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Development and validation of a novel risk score for asthma exacerbations, the RSE

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Abstract

Background: Identifying patients at risk of future severe asthma exacerbations and/or whose asthma may be less treatment responsive may guide selection of treatment.

Objective: To investigate predictors for failure to achieve 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 dataset from three studies comparing budesonide/formoterol maintenance and reliever therapy with fixed-dose ICS/LABA 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 three studies, was based on the dominant predictors for exacerbations in two-thirds of the dataset and validated in one-third.

Results: Patients (n = 7,446) not controlled on GINA treatment Steps 3–4 and with ≥1 exacerbation (as judged by a clinician based on patient records and/or history) in the previous year were included. On multivariate analysis, GINA Step, reliever use, post-bronchodilator FEV_1, and ACQ-5 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 score, and for severe exacerbations, body mass index. An exponential increase in risk was observed with increments in RSE, based on five 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 may guide asthma patient management.

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.

Capsule summary

Asthma features predicting failure to achieve asthma control and risk of a severe exacerbation within 12 months were used to develop a risk score for exacerbations (RSE) for prospective use in higher-risk patients.

Key words

Asthma, asthma control, budesonide/formoterol maintenance and reliever therapy, exacerbations, GINA, predictors, risk score.

Abbreviations used

ACQ-5: 5-item Asthma Control Questionnaire;

ADAS: Asthma Disease Activity Score;

BDP: beclomethasone dipropionate equivalents (chlorofluorocarbon);

BMI: body mass index;

BUD: budesonide;

FEV_1: forced expiratory volume in 1 second

FORM: formoterol;

GINA: Global Initiative for Asthma;

GOAL: Gaining Optimal Asthma controL study;

HR: hazard ratio;

ICS: inhaled corticosteroid;

LABA: long-acting β_2-agonist;

MRT: maintenance and reliever therapy;

OR: odds ratio;

PEF: peak expiratory flow;

PN: predicted normal;

RC: regression coefficient;

RSE: risk of severe exacerbation;

SABA: short-acting β_2-agonist.

Introduction

Typically, the management of asthma 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. Further, patients with severe asthma usually fail to achieve and maintain control; therefore, treatment may primarily aim at reducing exacerbations. Several proposed measures can assist clinicians in their assessment of risk. Some measures are based on single predictors, e.g., forced expiratory volume in 1 second (FEV_1) or exacerbations in the previous year, others on composites of several risk indicators; with the latter, indicators predicting failure to achieve symptomatic control may differ from those predicting exacerbations.[12, 13] Greenberg *et al*. 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;[14] it is, however, not suitable for clinical use. Clinical predictor tools are mainly used to guide clinical decision making, especially in severe asthma to identify those patients who may benefit from intensified and/or alternative treatments (e.g., biologicals, bronchial thermoplasty) that primarily address future risk. Additionally, the use of such tools may reduce futile escalation of treatment in patients unlikely to achieve total symptomatic control.

We analyzed a large dataset of patients with asthma 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, in order to develop a prediction tool for severe exacerbations (risk score for exacerbations [RSE]). Since 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 three double-blind, randomized, parallel-group clinical studies[15-17] 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 the Online Repository. The studies investigated the efficacy of BUD/FORM MRT compared with the following fixed-dose comparator therapies: i) the same maintenance dose of inhaled corticosteroid/long-acting β_2-agonist (ICS/LABA; BUD/FORM [Symbicort®, AstraZeneca AB, Mölndal, Sweden]) plus as-needed short-acting β_2-agonist (SABA; terbutaline)[17] or ii) a higher maintenance dose of ICS/LABA (BUD/FORM or salmeterol/fluticasone [Seretide®, GlaxoSmithKline, Uxbridge, UK]) plus as-needed SABA (terbutaline).[15, 16] All drugs were administered via Turbuhaler® (AstraZeneca AB, Mölndal, Sweden) with the exception of salmeterol/fluticasone, which was delivered via Diskus™[16] or Evohaler™[15] (GlaxoSmithKline, Uxbridge, UK).

Patients and primary endpoints

Patients receiving Global Initiative for Asthma (GINA) treatment Step 3–4 with a pre-bronchodilator FEV_1 ≥50% of predicted normal and ≥1 exacerbation (as judged by a clinician based on patient records and/or history) 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 run-in. GINA-defined uncontrolled asthma was determined retrospectively from clinical data on patient diaries from the last week of 3 months' treatment.[18] All studies had, as the primary endpoint, time to first severe exacerbation, defined as asthma worsening requiring ≥3 days of oral corticosteroids and/or emergency-room treatment/hospitalization. For univariate analyses, to attain the highest power, exacerbation data were analyzed for the whole treatment period (6 or 12 months) in each study. For development of the RSE, in order to enable inclusion of the data from both the 6-month- and 12-month studies, these data were right-censored and analyzed separately at 6 months.

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 datasets of all three studies, which used similar methodologies and inclusion/exclusion criteria, for ease and reliability of comparison. These characteristics were age, gender, body mass index (BMI, kg/m^2), smoking status (current, previous, never), time since asthma diagnosis (years), pre- and post-bronchodilator FEV_1 percentage of predicted normal, 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 = one inhalation of terbutaline), number of night-time awakenings with asthma symptoms, GINA treatment Step (3 or 4, based on pre-study medication), pre-study ICS dose (beclomethasone dipropionate equivalents [chlorofluorocarbon], μg/day), LABA use, and presence of allergic rhinitis. Mean PEF variability ([morning PEF–evening PEF]/morning PEF), mean number of night-time 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. Exacerbation history,was not included in the model since all participants had ≥1 exacerbation in the previous year.

Statistical analyses

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

The final selection of predictors was performed using a multiple regression model to assess potential co-variation among the predictors. From this full multiple regression model, predictors were identified by 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] Using this selection by *P*-value, the predictive factor judged to have the smallest influence was removed and the process 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 < 0.05. Dominant predictors were defined by a *P*-value < .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 non-linear nature of the risk profile of each identified predictor, for uncontrolled asthma and exacerbations, was further described with adaptive non-linear curves (splines) as interaction by treatment (BUD/FORM MRT versus fixed-dose maintenance ICS/LABA plus SABA) and adjusted for study.[20]

Risk score for exacerbations (RSE)

In order to construct the RSE, the complete dataset was split 2:1 into an analysis dataset used to develop the formula, and a validation dataset to test the performance of the RSE in predicting the likelihood of an exacerbation in the next 6 months. A RSE score was constructed based on the dominant predictors and then

using categorization of continuous variables in a complementary loglog logistic regression model, adjusting for individual treatment duration.[20] Continuous variables were categorized based on previous literature and clinical relevance, and guided by visual spline analysis, with rounding where appropriate (e.g., BMI was categorized as ≥ versus <30 kg/m^2). 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 dataset into 10 and 5 groups (~500 patients/group) with increasing RSE, respectively.

Results

Study populations and baseline demographics

Demographic and baseline data were similar between the two treatment groups (BUD/FORM MRT, n = 3172; fixed-dose ICS/LABA, n = 4274); mean age was 39.5 years, 59% were females, mean time since asthma diagnosis was 14.6 years, and 79% of patients had never smoked. The mean pre-bronchodilator FEV_1 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 eight of the 16 baseline variables were significant (see Table E3a in the Online Repository). The multivariate analysis (obtained by Cox regression) with backward *P*-value selection identified six dominant baseline predictors ($P < .001$) associated with uncontrolled asthma: mean asthma symptom scores, mean daily number of as-needed reliever inhalations, post-bronchodilator FEV_1, smoking status (current versus never-smokers and previous versus never-smokers), ACQ-5 score, and GINA Step (4 versus 3) (Fig 1). Diurnal PEF variation, night-time awakenings, and gender were also statistically significant but were deselected during backward selection to $P < .001$.

A higher baseline level of symptoms, measured either as ACQ-5 or mean asthma symptom score, 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 inhalation per day, independent of symptoms. Lower lung function (10% higher risk per 10% decrement in post-bronchodilator FEV_1 at baseline) and smoking (current versus never, 92%; previous versus 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 ($P < .001$).

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 E3b in the Online Repository. Fifteen of 16 variables were shown to be statistically significant, only a positive history of allergic rhinitis being non-significant. The multivariate analysis with backward *P*-value selection method (using a threshold *P*-value of < .001) yielded five dominant baseline predictors of increased exacerbation risk within 12 months: GINA treatment Step, mean daily number of as-needed reliever inhalations, post-bronchodilator FEV_1, ACQ-5 score, and BMI (Fig 3). An

increased number of night-time awakenings due to 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 on GINA Step 4 versus Step 3; 15% higher risk with each as-needed reliever inhalation per day; 10% higher risk for each 10% lower post-bronchodilator value for FEV_1; 8% higher risk for each increase of 0.5 unit 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 4A. The risk of exacerbation within 6 months predicted by the RSE score was approximately 5–40% for a RSE score of 0–100. 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 4A). 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 4B).

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 and/or emergency-room treatment/hospitalization. By examining factors associated with increased risk of an exacerbation, we have developed a 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, post-bronchodilator FEV_1, and GINA Step at enrolment. However, there were significant differences in the strength of these associations between the two outcomes, and additional endpoints 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 impact exacerbation risk. GINA treatment Step at enrolment 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 have previously been reported in the Gaining Optimal Asthma controL (GOAL) study.[21] In both the current analysis and the GOAL study, patients with even a modest history (<10 pack-years) of smoking, past or current, were less likely to achieve satisfactory asthma control. Patients on GINA Step 4 treatment were also less likely to achieve good control providing support for considering prior treatment step as both a descriptor of asthma "severity" and a predictor of likely future treatment response. It should be noted, however, that the majority of patients in the current trials were uncontrolled on Step 3 or 4 treatment at randomization. The finding that baseline post- rather than pre-bronchodilator FEV_1 predicted both control and exacerbation risk is consistent with the fact that the post-bronchodilator FEV_1 represents persistent airflow limitation, also a feature of severity and/or partially refractory asthma, while the pre-bronchodilator FEV_1 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 since all participants had ≥1 exacerbation in the previous year. Finally, the association between BMI and exacerbation risk is of interest since 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 due to other, more complex, associations between obesity and asthma.[23, 25, 26]

The fact that measures that predict future clinical asthma control and exacerbations may differ supports other sources.[7, 27] We have previously reported a separate analysis of five asthma trials, some of which have been included in the current analysis, comparing fixed high-dose ICS, and two 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 impact 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/LABAs, and MRT were similar, but higher doses of ICS reduced exacerbation rates more than lower doses of ICS and LABA. 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 in patients receiving Step 3 or 4 treatment.[31] 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 children and adults with asthma 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 healthcare utilization (emergency unit visits, oral corticosteroid use, and SABA use).[4, 6, 32-35] These measures range from clinical features like symptoms, PEF, and exacerbation history,[27, 36] to complex validated tools like 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 (e.g., the Short Form-12 questionnaire).[4, 6, 32-35, 37] The use of biomarkers reflecting airway inflammation (e.g., 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 impact 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 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.[14] Novel features are the weighting applied to each component, but the requirement for 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.*, who developed a tool for classifying asthmatics as being at low, moderate, or high risk for acute healthcare utilization.[37] In this group of patients receiving a variety of treatments, pre-bronchodilator FEV_1 was the strongest predictor; and, amongst the modifiable risk factors examined, current cigarette-smoke exposure was the strongest predictor of exacerbations requiring healthcare utilization. The differences between these results and ours may be explained by our analysis focusing on high-risk patients, all of whom had impaired lung function, current treatment with ICS or ICS/LABA and ≥1 exacerbation 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 may be particularly useful and could guide selection of therapy for patients whose asthma is uncontrolled on current treatment, such as those in the current analysis, all of whom were on moderate-to-high doses of ICS and 52% on LABA (GINA Steps 3 or 4), with an asthma exacerbation in the previous year. In such patients, achievement of optimal current asthma control may be less likely, and treatments that are more effective in reducing exacerbation rates may be considered. Thus, while the findings of the current analysis and RSE developed cannot be extrapolated or applied to the wider asthma population – a limitation of the analysis – its potential application is clear. However, this requires prospective evaluation.

The RSE, developed and validated in our large cohort of patients, provides an estimate of the risk of exacerbation over 6 months ranging from low risk (5%) to high risk (40%). 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 may be changed to one that targets a specific component of risk: lack of control and/or exacerbation risk. The comparison of impact of different treatments on exacerbation risk across different RSE scores (Fig 4A) confirms the potential value of this approach.

Our analysis has strengths, including its size and the completeness of data, the consistent clinically relevant endpoints, the clinical category of asthma 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 patient diaries. Further, the assessment of clinical asthma control was based on a 1-week

assessment at 3 months, which may 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 doses of ICS/LABA), and so 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 on previous treatment. Further, 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.

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Tables

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, n (%)	1286 (41)	1733 (41)	3019 (41)
Mean age, years (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, n (%)			
Never	2,518 (79)	3,388 (79)	5,906 (79)
Previous	488 (15)	642 (15)	1,130 (15)
Current	166 (5)	244 (6)	410 (6)
History of allergic rhinitis, n (%)	1,131 (36)	1,473 (34)	2,604 (35)
Mean ICS dose, BDP µg/day (SD)*	1,100 (0.4)	1,100 (0.4)	1,100 (0.4)
LABA use, n (%)	1,689 (53)	2,200 (51)	3,889 (52)
Mean asthma duration, years (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 pre-bronchodilator FEV_1, % PN (SD)	71.8 (13.4)	72.1 (13.9)	72.0 (13.7)
Mean as-needed reliever use, occasions/day (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)
Night-time 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, n (%)			
3	1685 (53)	2245 (53)	3930 (53)
4	1487 (47)	2029 (47)	3516 (47)

Patients' demographic data and medication (calculation of GINA treatment Step) were collected at study entry. Pre- and post-bronchodilator FEV_1 and the ACQ-5 score were assessed at randomization, while PEF and asthma symptom scores were collected mean (SD) 7 (±10) days before randomization. All patients had experienced ≥1 exacerbation in the 12 months prior to study entry. PEF variability was calculated as: (morning PEF–evening PEF)/morning PEF.

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

** One occasion represents one inhalation of terbutaline administered via a Turbuhaler®.

ACQ-5, 5-item Asthma Control Questionnaire; *BDP,* beclomethasone dipropionate equivalents (chlorofluorocarbon); *BMI,* body mass index; *BUD/FORM,* budesonide/formoterol; *FEV_1,* forced expiratory volume in 1 second; *GINA,* Global Initiative for Asthma; *ICS,* inhaled corticosteroid; *LABA,* long-acting β_2-agonist; *PEF,* peak expiratory flow; *PN,* predicted normal; *SABA,* short-acting β_2-agonist.

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
Post-bronchodilator FEV_1, % PN	≥90%	–
	80–90%	13
	<80%	20
Reliever use, occasions/day**	<2	–
	2–4	11
	≥4	26
GINA treatment Step	3	–
	4	27

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

** One occasion represents one inhalation of terbutaline, or budesonide/formoterol used as reliever.

ACQ-5, 5-item Asthma Control Questionnaire; *BMI,* body mass index; *FEV_1,* forced expiratory volume in 1 second; *GINA,* Global Initiative for Asthma; *PN,* predicted normal.

Table E1. Summary of the three clinical trials used in this *post-hoc* analysis

Study	Treatment arms	Study duration (months)	N	Mean ICS µg/day (BDP equiv)*†	Study code
Rabe *et al*. 2006[14]	BUD/FORM maintenance + reliever (160/4.5 µg BID + as needed) vs	12	1113	483 (755)	SD-039-0734
	BUD/FORM (160/4.5 µg BID) + terbutaline 0.4 mg or FORM 4.5 µg† as needed		2281	320 (500)	
Kuna *et al*. 2007[12]	BUD/FORM maintenance + reliever (160/4.5 µg BID + as needed) vs	6	1107	483 (755)	SD-039-0735
	BUD/FORM (320/9 µg BID) + terbutaline 0.4 mg as needed		1105	640 (1000)	
	SAL/FLU (2 x 25/125 µg BID) + terbutaline 0.4 mg as needed		1123	500 (1000)	
Bousquet *et al*. 2007[13]	BUD/FORM maintenance + reliever (2 × 160/4.5 µg BID + as needed) vs	6	1154	792 (1238)	NCT00242775
	SAL/FLU (50/500 µg BID) + terbutaline 0.4 mg as needed		1155	1000 (2000)	

† Only data from the terbutaline as-needed arm were included in the present analysis (n = 1,141); data from the FORM as-needed arm (n = 1,140) were excluded. * Different preparations of ICS were standardized to chlorofluorocarbon BDP equivalents. All patients had experienced ≥1 exacerbation.

BDP, beclomethasone dipropionate; *BUD,* budesonide; *FORM,* formoterol; *FLU,* fluticasone; *ICS,* inhaled corticosteroid; *LABA,* long-acting β_2-agonist; *SAL,* salmeterol.

Table E2. Summary of the statistical analysis steps

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

1) Univariate analysis to assess the individual impact of the candidate set of predictors.

2) In order to select a more manageable set of predictors from the full model, multiple regression analysis was performed using a backward stepwise selection method. A full model that included all predictors was estimated, followed by the steps below:

a) the smallest *P*-value (= *Pmin*) of the predictors was obtained

b) if *Pmin* < 0.05, 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 selected.

Table E3a. Univariate analysis (n = 7446) of baseline predictors for GINA-defined uncontrolled asthma at 3 months. The base model is a logistic regression, stratified by study and treatment

Baseline variable	Comparison	OR (95% CI)	*P* 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
Post-bronchodilator FEV_1		0.991 (0.984, 0.997)	.004
Night-time awakenings		0.997 (0.996, 0.999)	.004
Gender	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
Pre-bronchodilator FEV_1		1.001 (0.993, 1.008)	.820

PEF variability was calculated as: (morning PEF–evening PEF)/morning PEF.

The degrees of freedom is one for all parameters, with the exception of smoking status (two).

* Overall *P*-value for smoking status is < .001.

ACQ-5, 5-item Asthma Control Questionnaire; *BMI,* body mass index; *FEV_1,* forced expiratory volume in 1 second; *GINA,* Global Initiative for Asthma; *ICS,* inhaled corticosteroid; *LABA,* long-acting β_2-agonist; *OR,* odds ratio; *PEF,* pulmonary expiratory flow.

Table E3b. Univariate analysis (n = 7446) of baseline predictors for a severe asthma exacerbation within 12 months. The base model is a Cox regression analysis, stratified by treatment

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
Post-bronchodilator 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
Pre-bronchodilator 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
Gender	Female vs male	1.265 (1.107, 1.446)	< .001
Night-time awakenings		1.003 (1.001, 1.004)	.005
History of allergic rhinitis	Yes vs no	0.974 (0.851, 1.114)	.702

PEF variability was calculated as: (morning PEF–evening PEF)/morning PEF.

The degrees of freedom is one for all parameters, with the exception of smoking status (two).

* Overall *P*-value for smoking status is < .001.

ACQ-5, 5-item Asthma Control Questionnaire; *BMI,* body mass index; *FEV_1,* forced expiratory volume in 1 second; *GINA,* Global Initiative for Asthma; *HR,* hazard ratio; *ICS,* inhaled corticosteroid; *LABA,* long-acting β_2-agonist.

Figure legends

FIG 1. Baseline continuous variables (A) BMI, (B) ACQ-5 score, (C) reliever use, and (D) post-bronchodilator FEV_1 as spline predictors for the log for hazard of a severe asthma exacerbation in the next 3 months.

ACQ-5, 5-item Asthma Control Questionnaire; *BMI,* body mass index; *BUD/FORM,* budesonide/formoterol; *FEV_1,* forced expiratory volume in 1 second; *ICS,* inhaled corticosteroid; *LABA,* long-acting β_2-agonist; *PN,* predicted normal.

FIG 2. Dominant ($P < .001$) baseline predictors for the risk of uncontrolled asthma at 3 months in patients on GINA treatment Steps 3 or 4 at enrolment and ≥1 exacerbation in the previous 12 months. [a] Per 1 occasion/day higher use of budesonide/formoterol or short-acting β_2-agonist use (terbutaline); [b] per 0.5-point lower ACQ-5 score; [c] per 10% lower post-bronchodilator FEV_1 (% of PN); * regression coefficient; † odds ratio.

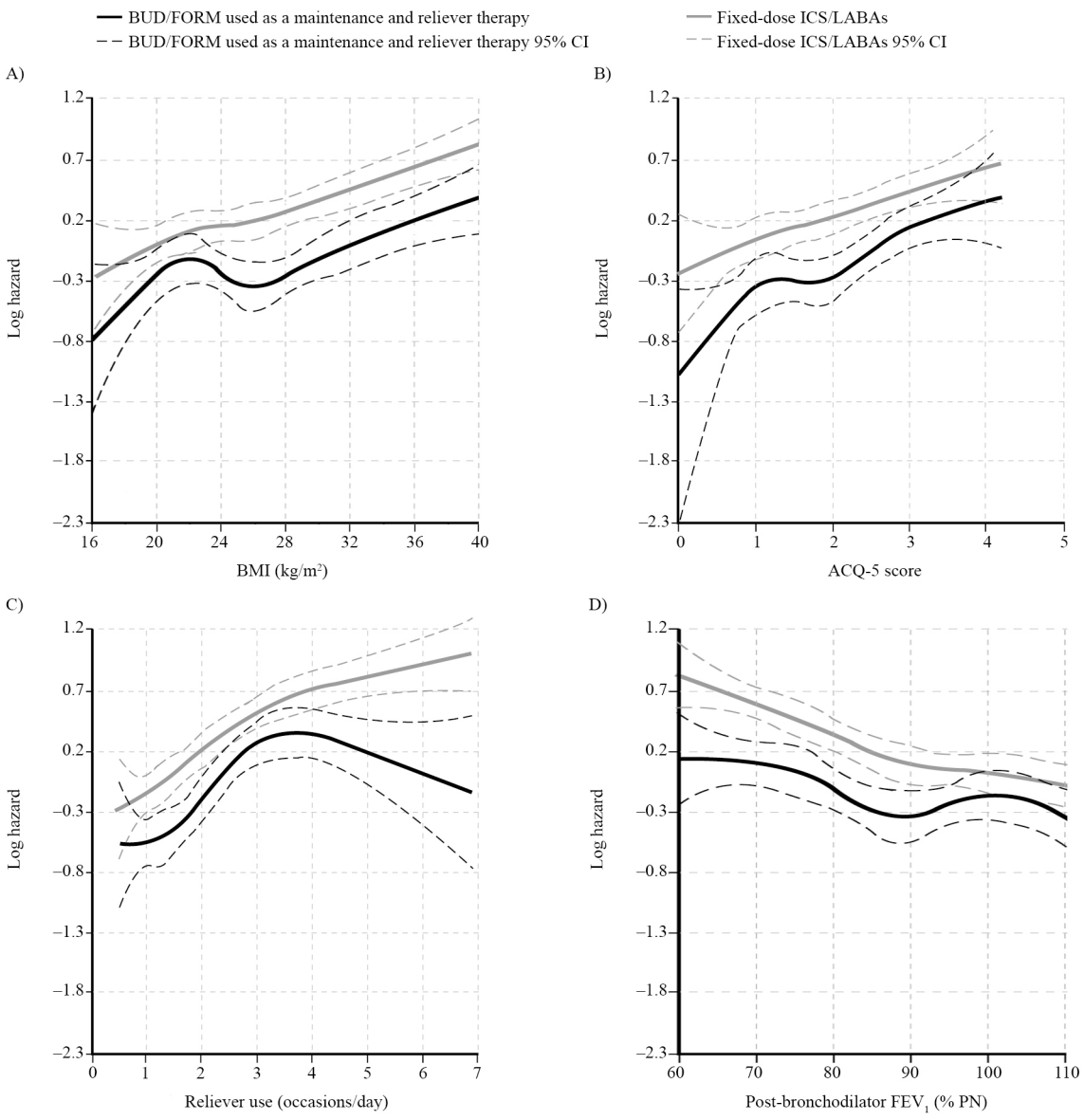
ACQ-5, 5-item Asthma Control Questionnaire; *FEV_1,* forced expiratory volume in 1 second; *GINA,* Global Initiative for Asthma; *PN,* predicted normal.

FIG 3. Dominant ($P < .001$) baseline predictors for a severe asthma exacerbation within the next 6 months in patients on GINA treatment Steps 3 or 4 at enrolment and ≥1 exacerbation in the previous 12 months. [a] Per 1 occasion/day higher use of budesonide/formoterol or short-acting β_2-agonist use (terbutaline); [b] per 10% lower post-bronchodilator FEV_1 (% of PN); [c] per 0.5-point higher ACQ-5 score; per 5-kg/m^2 higher BMI.

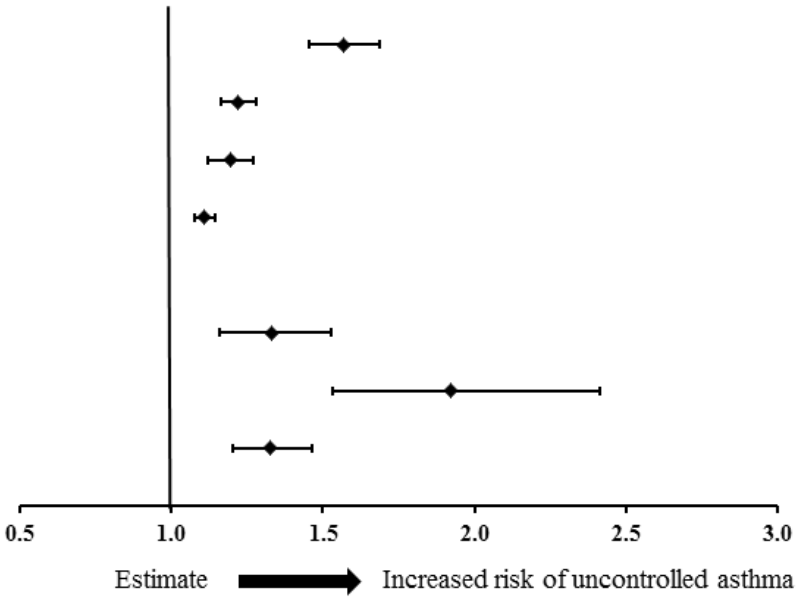
ACQ-5, 5-item Asthma Control Questionnaire; *FEV_1,* forced expiratory volume in 1 second; *GINA,* Global Initiative for Asthma; *HR,* hazard ratio; *PN,* predicted normal.

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

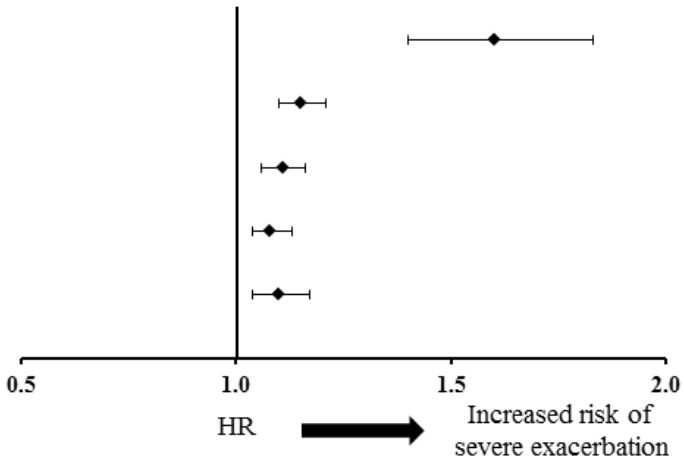
BUD, budesonide; *FORM,* formoterol; *ICS,* inhaled corticosteroid; *LABA,* long-acting β_2-agonist; *RSE,* risk of severe exacerbation.

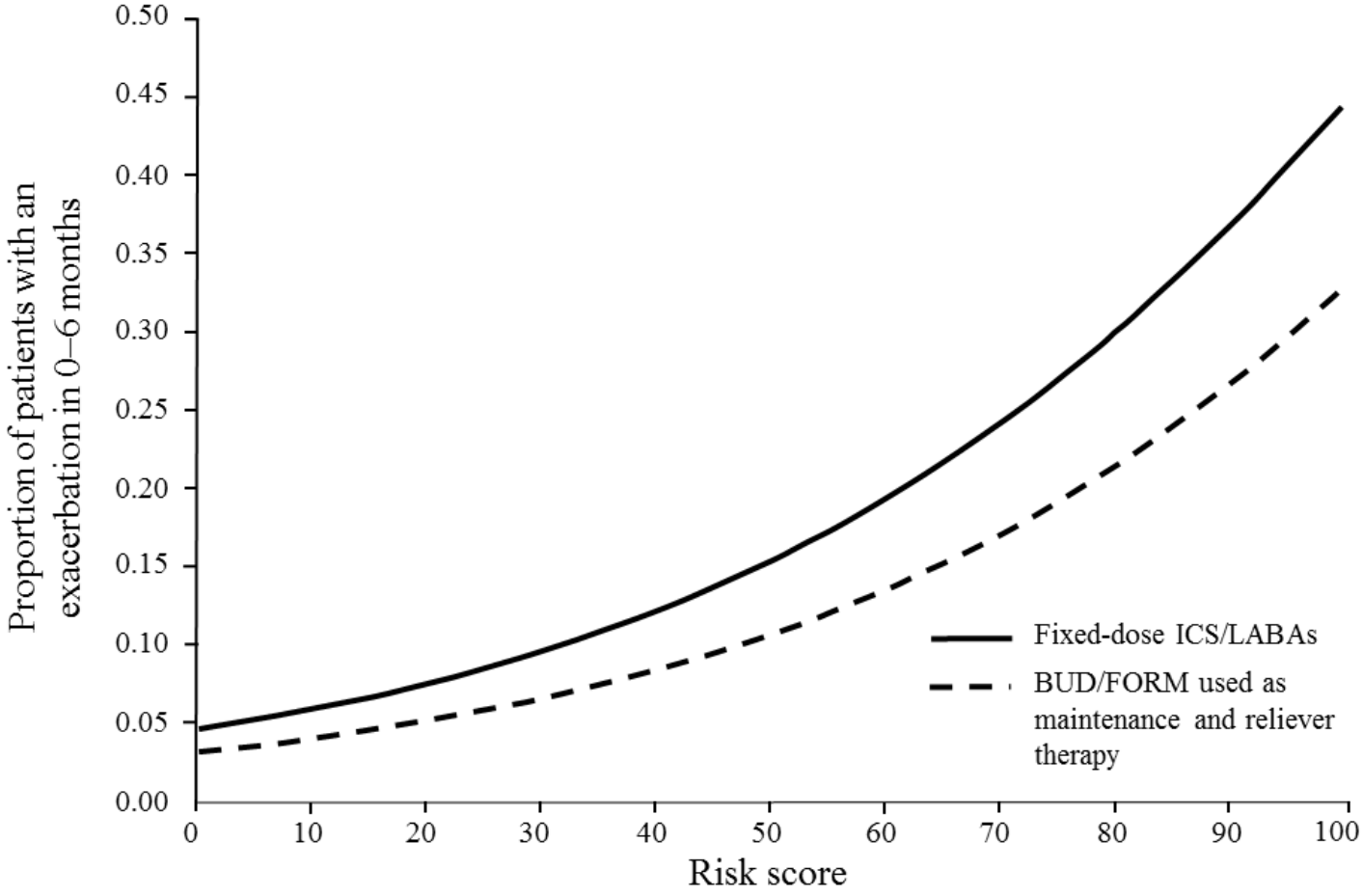

BUD/FORM used as a maintenance and reliever therapy
BUD/FORM used as a maintenance and reliever therapy 95% CI
Fixed-dose ICS/LABAs
Fixed-dose ICS/LABAs 95% CI
A)
B)
C)
D)
Log hazard
1.2
0.7
0.2
–0.3
–0.8
–1.3
–1.8
–2.3
16 20 24 28 32 36 40
BMI (kg/m²)
0 1 2 3 4 5
ACQ-5 score
0 1 2 3 4 5 6 7
Reliever use (occasions/day)
60 70 80 90 100 110
Post-bronchodilator FEV1 (% PN)

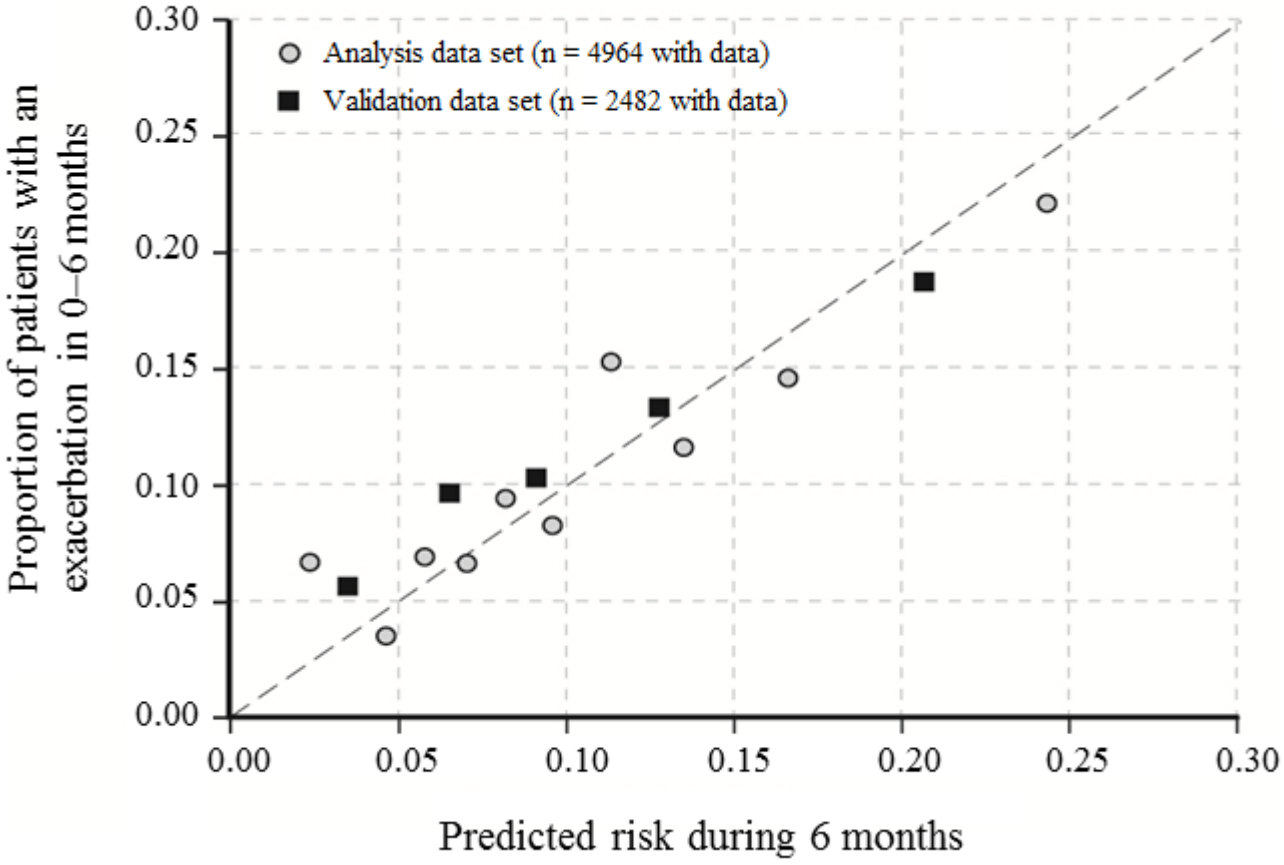
Baseline variable	OR/RC (95% CI)
Mean asthma symptom score, 0–6 *	1.57 (1.45, 1.69)
Mean as-needed reliever use, occasions/day[a] *	1.22 (1.16, 1.28)
ACQ-5 score, 0–6[b] *	1.19 (1.12, 1.27)
Post-bronchodilator FEV_1, 10% PN[c] †	1.10 (1.07, 1.14)
Smoking status †	
Previous vs never	1.33 (1.16, 1.53)
Current vs never	1.92 (1.53, 2.41)
GINA treatment Step (4 vs 3) †	1.33 (1.20, 1.47)



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)




Proportion of patients with an exacerbation in 0–6 months
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
0
10
20
30
40
50
60
70
80
90
100
Risk score
Fixed-dose ICS/LABAs
BUD/FORM used as maintenance and reliever therapy


Analysis data set (n = 4964 with data)
Validation data set (n = 2482 with data)
Proportion of patients with an exacerbation in 0–6 months
Predicted risk during 6 months
0.00
0.05
0.10
0.15
0.20
0.25
0.30