Original Investigation

Anticholinergic vs Long-Acting β-Agonist in Combination With Inhaled Corticosteroids in Black Adults With Asthma
The BELT Randomized Clinical Trial

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IMPORTANCE The efficacy and safety of long-acting β-agonists (LABAs) have been questioned. Black populations may be disproportionately affected by LABA risks.

OBJECTIVE To compare the effectiveness and safety of tiotropium vs LABAs, when used with inhaled corticosteroids (ICS) in black adults with asthma and to determine whether allelic variation at the Arg16Gly locus of the β_2-adrenergic receptor (*ADRB2*) gene is associated with treatment response.

DESIGN, SETTING, AND PARTICIPANTS A multisite (n = 20), open-label, parallel-group, pragmatic randomized clinical trial conducted from March 2011 through July 2013, enrolling black adults with moderate to severe asthma in the United States.

INTERVENTIONS Patients eligible for, or receiving, step 3 or step 4 combination therapy per National Heart, Lung, and Blood Institute guidelines, received ICS plus either once-daily tiotropium (n = 532) or twice-daily LABAs (n = 538,) and were followed up for up to 18 months. Patients underwent genotyping, attended study visits at baseline, 1, 6, 12, and 18 months, and completed monthly questionnaires.

MAIN OUTCOMES AND MEASURES The primary outcome was time to asthma exacerbation, defined as a worsening asthma event requiring oral or parenteral corticosteroids. Secondary outcomes included patient-reported outcomes (Asthma Quality of Life Questionnaire, Asthma Control Questionnaire [ACQ], Asthma Symptom Utility Index, and Asthma Symptom-Free Days questionnaire), spirometry (FEV_1), rescue medication use, asthma deteriorations, and adverse events.

RESULTS There was no difference between LABA + ICS vs tiotropium + ICS in time to first exacerbation (mean No. of exacerbations/person-year, 0.42 vs 0.37 (rate ratio, 0.90 [95% CI, 0.73 to 1.11], log-rank $P = .31$). There was no difference in change in FEV_1 at 12 months (0.003 L for LABA + ICS vs −0.018 L for tiotropium + ICS; between-group difference, 0.020 [95% CI, −0.021 to 0.061], $P = .33$) and at 18 months (−0.053 L vs −0.078 L; between-group difference, 0.025 [95% CI, −0.045 to 0.095], $P = .49$). There were no differences in ACQ score at 18 months (change in score from baseline, −0.68 for LABA + ICS vs −0.72 for tiotropium + ICS; between-group difference, 0.04 [95% CI, −0.18 to 0.27], $P = .70$). There were no differences in other patient-reported outcomes. Arg16Gly *ADRB2* alleles were not associated with differences in the effects of tiotropium + ICS vs LABA + ICS (hazard ratio for time to first exacerbation, 0.84 [95% CI, 0.47 to 1.51] for Arg/Arg vs 0.85 [95% CI, 0.63 to 1.15] for Arg/Gly or Gly/Gly, $P = .97$).

CONCLUSIONS/RELEVANCE Among black adults with asthma treated with ICS, adding a LABA did not improve time to asthma exacerbation compared with adding tiotropium. These findings were not affected by polymorphisms at the Arg16Gly locus of *ADRB2*. These findings do not support the superiority of LABA + ICS compared with tiotropium + ICS for black patients with asthma.

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National treatment recommendations suggest increasing inhaled corticosteroid (ICS) dose or adding a long-acting β-agonist (LABA) to asthma patients with poor asthma control on low-dose ICS.[1,2] However, asthma experts and the US Food and Drug Administration have questioned the safety of LABA therapy,[3-5] noting possible increases in serious events, including hospitalizations and death. Data suggest that LABA risks, if they exist, may disproportionately affect black populations[6] and that black individuals may not benefit from LABAs to the same degree as individuals of other races.[7-9] Some studies have suggested that allelic variation at the Arg16Gly locus of the β_2-adrenergic receptor (*ADRB2* [NCBI Entrez Gene 109690]) gene may be associated with increased rates of adverse outcomes when LABAs are used for asthma,[10-12] especially among black patients.[13]

ACQ *Asthma Control Questionnaire*

AQLQ *Asthma Quality-of-Life Questionnaire*

ASFD *Asthma Symptom-Free Days*

ASUI *Asthma Symptoms Utility Index*

FEV_1 *forced expiratory volume in first second of expiration*

ICS *inhaled corticosteroids*

LABA *long-acting β-agonist*

Investigations in predominantly white populations have attempted to determine if long-acting anticholinergics can substitute for LABAs in asthma. One trial showed that tiotropium, a long-acting anticholinergic, was not inferior to LABA when added to ICS for the outcomes of lung function or symptoms.[14] Another study found tiotropium to be noninferior to LABA in patients with 2 arginine alleles (Arg/Arg) at the Arg16Gly locus of *ADRB2*. Neither trial was powered to assess one of the outcomes most important to patients, prescribers, and policy makers—asthma exacerbations.

In view of the paucity of data on outcomes related to using tiotropium instead of LABA as an add-on therapy to ICS, concerns related to the use of LABAs, particularly in black populations, and the possibility that clinical efficacy trials, which temporarily control patient behavior, may not reflect the real therapeutic environment, we conducted a trial in black adults with asthma in geographically diverse practices in the United States. We examined whether LABA in combination with ICS was superior to tiotropium combined with ICS. Because black patients with Arg16Arg of *ADRB2* might not gain as great a benefit from LABAs,[13] we sought to determine whether this polymorphism was associated with differential outcomes. We also compared the relative safety of these combination therapies.

Methods

The trial protocol (Supplement 1) and statistical analysis plan (Supplement 2) for this trial are available online. The trial was conducted at 20 practice sites (eFigure 2 in Supplement 3) from March 2011 through July 2013, with a data coordinating center (Harvard Clinical Research Institute), a clinical coordinating center (Brigham and Women's Hospital), and site-management coordinating centers (Olmsted Medical Center Department of Research and American Academy of Family Physicians National Research Network). A data and safety monitoring board oversaw all aspects of trial conduct. The study was approved by individual institutional review boards, and all patients provided written informed consent.

The Blacks and Exacerbations on LABA vs Tiotropium (BELT) study was a parallel-group, randomized pragmatic trial that enrolled black adults with asthma from primary care and specialty practices in the United States. Enrollees receiving, or eligible for, step 3 or step 4 combination ICS and LABA therapy according to National Heart, Lung, and Blood Institute asthma guidelines[1] were randomly assigned 1:1 to receive either daily LABA (salmeterol or formoterol, depending on the initial prescription by the treating physician) or tiotropium, each in addition to their prior dose of ICS (**Figure 1**). Following the initial enrollment and randomization visit, clinic visits occurred at 1 month and 6 months, and depending on time of enrollment, at 12 and 18 months (eFigure 1 in Supplement 3). We expanded the potential observation time to 6 to 18 months to increase the study power. Monthly questionnaires were sent to patients using standardized asthma control questionnaires,[15-20] as well as questions related to asthma exacerbations developed for this study (eMethods 4 in Supplement 3). The trial was originally powered to detect the effects of treatment at 1 year using the time to first exacerbation outcome. Patients who were enrolled early were eligible for up to 18 months of follow-up, whereas patients who were enrolled late in the study were followed for a minimum of 6 months.

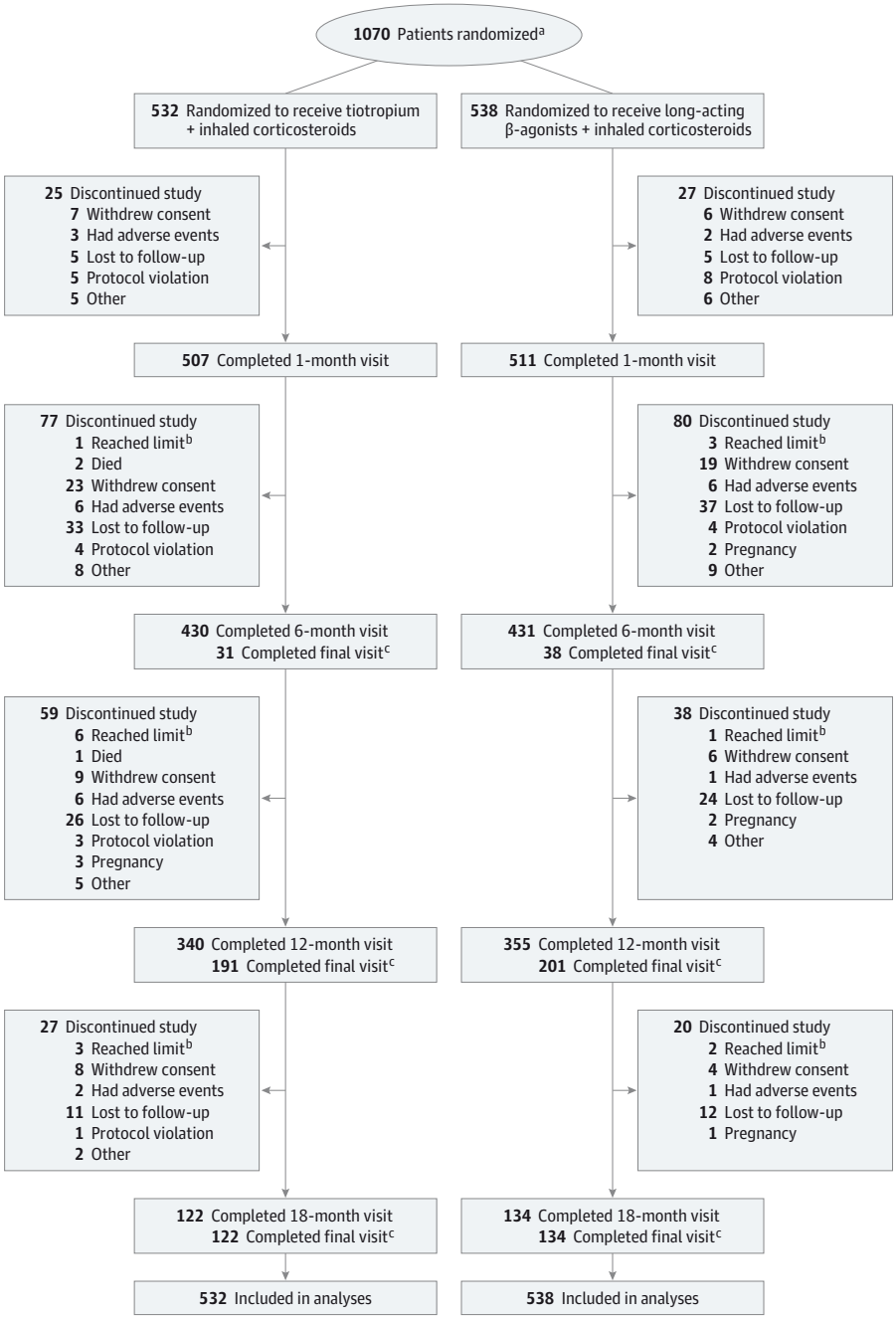
Self-identified black patients, aged 18 through 75 years, with physician-diagnosed asthma and receiving combination LABA + ICS or taking ICS and having an Asthma Control Questionnaire (ACQ)[16,19] score higher than 1.25, were enrolled. Patients were excluded if they were current smokers, had a history of smoking of less than 10 pack-years, had a prebronchodilator forced expiratory volume in first second of expiration (FEV_1) of less than 40% predicted, had asthma-related intensive care unit use or intubation within the previous 5 years, or had an exacerbation requiring oral steroids within 3 months. Full entry criteria are in eMethods 3 in Supplement 3.

Patients continued taking their baseline ICS dose and were randomized to either once-daily tiotropium (18 μg) via hand inhaler (tiotropium + ICS) or twice-daily LABA (LABA + ICS; either salmeterol [50 μg] or formoterol [9 μg]). Each study medication was provided in a separate inhaler because no combination tiotropium + ICS inhalers are available. Costs of study medications not covered by the patient's insurance were paid for using study-supplied pharmacy credit cards (ClinCards).[21]

Randomization was computer-generated, performed in a blinded fashion, and stratified in blocks of 4 within each stratum based on patient age (<40 years or ≥40 years), baseline LABA use (yes or no), FEV_1 (<60%, 60%-79%, or ≥80% predicted), and smoking environment (smoker in the home [yes or no]). Allocation was accessed by site personnel using an automated web-based system.

The study was designed to compare the effectiveness of tiotropium + ICS vs LABA + ICS in delaying time to first exacerbation (primary outcome; defined as asthma deterioration that resulted in a prescription of systemic steroids or, even if no steroids were prescribed, a hospitalization for asthma)

Figure 1. Flow of Patients Through the BELT Trial



BELT indicates Blacks and Exacerbations on Long-Acting β-Agonists vs Tiotropium. Final visit indicates completion of the expected term of participation based on time of enrollment.

[a] Data on numbers of patients screened and excluded are not available.

[b] Reached limit due to asthma exacerbation (patients who had >2 asthma exacerbations within any 6-month treatment period or >3 asthma exacerbations during the 12-month treatment period were withdrawn from the study).

[c] Completed final visit indicates patients who were enrolled for 6, 12, or 18 months depending on time left in study period on the date of their enrollment.

(eMethods 1 in Supplement 3). The second primary outcome was to explore whether allelic variation in Arg16Gly of *ADRB2* was associated with an effect of LABA or tiotropium on the delay in time to first exacerbation.

Worsening of asthma symptoms reported on monthly patient questionnaires was followed up by nurse telephone calls. Episodes requiring an increase in asthma therapy for 2 days or more without steroids or hospitalizations were adjudicated as deteriorations (eMethods 1 in Supplement 3) in a blinded fashion. Pulmonary function tests were performed using a spirometer system (EasyOne, ndd Medical Technologies). All results were sent electronically to the central clinical site for quality grading and interpretation. Except for the 1-month visit, LABA or tiotropium were not withheld prior to the visit. Genomic DNA was collected via a saliva DNA self-collection kit (Oragene DNA, DNA Genotek). DNA was extracted and genotyped at the Arg16Gly locus using a gene expression assay (TaqMan, Thermo Fisher Scientific).[22]

Asthma medication adherence was assessed using information from the ClinCard[21] system used to pay for study drugs, and where necessary, site and pharmacy information. Percentage of adherence was defined as the number of months of tiotropium

or LABA and ICS fills divided by the number of months in the study, using the date of the last visit or last returned survey as duration of enrollment. Use of rescue medication was estimated from patient response to question 6 on the ACQ. The median number of puffs per day was truncated at 16.

Hospitalizations, which almost always included administration of corticosteroids, and deaths were investigated by obtaining primary data from clinical sites. Attribution of asthma-relatedness was determined by agreement of 2 physician investigators blinded to treatment assignment.

Outcomes

The primary outcome was time to asthma exacerbation, defined as an event of worsening asthma requiring oral or parenteral corticosteroids, such as an unscheduled physician visit, emergency department visit, hospitalization, or physician judgment of clinical asthma status over the follow-up duration of the study. Patients experiencing more than 2 asthma exacerbations within any 6-month treatment period, more than 3 asthma exacerbations during the 12-month treatment period, or more than 4 asthma exacerbations during the 18-month treatment period were withdrawn from the study to prevent any harm when patients were randomized to a given treatment group.

Secondary outcomes included patient-reported outcomes (Asthma Quality of Life Questionnaire [AQLQ], ACQ, Asthma Symptom Utility Index [ASUI], and Asthma Symptom-Free Days [ASFD] questionnaire), spirometry (FEV_1), rescue medication use, asthma deteriorations, and adverse events.

The AQLQ score ranges from 1 (severely impaired) through 7 (not impaired at all) with a minimal clinically important difference evaluated to be 0.5 points.[19] The ACQ score ranges from 0 (no impairment) through 6 (maximum impairment) with a minimal clinically important difference for an individual patient of 0.5 points.[23] The ASUI score ranges from 0 (worst possible symptoms) through 1 (no symptoms) with a minimum clinically important difference defined as 0.09 points.[24] The ASFD annualized score ranges from 0 (no symptom-free days) through 365 (no days with symptoms). A minimal clinically important difference is not available for this instrument.

Statistical Analysis

Power computations were performed by using PASS (NCSS) and assumed a 2-tailed *P* value of .05. The final sample size was determined assuming constant hazards corresponding to annual rates of exacerbations of 0.20 in the LABA + ICS group and 0.28 in the tiotropium + ICS group requiring 10 600 months of observation (1060 patients followed up for an average of 10 months each) to attain 80% power with the 2-sided log-rank *P* value of .05. This sample size was also calculated to provide 80% power to detect an interaction associated with a 2.72-fold increase in the group-specific hazard in the LABA + ICS group (Arg/Arg vs 2 glycine alleles [Gly/Gly] and 1 arginine allele and 1 glycine allele [Arg/Gly]) compared with no increase in the tiotropium + ICS group using a χ^2 test in a time-to-event regression model.

SAS software (SAS Institute), version 9.1, was used for analyses. Primary and secondary outcomes were evaluated with an intention-to-treat analysis. Time to first asthma exacerbation distributions were compared between treatment groups using a log-rank test. A prespecified secondary analysis compared groups after adjusting for age, sex, baseline FEV_1, and geographic region (Florida, Northeast, and South and Midwest), using Cox proportional hazards regression. To assess for possible study site effects, we performed a post hoc analysis comparing the 2 interventions using Cox regression frailty models for time to first exacerbation and mixed-effects Poisson regression models for mean number of exacerbations with study site included as a random effect. Fixed effects in the model included treatment, baseline age, sex, and percentage of FEV_1 predicted.

Mean number of exacerbations and mean number of hospitalizations were compared between groups using Poisson regression. Changes from baseline in FEV_1, percentage of predicted FEV_1, and the mean score outcomes of questionnaires (ACQ, AQLQ,[19] Asthma Symptom-Free Days questionnaire, and ASUI[15]) were compared between groups using a linear mixed-effect model for repeated measurements. The association between treatment (tiotropium + ICS vs LABA + ICS) responsiveness (6-month change from baseline FEV_1) and baseline FEV_1 divided by forced vital capacity (FEV_1/FVC) was tested using linear regression with baseline FEV_1/FVC, treatment, and their interactions as main predictors. In exploratory analyses, we also examined the statistical effect modification of body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), prior smoking history, and bronchodilator reversibility on hazard ratios.

Interactions between genotype (Arg/Arg vs Arg/Gly and Gly/Gly) and treatment were examined using the above models. To quantify the effect of missing data, sensitivity analyses were conducted following the pattern-mixture approach outlined in the study by Little et al.[25] Further statistical methods details are in eMethods 2 in Supplement 3.

Results

From March 2011 through December 2012, 1070 patients were randomized, with 532 patients assigned to tiotropium + ICS and 538 patients assigned to LABA + ICS (Figure 1); based on baseline LABA usage, 116 patients randomized to LABA + ICS received formoterol, and 422 patients received salmeterol. Twenty centers enrolled patients. There were no significant differences in any baseline characteristics (**Table**) with the exception of years since asthma diagnosis (mean, 25.6 years for LABA + ICS vs 23.3 years for tiotropium + ICS; between-group difference, 2.3 years [95% CI, 0.3 to 4.3], *P* = .02). Approximately 30% of patients had not been on combination therapy, and 60% reported an asthma exacerbation requiring corticosteroids in the prior year. More than 75% of the patients were women.

The mean duration of follow-up was 310 days for a total of 10 963 patient-months of follow-up. There was no difference in the rates of discontinuation between treatment groups (discontinuations: 31% for LABA + ICS vs 35% for tiotropium + ICS; between-group proportion difference, 4.7% [95%

Table. Baseline Characteristics for BELT Study Patients by Randomization Group

Patient Characteristics	No./Total No. (%) LABA + ICS (n = 538)	Tiotropium + ICS (n = 532)
Age, mean (SD), y	45.1 (12.6)	45.2 (12.6)
Sex		
Men	130/538 (24.2)	127/532 (23.9)
Race/ethnicity		
Hispanic/Latino	36/538 (6.7)	31/532 (5.8)
Not Hispanic/Latino	502/538 (93.3)	501/532 (94.2)
Region		
Florida	144/538 (26.8)	128/532 (24.1)
South	121/538 (22.5)	122/532 (22.9)
Northeast	148/538 (27.5)	153/532 (28.8)
Midwest	125/538 (23.2)	129/532 (24.3)
Height, mean (SD), cm	166.7 (9.2)	166.8 (9.6)
Weight, mean (SD), kg	94.9 (26.8)	95.5 (25.8)
BMI, mean (SD)	34.2 (9.5)	34.4 (9.2)
Genotype		
Arg/Arg	130/501 (25.9)	110/487 (22.6)
Gly/Gly	116/501 (23.2)	127/487 (26.1)
Arg/Gly	255/501(50.9)	250/487 (51.3)
Smoking environment		
Yes	86/538 (16.0)	83/532 (15.6)
Former smoker	180/538 (33.5)	195/531 (36.7)
FEV_1, % predicted		
<60	70/475 (14.7)	72/470 (15.3)
60-79	179/475(37.7)	170/470 (36.2)
≥80	226/475 (47.6)	228/470 (48.5)
Pulmonary values	n = 475	n = 470
FEV_1, L	2.1 (0.6)	2.1 (0.7)
FEV_1, mean (SD), % predicted	78.7 (18.6)	78.6 (17.6)
FVC, mean (SD), L	2.8 (0.8)	2.9 (0.8)
FVC, mean (SD), % predicted	87.0 (17.1)	86.0 (16.0)
Years from first asthma diagnosis, mean (SD), y[a]	25.6 (16.0) n = 509	23.3 (15.8) n = 493

(continued)

CI, −1.1% to 10.5%], P = .12). Detailed reasons for study discontinuation are presented in Figure 1. The median adherence (the average percentage of time patients took the medication) calculated from the ClinCard was 60% for both tiotropium + ICS and LABA + ICS (P = .80). ICS adherence was not different between the groups randomized to LABA + ICS vs tiotropium + ICS (median, 60% for LABA + ICS vs 60% for tiotropium + ICS, P = .73).

The primary outcome of time to first exacerbation, did not differ significantly between groups (log-rank P = .47) (**Figure 2**, panel A). When comparing LABA + ICS and tiotropium + ICS, the mean number of exacerbations was 0.42 exacerbations per person-year for LABA + ICS vs 0.37 exacerbations per person-year for tiotropium + ICS (rate ratio [RR], 0.90 [95% CI, 0.73 to 1.11], P = .31), and the probability of being free of exacerbation at 1 year was 74.0% for LABA + ICS vs 75.7% for tiotropium + ICS (hazard ratio [HR], 0.91 [95% CI, 0.70 to 1.18], P = .47). There was no significant difference in proportions of patients who had at least 1 exacerbation (22.7% of the LABA + ICS group vs 20.9% of the tiotropium + ICS group; between-group proportion difference, 1.8% [95% CI, −3.1% to 6.8%], P = .51) and there was no significant difference between groups with regard to number of exacerbations per patient (eTable 1 in Supplement 3). Results remained similar after adjusting for geographic region, age, sex, and baseline percentage of FEV_1 predicted. To address variation across the 20 investigation sites, we performed a post hoc analysis and found that there was no difference in the time to first exacerbation or in rate of events when adjusted for study site as a random effect in addition to age, sex, and baseline percentage of FEV_1 predicted. In exploratory analyses, we noted no significant difference between treatments with regard to exacerbations when stratified by prior smoking history (P = .98, comparing former smokers vs never smokers) and no treatment effect modification by BMI (P = .26). In other exploratory analyses, bronchodilator reversibility (>12% change in FEV_1) at the

Table. Baseline Characteristics for BELT Study Patients by Randomization Group (continued)

Patient Characteristics	No./Total No. (%) LABA + ICS (n = 538)	Tiotropium + ICS (n = 532)
Asthma episodes in the past 12 mo requiring an unscheduled visit to physician, emergency department, or hospital	322/538 (59.9)	314/531 (59.1)
Medication use		
ICS use		
Any ICS alone	148/538 (27.5)	149/532 (28.0)
Low-dose (≤500 µg)	130/148 (87.8)	130/149 (87.2)
High-dose (>500 µg)	18/148 (12.2)	19/149 (12.8)
Combination therapy with 1 device	370/538 (68.8)	375/532 (70.5)
Fluticasone + salmeterol		
100 µg + 50 µg	43/370 (11.6)	43/375 (11.5)
250 µg + 50 µg	186/370 (50.3)	158/375 (42.1)
500 µg + 50 µg	54/370 (14.6)	63/3750 (16.6)
Fluticasone + salmeterol		
45 µg + 21 µg	3/370 (0.8)	2/375 (0.5)
115 µg + 21 µg	6/370 (1.6)	4/375 (1.1)
230 µg + 21 µg	1/370 (0.3)	2/375 (0.5)
Budesonide + formoterol		
80 µg + 4.5 µg	13/370 (3.5)	20/375 (5.3)
160 µg + 4.5 µg	58/370 (15.7)	67/375 (17.9)
Mometasone + formoterol		
100 µg + 5 µg	3/370 (0.8)	12/375 (3.2)
200 µg + 5 µg	3/370 (0.8)	4/375 (1.1)
Combination therapy with 2 devices		
Low-dose ICS + LABA	4/538 (0.9)	0/532 (0.0)
High-dose ICS + LABA	1/538 (0.2)	0/532 (0.0)
Combination ICS + LABA + extra ICS, LABA, or both	9/538 (1.7)	5/532 (0.9)
No controller therapy	6/538 (1.1)	3/532 (0.6)
Questionnaire results, mean (SD)[b]		
AQLQ	4.04 (1.36) n = 537	4.01 (1.36) n = 525
ACQ	2.11 (1.17) n = 537	2.13 (1.15) n = 527
ASUI	0.68 (0.23) n = 511	0.68 (0.23) n = 510
No. of symptom-free days, mean (SD)	197.60 (124.32) n = 530	199.95 (123.97) n = 511
Rescue medication, mean (SD), puffs per day	3.53 (3.70) n = 535	3.41 (3.48) n = 526
Median (IQR)	1.50 (1.50-3.50)	1.50 (1.50-3.50)

Abbreviations: ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality-of-Life Questionnaire; ASUI, Asthma Symptoms Utility Index; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); FEV_1, forced expiratory volume in first second of expiration; FVC, forced vital capacity; ICS, inhaled corticosteroids; IQR, interquartile range; LABA, long-acting β-agonist.

[a] Patient-reported duration of asthma in years.

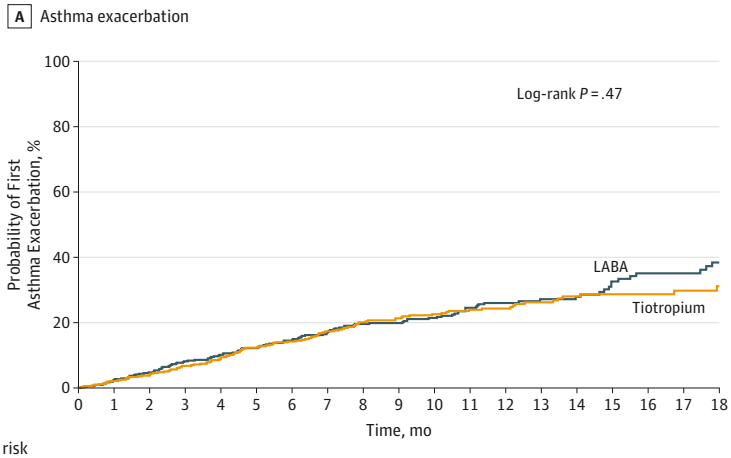
[b] AQLQ score ranges from 1 (severely impaired) to 7 (not impaired at all); ACQ score ranges from 0 (no impairment) to 6 (maximum impairment); ASUI score ranges from 0 (worst possible symptoms) to 1 (no symptoms). Further details about each of the questionnaires (including minimal clinically important difference) are in Supplement 3.

1-month visit was associated with a higher likelihood of exacerbation in response to tiotropium + ICS compared with LABA + ICS (HR, 1.82 [95% CI, 1.05 to 3.16], $P = .03$), and lack of bronchodilator reversibility at this visit was associated with a lower likelihood of exacerbation with tiotropium + ICS compared with LABA + ICS (HR, 0.74 [95% CI, 0.52 to 1.05], $P = .09$ [P for interaction <.01]). FEV_1/FVC was not associated with a difference in outcomes between the treatments.

A total of 67% of patients had protocol-defined asthma deteriorations, in which therapy was intensified over the course of the trial. There was no difference in time to first asthma deterioration or in mean number of deteriorations between groups (Figure 2, panel B).

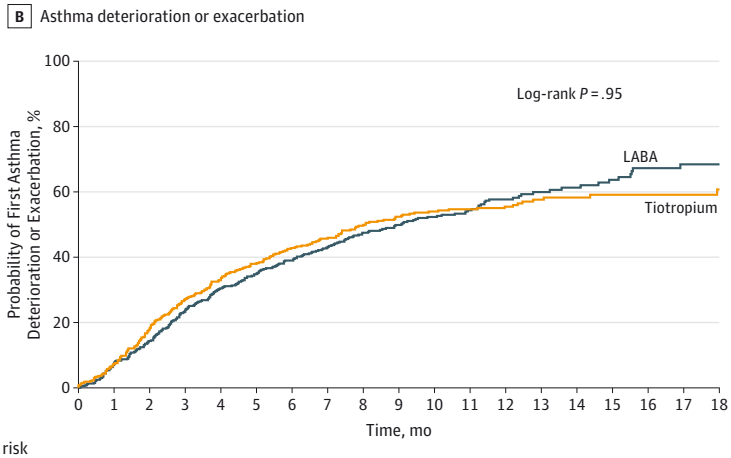
The secondary outcomes of ACQ score, AQLQ score, ASFD annualized score, and ASUI score all improved within both groups ($P < .001$), but there was no difference between groups (**Figure 3**, panels A-D). For ACQ score, there was no difference over the course of the entire study (Figure 3, panel A). At 12 months the mean change in ACQ score was 0.66 for LABA + ICS and −0.70 for tiotropium + ICS (between-group difference, 0.04 [95% CI, −0.11 to 0.20], $P = .573$) and at 18 months −0.68 for LABA + ICS vs −0.72 for tiotropium + ICS (between-group difference, 0.04 [95% CI, −0.18 to 0.27], $P = .70$). There was also no between-group difference in change in lung function as measured by FEV_1 over the course of the entire study (Figure 3, panel E), nor at the 12-month

Figure 2. Time to First Asthma Exacerbation, Asthma Deterioration or Exacerbation, and Exacerbation



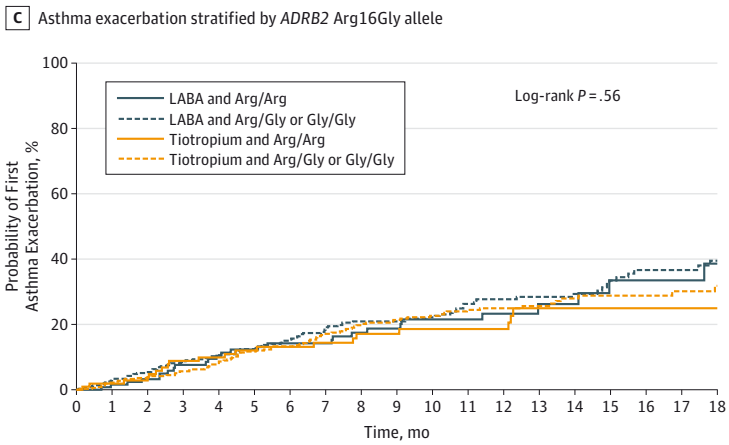
No. at risk

LABA	538	491	456	421	400	384	358	286	241	170	104	75	48
Tiotropium	532	487	456	431	410	381	356	274	236	182	111	87	43



No. at risk

LABA	538	467	408	349	306	283	254	185	148	96	53	36	23
Tiotropium	532	461	388	335	298	266	231	169	139	104	57	45	22



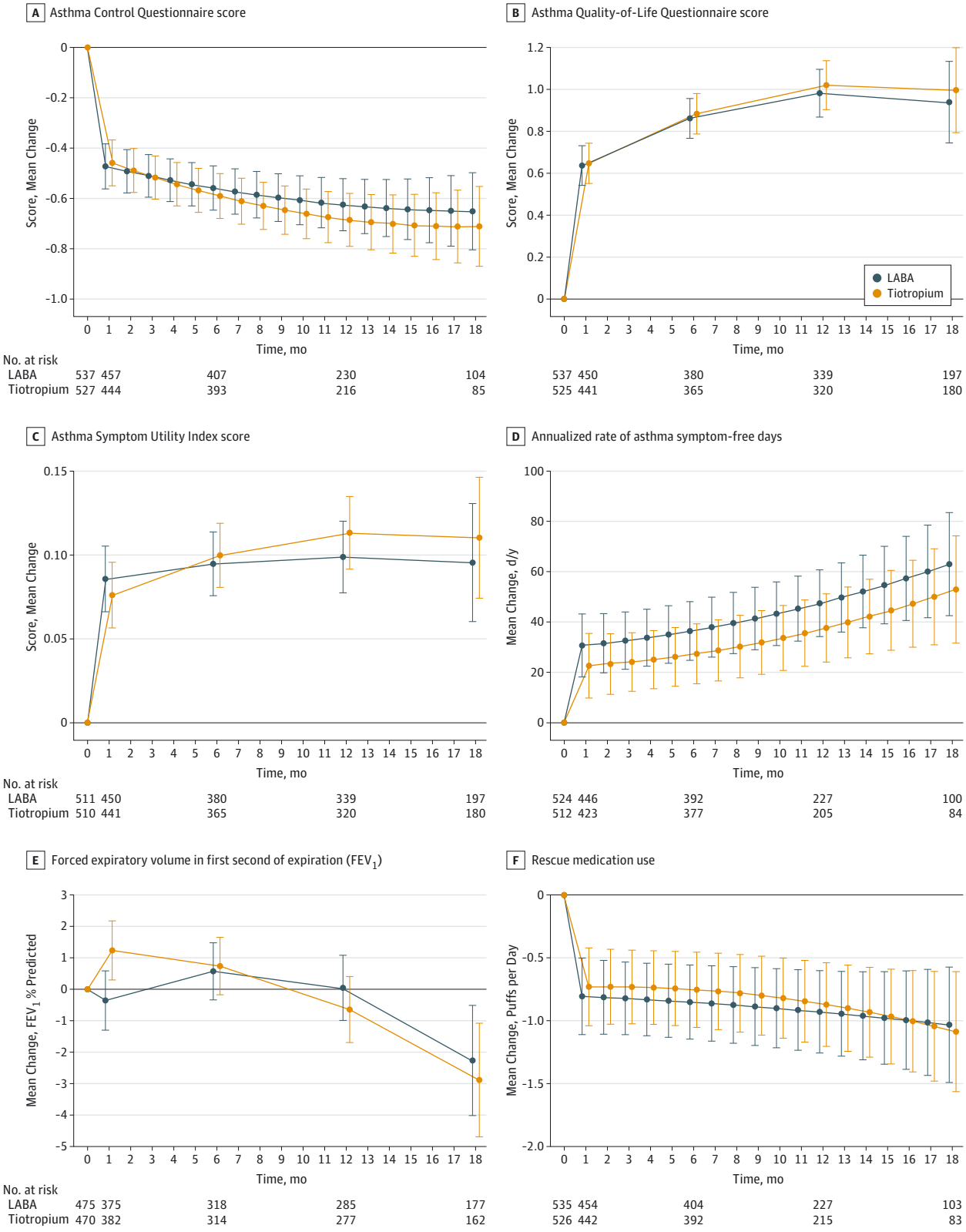
No. at risk

LABA and Arg/Arg	130	122	114	102	95	92	87	69	51	37	23	17	9
LABA and Arg/Gly or Gly/Gly	371	342	318	299	288	276	256	206	180	129	79	56	38
Tiotropium and Arg/Arg	110	104	99	87	85	81	75	57	50	42	22	13	8
Tiotropium and Arg/Gly or Gly/Gly	377	351	332	320	305	283	266	207	178	135	85	71	35

ADRB2 indicates β_2-adrenergic receptor; Arg/Arg, 2 arginine alleles; Arg/Gly, 1 arginine allele and 1 glycine allele; Gly/Gly, 2 glycine alleles; LABA, long-acting β-agonists.

Exacerbations are defined as worsening asthma that resulted in a prescription of systemic steroids or, even if no steroids were prescribed, a hospitalization for asthma. Deteriorations are defined as an increase in asthma symptoms that does not result in an asthma exacerbation but includes 1 or both of the following: (1) 2 days or more of an increase in either usual asthma medications (eg, inhaled corticosteroids, LABA, long-acting antimuscarinic) or rescue medications (short-acting β-agonists); (2) an emergency department visit for asthma (eg, for sick care), not resulting in systemic corticosteroids or in a hospitalization. For panel C, only patients with the identified genotype were included.

Figure 3. Mean Change from Baseline for Additional Asthma Outcomes in the Intention-to-Treat Population



LABA indicates long-acting β-agonists. Error bars indicate the 95% CIs. The No. at risk represent the number of patients at the respective time points in LABA or tiotropium groups with nonmissing results for the respective questionnaire measure.

time point (0.003 L for LABA + ICS vs −0.018 L for tiotropium + ICS; between-group difference, 0.020 [95% CI, −0.021 to 0.061], *P* = .33) or 18-month time point (−0.053 L for LABA + ICS vs −0.078 L for tiotropium + ICS; between-group difference, 0.025 [95% CI, −0.045 to 0.095], *P* = .49). There was no difference in average rescue medication use, which decreased when compared with baseline rescue medication use in both groups (Figure 3, panel F).

With regard to the *ADRB2* Arg16Gly alleles, the population was in Hardy-Weinberg equilibrium (*P* = .50). When stratified by genotype, there were no differences in the HRs for time to first exacerbation (HRs for tiotropium + ICS vs LABA + ICS: 0.84 [95% CI, 0.47 to 1.51] for Arg/Arg vs 0.85 [95% CI, 0.63 to 1.15] for Arg/Gly or Gly/Gly, *P* = .97) (Figure 2, panel C), mean number of exacerbations (RRs for tiotropium + ICS vs LABA + ICS: 0.77 [95% CI, 0.47 to 1.27] for Arg/Arg vs 0.86 [95% CI, 0.68 to 1.09] for Arg/Gly or Gly/Gly, *P* = .69) or lung function at 6, 12, or 18 months (*P* > .2).

The percentage of patients experiencing non-asthma-related or asthma-related adverse events and serious adverse events did not differ between treatments (2% of LABA + ICS patients vs 3% of tiotropium + ICS patients, *P* = .16). Given specific concerns regarding the safety of LABA therapy, particularly among black patients, we evaluated in an exploratory manner the frequency of asthma-related hospitalizations and deaths using our prespecified adjustments. There were 19 asthma-related hospitalizations in the tiotropium + ICS group vs 10 in the LABA + ICS group. The adjusted rates of asthma-related hospitalizations were 0.018 hospitalizations/patient/year for LABA + ICS vs 0.046 hospitalizations/patient/year for tiotropium + ICS (RR, 2.60 [95% CI, 1.14 to 5.91], *P* = .02) (eTable 2 in Supplement 3). There were a total of 67 hospitalizations in the tiotropium + ICS group and 58 in the LABA + ICS group. Three deaths occurred, all in the tiotropium + ICS group (*P* = .12); 2 of those deaths were asthma-related (*P* = .25) (eResults 1 in Supplement 3).

Discussion

We examined whether patients assigned to treatment with LABA + ICS had better outcomes compared with patients assigned to treatment with tiotropium + ICS. The study was performed in a population that bears a disproportionate burden of asthma morbidity and in whom questions have been raised about the relative efficacy and safety of LABAs. Because questions have been raised about whether efficacy studies correctly capture all the causes of morbidity, we conducted a clinical effectiveness study primarily in practicing physician offices. We used an outcome important to patients, physicians, and policy makers—asthma exacerbations.

We did not find LABA + ICS to be more effective than tiotropium + ICS in delaying asthma exacerbations (primary outcome). The risk ratio of a severe asthma exacerbation (requiring corticosteroids or hospitalization) when tiotropium + ICS was used compared with use of a LABA + ICS was 0.90 (95% CI, 0.73 to 1.11). Furthermore, LABA + ICS was not superior to tiotropium + ICS for the secondary outcomes that addressed additional dimensions of asthma control.

The Arg16Gly *ADRB2* polymorphism has been shown to be associated with the responses to regular use of short-acting β-agonists used without ICS.[10] A few studies have suggested that even when LABAs were used with ICS, allelic variation at this locus may affect outcomes.[11,12] However, several prospective and cross-sectional studies have not detected an adverse association in patients using ICS,[26,27] other than a possible association in black populations.[13] Our study did not detect a difference in the responses to LABA among the *ADRB2* Arg16Gly alleles or a difference between tiotropium + ICS and LABA + ICS in the black patients with Arg16Arg. No differences were observed for exacerbations or pulmonary function. A recent study suggested that a genotype-specific effect at this locus occurs in relation to use of LABAs in chronic obstructive pulmonary disease.[28] Furthermore, another study suggested that rare polymorphisms in *ADRB2* may affect responses to β-agonists.[29] Whether there is a difference in the prevalence of these rare polymorphisms in black populations is not known.

One of the strengths of this pragmatic trial was that it was conducted chiefly in primary care settings with minimal additional interventions. Except for the 1-month visit, patients were seen only every 6 months. Nonetheless, as this was an open-label study, the results may have been influenced by patient and prescriber knowledge of treatment. However, the adherence data suggest that it is unlikely that these differences were related to differential use of the medications because there was no difference in prescription refills between tiotropium + ICS and LABA + ICS, nor in the refills for ICS between the groups. The similar dropout data for both treatments are reassuring in this regard as well. Because 70% of the population was already taking a LABA + ICS before randomization, it is possible that the patients did not require combination therapy. However, the degree of exacerbations (>25% of the cohort) suggests that this is not the case. In addition, lung function, symptoms, and quality-of-life scores all improved to a clinically significant degree (eg, quality-of-life scores improved by >0.5 on the AQLQ scale) in patients, suggesting that there was significant room for improvement in this population.

Hospitalizations were analyzed in an exploratory manner in our safety analysis. The adjusted rates of hospitalizations due to asthma were higher with tiotropium + ICS compared with LABA + ICS. However, because hospitalizations were not a prespecified outcome for this trial, no conclusions can be reached regarding rates of hospitalizations among patients receiving LABA + ICS vs those receiving tiotropium + ICS. A dissociation between therapeutic effects of interventions on common measures of asthma control (including asthma exacerbations) and more serious asthma events such as hospitalizations, intubations, and deaths has been identified in a prior study[30] and has resulted in a US Food and Drug Administration–mandated study of more than 25 000 people to try to assess whether such an effect occurs.[31] No conclusions can be reached regarding dissociation of distinct measures of asthma control in the BELT trial, because hospitalizations were not a prespecified outcome.

We noted the relatively high mean BMI of 34 among our patients. However, we tested for treatment effect modification by BMI and found no significant difference. A prior smoking history was not associated with differential outcomes. The population in our study was mostly women (74%). Although this represents a relatively large percentage of the study population, a recent US Department of Health and Human Services report[32] noted that more than 62% of black individuals with asthma are women. Regardless, all our analyses were adjusted for sex.

A recent retrospective study suggested that patients with higher cholinergic tone (inferred from a lower resting heart rate), increased bronchodilator reversibility, or a lower FEV_1/FVC ratio were more likely to have improved airway function in response to tiotropium.[33] We did not assess resting heart rate. We observed no association between FEV_1/FVC and a difference in outcomes between the treatments. Although bronchodilator response was not assessed until patients had received 1 month of treatment, we observed that bronchodilator reversibility (>12% change in FEV_1) at the 1-month visit was associated with a lower likelihood of exacerbation in response to LABA + ICS compared with tiotropium + ICS, and lack of bronchodilator reversibility at this visit was associated with a lower likelihood of exacerbation with tiotropium + ICS compared with LABA + ICS.

Study Limitations

This study has several limitations that may affect generalizability of results. First, this was an open-label study that was not placebo-controlled and was limited to a single racial group. Second, patients' asthma status was based on physician diagnosis with no required objective testing as is common in community practice. Third, the population in this pragmatic trial had a relatively high discontinuation rate (31%-35%) and relatively poor adherence rate (60%) to medications. However, the adherence rate is comparable with published "real world" asthma medication adherence rates of 30% to 60%.[34] For each of these parameters, there was no significant difference between treatment groups. Fourth, although this study was powered to examine differences in exacerbations, it was not adequately powered to examine other significant outcomes such as hospitalization or death.

In summary, in a practice-based effectiveness trial, we studied black adults with asthma who were already treated with LABA + ICS or who were symptomatic and taking ICS. We found that the addition of twice-daily LABA to ICS was not superior to the addition of once-daily anticholinergic therapy with tiotropium as judged by asthma exacerbations, asthma deteriorations, lung function, and patient-reported outcomes. The Arg16Gly polymorphism of the *ADRB2* was not associated with differential responses to therapy. Although we could not detect a difference in exacerbations between either combination therapy, we found that, despite combination therapy, this population experienced a high rate of exacerbations. Additional targeted interventions and further study are needed to reduce the rate of asthma exacerbations in this population.

Conclusions

Among black adults with asthma treated with ICS, adding a LABA did not improve time to asthma exacerbation compared with adding tiotropium. These findings were not affected by polymorphisms at the Arg16Gly locus of *ADRB2*. These findings do not support the superiority of LABA + ICS compared with tiotropium + ICS for black patients with asthma.

ARTICLE INFORMATION

Author Contributions: Drs Israel and Wechsler had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
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