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Risk of Adverse Gastrointestinal Events from Inhaled Corticosteroids

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Abstract

Study Objective—Previous studies suggest a risk of gastrointestinal events in patients prescribed oral corticosteroids, but gastrointestinal events have not commonly been documented in patients prescribed inhaled corticosteroids. We explored whether patients prescribed inhaled corticosteroids are at risk of adverse gastrointestinal effects.

Design—A retrospective cohort study was conducted using 25 years of electronic medical record data.

Setting—An urban health center with an academic affiliation.

Patients—The incidence of adverse gastrointestinal events in patients prescribed inhaled corticosteroids and albuterol (n = 7,156) was compared to those prescribed albuterol alone (n = 12,287).

Measurements and Main Results—Adverse gastrointestinal outcomes included events such as gastritis, ulcers, and bleeding. Cox proportional hazards models were used to determine the risk of adverse events controlling for possible confounders such as alcohol use or non-steroidal anti-inflammatory drug use. Adverse gastrointestinal events were observed in 461 (6.4%) patients prescribed inhaled corticosteroids and albuterol and in 302 (2.5%) patients prescribed only albuterol. Patients prescribed inhaled albuterol and inhaled corticosteroids had an increased risk of adverse gastrointestinal events compared to patients prescribed only albuterol [hazard ratio 1.26 (95% confidence interval 1.02 to 1.56)] after controlling for potential confounders. A prescription for a spacer device reduced this risk among patients prescribed inhaled steroid [hazard ratio 0.26 (95% confidence interval 0.20 to 0.34)].

Conclusions—Patients prescribed inhaled corticosteroids appear to have a slight risk of adverse gastrointestinal events that is mitigated in patients prescribed a spacer device.

Keywords

inhaled corticosteroids; gastrointestinal adverse events; spacer; obstructive airways disease

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INTRODUCTION

Inhaled corticosteroids are commonly used to treat obstructive airways diseases including asthma and chronic obstructive pulmonary disease (COPD). For asthma, inhaled corticosteroids are the primary treatment of underlying airway inflammation and have been shown to reduce morbidity, mortality, and the costs of health care.[1-5] Inhaled corticosteroids also are used in treating patients with COPD, although the benefits are less well confirmed.[6-8] For both asthma and COPD, inhaled corticosteroids are preferred over oral corticosteroids for long-term treatment because of their high levels of topical anti-inflammatory activity and low levels of systemic activity.[9, 10] While inhaled corticosteroids are relatively safe and effective, adverse effects may occur in patients receiving chronic treatment. Documented adverse effects include adrenal suppression,[11-13] osteoporosis in adults[14, 15] or reduced growth rates in children,[16] cataracts,[17-20] glaucoma,[21, 22] and dermal thinning.[23-25]

Although evidence is conflicting, gastrointestinal complications such as ulcers and bleeding may occur in patients treated with chronic oral corticosteroids. For example, a pooled analysis of 71 controlled trials revealed a risk of gastrointestinal events with oral corticosteroids.[26] Similarly, a case-control study of Medicaid data found an increased risk of gastrointestinal events with corticosteroids, but also found that it was primarily restricted to patients treated with non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids concomitantly.[27] An analysis of the United Kingdom General Practice Research Database confirmed the additional risk associated with concomitant NSAID administration, although this study also found monotherapy with oral corticosteroids to pose significant risk of gastrointestinal adverse events.[28]

Although evidence is somewhat contradictory, oral corticosteroids appear to have some degree of heightened risk for adverse gastrointestinal events. Prior evidence suggests that *inhaled* corticosteroids are not associated with gastrointestinal adverse events,[29, 30] even though studies have indicated that inhaled corticosteroids produce systemic effects, and there is some degree of gastric exposure with inhaled products.[11-25] We conducted an exploratory analysis to ascertain whether inhaled corticosteroids are associated with gastrointestinal adverse events.

METHODS

Patients

Patients received their care and medications from Wishard Health Services, Indianapolis, Indiana between 1977 and 2002. During this time, we identified adult patients (≥ 18 years of age) with airways disease defined as a diagnosis of asthma or COPD prescribed an inhaled sympathomimetic (i.e., albuterol). We required that patients had at least one clinic encounter 6 months before their first prescription for an inhaled steroid or albuterol. We excluded patients with any evidence contained in their automated medical records of an adverse gastrointestinal event (e.g., gastritis, gastrointestinal bleed, ulcer, and esophagitis) during the 6 months prior to initiation of an inhaled steroid or albuterol. The study was approved by the Indiana University - Purdue University Institutional Review Board.

Data Source

We used automated data from Regenstrief Medical Record System (RMRS). Beginning in 1974, the RMRS has been the central repository for clinical data for outpatients and inpatients seeking care at Wishard Health Services, an inner-city medical center in Indianapolis, Indiana, USA. The RMRS is a modular system containing registration and appointment data, prescriptions (including over-the-counter products filled through a Wishard Pharmacy), and diagnostic data from laboratory, radiology, and endoscopic procedures. Prescription data

derive from two sources. The first source is an archival database spanning back to 1974 containing the drug dispensed and the dispensing date. The second source is a prescription module spanning to 1992 created directly from the electronic prescription records containing virtually all data on each drug dispensed including the physician's instructions for use. In this database, physicians' orders for spacer devices were stored the same as all other prescriptions. These modules capture both prescription and over-the-counter products, as long as they were provided by the Wishard Health System. During the past decade, two internal surveys of adult outpatients with uncomplicated hypertension, coronary artery disease, heart failure, and obstructive airways disease indicated that patients seen at Wishard receive >95% of their prescription and over-the-counter drugs at Wishard Health System pharmacies.[31] Radiologic and endoscopic data include the procedural dates and diagnoses of upper gastrointestinal radiological examination and endoscopy.

Study Design

A retrospective cohort study design was used (Figure 1). Two groups were formed to represent patients treated with an inhaled corticosteroid and a comparison group not prescribed an inhaled corticosteroid. All study patients were required to have at least one sympathomimetic prescription for the β_2-adrenergic agonist albuterol. Patients in the inhaled steroid group were those prescribed both inhaled corticosteroids and albuterol and patients in the albuterol group were prescribed inhaled albuterol only. Because nasally administered corticosteroids ultimately reach the stomach and duodenum, we also considered their use.

The index date for patients in the steroid cohort was the date of the patient's first prescription for one of the following inhaled corticosteroids: beclomethasone, flunisolide, fluticasone, or triamcinolone. The index date for patients in the albuterol group was the date of the patient's first prescription for albuterol. The inhaled steroids budesonide and mometasone were not on the Health System's formulary during the time of this study, and thus were not included in our analysis.

Main Outcome Measures

The primary endpoint was incident gastrointestinal ulcer, perforation, or bleeding as diagnosed by a physician or identified by diagnostic procedure (radiology, endoscopy, sigmoidoscopy, or colonoscopy). Qualifying diagnoses on patients' problem lists included any gastrointestinal ulceration, perforation, esophagitis, gastritis, hemorrhage, hematemesis, hematochezia, or melena. We searched for evidence of patients reaching the endpoint after their index date but before their last prescription for inhaled steroid in the inhaled steroid group or inhaled albuterol in the albuterol group. For this analysis, we used prescription and endpoint data for the period November 14, 1977 to February 19, 2002.

Statistical Methods

We followed patients from the index prescription date to endpoint or censoring. Patients reaching the endpoint were considered as having experienced an adverse gastrointestinal event; otherwise, follow-up was censored one month after their last prescription for inhaled steroid or albuterol. Observations also were censored with death or when no additional observations were recorded in the RMRS. The outcome represented the duration from the index prescription to endpoint or censoring. The distribution of duration from the index date to the event (or censoring) time was quantified by a survival function for each treatment group. Kaplan-Meier curves were used to depict the estimated survival functions of patients in the inhaled steroid and albuterol groups. The method also was used to illustrate the difference in survival experience between inhaled steroid users with or without spacer devices. We conducted subgroup analyses for patients without any evidence of prescriptions for NSAIDs because of

previous work suggesting that concomitant NSAID use significantly increases risk with oral steroids.[27, 28]

Cox proportional-hazards regression models were used to examine the association between inhaled corticosteroids use and the development of the adverse gastrointestinal endpoint while controlling for confounders and effect modifiers. These variables included baseline demographics (age, race, sex) and relevant behavioral characteristics (smoking and alcohol use), and comorbidities that could represent diagnostic biases (evidence of oral thrush or gastroesophageal reflux disease). We also assessed the impact of short-term administration of effect modifying medications that are known to have acute gastrointestinal effects administered within six months prior to endpoint or censoring (e.g., acute administrations of oral corticosteroids, iron containing medications, NSAIDs, theophylline, and alendronate). We considered other potential effect modifying medications such as risedronate and etidronate, but these drugs were not on formulary at the time of this study. Cox regression models were created to adjust for the main effects (e.g., oral corticosteroids) and interactions such as treatment by NSAIDs, smoking by alcohol use, gender by iron medication use. The final model selected was based on the significance of the model predictors. The adjusted effect of the inhaled corticosteroids was then tested using the Wald Chi-square test and the magnitudes of effects quantified by the hazard ratios of the covariates and their confidence intervals.

Data from the prescription module of the RMRS from 1992 to 2001 were used to examine the dose effect (as low, moderate, and high dose) of inhaled and nasal steroid. The definition of low, moderate, and high dose was that used by the National Asthma Education and Prevention Program Expert Panel Report.[10] Patients receiving low dose inhaled steroid AND nasal steroid were elevated to the moderate dose level and those receiving moderate dose inhaled steroid AND nasal steroid were elevated to the high dose level.

A priori we wished to determine the effect of a spacer device on any observed risk of adverse gastrointestinal events. As such, we conducted additional analyses to gain insights into the effect of spacer use. We evaluated the effect of a prescription for a spacer on the development of adverse gastrointestinal events in all study patients and then restricted our analysis to the inhaled corticosteroid group. Analyses were conducted using SAS version 8.2 (SAS Institute, Inc., Cary, NC, USA). Two-sided P values of less than 0.05 were used in statistical inferences.

RESULTS

Patient Characteristics

Of 28,272 patients prescribed an inhaled steroid or albuterol, 8,829 patients were excluded because of a prior history of one of the endpoint diagnoses before their index prescription date. Of the remaining 19,443 patients, there were 7,156 patients who had been prescribed both an inhaled steroid and albuterol and 12,287 patients prescribed albuterol only. Beclomethasone (59.5%) was the most commonly prescribed inhaled steroid followed by fluticasone (24.6%), triamcinolone (13.9%), and flunisolide (2.1%). Among the inhaled steroid group, 5,695 (79.6%) used only an orally inhaled product and 1,461 (20.4%) used both orally and nasally inhaled products. Patient characteristics of the inhaled steroid and albuterol study groups are shown in Table 1. Patients in the inhaled steroid group were more likely older, a female, a smoker, diagnosed with gastroesophageal reflux disease, and a recipient of NSAIDs, oral corticosteroids, and a spacer device ($p<0.0001$). The mean (SD) duration of follow-up was 5.7 year (3.7), the median was 4.8 years, and the range was 1 to 24.3 years.

Incident Adverse Gastrointestinal Events

Incident adverse gastrointestinal were observed in 763 (3.9 percent) of the 19,443 study patients during the course of observation. Of the 7,156 patients in the inhaled steroid group, 461 (6.4 percent) experienced an event while receiving an inhaled steroid. The most common events documented in the inhaled steroid group were gastritis (N = 163; 2.3 percent), gastrointestinal bleed (N = 152; 2.1 percent), ulcer (N = 101; 1.4 percent), and esophagitis (N=45; 0.6%). Of the 12,287 patients in the albuterol group, 302 patients (2.5 percent) experienced an adverse gastrointestinal event, including: gastritis (N = 91; 0.7 percent), gastrointestinal bleed (N = 121; 1.0% percent), ulcer (N = 64; 0.5 percent), and esophagitis (N=26; 0.2%). The proportion of patients experiencing a gastrointestinal event was greater in the inhaled steroid group than the albuterol group, regardless of event type (P<0.05 for all).

Crude survival function estimates using Kaplan-Meier curves (Figure 2) show the change in hazard function for all patients (Panel A) and the probability for patients who had not received an NSAID (Panel B). Regardless of NSAID use, patients in the inhaled steroid group experienced a greater risk of a gastrointestinal disorder than patients in the albuterol group suggesting an association between the use of inhaled steroid and an incident gastrointestinal disorder. However, such graphical representations do not control for other confounders.

Cox regression models further confirmed the finding after controlling for other risk factors and covariates (Table 2). Patients in the inhaled steroid group had a greater risk of adverse gastrointestinal events despite their NSAID status. For all patients, the risk (i.e., hazard ratio) of adverse gastrointestinal event was 1.27 (95 percent confidence interval, 1.09 to 1.48), whereas for those without evidence of NSAID use the risk was 1.26 (95 percent confidence interval, 1.02 to 1.56). In other words, the risk of a gastrointestinal disorder was approximately 26% greater among patients prescribed an inhaled steroid and albuterol compared to patients prescribed albuterol only. Other significant factors associated with the endpoint included older age (P<0.001, hazard ratio=1.02), asthma (P=0.004, hazard ratio 0.74), cigarette smoking (P<0.001, hazard ratio=1.40), alcohol use (P<0.001, hazard ratio=1.60), and the use of iron containing medication (P=0.001, hazard ratio=1.55), NSAIDs (P<0.001, hazard ratio=1.31) or theophylline (P<0.001, hazard ratio=1.43). Interestingly, the use of oral steroids was not significant. We repeated our analyses excluding patients prescribed oral corticosteroids and the inhaled steroid effect remained significant (data not shown, P=0.02). Moreover, in the subset of patients prescribed inhaled corticosteroid between 1992 to 2001 (when more detailed data on drug dispensing and directions for use were available), we found that the risk of adverse gastrointestinal event was 3.7% among patients prescribed relatively low doses of inhaled steroid, 4.5% among those prescribed moderate doses, and 8.8% among patients prescribed high doses (P=0.03 for trend).

Effect of Receipt of a Spacer Device

Among all patients, receipt of a spacer (Table 2) had a significant mitigating effect on the risk of adverse gastrointestinal events (P<0.001, hazard ratio=0.34). These results imply that the risk of developing the adverse gastrointestinal events among patients prescribed a spacer was 66% lower than patients whom had not received a spacer.

To assess whether receipt of a spacer reduced the risk of adverse gastrointestinal event rates specifically within the inhaled corticosteroid-treated patients, we compared the Kaplan-Meier estimates of the hazard function of inhaled corticosteroid patients who had been prescribed a spacer with that of patients who had not (Figure 3, Panels A and B). The evidence from Figure 2 suggests that receipt of a spacer device is indeed associated with a reduced risk of an adverse gastrointestinal event. Cox regression models further confirmed this observation (Table 3). The hazard ratio for receipt of a spacer was 0.29 (95 percent confidence interval, 0.24 to 0.35)

among all patients prescribed inhaled corticosteroids and 0.26 (95 percent confidence interval, 0.20 to 0.34) among the subset of patients who had not been prescribed an NSAID. The results imply that the risk of adverse gastrointestinal event is 71% less among patients who receive a spacer device compared to those who do not.

DISCUSSION

Our results suggest that patients prescribed inhaled corticosteroids have a slight risk of adverse gastrointestinal events (primarily gastritis), which is mitigated when patients receive a spacer device. Oral corticosteroids have been implicated as a risk factor for adverse gastrointestinal events such as ulcers for many years, but the current study is the first suggesting a possible effect from inhaled corticosteroids.

While the target of inhaled drug is the lung, a considerable amount of inhaled corticosteroid appears in the gastrointestinal tract including the lining of the esophagus, the stomach, intestine, and colon.[32, 33] Scintillation studies have revealed large boluses of radiolabeled drug appearing in the stomach when metered dose inhalers are used without spacer devices.[34] However, little drug is observed when the spacer device is used with the metered dose inhaler. Presumably, the reduced amount of inhaled steroid that is swallowed or deposited in the oropharynx and ultimately swallowed reduces the risk of adverse gastrointestinal events such as gastritis, ulceration, and bleeding.

Our findings should be viewed in light of the conflicting evidence from previous studies assessing risk with oral corticosteroids. Although a large meta-analysis[26] indicated a risk of ulceration from oral corticosteroids, this evidence is contradicted by a case control study[27] that concluded the increased risk of developing peptic ulcer disease was limited to patients with concurrent NSAID use. In our study, despite NSAID use, we found that patients treated with oral steroids were not at a statistically significant higher risk of developing gastrointestinal adverse events. However, inhaled corticosteroid-treated patients had a greater risk of gastrointestinal adverse events even after controlling for NSAID use. A possible explanation for the association of inhaled but not oral corticosteroids with gastrointestinal adverse events may be related to the intensity or duration of exposure. The average duration of inhaled corticosteroid exposure was roughly 1 year, while oral steroid use generally covered a shorter time intervals (e.g., median duration = 1 month). Thus, part of the reason we identified a risk of gastrointestinal adverse events with inhaled but not oral corticosteroids could be related to differences in exposure. We measured both acute bursts and regular use for oral steroids, while inhaled steroids were typically administered on a regular basis over longer periods of time. This distinction likely biased our estimate of risk downward for oral steroids. More research is needed to examine how long-term oral steroid use compares to long-term inhaled steroid use.

We acknowledge several important limitations of this study. First, we used automated observational data from a large health care system over a long duration assuming that drug use during the interval between first and last prescription represented continuous use of drug. Such practice data may have been collected differently over time, important changes may have occurred with diagnostic instrumentation and procedures, and inhaled corticosteroids have become increasingly potent. These factors could bias our findings. Second, although we were able to account for patient level variables like smoking, alcohol use, and over-the-counter drug use - variables often missed in observational studies such as ours - residual confounding could exist and could possibly explain the small associations found. Third, comparison of an albuterol group to an albuterol plus inhaled steroid group could be biased by severity or type of disease (asthma versus COPD). Most of our sample included patients with a diagnosis of asthma and we controlled for this in our analyses. Patients with COPD were at higher risk for

gastrointestinal events than patients with asthma, which could be related to COPD patient's greater numbers of comorbidities and incidence of hospitalization. Fourth, we chose not to match the index date of the albuterol cohort to the index date of the albuterol plus inhaled steroid cohort because of the extent to which this would limit our sample size. However, this decision could introduce a time bias that potentially could bias our hazard ratio upward. Fifth, our endpoint was a diagnosis made by a physician using a variety of means including clinical acumen or diagnostic procedures such as endoscopy. Our study results would have been more compelling were we to use only endoscopic results. However, such procedural data were available on a limited number of patients whom are not likely generalizable to our overall patient population prescribed inhaled pharmacotherapy for airway disease. Sixth, we did not adjust our analysis for use of antacids or gastro-protective drugs because of the sporadic use of these drugs, and primarily with the drugs available during the early years of observation (e.g., liquid antacids and histamine antagonists). Future studies should consider this important confounder. Finally, our earlier archived data only accurately and consistently reflect prescription date and drug but not dosage, which was the reasoning for using more recent data to explore dose-effect. To some extent our design accounted for the length of drug exposure by censoring observations at the time the drug no longer appeared in the records, but we were unable to control for adherence. We are also limited in our understanding of the relationship between drug potency, device, and variability in administration technique - factors that could affect drug absorption in the gastrointestinal tract.[33, 35] While our study did not include dry powder delivery devices, market shift towards such formulations warrants further study of the effect of delivery device. Our indicator of spacer use is based on whether a patient received one, not whether the spacer was used properly or at all.

We conclude that patients prescribed inhaled corticosteroids may have a risk of adverse gastrointestinal events that is mitigated with the use of spacer devices. Although the incidence of such events is low (approximately 6%), these results provide further support for the use of spacer devices with inhaled corticosteroids. Although we cannot determine whether patients using dry powder devices are at increased risk for gastrointestinal events, our findings have potential implications for these newer devices since spacers cannot be used. Additional research should focus on dry powder delivery devices to determine whether recommendations might be strengthened in this area.

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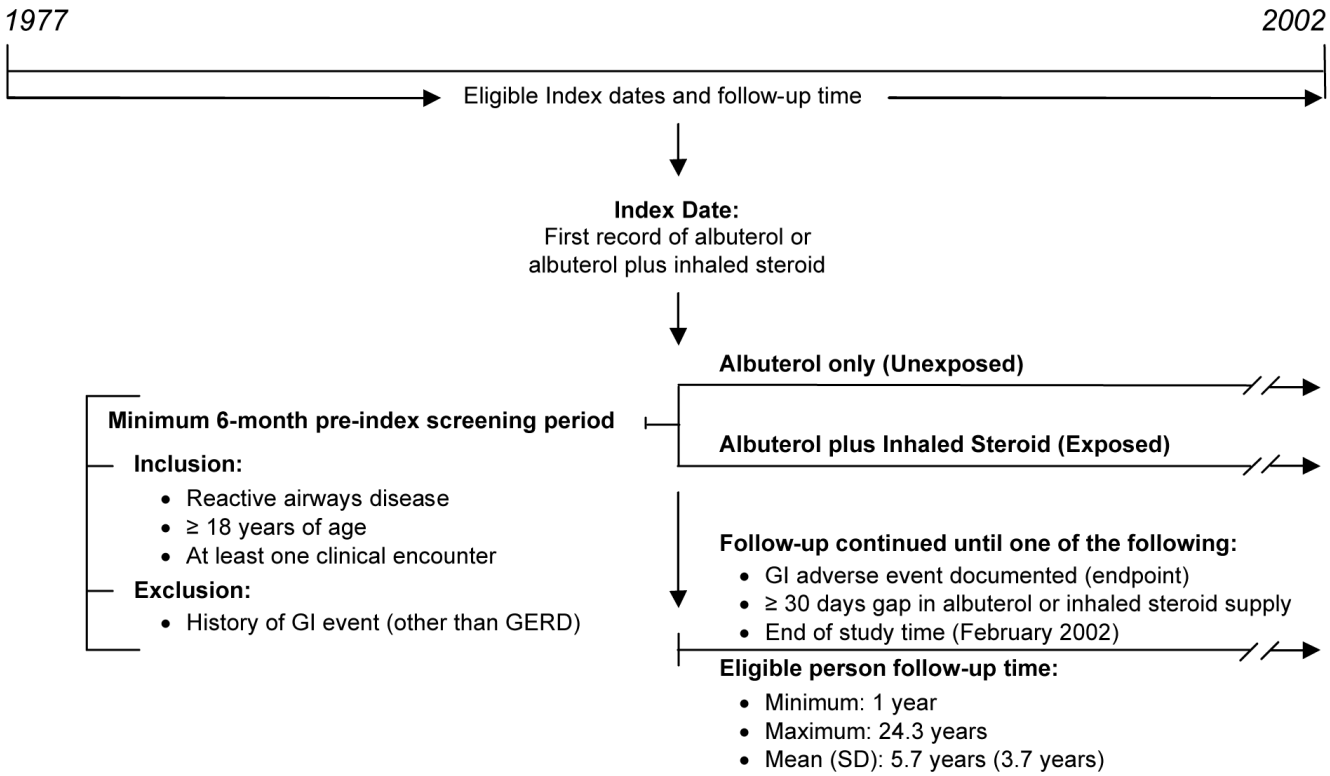

Figure 1. Study Design

COPD - chronic obstructive pulmonary disease; GERD - gastroesophageal reflux disease; GI - gastrointestinal; SD - standard deviation

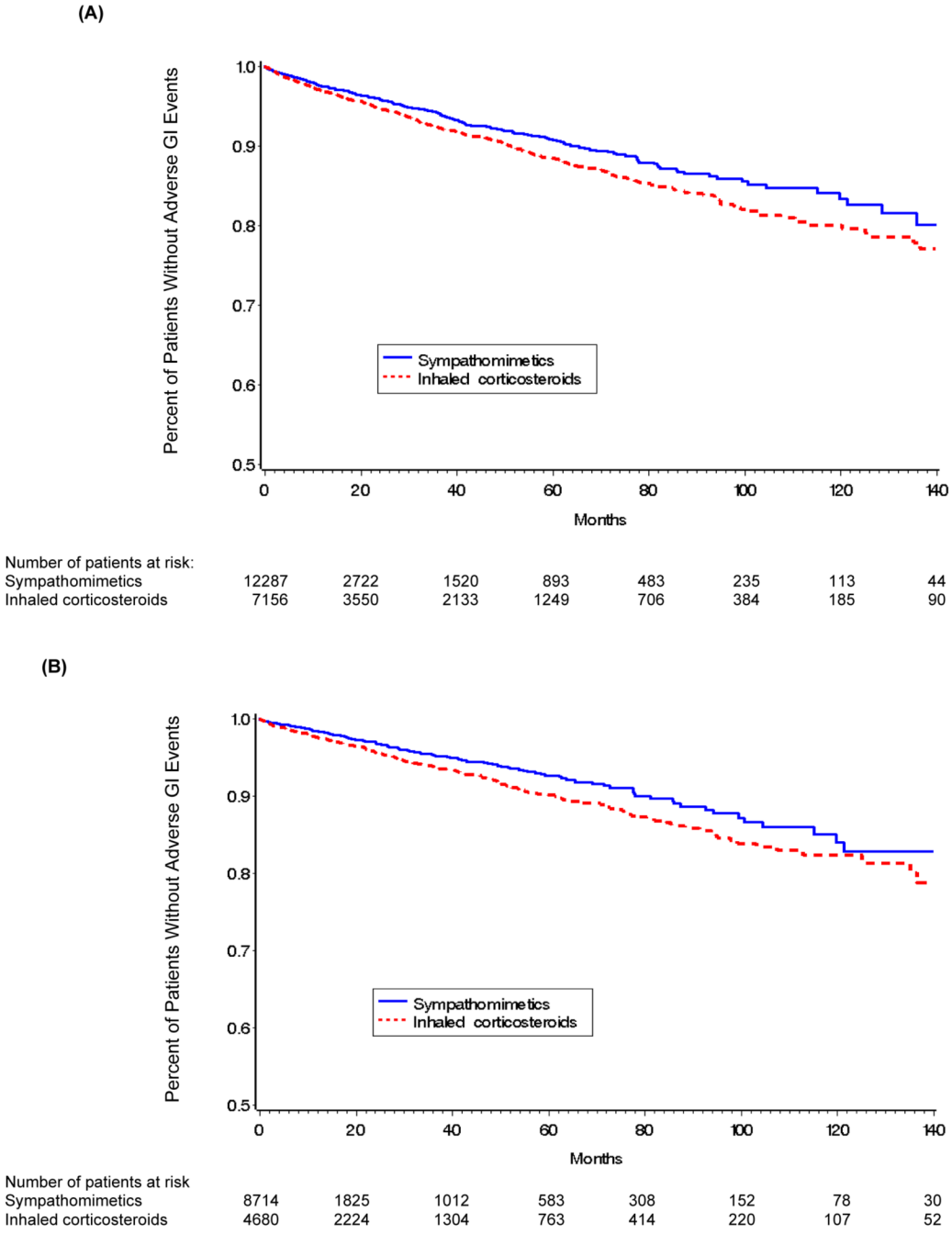

Figure 2. Kaplan-Meier Estimates of the Percentage of Patients in Corticosteroid and Albuterol Only (Sympathomimetics) Groups

Panel (A) All Patients, Panel (B) Patients who had not used NSAIDs within six months of the event or censoring date; NSAID - Non-steroidal anti-inflammatory drug

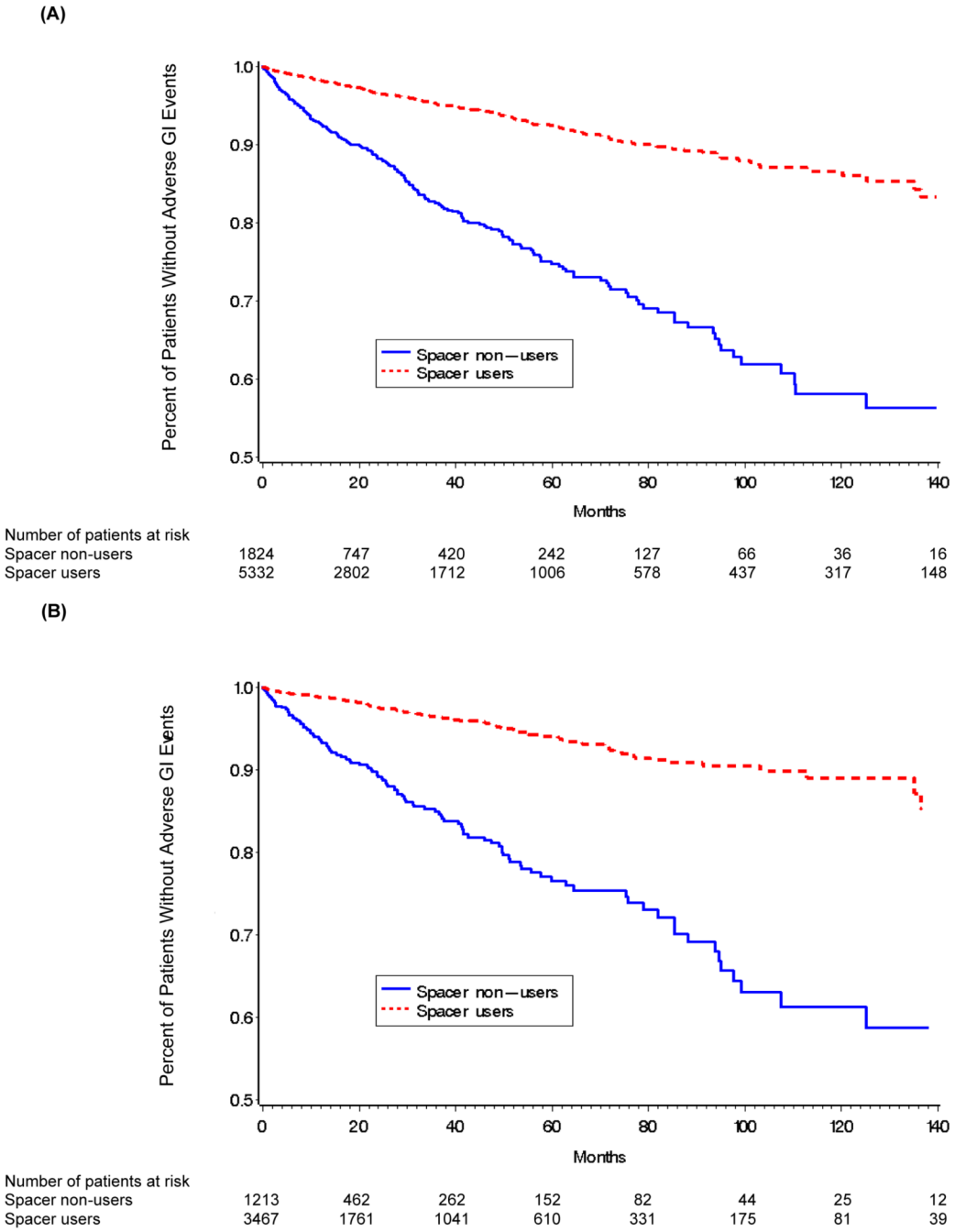

Figure 3. Kaplan-Meier Estimates of the Percentage of Patients Prescribed Inhaled corticosteroids (With or Without Spacer)

Panel (A) All inhaled corticosteroids users, Panel (B) Inhaled corticosteroid users who had not used NSAIDs within six months of the event or censoring date; NSAID - Non-steroidal anti-inflammatory drug

Table 1

Clinical Characteristics of the Study Sample

Variable	Inhaled Corticosteroid & Albuterol (N = 7,156)	Albuterol Only (N = 12,287)	Total (N = 19,443)
Age, mean (SD), y at index	34.0 (18.0)	30.5 (18.6)	31.8 (18.5)
Women, No. (%)	4,709 (65.8)	7,151 (58.2)	11,860 (61.0)
Black race, No. (%)	3,714 (51.9)	6,303 (51.3)	10,017 (51.5)
Asthma, No. (%)	6,083 (85.0)	11,181 (91.0)	17,264 (88.8)
COPD	1,073 (15.0)	1,106 (9.0)	2,179 (11.2)
Cigarette smoking, No. (%)	1,169 (16.3)	1,119 (9.1)	2,288 (11.8)
Alcohol use, No. (%)	973 (13.6)	1,769 (14.4)	2,742 (14.1)
Oral thrush[a], No. (%)	14 (0.2)	12 (0.1)	26 (0.1)
GERD[a], No. (%)	651 (9.1)	369 (3.0)	1,020 (5.2)
Iron medications[a], No. (%)	372 (5.2)	700 (5.7)	1,072 (5.5)
NSAIDs[a], No. (%)	2,476 (34.6)	3,576 (29.1)	6,052 (31.1)
Potassium supplements, No. (%)	964 (13.5)	750 (6.1)	1,714 (8.8)
Oral Steroid[a], No. (%)	1,553 (21.7)	1,290 (10.5)	2,843 (14.6)
Spacer device[a], No. (%)	5,331 (74.5)	7,077 (57.6)	12,408 (63.8)
Theophylline[a], No. (%)	444 (6.2)	491 (4.0)	935 (4.8)
Alendronate[a], No. (%)	7 (0.1)	12 (0.1)	19 (0.1)

SD = standard deviation

COPD = chronic obstructive pulmonary disease

GERD = gastroesophageal reflux disease

NSAID = non-steroidal anti-inflammatory drug

[a]Recorded after the index date but within 6 months of the event or censoring date.

Table 2

Results of Multivariable Cox Regression Models Examining the Relationship between Inhaled Corticosteroid Use and the Risk of Adverse Gastrointestinal Events

	All patients (N=19,442)		Patients who were not prescribed NSAIDS within 6 months before the event or censoring time (N = 13,393)	
Variables in the model	**Hazard Ratio (95% CI)**	**P-Value**	**Hazard Ratio (95% CI)**	**P-Value)**
Inhaled corticosteroids (yes=1)	1.27 (1.09-1.48)	0.002	1.26 (1.02-1.56)	0.03
Sex (male=1)	0.98 (0.84-1.15)	0.81	0.90 (0.72-1.12)	0.33
Race (black=1)	0.80 (0.69-0.93)	0.003	0.84 (0.69-1.03)	0.09
Age (years, on the index date)	1.02 (1.02-1.03)	<0.001	1.02 (1.01-1.02)	<0.001
Asthma (yes=1)	0.74 (0.59-0.91)	0.004	0.68 (0.51-0.90)	0.006
Smoking (yes=1)	1.40 (1.19-1.65)	<0.001	1.40 (1.10-1.77)	0.01
Alcohol use (yes=1)	1.60 (1.36-1.89)	<0.001	1.86 (1.48-2.34)	<0.001
Oral thrush [a](yes=1)	2.45 (0.78-7.66)	0.13	1.68 (0.23-12.11)	0.61
GERD [a](yes=1)	1.07 (0.86-1.32)	0.56	1.28 (0.95-1.71)	0.10
Iron-medications [a](yes=1)	1.55 (1.19-2.01)	0.001	1.45 (0.98-2.14)	0.07
NSAIDs [a](yes=1)	1.31 (1.13-1.51)	<0.001	-	-
Potassium supplements (yes=1)	1.27 (1.06 - 1.52)	0.008	1.16 (0.98-1.52)	0.27
Oral steroid [a](yes=1)	1.09 (0.90-1.32)	0.36	1.09 (0.84-1.40)	0.52
Spacer [a](yes=1)	0.34 (0.30-0.40)	<0.001	0.34 (0.28-0.42)	<0.001
Theophylline [a](yes=1)	1.43 (1.16-1.75)	<0.001	1.79 (1.36-2.34)	<0.001

NSAID = non-steroidal anti-inflammatory drug

CI = confidence interval

GERD = gastroesophageal reflux disease

[a]Referring to the time period after the index date but within 6 months of the event or censored date. One patient was removed from the analyses because of a missing response.

Table 3

Results of Multivariable Cox Regression Models Examining the Relationship between Spacer Use and the Risk of Adverse Gastrointestinal Events in Patients Prescribed Inhaled Corticosteroids

	All patients using inhaled corticosteroids (N = 7,155)		Patients using inhaled corticosteroids but were not prescribed NSAIDs within 6 months of the event or censoring date (N = 4,679)	
Variables in the model	**Hazard Ratio (95% CI)**	**P Value**	**Hazard Ratio (95% CI)**	**P Value**
Spacer (yes=1)	0.29 (0.24-0.35)	<0.001	0.26 (0.20-0.34)	<0.001
Sex (male=1)	1.03 (0.84-1.27)	0.77	0.92 (0.69-1.23)	0.59
Race (black=1)	0.84 (0.69-1.01)	0.06	0.86 (0.66-1.12)	0.26
Age on index date (years)	1.02 (1.01-1.02)	<0.001	1.01 (1.01-1.02)	0.002
Asthma (yes=1)	0.76 (0.59-0.99)	0.044	0.64 (0.45-0.90)	0.01
Smoking (yes=1)	1.44 (1.17-1.77)	<0.001	1.45 (1.08-1.95)	0.01
Alcohol use (yes=1)	1.53 (1.23-1.91)	<0.001	1.80 (1.33-2.44)	<0.001
Iron-medications *(yes=1)	1.62 (1.15-2.28)	0.006	1.67 (1.02-2.71)	0.04
NSAIDs *(yes=1)	1.35 (1.12-1.62)	0.002	-	-
Potassium supplements (yes=1)	1.37 (1.10-1.72)	0.006	1.36 (0.98-1.90)	0.06
Oral steroid *(yes=1)	1.24 (0.99-1.54)	0.06	1.23 (0.92-1.65)	0.16
Theophylline *(yes=1)	1.47 (1.15-1.88)	0.002	1.80 (1.30-2.49)	<0.001

NSAID = non-steroidal anti-inflammatory drug

CI = confidence interval

*Referring to the time period after index date but within 6 months of the event or censoring date. One patient was removed from the analyses because of a missing response.