Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

This clinical study synopsis is provided in line with **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country..

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's Policy on Transparency and Publication of Clinical Study Data**.

The synopsis is supplied for informational purposes only in the interests of scientific disclosure. It must not be used for any commercial purposes and must not be distributed, published, modified, reused, posted in any way, or used for any other purpose without the express written permission of Boehringer Ingelheim.

[redacted]

Boehringer Ingelheim

The effectiveness of Tiotropium add-on therapy for patients with asthma in a real-world cohort

September 11, 2019

Retrospective Data Analysis

We conducted a retrospective cohort study comparing asthma patients taking ICS/LABA therapy that added tiotropium Respimat® 1.25 mcg to those that increased their ICS/LABA dose. We found the group that added tiotropium were at a lower risk of exacerbation, were less likely to be hospitalized, and required less asthma rescue medication, and had lower all-cause and asthma-related emergency room visits. Results of this study highlight the benefit of adding tiotropium Respimat® 1.25 mcg for patients with Asthma.

[redacted]

Background

Asthma imposes a substantial burden on the healthcare system with poor symptom control doubling treatment cost versus patients with adequate control (ACAAI). The European National Health and Wellness Survey and the Real-world Evaluation of Asthma Control and Treatment (US) survey both found that 55% of asthma patients were uncontrolled, even among those who are treated (Peters 2007, Braido 2013). Asthma therapy involves a stepwise approach depending on control and severity levels. Uncontrolled asthma, which may present regardless of severity level, results in exacerbations, use of systemic corticosteroids, and declined lung function (Chung 2014). When asthma is not controlled, guidelines recommend increased ICS dose, and use of ICS in combination with long-acting β2-agonists (LABA), and/or other add-on therapy, including leukotriene receptor antagonists (LTRA), antibody biologics or oral corticosteroids. The ERS/ATS guidelines (Chung 2014) define severe asthma as that which remains uncontrolled despite use of high dose ICS as well as controller medications or systemic corticosteroids. Uncontrolled asthma is associated with an increased risk of exacerbation, which results in impaired lung function, reduced patient quality of life and increased health care resource use. To better guide treatment decision making, it is imperative to understand the impact of different treatment choices on health outcomes in a real-world setting for patients taking ICS/LABA combinations. This study was conducted to assess the impact of tiotropium add-on therapy on important health outcomes in patients with asthma.

Objective

To evaluate the effectiveness of add on therapy with tiotropium Respimat® compared to increasing the dose of ICS/LABA in patients with a diagnosis of asthma started on ICS/LABA.

Methods

Data sources

This study included asthma patients from two retrospective data sources described below. Both databases have been widely published in the academic asthma literature. Data from January 2014- December 2018 was extracted, with the first patient follow-up period for tiotropium 1.25 mcg dose patients starting January 2016.

IMS Pharmetrics

Data from January 2014-2018 was extracted, with the first recorded use of tiotropium 1.25 mcg starting at January 2016. This database is one of the largest US health plan claims database. It contains administrative insurance data of medical and pharmacy claims and enrolment information derived from approximately 150 million commercially insured and Medicare lives. This longitudinal database allows documentation and analysis of the patient journey from diagnosis to intervention and follow-up. It is nationally representative of the commercially insured population and also covers 90% of US hospitals.

EMRClaims+

EMRClaims+® is an integrated health services database containing more than 20 million medical records across seven states in the Midwestern region of the United States. The database includes administrative insurance claims of approximately 690,000 lives linked to an overlapping healthcare provider database of EMR, including laboratory values, and provider billing files. The database also offers lung function results, Asthma Control Test (ACT) scores, as well as eosinophil counts for asthma patients in addition to administrative data.

Study design and Measures

All patients with asthma were required to have used ICS/LABA therapy [Advair (Diskus and HFA), Airduo, Breo, Dulera, or Symbicort]. The date of the first ICS/LABA within the study period was defined as ICS/LABA-initiation (ICS/LABAi) date. These patients were followed to identify use of tiotropium Respimat® 1.25 mcg, or a dose increase of ICS/LABA. Patients who used tiotropium Respimat® 1.25 mcg were classified as 'Tio' group. Other patients who did not receive tiotropium during the study period but received a 'step-up' from baseline low-dose ICS/LABA to medium/high dose ICS/LABA or from baseline medium dose ICS/LABA to high dose ICS/LABA or persistent use of high-dose-ICS/LABA following the first prescription of baseline high dose ICS/LABA within the study period, were classified as the 'Non-Tio' group. The date of the first prescription for tiotropium Respimat® 1.25 mcg was defined as the index date for the 'Tio' group. Similarly the date of the first step-up from baseline low-dose ICS/LABA to medium/high dose ICS/LABA or from baseline medium dose ICS/LABA to high dose ICS/LABA or an additional prescription/refill of high-dose-ICS/LABA following the first prescription of baseline high dose ICS/LABA within the study period was defined as the index date for the 'Non-Tio' group. Patients were required to have continuous enrollment for 6 months prior to ("baseline period") and at least one month after ("follow-up period") the index date.

Patient gender and age at ICS/LABA initiation date was recorded. Comorbidities included in the Charlson Comorbidity Index (CCI) were identified during the baseline period and a composite CCI score was calculated. Other specific comorbidities identified were hypertension, gastro-esophageal reflux disease, anxiety and depression, and endocrine and metabolic disorder. Polypharmacy at baseline, was calculated as total number of drug claims identified during baseline. Baseline asthma control status was classified as a binary measure as 'Well' If patients had no prescriptions for an oral corticosteroid (OCS), and no asthma-related emergency department visits or hospitalizations other than the first diagnosis, and as 'Poor' for all others. Where available, Asthma Control Test (ACT) score and eosinophil blood count (EOS) levels as available, were identified at baseline for data extracted from EMRClaims+® only.

The primary outcome of interest was the risk of exacerbation after the index date. Exacerbations were defined as as either a hospitalization or an ER visit with a primary diagnosis of asthma. Secondary outcomes of interest included rate of exacerbation, health care resource use (HCRU) defined as all-cause and asthma related hospitalizations, ER visits, and outpatient visits, and associated costs as well as use of rescue medication and time to biologic use. Additional data-dependent secondary measures with limited availability were evaluated for feasibility of comparative subgroup analyses including EOS levels, ACT scores, and Lung Function Test Results (% Forced Expiratory Volume).

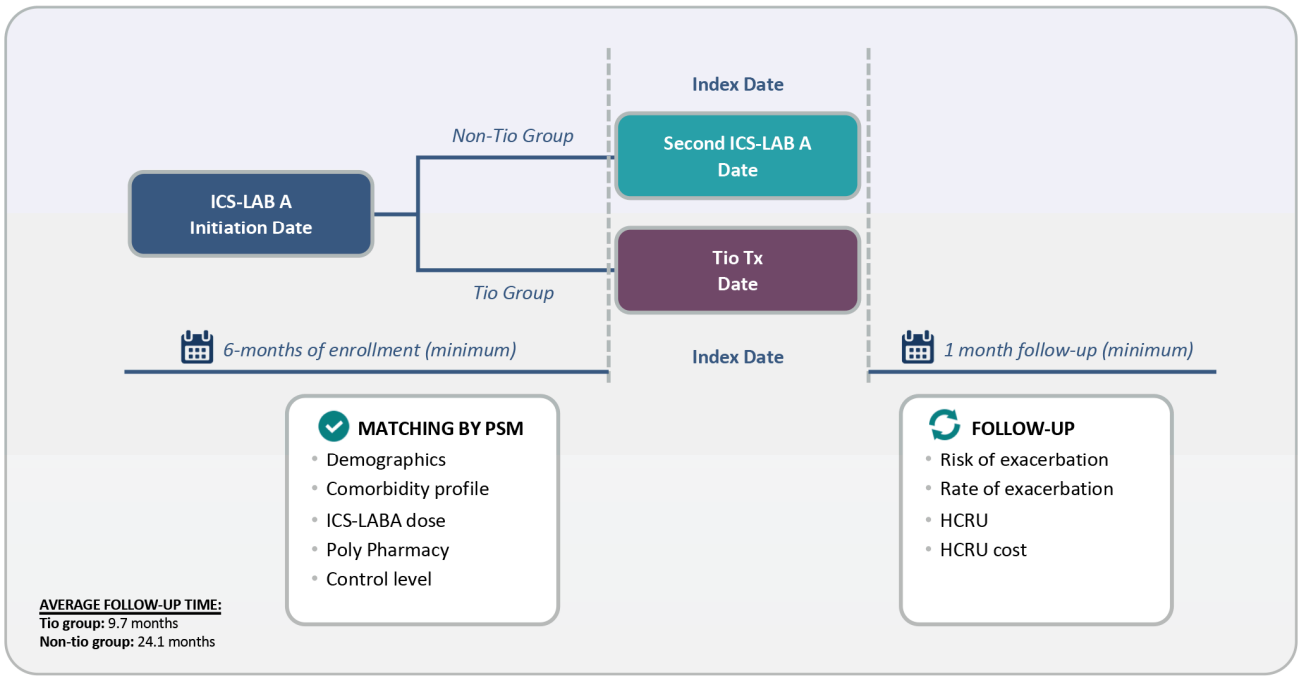
Propensity Score Modeling

To account for population and group differences we conducted propensity score matching (PSM) to create matched case and control groups. Baseline differences in patient characteristics, comorbidity levels, and disease status can cause confounding in interpretation of the outcome in relation to the intervention of interest. PSM matches each patient in the case group to 2 similar patients from the control group and creates a balanced dataset for comparison of groups based on the intervention of interest. In this study, PSM was conducted to match patients based on the parameters shown in Table 1.

TABLE 1: MATCHING PARAMETERS FOR PSM

VARIABLE NAME AND TYPE	DESCRIPTION
ICS/LABA dose on initiation date	The dose level of the first prescription on the ICS/LABA initiation date (low, medium, or high)
Demographics	Age (5-year increments) and Gender Male/Female), Region (Northeast, Midwest, South, West)
CCI score	Charlson Comorbidity Index score
Specific comorbidities (categorical variables)	Hypertension, diabetes, metabolic and endocrine comorbidities, anxiety and depression, gastro-esophageal reflux disease.
Medications	Polypharmacy level matched within a range of 2 drugs (for example, 0-2,3-5,6-8,8-10 and so on).
Asthma Control Status: Well Control or Poor Control	'Well Controlled' if patient has no prescriptions for an OCS, and no asthma-related emergency department visits or hospitalizations other than the first diagnosis recorded in the data extracted

FIGURE 1: STUDY DESIGN



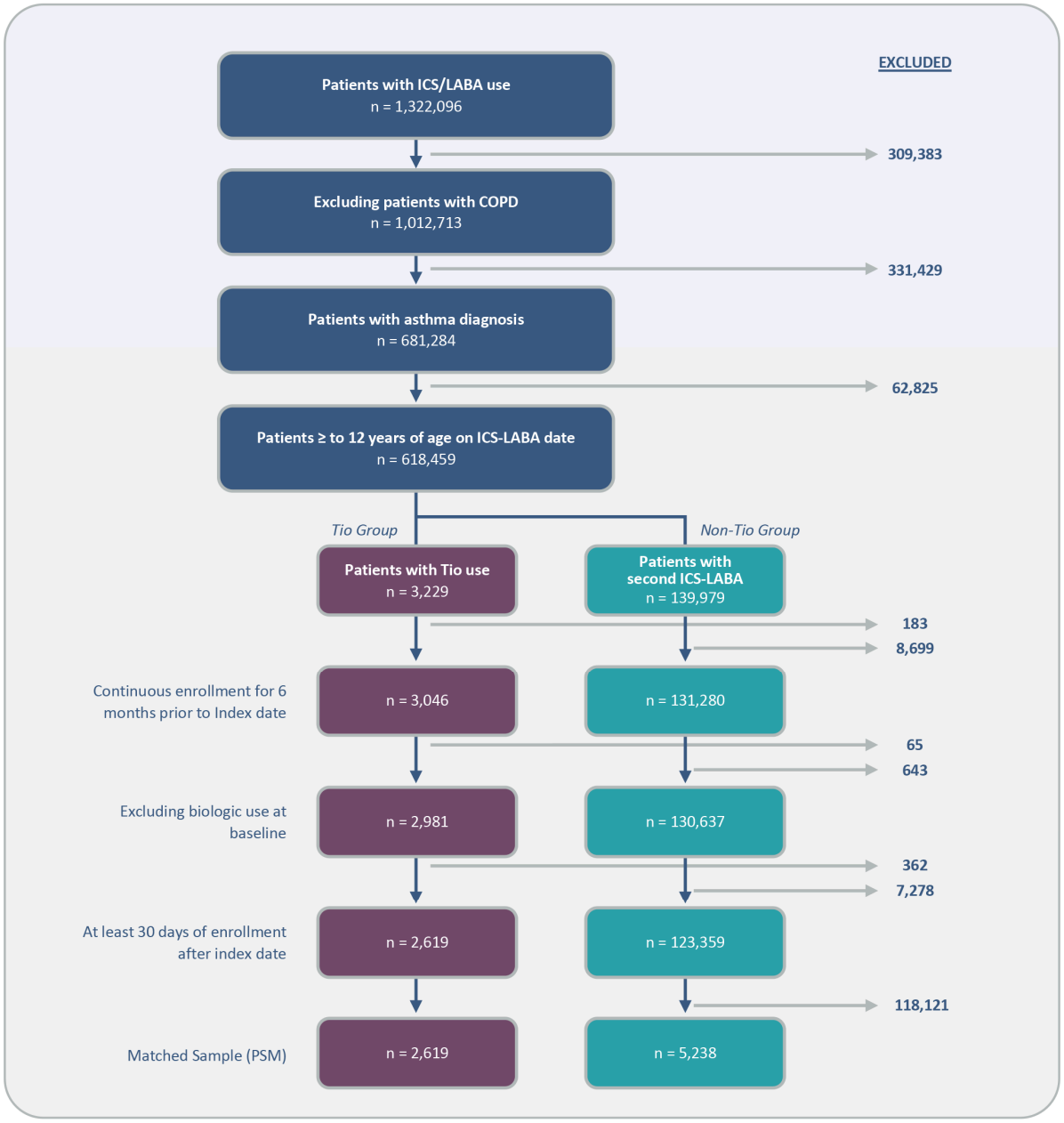
Data Analysis

The primary end point (risk of exacerbation) was assessed using Cox Proportional Hazards model that considers both occurrence of and time-to occurrence of the first event. For the secondary outcomes, we calculated the proportion of patients with at least one exacerbation within 6 months and 1 year after the index date. For health care resource use measures, we calculated the rate (per 100 person years) of all-cause and asthma related hospitalizations, or ER visits, or outpatient visits after the index date. Since patients had different follow-up times in the study, mean cost measures were averaged to a monthly level for all patients and compared between groups.

Results

A total of 2,619 patients were included in the Tio group along with 123,359 non-Tio patients available for matching.

FIGURE 2: SAMPLE ATTRITION



PSM resulted in a match of each Tio patient to 2 non-Tio patients. Table 2 compares the groups prior to and after matching. Except for age distribution, PSM was able to balance out all other covariates as shown by the lack of significant differences between the two groups for these parameters in the matched population.

TABLE 2: PSM RESULTS

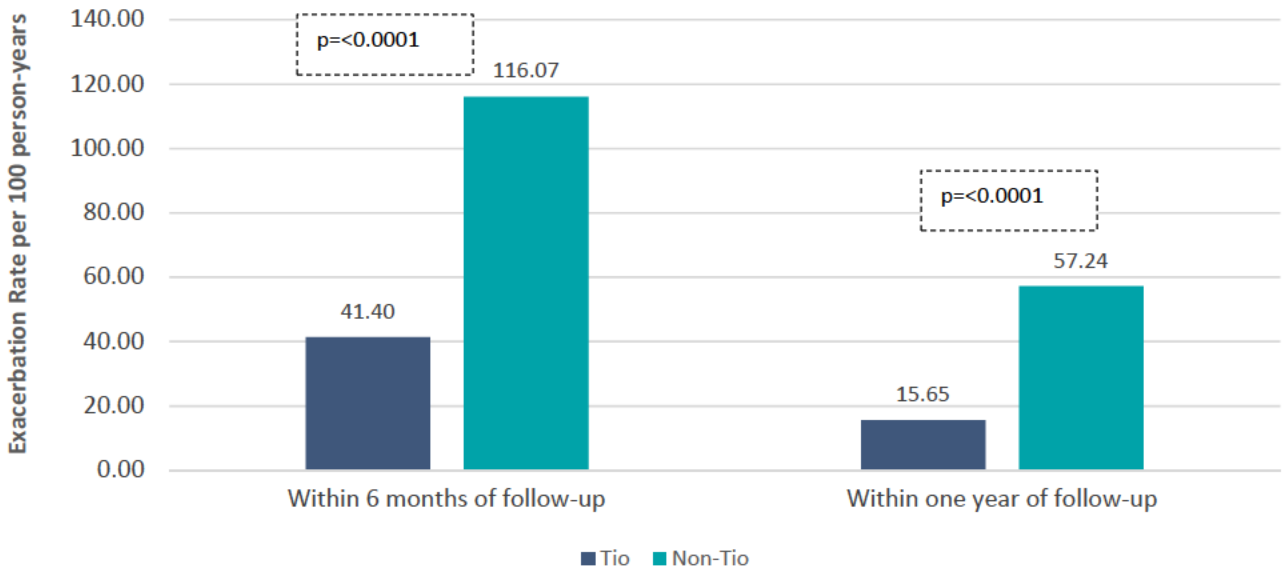
	UNMATCHED POPULATION					MATCHED POPULATION				
	Case/Tiotropium		Control/Non-Tio		P value	Case/Tiotropium		Control/Non-Tio		P value
	2,619		123,359			2,619		5,238		
	n	%	n	%		n	%	n	%	
Gender										
Female	1,802	69%	75,975	62%	<0.0001	1,802	69%	3,576	68%	0.631
Male	817	31%	47,383	38%		817	31%	1,662	32%	
Unknown	-	0%	1	0%		-	0%	1	0%	
Age groupings										
<=17	167	6%	9,516	8%	<0.0001	167	6%	346	7%	0.02
18-22	117	4%	6,559	5%		117	4%	218	4%	
23-27	109	4%	7,220	6%		109	4%	249	5%	
28-32	154	6%	8,629	7%		154	6%	353	7%	
33-37	283	11%	12,857	10%		283	11%	565	11%	
38-42	218	8%	10,143	8%		218	8%	361	7%	
43-47	313	12%	14,466	12%		313	12%	652	12%	
48-52	306	12%	15,311	12%		306	12%	685	13%	
53-57	336	13%	15,116	12%		336	13%	648	12%	
58-62	354	14%	13,609	11%		354	14%	586	11%	
63-67	142	5%	7,060	6%		142	5%	344	7%	
68-72	57	2%	1,657	1%		57	2%	123	2%	
73-77	35	1%	679	1%		35	1%	48	1%	
78-82	17	1%	467	0.4%		17	1%	36	1%	
>=83	11	0.4%	70	0.1%		11	0.4%	24	0.5%	
Region										
E	528	20%	30,846	25%	<0.0001	528	20%	1,042	20%	0.952
MW	881	34%	34,212	28%		881	34%	1,792	34%	
S	974	37%	41,356	34%		974	37%	1,955	37%	
W	225	9%	14,786	12%		225	9%	430	8%	
Unknown	11	0%	2,159	2%		11	0%	19	0%	

TABLE 2: PSM RESULTS (CONTINUED)

	UNMATCHED POPULATION					MATCHED POPULATION				
	Case/Tiotropium		Control/Non-Tio		P value	Case/Tiotropium		Control/Non-Tio		P value
	2,619		123,359			2,619		5,238		
	n	%	n	%		n	%	n	%	
First ICS-LABA dose level										
0	591	23%	17,074	14%	<0.0001	591	23%	1,237	24%	0.065
1	506	19%	8,146	7%		506	19%	902	17%	
2	1,522	58%	98,139	80%		1,522	58%	3,099	59%	
Control level										
Not well controlled	1,599	61%	53,280	43%	<0.0001	1,599	61%	3,172	61%	0.671
Well controlled	1,020	39%	70,079	57%		1,020	39%	2,066	39%	
Polypharmacy (number of claims)										
0	195	7%	2,642	2%	<0.0001	195	7%	303	6%	0.352
2-3	72	3%	6,571	5%		72	3%	129	2%	
3-4	97	4%	13,319	11%		97	4%	218	4%	
5-6	182	7%	15,594	13%		182	7%	374	7%	
7-8	211	8%	15,433	13%		211	8%	432	8%	
9-10	194	7%	13,943	11%		194	7%	421	8%	
11-12	220	8%	11,769	10%		220	8%	468	9%	
13-14	217	8%	9,497	8%		217	8%	435	8%	
15-16	208	8%	7,616	6%		208	8%	409	8%	
17-18	180	7%	6,121	5%		180	7%	378	7%	
>=19	843	32%	20,854	17%		843	32%	1,671	32%	
Hypertension	806	31%	32,778	27%	<0.0001	806	31%	1,594	30%	0.755
GERD	770	29%	22,356	18%	<0.0001	770	29%	1,517	29%	0.686
Anxiety/ depression	605	23%	23,858	19%	<0.0001	605	23%	1,228	23%	0.734
Endocrine/ Metabolic disorders	1,382	53%	39,969	32%	<0.0001	1,382	53%	2,673	51%	0.146
CCI score	**0.460**		**0.357**		**<0.0001**	**0.460**		**0.407**		**0.045**

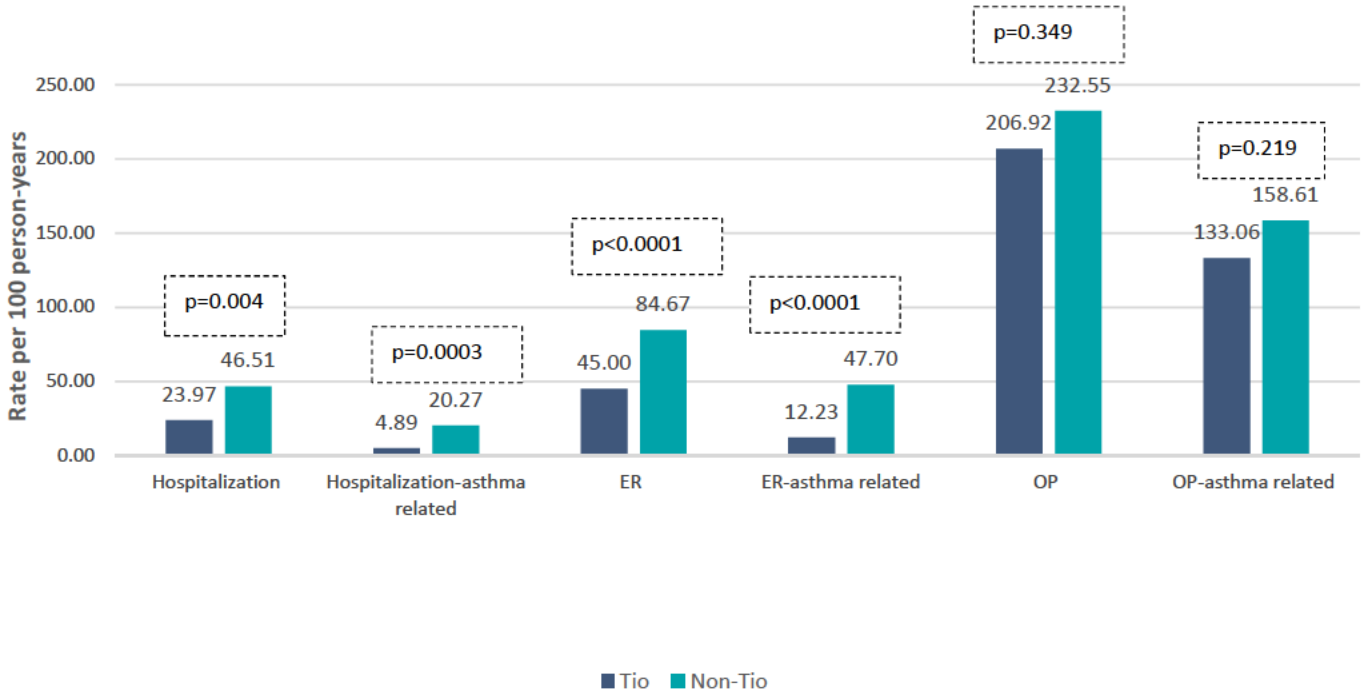
Cox Proportional Hazard models were estimated with group status as the only independent variable. Risk of exacerbation was 35% lower in the Tio group compared to Non-Tio [HR: 0.65, 95% CI: 0.427-0.990, p=0.044]. Within 6 months of follow-up, the rate of exacerbation was 64% lower for the Tio group (41.4 [n=26] vs. 116.07 [n=37] cases per 100 person-years, p<0.0001). Within 12 months of follow-up, the Tio group also showed a 73% lower exacerbation rate compared to the Non-Tio group (15.65 [n=32] vs. 57.24 [n=48] cases per 100 person-years, p<0.0001). (Figure 3).

FIGURE 3: RATE OF EXACERBATIONS



Within one year of follow-up, the rate per 100 person-years of all-cause hospitalizations was 48% lower and asthma-related hospitalizations were 76% lower in the Tio group (all-cause: Tio n=49, non-Tio=39 [p=0.004]; asthma-related Tio n=10, non-Tio=17 [p=0.0003]). The rate per 100 person-years of all-cause ER visits was 47% lower (p<0.0001) and asthma-related ER visits was 74% lower (p<0.0001) in the Tio group (all-cause: Tio n=92, non-Tio=71; asthma-related: Tio n=25, non-Tio=40) during one year of follow up (Figure 4). No differences were noted in outpatient visits (all-cause: Tio n=423, non-Tio n=195 [p=0.349]; asthma-related Tio n=272, non-Tio n=133 [p=0.219]).

FIGURE 4: RESOURCE USE



There were no significant differences found in mean monthly hospitalization and ER visit costs. Mean monthly outpatient costs were significantly greater for the Tio group (Table 3). It should be noted that observation of greater outpatient-related cost is often reported in retrospective asthma studies, reflecting patient-provider engagement. These regularly scheduled office visits in turn are expected to result in fewer or emergency encounters requiring urgent and prolonged care. Researchers commonly report and interpret higher outpatient cost in the group with better health outcomes.

TABLE 3: MEAN MONTHLY COST

Mean monthly cost related to	TIO		NON-TIO		P VALUE
	Mean	Std	Mean	Std	
Hospitalization (all cause)	$277	1661.3	$276	1735.6	0.992
Hospitalization (asthma)	$14	185.3	$24	191.8	0.337
ER visit (all cause)	$35	210.2	$34	153.8	0.919
ER visit (asthma)	$6	78.9	$5	33.1	0.825
Outpatient visit (all cause)	$724	2146.9	$374	779.4	<0.0001
Outpatient visit (asthma)	$145	749.2	$49	201.5	0.001

Based on power calculations used in determining the sample requirements in this study, Insufficient data were available to make reliable comparisons for the data-dependent sub-group measures including EOS, ACT, Lung Function, and Time-to-Biologics (sample of patients with these measures reported: EOS, ACT, Lung Function each n < 100; biologics use n=15). The study required 6,300 patients overall to show significance based on the effect size in the power calculation for the primary study endpoints. We estimate that these secondary measures would require a similar sample to show significant differences. The proportion of patients with rescue medication use within 12 months of index date was significantly lower in the Tio group compared to the non-Tio group (56% vs. 67% p<0.0001). Among those showing use, Tio patients had fewer rescue medications on average (Mean [SD]: 2.95[3.04] vs 3.61 [4.39], p=0.019).

Conclusion

Asthma patients who add tiotropium to ICS/LABA show a substantial reduction in risk and rate of exacerbation. These significant clinical improvements translate to reduced reliance on rescue medication, a lower likelihood of all-cause and asthma-related hospital admissions. There was significantly lower rate of hospitalization and ER visits for these patients as well. The findings of this real-world study support expanded use of tiotropium add-and on therapy for asthma patients taking ICS/LABA.

References

Braido F. Failure in Asthma control: Reasons and Conseuqences. Scientifica 2013. 549252 (2013)

Chung KF et al. International ERS/ATS Guidelines on definition evaluation and treatment of severe asthma. Eur Respir J 43, 343-373 (2014)

Guidelines for Good Pharmacoepidemiology Practices (GPP) (revision 2: April 2007). http://www.pharmacoepi.org/resources/guidelines_0827.cfm (access date: 13 September 2011) ; Bethesda: International Society for Pharmacoepidemiology (ISPE); 2007.

Keene ON, Calverley PMA, Jones PW, Vestbo J, Anderson JA. Statistical Analysis on exacerbation rates in COPD, TRISTAN, and ISOLDE revisited. Eur Respir J 32 (1) 17-24 (2008)

Kerstjens HA et al. Tiotropium and salmeterol as add-on therapies to inhaled corticosteroids for patients with symptomatic asthma: two replicate, double-blind, placebo-controlled, parallel-group, active-comparator, randomised trials. Lancet Respir Med. 2015 May;3(5):367-76

Peters SP, Jones CA, Haselkorn T, Mink DR, Valacer DJ, Weiss ST. Real- world Evaluation of Asthma Control and Treatment (REACT): findings from a national web-based survey. J Allergy Clin Immunol 119 (6) 1454-1461 (2007)