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The relationship between combination inhaled corticosteroid and long-acting beta-agonist use and severe asthma exacerbations in a diverse population

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Abstract

Background—Safety concerns surround the use of long-acting beta agonists (LABA) for the treatment of asthma, even in combination with inhaled corticosteroids (ICS) and particularly in high-risk subgroups.

Objective—To estimate the effect ICS therapy and fixed-dose ICS/LABA combination therapy on severe asthma exacerbations in a racially diverse population.

Methods—Inhaled corticosteroid and ICS/LABA exposure was estimated from pharmacy data for patients with asthma age 12 to 56 years who were members of a large health maintenance organization. Inhaled corticosteroid and ICS/LABA use was estimated for each day of follow-up to create a moving window of exposure. Proportional hazard models were used to assess the relationship between ICS and ICS/LABA combination therapy and severe asthma exacerbations (i.e., use of oral corticosteroids, asthma-related emergency department visit, or asthma-related hospitalization).

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Clinical Implications When used in fixed dose combinations with inhaled corticosteroids, inhaled long-acting beta-agonist medication appears to additionally reduce severe asthma exacerbations. This beneficial effect appears consistent even among high-risk subgroups.

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Results—Among the 1,828 patients who met the inclusion criteria, 37% were African American, 46% were treated with ICS therapy alone, and 54% were treated with an ICS/LABA combination. Models assessing the risk of severe asthma exacerbations among individuals using ICS treatment alone and ICS/LABA combination therapy suggested that the overall protective effect was as good or better for ICS/LABA combination therapy when compared with ICS treatment alone (hazard ratio [HR]=0.65 vs. HR=0.72, respectively). Analyses in several subgroups, including African American patients, showed a similar statistically significant protective association for combination therapy.

Conclusion—Treatment with ICS/LABA fixed combination therapy appeared to perform as well or better than ICS alone in reducing severe asthma exacerbations; this included multiple high-risk subgroups.

Keywords

Long-acting beta-agonist; inhaled corticosteroid; severe asthma exacerbation; safety; racially and ethnically diverse population; observational study

INTRODUCTION

The safety of long-acting beta-agonists (LABA) has been called into question since they first entered the market in the early 1990's.¹⁻³ In response to these safety concerns, the Food and Drug Administration (FDA) held a series of joint advisory committee meetings to discuss the benefits and risks of using LABA to treat asthma. These meetings were held subsequent to the much publicized termination, in 2003, of the Salmeterol Multicenter Asthma Research Trial (SMART), in which there was a higher proportion of deaths and serious asthma-related events with salmeterol, particularly in African Americans, than in the placebo group.⁴ The FDA concluded that, because of the symptomatic benefits of bronchodilation and asthma control, LABAs should remain on the market, but with a black-box warning.⁵⁻⁷ In addition, the FDA recommended that LABA medication not be used as monotherapy, but rather, concurrently with an asthma-controller medication such as an inhaled corticosteroid (ICS).⁵⁻⁷

Current U.S. guidelines recommend adding an inhaled LABA to a low or medium dose of ICS as an acceptable step-up therapy rather than using a higher dose of ICS in order to achieve or maintain asthma control.⁸ Accordingly, many patients with asthma are prescribed ICS/LABA combination therapy in order to achieve asthma control.⁹ In the U.S. alone, combined sales of Advair and Symbicort reached nearly \$5 billion in 2010. However, an important unanswered question remains whether LABA in fixed-dose combination with ICS increases the risk of serious asthma outcomes. Most of the meta-analyses examining the safety of LABA therapy in asthma focused on clinical trials that were conducted when LABA monotherapy was common, therefore, the trials had not been designed to evaluate the effect of ICS in mitigating the risk of serious asthma outcomes.^{5;6} A review of the meta-analyses of LABA with concomitant ICS use was inconclusive regarding the safety and efficacy of combined therapy in the treatment of asthma, particularly in African Americans.¹⁰⁻¹³ Additionally, none of the studies reviewed addressed patients' adherence to medication regimens which, for asthma, has historically been poor.¹⁴⁻¹⁶

Because of these uncertainties, the FDA has recently called for five post-market clinical trials to investigate the benefits of a LABA added to ICS treatment as compared with ICS therapy alone.¹⁷ Unfortunately, results from these studies are not anticipated until 2017. In the absence of these clinical trial results, well-designed observational studies may assist clinicians in deciding whether the addition of a LABA to ICS therapy is likely to provide a benefit or be a detriment to their patient with asthma.

In the current study, we assessed time to severe asthma exacerbation among individuals treated with ICS therapy and fixed-dose ICS/LABA combination therapy in a large, diverse managed care population with detailed longitudinal tracking of healthcare utilization and medication use.

METHODS

Study Population and Data Sources

The study protocol was reviewed and approved by the Institutional Review Boards of Henry Ford Hospital and Wayne State University. Subjects were identified from an integrated health system serving the primary and specialty health care needs of individuals in southeastern Michigan. The population was limited to individuals who were enrolled in the affiliated health maintenance organization (HMO) and therefore had electronic information available for health care visits and prescription fills both within and outside of the health system. Information on race-ethnicity was also available electronically and is usually self-reported, but may occasionally be assigned by the healthcare staff. We have previously found excellent agreement between self-reported race-ethnicity and that which is recorded in the electronic database.¹⁸

We identified individuals with the following characteristics: age 12 - 56 years, African American or white race-ethnicity, at least one asthma-related encounter between January 1, 2003 and December 31, 2010, and at least two prescription fills of an ICS or ICS/LABA combination within this same timeframe. Patients were excluded if they had a prior diagnosis of congestive heart failure or chronic obstructive pulmonary disease, or if they had any period of treatment with LABA monotherapy. The date of the first fill for an ICS or ICS/LABA prescription during the study period was termed the "index date." Patients were followed from their index date until their last fill before December 31, 2010. In order to assess the separate effects of ICS and ICS/LABA therapy, individuals were censored at the time of a switch between medication classes (i.e. from index ICS to ICS/LABA therapy or vice versa). Patients were enrolled in the health plan for at least one year prior to (i.e., the baseline year) and six months following the index date. To insure that the patients included in the analysis were consistently exposed to either an ICS or an ICS/LABA combination medication, participants were required to have at least one fill in each 6-month period following the index prescription for the duration of follow-up (e.g. at least one fill between days 0 - 180 days, one fill between days 181 - 360 days, etc.).

Measuring ICS and LABA Exposure

Patients were classified in either the ICS only or ICS/LABA combination group based on their index prescription. To calculate ICS exposure and account for differences in strength within and between steroid preparations and account for differences in individual use patterns over time, we took the number of actuations contained in each prescribed inhaler and weighted (i.e., multiplied) this value by the proportion of each actuation to the minimal recommended dose for that preparation as found in the current U.S. asthma guidelines.⁸ For example, a beclomethasone hydrofluoroalkane inhaler with 40 micrograms (mcg) per actuation was given a weight of 0.5 since the minimal recommended dose is 80mcg per day (see Table E1 in the Online Repository for a complete list of weighted ICS strengths). This calculated measure was divided by the number of days between prescription fill events to obtain the average amount of daily exposure for each day between fills. An individual's ICS exposure over the preceding 180 days was the sum of each day's exposure divided by 180 days, and could therefore overlap fill events. For *each* day of follow-up for an individual we calculated a moving window of mean ICS exposure representing the preceding 180 days. We also calculated an unweighted measure of medication use which did not account for ICS

strength, but which could be more directly interpreted as the average number of medication uses per day. Since LABA medication was included as a fixed dose combination medication with varying ICS strengths (and therefore taken contemporaneously with the ICS), we accounted for LABA use as a dichotomous, indicator variable.

Classifying Asthma Severity

We used the methods described in detail elsewhere to account for underlying asthma severity.^{19;20} Briefly, to account for baseline asthma severity, patients were classified into one of four severity levels based on short-acting beta-agonist (SABA) fills and oral corticosteroid (OCS) fills in the baseline year.¹⁹ The most severe group (Group 4) had either 3 OCS fills OR 2 OCS fills and >6 SABA fills. The moderate to severe group (Group 3) had either 2 OCS fills OR >6 SABA fills OR 1 OCS fill and 4 SABA fills. The low severity group (Group 1) had no OCS fills and 1 SABA fill. All other combinations of SABA and OCS fills made up the low to moderate severity group (Group 2). To account for changing levels of disease severity, we included a time-updated measure of SABA use, as we have done previously and which we have shown to be associated with future asthma exacerbations.²⁰ Here we calculated separate moving windows of SABA metered dose inhaler (MDI) and nebulizer exposure for each day of study follow-up, representing use of the preceding 180 days (i.e., contemporaneous with the ICS exposure window).

Statistical Analysis

Our primary outcome was a severe asthma exacerbation defined as the occurrence of any one of the following events: the need for burst oral corticosteroids, an asthma-related emergency department visit, or an asthma-related hospitalization.²¹ We have previously validated the algorithm for identifying these events from electronic data sources.¹⁶

Chi squared and t-test statistics were used to compare differences in the characteristics of patients treated with ICS medication and ICS/LABA combination therapy. Cox proportional hazard models were used to assess the relationship between ICS and ICS/LABA combination therapy and the composite primary outcome. The time-updated continuous measure of ICS exposure variable was log transformed to normalize the distribution and minimize the effects of outliers. Because LABA is dispensed simultaneously with an ICS in a fixed-dose inhaler, the models also included an indicator variable for the addition of LABA when used in combination with ICS. Given the contemporaneous use of ICS and LABA in combination inhalers, we used the dichotomous indicator variable for the additional effect of LABA with an ICS-LABA interaction term to account for differences in the effect combination medication use (when compared with ICS use alone). The overall effect estimate for ICS/LABA use was generated by combining the parameter estimates for ICS, LABA, and the interaction term.²² Similarly, the confidence intervals for combination therapy were computed by using both the variance estimates for each individual parameter (i.e., ICS, LABA, and the interaction term) and the corresponding covariance between parameters. Separate models were run for the weighted and unweighted ICS exposure variables. We included separate covariates for contemporaneous SABA use (i.e., separate variables for SABA metered dose inhaler and SABA nebulizer use) and a covariate for non-ICS asthma controller medication use at baseline (i.e., antileukotrienes, cromolyn sodium, omalizumab, or theophylline derivatives). We calculated effect estimates for both ICS and ICS/LABA use stratified by age (<18 and ≥18 years), sex, race-ethnicity, and baseline asthma severity (Severity groups 1 & 2 and groups 3 & 4).

Given our available sample size, we had 80% power to detect a 25% difference in the risk of the composite primary outcome among those receiving ICS/LABA combination treatment when compared to those without such treatment. Similarly, we had 80% power to detect the

following risk reduction (or increase, as this was a two-tailed analysis) in the composite outcome among our subgroups: a 30% reduction in white individuals, a 37% reduction in African American individuals, a 38% reduction in males, a 29% reduction in females, a 53% reduction in individuals <18 years of age, a 26% reduction in individuals ≥18 years of age, a 29% reduction in those individuals with low to low-moderate asthma severity, and a 45% reduction in those individuals with moderate-severe to severe asthma severity. In other words, we had adequate power to detect the reported association for ICS/LABA combination therapy in all subgroups with the exception individuals <18 years of age.

A P-value <0.05 was considered statistically significant. Analyses were performed using SAS v9.2 (SAS Institute Inc., Cary, NC).²³

RESULTS

We identified 1,828 individuals with asthma who met the study criteria and who received at least two prescriptions for an ICS (n=846) or an ICS/LABA combination (n=982) between January 1, 2003 and December 31, 2010. These individuals had a total of 3,791 person-years of follow up (i.e., a mean follow-up of 2.1 years per person; standard deviation [SD], 2.0 years); 1,368 person-years for individuals on ICS therapy (mean, 1.6 years per person; SD, 1.7 years) and 2,423 person-years of follow-up for individuals on ICS/LABA combination therapy (mean, 2.5 years per person; SD, 2.1 years). The characteristics of the study population stratified by treatment group are presented in Table 1. Individuals in the ICS and ICS/LABA combination groups significantly differed in mean age at baseline (33.7 vs. 37.4 years, respectively). Individuals in the ICS/LABA combination group were also more likely to use other concomitant asthma controller medications when compared with individuals on ICS therapy (20.5% vs. 12.9%, respectively).

The multivariable time-to-event analysis that adjusted for patient age, sex, race-ethnicity, baseline asthma severity, use of additional asthma controller medication, and contemporaneous SABA use is shown in Table 2. This analysis indicated significant differences in the effect of ICS therapy and ICS/LABA combination therapy with increasing ICS use, as evidenced by a significant ICS-LABA interaction (see Table E2 in the Online Repository for complete model parameter estimates). This suggests that the overall protective effect was greater with ICS/LABA combination therapy when compared with ICS only treatment (HR=0.41 vs. HR=0.56, respectively for the unweighted analysis and HR=0.65 vs. HR=0.72, respectively for the weighted analysis accounting for ICS strength) as shown in Table 2. This was also supported by a protective association for the LABA covariate in the fully adjusted model (P-value = 0.049, data not shown), suggesting that the addition of LABA in combination inhalers had a significantly beneficial effect. We performed the same analysis limiting the outcome to asthma-related hospitalizations only so that we could assess whether the relative protective effect of ICS/LABA combination therapy as compared with ICS only therapy existed for the most serious of our outcomes. The overall protective effect, although not statistically significant, was nearly the same for both ICS/LABA combination therapy and ICS only treatment (HR= 0.82, 95% confidence interval [CI] 0.16 – 4.18 vs. HR=0.81, 95% CI 0.18 – 3.65, respectively for the weighted analysis – data not shown).

The graphical representation for differences in ICS and ICS/LABA combination treatment on severe asthma events as implied by the model are shown in Figure 1. As can be seen, these suggested that the relative protective effect of ICS/LABA combination therapy as compared with ICS only therapy was better when ICS levels are low. However, the benefit of increasing ICS exposure appeared diminished with concomitant LABA use, such that ICS

only therapy appeared preferentially beneficial at the highest levels of ICS exposure (Figure 1B).

In order to assess the relative effect of higher strength ICS exposure while excluding the potential effect of higher than recommended doses of LABA, we performed a subgroup analysis limiting individuals in the combination inhaler group to those who on average used 2 puffs per day of their combination inhaler (n=972), but included all in the ICS only group (n=846). The same multivariable time-to-event weighted analysis of this subgroup revealed a similar significantly protective association for ICS/LABA combination therapy when compared with ICS only treatment (HR=0.65, 95% CI 0.47 – 0.89 vs. HR=0.72, 95% CI 0.53 – 0.98, respectively – data not shown). This suggested that the overall beneficial effect of ICS/LABA did not appear to diminish when excluding individuals who on average were taking more than the recommended dose.

Both ICS and ICS/LABA combination therapy consistently showed a protective association in all other subgroup analyses with the exception of individuals <18 years of age, although these latter results were not statistically significant (Table 2). Moreover, in these subgroup analyses the overall effect of ICS/LABA combination therapy was consistently as good or better than the effect of ICS therapy alone. The protective association for ICS/LABA combination therapy was most pronounced and statistically significant in individuals ≥18 years of age (HR=0.58, 95% CI 0.41 – 0.83), males (HR=0.46, 95% CI 0.25 – 0.83), African American individuals (HR=0.59, 95% CI 0.36 – 0.98), and individuals with either moderate-severe or severe asthma at baseline (HR=0.39, 95% CI 0.23 – 0.68).

To exclude the potential influence of other asthma medication, we conducted a post hoc analysis removing individuals treated with other asthma controller medications (i.e., antileukotrienes, cromolyn sodium, omalizumab, or theophylline derivatives). The protective association for ICS/LABA combination therapy was even stronger after excluding individuals on additional asthma controller medication (HR=0.59, 95% CI 0.42 – 0.84, data not shown).

DISCUSSION

In this large, population-based observational study we found that exposure to ICS/LABA combination therapy appeared to have an overall protective effect on asthma exacerbations that was as good or better than that observed for ICS treatment alone. To our knowledge this is the first study to attempt to measure actual ICS and ICS/LABA exposure (and variation in exposure over time) with regard to asthma exacerbations. Moreover, we demonstrated that the protective effect of ICS/LABA combination therapy appeared particularly effective in the following clinically relevant subgroups: individuals ≥18 years of age, males, African American individuals, and individuals with either moderate-severe or severe asthma at baseline.

The significant protective effect of ICS/LABA combination therapy among individuals with moderate to severe asthma is consistent with current guideline recommendations regarding the timing of supplemental LABA therapy.⁸ These findings are also consistent with the GOAL trial which showed that at the recommended dosage, combination therapy preferentially achieves asthma control when compared to ICS therapy alone.²⁴

Our study is based on current clinical practice-based data in a racially diverse managed care environment. Thus, the statistically significant protective effect in African American individuals is of particular interest since previous similar observational studies have not addressed the effect of ICS/LABA combination therapy in African American individuals separate from white individuals. Our findings are consistent with one recent randomized trial

among 475 African Americans which found no significant difference in the rate of asthma exacerbations when LABA was added to ICS. In other words, in this study as in ours, African American patients did not appear to be uniquely susceptible to untoward asthma outcomes when LABA medication was combined with an ICS.²⁵

Our results are also similar to three other randomized clinical trials. In a study by Lemanske and colleagues, 12.2% of patients treated with both an ICS and add-on salmeterol experienced treatment failure (i.e., use of oral corticosteroids, asthma-related emergency department visit, or asthma-related hospitalization) when compared with 47.4% of patients treated with ICS alone.²⁶ In the Oxis and Pulmicort Turbuhaler in the Management of Asthma trial, adding formoterol to the treatment regimen of patients already taking budesonide reduced the risk of an asthma exacerbation by 43%.²⁷ Similarly, the Formoterol and Corticosteroids Establishing Therapy trial found that adding formoterol to either a lower or higher dose of budesonide had an additive protective effect on reducing asthma exacerbations.²⁸

Several recent observational studies have examined the effect of combining LABA and ICS on severe asthma exacerbations. For example, Thomas et al. estimated ICS and LABA exposure from prescription data; they observed better control, but more serious adverse outcomes, in patients treated with LABA step-up therapy as opposed to step-up with a higher ICS dose.²⁹ In another retrospective study using administrative data, the addition of LABA therapy to existing ICS treatment appeared to improve asthma outcomes.³⁰ These authors also found adherence to be significantly better for the ICS/LABA combination preparation when compared to separate inhalers for ICS and LABA. Importantly, our study accounts for patient use or adherence such that we calculate the effect of therapy in only those with apparently consistent use. We also account for changing levels of patient medication use over time, which we have recently shown varies widely, especially around asthma exacerbation.³¹

Our results also appear to demonstrate that the beneficial effects of ICS/LABA combination therapy may be diminished when the level of use exceeds the recommended dose (i.e. >2 puffs per day). In fact, using an ICS alone appears more beneficial when compared with ICS/LABA use that exceeds the recommended dose. These results are also supported by meta-analyses of existing clinical trials data.³²

The present study must be interpreted in light of its limitations. First, as in all observational studies, we have not accounted for any unknown confounders between treatment groups. However, the consistency of our results with the findings of others suggests that this is unlikely. Moreover, our measures of medication use approximate actual exposure and therefore are not limited to the intention to treat analysis (i.e., analysis in the assigned treatment arm regardless of actual use) employed in many clinical trials. This is important since adherence to asthma controller medication is frequently low, even in clinical trials.¹⁴⁻¹⁶ We also limited the influence of non-adherence by requiring both a total of 2 ICS fills and at least one fill every 6 months. While frequent prescription fills do not ensure patient use, they are a necessary requirement for regular use. And as we have previously shown that we have near complete capture of fills in our covered patient population, we likely accounted for most of the available ICS and ICS/LABA combination medication in this study group.³³

Since all study individuals were members of a single, large integrated health system, our findings may not be generalizable to other patient populations. Nevertheless, the patient population is generally reflective of the larger census population from which they derive, including its racial and ethnic diversity.³⁴ Finally, our study was not of sufficient size to

analyze rare asthma-related events such as intubations and/or death. These events are infrequent and studies that have examined the relative effect of ICS/LABA combination therapy on these outcomes have been inconclusive.^{10;35} Nevertheless, likely preceding events, such as oral steroid prescriptions, asthma-related ER visits, and asthma-related hospitalizations, were not more likely with combination therapy, suggesting that ICS/LABA therapy does not increase the likelihood of severe exacerbations.

In summary, this study suggests that treatment with ICS/LABA performs as well or better than ICS alone in reducing severe asthma exacerbations. Equally important, is that African American patients, who appeared to experience more severe outcomes from add-on long-acting beta-agonist therapy,⁴ had similar benefits as compared with white patients when using fixed-dose ICS/LABA combination therapy. Further studies are underway to investigate whether the use of combination ICS/LABA therapy is associated with rarer asthma-related outcomes, such as intubation and death. However, our study provides important interim evidence suggesting that the more common, and presumably antecedent, type of asthma exacerbations would be reduced by fixed-dose combination therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used

ICS	Inhaled corticosteroid
LABA	Long-acting beta-agonist
SABA	Short-acting beta-agonist
OCS	Oral corticosteroid
MDI	Metered dose inhaler
HR	Hazard ratio
CI	Confidence interval

Figure 1.

Unweighted (A) and weighted (B) relationship between inhaled corticosteroid (ICS) use alone (solid line) and fixed-dose combination ICS and long-acting beta-agonist (LABA) use and severe asthma exacerbation (i.e., burst oral corticosteroid use, asthma-related emergency department visit, or asthma-related hospitalization). The unweighted analysis does not account for ICS strength, whereas the weighted analysis does account for ICS strength (see Table E1 in the Online Repository of ICS weights).

Table I

Characteristics of patients with asthma stratified by treatment group (N = 1,828)

Characteristic	ICS (n=846)	ICS/LABA (n=982)
Age categories – no. (%) ^{*†}		
<18 years	213 (25.2)	94 (9.6)
18 years	633 (74.8)	888 (90.4)
Female – no (%)	555 (65.6)	641 (65.3)
Race-ethnicity – no. (%)		
African American	308 (36.4)	360 (36.6)
White	538 (63.6)	622 (63.3)
Asthma severity categories – no. (%) [‡]		
Low	246 (29.1)	307 (31.3)
Low-Moderate	374 (44.2)	413 (42.1)
Moderate-Severe	171 (20.2)	189 (19.3)
Severe	55 (6.5)	73 (7.4)
Index ICS medication – no. (%)		
Fluticasone	496 (58.6)	--
Triamcinolone acetonide	185 (21.9)	--
Budesonide	158 (18.7)	--
Flunisolide	4 (0.5)	--
Beclomethasone	3 (0.4)	--
Index ICS/LABA medication – no. (%)		
Fluticasone/salmeterol	--	976 (99.4)
Budesonide/formoterol	--	6 (0.6)
Other asthma controller medication use -no. (%) [*]	109 (12.9)	201 (20.5)
Antileukotrienes	96 (11.4)	190 (19.4)
Cromolyn sodium	2 (0.2)	5 (0.5)
Omalizumab	0 (0.0)	2 (0.2)
Theophylline derivatives	16 (1.9)	18 (1.8)

ICS denotes inhaled corticosteroid treatment; ICS/LABA, combined inhaled corticosteroid and long-acting beta-agonist treatment; and SD, standard deviation.

^{*} P-value <.05 for the ICS treatment vs. ICS/LABA combination treatment group comparison.

[†] Age calculated at index date

[‡] Asthma severity categories correspond to severity groups 1-4 described in the methods section and are based on the results of Ramey et al., J Manag Care Pharm. 2006 May;12(4):310-21.

Table II

Relationship between inhaled corticosteroid and inhaled corticosteroid/long-acting beta agonist combination therapy use and severe asthma exacerbations*

Overall	aHR (95% CI) [†]	
	ICS	ICS/LABA
Unweighted controller	0.56 (0.42 - 0.76)	0.41 (0.29 - 0.60)
Weighted controller	0.72 (0.53 - 0.98)	0.65 (0.47 - 0.90)
Age		
<18 years	1.59 (0.70 - 3.65)	1.36 (0.61 - 3.04)
18 years	0.64 (0.46 - 0.88)	0.58 (0.41 - 0.83)
Sex		
Female	0.78 (0.54 - 1.12)	0.75 (0.51 - 1.10)
Male	0.60 (0.34 - 1.07)	0.46 (0.25 - 0.83)
Race-ethnicity		
African American	0.66 (0.39 - 1.13)	0.59 (0.36 - 0.98)
White	0.76 (0.52 - 1.12)	0.69 (0.45 - 1.05)
Asthma severity [‡]		
Low/low-moderate	0.70 (0.48 - 1.01)	0.72 (0.49 - 1.06)
Moderate-severe/severe	0.58 (0.35 - 0.95)	0.39 (0.23 - 0.68)

aHR denotes adjusted hazard ratio; CI, confidence interval; ICS, inhaled corticosteroid treatment; and ICS/LABA, inhaled corticosteroid and long-acting beta-agonist combined treatment.

* Serious asthma exacerbations were a composite outcome of the following: need for burst oral corticosteroids, an asthma-related emergency department visit, or an asthma-related hospitalization.

[†] Models adjusted for patient age, sex, race-ethnicity, baseline asthma severity, use of asthma controller medication, and concomitant short-acting beta-agonist use.

[‡] Asthma severity categories correspond to severity groups 1-4 described in the methods section and are based on the results of Ramey et al., *J Manag Care Pharm.* 2006 May;12(4):310-21.

Severity groups 1 and 2 represent the low to low-moderate categories and severity groups 3 and 4 represent the moderate-severe to severe categories.