6)	2.22 (0.87-5.64)
Drugs affecting cerebrovascular and cardiovascular diagnosis				
Nitrates	380 (5.6)	10 (12.0)	249 (6.3)	1.80 (0.90-3.59)
Platelet inhibitors	1,022 (15.1)	24 (28.9)	827 (20.8)	1.61 (0.99-2.62)
Anti-arrhythmics	70 (1.0)	4 (4.8)	76 (1.9)	NA
Anti-hypertensives	2,361 (34.8)	55 (66.3)	1,668 (42.0)	**2.77 (1.74-4.40)**
Diuretics	1,187 (17.5)	32 (38.6)	810 (20.4)	**2.35 (1.48-3.72)**
β-blockers	738 (10.1)	15 (18.1)	438 (11.0)	**1.74 (0.98-3.10)**
Calcium channel blockers	671 (9.9)	17 (20.5)	478 (12.0)	**2.01 (1.16-3.46)**
ACE - inhibitors	1,046 (15.4)	32 (38.6)	833 (21.0)	**2.54 (1.61-4.01)**
Corticosteroids (systemic)	579 (8.5)	11 (13.3)	371 (9.3)	1.57 (0.82-3.00)
Estrogens	197 (2.9)	2 (2.4)	32 (0.8)	NA
Antibiotics	741 (10.9)	11 (13.3)	358 (9.0)	1.50 (0.78-2.88)
NSAIDs	519 (7.6)	11 (13.3)	266 (6.7)	1.89 (0.99-3.64)
Vitamin K antagonists	385 (5.7)	17 (20.5)	384 (9.7)	**2.60 (1.51-4.49)**
Lipid lowering drugs	620 (9.1)	25 (30.1)	451 (11.3)	**3.93 (2.39-6.46)**
Other respiratory drugs				
Antihistamines	188 (2.8)	2 (2.4)	125 (3.1)	NA
Mucolytics	393 (5.8)	10 (12.0)	266 (6.7)	1.94 (0.99-3.80)
Cough suppressants	190 (2.8)	4 (4.8)	70 (1.8)	NA
Leukotriene receptor antagonists	16 (0.2)	0 (0)	20 (0.5)	NA
Systemic β_2 agonists	23 (0.3)	0 (0)	13 (0.3)	NA
Short-acting β_2 agonists	1,427 (21.0)	21 (25.3)	836 (21.0)	1.03 (0.58-1.84)
Long-acting β_2 agonists	768 (11.3)	17 (20.5)	946 (23.8)	0.73 (0.39-1.35)
Inhaled corticosteroids	1,919 (28.3)	24 (28.9)	1,413 (35.5)	0.79 (0.45-1.39)
Xanthines (theophyline)	182 (2.7)	5 (6.0)	112 (2.8)	2.09 (0.82-5.32)

ORs are not displayed if fewer than 5 subjects exposed to comparison of interest (NA= not applicable as fewer than 5 exposed subjects)

*Matched on age, gender and index date.

Abbreviations: GP (general practitioner), NSAIDs (non-steroid anti-inflammatory drugs), OR (odds ratio), SD (standard deviation).

Table 2 Inhaled anticholinergics and renal failure

Drug class*	Cases N=83(%)	Control moments N=3,975(%)	Matched OR (95%CI)**	Adjusted OR (95%CI) Model 1	Adjusted OR (95%CI) Model 2
Inhaled Anticholinergics[1]					
No use	29 (34.9)	1,372 (34.5)	Reference	Reference	Reference
Current use	25 (30.1)	1,321 (33.2)	0.90 (0.52-1.55)	0.77 (0.42-1.43)	0.78 (0.43-1.42)
Recent past*	13 (15.7)	406 (10.2)	1.45 (0.74-2.84)	1.30 (0.63-2.69)	1.30 (0.63-2.66)
Distant past*	16 (19.3)	876 (22.0)	0.78 (0.42-1.46)	0.78 (0.41-1.51)	0.81 (0.42-1.56)
Individual inhaled anticholinergics					
Current use tiotropium	5 (6.0)	172 (4.3)	1.22 (0.45-3.33)	1.01 (0.36-2.84)	1.01 (0.36-2.82)
Current use ipratropium	19 (22.9)	1,123 (28.3)	0.83 (0.46-1.49)	0.71 (0.36-1.37)	0.71 (0.37-1.36)
Combined use of tiotropium and ipratropium	1 (1.2)	26 (0.7)	NA	NA	NA
Dosage (ipratropium only)					
Low	2 (2.4)	268 (6.7)	NA	NA	NA
Middle	16 (19.3)	841 (21.2)	0.92 (0.49-1.71)	0.79 (0.39-1.59)	0.80 (0.40-1.59)
High	2 (2.4)	40 (1.0)	NA	NA	NA
Formulation (ipratropium only)					
Aerosol	8 (9.6)	551 (13.9)	0.66 (0.30-1.46)	0.54 (0.23-1.29)	0.56 (0.24-1.33)
Powder	10 (12.0)	552 (13.9)	0.93 (0.45-1.94)	0.88 (0.40-1.94)	0.87 (0.40-1.90)
Nebulizer	2 (2.4)	46 (1.2)	NA	NA	NA
Cumulative duration					
< 30 days	2 (2.4)	44 (1.1) (0.7)	NA	NA	NA
≥ 30 and <365 days	8 (9.6)	404 (10.2))	0.93 (0.42-2.05)	0.78 (0.34-1.82)	0.77 (0.34-1.76)
≥ 365 days	15 (18.1)	873 (22.0)	0.83 (0.44-1.56)	0.69 (0.34-1.40)	0.71 (0.35-1.43)
Mutually exclusive groups					
Current use LABA or SABA***	10 (12.0)	745 (18.7)	Reference	Reference	Reference
Current use inhaled anticholinergic drugs***	9 (10.8)	488 (12.3)	1.35 (0.54-3.35)	1.41 (0.57-3.52)	1.42 (0.57-3.54)
Current use of Xanthines***	1 (1.2)	17 (0.4)	NA	NA	NA
Current use of combinations of drug classes*** (either fixed or individual preparations)	18 (21.7)	854 (21.5)	1.58 (0.72-3.44)	1.62 (0.73-3.60)	1.69 (0.76-3.74)

Reference category "no use" is different for the different drug exposure groups and this implicates that the OR are not comparable across the drugs of interest. ORs are not displayed if fewer than 5 subjects exposed to comparison of interest (NA= not applicable as fewer than 5 exposed subjects)

**Matched on age, gender and index date

*** Might include use ICS

Model 1: adjusted for severity of COPD at index date, duration of COPD and smoking

Model 2: adjusted for severity of COPD one year prior to the index date, duration of COPD and smoking

Model 2 is the final model in the analysis.

1 Additionally adjusted for use of β_2 agonists, mucolytics, antihypertensive drugs, lipid lowering drugs, GP visits and heart failure.

Table 3 Inhaled anticholinergics and renal failure – stratified by acute renal failure or chronic kidney disease

Chronic Kidney Disease					
Drug class*	**Cases N=73(%)**	**Control moments N=3,420(%)**	**Matched OR (95%CI)****	**Adjusted OR (95%CI) Model 1**	**Adjusted OR (95%CI) Model 2**
Inhaled Anticholinergics[1]					
No use	27 (37)	1,165 (34.1)	Reference	Reference	Reference
Current use	21 (28.8)	1,136 (33.2)	0.80 (0.45-1.43)	0.75 (0.39-1.45)	0.74 (0.39-1.42)
Recent past*	12 (16.4)	350 (10.2)	1.41 (0.69-2.84)	1.30 (0.61-2.77)	1.30 (0.61-2.76)
Distant past*	13 (17.8)	769 (22.5)	0.66 (0.33-1.29)	0.65 (0.32-1.32)	0.67 (0.33-1.35)
Mutually exclusive groups					
Current use LABA or SABA***	8 (11.0)	644 (18.8)	Reference	Reference	Reference
Current use inhaled anticholinergic drugs***	9 (12.3)	428 (12.5)	1.65 (0.63-4.31)	1.75 (0.66-4.61)	1.77 (0.67-4.66)
Current use of Xanthines***	1 (1.4)	15 (0.4)	NA	NA	NA
Current use of combinations of drug classes*** (either fixed or individual preparations)	14 (19.2)	724 (21.2)	1.55 (0.64-3.73)	1.69 (0.69-4.14)	1.78 (0.80-3.97)
Acute Renal Failure					
Drug class*	Cases N=10(%)	Control moments N=555(%)	Matched OR (95%CI)**	Adjusted OR (95%CI) Model 1	Adjusted OR (95%CI) Model 2
Inhaled Anticholinergics[1]					
No use	2 (20.0)	207 (37.3)	Reference	Reference	Reference
Current use	4 (40.0)	185 (33.3)	2.23 (0.40-12.40)	0.83 (0.09-7.83)	1.21 (0.14-10.41)
Recent past*	1 (10.0)	56 (10.1)	NA	NA	NA
Distant past*	3 (30.0)	107 (19.3)	2.74 (0.45-16.73)	2.49 (0.24-25.92)	4.96 (0.42-46.89)
Mutually exclusive groups					
Current use LABA or SABA***	2 (20.0)	101 (18.2)	Reference	Reference	Reference
Current use inhaled anticholinergic drugs***	0	60 (10.8)	NA	NA	NA
Current use of Xanthines***	0	2 (0.4)	NA	NA	NA
Current use of combinations of drug classes*** (either fixed or individual preparations)	4 (40.0)	130 (23.4)	NA	NA	NA

ORs are not displayed if fewer than 5 subjects exposed to comparison of interest (NA= not applicable as fewer than 5 exposed subjects)

* Including fixed combination products, **Matched on age, gender and index date, *** Might include use ICS

Model 1: adjusted for severity of COPD at index date, duration of COPD and smoking

Model 2: adjusted for severity of COPD one year prior to the index date, duration of COPD and smoking

Model 2 is the final model in the analysis.

1 Additionally adjusted for use of β_2 agonists, mucolytics, antihypertensive drugs, lipid lowering drugs, GP visits and heart failure.

current use of inhaled anticholinergics, as compared to no-use, was not associated with an increased risk. Due to low exposure numbers, the association between current use of inhaled anticholinergic drugs, using inhaled β_2-agonists as reference category, and the risk of acute renal failure could not be investigated.

Discussion

In this study, we did not observe an increased risk of renal failure (either acute or chronic) in patients currently using inhaled anticholinergic drugs. We did observe a slightly increased risk - although not statistically significant - of CKD in patients currently exposed to inhaled anticholinergic drugs using current use of inhaled β_2-agonists as reference category.

In animals, the cholinergic vasodilator - acetylcholine - has been shown to produce decreases in both afferent and efferent arteriolar resistance when infused into rats [165], dogs [166] and rabbits, through a relaxation of both interlobular arteries as well as glomerular arterioles [167]. In addition, Vander et al [168] and Yun et al [169] demonstrated that the renal vasodilatation in animals, could be blocked by administration of an acetylcholine receptor antagonist, suggesting a role of the muscarinic receptor in the renal vasodilatory response [169]; probably of M3 subtype [170]. Wierema et al also demonstrated that atropine blocked the acetylcholine-induced vasodilatation in the human kidney [171]. By analogy, one could expect a similar mechanism for anticholinergic drugs such as ipratropium and tiotropium used for the treatment of COPD but this is not confirmed by our findings.

Few data exist on the association between the use of inhaled anticholinergic drugs and the risk of renal failure. Kesten et al conducted a pooled analysis of adverse events reported from phase III and phase IV tiotropium HandiHaler® clinical trials and found a non-significant risk difference for renal failure (as serious adverse event) in patients treated with tiotropium compared to placebo (RD 0.07, 95% CI -0.06,0.20) [154]. To our knowledge, the association between the used of ipratropium and the risk of renal failure has not been published. Based on the mechanism as described above, the association between the use of inhaled anticholinergic drugs and risk of renal failure is assumable. If anticholinergic drugs impair the renal blood flow, and through this mechanism, induce renal failure, one would expect that especially the systemic administration of anticholinergic drugs is associated with the highest risk. As part of our analysis, we investigated the association between the current use of non-respiratory drugs with anticholinergic effects (such as tricyclic antidepressants, antipsychotics, drugs given for the treatment of overactive bladder). In the crude analysis, use of these drugs was associated with a two-fold increased risk of renal failure but this association was not statistically significant and might be confounded by underlying co-morbidity. When stratifying between acute or CKD, the association between current used of inhaled anticholinergics, as compared to inhaled β_2-agonists, increased slightly but was still not statistically significant.

From the available literature, it is hard to tell whether use of inhaled anticholinergic drugs would mainly increase the risk of CKD as opposed to acute renal failure. If the association is real, use of inhaled anticholinergic drugs probably does not cause noticeable dramatic drop in renal blood flow, making the association with acute renal failure less likely.

As for all observational studies, our study has strengths, but also limitations. The main strength is the quality of our data. Great emphasis was put on the validity of the disease severity and endpoints that were all manually validated by at least two medically trained persons. The external validity of our data is also a strong point. Being observational, the study is sensitive to bias and confounding. We tried to avoid information bias and misclassification of the outcome by manually reviewing the electronic medical records of all cases by two medically trained researchers who were blinded to drug exposure and unaware of the research hypothesis. In case of doubt, a third medically trained person overruled the validation. Only the definite cases of renal failure were included in our analysis. In order to stratify by type of renal failure, all cases of renal failure were categorized into acute or CKD. Using primary care data, this categorization is not easy as criteria to decide whether an event is acute or chronic might be missing. Misclassification of exposure might be an issue in our study as exposure was assessed based on the prescription data, rather than dispensing data or actual patient intake, and could thus underestimate or overestimate patient exposure. In addition, in a chronic disease such as COPD, prescriptions initiated by the specialist may have been missed. Our main limitation was the low number of exposed cases making our study underpowered to identify a statistically significant association between the use of anticholinergic drugs and the risk of renal failure.

In conclusion, from our data, we cannot conclude that the use of inhaled anticholinergic drugs increases the risk of renal failure. As COPD is a very prevalent disease requiring chronic treatment with bronchodilating drugs including anticholinergic agents, further research on this topic is needed, preferably in a much larger dataset allowing stratification into acute or CKD and stratification by type of inhaled anticholinergic drugs (long or short acting ones).

4.4

Tiotropium and the risk of cardiovascular events and all cause mortality

Abstract

Background: Results from previous research hypothesized that the use of tiotropium might be associated with an increased risk of mortality and/or cardiovascular (CV) events. The safety of tiotropium was closely monitored by the FDA and based on recent data they stated in 2010 that the available data do not support an association between tiotropium and an increased risk of death or CV events. This potential association has not yet been investigated under routine clinical care.

Methods: We conducted 2 nested case-control studies in a COPD cohort using data from the Dutch IPCI database. The cohort consisted of COPD patients, ≥ 40 years, with at least 1 year of valid history. In the first case-control study, cases had a cardiovascular or cerebrovascular endpoint (CCVE): stroke and TIA, myocardial infarction, heart failure, and/or ventricular arrhythmia. In the second case-control study, cases were all patients who died. To each case, all eligible controls were matched on age, sex and index-date. Conditional logistic regression analysis was used to calculate adjusted odds ratios (OR_{adj}) with 95% confidence intervals (CI) for use of tiotropium with LABA as reference.

Results: Within the COPD cohort of 6,788 patients, 784 cases with a CCVE were identified and 1,032 patients died. Compared to current use of LABA, current use of tiotropium was not associated with an increased risk of a CCVE (OR_{adj} 0.89, 95% 0.55-1.44) nor with an increased risk of death (OR_{adj} 0.79, 95% CI 0.49-1.28).

Conclusions: Use of tiotropium in COPD patients is not associated with an increased risk of a CCVE or mortality, when compared to LABA.

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of chronic morbidity and mortality worldwide. According to data from the World Health Organization (WHO), COPD is expected to become the third leading cause of death by 2020. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, bronchodilators are the mainstay of symptomatic management of COPD [59]. Bronchodilator treatments include β_2-agonists, anticholinergics (AC), and methylxanthines, used alone or in combination. Long-acting bronchodilators are found to be more effective and convenient than the short-acting agents [59]. Tiotropium (marketed as Spiriva®) 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 described in randomized controlled trials, with imprecise reductions observed for mortality and a significantly lower risk observed for COPD exacerbations [62].

In March 2008, the FDA made an early communication on a small excess risk of stroke (2 cases per 1,000) with tiotropium over placebo based on a pooled analysis of 29 clinical trials. In the same year, 2 other publications reported an increased risk for mortality and/or cardiovascular (CV) events in patients who received inhaled ACs (ipratropium or tiotropium) [118, 119]. In 2008 the result of the UPLIFT study (Understanding Potential Long term Impacts on Function with Tiotropium) were published showing a reduced risk of cardiovascular events in the tiotropium group as compared to the placebo group (RR 0.84, 95% CI 0.73-0.98). In addition, this study showed a non-significant trend for a decrease of death from any cause in tiotropium treated patients compared to placebo treated patients (HR 0.89, 95 % CI 0.79-1.02) for the intention to treat analysis and a significant reduction in mortality (HR 0.87, 95% CI 0.76-0.99) for the on-treatment analysis [68]. In November 2009, the FDA convened a meeting of the Pulmonary – Allergy Drugs Advisory Committee to discuss the data on cardiovascular risk and mortality. The FDA concluded that the current data do not support the conclusion that there is an increased risk of stroke, heart attack or death associated with tiotropium Handihaler® [120].

As tiotropium continues to be used in a wider population, there is a need to better examine safety under non-experimental real-life conditions. For this reason, we studied the cardiovascular safety and risk of mortality of tiotropium compared to LABA in a cohort of well-defined COPD patients from the general population in clinical practice.

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 [86]. 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 1 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 [162]. 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, 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 [90]. 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 [91]. Guidelines on good pharmaco-epidemiological research are rigorously followed by all researchers working on the IPCI database [92].

Source population

The source population consisted of all patients in the IPCI database who were 40 years of age or older, and with at least one year of valid history available in the database. This meant that the practice had contributed data to the IPCI database and that patients had registered with the GP for at least one year. A one-year pre-enrollment period was required in order to be able to characterize the patients. The study period started in January 2000 and ended in May 2007.

COPD cohort

COPD patients were identified from diagnoses and narratives. The medical records of all potential cases were reviewed by a medical doctor and classified as: definite COPD - diagnosis by a specialist or a GP diagnosis confirmed by spirometry (FEV1/FVC<70%); probable COPD - COPD diagnosed by the GP with at least two records of COPD within one year of the

first record of COPD. All doubtful COPD patients were further reviewed and classified by a pulmonologist (GB). All remaining COPD patients were further categorized into prevalent or incident COPD. Pa tients with a COPD diagnosis prior to cohort entry were classified as prevalent (existing) COPD. If patients were disease free in the pre-enrollment period and developed COPD during the study period, they were considered as having incident (newly onset) COPD. The COPD cohort entry date was the first date of diagnosis of COPD for incident COPD patients and for prevalent COPD patients the date of study entry (1st January 2000), the date of the 40th birthday or the date at which one year of valid database history was reached, whichever occurred last.

COPD severity was assessed at the time of cohort entry and changes in COPD severity were captured during follow-up. If spirometry was available, severity of COPD was determined according to the GOLD guidelines; in all other patients, previously published algorithms for COPD severity assessment were used [76-78]. In summary, patients were considered to have mild COPD at the time of their first symptoms of COPD, moderate COPD if patients were on regular bronchodilatory treatment (defined as at least 2 prescriptions of the same drug class within 6 months of the first prescription), and severe COPD if they were hospitalized for COPD, or at the time they had their third courses of antibiotics for the treatment of respiratory infections in one year time, or at the time they had their second systemic corticosteroid course for the treatment of COPD exacerbations. Finally, patients were considered to have very severe COPD when they were prescribed oxygen therapy or were scheduled for lung transplantation because of COPD.

Design

In the cohort of COPD patients, two case control studies were nested, one to study the association with cardio-cerebrovascular endpoints and one to study the association with death.

Cases

Cardiovascular endpoints

Within the cohort of COPD patients, all newly (re)occurring cases of the following cardio-cerebrovascular endpoints (CCVE) were identified: stroke & TIA, myocardial infarction, heart failure, and/or ventricular arrhythmia (ventricular tachycardia, ventricular fibrillation/flutter and Torsade de Pointes). Potential cases were identified through a detailed search on both diagnosis codes and narratives. Potential cases were independently reviewed by 2 medical doctors according to a predefined algorithm. In case of doubt, a final review was done by a third medical doctor. Patients with a medical history of heart failure prior to cohort entry were excluded from the analysis. The index date was the date of the first CCVE since cohort entry.

Death

Mortality was studied separately from CCVE. All deaths recorded in the COPD cohort were identified and the complete medical files, including patient's referral and discharge letters, were reviewed to classify cause of death as respiratory, cardiovascular or death due to other reasons. The cause of death, as adjudicated by the medical doctors, was verified with the GP in an initial sample of 10% of respiratory or CV related deaths. Since the positive predictive value was high (>90%), confirmation of the cause of death by the GP was not requested for the remaining deaths.

Controls

To each case, all available controls were matched from the COPD cohort on index date, gender and year of birth. Due to this sampling approach (similar to Cox-survival analysis), controls could be re-sampled at different moments in time. Therefore, contribution represents person-time (moments) rather than subjects.

Exposure

Exposure was categorized by type of drug, timing, duration and dose. All information was obtained from the prescription records. The following types of bronchodilating and anti-inflammatory drugs were considered as study drugs: tiotropium as long-acting AC (LAAC), short-acting AC (SAAC), single-ingredient long-acting β_2-agonists (LABA), single-ingredient short-acting β_2-agonists (SABA), inhaled corticosteroids (ICS), xanthines and fixed combination therapies (corticosteroids and bronchodilators). Drugs were grouped in order to investigate class effects. The ACs as a class consisted of LAAC and SAAC, and the class of β_2-agonists comprised of SABA and LABA. ICS was either classified separately or adjusted for depending on the analysis (patients with fixed combinations of steroids and bronchodilators counted in the respective bronchodilator class). Drug exposure was further categorized by timing of use in current use (last prescription covered the index date or ended less than 30 days prior to the index date), past use (last prescription ended more that 30 days prior to the index date), or no use. In the analysis, we compared the effect on CCVE events and death between current use of tiotropium and LABA while controlling for other drug use and comorbidities.

Covariates

As potential confounders we considered the severity of COPD as well as various co-morbidities and concomitant drug use. For the primary analysis we used the COPD severity status one year prior to the index date since severity could be an intermediate factor between the exposure and CV events and/or death. In addition, we conducted a sensitivity analysis in which we adjusted for severity just prior to the index date.

Other covariates included were smoking history, use of concomitant medication (at least use in the month prior to the index date) and concomitant diseases such as heart diseases,

diabetes mellitus, lipid disorders, malignancies and diseases affecting the central nervous system. Finally, resource use, by means of the number of GP office and home visits as well as a home bound life style (two or more home visits in the last month prior to the index date) were taken into account.

Analysis

To study potential differences in co-morbidity between patients being prescribed LABA, tiotropium, or LABA and tiotropium together (same prescription dates), we compared patient characteristics between the three groups at the time of the first prescription of any of these drugs after cohort entry. Differences in co-morbidity and use of concomitant medication were tested using a non-parametric, Mann-Whitney U test for continuous variables and the Chi Square test for categorical variables.

Conditional logistic regression analysis was used to estimate the matched unadjusted and adjusted risk estimates and 95% CI for the comparison between tiotropium and LABA. All models were adjusted for at least COPD severity, duration of COPD, and smoking. In addition we adjusted for all factors that were univariately associated with the outcomes ($p<0.10$), and also changed the effect estimate of tiotropium by more than 5%. Stratified analyses were conducted by gender, calendar year, severity of COPD (mild/moderate versus severe/very severe) and, incident or prevalent COPD at study entry. We tested effect modification by adding an interaction term in the conditional logistic regression model (multiplicative interaction). Only if the interaction term based on the effect modifier of interest and current use of tiotropium turned out to be statistically significant ($p<0.05$) in the adjusted model, effect measure modification was considered to be present. All statistical analyses were conducted with the statistical software packages SPSS/PC 15.0 (SPSS Inc, Chicago, Ill).

Results

COPD Cohort

From the source population of 185,325 participants 40 years and older, 6,788 patients were diagnosed with COPD of which 23% were newly diagnosed during the study period (incident COPD). The median follow-up time per COPD patient was 3.5 years, with a total follow-up time of 23.930 person-years. Baseline characteristics of the COPD cohort are described in table 1. For 30% of COPD patients we could estimate the severity based on FEV1 (spirometry). In the remaining 70%, the severity of COPD was a proxy as described above. Up to 80% of patients had mild or moderate COPD at cohort entry. Since COPD has lately been recognized as a systemic disease, we thoroughly characterized extra-pulmonary co-morbidities in the COPD cohort. The most frequent co-morbidities were angina pectoris, hypertension, heart failure, hyperlipidemia, diabetes mellitus and tumors (table 1).

Table 1 Patient characteristics at time of cohort entry and at time of first prescriptions for LABA or tiotropium or tiotropium plus LABA during the study period

	At cohort entry	At start of first prescription during follow-up		
Characteristics	**COPD cohort No.(%)**	**Tiotropium No.(%)*#**	**LABA No.(%)***	**Tiotropium plus LABA No.(%)*#1**
Number of patients	6,788	1,048	3,214	153
Gender				
♂	3,889 (57.3)	639 (61.0)	1,829 (56.9)	84 (54.9)
♀	2,899 (42.7)	409 (39.0)	1,385 (43.1)	69 (45.1)
Age (mean, SD)	67.3 (±12.2)	69.1 (±11.0)	67.6 (±11.9)	67.3 (±11.0)
40-59 (No.,%)	1,797 (26.5)	**225 (21.5)**	863 (26.9)	39 (25.5)
60-69 (No.,%)	1,739 (25.6)	**278 (26.5)**	828 (25.8)	43 (28.1)
70+ (No.,%)	3,252 (47.9)	**545 (52.0)**	1,523 (47.3)	71 (46.4)
Smoking history				
no smoking	525 (7.7)	**82 (7.8)**	265 (8.2)	**6 (3.9)**
current smoking	2,737 (40.3)	**520 (49.6)**	1,413 (44.0)	**66 (43.1)**
past smoking	417 (6.1)	**105 (10.0)**	202 (6.3)	**11 (7.2)**
smoking unknown	3,101 (45.7)	**340 (32.4)**	1,334 (41.5)	**70 (45.8)**
COPD Severity at cohort entry**				
Mild	2,694 (39.7)	237 (22.6)	763 (23.8)	**29 (19.0)**
Moderate	2,713 (40.0)	489 (46.7)	1,508 (46.9)	**70 (45.8)**
Severe	1,280 (18.9)	301 (28.7)	874 (27.2)	**50 (32.7)**
Very Severe	101 (1.5)	21 (2.0)	69 (2.1)	**4 (2.5)**
Co-morbidity				
History of asthma	1,042 (15.4)	176 (16.8)	625 (19.4)	17 (11.1)
History of myocardial infarction	457 (6.7)	80 (7.6)	231 (7.2)	13 (8.5)
Angina pectoris	994 (14.6)	166 (15.8)	518 (16.1)	26 (17.0)
Ischemic heart disease	188 (2.8)	**46 (4.4)**	98 (3.0)	5 (3.3)
History of stroke or TIA	391 (5.8)	69 (6.6)	193 (6.0)	7 (4.6)
Peripheral arterial disease	441 (6.5)	**107 (10.2)**	233 (7.2)	**20 (13.1)**
Heart failure	793 (11.7)	136 (13.0)	395 (12.3)	17 (11.1)
Ventricular arrhythmia	335 (6.3)	9 (0.9)	15 (0.5)	0
Hypertension	1,422 (21.0)	**266 (25.4)**	334 (10.4)	**22 (14.4)**
Lipid disorder	1,769 (26.1)	**387 (36.9)**	937 (29.2)	**58 (37.9)**
Diabetes	767 (11.3)	151 (14.4)	382 (11.9)	22 (14.4)
Renal insufficiency	184 (2.7)	37 (3.5)	85 (2.6)	4 (2.6)
History of malignancy	673 (10.0)	**147 (14.0)**	389 (12.1)	**22 (14.4)**
Pneumonia	571 (8.4)	**149 (14.2)**	353 (11.0)	**18 (11.8)**
Parkinsonism	21 (0.3)	**4 (0.4)**	4 (0.1)	1 (0.7)
Depressive disorders	540 (8.0)	105 (10.0)	305 (9.5)	24 (15.7)
Dementia	23 (0.3)	3 (0.3)	14 (0.4)	2 (1.3)

Table 1 (continued)

	At cohort entry	At start of first prescription during follow-up		
Characteristics	**COPD cohort No.(%)**	**Tiotropium No.(%)*#**	**LABA No.(%)***	**Tiotropium plus LABA No.(%)*#1**
Number GP visits (mean, SD)	5.7 (±5.0)	6.2 (±4.8)	6.2 (±5.1)	5.9 (±5.2)
Home bound lifestyle	58 (1.1)	**9 (0.9)**	7 (0.2)	1 (0.7)
Previous use of drugs				
Ipratropium	1,393 (20.5)	**438 (41.8)**	1,117 (34.8)	**39 (25.5)**
SABA	1,427 (21.0)	394 (37.6)	1,190 (37.0)	**49 (32.0)**
ICS	1,919 (28.3)	**543 (51.8)**	2,290 (71.3)	**114 (74.5)**
Xanthines	182 (2.7)	48 (4.6)	127 (4.0)	**5 (3.3)**
Oral steroids	579 (8.5)	**561 (44.0)**	990 (30.8)	**52 (34.0)**
Leukotriens	0	0	0	0

The values in bold were statistic significant in Chi-square test comparing tiotropium, or Tiotropium+LABA against LABA. Patients can only appear in Tiotropium and in LABA group if with different dates, but not in the Tiotropium+LABA group and then Tiotropium alone or LABA alone. *First prescription of tiotropium in tiotropium group or LABA in LABA group. #LABA is the reference category. #1 First prescription of tiotropium and LABA at the same date.

** For 30% of COPD patients severity was based on FEV1 (spirometry). In all other patients, previously published algorithms for COPD severity assessment were used.

Abbreviations: ICS (inhaled corticosteroids), GP (general practitioner), LABA (long-acting β_2-agonists), SABA (short-acting β_2-agonists), TIA (transient ischemic attack), SD (standard deviation)

Table 1 also describes the characteristics of cohort members starting with LABA, tiotropium or tiotropium & LABA (same prescription dates), during follow-up. Approximately 47% of COPD patients had moderate COPD at the time of first prescription of tiotropium and or LABA during follow-up (table 1). The number of patients with severe or very severe COPD at time of first prescription was higher for patients who started on a combination of tiotropium and LABA (32.7% were severe and 2.6% very severe), than in patients who started with tiotropium or LABA alone. The CV risk profile was quite similar between LABA, tiotropium and tiotropium plus LABA group; apart from a medical history of hypertension, renal failure, pneumonia which were more frequently observed in patients being treated with tiotropium. Patients starting on LABA more frequently had a medical history of asthma (19.4% vs. 16.8 % in tiotropium users). Tiotropium users had a higher prevalence of ipratropium use (41.8% vs. 34.8 in LABA users) while LABA users had a higher prevalence of ICS use (71.3% vs. 51.8% in tiotropium users). Differences in age, smoking history, COPD severity and medical history between tiotropium and LABA users were statistically significant (table 1). In general, patients receiving tiotropium were slightly older and had more co-morbidities than patients starting on LABA, whereas the combined LABA and tiotropium group had more severe COPD than the patients starting on either LABA or tiotropium alone.

Table 2(a) Characteristics for cases and controls for a combined cardiovascular and cerebrovascular endpoint & death

	Combined cardiovascular and cerebrovascular endpoint			Death		
Characteristics	**Cases N=784 (%)**	**Control moments N=25,899 (%)**	**Matched OR* (95% CI)**	**Cases N=1,032 (%)**	**Control moments N=40,615 (%)**	**Matched OR* (95% CI)**
Male	490 (62.5)	18,844 (72.8)		681 (66.0)	30,946 (76.2)	
Age (mean,SD)	74.6 (9.4)	73.2 (7.3)		78.1 (9.2)	75.9 (6.9)	
Smoking history						
Never	75 (9.6)	2,598 (10)	Reference	38 (3.7)	3,978 (9.8)	Reference
Current	291 (37.1)	9,659 (37.3)	1.1 (0.85-1.43)	342 (33.1)	13,538 (33.3)	2.86 (2.03-4.04)
Past	47 (6)	1,964 (7.6)	0.94 (0.65-1.37)	41 (4.0)	3,216 (7.9)	1.58 (1.01-2.48)
Unclear	371 (47.3)	11,653 (45)	0.94 (0.73-1.22)	609 (59.0)	19,847 (48.9)	2.77 (1.98-3.89)
Passive	0 (0)	25 (0.1)	NA	2 (0.2)	36 (0.1)	NA
COPD severity						
Mild	184 (23.5)	5,941 (22.9)	Reference	98 (9.5)	8,319 (20.5)	Reference
Moderate	358 (45.7)	12,595 (48.6)	0.89 (0.74-1.06)	365 (35.4)	19,391 (47.7)	1.51 (1.20-1.89)
Severe	212 (27)	6,991 (27)	0.95 (0.77-1.16)	468 (45.3)	12,114 (29.8)	3.17 (2.54-3.97)
Very severe	30 (3.8)	360 (1.4)	**2.70 (1.80-4.06)**	101 (9.8)	782 (1.9)	11.4 (8.52-15.4)
Number of GP visits (mean, SD)	6.7 (5.0)	5.4 (4.5)	**1.04 (1.03-1.06)**	11.6 (9)	6 (4.9)	1.12 (1.11-1.13)
Home bound lifestyle	30 (3.8)	177 (0.7)	**4.69 (3.08-7.13)**	327 (31.7)	480 (1.2)	36.4 (30.4-43.6)
Co-morbidity						
Prior myocardial infarction	68 (8.7)	1,786 (6.9)	**1.39 (1.07-1.79)**	282 (27.3)	8,479 (20.9)	**1.32 (1.14-1.52)**
Angina pectoris	170 (21.7)	4,034 (15.6)	**1.48 (1.24-1.77)**	45 (4.4)	1,838 (4.5)	1.01 (0.74-1.38)
Other ischemic heart disease	35 (4.5)	1,051 (4.1)	1.16 (0.82-1.64)	134 (13)	4,037 (9.9)	**1.30 (1.08-1.58)**
Peripheral arterial disease	73 (9.3)	2,179 (8.4)	1.07 (0.84-1.38)	180 (17.4)	4,116 (10.1)	**1.68 (1.41-1.99)**
Stroke	75 (9.6)	1,401 (5.4)	**1.85 (1.44-2.39)**	174 (16.9)	5,221 (12.9)	**1.27 (1.07-1.51)**
Arrhythmia (atrial fibrillation, other)	108 (13.8)	2,144 (8.3)	**1.69 (1.36-2.09)**	248 (24)	10,539 (25.9)	0.89 (0.77-1.03)
Hypertension	242 (30.9)	6,481 (25)	**1.34 (1.15-1.57)**	420 (40.7)	8,021 (19.7)	**2.53 (2.21-2.9)**
Hyperlipidemia	262 (33.4)	8,485 (32.8)	**1.20 (1.03-1.41)**	264 (25.6)	13,488 (33.2)	0.83 (0.72-0.96)
Diabetes mellitus (type I, type II)	129 (16.5)	3,368 (13)	**1.33 (1.1-1.62)**	188 (18.2)	6,310 (15.5)	**1.27 (1.08-1.50)**
Renal disease	49 (6.3)	669 (2.6)	**2.71 (1.99-3.69)**	82 (7.9)	2,103 (5.2)	**1.60 (1.26-2.03)**
Migraine	10 (1.3)	269 (1)	1.02 (0.53-1.94)	10 (1)	404 (1)	0.92 (0.49-1.74)
Concussion and head injury	5 (0.6)	131 (0.5)	1.34 (0.55-3.28)	9 (0.9)	176 (0.4)	**2.26 (1.15-4.48)**
Pneumonia (year prior)	104 (13.3)	3,289 (12.7)	1.05 (0.85-1.3)	228 (22.1)	5,815 (14.3)	**1.62 (1.39-1.89)**
Parkinsonism	7 (0.9)	111 (0.4)	1.71 (0.79-3.74)	16 (1.6)	218 (0.5)	**2.14 (1.25-3.65)**
Depressive disorders	83 (10.6)	2,099 (8.1)	1.17 (0.92-1.48)	150 (14.5)	3,281 (8.1)	**1.75 (1.46-2.10)**
Dementia	6 (0.8)	98 (0.4)	1.59 (0.68-3.74)	20 (1.9)	275 (0.7)	**2.13 (1.30-3.49)**
Tumors (non-cerebral)	110 (14)	3,853 (14.9)	0.92 (0.74-1.13)	313 (30.3)	6,653 (16.4)	**2.33 (2.03-2.68)**

Table 2(b) Characteristics for cases and controls for a combined cardiovascular and cerebrovascular endpoint & death

	Combined cardiovascular and cerebrovascular endpoint			Death		
Central nervous system drugs						
Opioids	21 (2.7)	596 (2.3)	1.18 (0.76-1.84)	231 (22.4)	991 (2.4)	**10.90 (9.20-12.90)**
Hypnotics and sedatives	93 (11.9)	2,445 (9.4)	1.09 (0.87-1.36)	212 (20.5)	4,429 (10.9)	**1.88 (1.6-2.21)**
Anxiolytics	99 (12.6)	2,301 (8.9)	**1.36 (1.09-1.7)**	204 (19.8)	3,509 (8.6)	**2.48 (2.1-2.92)**
Antipsychotics (typical, atypical)	8 (1)	250 (1)	0.90 (0.44-1.86)	66 (6.4)	373 (0.9)	**6.18 (4.63-8.25)**
Antidepressants (SSRI)	30 (3.8)	717 (2.8)	1.21 (0.83-1.76)	55 (5.3)	1,148 (2.8)	**1.82 (1.36-2.42)**
Antiepileptic drugs	8 (1)	343 (1.3)	0.74 (0.37-1.51)	35 (3.4)	581 (1.4)	**2.38 (1.68-3.39)**
Anticholinergic drugs (except respiratory)						
Cholinesterase inhibitors	1 (0.1)	23 (0.1)	NA	0 (0)	56 (0.1)	NA
Parkinson drugs: anticholinergics	2 (0.3)	28 (0.1)	NA	1 (0.1)	34 (0.1)	NA
Disopyramide	1 (0.1)	15 (0.1)	NA	0 (0)	31 (0.1)	NA
Antispasmodics	1 (0.1)	8 (0)	NA	1 (0.1)	23 (0.1)	NA
Atropine	0 (0)	0 (0)	NA	0 (0)	0 (0)	NA
Tricylic/tetracyclic antidepressants	12 (1.5)	387 (1.5)	0.94 (0.52-1.69)	24 (2.3)	498 (1.2)	**1.71 (1.12-2.61)**
H1-antihistamines	1 (0.1)	29 (0.1)	NA	8 (0.8)	55 (0.1)	**3.60 (1.62-7.97)**
Anticholinergics (overactive bladder)	12 (1.5)	196 (0.8)	**1.83 (1.01-3.3)**	12 (1.2)	452 (1.1)	1.07 (0.60-1.91)
Drugs affecting cerebro- and cardiovascular dx						
Nitrates	63 (8)	1,243 (4.8)	**1.55 (1.18-2.04)**	129 (12.5)	3,063 (7.5)	**1.5 (1.23-1.82)**
Platelet inhibitors	178 (22.7)	4,412 (17)	**1.51 (1.27-1.8)**	213 (20.6)	8,700 (21.4)	0.94 (0.81-1.1)
Anti-arrhythmics	22 (2.8)	329 (1.3)	**2.43 (1.56-3.78)**	26 (2.5)	863 (2.1)	1.36 (0.91-2.03)
Anti-hypertensives	350 (44.6)	9,411 (36.3)	**1.35 (1.17-1.57)**	574 (55.6)	17,940 (44.2)	**1.55 (1.36-1.76)**
Corticosteroids (systemic):	133 (17)	2,211 (8.5)	**2.15 (1.77-2.61)**	278 (26.9)	3,971 (9.8)	**3.40 (2.94-3.93)**
Estrogens	14 (1.8)	290 (1.1)	1.13 (0.64-1.97)	6 (0.6)	389 (1)	0.47 (0.21-1.06)
Antibiotics	112 (14.3)	2,059 (8)	**1.92 (1.56-2.37)**	228 (22.1)	3,536 (8.7)	**2.82 (2.41-3.29)**
NSAIDs	69 (8.8)	1,830 (7.1)	1.24 (0.96-1.6)	101 (9.8)	2,759 (6.8)	**1.36 (1.10-1.69)**
Vitamin K antagonists	67 (8.5)	1,519 (5.9)	**1.52 (1.18-1.97)**	132 (12.8)	3,831 (9.4)	**1.45 (1.20-1.76)**
Lipid lowering drugs	87 (11.1)	2,720 (10.5)	1.22 (0.97-1.53)	75 (7.3)	4,543 (11.2)	0.73 (0.58-0.93)
Other respiratory drugs						
Antihistamines	29 (3.7)	817 (3.2)	1.16 (0.79-1.70)	65 (6.3)	1,292 (3.2)	**1.98 (1.53-2.58)**
Mucolytics	78 (9.9)	1,578 (6.1)	**1.72 (1.35-2.2)**	148 (14.3)	2,746 (6.8)	**2.36 (1.96-2.83)**
Cough suppressants	20 (2.6)	439 (1.7)	**1.57 (1-20.48)**	33 (3.2)	693 (1.7)	**2.13 (1.49-3.05)**
Leukotrien receptor antagonists	4 (0.5)	176 (0.7)	NA	10 (0.1)	267 (0.7)	1.51 (0.80-2.87)
Systemic β_2 agonists	2 (0.3)	79 (0.3)	NA	10 (1.0)	167 (0.4)	1.79 (0.88-3.63)
Short-acting anticholinergics	240 (30.6)	6,746 (26)	**1.29 (1.08-1.54)**	348 (33.7)	11,032 (27.2)	**1.84 (1.56-2.18)**
Short-acting β_2 agonists	198 (25.3)	5,461 (21.1)	1.11 (0.92-1.36)	313 (30.3)	8,661 (21.3)	1.9 (1.58-2.27)
Inhaled corticosteroids	307 (39.2)	9,267 (35.8)	0.99 (0.83-1.17)	337 (32.7)	14,214 (35)	1.1 (0.93-1.3)
Xanthines	26 (3.3)	600 (2.3)	1.51 (1.01-2.27)	75 (7.3)	1,205 (3)	3.05 (2.38-3.9)

ORs are not displayed if fewer than 5 subjects exposed to comparison of interest (NA= not applicable as fewer than 5 exposed subjects)

*matched on age, gender and indexdate

Cardiovascular endpoint

Within the COPD cohort, 784 (11.5%) new cases of a CCVE (254 cases of stroke & TIA, 116 cases of MI, 413 cases of heart failure and 6 cases of ventricular arrhythmia) were identified. CV co-morbidity as well as the use of concomitant CV drugs were associated with CCVE (table 2) among cases and control moments. Severity of COPD was not associated with CCVE apart from a significantly increased risk in patients with very severe COPD (OR matched 2.70, 95% CI 1.80-4.06). Current use of respiratory drugs was not associated with an increased risk of a CV endpoint apart from mucolytics, cough suppressants and short acting AC drugs. Table 3 describes the association between current use of tiotropium and the risk of a CCVE using current use of LABA as reference category. In this analysis, SABA is an exposure category only

Table 3 Associations for mutually exclusive bronchodilating drug use with a combined cardiovascular and cerebrovascular endpoint (independent of ICS and SABA)

Mutually exclusive groups (LABA as reference)	Cases No. (%) N=784	Control moments No. (%) N=25,899	Matched OR (95% CI)**	Adjusted OR (95%CI) Model 1	Adjusted OR (95%CI) Model 2 (main model)
Current use LABA*	115(14.7)	3,590 (13.9)	Reference	Reference1	Reference1
Current use Tiotropium*1	21 (2.7)	656 (2.5)	0.92 (0.57-1.49)	0.88 (0.54-1.43)	0.89 (0.55-1.44)
Duration of use					
LABA <30 days	9 (1.1)	97 (0.4)	Ref.	Ref.	Ref.
Tiotropium <30 days	2 (0.3)	56 (0.2)	NA	NA	NA
LABA ≥30 days	106(13.5)	3,493 (13.5)	Ref	Ref	Ref
Tiotropium ≥30 days	19 (2.4)	600 (2.3)	0.95 (0.57-1.58)	0.92 (0.55-1.53)	0.93 (0.56-1.54)
Current use Ipratropium*	143(18.2)	4,393 (17)	1.05 (0.82-1.35)	1.01 (0.78-1.30)	1.02 (0.79-1.32)
Current use of Xanthines*	6 (0.8)	192 (0.7)	1.11 (0.48-2.56)	1.00 (0.43-2.33)	1.03 (0.44-2.38)
Current use combinations of drug classes*** (either fixed or individual preparations)	120(15.3)	3,098 (12)	1.23 (0.95-1.6)	1.12 (0.86-1.47)	1.14 (0.87-1.5)
Current use SABA (when used without any other bronchodilating drug)	54 (6.9)	1,830 (7.1)	0.96 (0.69-1.34)	0.94 (0.68-1.32)	0.95 (0.68-1.32)
Past use of respiratory drugs****	226(28.8)	9,218 (35.6)	0.75 (0.6-0.95)	0.77 (0.61-0.97)	0.77 (0.61-0.97)
No use of respiratory drugs	99 (12.6)	2,922 (11.3)	1.09 (0.82-1.43)	1.01 (0.75-1.37)	1.01 (0.75-1.35)

ORs are not displayed if fewer than 5 subjects exposed to comparison of interest (NA = not applicable if fewer than 5 exposed cases)

*might include use ICS and/or SABA

** matched on age, gender and indexdate

***combinations of fixed or individual respiratory preparations other than SABA

**** past use is always overruled by current use

Model 1 Adjusted for COPD severity at index date, duration of COPD and smoking

Model 2 Adjusted for COPD severity 1 year prior to index date, duration of COPD and smoking

Model 2 is the final model in the analysis

1: Additionally adjusted for use of systemic corticosteroids

Table 4 Stratified and sensitivity analyses on association between Tiotropium vs. LABA and the association with a combined cardiovascular and cerebrovascular endpoint (independent of ICS use and SABA)

	Current use Tiotropium*		
	Cases No. (%)	**Control moments No. (%)**	**Adjusted OR (95%CI)**
Subgroup analyses (pre-specified)			
Gender			
Female	6 (2)	176 (2.5)	1.02 (0.42-2.49)
Male	15 (3.1)	480 (2.5)	0.83 (0.47-1.49)
Calendar time			
<2002 (prior to Tiotropium marketing)	NA	NA	NA
>2002	21 (4.3)	656 (4.3)	0.93 (0.56-1.54)
COPD severity#			
Mild & Moderate	18 (3.3)	469 (2.5)	0.96 (0.56-1.64)
Severe & Very severe	3 (1.2)	187 (2.5)	NA
Incident vs. Prevalent COPD			
Incident COPD	10 (6)	244 (5.2)	1.28 (0.55-2.98)
Prevalent COPD	11 (1.8)	412 (1.9)	0.74 (0.38-1.43)
Smoking status##			
Ever smoker	12 (3.6)	392 (3.4)	0.72 (0.36-1.46)
Never smoker	3 (4.0)	66 (2.5)	NA
Smoking status unclear	6 (1.6)	198 (1.7)	0.83 (0.33-2.04)
Sensitivity analyses focusing on assessing effect of choice in methods			
COPD severity assessment			
By Spirometry	6 (2.2)	306 (3.2)	0.55 (0.22-1.35)
Proxy assessment	15 (2.9)	350 (2.1)	1.14 (0.63-2.07)
Certainty COPD diagnosis			
Definite COPD	12 (2.4)	422 (2.6)	0.91 (0.48-1.73)
Probable COPD	9 (3.1)	234 (2.4)	0.89 (0.41-1.92)
Consultation with pulmonologist vs. no consultation with pulmonologist			
Patients seen by pulmonologist	9 (2)	356 (2.5)	0.73 (0.35-1.52)
Patients not seen by pulmonologist	12 (3.5)	300 (2.5)	0.88 (0.44-1.73)
Asthma vs. no Asthma			
Patients with asthma	2 (1.8)	77 (2.2)	NA
Patients without asthma	19 (2.8)	579 (2.6)	0.85 (0.51-1.42)

ORs are not displayed if fewer than 5 subjects exposed to comparison of interest (NA = not applicable if fewer than 5 exposed cases) *might include use ICS and/or SABA

Adjusted for COPD severity 1 year prior to index date, duration of COPD, smoking and use of systemic corticosteroids

#: Adjusted for duration of COPD, smoking and use of systemic corticosteroids

##: Adjusted for COPD severity 1 year prior to index date, duration of COPD and use of systemic corticosteroids

NA= not applicable as tiotropium registered from 2002 on

if it is not used in combination with another bronchodilating drug. Current use of tiotropium was not associated with an increased risk of a CCVE (OR_{adj} 0.89, 95% CI 0.55-1.44), nor was any current use of other bronchodilating drugs.

We conducted stratified and sensitivity analysis to inspect effect modification, but no major change in effect estimates of tiotropium against LABA was seen across different age, calendar time, smoking and severity strata (table 4).

Mortality

Within the COPD cohort, 1,032 (15.2%) patients died. Cause of death was distributed as following: 245 cases of CV related death (23.0% of total number of deaths), 346 cases of respiratory related death (33.0%), 83 cases of CV & respiratory related death (8.0%), 111 cases

Table 5 Associations between COPD drug use and all-cause death (mutually exclusive bronchodilator use but independent of ICS and SABA)

Mutually exclusive groups (LABA as reference)	Cases n=1,032 No. (%)	Control moments n=40,615 No. (%)	Matched OR (95%CI)**	Adjusted OR (95% CI) model 1	Adjusted OR (95% CI) model 2
Current use LABA*	116 (11.2)	5,378 (13.2)	Reference	Reference1	Reference1
Current use of Tiotropium*	23 (2.2)	1,265 (3.1)	0.74 (0.46-1.18)	0.79 (0.49-1.28)	0.79 (0.49-1.28)
Duration of use					
LABA <30 days	6 (0.6)	165 (0.4)	Ref	Ref	Ref
Tiotropium <30 days	1 (0.1)	91 (0.2)	NA	NA	NA
LABA ≥30 days	110 (10.7)	5,213 (12.8)	Ref	Ref	Ref
Tiotropium ≥30 days	22 (2.1)	1,174 (2.9)	0.77 (0.48-1.25)	0.83 (0.51-1.37)	0.84 (0.51-1.38)
Current use of Ipratropium*	201 (19.5)	6,883 (16.9)	1.34 (1.06-1.69)	1.13 (0.89-1.45)	1.17 (0.91-1.49)
Current use of Xanthines*	22 (2.1)	349 (0.9)	3.04 (1.88-4.93)	2.11 (1.27-3.50)	2.20 (1.33-3.64)
Current use of combinations of drug classes*** (either fixed or individual preparations)	183 (17.7)	5,406 (13.3)	1.59 (1.25-2.02)	0.96 (0.75-1.24)	1.01 (0.78-1.30)
Current use of SABA	66 (6.4)	2,620 (6.5)	1.12 (0.82-1.53)	1.11 (0.81-1.53)	1.10 (0.8-1.52)
Past use of respiratory drugs****	344 (33.3)	14,702(36.2)	1.03 (0.83-1.28)	1.30 (1.04-1.63)	1.27 (1.02-1.59)
No use of respiratory drugs	77 (7.5)	4,012 (9.9)	0.85 (0.63-1.14)	1.63 (1.17-2.26)	1.46 (1.06-2.01)

ORs are not displayed if fewer than 5 subjects exposed to comparison of interest (NA = not applicable if fewer than 5 exposed cases)

*might include use ICS and/or SABA

** matched on age, gender and indexdate

***combinations of fixed or individual respiratory preparations other than SABA

**** past use is always overruled by current use

Model 1: adjusted for severity of COPD at index date, duration of COPD and smoking

Model 2: adjusted for severity of COPD one year prior to the index date, duration of COPD and smoking

Model 2 is the final model in the analysis

1: Additionally adjusted for use of AHT drugs, systemic corticosteroids, and mucolytics

Table 6 Stratified and sensitivity analyses on association between mutually exclusive COPD bronchodilating drug use and the association with death independent of ICS use and SABA

Current use Tiotropium*	**Cases No. (%)**	**Control moments No. (%)**	**Adjusted OR (95%CI)**
Subgroup analyses (pre-specified)			
Gender			
Female	6 (1.7)	255 (2.6)	0.97 (0.4-2.36)
Male	17 (2.5)	1,010 (3.3)	0.73 (0.41-1.29)
Calendar time			
<2002 (prior to Tiotropium marketing)	NA	NA	NA
>2002	23 (3.2)	1,265 (4.6)	0.82 (0.5-1.34)
COPD severity#			
Mild & Moderate	8 (1.7)	896 (3.2)	0.54 (0.24-1.21)
Severe & Very severe	15 (2.6)	369 (2.9)	0.90 (0.48-1.71)
Incident vs .Prevalent COPD			
Incident COPD	6 (3.8)	416 (5.4)	0.64 (0.22-1.87)
Prevalent COPD	17 (1.9)	849 (2.6)	0.86 (0.49-1.51)
Smoking status##			
Ever smoker	13 (3.4)	675 (4)	0.66 (0.32-1.39)
Never smoker	0 (0)	159 (4)	NA
Smoking status unclear	10 (1.6)	431 (2.2)	1.01 (0.49-2.05)
Sensitivity analyses focusing on assessing effect of choice in methods			
COPD severity assessment			
By Spirometry	9 (3)	567 (4)	0.69 (0.30-1.59)
Proxy assessment	14 (1.9)	698 (2.7)	0.91 (0.49-1.69)
Certainty COPD diagnosis			
Definite COPD	14 (2.1)	817 (3.2)	0.74 (0.39-1.37)
Probable COPD	9 (2.4)	448 (2.9)	0.92 (0.4-2.12)
Consultation with pulmonologist vs. no consultation with pulmonologist			
Patients seen by pulmonologist	15 (2)	718 (3.1)	0.91 (0.51-1.6)
Patients not seen by pulmonologist	8 (2.9)	547 (3.1)	0.76 (0.3-1.89)
Asthma vs. no Asthma			
Patients with asthma	4 (4.2)	153 (3)	NA
Patients without asthma	19 (2)	1,112 (3.1)	0.75 (0.44-1.27)
Types of death			
Cardiovascular death	4 (1.6)	258 (2.5)	NA
Respiratory related death	11 (3.2)	459 (3.2)	1.09 (0.52-2.28)
Cardiovascular & Respiratory related death	2 (2.4)	99 (3.3)	NA
Cancer related death	4 (3.6)	209 (4.5)	NA
Death due to other cause	0 (0)	70 (2.6)	NA
Cause of death unknown	2 (1.2)	170 (2.9)	NA

ORs are not displayed if fewer than 5 subjects exposed to comparison of interest (NA = not applicable if fewer than 5 exposed cases) *might include use ICS and/or SABA #: Adjusted for duration of COPD, smoking and use of systemic corticosteroids, AHT drugs, and mucolytics ##: Adjusted for COPD severity 1 year prior to index date, duration of COPD and use of systemic corticosteroids, AHT drugs and mucolytics Adjusted for COPD severity 1 year prior to index date, duration of COPD, smoking, use of systemic corticosteroids, AHT drugs and mucolytics NA= not applicable as tiotropium registered from 2002 on

of cancer related death (11.0%), 78 cases of death due to other causes (7.5%), and 169 cases with unknown cause of death (16.4%). Co-morbidity and use of concomitant medication (as proxy for underlying co-morbidity) were related to death (table 2). COPD severity was a strong risk factor for dying especially in the severe to very severe COPD category. Table 5 describes the association between current use of tiotropium and the risk of death using current use of LABA as reference category. In this analysis, SABA is an exposure category only if it is not used in combination with another bronchodilating drug. Compared to LABA, current use of tiotropium (OR_{adj} 0.79, 95% CI 0.49-1.28), ipratropium (OR_{adj} 1.17, 95% CI 0.91-1.49), SABA (OR_{adj} 1.10, 95% CI 0.80-1.52) and the combination of respiratory drugs (OR_{adj} 1.01, 95% CI 0.78-1.30) was not associated with an increased risk of death. Current use of xanthines increased the risk of dying compared to LABA (OR_{adj} 2.20, 95% CI 1.33-3.64). Past use or no use of respiratory drugs increased the risk of death (table 5).

Stratified analyses were conducted to inspect effect modification, however no major heterogeneity in effect estimates of tiotropium against LABA was seen across different age, calendar time, smoking and severity strata (table 6).

Subananalyses were conducted to assess whether there is a potential association between tiotropium and the causes of death namely: CV, respiratory, CV & respiratory, cancer related deaths, death due to other causes and cause of death unknown. Due to low numbers; this analysis did not inform on the potential association between the current use of tiotropium and risk of dying from specific causes (table 6).

Discussion

Since long acting bronchodilators, including the long-acting anticholinergic tiotropium (Spiriva®) are the main stem in the treatment of patients with moderate to very severe COPD (GOLD stage II till IV), it is crucial to explore any potential safety signals. Pooled analysis of data from randomized controlled trials provided conflicting information on the potential of CV events in patients being treated with inhaled ACs. We conducted a nested case control study in a cohort of COPD patients to further elaborate the potential CV risks of tiotropium. We did not observe an increased risk for CCVE and/or mortality in patients currently treated with tiotropium and we had the power to exclude excess risks of more than 50%.

The debate on the potential association between the use of inhaled ACs and the risk of CV events started in 2002 with the publication of the results of the 5-year Lung Health Study. That study illustrated that ipratropium did not reduce mortality compared to placebo. In contrast, the proportion of patients with CV events and CV death was higher in the ipratropium arm compared to placebo but this was mainly observed in the non-compliant patients [172, 173]. Lee et al and Macie et al, both studied the CV safety of ipratropium using a nested case control study in a cohort of COPD patients, using data from the U.S. Veterans Health Administration health care system and the Canadian Manitoba Health database respectively and found that ipratropium was associated with an increased risk of death (OR 1.34, 95% CI 1.22-1.47) and hospitalization for CV events mainly heart failure (OR 1.47, 95% CI 1.31-1.64). [118, 174] It should be noted however, that the study from Macie et al included as well asthma, COPD and bronchitis patients and did not include information on smoking status. Lee et al conducted his study in a cohort of patients newly diagnosed with COPD but lacked information on COPD severity and smoking status, and therefore the results could be explained by residual confounding. In March 2008, the FDA released an early communication on a potential increased risk of stroke in patients being treated with tiotropium based on a preliminary report by Boehringer-Ingelheim (manufacturer of Spiriva) [121]. This report was based on an analysis of 29 clinical trials that showed an excess rate of stroke of 2/1,000 in patients treated with tiotropium compared to patients being treated with placebo. Soon after the FDA communication, the meta-analysis of Singh et al was published showing an increased risk (RR 1.58, 95% CI 1.21-2.06) of composite CV endpoints (stroke, MI and CV death) in patients being treated with inhaled ACs, including tiotropium, compared to patients receiving control therapy. [119] Later that year, the results of the UPLIFT study were published [68]. This randomized double blind trial compared 4 years of therapy with either tiotropium or placebo in 6,000 patients with COPD who were permitted to use all respiratory medication except inhaled AC drugs. At 4 years, there was a non-significant trend for a decrease in death from any cause in tiotropium treated patients compared to placebo treated patients (HR 0.89, 95 % CI 0.79-1.02). Regarding combined CV endpoints (angina pectoris, atrial fibrillation, cardiac failure, congestive heart failure, coronary artery disease and myocardial infarction); there was a reduced incidence in the tiotropium group as compared to the placebo group (3.56 vs. 4.21 per 100 PY, RR 0.84, 95% CI 0.73-0.98). The meta-analysis by Singh et al, also published in 2008, was strongly criticized because of methodological flaws such as the integration of placebo controlled trials with active controlled trials, the ignorance of the effect of differential discontinuation and the fact that most of the evidence (weight) was provided by a single study namely the Lung Health Study [119, 172]. In the mean time, the meta-analysis of Singh has been repeated by 3 different groups taking into account more recent studies including the UPLIFT study. These updated meta-analyses did no longer find an increased risk for CV events and mortality associated with the use of tiotropium. [175-177] Based on the available evidence, the FDA concluded in January 2010, that the available data do not support an as-

sociation between the use of tiotropium and an increased risk of stroke, heart attack or death from CV causes [120].

Most of the safety information on tiotropium is based on data from randomized controlled trials (RCTs) which hampers external validity as RCTs use stringent inclusion and exclusion criteria. Also, sample size and time of follow-up is often limited which reduces the chance to detect rare safety or long term events. Few observational studies studied the effectiveness and safety of tiotropium in real life. De Luise et al studied the risk of CV and respiratory hospitalizations and mortality in COPD patients treated with tiotropium using data from the Danish healthcare registries. Compared to no use of tiotropium (but allowing use of other respiratory drugs), tiotropium was associated with a reduced respiratory and overall mortality rate and was not associated with increased cardiac mortality. [178] Jara et al compared the risk of total mortality and CV safety in tiotropium users compared to users of LABA using data from the UK THIN database. [179] The authors concluded that both exposure groups had similar risks regarding overall mortality and CV endpoints. These observational studies had methodological limitations as information on important confounders such as smoking status and COPD severity was lacking. In addition, Jara et al did not restrict the study population to patients with COPD but included patients being treated with long acting bronchodilators whatever the indication for use. To our knowledge, our study is the first to study the association between the use of tiotropium and CV events and mortality in clinical practice. In addition we did put great efforts in identifying important confounders such as smoking history and COPD severity. It should be noted however that information on smoking status is often incomplete in health care databases as this is not routinely asked for nor reported in a consistent manner.

As for all observational studies, our study has strengths, but also limitations. The main strengths are the size and quality of our data. Great emphasis was put on the assessment of COPD, the COPD severity and clinical endpoints. The external validity of our data can be deducted by the fact that our risk estimates are in line with published data. Being observational, the study is sensitive to bias and confounding. We tried to adjust for COPD severity as much as possible, by assessing COPD severity longitudinally which allowed for flexibility in the timing for adjustment. Despite these measures, remaining confounding by indication, including severity might still be an issue. In addition, as COPD severity was assessed either via spirometry, using GOLD criteria, or via proxy using a pre-defined algorithm, potential misclassification of COPD severity was a concern. For this reason, we used current use of LABA as reference category, as long acting bronchodilators (including LABA) are indicated in COPD stage GOLD II-IV and users of LABA and tiotropium had similar CV risk profiles. To control for misclassification of the outcome we conducted a broad search and used a strict validation algorithm. In addition, all endpoints were validated by 2 medically trained researchers who were blinded to the exposure and were unaware of the research hypothesis. In case of doubt, the validation was overruled by a third medically trained person. Remaining misclassifica-

tion of the outcome can never be completely overruled. If present, this misclassification is probably non-differential resulting meaning that the observed OR is a conservative estimate (shifted towards the 1) meaning that the actual effect is probably lower. Due to the nature of the database, exposure was based on prescription data rather than on actual drug intake. In chronic diseases like COPD, we might have missed prescriptions initiated by the specialist. To study the potential of exposure bias, we conducted a sensitivity analysis, stratifying on patients seen by the GP only. For this group of patients, all prescriptions for respiratory drugs are available in the database - the results within this stratum were similar to the results of the overall dataset suggesting that exposure bias is minimal.

In conclusion, our analyses in a cohort of well-defined COPD patients did not show an increased risk of CV endpoints or mortality in COPD patients being treated with tiotropium compared to use of LABA.

4.5

β-blockers and the risk of severe COPD exacerbation in patients with COPD

Abstract

Background: Contrary to the traditional dogma that the use of β-blockers is dangerous in patients with chronic obstructive pulmonary disease (COPD), there is emerging evidence that treatment with β-blockers, particularly those that are cardioselective, might be safe and well tolerated and may produce good clinical outcomes in patients with COPD, especially if they have co-existing heart failure. Although there is reason to believe there may be some potential beneficial effect, we believe that the recently published degree of protection by Rutten *et al.* might be too optimistic and due to various design issues such as confounding and immortal time bias.
Objectives: To study the effect of β-blockers on the risk of severe COPD exacerbations leading to hospitalization in patients with COPD.
Methods: We conducted several analyses to study the effects of β-blockers on exacerbations by 1) mimicking the design of the previously published study by Rutten *et al.*; 2) avoidance of immortal time bias and fixed exposure bias by conducting a nested case-control study in a cohort of COPD patients; 3) reducing of confounding by indication for β-blockers by restricting the case control analyses to patients who had received a β-blocker during the study period. All studies were based on data from the Dutch Integrated Primary Care Information (IPCI) medical record database during the period 2000 to 2007. Cases were all COPD patients with a first COPD exacerbation requiring hospitalization. To each case, all eligible controls were matched on age, gender and index-date. Cox proportional hazard regression analysis (cohort) and conditional logistic regression analyses (case-control) were used.
Results: Within the cohort of 6,788 COPD patients, 619 patients had at least one COPD exacerbation requiring hospitalization. Current use of β-blockers significantly reduced the risk of severe COPD exacerbations by in the first analysis mimicking Rutten *et al.* (adjusted hazard ratio (HR) 0.73, 95%CI 0.60-0.90). When applying a case control analyses the use of β-blockers reduced the risk of exacerbations by 40% (OR_{adj} 0.60, 95% CI 0.44-0.82). When dealing by confounding by indication in the third analysis the protective effect was much attenuated (OR_{adj} 0.87, 95% CI 0.52-1.45). However, in patients with co-existing heart failure a significant protective effect was still observed (OR_{adj} 0.15, 95% CI 0.03-0.80).
Conclusions: The design is important when assessing the effect of β-blockers on COPD outcomes, especially since they were contra-indicated for a long time. Overall there may be a small protective effect, which is more pronounced in patients with co-existing heart failure.

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of chronic morbidity and mortality worldwide, with a marked negative impact on quality of life as well as increased hospitalization and mortality rates [105]. The disease is often complicated by frequent and recurrent exacerbations that ensue with increasing severity [54] and contribute to declining lung function [55]. Exacerbations contribute considerably to the morbidity associated with COPD [104]. Moreover, exacerbations lead to an increase in health care costs, disability, and result in premature death. As a consequence, exacerbations are currently considered to be one of the most relevant outcome parameters in randomized controlled trials in patients with COPD [103].

COPD is accompanied by systemic inflammation [105] which leads to atherosclerotic disease progression independent of age, smoking, or other cardiovascular risk factors [180]. Hence, patients with COPD are prone to develop cardiovascular diseases, which account for the majority of deaths in these patients [180, 181]. Heart failure is very common in patients with COPD as both conditions are diseases of the elderly and have the same risk factors, in particular smoking. In addition it is very difficult to differentiate between COPD and heart failure where symptoms of breathlessness might be interpreted as COPD-related symptoms and vice-versa [182, 183].

Treatment with cardiovascular drugs, especially β-blockers is known to improve the survival of patients with a large spectrum of cardiovascular diseases, including heart failure [184]. The traditional belief states however that β-blockers are contra-indicated in patients with COPD because of their presumed broncho-constrictive properties and their competition with β_2-agonists [185], which leads to lower prescription rates in COPD patients [186]. However, COPD as contra-indication for the use of β-blockers is currently revisited since β-blockers may actually have beneficial effects in patients with COPD through tempering of the sympathetic nervous system or by reducing the ischemic burden [187]. Meta-analyses of 20 randomized blinded clinical trials that studied the effects of cardioselective β-blockers in patients with COPD, have demonstrated that especially cardioselective β-blockers are well tolerated in patients with COPD [188]. In addition, two observational studies have shown that β-blocker use in patients with COPD and concomitant cardiovascular disease reduces the risk of dying [189, 190]. In their observational retrospective study of 3,371 patients who underwent vascular surgery, van Gestel *et al.* concluded that cardioselective β-blockers were associated with reduced mortality in patients with COPD undergoing vascular surgery [190]. In their observational study using hospital claims data from 201,752 patients with myocardial infarction, Gottlieb *et al.* concluded that after myocardial infarction, patients with conditions that are often considered contra-indications for β-blockade such as COPD, benefit from a beta-blocker therapy [189]. More recently, a small observational cohort study in the Netherlands showed that β-blockers might reduce the risk of exacerbations and improve survival

in patients with COPD, possibly as a result of dual cardiopulmonary protective properties. However time varying exposure exposure was not handled correctly and immortal time bias was an issue [191]. We hypothesized that the study of Rutten *et al.* on the protective effect of β-blockers on the risk of COPD exacerbation might suffer from exposure and immortal bias plus residual confounding. For this reason, we first mimicked the study by Rutten *et al.* to see whether we would obtain similar results, and subsequently we conducted two studies with better designs to capture biases. The conducted studies were a 1) nested case-control study in a cohort of COPD patients and 2) a nested case control study in a cohort of COPD patients who received β-blockers during the study period. In all analyses we have stratified by heart failure.

Methods

Setting

The study was conducted in a cohort of COPD patients from the Integrated Primary Care Information Project (IPCI) database. IPCI is a population-based longitudinal database that contains the complete computer-based medical records of currently more than 400 General Practitioners (GPs) throughout the Netherlands [86]. In the Dutch health care system, patients are registered with a single GP who acts as a gatekeeper of medical care. Therefore the medical records do not only capture GP diagnoses and symptoms, but also the results and summaries of specialist care. At present, the IPCI database contains information on more than 1 million patients. This database contains anonymized patient identification information (age, sex, patient identification number, and GP registration information), narratives, symptoms, signs, GP and specialist diagnoses, prescriptions, laboratory values, and summaries of specialist letters [86, 88]. The system complies with European Union guidelines on the secondary use of healthcare data for medical research and has been proven valid for pharmaco-epidemiological studies [91]. All observational research on the IPCI database is being conducted according to good pharmaco-epidemiological guidelines [92].

The source population consisted of all patients in the IPCI database who were 40 years of age or older, and with at least one year of valid history available in the database. The study period started in January 2000 and ended in May 2007. Practices included in the previous Dutch paper were not included in this study.

Design

In this study we used three designs to study the effects of β-blockers on COPD exacerbations and to explore the effects of design choices and confounding. The designs were 1) a fixed cohort design in COPD patients similar to Rutten *et al.* where follow-started at COPD cohort entry and use of β-blockers during follow-up was used to assign patients to expo-

sure cohorts; 2) a nested case control study in a cohort of COPD patients, where follow-up started at COPD cohort entry; 3) a nested case control study in a cohort of COPD patients who received β-blockers during the study period, where follow-up started at the day of first β-blocker prescription after the diagnosis of COPD. We hypothesized that the first design would overestimate the effect of β-blockers on exacerbations due to exposure misclassification such as immortal time bias [192].

COPD cohort

COPD patients were identified from diagnoses and narratives. The medical records of all potential cases were reviewed by a medical doctor and classified as: definite COPD - diagnosis by a specialist or a GP diagnosis confirmed by spirometry (FEV1/FVC<70%); probable COPD - COPD diagnosed by the GP with at least two records of COPD within one year of the first record of COPD. All doubtful COPD patients were further reviewed and classified by a pulmonologist (GB). All COPD patients were further categorized into prevalent or incident COPD. Patients with a COPD diagnosis prior to study entry were classified as prevalent (existing) COPD. If patients were disease free at cohort entry and developed COPD during the study period, they were considered as having incident (newly onset) COPD.

COPD severity was assessed at the time of cohort entry and changes in COPD severity were captured during follow-up. If spirometry was available, severity of COPD was determined according to the GOLD guidelines; in all other patients, previously published algorithms for COPD severity assessment were used [59, 76-78]. In summary, patients were considered to have mild COPD at the time of their first symptoms of COPD, moderate COPD if patients were on regular bronchodilatory treatment (defined as at least 2 prescriptions of the same drug class within 6 months of the first prescription), and severe COPD if they were hospitalized for COPD, had a third course of antibiotics for the treatment of respiratory tract infections in one year time, or had a second systemic corticosteroid course for the treatment of COPD exacerbations. Finally, patients were considered to have very severe COPD when they were prescribed oxygen therapy or were scheduled for lung transplantation because of COPD.

All COPD patients were followed from cohort entry until transferring out, last data download, the end of the study period, the first COPD exacerbation requiring hospitalization, death or end of follow-up, whichever event occurred the earliest.

Cases and controls

All COPD exacerbations were identified in the electronic medical records and adjudicated by two medical doctors, a third doctor arbitrated in case of discrepancies. For this study we only considered COPD exacerbations resulting in hospitalization. The index date was the date of the first COPD exacerbation leading to hospitalization after study entry.

For the case control studies to each case we matched all available controls from the COPD cohort on index date (controlling for differences between calendar years), gender and year

of birth. Due to this greedy sampling approach, controls could be re-sampled at different moments in time and their contribution should be considered in person-time (moments) rather than subjects (32).

Exposure to β-blockers

Exposure to β-blockers was categorized by type of drug (cardioselective and non-cardioselective β-blockers), timing, duration and dose. Drug exposure was categorized by timing of use in current use (last prescription covered the index date or ended less than 30 days prior to the index date), past use or no use, we distinguished also between those switched between types. For current users of β-blockers, the effect of daily dose and time since first use were investigated. Daily dose was expressed in daily doses (DDD); 1DDD is the average dose of a drug for an adult for the main indication, as defined by the WHO [89]. To study the effect of time since first use, we categorized current users of β-blockers into recent starters (patients who received their prescriptions for a β-blocker within 2 weeks prior to the index date) and chronic users (patients currently using β-blockers for more than 2 weeks).

Covariates

Heart failure was identified from ICPC specific codes for heart failure (K77, K82) and free text. Two medical doctors adjudicated all potential cases of heart failure, and a third doctor arbitrated in case of discrepancies. Heart failure was defined as being present in case of diagnosis by the specialist (cardiologist or specialist in internal medicine) or GP diagnosis, according to the Framingham criteria for the diagnosis of congestive heart failure [193].

As other covariates we considered the severity of COPD as well as underlying co-morbidities and concomitant drug use. These covariates included smoking history, use of concomitant medication (at least use in the month prior to the index date) and concomitant diseases such as heart diseases (excluding heart failure), diabetes mellitus, lipid disorders, malignancies and diseases affecting the central nervous system. Finally, resource use, by means of the number of GP office and home visits as well as a homebound lifestyle (two or more home visits in the last month prior to the index date) was taken into account.

Analysis

To mimic the paper by Rutten *et al*., we conducted a fixed cohort study with Cox proportional hazards regression analyses to calculate crude (unadjusted) and adjusted hazard ratios (HR) and their 95% confidence intervals (95%CI) for the risk of COPD exacerbations requiring hospitalization associated with the use of β-blockers. Exposure was classified on the basis of the first β-blocker prescription during follow-up and follow-up started at COPD cohort entry even if β-blockers were prescribed much later during follow-up. Adjusted HRs were calculated after correction for the following (potential confounding) variables: age, sex, smoking history, heart failure and history of cardiovascular disease (excluding heart failure).

In the case control studies, we used conditional logistic regression analysis for estimating the matched unadjusted and adjusted risks and 95% CI. The risk of exacerbation during current use of β-blockers was compared to the risk during no use (analysis 2) or past use of β-blockers (analysis 3). The third analysis was conducted in the cohort of COPD patients who received a β-blocker prescription during follow up. All models were adjusted for at least COPD severity, duration of COPD, and smoking. In addition we adjusted for all factors that changed the effect estimate of β-blockers by more than 5%.

Stratified analyses were conducted for co-existing heart failure in the final design. We tested effect modification by adding an interaction term in the conditional logistic regression model (multiplicative interaction). Only if the interaction term based on the effect modifier of interest and use of β-blockers turned out to be statistically significant ($p<0.05$) in the adjusted model, effect measure modification was considered to be present.

All statistical analyses were conducted with the statistical software packages SPSS/PC 15.0 (SPSS Inc, Chicago, Ill).

Results

COPD Cohort

From the source population of 185,325 participants 40 years and older, 6,788 patients were diagnosed with COPD of which 23% were newly diagnosed during the study period (incident COPD). The median follow-up time per COPD patient was 3.5 years, with a total follow-up time of 23.930 person-years. Baseline characteristics of the COPD cohort are described in table 1. The most frequent co-morbidities were hyperlipidemia, hypertension, angina pectoris, heart failure, diabetes mellitus and tumors.

Approximately 23% of the cohort received a prescription of a β-blocker during follow-up (including use of β-blocker at time of cohort-entry). Characteristics of patients at time of first prescription during follow-up (including use at time of cohort-entry) were compared to the general COPD cohort (table 1). Patients receiving a β-blocker tended to be older mainly had moderate COPD and had more cardiovascular comorbidity. Use of concomitant medications, including other cardiovascular drugs and respiratory drugs, was also more present in patients being prescribed a β-blocker.

β-blocker and hospitalization for COPD exacerbation

Within the COPD cohort, 619 patients were hospitalized for a COPD exacerbation of which 351 (56.7%) were male (table 2). The mean age of the cases was 72.2 (SD=±10.2) years. COPD severity (severe/very severe) was strongly related to hospitalization for COPD. Underlying co-morbidities that increased the risk of hospitalization were angina pectoris, peripheral arterial disease, heart failure, renal disease and depression. Use of concomitant medication

Table 1(a) Patients characteristics at cohort entry and at start of first presciption during follow-up

	At cohort entry	At start of first prescription during FU
	COPD cohort No.(%)	β-blocker No.(%)
Number of patients	6,788	1,553
♂ Male	3,889 (57.3)	880 (56.7)
♀ Female	2,899 (42.7)	673 (43.3)
Age (mean,SD)	67.3 (±12.1)	70.7 (±10.6)
40-59 (No.,%)	1,797 (26.5)	252 (16.2)
60-69 (No.,%)	173 (25.6)	414 (26.7)
70+ (No.,%)	3,252 (47.9)	887 (57.1)
Smoking history		
no smoking (reference)	525 (7.7)	137 (8.8)
current smoking	2,737 (40.3)	630 (40.6)
past smoking	417 (6.1)	117 (7.5)
smoking unspecified	3,101 (45.7)	669 (43.1)
passive smoking	8 (0.1)	
Severity at cohort entry		
mild (GOLD I)	2,694 (39.7)	508 (32.7)
moderate (GOLD II)	2,713 (40.0)	727 (46.8)
severe (GOLD III)	1,280 (18.9)	306 (19.7)
very severe (GOLD IV)	101 (1.5)	12 (0.8)
Co-morbidity /history		
History of asthma	1,042 (15.4)	233 (15.0)
History of myocardial infaction	457 (6.7)	247 (15.9)
Angina pectoris	994 (14.6)	524 (33.7)
Ischemic heart disease	188 (2.8)	95 (6.1)
History of stroke or TIA	391 (5.8)	185 (11.9)
Peripheral arterial disease	441 (6.5)	164 (10.6)
Heart failure	793 (11.7)	322 (20.7)
Ventricular arrhythmia	401 (5.9)	19 (1.2)
Hypertension	1,422 (21.0)	642 (41.3)
Hyperlipidemia (TC>5)	1,769 (26.1)	692 (44.6)
Diabetes mellitus	767 (11.3)	269 (17.3)
Renal insufficiency	184 (2.7)	87 (5.6)
Migraine	95 (1.4)	32 (2.1)
Concussion and head injury	26 (0.4)	13 (0.8)
History of malignancy	673 (10.0)	201 (12.9)
Pneumonia	571 (8.4)	144 (9.3)
Parkinsonism	21 (0.3)	4 (0.3)
Depressive disorders	540 (8.0)	138 (8.9)
Dementia	23 (0.3)	7 (0.5)
Number of GP visits (mean,SD)	5.7 (±5.0)	7.2 (±5.1)

Table 1(b) Patients characteristics at cohort entry and at start of first prescription during follow-up

	At cohort entry	At start of first prescription during FU
	COPD cohort All No. (%)	β-blocker No. (%)
Previous use of drugs		
Central nervous system drugs		
Opioids (N02A)	122 (2.3)	123 (7.9)
Hypnotics and sedatives (N05C)	519 (9.8)	231 (14.9)
Anxiolytics (N05B)	504 (9.5)	301 (19.4)
Antipsychotics (typical, atypical) (N05A)	49 (0.9)	17 (1.1)
Antidepressants (SSRI) (N06AB)	189 (3.6)	78 (5.0)
Antiepileptic drugs (N03)	65 (1.2)	40 (2.6)
Anticholinergic drugs (no respiratory)	155 (2.3)	
Drugs affecting cerebrovascular and cardiovascular dx		
Nitrates (C01DA)	380 (5.6)	311 (20.0)
Platelet inhibitors (B01AC)	1,022 (15.1)	602 (38.8)
Anti-arrhythmics (C01)	70 (1.0)	41 (2.6)
Anti-hypertensives noBB (C03/C08/C09)	2,084 (30.7)	816 (52.5)
Corticosteroids (systemic): (H02)	579 (8.5)	373 (24.0)
Estrogens (G03)	197 (2.9)	68 (4.4)
Antibiotics (J01)	741 (10.9)	549 (35.4)
NSAIDs (M01A)	519 (7.6)	358 (23.1)
Diuretics	1,187 (17.5)	543 (35.0)
Vitamin K antagonists (B01AA)	385 (5.7)	
Lipid lowering drugs (C10)	620 (9.1)	380 (24.5)
Other respiratory drugs		
Antihistaminics (R06)	188 (2.8)	
Mucolytics (R05CB)	393 (5.8)	173 (11.1)
Cough suppressants (R05D)	190 (2.8)	157 (10.1)
Anticholinergics	1,560 (23.0)	612 (39.4)
Systemic β_2 agonists	23 (0.3)	10 (0.6)
Leukotriene receptor antagonists (R03DC)	16 (0.2)	20 (1.3)
Inhaled β_2 agonists	2,195 (32.3)	710 (45.7)
Inhaled corticosteroids	1,919 (28.3)	652 (42.0)
Xanthines	182 (2.7)	38 (2.4)

(as proxy for underlying co-morbidities) such as opioids, hypnotics & sedatives, anxiolytics, and antidepressants were also related to the outcome (table 2).

According to the methods mimicking the design of Rutten et al, the risk of severe COPD exacerbation was 27% lower in patients being treated with β-blockers (crude HR 0.73, 95%CI 0.60-0.90), some covariates had strong effects (table 3). The fully adjusted HR for any

Table 2(a) Patients characteristics for cases (COPD exacerbations requiring hospitalization) and controls

	Outcome = COPD Exacerbation requiring hospitalization		
	Cases No.(%)	**Controls No. (%)**	**Matched OR* (95%CI)**
Number of patients	619	24,820	
Gender			
♂ Male	351 (56.7)	17,055 (68.7)	Nap
♀ Female	268 (43.3)	7,765 (31.3)	Nap
Age (mean,SD)	70.1 (±10.1)	70.7 (±7.9)	
40-59 (No.,%)	109 (17.6)	2,761(11.1)	Nap
60-69 (No.,%)	159 (25.7)	6,730 (27.1)	Nap
70+ (No.,%)	351 (56.7)	15,329 (61.8)	Nap
Smoking history			
no smoking (reference)	43 (6.9)	2,510 (10.1)	Reference
current smoking	260 (42.0)	9,361 (37.7)	**1.59 (1.14-2.21)**
past smoking	27 (4.4)	1,896 (7.6)	0.89 (0.54-1.45)
smoking unspecified	289 (46.7)	11,033 (44.5)	**1.46 (1.05-2.03)**
passive smoking	0 (0.0)	20 (0.10)	NA
Severity at cohort entry			
mild (GOLD I)	67 (10.8)	5,648 (22.8)	Reference
moderate (GOLD II)	155 (25.0)	12,503 (50.4)	1.03 (0.77-1.34)
severe (GOLD III)	344 (55.6)	6,305 (25.4)	**4.75 (3.64-6.21)**
very severe (GOLD IV)	53 (8.6)	358 (1.4)	**12.2 (8.33-18.0)**
Co-morbidity /history			
History of asthma	117 (18.9)	3,355 (13.5)	**1.37 (1.10-1.68)**
History of myocardial infaction	60 (9.7)	2,346 (9.5)	1.17 (0.89-1.54)
Angina pectoris	134 (21.6)	4,444 (17.9)	**1.33 (1.09-1.63)**
Ischemic heart disease	24 (3.9)	1,044 (4.2)	1.01 (0.67-1.54)
History of stroke or TIA	52 (8.4)	2,140 (8.6)	0.98 (0.73-1.32)
Peripheral arterial disease	71 (11.5)	2,175 (8.8)	**1.36 (1.05-1.75)**
Heart failure	181 (29.2)	3,759 (15.1)	**2.56 (2.11-3.09)**
Ventricular arrhythmia	57 (9.2)	2,559 (10.3)	0.88 (0.67-1.17)
Hypertension	145 (23.4)	6,319 (25.5)	0.88 (0.73-1.06)
Hyperlipidemia (TC>5)	174 (28.1)	8,584 (34.6)	0.78 (0.65-0.94)
Diabetes mellitus	103 (16.6)	3,595 (14.5)	1.22 (0.98-1.51)
Renal insufficiency	34 (5.5)	1,029 (4.1)	**1.46 (1.02-2.10)**
History of malignancy	109 (17.6)	3,633 (14.6)	**1.27 (1.03-1.58)**
Pneumonia	152 (24.6)	3,053 (12.3)	**2.29 (1.89-2.77)**
Parkinsonism	3 (0.5)	90 (0.4)	1.19 (0.37-3.80)
Depressive disorders	71 (11.5)	2,004 (8.1)	**1.31 (1.02-1.69)**
Dementia	0 (0.0)	128 (0.5)	NA
Number of GP visits (mean, SD)	7.8 (±6.3)	5.7 (±4.7)	**1.07 (1.06-1.08)**
Home bound lifestyle	26 (±4.2)	221 (±0.9)	**4.83 (3.15-7.40)**

Table 2(b) Patients characteristics for cases (COPD exacerbations requiring hospitalization) and controls

	Outcome = COPD Exacerbation requiring hospitalization		
	Cases No. (%)	**Controls No. (%)**	**Matched OR* (95%CI)**
Previous use of drugs			
Central nervous system drugs			
Opioids	40 (6.5)	615 (2.5)	**2.59 (1.85-3.63)**
Hypnotics and sedatives	96 (15.5)	2,524 (10.2)	**1.54 (1.23-1.94)**
Anxiolytics	83 (13.4)	2,206 (8.9)	**1.49 (1.18-1.90)**
Antipsychotics (typical, atypical)	3 (0.5)	204 (0.8)	0.61 (0.19-1.92)
Antidepressants (SSRI)	31 (5)	755 (3)	**1.51 (1.04-2.19)**
Antiepileptic drugs	8 (1.3)	357 (1.4)	0.87 (0.43-1.76)
Anticholinergic drugs (except respiratory)	19 (3.1)	608 (2.4)	1.25 (0.78-1.99)
Drugs affecting cerebrovascular and cardiovascular dx			
Nitrates	52 (8.4)	1,481 (6.0)	**1.43 (1.06-1.92)**
Platelet inhibitors	118 (19.1)	4,749 (19.1)	1.08 (0.88-1.33)
Anti-arrhythmics	6 (1.0)	432 (1.7)	0.65 (0.29-1.45)
Anti-hypertensives (β-blocker excluded)	555 (53.8)	16,259 (40.0)	**1.69 (1.48-1.92)**
Corticosteroids (systemic):	207 (33.4)	2,044 (8.2)	**5.93 (4.97-7.09)**
Estrogens	16 (2.6)	366 (1.5)	1.18 (0.70-1.99)
Antibiotics	147 (23.7)	2,030 (8.2)	**3.50 (2.89-4.25)**
NSAIDs	35 (5.7)	1,834 (7.4)	0.73 (0.52-1.03)
Diuretics	181 (29.2)	4,980 (20.1)	**1.66 (1.38-1.99)**
Vitamin K antagonists	56 (9.0)	2,013 (8.1)	1.20 (0.90-1.59)
Lipid lowering drugs	60 (9.7)	2,862 (11.5)	0.87 (0.66-1.15)
Other respiratory drugs			
Antihistaminics	18 (2.9)	758 (3.1)	0.92 (0.57-1.47)
Mucolytics	105 (17.0)	1,454 (5.9)	**3.52 (2.82-4.39)**
Cough suppressants	17 (2.7)	472 (1.9)	1.46 (0.89-2.38)
Anticholinergics	100 (16.2)	1,109 (4.5)	**4.67 (3.56-6.14)**
Systemic β_2 agonists	3 (0.5)	77 (0.3)	1.62 (0.50-5.21)
Leukotriene receptor antagonists	15 (2.4)	137 (0.6)	**4.58 (2.63-7.97)**
Inhaled β_2 agonists	379 (61.2)	9,635 (38.8)	**2.53 (2.15-2.99)**
Inhaled corticosteroids	274 (44.3)	8,718 (35.5)	**1.50 (1.28-1.77)**
Xanthines	44 (7.1)	636 (2.6)	**3.27 (2.37-4.52)**

*matched on age, gender and indexdate

β-blockers was 0.73, 95%CI 0.60-0.90, which is similar to the estimates provided by Rutten *et al*.

In the case control study in the COPD cohort (analysis 2) current use of β-blockers seemed to reduce the risk of COPD exacerbation requiring hospitalizations (table 4). No clear dose-response relationship was observed. In the third analysis that controlled most strictly for con-

Table 3 Crude and adjusted risk ratios for COPD exacerbations requiring hospitalization according to β-blocker use in patients with COPD according to the design by Rutten *et al*.

Variable	Any β-blocker	Cardioselective β-blocker	Nonselective β-blocker
IPCI data			
Unadjusted (crude)	**0.77 (0.63-0.93)**	**0.75 (0.61-0.93)**	0.90 (0.64-1.27)
Covariates included in Cox model for HR +			
Age	**0.72 (0.59-0.88)**	**0.72 (0.58-0.89)**	0.85 (0.60-1.20)
Sex	**0.72 (0.59-0.88)**	**0.72 (0.58-0.89)**	0.85 (0.60-1.20)
Smoking	**0.72 (0.59-0.88)**	**0.72 (0.58-0.89)**	0.84 (0.59-1.18)
Diabetes, hypertension, cardiovascular diseases	**0.70 (0.57-0.85)**	**0.69 (0.56-0.86)**	0.83 (0.56-1.17)
Cardiovascular drugs other than β-blockers	**0.68 (0.56-0.83)**	**0.68 (0.54-0.85)**	0.82 (0.58-1.16)
Respiratory drugs	**0.71 (0.58-0.87)**	**0.71 (0.57-0.88)**	0.85 (0.60-1.19)
GP visits	**0.69 (0.57-0.85)**	**0.69 (0.56-0.87)**	0.83 (0.59-1.17)
Referral to a pulmonologist	**0.73 (0.60-0.90)**	**0.74 (0.54-0.92)**	0.84 (0.59-1.18)
Estimates by Rutten *et al*. (reference)			
Crude	**0.73 (0.63-0.83)**	**0.75 (0.65-0.87)**	**0.72 (0.57-0.90)**
Fully adjusted	**0.71 (0.60-0.83)**	**0.78 (0.66-0.92)**	0.74 (0.58-0.94)

Table 4 Association between use of β-blockers (no use as reference category) and COPD exacerbations requiring hospitalization using a nested case control design in a cohort of COPD patients

β-blocker use	Cases n=619 (%)	Controls n=24,820 (%)	Matched OR (95%CI)	Adjusted OR* (95% CI)
No use of β-blocker*	496 (80.1)	18,599 (74.9)	reference	reference
Current use of β-blocker	51 (8.2)	3,002 (12.1)	**0.64 (0.47-0.85)**	**0.60 (0.44-0.82)**
Recent start (<= 1 month)	2 (0.3)	82 (0.3)	NA	NA
Non-recent start (> 1 month)	49 (7.9)	2,920 (11.8)	**0.63 (0.46-0.84)**	**0.58 (0.42-0.80)**
Dosage				
PDD ≤ 0.5 (low)	26 (4.2)	1,426 (5.7)	0.69 (0.46-1.02)	**0.58 (0.38-0.88)**
PDD > 0.5 (moderate-normal)	25 (4.0)	1,576 (6.3)	**0.59 (0.39-0.89)**	**0.62 (0.41-0.96)**
Type of β-blocker				
Cardioselective no switching	33 (5.3)	2,215 (8.9)	**0.54 (0.38-0.81)**	**0.49 (0.34-0.72)**
Cardioselective with switching	4 (0.6)	144 (0.6)	1.03 (0.38 – 2.82)	0.89 (0.31-2.56)
Non-Cardioselective no switching	11 (1.8)	602 (2.4)	0.79 (0.43-1.44)	0.78 (0.42-1.46)
Non-Cardioselective with switching	1 (0.2)	59 (0.2)	NA	NA
Combination	2 (0.3)	24 (0.1)	NA	NA
Past use of β -blockers	72 (11.6)	3,219 (13.0)	0.81 (0.63-1.04)	**0.76 (0.58-0.99)**

*adjusted for smoking, COPD severity, duration COPD, GP visits, angina, heart failure, diuretics, xanthines (covariates assessed at index date)
NA: not assessable as less than 3 exposed cases

Table 5 Association between use of β-blockers (past use as reference category) and COPD exacerbations requiring hospitalization using a nested case control design in a cohort of COPD patients who received a β-blocker prescription during follow-up

β-blocker use	Cases n=90 (%)	Controls n=5,121 (%)	Matched OR (95%CI)	Adjusted OR* (95% CI)
Past use of β-blocker*	39 (43.3)	2,110 (41.3)	Reference	Reference
Current use of β-blocker	51 (56.7)	3,002 (58.7)	0.96 (0.61-1.51)	0.87 (0.52-1.45)
Recent start (<= 1 month)	2 (2.2)	82 (1.6)	NA	NA
Non-recent start (> 1 month)	49 (54.5)	2,920 (57.1)	0.95 (0.60-1.50)	0.86 (0.51-1.44)
Dosage				
PDD ≤ 0.5 (low)	26 (28.9)	1,426 (27.9)	1.01 (0.58-1.75)	0.84 (0.46-1.55)
PDD > 0.5 (moderate-normal)	25 (27.8)	1,576 (30.8)	0.91 (0.53-1.57)	0.90 (0.48-1.69)
Type of β-blocker				
Cardioselective no switching	33 (36.7)	2,215 (43.3)	0.84 (0.51-1.40)	0.72 (0.41-1.29)
Cardioselective with switching	4 (4.4)	144 (2.8)	1.05 (0.30-3.66)	1.41 (0.32-6.15)
Non-Cardioselective no switching	11 (12.2)	560 (11.0)	1.24 (0.60-2.61)	1.19 (0.52-2.76)
Non-Cardioselective with switching	1 (1.1)	59 (1.2)	NA	NA
Combination	2 (2.2)	24 (0.5)	NA	NA
Patients without heart failure				
	Cases n=57 (%)	**Controls n=3,912 (%)**	**Matched OR (95%CI)**	**Adjusted OR* (95% CI)**
Past use of β-blocker*	20 (35.1)	1,558 (39.8)	Reference	Reference
Current use	37 (64.9)	2,354 (60.2)	1.32 (0.71-2.47)	1.13 (0.55-2.33)
Type of β-blocker				
Cardioselective no switching	23 (40.3)	1,750 (44.7)	1.11 (0.57-2.19)	0.86 (0.38-1.96)
Cardioselective with switching	3 (5.3)	110 (2.8)	1.39 (0.28-6.89)	2.64 (0.36-19.1)
Non-Cardioselective no switching	8 (14.0)	437 (11.2)	1.80 (0.69-4.68)	1.80 (0.62-5.29)
Non-Cardioselective with switching	1 (1.8)	35 (0.9)	NA	NA
Combination	2 (3.5)	22 (0.6)	NA	NA
Patients with heart failure				
	Cases n=33 (%)	**Controls n=1,200 (%)**	**Matched OR (95%CI)**	**Adjusted OR* (95% CI)**
Past use of β-blocker*	19 (57.6)	552 (46.0)	Reference	Reference
Current use	14 (42.4)	648 (54.0)	0.39 (0.15-1.02)	**0.15 (0.03-0.80)**
Type of β -blocker				
Cardioselective no switching	10 (30.3)	465 (38.7)	0.40 (0.14-1.12)	**0.12 (0.02-0.82)**
Cardioselective with switching	1 (3.0)	34 (2.8)	NA	NA
Non-Cardioselective no switching	3 (9.1)	123 (10.3)	0.38 (0.07-2.05)	0.19 (0.01-3.85)
Non-Cardioselective with switching	0 (0)	24 (2.0)	NA	NA
Combination	0 (0)	2 (0.2)	NA	NA

*adjusted for smoking, COPD severity, duration COPD, GP visits 4 weeks prior to BB, duration BB, depression, hypnotics and sedatives, corticosteroids, diuretics

NA: not assessable as less than 3 exposed cases

founding by contra-indication current use of β-blockers was not associated with a significant reduced risk of exacerbations (OR_{adj} 0.87, 95% CI 0.52-1.45). Only in patients with co-existing heart failure, the protective effect of β-blockers remained (OR_{adj} 0.15, 95% CI 0.03-0.80), very small in terms of numbers (table 5).

Discussion

In this observational study we demonstrated that studying the effect of β-blocker use on the risk of severe COPD exacerbations is highly dependent on design choice. Confounding is very strong; the protective effect disappeared when limiting the analysis to patients ever prescribed a β-blocker, comparing current use of a β-blocker to past use, although in heart failure patients still some effect was observed.

COPD is a chronic condition with systemic manifestations including cardiovascular diseases [194]. In patients with COPD, right heart failure – the so called cor pulmonale, is common, especially in patients with more severe COPD but the evidence on the association between COPD and left heart failure is less convincing. Overlapping sigs and symptoms complicated the diagnosis of heart failure in COPD. In addition, it is very difficult to distinguish acute COPD exacerbations from symptoms related to decompensated heart failure. As we hypothesize that COPD patients with or without heart failure consist of a totally different population group with differences in treatment response and outcomes, we stratified our analysis in COPD patients with or without co-existing heart failure at the time of the index date. Our final data showed that β-blockers significantly reduced the risk of severe COPD exacerbations in patients with co-existing heart failure but not in COPD patients without heart failure. These findings might in part be explained by misclassification of the outcome, where GPs or specialists label the event as being a COPD exacerbation whereas the underlying symptoms of cough and breathlessness are probably related to decompensated heart failure. Apart from the difficulties to distinguish acute COPD exacerbations from decompensated heart failure, decompensated heart failure might trigger COPD exacerbation through congestion of the lung parenchyma. In contrast to our findings, Rutten *et al.* did not observe a difference in risk estimate for COPD exacerbation in patients with or without underlying cardiovascular disease. It should be noted however that Rutten *et al.* grouped all cardiovascular diseases together namely angina pectoris, myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention, atrial fibrillation, heart failure, peripheral arterial disease, stroke or diabetes whereas the protective effect of β-blockers on mortality has only been described for patients with co-existing heart failure [195].

Our data showed that the risk of COPD exacerbations was mainly reduced in patients using cardioselective β-blockers, both in patients with or without heart failure. These findings are in line with studies that have shown that cardioselective β-blockers can be safely used in COPD patients with heart failure, as they do not alter pulmonary function on the short term [196].

In contrast to the study by Rutten *et al*., we did not only conduct a Cox regression analysis, but also analyzed our data via a case-control approach. This case-control design not only reduces misclassification of exposure through time-varying exposure assessment but also tackles the issue of immortal time bias [197]. The cohort analysis conducted by by Rutten *et al.* suffered from immortal time as β-blocker exposed COPD patients who received β-blockers during follow-up; by definition have an event free survival starting from cohort-entry until the time of first prescription. Our first case-control analysis showed that taking out immortal time bias did not adequately control for all potential distortions, such as confounding as the strong protective effect remained. This effect of β-blockers attenuated in our second case-control analysis when using past use as reference category. This shows that confounding by contra-indication is strong. In patients with COPD, β-blockers are probably only prescribed to patients with a better pulmonary function and thus less at risk of COPD exacerbation.

As for all observational studies, our study has strengths, but also limitations. The main strengths are the size and quality of our data. Great emphasis was put on the assessment of COPD, and the disease severity and endpoints that were all manually validated by at least 2 medically trained persons. Being observational, the study is sensitive to bias and confounding. We tried to adjust for COPD severity as much as possible, by assessing COPD severity longitudinally, which allowed for flexibility in the timing for adjustment. Despite these measures, remaining confounding by indication and/or contraindication, including severity might still be an issue. Conducting a sensitivity analysis comparing current use of β-blockers to past use further controlled for this remaining confounding by underlying COPD severity. In the overall analysis, the protective effect of current use of β-blockers disappeared and could only be observed in the sub-set of COPD patients with co-existing heart failure. To control for misclassification of the outcome we conducted a broad search and used a strict validation algorithm. In addition, two medically trained researchers who were blinded to the exposure and were unaware of the research hypothesis validated all endpoints. In case of doubt, a third medically trained person overruled the validation. Due to the nature of the database, exposure was based on prescription data rather than on actual drug intake. In chronic diseases like COPD, we might have missed prescriptions initiated by the specialist. To study the potential of exposure bias, we conducted a sensitivity analysis, stratifying on patients seen by the GP only. For this group of patients, all prescriptions are available in the database - the results within this stratum were similar to the results of the overall dataset suggesting that exposure bias is minimal.

To conclude, we found that β-blockers may have some protective effect on exacerbations in patients with COPD, but due to the confounding and potentially biases utmost care should be taken in designing studies addressing this question.

CHAPTER 5
General Discussion

Background

Chronic obstructive pulmonary disease (COPD) is a leading and still-increasing cause of chronic morbidity and mortality worldwide [3]. Chapman *et al*. [80] and Mannino *et al.* [15] projected that in 2020, COPD will become the third most common cause of death worldwide. Over the last decades, many interesting studies on the epidemiology of COPD have been published. Some of the epidemiology data were based on results from cross-sectional studies. These studies are often debated due to limitations in their design, including the impossibility to distinguish between cause and effect in the association between an exposure and disease, the often-unequal distribution of confounding factors between the groups being compared, and errors in the recall of exposures in patients with the disease.

Alternatively, the "gold standard", randomized controlled trials (RCTs), also present weaknesses. They are often expensive and cumbersome to perform, have a short follow-up time and regularly use surrogate endpoints, rather than clinical outcomes, and involve a limited number of highly selected participants, which may hinder the extrapolation of the results into clinical practice [198]. Observational database studies include a large representative sample of the general population and often have a long duration of follow-up. These characteristics make these studies well suited to study the epidemiology and management of COPD, and to explore the effectiveness and safety of respiratory drugs under real life circumstances.

The aims of the studies described in this thesis were 1) to study the epidemiology of COPD, and 2) to explore the effectiveness and safety of drugs given for the treatment of COPD, using data from the Integrated Primary Care Information (IPCI) project, a general practitioners (GP) database in the Netherlands. For this research, we defined three different cohorts of COPD. I) For the study on the association between the use of inhaled anticholinergic drugs and the risk of acute urinary retention; COPD was defined based on the presence of ICPC codes specific to COPD (ICPC R95 or R91), a diagnosis of COPD as free text and/or the use of at least 2 bronchodilating drugs during follow-up (chapter 4.2). II) For the studies on the a) epidemiology of COPD, b) the effectiveness study and the c) safety studies of tiotropium and the use of β-blockers in patients with COPD, we used data from 2000-2007 and defined a cohort of COPD patients based on a broad automated search on COPD specific ICPC codes and free text. All potential COPD patients were manually validated based on a strict algorithm. Of all potential COPD patients, only 6,788 remained: (chapters 2, 3, 4.3, 4.4 and 4.5). III) Finally, to study the association between the use of tiotropium Respimat® vs. tiotropium HandiHaler® and risk of dying, we defined a cohort of tiotropium users (either tiotropium Respimat® or tiotropium HandiHaler®). The study period ran from 2000 to 2010. Within this cohort, COPD was defined as a patient characteristic based on the presence of COPD specific ICPC codes (ICPC R95 or R91) or a free text search on "COPD" or "emphysema" (chapter 4.1).

In this discussion, the most important findings are summarized and the study setting and related methodological considerations are clarified. In addition, the clinical implications of this research and potential directions for future research are discussed.

Main findings

I) Epidemiology: Prevalence, incidence and mortality of COPD

Since 2002, large-scale epidemiologic studies on COPD, such as the Latin America Project for the Investigation of Obstructive Lung Disease (PLATINO) [12] and the worldwide project namely Burden of Obstructive Lung Diseases (BOLD) [11], have provided better estimates of the prevalence of COPD in different countries. Only few studies investigated the incidence of COPD and its related mortality.

In chapter 2 we describe the prevalence, incidence, mortality and lifetime risk of COPD as a function of age and sex in the general population.

In our population-based cohort study in the general Dutch population of 40 years and older and registered in the IPCI database, we identified 7,308 COPD patients, including 1,713 (23%) incident cases. The overall prevalence of COPD was 3.02% (95%CI 2.94-3.10%). The prevalence estimates were higher in men than in women, and rose progressively with age until the age of 81 years in men and 83 years in women.

The overall incidence rate (IR) of diagnosed COPD was 2.92/1,000 person-years (PY). Similar to the prevalence pattern, the IR was higher in men than in women (with a relative risk (RR) of 1.5 in men). The incidence rate increased almost 10-fold from 0.78/1,000PY at the age of 40-44 to 6.82/1,000PY at the age of 75-79. Other studies investigated the incidence and prevalence of COPD as well, using data from healthcare databases [22-24]. The most recent Canadian study on the incidence of COPD reported higher rates of incidence and prevalence (even after standardization) [24]. Our COPD incidence rate and prevalence can be compared to other Dutch data, namely data from the Rotterdam Study, a population based prospective cohort study with spirometry data and medical records. The overall COPD incidence rate in the Rotterdam study was 9.2/1,000PY. Our age standardized rate was 35% lower showing the level of under-diagnosis due to lack of systematic spirometry data in clinical practice [17]. Our IR is in line with results from the United Kingdom General Practitioners Research Database (GPRD), a general practitioner medical record based system, which is similar to IPCI. In GPRD the overall incidence rate (40-89 years) was 2.6/1,000PY.

Based on our data, the risk to be diagnosed with COPD in the coming 40 years was 12.7% for a 40-year-old man and 8.3% for a 40-year-old woman – assuming that COPD diagnostic work-up and awareness would remain similar. Mortality was high, especially in very severe COPD patients. In very severe COPD patients, the one-year mortality risks were nearly 10-fold that of non-COPD subjects of the same age. Mortality rates were 2.0-fold higher for COPD

patients than for the age and sex matched reference population, and increased with COPD severity. Our mortality rate of 6.1% in COPD patients is much in line with the data from Soriano *et al*. [28], who reported an overall death rate of 8.5% per year, and Gershon *et al*. [24], who described mortality rates between 5.7% in 1996 and 4.3% in 2007.

II) Effectiveness: Risk of COPD exacerbations requiring hospitalization in COPD patients treated with tiotropium versus LABA

In chapter 3 we compared the effectiveness of tiotropium to that of long-acting β_2-agonists (LABA) in the prevention of hospitalization for COPD exacerbation in clinical practice.

In a cohort of 6,788 COPD patients from the IPCI database, 619 patients were hospitalized for a COPD exacerbation during the follow-up period. In this cohort we demonstrated that tiotropium reduced the risk of COPD exacerbations leading to hospitalizations in COPD patients as compared to LABA (OR_{adj} 0.69; 95%CI 0.40-1.19). Most of the published RCTs have shown that both LABA and tiotropium were efficacious in reducing the risk of hospitalization related to COPD compared to placebo with risk estimates around 0.70 [68, 70, 71, 107, 131]. Only few RCTs compared the effect of long-acting bronchodilators on intermediate or surrogate endpoints. The few RCTs who did, reported that tiotropium is more effective than LABA in preventing COPD exacerbations, which is in line with our findings [72, 73, 131].

III) Safety studies

1) Mortality in tiotropium users by type of formulation

In the past, use of tiotropium HandiHaler® has been associated with an increased risk of dying and cardio-cerebro vascular events. In 2010, based on data from the UPLIFT study, the FDA revised their safety warning on the use of tiotropium HandiHaler®, 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" [120]. As the UPLIFT study only included a treatment regimen of tiotropium HandiHaler® versus placebo, the current available data does not allow drawing strong conclusions on the risk of mortality in patients treated with tiotropium Respimat® SMI. In their communication to the FDA, Boehringer Ingelheim, the manufacturer of tiotropium, reported an increased risk of mortality with tiotropium Respimat® SMI device based on unpublished data from 3 one-year placebo controlled trials [120]. These facts triggered us to conduct an observational study on the risk of dying in users of tiotropium Respimat® SMI versus HandiHaler®. (chapter 4.1)

Within an IPCI source population of patients, 40 years or older, we defined a cohort of 11,753 tiotropium users. 272 patients died while being exposed to either tiotropium HandiHaler® or Respimat® SMI. Use of tiotropium Respimat® SMI, compared to tiotropium HandiHaler®, was not associated with an increased risk of dying with a HR_{adj} of 1.21 (95%CI 0.85-1.73). Upon

stratification by cause of death, use of tiotropium Respimat® SMI was not associated with an increased risk of cardiovascular and cerebrovascular death (HR_{adj} 0.97, 95%CI 0.46-2.04).

2) Risk of acute urinary retention, renal failure, cardiovascular events and all cause mortality associated with the use of tiotropium

So far, tiotropium is the only long-acting inhaled anticholinergic bronchodilator, which can be used once daily for long-term maintenance treatment of COPD. The efficacy and safety of tiotropium have been demonstrated in several RCTs including RCTs with active comparisons such as ipratropium and LABA [60, 61, 63-71, 107, 131, 154], with imprecise reductions observed for mortality [131], reduced risk for cardiovascular events [68], and strong associations for unintended adverse events such as dry mouth and urinary retention [68, 70]. Safety data from RCTs hamper external validity as RCTs use stringent inclusion and exclusion criteria. Also, sample size and time of follow-up is often limited which reduces the chance to detect rare safety issues or long-term events. Observational studies offer the advantage to explore the safety of drugs in real life but few observational studies on tiotropium have been conducted so far.

A) In chapter 4.2) we investigated the association between use of inhaled anticholinergic drugs and the risk of acute urinary retention (AUR). Case series and RCTs reported on the risk of AUR in patients treated with inhaled anticholinergic drugs, but this association had never been quantified. Within a cohort of 22,579 COPD patients, 45 years or older, 209 cases of AUR were indentified. Use of inhaled anticholinergic drugs increased the risk of AUR with 40% (OR_{adj} 1.40, 95%CI, 1.21-7.98). The risk was the highest in recent starters, in men with benign prostatic hyperplasia (BPH) (OR_{adj} 4.67, 95%CI, 1.56-14.0) and in those using nebulizers (OR_{adj} 2.92, 95%CI, 1.17-7.31). Moreover, there were no differences in the risk of AUR between tiotropium and ipratropium (OR_{adj} 1.55, 95%CI, 0.80-3.00 and OR_{adj} 1.37, 95%CI, 0.96-1.98, respectively).

B) In 2009, data from a pooled analysis on the safety of tiotropium reported the occurrence of renal failure related to the use of tiotropium against placebo [154]. In chapter 4.3) we conducted a nested-case control study in the thoroughly validated COPD cohort of 6,788 patients (see chapter 3) to compare the risk of renal failure, in patients treated with tiotropium compared to no use or to the use of inhaled β_2-agonists. Within our COPD cohort, 83 new cases of renal failure were identified. We did not observe an increased risk of renal failure (either acute or chronic) in patients currently using inhaled anticholinergic drugs, OR_{adj} 0.78, 95%CI 0.43-1.42 (compared to no use of anticholinergic drugs), and OR_{adj} 1.42, 95%CI 0.57-3.54 (compared to current use of β_2-agonists). When stratifying between acute renal failure and chronic kidney disease, the risk of chronic kidney disease increased in current users of anticholinergics, using current use of β_2-agonists as reference (OR_{adj} 1.77, 95%CI 0.67-4.66), but this association was not statistically significant. Based on animal models, human studies, and a few case reports on renal failure in patients treated with tiotropium, we hypothesized

on the association between the use of inhaled anticholinergic drugs and the risk of renal failure, which could not be confirmed by our data. As acetylcholine is important for the preservation of renal blood flow, it seems plausible that inhibition of renal blood flow, through anticholinergic drugs, might increase the risk of renal failure. Further research on this topic might be warranted preferably not only considering inhaled anticholinergic drugs and also stratifying between acute renal failure and chronic kidney disease.

C) In 2008, concerns were raised on the cardiovascular and cerebrovascular safety of tiotropium. 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 case-control study reporting an increased risk for mortality and/or cardiovascular events in patients who received inhaled anticholinergics (ipratropium or tiotropium) [112, 118, 119]. 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 data from 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 [120]. Very few observational studies that investigated the association between the use of tiotropium and risk of cardiovascular events are generated from data from RCTs. In chapter 4.4) we describe the cardiovascular safety and risk of mortality in patients with COPD using tiotropium compared to LABA, under real life circumstances, using data from our cohort of validated COPD patients. Within our COPD cohort of 6,788 patients, 784 new cases of a cardiovascular endpoint (254 cases of stroke and transient ischemic attack (TIA), 116 cases of myocardial infarction, 413 cases of heart failure and 6 cases of ventricular arrhythmia) were identified, and 1,032 patients died during follow-up. We did not observe an increased risk for cardiovascular endpoint and/or mortality in patients currently treated with tiotropium compared to no use. Compared to LABA, current use of triotropium was not associated with an increased risk of a cardiovascular endpoint (OR_{adj} 0.89, 95%CI 0.55-1.44) neither with an increased risk of death (OR_{adj} 0.79, 95%CI 0.49-1.22).

3) Risk of COPD exacerbations requiring hospitalization in patients treated with β-blockers

Treatment with cardiovascular drugs, especially the use of β-blockers is known to improve the survival of patients with a large spectrum of cardiovascular diseases, including heart failure [184]. The traditional belief states that β-blockers are contra-indicated in COPD because of their presumed broncho-constrictive properties and their competition with β_2-agonists [185], which leads to lower prescription rates in COPD patients [186]. However, COPD as contra-indication for the use of β-blockers is currently revisited as β-blockers could actually have beneficial effects in patients with COPD through tempering of the sympathetic nervous system or by reducing the ischemic burden [187]. More recently, Rutten *et al.* showed that β-blockers might reduce the risk of exacerbations and improve survival in patients with

COPD, possibly as a result of dual cardiopulmonary protective properties [191]. The study from Rutten *et al*. suffered from major methodological weaknesses such as immortal time bias and residual confounding. For this reason, we investigated the association between the use of β-blockers and risk of COPD exacerbation requiring hospitalization, first by mimicking the study of Rutten *et al*., using a fixed cohort approach with immortal time bias. Subsequently we conducted two nested-case control studies. The first case-control approach eliminated the issue of immortal time bias and in the second case-control study, we only considered COPD patients ever exposed to β-blocker to deal with confounding by indication (or contra-indication). Results of these analyses are described in chapter 4.5) Within the COPD cohort, 619 patients were hospitalized for a COPD exacerbation. When mimicking the analysis of Rutten *et al.*, current use of β-blockers significantly reduced the risk of severe COPD exacerbations (HR_{adj} 0.73, 95%CI 0.60-0.90). In the case-control analysis, we found that the use of β-blockers reduces the risk of severe COPD exacerbations by 40% (OR_{adj} 0.60, 95%CI 0.44-0.82). When controlling for confounding-by-indication, the protective effect was greatly attenuated (OR_{adj} 0.87, 95%CI 0.52-1.45). However, in patients with co-existing heart failure, a significant protective effect was still observed (OR_{adj} 0.15, 95%CI 0.03-0.80) but the numbers became very low.

Methodological considerations

Population based COPD research

For all studies in this thesis, data was obtained from the Integrated Primary Care Information (IPCI) database that contains information from computer-based records of more than 400 GPs in the Netherlands. The anonymized medical records of approximately one million patients registered with GPs consist of detailed data on patient demographics, symptoms, diagnosis, lab results, referrals, drug prescription and hospitalizations [86, 91]. The IPCI database is representative for the Dutch population regarding age and sex. In the Netherlands, GPs act as gatekeepers for secondary care [87]. Consequently, their records can be considered to hold most relevant medical information about a patient. No paper records are being kept by GPs participating in the project except for hardcopy specialist letters, which can be requested for the case validation process. IPCI has been used and proven valid for pharmacoepidemiological research [199].

Using data from the IPCI project was essential to study the epidemiology of COPD for the following reasons. First of all, we had access to a very large population of COPD patients that were followed over time. Furthermore, as the IPCI project contains the complete medical records of all patients, it gave us good insight into the patient's characteristics, comorbidity and treatment of patients with COPD. However, as data was collected in relation to routine primary care, some information such as COPD severity was often incomplete. In addition,

not all data in the IPCI database was coded which made the case identification, through free text validation very labor-intensive. Finally, as the IPCI database is not linked to a pharmacy database, we did not have information on drug dispensing. Neither did we have information on "over-the-counter" drug use or actual drug intake [200]. This implies that we might have under- or overestimated the pharmacological treatment.

IPCI COPD cohorts

For this research, we defined three different cohorts. I) The first cohort of COPD patients was defined, between 1996 and 2006, to study the association between inhaled anticholinergic drugs and the risk of acute urinary retention (AUR). In this cohort of 22,579 patients - ≥ 45 years - with COPD (both incident and prevalent), a patient was considered to have COPD if there was a coded diagnosis for COPD (International classification of primary care (ICPC) R95 or R91), a diagnosis of COPD in the narratives (free text search) or the use of at least two bronchodilating drugs during follow-up [137]. Disease severity was defined by the algorithm of Ernst *et al*. [75] (chapter 4.2). II) The second cohort was later defined, with a study period between 2000 and 2007. A cohort of patients - ≥ 40 years - with potential COPD was defined based on information from diagnoses and narratives. All potential cases were then classified in definite COPD - diagnosis by a specialist or a GP diagnosis confirmed by spirometry (FEV1/FVC<70%); probable COPD - diagnosis by the GP with at least two records of COPD within one year of the first record of COPD. All doubtful COPD patients were further reviewed and classified by a pulmonologist (GB). And this led to two different cohorts: in chapters 3, 4.3, 4.4 and 4.5, we had 6,788 definite COPD patients, and in chapter 2, 7,308 definite COPD patients, as 520 doubtful cases were later revised and included as definite COPD patients. In addition, patients were classified as prevalent COPD if they had a COPD diagnosis prior to entry in the source population; and were classified as incident COPD if they were disease free at time of start, and later developed COPD. III) In chapter, 4.1 a third - tiotropium - cohort was defined. All patients who received a prescription for tiotropium between 2000 and 2010 were included. This cohort differed from the previously described ones, as for reasons of power, we considered all prescriptions of tiotropium, irrespective of indication of use. Co-existing COPD was considered a separate variable in the analysis.

Within these 3 COPD cohorts, COPD severity was assessed based on the GOLD criteria, for patients having data on lung function, or based on proxies based on published algorithms for the validation of COPD severity.

Study design

Our research on the epidemiology and treatment effects of COPD applied descriptive and analytical epidemiological techniques. Descriptive epidemiological studies focus on the occurrence of a disease in a population [201] and thus this method we used to study the

incidence, prevalence and lifetime risk of COPD in the general population and to study the risk of dying in patients with COPD.

If the aim of the research is to investigate the determinants or risk factors of the disease, analytical epidemiological designs are used [201, 202]. Analytical studies can be divided into observational or intervention studies (clinical trials). In observational studies, the natural course of events are studied through case-control or cohort designs [200]. Both designs were used in our research.

Cohort study

In cohort studies, subjects are classified on the basis of the presence of exposure to a particular factor and then followed for a specific period of time to determine the development of disease in each exposure group.

Using data from the IPCI database, we retrospectively defined a disease cohort of COPD patients to study the incidence and prevalence of COPD and, it's related mortality. Within this cohort, we studied the hazard ratio of COPD exacerbations requiring hospitalization in patients exposed to β-blockers versus non-exposed patients. Finally we defined a cohort of tiotropium users (either tiotropium HandiHaler® or tiotropium Respimat® SMI) to study the association between the use of tiotropium Respimat® SMI and risk of dying, using tiotropium HandiHaler® as reference category.

Case-control study

In a case-control study, a group of patients who have the outcome of interest and a control group of individuals without the outcome at the time of case occurrence are studied, and the odds of exposure in each group are compared. This design is particularly efficient to investigate of time varying exposures and multiple exposures. In our research we applied a nested case-control design where case-control studies were "nested" in a cohort of COPD patients. This design was applied for all safety studies and for the study on the effectiveness of tiotropium in the prevention of severe COPD exacerbations.

Internal and external validity

The internal validity of a study refers to the appropriateness of the design to answer the research question [203]. Observational studies on the association between drugs and several outcomes, using data from electronic medical record database, is challenging due to a variety of potential biases and mechanisms of confounding. In all observational studies, various types of bias, such as selection bias, protopathic bias, information bias, immortal time bias and confounding may hamper the internal validity [201, 202, 202, 205].

Selection bias results from an absence of comparability between the groups that are being compared due to differential participation rates [200-202, 204, 205]. As the IPCI data encom-

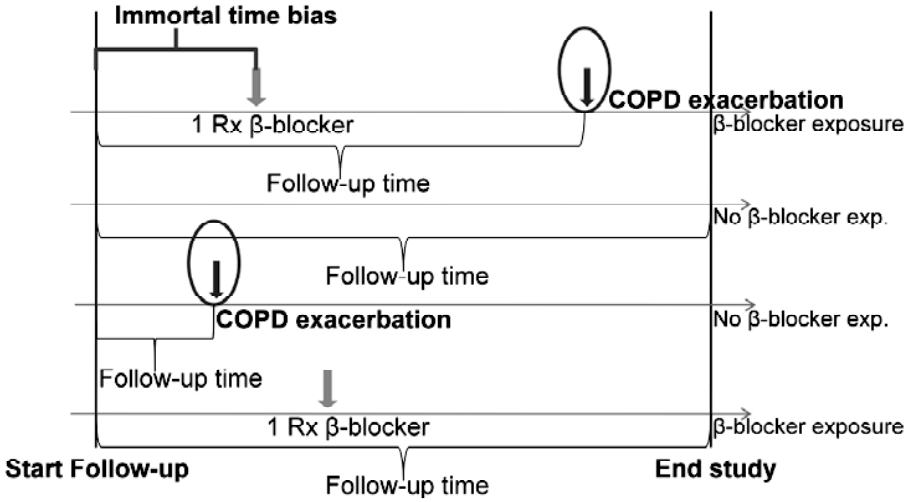
passes the total population and patients do not need to be asked for participation (opt-out system) the magnitude of selection bias is negligible.

Information bias, also known as observation, recall or misclassification bias, results from an incorrect determination of outcome or exposure [205]. This information bias might be random (non-differential) or systematic (differential). Non-differential misclassification bias usually shifts the risk towards 1 (except for dose response), whereas differential misclassification may result in an overestimation as well as an underestimation of the actual risk [200, 202, 204]. To minimize the potential effect of information bias by misclassification of the outcome, a three-step validation process, if feasible, was undertaken on all of the studied outcomes. First, all potential cases were identified by means of a broad search of coded diagnoses and free text narratives in the electronic medical records of all patients. Second, the complete electronic medical records of all potential cases were manually reviewed and validated by a medical doctor. All doubtful cases were further reviewed and classified by a specialist or a third independent MD. During the validation process, reviewers were blinded to drug exposure. Due to this extensive validation process, false positives are highly unlikely among the cases. Through this extensive validation process, we did encounter the risk of false negatives, which was not a concern in our safety studies but was an issue in our study on the incidence and prevalence of COPD. Misclassification of the exposure is a potential concern in our pharmacoepidemiological studies since we only used prescription data and did not have information on dispensing or actual drug intake. In addition, we missed prescriptions initiated by the specialist. Since data were obtained from medical records, independent of the study question, the exposure misclassification is probably non-differential and therefore the reported risk estimates between drug use and outcome are an underestimate of the actual risk. To tackle potential misclassification of exposure, due to irregular intake, we performed sensitivity analysis in our studies by varying the exposure window and by excluding or stratifying for patients who were referred to specialists.

Studies run the risk of *protopathic bias* when a pharmacological agent is prescribed for an early manifestation of a disease that has not yet been diagnosed [206]. In statistical analysis it may appear as if the drug is positively associated with the outcome [206] and thus one could erroneously conclude that the drug causes the outcome of interest. In our effectiveness study, protopathic bias was a concern; as one could hypothesize that GPs initiate the use of long-acting bronchodilators as treatment for the first symptoms of COPD exacerbations. Conducting a sensitivity analysis only including those patients who used the drugs for more than 30 days addressed this bias.

Immortal time bias is a span of cohort follow-up time during which, because of exposure definition, the outcome under study cohort can not occur [192]. If exposure effects are then compared to non-use of the drugs, extreme protective effects result [207]. The study per-

Figure 1: Immortal time bias

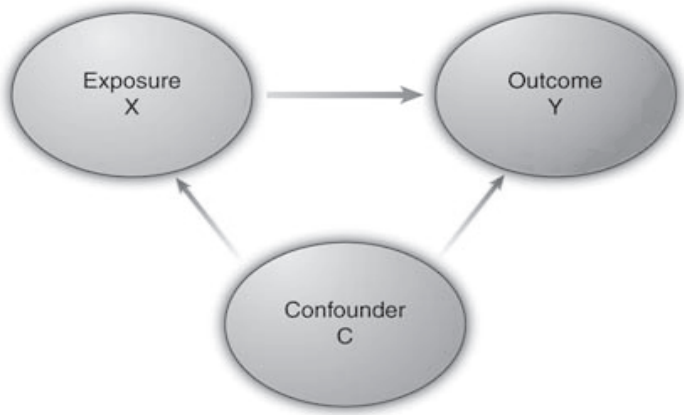


formed by Rutten *et al.* [191] suffered from immortal bias, in which the protective effect of the use of β-blockers on the risk of dying and COPD exacerbation is extreme (figure 1). In order to verify this we mimicked their study and subsequently conducted a case-control study, which avoided immortal time by design.

Confounding is one of the major concerns in epidemiological research, as it is one of the most difficult biases to detect and to control for. A confounding variable is a variable that can cause the disease under study and is also associated with the exposure of interest (figure 2). There are three criteria for a variable to be a confounder: 1) it must be an independent risk factor for the disease (also in the non-exposed), 2) it must be associated with the exposure (also in the non-diseased) and 3) it must not be an intermediate step in the causal pathway [200-202, 204, 205].

Confounding can lead to overestimation or underestimation of the true association between exposure and outcome, depending on the direction of the associations between the confounding factor and the exposure and outcome. It can be controlled for via restriction, matching, stratification or statistical adjustment such as mathematical modeling via multivariate logistic regression or proportional hazard analysis [200, 202, 205]. With restriction, the control of confounding is achieved by including only those individuals with certain homogeneous levels of potential confounders. Matching involves removing the effect of the confounder by making the case group and the control group equivalent regarding the confounders [200-202, 205]. Both techniques were applied as, first of all, we controlled for confounding by age by restricting our population to 40 years or older, and in the case-control studies, we matched on age, sex and index date (to control for calendar time).

Figure 2: Confounding



The risk of confounding by indication and confounding by COPD severity was substantial in our research. Confounding by indication may arise when the indication for the treatment is a risk factor for the outcome under study [208, 209], and it refers to an extraneous determinant of the outcome parameter that is present if a perceived high risk or poor prognosis is an indication for medical intervention. In our studies, COPD severity is a confounder because it correlates with the drug prescription and is a risk indicator for the different outcomes [209]. To control for confounding by COPD severity, we first of all assessed COPD severity via lung function or via proxies based on predefined algorithms. In all our analysis, we then adjusted for COPD severity. In addition, we dealt with confounding by indication by using reference drugs having the same indication of use as the indication of use of the drug of interest. E.g. in our studies on the safety and effectiveness of tiotropium, we used LABA as reference category because, similar to tiotropium, LABA is used for the symptomatic treatment of patients with moderate to severe COPD. For this same reason, the association between the use of tiotropium Respimat® SMI and the risk of dying was studied using tiotropium HandiHaler® as reference category. The high impact of confounding by indication is illustrated in the study on the use of β-blockers and the risk of severe COPD exacerbations where the strong protective effect disappears using past use of β-blockers as reference category.

The external validity of epidemiological research implies that the observed findings can be generalized to the general population. External validity can be an issue in RCTs, as participating patients tend to be different from patients who wish or cannot participate, due to stringent inclusion and exclusion criteria [200, 205]. Since all our data rely on routine clinical care data, the external validity is high and our findings can be extrapolated to the general population of COPD patients, 40 years or older.

Clinical implications

In the study on the incidence, prevalence and survival in COPD, we found that in the Netherlands, around 3 on 1000 subjects are newly diagnosed with COPD per year, although the true incidence of COPD based on spirometry criteria, may be 30-40% higher. Moreover, mortality rates are substantially higher in patients with COPD compared to the general population, which emphasizes the need for better care, including control of underlying comorbidity in patients with COPD. Not only GPs should be aware of increasing number of COPD cases, and assess lung function at earlier symptoms, but also specialists should diagnose and start treating COPD at an early disease stage, re-inforcing the importance to stop smoking.

In the comparative effectiveness study, we demonstrated a statistically non-significant trend towards a reduced risk for COPD exacerbations requiring hospitalization for tiotropium compared to LABA (salmeterol or formeterol). To our knowledge, our data are the first to compare the effectiveness of tiotropium and LABA in clinical practice. This is an important finding as both bronchodilators are the mainstay for symptomatic management of COPD. In clinical practice, this could lead to a preference in tiotropium prescribing, as it seems to perform better than LABA and tiotropium is administered once daily whereas LABA's twice a day.

There have been some concerns on the safety of tiotropium, especially related to a potential increased risk of cardiovascular and cerebrovascular events and risk of dying. This discussion on the safety of tiotropium HandiHaler® already tempered after the publication of the UPLIFT study. Our findings enforce the recent communication from the FDA 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".

Although there were concerns on the safety of tiotropium Respimat® SMI based on data from RCTs; this could not be confirmed by our data. This is of importance especially as tiotropium Respimat® SMI has been introduced because it has a better lung drug deposition and it's easiness of use. For these reasons, it is mainly prescribed to patients with more severe COPD and thus a more vulnerable patient group. Although our data need to be confirmed by other studies, it is important to know that the risk of dying is not higher for tiotropium Respimat® SMI versus HandiHaler® study.

We studied the association between the use of inhaled anticholinergic drugs and the risk of AUR and concluded that the risk of AUR is increased, especially in COPD patients with BPH. As BPH and COPD are highly prevalent diseases in elderly men, it might be advisable that GPs and urologists consider alternatives for anticholinergics (e.g. LABA) in COPD patients with BPH.

Finally, in the β-blockers study, we found that β-blockers may have some protective effect on COPD exacerbations in patients with COPD, especially in patients with underlying heart failure. Due to the great impact of confounding by (contra) indication, this association was

difficult to be addressed with the common methods in pharmacoepidemiology. The available data suggests that it is safe to prescribe β-blockers in patients with COPD, but their protective effect is probably more of a cardiovascular than of a respiratory one.

Recommendations for future research

Widely recognized as self-inflicted by smoking, COPD was in the past a neglected area of research and drug development. At present, COPD has become the fifth leading cause of death worldwide; and it is known that approximately 210 million people suffer from COPD, numbers confirming for epidemic disease [198].

The studies described in this thesis show the advantages and limitations of the use of electronic medical records for assessing associations between drug use and several outcomes in patients with COPD.

RCTs are the gold standard to address the efficacy of a drug – observational studies, using million records of health care databases, allow us to study the safety and effectiveness of respiratory drugs under real life circumstances.

Because of the large size number and long-term follow-up, these studies also allow using hard clinical outcomes, such as severe COPD exacerbations, instead of surrogate endpoints, such as improvement of FEV1, which correlate poorly with quality of life and mortality. The introduction of the new long acting β_2-agonist - indacaterol - and - aclidinium bromide - a new long-acting anticholinergic drug, drugs that so far have only been tested in small RCTs with limited follow-up time, warrant the importance of pharmaco-epidemiological studies to closely monitor the safety of these new drugs. The importance of safety studies in the field of COPD treatment is underlined by the recent FP7 call (HEALTH-2011-4.2-2: Adverse drug reaction research [210]) promoting research on the safety of bronchodilating and anti-inflammatory drugs. In particular, this call stimulates research on the cardiovascular safety on anticholinergic drugs and research on the use of ICS and risk of pneumonia in patients with COPD.

Effectiveness studies in the field of COPD research have been criticized because of concerns of remaining confounding by COPD severity, which might spur the associations. COPD severity is usually measured by means of pulmonary function, an assessment that, unfortunately, is not routinely done in primary care, and often not registered in a uniform manner. To improve the validity of, not only the effectiveness but also the safety studies, we would recommend that GPs perform spirometry in all patients with respiratory symptoms and that these lung function results are registered in a uniform manner in the database. The GOLD guidelines define a fixed FEV_1/FVC ratio below 0.7 to decide whether a patient has COPD or not. This fixed ratio overestimates COPD in the elderly and underestimates COPD in the

young. If pulmonary function becomes one of the parameters standard reported in primary care databases, it might be worthwhile considering the lower limit of normal to define COPD.

Genetics should be considered in COPD research, not only because of genetic variability in COPD development and COPD progression but also in terms of genetic variability in treatment response. Enriching electronic health care databases with information on genetic status would be an added value.

Gender is probably an important effect modifier in the association between respiratory drug exposure and outcome in patients with COPD. So far, we only addressed gender in our COPD incidence and prevalence studies. Although it is believed that gender also modifies the treatment response to respiratory drugs, very few data are available, as the existing RCTs were not designed to assess the impact of gender. In future research, the effect of gender should be further investigated and one of the topics that can be addressed by our data is the association between hormone replacement therapy and risk of COPD [49, 198].

Finally, the systemic inflammation observed in COPD implies that patients with COPD often suffer from other concomitant disease especially cardiovascular diseases. Studies on the epidemiology of both diseases and how they relate to each other in terms of disease progression would add great value. Within this field, treatment response to respiratory and cardiovascular drugs and effect modification by underlying disease and disease severity would be of utmost importance.

To conclude, we are convinced that the use of data from RCTs, in combination with observational studies using data from large electronic health care databases is important to give both the health care professionals and the patients' complete and up-to-date information on the safety and efficacy/ effectiveness of (respiratory) drugs.

CHAPTER 6
Summary

6.1
Summary

Chronic obstructive pulmonary disease (COPD) is a leading and still-increasing cause of chronic morbidity and mortality worldwide. It is estimated that by 2020 it will become the third most common cause of death. Because of its burden and the impact on health care, we studied the epidemiology of COPD, and explored the effectiveness and safety of drugs given for the treatment of COPD, using data from the Integrated Primary Care Information (IPCI) project, a general practitioners' (GP) database in the Netherlands. For this research we defined different cohorts of COPD patients and tiotropium users. Within the IPCI database, these patients were followed over time until the end of study period or the endpoint of interest whichever occurred first.

In chapter 1 we present a general introduction of COPD (definition, epidemiology, pathophysiology, risk factors, and symptoms), the national history of COPD and COPD treatment.

In chapter 2 – *epidemiology* – we describe the incidence, prevalence, mortality, and lifetime risk of COPD, as a function of age and gender. In addition, we compared mortality rates, both in the general population and in the COPD cohort. The cohort consisted of 7,308 COPD patients of whom 1,713 were incident COPD cases. The overall incidence rate (IR) of diagnosed COPD was 2.92/1,000 person-years (PY) and the overall prevalence was 3.02% (95%CI 2.94-3.10%). Mortality was high, especially in very severe COPD patients. The one-year mortality risk in patients with very severe COPD was nearly 10-fold that of non-COPD subjects of the same age and gender. Overall, mortality rates were 2-fold higher for COPD patients than for the age and sex matched reference population, and increased with COPD severity.

In chapter 3 – *effectiveness* – we investigated the association between the use of inhaled respiratory drugs and the risk of hospitalization for COPD exacerbations. The effectiveness of tiotropium, a long acting anticholinergic drug is compared with long-acting β_2-agonists (LABA). Tiotropium reduced the risk of COPD exacerbations leading to hospital admission in COPD patients as compared to LABA, but this association was not statistically significant (OR_{adj} 0.69; 95%CI 0.40-1.19).

In chapter 4 – safety – we present the results of our observational studies on the safety of respiratory drugs for the treatment of COPD. In addition, in this chapter, we describe the association between the use of β-blockers and the risk of COPD exacerbation requiring hospitalization.

Data from (unpublished) RCTs showed an increased risk of dying in patients treated with tiotropium Respimat® Soft Mist Inhaler versus placebo. Very few RCTs compared the safety and efficacy of tiotropium Respimat® Soft Mist Inhaler (SMI) versus tiotropium HandiHaler®, and the studies that did had a short duration of follow-up. We conducted a population

based cohort study to compare the mortality rates in users of tiotropium Respimat® Soft Mist Inhaler (SMI) versus users of tiotropium HandiHaler® under real life circumstances with maximal follow-up. The results of this study are described in part 4.1 of this chapter. In a cohort of 11,753 tiotropium users, 272 patients died while being exposed to either tiotropium Respimat® or HandiHaler®. In our study we found that, the risk of all-cause mortality was very similar in patients being exposed to Respimat® compared to tiotropium HandiHaler®, (HR_{adj} 1.21; 95%CI 0.85-1.73).

Results driven from RCTs have shown that use of tiotropium users developed unintended adverse events such as dry mouth and urinary retention. This association was not yet quantified nor investigated under real life circumstances. For this reason, we studied the association between the use of inhaled anticholinergic drugs and the risk of acute urinary retention (AUR) (chapter 4.2). Within a cohort of 22,579 COPD patients, 209 cases of AUR were identified. The use of inhaled anticholinergic drugs increased the risk of AUR with 40% (OR_{adj} 1.40; 95%CI 1.21-7.98). The risk was the highest in men with benign prostatic hyperplasia (OR_{adj} 4.67; 95%CI 1.56-14.0).

Data from a pooled analysis on tiotropium safety reported the occurrence of renal failure during use of tiotropium. In chapter 4.3 we describe a study on the association between the use of inhaled anticholinergic drugs and the risk of renal failure. Within a cohort of 6,788 COPD patients, 83 new cases of renal failure were identified. We did not observe an increased of renal failure (either acute or chronic) in patients currently using inhaled anticholinergics (OR_{adj} 0.78; 95%CI 0.43-1.42) compared to no use. A tendency for an increased risk of chronic kidney disease in current users of inhaled anticholinergics compared to current use of β_2-agonists was observed (OR_{adj} 1.77; 95% CI 0.67-4.66).

In part 4.4 we evaluate the cardiovascular safety and risk of death during the use of inhaled anticholinergic drugs when compared to LABA. This research was driven by the safety warning issued by the FDA in 2008, on a small excess risk of stroke in patients treated with tiotropium compared to placebo. Within our cohort of 6,788 patients with COPD, 784 new cases of a cardiovascular endpoint (254 stroke, 116 myocardial infarction, 413 heart failure and 6 ventricular arrhythmia) were identified, and 1032 patients died during follow-up. Compared to LABA, current use of tiotropium was not associated with an increased risk of a cardiovascular endpoint (OR_{adj} 0.89; 95%CI 0.55-1.44), neither with an increased risk of death (OR_{adj} 0.79; 95%CI 0.49-1.22).

β-blockers are generally contra-indicated in COPD patients, but recently published studies reported on a protective effect on mortality and severe COPD exacerbations in COPD patients treated with β-blockers. As the study results may be prone to bias and residual confounding, we applied different research designs to study this association (chapter 4.5). Within a cohort of 6,788 COPD patients, 619 patients were hospitalized for a COPD exacerbation during follow-up. Using a cohort analysis, current use of β-blockers significantly reduced the risk of severe COPD exacerbations (HR_{adj} 0.73; 95%CI 0.69-0.90). This protective effect was

confirmed in a case-control design where the use of β-blockers reduced the risk of severe COPD exacerbations by 40% (OR_{adj} 0.60; 95%CI 0.44-0.82). To control for confounding by (contra)-indication we repeated the analysis, only selecting those patients ever treated with a β-blocker. In this analysis the protective effect was greatly attenuated (OR_{adj} 0.87; 95%CI 0.52-1.45). This study shows the importance of the correct choice of study design for drugs where a huge impact of confounding by (contra)-indication is suspected.

Chapter 5 includes a general discussion in which the results and conclusions of the studies in this thesis are summarized and interpreted. Furthermore, methodological considerations are discussed and suggestions are given for future research.

6.2
Samenvatting

Chronisch obstructief longlijden, wat we verder zullen benoemen als "COPD", is een chronische longaandoening die gepaard gaat met een belangrijke morbiditeit en een verhoogde mortaliteit. De voorspellingen zijn dat tegen 2020, COPD de derde belangrijkste doodsoorzaak is. De huidige behandeling van COPD bestaat uit een symptomatische aanpak van de respiratoire klachten via het toedienen van bronchodilatoren en anti-inflammatoire middelen.

COPD is een belangrijke kostenpost voor de gezondheidszorg. Om die reden vonden wij het belangrijk om de epidemiologie van COPD nader te onderzoeken en tevens de effecten van de geneesmiddelen die gebruikt worden bij COPD te bestuderen. Voor dit onderzoek werden de gegevens van de IPCI (Integrated Primary Care Information) database gebruikt. De IPCI database is een Nederlandse database met de electronische geanonimiseerde medische dossiers van ongeveer 1 miljoen patiënten. Binnen de IPCI database definieerden we 2 verschillende COPD cohorten en één tiotropium gebruikers cohort.

Hoofdstuk 1 geeft een algemene inleiding over COPD (definitie, epidemiologie, pathofysiologie, risico factoren en symptomen) en gaat dieper in op de behandeling.

In hoofdstuk 2 – *epidemiologie* – beschrijven we de incidentie, prevalentie, mortaliteit en de cumulatieve incidentie van COPD in functie van leeftijd en geslacht. Daarnaast wordt het risico op overlijden vergeleken tussen COPD patiënten en patiënten zonder COPD. Het COPD cohort bestond uit 7308 patiënten. De incidentie van COPD was 2.92/1,000 persoonsjaren en de prevalentie was 3.02% (95%CI 2.94-3.10%). Het risico op overlijden was hoog, vooral in patiënten met zeer ernstig COPD. Het risico op overlijden was namelijk 10 maal hoger in patiënten met zeer ernstig COPD in vergelijking met niet-COPD patiënten van dezelfde leeftijd en geslacht. Algemeen zagen we dat het risico op overlijden 2 maal hoger was voor COPD patiënten versus niet-COPD patiënten met dezelfde leeftijd en geslacht.

In hoofdstuk 3 – *effectiviteit* – onderzochten we de relatie tussen het gebruik van respiratoire geneesmiddelen, toegediend via inhalatie, en het risico op hospitalisatie omwille van een COPD exacerbatie. In dit onderzoek werd het risico op hospitalisatie (voor COPD exacerbatie) vergeleken tussen patiënten die behandeld werden met tiotropium HandiHaler®, een langwerkend anticholinergicum, en patiënten die behandeld werden met een langwerkend β_2 agonist. Binnen het COPD cohort werden 619 patiënten tenminste een keer opgenomen voor een COPD exacerbatie. Het risico op ziekenhuis opname was iets lager tijdens gebruik van tiotropium HandiHaler® dan tijdens het gebruik van een langwerkende β_2 agonist maar deze associatie was niet statistisch significant (OR_{adj} 0.69; 95%CI 0.40-1.19).

Hoofdstuk 4 – *veiligheid* – beschrijft de resultaten van de observationele studies naar de veiligheid van respiratoire geneesmiddelen ter behandeling van COPD. In dit hoofdstuk

wordt ook de relatie onderzocht tussen het gebruik van β-blockers en het risico op ziekenhuisopname vanwege een COPD exacerbatie.

Aangezien er twijfel bestond over de veiligheid van tiotropium Respimat hebben we in deel 4.1 van dit hoofdstuk onderzocht of er een verschil is in mortaliteit tussen personen die tiotropium gebruiken via de HandiHaler of via de Respimat als toedieningsvorm. Binnen een cohort van 11,753 tiotropium gebruikers overleden 272 patiënten. In de niet geadjusteerde analyse was het risico op overlijden iets hoger voor gebruikers van tiotropium Respimat® maar dit effect verdween bijna geheel na correctie voor mogelijk verstorende factoren (HR_{adj} 1.21; 95%CI 0.85-1.73).

Uit klinische studies en uit spontane meldingen blijkt dat het gebruik van tiotropium geassocieerd is met een verhoogd risico op urine retentie. Dit risico was voorheen niet eerder gekwantificeerd noch onderzocht buiten studieverband. In deel 4.2 worden de resultaten besproken van de case-controle studie naar de associatie tussen het gebruik van inhalatie anticholinergica en het risico op acute urine retentie. Binnen een cohort van 22,579 COPD patiënten werden 209 nieuwe gevallen van acute urine retentie opgepikt tijdens de follow-up. Het gebruik van inhalatie anticholinergica verhoogt het risico op acute urine retentie met 40% (OR_{adj} 1.40; 95%CI 1.21-7.98). Het risico op acute urine retentie was het hoogst bij COPD patiënten met benigne prostaat hyperplasie (OR_{adj} 4.67; 95%CI 1.56-14.0).

Uit een gepoolde analyse naar de veiligheid van tiotropium bleek het risico op nierlijden hoger bij tiotropium vs. placebo maar dit verschil was niet statistisch significant. Deze associatie was tot dan niet onderzocht via observationeel onderzoek. Hoofdstuk 4.3 van dit proefschrift beschrijft de resultaten van de case-controle studie naar de associatie tussen gebruik van inhaleerbare anticholinergica en het risico op nierlijden (zowel acuut als chronisch). Binnen het COPD cohort van 6788 patiënten traden 83 nieuwe gevallen van nierlijden op. Het risico op nierlijden (zowel acuut als chronisch) was niet hoger in patiënten die inhaleerbare anticholinergica gebruikten ten opzichte van patiënten die geen anticholinergica gebruikten (OR_{adj} 0.78; 95%CI 0.43-1.42). Indien het optreden van nierlijden werd vergeleken tussen gebruikers van anticholinergica en gebruikers van β_2-mimetica werd een licht verhoogd risico op chronisch nierlijden gevonden voor anticholinergica, maar deze associatie was niet statistisch significant (OR_{adj} 1.77; 95% CI 0.67-4.66).

In deel 4.4 wordt de cardiovasculaire veiligheid en overlijden vergeleken tussen gebruikers van inhalatie anticholinergica en gebruikers van langwerkende β_2 mimetica. Dit onderzoek werd opgezet naar aanleiding van een waarschuwing van de FDA over een licht verhoogd risico op een beroerte bij patiënten die werden behandeld met tiotropium. Binnen het COPD cohort van 6,788 patiënten traden 784 nieuwe gevallen van cardiovascular uitkomsten (bijv. myocardinfarct, beroerte) opgepikt (254 beroertes, 116 myocard infarcten, 413 gevallen van hartfalen and 6 ventriculaire ritmestoornissen), 1032 patiënten overleden gedurende de follow-up. Het risico op een cardiovasculair eindpunt verschilde niet tussen gebruikers van tiotropium en patiënten die behandeld werden met een langwerkend β_2 mimeticum

(OR_{adj} 0.89; 95%CI 0.55-1.44). Ook het risico op overlijden was vergelijkbaar (OR_{adj} 0.79; 95%CI 0.49-1.22).

In deel 4.5 van dit hoofdstuk onderzochten we het risico op ernstige COPD exacerbaties in patiënten die behandeld met een β-blokker, β-blokkers zijn in principe gecontra-indicieerd in COPD patiënten maar recente studies laten zien dat er een beschermend effect kan zijn op overlijden en COPD exacerbaties. Omdat een contra-indicatie sterke vertekening kan geven hebben we verschillende onderzoeksopzetten geprobeerd. Uit de cohort analyse bleek inderdaad dat het risico op ziekenhuis opname duidelijk lager was bij gebruikers van β-blokkers dan bij niet-gebruikers (HR_{adj} 0.73; 95%CI 0.69-0.90). Dit beschermende effect werd nog sterker als een case controle onderzoek werd gedaan (OR_{adj} 0.60; 95%CI 0.44-0.82). Om te corrigeren voor confounding door (contra)indicatie herhaalden we de case-control analyse maar nu enkel bij die patiënten die gedurende follow-up behandeld werden met een β-blocker. In die analyse zagen we dat het beschermend effect op hospitalisatie voor COPD exacerbaties sterk was afgezwakt (OR_{adj} 0.87; 95%CI 0.52-1.45). Uit deze studie blijkt dat de keuze van de studie opzet extreem belangrijk is voor het vaststellen van de effectiviteit van geneesmiddelen waar men een sterk risico op confounding door (contra)indication verwacht.

Hoofdstuk 5 is een algemene discussie waarbij de belangrijkste resultaten en conclusies worden besproken en in perspectief worden geplaatst. Ook worden methodologische aspecten toegelicht en wordt er ingegaan op toekomstige onderzoeksvragen.

CHAPTER 7

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Acknowledgements

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PhD Portfolio

About the Author

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Bibliography

Manuscripts based on this thesis

Chapter 2.1

Afonso ASM, Verhamme KMC, Sturkenboom MCJM, Brusselle GGO. COPD in the general population: prevalence, incidence and survival. Submitted.

Chapter 3.1

Afonso ASM, Verhamme KMC, van Noord C, Haag MDM, Brusselle GGO, Sturkenboom MCJM. Comparative effectiveness of tiotropium and long-acting β_2-agonists in preventing severe COPD exacerbations. Submitted.

Chapter 4.1

Afonso ASM, Verhamme KMC, Brusselle GGO, Sturkenboom MCJM. Use of tiotropium Respimat® SMI versus tiotropium HandiHaler® and mortality in patients with COPD. Submitted.

Chapter 4.2

Afonso ASM, Verhamme KMC, Stricker BHC, Brusselle GGO, Sturkenboom MCJM. Inhaled anticholinergic drugs and risk of acute urinary retention. BJU International 2010, 2010 Sep 29. doi: 10.1111/j.1464-410X.2010.09600.x. [Epub ahead of print]

Chapter 4.3

Afonso ASM, Verhamme KMC, de Bie S, van Blijderveen J, Brusselle GGO, Sturkenboom MCJM. Inhaled anticholinergic drugs and the risk of renal failure. Submitted.

Chapter 4.4

Verhamme KMC, Afonso ASM, van Noord C, Haag MDM, Koudstaal PJ, Brusselle GGO, Sturkenboom MCJM. Tiotropium and the risk of cardiovascular events and all cause mortality. Submitted.

Chapter 4.5

Afonso ASM, Verhamme KMC, Suissa S, Brusselle GGO, Sturkenboom MCJM. β-blockers an risk of exacerbations in patients with COPD. Submitted.

PhD Portfolio

Research skills

2006-2008 Master of Science in Clinical Epidemiology, Netherlands Institute for Health Sciences (NIHES), Erasmus Medical Center, Rotterdam, the Netherlands

International conference presentations

2010 20th European Respiratory Society Congress, Barcelona, Spain; e-communication "Tiotropium and the risk of cardiovascular events and all cause mortality".

2010 26th International Conference on Pharmacoepidemiology, Brighton, United Kingdom; poster presentation "Comparative effectiveness of tiotropium and long-acting β_2-agonists in preventing severe COPD exacerbations". Award 2nd Place.

2008 18th European Respiratory Society Congress, Berlin, Germany; poster presentation "Inhaled anticholinergic drugs and the risk of acute urinary retention".

2008 24th International Conference on Pharmacoepidemiology, Copenhagen, Denmark; oral presentation "Inhaled anticholinergic drugs and the risk of acute urinary retention".

Attending international meetings

2010 26th International Conference on Pharmacoepidemiology, Brighton, United Kingdom.

2009 19th European Respiratory Society Congress, Vienna, Austria.

2008 24th International Conference on Pharmacoepidemiology, Copenhagen, Denmark.

Other

Since 2009 Referee activities for various international journals ("Archives of Internal Medicine", "American Journal of Respiratory and Critical Care Medicine", "International Society of Pharmacoepidemiology", and Progress in Neuro-Psychopharmacology & Biological Psychiatry).

About the author

Ana Sofia Maciel Afonso was born on 27 June 1978, in Porto, Portugal. In 1996 she finished her High School education at Carolina Michaelis Secondary School in Porto, Portugal. In 2002 she obtained her veterinary medicine degree at the University of Trás-os-Montes e Alto Douro in Vila Real, Portugal. In 2002 she did two internships: in the University of León, Spain and in the University of Tennessee Veterinary Teaching Hospital in Knoxville, Tennessee, USA. In 2005 she did her post-graduate specialization in Food Safety, at the Catholic University of Porto, Portugal, and one year later, in 2006, she obtained her specialization degree in the Master of Public Health, at the Faculty of Medicine of Porto, Portugal. Between 2002 and 2006 she worked as a veterinarian inspector for food safety at the Portuguese Ministry of Agriculture. In 2006 she moved to the Netherlands and started a Master of Science in the Erasmus Medical Center, and in 2008 she obtained her Master of Science degree in Clinical Epidemiology at the National Institute of Health Sciences (NIHES) in Rotterdam. During her Master program, she conducted research at the department of Medical Informatics of the Erasmus Medical Center, in Rotterdam, under the supervision of Dr. Verhamme and Prof. Sturkenboom. In April 2008 she started her PhD research described in this thesis at the same department.

In November 2010, she moved to Madrid, Spain, where she is currently working with the BIFAP general practitioners database at the Spanish Agency of Medicines (AEMPS), where she works as an epidemiologist (pharmacoepidemiology).