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Outcomes Associated With Tiotropium Use in Chronic Obstructive Pulmonary Disease Patients

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Abstract

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 versus other medication regimens for chronic obstructive pulmonary disease (COPD) in real-world clinical settings.

Methods: We conducted a cohort study on two separate cohorts with a diagnosis of COPD in the VA healthcare system. Patients with a COPD diagnosis 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 employed to evaluate outcomes.

Results: For 42,090 patients in the base case, the regimen of tiotropium plus inhaled corticosteroids plus long-acting beta-agonists was associated with 40% reduced risk of death (HR=0.60 [95% CI 0.45, 0.79]) compared to inhaled corticosteroids plus long-acting beta-agonists. This combination was associated with reduced rates of COPD exacerbations (HR=0.84 [0.73, 0.97]) and COPD hospitalizations (HR=0.78 [0.62, 0.98]). Tiotropium in combination with two other medications was associated with increased risk of mortality, exacerbations and hospitalizations.

Conclusions: When used with inhaled corticosteroids and long-acting beta-agonists, tiotropium use was associated with a decreased risk of mortality compared to treatment with inhaled corticosteroids and long-acting beta-agonists. However, this result was not consistent in other medication regimens that included tiotropium.

Introduction

Patients and providers are often confronted by treatment alternatives with limited information by which to make decisions. One prominent gap in clinical information is lack of direct comparisons between treatments, as much of the evidence in clinical practice guidelines come directly from placebo control trials rather than head-to-head comparisons. Patients enrolled in trials, which employ rigid inclusion and exclusion criteria, often lead to selected populations who may be different from those ultimately using the medication.[1,2] Thus, in order to complement results from placebo control 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 endpoints and consensus of COPD experts.[4,5] Importantly, 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 Towards a Revolution in COPD Health (TORCH) study that focused on combination inhaled corticosteroids and long-acting beta-agonists, yet concerns about the generalizability of the sample remains.[8]

Tiotropium is the most recent addition to the treatment options available for patients with COPD. Several short-term clinical trials[9-12] and trials of longer than 12 months[13,14] have shown tiotropium improves lung function, symptoms and quality of life, while a six-month trial in the VA healthcare system showed tiotropium was associated with reduced COPD exacerbations.[15] The recently completed Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) study showed tiotropium was associated with a reduced rate of exacerbations and COPD hospitalizations and improvement in respiratory-related quality of life.[16]

While evidence is growing on the efficacy of tiotropium, controversy exists with respect to overall safety. A recent meta-analysis showed an increased risk of cardiovascular mortality,[17] while this meta-analysis and others have not found a significant increase in overall mortality associated with tiotropium use.[18,19] As noted above, 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.

The objective of this study was to evaluate the comparative effectiveness of regimens containing tiotropium versus other medication regimens for COPD. Because of medication policies in place for the use of tiotropium in the VA healthcare system, we sought to compare outcomes among a group of patients switched from to a regimen that either included (1) tiotropium or (2) inhaled corticosteroids plus long-acting beta-agonists.

Methods

We conducted a cohort study in patients with COPD using national Veterans Affairs (VA) inpatient, outpatient, pharmacy, and mortality data. Tiotropium was not

available prior to February 2004, and there were initial restrictions on use when introduced. For these reasons, both contemporary and historic controls were used to identify patients with characteristics similar to those treated with tiotropium. Initial restrictions required patients to see a pulmonologist and have 'failed' treatment with other COPD medications. Failure was indicated by an exacerbation that resulted in a hospitalization or at least two 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 significant symptoms. Because of the use restrictions and the fact tiotropium was not used as first-line treatment for patients with COPD in the VA, we compared tiotropium to other medication regimens following a regimen change.

Cohort

Patients were identified for inclusion during two periods. During the first period, patients were identified for inclusion as historic controls in order to identify patients who possessed similar characteristics to those switched to 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 it is not used as first-line treatment for COPD in the VA.

To be included patients had to have a COPD diagnosis (ICD-9 491.x, 492.x, 496) during a twelve month period on at least two 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 switched to a regimen that included either tiotropium or inhaled corticosteroids plus long-acting beta-agonists. Patients who died less than 30 days following their medication switch and those with an asthma diagnosis were excluded. Patients from the first cohort (historic cohort) were identified between October 1, 2002 and September 30, 2003. Patients from the second cohort were identified between October 1, 2004 and March 31, 2006 (contemporary cohort).

Follow-Up Period

We defined the index date based on the date of switch to an eligible regimen. Patients were followed for up to 547 days. Patients were followed until they died, had not filled a prescription for 180 days, or 547 days, which ever occurred first.

Outcomes

During follow-up, we measured three outcomes: (1) all-cause mortality; (2) COPD exacerbations; and (3) COPD hospitalizations. Events occurring within 30 days following 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 does not introduce immortal time bias into the analysis.[20-22]

Deaths were identified using the VA Vital Status file, which captures approximately 98% of deaths.[23] Exacerbations were identified based on ICD-9 codes related to COPD present in combination with one of the following: (1) hospitalization; (2) emergency department visit; or (3) outpatient visit with either an oral steroid or antibiotic dispensing within five days of the visit.[24,25] 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: inhaled corticosteroids (ICS), ipratropium bromide (IPRA), long-acting beta-agonists (LABA), short-acting beta-agonists (SABA), theophylline (THEO) and tiotropium (TIO). 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.

Short-acting beta-agonists were not included 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 short-acting beta-agonists or no respiratory medication. Because of relatively small amounts of exposure in some regimens, we collapsed regimens with less than 1% of exposure time during follow-up. This resulted in 17 medication regimens included in the analysis.

Covariates

We defined covariates from the 12 months preceding the index date. Demographic characteristics, healthcare utilization and co-existing conditions were determined from inpatient and outpatient data. For healthcare utilization, we measured COPD-related and non-COPD healthcare. We measured 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 co-payment.[26]

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.[27-33] 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 fit for the initial medication (i.e. switch to ICS+LABA or 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 between 0.1 and 0.4 were included.

Analysis

Analyses were done 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 inhaled corticosteroid plus long-acting beta-agonist group from 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 non-tiotropium patients from both historic and contemporary cohorts. Second, only non-tiotropium patients from the contemporary cohort were used as controls. Third, the timeframe 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 one-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 from 0.4 to 0.7. Analyses were conducted with Stata/MP 10.0 for Windows (StataCorp LP, College Station, TX USA) and SAS 9.2 for Windows (SAS Institute Inc., Cary NC USA).

Results

We identified 135,422 patients for inclusion, of which 42,090 were included in the base case. There were 38,850 patients that switched to a regimen that included inhaled corticosteroids and long-acting beta-agonists in the historic cohort, while 3,240 switched to a regimen that included tiotropium. The average age in both groups was around 70 years and nearly 98% were male (Table 1). Those that switched to tiotropium had more COPD exacerbations at baseline and had a slightly larger percentage with 3 or more outpatient visits in the preceding 12 months.

During follow-up there were more than 17.1 million person-days of medication exposure. The most commonly used regimen was inhaled corticosteroids plus long-acting beta-agonists plus ipratropium (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 inhaled corticosteroids plus long-acting beta-agonists was used by 20.5% of the cohort over nearly one million person-days of exposure. Of the tiotropium regimens, the most frequently used regimen was tiotropium in combination with inhaled corticosteroids and long-acting beta-agonists 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 plus inhaled corticosteroids plus long-acting beta-agonists plus ipratropium (1.7% of exposure days).

For each outcome, the crude rate was higher in the tiotropium exposed group than in the non-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 non-tiotropium group (Table 3). The difference equates to a rate ratio of 1.25 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 for combination tiotropium plus inhaled corticosteroids plus long-acting beta-agonists showed a 40% reduction in mortality risk (HR 0.60, 95% CI 0.45, 0.79) compared to treatment with inhaled corticosteroids plus long-acting beta-agonists (Table 4). This was in contrast to tiotropium in combination with two other respiratory medications, excluding inhaled corticosteroids plus long-acting beta-agonists, (e.g. TIO+IPRA+ICS, TIO+LABA+IPRA, TIO+THEO+IPRA, etc.) 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 plus ipratropium plus inhaled corticosteroids and tiotropium plus ipratropium plus long-acting beta-agonists which contributed 84% of the exposure days in this group. The combination of tiotropium plus inhaled corticosteroids plus long-acting beta-agonists plus ipratropium was associated with a 36% increase in risk of death compared to inhaled corticosteroids plus long-acting beta-agonists.

For the most part, findings for exacerbations and hospitalizations were similar to mortality. For example, tiotropium plus inhaled corticosteroids plus long-acting beta-agonists 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) while there was a 22% reduction (HR 0.78, 95% CI 0.62, 0.89) for COPD-related hospitalizations. The exception to the consistent results was regimens that included tiotropium plus inhaled corticosteroids plus long-acting beta-agonists plus ipratropium where there was no significant association between exacerbations and hospitalizations compared to inhaled corticosteroids plus long-acting beta-agonists.

The reduced risk associated with tiotropium plus inhaled corticosteroids plus long-acting beta-agonists was consistently seen in each sensitivity analysis for all three outcomes (Figure 1). Only in the analysis in which patients with baseline hospitalizations were excluded did we not find a significant protective effect for combination tiotropium plus inhaled corticosteroids plus long-acting beta-agonists 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 plus two other medications and tiotropium plus inhaled corticosteroids plus long-acting beta-agonists plus ipratropium. In this analysis, these regimens were associated with a protective effect for mortality relative to inhaled corticosteroids plus long-acting beta-agonists while in the base case and all of the other sensitivity analyses they were associated with an increased risk of mortality.

Discussion

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 plus inhaled corticosteroids plus long-acting beta-agonists in combination were associated with reduced risk of all-cause mortality, COPD exacerbations and COPD hospitalizations compared to inhaled corticosteroids plus long-acting beta-agonists. Other three combination regimens that included tiotropium and the four combination regimen that included tiotropium plus inhaled corticosteroids plus long-acting beta-agonists plus ipratropium were associated with increased mortality risk.

Results from our study are similar to those reported from UPLIFT. This was a four year, multinational, randomized controlled trial that compared tiotropium to placebo while allowing the use of other COPD medications during the study period.[34] Nearly 6,000 patients were enrolled and the results showed reduced rates of exacerbations (RR 0.86, 95% CI 0.81, 0.91) and improvements in respiratory-related quality of life. The reduced rate of exacerbations was similar to the 16% reduction we observed in this analysis for the combination of tiotropium plus inhaled corticosteroids plus long-acting beta-agonists. In UPLIFT 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 four-year + 30 day period was used, while 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 four year study period. The effect in UPLIFT are substantially lower than the decreased risk of mortality we observed in patients on tiotropium plus inhaled corticosteroids plus long-acting beta-agonists. Importantly our comparison of tiotropium plus inhaled corticosteroids plus long-acting beta-agonists relative to inhaled corticosteroids plus long-acting beta-agonists is probably most similar to the comparisons in UPLIFT given that nearly three out of four patients reported using inhaled corticosteroids (74%) or long-acting beta-agonists (72%) during the study period. The regimens with ipratropium evaluated in our analysis were not included in UPLIFT as use of short-acting anticholinergics was prohibited except if deemed medically necessary to treat an acute exacerbation.

Our study suggests 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 was combination inhaled corticosteroids plus long-acting beta-agonists. The addition of tiotropium to medication regimens that are less effective than inhaled corticosteroids plus long-acting beta-agonists 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 to the reference group (e.g., 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.

While 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 identifying risks associated with tiotropium, while we identify new tiotropium users many patients had previously used ipratropium which may limit our ability in identifying adverse effects of anticholinergics.[35] The same is true for UPLIFT, where 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 Strom describes, 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.[36] Our study suffers from an inability to differentiate severity using a clinical marker of disease. In addition, the VA instituted criteria for 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 in order 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 combination of inhaled corticosteroids and long-acting beta-agonists were used as the highest step in COPD treatment. Estimation of the propensity to use tiotropium showed nearly one-third of tiotropium users we identified were different from those who switched to inhaled corticosteroids and long-acting beta-agonists. 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, as the findings may not apply to all users of tiotropium and are most applicable to males given that 98% of the population was male.

While taking advantage of a timeframe 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 impacting findings, which may be particularly true when a mortality benefit is found in a more recent cohort as advances in medical technology may contribute to these differences. However, the time period in which the groups are identified is only two years apart which may limit some of the secular concerns. Importantly, 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 similar baseline characteristics to the tiotropium patients when the sample was restricted by propensity score. Other limitations of the analysis are that we are unable to capture out of system use; however we do not expect out of system use to be differential between exposure groups would bias results toward the null. We are also unable to measure other important covariates like smoking status which may lead 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 were reported that have not previously been investigated. However, a subset of comparisons was of primary relevance, specifically the referent combination (inhaled corticosteroids plus long-acting beta-agonists) compared to tiotropium plus inhaled corticosteroids plus long-acting beta-agonists. Unlike placebo controlled trials, this study provides evidence as to the comparative effectiveness of treatments in COPD which are important for patients and providers when making treatment decisions in an effort to tailor therapies that are likely to optimize outcomes. Our findings show, when used in combination with inhaled corticosteroids and long-acting beta-agonists, tiotropium was associated with a decreased risk of

mortality, COPD exacerbations, and COPD hospitalizations compared to treatment with inhaled corticosteroids and long-acting beta-agonists. Importantly, there is the need for additional information on the comparative effectiveness of COPD treatment regimens so that patients and providers 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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Tables and Figure

Table 1. Baseline characteristics of the cohort by initial tiotropium exposure

	Switch to ICS+LABA		Switch to TIO	
	N	%	N	%
N	38,850		3,240	
Demographics				
age, mean (SD)	69.98	(9.66)	70.74	(9.13)
Male	38,009	(97.8%)	3,153	(97.3%)
Race				
White	19,762	(50.9%)	1,659	(51.2%)
Black	2,158	(5.6%)	159	(4.9%)
Other	652	(1.7%)	81	(2.5%)
Unknown	16,278	(41.9%)	1,341	(41.4%)
Comorbidities				
Hypertension	24,758	(63.7%)	2,066	(63.8%)
Heart Disease	12,665	(32.6%)	1,114	(34.4%)
Osteoarthritis	7,552	(19.4%)	567	(17.5%)
Diabetes	8,634	(22.2%)	744	(23.0%)
Depression	5,782	(14.9%)	503	(15.5%)
Cancer	8,496	(21.9%)	793	(24.5%)
CHF	5,736	(14.8%)	606	(18.7%)
Resource Utilization				
Distance to VA (miles), mean	41.18	(63.00)	36.12	(58.80)
Level of Copayment				
No Copayment	6,569	(16.9%)	616	(19.0%)
Some Copayment	23,409	(60.3%)	2,013	(62.1%)
Full Copayment	7,851	(20.2%)	555	(17.1%)
Missing	1,021	(2.6%)	56	(1.7%)
Baseline Exacerbations				
0	25,293	(65.1%)	1,249	(38.6%)
1	7,497	(19.3%)	712	(22.0%)
2+	6,060	(15.6%)	1,279	(39.5%)
Baseline Hospitalizations				
0	30,100	(77.5%)	2,127	(65.7%)
1	1,833	(4.7%)	571	(17.6%)
2+	6,917	(17.8%)	542	(16.7%)
ER Visits				
0	32,314	(83.2%)	2,457	(75.8%)
1	3,181	(8.2%)	325	(10.0%)
2+	3,355	(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%)	3,207	(99.0%)
PC Visits				
0	768	(2.0%)	69	(2.1%)
1	3,298	(8.5%)	224	(6.9%)
2+	34,784	(89.5%)	2,947	(91.0%)
Baseline Medication Use				
COPD				
ICS	18,476	(47.6%)	2,145	(66.2%)
LABA	15,125	(38.9%)	2,223	(68.6%)
IPRA	23,035	(59.3%)	2,340	(72.2%)
THEO	4,022	(10.4%)	495	(15.3%)
Cardiac Medications				
Digitalis	3,660	(9.7%)	336	(10.7%)
Beta Blockers	10,689	(28.2%)	875	(27.8%)
Alpha Blockers	8,402	(22.2%)	700	(22.2%)
Calcium Channel Blockers	11,475	(30.3%)	944	(30.0%)
Antianginals	7,917	(20.9%)	724	(23.0%)
Antiarrhythmics	1,169	(3.1%)	96	(3.1%)
Antilipemics	18,613	(49.2%)	1,568	(49.8%)

	Switch to ICS+LABA		Switch to TIO	
	N	%	N	%
Vasodilators	16	(0.0%)	2	(0.1%)
Diuretics	16,296	(43.1%)	1,373	(43.6%)
ACE Inhibitors	2,606	(6.9%)	191	(6.1%)
Angiotensin II inhibitor	17,397	(46.0%)	1,503	(47.7%)

Table 2. Medication exposure for each mutually exclusive treatment regimen during follow-up

	Patients Exposed		Cumulative Person-Days of Exposure		Duration of Exposure (days)	
	N	%	Total	(% of total)	Mean	(SD)
No Trt/ SABA only	1,749	(4.2%)	105,840	(0.6%)	60.5	(70.2)
ICS	2,391	(5.7%)	139,706	(0.8%)	58.4	(69.6)
IPRA	5,870	(13.9%)	509,173	(3.0%)	86.7	(90.1)
LABA	4,343	(10.3%)	278,971	(1.6%)	64.2	(79.4)
THEO	818	(1.9%)	55,205	(0.3%)	67.5	(84.5)
ICS+IPRA	7,199	(17.1%)	750,815	(4.4%)	104.3	(106.0)
ICS+LABA	8,659	(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	7,614	(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	1,565	(3.7%)	164,756	(1.0%)	105.3	(106.9)
ICS+LABA+THEO	2,577	(6.1%)	446,209	(2.6%)	173.2	(166.9)
IPRA+LABA+THEO	1,489	(3.5%)	143,173	(0.8%)	96.2	(97.9)
ICS+LABA+IPRA+THEO	7,186	(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%)	6,191	(0.0%)	80.4	(85.1)
ICS+IPRA+TIO	832	(2.0%)	73,785	(0.4%)	88.7	(73.0)
ICS+LABA+TIO	2,685	(6.4%)	403,767	(2.4%)	150.4	(120.9)
ICS+THEO+TIO	92	(0.2%)	9,173	(0.1%)	99.7	(100.6)
IPRA+LABA+TIO	1,190	(2.8%)	112,083	(0.7%)	94.2	(76.1)
IPRA+THEO+TIO	95	(0.2%)	7,044	(0.0%)	74.2	(72.3)
LABA+THEO+TIO	156	(0.4%)	18,865	(0.1%)	120.9	(104.7)
ICS+LABA+IPRA+TIO	2,669	(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)

Table 3. Unadjusted rate of events per 100 person-years by medication regimen compared to ICS + LABA

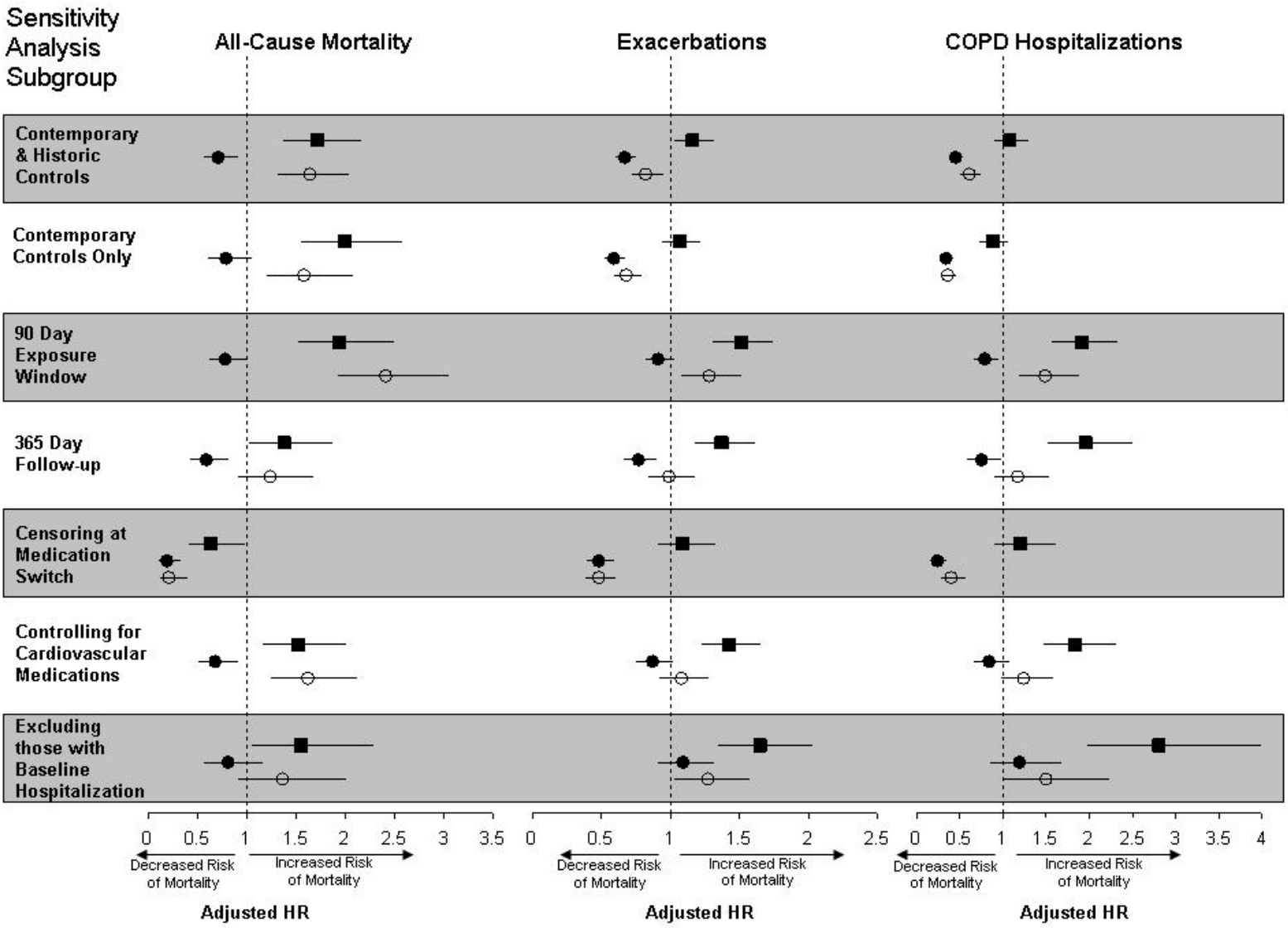
	Crude Mortality Rate*	RR	Crude Exacerbation Rate*	RR	Crude Hospitalization Rate*	RR
ICS+LABA (Ref)	8.38	–	31.41	–	12.83	–
Non-Tiotropium Regimens						
ICS+IPRA	14.45	1.72	29.19	0.93	17.32	1.35
IPRA+LABA	11.25	1.34	31.60	1.01	15.90	1.24
ICS+LABA+IPRA	11.47	1.37	37.75	1.20	19.04	1.48
ICS+LABA+THEO	9.00	1.08	24.97	0.79	5.89	0.46
ICS+IPRA+LABA+THEO	13.06	1.56	40.92	1.30	17.92	1.40
Tiotropium Regimens						
TIO+ 1 Other Med	10.63	1.27	48.21	1.53	27.65	2.16
TIO+ 2 Other Meds	44.96	5.37	58.52	1.86	28.76	2.24
ICS+LABA+TIO	8.87	1.06	40.07	1.28	16.10	1.26
ICS+LABA+IPRA+TIO	0.75	0.09	47.08	1.50	22.22	1.73
TIO+ 3 or 4 Other Meds	18.09	2.16	47.08	1.50	21.28	1.66

* Rates per 100 person-years

Table 4. Association between medication regimen and mortality, exacerbation, and hospitalization

	Mortality		Exacerbations		Hospitalizations	
	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
ICS+LABA (Ref)	1		1		1	
Non-Tiotropium Regimens						
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 Regimens						
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)
TIO+ 3 or 4 Other Meds	1.28	(0.93, 1.76)	1.02	(0.84, 1.24)	0.98	(0.73, 1.32)

Figure 1. Sensitivity analysis results from three tiotropium containing regimens compared to inhaled corticosteroids plus long-acting beta-agonists for each of the study outcomes



Results from tiotropium plus 2 other meds [TIO + 2 Other Meds, excluding TIO+ICS+LABA)] (solid square ■); tiotropium plus inhaled corticosteroids plus long-acting beta-agonists [TIO+ICS+LABA] (solid circle ●); tiotropium plus inhaled corticosteroids plus long-acting beta-agonists plus ipratropium [TIO+ICS+LABA+IPRA] (open circle ○). Symbol represents the point estimate and the bars represent the 95% confidence intervals.