Outcomes Associated With Tiotropium Use in Patients With Chronic Obstructive Pulmonary Disease

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Background: To date, there is mixed evidence on the safety and effectiveness of tiotropium. Our objective was to evaluate the comparative effectiveness of regimens containing tiotropium bromide vs other medication regimens for chronic obstructive pulmonary disease (COPD) in real-world clinical settings.

Methods: We conducted a cohort study on 2 separate cohorts with a diagnosis of COPD in the Veterans Affairs health care system. Patients with a diagnosis of COPD prescribed tiotropium and patients in a historic cohort prior to the introduction of tiotropium were selected for comparison using propensity scores, with the base case including scores from 0.1 to 0.4. Outcomes identified during follow-up were all-cause mortality, COPD exacerbations, and COPD hospitalizations. Exposure to COPD medication regimens was defined in a time-varying manner and Cox proportional hazards regression were used to evaluate outcomes.

Results: For 42 090 patients in the base case, the regimen of tiotropium + inhaled corticosteroids (ICS) + long-acting β-agonists (LABA) was associated with 40% reduced risk of death (hazard ratio [HR], 0.60; 95% confidence interval [CI], 0.45-0.79) compared with ICS + LABA. This combination was associated with reduced rates of COPD exacerbations (HR, 0.84; 95% CI, 0.73-0.97) and COPD hospitalizations (HR, 0.78; 95% CI, 0.62-0.98). Tiotropium in combination with 2 other medications was associated with increased risk of mortality, exacerbations, and hospitalizations.

Conclusions: When used with ICS and LABA, tiotropium use was associated with a decreased risk of mortality compared with treatment with ICS and LABA. However, this result was not consistent in other medication regimens that included tiotropium.

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PATIENTS AND HEALTH CARE PROviders are often confronted by treatment alternatives with limited information by which to make decisions. One prominent gap in clinical information is the lack of direct comparisons between treatments, because much of the evidence in clinical practice guidelines comes directly from placebo-controlled trials rather than head-to-head comparisons. Enrolling patients in trials that use rigid inclusion and exclusion criteria often leads to selected populations who may be different from those ultimately using the medication.[1,2] Thus, to complement results from placebo-controlled trials, comparative effectiveness studies of treatment interventions are increasingly conducted to inform decision making for more general populations.[3] For the most part, guidelines for chronic obstructive pulmonary disease (COPD) are based on results of short-term clinical trials using intermediate end points and consensus of COPD experts.[4,5] It is important to note that the recent focus of COPD clinical trials has been on overall mortality.[6,7] These trials have contributed evidence on longer-term effects of COPD medications; however, they often fail to provide evidence on comparative effectiveness of medication regimens because they focus on monotherapy. An exception is the Toward a Revolution in COPD Health (TORCH) study[6] that focused on combination inhaled corticosteroids (ICS) and long-acting β-agonists (LABA), yet concerns about the generalizability of the sample remains.

Tiotropium bromide is the most recent addition to the treatment options available for patients with COPD. Several short-term clinical trials[8-11] and trials of longer than 12 months[12,13] have shown that tiotropium improves lung function, symptoms, and quality of life, whereas a 6-month trial in the Veterans Affairs (VA) health care system showed that tiotropium was associated with reduced COPD exacerbations.[14] The recently completed

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Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) study[7] showed that tiotropium was associated with a reduced rate of exacerbations and COPD hospitalizations and improvement in respiratory-related quality of life.[7]

Although evidence is growing on the efficacy of tiotropium, controversy exists with respect to overall safety. A recent meta-analysis[15] showed an increased risk of cardiovascular mortality, whereas our meta-analysis and others have not found a significant increase in overall mortality associated with tiotropium use.[16,17] As noted, clinical trial populations may be quite different from those treated in clinical practice, and the primary aim of these studies is not to evaluate the overall safety of the medication. Therefore, examining outcomes outside of clinical trials is important.

Our objective was to evaluate the comparative effectiveness of regimens containing tiotropium vs other medication regimens for COPD. Owing to medication policies in place for the use of tiotropium in the VA health care system, we sought to compare outcomes among a group of patients switched to a regimen that either included (1) tiotropium or (2) ICS + LABA.

METHODS

We conducted a cohort study in patients with COPD using national VA inpatient, outpatient, pharmacy, and mortality data. Tiotropium was not available prior to February 2004, and there were initial restrictions on use when it was introduced. For these reasons, both contemporary and historic controls were used to identify patients with characteristics similar to those of patients treated with tiotropium. Initial restrictions required patients to see a pulmonologist and to have failed treatment with other COPD medications. Failure was indicated by an exacerbation that resulted in a hospitalization or at least 2 outpatient exacerbations in the last 12 months. Subsequently, these restrictions were modified such that a visit to a pulmonologist was no longer required and failure could include clinically significant symptoms. Because of the use restrictions and the fact that tiotropium was not used as first-line treatment for patients with COPD in the VA, we compared tiotropium with other medication regimens following a regimen change.

COHORT

Patients were identified for inclusion during 2 periods. During the first period, patients were identified for inclusion as historic controls to identify patients who possessed similar characteristics with those switched to treatment with tiotropium in a more contemporary cohort. In this way, we took advantage of the fact that tiotropium was not a treatment option during identification of the historic cohort and that it is not used as a first-line treatment for COPD in the VA health care system.

To be included, patients had to have a diagnosis of COPD (*International Classification of Diseases, Ninth Revision [ICD-9]* codes 491.x, 492.x, or 496) during a 12-month period on at least 2 outpatient encounters or a single inpatient discharge diagnosis and be at least 45 years of age. Patients had to have received COPD medications from the VA and been switched to a regimen that included either tiotropium or ICS + LABA. Patients who died less than 30 days following their medication switch and those with a diagnosis of asthma were excluded. Patients from the first cohort (hereinafter, historic cohort) were identified from October 1, 2002, through September 30, 2003. Patients from the second cohort were identified from October 1, 2004, through March 31, 2006 (hereinafter, contemporary cohort).

FOLLOW-UP PERIOD

We defined the index date based on the date that a patient was switched to an eligible regimen. Patients were followed up for up to 547 days. Patients were followed up until they died, had not filled a prescription for 180 days, or 547 days, whichever occurred first.

OUTCOMES

During follow-up, we measured 3 outcomes: (1) all-cause mortality, (2) COPD exacerbations, and (3) COPD hospitalizations. Events occurring within 30 days following the index date were not included. Because a medication switch may have been related to an event or an indicator of symptoms that may have preceded this event, we did not want to attribute those events to exposure to the medications during the switch. Therefore, each patient was given a 30-day immortal period following the switch. Because this period was equal for all patients, it did not introduce immortal time bias into the analysis.[18-20]

Deaths were identified using the VA Vital Status file, which captures approximately 98% of deaths.[21] Exacerbations were identified based on *ICD-9* codes related to COPD present in combination with 1 of the following: (1) hospitalization, (2) emergency department visit, or (3) outpatient visit with either an oral steroid or antibiotic dispensing within 5 days of the visit.[22,23] The first hospitalization with a primary diagnosis of COPD during follow-up was used to identify COPD-related hospitalizations.

EXPOSURE

Medication exposure was measured as a time-varying covariate during follow-up. Exposure was measured as the presence of a prescription for a respiratory medication in the 180-day period prior to each day of the follow-up period. Specifically, an individual's medication exposure was redefined each time there was an event during follow-up and the individual remained at risk. Exposure was defined using the 180-day period prior to the day of the event. We identified use of ICS, ipratropium bromide, LABA, short-acting β-agonists (SABA), theophylline, and tiotropium. For each exposure day, we defined medication regimens based on the combination of medication used during that period. Time-varying exposure allowed for different medication regimens to be attributed to the same individual.

We did include SABA in regimen definitions because of their nearly universal use by patients in the cohort. There were 32 possible medication regimens for exposure during follow-up, which includes exposure to only SABA or no respiratory medication. Owing to relatively small amounts of exposure in some regimens, we combined regimens with less than 1% of exposure time during follow-up. This resulted in 17 medication regimens or regimen combinations included in the analysis.

COVARIATES

We defined covariates from the 12 months preceding the index date. Demographic characteristics, health care utilization, and coexisting conditions were determined from inpatient and outpatient data. For health care utilization, we measured COPD-related and non–COPD-related health care. We measured the use of respiratory and other medications that preceded the medication switch. Other important covariates included distance to the nearest VA hospital and level of prescription medication copayment.[24]

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Table 1. Baseline Characteristics of the Cohort by Initial Tiotropium Bromide (TIO) Exposure[a]

Characteristic	Switch to ICS + LABA	Switch to TIO
No.	38 850	3240
Demographics		
Age, mean (SD), y	69.98 (9.7)	70.74 (9.1)
Male	38 009 (97.8)	3153 (97.3)
Race		
White	19 762 (50.9)	1659 (51.2)
Black	2158 (5.6)	159 (4.9)
Other	652 (1.7)	81 (2.5)
Unknown	16 278 (41.9)	1341 (41.4)
Comorbidities		
Hypertension	24 758 (63.7)	2066 (63.8)
Heart disease	12 665 (32.6)	1114 (34.4)
Osteoarthritis	7552 (19.4)	567 (17.5)
Diabetes mellitus	8634 (22.2)	744 (23.0)
Depression	5782 (14.9)	503 (15.5)
Cancer	8496 (21.9)	793 (24.5)
CHF	5736 (14.8)	606 (18.7)
Resource utilization		
Distance to VA health center, mean (SD), miles	41.18 (63.0)	36.12 (58.8)
Level of copayment		
No copayment	6569 (16.9)	616 (19.0)
Some copayment	23 409 (60.3)	2013 (62.1)
Full copayment	7851 (20.2)	555 (17.1)
Missing	1021 (2.6)	56 (1.7)
Baseline exacerbations		
0	25 293 (65.1)	1249 (38.6)
1	7497 (19.3)	712 (22.0)
≥2	6060 (15.6)	1279 (39.5)
Baseline hospitalizations		
0	30 100 (77.5)	2127 (65.7)
1	1833 (4.7)	571 (17.6)
≥2	6917 (17.8)	542 (16.7)
Emergency department visits		
0	32 314 (83.2)	2457 (75.8)
1	3181 (8.2)	325 (10.0)
≥2	3355 (8.6)	458 (14.1)
Outpatient visits		
0	64 (0.2)	6 (0.2)
1	819 (2.1)	27 (0.8)
≥2	37 967 (97.7)	3207 (99.0)
PC visits		
0	768 (2.0)	69 (2.1)
1	3298 (8.5)	224 (6.9)
≥2	34 784 (89.5)	2947 (91.0)
Baseline medication use		
COPD		
ICS	18 476 (47.6)	2145 (66.2)
LABA	15 125 (38.9)	2223 (68.6)
IPRA	23 035 (59.3)	2340 (72.2)
THEO	4022 (10.4)	495 (15.3)
Cardiac medications		
Digitalis	3660 (9.7)	336 (10.7)
β-Blockers	10 689 (28.2)	875 (27.8)
α-Blockers	8402 (22.2)	700 (22.2)
Calcium channel blockers	11 475 (30.3)	944 (30.0)
Antianginals	7917 (20.9)	724 (23.0)
Antiarrhythmics	1169 (3.1)	96 (3.1)
Antilipemics	18 613 (49.2)	1568 (49.8)
Vasodilators	16 (0.0)	2 (0.1)
Diuretics	16 296 (43.1)	1373 (43.6)
ACE inhibitors	2606 (6.9)	191 (6.1)
Angiotensin II inhibitor	17 397 (46.0)	1503 (47.7)

Abbreviations: ACE, angiotensin-converting enzyme; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids; IPRA, ipratropium bromide; LABA, long-acting β-agonists; PC, primary care; THEO, theophylline; VA, Veterans Affairs.

[a] Data are given as number (percentage) except where noted.

PROPENSITY SCORE

We calculated propensity scores to balance groups on baseline characteristics in an effort to reduce concerns related to confounding by indication and other biases that may exist.[25-31] Using baseline characteristics as covariates, we estimated the likelihood of switching to tiotropium only in the contemporary cohort because tiotropium was not available in the historic cohort and the probability of switching to tiotropium was zero. The propensity score model was fitted for the initial medication (ie, a switch to ICS + LABA or a switch to tiotropium) and then applied to both cohorts for each individual. Because of differences in the distribution of propensity scores between groups, only those with a propensity score of 0.1 to 0.4 were included.

STATISTICAL ANALYSIS

Analyses were performed separately for each outcome. We used Cox proportional hazards models, controlling for propensity score, to examine the association between medication regimen exposure and risk of event. We used the group prescribed ICS + LABA during the period in which tiotropium was not available (historic controls) as the reference group. We conducted several sensitivity analyses to evaluate the impact on study results. First, we used patients not treated with tiotropium (nontiotropium groups) from both the historic and contemporary cohorts. Second, only those in the nontiotropium group from the contemporary cohort were used as controls. Third, the time frame for identifying exposure was reduced to 90 days from 180 days in the base case. Fourth, follow-up was stopped after 365 days to evaluate results over a 1-year period. Fifth, patients were censored when they had a medication change from their index medication regimen. Sixth, we controlled for baseline cardiovascular medication use in regression models. Seventh, patients with a hospitalization during baseline were excluded in an attempt to focus on a more homogeneous patient population. Eighth, treatments were compared among patients with propensity scores of 0.4 to 0.7. We conducted analysis with Stata/MP statistical software (version 10.0 for Windows; StataCorp LP, College Station, Texas) and SAS software (version 9.2 for Windows; SAS Institute Inc, Cary, North Carolina).

RESULTS

We identified 135 422 patients for inclusion, of whom 42 090 were included in the base case. A total of 38 850 patients were switched to a regimen that included ICS and LABA in the historic cohort, whereas 3240 were switched to a regimen that included tiotropium. The mean age in both groups was around 70 years, and nearly 98% were male (**Table 1**). The group that was switched to tiotropium had more COPD exacerbations at baseline and had a slightly

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Table 2. Medication Exposure for Each Mutually Exclusive Treatment Regimen During Follow-Up[a]

Drug Regimen	Patients Exposed, No. (%)	Cumulative Person-Days of Exposure, Total (% of Total)	Duration of Exposure, Mean (SD), d
No treatment or SABA only	1749 (4.2)	105 840 (0.6)	60.5 (70.2)
ICS	2391 (5.7)	139 706 (0.8)	58.4 (69.6)
IPRA	5870 (13.9)	509 173 (3.0)	86.7 (90.1)
LABA	4343 (10.3)	278 971 (1.6)	64.2 (79.4)
THEO	818 (1.9)	55 205 (0.3)	67.5 (84.5)
ICS + IPRA	7199 (17.1)	750 815 (4.4)	104.3 (106.0)
ICS + LABA	8659 (20.5)	976 805 (5.7)	112.8 (120.0)
ICS + THEO	556 (1.3)	41 614 (0.2)	74.9 (93.3)
IPRA + LABA	7614 (18.1)	746 623 (4.4)	98.1 (101.4)
IPRA + THEO	944 (2.2)	82 427 (0.5)	87.3 (89.9)
LABA + THEO	793 (1.9)	60 179 (0.4)	75.9 (85.6)
ICS + IPRA + LABA	31 937 (75.8)	9 404 072 (54.8)	294.5 (171.8)
ICS + IPRA + THEO	1565 (3.7)	164 756 (1.0)	105.3 (106.9)
ICS + LABA + THEO	2577 (6.1)	446 209 (2.6)	173.2 (166.9)
IPRA + LABA + THEO	1489 (3.5)	143 173 (0.8)	96.2 (97.9)
ICS + LABA + IPRA + THEO	7186 (17.0)	2 013 658 (11.7)	280.2 (164.7)
TIO	478 (1.1)	33 809 (0.2)	70.7 (75.8)
ICS + TIO	416 (1.0)	37 318 (0.2)	89.7 (83.9)
IPRA + TIO	286 (0.7)	15 617 (0.1)	54.6 (58.0)
LABA + TIO	919 (2.2)	95 435 (0.6)	103.9 (95.8)
THEO + TIO	77 (0.2)	6191 (0.0)	80.4 (85.1)
ICS + IPRA + TIO	832 (2.0)	73 785 (0.4)	88.7 (73.0)
ICS + LABA + TIO	2685 (6.4)	403 767 (2.4)	150.4 (120.9)
ICS + THEO + TIO	92 (0.2)	9173 (0.1)	99.7 (100.6)
IPRA + LABA + TIO	1190 (2.8)	112 083 (0.7)	94.2 (76.1)
IPRA + THEO + TIO	95 (0.2)	7044 (0.0)	74.2 (72.3)
LABA + THEO + TIO	156 (0.4)	18 865 (0.1)	120.9 (104.7)
ICS + LABA + IPRA + TIO	2669 (6.3)	290 950 (1.7)	109.0 (76.6)
ICS + IPRA + THEO + TIO	166 (0.4)	15 297 (0.1)	92.2 (77.1)
ICS + LABA + THEO + TIO	422 (1.0)	54 073 (0.3)	128.1 (108.5)
IPRA + LABA + THEO + TIO	194 (0.5)	18 117 (0.1)	93.4 (75.7)
ICS + LABA + IPRA + THEO + TIO	481 (1.1)	49 843 (0.3)	103.6 (65.8)

Abbreviations: ICS, inhaled corticosteroids; IPRA, ipratropium bromide; LABA, long-acting β-agonists; SABA, short-acting β-agonists; THEO, theophylline; TIO, tiotropium bromide.

[a] Regimens with less than 1% of cumulative person-days of exposure were combined in the analysis.

larger percentage of patients with 2 or more outpatient visits in the preceding 12 months (99.0% vs 97.7%).

During follow-up there were more than 17.1 million person-days of medication exposure. The most commonly used regimen was ICS + ipratropium + LABA (**Table 2**). This regimen was used during slightly more than 50% of exposure days and was used by 76% of patients at some point during follow-up. The reference regimen of ICS + LABA was used by 20.5% of the cohort over nearly 1 million person-days of exposure. Of the tiotropium regimens, the most frequently used regimen was tiotropium in combination with ICS and LABA, which was used in 2.4% of the exposure days and by 6.4% of the overall group. The second most commonly used regimen with tiotropium was tiotropium + ICS + LABA + ipratropium (1.7% of exposure days).

For each outcome, the crude rate was higher in the tiotropium-exposed group than in the tiotropium groups. The crude mortality rate was 14.6 per 100 person-years in the tiotropium group and 11.7 per 100 person-years in the nontiotropium group (**Table 3**). The difference equates to a rate ratio of 1.3 for those switched to a tiotropium regimen relative to those not switched to tiotropium. Similar rate ratios were seen for exacerbation and hospitalization rates between groups. When accounting for differences in propensity score between treatment regimens, it was clear there was heterogeneity in the association between the outcomes and regimens that contained tiotropium. The adjusted hazard ratio (HR) for the combination of tiotropium + ICS + LABA showed a 40% reduction in mortality risk (HR, 0.60; 95% confidence interval [CI], 0.45-0.79) compared with treatment with ICS + LABA (**Table 4**). This was in contrast to tiotropium in combination with 2 other respiratory medications, excluding ICS + LABA (eg, tiotropium + IPRA + ICS, tiotropium + LABA + IPRA, tiotropium + theophylline + IPRA), where there was an increased risk of mortality (HR, 1.38; 95% CI, 1.06-1.81). The most common combinations in this group were tiotropium + ipratropium + ICS and tiotropium + ipratropium + LABA, which contributed 84% of the exposure days in this group. The combination of tiotropium + ICS + LABA + ipratropium was associated with a 36% increase in risk of death compared with ICS + LABA.

For the most part, findings for exacerbations and hospitalizations were similar to those for mortality. For example, tiotropium + ICS + LABA was consistently associated with a reduced risk of events. For exacerbations there was a 16% reduction in risk (HR, 0.84; 95% CI, 0.79-0.97), whereas there was a 22% reduction (HR, 0.78; 95%

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Table 3. Unadjusted Rate of Events Per 100 Person-Years by Medication Regimen Compared With ICS + LABA

Drug Regimen	Crude Mortality Rate[a]	RR	Crude Exacerbation Rate[a]	RR	Crude Hospitalization Rate[a]	RR
ICS + LABA[b]	8.4		31.4		12.8	
Non-TIO regimen						
ICS + IPRA	14.5	1.72	29.2	0.93	17.3	1.35
IPRA + LABA	11.3	1.34	31.6	1.01	15.9	1.24
ICS + LABA + IPRA	11.5	1.37	37.8	1.20	19.0	1.48
ICS + LABA + THEO	9.0	1.08	25.0	0.79	5.9	0.46
ICS + IPRA + LABA + THEO	13.1	1.56	40.9	1.30	17.9	1.40
TIO regimen						
TIO + 1 other med	10.6	1.27	48.2	1.53	27.7	2.16
TIO + 2 other meds	45.0	5.37	58.5	1.86	28.8	2.24
ICS + LABA + TIO	8.9	1.06	40.1	1.28	16.1	1.26
ICS + LABA + IPRA + TIO	0.8	0.09	47.1	1.50	22.2	1.73
TIO + 3 or 4 other meds	18.1	2.16	47.1	1.50	21.3	1.66

Abbreviations: ICS, inhaled corticosteroids; IPRA, ipratropium bromide; LABA, long-acting β-agonists; med, medication; RR, relative risk; THEO, theophylline; TIO, tiotropium bromide.
[a] Rate per 100 person-years.
[b] Reference category.

Table 4. Association Between Medication Regimen and Mortality, Exacerbation, and Hospitalization

	HR (95% CI)		
Drug Regimen	Mortality	Exacerbations	Hospitalizations
ICS + LABA	1 [Reference]	1 [Reference]	1 [Reference]
Non-TIO regimen			
ICS + IPRA	1.81 (1.42-2.31)	1.30 (1.11-1.52)	1.72 (1.37-2.15)
IPRA + LABA	1.27 (0.97-1.66)	1.33 (1.14-1.55)	1.47 (1.17-1.86)
ICS + LABA + IPRA	1.20 (0.99-1.45)	1.14 (1.02-1.27)	1.46 (1.23-1.72)
ICS + LABA + THEO	0.86 (0.62-1.20)	0.58 (0.47-0.71)	0.44 (0.30-0.63)
ICS + IPRA + LABA + THEO	1.07 (0.86-1.33)	1.03 (0.91-1.16)	1.08 (0.90-1.31)
Tiotropium regimen			
TIO + 1 other med	0.95 (0.66-1.35)	1.31 (1.10-1.56)	1.85 (1.44-2.37)
TIO + 2 other meds	1.38 (1.06-1.81)	1.40 (1.21-1.62)	1.81 (1.45-2.26)
ICS + LABA + TIO	0.60 (0.45-0.79)	0.84 (0.73-0.97)	0.78 (0.62-0.98)
ICS + LABA + IPRA + TIO	1.36 (1.05-1.77)	1.03 (0.88-1.21)	1.15 (0.90-1.46)
IO + 3 or 4 other meds	1.28 (0.93-1.76)	1.02 (0.84-1.24)	0.98 (0.73-1.32)

Abbreviations: CI, confidence interval; HR, hazard ratio: ICS, inhaled corticosteroids; IPRA, ipratropium bromide; LABA, long-acting β-agonists; med, medication; THEO, theophylline; TIO, tiotropium bromide.

CI, 0.62-0.89) for COPD-related hospitalizations. The exception to the consistent results was regimens that included tiotropium + ICS + LABA + ipratropium where there was no significant association between exacerbations (HR, 1.03; 95% CI, 0.88-1.21) and hospitalizations (HR, 1.15; 95% CI, 0.90-1.46) compared with ICS + LABA.

The reduced risk associated with tiotropium + ICS + LABA was consistently seen in each sensitivity analysis for all 3 outcomes (**Figure**). Only in the analysis in which patients with baseline hospitalizations were excluded did we not find a protective effect for the combination of tiotropium + ICS + LABA across each outcome. The sensitivity analysis in which patients were censored at the point of a medication switch resulted in a change in the direction of the association observed with tiotropium + 2 other medications and tiotropium + ICS + LABA + ipratropium. In this analysis, these regimens were associated with a protective effect for mortality relative to ICS + LABA, whereas in the base case and all of the other sensitivity analyses they were associated with an increased risk of mortality.

COMMENT

This study contributes evidence on the safety and comparative effectiveness of tiotropium for treatment of COPD for patient populations that have not previously been examined, using real-world data. In this analysis, we found regimens that included tiotropium + ICS + LABA in combination were associated with reduced risk of all-cause mortality, COPD exacerbations, and COPD hospitalizations compared with ICS + LABA. The other 3 combination regimens that included tiotropium and the 4 combination regimens that included tiotropium + ICS + LABA + ipratropium were associated with increased mortality risk.

Results from our study are similar to those reported from the UPLIFT study,[7] a 4-year, multinational, ran-

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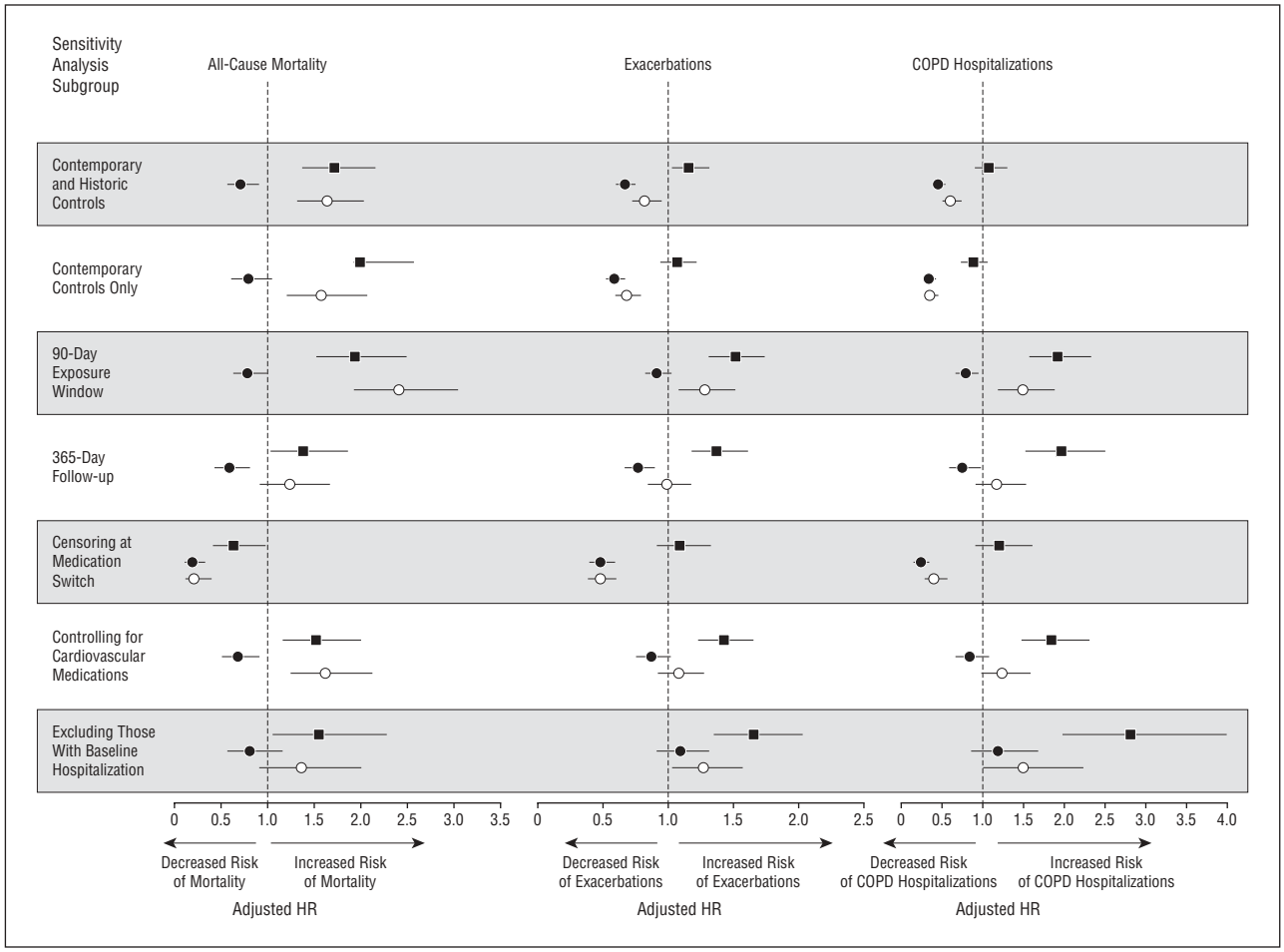

Figure. Sensitivity analyses results from 3 tiotropium bromide–containing regimens compared with inhaled corticosteroids (ICS) + long-acting β-agonists (LABA) for each of the study outcomes. Results from tiotropium + 2 other medications (TIO + 2 other medications, excluding TIO + ICS + LABA) (solid square); TIO + ICS + LABA (solid circle); TIO + ICS + LABA + ipratropium bromide (open circle). The symbols represent the point estimates, and the bars represent the 95% confidence intervals. HR indicates hazard ratio.

domized controlled trial that compared tiotropium with placebo while allowing the use of other COPD medications during the study period. Nearly 6000 patients were enrolled, and the results showed reduced rates of exacerbations (relative risk, 0.86; 95% CI, 0.81-0.91) and improvements in respiratory-related quality of life. The reduced rate of exacerbations in the UPLIFT study[7] was similar to the 16% reduction we observed in this analysis for the combination of tiotropium + ICS + LABA. In the UPLIFT study,[7] tiotropium was associated with an 11% reduction in the risk of death (HR, 0.89; 95% CI, 0.79-1.02), which was not statistically significant, when the 4-year plus 30-day period was used, whereas tiotropium was associated with a 13% reduction in mortality (HR, 0.87; 95% CI, 0.79-0.99) when the analysis was limited to the 4-year study period. The effects in the UPLIFT study[7] are substantially lower than the decreased risk of mortality we observed in patients prescribed tiotropium + ICS + LABA. It is important to note that our comparison of tiotropium + ICS + LABA relative to ICS + LABA is probably most similar to the comparisons in the UPLIFT study[7] given that nearly 3 of 4 patients reported using ICS (74%) or LABA (72%) during the study period. The regimens with ipratropium evaluated in our analysis were not included in the UPLIFT study[7] because the use of short-acting anticholinergics was prohibited except if deemed medically necessary to treat an acute exacerbation.

Our study suggests that there is heterogeneity in the effects observed for treatment regimens that included tiotropium. There are several potential explanations for this finding. First, our reference group comprised those who received the combination of ICS + LABA. The addition of tiotropium to medication regimens that are less effective than ICS + LABA may not improve overall outcomes. Second, medications used in combination with tiotropium may be associated with increased risks, and therefore regimens that included these medications and tiotropium may be associated with an elevated risk compared with the reference group (eg, concurrent use of short-acting anticholinergics). Finally, use of more medications may be indicative of more severe disease, and even though we controlled for markers of disease, severity differences may remain between groups.

Although our findings did not show harm associated with tiotropium in several regimens, it does not alleviate all potential concerns regarding tiotropium safety. This is particularly true if risks reported for ipratropium represent a class effect for anticholinergic medications. If this is the case, our study design is not optimal for identify-

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ing risks associated with tiotropium; although we identify new tiotropium users, many patients had previously used ipratropium, which may limit our ability in identifying adverse effects of anticholinergics.[32] The same is true for the UPLIFT study,[7] in which nearly 50% of patients enrolled used anticholinergics prior to beginning the study. Thus, there is still need to evaluate tiotropium safety in patient populations who are treatment naïve to anticholinergic medications.

One important consideration in interpreting these results is whether we have adequately controlled for severity differences. As described by Strom,[33] a weakness of comparative effectiveness studies using observational data is that, absent randomization, we cannot be certain there were not other differences between groups, unmeasured and uncontrolled, creating a selection bias. Our study suffers from an inability to differentiate severity using a clinical marker of disease. In addition, the VA instituted criteria for the use of tiotropium in patients with COPD that restricted use of the medication. Because of concerns about confounding by indication, we felt it was important to find a comparable group of patients to minimize differences in disease severity and further adjust for differences using propensity scores. Therefore, we selected a cohort from a period when tiotropium was not available and where the combination of ICS and LABA were used as the highest step in COPD treatment. Estimation of the propensity to use tiotropium showed that nearly one-third of tiotropium users we identified were different from those who switched to ICS and LABA. As a result, we limited our cohort to those with similar propensity scores so groups of patients with similar baseline characteristics were compared. Limiting our sample to this group strengthens the internal validity of the findings, but at the expense of generalizability, because the findings may not apply to all users of tiotropium and are most applicable to males given that 98% of the population was male.

Although taking advantage of a time frame in which tiotropium was not available may help balance groups, it also introduces limitations associated with historic controls. Historic controls can raise concerns about secular trends having an impact on findings, which may be particularly true when a mortality benefit is found in a more recent cohort because advances in medical technology may contribute to these differences. However, the time period in which the groups are identified is only 2 years apart, which may limit some of the secular concerns. It is important to note that we conducted sensitivity analyses in which we used controls from both periods as well as controls from only the current period, and the results were consistent across groups. The control group from the same period that the tiotropium users were selected from had baseline characteristics similar to those of the tiotropium users when the sample was restricted by propensity score. Another limitation of the analysis is that we were unable to capture out-of-system use; however, we do not expect out-of-system use to be different between exposure groups, which would bias results toward the null. We were also unable to measure other important covariates, such as smoking status, which may have led to unmeasured confounding in the analysis.

The strength of the present study is that, compared with a randomized trial, we evaluated effects of exposure to respiratory-related drugs in real-life clinical practice. Many combinations of medications that were reported have not, to our knowledge, been previously investigated. However, a subset of comparisons was of primary relevance, specifically the referent combination (ICS + LABA) compared with tiotropium + ICS + LABA. Unlike placebo-controlled trials, this study provides evidence as to the comparative effectiveness of treatments in COPD, which is important for patients and physicians when making treatment decisions in an effort to tailor therapies that are likely to optimize outcomes. Our findings show that, when used in combination with ICS and LABA, tiotropium was associated with a decreased risk of mortality, COPD exacerbations, and COPD hospitalizations compared with treatment with ICS and LABA. However, there is a need for additional information on the comparative effectiveness of COPD treatment regimens so that patients and physicians can make informed treatment decisions by weighing the harms and benefits of each of the medications and medication regimens from direct comparisons.

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Correction

Error in Abstract and Introductory Paragraph of the Main Article. In the article titled "Outcomes Associated With Tiotropium Use in Patients With Chronic Obstructive Pulmonary Disease" by Lee et al, published in the August 10/24 issue of the *Archives* (2009;169[15]: 1403-1410), part of the first paragraph of the article was published in the "Conclusions" section of the abstract. The last sentence of the abstract should have read "However, this result was not consistent in other medication regimens that included tiotropium." (The last 4 sentences of the abstract "Conclusions" should have been the first 4 sentences of the main article.)

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