

Comparative outcomes of leukotriene receptor antagonists and long-acting β -agonists as add-on therapy in asthmatic patients: A population-based study

Mohsen Sadatsafavi, MD, PhD,^{a,b,c} Larry Lynd, PhD,^{c,d} Carlo Marra, PharmD, PhD,^{c,d} Pierrick Bedouch, PharmD, PhD,^e and Mark FitzGerald, MD^{a,b} Vancouver, British Columbia, Canada, and Grenoble, France

Background: Recent evidence suggests that the use of leukotriene receptor antagonists (LTRAs) in addition to inhaled corticosteroids (ICSs) in asthmatic patients provides comparable benefits to the addition of long-acting β -agonists (LABAs) to ICSs.

Objective: We sought to compare, in a unified framework, adherence, outcomes, and costs associated with ICS+LTRA versus ICS+LABA as step-up therapies for asthma.

Methods: Using the administrative databases of British Columbia, Canada (years 1997-2007), we created a propensity score-matched sample of asthmatic patients (12-45 years old) receiving ICS+LTRA therapy versus ICS+LABA therapy after a period of monotherapy with an ICS. We compared the outcomes using 2 analyses: an intention-to-treat (ITT) analysis that followed subjects for a fixed period of 2 years and an uninterrupted treatment analysis that followed subjects for as long as they continuously dispensed their index medications.

Results: The matched cohort consisted of 1032 subjects in each group (mean age at entry, 27.4 years; 52.5% female).

Adherence, which was defined as the proportion of days covered, was higher in the ICS+LABA group compared with the ICS+LTRA group. In both the ITT and uninterrupted treatment analyses, use of ICS+LTRA therapy was associated with more asthma-related outpatient visits, asthma-related medication dispensations, and dispensation of reliever

medications. Dispensation of oral corticosteroids and rate of asthma exacerbations were higher in the ICS+LTRA group in the uninterrupted treatment analysis but not in the ITT analysis.

Conclusions: In a real-world clinical setting subjects were more adherent to ICS+LABA therapy than ICS+LTRA therapy. ICS+LABA therapy seems to be more effective than ICS+LTRA therapy in the management of asthma, regardless of adherence. (J Allergy Clin Immunol 2013;■■■■:■■■■-■■■■.)

Key words: Asthma, leukotriene receptor antagonists, long-acting β -agonists, inhaled corticosteroids, outcome research, costs, administrative data, Canada

The primary goal of asthma management is to achieve and maintain clinical control.¹ Lack of proper asthma control is associated with poorer quality of life and higher costs relative to controlled asthma.^{2,3} Currently, inhaled corticosteroids (ICSs) are accepted as a first-line controller therapy for asthma. Established guidelines recommend a step-up approach in the management of asthma if the patient does not respond to mild-to-moderate doses of ICSs.^{1,4} Such a step-up approach can consist of either increasing the dose of ICS or the addition of a second class of controller medication, either a long-acting β -agonist (LABA) or a leukotriene receptor antagonist (LTRA).^{1,5,6} Head-to-head randomized controlled trials (RCTs) comparing the addition of LABAs or LTRAs to ICSs have generally shown better results for ICS+LABA therapy than ICS+LTRA therapy.⁷⁻⁹ A pooled analysis of all efficacy studies reported ICS+LABA therapy to be superior to ICS+LTRA therapy in reducing oral corticosteroid use, with modest but significant improvements in lung function, functional status, and quality of life.¹⁰ Nevertheless, most RCTs comparing ICS+LABA and ICS+LTRA therapy have been efficacy trials that involved strict intervention protocols, included specific subgroups of patients, and mostly had short follow-up times. In a chronic disease, such as asthma, the real-world effectiveness of treatments is affected by patients' characteristics, adherence, and proper intake of interventions over the long term, important factors that efficacy trials often do not capture. For the comparison of LTRAs and LABAs, this issue might be of particular importance given that LTRAs are orally administered, whereas LABAs are provided in inhalers. It is hypothesized that oral administration of an LTRA, compared with use of an inhaler, might result in higher adherence without the risk of improper administration (ie, poor inhaler technique) and the resulting suboptimal intake of the medication.^{11,12} Therefore LTRAs might have advantages over inhaled therapies in real-world clinical practice.

This hypothesis is supported by the results of a recent pragmatic RCT showing that ICS+LTRA therapy and ICS+LABA therapy resulted in comparable improvements in

From ^athe Institute for Heart and Lung Health, Faculty of Medicine; ^bthe Centre for Clinical Epidemiology and Evaluation, Vancouver Coastal Health Institute; ^cCollaboration for Outcomes Research and Evaluation, Faculty of Pharmaceutical Sciences; and ^dthe Centre for Health Evaluation and Outcome Sciences, University of British Columbia, Vancouver, and ^ethe Pharmacy Department, Grenoble University Hospital.

This study is part of the project "Platform for Outcomes Research and Translation in Asthma and Allergy (PORTAL)" funded by Allergan National Center of Excellence, a peer-reviewed government funding agency. The agency did not have any input in the design, analysis, and preparing the reports of the present study.

Disclosure of potential conflict of interest: All of the authors have been supported by one or more grants from the Allergan National Center of Excellence. M. FitzGerald is an Advisory Board member for GlaxoSmithKline, AstraZeneca, Novartis, Pfizer, Boehringer-Ingelheim, Altana, Merck, and Topping; has received one or more grants from or has one or more grants pending with AstraZeneca, GlaxoSmithKline, Boehringer-Ingelheim, Merck, Wyeth, Schering, Genentech, and Topping; has received one or more payments for lecturing from or is on the speakers' bureau for GlaxoSmithKline, AstraZeneca, Boehringer-Ingelheim, Pfizer, and Merck; and has received one or more payments for travel/accommodations/meeting expenses from GlaxoSmithKline, AstraZeneca, Novartis, Pfizer, Boehringer-Ingelheim, Altana, Merck, and Topping.

Received for publication July 10, 2012; revised February 7, 2013; accepted for publication February 8, 2013.

Corresponding author: Mohsen Sadatsafavi, MD, PhD, Centre for Clinical Epidemiology and Evaluation, 7th Floor, 828 W 10th Ave, Research Pavilion, Vancouver, British Columbia V5Z 1M9, Canada. E-mail: msafavi@mail.ubc.ca.

0091-6749/\$36.00

© 2013 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaci.2013.02.007>

Abbreviations used

BC:	British Columbia
ICD:	International Classification of Diseases
ICS:	Inhaled corticosteroid
ITT:	Intention-to-treat
LABA:	Long-acting β -agonist
LTRA:	Leukotriene receptor antagonist
PDC:	Proportion of days covered
RCT:	Randomized controlled trial
RIW:	Resource intensity weight

patient-reported asthma-related quality of life, asthma control, and rate of exacerbation.¹³ RCTs are not the only methods of addressing comparative safety and effectiveness concerns. Well-designed quasiexperimental studies with high-quality data and proper statistical methods can provide real-world estimates of adherence and comparative outcomes at a fraction of the cost of an RCT.^{14–16}

We conducted a population-based study using the administrative health data of the province of British Columbia (BC), Canada, which includes data on all legal BC residents. The purpose of this study was to compare the outcomes between patients who step up therapy from an ICS alone to ICS+LABA therapy with those who step up to ICS+LTRA therapy. We specifically designed this study to evaluate whether any differences in effectiveness can be attributed to better adherence to one study drug versus another. Compared with similar studies based on commercial health care plans in the United States,^{17,18} our study is based on population-based administrative data in a well-defined geographic area and is the first to evaluate the effect of adherence to medications and observed outcomes and costs in a unified framework.

METHODS

The BC provincial health insurance program collects administrative data on the health resource use of all BC residents. Population Data BC provides data linkage and access to the health services database.¹⁹ Data for the fiscal years 1997–2007 were obtained for this study. The following components of health resource use were retrieved. First are the vital statistics, registry, and census databases containing basic demographics, neighborhood income, and longitudinal information on the registration status of the subjects with the provincial health plan. Second is the Discharge Abstract Database, which includes hospital separation records, including admission date, length of stay, and up to 25 discharge diagnostic codes (coded in International Classification of Diseases [ICD], 9th revision [ICD-9] or 10th revision [ICD-10]), as well as a resource intensity weight (RIW), which represents the relative weight of the episode of hospitalization in terms of resource use. An RIW of 1 means that the current episode of hospitalization costs the average hospitalization episode within the province in the corresponding fiscal year.²⁰ Third is the Medical Services Plan, which captures all the outpatient services resulting in a billing record and includes one ICD-9 code for the reason for the service, cost of the service, and specialty of the health care professional issuing the code. Finally, there is BC PharmaNET, which records all drug dispensations (regardless of the coverage status of the individual) in the province, except those belonging to first nations, Royal Canadian Mounted Police, and the military.

Within this database, patients were considered to have asthma if, during a 12-month rolling time window, they filled 3 or more prescriptions for asthma-related medications and had at least 1 outpatient service record with an ICD-9 code for asthma (493.xx; see Table E1 in this article's Online Repository at www.jacionline.org for a list of asthma-related medications).²¹ To robustly assess the covariates and measures of asthma activity before controller use, we

required each patient to be registered with the provincial health care system for at least 12 months before and 24 months after the index date. We restricted the enrollment to subjects who were between 12 and 45 years of age and who satisfied this case definition.²¹

A schematic illustration of cohort construction is provided in Fig 1. Within the population of asthmatic patients receiving ICS monotherapy, we identified those who filled a prescription for an ICS and a LABA (the ICS+LABA group) or an ICS and an LTRA (ICS+LTRA group) within 90 days of each other. The date of the second dispensation was considered the index date. In addition, a dispensation of a single-inhaler ICS+LABA would satisfy this definition for the ICS+LABA group, and the date of this dispensation was considered the index date. To include only subjects who stepped up their medication from monotherapy with an ICS, we required the patient to have received at least 2 dispensations of an ICS in the 12 months before the index date and not to have received any other controller medications during this period.

Within this cohort, each subject in the ICS+LTRA group was matched with a subject in the ICS+LABA group based on the propensity score (1:1 matching with a “greedy” algorithm²²). The propensity score, which was defined as the predicted probability of belonging to the ICS+LTRA group, was constructed by using a logistic regression model, with exposure group membership as the dependent variable (ICS+LABA = 0, ICS+LTRA = 1) and several covariates, all assessed in the 12-month period before the index date. Matching on the propensity score was chosen because it can yield precise comparisons with a relatively small number of experimental units.²³ We chose a nonparsimonious approach and used several variables in constructing the propensity score model.²⁴ The variables used to construct the propensity score were basic demographics, socioeconomic status, measures of asthma severity (asthma-related outpatient services, general practitioner and specialist visits, and dispensation of reliever medication), presence of other respiratory diseases (eg, allergic rhinitis), and general measures of comorbidity (dispensations of any medication and the Charlson comorbidity index²⁵). A complete list of variables used for propensity score calculations is provided in Table E2 in this article's Online Repository at www.jacionline.org.

Follow-up: Intention-to-treat and uninterrupted treatment definitions

One of our objectives was to assess whether potential differences in the effectiveness of 2 treatments are due to differential adherence. To achieve this, we evaluated the comparative effectiveness of both drug combinations under 2 follow-up schemes. First, and similar to the concept of the intention-to-treat (ITT) analysis in RCTs,²⁶ follow-up was defined as the 2-year period after the index date, regardless of treatment discontinuation or switch. Alternatively, the follow-up period was continued from the index date to the end of the uninterrupted treatment phase (uninterrupted treatment analysis). The uninterrupted treatment period started at the index date and stopped at 30 days after the last day of supply of the index medication, after which there was either no further dispensations or a gap of more than 30 days to the next dispensation of the study medication. This was calculated separately for the ICS and the add-on component of combination therapy, and the end of uninterrupted use was considered the earliest day of such a date for the ICS or the add-on component. Because this definition of follow-up includes only person time, in which subjects are adherent to their index medication, it mitigates the effect of differential adherence on the outcomes. As such, any difference between outcomes in the ITT analysis that is due to differential adherence will tend to disappear in the uninterrupted treatment analysis.

Outcomes

The outcomes for this study were measures of adherence to the index medication, rates of various asthma-related resource use and outcomes, and direct asthma-related medical costs.

The main outcome for adherence was the proportion of days covered (PDC),²⁷ which was computed as the percentage of days in the 2 years after the index date for which the index medication was dispensed, adjusting for overlapped supply time.²⁷ PDC was calculated separately for the ICS and the add-on component, and an overall PDC was calculated as the proportion of days

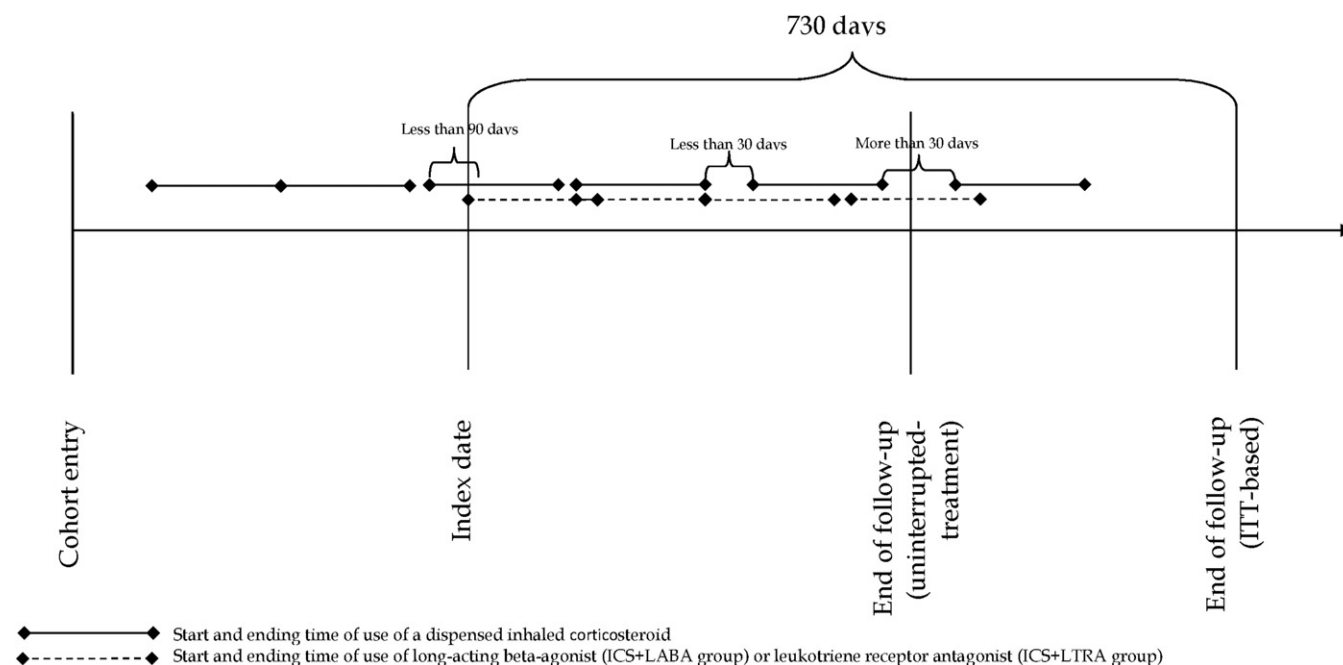


FIG 1. Schematic illustration of the cohort construction and analysis type. *Horizontal lines with nodes at the end represent a dispensed medication. The left node is the dispensation date, and the length of each line represents the intended days of supply of the medication. The index date defines the first time the patient is considered exposed to ICS+LABA or ICS+LTRA. This date is the date of the second of 2 dispensations, one for ICS and another for the non-ICS component of the study medication, if such dispensations occur within 90 days of each other. Follow-up is fixed at 2 years for the ITT-based analysis. For the uninterrupted treatment analysis, it ends 30 days after the patient does not renew his or her dispensations within 30 days of the end of the supply of a previous dispensation.*

the patient was covered by both ICS and the add-on component. An alternative outcome for adherence, which is a direct product of the follow-up (see above), was the time on uninterrupted treatment between the 2 groups.

We defined several primary asthma-related outcomes to provide a relatively comprehensive picture of resource use between the 2 competing interventions. Such outcomes were the relative rates of asthma-related hospitalizations, outpatient visits, and medication dispensations during follow-up. An asthma-related hospitalization was defined as a record in the discharge abstract database with asthma (ICD-9 493.xx or ICD-10 J45/J46) as the most responsible diagnosis for the admission. An asthma-related outpatient visit was defined as a visit with a diagnostic ICD-9 code for asthma. We calculated the total number of dispensations of asthma-related medications from a prespecified list of such medications (see Table E1) during the follow-up period. We also compared the rate of asthma exacerbations, which were defined as episodes of hospitalization caused by asthma or dispensation of oral corticosteroids.²⁸ If such records were within 7 days of each other, they were considered to belong to 1 episode of exacerbation.

Finally, asthma-related direct medical costs were calculated for each group. Costs were the sum of 3 components: hospitalizations, outpatient visits, and medications. We used the case-mixed group methodology for the calculation of hospitalization costs in which the RIW was multiplied by the average cost of hospitalization in the province for the corresponding fiscal year (provided by the Canadian Institution of Health Information) to calculate the cost of hospitalization associated with each discharge record.²⁰ For both the outpatient visits and medications, the exact amount paid, as recorded in the database, was used for cost calculations. Details of our cost calculations have been published previously.^{29,30} All costs were adjusted to 2008 Canadian dollars by using the provincial consumer price index.³¹

Statistical analysis

We compared the ICS+LTRA and ICS+LABA groups with regard to baseline demographic and socioeconomic factors and measures of asthma

severity estimated from the data. In line with recommendations, the final propensity score model was considered satisfactory if the standardized difference in the mean of all the baseline variables between the 2 groups in the matched set was less than 10%.³²

We used the paired *t* test for comparing the PDCs within matched pairs between the 2 groups. The comparison of the uninterrupted treatment time between the 2 groups was performed with proportional-hazards (Cox) regression modeling, with stratification on matched pairs. We used Poisson regression (with overdispersion) stratified on matched pairs to compare the rates of asthma-related outcomes.³³ Nonparametric methods based on 1000 bootstraps were used to draw inference on annual costs between the 2 treatments, considering the skewed nature of the costs and the variable follow-up period in the uninterrupted treatment analysis.³⁴

We performed additional secondary and sensitivity analyses, details of which are provided in the Methods section in this article's Online Repository at www.jacionline.org. We compared measures of uninterrupted treatment and adherence within the ICS+LABA group between those who took their index medication as a single inhaler versus separate inhalers. Next, the ITT analysis was repeated with only 6 months of follow-up to reduce the effect of treatment discontinuation and switching. In another sensitivity analysis we trimmed the follow-up time for each matched pair to the shorter follow-up time within that pair to adjust for temporal trends in outcomes after the index date. All analyses were performed with SAS version 9.3 software (SAS Institute, Cary, NC). *P* values were considered significant at the 5% level (2-sided).

RESULTS

Eighty-seven thousand seven hundred seventy patients satisfied the case definition for asthma, with an average of 5.8 years of follow-up for each subjects. The unmatched cohort consisted of 2992 subjects in the ICS+LABA group and 1032 subjects in the ICS+LTRA group; all subjects in the latter group were matched

TABLE I. Characteristics of the original and matched cohorts and performance of matching

Variable	Unmatched cohort			Matched cohort		
	ICS+LABA group (n = 2992)	ICS+LTRA group (n = 1032)	Std. dist.*	ICS+LABA group (n = 1032)	ICS+LTRA group (n = 1032)	Std. dist.*
Age at index date (y)	31.29 (11.8)	27.46 (12.2)	−31.9%	27.40 (11.7)	27.46 (12.2)	0.5%
Proportion female	0.57 (0.5)	0.52 (0.5)	−10.3%	0.53 (0.5)	0.52 (0.5)	−1.4%
Interval (y) between January 1, 1997, and index date	4.73 (2.1)	3.20 (2.2)	−70.2%	3.34 (2.1)	3.20 (2.2)	−6.2%
Annual rate of outcomes in the year before the index date						
Asthma-related hospitalizations†	0.07 (0.4)	0.05 (0.3)	−5.4%	0.06 (0.4)	0.05 (0.3)	−2.7%
[0, 1, 2, ≥3]	[95.0%, 3.8%, 0.8%, 0.4%]	[95.8%, 3.3%, 0.8%, 0.1%]		[95.5%, 4.0%, 0.2%, 0.4%]	[95.8%, 3.3%, 0.8%, 0.1%]	
Asthma-related outpatient visits‡	3.42 (3.5)	3.58 (3.5)	4.7%	3.66 (3.5)	3.58 (3.5)	−2.1%
Asthma-related outpatient visits by specialist†‡ [0, 1, 2, ≥3]	0.36 (1.2)	0.28 (1.2)	−6.7%	0.30 (0.9)	0.28 (1.2)	−1.4%
	[82.3%, 7.5%, 4.9%, 5.3%]	[86.1%, 7.4%, 2.2%, 4.3%]		[82.7%, 8.4%, 4.8%, 4.2%]	[86.1%, 7.4%, 2.2%, 4.3%]	
Asthma-related medication dispensations	10.33 (7.2)	11.00 (7.5)	9.1%	10.58 (7.4)	11.00 (7.5)	5.7%
Dispensations of short-acting β-agonists	5.69 (5.5)	5.67 (5.5)	−0.4%	5.50 (5.4)	5.67 (5.5)	3.1%
Dispensations of oral corticosteroids†	0.56 (1.3)	0.63 (1.4)	5.7%	0.69 (1.5)	0.63 (1.4)	−4.3%
[0, 1, 2, ≥3]	[72.0%, 15.8%, 6.2%, 6.1%]	[69.5%, 16.0%, 7.6%, 7.0%]		[67.9%, 16.9%, 6.6%, 8.6%]	[69.5%, 16.0%, 7.6%, 7.0%]	
Dispensations of ICSs	3.46 (2.1)	3.23 (2.3)	−10.2%	3.26 (2.1)	3.23 (2.3)	−1.3%
Outpatient services for allergic rhinitis†	0.28 (1.5)	0.55 (2.5)	13.1%	0.45 (2.3)	0.55 (2.5)	4.2%
[0, 1, 2, ≥3]	[89.6%, 4.7%, 3.1%, 2.5%]	[86.0%, 5.5%, 3.0%, 5.5%]		[89.6%, 4.7%, 3.1%, 2.5%]	[86.0%, 5.5%, 3.0%, 5.5%]	
All-cause hospitalizations† [0, 1, 2, ≥3]	0.27 (0.7)	0.19 (0.5)	−11.5%	0.20 (0.6)	0.19 (0.5)	−0.3%
	[82.2%, 12.6%, 3.4%, 1.8%]	[84.8%, 12.2%, 2.2%, 0.8%]		[86.1%, 10.6%, 2.3%, 1.1%]	[84.8%, 12.2%, 2.2%, 0.8%]	
All-cause outpatient services	16.85 (16.4)	15.33 (13.4)	−10.1%	15.44 (12.5)	15.33 (13.4)	−0.8%
All-cause medication dispensations	23.18 (32.6)	19.39 (19.8)	−14.1%	19.17 (21.0)	19.39 (19.8)	1.1%
Charlson comorbidity index	0.97 (0.6)	0.95 (0.4)	−4.4%	0.95 (0.4)	0.95 (0.4)	0.5%

*Standardized distance.

†For rates of less than 1, frequency breakdown is also provided.

‡Outpatient visits are calculated by grouping all outpatient services that occur on the same day into 1 service and counting the number of such groups.

to a unique subject in the former group, and therefore the matched cohort consisted of 2064 subjects equally divided between the 2 groups. Demographic characteristics and baseline variables for the unmatched and matched cohorts are presented in Table I. The distribution of several variables was substantially imbalanced in the unmatched cohort. Specifically, subjects receiving ICS+LTRA were younger, were more likely to be male, satisfied the exposure definition earlier during their follow-up, and generally had more outpatient encounters and asthma-related dispensations. On the other hand, matching on the propensity score achieved a good balance, with standardized distance not exceeding 10% for any variable (see Table E2).

Adherence

Table II provides the PDCs for treatment groups. The PDCs for the ICS component of the ICS+LABA and ICS+LTRA groups were 0.45 (95% CI, 0.43-0.46) and 0.36 (95% CI, 0.35-0.38), respectively, indicating a significantly better adherence to ICSs in the ICS+LABA group ($P < .001$). On the other hand, the difference in PDCs between the non-ICS components of ICS+LABA (0.37 [95% CI, 0.36-0.39]) and ICS+LTRA (0.37 [95% CI, 0.35-0.38]) was similar ($P = .64$).

Overall, the time on uninterrupted treatment of the index medication was very low. By the end of the first year, only 9% and 3% of subjects had uninterruptedly refilled their index prescriptions in the ICS+LABA and ICS+LTRA groups, respectively (see Fig E2 in this article's Online Repository at www.jacionline.org).

TABLE II. PDCs in the 2 years after the index date

	ICS+LABA group, mean (95% CI)	ICS+LTRA group, mean (95% CI)	Difference	P value
ICS component	0.45 (0.43-0.46)	0.36 (0.35-0.38)	−0.09	<.001
Other component	0.37 (0.36-0.39)	0.37 (0.35-0.38)	−0.01	.64
Overall PDC*	0.32 (0.30-0.33)	0.16 (0.15-0.17)	0.25	<.001

*The overall PDC was calculated as the proportion of days the person was covered with both ICS and non-ICS components.

org). Patients stepping up from ICS monotherapy to ICS+LTRA therapy had a shorter period of uninterrupted treatment (hazard ratio for the end of uninterrupted treatment, 1.25 [95% CI, 1.12-1.39] for the ICS+LTRA group vs the ICS+LABA group).

Outcomes

Table III provides the comparative outcomes between the ICS+LABA and ICS+LTRA groups for both the ITT-based and uninterrupted treatment analyses.

The total patient-years of follow-up for the ITT analysis was 2064 years for each group. In the ITT analysis the outcomes were generally better for the ICS+LABA group compared with the ICS+LTRA group. Compared with patients in the ICS+LABA group, patients in the ICS+LTRA group had a 12% higher rate of outpatient visits, a 37% higher rate of specialist visits, an 11% higher rate of asthma-related medication dispensations, and a

TABLE III. Annual rate of outcomes (per patient year) associated with exposure groups during follow-up in the matched cohort

Outcome	ITT analysis				Uninterrupted treatment analysis			
	ICS+LABA rate (95% CI)	ICS+LTRA rate (95% CI)	RR (95% CI)	P value	ICS+LABA rate (95% CI)	ICS+LTRA rate (95% CI)	RR (95% CI)	P value
Asthma-related hospitalizations	0.04 (0.03-0.05) [95.2%, 3.7%, 0.6%, 0.6%]	0.04 (0.03-0.04) [94.6%, 4.4%, 0.6%, 0.5%]	1.00 (0.67-1.51)	.98	0.06 (0.03-0.08) [98.5%, 1.4%, 0.1%, 0.1%]	0.04 (0.02-0.07) [99.1%, 0.8%, 0.1%, 0.0%]	0.57 (0.22-1.49)	.25
Asthma-related outpatient visits [‡]	2.69 (2.62-2.76)	3.01 (2.94-3.09)	1.12 (1.04-1.21)	<.01*	3.98 (3.77-4.19)	5.07 (4.79-5.35)	1.28 (1.15-1.43)	<.01*
Asthma-related outpatient visits by specialist [‡]	0.32 (0.30-0.35) [74.5%, 11.1%, 5.4%, 9.0%]	0.40 (0.37-0.42) [80.3%, 7.1%, 4.7%, 8.0%]	1.37 (1.10-1.69)	<.01*	0.42 (0.35-0.49) [86.5%, 7.3%, 4.1%, 2. %1]	0.99 (0.87-1.12) [30.8%, 66.0%, 2.3%, 0.9%]	1.38 (1.01-1.90)	.05
Asthma-related medication dispensations	10.85 (10.71-10.99)	12.37 (12.22-12.53)	1.11 (1.06-1.16)	<.01*	16.49 (16.06-16.92)	20.94 (20.37-21.51)	1.25 (1.20-1.31)	<.01*
Asthma-related medication dispensations other than the study drugs	5.25 (5.15-5.35)	6.86 (6.75-6.98)	1.27 (1.19-1.35)	<.01*	5.47 (5.22-5.72)	7.92 (7.56-8.27)	1.45 (1.33-1.58)	<.01*
Dispensation of short-acting β -agonists	3.97 (3.88-4.06)	5.09 (5.00-5.19)	1.25 (1.18-1.33)	<.01*	4.17 (3.96-4.39)	6.27 (5.96-6.59)	1.52 (1.41-1.65)	<.01*
Dispensations of parenteral corticosteroids	0.47 (0.44-0.50) [65.2%, 15.3%, 8.6%, 10.9%]	0.50 (0.47-0.53) [63.4%, 16.0%, 8.4%, 12.2%]	1.02 (0.87-1.19)	.81	0.55 (0.47-0.62) [86.6%, 10.0%, 2.5%, 0.9%]	0.70 (0.59-0.80) [87.3%, 9.6%, 2.4%, 0.7%]	1.32 (1.01-1.73)	<.01*
Moderate-to-severe exacerbations	0.46 (0.43-0.49) [65.0%, 16.8%, 8.0%, 10.2%]	0.48 (0.45-0.51) [63.0%, 16.7%, 8.4%, 11.9%]	1.02 (0.87-1.19)	.81	0.53 (0.45-0.60) [86.5%, 10.6%, 2.0%, 0.9%]	0.67 (0.57-0.77) [86.9%, 10.8%, 1.9%, 0.4%]	1.30 (1.00-1.69)	.19
Non-asthma-related hospitalizations	0.16 (0.14-0.17) [76.8%, 14.2%, 5.2%, 3.8%]	0.16 (0.14-0.18) [76.7%, 15.8%, 4.1%, 3.5%]	0.95 (0.77-1.17)	.64	0.22 (0.17-0.27) [94.9%, 4.0%, 0.7%, 0.5%]	0.16 (0.11-0.21) [96.7%, 2.9%, 0.3%, 0.1%]	0.71 (0.42-1.19)	.04*
Non-asthma-related outpatient services	12.14 (11.99-12.29)	12.31 (12.16-12.46)	0.99 (0.93-1.06)	.87	16.50 (16.07-16.93)	18.38 (17.84-18.92)	1.03 (0.94-1.12)	.19
Non-asthma-related dispensations	9.86 (9.73-10.00)	9.66 (9.52-9.79)	0.97 (0.89-1.07)	.55	26.62 (26.08-27.17)	30.82 (30.12-31.52)	1.00 (0.91-1.10)	.50

RR, Relative risk estimated from conditional Poisson regression model stratified on matched pairs.

*Significant at .05 level.

[†]For rates of less than 1, frequency breakdown is also provided, with percentages of those with 0, 1, 2, and 3 or more instances of the outcome.[‡]Outpatient visits are calculated by grouping all outpatient services that occur on the same day into 1 service and counting the number of such groups.

25% higher rate of reliever medication dispensations (all $P < .01$). Differences in the rate of asthma-related hospitalization, parenteral corticosteroid use, and exacerbations were not statistically significant.

The total follow-up for the uninterrupted treatment analysis was 346.6 years for the ICS+LABA group and 244.4 years for the ICS+LTRA group. Outcome rates were generally higher during the uninterrupted treatment period compared with the ITT period. However, the measures of association remained generally the same, favoring the ICS+LABA group. In addition, the rate of parenteral corticosteroid dispensations in this analysis was 32% higher for the ICS+LTRA group compared with the ICS+LABA group ($P < .01$).

Asthma-related costs

Table IV presents the average asthma-related annual costs for the 2 cohorts. The only component of the cost that was significantly different between the 2 groups was the cost of outpatient

services, which was \$25.9 per year higher for the ICS+LTRA group ($P = .02$).

Secondary and sensitivity analyses

Four hundred thirty-one (41.8%) subjects of the final matched cohort in the ICS+LABA group received a single combined ICS+LABA inhaler as their index medication. On average, this group had 51.5 more days of uninterrupted treatment per subject compared with those who received their index ICS+LABA therapy in separate inhalers ($P < .01$). In addition, the PDC was significantly higher among the single-inhaler ICS+LABA group (40.7%) compared with the separate-inhaler (25.4%) subgroup ($P < .01$). No major changes in the results were observed when the follow-up period was set at 6 months (see Table E3 in this article's Online Repository at www.jacionline.org). When the follow-up period in the matched cohort was set to be equal within pairs, there were no significant differences in the rates of reliever medication and parenteral corticosteroid use (see Table E4 in this article's Online Repository at www.jacionline.org).

TABLE IV. Asthma-related annual costs*

	ITT analysis				Uninterrupted treatment analysis			
	ICS+LABA group, mean (SD)	ICS+LTRA group, mean (SD)	Difference, mean (SD)	P value	ICS+LABA group, mean (SD)	ICS+LTRA group, mean (SD)	Difference, mean (SD)	P value
Hospital cost	251.6 (38.8)	226.9 (25.8)	−24.7 (47.5)	.32	356.4 (78.7)	252.2 (2976.8)	−104.2 (100.6)	.14
Outpatient services costs	128.1 (3.7)	136.1 (3.6)	8.1 (5.2)	.06	201.6 (9.1)	227.4 (375.3)	25.9 (12.6)	.02†
Medication dispensation costs	1189.1 (29.5)	1145.3 (25.4)	−43.9 (39.2)	.14	1824.6 (86.9)	1799.1 (1755.9)	−25.5 (96.4)	.38
Total asthma-related costs	1568.8 (52.6)	1508.3 (38.3)	−60.5 (65.8)	.17	2382.6 (120.1)	2278.8 (3702.5)	−103.9 (146.7)	.26

*All costs are adjusted to 2008 Canadian dollars.

†Significant at .05 level.

DISCUSSION

Ours is the first observational study to use administrative databases to comprehensively investigate the relationship between adherence, asthma-related outcomes, and the costs of 2 combination step-up therapies for asthma. Contrary to our initial hypothesis, we observed that stepping up to ICS+LABA therapy generally resulted in better adherence to controlled medications relative to ICS+LTRA therapy. We found that in a real-world setting, patients who stepped up to ICS+LABA therapy generally experienced better asthma-related outcomes than those who switched to ICS+LTRA therapy, although for some important outcomes, such as exacerbation, there was no difference between the 2 groups when outcomes over a fixed period of 2 years were considered. However, we also showed that within the time patients were adherent to their medication, ICS+LABA therapy was still associated with better outcomes, supporting the hypothesis that the superiority of ICS+LABA therapy is not solely attributable to better adherence. These results overall indicate that ICS+LABA therapy improves measures of impairment. However, our data do not provide convincing evidence of the superiority of ICS+LABA therapy in terms of reducing the future risk of adverse asthma-related outcomes (eg, exacerbations) because the difference in such outcomes was only observed in the uninterrupted time analysis and not in the ITT analysis. This might be because of insufficient statistical power due to the rarity of such outcomes and the fact that treatment switching and discontinuation could have resulted in the dilution of exposure in the ITT analysis.

Other authors have used administrative health databases in different jurisdictions to compare the addition of LABA or LTRA therapy to an ICS in adolescents or adults with asthma.^{11,17,35-39} Lee et al⁴⁰ compared asthma-related and total medical costs among several controller therapies, including ICS+LABA and ICS+LTRA regimens. They observed that higher costs for ICS+LTRA therapy were attributable to more frequent exacerbations compared with ICS+LABA therapy, despite similar adherence. Allen-Ramey et al³⁶ used propensity scores to match 608 ICS+LTRA users to an equal number of ICS+LABA users. Although there were no differences in the rate of filling a prescription for an oral corticosteroid between groups (a proxy for uncontrolled asthma), ICS+LTRA therapy resulted in a lower risk of an emergency department visit and asthma-related hospitalization relative to ICS+LABA therapy but more frequent use of reliever medications. Zeiger et al³⁹ reported significantly lower costs (adjusted difference of \$1193) associated with the use of ICS+LTRA therapy (n = 1235) compared with ICS+LABA therapy (n = 8125) in an analysis of data from the Kaiser Permanente Southern California health plan. Nevertheless, this study also involved several other groups of treatments, and as such,

the efforts in making the ICS+LTRA and ICS+LABA groups comparable in terms of baseline variables and asthma severity measures might not have been as comprehensive.

Like many other studies based on administrative health data, the case definition of asthma in our study was not perfect and might have resulted in the inclusion of subjects without asthma in the cohort. However, this is not necessarily a limitation of the study. Not all subjects in real-world clinical practice receive a correct diagnosis of asthma (especially considering the over-diagnosis of asthma in Canada⁴¹), but such subjects nonetheless continue to receive study medications and consume health care resources because of their diagnosis of asthma. A study that attempts to provide external validity needs to include patients across the entire spectrum of the disease.⁴² Exposure to ICSs, LABAs, and LTRAs in this study was estimated from the dispensation records, which do not necessarily correspond with drug use. Furthermore, a decision to step up the controller medication can be made for a variety of reasons (eg, worsening of symptoms and occurrence of exacerbation), and the effectiveness of step-up therapies might be affected by such indications; we could not reliably determine the underlying reason for change in treatment. Another recommended option for step-up therapy is to increase the dose of ICS¹; in our exploratory analysis we found it difficult to reliably select such subjects because an increased dispensed amount between a first and a second dispensation might indicate a bulk purchase rather than an increased daily dose. Furthermore, like any other observational study in which the treatment is not randomized, the potential for residual confounding by indication or disease severity certainly exists. In the context of the present study, such a bias means patients who step up to ICS+LTRA therapy might be systematically different than those stepping up to ICS+LABA therapy (eg, having milder asthma or being more likely to have concomitant allergic rhinitis), which will affect the chance of the outcomes independently of the effect of treatment. We have taken several steps to minimize the effect of such biases (ie, a restrictive case definition of asthma, propensity score matching, adjusting for many potential confounders, and an exposure definition based on ≥ 2 dispensations) and achieved very good balance in measured confounders in the matched cohort. Nevertheless, it is difficult to estimate any residual effect of unmeasured confounders in this study. Finally, some traditional measures of asthma control, such as the use of short-acting β -agonists, might not be reliable in this context because LABAs might act as a direct substitute for short-acting agents, regardless of the level of asthma control.

Although the recent pragmatic trial showed no differences in patient-reported, asthma-related quality of life and asthma-related outcomes between subjects receiving ICS+LABA

therapy and those receiving ICS+LTRA therapy,¹³ we showed better outcomes and health services use for the former in a population-based study. Asthma is a prevalent and chronic disease that imposes a tremendous burden on patients and society. Informed changes in the management of asthma have the potential to translate into significant gains in the efficiency of health care systems in terms of improving quality of life and reducing costs. Providing evidence on the benefit of treatment with high external validity should be on the research agenda.⁴²

Key messages

- Subjects who step up from monotherapy with ICSs to combination therapy with an ICS and a LABA seem to be more adherent to their medication than those who step up to an ICS and an LTRA.
- ICS+LABA therapy is associated with better outcomes, even when one accounts for the effect of differential adherence.

REFERENCES

- Global Initiative for Asthma (GINA). GINA report, global strategy for asthma management and prevention. Available at: http://www.ginasthma.org/pdf/GINA_Report_2010.pdf. Accessed February 5, 2013.
- Accordini S, Bugiani M, Arossa W, Gerzeli S, Marinoni A, Olivieri M, et al. Poor control increases the economic cost of asthma. A multicentre population-based study. *Int Arch Allergy Immunol* 2006;141:189-98.
- Vollmer WM, Markson LE, O'Connor E, Sanocki LL, Fitterman L, Berger M, et al. Association of asthma control with health care utilization and quality of life. *Am J Respir Crit Care Med* 1999;160:1647-52.
- The National Asthma Education Prevention Program (NAEPP II) guidelines for the treatment of asthma: implications for the pharmacist (manuscript updated December 2000). 2009. Available at: <http://www.inetce.com/articles/pdf/146-000-01-001-H01.pdf>. Accessed February 5, 2013.
- Canadian Thoracic Society. 2010 CTS guideline—asthma management continuum—consensus summary for children six years of age and over, and adults. Available at: <http://www.respiratoryguidelines.ca/canadian-thoracic-society-asthma-management-continuum-%E2%80%932010-consensus-summary-for-children-six-year>. Accessed February 5, 2013.
- Expert panel report 3 (EPR-3): guidelines for the diagnosis and management of asthma—summary report 2007. *J Allergy Clin Immunol* 2007;120(suppl):S94-138.
- Nelson HS, Busse WW, Kerwin E, Church N, Emmett A, Rickard K, et al. Fluticasone propionate/salmeterol combination provides more effective asthma control than low-dose inhaled corticosteroid plus montelukast. *J Allergy Clin Immunol* 2000;106:1088-95.
- Fish JE, Israel E, Murray JJ, Emmett A, Boone R, Yancey SW, et al. Salmeterol powder provides significantly better benefit than montelukast in asthmatic patients receiving concomitant inhaled corticosteroid therapy. *Chest* 2001;120:423-30.
- Ringdal N, Eliraz A, Pruzinec R, Weber HH, Mulder PGH, Akveld M, et al. The salmeterol/fluticasone combination is more effective than fluticasone plus oral montelukast in asthma. *Respir Med* 2003;97:234-41.
- Ducharme FM, Lasserson TJ, Cates CJ. Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma. *Cochrane Database Syst Rev* 2011;(5):CD003137.
- Latry P, Pinet M, Labat A, Magand J-P, Peter C, Robinson P, et al. Adherence to anti-inflammatory treatment for asthma in clinical practice in France. *Clin Ther* 2008;30(Spec No):1058-68.
- Ducharme FM, Noya FJD, Allen-Ramey FC, Maiese EM, Gingras J, Blais L. Clinical effectiveness of inhaled corticosteroids versus montelukast in children with asthma: prescription patterns and patient adherence as key factors. *Curr Med Res Opin* 2012;28:111-9.
- Price D, Musgrave SD, Shepstone L, Hillyer EV, Sims EJ, Gilbert RFT, et al. Leukotriene antagonists as first-line or add-on asthma-controller therapy. *N Engl J Med* 2011;364:1695-707.
- Black N. Why we need observational studies to evaluate the effectiveness of health care. *BMJ* 1996;312:1215-8.
- Persaud N, Mamdani MM. External validity: the neglected dimension in evidence ranking. *J Eval Clin Pract* 2006;12:450-3.
- Sanson-Fisher RW, Bonevski B, Green LW, D'Este C. Limitations of the randomized controlled trial in evaluating population-based health interventions. *Am J Prev Med* 2007;33:155-61.
- Allen-Ramey FC, Bukstein D, Luskin A, Sajjan SG, Markson LE. Administrative claims analysis of asthma-related health care utilization for patients who received inhaled corticosteroids with either montelukast or salmeterol as combination therapy. *J Manag Care Pharm* 2006;12:310-21.
- Stempel D, O'Donnell J, Meyer J. Inhaled corticosteroids plus salmeterol or montelukast: effects on resource utilization and costs. *J Allergy Clin Immunol* 2002;109:433-9.
- British Columbia Ministry of Health. Population Data BC. Available at: <http://www.popdata.bc.ca/data>. Accessed November 20, 2011.
- Pink GH, Bolley HB. Physicians in health care management: 4. case mix groups and resource intensity weights: physicians and hospital funding. *CMAJ* 1994;150:1255-61.
- Suissa S, Ernst P, Kezouh A. Regular use of inhaled corticosteroids and the long term prevention of hospitalisation for asthma. *Thorax* 2002;57:880-4.
- Gu XS, Rosenbaum PR. Comparison of multivariate matching methods: structures, distances, and algorithms. *J Comput Graph Stat* 1993;2:405-20.
- Glynn RJ, Schneeweiss S, Stürmer T. Indications for propensity scores and review of their use in pharmacoepidemiology. *Basic Clin Pharmacol Toxicol* 2006;98:253-9.
- Weitzen S, Lapane KL, Toledano AY, Hume AL, Mor V. Principles for modeling propensity scores in medical research: a systematic literature review. *Pharmacoepidemiol Drug Saf* 2004;13:841-53.
- Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol* 1994;47:1245-51.
- Hollis S, Campbell F. What is meant by intention to treat analysis? Survey of published randomised controlled trials. *BMJ* 1999;319:670-4.
- Hess LM, Raebel MA, Conner DA, Malone DC. Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. *Ann Pharmacother* 2006;40:1280-8.
- Yong PL, Werner RM. Process quality measures and asthma exacerbations in the Medicaid population. *J Allergy Clin Immunol* 2009;124:961-6.
- Sadat Safavi M, Lynd L, Marra C, Carleton B, Tan W, Sullivan S, et al. Direct health care costs associated with asthma in British Columbia. *Can Respir J* 2010;17:74-80.
- Bedouch P, Marra CA, Fitzgerald JM, Lynd LD, Sadat Safavi M. Trends in asthma-related direct medical costs from 2002 to 2007 in British Columbia, Canada: a population based-cohort study. *PLoS One* 2012;7:e50949.
- Latest release from the Consumer Price Index. Available at: <http://www.statcan.ca/english/Subjects/Cpi/cpi-en.htm>. Accessed February 5, 2013.
- Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009;28:3083-107.
- Gardner W, Mulvey EP, Shaw EC. Regression analyses of counts and rates: Poisson, overdispersed Poisson, and negative binomial models. *Psychol Bull* 1995;118:392-404.
- Mihaylova B, Briggs A, O'Hagan A, Thompson S. Review of statistical methods for analysing healthcare resources and costs. *Health Econ* 2011;20:897-916.
- Stempel D, Meyer J, Stanford R, Yancey S. One-year claims analysis comparing inhaled fluticasone propionate with zafirlukast for the treatment of asthma. *J Allergy Clin Immunol* 2001;107:94-8.
- Allen-Ramey FC, Duong PT, Goodman DC, Sajjan SG, Nelsen LM, Santanello NC, et al. Treatment effectiveness of inhaled corticosteroids and leukotriene modifiers for patients with asthma: an analysis from managed care data. *Allergy Asthma Proc* 2003;24:43-51.
- Dorais M, Blais L, Chabot I, LeLorier J. Treatment persistence with leukotriene receptor antagonists and inhaled corticosteroids. *J Asthma* 2005;42:385-93.
- Tan H, Sarawate C, Singer J, Elward K, Cohen RI, Smart BA, et al. Impact of asthma controller medications on clinical, economic, and patient-reported outcomes. *Mayo Clin Proc* 2009;84:675-84.
- Zeiger RS, Hay JW, Contreras R, Chen W, Quinn VP, Seal B, et al. Asthma costs and utilization in a managed care organization. *J Allergy Clin Immunol* 2008;121:885-92.e5.
- Lee TA, Chang C-L, Stephenson JJ, Sajjan SG, Maiese EM, Everett S, et al. Impact of asthma controller medications on medical and economic resource utilization in adult asthma patients. *Curr Med Res Opin* 2010;26:2851-60.
- Aaron SD, Vandemheen KL, Boulet L-P, McIvor RA, Fitzgerald JM, Hernandez P, et al. Overdiagnosis of asthma in obese and nonobese adults. *CMAJ* 2008;179:1121-31.
- Travers J, Marsh S, Williams M, Weatherall M, Caldwell B, Shirlcliffe P, et al. External validity of randomised controlled trials in asthma: to whom do the results of the trials apply? *Thorax* 2007;62:219-23.

Figure E1: Cohort size and cohort construction steps

1	Index dates by category, after having at least 2 ICS prescriptions
2	Index dates by category, after error check and removing erroneous records
3	Index dates by category, after excluding duplicates before index
4	Index dates for first users by category, after excluding those with not enough presence in the data
5	Index dates for first users by category, after excluding those who do not satisfy look back a
6	Index dates by category, after calculating exposure to index medications, and removing expose
7	Index dates by category, after calculating comorbidity measures
8	Index dates for first users by category, after calculating covariates
9	Index dates for first users by category, after removing the outliers
10	Index dates for first users by category, after 1:1 matching

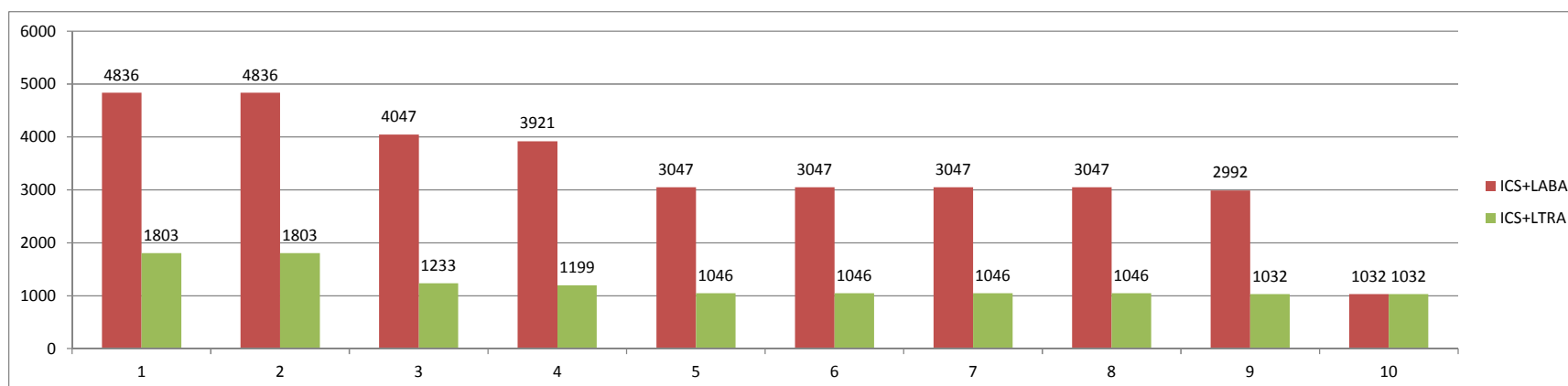


Figure E2: Kaplan-Meier curves for time to end of uninterrupted treatment

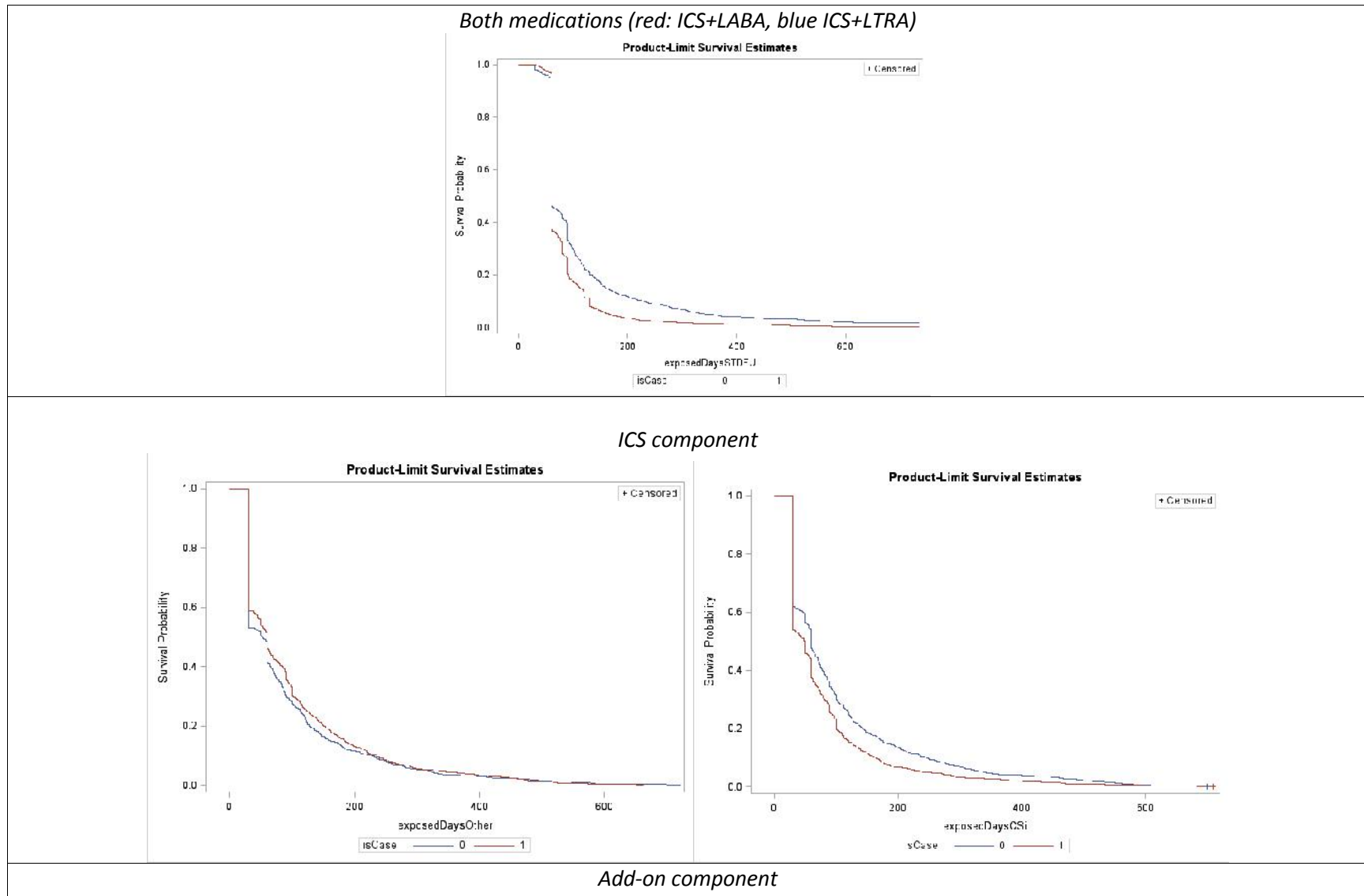


Table E1: Asthma-related medications per Categories, Active ingredients, Anatomical Therapeutic Chemical (ATC) codes and Drug Identification Numbers (DIN) selected in the PharmaNet database

All medications are used in calculating the number of asthma-related dispensations as a measure of asthma severity; but only a subset of the list is used for the case definition (refer to the right-most column)

Medication categories	Active ingredient(s)	ATC	DIN	Used in case definition?
Used in the 'narrow definition' of resource use (short list), also used for case-definition of asthma (see text)				
Inhaled corticosteroids (ICS)	Beclometasone	R03BA01	2242030, 2242029, 374407, 828521, 828548, 872334, 893633, 897353, 1949993, 1950002, 2079976, 2213710, 2213729, 2215039, 2215047, 2215055, 2216531	Y
	Budesonide	R03BA02	2229099, 1978918, 1978926, 852074, 851752, 851760	Y
	Fluticasone	R03BA05	2237247, 2237246, 2237245, 2237244, 2244293, 2244292, 2244291, 2174731, 2174758, 2174766, 2174774, 2213583, 2213591, 2213605, 2213613	Y
	Ciclesonide	R03BA08	2285614, 2285606, 2303671	Y
Short-acting beta-agonists (SABA)	Salbutamol	R03AC02	790419, 812463, 832758, 832766, 851841, 860808, 867179, 897345, 1926934, 1938851, 1938878, 1945203, 1947222, 1986864, 2022125, 2046741, 2048760, 2069571, 2084333, 2148617, 2154412, 2173360, 2208229, 2208237, 2208245, 2212315, 2212323, 2213400, 2213419, 2213427, 2213478, 2213486, 2214997, 2215004, 2215616, 2215624, 2215632, 2216949, 2231430, 2231488, 2231678, 2231783, 2231784, 2232570, 2232987, 2236931,	Y

			2236932, 2236933, 2239365, 2239366, 2241497, 2243115, 2243828, 2244914, 2245669, 2259583, 2326450	
		R03CC02	620955, 620963, 874086, 894249, 894257, 1932691, 2035421, 2063689, 2091186, 2146843, 2146851, 2164434, 2164442, 2165368, 2165376, 2212390, 2213435, 2213443, 2213451, 2261324	Y
	Terbutaline	R03AC03	786616	Y
	Orciprenaline	R03CB03	249920, 3891, 2236783, 2229862, 2152568, 2192675	Y
Long-acting beta-agonists (LABA)	Salmeterol	R03AC12	2211742, 2214261, 2231129, 2136139, 2136147	Y
	Formoterol	R03AC13	2230898, 2237224, 2237225	Y
ICS and LABA in combination (ICS+LABA)	Budesonide, formoterol	R03AK07	2245385, 2245386	Y
	Fluticasone, salmeterol	R03AK06	2240835, 2245126, 2245127, 2240836, 2240837	Y
Leukotriene receptor antagonists (LTRA)	Montelukast	R03DC03	2247997, 2238217, 2243602, 2238216	Y
	Zafirlukast	R03DC01	2236606	Y
Anti-immunoglobulin E monoclonal antibody	Omalizumab	R03DX05	2260565	Y
Inhaled mast cell stabilizers	Cromoglicic acid	R03BC01	2231431, 2231671, 2046113, 534609, 555649,	Y

			261238, 638641, 2049082, 2219468	
Theophylline	Choline theophyllinate	R03DA02	346071, 405310, 441724, 441732, 451282, 458708, 458716, 476366, 476390, 476412, 503436, 511692, 536709, 565377, 589942, 589950, 792934	Y
	Theophylline	R03DA04	156701, 261203, 460982, 460990, 461008, 466409, 488070, 532223, 556742, 575151, 599905, 627410, 631698, 631701, 692689, 692697, 692700, 722065, 1926586, 1926594, 1926608, 1926616, 1926640, 1966219, 1966227, 1966235, 1966243, 1966251, 1966278, 1966286, 2014165, 2014181, 2230085, 2230086, 2230087	Y
	Aminophylline	R03DA05	14923, 178497, 497193, 497193, 497207, 582654, 582662, 868450, 2014270, 2014289	Y
Inhaled anticholinergics	Ipratropium bromide	R01AX03	2246084, 2246083, 2163705, 2163713, 2240508, 2240072	N
		R03BB01	2126222, 2243827, 2231494, 731439, 576158, 2247686, 824216, 2026759, 1950681, 2239131, 2216221, 2210479, 2231785, 2236934, 2236935, 2237134, 2237135, 2239627, 2231135, 2231136, 2231245, 2231244, 2097141, 2097176, 2097168	N
	Ipratropium bromide, fenoterol	R03AK03	02148633	N
	Tiotropium bromide	R03BB04	02246793	N
	Epinephrine	R03AA01	2017555, 466417, 525103, 1927582	N

	Ephedrine	R03CA02	2237085, 2229698, 2100231, 2100258, 2243148, 2236722, 2229678, 2219743, 2012111, 2229711, 38121, 2242961, 876534, 893323, 893331, 438847, 2242639, 2126419, 2126400	N
	Isoprenaline	R03AB02	2017652	N
	Orciprenaline	R03AB03	1923870, 1928449, 2017660, 254134, 3859	N
Other corticosteroids	Cortisone	H02AB10	280437, 16241, 16446, 16438	N
	Triamcinolone	H02AB08	2194090, 15016, 15024, 2194082	N
	Prednisone	H02AB07	610623, 598194, 550957, 312770, 252417, 210188, 868426, 868434, 868442, 21695, 232378, 607517, 508586, 156876, 271373, 271381	N
	Prednisolone	H02AB06	21679, 2230619, 2152541, 2245532	N
	Methylprednisolone	H02AB04	1934325, 1934333, 1934341, 30759, 30767, 36129, 30988, 2245406, 2245400, 2245408, 2245407, 2241229, 2231893, 2231894, 2231895, 2232750, 2232748, 2063727, 2063697, 2063719, 2063700, 36137, 2230210, 2230211, 30678, 30651, 30643	N
	Betamathasone	H02AB01	2237835, 36366, 2063190, 176834, 28096, 28185	N
	Hydrocortisone	H02AB09	888222, 888230, 888206, 888214, 30910, 30929, 872520, 872539, 878618, 878626, 30635, 30600, 30619, 30627	N
	Dexamathasone	H02AB02	2261081, 2250055, 213624, 16462, 354309, 716715, 874582, 1977547, 664227, 2204274,	N

			2204266, 295094, 285471, 489158, 2239534, 732893, 732885, 2260301, 2237044, 2260298, 2237046, 2237045, 1946897, 1964976, 1964968, 1964070, 2279363, 783900, 751863, 2311267, 2240687, 2240685, 2240684	
Other xanthines	Theophylline, combination	R03DA54	545090, 476374, 334510, 356123, 792942, 721301, 317225, 828718, 640093, 828726, 828742, 307548	N
Other anti-allergic agents	Levocabastine	R01AC02	2020017	N
	Ketotifen	R06AX17	2221330, 2176084, 2230730, 2218305, 2231680, 2231679, 600784, 577308	N

Table E2: Variables estimated in the twelve months prior to index date which were used to calculate propensity scores

Label	Unmatched cohort					Matched cohort				
	Mean in ICS+LABA	SD in ICS+LABA	Mean in ICS+LTRA	SD in ICS+LTRA	Standardized distance	Mean in ICS+LABA	SD in ICS+LABA	Mean in ICS+LTRA	SD in ICS+LTRA	Standardized distance
Age at index date	31.29	11.83	27.46	12.19	-0.32	27.40	11.68	27.46	12.19	0.00
Percent female	0.57	0.49	0.52	0.50	-0.10	0.53	0.50	0.52	0.50	-0.01
Interval (years) between 1/1/1997 and index date	4.73	2.14	3.20	2.23	-0.70	3.34	2.08	3.20	2.23	-0.06
Cohort entry date	-0.73	0.76	-0.79	0.62	-0.10	-0.77	0.61	-0.79	0.62	-0.04
Number of asthma-related hospitalizations in the year before the index date	0.07	0.36	0.05	0.28	-0.05	0.06	0.35	0.05	0.28	-0.03
Number of asthma-related outpatient services	3.42	3.51	3.58	3.51	0.05	3.66	3.53	3.58	3.51	-0.02
Number of asthma-related outpatient services made by specialist	0.36	1.22	0.28	1.16	-0.07	0.30	0.88	0.28	1.16	-0.01
Number of asthma-related outpatient services made by allergists	0.03	0.20	0.02	0.14	-0.04	0.02	0.21	0.02	0.14	-0.01
Number of asthma-related medication dispensations	10.33	7.21	11.00	7.50	0.09	10.58	7.36	11.00	7.50	0.06
Number of dispensations of short-acting beta agonists in the year before the index date	5.69	5.46	5.67	5.53	0.00	5.50	5.40	5.67	5.53	0.03
Number of dispensations of oral corticosteroids	0.56	1.26	0.63	1.39	0.06	0.69	1.46	0.63	1.39	-0.04
Number of dispensations of inhaled corticosteroids	3.46	2.14	3.23	2.32	-0.10	3.26	2.06	3.23	2.32	-0.01
Number of outpatient services for allergic rhinitis	0.28	1.55	0.55	2.47	0.13	0.45	2.32	0.55	2.47	0.04
Number of hospitalizations in the year before the index date	0.27	0.73	0.19	0.54	-0.11	0.20	0.60	0.19	0.54	0.00
Number of outpatient services in the year	16.85	16.36	15.33	13.40	-0.10	15.44	12.53	15.33	13.40	-0.01

before the index date										
Number of medication dispensations in the year before the index date	23.18	32.57	19.39	19.82	-0.14	19.17	20.99	19.39	19.82	0.01
Charlson comorbidity index	0.97	0.56	0.95	0.43	-0.04	0.95	0.40	0.95	0.43	0.00
Income Quintile 1	0.19	0.39	0.18	0.39	-0.01	0.19	0.39	0.18	0.39	0.00
Income Quintile 2	0.20	0.40	0.17	0.38	-0.08	0.16	0.37	0.17	0.38	0.02
Income Quintile 3	0.21	0.40	0.22	0.41	0.03	0.22	0.42	0.22	0.41	-0.02
Income Quintile 4	0.20	0.40	0.20	0.40	0.02	0.21	0.41	0.20	0.40	-0.01
Income Quintile 5	0.18	0.38	0.19	0.39	0.03	0.19	0.39	0.19	0.39	0.00
Asthma-related inpatient direct costs	723.29	2,869.34	354.65	1,157.67	-0.17	356.21	1,441.88	354.65	1,157.67	0.00
Inpatient direct costs	444.38	2,334.62	326.62	1,738.37	-0.06	376.49	2,236.03	326.62	1,738.37	-0.02
Cost of asthma-related outpatient services	974.81	1,183.49	778.97	785.59	-0.19	791.57	733.34	778.97	785.59	-0.02
Cot of outpatient services	169.06	245.17	172.12	203.97	0.01	180.00	220.15	172.12	203.97	-0.04
Cot of asthma-related medications	1,035.14	1,812.49	829.76	968.66	-0.14	818.11	920.43	829.76	968.66	0.01
Cot of medications	1,035.14	1,812.49	829.76	968.66	-0.14	818.11	920.43	829.76	968.66	0.01
Total dispensations of cromons	0.03	0.39	0.09	0.77	0.10	0.06	0.48	0.09	0.77	0.06
Total dispensations of theophyllines	0.00	0.00	0.00	0.05	0.08	0.00	0.00	0.00	0.05	0.08
Total dispensations of xanthines	0.12	0.93	0.17	0.92	0.06	0.16	1.02	0.17	0.92	0.02
Total dispensations of anti-allergics	0.02	0.33	0.06	0.54	0.09	0.05	0.53	0.06	0.54	0.02
Total dispensations of anti-cholinergics	0.15	0.92	0.13	0.78	-0.01	0.13	0.63	0.13	0.78	0.01
List of ICD-9 codes 001–139: infectious and parasitic diseases	0.30	1.26	0.23	0.81	-0.07	0.23	1.01	0.23	0.81	-0.01
List of ICD-9 codes 140–239: neoplasms	0.15	0.93	0.16	1.24	0.01	0.12	0.73	0.16	1.24	0.04
List of ICD-9 codes 240–279: endocrine, nutritional and metabolic diseases, and immunity disorders	0.38	2.92	0.19	0.97	-0.08	0.22	1.00	0.19	0.97	-0.03
List of ICD-9 codes 280–289: diseases of the blood and blood-forming organs	0.05	0.63	0.03	0.47	-0.03	0.08	0.94	0.03	0.47	-0.06

List of ICD-9 codes 290–319: mental disorders	2.03	11.06	0.99	7.78	-0.11	1.08	6.68	0.99	7.78	-0.01
List of ICD-9 codes 320–359: diseases of the nervous system	0.29	2.88	0.11	0.58	-0.09	0.12	0.73	0.11	0.58	-0.01
List of ICD-9 codes 360–389: diseases of the sense organs	0.76	2.03	0.85	2.05	0.04	0.88	2.26	0.85	2.05	-0.02
List of ICD-9 codes 390–459: diseases of the circulatory system	0.42	2.42	0.27	1.86	-0.07	0.29	1.60	0.27	1.86	-0.01
List of ICD-9 codes 460–519: diseases of the respiratory system	7.30	7.23	7.24	7.05	-0.01	7.51	7.13	7.24	7.05	-0.04
List of ICD-9 codes 520–579: diseases of the digestive system	0.37	1.62	0.29	1.11	-0.06	0.30	1.29	0.29	1.11	0.00
List of ICD-9 codes 580–629: diseases of the genitourinary system	0.93	2.94	0.64	1.90	-0.12	0.56	1.45	0.64	1.90	0.05
List of ICD-9 codes 630–679: complications of pregnancy, childbirth, and the puerperium	0.19	1.73	0.08	1.67	-0.06	0.06	0.56	0.08	1.67	0.02
List of ICD-9 codes 680–709: diseases of the skin and subcutaneous tissue	0.63	2.11	0.47	1.41	-0.09	0.51	1.41	0.47	1.41	-0.03
List of ICD-9 codes 710–739: diseases of the musculoskeletal system and connective tissue	2.35	7.33	2.56	8.03	0.03	2.44	7.35	2.56	8.03	0.02
List of ICD-9 codes 740–759: congenital anomalies	0.02	0.27	0.02	0.18	0.00	0.02	0.23	0.02	0.18	0.00
List of ICD-9 codes 760–779: certain conditions originating in the perinatal period	0.01	0.23	0.01	0.15	-0.02	0.02	0.33	0.01	0.15	-0.04
List of ICD-9 codes 780–799: symptoms, signs, and ill-defined conditions	3.65	6.20	2.75	5.22	-0.16	2.70	4.19	2.75	5.22	0.01
List of ICD-9 codes 800–999: injury and poisoning	1.94	5.15	1.90	4.85	-0.01	1.79	4.60	1.90	4.85	0.02
List of ICD-9 codes E and V codes: external causes of injury and supplemental classification (E codes)	0.02	0.20	0.03	0.22	0.05	0.03	0.27	0.03	0.22	-0.02

List of ICD-9 codes E and V codes: external causes of injury and supplemental classification (V codes)	0.22	0.92	0.11	0.65	-0.13	0.13	0.61	0.11	0.65	-0.04
--	------	------	------	------	--------------	------	------	------	------	--------------

Table E3: Intention-to-treat analysis with 6 months of follow-up (annual rates)

Outcome	Intention-to-treat (ITT) analysis			
	ICS+LABA Rate (95%CI)	ICS+LTRA Rate (95%CI)	RR (95%CI)	P
Asthma-related hospitalizations	0.06 (0.04 - 0.08)	0.05 (0.03 - 0.07)	0.93 (0.53 - 1.62)	0.79
Asthma-related outpatient visits	3.90 (3.74 - 4.07)	4.37 (4.20 - 4.55)	1.14 (1.05 - 1.25)	<0.01*
Asthma-related outpatient visits by specialist	0.56 (0.50 - 0.63)	0.68 (0.62 - 0.75)	1.25 (0.98 - 1.57)	0.07
Asthma-related medication dispensations	15.12 (14.80 - 15.44)	16.44 (16.11 - 16.78)	1.10 (1.06 - 1.15)	<0.01*
Asthma-related medication dispensations other than the study drugs	6.53 (6.32 - 6.74)	7.70 (7.47 - 7.93)	1.21 (1.14 - 1.30)	<0.01*
Dispensation of short-acting beta-agonists	4.75 (4.57 - 4.93)	6.05 (5.85 - 6.25)	1.31 (1.22 - 1.40)	<0.01*
Dispensations of oral corticosteroids	0.67 (0.61 - 0.74)	0.61 (0.55 - 0.68)	1.00 (0.83 - 1.20)	0.97
Moderate-severe exacerbations	0.64 (0.58 - 0.71)	0.60 (0.53 - 0.66)	1.01 (0.85 - 1.21)	0.17
<i>*All rates are over two years.</i> <i># Outpatient visits are calculated by grouping all outpatient services that belong to the same day into one and counting the number of such groups.</i> <i>RR: Relative Risk, estimated from conditional Poisson regression model stratified on matched pairs</i>				

Table E4: Equal follow-up uninterrupted treatment analysis

Total follow-up time for this analysis was 186.04 years for each exposure group. Note that the same cohort of individuals as in the main analysis is included in this study, and that the ITT analysis is not affected.

Outcomes for uninterrupted treatment analysis				
Outcome	Uninterrupted treatment analysis			
	ICS+LABA Rate (95%CI)	ICS+LTRA Rate (95%CI)	RR (95%CI)	P
Asthma-related hospitalizations	0.11 (0.06 - 0.15)	0.05 (0.02 - 0.09)	0.44 (0.19 - 1.00)	0.06
Asthma-related outpatient visits	7.42 (7.03 - 7.81)	6.66 (6.29 - 7.03)	0.90 (0.80 - 1.01)	0.08
Asthma-related outpatient visits by specialist	0.78 (0.65 - 0.91)	1.31 (1.14 - 1.47)	1.90 (1.42 - 2.55)	<0.01*
Asthma-related medication dispensations	27.50 (26.75 - 28.26)	30.72 (29.92 - 31.52)	1.13 (1.03 - 1.24)	0.01*
Asthma-related medication dispensations other than the study drugs	10.19 (9.73 - 10.65)	10.40 (9.93 - 10.86)	1.01 (0.91 - 1.12)	0.90
Dispensation of short-acting beta-agonists	7.78 (7.37 - 8.18)	8.24 (7.83 - 8.65)	1.06 (0.95 - 1.19)	0.30
Dispensations of oral corticosteroids	1.02 (0.87 - 1.16)	0.92 (0.78 - 1.06)	0.89 (0.69 - 1.14)	0.34
Moderate-severe exacerbations	0.98 (0.84 - 1.13)	0.88 (0.75 - 1.02)	0.88 (0.69 - 1.12)	0.29
*All rates are over two years. # Outpatient visits are calculated by grouping all outpatient services that belong to the same day into one and counting the number of such groups. RR: Relative Risk, estimated from conditional Poisson regression model stratified on matched pairs				

Figure E1. Cohort size and cohort construction steps

Figure E2. Kaplan-Meier curves for time to end of uninterrupted treatment