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

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**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 $\beta_2$-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 $FEV_1$, 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**

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**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 $FEV_1$ 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 al[14] 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 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 this article's Online Repository at www.jacionline.org. The studies investigated the efficacy of BUD/FORM MRT compared with the following fixed-dose comparator therapies: (1) the same maintenance dose of inhaled corticosteroid (ICS)/long-acting $\beta_2$-agonist (LABA; BUD/FORM [Symbicort; AstraZeneca AB, Mölndal, Sweden]) plus as-needed short-acting $\beta_2$-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 Diskus[16] or Evohaler[15] (GlaxoSmithKline).

*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 $\beta_2$-agonist
MRT: Maintenance and reliever therapy
PEF: Peak expiratory flow
RSE: Risk score for exacerbations
SABA: Short-acting $\beta_2$-agonist

### Patients and primary end points

Patients receiving Global Initiative for Asthma (GINA) treatment steps 3 and 4 with a prebronchodilator $FEV_1$ 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 $FEV_1$ 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.

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