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Mortality Risk in Chronic Obstructive Pulmonary Disease Patients Using Theophylline

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Abstract

Study objective: To evaluate the comparative effectiveness of treatment regimens with theophylline compared to the regimen without theophylline.

Design: Retrospective cohort study.

Setting: United States Veterans Affairs healthcare system from October 2001 through September 2005.

Patients: Patients with a diagnosis of chronic obstructive pulmonary disease that were 45 years or older.

Measurements and main results: Primary outcome measures were all-cause mortality, chronic obstructive pulmonary disease exacerbations and chronic obstructive pulmonary disease-related hospitalizations. Two approaches were used, the first where treatment assignment was based on medication use at baseline, and the second where exposure was measured as a time-varying covariate. Treatment groups were stratified based on propensity to receive theophylline. Mortality was compared using Cox proportional hazards models and other outcomes were compared using negative binomial models. Comparisons were conducted within individual treatment regimens that were the same with the exception of theophylline. A total of 183,573 patients were included. In the largest group, patients treated with ipratropium plus theophylline, compared to ipratropium alone, had a 1.11-fold increase in the risk of death (95% CI, 1.04-1.18). In comparisons of other regimens the risk of mortality associated with theophylline in the regimen was greater than regimens without theophylline (HRs from 1.17 to 1.31). In the time-varying exposure analysis, theophylline (HR=1.23 [95% CI 1.09 to 1.39]) was associated with an increased mortality risk.

Conclusion: Compared to similar regimens, patients in regimens that included theophylline had slightly increased risks of mortality, chronic obstructive pulmonary disease exacerbations and chronic obstructive pulmonary disease hospitalizations; however we are unable to measure the impact on other factors including symptoms and quality of life.

Introduction

The burden of chronic obstructive pulmonary disease (COPD) is substantial throughout the world.[1] Medication management is an integral part of treatment; yet, there remains uncertainty in optimizing pharmacotherapy. Clinical practice guidelines recommend stepped treatment beginning with bronchodilators and then adding inhaled corticosteroids; however, the guidelines, for the most part, are based on results of short-term clinical trials of intermediate endpoints and expert consensus.[2,3] For some treatments, such as inhaled corticosteroids (ICS), long-acting beta-agonists (LABA) and tiotropium, there is growing literature on long-term outcomes.[4-11] However, there remains a need for additional evaluations of COPD treatments, particularly the comparative effectiveness of treatments in real world settings and especially combination therapy.

Theophylline has been used in COPD for many years despite limited research associating its use with improved outcomes. The GOLD guidelines indicate theophylline may benefit patients on long-acting bronchodilators that are still experiencing symptoms.[3] Recently, use of theophylline has received renewed attention. While inhaled anticholinergics and $beta_2$-agonists are preferred therapy for bronchodilation,[12] theophylline has been shown to add clinical benefit when given with long-acting $beta_2$-agonists.[13] Theophylline restores steroid sensitivity *in vitro*[14] and may reduce inflammation and restore steroid responsiveness.[15] It has been suggested that theophylline use may increase because of potential anti-inflammatory and immunomodulatory effects, which occur at low doses where side effects are uncommon and fewer drug interaction issues arise.[16]

Most theophylline studies have been controlled trials which demonstrate short-term clinical efficacy.[13,17-19] The objective of this study was to evaluate outcomes associated with theophylline use in patients with COPD outside the clinical trial setting. Specifically, we compared mortality, COPD exacerbations, and COPD-related hospitalizations among patients on medication regimens that included theophylline to similar patients on the same regimens with the exception of theophylline.

Methods

National Veterans Affairs (VA) inpatient, outpatient, pharmacy and mortality databases were used for this study. The research was approved by IRBs at Hines VA Hospital and Northwestern University.

Cohort Identification

Patients with a COPD diagnosis (ICD-9 491.x, 492.x, 496) between October 1, 2002 and September 30, 2003 were identified. The cohort was limited to patients that received respiratory medication on two separate dates between October 1, 2002 and March 31, 2003, were ≥45 years old and alive on April 1, 2003.

Analysis Period

Data from October 1, 2001 to September 30, 2002 was used as a baseline period to characterize patients. The treatment identification period was the six months from October 1,

2002 through March 31, 2003. Patients were followed for events from April 1, 2003 to September 30, 2005.

Analytic Approach

Two approaches for examining outcomes associated with theophylline were used. The first assigned patients to groups based on combinations of medication received during the six month baseline period, and outcomes were compared between groups. The second approach evaluated outcomes associated with various medication regimens by allowing categorization of medication exposure to vary over time when regimens changed.

Treatment Assignment

Treatment group assignment was based on medications dispensed between October 1, 2002 and March 31, 2003. Medications were grouped by classes: anticholinergics (IPRA), inhaled corticosteroids (ICS), long-acting beta-agonists (LABA), methylxanthines (THEO) cromolyn (CROMO), and short-acting beta-agonists (SABA). Treatment regimens were defined based on classes dispensed. All possible combinations were defined and patients were allocated to mutually exclusive groups. SABAs were not used to define regimens.

Because the focus was on the incremental effect of theophylline, all comparisons were stratified by baseline regimen. Comparisons were made within regimens that included theophylline (THEO) versus those that did not include theophylline (NO THEO). For example, the ICS+LABA group was compared to the ICS+LABA+THEO group.

Dose

For each medication class the average daily dose over the treatment identification period was determined. Average daily dose was calculated by dividing the cumulative amount of medication by the number of days from the first dispensing until March 31, 2003. For THEO, the dose of medications was calculated in units of theophylline. For ICS, doses were converted to beclomethasone equivalents.[20] For LABA, doses were converted to salmeterol equivalents.

Doses were categorized into high dose or low dose for each medication class. For ICS, high doses were defined as average daily doses ≥700 μg per day.21, 22 High dose categories for other classes were average daily doses ≥500 mg for THEO, >50 μg for LABA and >144 μg for IPRA.

Theophylline Level

Theophylline levels were available for a subset of patients. We determined whether patients were ever in the therapeutic range (10-20 μg/mL), ever had a high theophylline level or ever had a low theophylline level during the baseline period. We compared levels by dose of theophylline and medication regimen. Among patients with a theophylline level, we compared risk of mortality in those with high levels to those without high levels.

Treatment Regimen Change

We examined changes in respiratory treatment regimens over follow-up. Respiratory medication regimens were defined for each six month increment during follow-up. We identified patients as having a regimen change if there were any changes in the medication

regimen during follow-up. We also determined use of theophylline during follow-up for each group.

Time-Varying Exposure

Because theophylline was not used by everyone and was the focus of this analysis, we used a two-stage sampling approach when identifying patients to include in the time-varying exposure analysis (Figure 1). Our sampling frame was selected to provide sufficient power to detect differences in the theophylline group. We included patients with theophylline (N=27,052) and a 35% random sample of the remaining cohort from the top six regimens (N=51,342). From this combined group we randomly sampled 10% to form the analytic group for time-varying exposure analysis.

For each person in the analysis, medication exposure during the six months preceding each day during follow-up was identified. We selected six months as our time frame for exposure measurement because we did not want associations between events and medication use to be a result of changing clinical status of the patient, which can happen if a shorter time frame or one that only considers medication use on the event date is used to characterize exposure. Additionally, six months ensures sufficient time for chronic exposure and includes two dispensings of 90-days supplies from VA pharmacies. Thus, each individual had information on medication exposure for each day they were at risk for death during follow-up. An example of how exposure was measured for several hypothetical patients is shown in Figure 2. Patients were defined as exposed if they had a dispensing for that medication during the six month exposure window. We also measured COPD exacerbations as a time-varying covariate as an indicator for disease severity that changed over the study period.

Outcomes

Three outcomes were measured: mortality, exacerbations (using a previously defined algorithm[23]) and COPD-related hospitalizations (primary diagnosis of COPD).

Covariates

Data from October 1, 2001 to September 30, 2002 was used to define baseline characteristics. Patients were defined as incident cases if they used VA healthcare services for two years prior to FY2003 but did not have any diagnoses for COPD during that period. Respiratory regimens prior to baseline were defined based on FY2002 prescriptions.

We identified types of providers, use of spirometry and comorbidities. The comorbidities identified were the most prevalent conditions in veterans[24] and those comorbidities that may influence the likelihood of receiving theophylline (e.g. those likely to reduce theophylline use: peptic ulcer disease, gastroesophogeal reflux disease, arrhythmias).[16,25,26] Comorbidities identified were peptic ulcer disease (PUD), gastroesophogeal reflux disease (GERD), arrhythmias, depression, hypertension, ischemic heart disease (IHD), osteoarthritis, rheumatoid arthritis, diabetes, stroke, mental health (non-depression), substance abuse, benign prostatic hypertrophy (BPH), cancer (non-melanoma), lung cancer, chronic heart failure (CHF), alcoholism, and HIV. Finally, we determined baseline COPD-related healthcare utilization which includes hospitalizations with a primary diagnosis of COPD, outpatient encounters with any diagnosis of COPD and COPD exacerbations, as it has been shown that these measures

represent important predictors of disease severity for COPD patients[27] and thus serve as proxies for COPD severity in this analysis.

Analysis

Baseline treatment regimens were used to define comparison groups. Regimens with more than 10,000 total patients in the THEO and NO THEO groups combined were included. To compare incremental effects of theophylline, analyses were stratified by treatment groups.

Propensity scores were calculated to balance groups on baseline characteristics in an effort to reduce concerns related to confounding by indication and other biases.[28-34] Propensity scores were estimated based on likelihood of receiving theophylline during the treatment identification period based on characteristics measured during the baseline period including demographics, comorbidities, region, COPD-related healthcare use, provider types and previous medication use. Logistic regression was used to estimate the propensity to use theophylline and separate models were created for each comparison group (i.e. six separate propensity models were developed) (see Tables A1-A6 for specific covariates included in each propensity model).

A propensity score for each individual was calculated and five equal size groups were created based on quintiles of the combined propensity score.[30,32] Groups were stratified by quintiles and baseline characteristics of NO THEO and THEO patients compared.

Evaluation of outcomes was conducted within quintiles. Cox proportional hazards models and negative binomial regression models were used to account for remaining differences between THEO and NO THEO groups within quintiles. Criteria for inclusion in regression models were: (1) factors not balanced within quintiles; (2) factors associated with differences in outcome (e.g. baseline exacerbation rates); and (3) factors that changed the point estimate for the effect of theophylline more than 10%.[35] An overall estimate across quintiles was calculated by combining within quintile results using Mantel-Haenszel methods.

For the time-varying covariate analysis, Cox proportional hazards models were used to evaluate the association between medication exposure and risk of mortality during follow-up, while adjusting for propensity to receive theophylline at baseline and COPD exacerbations. All analyses were done using STATA/MP v10.1 for Windows (StataCorp., College Station, TX, USA).

Role of Funding Source

The Agency for Healthcare Research and Quality funded the research but had no role in the design, analysis, interpretation, or manuscript preparation.

Results

A total of 183,573 patients were identified for inclusion. The most frequently occurring treatment regimen was ipratropium alone (Table 1). The top six regimens included more than 10,000 patients and were included in the evaluation. The proportion of patients using theophylline in each regimen ranged from 11.2% in the IPRA regimen to 20.8% in the ICS+LABA+IPRA regimen.

Generally, there were differences in baseline characteristics of THEO and NO THEO patients (Table 2). Patients using theophylline were more likely to have seen a pulmonologist, were less likely to be considered an incident diagnosis of COPD and had higher rates of COPD exacerbations and hospitalizations. Patients treated with theophylline tended to fill more

prescriptions for a respiratory medication during the baseline period than the NO THEO group (Table 3). Additionally, patients in the THEO group had higher average daily doses than the NO THEO group. The majority of patients experienced a change in their medication regimen during follow-up. Within the NO THEO groups, there was very little use of theophylline during follow-up, with no group having more than 4% of their patients exposed to theophylline during follow-up (Table 3). Within the THEO group, the persistence of theophylline use decreased over the follow-up period. The rates of use were approximately 70% or higher over the first 18 months and then decreased in each group. Characteristics were relatively balanced within quintiles following stratification by propensity score (Tables A1-A6).

There was some heterogeneity in effects across quintiles within each of the regimens (Table A8). When summarized by regimen, THEO patients were at increased risk of death (Figure 2). The risk ranged from 1.11 (95% CI, 1.04, 1.18) for IPRA+THEO to 1.31 (95% CI, 1.11, 1.55) for ICS+LABA+THEO. For COPD exacerbations, there were three regimens where exacerbation rates were significantly higher in THEO groups (Figure 2). THEO was associated with an increased hospitalization rate for two regimens, with a trend towards higher rates for all regimens (Figure 2).

When the analysis was restricted to patients that never changed treatment during follow-up, point estimates varied where in some cases they were higher than the base case and in others they were lower. However, because of the small sample of patients none of the results were statistically significant. The hazard ratios for the three largest groups were: IPRA+THEO=0.54 (0.29, 1.00); ICS+IPRA+THEO=1.35 (0.81, 2.26); and ICS+LABA+IPRA+THEO=1.52 (0.79, 2.95). Finally, there were no differences in hazard ratios between patients with and without a history of exacerbations.

Theophylline Level

Among patients using theophylline at baseline, 28.4% had a theophylline laboratory result available during the baseline period. Of these, 35.5% had a level in the therapeutic range. A small percentage of patients (3.0%) had a theophylline level above the therapeutic range, while the majority of the patients (70.5%) had at least one level measured during that period that was below the therapeutic range. The proportion of patients with a level above the therapeutic range did not differ by regimen. A higher proportion of those using high dose theophylline had at least one theophylline level above the therapeutic range compared to those not using high dose theophylline (4.1% vs. 2.0%, $p<0.001$).

During follow-up there were 35,025 patients that had at least one theophylline level available. Among those, 2,032 (5.8%) had at least one level above the therapeutic range. There were 7,408 (21.2%) patients that died during follow-up among those with at least one theophylline level, and of those that died, 565 (7.6%) had at least one level above the therapeutic range. The mortality rate in patients with at least one high theophylline level was higher than those that did not have at least one high theophylline level (27.8% vs. 20.7%, $p<0.001$).

Time-Varying Exposure

There were 7,840 patients included in the time-varying exposure analysis. There were 1,203 patients (15.3%) that died. Of those, at some point during follow-up 67.5% were exposed to ICS, 48.2% to LABA, 88.2% to IPRA and 36.1% to THEO. After adjustment for baseline propensity to receive theophylline, exacerbations and age, exposure to ICS in the preceding six months was associated with decreased risk of mortality (HR=0.87 [95% CI 0.77, 0.99]) (Table 4).

Exposure to LABA was not associated with a statistically significant difference in mortality risk (HR=0.91 [95% CI 0.80, 1.03]). Exposure to THEO (HR=1.23 [95% CI 1.09, 1.39]) or IPRA (HR=1.45 [95% CI 1.20, 1.75]) was associated with increased risk of mortality.

Discussion

The objective of this study was to evaluate outcomes associated with theophylline present in a treatment regimen to that regimen without theophylline in patients with COPD. Across regimens, we consistently found theophylline was not associated with improved outcomes for COPD patients. Importantly, in several cases theophylline was associated with an increased risk of events; however, these increased risks were generally small (HR of 1.1 to 1.3).

Evidence supporting use of theophylline is based on short-term clinical trials that have shown benefit in lung function.[17-19] These efficacy studies are limited by duration and outcome measures included. None were long enough to examine mortality or to compare exacerbation rates. Thus, there has been a lack of information on the effectiveness of theophylline in COPD compared to other therapies outside clinical trials. Despite this, theophylline was used in more than one in five COPD patients in the VA.

In our analysis, theophylline was not associated with improvement in rate of exacerbations, hospitalizations or mortality, but these are not the only factors important to patients when considering COPD treatment options. We were unable to measure symptoms or functioning which may be improved because of the bronchodilatory effects of theophylline. Therefore, if theophylline reduces symptoms, makes patients feel better and improves activities of daily living it may still have a role in the clinical management of COPD. However, these benefits would need to be quantified and weighed against the potential for a slight increase in mortality risk.

There are limitations that need to be acknowledged. We used two approaches; the first was a simple approach to characterizing treatment groups. Treatment group assignment was based on medication use during a fixed time point, in this case, a six month window. However, this may not reflect long-term medication use and ultimately may not reflect the association between exposure and outcomes. As noted, switching medications was common and if short-term use of medications affects outcomes in patients with COPD then our results may not reflect the true association between theophylline and outcomes that were measured. In addition, we do not measure medication adherence, and therefore do not know if the observed association is a result of adverse effects associated with theophylline use or from non-adherence with the medication.

To address this we used a time-varying exposure approach, where exposure reflects medications used in the preceding six months rather than a fixed time point. We found ICS use was protective with nearly a 13% reduction in risk of death, similar to estimates from a meta-analyses of ICS in COPD.[36,37] In addition, we found consistent results for theophylline exposure in both analyses. When exposure was measured as a time-varying covariate, we found an increased risk of mortality in patients exposed to theophylline, similar to results when exposure was defined based on a fixed six month period. In the time-varying exposure analysis ipratropium was associated with increased risk of mortality. This was not apparent in the initial analysis as we did not compare addition of ipratropium to a regimen. This finding is consistent with other studies on the safety of ipratropium and suggests the need for additional research on anticholinergic safety.[38-40] This finding was also consistent with a study we recently published evaluating the risk of mortality associated with COPD medication use in patients with newly

diagnosed COPD.[41] That analysis focused on newly diagnosed patients while this analysis included all patients with a diagnosis of COPD since the focus of this study was on patients using theophylline. Additionally, this study was conducted in a more recent cohort than our previous study.

Most of the cohort was prevalent cases of COPD and using COPD medications prior to identification. By not using an inception cohort we may introduce survivorship bias into the analysis. That is, these patients have already survived treatment with medications or they would not be in the analysis. However, we expect this to be non-differential between groups and should not bias the results. It is important to focus on prevalent cases of COPD because those are individuals that require treatment and often with more than one medication. It is in these patients where it was important to understand if theophylline was associated with improved outcomes.

An overriding concern is that the increased risk of events with theophylline may be a result of disease severity and not related to the medication (i.e. confounding by indication). By definition, patients in the theophylline group had an additional medication in their regimen relative to the group to which they were compared. Therefore, patients with more severe disease may be more likely to be in THEO groups. This is supported by differences in markers of disease severity, pulmonologist visits, exacerbations and COPD hospitalizations, between groups. Unadjusted results are likely confounded by severity of disease; however, we used propensity scores to account for differences in patients. When we were able to remove differences in markers of disease severity we still observed theophylline was associated with an increased risk of events. However, we do not have measures of lung function that would allow us to account for differences in disease severity as measured by lung function. Measures of symptoms are also not available, and while our propensity scores account for many of the factors used in the clinical management of patients with COPD, there is the potential that these unmeasured factors contribute to observed differences between groups.

We relied solely on VA data to conduct this analysis. Thus, the population was predominantly male and results may not generalize to females. Also, it is possible that patients utilized services outside the VA healthcare system that we would not have identified. This may be particularly true for acute events that require treatment at the nearest healthcare facility. Thus, we may underestimate COPD hospitalizations and exacerbations if care happens outside the VA. There is no reason to suspect there would be differential rates between groups based on treatment and this should not bias the findings. It may simply represent an underestimate of events.

In conclusion, patients with a regimen that included theophylline did not have improved outcomes. Theophylline was associated with a slight increase in the risk of mortality, COPD exacerbations and COPD hospitalizations in nearly all treatment regimens examined. We were unable to determine the benefit of theophylline on important patient outcomes such as symptoms, quality of life and activities of daily living in this analysis. Thus it is important that patients and providers consider all of the potential benefits and harms associated with theophylline when making treatment decisions. Future studies that capture medication use patterns, measures of lung function, and patient-reported outcomes in a real-world setting will be necessary to quantify both the benefits and risks associated with theophylline use in patients with COPD.

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Abbreviations

COPD = chronic obstructive pulmonary disease

ICS = inhaled corticosteroids

LABA = long-acting beta-agonists

VA = Veterans Affairs

VHA = Veterans Health Administration

IPRA = ipratropium

THEO = theophylline

HR = hazard ratio

RR = rate ratio

CI = confidence interval

Tables and Figures

Table 1. Baseline treatment regimens where the top six regimens were included in the analysis

			+ THEO	
N	151,716		31,857	
Baseline Regimen, n (%)				
IPRA	57,195	(37.7)	7,213	(22.6)
ICS + IPRA	34,560	(22.8)	7,015	(22.0)
ICS + LABA + IPRA	23,634	(15.6)	6,218	(19.5)
LABA + IPRA	11,241	(7.4)	2,245	(7.1)
ICS	10,816	(7.1)	1,850	(5.8)
ICS + LABA	9,244	(6.1)	1,553	(4.9)
LABA	4,589	(3.0)	775	(2.4)
ICS + LABA + IPRA + CROMO	100	(0.1)	45	(0.1)
ICS + IPRA + CROMO	86	(0.1)	36	(0.1)
CROMO	60	(<0.1)	11	(<0.1)
ICS + LABA + CROMO	48	(<0.1)	24	(0.1)
IPRA + CROMO	47	(<0.1)	11	(<0.1)
ICS + CROMO	47	(<0.1)	35	(0.1)
LABA + CROMO	26	(<0.1)	7	(<0.1)
LABA + IPRA + CROMO	23	(<0.1)	14	(<0.1)
			4,805	(15.1)

Abbreviations: LABA = long-acting beta-agonists; ICS = inhaled corticosteroids; IPRA = ipratropium; THEO = theophylline; CROMO = cromolyn

Table 2. Baseline characteristics for each group

	Group 1			Group 2			Group 3		
	IPRA	+ THEO	p-value	ICS + IPRA	+ THEO	p-value	ICS+LABA+IPRA	+ THEO	p-value
N	56,162	7,040		33,991	6,895		23,248		6,103
White, %	61.1	60.8	0.658	60.5	62.8	<0.001	58.4	60.1	0.009
Age (yrs), mean	68.6	70.7	<0.001	69.4	70.4	<0.001	69.4	69.2	0.177
Male, %	94.2	95.7	<0.001	94.5	96.0	<0.001	93.8	94.9	0.007
Incident COPD[a], %	10.3	4.0	<0.001	6.6	2.5	<0.001	4.2	1.7	<0.001
Pulmonologist Visit, %	12.5	15.9	<0.001	15.4	19.4	<0.001	28.2	32.1	<0.001
Exacerbations, %									
0	76.9	68.5	<0.001	71.0	62.3	<0.001	45.3	39.4	<0.001
1	15.7	18.9		18.4	21.0		19.4	18.6	
2	4.8	7.4		6.6	9.6		11.7	12.6	
3+	2.6	5.2		4.0	7.1		23.7	29.5	
Hospitalizations[b], %									
0	97.6	96.1	<0.001	96.4	94.4	<0.001	94.1	93.2	0.055
1	2.0	2.8		2.9	4.2		4.4	4.9	
2	0.3	0.7		0.5	1.0		1.0	1.2	
3+	0.1	0.4		0.3	0.5		0.5	0.7	

[a]No COPD related visits in previous 24-month period
[b]Hospitalizations with primary COPD diagnosis

Table 2. Baseline characteristics for each group

	Group 4			Group 5			Group 6		
	LABA + IPRA	+ THEO	p-value	ICS	+ THEO	p-value	ICS + LABA	+ THEO	p-value
N	11,004	2,186		10,698	1,824		9,160	1,531	
White, %	60.8	62.3	0.155	53.7	56.5	0.034	47.6	50.9	0.008
Age (yrs), mean	69.8	70.4	0.012	69.0	71.4	<0.001	70.3	70.3	0.167
Male, %	94.7	96.6	0.001	91.5	94.0	0.001	89.7	92.8	0.001
Incident COPD[a], %	5.6	2.1	<0.001	8.6	3.6	<0.001	6.4	2.1	<0.001
Pulmonologist Visit, %	24.0	27.4	0.001	10.5	11.1	0.481	17.5	18.9	<0.001
Exacerbations, %									
0	68.2	59.8	<0.001	83.6	77.1	<0.001	82.5	72.5	<0.001
1	19.7	20.9		12.1	15.2		12.2	18.9	
2	7.2	10.7		2.9	5.3		3.5	5.8	
3+	4.9	8.7		1.4	2.4		1.8	2.7	
Hospitalizations[b], %									
0	95.6	93.5	<0.001	98.8	98.8	0.772	98.8	98.1	0.076
1	3.4	4.6		0.9	0.9		1.0	1.4	
2	0.7	1.5		0.2	0.2		0.2	0.4	
3+	0.3	0.5		0.1	0.1		0.1	0.1	

[a]No COPD related visits in previous 24 month period
[b]Hospitalizations with primary COPD diagnosis

Table 3. Medication use for each group

	Group 1			Group 2			Group 3		
	IPRA	+ THEO	p-value	ICS + IPRA	+ THEO	p-value	ICS + LABA +IPRA	+ THEO	p-value
SABA use, %	93.1	93.9	<0.010	95.9	96.8	<0.001	93.8	95.9	<0.001
Rx fills, mean (sd)	2.7 (2.2)	5.3 (3.1)	<0.001	4.6 (3.2)	7.1 (3.9)	<0.001	6.1 (3.8)	8.3 (4.2)	<0.001
High Dose, %									
IPRA	33.2	42.4	<0.001	43.3	51.1	<0.001	45.4	52.1	<0.001
ICS	–	–		64.5	68.1	<0.001	55.4	58.0	<0.001
LABA	–	–		–	–		18.8	20.8	<0.001
THEO	–	45.5		–	48.9		–	48.8	
Medication switch during follow-up, %	77.9	86.2	<0.001	84.0	87.1	<0.001	82.9	87.0	<0.001
Theophylline use during follow-up, %									
Apr 03-Sep 03	1.3	84.6		1.8	86.2		2.4	84.6	
Oct 03-Mar 04	1.7	76.8		2.4	79.6		3.2	77.9	
Apr 04-Sep 04	1.7	69.4		2.6	72.6		3.4	70.8	
Oct 04-Mar 05	1.8	63.8		2.9	66.3		3.7	66.0	
Apr 05-Sep 05	1.7	56.5		2.9	60.1		3.8	60.0	

Table 3. Medication use for each group

	Group 4			Group 5			Group 6		
	LABA+IPRA	+ THEO	p-value	ICS	+ THEO	p-value	ICS + LABA	+ THEO	p-value
SABA use, %	90.0	92.6	<0.001	78.7	73.9	<0.001	59.5	66.0	<0.001
Rx fills, mean (sd)	4.5 (3.1)	6.8 (3.6)	<0.001	2.9 (2.2)	5.1 (2.9)	<0.001	4.0 (2.7)	6.1 (3.5)	<0.001
High Dose, %									
IPRA	41.2	48.0	<0.001	–	–		–	–	
ICS	–	–		58.9	62.8	0.001	50.7	53.9	0.019
LABA	12.6	13.3	0.338	–	–		17.3	19.8	0.014
THEO	–	47.2		–	51.3		–	49.5	
Medication switch during follow-up, %									
	90.5	93.2	<0.001	85.4	88.3	0.001	83.3	88.4	<0.001
Theophylline use during follow-up, %									
Apr 03-Sep 03	1.9	84.2		1.3	85.8		1.4	86.8	
Oct 03-Mar 04	2.6	75.8		1.7	78.8		1.9	80.6	
Apr 04-Sep 04	2.8	70.6		1.8	74.0		1.9	74.5	
Oct 04-Mar 05	2.9	64.1		1.9	68.8		2.0	69.1	
Apr 05-Sep 05	2.9	58.9		1.9	63.5		2.0	62.3	

Table 4. Time-varying exposure sensitivity analysis: Risk of mortality by treatment exposure in the preceding six months

Treatment	Crude HR	(95% CI)	Adjusted HR[a]	(95% CI)
No Treatment[b]	1		1	
ICS	0.94	(0.84 to 1.07)	0.87	(0.77 to 0.99)
LABA	0.98	(0.87 to 1.11)	0.91	(0.80 to 1.03)
IPRA	1.62	(1.35 to 1.95)	1.45	(1.20 to 1.75)
THEO	1.34	(1.19 to 1.50)	1.23	(1.09 to 1.39)

[a]Adjusted for baseline propensity to receive theophylline, exacerbations in the preceding six months, age
[b]No treatment indicates no use of ICS, LABA, IPRA or THEO in preceding six months

Figure 1. Sample selection used to identify the analytic cohort included in the time-varying exposure analysis

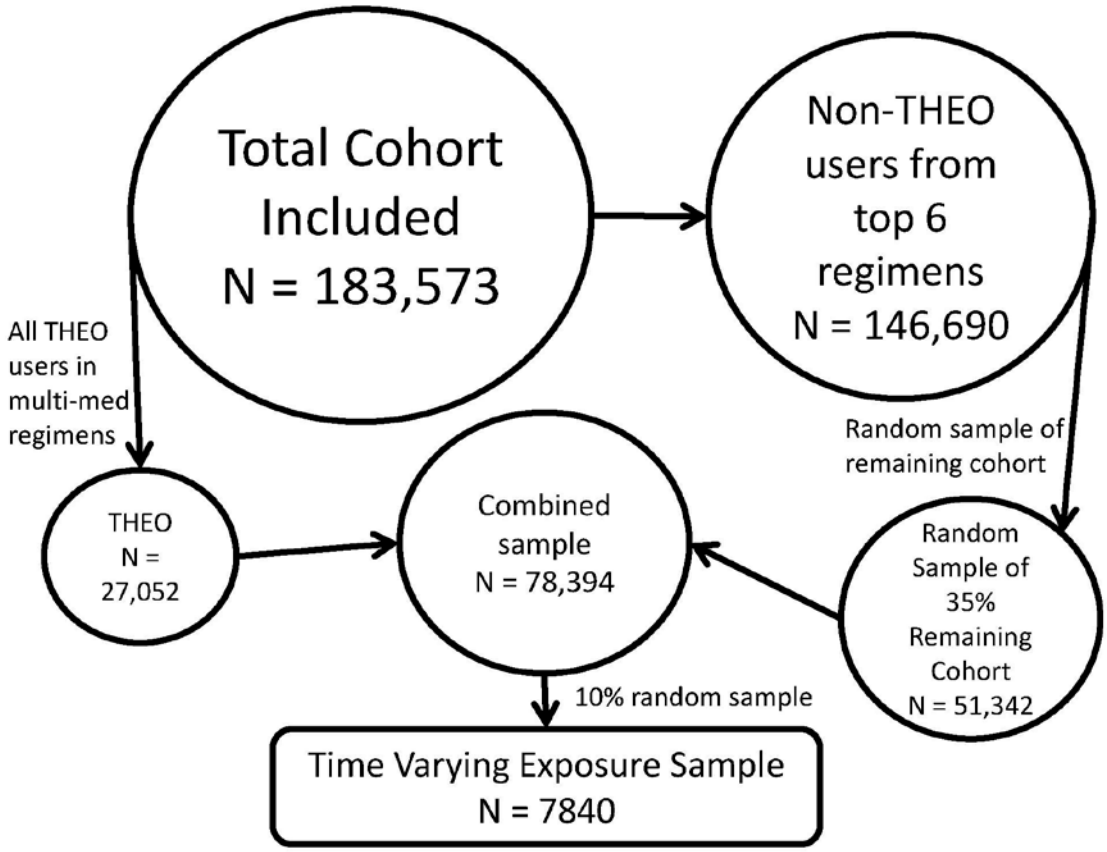
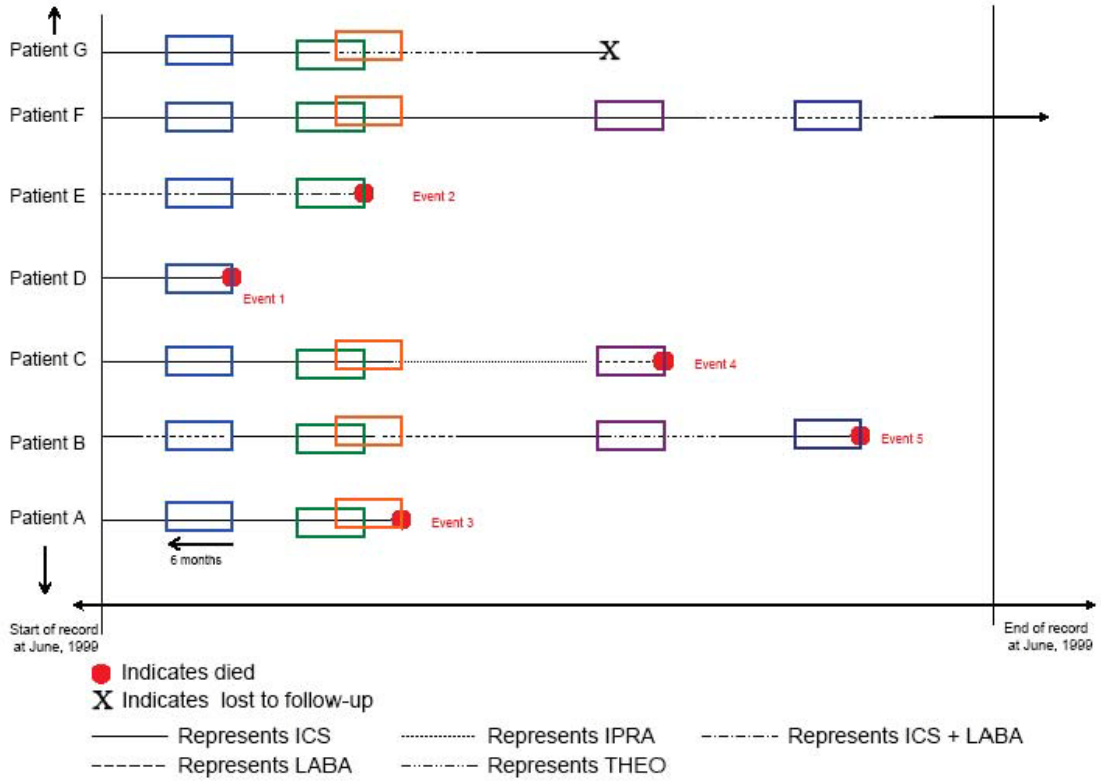
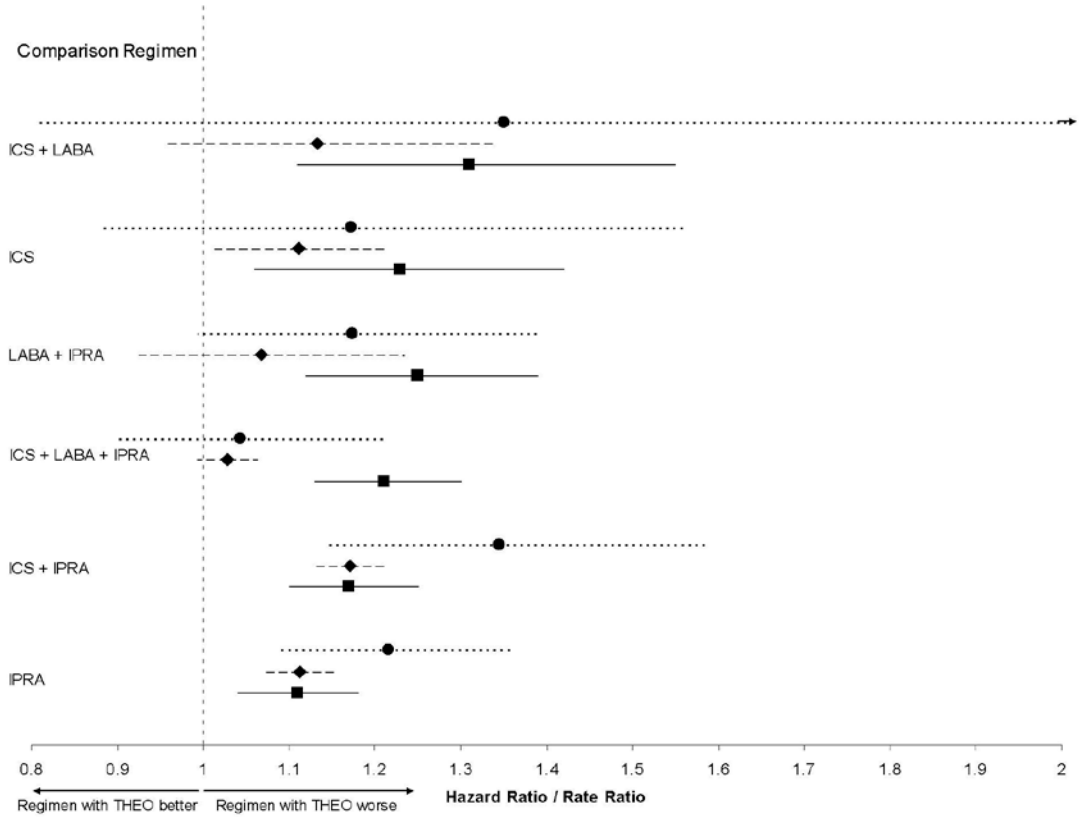


Figure 2. Example of measurement of medication exposure as a time-varying covariate for seven hypothetical patients in the time-varying exposure sensitivity analysis



Each box represents a 6-month period for which medication exposure was measured.

Figure 3. Adjusted risk of mortality (■), COPD exacerbations (◆) and hospitalizations (●) during follow-up in each regimen with theophylline compared to the regimen without theophylline



Point estimates represent hazard ratio for mortality and rate ratio for hospitalizations and exacerbations. Lines represent 95% confidence intervals.

Appendix A. Characterization of Propensity Score Models for Each Medication Regimen

Table A1. Baseline characteristics by treatment regimen after stratification by propensity score in Group 1 (IPRA vs. IPRA + THEO)

	Quintile 1			Quintile 2			Quintile 3			Quintile 4			Quintile 5		
	IPRA	+ THEO		IPRA	+ THEO		IPRA	+ THEO		IPRA	+ THEO		IPRA	+ THEO	
N	12,405	477		12,037	845		11,720	1,174		11,125	1,737		9,908	2,980	
White, %	62.5	60.8		65.7	64.9		55.1	55.7		60.6	58.9		61.1	62.8	
Age, mean	62.7	63.7		67.5	68.6	*	70.3	71.2	*	71.6	71.6		72.1	71.8	*
Male, %	93.3	93.5		97.9	97.9		85.0	85.0		97.5	97.5		98.1	98.7	*
Incident COPD, %	34.5	25.8	**	9.8	9.5		2.3	2.4		0.9	1.4		0.5	1.0	**
Pulmonologist Visit, %	8.4	11.1	*	10.8	10.8		10.4	8.5	*	13.8	12.7		20.9	23.0	*
Exacerbations, %															
1+	12.8	15.9	*	18.3	16.5		18.3	17.0		26.4	27.4		43.9	46.4	*
Hospitalizations – primary COPD, %															
1+	0.9	0.8		1.6	1.9		1.9	2.0		2.5	2.5		5.7	6.5	

* ≤ 0.05
** ≤ 0.01

Abbreviations: LABA = long-acting beta-agonists; ICS = inhaled corticosteroids; IPRA = ipratropium; THEO = theophylline

Propensity model adjusted for age, race, VISN, incident COPD, mental health diagnosis, substance abuse, cancer, alcoholism, depression, arrhythmias, pulmonologist, cardiologist, baseline exacerbations, COPD-related hospitalizations, treatment change from FY2002, IPRA FY2002, LABA FY2002, ICS FY2002

Table A2. Baseline characteristics by treatment regimen after stratification by propensity score in Group 2 (ICS+IPRA vs. ICS+IPRA+THEO)

	Quintile 1			Quintile 2			Quintile 3			Quintile 4			Quintile 5		
	ICS+ IPRA	+ THEO		ICS + IPRA	+ THEO		ICS + IPRA	+ THEO		ICS + IPRA	+ THEO		ICS + IPRA	+ THEO	
N	7,553	624		7,146	1,031		6,941	1,236		6,550	1,627		5,801	2,377	
White, %	58.0	57.4		53.2	51.5		61.7	63.8		63.9	62.0		67.2	69.2	
Age, mean	65.5	66.4		69.2	70.0	*	70.5	70.5		71.0	70.8		71.5	71.3	
Male, %	97.7	98.6		98.0	98.7		98.0	98.7		98.1	98.8		98.4	98.6	
Incident COPD, %	24.8	15.5	**	3.4	3.7		1.3	1.8		0.4	0.6		<0.1	0.2	*
Pulmonologist Visit, %	9.3	10.1		10.9	9.3		14.4	15.2		17.8	17.6		27.4	29.5	
Exacerbations, %															
1+	15.5	17.0		18.9	16.0	*	25.4	26.5		34.5	35.3		57.2	60.0	*
Hospitalizations – primary COPD, %															
1+	1.2	1.6		1.8	2.0		2.9	2.8		3.9	3.9		9.7	10.9	

* ≤ 0.05
** ≤ 0.01

Abbreviations: LABA = long-acting beta-agonists; ICS = inhaled corticosteroids; IPRA = ipratropium; THEO = theophylline

Propensity model included age, race, VISN, incident, hypertension, IHD, non-depression mental health, substance abuse, cancer, lung cancer, alcoholism, CHF, stroke, depression, GERD, PUD, arrhythmias, pulmonologist, cardiologist, GP, baseline exacerbations, baseline COPD hospitalizations, treatment change from FY02, FY02 treatment regimen

Table A3. Baseline characteristics by treatment regimen after stratification by propensity score in Group 3 (ICS+LABA+IPRA vs. ICS+LABA+IPRA+THEO)

	Quintile 1			Quintile 2		Quintile 3		Quintile 4		Quintile 5	
	ICS + LABA + IPRA	+ THEO		ICS + LABA + IPRA	+ THEO	ICS + LABA + IPRA	+ THEO	ICS + LABA + IPRA	+ THEO	ICS + LABA + IPRA	+ THEO
N	5,202	668		4,879	980	4,700	1,182	4,468	1,402	3,999	1,871
White, %	55.9	53.9		52.8	52.6	58.0	58.5	62.2	61.8	64.5	66.0
Age, mean	69.7	70.3		70.1	70.0	69.8	69.6	68.9	69.2	68.4	68.2
Male, %	97.4	98.2		98.6	98.6	97.5	98.3	97.6	97.7	98.2	98.4
Incident COPD, %	15.5	10.3	**	2.0	2.1	0.9	0.7	0.4	0.5	0.1	0.1
Pulmonologist Visit, %	19.1	18.9		22.1	20.9	28.8	27.5	34.4	36.0	40.0	42.7
Exacerbations, %											
1+	41.5	43.7		42.7	41.9	55.1	54.2	63.4	63.6	76.5	78.3
Hospitalizations – primary COPD, %											
1+	4.7	5.1		4.6	3.6	5.1	5.4	7.0	7.3	8.9	9.6

* ≤ 0.05
** ≤ 0.01

Abbreviations: LABA = long-acting beta-agonists; ICS = inhaled corticosteroids; IPRA = ipratropium; THEO = theophylline

Propensity model included age, race, VISN, incident, hypertension, IHD, non-depression mental health, substance abuse, cancer, lung cancer, alcoholism, CHF, stroke, depression, GERD, PUD, arrhythmias, pulmonologist, cardiologist, GP, baseline exacerbations, baseline COPD hospitalizations, treatment change from FY02, FY02 treatment regimen

Table A4. Baseline characteristics by treatment regimen after stratification by propensity score in Group 4 (LABA+IPRA vs. LABA+IPRA+THEO)

	Quintile 1			Quintile 2		Quintile 3		Quintile 4			Quintile 5	
	LABA + IPRA	+ THEO		LABA + IPRA	+ THEO	LABA + IPRA	+ THEO	LABA + IPRA	+ THEO		LABA + IPRA	+ THEO
N	2,453	185		2,316	322	2,241	397	2,124	513		1,870	769
White, %	59.6	60.0		57.0	56.5	61.6	60.0	61.5	62.2		65.1	66.5
Age, mean	67.5	68.6		70.3	70.2	70.1	70.6	70.6	70.6		71.0	70.6
Male, %	98.0	98.4		98.3	98.5	97.8	98.7	97.8	99.4	*	98.2	98.1
Incident COPD, %	20.0	12.4	*	4.0	5.6	1.5	1.3	0.1			0.1	
Pulmonologist Visit, %	17.1	20.0		19.4	21.4	25.4	22.7	28.3	28.9		32.3	33.2
Exacerbations, %												
1+	19.5	19.5		22.0	24.2	30.2	27.2	36.2	39.0		57.3	59.3
Hospitalizations – primary COPD, %												
1+	1.9	2.7		2.3	2.2	3.7	4.3	5.0	4.5		10.4	11.8

* ≤ 0.05
** ≤ 0.01

Abbreviations: LABA = long-acting beta-agonists; ICS = inhaled corticosteroids; IPRA = ipratropium; THEO = theophylline

Propensity model adjusted for age, race, VISN, incident COPD, mental health diagnosis, substance abuse, cancer, alcoholism, depression, arrhythmias, pulmonologist, cardiologist, baseline exacerbations, COPD-related hospitalizations, treatment change from FY2002, IPRA FY2002, LABA FY2002, ICS FY2002

Table A5. Baseline characteristics by treatment regimen after stratification by propensity score in Group 5 (ICS vs. ICS+THEO)

	Quintile 1		Quintile 2		Quintile 3		Quintile 4		Quintile 5	
	ICS	+ THEO	ICS	+ THEO	ICS	+ THEO	ICS	+ THEO	ICS	+ THEO
N	2,345	158	2,227	268	2,182	333	2,66	452	1,878	613
White, %	50.1	55.1	50.9	47.8	48.4	47.5	55.0	57.1	66.0	65.1
Age, mean	61.0	60.7	66.6	67.4	71.3	72.2	73.2	72.9	74.3	74.4
Male, %	93.9	94.9	95.6	96.6	97.1	98.5	97.1	98.2	97.9	98.4
Incident COPD, %	31.7	27.9	6.0	4.9	1.8	1.5	0.2	0.4	–	0.1
Pulmonologist Visit, %	9.5	10.1	11.0	14.6	8.9	9.6	12.0	8.9	11.6	12.2
Exacerbations, %										
1+	7.0	8.9	10.0	9.0	11.8	12.3	19.9	20.1	37.4	40.5
Hospitalizations – primary COPD, %										
1+	1.2	1.3	1.1	0.4	1.1	1.5	1.4	2.0	1.1	0.8

* ≤ 0.05
** ≤ 0.01

Abbreviations: LABA = long-acting beta-agonists; ICS = inhaled corticosteroids; IPRA = ipratropium; THEO = theophylline

Propensity model adjusted for age, race, VISN, incident COPD, mental health diagnosis, substance abuse, cancer, alcoholism, depression, arrhythmias, pulmonologist, cardiologist, baseline exacerbations, COPD-related hospitalizations, treatment change from FY2002, IPRA FY2002, LABA FY2002, ICS FY2002

Table A6. Baseline characteristics by treatment regimen after stratification by propensity score in Group 6 (ICS+LABA vs. ICS+LABA+THEO)

	Quintile 1			Quintile 2			Quintile 3			Quintile 4			Quintile 5		
	ICS + LABA	+ THEO		ICS + LABA	+ THEO		ICS + LABA	+ THEO		ICS + LABA	+ THEO		ICS + LABA	+ THEO	
N	1,980	158		2,064	268		1,680	264		1,824	315		1,612	526	
White, %	45.0	39.9		36.3	35.1		45.8	51.5		53.5	49.5		60.4	62.7	
Age, mean	67.8	68.8		71.1	70.9		70.7	70.6		71.2	70.7		71.1	71.2	
Male, %	96.4	97.5		97.3	97.8		95.7	98.1		96.4	97.1		97.3	98.9	*
Incident COPD, %	29.1	17.1	**	0.5	1.5	*	0.1	0.4		0.1	0.0		0.0	0.0	
Pulmonologist Visit, %	16.6	17.7		14.1	13.1		17.9	15.9		16.7	19.4		23.5	23.6	
Exacerbations, %															
1+	3.2	3.8		5.1	3.0		10.1	12.1		19.9	19.7		56.0	59.5	
Hospitalizations – primary COPD, %															
1+	0.3	1.3		0.6	0.0		0.8	0.4		0.7	1.0		4.0	4.4	

* ≤ 0.05
** ≤ 0.01

Abbreviations: LABA = long-acting beta-agonists; ICS = inhaled corticosteroids; IPRA = ipratropium; THEO = theophylline

Propensity model adjusted for age, rage, VISN, incident COPD, hypertension, IHD, lung cancer, CHF, stroke, GERD, PUD, arrhythmias, pulmonologist, cardiologist, baseline exacerbations, COPD-related hospitalizations, treatment change from FY2002, ipratropium in FY2002, ICS in FY2002 and LABA in FY2002

Table A7. Unadjusted Outcomes by Treatment Group

		Deaths			Exacerbations[a]				Hospitalizations[a]			
	N	(%)	HR	(95% CI)	Mean	(sd)	RR	(95% CI)	Mean	(sd)	RR	(95% CI)
IPRA	8,690	(15.5)	—		1.00	(1.63)	—		0.11	(0.54)	—	
IPRA + THEO	1,265	(18.0)	1.19	(1.12, 1.26)	1.26	(2.03)	1.28	(1.23, 1.33)	0.16	(0.65)	1.60	(1.43, 1.79)
ICS + IPRA	5,035	(14.8)	—		1.27	(1.97)	—		0.16	(0.64)	—	
ICS + IPRA + THEO	1,241	(18.0)	1.24	(1.16, 1.32	1.64	(2.31)	1.31	(1.26, 1.36)	0.25	(0.88)	1.60	(1.45, 1.76)
ICS + LABA + IPRA	3,524	(15.1)	—		1.63	(2.37)	—		0.23	(0.82)	—	
ICS + LABA + IPRA + THEO	1,065	(17.4)	1.17	(1.09, 1.25)	2.00	(2.64)	1.24	(1.18, 1.29)	0.29	(0.94)	1.30	(1.17, 1.43)
LABA + IPRA	1,769	(16.3)	—		1.33	(2.05)	—		0.18	(0.73)	—	
LABA + IPRA + THEO	438	(20.0)	1.25	(1.13, 1.39)	1.62	(2.39)	1.23	(1.15, 1.32)	0.26	(0.95)	1.49	(1.24, 1.78)
ICS	1,116	(10.4)	—		0.72	(1.43)	—		0.06	(0.36)	—	
ICS + THEO	244	(13.4)	1.30	(1.14, 1.50)	0.90	(1.55)	1.25	(1.13, 1.37)	0.08	(0.40)	1.43	(1.07, 1.92)
ICS + LABA	813	(8.9)	—		0.70	(1.43)	—		0.06	(0.35)	—	
ICS + LABA + THEO	183	(12.0)	1.36	(1.16, 1.60)	0.99	(1.73)	1.43	(1.28, 1.59)	0.09	(0.51)	1.73	(1.26,2.37)

[a]Reported as average rate per patient per year

Table A8. Adjusted[a] outcomes within comparison groups by quintile

		Mortality		Exacerbations		Hospitalizations	
Regimen + THEO		HR	(95% CI)	RR	(95% CI)	RR	(95% CI)
IPRA	Quintile 1	1.29	(1.01, 1.65)	1.11	(0.95, 1.31)	1.13	(0.70, 1.81)
	Quintile 2	1.18	(0.99, 1.41)	1.11	(0.99, 1.25)	1.51	(1.09, 2.08)
	Quintile 3	1.14	(0.97, 1.34)	1.12	(1.00, 1.25)	1.22	(0.89, 1.68)
	Quintile 4	1.04	(0.91, 1.18)	1.11	(1.02, 1.21)	1.28	(1.02, 1.61)
	Quintile 5	1.08	(0.99, 1.19)	1.11	(1.05, 1.18)	1.13	(0.97, 1.33)
ICS + IPRA	Quintile 1	1.06	(0.84, 1.34)	1.09	(0.95, 1.24)	1.27	(0.89, 1.83)
	Quintile 2	1.19	(1.00, 1.41)	1.22	(1.09, 1.36)	1.97	(1.51, 2.58)
	Quintile 3	1.29	(1.12, 1.50)	1.17	(1.07, 1.28)	1.18	(0.93, 1.51)
	Quintile 4	1.24	(1.09, 1.42)	1.19	(1.10, 1.29)	1.29	(1.07, 1.57)
	Quintile 5	1.08	(0.97, 1.21)	1.17	(1.10, 1.24)	1.22	(1.06, 1.40)
ICS + LABA + IPRA	Quintile 1	0.97	(0.79, 1.18)	1.10	(0.95, 1.27)	1.29	(0.96, 1.74)
	Quintile 2	1.14	(0.96, 1.37)	1.01	(0.90, 1.15)	1.01	(0.77, 1.33)
	Quintile 3	1.22	(1.04, 1.44)	1.00	(0.92, 1.10)	0.82	(0.65, 1.04)
	Quintile 4	1.43	(1.24. 1.66)	1.05	(0.98, 1.13)	1.22	(1.01, 1.47)
	Quintile 5	1.21	(1.06, 1.39)	1.02	(0.97, 1.07)	0.97	(0.83, 1.13)
LABA + IPRA	Quintile 1	1.10	(0.76, 1.60)	0.68	(0.53, 0.86)	0.70	(0.37, 1.33)
	Quintile 2	1.16	(0.88, 1.54)	1.21	(1.00, 1.45)	1.49	(0.97, 2.31)
	Quintile 3	1.51	(1.19, 1.92)	1.16	(0.99, 1.36)	1.22	(0.81, 1.83)
	Quintile 4	1.16	(0.92, 1.46)	1.15	(1.01, 1.32)	1.26	(0.88, 1.79)
	Quintile 5	1.23	(1.01, 1.49)	1.13	(1.02, 1.26)	1.11	(0.85, 1.45)
ICS	Quintile 1	0.99	(0.53, 1.85)	1.35	(1.00, 1.83)	1.79	(0.71, 4.50)
	Quintile 2	1.21	(0.78, 1.88)	0.98	(0.75, 1.28)	1.23	(0.57, 2.63)
	Quintile 3	1.27	(0.90, 1.78)	1.17	(0.93, 1.47)	0.89	(0.38, 2.09)
	Quintile 4	0.94	(0.69, 1.28)	1.11	(0.92, 1.34)	1.02	(0.58, 1.79)
	Quintile 5	1.32	(1.06, 1.66)	1.08	(0.94, 1.25)	1.23	(0.78, 1.93)
ICS + LABA	Quintile 1	1.35	(0.80, 2.27)	1.08	(0.78, 1.50)	1.12	(0.42, 3.05)
	Quintile 2	1.12	(0.70, 1.81)	1.19	(0.78, 1.82)	2.30	(0.65, 8.18)
	Quintile 3	1.25	(0.85, 1.86)	1.27	(0.85, 1.90)	1.54	(0.43, 5.49)
	Quintile 4	1.36	(0.94, 1.97)	1.07	(0.72, 1.58)	0.97	(0.28, 3.33)
	Quintile 5	1.42	(1.08, 1.88)	1.11	(0.77, 1.59)	1.34	(0.45, 3.99)

[a]Each model was adjusted for factors that were imbalanced within quintile following creation of propensity scores