ORIGINAL RESEARCH ARTICLE

Drug Safety 2007; 30 (12): 1151-1160
0114-5916/07/0012-1151/$44.95/0

Comparative Safety of Long-Acting Inhaled Bronchodilators

A Cohort Study Using the UK THIN Primary Care Database

Michele Jara,[1] *Stephan F. Lanes*,[1] *Charles Wentworth III*,[2] *Corey May*[2] and *Steven Kesten*[1]

1 Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, Connecticut, USA
2 Analytic Consulting Solutions Inc., Warwick, Rhode Island, USA

Abstract

Background: Use of a long-acting inhaled bronchodilator, either an anticholinergic or a β-adrenergic receptor agonist (β-agonist), is recommended for maintenance treatment of chronic obstructive pulmonary disease (COPD). In COPD, the organ system most frequently requiring medical care, other than the respiratory system, is the cardiac system.

Objectives: To compare the risk of total mortality and certain respiratory and cardiac adverse events among users of the two types of recommended long-acting bronchodilators, we conducted a cohort study. Specifically, the study compared the safety of the only approved long-acting anticholinergic, tiotropium bromide, with the single-ingredient long-acting β-agonists (LABAs) salmeterol or formoterol in a broad population of users.

Methods: We used automated general practitioner data from the UK THIN (The Health Information Network) database as the data source for this study. We used Cox proportional hazards models to compute hazard ratio (HR) estimates and 95% CI controlling for propensity scores comprising various baseline demographic variables, medical therapies and illnesses.

Results: The 1061 tiotropium users and 1801 LABA users were similar with regard to risk of total mortality (HR 0.93; 95% CI 0.59, 1.44) and most cardiac events, including angina (HR 0.77; 95% CI 0.37, 1.59), atrial fibrillation or flutter (HR 0.60; 95% CI 0.25, 1.42), myocardial infarction (HR 1.29; 95% CI 0.45, 3.66) and tachycardia (HR 0.66; 95% CI 0.29, 1.51). Though imprecise, there was evidence of a decreased risk of heart failure (HR 0.65; 95% CI 0.37, 1.12) in tiotropium users. As regards respiratory endpoints, the risk of COPD exacerbation (HR 1.15; 95% CI 0.79, 1.67) and pneumonia (HR 1.11; 95% CI 0.38, 3.26) were similar among users of each type of drug, although there was a decreased risk of asthma exacerbation (HR 0.41; 95% CI 0.26, 0.64) in tiotropium users compared with LABA users.

Conclusions: Users of tiotropium and single-ingredient LABA had similar risk of total mortality and cardiovascular endpoints. The decreased risk of asthma exacerbations with tiotropium may be due to residual confounding by indication. Confidence limits for most events include reduced risks for tiotropium and also small increases in risk. Nevertheless, the point estimates suggest that tiotropium was associated with a lower risk of each cardiac event except myocardial

infarction. However, the small number of cases means that further studies are needed to confirm these results.

Background

Use of a long-acting inhaled bronchodilator, either an anticholinergic or a β-adrenergic receptor agonist (β-agonist), is recommended for maintenance treatment of chronic obstructive pulmonary disease (COPD).[1] In COPD, the organ system most frequently requiring medical care, other than the respiratory system, is the cardiac system.[2]

To compare the risk of total mortality and certain respiratory and cardiac adverse events among users of the two types of recommended long-acting bronchodilators, we conducted a cohort study. Specifically, the study compared the safety of the only approved long-acting anticholinergic, tiotropium bromide, with long-acting β-agonists (LABAs) in a broad population of users. LABAs are marketed both as single-ingredient formulations and in combination with an inhaled corticosteroid, whereas tiotropium is only marketed as a single-ingredient formulation. Therefore, to enhance the comparability in this cohort study, we compared the use of tiotropium with the use of single-ingredient formulation LABA.

Tiotropium (tiotropium bromide monohydrate, marketed as Spiriva®)[1] is used for the long-term, once-daily maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema.[3] Tiotropium 18μg once daily delivered via the HandiHaler® device has been shown to improve lung function, dyspnoea, exacerbations, exercise tolerance and quality of life.[4-6] In clinical trials, tiotropium has a safety profile consistent with anticholinergic effects, particularly decreased salivation and gastrointestinal motility.[7-9]

LABAs include salmeterol (salmeterol xinafoate, marketed as Serevent®) and, less frequently, formoterol (formoterol, marketed under various trade names including Foradil® and Oxis®). Both compounds have been approved for the maintenance treatment of COPD and require twice-daily administration. Unintended effects associated with LABA include tachycardia, tremor and hypokalaemia.[10] In asthma patients, LABA bronchodilators may increase the risk of respiratory death;[11,12] nevertheless, no studies have been conducted to assess such an effect in patients with COPD.[12]

Methods

Data Source

The data source for this project was UK THIN (The Health Information Network) general practitioner (GP) primary care database provided by Epidemiology and Pharmacology Information Core (EPIC).[13] THIN data are collected from the daily record keeping of UK general practices using the Vision Information Management System. The data are similar to an automated GP record. THIN provides anonymous patient data, including demographics, past history and prescriptions. THIN also contains information on referral to specialists, diagnostics and laboratory results, some lifestyle characteristics and other measurements taken within the general practice. The data are organised in files by individual practice after evaluation, verification and validation of the raw data and provide a longitudinal medical record for each patient.[13,14] The database included 3 425 028 people registered in 220 general practices at the time of this study. All variables were identified from the automated patient records. The analysis database was developed in Oracle® 9i[15] and the epidemiological analyses were done using STATA 7.0.[16]

This study received ethical approval from the UK Department of Health Multicentre Research Ethics Committee.

Study Population

The source population included patients in the UK enrolled with a GP who contributed to the THIN primary care database. Patients eligible for inclusion had at least one prescription for a long-acting in-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

haled anticholinergic (tiotropium) or a LABA (salmeterol or formoterol), from November 2002 (the earliest use of tiotropium) until the last collection date of data from their participating practice. Last collection dates ranged from February 2003 to 3 June 2004, although only 6% of the practices had last collection dates in 2003.

In addition, to be eligible for inclusion, a patient had to be registered at least 1 year before their first or 'index' prescription for tiotropium or LABA. This criterion ensures a cohort of patients with new prescriptions (within 1 year) for a long-acting bronchodilator.

β-Agonists are more widely used than anticholinergic medications in treating asthma. In addition, COPD is more strongly related to mortality and serious morbidity than is asthma.[17,18] Therefore, to reduce confounding by indication, patients who had a recorded diagnosis of asthma as their only respiratory diagnosis were excluded. Furthermore, because asthma is more common in the young than COPD, patients aged <40 years old were excluded from the study.

In summary, the study population included all patients enrolled in THIN practices who were at least 40 years old, prescribed a long-acting bronchodilator between November 2002 and June 2004, had at least 1 year of baseline data prior to the prescription for long-acting bronchodilator and did not have asthma listed as their only respiratory diagnosis. The study population was not restricted to COPD patients only.

Endpoints

The main study endpoints were death from any cause; cardiac events, including angina, atrial fibrillation and flutter, heart failure, myocardial infarction, and tachycardia; and COPD exacerbation. Secondary study endpoints included two additional respiratory adverse events, asthma exacerbation and pneumonia, and constipation. Constipation is a recognised adverse effect of tiotropium and is described in drug labelling. We included this endpoint to check the sensitivity of our study to identify known effects.

Confounding Variables

We controlled for differences in baseline risk measured in the year before the first prescription for a long-acting bronchodilator. Covariates considered included indication for tiotropium use (COPD, COPD and asthma, COPD symptoms), age, sex, months since market introduction of tiotropium, smoking, body mass index (BMI), alcohol use, number of hospitalisations in the year prior to cohort entry, number of GP visits in the year prior to cohort entry, cardiac co-morbidities (ischaemic heart disease, arrhythmias, hypertension), number of prescriptions for respiratory medications (including short-acting anticholinergics, short-acting β-agonists, inhaled corticosteroids, oral corticosteroids, theophyllines, cromoglycates), number of prescriptions for cardiac medications (including antiarrhythmics, anticoagulants, antihypertensives, ACE inhibitors, aspirin [acetylsalicylic acid], diuretics, inotropics, lipid regulators, β-adrenoceptor antagonists [β-blockers], nitrates), use of other medications (including medications for gastrointestinal, vascular, CNS, gynaecological and urinary, nutrition and blood disorders, malignancies and anti-infectives) and oxygen use.

Statistical Analysis

Main Analyses

The duration of drug use was estimated from the prescription quantity and doses per day fields, and the formulation of the prescribed bronchodilator. People were classified as exposed to study medication for the duration of prescribed therapy plus 30 days. Patients could not contribute time to both exposures during the course of the observation period. A switch to or addition of the other long-acting bronchodilator terminated follow-up. We followed patients from the date of their first eligible prescription until the earliest of the following: date of study endpoint; date of long-acting bronchodilator switch or add-on; date of transfer to a new practice; date of death; or last collection date of the participating practice.

We used propensity score matching to enhance efficiency of analytical control of confounding.[19-22] We conducted multiple cross-tabulations to examine the relationship of each covariate listed in the pre-

vious section with type of long-acting bronchodilator assigned and each study endpoint. We used logistic regression models to create propensity scores that we categorised into quintiles of propensity to receive one or the other study medications. We then conducted multivariate analysis using Cox proportional hazard models with adjustment for indicators of propensity score quintile to compute estimates of hazard ratio (HR) and 95% CIs.[19-22] We used the width of the 95% CI to convey the precision of the estimate and position of the p-value function.[23]

Secondary Analyses

Several sensitivity analyses were conducted primarily to assess residual confounding by indication. First, we conducted analyses restricted to patients with diagnosed COPD without an asthma diagnosis, excluding patients with asthma and COPD or symptoms only. We also conducted probabilistic sensitivity analysis using the SensTool[24] Excel programme provided by Fox et al.[25] to quantify the likely effects of misclassification of drug exposure and the presence of an unmeasured confounder, a hypothetical COPD severity indicator, while accounting for random error. We assumed non-differential exposure misclassification error with sensitivity ranging from 0.97 to 1.00 and specificity ranging from 0.90 to 1.00.[26] We assumed the prevalence of the unmeasured COPD severity confounder to range from 0.25 to 0.35 among tiotropium patients and 0.10 to 0.20 among LABA patients. Based on the natural history of COPD,[27] we assumed relationships between the unmeasured COPD severity confounder and death, negative cardiovascular outcomes, COPD exacerbation and pneumonia with the odds of death ranging from 1.5 to 5.0 times higher in patients with 'severe' COPD compared with 'non-severe' COPD, the odds of heart failure from 1.5 to 4.0 times higher, the odds of angina, atrial fibrillation or flutter, myocardial infarction and tachycardia up to 2.0 times higher, the odds of COPD exacerbation from 1.5 to 6.0 times higher and the odds of pneumonia from 1.0 to 2.5 higher.

Tiotropium was introduced in the UK more recently than the LABAs. The impact of differences in time since introduction is unclear, but new medications may initially be prescribed to patients for whom existing therapies are unsatisfactory (e.g. those with more advanced disease). To identify any relevant changes in the propensity score of the tiotropium population over time, we stratified by calendar time intervals.

To restrict the study population to a more homogeneous group of patients at risk of cardiac disease, we conducted analysis among patients who used nitrates in the 365 days prior to index date. Mean duration of exposure was 5 months, making analysis by duration of exposure impractical.

Results

The study population included 2862 patients (1061 tiotropium patients and 1801 LABA patients), contributing 470 person-years of exposure to tiotropium and 746 person-years of exposure to a single-ingredient LABA (table I). The vast majority of LABA prescriptions were for salmeterol; only 6.4% of all prescriptions issued for a single-ingredient LABA were for formoterol. Tiotropium patients were more likely to be male, somewhat older and have lower BMI than LABA patients. Tiotropium patients had a lower BMI than LABA patients regardless of sex, although the difference was greater in women (17.5% with low BMI in tiotropium patients, 10.9% in LABA patients) than in men (11.2% with low BMI in tiotropium patients, 9.6% in LABA patients). Approximately one-third of patients in both groups were noted as current smokers. Although current smoking is noted frequently, smoking history does not appear to be reliably documented as evidenced by the large proportion of patients with no evidence of smoking (i.e. the medical record contained no indication that the patient was a smoker) regardless of type of long-acting bronchodilator used. With regard to medication history in the year prior to first prescription of a long-acting bronchodilator, patients receiving tiotropium were more likely to use short-acting anticholinergic and β-agonist bronchodilators and less likely to use inhaled corticosteroids than were patients receiving LABA.

HR estimates are presented in table II. Tiotropium and LABA users were similar with regard to risk of total mortality (HR 0.93; 95% CI 0.59, 1.44) and most cardiac endpoints, including angina (HR 0.77; 95% CI 0.37, 1.59), atrial fibrillation or flutter (HR 0.60; 95% CI 0.25, 1.42), myocardial infarction (HR

1.29; 95% CI 0.45, 3.66) and tachycardia (HR 0.66; 95% CI 0.29, 1.51). Though imprecise, there was evidence of a decreased risk of heart failure (HR 0.65; 95% CI 0.37, 1.12) in tiotropium users.

With regard to respiratory events, there was a decreased risk of asthma exacerbation in patients using tiotropium compared with patients using a single-ingredient LABA (HR 0.41; 95% CI 0.26, 0.64). The risks of COPD exacerbation (HR 1.15; 95% CI 0.79, 1.67) and pneumonia (HR 1.11; 95% CI 0.38, 3.26) were similar in patients using tiotropium and patients using a single-ingredient LABA users.

Results of analyses restricted to patients with COPD without identified asthma were similar to those seen in the analysis of the full study population, except there was a upward shift in the HR of asthma (from 0.41 to 0.77; 95% CI 0.31, 1.91) and slight downward shift in the HR of COPD exacerbations (from 1.15 to 1.03; 95% CI 0.60, 1.76) and death (from 0.93 to 0.71; 95% CI 0.35, 1.45) in the restricted population. There was no consistent effect on cardiovascular endpoints detected; however, the analysis was limited by the small number of most cardiac endpoints. The HR of heart failure, the most numerous cardiac endpoint, remained similar in both the restricted and unrestricted study populations.

There was a small, imprecise, increased risk of constipation in patients using tiotropium compared with patients using a single-ingredient LABA (HR 1.38; 95% CI 0.81, 2.36).

The odds of being prescribed tiotropium versus a single-ingredient LABA at first prescription for a long-acting bronchodilator differed by time since introduction to the UK market. In the first 5-month period following introduction of tiotropium to the market, patients with oxygen use in the 365 days prior to study entry were 3.22 times (95% CI 1.55, 6.69) more likely to be prescribed tiotropium when they began a long-acting bronchodilator than a single-ingredient LABA. This increased propensity to be assigned to tiotropium versus LABA when oxygen use was noted in the year prior to study entry date decreased over time and had largely dissipated by 10–15 months after tiotropium was first sold (adjusted odds ratio [OR] 1.21; 95% CI 0.56, 2.60). Oxygen use was the only predictor of tiotropium use that appeared to vary by time since introduction to the market of tiotropium.

With regard to the use of nitrates in the year prior to index, the relative risk (RR) of myocardial infarction in patients with a history of nitrate use was 0.70 (95% CI 0.11, 4.55).

The results of our sensitivity analyses simulating the effects of exposure misclassification and unmeasured confounding by a hypothetical COPD severity indicator suggest that effect estimates adjusted for a single dichotomous confounder consistently overestimate the relative risk of all study endpoints with tiotropium by 11–17%. The greater uncertainty surrounding the effect estimates in light of possible misclassification and unmeasured confounding was reflected in the simulated 95% intervals, which were as much as twice the width of the conventional limits. The effect of exposure misclassification alone was minor, with all effect estimates remaining similar within one decimal place of the crude estimates.

Discussion

This study suggests new users of long-acting anticholinergic and β-agonist bronchodilators are similar with regard to risk of total mortality over a mean follow-up time of 5 months. With regard to cardiac endpoints, we did not observe important differences between the treatments, although the point estimates indicate a lower risk of each cardiac event with tiotropium, except myocardial infarction, which was the rarest cardiac event with the widest confidence interval.

Two published studies compared tiotropium with salmeterol, but neither study was sufficiently large to detect rare adverse events.[28,29] Nevertheless, pooled analyses of these trials found fewer deaths in patients receiving tiotropium (n = 1) relative to patients receiving salmeterol (n = 6) [RR 0.17; 95% CI 0.02, 1.39].[28] Although the current study found the risk of death in patients treated with tiotropium or a LABA to be similar, our sensitivity analysis suggested the possibility of uncontrolled confounding by indication may have inflated the HR of death. Salmeterol has been found to be related to increased risk of respiratory death, but not to overall mortality.[11] Direct comparison of tiotropium with

Table I. Selected baseline characteristics of the study population[a]

Characteristics	Tiotropium [n (%)]	LABA[b] [n (%)]
Total patients	1061 (100)	1801 (100)
Total person-years	470 (100)	746 (100)
Mean person-years of follow-up	0.44 (100)	0.41 (100)
Age (y)		
40–49	26 (2)	111 (6)
50–59	130 (12)	284 (16)
60–79	735 (69)	1114 (62)
80+	170 (16)	292 (16)
Sex		
Male	616 (58)	894 (50)
Female	445 (42)	907 (50)
Weight		
Low body mass index	147 (14)	185 (10)
Smoking		
No evidence of smoking	388 (37)	728 (40)
Ex-smoker	287 (27)	495 (27)
Current smoker	386 (36)	578 (32)
Indication for use		
COPD	474 (45)	567 (31)
COPD and asthma	319 (30)	659 (37)
Other	268 (25)	575 (32)
Use of respiratory medications		
Short-acting anticholinergics		
no use	496 (47)	1077 (60)
1–6 prescriptions	280 (26)	425 (24)
7+ prescriptions	285 (27)	299 (17)
Short-acting β-agonists		
no use	250 (24)	327 (18)
1–5 prescriptions	324 (31)	709 (39)
6–10 prescriptions	183 (17)	369 (20)
11+ prescriptions	304 (29)	396 (22)
Inhaled corticosteroids		
no use	545 (51)	672 (37)
1–6 prescriptions	311 (29)	796 (44)
7+ prescriptions	205 (19)	333 (18)
Oral corticosteroids		
no use	678 (64)	1122 (62)
1 prescription	172 (16)	328 (18)
2+ prescriptions	211 (20)	351 (19)
Use of cardiac medications		
Antihypertensives	511 (48)	803 (45)
Diuretics	462 (44)	680 (38)

Continued next page

Table I. Contd

Characteristics	Tiotropium [n (%)]	LABA[b] [n (%)]
ACE inhibitors	246 (23)	384 (21)
Nitrates	167 (16)	258 (14)
Anticoagulants	333 (31)	508 (28)
β-Adrenoceptor antagonists (β-blockers)	91 (9)	153 (9)
Lipid-regulators	89 (8)	134 (7)
Antiarrhythmics	52 (5)	85 (5)
Cardiac events		
Ischaemic heart disease	247 (23)	368 (20)
Arrhythmia	109 (10)	163 (9)
Hospital admissions		
No	956 (90)	1586 (88)
Yes	105 (10)	215 (12)

a 365 days prior to index date.

b Single-ingredient formulation.

COPD = chronic obstructive pulmonary disease; **LABA** = long-acting β-adrenergic receptor agonist.

salmeterol in trials did not elucidate any differences in the risk of cardiovascular adverse events.[28,29]

Tiotropium users in our study had a reduced risk of heart failure relative to use of a LABA. The apparent decreased risk is based on a greater number of cases than other cardiac endpoints and, though imprecise, is most consistent with a range of effects that lies almost entirely in the region of a lower risk for tiotropium. Relative to placebo, tiotropium has been found to have a reduced risk of left heart failure (RR 0.46; 95% CI 0.21, 1.00) in analysis of pooled clinical trial data.[7]

Tiotropium users in our study had an HR of myocardial infarction value slightly above one, which was imprecise and diminished when the study population was restricted to COPD patients without a diagnosis of asthma. In analyses restricted to patients prescribed nitrates in the year prior to study entry, we found no increased risk of myocardial infarction.

Although imprecise, the incidence rate of tachycardia in tiotropium users in our study was compatible with that of patients using a single-ingredient LABA. Anticholinergics and β-agonists can potentially increase heart rate in patients with COPD.[30-32] Relative to placebo, tiotropium has been found to have a somewhat elevated risk of tachycardia (including tachyarrhythmia, but excluding ventricular tachyarrhythmias) [RR 1.68; 95% CI 0.69, 4.11] in analysis of pooled clinical trial data.[7] Ferguson and colleagues[33] conducted a similar analysis pooling data from placebo-controlled clinical trial data of salmeterol. Calculations based on the data reported indicate that salmeterol is associated with an elevated though imprecise risk of tachycardia (RR 1.9; 95% CI 0.76, 4.7), tachyarrhythmia (RR 2.05; 95% CI 0.83, 5.06) as well as serious tachyarrhythmia (RR 3.07; 95% CI 0.62, 15.09).[33]

Ferguson and colleagues[33] found an increased risk of serious angina with salmeterol use (crude RR 4.09; 95% CI 0.87, 19.24). In analysis of pooled clinical trial data, tiotropium was not found to have an increased risk of serious angina (RR 0.92; 95% CI 0.46, 1.87) relative to placebo.[7] Although wide confidence intervals indicate imprecision, patients using tiotropium in our study developed angina at a rate similar to that observed in patients using a LABA.

The negative association of tiotropium with asthma exacerbation and weak positive association with COPD exacerbation may be due to residual confounding by indication for long-acting bronchodilator use. LABAs are approved for both COPD and asthma indications, whereas tiotropium is currently approved for maintenance treatment of bronchospasm associated with COPD. In this study, both tiotropium and LABA were prescribed to patients with respiratory symptoms but without diagnosis of COPD or asthma. As the goal of our study was to compare the safety of inhaled long-acting broncho-

dilators in users of these drugs, we did not restrict the study population to patients with diagnosed COPD. The study population included patients with asthma in addition to COPD and patients with respiratory symptoms. We attempted to limit confounding by indication through restrictions on age and the requirement of a diagnosis of COPD if the patient had a concomitant diagnosis of asthma. These restrictions effectively reduced the cohort of LABA users, comprised largely of young asthmatics, by 74%, and tiotropium users by 12%. Nevertheless, roughly one-third of the remaining patients in each treatment group had neither a diagnosis of COPD nor asthma, and the underlying respiratory disease in these patients is uncertain. We also used propensity score modelling to reduce the potential for confounding. Propensity scores can be used effectively in situations where the number of outcomes is limited, treatment is common and there are multiple prognostic variables.[19,34] Nevertheless, propensity scores may not balance unobserved covariates, so the potential for residual confounding exists.

Even after the abovementioned restrictions to the study cohort, it was not possible to fully characterise underlying respiratory disease, and LABA users were more likely to have a concomitant diagnosis of asthma with COPD than were tiotropium users. Consequently, a higher risk of asthma exacerbations in LABA users relative to tiotropium users is expected. The continuing presence of residual confounding by indication was illustrated when analysis restricted to COPD patients without asthma increased the HR of asthma exacerbation, bringing it closer to the null value (HR = 1). In sensitivity analyses the traditionally adjusted effect estimates consistently overestimate the RR of all study endpoints, in particular, COPD exacerbations. This result supports the argument that any bias due to a larger proportion of sicker patients with COPD being prescribed tiotropium rather than a LABA would bias RR estimates upwards, and tend to overestimate the risk of COPD exacerbation and cardiovascular endpoints in patients receiving tiotropium compared with patients receiving a LABA. Finally, the limited data available from direct comparison of tiotropium and salmeterol support a lower risk of COPD exacerbation in patients receiving tiotropium. Brusasco et al.[29] found a lower rate of COPD exacerbations per patient year in the tiotropium group (1.07) than

Table II. Incidence rates and hazard ratio (HR) estimates of death and adverse events[a]

Endpoints	Tiotropium [n (rate[b])]	LABA[c] [n (rate[b])]	Crude HR	Adjusted HR[d]	Adjusted 95% CI
Total treated (n = 2862)	1061	1801			
Total person-years (n = 1216)	470	746			
Death	35 (7.45)	53 (7.10)	1.04	0.93	0.59, 1.44
Cardiac events					
Angina	11 (2.34)	26 (3.49)	0.67	0.77	0.37, 1.59
Atrial fibrillation and flutter	8 (1.70)	18 (2.41)	0.71	0.60	0.25, 1.42
Heart failure	20 (4.26)	44 (5.90)	0.73	0.65	0.37, 1.12
Myocardial infarction	7 (1.49)	9 (1.21)	1.27	1.29	0.45, 3.66
Tachycardia	9 (1.91)	18 (2.41)	0.80	0.66	0.29, 1.51
Respiratory events					
Asthma exacerbation	24 (5.11)	132 (17.69)	0.28	0.41	0.26, 0.64
COPD exacerbation	54 (11.49)	68 (9.12)	1.28	1.15	0.79, 1.67
Pneumonia	6 (1.28)	9 (1.21)	1.06	1.11	0.38, 3.26
Other events					
Constipation	27 (5.74)	31 (4.16)	1.38	1.38	0.81, 2.36

a Relative hazard was estimated using Cox proportional hazards model.

b Rates are per 100 person-years at risk.

c Single-ingredient formulation.

d Adjusted using a propensity score.

COPD = chronic obstructive pulmonary disease; **LABA** = long-acting β-adrenergic receptor agonist.

in the salmeterol group (1.23) and a lower rate of COPD-related hospital admissions per patient year in the tiotropium group (0.10) than in the salmeterol group (0.17).

Tiotropium was associated with a small increased risk of constipation, a recognised anticholinergic effect. The result from our study, though imprecise, is similar to the result obtained in clinical trials, and provides some reassurance about the validity of our study.[7]

This study shares limitations with other studies using automated administrative databases, especially the potential for misclassification. For example, THIN data record prescriptions are issued, but do not confirm that the patient actually took a medication. It is assumed that patients use prescribed medication. This limitation has not been considered an important source of error in previous epidemiological studies since systematic overestimation of exposure that is independent of study endpoints tends to dilute the strength of the effect estimate; however, for studies with null results, misclassification needs to be considered as a reason for the null result. The results of our sensitivity analyses suggest that exposure misclassification did not introduce important bias.

There may be some residual confounding due to incomplete recording of information in THIN data of variables such as smoking, test results and hospitalisation. We controlled for prior hospitalisation and number of GP visits to the extent possible, although we were unable to control for spirometry results or other direct measures of COPD severity, which were not available for >99% of patients in the study population. Patients prescribed tiotropium in the initial period after market introduction of the drug appeared to have more severe COPD than patients prescribed tiotropium later in the study period, as illustrated by the decrease over time of patients using respiratory oxygen. This analysis illustrates that although confounding by indication due to unmeasured COPD severity may be affecting the RRs, the main study conclusions remain valid and any bias would tend to underestimate the safety of tiotropium relative to LABA.

Both tiotropium and the LABA salmeterol have one recommended daily dose in patients with COPD; however, the daily dose of the other LABA, formoterol, may vary in patients with COPD. We analysed formoterol exposure as a dichotomous variable that did not take dose into account. COPD patients with pre-existing cardiac arrhythmias and hypoxaemia in one crossover placebo-controlled study undergoing 24-hour Holter monitoring showed a higher heart rate and supraventricular or ventricular premature beats more often following formoterol 24μg than after formoterol 12μg and salmeterol 50μg. Patients receiving higher-dose formoterol also showed reduced plasma potassium levels for longer compared with placebo than did patients receiving lower-dose formoterol and salmeterol.[35] Nevertheless, the small proportion of formoterol users (6.4%) in our study precluded a meaningful assessment of dose effects.

Conclusion

This study found that users of tiotropium and LABA are similar with regard to risk of total mortality and cardiac endpoints. Although cardiac events, in general, tended to occur at a lower rate in the tiotropium group, the low frequencies and the small number of cases mean continued monitoring is necessary to obtain reliable estimates.

Acknowledgements

This study was funded by Boehringer Ingelheim Pharmaceuticals Incorporated. Michele Jara, Steven Kesten and Stephan F. Lanes are employees of Boehringer Ingelheim. Charles Wentworth III and Corey May are consultants for Boehringer Ingelheim. The authors were responsible for all aspects of this study, including design, analysis and interpretation.

References

1. Pauwels RA, Buist AS, Calverley PM, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. Am J Respir Crit Care Med 2001; 163: 1256-76
2. Sin DD, Man P. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? Circulation 2003; 107 (11): 1514-9
3. Disse B, Speck GA, Rominger KL, et al. Tiotropium (Spiriva): mechanistical considerations and clinical profile in obstructive lung disease. Life Sci 1999; 64: 457-64
4. Casaburi R, Kukafka D, Cooper CB, et al. Improvement in exercise tolerance with the combination of tiotropium and pulmonary rehabilitation in patients with COPD. Chest 2005; 127 (3): 809-17
5. Niewoehner DE, Rice K, Cote C, et al. Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropi-

um, a once-daily inhaled anticholinergic bronchodilator: a randomized trial. Ann Intern Med 2005; 143 (5): 317-26

6. Maltais F, Hamilton A, Marciniuk D, et al. Improvements in symptom-limited exercise performance over 8 hours with once-daily tiotropium in patients with COPD. Chest 2005; 128 (3): 1168-78
7. Kesten S, Jara M, Wentworth C, et al. Pooled clinical trial analysis of tiotropium safety. Chest 2006; 130: 1695-703
8. Morganroth J, Golisch W, Kesten S. Lack of cardiac safety signals in COPD patients receiving tiotropium as defined by electrocardiographic monitoring in placebo controlled trials. J COPD 2004; 1: 181-90
9. Covelli H, Bhattacharya S, Cassino C, et al. Absence of electrocardiographic findings and improved function with daily tiotropium in patients with chronic obstructive pulmonary disease. Pharmacotherapy 2005; 25: 1708-18
10. Currie GP, Lipworth BJ. ABC of chronic obstructive pulmonary disease: pharmacologic management-inhaled treatment. BMJ 2006; 332: 1439-41
11. Nelson HS, Weiss ST, Bleecker ER, et al. The salmeterol multicenter asthma research trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest 2006; 129: 15-26
12. GlaxoSmithKline. Serevent® product information, RL-2033. Research Triangle Park (NC): GlaxoSmithKline, 2003 Aug
13. Bourke A, Dattani H, Robinson M. Feasibility study and methodology to create a quality-evaluated database of primary care data. Inform Prim Care 2004; 12: 171-7
14. Lewis JD, Schinnar R, Bilder WB, et al. Validation studies of The Health Improvement Network (THIN) database for Pharmacoepidemiology research. Pharmacoepidemiol Drug Saf 2007; 16: 393-401
15. Oracle9i database. Redwood Shores (CA): Oracle Corporation, 2000
16. STATA 7.0. College Station (TX): StataCorp, 2002
17. CDC. Chronic obstructive pulmonary disease surveillance: United States, 1971-2000 [online]. Available from URL: http://www.cdc.gov/mmwr/preview/mmwrhtml/ss5106a1.htm [Accessed 2006 May 12]
18. CDC. Surveillance for asthma: United States, 1980-1999 [online]. Available from URL: http://www.cdc.gov/mmwr/preview/mmwrhtml/ss5101a1.htm [Accessed 2006 May 12]
19. Braitman LE, Rosenbaum PR. Rare outcomes, common treatments: analytic strategies using propensity scores. Ann Intern Med 2002; 137: 693-6
20. Joffe MM, Rosenbaum PR. Invited commentary: propensity scores. Am J Epidemiol 1999, 333
21. Robins JM, Mark SD, Newey WK. Estimating exposure effects by modelling the expectations of exposure conditional on confounders. Biometrics 1992; 48: 479-95
22. Rubin DB. On principles for modeling propensity scores in medical research. Pharmacoepidemiol Drug Saf 2005; 13: 855-7
23. Rothman KJ, Greenland S. Approaches to statistical analysis. In: Rothman KJ, Greenland S, editors. Modern epidemiology. 2nd ed. Philadelphia (PA): Lippincott-Raven Publishers, 1998: 183-99
24. SensTool.xls from the Boston University School of Public Health [online]. Available from URL: http://www.bu.edu/dbin/sph/departments/epidemiology/epidemiologic_methods_research.php [Accessed 2006 Feb 8]
25. Fox MP, Lash TL, Greenland S. A method to automate probabilistic sensitivity analyses of misclassified binary variables. Int J Epidemiol 2005; 34: 1370-6
26. Garcia Rodriguez LA, Pérez-Gutthann S, Jick S. The UK General Practice Research Database. In: Strom BL, editor. Pharmacoepidemiology. 3rd ed. New York: John Wiley & Sons, Ltd, 2000: 375-85
27. Curkendall SM, DeLuise C, Jones JK, et al. Cardiovascular disease in patients with chronic obstructive pulmonary disease, Saskatchewan Canada: cardiovascular disease in COPD patients. Ann Epidemiol 2006; 16: 63-70
28. Donohue JF, van Noord JA, Bateman ED, et al. A 6-month, placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol. Chest 2002; 122: 47-55
29. Brusasco V, Hodder R, Miravitlles M, et al. Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. Thorax 2003; 58: 399-404
30. Mintzer J, Burns A. Anticholinergic side-effects of drugs in elderly people. J R Soc Med 2000; 93: 457-62
31. Costello R. Pharmacology. In: Calverly PMA, MacNee W, Pride NB, et al., editors. Chronic obstructive pulmonary disease. 2nd ed. London: Arnold, 2003: 341-56
32. Sovani MP, Whale CI, Tattersfield AE. A benefit-risk assessment of inhaled long-acting β2-agonists in the management of obstructive pulmonary disease. Drug Saf 2004; 27 (10): 689-715
33. Ferguson GT, Funck-Brentano C, Fisher T, et al. Cardiovascular safety of salmeterol in COPD. Chest 2003; 123: 1817-24
34. Cepeda MS, Boston R, Farrar JT, et al. Comparison of logistic regression versus propensity score when the number of events is low and there are multiple confounders. Am J Epidemiol 2003; 158: 280-7
35. Cazzola M, Imperatore F, Salzillo A, et al. Cardiac effects of formoterol and salmeterol in patients suffering from COPD with preexisting cardiac arrhythmias and hypoxemia. Chest 1998; 114: 411-5

Correspondence: Dr *Michele Jara*, Boehringer Ingelheim Pharmaceuticals Inc., 900 Ridgebury Road, Ridgefield, CT 06877-0368, USA.
E-mail: mjara2@rdg.boehringer-ingelheim.com