

Original Article

Predictors of Severe Exacerbations, Poor Asthma Control, and β -Agonist Overuse for Patients with Asthma

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What is already known about this topic? Assessment of the future risk of adverse outcomes is an important component of the clinical management of patients with asthma, and some predictors have been identified.

What does this article add to our knowledge? Lower FEV₁ % predicted, previous severe exacerbations, standard management (when compared with single budesonide-formoterol inhaler as maintenance and reliever therapy) and female sex predict risk of severe exacerbations. A higher Asthma Control Questionnaire–5 score and older age predict poorly controlled asthma. Higher self-reported reliever use, Māori ethnicity, and lower FEV₁ % predicted were predictors of extreme β -agonist overuse.

How does this study impact current management guidelines? We confirmed the clinical utility of existing predictors of severe exacerbations and poor control. Novel data are presented on predictors of β -agonist overuse. Different clinical and demographic characteristics predict the future risk of different adverse outcomes.

BACKGROUND: Predictors of asthma exacerbations, poor asthma control, or extreme β -agonist overuse may be of clinical utility in the management of asthma.

OBJECTIVE: To investigate characteristics that predict subsequent adverse outcomes in asthma.

METHODS: An independent 24-week, randomized controlled trial of 303 adult patients with asthma who are at risk, which compared the efficacy of SMART (single budesonide-formoterol inhaler as maintenance and reliever therapy) with a fixed-dose regimen with salbutamol as reliever (“Standard”). Inhaled

medication use was measured by electronic monitoring. Baseline characteristics that were predictors of subsequent severe asthma exacerbations, poor asthma control (Asthma Control Questionnaire –5 score ≥ 1.5), and “extreme” β -agonist overuse (>16 budesonide-formoterol actuations/d in SMART and >32 salbutamol actuations/d in Standard) were assessed by multivariate analyses.

RESULTS: FEV₁ % predicted (rate ratio [RR] 1.14 [95% CI, 1.03–1.27] per 10% lower), more previous exacerbations (RR 1.15 [95% CI, 1.01–1.31]), Standard therapy (RR 1.62 [95% CI, 1.07–2.47]), and female sex (RR 2.18 [95% CI, 1.29–3.67])

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*Abbreviations used**ACQ- Asthma Control Questionnaire**ICS- Inhaled corticosteroid**IQR- Interquartile range**LABA- Long-acting β -agonist**MDI- Metered-dose inhaler**RR- Rate ratio**SMART- Single budesonide-formoterol inhaler as maintenance and reliever therapy**Standard- Fixed-dose budesonide-formoterol inhaler as maintenance therapy with salbutamol as reliever*

were associated with future severe exacerbations. Asthma Control Questionnaire—5 (regression coefficient 0.20 [95% CI, 0.13-0.27] per 0.5 points higher) and age (regression coefficient 0.09 [95% CI, 0.01-0.17] per decade older) were associated with future poorly controlled asthma. Higher reliever use (RR 1.63 [95% CI, 1.36-1.95] per categorical score in Asthma Control Questionnaire question no. 6), Māori ethnicity (RR 2.20 [95% CI, 1.43-3.38]) and FEV₁ % predicted (RR 1.16 [95% CI, 1.03-1.31] per 10% lower) were associated with future extreme β -agonist overuse.

CONCLUSION: Future severe asthma exacerbations, poor asthma control, and extreme β -agonist overuse are predicted by different baseline clinical and demographic characteristics and management approaches in at-risk asthma. © 2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;■:■-■)

Key Words: Asthma; β -agonist; Electronic monitoring; Predictors; Risk

The focus of clinical practice guidelines for asthma has shifted to include not only the conventional assessment of symptoms, reliever use, and activity limitation but also assessment of the patient's future risk of adverse outcomes, such as exacerbations, future poor asthma control, accelerated decline in lung function, and adverse effects of medications.^{1,2} Although current poorly controlled asthma is a significant risk factor for future poor control and exacerbations,^{3,4} other factors, including clinical and demographic factors, may contribute to a patient's risk profile.⁵ Identification of these characteristics in asthma is important to enable recognition of patients at high risk. Known predictors of severe exacerbation include prior severe exacerbation,⁶ lower lung function,⁷ higher reliever medication use,⁸ more symptoms,⁹ higher age,¹⁰ female sex,^{10,11} and African American race.⁹ Predictor factors for future poor asthma control include prior hospital admission for asthma,¹² lower lung function,⁹ worse baseline asthma control as measured by Asthma Control Questionnaire (ACQ) 5³ or the Asthma Control Test,^{4,13,14} and ethnicity.¹² Observational studies have reported that overuse of β -agonist drugs is associated with an increased risk of severe exacerbations, including death.^{15,16} There are few data to guide clinicians as to which, if any, patient characteristics might predict extreme β -agonist overuse, which may be of value in identifying patients at high risk.

In a recent 6-month randomized controlled trial, we studied the efficacy and safety of combination inhaled corticosteroid long-acting β -agonist therapy (budesonide-formoterol metered-dose inhaler [MDI]) (Vannair, AstraZeneca Limited, Auckland, New Zealand [this is marketed as Symbicort Inhalation Aerosol in the

United States]) when used as a single budesonide-formoterol inhaler as maintenance and reliever therapy (SMART) or as a fixed-dose treatment with short-acting β -agonist as reliever ("Standard" therapy).¹⁷ We conducted the trial in real-world patients with asthma who were at risk of severe exacerbations, and we used electronic monitoring to measure their medication use. In this current exploratory analysis, we sought to determine the baseline characteristics that were predictors of future severe asthma exacerbations, poor asthma control, and extreme β -agonist overuse.

METHODS

Study design

This analysis was based on an independent 24-week multicenter, prospective, open-label, randomized controlled trial of SMART versus Standard therapy of patients with asthma (ages 16-65 years) (Australian New Zealand Clinical Trials Registry number ACTRN12610000515099). Full details of the trial have been published elsewhere.¹⁷ Eligible patients had a physician's diagnosis of asthma and a current prescription for inhaled corticosteroid, with at least 1 asthma exacerbation in the preceding year (defined as a presentation to a general practice or emergency department, which resulted in a prescription of oral corticosteroids and/or treatment with spacer-delivered or nebulized bronchodilator, or self-administration of prednisone for asthma for at least 3 days). Key exclusion criteria included a diagnosis of chronic obstructive pulmonary disease or onset of respiratory symptoms after the age of 40 years in current or ex-smokers with a ≥ 10 pack year smoking history. The study was undertaken at 5 centers in New Zealand (4 primary care centers and 1 secondary care center).

The participants were randomized 1:1 to receive 200 μ g budesonide and 6 μ g formoterol via a single combination MDI; 2 actuations twice daily as maintenance, with extra doses for relief of symptoms as per SMART¹⁸ (SMART group), or 200 μ g budesonide and 6 μ g formoterol via a single combination MDI 2 actuations twice daily as maintenance with as-needed salbutamol via MDI (100 μ g per actuation [Ventolin; GlaxoSmithKline NZ Limited, Auckland, New Zealand]) for relief of symptoms (Standard group). Five study visits occurred over 24 weeks, at weeks 0 (randomization visit), 3, 10, 17, and 24. At visit 1, baseline data were collected from all the participants, which included self-reported history of severe asthma exacerbations in the preceding 12 months and hospital admissions for asthma.

The ACQ-7 was completed as a composite score of current asthma control.¹⁹ The ACQ-7 comprises 5 self-reported questions that relate to asthma symptoms (ACQ question nos. 1-5), 1 self-reported question that relates to average reliever use in the preceding 1 week (ACQ question no. 6), and 1 question that relates to FEV₁ % predicted (ACQ question no. 7). Each question is scored on a scale of 0 to 6, with higher values reflecting worse control. The ACQ-5 score is calculated as the mean of the responses to question nos. 1 to 5, and is a validated measure of asthma control.²⁰ Question no. 6 is a categorical score of reliever use in the following bands: score 0, none; score 1, 1 to 2 inhalations most days; score 2, 3 to 4 inhalations most days; score 3, 5 to 8 inhalations most days; score 4, 9 to 12 inhalations most days; score 5, 13 to 16 inhalations most days; and score 6, more than 16 inhalations most days. Spirometry was measured "on treatment,"²⁵ that is, without withholding inhaled

medication, and FEV₁ % predicted was calculated by using reference values.²¹ All the participants provided written informed consent, and the New Zealand Multi-Region Ethics Committee approved the study protocol.

Collection of electronic medication use data

All Vannair and Ventolin MDIs dispensed in the study were fitted with SmartInhaler Tracker (Nexus6 Limited, Auckland, New Zealand) electronic monitors.²² These validated monitors were used in accordance with detailed trial quality control procedures.^{23,24} Actuations of the MDI resulted in date and time logs, which were uploaded at the next study visit. The participants were informed that their inhalers contained an electronic device that measured the total number of actuations used, but they were unaware of the detailed capabilities of the monitor to record patterns of use.

Definition of severe asthma exacerbation

A severe exacerbation was defined in accordance with the American Thoracic Society/European Respiratory Society criteria: (a) the use of systemic corticosteroids for at least 3 days, or (b) a hospitalization or emergency department visit because of asthma and that required systemic corticosteroids. Courses of corticosteroids separated by 7 days or more were treated as separate severe exacerbations.⁵ Exacerbation details and data on unscheduled consultations for asthma were collected from participant records (by using events noted contemporarily on the participant's study appointment card), spontaneous report, and answers to the following standardized questions at study visits:

"Since the last study visit, have you taken a course of systemic steroids for your asthma?"

"Since the last study visit, has troublesome asthma led you to seek unplanned or urgent help for your asthma?"

"Have you needed to attend the emergency department for your asthma?"

Cross-checks with primary care general practice databases and hospital records were performed if there was uncertainty about events.

Definition of poor asthma control

Future poor asthma control was defined as an ACQ-5 score of ≥ 1.5 ^{20,25} at 6 months (ie, at visit 5, study completion).

Definition of extreme β -agonist overuse

Extreme β -agonist overuse was defined from electronically monitored data throughout the study. For the SMART group, extreme overuse was defined as >16 actuations of budesonide-formoterol in excess of the prescribed 4 maintenance doses (ie, equivalent to >20 actuations in total) in any 24-hour period. For the Standard group, extreme overuse was defined as >32 actuations of salbutamol in any 24-hour period. These thresholds were based on use which would be twice the limit of β -agonist use at which the respective self-management plans for the 2 regimens recommended that the participants should obtain medical review.^{18,26} They were also supported by the short-term bronchodilator equivalence of 6 μ g formoterol to 200 μ g salbutamol with repeated dosing in acute asthma.^{27,28}

Baseline predictors of severe exacerbation, poor asthma control, and extreme β -agonist overuse

The baseline characteristics that were selected as the predictor variables were age, sex, ethnicity (Māori versus non-Māori), the number of severe asthma exacerbations in the preceding 12 months, the number of hospital admissions for asthma ever, ACQ-5 score at visit 1, self-reported reliever use at visit 1 from ACQ question no. 6, lung function measured by % predicted FEV₁, and randomized treatment (SMART or Standard therapy). The ACQ-5 score was used as the validated measure of asthma control²⁰ because reliever use and lung function were separate individual predictors in the model.

Statistical analysis

The associations between potential predictors and severe asthma exacerbations were by Poisson regression, with an offset for days in the trial. Overdispersion was not present for this analysis, and the results are presented as rate ratios (RR). The associations with extreme β -agonist overuse also were evaluated by Poisson regression, with an offset for days of exposure to β -agonist therapy; however, this variable was overdispersed and a deviance-based overdispersion adjustment was used. Asthma control was treated as a continuous variable based on the ACQ score at the fifth visit. The regression coefficients represent the unit change in the ACQ (1 unit represents a difference in ACQ score of 0.5, which corresponds to the published minimal important difference for this tool)²⁰ per unit change in predictor. In the multivariate analyses, all of the prespecified predictors were left in the model. SAS version 9.3 (SAS Institute Inc, Cary, NC) was used.

RESULTS

A total of 303 participants (151 randomized to the SMART group and 152 randomized to the Standard group) were enrolled between June 2010 and September 2011. The baseline characteristics of the participants are shown in Table I. Complete electronic data were available from 2498 of 2642 dispensed monitors (94.5%) and 2498 of 2549 returned monitors (98.0%).²⁴

Predictors of severe asthma exacerbations

Overall, 1 or more severe exacerbations were experienced during the study by 78 of the 303 participants (26%). Baseline characteristics of the participants by occurrence of severe exacerbation are shown in Table E1 (in this article's Online Repository at www.jaci-inpractice.org). In univariate analyses, older age, female sex, a higher number of severe exacerbations in the preceding 12 months, a higher ACQ score (worse asthma control), higher baseline self-reported reliever use, lower FEV₁ % predicted, and treatment with Standard therapy were all associated with an increased risk of subsequent severe asthma exacerbation (Table II). In multivariate analyses, lower baseline FEV₁ % predicted (RR 1.14 [95% CI, 1.03-1.27] per 10% lower), a higher number of severe exacerbations in the preceding 12 months (RR 1.15 [95% CI, 1.01-1.31] per 1 in the preceding 12 months), treatment with Standard therapy (RR 1.62 [95% CI, 1.07-2.47]), and female sex (RR 2.18 [95% CI, 1.29-3.67]) were all associated with risk of severe exacerbation (Table II).

TABLE I. Baseline characteristics of the study participants

Characteristic	SMART group (n = 151)	Standard group (n = 152)
Age (y), mean $\pm$ SD	41.3 $\pm$ 13.7	42.6 $\pm$ 14.5
Men, no. (%)	48 (31.8)	46 (30.3)
Ethnicity, no. (%)		
European	113 (74.8)	118 (77.6)
Māori	25 (16.6)	19 (12.5)
Pacific Islander	5 (3.3)	10 (6.6)
Other	8 (5.3)	5 (3.3)
Baseline self-reported reliever use score, median (IQR)*	2 (1-3)	2 (1-3)
Baseline self-reported reliever use score, no. (%)*		
0 (0 inhalations)	26 (17.2)	22 (14.5)
1 (1-2 inhalations most days)	45 (29.8)	49 (32.2)
2 (3-4 inhalations most days)	39 (25.8)	40 (26.3)
3 (5-8 inhalations most days)	25 (16.6)	21 (13.8)
4 (9-12 inhalations most days)	8 (5.3)	11 (7.2)
5 (13-16 inhalations most days)	5 (3.3)	3 (2.0)
6 (>16 inhalations most days)	3 (2.0)	6 (3.9)
ACQ-5 score, mean $\pm$ SD	1.78 $\pm$ 0.99	1.79 $\pm$ 1.24
ACQ-5 score, no. (%)		
≤ 0.75	23 (15.2)	33 (21.7)
0.76-1.49	35 (23.2)	43 (28.3)
≥ 1.5	93 (61.6)	76 (50.0)
On-treatment FEV ₁ (L), mean $\pm$ SD†	2.62 $\pm$ 0.91	2.50 $\pm$ 0.78
On-treatment FEV ₁ % predicted, mean $\pm$ SD†	81.6 $\pm$ 18.9	80.4 $\pm$ 20.5
On-treatment FEV ₁ % predicted, no. (%)†		
<40%	0 (0)	3 (2.0)
40%-60%	22 (14.6)	25 (16.4)
60%-80%	46 (30.5)	39 (25.7)
80%-100%	58 (38.4)	61 (40.1)
>100%	25 (16.6)	24 (15.8)
Severe exacerbations in the prior 12 mo, mean $\pm$ SD‡	1.55 $\pm$ 1.31	1.73 $\pm$ 1.22
Severe exacerbations in the prior 12 mo, no. (%)‡		
0	14 (9.3)	11 (7.2)
1	86 (57.0)	75 (49.3)
2	29 (19.2)	31 (20.4)
3	10 (6.6)	22 (14.5)
4	5 (3.3)	6 (3.9)
≥ 5	7 (4.6)	7 (4.6)
No. hospital admissions ever for asthma, median (IQR)	1 (0-4)	1 (0-4)
Medication use§		
Daily ICS dose (budesonide or equivalent) (μ g), mean $\pm$ SD	804.5 $\pm$ 352.7	812.6 $\pm$ 370.4
LABA, no. (%)	92 (60.9)	103 (67.8)
Step up, no. (%)	76 (50.3)	64 (42.1)
Step neutral, no. (%)¶	75 (49.7)	88 (57.9)
ICS dose reduction, no. (%)#	14 (9.2)	15 (9.9)
Smoking status, no. (%)		
Current smokers	30 (19.9)	29 (19.1)
Ex-smokers	49 (32.5)	48 (31.6)
Nonsmokers	72 (47.7)	75 (49.3)

ICS, Inhaled corticosteroid; IQR, interquartile range; LABA, long-acting β -agonist.*ACQ question no. 6, authorized New Zealand Version; ACQ question no. 6 is a categorical score of self-reported β -agonist use over the preceding 7 days.

†Performed without withholding medications (see Ref 5).

‡Defined according to the American Thoracic Society/European Respiratory Society criteria as (a) the use of systemic corticosteroids for at least 3 days, or (b) a hospitalization or emergency department visit because of asthma, which required systemic corticosteroids (Ref 5).

§ICS dose conversion: 500 μ g fluticasone = 800 μ g budesonide; 1000 μ g beclomethasone = 800 μ g budesonide; a low daily budesonide dose was defined as 200-400 μ g; a medium daily budesonide dose was defined as >400-800 μ g; high daily budesonide dose was defined as >800 μ g.

||Defined as having no prestudy treatment with LABA (at any ICS dose) or prestudy treatment with low-dose budesonide and LABA (from Ref 1).

¶Defined as prestudy treatment with medium- or high-dose budesonide and LABA (from Ref 1).

#Defined as the subgroup of step-neutral patients who were on prestudy high-dose budesonide and LABA (from Ref 1).

TABLE II. Poisson regression for baseline factors as predictors of future severe asthma exacerbation*

Predictor	Univariate, RR (95% CI)	P	Multivariate, RR (95% CI)	P
Age (per decade older)	1.15 (1.00-1.33)	.043	1.14 (0.98-1.33)	.08
Women vs men	2.08 (1.25-3.46)	.005	2.18 (1.29-3.67)	.004
Māori vs non-Māori	1.03 (0.59-1.78)	.92	0.77 (0.43-1.36)	.37
Previous severe exacerbations (per 1 in the preceding 12 mo)	1.24 (1.11-1.38)	<.001	1.15 (1.01-1.31)	.033
Hospital admissions (per 1 ever)	1.00 (0.98-1.02)	.66	0.99 (0.97-1.02)	.68
ACQ-5 score (per 0.5 points higher)†	1.12 (1.03-1.21)	.006	0.99 (0.88-1.12)	.88
Self-reported reliever use (per 1 category on ACQ question no. 6)	1.21 (1.07-1.37)	.002	1.17 (0.90-1.52)	.25
FEV ₁ % predicted (per 10% lower)	1.20 (1.09-1.33)	<.001	1.14 (1.03-1.27)	.015
Standard vs SMART groups	1.84 (1.22-2.77)	.004	1.62 (1.07-2.47)	.024

RR, Rate ratio.

*This analysis treats exacerbations as a Poisson count variable (with an offset for time of observation within the study), so the outcome is the ratio of the number of exacerbations per unit time; there was no evidence of overdispersion for this analysis and no overdispersion adjustment was used; a severe asthma exacerbation was defined as (a) the use of systemic corticosteroids for at least 3 days, or (b) a hospitalization or emergency department visit because of asthma, which required systemic corticosteroids (from Ref 5).

†ACQ-5 is a composite score for asthma control (from Ref 20).

Predictors of poor asthma control

Overall, 56 of 277 of the participants (20%) had an ACQ-5 score ≥ 1.5 at 6 months compared with 169 of 303 (56%) at study entry. Baseline characteristics of participants by poor asthma control at 6 months are shown in Table E2 (in this article's Online Repository at www.jaci-inpractice.org). In univariate analysis, a higher number of severe exacerbations in the preceding 12 months, a higher baseline ACQ-5 score (worse asthma control), higher baseline self-reported reliever use, lower FEV₁ % predicted, and treatment with Standard therapy were predictors of poor control at 6 months (Table III). In multivariate analyses, a higher baseline ACQ-5 score (regression coefficient 0.20 [95% CI, 0.13-0.27] per 0.5 points higher) and greater age (regression coefficient 0.09 [95% CI, 0.01-0.17] per decade older) were predictors of poor control at 6 months (Table III).

Predictors of extreme β -agonist overuse

Overall, 81 of 303 participants (27%) had 1 or more episodes of extreme overuse during the study. Baseline characteristics of participants by occurrence of extreme overuse are shown in Table E3 (in this article's Online Repository at www.jaci-inpractice.org). In univariate analysis, Māori ethnicity, a higher number of severe exacerbations in the preceding 12 months, a higher number of hospital admissions ever, higher self-reported reliever use, lower FEV₁ % predicted, and the Standard therapy were all associated with an increased risk of subsequent extreme β -agonist overuse (Table IV). In multivariate analyses, higher baseline self-reported reliever use (RR 1.63 [95% CI, 1.36-1.95] per ACQ question no. 6 category), Māori ethnicity (RR 2.20 [95% CI, 1.43-3.38]), and lower FEV₁ % predicted (RR 1.16 [95% CI, 1.03-1.31] per 10% lower) were associated with a greater risk of extreme β -agonist overuse (Table IV).

DISCUSSION

Our study demonstrated that future severe asthma exacerbations, poor asthma control, and extreme β -agonist overuse are predicted by different baseline clinical and demographic characteristics and management approaches for patients with asthma who are at risk. In keeping with previous findings, previous severe exacerbations,^{6,11,29} lower lung function,^{7,30} treatment with the Standard therapy compared with the SMART,^{31,32} and female sex^{10,11} were associated with increased risk of severe asthma exacerbations. Increased baseline asthma symptoms, as measured

by ACQ-5 score³ and age were associated with future poor asthma control. Higher baseline self-reported reliever medication use, Māori ethnicity, and lower FEV₁ were significantly associated with future extreme β -agonist overuse. Our findings support the use of clinical and demographic characteristics that may be predictors of future adverse events in patients with asthma who are at risk as an important component of asthma management.

Our present analysis confirms the importance of lung function (FEV₁ % predicted) as an independent predictor of future severe exacerbations.^{7,30} In our study, inhaled medications were not withheld before FEV₁ measurements, which allows our findings to be generalizable to primary care. The number of previous severe exacerbations was significant in this model but only weakly; previous reports of a strong association between past and future severe exacerbations were based on a comparison of none versus 1 or more past exacerbations,^{6,11,29} whereas, in the present study, almost all the participants had at least 1 severe exacerbation in the previous year. Our study confirmed previous reports in adults, female sex is also associated with increased risk of severe exacerbations^{10,11}; a number of potential mechanisms have been proposed to account for this finding.^{33,34} In univariate analyses, but not in multivariate analyses, the baseline ACQ-5 score was a predictor of future severe exacerbations. There was a more consistent association with future poor asthma control. Although this differential association, based on these particular outcome variables, may be due to the relatively small number of events in relation to potential predictors, it could also be consistent with different baseline characteristics that predict different adverse outcomes in asthma, which, in turn, is consistent with the multidimensional nature of future risk. In general, the point estimates for associations with future poor outcomes for individual predictors were weakened in the multivariate analyses. This again may be due to the large number of predictors in relation to events or collinearity among predictors. It might also support that a number of factors contribute together to increased risk. We were unable to explore interactions between predictors because of the modest size of this data set.

Our study presents novel data on predictors of extreme β -agonist overuse by patients, defined as >32 actuations of salbutamol (or equivalent) in any 24-hour period. In case series, the self-administration of very high doses of β -agonist has been reported in fatal and near-fatal asthma.^{35,36} Analysis of results of epidemiologic studies indicated that β -agonist overuse is a risk factor

TABLE III. Linear regression for baseline factors as predictors of future ACQ scores*

Predictor	Univariate, regression coefficient (95% CI)	P	Multivariate, regression coefficient (95% CI)	P
Age (per decade older)	0.03 (−0.005 to 0.01)	.45	0.09 (0.01–0.17)	.03
Women vs men	0.10 (−0.15 to 0.36)	.43	0.02 (−0.22 to 0.26)	.86
Māori vs non-Māori	0.20 (−0.15 to 0.54)	.26	0.07 (−0.25 to 0.38)	.67
Previous severe exacerbations (per 1 in the preceding 12 mo)	0.10 (0.01–0.20)	.027	0.02 (−0.06 to 0.11)	.60
Hospital admissions (per 1 ever)	0.01 (−0.01 to 0.02)	.32	0.002 (−0.01 to 0.01)	.78
ACQ-5 score (per 0.5 points higher)†	0.19 (0.14–0.24)	<.001	0.20 (0.13–0.27)	<.001
Self-reported reliever use (per 1 category on ACQ question no. 6)	0.20 (0.12–0.28)	<.001	−0.01 (−0.12 to 0.09)	.79
FEV ₁ % predicted (per 10% lower)	0.07 (0.01–0.13)	.015	0.01 (−0.05 to 0.07)	.67
Standard vs SMART groups	0.25 (0.01–0.48)	.042	0.21 (−0.01 to 0.42)	.065

*This analysis treats the ACQ-5 variable as a continuous outcome variable and the regression coefficients represent the number of units change in ACQ-5 per unit change in the predictor variable; a higher ACQ-5 represents worse control.

†ACQ-5 is a composite score for asthma control (from Ref 20). Future poor asthma control was defined as an ACQ-5 score of ≥ 1.5 (from Ref 25) at 6 mo (ie, at visit 5, study completion).

TABLE IV. Poisson regression for baseline factors that are predictors of extreme β -agonist overuse*

Predictor	Univariate, RR (95% CI)	P	Multivariate RR (95% CI)	P
Age (per decade older)	0.85 (0.72–1.00)	.057	0.97 (0.82–1.14)	.47
Women vs men	1.35 (0.78–2.33)	.29	1.09 (0.67–1.76)	.74
Māori vs non-Māori	3.45 (2.14–5.55)	<.001	2.20 (1.43–3.38)	<.001
Previous severe exacerbations (per 1 in the preceding 12 mo)	1.29 (1.14–1.46)	<.001	1.06 (0.94–1.20)	.34
Hospital admissions (per 1 ever)	1.01 (0.99–1.03)	<.001	1.0 (0.97–1.02)	.84
ACQ-5 score (per 0.5 point higher)	1.44 (1.33–1.55)	.27	1.04 (0.92–1.17)	.53
Self-reported reliever use (per 1 category on ACQ question no. 6)	1.89 (1.69–2.11)	<.001	1.63 (1.36–1.95)	<.001
FEV ₁ % predicted (per 10% lower)	1.34 (1.19–1.51)	<.001	1.16 (1.03–1.31)	.014
Standard vs SMART groups	1.80 (1.10–2.94)	.02	1.39 (0.90–2.15)	.13

RR, Rate ratio.

*This analysis treats the number of days of extreme overuse as a Poisson count variable (with an offset for time of exposure to medication within the study), so the outcome is the ratio of the number of days of extreme overuse per unit time; there was evidence of overdispersion for this analysis the scaled deviance (deviance divided by degrees of freedom) was used to correct for overdispersion; for the Standard group, extreme overuse was defined as >32 actuations of salbutamol in any 24-h period; for the SMART group, data from all budesonide-formoterol inhalers for the period were combined, and extreme overuse was defined as >16 actuations of budesonide-formoterol in excess of the prescribed four maintenance doses (ie, equivalent to >20 actuations in total) in any 24-h period.

for death.^{15,16} These studies^{15,16} relied on prescription databases, which are only able to estimate sustained overuse over long periods rather than actual episodes of extreme β -agonist overuse, which was measured by validated covert electronic monitors in our study.^{23,24}

We observed that patient self-reported reliever medication use at baseline was a strong predictor of the likelihood of episodes of extreme β -agonist overuse in the following 6 months. Obtaining a history of reliever medication overuse may have utility in clinical practice because it could identify patients at risk of subsequent β -agonist overuse to a level that is associated with a risk of mortality. This approach may be particularly important in ethnic groups that are disadvantaged and at risk of poor asthma outcomes. Māori patients were found to be at a higher risk of extreme β -agonist overuse and have previously been reported to have disproportionately poorer outcomes compared with non-Māori, including symptom control,³⁷ asthma-related hospitalizations^{37,38} and deaths.³⁸ The importance of recognizing the significance of ethnicity may not be unique to New Zealand, because at-risk ethnic groups have been identified in a number of countries, including Australia,³⁹ the United Kingdom,⁴⁰ America,⁴¹ and Canada.⁴²

In keeping with prior studies,^{31,32} results of analysis of our data indicate that the SMART approach reduces the risk of future severe exacerbations compared with fixed-dose budesonide-

formoterol with salbutamol for relief. Our study extends the generalizability of this previous finding because our trial included patients who smoked and patients with high baseline reliever medication use, and there was no step down in baseline treatment on randomization.¹⁷ As previously reported, use of electronic monitoring allowed us to identify that both reduction in inhaled corticosteroid nonadherence and self-titrated budesonide-formoterol use during worsening asthma may have contributed to the reduction in severe exacerbations with the SMART regimen.¹⁷

Strengths of this analysis included study of a community-based population at risk on the basis of an exacerbation in the previous 12 months but not limited by smoking status or previous patterns of reliever use, and without constraints, such as study diaries and dummy medications. High-quality data were obtained about actual medication use for patients in both treatment arms, not only of maintenance medications but also of reliever medications, which allowed identification of episodes of extreme β -agonist overuse. However, there are a number of limitations to this analysis. The participants in the study were provided with their medications free of charge, which avoided the potential impact of cost on medication behavior. This was a *post hoc* analysis and may have limited power to identify or rule out predictor characteristics and is also vulnerable to type I error

rate inflation by performance of a relatively large number of statistical tests.

There were relatively limited numbers of participants with severe exacerbations, poor control, or extreme β -agonist overuse. In exploratory regression analyses, a general guideline is to have a minimum of 10 events per predictor, and we exceeded this. Nine variables for 78 events are shown in Table II. This may lead to biased estimates of association for both univariate and multivariate analyses; however, we think that it is still useful to present these estimates of association, with this caveat, because of the other strengths of the prospective data collection. Other risk factors of interest that might be usefully explored in future research are obesity, atopic status, smoking status, and previous treatment step. We acknowledge that self-reported measures of medication use may be limited by recall bias and social desirability bias; however, analysis of the present findings indicates that self-reported baseline reliever use is appropriate for identifying patients at risk in a clinical setting, in which electronic monitoring is not routinely available.

In conclusion, this analysis from a randomized controlled trial conducted with patients with asthma who were at risk has confirmed the clinical utility of existing predictors of subsequent severe asthma exacerbations and poor asthma control. We also examined the baseline characteristics that are predictors of future risk of extreme β -agonist overuse. We found different predictors for the 3 different adverse outcomes, which suggests that “future risk” may be considered as a multidimensional outcome. We recommend the use of different clinical and demographic characteristics as predictors of future risk of adverse outcomes to allow targeted treatment approaches.

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TABLE E1. Baseline characteristics of patients with and without a future severe asthma exacerbation

	Severe exacerbation (n = 78)	No severe exacerbation (n = 225)
ACQ-5 score, mean $\pm$ SD	1.96 $\pm$ 1.32	1.73 $\pm$ 1.04
Age (y), mean $\pm$ SD	44.1 $\pm$ 13.5	41.2 $\pm$ 14.3
FEV ₁ % predicted, mean $\pm$ SD	75.6 $\pm$ 21.0	82.9 $\pm$ 18.9
Prior hospital admissions ever, median (IQR)	1 (0-6)	1 (0-3)
Severe asthma exacerbation in the prior 12 mo, mean $\pm$ SD	1.95 $\pm$ 1.20	1.53 $\pm$ 1.27
Self-reported reliever use, mean ACQ question no. 6, mean $\pm$ SD	2.12 $\pm$ 1.64	1.76 $\pm$ 1.34
SMART, no. (%)	28 (18.5)	123 (81.5)
Standard, no. (%)	50 (32.9)	102 (67.1)
Māori, no. (%)	11 (25.0)	33 (75.0)
Non-Māori, no. (%)	67 (25.9)	192 (74.1)
Men, no. (%)	17 (18.1)	77 (81.9)
Women, no. (%)	61 (29.2)	148 (70.8)

TABLE E2. Baseline characteristics in patients with and without future poor asthma control

	Poor control (n = 56)	Not poorly controlled (n = 221)
ACQ-5 score, mean $\pm$ SD	2.5 $\pm$ 1.2	1.7 $\pm$ 1.0
Age (y), mean $\pm$ SD	45.2 $\pm$ 14.2	41.2 $\pm$ 14.1
FEV ₁ % predicted, mean $\pm$ SD	77.2 $\pm$ 20.1	81.9 $\pm$ 19.6
Prior hospital admissions ever, median (IQR)	1 (0-4.5)	1 (0-4)
Severe asthma exacerbation in the prior 12 mo, mean $\pm$ SD	1.8 $\pm$ 1.1	1.6 $\pm$ 1.3
Self-reported reliever use, mean ACQ question no. 6, mean $\pm$ SD	2.4 $\pm$ 1.7	1.7 $\pm$ 1.3
SMART, no./total no. (%)	22/135 (16.3)	113/135 (83.7)
Standard, no./total no. (%)	34/142 (23.9)	108/142 (76.1)
Māori, no./total no. (%)	9/39 (23.1)	30/39 (76.9)
Non-Māori, no./total no. (%)	47/238 (19.7)	191/238 (80.3)
Men, no./total no. (%)	16/85 (18.8)	69/85 (81.2)
Women, no./total no. (%)	40/192 (20.8)	152/192 (79.2)

TABLE E3. Baseline characteristics of patients with and without future extreme β -agonist overuse

	Overuse (n = 81)	No overuse (n = 222)
ACQ-5 score, mean $\pm$ SD	2.36 $\pm$ 1.16	1.57 $\pm$ 1.03
Age (y), mean $\pm$ SD	41.8 $\pm$ 13.4	42.0 $\pm$ 14.4
FEV ₁ % predicted, mean $\pm$ SD	75.5 $\pm$ 22.4	83.0 $\pm$ 18.3
Prior hospital admissions ever, median (IQR)	1 (0-6)	1 (0-3)
Severe asthma exacerbation in the prior 12 mo, mean $\pm$ SD	2.07 $\pm$ 1.31	1.48 $\pm$ 1.22
Self-reported reliever use, mean ACQ question no. 6, mean $\pm$ SD	2.72 $\pm$ 1.70	1.53 $\pm$ 1.17
SMART, no. (%)	41 (27.2)	110 (72.3)
Standard, no. (%)	40 (26.3)	112 (73.7)
Māori, no. (%)	19 (43.2)	25 (56.8)
Non-Māori, no. (%)	62 (23.9)	197 (76.1)
Men, no. (%)	18 (19.2)	76 (80.9)
Women, no. (%)	63 (30.1)	146 (69.9)