

Development and validation of a novel risk score for asthma exacerbations: The risk score for exacerbations

Eric D. Bateman, MD,^a Roland Buhl, MD,^b Paul M. O'Byrne, MB, FRCPC,^c Marc Humbert, MD,^d
Helen K. Reddel, MBBS, PhD, FRACP,^e Malcolm R. Sears, MB, FRACP, FRCPC,^c Christine Jenkins, MD, FRACP,^f
Tim W. Harrison, MD,^g Santiago Quirce, MD, PhD,^h Stefan Peterson, PhD,ⁱ and Göran Eriksson, MB, PhD^j

Cape Town, South Africa, Mainz, Germany, Hamilton, Ontario, Canada, Clamart, France, Sydney, Australia, Nottingham, United Kingdom, Madrid, Spain, and Lund, Sweden

Background: Identifying patients at risk of future severe asthma exacerbations, those whose asthma might be less treatment responsive, or both might guide treatment selection.

Objective: We sought to investigate predictors for failure to achieve Global Initiative for Asthma (GINA)-defined good current asthma control and severe exacerbations on treatment and to develop a simple risk score for exacerbations (RSE) for clinical use.

Methods: A large data set from 3 studies comparing budesonide/formoterol maintenance and reliever therapy with fixed-dose inhaled corticosteroid/long-acting β_2 -agonist therapy was analyzed. Baseline patient characteristics were investigated to determine dominant predictors for uncontrolled asthma at 3 months and for severe asthma exacerbations within 12 months

of commencing treatment. The RSE, right censored at 6 months to include all 3 studies, was based on the dominant predictors for exacerbations in two thirds of the data set and validated in one third.

Results: Patients (n = 7446) whose symptoms were not controlled on GINA treatment steps 3 and 4 and with 1 or more exacerbations (as judged by a clinician based on patient records, history, or both) in the previous year were included. On multivariate analysis, GINA step, reliever use, postbronchodilator FEV₁, and 5-item Asthma Control Questionnaire score were dominant (all $P < .001$) predictors for both the risk of uncontrolled asthma and severe exacerbations. Additional dominant predictors for uncontrolled asthma were smoking status and asthma symptom scores and an additional

From ^athe Division of Pulmonology, Department of Medicine, University of Cape Town; ^bthe Pulmonary Department, Mainz University Hospital; ^cMichael G DeGroot School of Medicine, Faculty of Health Sciences, McMaster University, Hamilton; ^dUniversité Paris-Sud 11, Service de Pneumologie et Réanimation Respiratoire, Hôpital Antoine Bécélère, APHP, Clamart; ^ethe Clinical Management Group, Woolcock Institute of Medical Research, University of Sydney; ^fthe Respiratory Group, The George Institute for Global Health, Sydney; ^gthe Respiratory Research Unit, City Hospital Campus, Nottingham University; ^hthe Department of Allergy, Hospital La Paz Institute for Health Research (IdiPAZ), Madrid; ⁱStatMind AB, Lund; and ^jthe Department of Respiratory Medicine and Allergology, University Hospital, Lund.

The analysis was sponsored by AstraZeneca. E.D.B. has served as a consultant to ALK-Abelló, Almirall, Cephalon, Hoffman La Roche, ICON, and MS Consulting Group; been involved with advisory boards for Almirall, AstraZeneca, Boehringer Ingelheim, Elevation Pharma, Forest, GlaxoSmithKline, Merck, Napp, Novartis, and Nycomed; and received lecture fees from ALK-Abelló, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Pfizer, and Takeda; his institution has received remuneration for participation in clinical trials sponsored by Actelion, Aeras, Almirall, AstraZeneca, Boehringer Ingelheim, Forest, GlaxoSmithKline, Hoffman La Roche, Merck, Novartis, Takeda, and TEVA. S.P. and G.E. were employees of AstraZeneca at the time this analysis was conducted. The analysis was funded by AstraZeneca AB, Mölndal, Sweden.

Disclosure of potential conflict of interest: E. D. Bateman has received consulting fees from AstraZeneca for participation in a working group that performed analyses of databases that led to this paper; has received compensation for board membership from Almirall, AstraZeneca, Boehringer Ingelheim, Elevation Pharma, Forest, GlaxoSmithKline, Merck, Napp, Novartis, and Nycomed; has received consultancy fees from ALK-Abelló, Almirall, Cephalon, ICON, and MS Consulting Group; has received or has grants pending from Actelion, Aeras, Almirall, AstraZeneca, Boehringer Ingelheim, Forest, GlaxoSmithKline, Roche/Genentech, Merck, Novartis, Takeda, TEVA, and Cephalon; and has received payment for delivering lectures from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Pfizer, and Takeda, as well as from Novartis for the development of education presentations. R. Buhl has received compensation for board membership from AstraZeneca, Boehringer Ingelheim, Chiesi, Novartis, and Roche; has received or has grants pending from Boehringer Ingelheim, Novartis, and Roche; and has received compensation for delivering lectures from AstraZeneca, Boehringer Ingelheim, Chiesi, Grifols, GlaxoSmithKline, Novartis, Roche, and Takeda. P. M. O'Byrne has received compensation for board membership from the Joint Oversight Board for an LABA safety study, and has received consultancy fees from AstraZeneca, GlaxoSmithKline, Merck,

Boehringer, and Novartis and has received or has grants pending from AstraZeneca, Amgen, Genentech, Axikin, and Novartis. M. Humbert has received consultancy fees from AstraZeneca, GlaxoSmithKline, TEVA, Novartis, and Roche. H. K. Reddel has received consultancy fees from AstraZeneca for a face-to-face meeting at which this manuscript and other studies were discussed; has received compensation for board membership from AstraZeneca, GlaxoSmithKline, Merck, and Novartis; has received consultancy fees from AstraZeneca, Mundipharma, and Novartis; has received or has grants pending from GlaxoSmithKline and AstraZeneca; and has received payment for delivering lectures from AstraZeneca, GlaxoSmithKline, and Novartis. C. Jenkins has received consultancy fees from AstraZeneca, as well as support for travel and other meeting-related expenses; has received compensation for board membership from AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, Novartis, and Mundipharma; has also received consultancy fees from GlaxoSmithKline, Boehringer Ingelheim, Novartis, and Mundipharma; has received payment for delivering lectures from GlaxoSmithKline, Boehringer Ingelheim, AstraZeneca, Novartis, and Mundipharma and payment for the development of educational presentations from GlaxoSmithKline, Boehringer Ingelheim, AstraZeneca, Novartis, Mundipharma; and has also been paid an hourly rate for face-to-face individual consultations and for offering advice on regulatory issues for airways disease medications from GlaxoSmithKline, Boehringer Ingelheim, AstraZeneca, Novartis, and Mundipharma. T. W. Harrison has received compensation for being a member of the NAPP advisory board; his institution has received or has grants pending from AstraZeneca; he has received payment from AstraZeneca, GlaxoSmithKline, and Chiesi for delivering lectures; and he has received compensation for travel and other meeting-related expenses from Boehringer Ingelheim. S. Quirce has received payment for delivering lectures from GlaxoSmithKline, AstraZeneca, Chiesi, Boehringer Ingelheim, and MSD (Merck). S. Peterson is employed by AstraZeneca and has received compensation for employment from Novo Nordisk A/S and StatMind AB. G. Eriksson was previously employed by AstraZeneca, from which he also received stock/stock options, and has received consultancy fees from G.Erik Medical Consulting AB.

Received for publication March 11, 2014; revised August 22, 2014; accepted for publication August 25, 2014.

Corresponding author: Eric D. Bateman, MD, Division of Pulmonology, Department of Medicine, University of Cape Town, George Street, Mowbray 7700, Cape Town, South Africa. E-mail: Eric.Bateman@uct.ac.za.

0091-6749/\$36.00

© 2014 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaci.2014.08.015>

predictor for severe exacerbation was body mass index. An exponential increase in risk was observed with increments in RSE based on 5 selected predictors for exacerbations. Conclusion: Risk of uncontrolled asthma at 3 months and a severe exacerbation within 12 months can be estimated from simple clinical assessments. Prospective validation of these predictive factors and the RSE is required. Use of these models might guide the management of asthmatic patients. (J Allergy Clin Immunol 2014;■■■:■■■-■■■.)

Key words: Asthma, asthma control, budesonide/formoterol maintenance and reliever therapy, exacerbations, Global Initiative for Asthma, predictors, risk score

Typically, asthma management involves achieving and maintaining current asthma control and reducing risk, primarily prevention of asthma exacerbations.¹⁻³ A relationship between levels of control and minimization of future risk has previously been confirmed,⁴⁻⁸ supporting the need to achieve and maintain optimal control as a treatment priority. However, there are several reports of dissociation between current control and exacerbation risk.⁹⁻¹¹ Thus patients might achieve control but remain at risk of exacerbations and *vice versa*. Furthermore, patients with severe asthma usually do not achieve and maintain control; therefore treatment might primarily aim at reducing exacerbations. Several proposed measures can assist clinicians in their assessment of risk. Some measures are based on single predictors, such as FEV₁ or exacerbations in the previous year, and others are based on composites of several risk indicators. With the latter, indicators predicting failure to achieve symptomatic control might differ from those predicting exacerbations.^{12,13} Greenberg et al¹⁴ have recently developed and validated the Asthma Disease Activity Score (ADAS), which they propose for use in clinical trials to both separate treatment effects and predict future asthma attacks, thereby reducing sample size requirements; however, it is not suitable for clinical use. Clinical predictor tools are mainly used to guide clinical decision making, especially in patients with severe asthma, to identify those patients who might benefit from intensified and/or alternative treatments (eg, biological agents and bronchial thermoplasty) that primarily address future risk. Additionally, the use of such tools might reduce futile escalation of treatment in patients unlikely to achieve total symptomatic control.

We analyzed a large data set of asthmatic patients enrolled in studies examining the efficacy of budesonide/formoterol (BUD/FORM) as maintenance and reliever therapy (MRT) to determine factors that predict future risk of uncontrolled asthma and severe asthma exacerbations to develop a prediction tool for severe exacerbations (the risk score for exacerbations [RSE]). Because the database contained data from studies comparing different treatments, we assessed the strength and consistency of these associations in patients who received different treatment regimens.

METHODS

Studies

This retrospective analysis included data from 3 double-blind, randomized, parallel-group clinical studies¹⁵⁻¹⁷ of 6 or 12 months' duration for which several candidate predictors were available. The detailed methodologies of the studies are summarized in Table E1 in this article's Online Repository at www.jacionline.org. The studies investigated the efficacy of

Abbreviations used

ACQ-5: 5-Item Asthma Control Questionnaire
 ADAS: Asthma Disease Activity Score
 BMI: Body mass index
 BUD/FORM: Budesonide/formoterol
 GINA: Global Initiative for Asthma
 ICS: Inhaled corticosteroid
 LABA: Long-acting β_2 -agonist
 MRT: Maintenance and reliever therapy
 PEF: Peak expiratory flow
 RSE: Risk score for exacerbations
 SABA: Short-acting β_2 -agonist

BUD/FORM MRT compared with the following fixed-dose comparator therapies: (1) the same maintenance dose of inhaled corticosteroid (ICS)/long-acting β_2 -agonist (LABA; BUD/FORM [Symbicort; AstraZeneca AB, Mölndal, Sweden]) plus as-needed short-acting β_2 -agonist (SABA; terbutaline)¹⁷ or (2) a higher maintenance dose of ICS/LABA (BUD/FORM or salmeterol/fluticasone [Seretide; GlaxoSmithKline, Uxbridge, United Kingdom]) plus as-needed SABA (terbutaline).^{15,16} All drugs were administered through a Turbuhaler (AstraZeneca AB), with the exception of salmeterol/fluticasone, which was delivered through a Diskus¹⁶ or Evohaler¹⁵ (GlaxoSmithKline).

Patients and primary end points

Patients receiving Global Initiative for Asthma (GINA) treatment steps 3 and 4 with a prebronchodilator FEV₁ of 50% or greater of predicted normal value and 1 or more exacerbations (as judged by a clinician based on patient records, history, or both) in the previous year were enrolled. The same definition for an asthma exacerbation was used in each study. Participants were required to have uncontrolled asthma at the end of the run-in period. GINA-defined uncontrolled asthma was determined retrospectively from clinical data on patients' diaries from the last week of 3 months' treatment.¹⁸ All studies had time to first severe exacerbation, as the primary end point, which was defined as asthma worsening requiring 3 or more days of oral corticosteroids, emergency department treatment/hospitalization, or both. For univariate analyses, exacerbation data were analyzed for the whole treatment period (6 or 12 months) in each study to attain the highest power. For development of the RSE, these data were right censored and analyzed separately at 6 months to enable inclusion of the data from both the 6-month and 12-month studies.

Candidate predictors

The analysis included 16 patient and baseline characteristics at study entry (Table I).¹⁵⁻¹⁷ These were selected on the basis of availability within the data sets of all 3 studies, which used similar methodologies and inclusion/exclusion criteria, for ease and reliability of comparison. These characteristics were age, sex, body mass index (BMI; in kilograms per square meter), smoking status (current, previous, or never), time since asthma diagnosis (years), prebronchodilator and postbronchodilator FEV₁ percentage of predicted normal value, diurnal peak expiratory flow (PEF) variability, 5-item Asthma Control Questionnaire (ACQ-5) score (0-6, with 6 representing worst control),¹⁹ asthma symptom score (0-6, with 6 representing most symptoms), reliever use (occasions per day, where 1 occasion = 1 inhalation of terbutaline), number of nighttime awakenings with asthma symptoms, GINA treatment step (3 or 4 based on prestudy medication), prestudy ICS dose (beclomethasone dipropionate equivalents [chlorofluorocarbon] in micrograms per day), LABA use, and presence of allergic rhinitis. Mean PEF variability ([Morning PEF – Evening PEF]/Morning PEF), mean number of nighttime awakenings, mean total daily asthma symptom score, and mean total daily reliever use were calculated for the last 10 days of the run-in period. The exacerbation history was not included in the model because all participants had 1 or more exacerbations in the previous year.

TABLE I. Pooled demographic and baseline data by treatment group

	BUD/FORM maintenance + reliever therapy (n = 3172)	Fixed maintenance dose ICS/LABA + SABA (n = 4274)	All (n = 7446)
Male sex, no. (%)	1286 (41)	1733 (41)	3019 (41)
Mean age (y; SD [range])	39.7 (16.5 [12-89])	39.4 (17.0 [12-83])	39.5 (16.8 [12-89])
Mean BMI (kg/m ² [SD])	25.8 (5.5)	25.9 (5.6)	25.8 (5.6)
Smoking status, no. (%)			
Never	2518 (79)	3388 (79)	5906 (79)
Previous	488 (15)	642 (15)	1130 (15)
Current	166 (5)	244 (6)	410 (6)
History of allergic rhinitis, no. (%)	1131 (36)	1473 (34)	2604 (35)
Mean ICS dose (BDP μ g/day [SD])*	1100 (0.4)	1100 (0.4)	1100 (0.4)
LABA use, no. (%)	1689 (53)	2200 (51)	3889 (52)
Mean asthma duration (y [SD])	14.7 (12.7)	14.6 (12.9)	14.6 (12.8)
Mean ACQ-5 score (points [SD])	1.9 (0.9)	1.9 (0.9)	1.9 (0.9)
Mean prebronchodilator FEV ₁ (% PN [SD])	71.8 (13.4)	72.1 (13.9)	72.0 (13.7)
Mean as-needed reliever use (occasions/d [SD])†	2.1 (1.3)	2.2 (1.4)	2.2 (1.4)
Mean asthma symptom score (points [SD])	1.9 (0.9)	1.9 (0.9)	1.9 (0.9)
Nighttime awakenings (% [SD])	32.3 (34.5)	31.6 (34.4)	31.9 (34.4)
Mean diurnal PEF variability (% [SD])	8.4 (6.4)	8.3 (6.2)	8.3 (6.3)
GINA treatment step, no. (%)			
3	1685 (53)	2245 (53)	3930 (53)
4	1487 (47)	2029 (47)	3516 (47)

Patients' demographic and medication (calculation of GINA treatment step) data were collected at study entry. Prebronchodilator and postbronchodilator FEV₁ and ACQ-5 scores were assessed at randomization, whereas PEF and asthma symptom scores were collected 7 $\pm$ 10 (mean $\pm$ SD) days before randomization. All patients had experienced 1 or more exacerbations in the 12 months before study entry. PEF variability was calculated as follows: (Morning PEF – Evening PEF)/Morning PEF.

BDP, Beclomethasone dipropionate equivalents (chlorofluorocarbon); PN, predicted normal value.

*Different preparations of ICSs were standardized to chlorofluorocarbon BDP equivalents.

†One occasion represents 1 inhalation of terbutaline administered through a Turbuhaler.

Statistical analyses

The statistical analysis steps are summarized in Table E2 in this article's Online Repository at www.jacionline.org. First, identification of individual predictors was performed by using a univariate model. The odds of a patient having uncontrolled asthma were assessed by using a logistic regression model, with study and treatment as fixed factors in the basal design. Time to first severe asthma exacerbation was determined by using a basic Cox regression model stratified by study and treatment (BUD/FORM MRT vs fixed-dose maintenance ICS/LABA plus SABA in each study).

The final selection of predictors was performed by using a multiple regression model to assess potential covariation among the predictors. From this full multiple regression model, predictors were identified by using a backward selection method ranked by *P* values in the logistic regression model for uncontrolled asthma or in the Cox regression model for exacerbations.²⁰ By using this selection by *P* value, the predictive factor judged to have the smallest influence was removed and the process was repeated on the remaining predictors until a final model was determined in which no predictor could be excluded in a single-step fashion; that is, *P* values for the remaining predictors were all less than .05. Dominant predictors were defined by a *P* value of less than .001. Imputation with median values was used for missing baseline variables to obtain the same number of patients for each baseline predictor in the analysis; however, the frequency of missing data at baseline was generally low (<1%).

The potentially nonlinear nature of the risk profile of each identified predictor for uncontrolled asthma and exacerbations was further described with adaptive nonlinear curves (splines) as interaction by treatment (BUD/FORM MRT versus fixed-dose maintenance ICS/LABA plus SABA) and adjusted for study.²⁰

RSE

The complete data set was split 2:1 into an analysis data set used to develop the formula and a validation data set to test the performance of the RSE in predicting the likelihood of an exacerbation in the next 6 months for construction of the RSE. An RSE score was constructed based on the dominant predictors and then using categorization of continuous variables in a

complementary log-log logistic regression model, adjusting for individual treatment duration.²⁰ Continuous variables were categorized based on previous literature and clinical relevance and guided by using visual spline analysis, with rounding where appropriate (eg, BMI was categorized as ≥ 30 vs <30 kg/m²). The RSE score was standardized to a maximal sum of 100, where a higher score represented a higher risk of exacerbation within 6 months. The agreement between the likelihood of exacerbations predicted by the RSE score and the actual exacerbation incidence recorded prospectively for the same patients was assessed by dividing the analysis and validation data set into 10 and 5 groups (approximately 500 patients per group), respectively, with increasing RSE scores.

RESULTS

Study populations and baseline demographics

Demographic and baseline data were similar between the 2 treatment groups (BUD/FORM MRT, n = 3172; fixed-dose ICS/LABA, n = 4274); mean age was 39.5 years, 59% were female, mean time since asthma diagnosis was 14.6 years, and 79% of patients had never smoked. The mean prebronchodilator FEV₁ was 72.0%, and the mean ACQ-5 score at randomization was 1.9 (Table I).

Predictors for uncontrolled asthma after 3 months

The univariate analysis of baseline predictors for the risk of uncontrolled asthma at 3 months showed that 8 of the 16 baseline variables were significant (see Table E3 in this article's Online Repository at www.jacionline.org). The multivariate analysis (obtained by using Cox regression) with backward *P* value selection identified 6 dominant baseline predictors (*P* < .001) associated with uncontrolled asthma: mean asthma symptom scores, mean daily number of as-needed reliever inhalations, postbronchodilator FEV₁, smoking status (current vs never

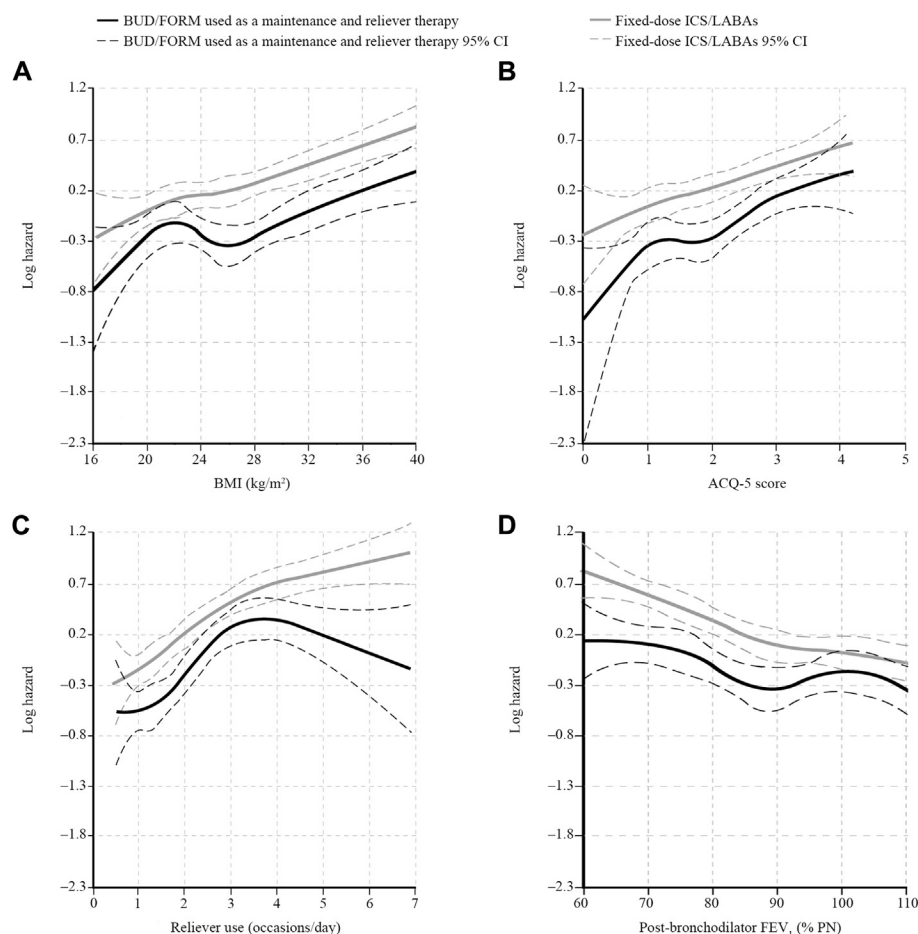


FIG 1. Baseline continuous variables BMI (A), ACQ-5 score (B), reliever use (C), and postbronchodilator FEV₁ (D) as spline predictors for the log for hazard of a severe asthma exacerbation in the next 3 months. PN, Predicted normal value.

Baseline variable	OR/RC (95% CI)
Mean asthma symptom score, 0–6 *	1.57 (1.45, 1.69)
Mean as-needed reliever use, occasions/day ^a *	1.22 (1.16, 1.28)
ACQ-5 score, 0–6 ^b *	1.19 (1.12, 1.27)
Post-bronchodilator FEV ₁ , 10% PN ^c †	1.10 (1.07, 1.14)
Smoking status †	
Previous vs never	1.33 (1.16, 1.53)
Current vs never	1.92 (1.53, 2.41)
GINA treatment Step (4 vs 3) †	1.33 (1.20, 1.47)

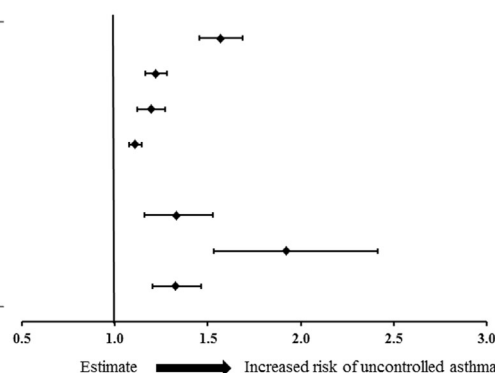


FIG 2. Dominant ($P < .001$) baseline predictors for the risk of uncontrolled asthma at 3 months in patients receiving GINA treatment steps 3 or 4 at enrollment and 1 or more exacerbations in the previous 12 months. ^aPer 1 occasion per day higher use of budesonide/formoterol or SABA use (terbutaline). ^bPer 0.5-point lower ACQ-5 score. ^cPer 10% lower postbronchodilator FEV₁ (percentage of PN). *RC, Regression coefficient. †OR, Odds ratio. PN, Predicted normal value.

smokers and previous vs never smokers), ACQ-5 score, and GINA step (4 vs 3, Fig 1). Diurnal PEF variation, nighttime awakenings, and sex were also statistically significant but were deselected during backward selection to a P value of less than .001.

A higher baseline level of symptoms, measured either as ACQ-5 or mean asthma symptom scores, increased the risk (9% per 0.5 unit and 56% per symptom score unit, respectively) of uncontrolled asthma at 3 months. Higher use of reliever medication increased the risk by 22% per each additional

Baseline variable	HR (95% CI)
GINA treatment Step (4 vs 3)	1.60 (1.40, 1.83)
Mean as-needed reliever use, occasions/day ^a	1.15 (1.10, 1.21)
Post-bronchodilator FEV ₁ , 10% PN ^b	1.11 (1.06, 1.16)
ACQ-5 score, 0–6 ^c	1.08 (1.04, 1.13)
Body mass index, kg/m ² ^d	1.10 (1.04, 1.17)

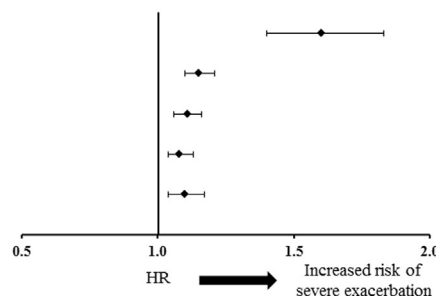


FIG 3. Dominant ($P < .001$) baseline predictors for a severe asthma exacerbation within the next 6 months in patients receiving GINA treatment steps 3 or 4 at enrollment and 1 or more exacerbations in the previous 12 months. ^aPer 1 occasion per day higher use of budesonide/formoterol or SABA use (terbutaline). ^bPer 10% lower postbronchodilator FEV₁ (percentage of PN). ^cPer 0.5-point higher ACQ-5 score. ^dPer 5-kg/m² higher BMI. HR, Hazard ratio; PN, predicted normal value.

TABLE II. Risk score for exacerbations

Baseline variable	Value	Normalized score*
BMI (kg/m ²)	<30	—
	≥30	14
ACQ-5 score (points [range, 0–6])	<1.5	—
	1.5–2.5	7
	≥2.5	13
Postbronchodilator FEV ₁ (% PN)	≥90%	—
	80% to 90%	13
	<80%	20
Reliever use (occasions/d) [†]	<2	—
	2–4	11
	≥4	26
GINA treatment step	3	—
	4	27

PN, Predicted normal value.

*Scores were adjusted to provide a maximum achievable score of 100.

[†]One occasion represents 1 inhalation of terbutaline or budesonide/formoterol used as reliever.

inhalation per day independent of symptoms. Lower lung function (10% higher risk per 10% decrement in postbronchodilator FEV₁ at baseline) and smoking (current vs never, 92%; previous vs never, 33%) also increased the risk (Fig 2). GINA step 4 treatment at baseline was associated with 33% higher risk of uncontrolled asthma versus GINA step 3 treatment ($P < .001$).

Predictors of severe asthma exacerbations

Results of the univariate analysis of the risk for a severe asthma exacerbation within 12 months associated with different baseline features are presented in Table E4 in this article's [Online Repository](http://www.jacionline.org) at www.jacionline.org. Fifteen of 16 variables were shown to be statistically significant, with only a positive history of allergic rhinitis being nonsignificant. The multivariate analysis with a backward P value selection method (using a threshold P value of $< .001$) yielded 5 dominant baseline predictors of increased exacerbation risk within 12 months: GINA treatment step, mean daily number of as-needed reliever inhalations, postbronchodilator FEV₁, ACQ-5 score, and BMI (Fig 3). An increased number of nighttime awakenings caused by asthma symptoms was also predictive of increased exacerbation risk ($P < .05$).

The higher risk of an exacerbation for each of the dominant predictors was as follows: 60% higher risk for patients receiving GINA step 4 versus step 3 treatment; 15% higher risk with each as-needed reliever inhalation per day; 10% higher risk for each 10% lower postbronchodilator value for FEV₁; 8% higher risk for each increase of 0.5 units in the ACQ-5 score; and 10% higher risk for each increase of 5 units in BMI at baseline (Fig 3).

Risk score for asthma exacerbation within 6 months

The risk formula for an asthma exacerbation based on the dominant risk factors is shown in Table II. A plot of the predicted risk of an exacerbation calculated for different treatments and expressed as the proportion of patients who will experience an exacerbation during this period is presented in Fig 4, A. The risk of exacerbation within 6 months predicted by the RSE score was approximately 5% to 40% for an RSE score of 0 to 100. The risk curves by treatment show that BUD/FORM MRT was associated with a lower risk over the entire score range than the fixed-dose ICS/LABA groups (Fig 4, A). After adjusting for all selected predictors, BUD/FORM was estimated to decrease the exacerbation risk by 32% versus the fixed-dose ICS/LABA arms.

The estimated risk shows good agreement with the actual outcome in most patient groups in the analysis and validation data sets (Fig 4, B).

DISCUSSION

In this analysis of data pooled from several similarly designed studies, we have identified clinical factors that are associated with not achieving a satisfactory level of current asthma control (defined by GINA as uncontrolled asthma). Similarly, we have identified clinical factors associated with increased risk for severe exacerbations requiring treatment with oral corticosteroids, emergency department treatment/hospitalization, or both. By examining factors associated with increased risk of an exacerbation, we have developed an RSE for identifying patients at higher risk of future asthma exacerbations. We have validated the latter in a separate cohort of patients from the same clinical trials. As expected, some factors associated with a greater likelihood of uncontrolled asthma were also associated with asthma exacerbation risk; these included mean daily reliever use, ACQ-5 score, postbronchodilator FEV₁, and GINA step at

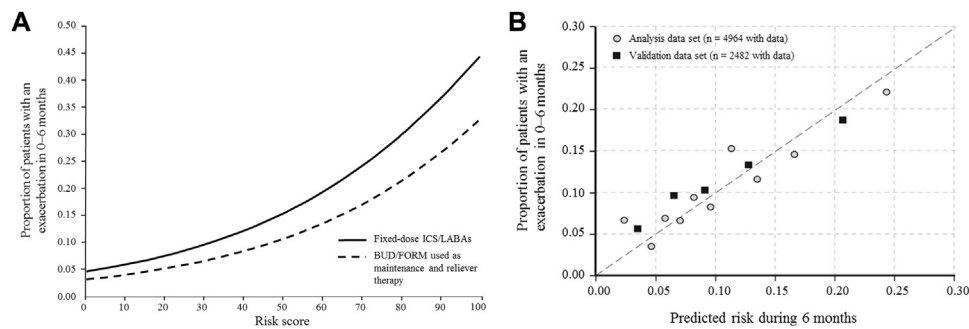


FIG 4. Risk of exacerbation over 6 months based on baseline RSE comparing BUD/FORM MRT with fixed-dose combination treatment of a LABA plus an ICS (**A**) and validation of the risk score formula (**B**). The analysis data set included two thirds of the cohort of patients divided by 10 percentiles in point score, with each group comprising approximately 500 patients. The validation data set, which comprised one third of the cohort, was divided into 5 groups, with approximately 500 patients in each group.

enrollment. However, there were significant differences in the strengths of these associations between the 2 outcomes, and additional end points emerged as significant for each. Whereas the baseline level of symptoms correlated inversely with the likelihood of achieving current asthma control (also termed “impairment”) independent of ACQ-5 score, it did not predict exacerbation risk. Similarly, past or current smoking increased the likelihood of uncontrolled asthma but did not affect exacerbation risk. GINA treatment step at enrollment identified both impairment and exacerbations but was by far the strongest predictor of exacerbation risk. High BMI emerged as an additional risk factor for exacerbations but did not influence the likelihood of uncontrolled asthma.

Factors associated with achieving asthma control in patients treated with ICS or ICS/LABA therapy have previously been reported in the Gaining Optimal Asthma Control study.²¹ In both the current analysis and the Gaining Optimal Asthma Control study, patients with even a modest history (<10 pack years) of smoking, past or current, were less likely to achieve satisfactory asthma control. Patients receiving GINA step 4 treatment were also less likely to achieve good control, providing support for considering the prior treatment step as both a descriptor of asthma “severity” and a predictor of likely future treatment response. However, it should be noted that the majority of patients in the current trials had uncontrolled symptoms on step 3 or 4 treatment at randomization. The finding that baseline postbronchodilator rather than prebronchodilator FEV₁ percent predicted both control and exacerbation risk is consistent with the fact that postbronchodilator FEV₁ represents persistent airflow limitation, which is also a feature of severe and/or partially refractory asthma, whereas prebronchodilator FEV₁ is usually considered a marker of adequacy of controller treatment. Exacerbation history, a strong predictor of future exacerbations in other analyses, was not included in the model because all participants had 1 or more exacerbations in the previous year. Finally, the association between BMI and exacerbation risk is of interest because the obese asthmatic phenotype is usually associated with high levels of persistent symptoms refractory to controller treatment rather than exacerbation risk.^{10,22-24} It is not clear whether increased BMI is a consequence of treatment (including frequent use of systemic corticosteroids) or caused by other, more complex associations between obesity and asthma.^{23,25,26}

The fact that measures that predict future clinical asthma control and exacerbations might differ supports other sources.^{7,27} We have previously reported a separate analysis of 5 asthma trials, some of which have been included in the current analysis, comparing fixed high-dose ICS and 2 doses of ICS/LABA and ICS/LABA MRT.⁷ In that analysis current levels of control reduced future risk and different treatments, and treatment approaches differed in their effect on stability of asthma control versus their influence on exacerbation rates.⁷ The proportion of patients achieving and maintaining good control over 6 or 12 months (as defined either by ACQ-5 scores or GINA categories of current control) with high-dose ICS, ICS/LABA, and MRT treatment were similar, but higher ICS doses reduced exacerbation rates more than lower ICS and LABA doses. The MRT regimen achieved the greatest reduction in exacerbation rates. This dissociation between different components of future risk, relatively independent from likelihood of sustained clinical control, is also evident in clinical trials of new asthma treatments, including bronchial thermoplasty,²⁸ omalizumab,²⁹ mepolizumab,³⁰ and tiotropium,³¹ in patients receiving step 3 or 4 treatment. This underlines the need to assess all components of “risk” (daily control, exacerbations, and lung function loss, as well as adverse effects) when evaluating new treatments.

The study of predictors of the future course of disease and events in both asthmatic children and adults has recently progressed. Some predictors are proposed for clinical use, but most are intended for application in research. Associations have been reported between various clinical and psychometric measures, and future clinical status and health care use (emergency department visits, oral corticosteroid use, and SABA use).^{4,6,32-35} These measures range from clinical features, such as symptoms, PEF, and exacerbation history,^{27,36} to complex validated tools, such as the Asthma Control Test, ACQ, Asthma Therapy Assessment Questionnaire, Asthma Quality of Life Questionnaire, Asthma Impact Survey, Asthma Outcomes Monitoring System, and non-disease-specific measures (eg, the Short-Form 12-item questionnaire).^{4,6,32-35,37} The use of biomarkers reflecting airway inflammation (eg, induced sputum examination and fractional exhaled nitric oxide measurement) has also been studied, either alone or in combination with clinical features. However, relatively few of the measures proposed have been evaluated with regard to their effect on the success of treatment. Their obvious application is likely to be in patients with severe or

relatively refractory asthma and in children in whom prediction of exacerbations is particularly problematic. Simple validated tools or risk scores have been developed for use in children.³⁸ Recently, Greenberg et al¹⁴ reported the development and validation of ADAS-6 and ADAS-4 as sensitive measures of asthma activity and predictors of future asthma attacks in clinical trials of patients 15 years and older. Novel features are the weighting applied to each component, but the requirement for a detailed once- or twice-daily asthma diary data make it unsuitable for clinical use. Our results differ in some respects from those reported by Osborne et al,³⁷ who developed a tool for classifying asthmatic patients as being at low, moderate, or high risk for acute health care use. In this group of patients receiving a variety of treatments, prebronchodilator FEV₁ was the strongest predictor, and among the modifiable risk factors examined, current cigarette smoke exposure was the strongest predictor of exacerbations requiring health care use. The differences between these results and ours might be explained by our analysis focusing on high-risk patients, all of whom had impaired lung function, current treatment with ICSs or ICSs/LABAs, and 1 or more exacerbations in the previous year, together with the exclusion of heavy smokers. In addition, we did not include cigarette smoke exposure but only personal use of tobacco.

The prediction of treatment outcome might be particularly useful and could guide selection of therapy for patients whose asthma symptoms are uncontrolled by current treatment, such as those in the current analysis, all of whom were receiving moderate-to-high ICS doses and 52% of whom were receiving LABAs (GINA steps 3 or 4), with an asthma exacerbation in the previous year. In such patients, achievement of optimal current asthma control might be less likely, and treatments that are more effective in reducing exacerbation rates might be considered. Thus although the findings of the current analysis and RSE developed cannot be extrapolated or applied to the wider asthmatic population, a limitation of the analysis, its potential application is clear. However, this requires prospective evaluation.

The RSE, which was developed and validated in our large cohort of patients, provides an estimate of the risk of exacerbation over 6 months ranging from low (5%) to high (40%) risk. In theory, risk can be improved either by addressing modifiable predictive factors or by changing treatment to one that reduces exacerbation risk. Of the predictors of poor response to treatment, only smoking status can be altered. On the basis of risk assessment, treatment can be changed to one that targets a specific component of risk: lack of control, exacerbation risk, or both. The comparison of effect of different treatments on exacerbation risk across different RSE scores (Fig 4, A) confirms the potential value of this approach.

Our analysis has strengths, including its size and the completeness of our data, the consistent clinically relevant end points, the clinical category of asthmatic patients selected, and the ability to compare different treatments. Weaknesses are that it is a *post hoc* analysis and that the GINA-defined levels of control were derived from data obtained from patients' diaries. Furthermore, the assessment of clinical asthma control was based on a 1-week assessment at 3 months, which might not adequately represent long-term control. However, our previous analysis of duration of control in this cohort has confirmed that asthma control is sustained and that most patients who achieve satisfactory control do so within 3 months, with relatively fewer additional patients

achieving satisfactory control thereafter.^{7,39} The ACQ-5, one of the components of the RSE for predicting exacerbations, has been developed for clinical use but is not commonly used.⁴⁰ Finally, in the validation study we compared MRT with pooled data from other controller treatment groups (fixed daily dosing with moderate and high ICS/LABA doses) and therefore are unable to provide separate risk curves for each of the individual treatment options. This requires further study. Furthermore, this model needs to be tested prospectively in a wider real-life setting in patients with varying degrees of asthma severity and with a variety of treatment regimens.

In conclusion, we have demonstrated differences in the factors that predict the likelihood of achieving and maintaining satisfactory daily clinical control of asthma and future exacerbation risk in at-risk patients who have not achieved a satisfactory level of daily asthma control with previous treatment. Furthermore, we have developed and validated an RSE that, although requiring prospective evaluation in other cohorts, might prove useful for comparing the efficacy of different treatments in improving asthma exacerbation risk across a range of risk categories and for identifying patients who require treatment to reduce the risk of exacerbations.

We thank Malin Fagerås and Anders Persson, AstraZeneca R&D, Mölndal, Sweden, for their assistance with the development of the RSE and this manuscript. Anna Mett from inScience Communications, Springer Healthcare, provided editorial assistance on behalf of AstraZeneca.

Clinical implications: For patients at risk of future severe asthma exacerbations, and/or whose asthma may be less responsive to treatment, improved prediction of treatment outcomes might serve as a guide to management.

REFERENCES

- Bateman ED, Hurd S, Barnes P, Bousquet J, Drazen J, FitzGerald M, et al. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008;31:143-78.
- Eid N. Update on National Asthma Education and Prevention Program pediatric asthma treatment recommendations. *Clin Pediatr* 2004;43:793-802.
- Reddel H, Taylor D, Bateman E, 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.
- Vollmer W, Markson L, O'Connor E, Frazier E, Berger M, Buist A. Association of asthma control with healthcare utilization: a prospective evaluation. *Am J Respir Crit Care Med* 2002;165:195-9.
- Miller MK, Lee JH, Miller DP, Wenzel SE. TENOR Study Group. Recent asthma exacerbations: a key predictor of future exacerbations. *Respir Med* 2007;101:481-9.
- Sullivan SD, Wenzel SE, Bresnahan BW, Zheng B, Lee JH, Pritchard M, et al. Association of control and risk of severe asthma-related events in severe or difficult-to-treat asthma patients. *Allergy* 2007;62:655-60.
- Bateman ED, Reddel HK, Eriksson G, Peterson S, Ostlund O, Sears MR, et al. Overall asthma control: the relationship between current control and future risk. *J Allergy Clin Immunol* 2010;125:600-8.
- Bateman E, Bousquet J, Busse W, Clark T, Gul N, Gibbs M, et al. Stability of asthma control with regular treatment: an analysis of the Gaining Optimal Asthma control (GOAL) study. *Allergy* 2008;63:932-8.
- Blakey JD, Woolnough K, Fellows J, Walker S, Thomas M, Pavord ID. Assessing the risk of attack in the management of asthma: a review and proposal for revision of the current control-centered paradigm. *Prim Care Respir J* 2013;22:344-52.
- Haldar P, Pavord I, Shaw D. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008;178:218-24.
- Lazarus SC, Boushey HA, Fahy JV, Chinchilli VM, Lemanske RF Jr, Sorkness CA, et al. Long-acting beta2-agonist monotherapy vs continued therapy with inhaled

- corticosteroids in patients with persistent asthma: a randomized controlled trial. *JAMA* 2001;285:2583-93.
12. Green R, Brightling C, McKenna S, Hargadon B, Parker D, Bradding P, et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet* 2002;360:1715-21.
 13. Wu A, Tantisira K, Li L, Schuemann B, Weiss S, Fuhlbrigge A. Predictors of symptoms are different from predictors of severe exacerbations from asthma in children. *Chest* 2011;140:100-7.
 14. Greenberg S, Lui N, Kaur A, Lakshminarayanan M, Zhou Y, Nelsen L, et al. The asthma disease activity score: a discriminating, responsive measure predicts future asthma attacks. *J Allergy Clin Immunol* 2012;130:1071-7.
 15. Kuna P, Peters MJ, Manjra AI, Jorup C, Naya IP, Martinez-Jimenez NE, et al. Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations. *Int J Clin Pract* 2007;61:725-36.
 16. Bousquet J, Boulet LP, Peters MJ, Magnussen H, Quirarte J, Martinez-Aguilar NE, et al. Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone. *Respir Med* 2007;101:2437-46.
 17. Rabe KF, Atienza T, Magyar P, Larsson P, Jorup C, Lalloo UG. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. *Lancet* 2006;368:744-53.
 18. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention 2006 revision. Available at: http://www.ginasthma.org/documents/5/documents_variants/31. Accessed January 23, 2014.
 19. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999;14:902-7.
 20. Harrell FE. Regression modeling strategies: with applications to linear models, logistic regression, and survival analysis. 2nd ed. New York (NY): Springer; 2001.
 21. Pedersen S, Bateman E, Bousquet J, Busse W, Yoxall S, Clark T. Determinants of response to fluticasone propionate and salmeterol/fluticasone propionate combination in the Gaining Optimal Asthma Control Study. *J Allergy Clin Immunol* 2007;120:1036-42.
 22. Lavoie K, Bacon S, Labrecque M, Cartier A, Ditto B. Higher BMI is associated with worse asthma control and quality of life but not asthma severity. *Respir Med* 2006;100:648-57.
 23. Mosen D, Schatz M, Magid D, Camargo CJ. The relationship between obesity and asthma severity and control in adults. *J Allergy Clin Immunol* 2008;122:507-11.
 24. Peters-Golden M, Swern A, Bird S, Hustad C, Grant E, Edelman J. Influence of body mass index on the response to asthma controller agents. *Eur Respir J* 2006;27:495-503.
 25. Farah C, Kermode J, Downie S, Brown N, Hardaker K, Berend N, et al. Obesity is a determinant of asthma control independent of inflammation and lung mechanics. *Chest* 2011;140:659-66.
 26. Pakhale S, Doucette S, Vandemheen K, Boulet L, McIvor R, Fitzgerald J, et al. A comparison of obese and nonobese people with asthma: exploring an asthma-obesity interaction. *Chest* 2010;137:1316-23.
 27. Covar R, Szeffler S, Zeiger R, Sorkness C, Moss M, Mauger D, et al. Factors associated with asthma exacerbations during a long-term clinical trial of controller medications in children. *J Allergy Clin Immunol* 2008;122:741-7.
 28. O'Byrne P, Naji N, Gauvreau G. Severe asthma: future treatments. *Clin Exp Allergy* 2012;42:706-11.
 29. Hanania NA, Wenzel S, Rosen K, Hsieh HJ, Mosesova S, Choy DF, et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. *Am J Respir Crit Care Med* 2013;187:804-11.
 30. Pavord I, Korn S, Howarth P, Bleecker E, Buhl R, Keene O, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012;380:651-9.
 31. Kerstjens H, Engel M, Dahl R, Paggiaro P, Beck E, Vandewalker M, et al. Tiotropium in asthma poorly controlled with standard combination therapy. *N Engl J Med* 2012;367:1198-207.
 32. Schatz M, Mosen D, Apter A, Zeiger R, Vollmer W, Stibolt T, et al. Relationship of validated psychometric tools to subsequent medical utilization for asthma. *J Allergy Clin Immunol* 2005;115:564-70.
 33. Schatz M, Zeiger R, Drane A, Harden K, Cibildak A, Oosterman J, et al. Reliability and predictive validity of the Asthma Control Test administered by telephone calls using speech recognition technology. *J Allergy Clin Immunol* 2007;119:336-43.
 34. Schatz M, Zeiger R, Mosen D, Vollmer W. Asthma-specific quality of life and subsequent asthma emergency hospital care. *Am J Manag Care* 2008;14:206-11.
 35. Schatz M, Zeiger R, Yang S-J, Chen W, Crawford W, Sajjan S, et al. The relationship of asthma impairment determined by psychometric tools to future exacerbations. *Chest* 2012;141:66-72.
 36. Tierney W, Roesner J, Seshadri R, Lykens M, Murray M, Weinberger M. Assessing symptoms and peak expiratory flow rate as predictors of asthma exacerbations. *J Gen Intern Med* 2004;19:237-42.
 37. Osborne M, Pedula K, O'Hollaren M, Ettinger K, Stibolt T, Buist A, et al. Assessing future need for acute care in adult asthmatics: the Profile of Asthma Risk Study: a prospective health maintenance organization-based study. *Chest* 2007;132:1151-61.
 38. Forno E, Fuhlbrigge A, Soto-Quirós M, Avila L, Raby B, Brehm J, et al. Risk factors and predictive clinical scores for asthma exacerbations in childhood. *Chest* 2010;138:1156-65.
 39. O'Byrne P, Reddel H, Eriksson G, Östlund O, Peterson S, Sears M, et al. Measuring asthma control: a comparison of three classification systems. *Eur Respir J* 2010;36:269-76.
 40. Juniper EF, Svensson K, Mörk A, Ståhl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respir Med* 2005;99:553-8.

TABLE E1. Summary of the 3 clinical trials used in this *post hoc* analysis

Study	Treatment arms	Study duration (mo)	No.	Mean ICS (μg/d [BDP equivalent])*†	Study code
Rabe et al, 2006 ¹⁷	BUD/FORM maintenance + reliever (160/4.5 μg BID + as needed) vs BUD/FORM (160/4.5 μg BID) + terbutaline 0.4 mg or FORM 4.5 μg [†] as needed	12	1113	483 (755)	SD-039-0734
			2281	320 (500)	
Kuna et al, 2007 ¹⁵	BUD/FORM maintenance + reliever (160/4.5 μg BID + as needed) vs BUD/FORM (320/9 μg BID) + terbutaline 0.4 mg as needed SAL/FLU (2 × 25/125 μg BID) + terbutaline 0.4 mg as needed	6	1107	483 (755)	SD-039-0735
			1105	640 (1000)	
			1123	500 (1000)	
Bousquet et al, 2007 ¹⁶	BUD/FORM maintenance + reliever (2 × 160/4.5 μg BID + as needed) vs SAL/FLU (50/500 μg BID) + terbutaline 0.4 mg as needed	6	1154	792 (1238)	NCT00242775
			1155	1000 (2000)	

BDP, Beclomethasone dipropionate; BID, twice daily; BUD, budesonide; FORM, formoterol; FLU, fluticasone; SAL, salmeterol.

*Different preparations of ICSs were standardized to chlorofluorocarbon BDP equivalents. All patients had experienced 1 or more exacerbations.

†Only data from the terbutaline as-needed arm were included in the present analysis (n = 1141); data from the FORM as-needed arm (n = 1140) were excluded.

TABLE E2. Summary of the statistical analysis steps

Analysis of both uncontrolled asthma at 3 mo and severe asthma exacerbations within 12 mo were performed in the following sequence:

1. Univariate analysis was used to assess the individual effect of the candidate set of predictors.
2. Multiple regression analysis was performed with a backward stepwise selection method to select a more manageable set of predictors from the full model. A full model that included all predictors was estimated, followed by the steps below:
 - A. The smallest P value ($= P_{min}$) of the predictors is obtained.
 - B. If P_{min} is less than .05, go to step (E); otherwise, go to step (C).
 - C. Remove the predictor associated with the highest P value.
 - D. Calculate new coefficients that include the remaining predictors and go to step (A).
 - E. Final model is selected.

TABLE E3. Univariate analysis (n = 7446) of baseline predictors for GINA-defined uncontrolled asthma at 3 months

Baseline variable	Comparison	OR (95% CI)	<i>P</i> value
Mean daily asthma symptom score		1.614 (1.495-1.743)	<.001
Mean as-needed daily reliever use		1.219 (1.161-1.280)	<.001
ACQ-5 score		1.234 (1.155-1.318)	<.001
Smoking status*	Previous vs never	1.271 (1.101-1.467)	.001
	Current vs never	1.839 (1.463-2.311)	<.001
Diurnal PEF variability		1.014 (1.006-1.022)	<.001
Postbronchodilator FEV ₁		0.991 (0.984-0.997)	.004
Nighttime awakenings		0.997 (0.996-0.999)	.004
Sex	Female vs male	0.888 (0.801-0.985)	.025
GINA treatment step	4 vs 3	1.184 (0.981-1.429)	.078
History of allergic rhinitis	Yes vs no	0.919 (0.828-1.021)	.114
LABA use	Yes vs no	1.145 (0.951-1.378)	.154
ICS dose		1.058 (0.927-1.208)	.401
Age		1.001 (0.998-1.005)	.407
Duration of asthma diagnosis		1.001 (0.997-1.005)	.620
BMI		0.998 (0.988-1.007)	.641
Prebronchodilator FEV ₁		1.001 (0.993-1.008)	.820

PEF variability was calculated as follows: (Morning PEF – Evening PEF)/Morning PEF. The base model is a logistic regression stratified by study and treatment. The degree of freedom is 1 for all parameters, with the exception of smoking status (ie, 2).
OR, Odds ratio.

*Overall *P* value for smoking status is less than .001.

TABLE E4. Univariate analysis (n = 7446) of baseline predictors for a severe asthma exacerbation within 12 months

Baseline variable	Comparison	HR (95% CI)	P value
Mean as-needed daily reliever use		1.212 (1.166-1.260)	<.001
GINA treatment step	4 vs 3	1.796 (1.575-2.047)	<.001
Postbronchodilator FEV ₁		0.855 (0.820-0.892)	<.001
Age		1.014 (1.010-1.018)	<.001
LABA use	Yes vs no	1.619 (1.417-1.849)	<.001
BMI		1.039 (1.028-1.050)	<.001
ACQ-5 score		1.262 (1.180-1.349)	<.001
Mean daily asthma symptom score		1.243 (1.165-1.326)	<.001
Prebronchodilator FEV ₁		0.984 (0.979-0.989)	<.001
ICS dose		1.447 (1.260-1.661)	<.001
Diurnal PEF variability		1.208 (1.111-1.314)	<.001
Duration of asthma diagnosis		1.010 (1.005-1.014)	<.001
Smoking status*	Previous vs never	1.321 (1.119-1.559)	.001
	Current vs never	1.435 (1.120-1.838)	.004
Sex	Female vs male	1.265 (1.107-1.446)	<.001
Nighttime awakenings		1.003 (1.001-1.004)	.005
History of allergic rhinitis	Yes vs no	0.974 (0.851-1.114)	.702

The base model is a Cox regression analysis, stratified by treatment. PEF variability was calculated as follows: (Morning PEF – Evening PEF)/Morning PEF. The degree of freedom is 1 for all parameters, with the exception of smoking status (ie, 2).

HR, Hazard ratio.

*Overall P value for smoking status is less than .001.