

Original Article

A Pragmatic Trial of Symptom-Based Inhaled Corticosteroid Use in African-American Children with Mild Asthma

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What is already known about this topic? Symptom-based, as-needed use of inhaled corticosteroids (ICS) has been shown to provide asthma control and event rates comparable to daily ICS in rigorous controlled trials and has been recently added to the global asthma guideline.

What does this article add to our knowledge? To our knowledge, our study is the first real-world, open-label pragmatic study assessing the effectiveness of intermittent symptom-based use of ICS in children with mild asthma implemented by community primary care pediatricians.

How does this study impact current management guidelines? Intermittent, symptom-based use of ICS can be considered as an alternative patient-centered strategy in mild asthma in the primary care setting, especially in those who have difficulty in adhering to daily therapy.

BACKGROUND: Symptom-based adjustment (SBA) of inhaled corticosteroids may be an alternative patient-centered approach in which day-to-day inhaled corticosteroid use is adjusted by symptoms and short-acting β -agonist need.

OBJECTIVE: To evaluate the effectiveness of SBA in the primary care setting.

METHODS: We conducted a randomized, open-label, pragmatic equivalence trial in African-American children (6-17 years old) with mild asthma managed by 12 primary care providers (PCPs). A total of 206 participants were randomized to SBA (as-needed beclomethasone 80 μ g with rescue short-acting β -agonist) or provider-based guideline-directed adjustment (PBA): maintenance beclomethasone 80 μ g/d (6-11 years old), 160 μ g/d (12-17 years old), with subsequent guideline-based

dose adjustment by PCPs. PCPs implemented both treatment assignments, with outcomes measured by blinded staff. All participants received symptom recognition and albuterol use education from peer educators. Primary outcome was change in asthma control (measured by Asthma Control Test [ACT]/childhood ACT [cACT]) over 12 months.

RESULTS: Participants had adequately controlled asthma (mean ACT or cACT score = 21.6 ± 2.8) at baseline. After 1 year, there was no significant between-group difference in change in ACT scores (SBA – PBA): ACT: -0.88 (95% CI, -2.19 to 0.42), cACT: -0.73 (-2.09 to 0.62), or combined ACT and cACT ($P = .10$), and was within the predefined statistical clinical equivalence. The proportion with an exacerbation and measures of lung function were similar between groups. Compared with

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Abbreviations used

ACT- Asthma Control Test
 cACT- Childhood Asthma Control Test
 ICS- Inhaled corticosteroids
 LABA- Long-acting β -agonist
 PBA- Provider-based guideline-directed adjustment
 PCP- Primary care provider
 SABA- Short-acting β -agonist
 SBA- Symptom-based adjustment

PBA, SBA led to less beclomethasone use (SBA: 526 μ g/mo [95% CI, 412–639 μ g] vs PBA: 1961 μ g/mo [95% CI, 1681–2241]; $P < .0001$). More parents in the SBA arm felt they were managing their child's asthma.

CONCLUSIONS: SBA in African-American children with mild asthma was similar to PBA in asthma control and events when implemented by PCPs with lower inhaled corticosteroid exposure. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;■:■-■)

Key words: Mild asthma; Primary care; Pragmatic; As-needed; Inhaled corticosteroids

INTRODUCTION

Asthma guidelines have recommended daily use of inhaled corticosteroids (ICS) for persistent asthma for the past 3 decades.^{1,2} However, adherence to daily asthma therapy remains low despite efforts,³ and concerns for side effects from ICS (such as growth effect⁴ and long-term steroid-induced complications⁵) negatively affect adherence.^{6,7} Moreover, the cost of asthma therapy is a major concern of the urban minority family.^{7,8} Reflecting this behavior and belief of the patients and families, primary care providers (PCPs) often elect not to recommend daily ICS to patients with persistent asthma,⁹ especially those with mild disease.¹⁰ These ongoing obstacles to guideline-based asthma management have led to consideration of alternative, nondaily strategies.

Intermittent, symptom-based adjustment (SBA) of ICS is a patient-centered strategy in which the dose of ICS is determined by the patient's rescue inhaler needs. Daily ICS is not used, but rather ICS is delivered whenever a short-acting β -agonist (SABA, albuterol) or a quick-onset long-acting β -agonist (LABA, formoterol) is used to treat symptoms. SBA of ICS with SABA was shown to be effective in controlling asthma and preventing exacerbation both in adults and in children with mild persistent asthma.^{11–13} The most recent update of the Global Initiative of Asthma published in April 2019 now recommends this strategy as one of the options for step 1 and step 2 therapy for the first time.¹⁴ Similarly, SBA of ICS combined with a LABA (budesonide + formoterol) has been recently shown to deliver better asthma control than SABA alone and resulted in a similar rate of asthma exacerbation compared with daily dose of budesonide + formoterol in patients with mild asthma.^{15,16} These studies have consistently shown that patients using SBA were exposed to a lower dose of ICS compared with daily therapy^{11–13} and associated with less adverse growth effect.¹³

However, these previous studies were conducted in a controlled clinical trial setting, which is often different from

usual clinical practice. Thus, there is a need to evaluate the SBA in a real-life, primary care setting, especially now that SBA is added to the Global Initiative of Asthma recommendation as a treatment option for mild asthma that is highly prevalent in the primary care practices.

We conducted our study in African-American children, a population in which provider-based guideline-directed adjustment (PBA) asthma care (current standard of care) has been inconsistently implemented.^{17,18} Adherence to daily ICS is low,¹⁹ and African Americans have concerns regarding the adverse effects of daily ICS.^{7,20,21} We hypothesized that the SBA strategy might be better accepted in this population, because the patient or caregiver can initiate therapy at the onset of symptoms (self-management) without direct guidance by the PCP to adjust the ICS dose. Therefore, we evaluated the effectiveness of ICS use by SBA compared with PBA by a pragmatic trial in African-American children with mild asthma at PCP offices in the community.

METHODS

Study design and participants

This study was a randomized, open-label, 2-arm, pragmatic trial in African-American children with mild asthma under the care of 12 participating PCPs in Saint Louis, MO (Clinicaltrials.gov: NCT02298205). We included African-American children, aged 6 to 17 years, under the care of the participating PCP with (1) physician-diagnosed asthma by the participant's PCP, (2) prescribed low-dose ICS, leukotriene receptor antagonist, or low-dose ICS plus LABA (for 12- to 17-year-olds), (3) prebronchodilator FEV₁ value of greater than or equal to 80% predicted, and (4) asthma symptoms up to 4 times a week (defined by Modified Asthma Evaluation Questionnaire score¹² of up to 2 in 2 of 3 questions, with total score ≤ 5 ; see Section E1 in this article's Online Repository at www.jaci-inpractice.org). We excluded those with asthma in which SBA might not be considered appropriate, which includes those with moderate-to-severe asthma: receiving medium- to high-dose ICS with LABA, and/or a history of intensive care unit admission (for full inclusion and exclusion criteria, see Section E2 in this article's Online Repository at www.jaci-inpractice.org). Possible candidates were identified by the practices using electronic health records, and were approached by study coordinators by phone and screened for eligibility at a visit at the PCP offices (Figure 1). This study was approved by the Institutional Review Board at Washington University. Parents or guardians provided written consent and the participant provided verbal or written assent.

Randomization and masking

After eligibility was confirmed, participants entered a 2- to 4-week run-in period. They were transitioned from their existing controller medication(s) and instructed to take a fixed dose of beclomethasone (40 μ g, 1 puff, twice daily for 6- to 11-year-olds and 40 μ g, 2 puffs, twice daily for 12- to 17-year-olds, with use of holding chamber) to standardize study ICS (beclomethasone dipropionate HFA: Qvar) used in the study. All participants received telephone-based education (2–4 sessions) by a trained peer educator during run-in. The peer educator delivered the same educational content that was predetermined regarding symptom recognition and appropriate use of albuterol. A minimum of 2 phone contacts were required, but additional calls were made until the full educational content was provided to the participant/caregivers. Completion of these calls was required to proceed with randomization. The peer educator made 1

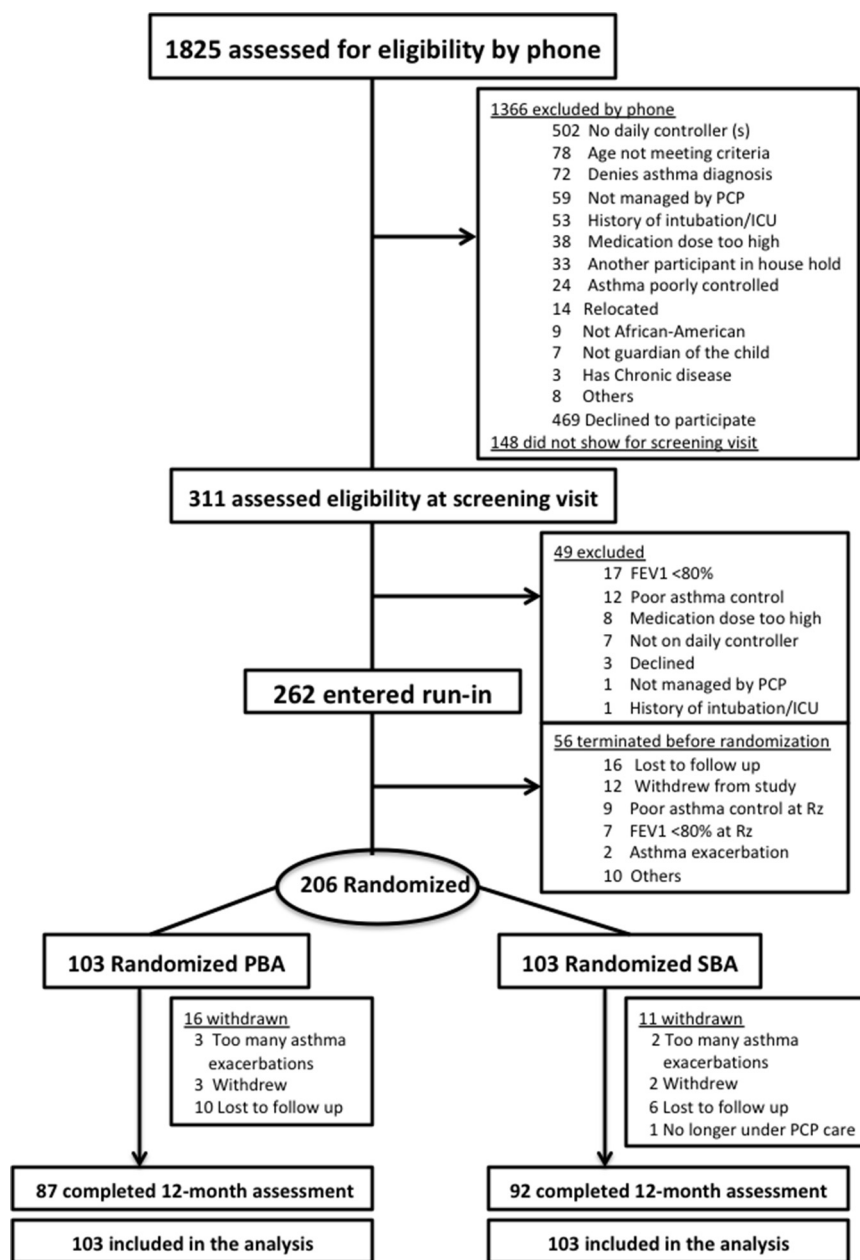


FIGURE 1. Flow of study participants. *ICU*, Intensive care unit; *Rz*, randomization.

additional reminder call at 6 months to review the initial education during run-in and asthma action plan given at randomization. Randomization was performed in a 1:1 ratio using REDCap data system using computer-generated random numbers stratified by practice with a blocked scheme. The unmasked study staff notified the assignment to the participants and their PCPs. This unmasked staff dealt with all assignment-related tasks, whereas other study staff members responsible for the outcome measurements were kept masked throughout the study (see details in Section E3 in this article's Online Repository at www.jaci-inpractice.org).

Procedures

Each PCP received 1 training session by the research team to review each treatment strategy and the asthma action plan before

enrolling any participant from the practice. In the SBA group, participants were instructed to take 2 puffs of beclomethasone 40 µg (total 80 µg) each time they took albuterol when they experienced symptoms identified with the peer educator including behavior changes (identified by the caregiver of the child), chest tightness, shortness of breath, coughing, wheezing, and underperforming due to asthma during physical activities. Participants were instructed to carry the albuterol and beclomethasone metered dose inhalers together (combination product was not available in the United States at the time of study initiation). In the PBA group, participants were instructed to take 1 puff of beclomethasone 40 µg twice daily (for 6- to 11-year-olds) or 2 puffs of beclomethasone 40 µg twice daily (for 12- to 17-year-olds). Subsequent dosing adjustments were made by the PCP according to the level of asthma control assessed by

TABLE I. Baseline demographic characteristics of study participants

Demographic characteristic	PBA (N = 103)	SBA (N = 103)
Age (y)	10.1 (3.2)	10.3 (3.4)
Age at diagnosis (y)	3.0 (2.8)	2.7 (2.8)
% Female*	39 (38)	56 (54)
% Parent married	33 (32)	23 (22)
Household income < \$35,000	55 (53)	63 (61)
Mother employed	80 (78)	74 (72)
Medicaid insured	58 (56)	66 (64)
Asthma characteristics		
No. of those with exacerbation in the past 12 mo	45 (44)	42 (41)
No. of those with ED visit for asthma in the past 12 mo	30 (29)	28 (27)
No. of asthma exacerbations in the past 12 mo	0.7 (1.0)	0.8 (1.2)
Controller medications		
ICS without LABA	89 (86)	88 (85)
Low-dose ICS/LABA	8 (8)	11 (11)
Leukotriene modifier	46 (45)	46 (45)
ACT score (range, ACT, 5-25; cACT, 0-27)		
ACT (n = 71)	22.0 (2.3)	21.1 (3.4)
cACT (n = 135)	21.6 (3.1)	21.8 (2.6)
ACT/cACT ≤ 19 (%)	21 (20)	23 (22)
Quality-of-life scores, median (IQR)		
Children's Health Survey for Asthma, Parent Version (range, 0-100) n = 135		
Physical, health	90 (78-95)	83 (75-95)
Activity, child	95 (80-100)	100 (85-100)
Activity, family	100 (92-100)	100 (92-100)
Emotion, child	100 (78-100)	95 (75-100)
Emotion, family	91 (80-99)	91 (81-100)
Children's Health Survey for Asthma, Child Version (range, 0-100) n = 72		
Physical, health, median (IQR)	93 (79-100)	89 (75-96)
Activities	95 (85-100)	100 (78-100)
Emotion	94 (92-100)	92 (87-98)
Lung function		
FEV ₁ , % predicted	99.8 (15.7)	98.6 (14.7)
FEV ₁ /FVC (%)	84.3 (6.9)	84.1 (7.1)

ED, Emergency department; FVC, forced vital capacity.

ACT (for 12-y-olds and above), cACT (for 6- to 11-y-olds). Data are mean (SD) or n (%) unless stated otherwise.

*There was a statistically significant difference in sex between groups ($P = .02$).

albuterol use, symptoms, and history of exacerbations following national guidelines.² This comparator arm was chosen to reflect the current standard of care for mild asthma (details of the study arm instructions are provided in [Section E3](#) in this article's Online Repository at www.jaci-inpractice.org).

Four to 6 weeks after randomization, every participant had a visit with their PCP to review their treatment instructions. Subsequently, for participants in both study arms, the PCP determined the frequency and intensity of the follow-up visits per routine practice and dealt with management issues including lack of adequate asthma control, missed visits, nonadherence to study assignment, and postexacerbation care. Provider and follow-up visits occurred at the provider's offices. All participants received a written asthma action plan specifically developed by the study team and instructed to keep during the study. All questions from participants regarding treatment assignments were forwarded to the PCP. Study inhalers (beclomethasone and albuterol metered dose inhalers) were provided to the participants to avoid access to medication as a confounder.

Primary outcome

Study outcomes were measured at in-person visits by a masked study staff every 3 months, independent of the PCP visits. The primary outcome was the change in Asthma Control Test (ACT) score (ACT for 12- to 17-year-olds; childhood ACT [cACT] for 6- to 11-year-olds) from baseline to 12 months. ACT and cACT are validated 5- and 7-item questionnaires, respectively, that assess asthma control over the previous 4 weeks (score range, ACT: 5-25; cACT: 0-27),^{22,23} with a score of 19 or less indicating inadequate control.^{23,24}

Secondary outcomes

Secondary outcomes included average monthly dose of beclomethasone (measured by built-in dose counter on the metered dose inhaler), proportion of participants with 1 or more asthma exacerbations during 12-month follow-up, change in quality-of-life scores (Children's Health Survey for Asthma for caregivers²⁵ for 6- to 11-year-olds and Children's Health Survey for Asthma Child Version²⁶ for 12- to 17-year-olds), change in prebronchodilator

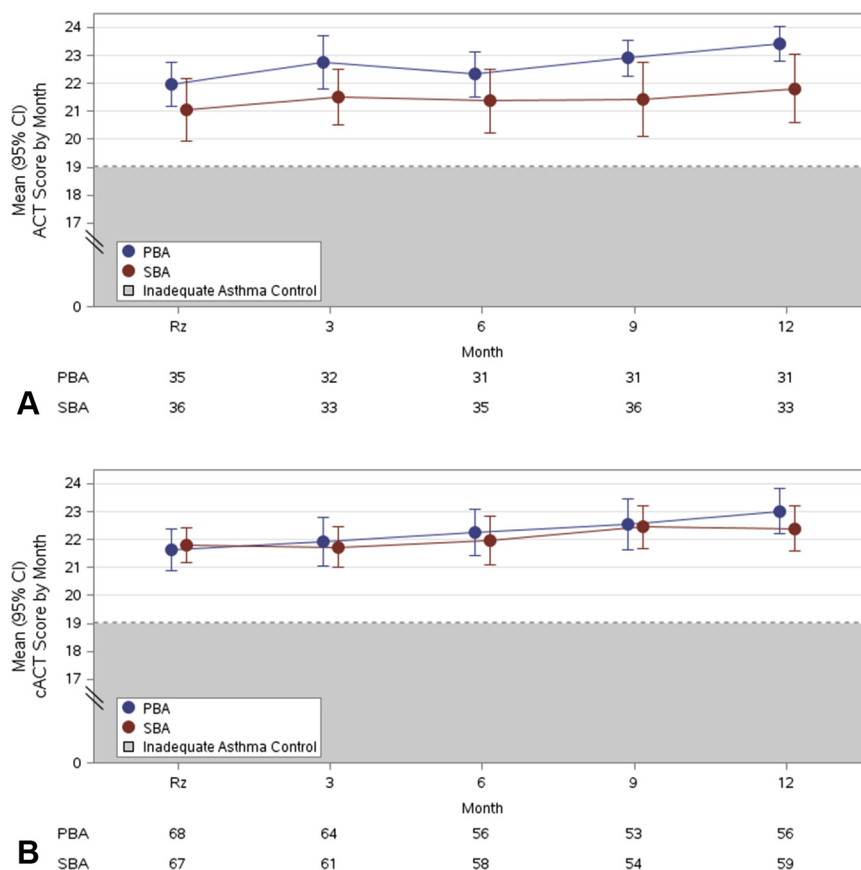


FIGURE 2. Scores of ACT (**A**) and cACT (**B**) at each visit. Mean score and 95% CI at each visit are shown. ACT and cACT scores were measured every 3 months after randomization. Gray zone (score below 19) indicates inadequate asthma control. Numbers below each visit indicate the number of completed tests at each study visit. *Rz*, Randomization.

percent predicted FEV₁ over 12 months, number of missed school days for asthma, and change in ACT/cACT scores at 6 months (see Section E4 in this article's Online Repository at www.jaci-inpractice.org). Asthma exacerbation, reported by the parent or PCP, was defined as an urgent care, PCP visit/phone contact for an "asthma attack" for which the participant was treated with oral corticosteroids, or an emergency department visit or hospitalization for asthma exacerbation requiring systemic steroids. Lung function was measured by staff trained to perform spirometry per American Thoracic Society standard using portable spirometer (KoKo spirometer) at baseline and 12 months at PCP offices. The participants and caregivers rated their degree of satisfaction with the treatment strategy and the estimated frequency with which they followed the study instruction at 12 months using a questionnaire developed by the study team (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org).

Statistical analysis

We determined that a total of 200 participants (100 in each group) would provide 90% power to establish equivalence with 5% type 1 error rate with a dropout rate of 15% with estimated SD for the change in ACT score to be 5.0 and defined the limit of the change in ACT score for equivalence to be 2.5, considering that the minimally important clinical difference had been determined to be 3 for the ACT²⁷ at the time of the study initiation. The details of the

sample size calculation and its justification are provided in Section E5 in this article's Online Repository at www.jaci-inpractice.org.

Outcome analysis was conducted including all available data from all randomized participants following intention-to-treat principle. For the primary outcome, a mixed-effects, repeated-measures ANOVA model was used to evaluate the longitudinal data (measurements at baseline and at 3, 6, 9, and 12 months), adjusting for sex, season of enrollment, random effect of practice site, and a dichotomous variable for test taken (ACT or cACT). For simultaneous analysis including data from all participants, ACT and cACT scores were combined and a variable was created to indicate which test was used. A data transformation (natural log of participant's score subtracted from 30) was performed for an appropriate model fit due to nonnormal distribution of combined ACT and cACT scores. Because of the 2 separate scales of measurements, we provide the mean and 95% CI using 2-sample *t* tests for the change in ACT and cACT scores separately, and the corresponding *P* value from the statistical contrast. Equivalence was assessed by comparing predetermined upper level of equivalence to the CIs.

For secondary outcomes, continuous variables were evaluated with a linear mixed model adjusted for sex, season of enrollment, and a random effect of practice site. Occurrence of an asthma exacerbation was evaluated by logistic regression adjusted for sex and season of enrollment. Monthly dose of beclomethasone was calculated on the basis of the number of actuations of beclomethasone measured by the

TABLE II. Change in ACT and cACT scores from baseline to 12 mo*

Tool	Difference (95% CI), 12 mo – baseline†			P value from model
	PBA	SBA	SBA – PBA	
ACT	1.55 (0.68 to 2.42)	0.67 (–0.33 to 1.66)	–0.88 (–2.19 to 0.42)	.10*
cACT	1.43 (0.45 to 2.41)	0.69 (–0.26 to 1.65)	–0.73 (–2.09 to 0.62)	

ACT (for 12-y-olds and above), cACT (for 6- to 11-y-olds).

*The *P* value corresponds to the test of no difference between treatment groups and is from a model of transformed combined ACT/cACT controlling for test, season, and sex, with random effect of clinic.

†Differences shown are raw values.

TABLE III. Proportion of participants experiencing an exacerbation in each group

Outcomes	Treatment group		P value*
	PBA	SBA	
Exacerbations			
No. of events	29	22	
No. with ≥1 events, n (%)	24 (23)	20 (19)	.620
Exacerbations resulting in ED visit			
No. of events	13	5	
No. with ≥1 events, n (%)	11 (11)	4 (4)	.072

ED, Emergency department.

**P* value is from model controlling for season and sex.

dose counter divided by the number of follow-up months. Quality of each spirometry was assessed and those who did not meet American Thoracic Society criteria²⁸ were excluded from the analysis. Exploratory analysis was performed for time to first exacerbation using survival analysis and the comparison of the proportion of those with equal to or more than a 3-point decline in the ACT or cACT score at 12 months in both groups. All analyses were performed using SAS version 9.4 (SAS Institute, Inc, Cary, NC).

RESULTS

Demographic characteristics of participants

Of 1825 potential participants, 311 attended the first visit, and 206 participants were randomized (PBA *n* = 103, SBA *n* = 103) between March 2015 and October 2016 (Figure 1). There were significantly more females in the SBA group (*P* = .02). Otherwise, the participant characteristics were similar between groups (Table I). Both groups received similar number of phone-based education calls during run-in (PBA: 3.4 ± 0.6 calls vs SBA: 3.3 ± 0.6 calls; *P* = .46). A total of 179 participants completed the 12-month visit (PBA: 87 vs SBA: 92); 27 participants (13%) withdrew or were withdrawn after randomization, with no difference between groups. After the follow-up visit by the PCP 4 to 6 weeks postrandomization, the frequency of PCP visits at which asthma management was discussed was similar between groups (PBA: 2.1 ± 1.5 times vs SBA 2.0 ± 1.4 times; *P* = .78).

Primary outcome

Participants in both treatment arms had evidence of well-controlled asthma at baseline, with mean ACT and cACT scores above 21^{23,24} (Table I and Figure 2). At 12 months, mean scores were as follows: PBA: ACT, 23.4 ± 1.7; cACT, 23.0 ± 3.0 and SBA: ACT, 21.8 ± 3.5; cACT, 22.4 ± 3.1 (Figure 2). The average changes in the scores at 12 months were as follows: PBA: ACT, 1.55 (*n* = 31); cACT, 1.43 (*n* = 56) and SBA: ACT, 0.67 (*n* = 33); cACT, 0.69 (*n* = 59) (Table II). When we

included both ACT and cACT in a single analysis, there was no significant difference in change in ACT/cACT scores between treatment groups (*P* = .10; Table II). The mean between-group difference in the change in asthma control from baseline to 12 months was less than 1 point (SBA – PBA: ACT, –0.88 [95% CI, –2.19 to 0.42]; cACT, –0.73 [95% CI, –2.09 to 0.62]), and was within the predefined statistical clinical equivalence limit of 2.5 (Table II). There was no significant difference between groups in the proportion of participants whose ACT or cACT score decreased by the previously defined minimally important difference^{27,29} of 3 or more points at 12 months (PBA: 12.6% vs SBA: 14.1%; *P* = .77).

Secondary outcomes

The groups did not differ in the proportion of participants who had an asthma exacerbation (PBA: 23% vs SBA: 19%; *P* = .62) (Table III), the time to first exacerbation (*P* = .49; see Figure E2 in this article's Online Repository at www.jaci-inpractice.org), or the proportion requiring emergency department visit (*P* = .072). Quality-of-life scores in all domains (Table IV), the self-reported, missed school days per year (PBA: 1.05 days [95% CI, 0.56–1.55]; SBA: 1.13 days [95% CI, 0.61–1.65]; *P* = .84), or change in ACT and cACT scores at 6 months (*P* = 0.71) did not differ between groups. There was a small, but significant, decline in prebronchodilator percent predicted FEV₁ and forced vital capacity in both groups at 12 months compared with baseline values (PBA: *P* = .002; SBA: *P* < .001; see Table E1 in this article's Online Repository at www.jaci-inpractice.org). On average, FEV₁ decreased 3.44% (–5.53 to –1.34) in the PBA group and 5.54% (–7.42 to –3.67) in the SBA group at 12 months compared with baseline, but the difference between groups was not significant (*P* = .14). The change in FEV₁/forced vital capacity ratio did not differ between groups (PBA: –0.05% [95% CI, –1.30 to 1.19] vs SBA: 0.57% [95% CI, –1.89 to 0.8]; *P* = 0.43) (Table IV).

A total of 2235 beclomethasone inhalers were provided to the participants and 1778 were recovered (80%); the recovery rate was similar between groups (PBA: 81%; SBA: 79%; *P* = .24). On average, participants in the PBA group used 1961 µg/mo (1681–2241 µg) of beclomethasone (~60% of the estimated dose of 3289 µg/mo), whereas those in the SBA group used 526 µg/mo (413–639 µg; *P* < .0001) (Figure 3).

Satisfaction and sense of self-management

The proportion of those who reported high satisfaction with the treatment strategies was similar between groups (very or mostly satisfied: PBA, 100%; SBA, 100%). More children and/or their caregivers in the SBA group felt that they were managing their asthma rather than their PCP (Table V: child: PBA: 44% vs SBA: 72%, *P* = .044; parent: PBA: 40% vs SBA: 63%, *P* = .001).

TABLE IV. Secondary outcomes

Outcome	Mean difference, 12 mo – baseline (95% CI)*				P value†
	N	PBA	N	SBA	
Children's Health Survey for Asthma score – Parent					
Physical health	54	−0.09 (−3.41 to 3.22)	58	−2.77 (−7.41 to 1.87)	.23
Activities, Child	55	3.14 (−1.61 to 7.89)	58	0.26 (−5.48 to 6.00)	.37
Emotional, Child	55	1.55 (−6.16 to 9.25)	58	3.71 (−1.94 to 9.36)	.57
Children's Health Survey for Asthma score – Child					
Physical health	31	2.67 (−1.20 to 6.54)	33	3.14 (−1.39 to 7.67)	.93
Activities	31	4.35 (2.25 to 6.46)	33	2.58 (−2.32 to 7.47)	.51
Emotional	31	1.48 (−1.92 to 4.87)	33	1.33 (−3.12 to 5.77)	.95
Lung function					
FEV ₁ % predicted	79	−3.44 (−5.53 to −1.34)	82	−5.54 (−7.42 to −3.67)	.14
FEV ₁ /FVC (%)	78	−0.05 (−1.30 to 1.19)	82	−0.57 (−1.89 to 0.86)	.43

FVC, Forced vital capacity.

*Differences shown are raw values.

†P value is from model controlling for season and sex, with random effect of clinic.

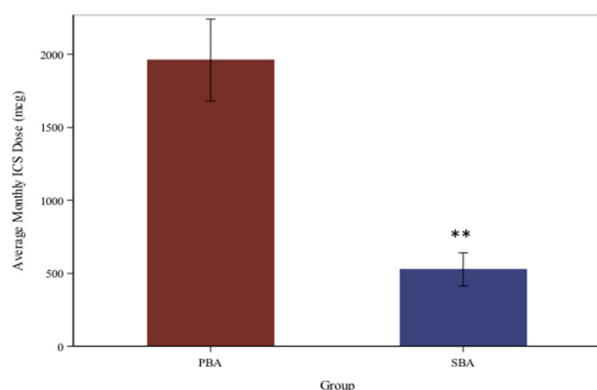


FIGURE 3. Average monthly ICS use. Use of beclomethasone was measured by the built-in dose counter at each follow-up visit. On average, participants in the PBA group used 1961 µg/mo (95% CI, 1681–2241 µg) of beclomethasone, whereas the mean use in the SBA group was 526 µg/mo (413–639 µg) (** $P < .0001$).

Furthermore, more caregivers in the PBA group reported they were not following the PBA instruction (use of daily ICS) (PBA: 28% vs SBA: 14%; $P = .023$).

Adverse events

The adverse events were similar among groups (see [Section E6](#) and [Table E2](#) in this article's Online Repository at www.jaci-inpractice.org). Five participants (3 in PBA and 2 in SBA) were withdrawn from the study per protocol because they had too many exacerbations (2 exacerbations within 6 months, or 3 within 12 months per protocol).

DISCUSSION

In this pragmatic trial conducted in the primary care setting, SBA of ICS with SABA among African-American children with well-controlled mild asthma at study entry was similar in effectiveness and safety to PBA over 1 year. SBA of ICS resulted in similar level of asthma control as PBA with almost one-fourth of the exposure to ICS. The mean difference in asthma control between groups was much smaller than the reported minimally

important difference,^{27,29} indicating that there is little difference in real-life effectiveness between SBA of ICS and the use of PBA of ICS in well-controlled mild asthma in children.

Previous studies have demonstrated that intermittent SBA of ICS is similarly effective to the daily use of ICS in controlling mild asthma and preventing exacerbations.^{11–13} In children with mild persistent asthma, SBA of beclomethasone with SABA achieved levels of asthma control with less growth impairment at 10 months similar to twice-daily use of beclomethasone.¹³ A 9-month study in adults took this evidence further and investigated its use as a treatment adjustment strategy and demonstrated that loss of asthma control was not significantly different between SBA and PBA by national asthma guidelines.¹² No previous studies have compared SBA of ICS with PBA in children nor in a primary care setting.

A unique aspect of our study was that we evaluated the effectiveness of SBA of ICS in a real-life primary care setting. In contrast to previous controlled studies in which highly selected and motivated patients with asthma used both daily and as-needed inhalers in a blinded fashion, our community-based, pragmatic design allowed the patients to take their inhalers in an open-label fashion, with providers implementing both strategies as they may do in real-life. The participating providers of these African-American children addressed management issues during the year-long study including episodes of worsening asthma control or exacerbations, nonadherence to medications, and patients missing scheduled visits. We designed our pragmatic trial to achieve the goal of evaluating an alternative asthma management strategy in the hands of PCPs in their medical home to fill the gap between controlled trials and real-life practice. Our study indicates that SBA of ICS with SABA can be considered as a patient-centered, alternative management strategy to daily use of ICS for mild asthma in a primary care setting.

It is important to point out several factors the practicing providers need to consider that may influence the choice of one asthma management strategy over another. First, in our study, the estimated adherence to the PBA daily ICS was approximately 60%, which was consistent with that in other studies in asthma.³ However, when treating individual patients in practice, those who are more adherent and willing to take daily ICS (current standard of care), daily ICS strategy may be used to achieve and

TABLE V. Self-reported adherence and sense of self-management

Outcome	Treatment group		P value
	PBA: Child (N = 35)	SBA: Child (N = 40)	
Who do you feel took charge in adjusting your asthma medication during the study?			
Mostly me and/or caregiver	14 (44)	28 (72)	.044
Doctor and me equally	10 (31)	8 (21)	
Not mostly me and/or caregiver	8 (25)	3 (8)	
How much do you think you were able to follow the instruction (do what you were supposed to do with your inhalers)?			
You followed mostly every day (75%-100% of the time)	24 (69)	29 (73)	0.71
You did not follow mostly every day	11 (31)	11 (28)	
	PBA: Parent (N = 84)	SBA: Parent (N = 90)	
Who do you feel took charge of your child's asthma management during the study?			
Mostly child and/or caregiver	33 (40)	55 (63)	.001
Doctor and child equally	32 (39)	27 (31)	
Not mostly child and/or caregiver	18 (22)	5 (6)	
How much do you think you (or your child) were able to follow the instruction (do what you/your child were supposed to do with the inhalers)?			
Your child followed mostly every day (75%-100% of the time)	60 (72)	76 (86)	.023
Your child did not follow mostly every day	23 (28)	12 (14)	

maintain asthma control. Second, patients/caregivers' preferences and beliefs regarding the benefits and risks of ICS should be taken into consideration. Doubts by the patient of the necessity and efficacy of ICS, along with concerns for adverse effects, contribute to nonadherence^{6,7,30} and consequently poor asthma control,³¹ especially prominent in minorities.^{7,31} Therefore, an intermittent SBA strategy may be more acceptable for those with such beliefs. In our study, we randomly assigned the treatment strategies and it was not within the scope of the study to include patient's preference in the selection of treatment. However, caregivers and PCPs of African-American children with asthma thought that SBA was in line with their goal of using less medication.⁸ Further studies reflecting patient/parent preference in the choice of the management strategy are needed. Third, the strategy tested in our study is different from intermittent use of high-dose ICS for a fixed duration in the setting of an asthma exacerbation. Studies of self-directed high-dose ICS at the onset of loss of asthma control have not shown reduction in the severity or length of subsequent exacerbations.^{32,33} Finally, it is important to note that all patients in our study received education from a peer educator about symptom recognition and effective use of albuterol via telephone calls during the run-in, with an additional reinforcement at 6 months. Asthma education provided by a peer is effective,³⁴ but is generally not provided as part of usual care. Therefore, this may limit the generalizability of our findings "in the real world."

Secondary outcomes including the frequency of exacerbations and quality of life were similar between the groups, which further supports that there is little difference between these management strategies. In addition, more children and caregivers in the SBA group felt that they were managing their own asthma rather than their PCP, indicating an increased sense of ownership of their asthma management by the use of SBA. There was a small

decrease in lung function at 1 year in both groups, although not significantly different between groups. The decrease at 12 months may be related to greater adherence to daily ICS in the run-in followed by lower levels of adherence over the subsequent year. Lower ICS exposure over the year in both groups may have contributed to this decline as well. We are unable to conclude whether this decrease in lung function represents true long-term decline because it was measured only once after randomization. Longitudinal studies of lung function would be needed to answer this question.

There are several limitations to our study. First, we included children with mild asthma, so the effectiveness of SBA in children with moderate asthma or with mild airflow obstruction was not tested. However, our findings are highly relevant to primary care management because mild asthma reflects most of the asthma population.³⁵ In addition, we included children on daily controller therapy (low-dose ICS and/or leukotriene receptor antagonist) at baseline, so children with mild intermittent asthma on albuterol only were not included. So, the effectiveness in the albuterol-only population was not tested. Second, our study included African-American children; therefore, the relevance to other racial populations or populations with low socioeconomic status may be questioned, although previous studies of SBA have included both white and African-American children and adults. Third, we did not include a placebo group in our study design, so we were unable to compare the effect of SBA or PBA with that of placebo. However, we decided not to add the placebo group because completely removing ICS from children with mild persistent asthma has been associated with adverse outcomes.¹³ Our study population was restricted to children with well-controlled asthma on daily asthma controller medications prescribed by their PCP. Although not all the enrolled children were adherent to the prescribed daily medications and might not have

required full daily dose to control their asthma at enrollment, there was little room for improvement in baseline asthma control. Fourth, we were unable to accurately measure adherence to the management strategy to evaluate the effect of adherence on the outcomes. Multiple options for accurate adherence monitoring were considered, but it was not feasible to fully capture the presence of symptoms and the implementation of SBA by daily self-report in primary care setting. Measuring adherence to symptom-driven therapy is challenging compared with measuring adherence for a scheduled therapy, especially in the community setting, because it requires comprehensive tracking of symptoms and then determining whether SBA was used when symptoms occurred. We did not include electronic remote monitoring of inhaler use because this is not generally provided as part of usual care in the primary care setting. We used SABA and beclomethasone inhaler separately because a combination product was not available in the United States, but use of a combination product may provide better option for monitoring adherence by the PCP once it becomes available.

In conclusion, the use of intermittent SBA of ICS with SABA among African-American children with mild and well-controlled asthma in a primary care setting resulted in similar levels of asthma control and asthma exacerbations compared with PBA, and did so with significantly less ICS exposure. There was a greater sense of self-management in those who practiced SBA. This patient-centered strategy can be considered as an alternative strategy for managing mild asthma in children, especially in those who have concerns regarding ICS or difficulty in adhering to daily ICS therapy.

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ONLINE REPOSITORY

Satisfaction and Adherence Questionnaire (at 12 month)

1. What were the good things about your (your child) treatment plan you were assigned to? (check all apply)
 1. Easy to follow the instruction
 2. Better asthma control (better symptoms)
 3. Less medicine
 4. Better quality of life (be able to do things you want to do)
 5. More involvement on treatment adjustments by you
 6. Being preventive (avoid asthma attacks)
 7. Others (please state: _____)
2. What were the bad things about your (your child) treatment plan you were assigned to? (check all apply)
 1. Difficult to take the medication as instructed (taking it every day, or taking them with albuterol)
 2. Worse asthma control (worse symptoms)
 3. More medicine
 4. Worse quality of life (not able to do things you want to do)
 5. Less involvement of on treatment adjustments by you
 6. Not being preventive (not avoiding asthma attack)
 7. Others (please state: _____)
3. What was your over all satisfaction on your (your child) treatment assignment?
 1. Very satisfied (80-100%)
 2. Mostly satisfied (50-79%)
 3. Mostly not satisfied (20-40%)
 4. Not satisfied (below 20%) (please state reason: _____)
4. Do you think you (your child) will continue to take your medicine as you were told during the study, even after the study is over?

Yes

No
5. Would you recommend your (your child) treatment plan to another child or friend with asthma?

Yes

No
6. Who do you feel took charge in adjusting your (your child) asthma medicine during the study? Was it you (and your caregiver, like your mom or dad), or your doctor, or both? Please select one best answer.

I feel:

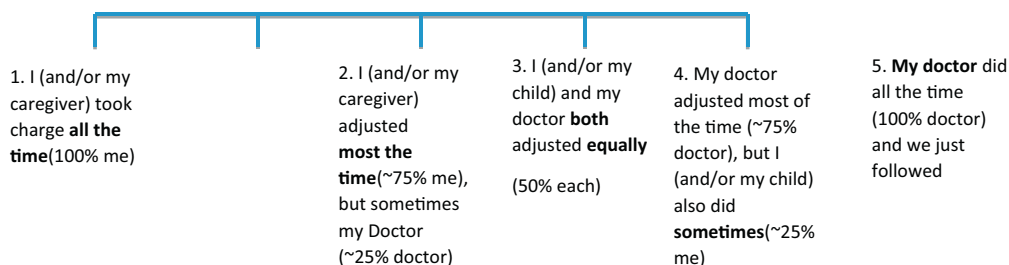


FIGURE E1. Satisfaction and Adherence Questionnaire (at 12 month).

7. During the study, you (your child) followed (or tried to follow) which direction during the study?
1. Take Qvar every day as directed by your doctor
 2. Take albuterol and Qvar as needed based on symptoms
 3. Others (please state: _____)
8. Regarding your given treatment plan above, how much do you think you (your child) were able to follow the instruction (do what your were supposed to do with their inhalers) ?
1. Your followed mostly every day (or 75-100% of the time)
 2. You followed few times a week (~50% of the time)
 3. Your followed few times a month (~25% of the time)
 4. Did not do what you were told to do most of the time (less than 25%)
9. Can you give us any comments about the treatment plan you were assigned to. Any comments are welcomed.
- Did you like it, not like it?
- Any issues you had?

FIGURE E1. (CONTINUED).

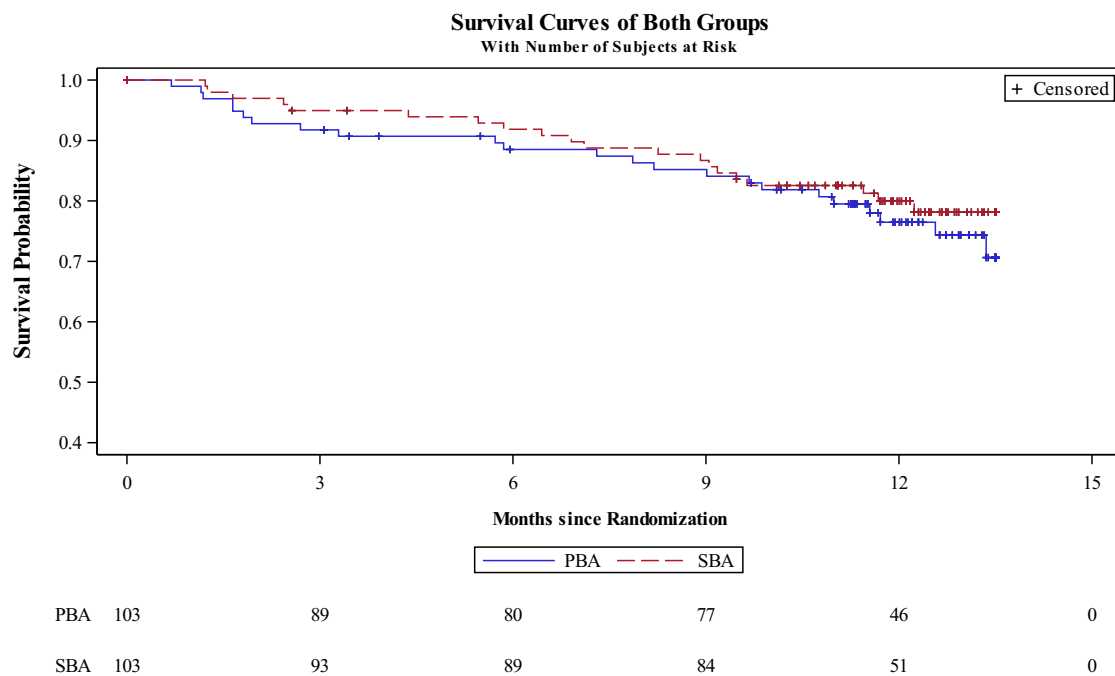


FIGURE E2. Time to first exacerbation.