

# Quantifying the proportion of severe asthma exacerbations attributable to inhaled corticosteroid nonadherence

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**Background:** Asthma is an inflammatory condition often punctuated by episodic symptomatic worsening, and accordingly, patients with asthma might have waxing and waning adherence to controller therapy.

**Objective:** We sought to measure changes in inhaled corticosteroid (ICS) adherence over time and to estimate the effect of this changing pattern of use on asthma exacerbations.

**Methods:** ICS adherence was estimated from electronic prescription and fill information for 298 participants in the Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-Ethnicity. For each patient, we calculated a moving average of ICS adherence for each day of follow-up. Asthma exacerbations were defined as the need for oral corticosteroids, an asthma-related emergency department visit, or an asthma-related hospitalization. Proportional hazard models were used to assess the relationship between ICS medication adherence and asthma exacerbations.

**Results:** Adherence to ICS medications began to increase before the first asthma exacerbation and continued afterward.

Adherence was associated with a reduction in exacerbations but was only statistically significant among patients whose adherence was greater than 75% of the prescribed dose (hazard ratio, 0.61; 95% CI, 0.41-0.90) when compared with patients

whose adherence was 25% or less. This pattern was largely confined to patients whose asthma was not well controlled initially. An estimated 24% of asthma exacerbations were attributable to ICS medication nonadherence.

**Conclusions:** ICS adherence varies in the time period leading up to and after an asthma exacerbation, and nonadherence likely contributes to a large number of these exacerbations. High levels of adherence are likely required to prevent these events. (*J Allergy Clin Immunol* 2011;128:1185-91.)

**Key words:** Medication adherence, inhaled corticosteroids, asthma, patient compliance, asthma exacerbations

Although inhaled corticosteroid (ICS) treatment is widely considered the cornerstone therapy for the control of asthma symptoms,<sup>1</sup> we and others have consistently documented poor adherence to this class of medications.<sup>2-5</sup> Despite the well-documented benefit of inhaled steroid use in mitigating asthma complications and exacerbations,<sup>6-8</sup> the methodology of quantifying the relationship between ICS adherence and these asthma-related outcomes poses particular challenges.

First, asthma exacerbations resulting in oral steroid use, an emergency department (ED) visit, or hospitalization can be infrequent; for example, in an earlier study we found that 45%, 25%, and 9% of adults experienced these events over a 2-year period.<sup>9</sup> Therefore ICS adherence needs to be estimated for a relatively large number of patients to detect an association with exacerbation.

Next, because asthma can be an episodic condition, so too can asthma medication use, especially with recent studies suggesting a potential benefit from as-needed ICS treatment.<sup>10</sup> Therefore assessing the relationship between ICS use and outcomes related to poor control might demonstrate a reverse causation bias, such that controller use might appear to be associated with exacerbations. At the other extreme, we have also shown that persons who never fill their asthma controller medications (ie, primary nonadherent patients) and thus have a measured adherence of 0% might have less severe disease and hence less inclination to ever use their medication.<sup>11</sup>

In an earlier study we looked at the cross-sectional relationship between adherence and asthma outcomes.<sup>9</sup> However, given the episodic nature of asthma, we hypothesized that ICS adherence changes with time. Therefore the purpose of this study was to measure changes in adherence over time and to estimate the effect of ICS adherence on asthma exacerbations (ie, burst therapy with oral corticosteroids, an asthma-related ED visit, or an asthma-related hospitalization), accounting for changing patterns of ICS use. Also novel to this analysis, we adjusted for contemporaneous measures of underlying asthma severity, such as changes

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*Abbreviations used*

ACT:	Asthma Control Test
ED:	Emergency department
HR:	Hazard ratio
ICS:	Inhaled corticosteroid
SABA:	Short-acting $\beta$ -agonist
SAPPHIRE:	Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-Ethnicity

in short-acting  $\beta$ -agonist (SABA) use,<sup>12</sup> so as to better estimate the relationship between ICS adherence and severe asthma exacerbations.

## METHODS

### Patient population

This study was approved by the Institutional Review Board of Henry Ford Health System and was consistent with its Health Insurance Portability and Accountability Act policy. All adult study participants signed written consent forms, and study participants less than age 18 years signed a written assent form, with a written consent form signed by a legal guardian. Participants were part of the Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-Ethnicity (SAPPHIRE), a prospective asthma cohort study that has been described in detail elsewhere.<sup>13,14</sup> Potentially eligible participants were first identified through health system electronic records and met the following criteria: age 12 to 56 years, a recorded clinical diagnosis of asthma, and no recorded diagnosis of chronic obstructive pulmonary disease or congestive heart failure. Patients meeting these criteria were invited to undergo a screening examination as part of the intake evaluation for SAPPHIRE, the parent pharmacogenomics study (ClinicalTrials.gov no. NCT01142947). The current analysis includes patients who confirmed that they had a physician's diagnosis of asthma at this initial visit for SAPPHIRE (henceforward referred to as the initial visit) and who had both medical and pharmacy coverage through an affiliated health maintenance organization. (The latter criterion allowed us to identify medication use and clinical outcomes retrospectively and prospectively.) In addition, because we were estimating the contribution of nonadherence to asthma exacerbation, we included only persons who had at least 1 ICS prescription fill (ie, SAPPHIRE participants with at least 1 nonzero measurement of ICS adherence during the study period).

The initial visit as part of SAPPHIRE also included pulmonary function testing, which followed 2005 American Thoracic Society/European Respiratory Society recommendations.<sup>15,16</sup> FEV<sub>1</sub> was measured in liters, and percent predicted FEV<sub>1</sub> was estimated by using the reference equations of Hankinson et al.<sup>17</sup> Bronchodilator response was assessed after administering albuterol sulfate hydrofluoroalkane. A 360- $\mu$ g dose of albuterol was delivered from a standard metered-dose inhaler with an AeroChamber Plus Z STAT spacer (Monahan Medical Corp, Plattsburgh, NY). Bronchodilator reversibility was calculated as the percentage change in FEV<sub>1</sub> before and after albuterol administration.<sup>15</sup>

### Calculation of ICS adherence

We defined ICS adherence as the percentage of the prescribed dose taken by a patient. ICS adherence was estimated by linking electronic prescription data with pharmacy claims data. We have previously shown that these data are nearly complete for our covered population, with very few prescriptions being filled through other providers.<sup>11,15</sup> To estimate the length of time each filled ICS canister would last, we linked dosage information from electronic prescription data to information on canister size as gleaned from National Drug Code information recorded at the time of the prescription fill. Together, these data were used to calculate a day's supply for each ICS fill. As we and others have done previously,<sup>2,18,19</sup> adherence was estimated as the cumulative days' supply divided by the number of days of observation (ie, a moving 6-month observation period for the current study). These calculations also accounted

for (ie, prorated) prescription fills that partially overlapped with the beginning and end of each observation period and incorporated when a medication was discontinued by a physician. Because a patient's medication use could change over time, we calculated a moving 6-month average of medication use for each day of study follow-up; that is, for each day of follow-up past the initial SAPPHIRE visit, we calculated the proportion of ICS medication taken as prescribed for the preceding 6-month period. We chose the 6-month window of exposure based on our prior experience showing that this time interval provides stable estimates of use when derived from electronic data sources (ie, electronic prescriptions and pharmacy claims); we have also shown that estimates using this time window are associated not only with asthma but also with outcomes for another disease condition.<sup>20</sup>

### Statistical analysis

The primary outcome was the composite of the following events: an asthma-related hospitalization, an asthma-related ED visit, or use of oral corticosteroids. Because we performed a time-to-event analysis, the primary analysis included follow-up to the occurrence of any of the aforementioned events. The events included in our composite measure of serious asthma exacerbations are also consistent with recent efforts to standardize the definition of asthma exacerbations for research studies and clinical practice.<sup>21</sup> Secondary outcomes analysis included follow-up to each of these event types in isolation (ie, only asthma-related hospitalizations, only asthma-related ED visit, or only burst oral corticosteroid use).

Cox proportional hazard models were used to assess the relationship between ICS medication adherence and the time to asthma-related outcomes. These time-to-event models estimate a hazard ratio (HR) for each covariate, which is similar to a relative risk but specific to regression models using survival analysis. Because events could happen multiple times for a given patient, we accounted for the intensity of repeated measures (ie, clustering of events per patients) using the methods described by Andersen and Gill.<sup>22</sup> Moreover, events occurring simultaneously were handled according to the method described by Breslow.<sup>23</sup> Patients were censored if and when they disenrolled from the health plan or at the end of observation on November 1, 2010. As mentioned above, adherence measures were updated for each day of follow-up (ie, entered into the regression models as time-updated covariates), and each day's measure approximated the proportion of the prescribed ICS dose taken over the preceding 6-month period per patient. Therefore adherence was a continuous measure for which we estimated the risk reduction (for an asthma exacerbation) per 0.25 increase in this proportion (ie, a 25% increase in adherence). Regression models adjusted for patients' age, sex, and race-ethnicity. To account for underlying disease severity and control, we included FEV<sub>1</sub> (in liters) and the degree of bronchodilator reversibility (as a percentage change in FEV<sub>1</sub>) taken at the time of the initial visit and a history of asthma exacerbations (ie, oral steroid use, asthma-related ED visits, and asthma-related hospitalizations) in the baseline period. The baseline period was defined as the 6 to 12 months before the initial visit and was chosen so as not to overlap with ICS adherence measured at the time of the initial visit (ie, the 6-month window of ICS use measured from 6 months before the initial visit to the time of the initial visit). The regression models also included separate indicator variables for whether patients were using a long-acting  $\beta$ -agonist or other asthma controller medications (ie, antileukotrienes, mast cell stabilizers, immunomodulatory medications, or theophylline derivatives) at the time of their initial visit. Because we previously showed that prospective measures of SABA use predict future asthma exacerbations,<sup>12</sup> we also included time-updated measures of SABA use in our regression models as a proxy for changing disease severity. Similar to the measure of ICS adherence, SABA use was calculated as the total number of doses dispensed over the preceding 6 months (ie, contemporaneous with the measurement of ICS adherence). Separate variables were created for SABA nebulizer and SABA metered-dose inhaler use based on our earlier published findings regarding their predictive import.<sup>12</sup> Therefore we had estimates of SABA use for each day of follow-up, and these measures were included in the regression models as time-updated covariates.

To assess for a potential threshold effect in the relationship between ICS adherence and outcomes, we categorized adherence (ie, the proportion of dose

taken) as follows: 0% to 25% (referent), 26% to 50%, 51% to 75%, and 75% to 100%. These categorical variables were included as time-updated dummy variables in the regression equations. We stratified the analysis for asthma control status based on participants' responses to the Asthma Control Test (ACT). Baseline ACT scores of 19 or less were considered uncontrolled asthma, and scores of greater than 19 were considered controlled asthma.<sup>24</sup> These regression models adjusted for all other covariates previously discussed.

Lastly, we estimated the proportion of serious asthma exacerbations (ie, the combined primary outcome) attributable to ICS medication nonadherence. We estimated the rate of events with perfect adherence by generating a hazard for each person in analysis, with ICS adherence set to 100%. This estimation included all other individual risk factors weighted by the model parameter estimates for that risk factor and for that patient. The number of avoidable events caused by nonadherence was the difference between the observed number of events and the sum of the calculated hazards for the analytic population. We divided this value by the sum of the observed events in the analytic population and the number of events in patients without ICS use (ie, conservatively assuming that these events are immutable) to estimate the proportion of exacerbations attributable to ICS nonadherence. Restated, we estimated the total proportion of asthma exacerbations that could have been avoided through improved ICS adherence in the entire study population by first estimating the number of events that could have been prevented in those taking an ICS and then incorporating the number of events in those not taking ICS medication in the denominator (this latter number was conservatively assumed to be fixed).

We accepted a type I error rate threshold of 5% (ie,  $P < .05$ ) for determining statistical significance. Analyses were performed with SAS version 9.2 software (SAS Institute, Inc, Cary, NC).<sup>25</sup>

## RESULTS

The characteristics of the 298 study participants with asthma from the SAPHIRE cohort are shown in Table I. Mean  $\pm$  SD age was  $34.5 \pm 15.7$  years, and 68.5% were female. Almost all patients (98.3%) were of African American race-ethnicity by self-report. At the initial screening visit, approximately half of the participants (48.7%) reported asthma that was not controlled based on their ACT scores. Mean adherence to ICS medication was 26.3% at the time of the initial visit.

The total duration of patient follow-up was 581.6 patient-years or an average duration of follow-up per study participant of 1.95 years ( $\pm 0.93$  SD). During follow-up, 40.6% had 1 or more treatments with an oral corticosteroid, 23.2% had an asthma-related ED visit, and 4.0% had an asthma-related hospitalization; 46.3% of participants had at least 1 of these events, for a total of 435 asthma exacerbations. Among the 138 patients with 1 or more asthma exacerbations, the median time between events was 84 days (minimum time, 0 days; maximum time, 1028 days).

Fig 1 demonstrates the variation in adherence with respect to the first asthma exacerbation (ie, burst therapy with oral corticosteroids, an asthma-related ED visit, or an asthma-related hospitalization). The first events among study participants were aligned to demonstrate the changes in adherence before and after the exacerbation. As can be seen, ICS use began to increase before the exacerbation and continued after the event.

The increased ICS use around the time of an exacerbation might result in a counterfactual relationship between ICS adherence and the risk of an exacerbation. This is demonstrated in Table II, in which the unadjusted relationship between ICS adherence and asthma exacerbations shows an increased risk (HR, 1.12; 95% CI, 1.04-1.20). However, adjusting for other markers of concomitant asthma severity (eg, concurrent SABA use) and historic

TABLE I. Characteristics of SAPHIRE participants (n = 298)\*

Variable	
Age (y), mean $\pm$ SD	35.4 $\pm$ 15.7
Female sex, no. (%)	204 (68.5)
Race-ethnicity, no. (%)	
African American	293 (98.3)
White	3 (1.0)
Other	2 (0.7)
ACT score†	
$\leq 19$ , no. (%)	145 (48.7)
$> 19$ , no. (%)	153 (51.3)
Pulmonary function‡	
FEV <sub>1</sub> (L), mean $\pm$ SD	2.44 $\pm$ 0.76
Percent predicted FEV <sub>1</sub> , mean $\pm$ SD	87.1 $\pm$ 19.9
FEV <sub>1</sub> bronchodilator reversibility (% change in FEV <sub>1</sub> ), mean $\pm$ SD§	1.08 $\pm$ 1.38
Oral steroid use in baseline period, no. (%)¶	79 (26.5)
Asthma-related ED visit in baseline period, no. (%)¶	20 (6.7)
Asthma-related hospitalization in baseline period, no. (%)¶	3 (1.0)
Use of an additional controller medication at the time of the initial visit, no. (%)	
Long-acting $\beta$ -agonist#	151 (50.7)
Other controller medication**	50 (16.8)
ICS adherence at the time of the initial visit (%), mean $\pm$ SD††	26.3 $\pm$ 25.4

\*Includes all participants from SAPHIRE with at least 1 nonzero measurement of ICS adherence during the study period.

†Asthma control was assessed at the initial screening visit. An ACT score of 19 or less implies uncontrolled asthma, and a score of greater than 19 implies controlled asthma.

‡Pulmonary function was measured during the initial screening visit at the time of enrollment.

§Bronchodilator reversibility was measured as the percentage change in FEV<sub>1</sub> between the initial measurement and after administration of a 360- $\mu$ g dose of albuterol sulfate hydrofluoroalkane.

¶Baseline oral steroid use, asthma-related ED visits, and asthma-related hospitalizations were measured before ICS adherence measurements (ie, 6-12 months before the initial screening visit).

||Initial visit denotes the time of the first examination for SAPHIRE.

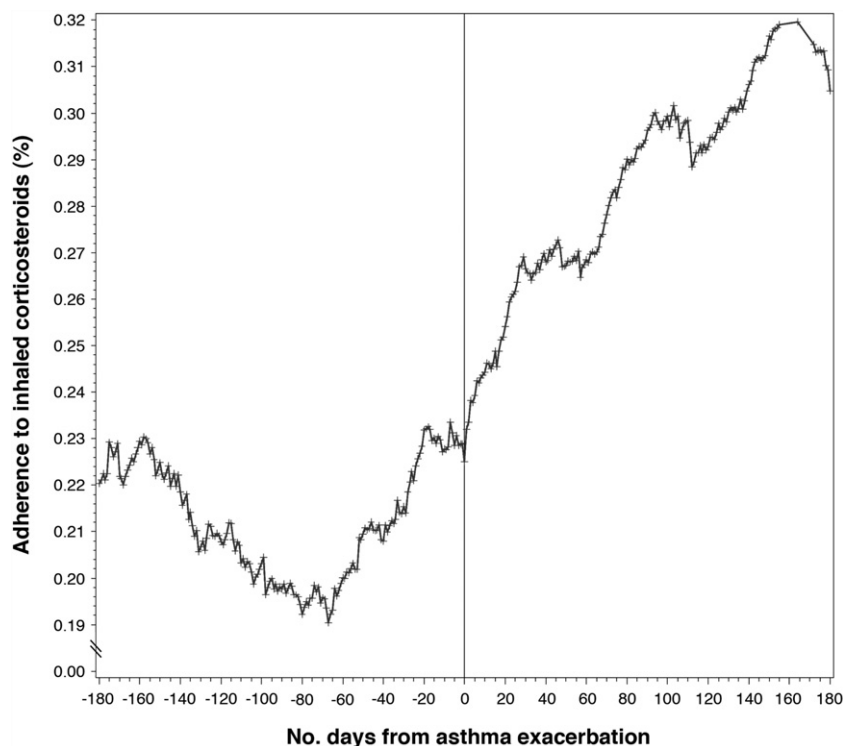
#Number of patients using an ICS who were concomitantly using an inhaled long-acting  $\beta$ -agonist medication.

\*\*Number of patients using an ICS who were concomitantly using 1 of the following additional asthma controller medications: an antileukotriene, a mast cell stabilizer, an immunomodulatory agent (ie, omalizumab), or a theophylline derivative medication.

††ICS adherence at the time of the initial evaluation represents the average proportion of prescribed ICS medication taken per patient for the time period starting 6 months before the initial visit to the time of the initial visit. The value presented represents the average across all study patients.

asthma severity (ie, prior history of oral steroid use, asthma-related ED visit, or asthma-related hospitalization) resulted in a consistent protective relationship between ICS adherence and asthma exacerbation (see Table E1 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org) for the parameter estimates for the other covariates).<sup>17</sup> Every 25% increase in ICS adherence was associated with an 11% decreased risk in the composite measure of asthma exacerbation (HR, 0.89; 95% CI, 0.81-0.97;  $P = .009$ ).

We also examined whether the relationship between the level of adherence and asthma exacerbations was linear. As can be seen, the largest and only statistically significant reduction in the risk of exacerbation was seen among patients whose ICS adherence exceeded 75% of that prescribed (Fig 2, A). However, after stratifying our sample by asthma control status at baseline (ie, an ACT score  $\leq 19$  for uncontrolled and  $> 19$  for controlled asthma), we found that the benefit of adherence was largely confined to patients whose asthma was not controlled at baseline. In this latter group



**FIG 1.** Change in corticosteroid adherence over time with respect to the first asthma exacerbation in SAPPHIRE participants. The first asthma exacerbation (ie, burst oral steroid use, asthma-related ED visit, or asthma-related hospitalization) is aligned at time zero. Average adherence for the 180 days before and after the exacerbation are shown.

the protected effect of ICS controller therapy was again largely confined to those with an adherence of greater than 75% (HR, 0.59; 95% CI, 0.37-0.95;  $P = .03$ ; Fig 2, B). Although increasing ICS adherence also appeared protective among patients whose reported asthma was controlled at baseline, these findings did not reach statistical significance, and there was no obvious threshold effect (Fig 2, C). These data can also be found in Table E2 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org).

Using the model parameter estimates (see Table E1), we estimated that there would have been 124 asthma exacerbations (ie, the combined outcome) in our analytic population per year were patients to have used their ICS medication as prescribed (ie, perfect adherence). One hundred ninety-six events were observed in this time period for this group, and an additional 99 events were noted for patients without ICS exposure. Therefore we estimate that 24.4% (ie,  $[196 - 124]/[196 + 99]$ ) of all asthma exacerbations in our study population could have been avoided through improved ICS adherence. Of these 295 events, 176 (59.7%) were oral steroid fills, 107 (36.3%) were ED visits, and 12 (4.1%) were hospitalizations.

## DISCUSSION

The effectiveness of ICSs to reduce asthma exacerbations has been well described,<sup>26,27</sup> as has the relationship between ICS non-adherence and increased exacerbations<sup>9,28-30</sup> and the lack of persistence in ICS use over time.<sup>31,32</sup> However, to our knowledge, this is the first study to quantify the likely effect of this varying use on severe asthma events. Moreover, our composite measure of severe asthma exacerbations was consistent with recent

recommendations to standardize the measurement of these events,<sup>21</sup> and hence our findings might be more easily generalized when compared with earlier studies.

Not surprisingly, we found that medication use as assessed through pharmacy claims increased in the time surrounding an asthma exacerbation. This observation has relevance when assessing the relationship between medication use and outcomes, such that one might observe a positive relationship between ICS adherence and asthma exacerbations if underlying severity is not adequately accounted for in the analysis. We have previously shown SABA rescue medication use to be a predictor of an impending asthma event<sup>12</sup> and again have observed that accounting for this use at least in part corrects underlying variation in disease severity,<sup>9</sup> as does accounting for a past history of asthma exacerbations.

We also report the somewhat surprising suggestion of a nonlinear reduction in asthma exacerbations with increasing ICS use. In particular, ICS adherence rates of greater than 75% of the prescribed dose appeared to be a threshold above which asthma exacerbations were significantly reduced. This finding suggests that the seemingly arbitrary thresholds between 70% and 80% often used to describe the level above which a patient is considered adherent might actually have clinical relevance<sup>33-35</sup> and is consistent with at least 1 other study finding increased asthma control among patients with greater than 80% ICS adherence.<sup>36</sup> However, this cut point might differ by condition, disease severity, and medication class, implying that its predictive validity also needs to be established for other clinical scenarios.<sup>37</sup>

Our findings do appear to conflict with those of a recent clinical trial suggesting that intermittent dosing of ICSs results in similar exacerbation rates when compared with ICS continuous dosing.<sup>10</sup>



**TABLE II.** Unadjusted and adjusted relationship between ICS medication adherence and asthma exacerbations\*

Outcome	Adherence to ICSs†			
	HR (95% CI)	P value	aHR (95% CI)‡	P value
Primary outcome				
Combined asthma exacerbations*	1.12 (1.04-1.20)	.002	0.89 (0.81-0.97)	.009
Secondary outcomes				
Oral corticosteroid use	1.12 (1.03-1.22)	.006	0.90 (0.80-1.00)	.043
Asthma-related ED visit	1.06 (0.92-1.22)	.428	0.87 (0.73-1.03)	.114
Asthma-related hospitalization	1.37 (1.03-1.81)	.029	0.99 (0.65-1.51)	.971

aHR, Adjusted HR.

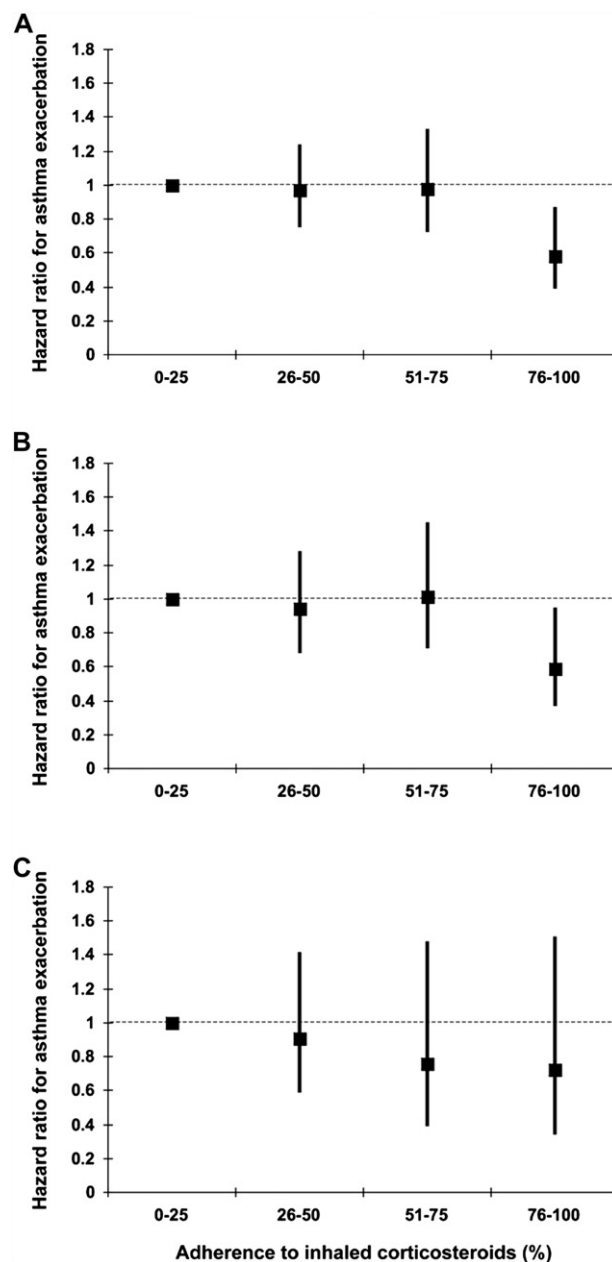
\*An asthma exacerbation was considered to be an event requiring the initiation of oral corticosteroids, an asthma-related ED visit, or an asthma-related hospitalization. These events combined comprised the primary study outcome.

†HRs for adherence represent the estimated effect for a 25% improvement in ICS adherence.

‡Adjusted for patients' age, sex, race-ethnicity, concomitant SABA use (ie, separately adjusting for metered-dose inhaler and nebulizer use), percent predicted FEV<sub>1</sub> at the time of the initial visit, degree of bronchodilator reversibility in FEV<sub>1</sub> at the time of the initial visit, historic exacerbations during the baseline period (ie, separate variables for oral steroid use, asthma-related ED visits, and asthma-related hospitalizations), use of a long-acting  $\beta$ -agonist as an ICS combination inhaler at the time of the initial visit, and use of other asthma controller medications at the time of the initial visit (ie, antileukotrienes, mast cell stabilizers, immunomodulatory medication, or theophylline derivatives).

However, this study was restricted to patients with mild persistent asthma, whereas our study was not. Although we did not categorize patients according to severity as outlined in the National Asthma Education and Prevention Program guidelines,<sup>1</sup> we do show that the largest benefit of ICS use was seen in patients whose asthma was deemed to be uncontrolled based on the ACT score, and in these patients only adherence levels of greater than 75% were associated with a lower rate of exacerbations. In the trial adherence was assessed by counting unused inhaler doses. Because study participants might dump medication in an attempt to appear compliant,<sup>38</sup> this method of assessing adherence could overestimate actual use and diminish the observed effect of continuous ICS therapy. It is possible that we were underpowered to detect the association between ICS adherence and exacerbations among those whose asthma was well controlled at baseline. However, because this group was actually larger than those with an ACT score of 19 or less, the relationship, if present, is likely smaller than that reported here.

Although we have again shown pharmacy claims–based estimates of medication adherence to be predictors of asthma-related outcomes, we must note that these metrics do not measure the erratic patterns of daily use, nor are they capable of assessing improper inhaler technique, both of which might be highly prevalent.<sup>39,40</sup> Moreover, we could not determine whether some filled medication was dumped or went unused. Nevertheless, we anticipate that this unmeasured deviation would result in underestimating the true effect of adherence to ICS medication on asthma exacerbations, and in this regard our estimates might be conservative. Similarly, because this is an observational study, it is possible that we did not account for other important confounders in our analysis. It is also uncertain whether our finding can be generalized to other groups because the patients analyzed were all members of a single health system and were predominantly African



**FIG 2.** Relationship between level of ICS adherence (ie, percentage of prescribed ICS medication taken) and the likelihood of an asthma exacerbation (ie, burst oral steroid use, asthma-related ED visit, or asthma-related hospitalization). The relationship between adherence and outcomes is shown for all study participants (**A**), for those whose asthma was uncontrolled at the initial visit (**B**), and for those whose asthma was controlled at the initial visit (**C**). Participants with an ICS adherence of 0% to 25% are the referent group against which the other adherence categories are compared. Effect estimates are adjusted for all covariates included in Table II and in model 5 from Table E1.

American. Excluding and including the few patients who did not report African American race-ethnicity had no significant effect on our results (data not shown). Moreover, we have recently shown that ICS treatment response is not likely to vary according to the proportion of one's African and European ancestry,<sup>14</sup> suggesting that the effect of ICS adherence observed here can be generalized to multiple population groups.

The low baseline level of ICS adherence that we measured here (26.3%) is consistent with other large population-based studies by us and others.<sup>2,41</sup> We estimate that approximately 24% of our combined exacerbation outcomes could have been avoided through improved ICS use. At first glance, this is lower than our previous estimate of 60% of asthma hospitalizations being attributable to ICS nonadherence,<sup>9</sup> yet it is important to note that hospitalizations are a rare event, and therefore our current estimates represent a much larger number of events avoided. Our estimates are also conservative in that they assume that events in patients without ICS exposure are fixed; however, we know from the work of others that even patients with severe asthma can be underprescribed ICS medication and therefore might benefit from treatment.<sup>42</sup>

In summary, we are able to demonstrate the relationship between ICS adherence and asthma exacerbations in a manner that accounts for the changing patterns of inhaler use over time. Not surprisingly, ICS adherence appears to be protective for these events. Although these findings are consistent with the results of clinical trials involving the use of ICS medication for asthma,<sup>27</sup> even these trials do not account for varying degrees of ICS use by participants. In this manner we were able to ascertain that the primary treatment benefit was experienced by those with relatively high degrees of use (>75% of the prescribed dose) over a 6-month period. Although these population-level estimates accounted for multiple proxies of disease severity, the exact strength and duration of ICS treatment needed for an individual patient will vary. Nevertheless, developing and refining these measures of medication use from automated data sources (ie, electronic prescription information, claims data, and the electronic medical record) has a number of exciting potentials. These include improvement in patient care through the identification of patients at high risk for poor outcomes and even application in the areas of pharmacoepidemiology and pharmacogenomics, in which accurate assessments of drug exposure are needed.<sup>13,43</sup>

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**Clinical implications: ICS nonadherence is a major contributor to serious asthma exacerbations, and efforts to reduce these events will likely need to achieve high adherence levels in patients with uncontrolled asthma.**

## REFERENCES

- 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.
- Williams LK, Peterson EL, Wells K, Campbell J, Wang M, Chowdhry VK, et al. A cluster-randomized trial to provide clinicians inhaled corticosteroid adherence information for their patients with asthma. *J Allergy Clin Immunol* 2010;126:225-31.
- Apter AJ, Boston RC, George M, Norfleet AL, Tenhave T, Coyne JC, et al. Modifiable barriers to adherence to inhaled steroids among adults with asthma: it's not just black and white. *J Allergy Clin Immunol* 2003;111:1219-26.
- Rand CS, Wise RA. Measuring adherence to asthma medication regimens. *Am J Respir Crit Care Med* 1994;149(suppl):S69-76.
- Bender B, Wamboldt FS, O'Connor SL, Rand C, Szefer S, Milgrom H, et al. Measurement of children's asthma medication adherence by self report, mother report, canister weight, and Doser CT. *Ann Allergy Asthma Immunol* 2000;85:416-21.
- Haahela T, Jarvinen M, Kava T, Kiviranta K, Koskinen S, Lehtonen K, et al. Comparison of a beta 2-agonist, terbutaline, with an inhaled corticosteroid, budesonide, in newly detected asthma. *N Engl J Med* 1991;325:388-92.
- Haahela T, Jarvinen M, Kava T, Kirviranta K, Koskinen S, Lehtonen K, et al. Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma. *N Engl J Med* 1994;331:700-5.
- Long-term effects of budesonide or nedocromil in children with asthma. The Childhood Asthma Management Program Research Group. *N Engl J Med* 2000;343:1054-63.
- Williams LK, Pladevall M, Xi H, Peterson EL, Joseph C, Lafata JE, et al. Relationship between adherence to inhaled corticosteroids and poor outcomes among adults with asthma. *J Allergy Clin Immunol* 2004;114:1288-93.
- Boushey HA, Sorkness CA, King TS, Sullivan SD, Fahy JV, Lazarus SC, et al. Daily versus as-needed corticosteroids for mild persistent asthma. *N Engl J Med* 2005;352:1519-28.
- Williams LK, Joseph CL, Peterson EL, Wells K, Wang M, Chowdhry VK, et al. Patients with asthma who do not fill their inhaled corticosteroids: a study of primary nonadherence. *J Allergy Clin Immunol* 2007;120:1153-9.
- Paris J, Peterson EL, Wells K, Pladevall M, Burchard EG, Choudhry S, et al. Relationship between recent short-acting beta-agonist use and subsequent asthma exacerbations. *Ann Allergy Asthma Immunol* 2008;101:482-7.
- Jin Y, Hu D, Peterson EL, Eng C, Levin AM, Wells K, et al. Dual-specificity phosphatase 1 as a pharmacogenetic modifier of inhaled steroid response among asthmatic patients. *J Allergy Clin Immunol* 2010;126:618-25.
- Gould W, Peterson EL, Karungi G, Zoratti A, Gaggin J, Toma G, et al. Factors predicting inhaled corticosteroid responsiveness in African American patients with asthma. *J Allergy Clin Immunol* 2010;126:1131-8.
- Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. *Eur Respir J* 2005;26:319-38.
- Miller MR, Crapo R, Hankinson J, Brusasco V, Burgos F, Casaburi R, et al. General considerations for lung function testing. *Eur Respir J* 2005;26:153-61.
- Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999;159:179-87.
- Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. *J Clin Epidemiol* 1997;50:105-16.
- Wells K, Pladevall M, Peterson EL, Campbell J, Wang M, Lanfear DE, et al. Racial/ethnic differences in factors associated with inhaled steroid adherence among adults with asthma. *Am J Respir Crit Care Med* 2008;178:1194-201.
- Habib ZA, Tzogiannis L, Havstad SL, Wells K, Divine G, Lanfear DE, et al. Relationship between thiazolidinedione use and cardiovascular outcomes and all-cause mortality among patients with diabetes: a time-updated propensity analysis. *Pharmacoepidemiol Drug Saf* 2009;18:437-47.
- Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med* 2009;180:59-99.
- Andersen PK, Gill RD. Cox's regression model for counting processes: a large sample study. *Ann Stat* 1982;10:1100-20.
- Breslow N. Covariance analysis of censored survival data. *Biometrics* 1974;30:89-99.
- Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, et al. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol* 2004;113:59-65.
- SAS Institute, Inc. SAS/STAT users guide. Version 9.2. Cary (NC): SAS Institute, Inc; 2008.
- 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.
- Sin DD, Man J, Sharpe H, Gan WQ, Man SF. Pharmacological management to reduce exacerbations in adults with asthma: a systematic review and meta-analysis. *JAMA* 2004;292:367-76.
- Stern L, Berman J, Lumry W, Katz L, Wang L, Rosenblatt L, et al. Medication compliance and disease exacerbation in patients with asthma: a retrospective study of managed care data. *Ann Allergy Asthma Immunol* 2006;97:402-8.
- Bender B, Zhang L. Negative affect, medication adherence, and asthma control in children. *J Allergy Clin Immunol* 2008;122:490-5.
- Milgrom H, Bender B. Nonadherence to asthma treatment and failure of therapy. *Curr Opin Pediatr* 1997;9:590-5.
- Marceau C, Lemiere C, Berbiche D, Perreault S, Blais L. Persistence, adherence, and effectiveness of combination therapy among adult patients with asthma. *J Allergy Clin Immunol* 2006;118:574-81.
- Breekveldt-Postma NS, Koerselman J, Erkens JA, van der Molen T, Lammers JW, Herings RM. Treatment with inhaled corticosteroids in asthma is too often discontinued. *Pharmacoepidemiol Drug Saf* 2008;17:411-22.
- Clerisme-Beatty EM, Bartlett SJ, Teague WG, Lima J, Irvin CG, Cohen R, et al. The Madison Avenue effect: how drug presentation style influences adherence and outcome in patients with asthma. *J Allergy Clin Immunol* 2011;127:406-11.

34. Apter AJ, Reisine ST, Affleck G, Barrows E, ZuWallack RL. Adherence with twice-daily dosing of inhaled steroids. Socioeconomic and health-belief differences. *Am J Respir Crit Care Med* 1998;157:1810-7.
35. Cochrane GM. Compliance and outcomes in patients with asthma. *Drugs* 1996; 52(suppl 6):12-9.
36. Lasmar L, Camargos P, Champs NS, Fonseca MT, Fontes MJ, Ibiapina C, et al. Adherence rate to inhaled corticosteroids and their impact on asthma control. *Allergy* 2009;64:784-9.
37. Pladevall M, Williams LK, Potts LA, Divine G, Xi H, Lafata JE. Clinical outcomes and adherence to medications measured by claims data in patients with diabetes. *Diabetes Care* 2004;27:2800-5.
38. Rand CS, Wise RA, Nides M, Simmons MS, Bleecker ER, Kusek JW, et al. Metered-dose inhaler adherence in a clinical trial. *Am Rev Respir Dis* 1992;146: 1559-64.
39. Cochrane MG, Bala MV, Downs KE, Mauskopf J, Ben Joseph RH. Inhaled corticosteroids for asthma therapy: patient compliance, devices, and inhalation technique. *Chest* 2000;117:542-50.
40. Milgrom H, Bender B, Ackerson L, Bowry P, Smith B, Rand C. Noncompliance and treatment failure in children with asthma. *J Allergy Clin Immunol* 1996;98:1051-7.
41. Bender BG, Pedan A, Varasteh LT. Adherence and persistence with fluticasone propionate/salmeterol combination therapy. *J Allergy Clin Immunol* 2006;118: 899-904.
42. Legorreta AP, Christian-Herman J, O'Connor RD, Hasan MM, Evans R, Leung KM. Compliance with national asthma management guidelines and specialty care. *Arch Intern Med* 1998;158:457-64.
43. Wilke RA, Xu H, Denny JC, Roden DM, Krauss RM, McCarty CA, et al. The emerging role of electronic medical records in pharmacogenomics. *Clin Pharmacol Ther* 2011;89:379-86.

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**TABLE E1.** Relationship between ICS medication adherence and asthma exacerbations\*

Variable	Risk of asthma exacerbation									
	Model 1†		Model 2‡		Model 3§		Model 4¶		Model 5	
	HR (95% CI)	P value	aHR (95% CI)	P value	aHR (95% CI)	P value	aHR (95% CI)	P value	aHR (95% CI)	P value
ICS adherence	1.12 (1.04-1.20)	.002	0.95 (0.88-1.03)	.244	0.93 (0.86-1.01)	.087	0.90 (0.83-0.99)	.022	0.89 (0.81-0.97)	.009
Female sex					1.24 (0.97-1.58)	.090	1.27 (0.99-1.62)	.063	1.30 (1.01-1.66)	.042
Race-ethnicity					1.42 (1.02-1.99)	.041	1.41 (0.94-2.11)	.097	1.44 (0.96-2.18)	.080
Age (y)					1.12 (1.04-1.20)	.003	1.10 (1.01-1.19)	.023	1.10 (1.02-1.19)	.020
SABA metered-dose inhaler use			1.11 (1.08-1.15)	.001	1.12 (1.09-1.16)	.001	1.12 (1.08-1.16)	.001	1.12 (1.08-1.16)	.001
SABA nebulizer use			1.07 (1.03-1.11)	.002	1.08 (1.04-1.12)	.001	1.08 (1.03-1.12)	.001	1.06 (1.01-1.11)	.014
History of oral steroid use			1.54 (1.40-1.70)	.001	1.51 (1.36-1.67)	.001	1.42 (1.27-1.59)	.001	1.47 (1.31-1.65)	.001
History of asthma-related ED visit			1.78 (1.42-2.22)	.001	1.90 (1.50-2.40)	.001	1.85 (1.45-2.38)	.001	1.76 (1.37-2.27)	.001
History of asthma-related hospitalization			0.16 (0.07-0.37)	.001	0.12 (0.05-0.29)	.001	0.17 (0.07-0.43)	.001	0.12 (0.05-0.31)	.001
FEV <sub>1</sub> percent predicted							0.94 (0.88-1.01)	.090	0.94 (0.88-1.01)	.087
FEV <sub>1</sub> reversibility							0.94 (0.87-1.03)	.176	0.94 (0.88-1.03)	.210
Use of long-acting $\beta$ -agonist combination inhaler									0.92 (0.74-1.15)	.473
Use of other asthma controller medication concomitantly									1.69 (1.35-2.12)	.001

aHR, Adjusted HR.

\*An asthma exacerbation was considered an event requiring the initiation of oral corticosteroids, an asthma-related ED visit, or an asthma-related hospitalization. These events combined comprised the primary study outcome.

†Model 1 includes the variable for ICS adherence alone. HRs for adherence represent the estimated effect for a 25% improvement in ICS adherence.

‡Model 2 included ICS adherence (as in model 1) but adjusts for SABA use (ie, both metered-dose inhaler and nebulizer use) and history of asthma exacerbation (ie, oral steroid use, asthma-related ED visit, and asthma-related hospitalization). SABA use is measured as the total pack size supplied (ie, sum) in a 6-month period and is contemporaneous with the measurement of ICS adherence. Pack size is the number of doses available per inhaler device or nebulizer prescription fill. History of asthma exacerbation is represented as oral steroid use, asthma-related ED visits, and asthma-related hospitalizations in the time period before any ICS adherence measurements (ie, 6-12 months before the initial screening visit).

§Model 3 is adjusted for all variables in model 2 and includes additional variables for patients' age, sex, and race-ethnicity. Age is coded for each year increase, female sex is coded as 1 for female and 0 for male patients, and race-ethnicity is coded as 1 for persons reporting African American race and 0 for all others.

¶Model 4 is adjusted for all variables in model 3 and includes additional variables for percent predicted FEV<sub>1</sub> and the degree of bronchodilator reversibility in FEV<sub>1</sub> at the initial screening visit. Predicted forced expiratory volume was calculated by using the predictive equations of Hankinson et al.<sup>17</sup> Bronchodilator FEV<sub>1</sub> reversibility was measured as the percentage change in FEV<sub>1</sub> after administration of a 360- $\mu$ g dose of albuterol sulfate hydrofluoroalkane.||Model 5 is adjusted for all variables in model 4 and includes additional variables for use of a long-acting  $\beta$ -agonist combination inhaler (ie, in combination with an ICS) or the use of other asthma controller medications (ie, antileukotrienes, mast cell stabilizers, immunomodulatory medication, or theophylline derivatives).



**TABLE E2.** Relationship between ICS medication adherence (categorized) and asthma exacerbations with and without stratification for initial level of patient-reported asthma control\*

ICS adherence	Time to asthma exacerbation					
	Total sample		Stratified by initial level of asthma control			
			ACT score ≤19 (uncontrolled asthma)†		ACT score >19 (controlled asthma)‡	
	aHR (95% CI)‡	P value	aHR (95% CI)‡	P value	aHR (95% CI)‡	P value
0% to 25% (Referent)	1.0	—	1.0	—	1.0	—
26% to 50%	0.97 (0.75-1.24)	.789	0.94 (0.68-1.28)	.682	0.91 (0.59-1.42)	.690
51% to 75%	0.98 (0.72-1.33)	.871	1.01 (0.71-1.45)	.941	0.76 (0.39-1.48)	.419
76% to 100%	0.58 (0.39-0.87)	.008	0.59 (0.37-0.95)	.030	0.72 (0.34-1.51)	.384

aHR, Adjusted HR.

\*The measure of adherence is an estimate of the percentage of prescribed ICS medication taken.

†Asthma control was assessed at the initial visit for SAPPHERE. An ACT score of 19 or less implies uncontrolled asthma, and a score of greater than 19 implies controlled asthma.

‡HRs for ICS adherence represent the estimated effect for that level of adherence when compared with the reference level of 0% to 25% of the prescribed dose taken. Models are adjusted for patients' age (in years), sex, race-ethnicity, percent predicted FEV<sub>1</sub> in liters at the initial visit, degree of bronchodilator reversibility in the FEV<sub>1</sub> (ie, percentage change in FEV<sub>1</sub>) at the initial visit, SABA metered-dose inhaler use, SABA nebulizer use, past history of asthma exacerbation (ie, oral steroid use, asthma-related ED visit, and asthma-related hospitalization) 6 to 12 months before the initial screening visit, use of an inhaled long-acting β-agonist medication, and use of other asthma controller medications (ie, antileukotrienes, mast cell stabilizers, immunomodulatory medication, or theophylline derivatives).