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A new user cohort study comparing the safety of long-acting inhaled bronchodilators in COPD

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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 β-agonist (LABA) monotherapy, and propensity scores were used to control confounding.

Setting: UK healthcare system general practitioner electronic medical record database.

Participants: 10 840 patients newly prescribed tiotropium (n=4767) or LABA (n=6073), 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 to 2.45), angina (HR=1.38, 95% CI 0.88 to 2.16) and myocardial infarction (HR=1.26, 95% CI 0.72 to 2.21). Groups had similar rates of chronic obstructive pulmonary disease exacerbation (HR=0.95, 95% CI 0.80 to 1.12) and pneumonia (HR=0.96, 95% CI 0.58 to 1.58). Tiotropium was associated with a lower rate of total mortality (HR=0.70, 95% CI 0.56 to 0.89) and asthma exacerbations (HR=0.46, 95% CI 0.36 to 0.57) than users of LABA.

Conclusion: Small increased risks of serious ischaemic cardiovascular events have been reported with inhaled anticholinergic medication from randomised 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.

ARTICLE 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 chronic obstructive pulmonary disease.
- The authors compared new users of long-acting anticholinergic therapy (tiotropium HandiHaler®) with new users of 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 ischaemic cardiovascular events.

Strengths and limitations of this study

- 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 end points of all-cause mortality and all strokes may attenuate associations for cardiovascular mortality and ischaemic stroke.

INTRODUCTION

Inhaled anticholinergic medications, including short-acting ipratropium bromide (ipratropium) and long-acting tiotropium bromide (tiotropium), are mainstays for the treatment of symptoms of chronic obstructive pulmonary disease (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 ischaemia, possibly secondary to tachyarrhythmias,[4 5] and could pose a risk to patients with cardiovascular complications.[6] Among patients with congestive heart failure, SVT is a risk factor for stroke, as well as cardiovascular

hospitalisation and death.[7] Furthermore, 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 (MI).

METHODS

Treatment guidelines for COPD consider long-acting bronchodilators as a class and make no distinction between anticholinergic drugs and long-acting β agonists (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 deidentified 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 and has been validated for COPD, as well as stroke and MI, 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 end points included various cardiovascular adverse events (aneurysm, atrial fibrillation, cardiac arrest, coronary artery disease, angina, MI, 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 end points 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 codes and enrolment dates.

Covariates were selected for inclusion in the analysis based on clinical importance and included respiratory diagnosis (COPD/no asthma, COPD and asthma, other (ie, asthma or COPD not recorded)), age, sex, calendar year of drug start, smoking, body mass index, number of hospitalisations in the year prior to cohort entry, number of general practitioner visits in the year prior to cohort entry, cardiac comorbidities (ischaemic heart disease, arrhythmias, hypertension), respiratory medications (number of prescriptions for short-acting anticholinergics, short-acting β-agonists, inhaled corticosteroids, oral corticosteroids and use of theophyllines and cromoglycates), cardiac medications (prescriptions for antiarrhythmics, anticoagulants, anti-hypertensives, ACE inhibitors, diuretics, inotropics, lipid regulators, β-blockers, nitrates), other medications (gastrointestinal, vascular, central nervous system, infectious disease, endocrine, gynaecologic/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 the analysis of each end point, patients were followed from the date of their first eligible prescription until the earliest of the following: date of treatment end, date of study end point, date of transfer to a new practice, death or January 2007. Each end point was analysed separately, so patients who experienced more than one end point under study were included in analyses of each event.

Incidence rates of the study end points 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% CIs.[15]

Some end points 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 HRs and corresponding 95% CIs.[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 end points where the

event was detected in at least five 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 6 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 V.7.0 and SAS V.9.1. This study received ethical approval from the UK Department of Health Multicentre Research Ethics Committee.

RESULTS

The study population included 4767 tiotropium patients and 6073 LABA patients who contributed 2775 person-years of exposure to tiotropium and 2303 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 per cent 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 codiagnosis (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 to 2.16), MI (HR=1.26, 95% CI 0.72 to 2.21) and stroke (HR=1.49, 95% CI 0.91 to 2.45). There were similar rates between treatment groups of aneurysm (HR=0.96, 95% CI 0.44 to 2.05), atrial fibrillation or flutter (HR=0.99, 95% CI 0.71 to 1.38), coronary artery disease (HR=1.11, 95% CI 0.84 to 1.47), hypertension (HR=1.03, 95% CI 0.81 to 1.29), syncope (HR=0.94, 95% CI 0.57 to 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 to 1.14) and all-cause mortality (HR=0.70, 95% CI 0.56 to 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 to 0.57). There were similar rates of COPD exacerbations (HR=0.95, 95% CI 0.80 to 1.12) and pneumonia (HR=0.96, 95% CI 0.58 to 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 to 8.78). The rate of constipation (HR=0.95, 95% CI 0.74 to 1.23), dysphagia (HR=1.02, 95% CI 0.62 to 1.69) and urinary retention (HR=0.97, 95% CI 0.55 to 1.70) was similar in both treatment groups. There was a higher rate of renal failure in tiotropium patients (HR=1.40, 95% CI 0.77 to 2.55) and a lower rate of tremor (HR=0.62, 95% CI 0.31 to 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 to 3.17), angina (HR=1.42, 95% CI 0.78 to 2.59) and MI (HR=1.65, 95% CI 0.63 to 4.27). The difference between groups in rates of total mortality diminished (HR=0.90, 95% CI 0.58 to 1.38). Associations for other cardiovascular events were weaker, including aneurysm (HR=0.82, 95% CI 0.27 to 2.45), atrial fibrillation/flutter (HR=1.17, 95% CI 0.70 to 1.94), heart failure (HR=0.77, 95% CI 0.47 to 1.24), hypertension (HR=1.07, 95% CI 0.79 to 1.45), syncope (HR=0.79, 95% CI 0.36 to 1.70) and tachycardia (HR=0.98, 95% CI 0.32 to 3.04).

Effect estimates for respiratory end points 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 to 0.65), COPD exacerbation (HR=0.82,

Table 1 Demographic characteristics of the study population

	Tiotropium, n=4767		LABA*, n=6073	
	n	%	n	%
Age group				
40–49	149	3	362	6
50–59	641	13	943	16
60–69	1391	29	1730	28
70–79	1759	37	1991	33
80–89	769	16	976	16
90+	58	1	71	1
Sex				
Male	2707	57	3073	51
Female	2060	43	3000	49
Body mass index				
Low	634	13	613	10
Normal	1500	31	1799	30
Overweight	1413	30	1895	31
Obese	1012	21	1467	24
Missing	208	4	299	5
Smoking				
Never	562	12	1077	18
Current	1765	37	1812	30
Former	2343	49	2960	49
Missing	97	2	224	4

*Long-acting β-agonist single-ingredient formulations.

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

	Tiotropium, n=4767		LABA*, n=6073	
	n	%	n	%
Prior respiratory diagnosis				
COPD and asthma	1807	38	3366	55
COPD only	2450	51	1960	32
Other	510	11	747	12
Use of respiratory medications†				
Short-acting anticholinergics	1948	41	2372	39
Short-acting β-agonists	3372	71	5053	83
Inhaled corticosteroids	1904	40	3610	59
Oral corticosteroids	1396	29	2227	37
Theophyllines	238	5	361	6
Cromoglycates	48	1	67	1
Use of oxygen	187	4	175	3
Use of cardiac medications†				
Anti-arrhythmics	219	5	312	5
Anti-coagulants	1834	38	2069	34
Anti-hypertensives	2424	51	2913	48
ACE inhibitors	1162	24	1380	23
Diuretics	1912	40	2336	38
Inotropics	254	5	286	5
Lipid regulators	1413	30	1509	25
β-Blockers	613	13	537	9
Nitrates	704	15	843	14
History of ischaemic heart disease	233	5	319	5
History of arrhythmia	139	3	165	3
History of hypertension	1785	37	2202	36
History of diabetes	456	10	591	10
Use of spirometry (at least once)	4225	89	5093	84
Number of general practitioner visits†				
0	357	6	288	7
1–5	2167	45	2577	42
6–10	1415	30	1902	31
11+	897	19	1237	20
Number of hospital admissions†				
0	4143	87	5097	84
1–2	502	11	791	13
3+	122	3	185	3

*Single-ingredient formulations.
†365 days prior to index date.
COPD, chronic obstructive pulmonary disease; N, number; LABA, long-acting β-agonists.

95% CI 0.63 to 1.05) and pneumonia (HR=1.42, 95% CI 0.68 to 2.96)). Effect estimates computed for other events included constipation (HR=0.97, 95% CI 0.69 to 1.37), dysphagia (HR=1.30, 95% CI 0.65 to 2.58), renal failure (HR=1.17, 95% CI 0.51 to 2.66), urinary retention (HR=1.17, 95% CI 0.51 to 2.66) and tremor (HR=0.57, 95% CI 0.23 to 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 to 3.63) than patients with only COPD (HR=0.93, 95% CI 0.49 to 1.77), while the association with MI was stronger in patients who had only COPD (HR=1.94, 95% CI 0.77 to 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 patients without coronary artery disease (HR=3.02, 95% CI 1.08 to 8.47) than among patients with coronary artery disease (HR=1.05, 95% CI 0.63 to 1.77). After stratification by corticosteroids, the association with angina was greater among patients without corticosteroids (HR=2.28, 95% CI 0.99 to 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 to 3.44) than without corticosteroids (HR=0.86, 95% CI 0.37 to 2.01).

DISCUSSION

This study found small increased risks of stroke, MI and angina along with a decreased risk of mortality with

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

	Tiotropium, n=4767			LABA,* n=6073			Crude	Adjusted	
Adverse events	**n**	**Pyrs**	**Rate†**	**n**	**Pyrs**	**Rate**	**RR**	**HR**	**95% CI**
Death (any)	152	2775	5.48	170	2303	7.38	0.74	0.70	0.56 to 0.89
Cardiovascular									
Aneurysm	17	2765	0.61	13	2298	0.57	1.09	0.96	0.44 to 2.05
Atrial fibrillation/flutter	87	2725	3.19	76	2272	3.34	0.95	0.99	0.71 to 1.38
Cardiac arrest	3	2774	0.11	4	2303	0.17	0.65	–	–
Coronary artery disease	125	2712	4.61	102	2255	4.52	1.02	1.11	0.84 to 1.47
Angina	53	2746	1.93	38	2275	1.67	1.16	1.38	0.88 to 2.16
Myocardial infarction	35	2765	1.27	23	2297	1.00	1.26	1.26	0.72 to 2.21
Heart failure	93	2738	3.40	105	2265	4.64	0.73	0.85	0.63 to 1.14
Hypertension	169	2654	6.37	163	2232	7.30	0.87	1.03	0.81 to 1.29
Stroke	45	2750	1.64	28	2296	1.22	1.34	1.49	0.91 to 2.45
Syncope	35	2762	1.27	35	2289	1.53	0.83	0.94	0.57 to 1.55
Tachycardia	15	2769	0.54	11	2296	0.48	1.13	1.08	0.48 to 2.41
Ventricular tachycardia	2	2774	0.07	1	2302	0.04	1.66	–	–
Respiratory									
Asthma exacerbation	98	2716	3.61	395	2140	18.46	0.20	0.46	0.36 to 0.57
COPD exacerbation	287	2637	10.88	313	2168	14.44	0.75	0.95	0.80 to 1.12
Pneumonia	35	2757	1.27	34	2297	1.48	0.86	0.96	0.58 to 1.58
Other									
Constipation	137	2708	5.06	124	2251	5.51	0.92	0.95	0.74 to 1.23
Dry mouth	26	2762	0.94	7	2299	0.30	3.09	3.66	1.52 to 8.78
Dysphagia	39	2757	1.41	32	2292	1.40	1.01	1.02	0.62 to 1.69
Paralytic ileus/bowel obstruction	4	2775	0.14	7	2301	0.30	0.47	–	–
Renal failure	34	2760	1.23	19	2295	0.83	1.49	1.40	0.77 to 2.55
Urinary retention	29	2765	1.05	25	2290	1.09	0.96	0.97	0.55 to 1.70
Tremor	16	2769	0.58	23	2292	1.00	0.58	0.62	0.31 to 1.22

*Single-ingredient formulations.
†Rate per 100 person-years.
'–' signifies the adjusted results are not presented as there are <5 events in either tiotropium or LABA users.
COPD, chronic obstructive pulmonary disease; 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.

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 randomised trial of an inhaled anticholinergic agent reported an increased incidence in the ipratropium group of hospitalisation due to SVT, angina, MI and death due to coronary heart disease.[18] Observational studies have reported associations between ipratropium and stroke,[19] cardiovascular hospitalisation[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, MI and no increased risk of stroke with tiotropium.[23] As in other studies, the stroke end point was a composite end point that included ischaemic and hemorrhagic stroke,[23] and the incidence of ischaemic 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 randomised 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 to 3.89).[27] A randomised 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 MI, cardiovascular mortality and total mortality.[30–32]

Perhaps the most relevant study is the recent 'POET' study, the largest tiotropium randomised trial conducted to date, with 7376 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 (eight tioptropium vs six 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 (nine tiotropium vs five salmeterol), myocardial ischaemia (11 tiotropium vs six salmeterol) and MI (20 tiotropium vs 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 USA.[35] (Tiotropium Respimat was not available in the UK at the time of this analysis.) It was hypothesised 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 ischaemic events, but not MI.[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 of both causal and non-causal explanations. For composite end points, 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, MI 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.

Non-randomized 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 that 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 ischaemic cardiovascular events in randomised 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 end points, results showed an increased risk of dry mouth with tiotropium, but not for other anticholinergic end points 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 end points as well, although we would expect that completeness of the medical record would be better for more serious cardiovascular events. Misclassification of certain serious end points still is a concern, however, as we examined total mortality and total strokes, but not cardiovascular mortality or ischaemic 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, MI 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 help explain these divergent conclusions. First, we consider the entire body of evidence pertaining to class effects, and we consider each study on its merits. In particular, studies should not be disregarded merely because they are not randomised[19–21 29] or they include an another medication as a control group instead of a placebo group.[28 33] Second, when considering the evidence pertaining to small effects on rare adverse events, we do 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 ischaemic stroke with tiotropium than placebo[24] and so can hardly provide reassurance about the absence of such risks. In addition, results from composite end points 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 ischaemic 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 non-causal 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 MI in the Uplift study does not negate increases in risk of MI 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 older people 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-randomised and randomised studies, of various sizes and durations, with ipratropium and tiotropium, compared with placebo and active comparators, and using different devices. Pharmacological 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 MI, 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.

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