

Step-Down Therapy for Asthma Well Controlled on Inhaled Corticosteroid and Long-Acting Beta-Agonist: A Randomized Clinical Trial



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What is already known about this topic? Current recommendations regarding stepping down combination inhaled corticosteroid (ICS)/long-acting beta-agonist (LABA) therapy when asthma is well controlled are based on limited data. Whether the ICS dose should be reduced first or whether LABA should be discontinued remains unclear.

What does this article add to our knowledge? No difference in treatment failure was identified in those with well-controlled asthma on medium-dose ICS/LABA following randomization to maintenance of medium-dose ICS/LABA, reduced-dose ICS/LABA, or stable-dose ICS and LABA discontinuation.

How does this study impact current management guidelines? Our results suggest similar outcomes with use of either strategy of reducing asthma therapy but also highlight significant rates of treatment failure over the course of 1 year in all 3 treatment arms.

BACKGROUND: Stepping down therapy when asthma is well controlled on combination inhaled corticosteroids (ICSs) and long-acting beta-agonists (LABAs) is recommended, but it is not known whether lowering the ICS dose or stopping LABA is superior.

OBJECTIVE: To evaluate whether step-down therapy with LABA is superior to one without; and, secondarily, to evaluate whether reducing the ICS dose while maintaining LABA is noninferior to remaining on stable-ICS/LABA.

METHODS: The study was a randomized, double-masked 3-arm parallel group trial in participants aged 12 years or older. Following an 8-week run-in, 459 participants were randomly assigned to continue medium-dose ICS/LABA, reduced-dose

ICS/LABA, or ICS alone (LABA-step-off) and followed for 48 weeks. The primary outcome was time to treatment failure, a composite of health care utilization, systemic corticosteroid use, increase in rescue therapy, decline in lung function, or participant or physician decision.

RESULTS: Time to treatment failure did not differ significantly between reduced- ICS/LABA and LABA-step-off (hazard ratio, 1.07; 95.3% CI, 0.69-1.65, $P = .76$). Nor was there a difference between stable-ICS/LABA and reduced-ICS/LABA (hazard ratio, 1.11; 95% CI, 0.70-1.76; $P = .67$), but the 10% non-inferiority margin was exceeded. Lung function declines and hospitalization rates were significantly greater in the LABA-step-off group.

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Abbreviations used

ACT- Asthma Control Test

FDA- Food and Drug Administration

FSC- Fluticasone-salmeterol combination

HR- Hazard ratio

ICS- Inhaled corticosteroid

LABA- Long-acting beta-agonist

CONCLUSIONS: The 2 step-down regimens did not differ in terms of treatment failure, although stopping LABA was associated with a decline in lung function and more hospitalizations. There was no evidence to support the noninferiority of reduced-ICS/LABA as compared with stable-ICS/LABA. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:633-43)

Key words: Asthma; Long-acting beta-agonist; Step-down therapy

Although asthma guidelines recommend stepping down therapy once asthma is controlled, the best approach for patients on combination inhaled corticosteroid (ICS) and long-acting beta-agonist (LABA) remains unclear. The 2007 National Asthma Education Program guidelines do not advocate a specific approach to stepping down therapy.¹ The Global Initiative for Asthma recommends reducing the ICS dose while maintaining the LABA dose, citing better symptom control.² Single maintenance and reliever therapy with adjustable ICS/LABA dosing is used worldwide; however, this strategy is not approved by US regulatory authorities.^{3,4} Concerned about LABA safety, the US Food and Drug Administration (FDA) recommends that LABAs should be used for the shortest duration required to achieve asthma control and then should be discontinued.⁵ In practice, many clinicians do not reduce therapy as long as asthma is well controlled.⁶ Most studies examining tapering of ICS/LABA therapy suggest that approaches where a LABA is maintained result in superior lung function compared with approaches where patients are “stepped off” to ICS alone.⁷⁻¹¹ These studies suggest that the ICS dose can be reduced by 50% when a LABA is maintained but that the ICS cannot be stopped without loss of control and LABA monotherapy is not recommended.¹²⁻¹⁴ Systematic reviews of step-down therapy suggested modestly

better asthma control and quality of life when the LABA was maintained; however, these were of insufficient duration to assess exacerbations and serious adverse events.^{15,16} Trials with a longer duration of follow-up and measurement of exacerbations have been recommended to evaluate the optimal tapering strategy for patients on ICS/LABA. Accordingly, the American Lung Association Airways Clinical Research Centers conducted the Long-acting Beta-Agonist Step Down Study to compare outcomes of ICS reduction, LABA discontinuation, or maintenance of stable treatment in patients well controlled on medium-dose ICS/LABA.

METHODS

Study design

This was a randomized, double-masked, parallel, 3-arm, 56-week trial comparing approaches to stepping down therapy for individuals with well-controlled asthma on ICS/LABA. Participants with well-controlled asthma on baseline treatment with moderate-dose ICS/LABA for at least 30 days were enrolled in an 8-week open-label treatment run-in with fluticasone propionate/salmeterol combination (FSC, Advair Diskus 250/50 twice daily) and were subsequently randomized if their asthma remained stable.

Study population

Eligible participants were aged 12 years or older with physician-diagnosed asthma on treatment with medium-dose FSC, well controlled for at least 4 weeks before enrollment. Participants were excluded if they had smoked more than 10 pack-years or had smoked in the past year (for full list of eligibility criteria, see this article's Online Repository at www.jaci-inpractice.org). Participants were recruited and enrolled between December 2011 and May 2014. Participants whose asthma remained stable while continuing medium-dose FSC during the run-in were randomly assigned to study treatment. Stable asthma was defined as an Asthma Control Test (ACT) score of 20 or more at week 4 and week 8, no unscheduled health care encounters, no change in asthma medication, pre-bronchodilator FEV₁ value of greater than or equal to 70% predicted, the use of fewer than 16 puffs of rescue beta-agonist per week and no more than 10 puffs of rescue beta-agonist on 2 consecutive days.

Study treatments

Participants were randomly assigned (1:1:1) to receive masked treatment for 48 weeks with FSC (Advair Diskus 250/50) twice daily referred to as stable-ICS/LABA or FSC 100/50 (Advair Diskus 100/50) twice daily referred to as reduced-ICS/LABA, or fluticasone

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propionate (Flovent Diskus 250 µg) twice daily referred to as LABA-step-off. The Data Coordinating Center prepared a permuted block randomization scheme stratified by clinic. Treatments were masked to participants, clinicians, and data analysts during follow-up.

Outcome measures

The primary outcome measure was time to treatment failure, defined as any of the following: hospitalization or urgent medical visit for asthma; systemic corticosteroids for asthma; increase in controller therapy; a decrease in prebronchodilator FEV₁ of 20% or more below the value measured at randomization; 2 consecutive days with a 35% decrease in morning peak expiratory flow rate from the baseline value as recorded on daily diaries (baseline defined as the mean over the final 2 weeks of the stable treatment phase); use of more than 10 puffs of rescue beta-agonist for 2 consecutive days; participant refusal to continue in the trial (eg, medication intolerance and inadequate symptom relief); or physician's judgment (reasons of safety).¹⁷ Secondary outcome measures included ACT score (range, 5-25, higher better)^{18,19}; pulmonary function; Asthma Symptoms Utility Index score (range, 0-1, higher better)²⁰; quality of life (EuroQol five-dimensional questionnaire, 5 level, range, 0.109-1, higher better)²¹; and asthma-specific quality-of-life scores (adults 18 years and older: Marks Asthma Quality of Life Questionnaire score [range, 0-80, lower better]²²; children aged 12-17 years: Children's Health Survey for Asthma [2-week version, range 0-100, higher better]).²³ Other outcomes include symptom-free days and fraction of exhaled nitric oxide. The detailed study schema and data collection schedule are available in this article's Online Repository at www.jaci-inpractice.org.

Study oversight

The Steering Committee of the American Lung Association Airways Clinical Research Centers designed, approved, and oversaw study implementation. GlaxoSmithKline funded the study with an unrestricted grant to the American Lung Association and also provided the active drug and placebo. GlaxoSmithKline reviewed the protocol before funding the trial but had no role in design, conduct, or analysis of the results. Study centers received institutional review board approval from their local boards and all participants signed institutional review board-approved consent statements. Participants younger than 18 years provided written assent. An independent data and safety monitoring committee that had access to unmasked data monitored the trial.

Sample size

The primary hypothesis compared LABA-step-off versus reduced-ICS/LABA. The planned sample size of 150 per group provided 80% power to detect a 0.15 increase in the proportion of participants experiencing treatment failure by 48 weeks from 0.20 for reduced-ICS/LABA to 0.35 for LABA-step-off assuming a 2-sided type 1 error rate and 10% loss to follow-up. Power based on a time to event analysis was similar (82%). The significance threshold for the primary hypothesis was adjusted to be 0.047 to account for 2 interim analyses. There was relatively low power (54%) for the secondary hypothesis that the reduced-ICS/LABA regimen was noninferior to continuing on the stable-ICS/LABA regimen based on a 10% noninferiority margin. *P* values for secondary outcomes were not adjusted for multiple comparisons or interim analyses.

Data analysis

All analyses were performed according to treatment assignment and all available data were included in the analyses. Participants' characteristics were compared using Kruskal-Wallis and chi-square tests for continuous and categorical outcomes, respectively. The analysis of the primary outcome, time to first treatment failure, was performed using Cox proportional hazards models. The cumulative proportions with treatment failure, hospitalization for any reason, or development of moderate or severe symptoms were estimated with 95% CIs using Kaplan-Meier techniques. Generalized estimating equations were used to model continuous outcomes (eg, FEV₁ and ACT scores) over time while adjusting for repeated measurements.²⁴ A saturated mean structure was used and the covariance structure (unstructured, Toeplitz, or exchangeable) was selected on the basis of empirical evaluations of correlations among repeated measures for each outcome. Kruskal-Wallis tests were used to compare adherence using data from daily diaries and inhaler dose counters. Analyses were performed using SAS (SAS/STAT User's Guide, Version 9.1, SAS Institute Inc, Cary, NC) and R (Version 2.11.1, R Project for Statistical Computing; <http://www.r-project.org/>).

RESULTS

Characteristic of participants

A total of 553 patients were enrolled in the trial and 459 successfully completed the 8-week run-in period and were randomized (see Figure 1); 94 enrolled participants were not eligible for randomization. The primary reason for exclusion was treatment failure during the run-in (43%) and the next most common reason was not returning for the second or third visit during the run-in period (30%). Four participants were excluded from the analysis after randomization because of data irregularities. There were more female participants and diverse representation of major racial/ethnic groups. Overall, participants had good asthma control and lung function although approximately one-fourth had used oral corticosteroids for an exacerbation in the previous year. The demographic and asthma characteristics of patients who were randomized did not significantly differ among the 3 groups (see Table 1).

Adherence and follow-up

Rates of missing visits in the trial were low (4.5%) and 89% of participants completed 48 weeks of follow-up. Adherence to study treatment was high for all treatment groups whether measured using diary cards (median of 98% for all) or Diskus counters (92%, 90%, and 86% for the reduced-ICS/LABA, LABA-step-off, and stable-ICS/LABA groups, respectively) with no significant differences among the groups (*P* = .09). The LABA-step-off group had the highest rate of discontinuation of study treatment during the trial but the difference in comparison to the other 2 study groups was not significant.

Primary outcome

The cumulative proportion of participants with treatment failure was 26%, 28%, and 31% in the stable-ICS/LABA, reduced-ICS/LABA, and LABA-step-off groups, respectively (see Figure 2). Time to treatment failure did not differ significantly between reduced-ICS/LABA and LABA-step-off groups (hazard ratio [HR], 1.07; 95.3% CI, 0.69-1.65; *P* = .76). There was not sufficient evidence to either establish or exclude non-inferiority of time to treatment failure for reduced-ICS/LABA as compared with stable-ICS/LABA (HR, 1.11; 95% CI, 0.70-

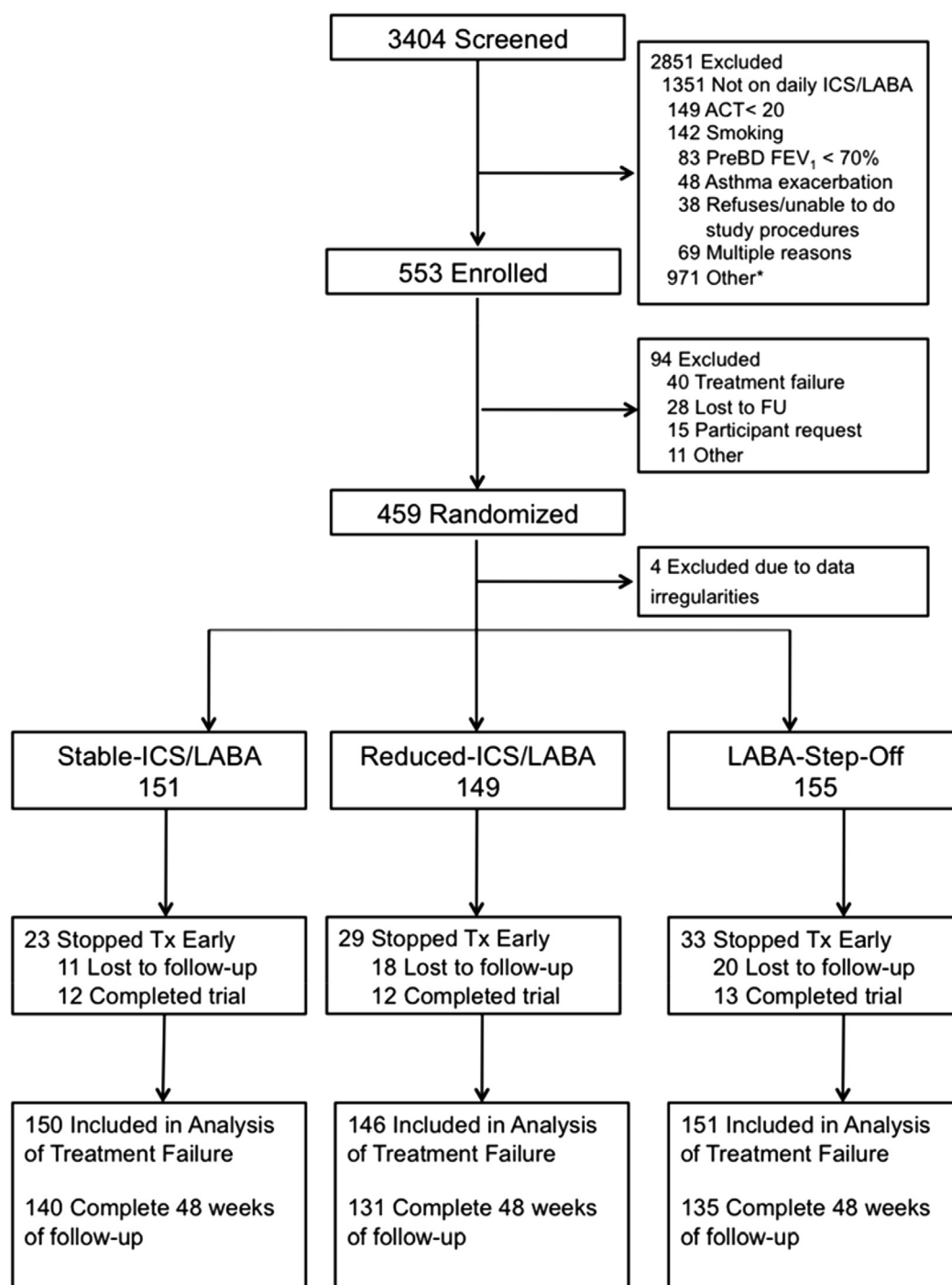


FIGURE 1. Flow of participants in the Long-acting Beta-Agonist Step Down Study. *BD*, Bronchodilator; *FU*, follow-up; *Tx*, treatment. *Other reasons for screening failures include a change in asthma medication within 4 weeks of screening ($N = 8$), lack of compensation ($N = 4$), not fluent in English or Spanish ($N = 3$), and unspecified reason ($N = 956$).

1.76; $P = .67$) as the 95% CI included the margin of 1.10. The most common reason for treatment failure in all 3 groups was use of systemic corticosteroids for asthma, contributing to 51% of treatment failures overall (see Table II) and did not differ among the groups. Hospitalizations or urgent care for asthma and decrease in FEV_1 of more than 20% contributed to treatment failure 30% and 27% of the time, respectively. Of the 26

pairwise comparisons of the components of failure, only 1 achieved statistical significance. LABA-step-off was less likely to have an increase in controller therapy contribute to failure than stable-ICS/LABA (HR, 0.20; 95% CI, 0.04-0.91; $P = .037$). However, the number of events was small (2 vs 10) and the expected number of significant results due to chance alone was 1.2. A number of subgroup analyses were performed stratifying

TABLE I. Characteristics of participants

Characteristic	Randomized (N = 455)	Stable- ICS/LABA (N = 151)	Reduced- ICS/LABA (N = 149)	LABA-step-off (N = 155)	P value*
Demographic characteristics at enrollment					
Age (y)					
Median (IQR)	35 (20-50)	36 (22-51)	33 (17-49)	35 (23-50)	.50
Age < 18 y, n (%)	100 (21)	31 (21)	39 (26)	30 (19)	.31
Sex: male, n (%)	168 (37)	55 (36)	61 (41)	52 (34)	.41
Former smoker, n (%)	62 (14)	23 (15)	25 (17)	14 (9)	.11
Secondhand smoke home/work, n (%)	56 (12)	18 (12)	21 (14)	17 (11)	.70
Race or ethnic group, n (%)					
White	221 (49)	72 (48)	74 (50)	75 (48)	.89
Black	151 (33)	52 (34)	48 (32)	51 (33)	
Hispanic	66 (15)	19 (13)	23 (15)	24 (15)	
Other	17 (4)	8 (5)	4 (3)	5 (3)	
Socioeconomic characteristics at enrollment, n (%)					
Household income†					
<\$14,999	49 (13)	17 (14)	18 (15)	14 (12)	.94
\$15,000-\$21,999	30 (8)	12 (10)	10 (8)	8 (7)	
\$22,000-\$43,999	84 (23)	24 (19)	28 (23)	32 (27)	
\$44,000-\$60,000	65 (18)	22 (18)	22 (17)	21 (18)	
More than \$60,000	136 (37)	49 (40)	45 (37)	42 (36)	
Unknown	91 (20)	27 (18)	26 (17)	38 (25)	
Insurance†					
Private insurance	271 (62)	93 (63)	87 (61)	91 (62)	.86
Public insurance	122 (28)	43 (29)	39 (27)	40 (27)	
Self-pay/no insurance	42 (10)	11 (7)	16 (11)	15 (10)	
Unknown	20 (4)	4 (3)	7 (5)	9 (6)	
Asthma characteristics at enrollment					
Age of asthma onset (y), median (IQR)	7 (2-20)	7 (3-21)	7 (2-18)	7 (2-20)	.78
Hospitalized for asthma in past year, n (%)	14 (3)	5 (3)	3 (2)	6 (4)	.53
Oral steroids in past year, n (%)	122 (27)	44 (29)	36 (24)	42 (27)	.62
Daily short-acting beta-agonist use, n (%)	29 (6)	7 (5)	12 (8)	10 (6)	.48
Daily antileukotriene use, n (%)	92 (20)	32 (21)	30 (20)	30 (19)	.92
FeNO (ppb), median (IQR)‡	17.5 (12.5-26)	18.5 (12.5-26.5)	17.5 (13.8-25.3)	16.5 (11.5-26.5)	.54
Atopy (phadiatop ≥0.35 kUA/L), n (%)‡	352 (79)	115 (78)	123 (84)	114 (74)	.09
Quality-of-life scores at randomization, median (IQR)					
Asthma Symptom Utility Index (↑) (range, 0-1)	0.95 (0.89-1.00)	0.95 (0.90-1.00)	0.94 (0.89-1.00)	0.98 (0.92-1.00)	.21
ACT score (↑) (range, 5-25)	23 (22-25)	23 (22-25)	23 (21-24)	23 (22-24)	.48
Mark's: ages 18 y and older (↓) (range, 0-80)	4.0 (2.0-8.0)	4.0 (1.5-8.0)	5.0 (2.0-9.0)	4.0 (2.0-7.0)	.37
Children's Health Survey for Asthma: ages 12-17 y (↑) (range, 0-100)					
Physical, child	93 (91-100)	93 (93-100)	93 (89-100)	96 (93-100)	.53
Activity, child§	100 (92-100)	100 (92-100)	100 (92-100)	100 (96-100)	.58
Emotion, child	93 (89-100)	93 (86-98)	95 (91-100)	93 (88-100)	.57
EQ-5D-5L	1.00 (0.86-1.00)	1.00 (0.86-1)	1.00 (0.86-1.00)	1.00 (0.86-1.00)	.90
Pulmonary function at randomization, median (IQR)					
Prebronchodilator FEV ₁ (L)	2.83 (2.30-3.43)	2.82 (2.24-3.31)	2.86 (2.35-3.44)	2.82 (2.38-3.49)	.46
Prebronchodilator FVC (L)	3.62 (3.00-4.44)	3.54 (2.99-4.30)	3.62 (2.97-4.54)	3.65 (3.03-4.56)	.60
Prebronchodilator peak flow (L/min)	430 (350-500)	420 (350-500)	430 (350-500)	430 (360-500)	.41
Postbronchodilator FEV ₁ (L)	2.92 (2.39-3.49)	2.88 (2.34-3.36)	2.96 (2.39-3.50)	2.93 (2.44-3.60)	.49
Postbronchodilator FVC (L)	3.62 (3.09-4.50)	3.59 (3.09-4.28)	3.72 (3.11-4.63)	3.65 (3.06-4.52)	.62
Prebronchodilator FEV ₁ (% predicted)	91 (83-100)	91 (82-99)	91 (83-101)	92 (83-101)	.54
Prebronchodilator FVC (% predicted)	99 (90-107)	98 (89-107)	100 (91-107)	98 (90-108)	.48
Prebronchodilator peak flow (% predicted)	98 (88-110)	96 (84-110)	100 (90-110)	98 (89-113)	.37

(continued)

TABLE I. (Continued)

Characteristic	Randomized (N = 455)	Stable- ICS/LABA (N = 151)	Reduced- ICS/LABA (N = 149)	LABA-step-off (N = 155)	P value*
Other conditions based on self-report at enrollment, n (%)					
Eczema	89 (20)	35 (23)	28 (19)	26 (17)	.35
Sinusitis†	125 (28)	50 (33)	41 (28)	34 (22)	.10
Allergic rhinitis†	246 (54)	85 (56)	73 (49)	88 (57)	.30
Food allergies‡	107 (24)	33 (22)	40 (27)	34 (22)	.52
Allergies worsen asthma‡	358 (79)	123 (81)	113 (76)	122 (79)	.49

FeNO, Fraction of exhaled nitric oxide; EQ-5D-5L, five-level EuroQol five-dimensional questionnaire; FVC, forced vital capacity; IQR, interquartile range.

† Higher scores represent better health; ‡ Lower scores represent better health.

*P values are based on the Kruskal-Wallis test for continuous variables and the chi-square test for categorical variables.

†The proportion missing is computed from the total number of individuals. The proportion within all other categories is computed out of the number of nonmissing entries.

‡FeNO measurements were missing for 12 individuals. Phadiatop measurements were missing for 8 individuals. Information for each of self-reported sinusitis, allergic rhinitis, food allergies, and allergies worsen asthma was missing for 1 individual.

§For 12-17-y-old participants, 1 did not provide the activity score for the Children's Health Survey for Asthma.

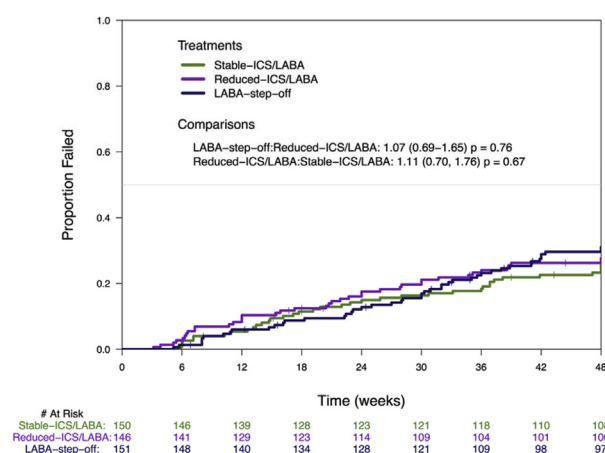


FIGURE 2. Comparison of time to first treatment failure.

by age (≥ 18 y vs < 18 y), sex (male vs female), race (white vs not white), age of asthma onset (> 30 y vs ≤ 30 y), emergency room visit in the past year (no vs yes), secondary smoke exposure (no vs yes), allergic rhinitis (no vs yes), albuterol use more than twice per week (no vs yes), prebronchodilator FEV₁ (% predicted < 80 vs ≥ 80), prebronchodilator forced vital capacity ($< 100\%$ vs $\geq 100\%$), and short-acting β -agonist use at enrollment (> 2 times/wk vs ≤ 2 times/wk). There were no statistically significant differences in the treatment effects between these subgroups (data not shown).

Secondary outcome

Lung function (as measured by prebronchodilator FEV₁, forced vital capacity, FEV₁/FVC, and peak flow) remained unchanged from randomization to 48 weeks among individuals assigned to the stable-ICS/LABA group (see Figure 3 and Figure E1 in this article's Online Repository at www.jaci-inpractice.org). In comparison, the prebronchodilator FEV₁ declined by -0.07 in the reduced-ICS/LABA group and by -0.13 in the LABA-step-off group. The decline in prebronchodilator lung function in the LABA-step-off group was significantly larger compared with that in the reduced-ICS/LABA group and the stable-ICS/LABA group. None of the lung function declines was greater than what is considered a minimal

clinically important difference of 230 mL for FEV₁ or 19 L/min for peak flow.²⁵ There was a small increase in exhaled nitric oxide during the study period, but the increase did not differ significantly among the 3 groups (see Table III). Asthma control as measured by the ACT and the Asthma Symptom Utility Index, and quality-of-life measures remained stable over follow-up and did not differ among the 3 treatment groups (see Table IV). We performed a time to event analysis for 2 ACT-based failure outcomes: drop of 3 or more in the ACT score and drop below 19 in the ACT score. For a decrease of 3 or more in the ACT score, a total of 227 events were observed within 48 weeks with cumulative proportions at 48 weeks of 51% (95% CI, 42%-59%), 49% (95% CI, 39%-57%), and 54% (95% CI, 44%-61%) for stable-ICS/LABA, reduced-ICS/LABA, and LABA-step-off groups, respectively. For a drop in the ACT score to below 19, a total of 125 events were observed within 48 weeks with cumulative proportions at 48 weeks of 26% (95% CI, 18%-33%), 28% (20%-35%), and 31% (95% CI, 23%-39%) for stable-ICS/LABA, reduced-ICS/LABA, and LABA-step-off groups, respectively. There were no statistically significant differences between the 3 treatment groups for either definition of failure. The percentage of asthma-free days was high in all 3 groups: 83% (interquartile range, 81%-99%) in the LABA-step-off group, 87% (interquartile range, 86%-99%) in the reduced-ICS/LABA group, and 88% (interquartile range, 86%-99%) in the stable-ICS/LABA group. There were 5 hospitalizations reported for asthma exacerbations (1 with pneumonia) during the trial, all in participants assigned to the LABA-step-off group. There were 23 all-cause hospitalizations: 1 in the run-in and 22 following randomization. For the latter, 13, 3, and 6 took place in the LABA-step-off, reduced-ICS/LABA, and stable-ICS/LABA groups, respectively. The rate of all-cause hospitalizations for the LABA-step-off group was higher compared with the rate for reduced-ICS/LABA (HR, 4.28; 95% CI, 1.21-15.01; $P = .023$) and stable-ICS/LABA groups (HR, 2.18; 95% CI, 0.82-5.74; $P = .12$), although the latter did not achieve statistical significance. Four of the hospitalizations were planned (2 knee replacements and 2 normal births). The results were similar (HR, 5.35; 95% CI, 1.18-24.14; $P = .029$ and HR, 2.22; 95% CI, 0.76-6.38; $P = .14$, respectively) if we restricted the analysis to unplanned or emergency hospitalizations. There were no deaths during the course of the study. The cumulative percentages of participants developing moderate or severe adverse effects were

TABLE II. Summary of the risk of and factors contributing to treatment failure

Factor	Overall	Stable- ICS/LABA	Reduced- ICS/LABA	LABA-step-off
Number at risk*	447	150	146	151
Number with an event	122	38	39	45
Cumulative proportion at 48 wk (95.3% CI)†	28% (23%-33%)	26% (18%-33%)	28% (19%-35%)	31% (23%-39%)
Components of failure, n (%)‡				
Hospitalization or urgent medical visit	37 (30)	10 (26)	13 (33)	14 (31)
Use of systemic corticosteroids	62 (51)	21 (55)	17 (44)	24 (53)
Increase in controller therapy	17 (14)	10 (26)	5 (13)	2 (4)
Decrease in prebronchodilator FEV ₁ >20% below the value at randomization	33 (27)	7 (18)	11 (28)	15 (33)
Decrease in PEF >35% below the BL§ value on 2 consecutive days	13 (11)	3 (8)	4 (10)	6 (13)
Use of 10 puffs or more per day of rescue beta-agonist for 2 consecutive days	13 (11)	3 (8)	3 (8)	7 (16)
Patient refusal	16 (13)	5 (13)	7 (18)	4 (9)
Physician judgment	12 (10)	6 (16)	5 (13)	1 (2)

BL, Baseline; PEF, peak expiratory flow (L/m).

*A total of 8 individuals were missing failure information and were excluded from the analysis: 1 in the stable-ICS/LABA, 3 in the reduced-ICS/LABA, and 4 in the LABA-step-off arms, respectively.

†Kaplan-Meier techniques were used to estimate the cumulative proportion at 48 wk to adjust for variable follow-up. A 95.3% CI was used to adjust for type I error spent on 2 interim analyses.

‡Individuals could have multiple factors contributing to failure simultaneously so the number of factors may exceed the number of individuals with an event. The percentage is computed on the basis of the number of individuals with an event.

§The baseline PEF is the mean of the final 2 wk of the stable treatment phase immediately before randomization.

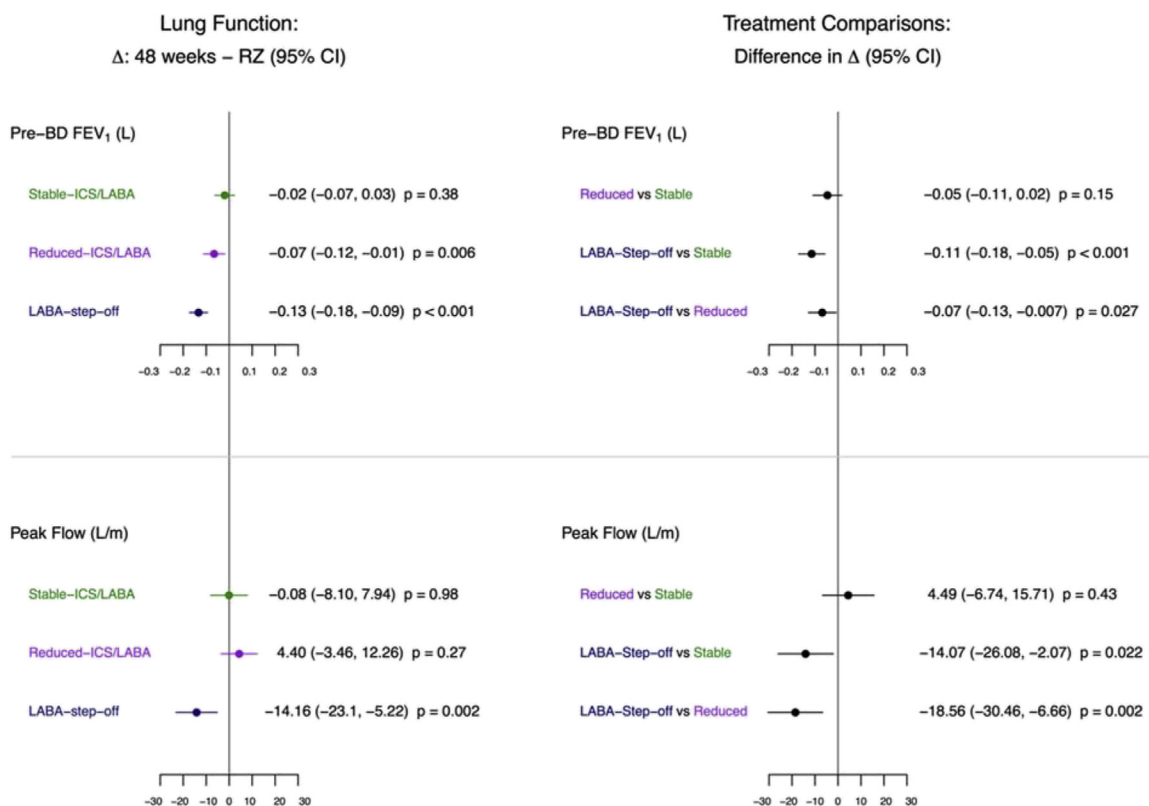


FIGURE 3. Change in the pre-FEV₁ and peak flow from randomization (left panel) and treatment effects (right panel) at 48 weeks. BD, Bronchodilator; RZ, randomization.

TABLE III. Model-based estimates of mean change from baseline to 48 wk for asthma scores and quality-of-life and laboratory markers by treatment group

Outcome	Secondary outcomes: Estimated Δ from RZ to 48 wk (SE)*			Treatment comparisons: Difference in Δ from RZ to 48 wk (95% CI)*		
	Stable- ICS/LABA	Reduced- ICS/LABA	LABA-step-off	Reduced- ICS/LABA – Stable- ICS/LABA	LABA-step-off – Stable- ICS/LABA	LABA-step-off – Reduced- ICS/LABA
Laboratory measurement						
FeNO (ppb)	3.52 (1.52)	4.38 (1.47)	6.16 (1.88)	0.86 (–3.28 to 5.00)	2.64 (–2.11 to 7.39)	1.78 (–2.91 to 6.46)
Questionnaire						
ACT score ($\uparrow$) (range, 5-25)	–0.23 (0.17)	0.06 (0.22)	–0.38 (0.23)	0.29 (–0.27 to 0.84)	–0.14 (–0.71 to 0.42)	–0.43 (–1.05 to 0.19)
Asthma Symptom Utility Index ($\uparrow$) (range, 0-1)	–0.004 (0.01)	0.002 (0.01)	–0.02 (0.01)	0.01 (–0.02 to 0.03)	–0.02 (–0.05 to 0.01)	–0.02 (–0.05 to 0.01)
EQ-5D-5L ($\uparrow$) (range, –0.109 to 1)	–0.001 (0.007)	–0.003 (0.007)	0.0001 (0.010)	–0.002 (–0.023 to 0.019)	0.001 (–0.023 to 0.026)	0.003 (–0.021 to 0.028)
Mark's AQLQ: age ≥ 18 y † ($\downarrow$) (range, 0-80)	0.35 (0.51)	0.47 (0.78)	1.89 (0.85)	0.12 (–1.72 to 1.96)	1.54 (–0.41 to 3.49)	1.42 (–0.85 to 3.69)
CHSA: ages 12-17 y † ($\uparrow$) (range, 0-100)						
Physical health	0.76 (1.41)	3.96 (1.47)	1.85 (1.64)	3.21 (–0.79 to 7.20)	1.10 (–3.15 to 5.34)	–2.11 (–6.43 to 2.21)
Child activities	0.22 (1.60)	1.68 (1.09)	–2.50 (1.59)	1.46 (–2.34 to 5.26)	–2.72 (–7.15 to 1.71)	–4.18 $_{\ddagger}$ (–7.97 to –0.40)
Emotional health	2.13 (2.35)	0.71 (1.35)	1.24 (0.90)	–1.43 (–6.73 to 3.88)	–0.90 (–5.83 to 4.03)	0.53 (–2.65 to 3.70)

Δ , Change; *AQLQ*, Asthma Quality of Life Questionnaire; *CHSA*, Children's Health Survey for Asthma; *EQ-5D-5L*, five-level EuroQol five-dimensional questionnaire; FeNO, fraction of exhaled nitric oxide; RZ, randomization.

$\uparrow$ Higher values indicate less severe disease. $\downarrow$ Lower values indicate less severe disease.

*Parameter estimates are calculated using generalized estimating equations with robust SEs. The models use a saturated mean structure and various covariance structures (unstructured: ACT, Asthma Symptom Utility Index, EQ-5D-5L; Toeplitz: Mark's AQLQ, CHSA physical health; exchangeable: CHSA child activities and emotional health, FeNO).

† Age is based on the age of enrollment as opposed to randomization.

$_{\ddagger}P = .030$.

TABLE IV. Development of previously undetected moderate or severe symptoms by treatment group

Symptom*	Number at risk†	Cumulative proportion at 48 wk (%)‡		
		Stable-ICS/LABA	Reduced-ICS/LABA	LABA-Step-off
Skin bruising	441	9	6	7
Upper respiratory tract infection	433	34	26	35
Sore throat	435	20	28	26
Hoarseness	432	21	26	16§
Chest pain	444	8	12	13
Cough	423	40	44	45
Musculoskeletal pain	420	26	20	20
Headache	414	29	22	31
Increased/irregular heartbeat	446	4	0.7	4
Restlessness or nervousness	444	13	11	9
Runny nose/congestion	383	49	46	46
Nausea/vomiting	445	12	13	8

*Only symptoms with 10 or more events are summarized. Seven individuals experienced moderate or severe tremors and thrush during follow-up.

†Individuals were at risk if they did not have moderate or severe symptoms at randomization and had follow-up available.

‡The cumulative proportion is estimated using Kaplan-Meier techniques to account for variable follow-up.

§The LABA-step-off group had significantly fewer individuals develop moderate or severe hoarseness as compared with the reduced-ICS/LABA group (HR, 0.54; $P = .027$). All other differences were not statistically significant.

similar among the groups (see Table IV). More participants assigned to the reduced-ICS/LABA group reported hoarseness than those assigned to the LABA-step-off group (26% vs 16%; $P = .03$). However, with 36 pairwise comparisons among the 3 treatment groups for the 13 symptoms, we would expect to observe 1.8 significant results at the .05 level by chance alone.

DISCUSSION

In this study, we compared 2 strategies for step down from ICS/LABA: LABA-step-off, as recommended by the FDA, or reduced-ICS/LABA, as recommended by the Global Initiative for Asthma. We also compared reduced-ICS/LABA to stable, moderate-dose ICS/LABA. We did not identify one strategy that was superior in terms of risk of treatment failure. Our study differed from previous studies by using a clinically relevant composite primary outcome, treatment failure, including outcomes important to both patients and providers. The design also included longer follow-up postrandomization (48 weeks), allowing for exposure during peaks in seasonal allergens and viral infections, and sufficient time to assess exacerbation rates. Previous systematic reviews of step-down randomized clinical trials were unable to assess differences in exacerbations specifically resulting in an urgent care visit or hospitalization due to short study duration after step-down (12-24 weeks).^{9,14-16,26-29} In a retrospective study, patients who reduced treatment had similar clinical outcomes including exacerbation rates, and modest cost savings at 2 years compared with stable treatment.³⁰ In recent FDA-mandated LABA safety studies, although not designed specifically to compare step-down strategies, adults and children

well controlled on ICS/LABA at baseline had a greater risk of exacerbation on LABA-step-off versus continuation of ICS/LABA.³¹⁻³³ Although we did not observe a difference in asthma exacerbations among the different step-down strategies, we observed significantly greater all-cause hospitalization in the LABA-step-off group compared with the reduced-ICS/LABA group, and a nonsignificant increase in hospitalization in the LABA-step-off group compared with the stable-ICS/LABA group. There were no deaths or intubations in our study, and the few asthma-specific hospitalizations all occurred in the LABA-step-off group with none in groups in which LABA was maintained. Overall, we did not observe a higher rate of asthma-related severe adverse events in adults or children over 48 weeks in groups in which LABA was maintained, results that are in accord with results of recently published FDA-mandated LABA safety studies.³¹⁻³³ Although all 5 of the hospitalizations for asthma in our study occurred in the LABA-step-off group, the small number of events makes it difficult to draw definite conclusions. Together with our results, current data do not support greater safety using a LABA step-down approach in patients well controlled on combination therapy, and suggest possible harm with this approach. Whether discontinuation of LABAs impacts the risk of rare events such as intubation or death awaits completion of the FDA safety studies and pooled analysis of the data.

The 2 groups in which LABA was maintained had statistically significantly higher lung function than the LABA-step-off group, in accord with previous studies.^{15,16} Many previous studies exploring the relative merit of differing step-down approaches were designed with lung function as the primary outcomes, which would inherently favor a LABA-containing regimen. When stepping up asthma therapy, addition of a LABA as opposed to escalating the ICS dose has resulted in better outcomes in randomized prospective clinical trials requiring demonstration of bronchodilator reversibility. However, increased ICS approaches behaved similarly or better than addition of LABA in retrospective studies and observational studies in which bronchodilator reversibility was not required.³⁴⁻³⁷ Our study resembled some of these “real-life” studies in that bronchodilator reversibility was not required for enrollment. We observed a decrement in lung function with LABA-step-off and did not observe a treatment difference according to bronchodilator response. Although lung function declined with LABA discontinuation, there was no difference in symptom scores or quality-of-life measures among the 3 groups and the lung function decrements were less than what is considered the minimal clinically important differences in these measures.^{37,38} Two previous systematic reviews comparing treatment reduction strategies found worse symptom control and quality of life when LABAs were stopped, but differences were small and of unclear clinical significance.^{15,16} Our study was designed to have 80% power to identify a 15% difference in treatment failure between the 2 step-down strategies, our primary hypothesis, assuming a treatment failure rate of 20% per year. The observed rates of treatment failure were all higher; however, the difference between groups was much less than 15%, indicating that none of the strategies was clearly superior. We cannot exclude a smaller but clinically significant difference between the 2 step-down strategies. In terms of our secondary hypothesis, we did not meet the prespecified 10% noninferiority margin between the stable and reduced ICS dose when LABA was maintained. A limitation of our study is a lack of power for the secondary hypothesis that

precluded either establishment or exclusion of noninferiority of reduced-dose ICS/LABA compared with stable-dose ICS/LABA. We also cannot exclude the possibility that overtreatment of patients on combination therapy as observed in previous step-down studies led to null results.⁷ Our inclusion criteria required at least 3 months of good asthma control by ACT, with 2 months of direct observation on open-label treatment. If the ACT score remained above 20, our study permitted somewhat greater use of beta-agonist than permitted strictly for good control under guidelines, and an FEV₁ as low as 70%. These factors, along with the fact that approximately a quarter of participants across groups experienced treatment failure, including the group in which higher dose ICS was maintained, suggest that enrollment of patients with very mild asthma did not likely account for our findings. In retrospective studies, longer duration of control was associated with a greater likelihood of successful treatment reduction, but 32% of patients who underwent step down of therapy still had an asthma exacerbation within 2 years.³⁹ Our findings raise a similar question of whether a 3-month period in which the ACT score was more than 20 and stable lung function is adequate to assess stability for stepping down therapy in all patients because 15% of patients in both the stable-ICS/LABA and LABA-step-off groups went on to have an exacerbation requiring oral corticosteroids over a 48-week period. Although the difference between low- and moderate-dose ICS did not result in different outcomes in our study, our data do not speak to whether “stepping up” therapy with higher dose ICS chronically or transiently with single maintenance and reliever therapy strategy, or via addition of other nonsteroid controllers, would reduce treatment failure in these patients, and raises questions for future studies. In conclusion, we found that reduced ICS dose or discontinuation of LABA as step-down strategies did not differ significantly in terms of treatment failure, nor did they differ compared with continuation of stable treatment with medium-dose ICS/LABA. However, LABA step-off was associated with a higher risk of all-cause hospitalization, more asthma hospitalizations, and a small decrease in lung function. Our data suggest that a significant proportion of patients remain at risk of exacerbation even when apparently controlled for short periods as measured by the ACT or lung function measures. With any step-down strategy, emphasis should be placed on the early recognition of loss of asthma control and reescalation of treatment to regain control. The ultimate strategy used depends on the assessment of the relative risks of adverse effects of higher doses of ICS and the relative safety and efficacy of LABA in a particular individual, as well as the preferences of the patient.

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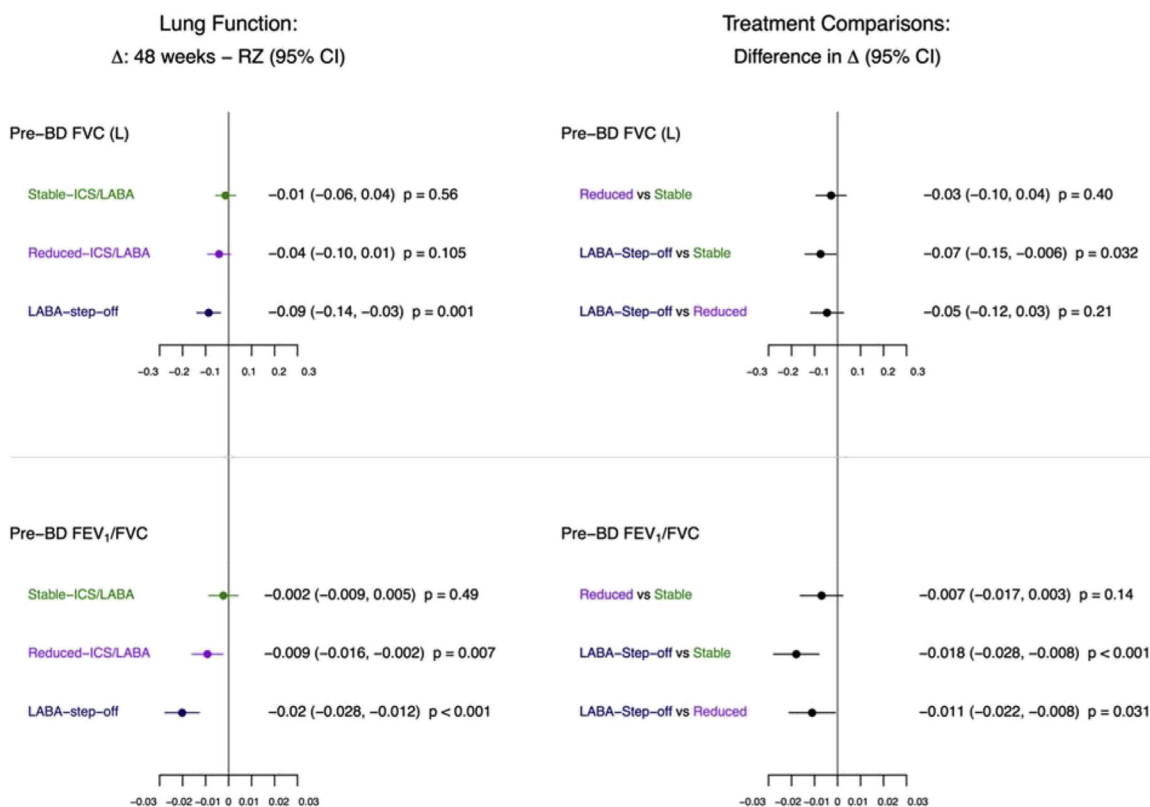


FIGURE E1. FVC and FEV₁/FVC ratio: change from baseline (*left panel*) and treatment effects (*right panel*) at 48 weeks. FVC, Forced vital capacity.

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