A Cohort Study Comparing the Safety of Long-Acting Inhaled Bronchodilators in COPD

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2012-000841
Article Type:	Research
Date Submitted by the Author:	26-Jan-2012
Complete List of Authors:	Lanes, Stephan; UnitedBiosource Corporation, Jara, Michele; Acorda Therapeutics, Wentworth, Charles; United BioSource Corp, Epidemiology and Datbase Analytics
Primary Subject Heading:	Pharmacology and therapeutics
Secondary Subject Heading:	Respiratory medicine, Epidemiology
Keywords:	Emphysema < THORACIC MEDICINE, Adverse events < THERAPEUTICS, Stroke < NEUROLOGY, Ischaemic heart disease < CARDIOLOGY

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

A Cohort Study Comparing the Safety of Long-Acting Inhaled Bronchodilators in COPD

Michele Jara, Charles Wentworth III, Stephan Lanes

Address correspondence to:

Michele Jara, Epidemiology Consulting, LLC, 5 Fox Den Road, Danbury, CT 06811 email: mjara@acorda.com

Disclosures: Drs. Lanes and Jara were employees of Boehringer Ingelheim Pharmaceuticals Inc. during the conduct of this study. Dr. Jara is employed by Acorda Therapeutics. Dr. Lanes and Mr. Wentworth are employed by United BioSource Corporation, Lexington, MA.

Contributions: Drs. Lanes and Jara were responsible for the study conception and design. Mr. Wentworth and Dr. Jara were responsible for data analysis. All authors were responsible for data interpretation. Drs. Lanes and Jara drafted the manuscript. All authors revised the manuscript and approved the final version.

Data sharing: Unpublished data from the study are not available.

Funding: Supported by Boehringer Ingelheim Pharmaceuticals

Subject Headings: cohort study, COPD, product safety, tiotropium, cardiovascular, stroke

Word count: Abstract: 197; Text: 2640

SUMMARY

Article focus

- This study investigated whether there are possible increased risks of stroke and other adverse events, including angina and myocardial infarction, with tiotropium use in COPD
- We compared new users of long-acting anticholinergic therapy (tiotropium Handihaler®) with new users of long-acting beta agonist (LABA) monotherapy

Key messages

- Imprecise increased risks of angina, myocardial infarction and stroke were observed in tiotropium users
- These results suggest that tiotropium may be associated with an increased risk of serious cardiovascular events

Strengths and Limitations

This study was conducted in a large population of COPD patients using primary care medical records. Nonrandomized studies must always be concerned with possible bias. Although we used propensity scores and multivariate models to control efficiently for available risk factors, certain variables, such as lung function results, were unavailable and could not be controlled. The results reported here and in other comparative tiotropium studies for angina, myocardial infarction and stroke are not statistically significant. The absence of statistical significance in studies that lack the power to detect small effects, however, should be expected and does not indicate the absence of an effect.

ABSTRACT

Background: To investigate a possible increased risk of stroke and other adverse events with tiotropium, we compared new users of long-acting anticholinergic therapy (tiotropium Handihaler®) with new users of long-acting beta agonist (LABA) monotherapy.

Methods: We used The Health Improvement Network (THIN) general practitioner database to identify patients newly prescribed a single-ingredient long-acting bronchodilator. Patients <40 years old or having asthma as their only respiratory diagnosis were excluded. We used Cox proportional hazards models to compute hazard ratio (HR) estimates comparing tiotropium with LABA adjusted for propensity scores comprising baseline demographic variables, medical therapies, and illnesses.

Results: We identified 10,840 patients newly prescribed tiotropium (n=4,767) or LABA (n=6,073). Tiotropium users had a lower rate of total mortality than users of LABA (HR=0.70, 95% CI= 0.56, 0.89). Tiotropium was associated with increased rates of stroke (HR=1.49, 95% CI=0.91, 2.45), angina (HR=1.38, 95% CI=0.88, 2.16), and myocardial infarction (HR=1.26, 95% CI=0.72, 2.21). Rates of COPD exacerbation (HR=0.95, 95%CI=0.80, 1.12) and pneumonia (HR=0.96, 95%CI=0.58, 1.58) were similar. Tiotropium was associated with a lower rate of asthma exacerbations (HR=0.46, 95%CI=0.36, 0.57).

Conclusion: Tiotropium users had lower rates of total mortality than LABA users, and higher rates of serious ischemic cardiovascular events.

INTRODUCTION

Inhaled anticholinergic medications, including short-acting ipratropium bromide (ipratropium), and long-acting tiotropium bromide (tiotropium), are mainstays for the treatment of symptoms of COPD. The safety profiles of these drugs comprise systemic anticholinergic events, including dry mouth, constipation, urinary retention and cardiac effects, including palpitations, tachycardia, and supraventricular tachycardia (SVT).[1-3] There has been concern that anticholinergic drugs could induce ischemia, possibly secondary to tachyarrhythmias,[3] and could pose a risk to patients with cardiovascular complications.[4] Among patients with congestive heart failure (CHF), SVTs are an independent risk factor for stroke, as well as cardiovascular hospitalization and death.[5] Further, among patients with sinus node dysfunction, asymptomatic atrial tachyarrhythmias increase the risk of stroke and death.[6]

We conducted this epidemiologic study to examine the possible association between tiotropium (Handihaler® powder formulation) and risk of stroke and other adverse events, including angina and myocardial infarction.

METHODS

Treatment guidelines for COPD consider long-acting bronchodilators as a class, but make no distinction between anticholinergic drugs and LABAs, resulting in clinical equipoise.[7] Therefore, new users of tiotropium were compared with new users of LABAs. Both long-acting bronchodilators are indicated for treating symptoms of COPD; LABAs are also indicated for the treatment of asthma.

The source population included patients in the UK enrolled with a general practitioner who contributes to The Health Improvement Network (THIN) primary care database. The THIN database

includes de-identified patient records containing demographic data, medical history, prescribed medications, diagnostic tests, laboratory results, specialist referrals, and some lifestyle characteristics.[8] The database is derived from the same software as the General Practice Research Database (GPRD) and has been validated for COPD, as well as stroke and myocardial infarction, and is widely used in epidemiologic research.[8-10]

Patients had to have at least one prescription for tiotropium (Handihaler formulation) or LABA (salmeterol or formoterol), from November 2002 (the earliest use of tiotropium) until January 2007. Because tiotropium is available only in a single-ingredient preparation, whereas LABAs are also available in combination with inhaled corticosteroids, the LABA group was restricted to patients prescribed single-ingredient LABAs. Patients had to have at least two years of baseline data with no use of a long-acting inhaler prior to their first or "index" prescription for tiotropium or LABA. To reduce confounding by indication, patients who had a recorded diagnosis of asthma as their only respiratory diagnosis were excluded, as were patients less than 40 years old.

Study endpoints included various cardiovascular adverse events (aneurysm, atrial fibrillation, cardiac arrest, coronary artery disease, angina, myocardial infarction, heart failure, hypertension, stroke, syncope, tachycardia, and ventricular tachycardia); respiratory adverse events (COPD exacerbation, asthma exacerbation, and pneumonia); and other adverse events of interest (constipation, dry mouth, dysphagia, paralytic ileus/bowel obstruction, renal failure, tremor, urinary retention). Information on causes of death was unavailable, but we were able to examine all-cause mortality. Study endpoints were defined using medical codes from the Read Clinical Classification Version 2, May 2006.

Covariates were selected for inclusion in the analysis based on clinical importance and included respiratory diagnosis (COPD/no asthma, COPD and asthma, other (i.e. asthma or COPD not recorded)), age, sex, calendar year of drug start, smoking, body mass index (BMI), number of hospitalizations in the year prior to cohort entry, number of general practitioner visits in the year prior to cohort entry, cardiac co-morbidities (ischemic heart disease, arrhythmias, hypertension), respiratory medications (number of prescriptions for short-acting anticholinergics, short-acting beta-agonists, inhaled corticosteroids, oral corticosteroids, and use of theophyllines and cromoglycates), cardiac medications (prescriptions for anti-arrhythmics, anticoagulants, anti-hypertensives, angiotensin converting enzyme (ACE) inhibitors, diuretics, inotropics, lipid regulators, beta-blockers, nitrates), other medications (gastrointestinal, vascular, central nervous system, infectious disease, endocrine, gynecologic/urinary tract, malignancy, nutrition/blood disorders), oxygen use, lung cancer diagnosis prior to index, and history of diabetes.

People were classified as exposed to study medication for the duration of prescribed therapy plus 30 days. For analysis of each endpoint, patients were followed from the date of their first eligible prescription until the earliest of the following: date of treatment end, date of study endpoint, date of transfer to a new practice, death, or January 2007. Each endpoint was analyzed separately, so patients who experienced more than one endpoint under study were included in analyses of each event.

Incidence rates of the study endpoints were calculated as the number of patients experiencing an event divided by the person-years at risk. Incidence rate ratios were calculated as the incidence rate in the tiotropium group divided by the incidence rate in the LABA group. Precision of effect estimates was evaluated from the width of the 95% confidence intervals (CI).[11]

Some endpoints were rare relative to the number of factors that needed to be controlled, so propensity scores (derived from logistic regression models) were used to enhance efficiency of analytic control of confounding.[12] The propensity score is the estimated chance of a patient receiving tiotropium compared with LABA, given a patient's observed set of covariates (prognostic variables). In constructing the logistic models used to calculate the propensity scores, all available variables described above were entered into the model.

Multivariate analysis was performed using Cox' proportional hazard model with adjustment for indicators of propensity score quintile to estimate adjusted hazard ratios (HR) and corresponding 95% confidence intervals (CI).[13] The assumption of proportionality of the hazards was tested by including time-dependent covariates in the Cox model.[13] We also computed effect estimates using Poisson regression. Effect estimates are presented for endpoints where the event was detected in at least 5 patients in each treatment group.

Analyses were stratified by respiratory diagnostic status (COPD and asthma, and COPD without asthma) and history of coronary artery disease. To identify a study population of more compliant, long-term users, we also restricted analyses to patients on treatment for greater than six months.

All analyses were performed using STATA 7.0 and SAS 9.1. This study received ethical approval from the UK Department of Health Multicentre Research Ethics Committee.

RESULTS

The study population included 4,767 tiotropium patients and 6,073 LABA patients who contributed 2,775 person-years of exposure to tiotropium and 2,303 person-years of exposure to a single-ingredient LABA (Table 1). Mean duration of exposure was 212 days for tiotropium patients and 139

days for LABA patients. Ninety-five percent of LABA prescriptions were for salmeterol. Though a similar proportion of tiotropium and LABA patients switched or added a different long-acting bronchodilator thereby terminating study participation, a lower proportion of tiotropium patients than LABA patients discontinued use of a long-acting bronchodilator prior to the administrative end of the study (58% compared with 73%). The proportion of current smokers was slightly higher in tiotropium users than in LABA users (37% compared with 30%). Other covariates were generally balanced between treatment groups.

Characteristics of medical history prior to study entry are shown in Table 2. A high proportion of patients in both groups had spirometry testing (89% of tiotropium patients and 84% of LABA patients) and a diagnosis of COPD (89% of tiotropium patients and 88% of LABA patients. More LABA patients than tiotropium patients also had an asthma co-diagnosis (42% vs. 63%).

Results from Cox models and Poisson models were similar, so estimates from Cox models are presented (Table 3). There was a lower rate of death due to all causes in patients using tiotropium (HR=0.70, 95% CI=0.56, 0.89). There were small increases in the tiotropium group in the rates of angina (HR=1.38, 95% CI=0.88, 2.16), myocardial infarction (HR=1.26, 95% CI=0.72, 2.21) and stroke (HR=1.49, 95% CI=0.91, 2.45). There were similar rates between treatment groups of aneurysm (HR=0.96, 95% CI=0.44, 2.05), atrial fibrillation or flutter (HR=0.99, 95% CI=0.71, 1.38), coronary artery disease (HR=1.11, 95% CI=0.84, 1.47), hypertension (HR=1.03, 95% CI=0.81, 1.29), syncope (HR=0.94, 95% CI=0.57, 1.55) and tachycardia (HR=1.08, 95% CI=0.48, 2.41). There was a decrease in the tiotropium group in the rate of heart failure (HR=0.85, 95% CI=0.63, 1.14).

With regard to respiratory events, there was a lower rate of asthma exacerbation in patients using tiotropium compared with patients using a LABA (HR=0.46, 95% CI=0.36, 0.57). There were similar rates of COPD exacerbations (HR=0.95, 95% CI=0.80, 1.12) and pneumonia (HR=0.96, 95% CI=0.58, 1.58).

Dry mouth was recorded at a higher rate in patients using tiotropium compared with patients using a LABA (HR=3.66, 95% CI=1.52, 8.78). The rate of constipation (HR=0.95, 95% CI=0.74, 1.23), dysphagia (HR=1.02, 95% CI=0.62, 1.69), and urinary retention (HR=0.97, 95% CI=0.55, 1.70) were similar in both treatment groups. There was a higher rate of renal failure in tiotropium patients (HR=1.40, 95% CI=0.77, 2.55), and a lower rate of tremor (HR=0.62, 95% CI=0.31, 1.22).

Among patients who had been receiving long acting bronchodilator therapy for at least 6 months, the difference between groups in rates of total mortality diminished (HR=0.90, 95% CI=0.58, 1.38). For cardiovascular endpoints, effect estimates increased for stroke (HR=1.63, 95% CI=0.83, 3.17), angina (HR=1.42, 95% CI=0.78, 2.59), and MI (HR=1.65, 95% CI=0.63, 4.27). Associations for other cardiovascular events were weaker, including aneurysm (HR=0.82, 95% CI=0.27, 2.45), atrial fibrillation/flutter (HR=1.17, 95% CI=0.70, 1.94), heart failure (HR=0.77, 95% CI=0.47, 1.24), hypertension (HR=1.07, 95% CI=0.79, 1.45), syncope (HR=0.79, 95% CI=0.36, 1.70), and tachycardia (HR=0.98, 95% CI=0.32, 3.04).

Effect estimates for respiratory endpoints among patients treated for at least 6 months were similar to those in the total population (asthma exacerbation (HR=0.47, 95% CI=0.33, 0.65); COPD exacerbation (HR=0.82, 95% CI=0.63, 1.05); and pneumonia (HR=1.42, 95% CI=0.68, 2.96)). Effect estimates computed for other events included constipation (HR=0.97, 95% CI=0.69, 1.37), dysphagia

(HR=1.30, 95% CI=0.65, 2.58), renal failure (HR=1.17, 95% CI=0.51, 2.66), urinary retention (HR=1.17, 95% CI=0.51, 2.66), and tremor (HR=0.57, 95% CI=0.23, 1.41).

DISCUSSION

This study found a decreased risk of mortality with tiotropium, along with imprecise increased risks of stroke, myocardial infarction and angina. Individual studies are often too small to identify with certainty associations between specific medications and rare adverse events, and elevated risks of stroke, angina, and myocardial infarction observed with tiotropium in this study should be considered in context with other evidence.

In 2002, the Lung Health Study, the first large placebo-controlled randomized trial of an inhaled anticholinergic agent, reported an increased incidence in the ipratropium group of hospitalization due to SVT, angina, myocardial infarction, and death due to coronary heart disease.[14] Observational studies also reported associations between ipratropium and stroke,[15] cardiovascular hospitalization,[16] and death.[17]

Tiotropium has a similar mechanism of action as ipratropium, and in 2008, the FDA issued an early communication after a pooled analysis of placebo-controlled clinical trials revealed an excess risk of stroke with tiotropium.[18] Subsequently, the Uplift trial reported a decreased risk of total mortality, and no increased risk of stroke with tiotropium.[19] The stroke endpoint included all types of strokes,[19] however, and the incidence of ischemic events (TIA, cerebral ischemia, ischemic stroke) in the Uplift study was greater in the tiotropium group than the placebo group.[20] In addition, the Uplift study reported an increased risk with tiotropium of certain tachyarrhythmias[21] and serious angina.[19]

Perhaps the most relevant study is the recent "POET" study, the largest tiotropium randomized trial conducted to date with 7376 COPD patients.[22] The POET study compared tiotropium with salmeterol, similar to the observational study reported here. Like this study, the POET study also found fewer deaths for tiotropium (n=64) compared with salmeterol (n=78), although there was no decrease in cardiac deaths (8 tioptropium vs. 6 salmeterol)[22] [Supplementary Appendix]. The POET study reported no increased risk of stroke, but found an increased risk with tiotropium of serious adverse events reported as angina (9 tiotropium vs. 5 salmeterol), myocardial ischemia (11 tiotropium v. 6 salmeterol), and myocardial infarction (20 tiotropium v. 13 salmeterol).[22 23] A pooled analysis of randomized trials reported an increased rate of arrhythmias with tiotropium compared with placebo or LABAs, and increased risks with tiotropium of both cardiovascular and cerebrovascular serious adverse events (RR=1.71, 95% CI 0.76, 3.89).[24] Finally, a randomized trial comparing tiotropium with salmeterol in combination with fluticasone reported increased cardiac adverse events with tiotropium.[25]

Thus, the increased risks of angina, MI and stroke and the decreased mortality risk observed in this study have also been reported in randomized clinical trials, and suggest that tiotropium may be associated with an increased risk of serious cardiovascular events, possibly secondary to tachyarrhythmias. The risk of serious angina with tiotropium is a consistent finding across multiple trials and is a concern because (1) angina itself is a serious clinical event and (2) angina is not included as a side effect of tiotropium in the summary of product characteristics.[1] Further, an ischemic mechanism that causes angina might also be related to other serious ischemic events such as myocardial infarction, TIA, and ischemic stroke.

Recently, safety concerns have been raised with the mist inhaler formulation of tiotropium (Respimat®), which is available in several countries but which was not approved for marketing in the US.[26] In evaluating the safety concerns with the tiotropium mist inhaler, it was hypothesized that the increased risk of deaths, mostly cardiac-related, seen with the mist formulation may derive from the device delivering a greater dose than the powder formulation.[27] Cardiovascular events reported inconsistently with the powder formulation, usually in the absence of increased deaths, are consistent with this hypothesis, and may indicate more subtle responses of patients susceptible to lower doses of tiotropium delivered in the Handihaler formulation.

In interpreting these results, one needs to consider the possible impact of both random error and systematic error. The results reported here and in other comparative tiotropium studies for angina, myocardial infarction and stroke are not statistically significant. The absence of statistical significance in studies that lack the power to detect small effects, however, should be expected and does not indicate the absence of an effect.[28 29] To the contrary, repeated findings of increased risks of similar magnitudes in several studies of different design and locations make chance an unlikely explanation.

Nonrandomized studies must always be concerned with possible bias arising from differences in baseline risks between treatment groups. We used propensity scores and multivariate models to control efficiently for available risk factors. Nevertheless, certain variables, such as lung function results, were unavailable and could not be controlled. We found more LABA patients than tiotropium patients had an asthma diagnosis in addition to COPD. The decreased risk of asthma exacerbations in the tiotropium group is consistent with a greater proportion of patients in the LABA group having an asthma component to their COPD. Nevertheless, COPD diagnoses and

exacerbations were similar between groups. It is possible that tiotropium patients had more severe COPD than LABA patients despite our efforts to control for baseline risk factors. The decreased mortality in the tiotropium group, however, makes it unlikely that tiotropium patients had more severe COPD than LABA patients. It seems more likely that whatever mechanism caused increased cardiovascular events in randomized trials also might have produced similar effects in the population studied here.

Anticholinergic medications are known to cause tachyarrhythmias,[3] and tiotropium has been consistently associated in clinical trials with tachyarrhythmias and angina. Tachycardia was only slightly more common in tiotropium users in this study, but LABAs are also associated with tachycardia, which may be asymptomatic and underreported.

Among non-cardiovascular and non-respiratory endpoints, results showed an increased risk of dry mouth with tiotropium, but not for other anticholinergic endpoints including constipation and urinary retention. The incidence of dry mouth was low, however, and it is likely that only a small proportion of these cases are reported to GPs and recorded in the database. Under-reporting of non-serious AEs could introduce misclassification that would dilute RR estimates for events such as dry mouth and constipation.[11] Misclassification could have occurred for more serious endpoints as well, although we would expect that completeness of the medical record d would be better for more serious cardiovascular events. Misclassification of serious endpoints still is a concern, however, as we examined total mortality and total strokes, but not cardiovascular mortality or ischemic strokes.

Additional research should examine more specifically the ischemic effects of tiotropium, and explore subgroups to identify patients who may be particularly susceptible to ischemic events.

REFERENCES

1. Boehringer Ingelheim International GmbH. Summary of Product Characteristics. Spiriva 18 microgram Inhalation Powder, hard capsule 2010.
2. Boehringer Ingelheim International GmbH. Summary of Product Characteristics, Atrovent Inhaler CFC-free 2011.
3. Mintzer J, Burns A. Anticholinergic side effects of drugs in elderly people. *J R Soc Med* 2000;93:457-62.
4. Parlow JL, van Vlyman JM, Odell MJ. The duration of impairment of autonomic control after anticholinergic drug administration in humans. *Anesth Analg* 1997;84:155-59.
5. Mathew J, Hunsberger S, Fleg J, et al. Incidence, prognostic factors, and prognostic significance of supraventricular tachyarrhythmias in congestive heart failure. *Chest* 2000;118:914-22.
6. Glotzer TV, Hellkamp AS, Zimmerman J, et al. Atrial high rate episodes detected by pacemaker diagnostics predict death and stroke. *Circulation* 2003;107:1614-19.
7. 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.
8. Bourke A, Dattani H, Robinson M. Feasibility study and methodology to create a quality-evaluated database of primary care data. *Inform Prim Care* 2004;12:171-77.
9. Feary JR, Rodrigues LC, Smith CJ, et al. Prevalence of major comorbidities in subjects with COPD and incidence of myocardial infarction and stroke: a comprehensive analysis using data from primary care *Thorax* 2010;65:956-62.
10. Lewis JD, Schinnar R, Bilker WB, et al. Validation studies of The Health Improvement Network (THIN) database for Pharmacoepidemiology research *Pharmacoepidemiol Drug Saf* 2007;16:393-401.
11. Rothman KJ, Greenland S. *Modern Epidemiology*. 2nd ed. Philadelphia: Lippincott–Raven Publishers, 1998.
12. Rosenbaum PR, Rubin DP. Reducing bias in observational studies using subclassification on the propensity score. *J Am Stat Assoc* 1984;79:516-24.
13. Rubin DB. On principles for modeling propensity scores in medical research. . *Pharmacoepidemiol Drug Saf* 2005;13:855-57.
14. Anthonisen NR, Connett JE, Enright PL, et al. Hospitalizations and mortality in the Lung Health Study *Am J Resp Crit Care Med* 2002;166:333-39.
15. Macie C, Wooldrage K, Manfreda J, et al. Cardiovascular morbidity and the use of inhaled bronchodilators. *J Chron Obstruct Pulmon Dis* 2008;3:163-69.

16. Ogale SS, Lee TA, Au DH, et al. Cardiovascular events associated with ipratropium bromide in COPD. *Chest* 2010;137:13-19.

17. Lee TA, Pickard AS, Au DH, et al. Risk for death associated with medications for recently diagnosed chronic obstructive pulmonary disease. *Ann Intern Med* 2008;149:380-90.

18. Food and Drug Administration. Early communication about an ongoing safety review of tiotropium (marketed as Spiriva HandiHaler). March 18, 2008 ed: FDA, 2008.

19. Tashkin DP, Celli B, Senn S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008;359:1534-54.

20. Boehringer Ingelheim International GmbH. Briefing document: Tiotropium (SPIRIVA®): Pulmonary Allergy Drug Advisory Meeting – November 2009. *Briefing Information for the November 19, 2009 Meeting of the Pulmonary-Allergy Drugs Advisory Committee*, 2009:115.

21. Food and Drug Administration Pulmonary-Allergy Drugs Advisory Committee Meeting. November 19. FDA Briefing Material. *Briefing Information for the November 19, 2009 Meeting of the Pulmonary-Allergy Drugs Advisory Committee*: FDA, 2009:115.

22. Vogelmeier C, Hederer B, Glabb T, et al. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. *N Engl J Med* 2011;364:1093-11-3.

23. National Institutes of Health. Effect of Inhalation of Tiotropium Once Daily 18 Mcg Versus Salmeterol Twice Daily 50 Mcg on Time to First Exacerbation in COPD Patients (a Randomised, Double-blind, Double-dummy, Parallel Group, One-year Study). March 29, 2011 ed: ClinicalTrials.gov, 2011.

24. Worth H, Chung KF, Felser JM, et al. Cardio- and cerebrovascular safety of indacaterol vs formoterol, salmeterol, tiotropium and placebo in COPD. *Resp Med* 2010;105:571-79.

25. Wedzicha JA, Calverly PMA, Seemungal TA, et al. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. *Am J Respir Crit Care Med* 2008;177:19-26.

26. Singh S, Loke YK, Enright PL, et al. Mortality associated with tiotropium mist inhaler in patients with chronic obstructive pulmonary disease: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2011;342.

27. Cates CJ. Safety of tiotropium. *BMJ* 2011;342.

28. Altman DG, Bland JM. Absence of evidence is not evidence of absence. *BMJ* 1995;311:485.

29. Rothman KJ. Significance questing. *Ann Int Med* 1986;105:445-47.

Table 1. Exposure distribution and demographic characteristics of the study population

	Tiotropium		LABA[1]	
	N	%	N	%
Age Group				
40-49	149	3	362	6
50-59	641	13	943	16
60-69	1,391	29	1,730	28
70-79	1,759	37	1,991	33
80-89	769	16	976	16
90+	58	1	71	1
Sex				
Male	2,707	57	3,073	51
Female	2,060	43	3,000	49
Body mass index				
Low	634	13	613	10
Normal	1,500	31	1,799	30
Overweight	1,413	30	1,895	31
Obese	1,012	21	1,467	24
Missing	208	4	299	5
Smoking				
Never	562	12	1,077	18
Current	1,765	37	1,812	30
Former	2,343	49	2,960	49
Missing	97	2	224	4

[1] Long-acting β-agonist single-ingredient formulations

Table 2. Medical history of the study population by long-acting bronchodilator

	Total Study Population n=10,840			
	Tiotropium		LABA[1]	
	N	%	N	%
Prior Respiratory Diagnosis				
COPD and asthma	1,807	38	3,366	55
COPD Only	2,450	51	1,960	32
Other	510	11	747	12
Use of Respiratory Medications[2]				
Short-acting anticholinergics	1,948	41	2,372	39
Short-acting Beta-agonists	3,372	71	5,053	83
Inhaled Corticosteroids	1,904	40	3,610	59
Oral Corticosteroids	1,396	29	2,227	37
Theophyllines	238	5	361	6
Cromoglycates	48	1	67	1
Use of Oxygen	187	4	175	3
Use of Cardiac Medications[2]				
Anti-arrhythmics	219	5	312	5
Anti-coagulants	1834	38	2,069	34
Anti-hypertensives	2424	51	2,913	48
ACE inhibitors	1162	24	1,380	23
Diuretics	1912	40	2,336	38
Inotropics	254	5	286	5
Lipid regulators	1413	30	1,509	25
Beta-blockers	613	13	537	9
Nitrates	704	15	843	14
History of Ischemic Heart Disease	233	5	319	5
History of Arrhythmia	139	3	165	3
History of Hypertension	1,785	37	2,202	36
History of Diabetes	456	10	591	10
Use of Spirometry (at least once)	4,225	89	5,093	84
Number of General Practitioner Visits[2]				
0	357	6	288	7
1-5	2,167	45	2,577	42
6-10	1,415	30	1,902	31

	Total Study Population n=10,840			
	Tiotropium		LABA[1]	
	N	%	N	%
11+	897	19	1,237	20
Number of Hospital Admissions[2]				
0	4143	87	5,097	84
1─2	502	11	791	13
3+	122	3	185	3

Abbreviations: N, number; LABA, long-acting beta-agonists, ─, not applicable
[1] Single-ingredient formulations; [2] 365 days prior to index date

Table 3. Incidence rates and adjusted rate ratio estimates in new users of long-acting bronchodilators

Adverse Events	Tiotropium N = 4,767			LABA[1] N = 6,073			Crude	Adjusted		
	N	Pyrs	Rate[2]	N	Pyrs	Rate	RR	HR	95% CI	
Death (any)	152	2,775	5.48	170	2,303	7.38	0.74	**0.70**	0.56	0.89
Cardiovascular										
Aneurysm	17	2,765	0.61	13	2,298	0.57	1.09	**0.96**	0.44	2.05
Atrial fibrillation/flutter	87	2,725	3.19	76	2,272	3.34	0.95	**0.99**	0.71	1.38
Cardiac arrest	3	2,774	0.11	4	2,303	0.17	0.65	—	—	—
Coronary artery disease	125	2,712	4.61	102	2,255	4.52	1.02	**1.11**	0.84	1.47
Angina	53	2,746	1.93	38	2,275	1.67	1.16	**1.38**	0.88	2.16
Myocardial infarction	35	2,765	1.27	23	2,297	1.00	1.26	**1.26**	0.72	2.21
Heart failure	93	2,738	3.40	105	2,265	4.64	0.73	**0.85**	0.63	1.14
Hypertension	169	2,654	6.37	163	2,232	7.30	0.87	**1.03**	0.81	1.29
Stroke	45	2,750	1.64	28	2,296	1.22	1.34	**1.49**	0.91	2.45
Syncope	35	2,762	1.27	35	2,289	1.53	0.83	**0.94**	0.57	1.55
Tachycardia	15	2,769	0.54	11	2,296	0.48	1.13	**1.08**	0.48	2.41
Ventricular tachycardia	2	2,774	0.07	1	2,302	0.04	1.66	—	—	—
Respiratory										
Asthma exacerbation	98	2,716	3.61	395	2,140	18.46	0.20	**0.46**	0.36	0.57
COPD exacerbation	287	2,637	10.88	313	2,168	14.44	0.75	**0.95**	0.80	1.12
Pneumonia	35	2,757	1.27	34	2,297	1.48	0.86	**0.96**	0.58	1.58
Other										
Constipation	137	2,708	5.06	124	2,251	5.51	0.92	**0.95**	0.74	1.23
Dry mouth	26	2,762	0.94	7	2,299	0.30	3.09	**3.66**	1.52	8.78
Dysphagia	39	2,757	1.41	32	2,292	1.40	1.01	**1.02**	0.62	1.69
Paralytic ileus/bowel obstruction	4	2,775	0.14	7	2,301	0.30	0.47	—	—	—
Renal failure	34	2,760	1.23	19	2,295	0.83	1.49	**1.40**	0.77	2.55
Urinary retention	29	2,765	1.05	25	2,290	1.09	0.96	**0.97**	0.55	1.70
Tremor	16	2,769	0.58	23	2,292	1.00	0.58	**0.62**	0.31	1.22

Abbreviations: LABA, long-acting β-agonists; N, number of patients; Pyrs, person-years at risk; RR, rate ratio; HR, relative hazard estimated using Cox' proportional hazards model adjusted for propensity score; CI, confidence interval.

[1] Single-ingredient formulations; [2] Rate per 100 person-years

'—' signifies the adjusted results are not presented as there are < 5 events in either tiotropium or LABA users.

A New User Cohort Study Comparing the Safety of Long-Acting Inhaled Bronchodilators in COPD

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2012-000841.R1
Article Type:	Research
Date Submitted by the Author:	15-Apr-2012
Complete List of Authors:	Jara, Michele; Acorda Therapeutics, Wentworth, Charles; United BioSource Corp, Epidemiology and Datbase Analytics Lanes, Stephan; UnitedBiosource Corporation,
Primary Subject Heading:	Pharmacology and therapeutics
Secondary Subject Heading:	Respiratory medicine, Epidemiology
Keywords:	Chronic airways disease < THORACIC MEDICINE, Adverse events < THERAPEUTICS, Stroke < NEUROLOGY, Ischaemic heart disease < CARDIOLOGY

A New User Cohort Study Comparing the Safety of Long-Acting Inhaled Bronchodilators in COPD

Michele Jara, Charles Wentworth III, Stephan Lanes

Address correspondence to:

Michele Jara, Epidemiology Consulting, LLC, 5 Fox Den Road, Danbury, CT 06811 email: mjara@acorda.com

Disclosures: Dr. Jara is employed by Acorda Therapeutics. Dr. Lanes and Mr. Wentworth are employed by United BioSource Corporation, Lexington, MA. The study was funded by Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT. Two of the authors (MJ, SL) were employees of Boehringer Ingelheim at the time the study was conducted. CW served as a consultant. Boehringer Ingelheim granted the authors permission to publish this study. The authors are solely responsible for the design, analysis, interpretation, and conclusions of the study.

Contributions: Drs. Lanes and Jara were responsible for the study conception and design. Mr. Wentworth and Dr. Jara were responsible for data analysis. All authors were responsible for data interpretation. Drs. Jara and Lanes drafted the manuscript. All authors reviewed and revised the manuscript and approved the final version.

Subject Headings: cohort study, COPD, product safety, tiotropium, salmeterol, cardiovascular, stroke

Word count: Abstract: 215; Text: 3400

SUMMARY

Article focus

- This study investigated whether there are possible increased risks of stroke and other adverse events, including angina and myocardial infarction, with tiotropium use in COPD
- The authors compared new users of long-acting anticholinergic therapy (tiotropium HandiHaler®) with new users of long-acting beta agonist (LABA) monotherapy

Key messages

- Compared with LABA, tiotropium HandiHaler was associated with increased risks of angina, myocardial infarction and stroke, and lower risk of total mortality
- The results of this study are similar to results from a recent clinical trial comparing tiotropium with salmeterol, and support the hypothesis that tiotropium HandiHaler can be associated with an increased risk of ischemic cardiovascular events

Strengths and Limitations

- Strengths of this study are the new user design and use of propensity scores to control for available risk factors, including demographic factors, history of respirator, cardiovascular, and other illness, and respiratory, cardiovascular, and other medications.
- Limitations of this study are that routine lung function measures were unavailable, and composite endpoints of all cause mortality and all strokes may attenuate associations for cardiovascular mortality and ischemic stroke.

ABSTRACT

Objective: To investigate a possible increased risk observed in tiotropium clinical trials of stroke and other adverse events.

Design: New users of long-acting anticholinergic therapy (tiotropium HandiHaler®) were compared with new users of long-acting beta agonist (LABA) monotherapy and propensity scores were used to control confounding.

Setting: United Kingdom healthcare system general practitioner electronic medical record database.

Participants: 10,840 patients newly prescribed tiotropium (n=4,767) or LABA (n=6,073), at least 40 years old, and not having asthma as their only respiratory illness.

Primary and secondary outcome measures: Incidence rates of total stroke, myocardial infarction, angina and other adverse events.

Results: Tiotropium was associated with increased rates of stroke (HR=1.49, 95% CI=0.91, 2.45), angina (HR=1.38, 95% CI=0.88, 2.16), and myocardial infarction (HR=1.26, 95% CI=0.72, 2.21). Groups had similar rates of COPD exacerbation (HR=0.95, 95%CI=0.80, 1.12) and pneumonia (HR=0.96, 95%CI=0.58, 1.58). Tiotropium was associated with a lower rate of total mortality (HR=0.70, 95% CI= 0.56, 0.89) and asthma exacerbations (HR=0.46, 95%CI=0.36, 0.57) than users of LABA.

Conclusion: Small increased risks of serious ischemic cardiovascular events have been reported with inhaled anticholinergic medication from randomized and nonrandomized studies of

ipratropium, tiotropium HandiHaler®, and tiotropium Respimat®. Additional research is needed to understand the full extent of cardiovascular effects of inhaled anticholinergic medications and the patients who may be most susceptible.

INTRODUCTION

Inhaled anticholinergic medications, including short-acting ipratropium bromide (ipratropium), and long-acting tiotropium bromide (tiotropium), are mainstays for the treatment of symptoms of COPD. The safety profiles of these drugs comprise systemic anticholinergic events, including dry mouth, constipation, urinary retention and cardiac effects, including palpitations, tachycardia, and supraventricular tachycardia (SVT).[1-5] There has been concern that anticholinergic drugs could induce ischemia, possibly secondary to tachyarrhythmias,[4 5] and could pose a risk to patients with cardiovascular complications.[6] Among patients with congestive heart failure (CHF), SVT is a risk factor for stroke, as well as cardiovascular hospitalization and death.[7] Further, among patients with sinus node dysfunction, asymptomatic atrial tachyarrhythmias increase the risk of stroke and death.[8]

We conducted this epidemiologic study to examine the possible association between tiotropium (HandiHaler® powder formulation) and risk of stroke and other cardiovascular adverse events, including angina and myocardial infarction.

METHODS

Treatment guidelines for COPD consider long-acting bronchodilators as a class, and make no distinction between anticholinergic drugs and LABAs, resulting in clinical equipoise.[9] Therefore, new users of tiotropium were compared with new users of LABAs.[10 11] Both long-acting bronchodilators are indicated for treating symptoms of COPD; LABAs are also indicated for the treatment of asthma.

The source population included patients in the UK enrolled with a general practitioner who contributes to The Health Improvement Network (THIN) primary care database. The THIN database

includes de-identified patient records containing demographic data, medical history, prescribed medications, diagnostic tests, laboratory results, specialist referrals, and some lifestyle characteristics.[12] The database is derived from the same software as the General Practice Research Database (GPRD) and has been validated for COPD, as well as stroke and myocardial infarction, and is widely used in epidemiologic research.[12-14]

Patients had to have at least one prescription for tiotropium (HandiHaler formulation) or LABA (salmeterol or formoterol), from November 2002 (the earliest use of tiotropium) until January 2007. Because tiotropium is available only in a single-ingredient preparation, whereas LABAs are also available in combination with inhaled corticosteroids, the LABA group was restricted to patients prescribed single-ingredient LABAs. Patients had to have at least two years of baseline data with no use of a long-acting inhaler prior to their first or "index" prescription for tiotropium or LABA. To reduce confounding by indication, patients who had a recorded diagnosis of asthma as their only respiratory diagnosis were excluded, as were patients less than 40 years old.

Study endpoints included various cardiovascular adverse events (aneurysm, atrial fibrillation, cardiac arrest, coronary artery disease, angina, myocardial infarction, heart failure, hypertension, stroke, syncope, tachycardia, and ventricular tachycardia); respiratory adverse events (COPD exacerbation, asthma exacerbation, and pneumonia); and other adverse events of interest (constipation, dry mouth, dysphagia, paralytic ileus/bowel obstruction, renal failure, tremor, urinary retention). Information on causes of death was unavailable, but we were able to examine all-cause mortality. Most endpoints were defined using medical codes from the Read Clinical Classification Version 2, May 2006. Mortality was identified from a combination of READ codes, registration status, additional health data (AHD) codes and enrollment dates.

Covariates were selected for inclusion in the analysis based on clinical importance and included respiratory diagnosis (COPD/no asthma, COPD and asthma, other (i.e. asthma or COPD not recorded)), age, sex, calendar year of drug start, smoking, body mass index (BMI), number of hospitalizations in the year prior to cohort entry, number of general practitioner visits in the year prior to cohort entry, cardiac co-morbidities (ischemic heart disease, arrhythmias, hypertension), respiratory medications (number of prescriptions for short-acting anticholinergics, short-acting beta-agonists, inhaled corticosteroids, oral corticosteroids, and use of theophyllines and cromoglycates), cardiac medications (prescriptions for anti-arrhythmics, anticoagulants, anti-hypertensives, angiotensin converting enzyme (ACE) inhibitors, diuretics, inotropics, lipid regulators, beta-blockers, nitrates), other medications (gastrointestinal, vascular, central nervous system, infectious disease, endocrine, gynecologic/urinary tract, malignancy, nutrition/blood disorders), oxygen use, lung cancer diagnosis prior to index, and history of diabetes.

People were classified as exposed to study medication for the duration of prescribed therapy plus 30 days. For analysis of each endpoint, patients were followed from the date of their first eligible prescription until the earliest of the following: date of treatment end, date of study endpoint, date of transfer to a new practice, death, or January 2007. Each endpoint was analyzed separately, so patients who experienced more than one endpoint under study were included in analyses of each event.

Incidence rates of the study endpoints were calculated as the number of patients experiencing an event divided by the person-years at risk. Incidence rate ratios were calculated as the incidence rate in the tiotropium group divided by the incidence rate in the LABA group. Precision of effect estimates was evaluated from the width of the 95% confidence intervals (CI).[15]

Some endpoints were rare relative to the number of factors that needed to be controlled, so propensity scores (derived from logistic regression models) were used to enhance efficiency of analytic control of confounding.[16] The propensity score is the estimated chance of a patient receiving tiotropium compared with LABA, given a patient's observed set of covariates (prognostic variables). In constructing the logistic models used to calculate the propensity scores, all available variables described above were entered into the model.

Multivariate analysis was performed using Cox' proportional hazard model with adjustment for indicators of propensity score quintile to estimate adjusted hazard ratios (HR) and corresponding 95% confidence intervals (CI).[17] The assumption of proportionality of the hazards was tested by including time-dependent covariates in the Cox model.[17] We also computed effect estimates using Poisson regression. Effect estimates are presented for endpoints where the event was detected in at least 5 patients in each treatment group.

To identify a study population of more compliant, long-term users, we also conducted analyses restricted to patients on treatment for greater than six months. In addition, analyses were stratified by respiratory diagnostic status (COPD and asthma, COPD without asthma, other), use of oral corticosteroids, and history of coronary artery disease.

All analyses were performed using STATA 7.0 and SAS 9.1. This study received ethical approval from the UK Department of Health Multicentre Research Ethics Committee.

RESULTS

The study population included 4,767 tiotropium patients and 6,073 LABA patients who contributed 2,775 person-years of exposure to tiotropium and 2,303 person-years of exposure to a single-

ingredient LABA (Table 1). Mean duration of exposure was 212 days for tiotropium patients and 139 days for LABA patients. Ninety-five percent of LABA prescriptions were for salmeterol. Though a similar proportion of tiotropium and LABA patients switched or added a different long-acting bronchodilator thereby terminating study participation, a lower proportion of tiotropium patients than LABA patients discontinued use of a long-acting bronchodilator prior to the administrative end of the study (58% compared with 73%). The proportion of current smokers was slightly higher in tiotropium users than in LABA users (37% compared with 30%). Other covariates were generally balanced between treatment groups.

Characteristics of medical history prior to study entry are shown in Table 2. A high proportion of patients in both groups had spirometry testing (89% of tiotropium patients and 84% of LABA patients) and a diagnosis of COPD (89% of tiotropium patients and 88% of LABA patients). More LABA patients than tiotropium patients also had an asthma co-diagnosis (42% vs. 63%).

Results from Cox models and Poisson models were similar, so estimates from Cox models are presented (Table 3). There were small increases in the tiotropium group in the rates of angina (HR=1.38, 95% CI=0.88, 2.16), myocardial infarction (HR=1.26, 95% CI=0.72, 2.21) and stroke (HR=1.49, 95% CI=0.91, 2.45). There were similar rates between treatment groups of aneurysm (HR=0.96, 95% CI=0.44, 2.05), atrial fibrillation or flutter (HR=0.99, 95% CI=0.71, 1.38), coronary artery disease (HR=1.11, 95% CI=0.84, 1.47), hypertension (HR=1.03, 95% CI=0.81, 1.29), syncope (HR=0.94, 95% CI=0.57, 1.55) and tachycardia (HR=1.08, 95% CI=0.48, 2.41). There was a decrease in the tiotropium group in the rate of heart failure (HR=0.85, 95% CI=0.63, 1.14) and all cause mortality (HR=0.70, 95% CI=0.56, 0.89).

With regard to respiratory events, there was a lower rate of asthma exacerbation in patients using tiotropium compared with patients using a LABA (HR=0.46, 95% CI=0.36, 0.57). There were similar rates of COPD exacerbations (HR=0.95, 95% CI=0.80, 1.12) and pneumonia (HR=0.96, 95% CI=0.58, 1.58).

Dry mouth was recorded at a higher rate in patients using tiotropium compared with patients using a LABA (HR=3.66, 95% CI=1.52, 8.78). The rate of constipation (HR=0.95, 95% CI=0.74, 1.23), dysphagia (HR=1.02, 95% CI=0.62, 1.69), and urinary retention (HR=0.97, 95% CI=0.55, 1.70) were similar in both treatment groups. There was a higher rate of renal failure in tiotropium patients (HR=1.40, 95% CI=0.77, 2.55), and a lower rate of tremor (HR=0.62, 95% CI=0.31, 1.22).

Among patients who had been receiving long acting bronchodilator therapy for at least 6 months, effect estimates increased for stroke (HR=1.63, 95% CI=0.83, 3.17), angina (HR=1.42, 95% CI=0.78, 2.59), and MI (HR=1.65, 95% CI=0.63, 4.27). The difference between groups in rates of total mortality diminished (HR=0.90, 95% CI=0.58, 1.38). Associations for other cardiovascular events were weaker, including aneurysm (HR=0.82, 95% CI=0.27, 2.45), atrial fibrillation/flutter (HR=1.17, 95% CI=0.70, 1.94), heart failure (HR=0.77, 95% CI=0.47, 1.24), hypertension (HR=1.07, 95% CI=0.79, 1.45), syncope (HR=0.79, 95% CI=0.36, 1.70), and tachycardia (HR=0.98, 95% CI=0.32, 3.04).

Effect estimates for respiratory endpoints among patients treated for at least 6 months were similar to those in the total population (asthma exacerbation (HR=0.47, 95% CI=0.33, 0.65); COPD exacerbation (HR=0.82, 95% CI=0.63, 1.05); and pneumonia (HR=1.42, 95% CI=0.68, 2.96)). Effect estimates computed for other events included constipation (HR=0.97, 95% CI=0.69, 1.37), dysphagia

(HR=1.30, 95% CI=0.65, 2.58), renal failure (HR=1.17, 95% CI=0.51, 2.66), urinary retention (HR=1.17, 95% CI=0.51, 2.66), and tremor (HR=0.57, 95% CI=0.23, 1.41).

After stratifying by subgroups, results were imprecise and generally similar to the overall results. With regard to concomitant asthma diagnosis, the association with angina was stronger in patients with asthma and COPD (HR=1.91, 95% CI=1.00, 3.63) than patients with only COPD (HR=0.93, 95% CI=0.49, 1.77), while the association with myocardial infarction was stronger in patients who had only COPD (HR=1.94, 95% CI=0.77, 4.94). Asthma exacerbations occurred only among patients with a concomitant diagnosis of asthma. After stratification by coronary artery disease, the association with angina was stronger among patient without coronary artery disease (HR=3.02, 95% CI=1.08, 8.47) than among patients with coronary artery disease (HR=1.05, 95% CI=0.63, 1.77). After stratification by corticosteroids, the association with angina was greater among patients without corticosteroids (HR=2.28, 95% CI=0.99, 5.26) than with corticosteroids (HR=1.09, 95%CI=0.63, 1.89), while the association with stroke was greater for patients with corticosteroids (HR=1.85, 95% CI=1.00, 3.44) than without corticosteroids (HR=0.86, 95% CI=0.37, 2.01).

DISCUSSION

This study found small increased risks of stroke, myocardial infarction and angina along with a decreased risk of mortality with tiotropium. Individual studies are often too small to identify with certainty associations between specific medications and rare adverse events, and these findings should be considered in context with other evidence.

In 2002, the Lung Health Study, the first large placebo-controlled randomized trial of an inhaled anticholinergic agent, reported an increased incidence in the ipratropium group of hospitalization due to SVT, angina, myocardial infarction, and death due to coronary heart disease.[18] Observational studies have reported associations between ipratropium and stroke,[19] cardiovascular hospitalization,[20] and death.[21]

Tiotropium has a similar mechanism of action to ipratropium, and in 2008, the FDA issued an early communication after a pooled analysis of placebo-controlled clinical trials revealed an excess risk of stroke with tiotropium.[22] Subsequently, the Uplift trial reported a decreased risk of total mortality, myocardial infarction, and no increased risk of stroke with tiotropium.[23] As in other studies, the stroke endpoint was a composite endpoint that included ischemic and hemorrhagic stroke, [23] and the incidence of ischemic stroke in the Uplift study was slightly greater in the tiotropium group than the placebo group.[24 25] In addition, the Uplift study showed an increased risk with tiotropium of certain tachyarrhythmias[26] and serious angina.[23]

A pooled analysis of randomized trials reported an increased rate of arrhythmias with tiotropium compared with placebo or LABAs, and increased risks with tiotropium of both cardiovascular and cerebrovascular serious adverse events (RR=1.71, 95% CI 0.76, 3.89).[27] A randomized trial comparing tiotropium with salmeterol in combination with fluticasone reported increased cardiac adverse events with tiotropium.[28] An observational study reported increased risk of mortality with tiotropium compared with LABA.[29] Pooled analyses of placebo-controlled tiotropium clinical trials have reported small increased rates with tiotropium of palpitations, SVT, angina and stroke, and lower rates of myocardial infarction, cardiovascular mortality and total mortality.[30-32]

Perhaps the most relevant study is the recent "POET" study, the largest tiotropium randomized trial conducted to date, with 7,376 COPD patients.[33] The POET study is similar to this study in that it compared tiotropium HandiHaler with salmeterol. The POET study also found fewer deaths for tiotropium (n=64) compared with salmeterol (n=78), although there was no decrease in cardiac deaths (8 tioptropium vs. 6 salmeterol)[33] [Supplementary Appendix]. The POET study reported no increased risk of stroke, but found an increased risk with tiotropium of several serious cardiovascular adverse events including angina (9 tiotropium vs. 5 salmeterol), myocardial ischemia (11 tiotropium v. 6 salmeterol), and myocardial infarction (20 tiotropium v. 13 salmeterol).[33 34]

Recently, safety concerns have been raised about increased mortality with the mist inhaler formulation of tiotropium (Respimat®), which is available in several countries but which was not approved for marketing in the US.[35] (Tiotropium Respimat was not available in the UK at the time of this analysis.) It was hypothesized that the increased risk of deaths, which were mostly cardiac and sudden or unexplained deaths, may be the result of the device delivering a greater dose than the powder formulation.[36] Tiotropium Respimat is also associated with a dose-related increased risk of angina and cardiac ischemic events, but not myocardial infarction.[37 38]

The decreased risk of mortality observed in this study with tiotropium is in agreement with the results reported in the Uplift[23] and POET[33] studies, but not in the ipratropium Lung Health Study[18] or several large tiotropium trials using the Respimat device.[37 39] These drugs have virtually identical safety profiles,[2 3 40] so it would be an oversimplification to suggest that they have either beneficial or harmful effects on mortality based solely on the device delivering similar active ingredients. Heterogeneity of results should be considered in light ob both causal and noncausal explanations. For composite endpoints, interpretation often can be clarified by evaluating components, especially

cardiovascular deaths. Thus, the POET study reports fewer total deaths with tiotropium,[33] but more cardiac deaths.[34]

The results for angina, myocardial infarction and stroke reported here and in other studies of inhaled anticholinergic drugs are usually not statistically significant. The absence of statistical significance in studies that lack the power to detect small effects should be expected, and does not indicate the absence of an effect.[41 42] For instance, repeated findings of an increased risk of angina of a similar magnitude in studies of different design and locations make chance an unlikely explanation for this finding.

Nonrandomized studies must always be concerned with possible bias arising from differences in baseline risks between treatment groups. We used propensity scores and multivariate models to control efficiently for available risk factors. Nevertheless, certain variables, such as lung function results, were unavailable and could not be controlled. We found more LABA patients than tiotropium patients had an asthma diagnosis in addition to their COPD diagnosis. The decreased risk of asthma exacerbations in the tiotropium group is consistent with a greater proportion of patients in the LABA group having an asthma component to their COPD. Nevertheless, COPD diagnoses and exacerbations were similar between groups, suggesting similar severity of COPD. Nevertheless, it is possible that tiotropium patients had more severe COPD than LABA patients despite our efforts to control for baseline risk factors. More severe COPD might account for higher rates of cardiovascular events, although the decreased mortality in the tiotropium group is inconsistent with this hypothesis. Increased risks of ischemic cardiovascular events in randomized trials also argue against confounding as an explanation.

All tiotropium effect estimates in this study are relative to effects of LABA. A valid effect estimate indicating a higher rate with tiotropium means that tiotropium increases risk more than LABA, but both drugs could be either increasing or decreasing risk. To the extent that LABA may increase the risk of cardiovascular adverse events, such an effect would attenuate an increased risk that might also exist for tiotropium.

Among non-cardiovascular and non-respiratory endpoints, results showed an increased risk of dry mouth with tiotropium, but not for other anticholinergic endpoints including constipation and urinary retention. The incidence of these less serious events was low, however, and it is likely that only a small proportion of these cases are reported to GPs and recorded in the database. Under-reporting of non-serious AEs could introduce misclassification that would dilute RR estimates for events such as dry mouth and constipation.[15] Misclassification could have occurred for more serious endpoints as well, although we would expect that completeness of the medical record would be better for more serious cardiovascular events. Misclassification of certain serious endpoints still is a concern, however, as we examined total mortality and total strokes, but not cardiovascular mortality or ischemic strokes. Finally, tiotropium HandiHaler is available in one dose, and this study was unable to evaluate dose-response. However, among patients using therapy for at least 6 months, the associations with angina, myocardial infarction and stroke became stronger, while the association with mortality became weaker.

Results of this study should be interpreted cautiously, but they lend modest support to a considerable body of evidence of a serious cardiovascular safety risk with inhaled anticholinergic drugs. Nevertheless, with regard to safety of inhaled anticholinergic drugs, the FDA recently concluded that “data from Uplift adequately addressed the potential safety signal of stroke and

adverse cardiovascular outcomes." [43] A few points go a long way towards explaining these divergent conclusions. First, we consider the entire body of evidence, and we consider each study on its merits. In particular, studies should not be disregarded merely because they are not randomized[19-21 29] or they include another treatment as a control group instead of a placebo group.[28 33] Secondly, when considering the evidence pertaining to small effects on rare adverse events, we did not assume that results that are not statistically significant provide evidence against an increased risk.[41 42] This is especially important when increases in risk are small or studies were not large enough to detect such risks as statistically significant. It is important to consider the magnitude of effect estimates and the precision with which they are measured.[41 42] The Uplift study, for instance, describes higher rates of serious angina and ischemic stroke with tiotropium than placebo,[24] and so can hardly provide reassurance about the absence of such risks. In addition, results from composite endpoints do not necessarily apply to each of their components. Thus, decreased rates of total mortality and total stroke can mask increased rates of cardiovascular mortality[24] or ischemic stroke.[34] Finally, adverse effects do not occur in every patient and may not be apparent in every population or every study. Heterogeneity of results is not evidence against a causal effect, but is an interesting finding that should be interpreted in consideration of the impact of both noncausal as well as causal explanations; the latter include differences in populations, durations of follow-up, and doses. Thus, the absence of an increased risk of myocardial infarction in the Uplift study does not negate increases in risk of myocardial infarction in the Lung Health Study,[18] POET study,[34] or this study, especially when each of these studies indicates an increased risk of angina.

Inhaled anticholinergic drugs are effective treatments in COPD and treatment decisions must balance benefits with risks for individual patients. It has long been suggested that the elderly are especially susceptible to anticholinergic effects, and angina has been described previously as a severe anticholinergic effect secondary to tachyarrhythmias.[1 4 5] Subsequently, increased risks of tachyarrhythmias and angina have been reported in association with inhaled anticholinergic drugs in non-randomized and randomized studies, of various sizes and durations, with ipratropium and tiotropium, compared with placebo and active comparators, and using different devices. Pharmacologic and clinical evidence, therefore, supports these cardiovascular events as class effects of inhaled anticholinergic drugs. Small increased rates of stroke have been observed fairly consistently across studies, while myocardial infarction, and cardiovascular death, have been associated in different studies both positively and negatively with anticholinergic medication. Additional research is needed to understand the full extent of cardiovascular effects of inhaled anticholinergic medications and the patients who may be susceptible.

REFERENCES

1. Peters NL. Snipping the thread of life. Antimuscarinic side effects of medications in the elderly. *Arch Int Med* 1989;149:2414-20.
2. Boehringer Ingelheim International. Summary of Product Characteristics. Spiriva 18 microgram Inhalation Powder, hard capsule 2010.
3. Boehringer Ingelheim International. Summary of Product Characteristics. Atrovent Inhaler CFC-free 2011.
4. Mintzer J, Burns A. Anticholinergic side effects of drugs in elderly people. *J R Soc Med* 2000;93:457-62.
5. Feinberg M. The problems of anticholinergic adverse effects in older patients. *Drugs Aging* 1993;3(4):335-48.
6. Parlow JL, van Vlyman JM, Odell MJ. The duration of impairment of autonomic control after anticholinergic drug administration in humans. *Anesth Analg* 1997;84:155-59.
7. Mathew J, Hunsberger, S., Fleg, J., et al. Incidence, prognostic factors, and prognostic significance of supraventricular tachyarrhythmias in congestive heart failure. *Chest* 2000;118:914-22.
8. Glotzer TV, Hellkamp, A.S., Zimmerman, J., et al, the MOST Investigators. Atrial high rate episodes detected by pacemaker diagnostics predict death and stroke *Circulation* 2003;107:1614-19.
9. Pauwels R, Buist A, Calverley P, 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.
10. Ray WA. Evaluating medication effects outside of clinical trials: New- user designs. *Am J Epidemiol* 2003;158(9):915-20.
11. Schneeweiss S. A basic study design for expedited safety signal evaluation based on electronic healthcare data. *Pharmacoepidemiol Drug Safety* 2010;19:858-68.
12. Bourke A, Dattani H, Robinson M. Feasibility study and methodology to create a quality-evaluated database of primary care data. *Inform Prim Care* 2004;12:171-77.
13. Feary JR, Rodrigues, L.C., Smith, C.J., et al. Prevalence of major comorbidities in subjects with COPD and incidence of myocardial infarction and stroke: a comprehensive analysis using data from primary care *Thorax* 2010;65(11):956-62.
14. Lewis JD, Schinnar, R., Bilker, W.B., et al . Validation studies of The Health Improvement Network (THIN) database for Pharmacoepidemiology research. . *Pharmacoepidemiol Drug Saf* 2007;16:393-401.
15. Rothman KJ, Greenland S. *Modern Epidemiology*. 2nd ed. Philadelphia: Lippincott–Raven Publishers, 1998.

16. Rosenbaum PR, Rubin DP. Reducing bias in observational studies using subclassification on the propensity score. *J Am Stat Assoc* 1984;79(387):516-24.

17. Rubin DB. On principles for modeling propensity scores in medical research. . *Pharmacoepidemiol Drug Saf* 2005;13:855-57.

18. Anthonisen NR, Connett, J.E., Enright, P.L., et al, and the Lung Health Study Research Group. Hospitalizations and mortality in the Lung Health Study *Am J Resp Crit Care Med* 2002;166:333-39.

19. Macie C, Wooldrage K, Manfreda J, et al. Cardiovascular morbidity and the use of inhaled bronchodilators. *J Chron Obstruct Pulmon Dis* 2008;3(1):163-69.

20. Ogale S, Lee T, Au D, et al. Cardiovascular events associated with ipratropium bromide in COPD. *Chest* 2010;137(1):13-19.

21. Lee TA, Pickard, A.S., Au, et al. Risk for death associated with medications for recently diagnosed chronic obstructive pulmonary disease. *Ann Intern Med* 2008;149(6):380-90.

22. Food and Drug Administration. Early communication about an ongoing safety review of tiotropium (marketed as Spiriva HandiHaler). March 18, 2008 ed: FDA, 2008.

23. Tashkin DP, Celli B, Senn S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008;359:1534-54.

24. National Institutes of Health. Evaluation of the Long- Term Effects of Spiriva on Lung Function in COPD Patients. NCT00144339 *NCT00144339*: NIH, 2005.

25. Boehringer Ingelheim International. Briefing document: Tiotropium (SPIRIVA®): Pulmonary Allergy Drug Advisory Meeting – November 2009. *Briefing Information for the November 19, 2009 Meeting of the Pulmonary-Allergy Drugs Advisory Committee*, 2009:115.

26. Food and Drug Administration Pulmonary-Allergy Drugs Advisory Committee Meeting. November 19. FDA Briefing Material. *Briefing Information for the November 19, 2009 Meeting of the Pulmonary-Allergy Drugs Advisory Committee*: FDA, 2009:115.

27. Worth H, Chung KF, Felser JM, et al. Cardio-and cerebrovascular safety of indacaterol vs formoterol, salmeterol, tiotropium and placebo in COPD. *Resp Med* 2010;105(4):571-79.

28. Wedzicha JA, Calverly, P.M.A., Seemungal, T.A., et al, Inspire Investigators. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. *Am J Respir Crit Care Med* 2008;177:19-26.

29. Gershon A CR, To T, Stanbrook MB, et al. Comparison of inhaled long-acting beta-agonist and anticholinergic effectiveness in older patients with chronic obstructive pulmonary disease. *Ann Intern Med* 2011;154:583-92.

30. Celli B DM, Leimer I, Vogel U, et al. Cardiovascular safety of tiotropium in patients with COPD. *Chest* 2010;137(1):20-30.

31. Kesten S CB, Decramer M, Leimer I, et al. Tiotropium HandiHaler in the treatment of COPD: A safety review. *Int J COPD* 2009;4:397-409.

32. Kesten S JM, Wentworth C, Lanes S. Pooled clinical trial analysis of tiotropium safety. *Chest* 2006;130:1695-703.

33. Vogelmeier C, Hederer B, Glabb T, et al. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. *N Engl J Med* 2011;364:1093-11-3.

34. National Institutes of Health. Effect of Inhalation of Tiotropium Once Daily 18 Mcg Versus Salmeterol Twice Daily 50 Mcg on Time to First Exacerbation in COPD Patients (a Randomised, Double-blind, Double-dummy, Parallel Group, One-year Study). NCT00563381. *NCT00563381*. March 29, 2011 ed: ClinicalTrials.gov, 2011.

35. Singh S, Loke, Y.K., Enright, P.L., et al. Mortality associated with tiotropium mist inhaler in patients with chronic obstructive pulmonary disease: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2011;342(d3215).

36. Cates CJ. Safety of tiotropium. *BMJ* 2011;342(d2970).

37. Bateman E, Singh D, Smith D, et al. Efficacy and safety of tiotropium Respimat SMI in COPD in two 1-year randomized studies. *Int J COPD* 2010;5:197-208.

38. Boehringer Ingelheim International. A randomized double-blind, placebo-controlled, parallel-group study to assess long term (one-year) efficacy and safety of tiotropium inhalation solution 5 mcg (2 puffs of 2.5 mcg) delivered by the Respimat inhaler in patients with chronic obstructive pulmonary disease *Boehringer Ingelheim Trial Results*, 2009.

39. Bateman ED TD, Siafakas N, Dahl R, et al. A one-year trial of tiotropium Respimat plus usual therapy in COPD pateints. *Resp Med* 2010;104:1460-72.

40. Boehringer Ingelheim International. Summary of Product Characteristics, Spiriva Respimat 2.5 micrograms solution for inhalation, 2010.

41. Altman DG, Bland, J.M. Absence of evidence is not evidence of absence. *BMJ* 1995;311(1):485.

42. Rothman KJ. Significance questing. *Ann Int Med* 1986;105(3):445-47.

43. Food and Drug Administration Pulmonary-Allergy Drugs Advisory Committee Meeting. February 23. FDA Main Presentations for the February 23, 2012 Meeting of the Pulmonary-Allergy Drugs Advisory Committee., 2012:Slide 60/109.

Table 1. Exposure distribution and demographic characteristics of the study population

	Tiotropium		LABA[1]	
	N	%	N	%
Age Group				
40-49	149	3	362	6
50-59	641	13	943	16
60-69	1,391	29	1,730	28
70-79	1,759	37	1,991	33
80-89	769	16	976	16
90+	58	1	71	1
Sex				
Male	2,707	57	3,073	51
Female	2,060	43	3,000	49
Body mass index				
Low	634	13	613	10
Normal	1,500	31	1,799	30
Overweight	1,413	30	1,895	31
Obese	1,012	21	1,467	24
Missing	208	4	299	5
Smoking				
Never	562	12	1,077	18
Current	1,765	37	1,812	30
Former	2,343	49	2,960	49
Missing	97	2	224	4

[1] Long-acting β-agonist single-ingredient formulations

Table 2. Medical history of the study population by long-acting bronchodilator

	Total Study Population n=10,840			
	Tiotropium		LABA[1]	
	N	%	N	%
Prior Respiratory Diagnosis				
COPD and asthma	1,807	38	3,366	55
COPD Only	2,450	51	1,960	32
Other	510	11	747	12
Use of Respiratory Medications[2]				
Short-acting anticholinergics	1,948	41	2,372	39
Short-acting Beta-agonists	3,372	71	5,053	83
Inhaled Corticosteroids	1,904	40	3,610	59
Oral Corticosteroids	1,396	29	2,227	37
Theophyllines	238	5	361	6
Cromoglycates	48	1	67	1
Use of Oxygen	187	4	175	3
Use of Cardiac Medications[2]				
Anti-arrhythmics	219	5	312	5
Anti-coagulants	1834	38	2,069	34
Anti-hypertensives	2424	51	2,913	48
ACE inhibitors	1162	24	1,380	23
Diuretics	1912	40	2,336	38
Inotropics	254	5	286	5
Lipid regulators	1413	30	1,509	25
Beta-blockers	613	13	537	9
Nitrates	704	15	843	14
History of Ischemic Heart Disease	233	5	319	5
History of Arrhythmia	139	3	165	3
History of Hypertension	1,785	37	2,202	36
History of Diabetes	456	10	591	10
Use of Spirometry (at least once)	4,225	89	5,093	84
Number of General Practitioner Visits[2]				
0	357	6	288	7
1-5	2,167	45	2,577	42
6-10	1,415	30	1,902	31

	Total Study Population n=10,840			
	Tiotropium		LABA[1]	
	N	%	N	%
11+	897	19	1,237	20
Number of Hospital Admissions[2]				
0	4143	87	5,097	84
1─2	502	11	791	13
3+	122	3	185	3

Abbreviations: N, number; LABA, long-acting beta-agonists, ─, not applicable
[1] Single-ingredient formulations; [2] 365 days prior to index date

Table 3. Incidence rates and adjusted rate ratio estimates in new users of long-acting bronchodilators

Adverse Events	Tiotropium N = 4,767			LABA[1] N = 6,073			Crude	Adjusted		
	N	Pyrs	Rate[2]	N	Pyrs	Rate	RR	HR	95% CI	
Death (any)	152	2,775	5.48	170	2,303	7.38	0.74	**0.70**	0.56	0.89
Cardiovascular										
Aneurysm	17	2,765	0.61	13	2,298	0.57	1.09	**0.96**	0.44	2.05
Atrial fibrillation/flutter	87	2,725	3.19	76	2,272	3.34	0.95	**0.99**	0.71	1.38
Cardiac arrest	3	2,774	0.11	4	2,303	0.17	0.65	—	—	—
Coronary artery disease	125	2,712	4.61	102	2,255	4.52	1.02	**1.11**	0.84	1.47
Angina	53	2,746	1.93	38	2,275	1.67	1.16	**1.38**	0.88	2.16
Myocardial infarction	35	2,765	1.27	23	2,297	1.00	1.26	**1.26**	0.72	2.21
Heart failure	93	2,738	3.40	105	2,265	4.64	0.73	**0.85**	0.63	1.14
Hypertension	169	2,654	6.37	163	2,232	7.30	0.87	**1.03**	0.81	1.29
Stroke	45	2,750	1.64	28	2,296	1.22	1.34	**1.49**	0.91	2.45
Syncope	35	2,762	1.27	35	2,289	1.53	0.83	**0.94**	0.57	1.55
Tachycardia	15	2,769	0.54	11	2,296	0.48	1.13	**1.08**	0.48	2.41
Ventricular tachycardia	2	2,774	0.07	1	2,302	0.04	1.66	—	—	—
Respiratory										
Asthma exacerbation	98	2,716	3.61	395	2,140	18.46	0.20	**0.46**	0.36	0.57
COPD exacerbation	287	2,637	10.88	313	2,168	14.44	0.75	**0.95**	0.80	1.12
Pneumonia	35	2,757	1.27	34	2,297	1.48	0.86	**0.96**	0.58	1.58
Other										
Constipation	137	2,708	5.06	124	2,251	5.51	0.92	**0.95**	0.74	1.23
Dry mouth	26	2,762	0.94	7	2,299	0.30	3.09	**3.66**	1.52	8.78
Dysphagia	39	2,757	1.41	32	2,292	1.40	1.01	**1.02**	0.62	1.69
Paralytic ileus/bowel obstruction	4	2,775	0.14	7	2,301	0.30	0.47	—	—	—
Renal failure	34	2,760	1.23	19	2,295	0.83	1.49	**1.40**	0.77	2.55
Urinary retention	29	2,765	1.05	25	2,290	1.09	0.96	**0.97**	0.55	1.70
Tremor	16	2,769	0.58	23	2,292	1.00	0.58	**0.62**	0.31	1.22

Abbreviations: LABA, long-acting β-agonists; N, number of patients; Pyrs, person-years at risk; RR, rate ratio; HR, relative hazard estimated using Cox' proportional hazards model adjusted for propensity score; CI, confidence interval.

[1] Single-ingredient formulations; [2] Rate per 100 person-years

'—' signifies the adjusted results are not presented as there are < 5 events in either tiotropium or LABA users.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1 (Title page)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Pages 3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 5
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 5
Methods			
Study design	4	Present key elements of study design early in the paper	Page 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Pages 5-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Pages 5-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable (NA)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Pages 6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Pages 5,6 and 8
Bias	9	Describe any efforts to address potential sources of bias	Pages 5,6 and 8
Study size	10	Explain how the study size was arrived at	NA (all available patients included)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Pages 7-8
		(*b*) Describe any methods used to examine subgroups and interactions	Page 8
		(*c*) Explain how missing data were addressed	Pages 6, 14, Limitations
		(*d*) If applicable, explain how loss to follow-up was addressed	NA

		(*e*) Describe any sensitivity analyses	Page 8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 8
		(b) Give reasons for non-participation at each stage	NA: all patients meeting criteria included
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 9; Tables 1-2
		(b) Indicate number of participants with missing data for each variable of interest	Table 1: BMI and smoking
		(c) Summarise follow-up time (eg, average and total amount)	Pages 8-9
Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 3
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 3
		(*b*) Report category boundaries when continuous variables were categorized	Tables 1-2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Pages 10-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 12-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	Pages 16-17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 1: title page

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

A New User Cohort Study Comparing the Safety of Long-Acting Inhaled Bronchodilators in COPD

Michele Jara, Charles Wentworth III, Stephan Lanes

Address correspondence to:

Michele Jara, Epidemiology Consulting, LLC, 5 Fox Den Road, Danbury, CT 06811 email: mjara@acorda.com

Disclosures: ~~Drs. Lanes and Jara were employees of Boehringer Ingelheim Pharmaceuticals Inc. during the conduct of this study. Dr.~~Dr. Jara is employed by Acorda Therapeutics. Dr. Lanes and Mr. Wentworth are employed by United BioSource Corporation, Lexington, MA. The study was funded by Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT. Two of the authors (MJ, SL) were employees of Boehringer Ingelheim at the time the study was conducted. CW served as a consultant. Boehringer Ingelheim granted the authors permission to publish this study. The authors are solely responsible for the design, analysis, interpretation, and conclusions of the study.

Contributions: Drs. Lanes and Jara were responsible for the study conception and design. Mr. Wentworth and Dr. Jara were responsible for data analysis. All authors were responsible for data interpretation. Drs. Jara and Lanes ~~and Jara~~ drafted the manuscript. All authors reviewed and revised the manuscript and approved the final version.

Subject Headings: cohort study, COPD, product safety, tiotropium, salmeterol, cardiovascular, stroke

Word count: Abstract: ~~197~~215; Text: ~~2640~~

3374

SUMMARY

Article focus

- This study investigated whether there are possible increased risks of stroke and other adverse events, including angina and myocardial infarction, with tiotropium use in COPD
- ~~We~~The authors compared new users of long-acting anticholinergic therapy (tiotropium ~~Handihaler~~HandiHaler®) with new users of long-acting beta agonist (LABA) monotherapy

Key messages

- ~~Imprecise~~ Compared with LABA, tiotropium HandiHaler was associated with increased risks of angina, myocardial infarction and stroke ~~were observed in tiotropium users~~, and lower risk of total mortality
- ~~These~~The results ~~suggest~~of this study are similar to results from a recent clinical trial comparing tiotropium with salmeterol, and support the hypothesis that tiotropium ~~may~~HandiHaler can be associated with an increased risk of ~~serious~~ischemic cardiovascular events

Strengths and Limitations

- ~~This~~Strengths of this study ~~was conducted in a large population of COPD patients using primary care medical records. Nonrandomized studies must always be concerned with possible bias. Although we used~~ are the new user design and use of propensity scores ~~and multivariate models~~ to control ~~efficiently~~ for available risk factors, ~~certain variables, such~~

~~as~~including demographic factors, history of respirator, cardiovascular, and other illness, and respiratory, cardiovascular, and other medications.

- Limitations of this study are that routine lung function ~~results,~~measures were unavailable ~~and could not be controlled. The results reported here and in other comparative tiotropium studies~~, and composite endpoints of all cause mortality and all strokes may attenuate associations for ~~angina, myocardial infarction~~cardiovascular mortality and ischemic stroke ~~are not statistically significant. The absence of statistical significance in studies that lack the power to detect small effects, however, should be expected and does not indicate the absence of an effect.~~

Formatted: Bulleted + Level: 1 + Aligned at: 0.25" + Indent at: 0.5"

Formatted: Font: Not Bold

ABSTRACT

~~Background:~~**Objective:** To investigate a possible increased risk observed in tiotropium clinical trials of stroke and other adverse events ~~with tiotropium, we compared new~~.

Design: New users of long-acting anticholinergic therapy (tiotropium ~~Handihaler®)~~ HandiHaler®) were compared with new users of long-acting beta agonist (LABA) monotherapy~~.~~ and propensity scores were used to control confounding.

Formatted: Font: Bold

~~Methods: We used The Health Improvement Network (THIN) general practitioner database to identify patients newly prescribed a single-ingredient long-acting bronchodilator. Patients <40 years old or having asthma as their only respiratory diagnosis were excluded. We used Cox proportional hazards~~

~~models to compute hazard ratio (HR) estimates comparing tiotropium with LABA adjusted for propensity scores comprising baseline demographic variables, medical therapies, and illnesses.~~

~~Results: We identified~~**Setting:** United Kingdom healthcare system general practitioner electronic medical record database.

Participants: 10,840 patients newly prescribed tiotropium (n=4,767) or LABA (n=6,073~~). Tiotropium users had a lower rate~~), at least 40 years old, and not having asthma as their only respiratory illness.

Primary and secondary outcome measures: Incidence rates of total ~~mortality than users of LABA (HR=0.70, 95% CI= 0.56, 0.89).~~stroke, myocardial infarction, angina and other adverse events.

Results: Tiotropium was associated with increased rates of stroke (HR=1.49, 95% CI=0.91, 2.45), angina (HR=1.38, 95% CI=0.88, 2.16), and myocardial infarction (HR=1.26, 95% CI=0.72, 2.21). ~~Rates~~Groups had similar rates of COPD exacerbation (HR=0.95, 95%CI=0.80, 1.12) and pneumonia (HR=0.96, 95%CI=0.58, 1.58~~) were similar.~~). Tiotropium was associated with a lower rate of total mortality (HR=0.70, 95% CI= 0.56, 0.89) and asthma exacerbations (HR=0.46, 95%CI=0.36, 0.57~~).~~) than users of LABA.

~~Conclusion: Tiotropium users had lower rates of total mortality than LABA users, and higher rates of serious ischemic cardiovascular events.~~

Conclusion: Small increased risks of serious ischemic cardiovascular events have been reported with inhaled anticholinergic medication from randomized and nonrandomized studies of ipratropium, tiotropium HandiHaler®, and tiotropium Respimat®. Additional research is needed to

Formatted: English (U.S.)

Formatted: English (U.K.)

understand the full extent of cardiovascular effects of inhaled anticholinergic medications and the patients who may be most susceptible.

INTRODUCTION

Inhaled anticholinergic medications, including short-acting ipratropium bromide (ipratropium), and long-acting tiotropium bromide (tiotropium), are mainstays for the treatment of symptoms of COPD. The safety profiles of these drugs comprise systemic anticholinergic events, including dry mouth, constipation, urinary retention and cardiac effects, including palpitations, tachycardia, and supraventricular tachycardia (SVT).~~[1 3]~~[1-5] There has been concern that anticholinergic drugs could induce ischemia, possibly secondary to tachyarrhythmias,[3 4 5] ~~and could pose a risk to patients with cardiovascular complications.[4] Among patients with congestive heart failure (CHF), SVTs are an independent risk factor for stroke, as well as cardiovascular hospitalization and death.[5]~~ and could pose a risk to patients with cardiovascular complications.[6] Among patients with congestive heart failure (CHF), SVT is a risk factor for stroke, as well as cardiovascular hospitalization and death.[7] Further, among patients with sinus node dysfunction, asymptomatic atrial tachyarrhythmias increase the risk of stroke and death.[6 8]

We conducted this epidemiologic study to examine the possible association between tiotropium (~~Handihaler~~HandiHaler® powder formulation) and risk of stroke and other cardiovascular adverse events, including angina and myocardial infarction.

METHODS

~~Treatment guidelines for COPD consider long-acting bronchodilators as a class, but make no distinction between anticholinergic drugs and LABAs, resulting in clinical equipoise.[7] Therefore, new users of tiotropium were compared with new users of LABAs. Both long-acting bronchodilators are indicated for treating symptoms of COPD; LABAs are also indicated for the treatment of asthma.~~

Field Code Changed

Treatment guidelines for COPD consider long-acting bronchodilators as a class, and make no distinction between anticholinergic drugs and LABAs, resulting in clinical equipoise.[9] Therefore, new users of tiotropium were compared with new users of LABAs.[10 11] Both long-acting bronchodilators are indicated for treating symptoms of COPD; LABAs are also indicated for the treatment of asthma.

The source population included patients in the UK enrolled with a general practitioner who contributes to The Health Improvement Network (THIN) primary care database. The THIN database includes de-identified patient records containing demographic data, medical history, prescribed medications, diagnostic tests, laboratory results, specialist referrals, and some lifestyle characteristics.[~~8~~12] The database is derived from the same software as the General Practice Research Database (GPRD) and has been validated for COPD, as well as stroke and myocardial infarction, and is widely used in epidemiologic research.[~~8 10~~12-14]

Patients had to have at least one prescription for tiotropium (~~Handihaler~~HandiHaler formulation) or LABA (salmeterol or formoterol), from November 2002 (the earliest use of tiotropium) until January 2007. Because tiotropium is available only in a single-ingredient preparation, whereas LABAs are also available in combination with inhaled corticosteroids, the LABA group was restricted to patients prescribed single-ingredient LABAs. Patients had to have at least two years of baseline data with no use of a long-acting inhaler prior to their first or "index" prescription for tiotropium or LABA. To reduce confounding by indication, patients who had a recorded diagnosis of asthma as their only respiratory diagnosis were excluded, as were patients less than 40 years old.

Study endpoints included various cardiovascular adverse events (aneurysm, atrial fibrillation, cardiac arrest, coronary artery disease, angina, myocardial infarction, heart failure, hypertension, stroke, syncope, tachycardia, and ventricular tachycardia); respiratory adverse events (COPD

exacerbation, asthma exacerbation, and pneumonia); and other adverse events of interest (constipation, dry mouth, dysphagia, paralytic ileus/bowel obstruction, renal failure, tremor, urinary retention). Information on causes of death was unavailable, but we were able to examine all-cause mortality. ~~Study~~Most endpoints were defined using medical codes from the Read Clinical Classification Version 2, May 2006.~~–~~ Mortality was identified from a combination of READ codes, registration status, additional health data (AHD) codes and enrollment dates.

Covariates were selected for inclusion in the analysis based on clinical importance and included respiratory diagnosis (COPD/no asthma, COPD and asthma, other (i.e. asthma or COPD not recorded)), age, sex, calendar year of drug start, smoking, body mass index (BMI), number of hospitalizations in the year prior to cohort entry, number of general practitioner visits in the year prior to cohort entry, cardiac co-morbidities (ischemic heart disease, arrhythmias, hypertension), respiratory medications (number of prescriptions for short-acting anticholinergics, short-acting beta-agonists, inhaled corticosteroids, oral corticosteroids, and use of theophyllines and cromoglycates), cardiac medications (prescriptions for anti-arrhythmics, anticoagulants, anti-hypertensives, angiotensin converting enzyme (ACE) inhibitors, diuretics, inotropics, lipid regulators, beta-blockers, nitrates), other medications (gastrointestinal, vascular, central nervous system, infectious disease, endocrine, gynecologic/urinary tract, malignancy, nutrition/blood disorders), oxygen use, lung cancer diagnosis prior to index, and history of diabetes.

People were classified as exposed to study medication for the duration of prescribed therapy plus 30 days. For analysis of each endpoint, patients were followed from the date of their first eligible prescription until the earliest of the following: date of treatment end, date of study endpoint, date of transfer to a new practice, death, or January 2007. Each endpoint was analyzed separately, so patients who experienced more than one endpoint under study were included in analyses of each event.

Incidence rates of the study endpoints were calculated as the number of patients experiencing an event divided by the person-years at risk. Incidence rate ratios were calculated as the incidence rate in the tiotropium group divided by the incidence rate in the LABA group. Precision of effect estimates was evaluated from the width of the 95% confidence intervals (CI).~~11~~15

Some endpoints were rare relative to the number of factors that needed to be controlled, so propensity scores (derived from logistic regression models) were used to enhance efficiency of analytic control of confounding.~~12~~16 The propensity score is the estimated chance of a patient receiving tiotropium compared with LABA, given a patient's observed set of covariates (prognostic variables). In constructing the logistic models used to calculate the propensity scores, all available variables described above were entered into the model.

Multivariate analysis was performed using Cox' proportional hazard model with adjustment for indicators of propensity score quintile to estimate adjusted hazard ratios (HR) and corresponding 95% confidence intervals (CI).~~13~~ ~~The assumption of proportionality of the hazards was tested by including time-dependent covariates in the Cox model.13 We also computed effect estimates using Poisson regression.~~17 The assumption of proportionality of the hazards was tested by including time-

dependent covariates in the Cox model.[17] We also computed effect estimates using Poisson regression. Effect estimates are presented for endpoints where the event was detected in at least 5 patients in each treatment group.

~~Analyses were stratified by respiratory diagnostic status (COPD and asthma, and COPD without asthma) and history of coronary artery disease.~~ To identify a study population of more compliant, long-term users, we also conducted analyses restricted ~~analyses~~ to patients on treatment for greater than six months. In addition, analyses were stratified by respiratory diagnostic status (COPD and asthma, COPD without asthma, other), use of oral corticosteroids, and history of coronary artery disease.

All analyses were performed using STATA 7.0 and SAS 9.1. This study received ethical approval from the UK Department of Health Multicentre Research Ethics Committee.

RESULTS

The study population included 4,767 tiotropium patients and 6,073 LABA patients who contributed 2,775 person-years of exposure to tiotropium and 2,303 person-years of exposure to a single-ingredient LABA (Table 1). Mean duration of exposure was 212 days for tiotropium patients and 139 days for LABA patients. Ninety-five percent of LABA prescriptions were for salmeterol. Though a similar proportion of tiotropium and LABA patients switched or added a different long-acting bronchodilator thereby terminating study participation, a lower proportion of tiotropium patients than LABA patients discontinued use of a long-acting bronchodilator prior to the administrative end of the study (58% compared with 73%). The proportion of current smokers was slightly higher in tiotropium users than in LABA users (37% compared with 30%). Other covariates were generally balanced between treatment groups.

Characteristics of medical history prior to study entry are shown in Table 2. A high proportion of patients in both groups had spirometry testing (89% of tiotropium patients and 84% of LABA patients) and a diagnosis of COPD (89% of tiotropium patients and 88% of LABA patients~~-~~). More LABA patients than tiotropium patients also had an asthma co-diagnosis (42% vs. 63%).

Results from Cox models and Poisson models were similar, so estimates from Cox models are presented (Table 3). ~~There was a lower rate of death due to all causes in patients using tiotropium (HR=0.70, 95% CI=0.56, 0.89).~~ There were small increases in the tiotropium group in the rates of angina (HR=1.38, 95% CI=0.88, 2.16), myocardial infarction (HR=1.26, 95% CI=0.72, 2.21) and stroke (HR=1.49, 95% CI=0.91, 2.45). There were similar rates between treatment groups of aneurysm (HR=0.96, 95% CI=0.44, 2.05), atrial fibrillation or flutter (HR=0.99, 95% CI=0.71, 1.38), coronary artery disease (HR=1.11, 95% CI=0.84, 1.47), hypertension (HR=1.03, 95% CI=0.81, 1.29), syncope (HR=0.94, 95% CI=0.57, 1.55) and tachycardia (HR=1.08, 95% CI=0.48, 2.41). There was a decrease in the tiotropium group in the rate of heart failure (HR=0.85, 95% CI=0.63, 1.14~~).~~) and all cause mortality (HR=0.70, 95% CI=0.56, 0.89).

With regard to respiratory events, there was a lower rate of asthma exacerbation in patients using tiotropium compared with patients using a LABA (HR=0.46, 95% CI=0.36, 0.57). There were similar rates of COPD exacerbations (HR=0.95, 95% CI=0.80, 1.12) and pneumonia (HR=0.96, 95% CI=0.58, 1.58).

Dry mouth was recorded at a higher rate in patients using tiotropium compared with patients using a LABA (HR=3.66, 95% CI=1.52, 8.78). The rate of constipation (HR=0.95, 95% CI=0.74, 1.23), dysphagia (HR=1.02, 95% CI=0.62, 1.69), and urinary retention (HR=0.97, 95% CI=0.55, 1.70) were

similar in both treatment groups. There was a higher rate of renal failure in tiotropium patients (HR=1.40, 95% CI=0.77, 2.55), and a lower rate of tremor (HR=0.62, 95% CI=0.31, 1.22).

Among patients who had been receiving long acting bronchodilator therapy for at least 6 months, ~~the difference between groups in rates of total mortality diminished (HR=0.90, 95% CI=0.58, 1.38). For cardiovascular endpoints,~~ effect estimates increased for stroke (HR=1.63, 95% CI=0.83, 3.17), angina (HR=1.42, 95% CI=0.78, 2.59), and MI (HR=1.65, 95% CI=0.63, 4.27).- The difference between groups in rates of total mortality diminished (HR=0.90, 95% CI=0.58, 1.38). Associations for other cardiovascular events were weaker, including aneurysm (HR=0.82, 95% CI=0.27, 2.45), atrial fibrillation/flutter (HR=1.17, 95% CI=0.70, 1.94), heart failure (HR=0.77, 95% CI=0.47, 1.24), hypertension (HR=1.07, 95% CI=0.79, 1.45), syncope (HR=0.79, 95% CI=0.36, 1.70), and tachycardia (HR=0.98, 95% CI=0.32, 3.04).

Effect estimates for respiratory endpoints among patients treated for at least 6 months were similar to those in the total population (asthma exacerbation (HR=0.47, 95% CI=0.33, 0.65); COPD exacerbation (HR=0.82, 95% CI=0.63, 1.05); and pneumonia (HR=1.42, 95% CI=0.68, 2.96)). Effect estimates computed for other events included constipation (HR=0.97, 95% CI=0.69, 1.37), dysphagia (HR=1.30, 95% CI=0.65, 2.58), renal failure (HR=1.17, 95% CI=0.51, 2.66), urinary retention (HR=1.17, 95% CI=0.51, 2.66), and tremor (HR=0.57, 95% CI=0.23, 1.41).

After stratifying by subgroups, results were imprecise and generally similar to the overall results. With regard to concomitant asthma diagnosis, the association with angina was stronger in patients with asthma and COPD (HR=1.91, 95% CI=1.00, 3.63) than patients with only COPD (HR=0.93, 95% CI=0.49, 1.77), while the association with myocardial infarction was stronger in patients who had

only COPD (HR=1.94, 95% CI=0.77, 4.94). Asthma exacerbations occurred only among patients with a concomitant diagnosis of asthma. After stratification by coronary artery disease, the association with angina was stronger among patient without coronary artery disease (HR=3.02, 95% CI=1.08, 8.47) than among patients with coronary artery disease (HR=1.05, 95% CI=0.63, 1.77). After stratification by corticosteroids, the association with angina was greater among patients without corticosteroids (HR=2.28, 95% CI=0.99, 5.26) than with corticosteroids (HR=1.09, 95%CI=0.63, 1.89), while the association with stroke was greater for patients with corticosteroids (HR=1.85, 95% CI=1.00, 3.44) than without corticosteroids (HR=0.86, 95% CI=0.37, 2.01).

Formatted: Space After: 0 pt, Line spacing: Double

DISCUSSION

This study found ~~a decreased risk of mortality with tiotropium, along with imprecise~~small increased risks of stroke, myocardial infarction and angina along with a decreased risk of mortality with tiotropium. Individual studies are often too small to identify with certainty associations between specific medications and rare adverse events, and ~~elevated risks of stroke, angina, and myocardial infarction observed with tiotropium in this study~~these findings should be considered in context with other evidence.

~~In 2002, the Lung Health Study, the first large placebo-controlled randomized trial of an inhaled anticholinergic agent, reported an increased incidence in the ipratropium group of hospitalization due to SVT, angina, myocardial infarction, and death due to coronary heart disease.[14] Observational studies also reported associations between ipratropium and stroke,[15] cardiovascular hospitalization,[16] and death.[17]~~

~~Tiotropium has a similar mechanism of action as ipratropium, and in 2008, the FDA issued an early communication after a pooled analysis of placebo-controlled clinical trials revealed an excess risk of stroke with tiotropium.[18] Subsequently, the Uplift trial reported a decreased risk of total mortality, and no increased risk of stroke with tiotropium.[19] The stroke endpoint included all types of strokes,[19] however, and the incidence of ischemic events (TIA, cerebral ischemia, ischemic stroke) in the Uplift study was greater in the tiotropium group than the placebo group.~~In 2002, the Lung Health Study, the first large placebo-controlled randomized trial of an inhaled anticholinergic agent, reported an increased incidence in the ipratropium group of hospitalization due to SVT, angina, myocardial infarction, and death due to coronary heart disease.[18] Observational studies have reported associations between ipratropium and stroke,[19] cardiovascular hospitalization,[20] and death.[21]

Tiotropium has a similar mechanism of action to ipratropium, and in 2008, the FDA issued an early communication after a pooled analysis of placebo-controlled clinical trials revealed an excess risk of stroke with tiotropium.[22] Subsequently, the Uplift trial reported a decreased risk of total mortality, myocardial infarction, and no increased risk of stroke with tiotropium.[23] As in other studies, the stroke endpoint was a composite endpoint that included ischemic and hemorrhagic stroke,[23] and the incidence of ischemic stroke in the Uplift study was slightly greater in the tiotropium group than the placebo group.~~[20][24][25] In addition, the Uplift study reported an increased risk with tiotropium of certain tachyarrhythmias[21] and serious angina.[19]~~

~~Perhaps the most relevant study is the recent "POET" study, the largest tiotropium randomized trial conducted to date with 7376 COPD patients.[22] The POET study compared tiotropium with salmeterol, similar to the observational study reported here. Like this study, the POET study also~~

Field Code Changed

found fewer deaths for tiotropium (n=64) compared with salmeterol (n=78), although there was no decrease in cardiac deaths (8 tioptropium vs. 6 salmeterol)[22] [Supplementary Appendix]. The POET study reported no increased risk of stroke, but found an increased risk with tiotropium of serious adverse events reported as angina (9 tiotropium vs. 5 salmeterol), myocardial ischemia (11 tiotropium v. 6 salmeterol), and myocardial infarction (20 tiotropium v. 13 salmeterol).[22 23] A pooled analysis of randomized trials reported an increased rate of arrhythmias with tiotropium compared with placebo or LABAs, and increased risks with tiotropium of both cardiovascular and cerebrovascular serious adverse events (RR=1.71, 95% CI 0.76, 3.89).[24] Finally, a randomized trial comparing tiotropium with salmeterol in combination with fluticasone reported increased cardiac adverse events with tiotropium.[25]

Thus, the increased risks of angina, MI and stroke and the decreased mortality risk observed in this study have also been reported in randomized clinical trials, and suggest that tiotropium may be associated with an increased risk of serious cardiovascular events, possibly secondary to tachyarrhythmias. The risk of serious angina with tiotropium is a consistent finding across multiple trials and is a concern because (1) angina itself is a serious clinical event and (2) angina is not included as a side effect of tiotropium in the summary of product characteristics.[1] Further, an ischemic mechanism that causes angina might also be related to other serious ischemic events such as myocardial infarction, TIA, and ischemic stroke.

Recently, safety concerns have been raised with the mist inhaler formulation of tiotropium (Respimat®), which is available in several countries but which was not approved for marketing in the US. In addition, the Uplift study showed an increased risk with tiotropium of certain tachyarrhythmias[26] and serious angina.[23]

A pooled analysis of randomized trials reported an increased rate of arrhythmias with tiotropium compared with placebo or LABAs, and increased risks with tiotropium of both cardiovascular and cerebrovascular serious adverse events (RR=1.71, 95% CI 0.76, 3.89).[27] A randomized trial comparing tiotropium with salmeterol in combination with fluticasone reported increased cardiac adverse events with tiotropium.[28] An observational study reported increased risk of mortality with tiotropium compared with LABA.[29] Pooled analyses of placebo-controlled tiotropium clinical trials have reported small increased rates with tiotropium of palpitations, SVT, angina and stroke, and lower rates of myocardial infarction, cardiovascular mortality and total mortality.[30-32]

Perhaps the most relevant study is the recent "POET" study, the largest tiotropium randomized trial conducted to date, with 7,376 COPD patients.[33] The POET study is similar to this study in that it compared tiotropium HandiHaler with salmeterol. The POET study also found fewer deaths for tiotropium (n=64) compared with salmeterol (n=78), although there was no decrease in cardiac deaths (8 tioptropium vs. 6 salmeterol)[33] [Supplementary Appendix]. The POET study reported no increased risk of stroke, but found an increased risk with tiotropium of several serious cardiovascular adverse events including angina (9 tiotropium vs. 5 salmeterol), myocardial ischemia (11 tiotropium v. 6 salmeterol), and myocardial infarction (20 tiotropium v. 13 salmeterol).[~~26~~33 34] ~~In evaluating the safety concerns with the tiotropium mist inhaler, it was hypothesized that the increased risk of deaths, mostly cardiac-related, seen with the mist formulation may derive from the device delivering a greater dose than the powder formulation.[27] Cardiovascular events reported inconsistently with the powder formulation, usually in the absence of increased deaths, are consistent with this hypothesis, and may indicate more subtle responses of patients susceptible to lower doses of tiotropium delivered in the Handihaler formulation.~~

Field Code Changed

~~In interpreting these results, one needs to consider the possible impact of both random error and systematic error.~~

Recently, safety concerns have been raised about increased mortality with the mist inhaler formulation of tiotropium (Respimat®), which is available in several countries but which was not approved for marketing in the US.[35] (Tiotropium Respimat was not available in the UK at the time of this analysis.) It was hypothesized that the increased risk of deaths, which were mostly cardiac and sudden or unexplained deaths, may be the result of the device delivering a greater dose than the powder formulation.[36] Tiotropium Respimat is also associated with a dose-related increased risk of angina and cardiac ischemic events, but not myocardial infarction.[37 38]

The decreased risk of mortality observed in this study with tiotropium is in agreement with the results reported in the Uplift[23] and POET[33] studies, but not in the ipratropium Lung Health Study[18] or several large tiotropium trials using the Respimat device.[37 39] These drugs have virtually identical safety profiles,[2 3 40] so it would be an oversimplification to suggest that they have either beneficial or harmful effects on mortality based solely on the device delivering similar active ingredients. Heterogeneity of results should be considered in light ob both causal and noncausal explanations. For composite endpoints, interpretation often can be clarified by evaluating components, especially cardiovascular deaths. Thus, the POET study reports fewer total deaths with tiotropium,[33] but more cardiac deaths.[34]

The results ~~reported here and in other comparative tiotropium studies~~ for angina, myocardial infarction and stroke ~~are not~~ reported here and in other studies of inhaled anticholinergic drugs are usually not statistically significant. The absence of statistical significance in studies that lack the

power to detect small effects~~, however,~~ should be expected, and does not indicate the absence of an effect.[28 29 41 42] ~~To the contrary~~For instance, repeated findings of an increased ~~risks~~risk of angina of a similar ~~magnitudes~~magnitude in ~~several~~ studies of different design and locations make chance an unlikely explanation for this finding.

Nonrandomized studies must always be concerned with possible bias arising from differences in baseline risks between treatment groups. We used propensity scores and multivariate models to control efficiently for available risk factors. Nevertheless, certain variables, such as lung function results, were unavailable and could not be controlled. We found more LABA patients than tiotropium patients had an asthma diagnosis in addition to their COPD diagnosis. The decreased risk of asthma exacerbations in the tiotropium group is consistent with a greater proportion of patients in the LABA group having an asthma component to their COPD. Nevertheless, COPD diagnoses and exacerbations were similar between groups~~. It~~, suggesting similar severity of COPD. Nevertheless, it is possible that tiotropium patients had more severe COPD than LABA patients despite our efforts to control for baseline risk factors. ~~The~~ More severe COPD might account for higher rates of cardiovascular events, although the decreased mortality in the tiotropium group~~, however, makes it unlikely that tiotropium patients had more severe COPD than LABA patients. It seems more likely that whatever mechanism caused increased~~ is inconsistent with this hypothesis. Increased risks of ischemic cardiovascular events in randomized trials also ~~might have produced similar effects in the population studied here.~~argue against confounding as an explanation.

~~Anticholinergic medications are known to cause tachyarrhythmias,[3] and tiotropium has been consistently associated in clinical trials with tachyarrhythmias and angina. Tachycardia was only slightly more common in tiotropium users in this study, but LABAs are also associated with~~

Field Code Changed

~~tachycardia, which may be asymptomatic and underreported.~~All tiotropium effect estimates in this study are relative to effects of LABA. A valid effect estimate indicating a higher rate with tiotropium means that tiotropium increases risk more than LABA, but both drugs could be either increasing or decreasing risk. To the extent that LABA may increase the risk of cardiovascular adverse events, such an effect would attenuate an increased risk that might also exist for tiotropium.

Among non-cardiovascular and non-respiratory endpoints, results showed an increased risk of dry mouth with tiotropium, but not for other anticholinergic endpoints including constipation and urinary retention. The incidence of ~~dry mouth~~these less serious events was low, however, and it is likely that only a small proportion of these cases are reported to GPs and recorded in the database. Under-reporting of non-serious AEs could introduce misclassification that would dilute RR estimates for events such as dry mouth and constipation.[~~11~~15] Misclassification could have occurred for more serious endpoints as well, although we would expect that completeness of the medical record ~~d~~ would be better for more serious cardiovascular events. Misclassification of certain serious endpoints still is a concern, however, as we examined total mortality and total strokes, but not cardiovascular mortality or ischemic strokes.~~-~~ Finally, tiotropium HandiHaler is available in one dose, and this study was unable to evaluate dose-response. However, among patients using therapy for at least 6 months, the associations with angina, myocardial infarction and stroke became stronger, while the association with mortality became weaker.

~~Additional research should examine more specifically the ischemic effects of tiotropium, and explore subgroups to identify patients who may be particularly susceptible to ischemic events.~~

Results of this study should be interpreted cautiously, but they lend modest support to a considerable body of evidence of a serious cardiovascular safety risk with inhaled anticholinergic drugs. Nevertheless, with regard to safety of inhaled anticholinergic drugs, the FDA recently concluded that "data from Uplift adequately addressed the potential safety signal of stroke and adverse cardiovascular outcomes." [43] A few points go a long way towards explaining these divergent conclusions. First, we consider the entire body of evidence, and we consider each study on its merits. In particular, studies should not be disregarded merely because they are not randomized[19-21 29] or they include another treatment as a control group instead of a placebo group.[28 33] Secondly, when considering the evidence pertaining to small effects on rare adverse events, we did not assume that results that are not statistically significant provide evidence against an increased risk.[41 42] This is especially important when increases in risk are small or studies were not large enough to detect such risks as statistically significant. It is important to consider the magnitude of effect estimates and the precision with which they are measured.[41 42] The Uplift study, for instance, describes higher rates of serious angina and ischemic stroke with tiotropium than placebo,[24] and so can hardly provide reassurance about the absence of such risks. In addition, results from composite endpoints do not necessarily apply to each of their components. Thus, decreased rates of total mortality and total stroke can mask increased rates of cardiovascular mortality[24] or ischemic stroke.[34] Finally, adverse effects do not occur in every patient and may not be apparent in every population or every study. Heterogeneity of results is not evidence against a causal effect, but is an interesting finding that should be interpreted in consideration of the impact of both noncausal as well as causal explanations; the latter include differences in populations, durations of follow-up, and doses. Thus, the absence of an increased risk of myocardial infarction in the Uplift study does not negate increases in risk of myocardial infarction in the Lung Health Study,[18]

POET study,[34] or this study, especially when each of these studies indicates an increased risk of angina.

Inhaled anticholinergic drugs are effective treatments in COPD and treatment decisions must balance benefits with risks for individual patients. It has long been suggested that the elderly are especially susceptible to anticholinergic effects, and angina has been described previously as a severe anticholinergic effect secondary to tachyarrhythmias.[1 4 5] Subsequently, increased risks of tachyarrhythmias and angina have been reported in association with inhaled anticholinergic drugs in non-randomized and randomized studies, of various sizes and durations, with ipratropium and tiotropium, compared with placebo and active comparators, and using different devices. Pharmacologic and clinical evidence, therefore, supports these cardiovascular events as class effects of inhaled anticholinergic drugs. Small increased rates of stroke have been observed fairly consistently across studies, while myocardial infarction, and cardiovascular death, have been associated in different studies both positively and negatively with anticholinergic medication. Additional research is needed to understand the full extent of cardiovascular effects of inhaled anticholinergic medications and the patients who may be susceptible.

REFERENCES

1. Peters NL. Snipping the thread of life. Antimuscarinic side effects of medications in the elderly. *Arch Int Med* 1989;149:2414-20.

2. Boehringer Ingelheim International ~~GmbH~~. Summary of Product Characteristics. ~~-~~Spiriva 18 microgram Inhalation Powder, hard capsule 2010.

~~2~~3. Boehringer Ingelheim International ~~GmbH~~. Summary of Product Characteristics~~,~~. Atrovent Inhaler CFC-free 2011.

~~3~~4. Mintzer J, Burns A. Anticholinergic side effects of drugs in elderly people. *J R Soc Med* 2000;93:457-62.

~~4.~~5. Feinberg M. The problems of anticholinergic adverse effects in older patients. *Drugs Aging* 1993;3(4):335-48.

6. Parlow JL, van Vlyman JM, Odell MJ. The duration of impairment of autonomic control after anticholinergic drug administration in humans. *Anesth Analg* 1997;84:155-59.

~~5~~7. Mathew J, Hunsberger, S~~.~~, Fleg, J~~, et al.~~, McSherry, F., Williford, W., Yusef, S. Incidence, prognostic factors, and prognostic significance of supraventricular tachyarrhythmias in congestive heart failure. *Chest* 2000;118:914-22.

~~6~~8. Glotzer TV, Hellkamp ~~AS,~~ A.S., Zimmerman, J~~, et al.~~, Sweeney, M.O., Yee, R., Marinchak, R., Cook, J., Paraschos, A., Love, J., Radoslovich, G., Lee, K.L., Lamas, G.A., the MOST Investigators. Atrial high rate episodes detected by pacemaker diagnostics predict death and stroke~~.~~ *Circulation* 2003;107:1614-19.

~~7~~9. Pauwels ~~RA~~R, Buist ~~AS~~A, Calverley ~~PM, et al~~P, Jenkins C, Hurd S. 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.

~~8~~10. Ray WA. Evaluating medication effects outside of clinical trials: New- user designs. *Am J Epidemiol* 2003;158(9):915-20.

11. Schneeweiss S. A basic study design for expedited safety signal evaluation based on electronic healthcare data. *Pharmacoepidemiol Drug Safety* 2010;19:858-68.

12. Bourke A, Dattani H, Robinson M. Feasibility study and methodology to create a quality-evaluated database of primary care data. *Inform Prim Care* 2004;12:171-77.

~~9~~13. Feary JR, Rodrigues ~~LC,~~ L.C., Smith ~~CJ, et al~~, C.J., Hubbard, R.B., Gibson, J.E. Prevalence of major comorbidities in subjects with COPD and incidence of myocardial infarction and stroke: a comprehensive analysis using data from primary care *Thorax* 2010;65~~:~~(11):956-62.

1014. Lewis JD, Schinnar, R,., Bilker WB, et al, W.B., Wang, X., Strom, B.L. . Validation studies of The Health Improvement Network (THIN) database for Pharmacoepidemiology research. . *Pharmacoepidemiol Drug Saf* 2007;16:393-401.

1115. Rothman KJ, Greenland S. *Modern Epidemiology*. 2nd ed. Philadelphia: Lippincott–Raven Publishers, 1998.

1216. Rosenbaum PR, Rubin DP. Reducing bias in observational studies using subclassification on the propensity score. *J Am Stat Assoc* 1984;79:(387):516-24.

1317. Rubin DB. On principles for modeling propensity scores in medical research. . *Pharmacoepidemiol Drug Saf* 2005;13:855-57.

1418. Anthonisen NR, Connett JE, J.E., Enright PL, et al, P.L., Manfreda, J., and the Lung Health Study Research Group. Hospitalizations and mortality in the Lung Health Study *Am J Resp Crit Care Med* 2002;166:333-39.

1519. Macie C, Wooldrage K, Manfreda J, et alAnthonisen N. Cardiovascular morbidity and the use of inhaled bronchodilators. *J Chron Obstruct Pulmon Dis* 2008;3:(1):163-69.

1620. Ogale SSS, Lee TAT, Au DH, et alD, DM B, SD S. Cardiovascular events associated with ipratropium bromide in COPD. *Chest* 2010;137:(1):13-19.

1721. Lee TA, Pickard AS, A.S., Au DH, et al, D.H., Bartle, B., Weiss, K.B. Risk for death associated with medications for recently diagnosed chronic obstructive pulmonary disease. *Ann Intern Med* 2008;149:(6):380-90.

1822. Food and Drug Administration. Early communication about an ongoing safety review of tiotropium (marketed as Spiriva HandiHaler). March 18, 2008 ed: FDA, 2008.

1923. Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008;359:1534-54.

2024. National Institutes of Health. Evaluation of the Long- Term Effects of Spiriva on Lung Function in COPD Patients. NCT00144339 *NCT00144339*: NIH, 2005.

25. Boehringer Ingelheim International GmbH. Briefing document: Tiotropium (SPIRIVA®): Pulmonary Allergy Drug Advisory Meeting – November 2009. *Briefing Information for the November 19, 2009 Meeting of the Pulmonary-Allergy Drugs Advisory Committee*, 2009:115.

2126. Food and Drug Administration Pulmonary-Allergy Drugs Advisory Committee Meeting. November 19. FDA Briefing Material. *Briefing Information for the November 19, 2009 Meeting of the Pulmonary-Allergy Drugs Advisory Committee*: FDA, 2009:115.

2227. Worth H, Chung KF, Felser JM, Hu H, Ruegg P. Cardio-and cerebrovascular safety of indacaterol vs formoterol, salmeterol, tiotropium and placebo in COPD. *Resp Med* 2010;105(4):571-79.

28. Wedzicha JA, Calverly, P.M.A., Seemungal, T.A., Hagan, G., Ansari, Z., Stockley, R.A., Inspire Investigators. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. *Am J Respir Crit Care Med* 2008;177:19-26.

29. Gershon A CR, To T, Stanbrook MB, Upshur R, Sanchez-Romeu P, Stukel T. Comparison of inhaled long-acting beta-agonist and anticholinergic effectiveness in older patients with chronic obstructive pulmonary disease. *Ann Intern Med* 2011;154:583-92.

30. Celli B DM, Leimer I, Vogel U, kesten S, Tashkin DP. Cardiovascular safety of tiotropium in patients with COPD. *Chest* 2010;137(1):20-30.

31. Kesten S CB, Decramer M, Leimer I, Tashkin D. Tiotropium HandiHaler in the treatment of COPD: A safety review. *Int J COPD* 2009;4:397-409.

32. Kesten S JM, Wentworth C, Lanes S. Pooled clinical trial analysis of tiotropium safety. *Chest* 2006;130:1695-703.

33. Vogelmeier C, Hederer B, Glabb T, Schmidt H, Rutten-van Molken MPMH, Beeh KM, et al. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. *N Engl J Med* 2011;364:1093-11-3.

~~23~~34. National Institutes of Health. Effect of Inhalation of Tiotropium Once Daily 18 Mcg Versus Salmeterol Twice Daily 50 Mcg on Time to First Exacerbation in COPD Patients (a Randomised, Double-blind, Double-dummy, Parallel Group, One-year Study). NCT00563381. *NCT00563381*. March 29, 2011 ed: ClinicalTrials.gov, 2011.

~~24. Worth H, Chung KF, Felser JM, et al. Cardio- and cerebrovascular safety of indacaterol vs formoterol, salmeterol, tiotropium and placebo in COPD. *Resp Med* 2010;105:571-79.~~

~~25. Wedzicha JA, Calverly PMA, Seemungal TA, et al. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. *Am J Respir Crit Care Med* 2008;177:19-26.~~

~~26~~35. Singh S, Loke ~~YK,~~ Y.K., Enright ~~PL, et al~~, P.L., Furberg, C. Mortality associated with tiotropium mist inhaler in patients with chronic obstructive pulmonary disease: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2011;342~~.~~(d3215).

~~27~~36. Cates CJ. Safety of tiotropium. *BMJ* 2011;342~~.~~(d2970).

~~28~~37. Bateman E, Singh D, Smith D, Disse B, Towse L, Massey D, et al. Efficacy and safety of tiotropium Respimat SMI in COPD in two 1-year randomized studies. *Int J COPD* 2010;5:197-208.

38. Boehringer Ingelheim International. A randomized double-blind, placebo-controlled, parallel-group study to assess long term (one-year) efficacy and safety of tiotropium inhalation solution 5 mcg (2 puffs of 2.5 mcg) delivered by the Respimat inhaler in patients with chronic obstructive pulmonary disease *Boehringer Ingelheim Trial Results*, 2009.

39. Bateman ED TD, Siafakas N, Dahl R, Towse L, Massey D, Pavia D, Zhong NS. A one-year trial of tiotropium Respimat plus usual therapy in COPD pateints. *Resp Med* 2010;104:1460-72.

40. Boehringer Ingelheim International. Summary of Product Characteristics, Spiriva Respimat 2.5 micrograms solution for inhalation, 2010.

41. Altman DG, Bland ~~JM~~, J.M. Absence of evidence is not evidence of absence. *BMJ* 1995;311~~:~~(1):485.

~~29~~42. Rothman KJ. Significance questing. *Ann Int Med* 1986;105~~:~~(3):445-47.

43. Food and Drug Administration Pulmonary-Allergy Drugs Advisory Committee Meeting. February 23. FDA Main Presentations for the February 23, 2012 Meeting of the Pulmonary-Allergy Drugs Advisory Committee., 2012:Slide 60/109.

Formatted: Indent: Left: 0", First line: 0", Space After: 10 pt

Formatted: Indent: Left: 0", Hanging: 0.5", Line spacing: 1.5 lines

Table 1. Exposure distribution and demographic characteristics of the study population

	Tiotropium		LABA[1]	
	N	%	N	%
Age Group				
40-49	149	3	362	6
50-59	641	13	943	16
60-69	1,391	29	1,730	28
70-79	1,759	37	1,991	33
80-89	769	16	976	16
90+	58	1	71	1
Sex				
Male	2,707	57	3,073	51
Female	2,060	43	3,000	49
Body mass index				
Low	634	13	613	10
Normal	1,500	31	1,799	30
Overweight	1,413	30	1,895	31
Obese	1,012	21	1,467	24
Missing	208	4	299	5
Smoking				
Never	562	12	1,077	18
Current	1,765	37	1,812	30
Former	2,343	49	2,960	49
Missing	97	2	224	4

[1] Long-acting β-agonist single-ingredient formulations

Table 2. Medical history of the study population by long-acting bronchodilator

	Total Study Population n=10,840			
	Tiotropium		LABA[1]	
	N	%	N	%
Prior Respiratory Diagnosis				
COPD and asthma	1,807	38	3,366	55
COPD Only	2,450	51	1,960	32
Other	510	11	747	12
Use of Respiratory Medications[2]				
Short-acting anticholinergics	1,948	41	2,372	39
Short-acting Beta-agonists	3,372	71	5,053	83
Inhaled Corticosteroids	1,904	40	3,610	59
Oral Corticosteroids	1,396	29	2,227	37
Theophyllines	238	5	361	6
Cromoglycates	48	1	67	1
Use of Oxygen	187	4	175	3
Use of Cardiac Medications[2]				
Anti-arrhythmics	219	5	312	5
Anti-coagulants	1834	38	2,069	34
Anti-hypertensives	2424	51	2,913	48
ACE inhibitors	1162	24	1,380	23
Diuretics	1912	40	2,336	38
Inotropics	254	5	286	5
Lipid regulators	1413	30	1,509	25
Beta-blockers	613	13	537	9
Nitrates	704	15	843	14
History of Ischemic Heart Disease	233	5	319	5
History of Arrhythmia	139	3	165	3
History of Hypertension	1,785	37	2,202	36
History of Diabetes	456	10	591	10
Use of Spirometry (at least once)	4,225	89	5,093	84
Number of General Practitioner Visits[2]				
0	357	6	288	7
1-5	2,167	45	2,577	42
6-10	1,415	30	1,902	31

	Total Study Population n=10,840			
	Tiotropium		LABA[1]	
	N	%	N	%
11+	897	19	1,237	20
Number of Hospital Admissions[2]				
0	4143	87	5,097	84
1—2	502	11	791	13
3+	122	3	185	3

Abbreviations: N, number; LABA, long-acting beta-agonists, —, not applicable
[1] Single-ingredient formulations; [2] 365 days prior to index date

Table 3. Incidence rates and adjusted rate ratio estimates in new users of long-acting bronchodilators

Adverse Events	Tiotropium N = 4,767			LABA[1] N = 6,073			Crude	Adjusted		
	N	Pyrs	Rate[2]	N	Pyrs	Rate	RR	HR	95% CI	
Death (any)	152	2,775	5.48	170	2,303	7.38	0.74	**0.70**	0.56	0.89
Cardiovascular										
Aneurysm	17	2,765	0.61	13	2,298	0.57	1.09	**0.96**	0.44	2.05
Atrial fibrillation/flutter	87	2,725	3.19	76	2,272	3.34	0.95	**0.99**	0.71	1.38
Cardiac arrest	3	2,774	0.11	4	2,303	0.17	0.65	—	—	—
Coronary artery disease	125	2,712	4.61	102	2,255	4.52	1.02	**1.11**	0.84	1.47
Angina	53	2,746	1.93	38	2,275	1.67	1.16	**1.38**	0.88	2.16
Myocardial infarction	35	2,765	1.27	23	2,297	1.00	1.26	**1.26**	0.72	2.21
Heart failure	93	2,738	3.40	105	2,265	4.64	0.73	**0.85**	0.63	1.14
Hypertension	169	2,654	6.37	163	2,232	7.30	0.87	**1.03**	0.81	1.29
Stroke	45	2,750	1.64	28	2,296	1.22	1.34	**1.49**	0.91	2.45
Syncope	35	2,762	1.27	35	2,289	1.53	0.83	**0.94**	0.57	1.55
Tachycardia	15	2,769	0.54	11	2,296	0.48	1.13	**1.08**	0.48	2.41
Ventricular tachycardia	2	2,774	0.07	1	2,302	0.04	1.66	—	—	—
Respiratory										
Asthma exacerbation	98	2,716	3.61	395	2,140	18.46	0.20	**0.46**	0.36	0.57
COPD exacerbation	287	2,637	10.88	313	2,168	14.44	0.75	**0.95**	0.80	1.12
Pneumonia	35	2,757	1.27	34	2,297	1.48	0.86	**0.96**	0.58	1.58
Other										
Constipation	137	2,708	5.06	124	2,251	5.51	0.92	**0.95**	0.74	1.23
Dry mouth	26	2,762	0.94	7	2,299	0.30	3.09	**3.66**	1.52	8.78
Dysphagia	39	2,757	1.41	32	2,292	1.40	1.01	**1.02**	0.62	1.69
Paralytic ileus/bowel obstruction	4	2,775	0.14	7	2,301	0.30	0.47	—	—	—
Renal failure	34	2,760	1.23	19	2,295	0.83	1.49	**1.40**	0.77	2.55
Urinary retention	29	2,765	1.05	25	2,290	1.09	0.96	**0.97**	0.55	1.70
Tremor	16	2,769	0.58	23	2,292	1.00	0.58	**0.62**	0.31	1.22

Abbreviations: LABA, long-acting β-agonists; N, number of patients; Pyrs, person-years at risk; RR, rate ratio; HR, relative hazard estimated using Cox' proportional hazards model adjusted for propensity score; CI, confidence interval.

[1] Single-ingredient formulations; [2] Rate per 100 person-years

'—' signifies the adjusted results are not presented as there are < 5 events in either tiotropium or LABA users.