

A Simple Score for Future Risk Prediction in Patients with Controlled Asthma Who Undergo a Guidelines-Based Step-Down Strategy



Luis Pérez de Llano, MD, PhD^a, Juan Luis García-Rivero, MD^b, Isabel Urrutia, MD, PhD^c, Eva Martínez-Moragón, MD, PhD^d, Jacinto Ramos, MD, PhD^e, Pilar Cebollero, MD, PhD^f, Francisco Carballada, MD, PhD^g, Marina Blanco-Aparicio, MD, PhD^h, María del Carmen Vennera, MD^{i,j,k}, María Merino, MSc^l, Yolanda Torralba-García, NR, MSc^{i,j,k}, and Vicente Plaza, MD, PhD^m *Lugo, Cantabria, Bizkaia, València, Salamanca, Navarra, A Coruña, Madrid, and Barcelona, Spain*

What is already known about this topic? International guidelines recommend that once asthma control is achieved and maintained for at least 3 months, clinicians should consider stepping-down treatment, but this approach carries an unpredictable risk of clinical deterioration.

What does this article add to our knowledge? We have developed a readily usable tool composed of 4 items (a medical-record documented postbronchodilator spirometry result of less than 70% forced expiratory volume in one second [FEV₁]/forced vital capacity, current FEV₁ < 80% predicted, ≥1 severe exacerbation in the prior 12 months, and Asthma Control Test score <25) to predict step-down failure in patients with asthma who are being considered for this strategy.

How does this study impact current management guidelines? This score helps clinicians to balance the benefits of stepping-down treatment with the risk of asthma control loss in a specific patient.

^aPneumology Service, Hospital Lucus Augusti, Lugo, Spain

^bPneumology Service, Hospital Comarcal de Laredo, Cantabria, Spain

^cPneumology Service, Hospital de Galdakao, Bizkaia, Spain

^dPneumology Service, Hospital Universitario Doctor Peset, València, Spain

^ePneumology Service, Complejo Asistencial de Salamanca, Salamanca, València, Spain

^fPneumology Service, Complejo Hospitalario de Navarra, Navarra, Spain

^gAllergology Unit, Hospital Lucus Augusti, Lugo, Spain

^hPneumology Service, Complejo Hospitalario Universitario A Coruña (CHUAC), A Coruña, Spain

ⁱServei de Pneumologia i Allèrgia Respiratòria, Hospital Clínic, Universitat de Barcelona, Barcelona, Spain

^jInstitut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

^kCentro de Investigaciones Biomédicas en Red de Enfermedades Respiratorias (CIBERES), Barcelona, Spain

^lHealth Outcomes Research Department, Weber, Economía y Salud, Madrid, Spain

^mDepartment of Respiratory Medicine, Hospital de la Santa Creu i Sant Pau, Institut d'Investigació Biomèdica Sant Pau (IIB Sant Pau), Universitat Autònoma de Barcelona, Department of Medicine, Barcelona, Spain

The study was funded by a grant from the Spanish Respiratory Society. The design, analysis, and writing of this report are entirely the work and responsibility of the authors, and L. P. de Llano had full access to all data and final responsibility for the decision to submit this work for publication.

Conflicts of interest: L. P. de Llano reports personal fees and nonfinancial support from Novartis, GlaxoSmithKline (GSK), Boehringer-Ingelheim, and Mundipharma; grants and personal fees from Astra-Zeneca and Chiesi; grants, personal fees, and nonfinancial support from Teva; personal fees from Sanofi; nonfinancial support from Menarini; personal fees and non-financial support from Esteve, outside the submitted work. J. L. García-Rivero has received speaker's fees from Boehringer-Ingelheim, Astra-Zeneca, Chiesi, GSK, Menarini, Teva, Ferrer, and Novartis; and consulting fees from Novartis, GSK, Boehringer-Ingelheim, ALK, and Menarini, outside the submitted work. E. Martínez-Moragón reports grants and personal fees from Astra-Zeneca and ALK; personal fees and nonfinancial

support from Teva, Boehringer-Ingelheim, Chiesi, and GSK, outside the submitted work. I. Urrutia reports personal fees from Novartis, Astra-Zeneca, Sanofi, Mundipharma, and personal fees from ALK, outside the submitted work. J. Ramos has received payments from Novartis, GSK, ROVI Pharmaceuticals, Menarini, Chiesi, Teva, and Boehringer-Ingelheim for lectures and traveling to scientific meetings and has provided expert testimony for ALK-Abelló, Astra-Zeneca, and Boehringer-Ingelheim, outside the submitted work. P. Cebollero reports personal fees and nonfinancial support from GSK, Novartis, Boehringer-Ingelheim; grants and personal fees from Astra-Zeneca and Chiesi; grants from TEVA; nonfinancial support from Menarini, Mundipharma; and nonfinancial support from Ferrer, outside the submitted work. F. Carballada reports personal fees and nonfinancial support from ALK-Abelló SA, Immunotek SL, and LETI SL; personal fees from Roal Medicina España, GSK, Chiesi, Astra-Zeneca, Meda Pharma SL, Mundipharma, Pfizer SL, Alpha BioResearch SL, Teva Pharma SL, and Menarini, outside the submitted work. M. Blanco reports personal fees from Novartis, Astra-Zeneca, Teva, Mundipharma, and Esteve, outside the submitted work. V. Plaza received honoraria for speaking at sponsored meetings from Astra-Zeneca, Chiesi, GSK, and Novartis; received help assistance to meeting travel from Chiesi and Novartis; acted as a consultant for ALK, Astra-Zeneca, Boehringer-Ingelheim, Mundipharma, and Sanofi; and received funding/grant support for research projects from a variety of government agencies and not-for-profit foundations, as well as Astra-Zeneca, Chiesi, and Menarini. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication July 7, 2018; revised October 13, 2018; accepted for publication October 15, 2018.

Available online October 25, 2018.

Corresponding author: Luis Pérez de Llano, MD, PhD, Pneumology Service, University Hospital Lucus Augusti, Calle Doctor Ulises Romero, 1, 27003, Lugo, Spain. E-mail: eremos26@hotmail.com.

2213-2198

© 2018 American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaip.2018.10.017>

Abbreviations used

ACT- Asthma Control Test
AUC- Area under the curve
BDR- Bronchodilator response
CI- Confidence intervals
FENO- Fraction of exhaled nitric oxide
FEV₁- Forced expiratory volume in 1 second
FVC- Forced vital capacity
GINA- Global Initiative for Asthma
ICS- Inhaled corticosteroids
LABA- Long-acting β_2 -agonist
MARS-A- Medication Adherence Report Scale for Asthma
OR- Odds ratio
ROC- Receiver operating characteristics

BACKGROUND: The minimum controlling dose of treatment must be established in patients with asthma, but the outcome of step-down is unpredictable.

OBJECTIVE: To identify factors associated with risk of control loss when stepping down asthma treatment and to develop a score to predict this risk.

METHODS: A prospective, multicenter study including adults with well-controlled asthma was performed. Treatment was stepped up or stepped down over a 12-month period to maintain asthma control. We determined associations between clinical and functional variables and step-down failure. Finally, we derived a score to predict loss of control in 1 cohort and validated it in an independent cohort.

RESULTS: The derivation cohort consisted of 228 patients; 218 completed at least 1 step-down episode and a total of 495 step-down episodes were evaluated. A medical-record documented postbronchodilator spirometry result of <70% forced expiratory volume in 1 second (FEV₁)/forced vital capacity (odds ratio [OR] = 2.08; 95% confidence interval [CI]: 1.26-3.43), current FEV₁ < 80% (OR = 1.80; 95% CI: 1.03-3.14), ≥ 1 severe exacerbation in the previous 12 months (OR = 2.43; 95% CI: 1.48-4.01), and Asthma Control Test score < 25 (OR = 2.30; 95% CI: 1.35-3.92) were independently associated with failure. The score showed an area under the curve of 0.690 (95% CI: 0.633-0.747; $P < .05$) in the derivation cohort and 0.76 (95% CI: 0.643-0.882; $P < .001$) in a validation cohort of 114 patients. A score <4.5 implies a low risk of failure (<20%), whereas a score ≥ 8 implies a high risk (>40%).

CONCLUSION: This score can facilitate the prediction of step-down failure before medication taper in patients with well-controlled asthma. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:1214-21)

Key words: Asthma; Asthma management; Asthma guidelines; Step-down; Inhaled corticosteroids

The aim of asthma treatment is to achieve control and to maintain it for long periods of time.^{1,2} International guidelines recommend that once asthma control is achieved and maintained for at least 3 months, step-down therapy can be attempted to employ the least amount of medication possible.^{1,2} However, these recommendations are supported by low levels of evidence, leading to considerable uncertainty about the risks and benefits

of this strategy. The reduced need for medication, once control is achieved, remains not fully understood, but it might reflect the modulation of some components of the ongoing inflammatory process in the airways. Whatever the explanation, the minimum controlling dose of treatment must be established in all patients through a process of regular follow-up and staged dose reductions, because it allows for lower costs and fewer side effects compared with maintaining the current treatment level.³ However, despite all the foreseeable precautions, a reduction of therapy entails a nonnegligible risk of unstable asthma, emergency visits, and hospital admissions.⁴⁻⁶ Recent meta-analyses conclude that reducing the dose of the inhaled corticosteroids (ICS) while maintaining long-acting β_2 -agonist (LABA) is safer than stopping this drug while keeping the ICS dose stable.^{7,8} In contrast, the risk appears to be significantly lower when the ICS dose is decreased by 50%.^{9,10} In general, the failure rates range from 13% to 78%, depending on the type of step-down procedure and the length of the study.¹¹ In view of all the above, it may be concluded that both physicians and patients would benefit from more confident risk estimates for asthma step-down decisions. The development and validation of predictors of failure—especially those that can be easily applied in multiple care settings—are fully warranted.

The purpose of this prospective study was to develop and externally validate a multivariable prediction tool to anticipate failure when stepping down asthma therapy in well-controlled patients.

MATERIAL AND METHODS

Study design

We carried out a prospective, multicenter study at 8 tertiary centers in cities across Spain. For the derivation cohort, we recruited 228 patients (10 were excluded because of protocol violations) in the outpatient clinic of the 8 centers, and for the validation cohort, we recruited 114 patients from 6 of these clinics. The first patient was included in December 2014 and the last patient's final visit was in June 2017.

The study was conducted in accordance with the Declaration of Helsinki, and the final study protocol was approved in writing by Galicia's Ethics Committee (Cod 10/439), by the independent ethics committees of the trial centers and registered in [ClinicalTrials.gov](https://www.clinicaltrials.gov) (Identifier: NCT01565031). Written consent was obtained from all participants.

Eligible subjects

The eligible subjects were adults (aged between 18 and 80 years) with asthma under control—Asthma Control Test (ACT) ≥ 20 and no exacerbations—during the previous 3 months, treated (in consonance with Global Initiative for Asthma [GINA] guidelines) with a combination of ICS and LABA.

Exclusion criteria

The exclusion criteria were as follows: active smoking, pregnancy, and treatment with oral corticosteroids, long-acting antimuscarinic agent, biological drugs, or immunotherapy.

Definitions

Asthma. Diagnosed—in accordance with the Spanish guidelines²—by the presence of symptoms of wheeze, breathlessness, or cough plus a positive bronchodilator test (a rise of at least 12% and at least 200 mL compared with the prebronchodilator test 10

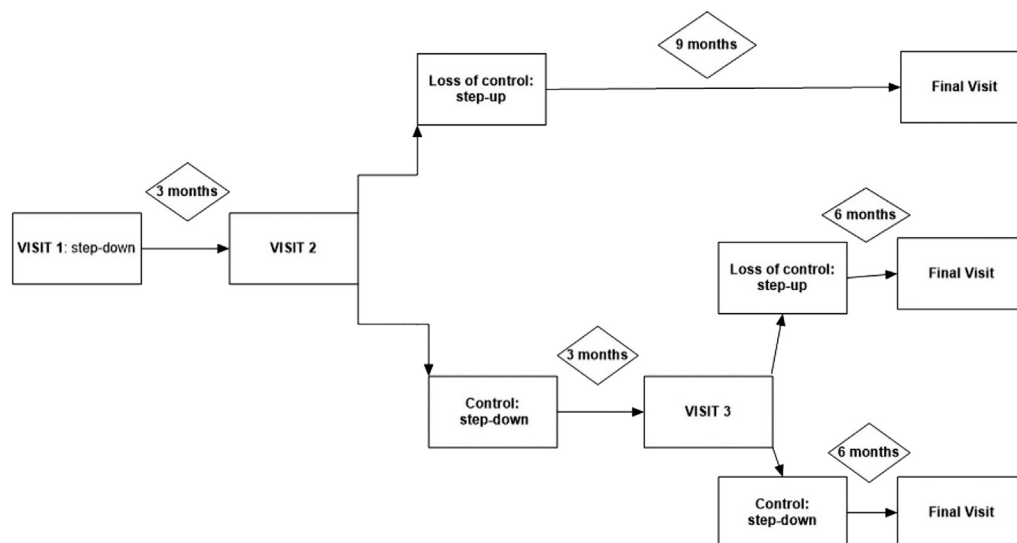


FIGURE 1. Study design.

minutes after the inhalation of 200 mg of salbutamol) or a positive methacholine challenge test (a provocative concentration of methacholine required to lower the forced expiratory volume in 1 second [FEV₁] by 20%—PC20—of <4 mg/mL) or high fraction of exhaled nitric oxide (FENO) levels (>50 ppb).

Controlled asthma. ACT score > 19, absence of exacerbations since the previous visit, and stability in pulmonary function (<20% decrease in FEV₁ with respect to baseline) during the follow-up period.

Loss of control. ACT score ≤ 19, development of an exacerbation (either severe or moderate), or FEV₁ decrease of ≥ 20% from baseline at any point of the follow-up period.

Asthma exacerbation. Event characterized by a change from the patient's previous status. These events must be clinically identified by being outside the patient's usual range of day-to-day asthma variation.¹²

Moderate exacerbations. Deterioration in symptoms that last for 2 days or more, but not severe enough to warrant systemic corticosteroid use and/or hospitalization. They were identified by the investigators via a detailed review of physicians' electronic records (primary, secondary, or emergency care) and confirmation of an exacerbation that did not meet criteria for severity.

Severe exacerbation. Deterioration in symptoms enough to warrant systemic corticosteroid use and/or hospitalization.

Comorbidities

Rhinitis, chronic sinusitis, nasal polyps, gastroesophageal reflux, obesity, sleep apnea syndrome, vocal cord dysfunction, allergic bronchopulmonary aspergillosis, anxiety, and depression were documented in every case.

Study protocol

The patients visited their chest physician at one of the participating outpatient clinics at 3, 6, and 12 months during the 1-year study period. Asthma control was reassessed at each study visit and controller medication was adjusted conforming to a stepwise

approach (Figure 1). The researchers obtained and recorded in an electronic clinical research database anthropometric data, smoking history, atopic status assessed by skin prick testing, clinical and functional data, presence of comorbidities, exacerbations, symptoms assessed by the validated Spanish version of the ACT,¹³ pharmacologic treatments, and the degree of compliance with inhalers estimated by the Medication Adherence Report Scale for Asthma (MARS-A). MARS-A is a 10-item self-reported scale to measure adherence to inhaled medications in patients with asthma that has demonstrated good psychometric performance; patients with a score of ≥4.5 are defined as good adherers.¹⁴ Loss of control was assessed in the entire period between visits. This means that, if a patient had an exacerbation at any time between 2 consecutive visits, the ACT fell below 20, or FEV₁ showed a decrease of ≥20% from baseline, loss of control was confirmed, and the patient was scheduled for the final follow-up visit. Otherwise, the patient was considered controlled and followed the step-down process as scheduled.

Spirometry and bronchodilator test

They were performed using equipment and techniques that met standards developed by the Spanish Respiratory Society.¹⁵ Spirometry results included pre/postbronchodilator FEV₁ (in liters and percent predicted value, forced vital capacity (FVC) (in liters and percent predicted), and FEV₁/FVC ratio. Bronchodilator response was defined as an increase in postbronchodilator FEV₁ > 12% and > 0.2 L (measured 15 minutes after inhalation of 200 µg of salbutamol, using a spacer) compared with prebronchodilator FEV₁.

FENO was measured by a chemoluminescence analyzer (NIOX; Aerocrine, Stockholm, Sweden) at a flow rate of 50 mL/s, in accordance with the recommendations of the American Thoracic Society (ATS)/European Respiratory Society (ERS) task force.¹⁶

Treatment schedule

Antileukotrienes, antihistamines, nasal corticosteroids, and comorbidity-related medication were allowed to be employed at the discretion of the investigator during the study period. However, these treatments had to be kept at stable dose during the entire study period. The medication was adjusted in accordance with each patient's level of control. Depending on the state of control of

asthma, the dose was adjusted up or down (step-up therapy and step-down therapy, respectively) in consonance with GINA guidelines.¹ If the patient had a good asthma control, the treatment was decreased by 1 step. For instance, if a patient remained controlled at visit 2, the treatment was reduced according to the predefined dosing schedule and the outcome was reassessed at visit 3. If the patient lost asthma control, treatment was increased by 1 step and remained unchanged until the final visit. All the possible therapeutic changes are summarized in Figure E1 in this article's Online Repository at www.jaci-inpractice.org.

Management and treatment of asthma exacerbations were left to discretion of the investigators, based on current standards. Maintenance treatment was stepped up and it was kept unchanged for the rest of the follow-up period if an exacerbation was diagnosed during the study. If a second exacerbation occurred in the same subject, treatment was stepped up once again, and the patient was removed from the study.

Statistical methods

Sample size. The main outcome measure was loss of control after medication reduction. For power calculations, we anticipated that 40% of the patients will lose control during the stepping-down process. Considering power of 80%, alpha of 5%, and confidence level of 95%, the required sample was calculated to be 225. The score model was subsequently validated in an independent set of 114 patients.

Statistical analysis

All step-down episodes were included in the analysis even if a subject discontinued at a later stage (intention-to-treat). Values for missing data were calculated using multiple imputation; imputed data were used only in the model-building process.

To describe the qualitative variables, absolute frequencies and percentages were employed. The description of quantitative variables was performed using mean and standard deviation. The Kolmogorov-Smirnov test was used to assess the normality of distributions. All the different variables were evaluated at every visit in accordance with the clinical outcome: loss or maintenance of control at the next visit after a step-down in asthma therapy. The results were regarded as significant when the *P* value was <.05. A medical-record documented postbronchodilator spirometry result of less than 70% FEV₁/FVC, history of severe exacerbations, current FEV₁ < 80%, coefficient of variation of peak expiratory flow >20%, presence of a significant BDR, FENO values >50 ppb, ACT score < 25, and adherence (MARS-A scale <4.5) were selected as potential prognostic variables of poor outcome. Quantitative variables were transformed to binary variables before inclusion in logistic models using the best predictive cutoff point of each selected. A final model was developed using logistic regression analysis including loss of control as a dependent variable. The results were described with odds ratios (OR), their 95% confidence intervals (CI), and *P* values.

Development of the prediction tool

To develop a practical prognostic score, we assigned the risk factors identified by multivariate analysis weighted points proportional to the β regression coefficient values, rounding to the nearest integer or a multiple of it. A risk score was then calculated for each patient and a receiver operating characteristics (ROC) curve was constructed to evaluate the discriminative ability of the prediction rule for loss of asthma control, both in the derivation and validation cohorts.

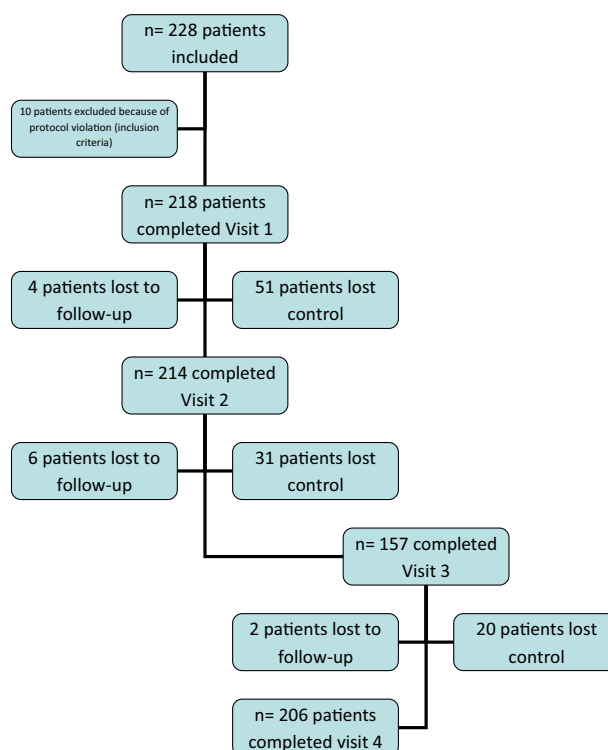


FIGURE 2. Flow diagram of the study population.

All analyses were performed using SPSS software version 23.0 (IBM Corporation, Armonk, NY).

RESULTS

Demographic characteristics

Two hundred and twenty-eight patients were included in the derivation cohort (68.8% women; mean age 62.9 years); 218 completed at least 1 step-down episode and a total of 495 step-down episodes were evaluated (214 from visit 1 to visit 2, 157 from visit 2 to visit 3, and 124 from visit 3 to visit 4). Twelve patients were lost to follow-up at any time during the study. Figure 2 shows the flow of the patients through the study. Considering the pulmonary function test results (mean FEV₁ 92%), the exacerbation rate (0.4 in the previous year), and the prescribed medication (ICS/LABA combination), patients could be classified as having moderate asthma. Demographic and clinical characteristics of the whole sample at visit 1 are shown in Table I.

Patient's clinical outcome

The overall loss of control rate was 46.8% (102 patients): 51 (19%) patients lost control in visit 2, 31 (15%) patients in visit 3, and 20 (15%) patients in visit 4 (Figure 2). Seventy-three percent of the episodes of loss of control occurred after reducing the dose of ICS while taking an ICS/LABA combination, 21.6% after stopping LABA, and 5.2% after reducing the dose of ICS given as monotherapy. We found 21 loss of control events in 108 step-down episodes in which LABA were stopped (19.4%) whereas the figures were 5 in 52 (9.6%) step-down episodes in which the dose of ICS given as monotherapy was reduced (*P* = .010). An exacerbation was recorded in 63 patients

TABLE I. Basal (at visit 1) demographic and clinical characteristics of the included patients

Characteristics	Values (n = 218)
Sex (% female)	68.8
Age (y), mean (SD)	52.9 (13.9)
BMI, mean (SD)	28.2 (5.4)
Disease debut (% before 12 y old)	17.9
Smoking habit (% nonsmoker)	64.7
Prick test (% positive)	59.6
Rhinitis (%)	75.2
Sinusitis (%)	27.3
Polyposis (%)	14.0
Aspirin intolerance (%)	6.5
Reflux (%)	30.7
Anxiety/depression (%)	26.6
COPD (%)	0.9
Allergic bronchopulmonary aspergillosis (%)	0.5
Vocal cord dysfunction (%)	0.9
Exacerbations in the last 12 mo, mean (SD)	0.4 (0.8)
≥1 exacerbation in the last 12 mo (%)	29.0
Documented bronchial obstruction (postbronchodilation FEV ₁ /FVC < 70%) (%)	45.6
ACT, mean (SD)	23.1 (2.0)
FEV ₁ liters, mean (SD)	2.7 (0.9)
FEV ₁ percentage over theoretical value, mean (SD)	92.9 (16.1)
FEV ₁ /FVC, mean (SD)	72.4 (9.8)
FVC, mean (SD)	3.7 (1.1)
FVC%, mean (SD)	99.6 (14.1)
FEV ₁ /FVC < 70% (%)	33.9
BDR (% positive)	22.1
MARS-A scale	4.6 (0.7)
Treatment (% patients)*	
BF 160	24.6
FS 500	22.3
BF 320	22.3
FS 250	14.4
BcF 100: 2-0-2	10.7
BcF 100: 1-0-1	3.7
FS 100	1.9

ACT, Asthma Control Test; BcF, beclomethasone-formoterol; BDR, bronchodilator response; BF, budesonide-formoterol; BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 second; FS, fluticasone-salmeterol; FVC, forced vital capacity; MARS-A, Medication Adherence Report Scale for Asthma; SD, standard deviation.

*BF 160, budesonide-formoterol 160/4.5 mcg; FS 500, fluticasone/salmeterol 500/50 mcg; BF 320, budesonide/formoterol 320/9 mcg; FS 250, fluticasone/salmeterol 250/50 mcg; BcF 100, beclomethasone/formoterol 100/6 mcg; FS 100, fluticasone/salmeterol 100/50 mcg.

(13 severe, 50 moderate), but none of them required hospitalization. Most of the patients (73.6%) who lost control in visit 2 or visit 3 regained it in visit 4.

Risk factors for loss of asthma control

The final multivariate model showed a greater probability of losing control in patients with a medical-record documented postbronchodilator spirometry result of less than 70% FEV₁/FVC (OR = 2.08; 95% CI: 1.26-3.43), FEV₁ < 80% (OR = 1.80; 95% CI: 1.03-3.14), ≥1 severe exacerbation in the

prior 12 months (OR = 2.43; 95% CI: 1.48-4.01), and ACT score < 25 (OR = 2.30; 95% CI: 1.35-3.92) (Table II). This model showed a moderate predictive power (AUC = 0.690; 95% CI: 0.633-0.747; *P* < .05) (Figure E2 in this article's Online Repository at www.jaci-inpractice.org). Complete calculations including sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic OR are provided in Table E1 in this article's Online Repository at www.jaci-inpractice.org.

Step-down failure score: predictive accuracy

A weighted step-down failure score was constructed by using the regression coefficients from the multivariate model. This score assigned points for the 4 variables that resulted significant at multivariate analysis (Table III). Table IV discloses the estimates of risk of step-down failure across different results of the score. A score <4.5 implies a low risk of failure (<20%; 53% of the step-down episodes scored <4.5), whereas a score >8 implies a high risk of failure (>40%; only 3.6% of the step-down episodes scored >8).

The fit of the step-down failure score with the predictive values from logistic regression is represented graphically in Figure E3 in this article's Online Repository at www.jaci-inpractice.org.

Application of the derived prediction tool in the validation cohort

The validation cohort consisted of 114 patients (64% women, 52.8 ± 15.5 years). There were no significant differences between the 2 cohorts in terms of prior exacerbations, ACT, and pulmonary function. After stepping down asthma medication, 27 patients (23.6%) lost control during the ensuing 3 months. The ROC curve showed a predictive accuracy of 0.76 (95% CI: 0.643-0.882; *P* < .001) for step-down failure (Figure E4 in this article's Online Repository at www.jaci-inpractice.org). Complete calculations including sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic OR are provided in Table E1 in this article's Online Repository at www.jaci-inpractice.org.

DISCUSSION

In this analysis, we have identified factors associated with loss of control during step-down therapy among individuals with well-controlled asthma. These factors include a medical-record documented postbronchodilator spirometry result of less than 70% FEV₁/FVC, current FEV₁ < 80%, ≥1 severe exacerbation in the previous 12 months, and ACT score <25. Using these data, we have computed a step-down failure score that can be used to predict the probability of failure for patients who are being considered for a step-down strategy. Given the fact that there is significant heterogeneity in asthma biology, severity, and in factors influencing risk of impairment, it seems unfeasible to set up a perfect clinical tool to predict loss of control. The ROC curves in the derivation and validation cohorts (AUC 0.69 and 0.76) for this score demonstrate moderate predictive capacity for step-down failure. Nonetheless, we believe that the score is of clinical value, because a step-down failure score of less than 4.5 predicts a low risk of control loss (<20%), whereas a score of greater than 8 is associated with a high risk of losing control (>40%). In this regard, more than 50% of the episodes could be classified as "low risk" irrespective of the therapy used. In the first

TABLE II. Univariate and multivariate logistic regression models for predicting loss of control

Variable	Univariate model		Multivariate model	
	OR (95% CI)	P value	OR (95% CI)	P value
Documented bronchial obstruction (postbronchodilation FEV ₁ /FVC < 70%)	2.034 (1.307-3.165)	.002	2.079 (1.260-3.431)	.004
Presence of exacerbations in the last 12 mo	2.739 (1.721-4.358)	<.001	2.434 (1.479-4.006)	<.001
FEV ₁ over theoretical value (<80%)	2.159 (1.341-3.477)	.002	1.795 (1.027-3.135)	.040
CV of morning PEF > 20%	0.957 (0.471-1.945)	.903	1.080 (0.623-1.872)	.784
BDR	1.204 (0.687-2.109)	.516	0.659 (0.334-1.303)	.229
FENO > 50 ppb	1.200 (0.694-2.076)	.514	1.242 (0.691-2.233)	.469
ACT score < 25	2.338 (1.399-3.907)	.001	2.299 (1.348-3.921)	.002
MARS-A scale score < 4.5	1.930 (1.157-3.218)	.012	1.737 (0.988-3.054)	.055

ACT, Asthma Control Test; BDR, bronchodilator response; CI, confidence interval; CV, coefficient of variation; FENO, fraction of exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; MARS-A, Medication Adherence Report Scale for Asthma (values < 4.5 were considered to indicate suboptimal adherence); OR, odds ratio; PEF, peak expiratory flow.

TABLE III. Step-down failure score

Variable	Points
FEV ₁ percentage over theoretical value	
≥80%	0
<80%	2.0
Documented bronchial obstruction (postbronchodilation FEV ₁ /FVC < 70%)	
No	0
Yes	2.5
ACT	
25	0
<25	2.5
Presence of exacerbations in the last 12 mo	
No	0
Yes	3.0

This score assigns points for the 4 variables and the final result ranges from 0 to 10. ACT, Asthma Control Test; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity.

TABLE IV. Predictive risk of control loss

Total points	Estimate of risk*
0.0	0.07
2.0	0.11
2.5	0.13
3.0	0.15
4.5	0.21
5.0	0.24
5.5	0.27
7.0	0.36
7.5	0.40
8.0	0.43
10.0	0.58

*Estimate of risk reflects the predicted risk of treatment failure derived from the step-down failure score.

situation, the step-down procedure can be safely carried out in most patients, but in the second situation, step-down should be avoided or, in the case of potentially harmful side effects, it should be undertaken with caution, although it is worth to mention that no patient required admission to hospital for asthma exacerbation. Because only 3.6% of the population was classified in the “high-risk stratum,” this prediction rule is more helpful to identify patients with low risk of failure. In cases with a score between 4.5 and 8, the risk of failure ranges from 0.21 to 0.4, and it could be acceptable, particularly if high doses of ICS are employed. On the other hand, because asthma is a frequent disorder and all the health care system levels are involved in its management, a tool to assess the step-down process should be easy to implement outside of select asthma clinics (although spirometry is not always available in primary care settings), as is the case with this predictive score.

International guidelines suggest to step down the ICS dose when asthma has been stable for at least 3 months.¹ These recommendations are supported by a number of clinical trials, real-life studies, and systematic reviews in both adults and children.^{4-10,17-21} Previous studies have reported different predictors for step-down failure that include clinical or demographic characteristics (age >40 years,^{22,23} disease duration >5 years,²⁴ length of time without clinical symptoms,²⁵ time of the year,²⁶

and asthma control assessed by a validated questionnaire²⁷), biologic markers (sputum eosinophils,^{23,24,28} serum eosinophil count,²⁴ and FENO^{25,28}), and physiologic measurements (bronchial hyperresponsiveness^{23,25} and FEV₁^{25,27}). However, virtually all of these studies were carried out in small groups of patients or they were of short duration (<12 months), and most of them focused on ICS reduction, not covering the whole spectrum of asthma therapeutic options. Of note, high FENO levels did not predict step-down failure in our study. The role of FENO as a predictor of asthma outcome remains controversial. In fact, Semprini et al²⁹ evaluated the association between type 2 biomarkers and time to severe exacerbation, and they found that those patients who had at least 1 severe exacerbation had lower baseline FENO levels than those who did not exacerbate. Lehtimäki et al³⁰ carried out a systematic review on the predictive value of FENO in the management of asthma, and they concluded that there are insufficient data to deduce whether or not low FENO predicts step-down success.

We have found an overall loss of control rate of 46.8%, which is consistent with many other studies,^{7,18} although higher than the one (10.6%) reported by Rank et al,³ probably because these authors used an observational data set unsuitable to capture events that are paramount in describing asthma control (symptoms and pulmonary function). Interestingly, no patient required hospitalization and the great majority (73.6%) of those who lost control regained it by increasing medication to the previous dosage.

The strengths of this study include a prospective design that reproduces international guideline's recommendations about asthma medication adjustment. The concept of asthma control was defined in accordance with this guideline, as was also done with the definition of exacerbation. It is important to note that we have only chosen simple predictive measures whose application is suitable in both primary care and specialists' offices. The low dropout rate may also be considered a strength.

Nonetheless, there are several limitations to this study that should be considered in the application of its findings to a larger and more diverse asthma population. First of all, the study was designed to target patients with moderate asthma. Thus, it is unclear that its results are applicable to a wider range of asthma severity. Second, although asthma guidelines suggest that step-down can be considered if asthma is stable for at least 3 months, it remains unknown whether control persists on the long term. In this sense, Rank et al⁵ found that 32% of individuals have an asthma exacerbation in the 2 years after a step-down episode, a figure even lower than the 47% we found (although we adopted a broader concept of control). Third, adherence was measured by a questionnaire of questionable validity, but pharmacy claims data were not available to all the investigators at the moment in which the study was designed. Fourth, lack of having considered blood eosinophil count—widely available—as a potential predictor of step-down failure is a clear limitation of the present study. Fifth, the unblinded observational design of this study can be considered a weakness. Finally, and probably most importantly, a study design incorporating a usual control comparison group would have been more valuable.

In summary, this investigation has identified several factors associated with step-down failure in patients with moderate asthma: a medical-record documented postbronchodilator spirometry result of less than 70% FEV₁/FVC, current FEV₁ < 80% predicted, ≥1 severe exacerbation in the previous 12 months, and ACT score < 25. We have developed a readily usable tool to predict step-down failure in patients with asthma who are being considered for step-down therapy. Such an index, which incorporates clinical and spirometric variables, would allow clinicians at different health care levels to anticipate the risk of failure before making the decision.

Acknowledgments

L. P. de Llano was responsible for the design of the study, the acquisition, analysis, interpretation and discussion of data, drafting the work; final approval of the version to be published; agreement to be accountable for all aspects of the study in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. M. Merino was responsible for the statistical analysis of the study, drafting the work; final approval of the version to be published; agreement to be accountable for all aspects of the study. J. L. García-Rivero, I. Urrutia, E. Martínez-Moragón, J. Ramos, P. Cebollero, F. Carballada, M.C. Vennera, Y. Torralba García, V. Plaza made substantial contributions to the conception and design of the work and to the acquisition of data; revising the work critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work.

REFERENCES

1. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention 2016 update. Available from: <http://ginasthma.org/2016-gina-report-global-strategy-for-asthma-management-and-prevention/>. Accessed January 10, 2017.
2. Plaza Moral V, Comité Ejecutivo de GEMA. GEMA^{4.0}. Guidelines for asthma management. *Arch Bronconeumol* 2015;51(Suppl 1):2-54.
3. Rank MA, Liesinger JT, Branda ME, Gionfriddo MR, Schatz M, Zeiger RS, et al. Comparative safety and costs of stepping down asthma medications in patients with controlled asthma. *J Allergy Clin Immunol* 2016;137:1373-9.
4. Waalkens HJ, Van Essen-Zandvliet EE, Hughes MD, Gerritsen J, Duiverman EJ, Knol K, et al. Cessation of long-term treatment with inhaled corticosteroid (budesonide) in children with asthma results in deterioration. *Am Rev Respir Dis* 1993;148:1252-7.
5. Rank MA, Johnson R, Branda M, Herrin J, van Houten H, Gionfriddo MR, et al. Long-term outcomes after stepping down asthma controller medications: a claims-based, time-to-event analysis. *Chest* 2015;148:630-9.
6. Godard P, Greillier P, Pigearias B, Nachbaur G, Desfougères JL, Attali V. Maintaining asthma control in persistent asthma: comparison of three strategies in a 6-month double blind randomised study. *Respir Med* 2008;102:1124-31.
7. Brozek JL, Kraft M, Krishnan JA, Cloutier MM, Lazarus SC, Li JT, et al. Long-acting β_2 -agonist step-off in patients with controlled asthma. *Arch Intern Med* 2012;172:1365-75.
8. Ahmad S, Kew KM, Normansell R. Stopping long-acting beta2-agonists (LABA) for adults with asthma well controlled by LABA and inhaled corticosteroids. *Cochrane Database Syst Rev* 2015;(6):CD011306.
9. Hawkins G, McMahon AD, Twaddle S, Wood SR, Ford I, Thomson NC. Stepping down inhaled corticosteroids in asthma: a randomized controlled trial. *BMJ* 2003;326:1115.
10. Hagan JB, Samant SA, Volcheck GW, Li JT, Hagan CR, Erwin PJ, et al. The risk of asthma exacerbation after reducing inhaled corticosteroids: a systematic review and meta-analysis of randomized controlled trials. *Allergy* 2014;69:510-6.
11. Rank MA, Peters SP. The risks, benefits, and uncertainties of stepping down asthma medications. *J Allergy Clin Immunol Pract* 2014;2:503-9.
12. Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med* 2009;180:59-99.
13. Vega JM, Badiá X, Badiola C, López-Viña A, Olaguibel JM, Picado C, et al. Validation of the Spanish version of the Asthma Control Test (ACT). *J Asthma* 2007;44:867-72.
14. Cohen JL, Mann DM, Wisnivesky JP, Home R, Leventhal H, Musumeci-Szabó TJ, et al. Assessing the validity of self-reported medication adherence among inner-city asthmatic adults: the Medication Adherence Report Scale for Asthma. *Ann Allergy Asthma Immunol* 2009;103:325-31.
15. García-Río F, Calle M, Burgos F, Casan P, Del Campo F, Galdiz JB, et al. Espirometría. Normativas SEPAR. *Arch Bronconeumol* 2013;49:388-401.
16. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide. *Am J Respir Crit Care Med* 2005;2005(171):912-30.
17. Usmani OS, Kempainen A, Gardener E, Thomas V, Konduru PR, Callan C, et al. A randomized pragmatic trial of changing to and stepping down fluticasone/formoterol in asthma. *J Allergy Clin Immunol Pract* 2017;5:1378-87.
18. Rogers L, Sugar EA, Blake K, Castro M, Dimango E, Hanania NA, et al. Step-down therapy for asthma well controlled on inhaled corticosteroid and long-acting beta-agonist: a randomized clinical trial. *J Allergy Clin Immunol Pract* 2018;6:633-43.
19. Anderson WC III, Szefer SJ. Controlling the risk domain in pediatric asthma through personalized care. *Semin Respir Crit Care Med* 2018;39:36-44.
20. DiMango E, Rogers L, Reibman J, Gerald LB, Brown M, Sugar EA, et al. Risk factors for asthma exacerbation and treatment failure in adults and adolescents with well-controlled asthma during continuation and step-down therapy. *Ann Am Thorac Soc* 2018;15:955-61.
21. Tsurikawa N, Oshikata C, Sato T, Kimura G, Mizuki M, Tsuburai T, et al. Low variability in peak expiratory flow predicts successful inhaled corticosteroid step-down in adults with asthma. *J Allergy Clin Immunol Pract* 2018;6:972-9.
22. Tonelli M, Bacci E, Dente FL, Bartoli ML, Cianchetti S, Di Franco A, et al. Predictors of symptom recurrence after low-dose inhaled corticosteroid cessation in mild persistent asthma. *Respir Med* 2006;100:622-9.

23. Leuppi JD, Salome CM, Jenkins CR, Anderson SD, Xuan W, Marks GB, et al. Predictive markers of asthma exacerbation during stepwise dose reduction of inhaled corticosteroids. *Am J Respir Crit Care Med* 2001;163:406-12.
24. Belda J, Parameswaran K, Lemiere C, Kamada D, O'Byrne PM, Hargreave FE. Predictors of loss of asthma control induced by corticosteroid withdrawal. *Can Resp J* 2006;13:129-33.
25. Tsurikisawa N, Oshikata C, Tsuburai T, Mitsui C, Tanimoto H, Takahashi K, et al. Markers for step-down of inhaled corticosteroid therapy in adult asthmatics. *Allergol Int* 2012;61:419-29.
26. Rank MA, Branda ME, McWilliams DB, Johnson SK, Samant SA, Podjasek JC, et al. Outcomes of stepping down asthma medications in a guideline-based pediatric asthma management program. *Ann Allergy Asthma Immunol* 2013;110:354-8.
27. Koskela HO, Purokivi MK, Kokkarinen J. Stepping down from combination asthma therapy: the predictors of outcome. *Respir Med* 2016;117:109-15.
28. Zacharasiewicz A, Wilson N, Lex C, Erin EM, Li AM, Hansei T, et al. Clinical use of noninvasive measurements of airway inflammation in steroid reduction in children. *Am J Respir Crit Care Med* 2005;171:1077-82.
29. Semprini R, Williams M, Semprini A, McDouall A, Fingleton J, Holweg C, et al. Type 2 biomarkers and prediction of future exacerbations and lung function decline in adult asthma. *J Allergy Clin Immunol Pract* 2018;6:1982-8.
30. Lehtimäki L, Csonka P, Mäkinen E, Isojärvi J, Hovi SL, Ahovuo-Saloranta A. Predictive value of exhaled nitric oxide in the management of asthma: a systematic review. *Eur Respir J* 2016;48:706-14.

ONLINE REPOSITORY

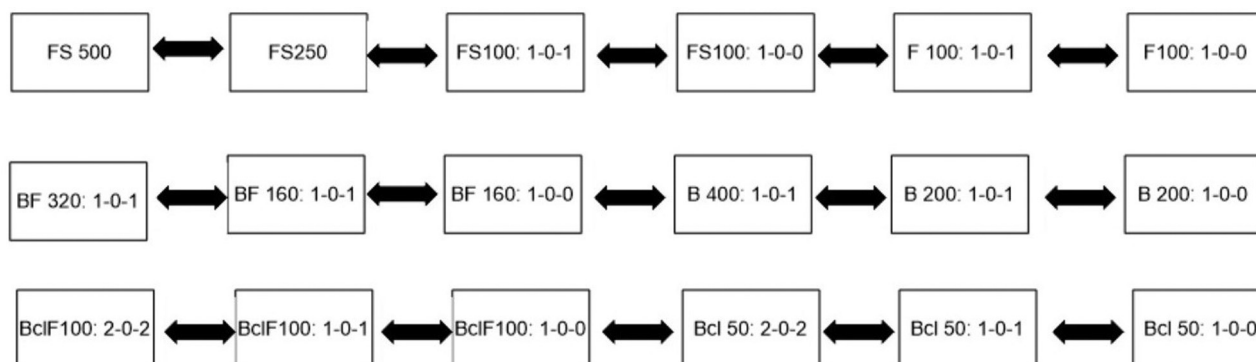


FIGURE E1. Medication adjustment over the 12-month intervention period. This figure illustrates the potential changes in patients' medication during the study period. Treatment could be stepped up or down according to the presence or absence of asthma control. ICS/LABA combination or ICS given as monotherapy were decreased by 1 step when asthma control was maintained, whereas treatment was increased by 1 step and remained unchanged until the final visit if control was lost. *B*, Budesonide; *Bc*, beclomethasone; *BcF*, beclomethasone/formoterol; *BF*, budesonide/formoterol; *F*, fluticasone; *FS*, fluticasone-salmeterol.

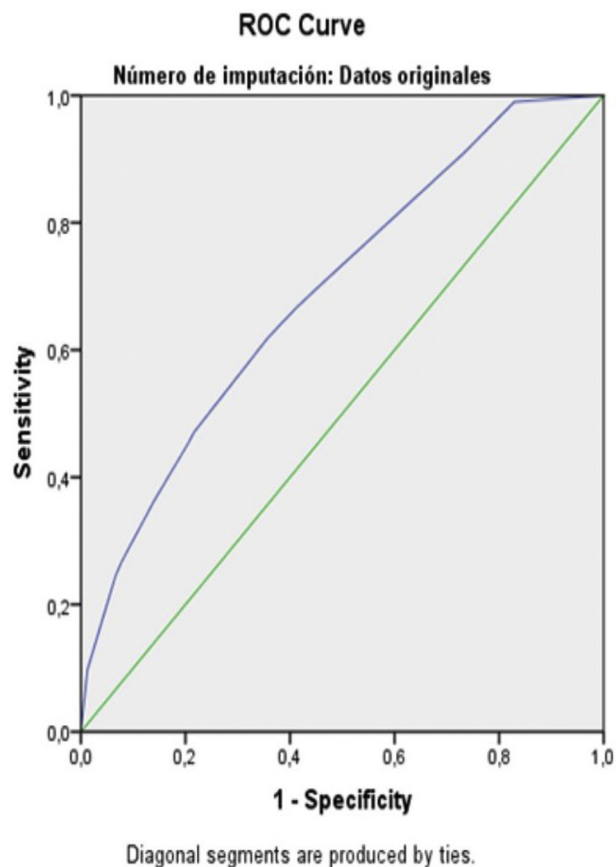


FIGURE E2. ROC curve of the score for step-down failure prediction in the derivation cohort. *ROC*, Receiver operating characteristics.

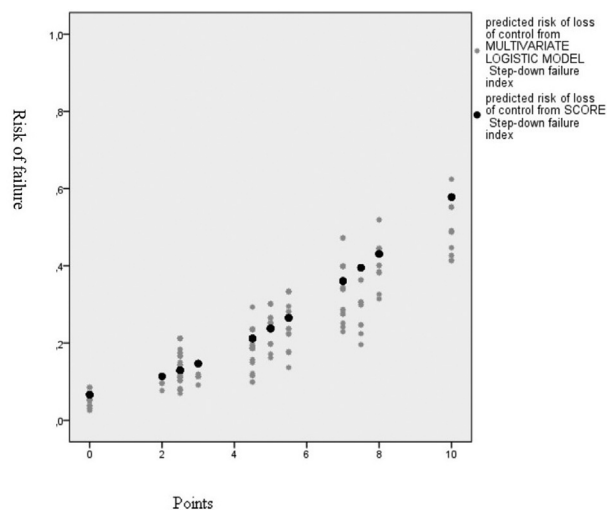


FIGURE E3. Comparison of the risk of failure predicted by the step-down failure score and logistic regression model. As can be seen, across a range of scores, the risk of failure was similar between the score and the logistic regression model. A high degree of agreement was present when quantitatively comparing the agreement between the step-down score and the logistic regression model. Spearman's rank correlation was 0.908 ($P < .001$).

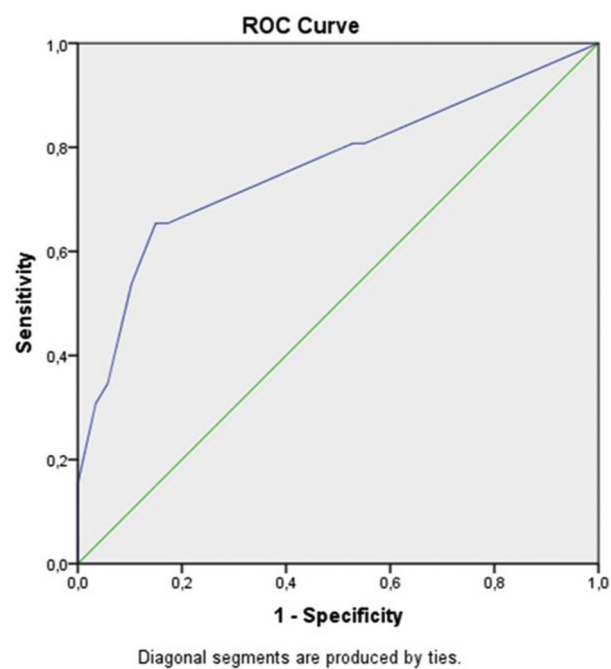


FIGURE E4. Receiver operating characteristics (ROC) curve analyses of the score for step-down failure prediction in a second cohort.

TABLE E1. Sensitivity, specificity, positive and negative predictive values, negative and positive likelihood ratios, and diagnostic odds ratios for step-down failure prediction in derivation and validation cohorts

Variable	Derivation cohort	Validation cohort
AUC	0.690 (0.633-0.747)	0.762 (0.643-0.882)
Positive test score	2.25	2.25
Sensitivity	0.980	0.808
Specificity	0.822	0.529
PPV (%)	23.6	31.3
NPV (%)	97.2	89.1
LLR+	1.19	1.53
LLR–	0.11	0.41
Diagnostic OR	10.84	3.74

AUC, Area under the ROC curve (95% confidence interval); LLR+, positive likelihood ratios; LLR–, negative likelihood ratios; NPV, negative predictive values; OR, odds ratios; PPV, positive predictive values; ROC, receiver operating characteristics.