ORIGINAL ARTICLE

Serious Asthma Events with Fluticasone plus Salmeterol versus Fluticasone Alone

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ABSTRACT

BACKGROUND

The safe and appropriate use of long-acting beta-agonists (LABAs) for the treatment of asthma has been widely debated. In two large clinical trials, investigators found a potential risk of serious asthma-related events associated with LABAs. This study was designed to evaluate the risk of administering the LABA salmeterol in combination with an inhaled glucocorticoid, fluticasone propionate.

METHODS

In this multicenter, randomized, double-blind trial, adolescent and adult patients (age, ≥12 years) with persistent asthma were assigned to receive either fluticasone with salmeterol or fluticasone alone for 26 weeks. All the patients had a history of a severe asthma exacerbation in the year before randomization but not during the previous month. Patients were excluded from the trial if they had a history of life-threatening or unstable asthma. The primary safety end point was the first serious asthma-related event (death, endotracheal intubation, or hospitalization). Noninferiority of fluticasone–salmeterol to fluticasone alone was defined as an upper boundary of the 95% confidence interval for the risk of the primary safety end point of less than 2.0. The efficacy end point was the first severe asthma exacerbation.

RESULTS

Of 11,679 patients who were enrolled, 67 had 74 serious asthma-related events, with 36 events in 34 patients in the fluticasone–salmeterol group and 38 events in 33 patients in the fluticasone-only group. The hazard ratio for a serious asthma-related event in the fluticasone–salmeterol group was 1.03 (95% confidence interval [CI], 0.64 to 1.66), and noninferiority was achieved (P=0.003). There were no asthma-related deaths; 2 patients in the fluticasone-only group underwent asthma-related intubation. The risk of a severe asthma exacerbation was 21% lower in the fluticasone–salmeterol group than in the fluticasone-only group (hazard ratio, 0.79; 95% CI, 0.70 to 0.89), with at least one severe asthma exacerbation occurring in 480 of 5834 patients (8%) in the fluticasone–salmeterol group, as compared with 597 of 5845 patients (10%) in the fluticasone-only group (P<0.001).

CONCLUSIONS

Patients who received salmeterol in a fixed-dose combination with fluticasone did not have a significantly higher risk of serious asthma-related events than did those who received fluticasone alone. Patients receiving fluticasone–salmeterol had fewer severe asthma exacerbations than did those in the fluticasone-only group. (AUSTRI ClinicalTrials.gov number, NCT01475721.)

The safe and appropriate use of short-acting beta-agonists (SABAs) and long-acting beta-agonists (LABAs) for the treatment of asthma has been widely debated.[1] In early reports, SABAs were associated with an increased risk of asthma-related death.[2,3] In the 1990s, analyses suggested that high use of SABAs (>1.5 to 2 canisters per month) might increase the risk of death or near-fatal asthma.[4-6] In one of these studies, the authors postulated that high use of SABAs was either a marker of poorly controlled asthma or a "toxic effect of the medications or their vehicles."[6]

Two large clinical trials, the Serevent Nationwide Surveillance (SNS) trial[7] and the Salmeterol Multicenter Asthma Research Trial (SMART),[8] were designed to address whether regular use of the LABA salmeterol was associated with an increased risk of serious asthma events. At that time, inhaled glucocorticoids were not part of routine asthma care. Although the SNS trial showed significantly fewer withdrawals because of worsening asthma with salmeterol than with salbutamol, the rate of asthma-related deaths was higher among salmeterol-treated patients, although the difference was not significant.[7] In SMART, more patients receiving salmeterol than receiving placebo died, both from respiratory-related events (24 vs. 11) and from asthma-related events (13 vs. 3).[8] This risk was greater among black patients than among white patients.[8] Although 47% of the patients were receiving inhaled glucocorticoids at baseline, SMART was not designed to address whether concurrent use of inhaled glucocorticoids altered the risk.[8]

In 2008, the Food and Drug Administration (FDA) requested that the four manufacturers of LABA-containing medications for the treatment of asthma assess the rates of asthma-related death, intubation, and hospitalization by analyzing the data in all their studies of LABAs. In response, GlaxoSmithKline, the manufacturer of salmeterol, compared data regarding salmeterol with non-LABA data in a meta-analysis[9]; this meta-analysis showed higher rates of asthma-related death and hospitalization among patients receiving salmeterol, with inhaled glucocorticoids dispensed in a separate inhaler (i.e., inhaled glucocorticoids were not part of the treatment protocol and may or may not have been used), than among patients receiving non-LABA treatment.[9] There were no asthma-related deaths or imbalances in the rates of asthma-related hospitalization when salmeterol was dispensed in a fixed-dose combination with fluticasone propionate.[9,10]

In 2010, the FDA requested that each of the four manufacturers undertake a large prospective trial to evaluate whether a LABA added to an inhaled glucocorticoid would be noninferior to an inhaled glucocorticoid alone with respect to the risk of a serious asthma-related event (hospitalization, endotracheal intubation, or death).[11] The composite of serious asthma-related events was selected since asthma-related deaths are rare in clinical trials.

We designed this prospective, multicenter, randomized, double-blind trial (AUSTRI) with a primary objective of establishing whether the risk of serious asthma-related events would be higher when salmeterol was used concomitantly with fluticasone as a fixed-dose combination (fluticasone–salmeterol) than if fluticasone was used alone. A secondary objective was to evaluate whether fluticasone–salmeterol was superior to fluticasone with respect to prespecified measures of efficacy.

Methods

Trial Design and Oversight

From November 2011 through June 2015, we enrolled adolescent and adult patients (age, ≥12 years) with moderate-to-severe asthma at 710 centers in 33 countries. All the patients attended a screening and randomization visit, which was followed by a 26-week active treatment period and a 1-week follow-up period (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

Members of a common joint oversight steering committee, a joint adjudication committee (which was responsible for uniform determination of asthma-relatedness for study end points), and a joint data and safety monitoring committee were charged with ensuring responsible conduct of the trial and the safety of all the patients. An independent, trial-specific data and safety monitoring committee reviewed trial-specific safety data for patients every 6 months, with one planned, formal interim statistical analysis performed after approximately half the expected 87 events had occurred (see the trial protocol, available at NEJM.org).

Scientific oversight of the trial was provided by employees of GlaxoSmithKline, including the authors, who were collectively responsible for the design and conduct of the trial. The joint steering committee and the FDA provided advice on the trial, which was harmonized with trials conducted by the other three manufacturers of LABA-containing medications. The initial draft of the manuscript was written by the first author, and all the authors worked collaboratively to prepare the final content. Editorial support was provided by a professional medical writer who was paid by GlaxoSmithKline. Statistical analyses were performed by employees of GlaxoSmithKline and PAREXEL International. All the authors had full access to the data and vouch for the accuracy and completeness of all data and analyses and agreed to the submission of the manuscript for publication.

Ethical approval was obtained from the relevant ethics committee or institutional review board at each site. The trial was conducted in accordance with Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki.

TRIAL POPULATION

Eligible patients had at least a 1-year history of asthma,[12,13] required daily medications for asthma control, and had received treatment with systemic glucocorticoids for an asthma exacerbation or had been hospitalized for an asthma exacerbation during the previous 12 months, with the exclusion of the 30 days before randomization.

Patients were excluded from the study if they had a history of life-threatening asthma, cigarette smoking for more than 10 pack-years, or unstable asthma. (A detailed description of the trial criteria is provided in the Methods section in the Supplementary Appendix.) All the patients or their legal guardians provided written informed consent.

STUDY RANDOMIZATION AND TREATMENTS

Randomization was performed with the use of an interactive voice–response system, with stratification of patients in six groups according to the patients' current asthma medications and assessment of asthma control (Table S1 in the Supplementary Appendix). Asthma control was assessed at screening and during office visits with the use of the Asthma Control Questionnaire 6 (ACQ-6), on which asthma symptoms are rated on a scale of 0 to 6, with higher values indicating worse symptoms.[14]

Patients were randomly assigned in a 1:1 ratio within stratification groups to receive a combination of fluticasone propionate and salmeterol (at a dose of 100 μg of fluticasone and 50 μg of salmeterol, 250 μg and 50 μg, respectively, or 500 μg and 50 μg, respectively) or fluticasone propionate alone (at a dose of 100 μg, 250 μg, or 500 μg), administered twice daily in a masked DISKUS dry-powder inhaler (GlaxoSmithKline). Study treatment was double-blinded with respect to fluticasone–salmeterol versus fluticasone alone but not with respect to the dose of inhaled glucocorticoid. All treatments were presented in identical packaging. Open-label rescue albuterol or salbutamol administered through a metered-dose inhaler was also supplied to all patients.

STUDY END POINTS

Safety

The primary safety end point was the first serious asthma-related event, a composite end point that included death, endotracheal intubation, and hospitalization. Events were reviewed by members of the joint adjudication committee who were unaware of the study-group assignments. All hospitalization events underwent initial screening by a member of the joint adjudication committee, and if the patient's condition was considered to be potentially asthma-related, a complete adjudication followed. All intubations and deaths were fully adjudicated.

All nonserious adverse events leading to withdrawal from the trial and all serious adverse events were documented. The vital status and mortality of all patients who received at least one dose of a study drug were assessed after the 6-month trial period.

Efficacy

The main efficacy end point was the first severe asthma exacerbation, which was defined as asthma deterioration that led to the use of systemic glucocorticoids for at least 3 days or an asthma-related hospitalization or emergency department visit that led to the use of systemic glucocorticoids.[15] A secondary measure of efficacy was the use of rescue albuterol or salbutamol.

STATISTICAL ANALYSIS

The primary safety objective was assessed by means of a stratified Cox proportional-hazards regression model of the time until the first serious asthma-related outcome, with a term for randomized treatment (fluticasone–salmeterol or fluticasone alone) and with the randomization stratum according to the asthma treatment being received and the level of asthma control at baseline as the stratification factor. Noninferiority of fluticasone–salmeterol to fluticasone alone was defined as an upper boundary of the 95% confidence interval for the risk of the primary safety end point of less than 2.0. In the two treatment groups, data from the three dose strata were combined.

We used a Cox proportional-hazards regression model to test the main efficacy end point. The study was not powered to allow formal statistical comparison or evaluation of fluticasone–salmeterol versus fluticasone alone in subgroups. However, for the key subgroups of age and race, descriptive analyses were performed, and results are expressed as hazard ratios and 95% confidence intervals.

In calculating the sample size for the primary safety end point, we assumed that the rate in the fluticasone-only group would be 0.0075 patients with an event during the 26-week trial. The sample size was adjusted to accommodate one interim statistical analysis when approximately half the expected number of composite end points had occurred. We used the Haybittle–Peto method for managing the alpha spending function over the interim analysis and the final analysis.[16,17] We determined that a sample size of 11,664 participants would allow the observation of 87 patients with the composite end point, which would give the study 90% power to show the noninferiority of fluticasone–salmeterol to fluticasone alone, with the use of the log-rank test, at a one-sided alpha level of 0.025, and to reject the null hypothesis that the risk associated with fluticasone–salmeterol, as compared with fluticasone alone, would be greater than the noninferiority margin.

The primary analysis was performed in the intention-to-treat population, which included all the patients who had undergone randomization and received at least one dose of fluticasone–salmeterol or fluticasone alone. For the primary analysis, the data included composite events that occurred within 6 months after the first dose or 7 days after the last dose of a study drug, whichever interval from randomization was greater. A modified intention-to-treat analysis included only data collected up to 7 days after each patient stopped the study drug. Four efficacy subgroups that were classified according to the level of asthma control at baseline (controlled or not controlled) and previous asthma therapy (inhaled glucocorticoids or inhaled glucocorticoids plus LABA) were prespecified for analysis (Table S2 in the Supplementary Appendix).

RESULTS

TRIAL POPULATION

A total of 11,751 patients underwent randomization at 694 of the 710 centers that participated in the trial. Of these patients, 72 (0.6%) did not receive a dose of a study drug, so 11,679 patients were included in the intention-to-treat population (5834 in the fluticasone–salmeterol group and 5845 in the fluticasone-only group) (Fig. 1, and Table S3 in the Supplementary Appendix). The demographic characteristics of the patients were similar in the two groups (Table 1). The median rate of adherence to study medications (as determined by the dose counter in the DISKUS device) was 95.1% in each of the two groups.

SAFETY

Serious Asthma-Related Events

Among the 11,679 patients, 67 had 74 serious asthma-related events, with 36 events in 34 patients in the fluticasone–salmeterol group and 38 events in 33 patients in the fluticasone-only group (Table 2). The hazard ratio for a serious asthma-related event in the fluticasone–salmeterol group was 1.03 (95% confidence interval [CI], 0.64 to 1.66). The upper boundary of the confidence interval did not exceed 2.0; therefore, fluticasone–salmeterol was shown to be noninferior to fluticasone alone ($P=0.003$). The Kaplan–Meier curve for the primary safety end point is shown in Figure 2.

There were no asthma-related deaths in either group. One or more asthma-related hospitalizations were reported in 34 patients in the fluticasone–salmeterol group and in 33 patients in the fluticasone-only group (with a total of 36 asthma-related hospitalizations in each group) (Table 2). There were no significant differences in the rates of asthma-related hospitalization accord-

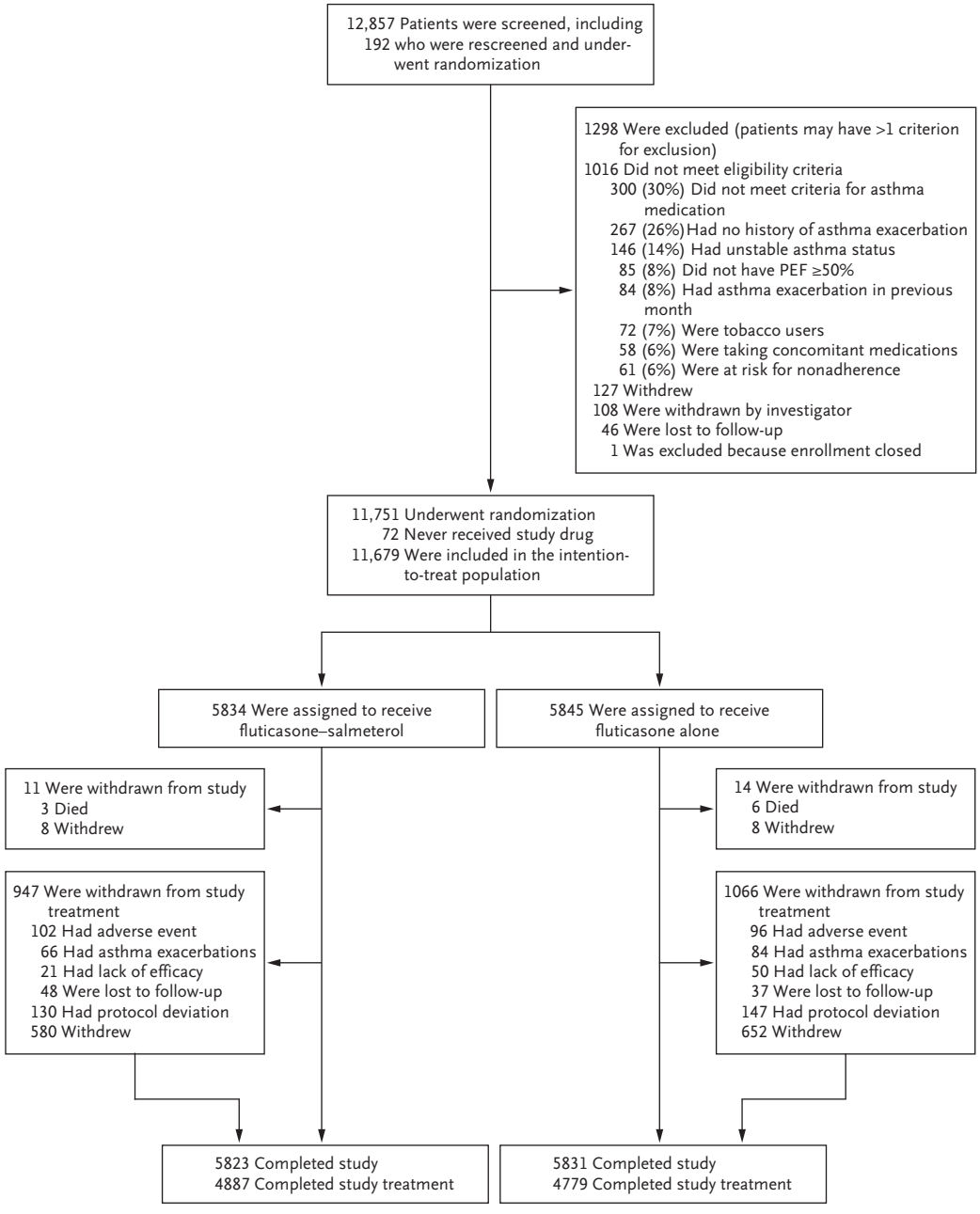


Figure 1. Enrollment and Outcomes.

A complete list of reasons for exclusion from the trial is provided in Table S3 in the Supplementary Appendix. PEF denotes peak expiratory flow.

ing to age group (12 to 17 years, 18 to 64 years, and >64 years) or race (white, black, or other), although the trial was not powered to detect noninferiority in these subgroups (Table S4 in the Supplementary Appendix). Asthma-related endotracheal intubations were reported in 2 patients in the fluticasone-only group and in no patients in the fluticasone–salmeterol group.

Other Safety Outcomes

Adverse events leading to withdrawal from a study treatment were reported in 165 of 5834 patients (3%) in the fluticasone–salmeterol group and in 180 of 5845 (3%) in the fluticasone-only group. The incidence of serious adverse events was 2% in each of the two groups (Table S5 in the Supplementary Appendix). Serious respiratory adverse events were observed in 33 patients (<1%) in the fluticasone–salmeterol group and in 38 patients (<1%) in the fluticasone-only group.

Nine deaths occurred during the study, three in the fluticasone–salmeterol group and six in the fluticasone-only group; none were independently adjudicated as being asthma-related. Vital status was determined for all but 2 patients. (Details are provided in Sections 3 and 4 in the Supplementary Appendix.)

SEVERE ASTHMA EXACERBATIONS AND USE OF RESCUE INHALER

At least one severe asthma exacerbation was reported in 480 of 5834 patients (8%) in the fluticasone–salmeterol group and in 597 of 5845 patients (10%) in the fluticasone-only group. The hazard ratio for a serious asthma exacerbation in the fluticasone–salmeterol group was 0.79 (95% CI, 0.70 to 0.89; P<0.001) when age was included as a covariate. For the four prespecified efficacy subgroups (Table S2 in the Supplementary Appendix), the risk of an asthma exacerbation was 16 to 32% lower in the fluticasone–salmeterol group than in the fluticasone-only group (Table 3). Among the four subgroups, the between-group difference was significant only in the one in which asthma was well controlled on a regimen of inhaled glucocorticoids plus LABA at baseline. In that subgroup, there was a 24% lower risk of a severe asthma exacerbation in the fluticasone–salmeterol group than in the fluticasone-only group.

In all age groups, the risk of a severe asthma exacerbation was consistently lower among those treated with fluticasone–salmeterol than among those treated with fluticasone alone (Table 3), with the largest difference (a 35% lower risk) seen among adolescents. A total of 79 black patients in each group had an exacerbation (hazard ratio for fluticasone–salmeterol vs. fluticasone alone, 0.96; 95% CI, 0.70 to 1.31). The mean and median number of puffs of rescue medication per day were slightly lower in the fluticasone–salmeterol group than in the fluticasone-only group (Table S6 in the Supplementary Appendix).

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Fluticasone–Salmeterol (N=5834)	Fluticasone Alone (N=5845)
Female sex — no. (%)	3851 (66)	3898 (67)
Age		
Mean	43.4±17.45	43.4±17.28
Distribution — no. (%)		
12–17 yr	615 (11)	615 (11)
18–64 yr	4576 (78)	4605 (79)
>64 yr	643 (11)	625 (11)
Race — no. (%)†		
White	4374 (75)	4409 (75)
Black	870 (15)	856 (15)
Other	590 (10)	580 (10)
Region — no. (%)		
North America	2623 (45)	2680 (46)
Latin America	339 (6)	338 (6)
Europe	2110 (36)	2091 (36)
Africa	477 (8)	474 (8)
Asia–Pacific	285 (5)	262 (4)

* Plus–minus values are means ±SD. The analysis was performed in the intention-to-treat population, which included all patients who had undergone randomization and who had received at least one dose of fluticasone–salmeterol or fluticasone alone. There were no significant differences between the two treatment groups in post hoc analysis.
† Race was self-reported.

Table 2. Summary of Safety End Points.*

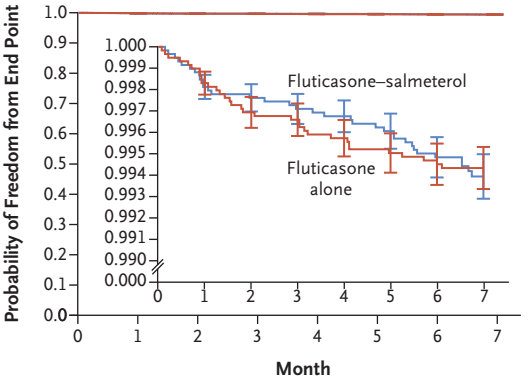
Safety End Point	Fluticasone–Salmeterol (N=5834)	Fluticasone Alone (N=5845)
Composite safety end point — no. (%)	34 (<1)	33 (<1)
Asthma-related death	0	0
Asthma-related intubation	0	2 (<1)
Asthma-related hospitalization	34 (<1)	33 (<1)
Total no. of asthma-related hospitalizations	36	36
Death from any cause — no. (%)†	3 (<1)	6 (<1)

* The analysis was performed in the intention-to-treat population.
† Details regarding all-cause mortality are provided in Section 4 in the Supplementary Appendix.

Table 3. First Severe Asthma Exacerbation, According to Subgroup.*

Subgroup	Severe Asthma Exacerbation		Hazard Ratio (95% CI)	P Value
	Fluticasone–Salmeterol	Fluticasone Alone		
	no./total no. (%)			
Asthma control				
Not well controlled on previous inhaled glucocorticoid or non-LABA therapy	91/1405 (6)	106/1398 (8)	0.83 (0.63–1.10)	0.20
Not well controlled on previous inhaled glucocorticoid plus LABA therapy	102/1016 (10)	124/1040 (12)	0.84 (0.65–1.09)	0.19
Well controlled on previous inhaled glucocorticoid plus LABA therapy	239/2652 (9)	304/2663 (11)	0.76 (0.65–0.91)	0.002
Well controlled on previous inhaled glucocorticoid therapy	38/612 (6)	54/608 (9)	0.68 (0.45–1.03)	0.07
Age				
12–17 yr	42/615 (7)	64/615 (10)	0.65 (0.44–0.95)	0.03
18–64 yr	386/4576 (8)	469/4605 (10)	0.81 (0.71–0.93)	0.002
>64 yr	52/643 (8)	64/625 (10)	0.78 (0.54–1.12)	0.17

* The analysis was performed in the modified intention-to-treat population, which included all the patients in the intention-to-treat population for whom data were available 7 days after the last dose of a trial medication was administered.



No. at Risk

Fluticasone–salmeterol	5834	5798	5761	5731	5707	5671	5625	527
Fluticasone alone	5845	5811	5770	5726	5695	5669	5621	529

Figure 2. Primary Safety End Point (Intention-to-Treat Population).

The primary safety end point was the first serious asthma-related event, a composite that included death, endotracheal intubation, and hospitalization. The end point was assessed in the intention-to-treat population, which included all the patients who had undergone randomization and received at least one dose of fluticasone–salmeterol or fluticasone alone. The inset shows the same data on an expanded y axis. I bars indicate standard errors.

DISCUSSION

We found that among patients with moderate-to-severe asthma and a history of exacerbation during the previous year, the risk of serious asthma-related events was no greater when salmeterol was delivered by inhaler in a fixed-dose combination with fluticasone propionate than when fluticasone was administered alone. This finding was consistent with the results of previous trials and meta-analyses of fluticasone–salmeterol,[9,10,18] which showed no greater risk of serious asthma-related events among patients receiving fluticasone–salmeterol than among those receiving fluticasone alone.

Several meta-analyses that have investigated possible links between the use of LABAs and asthma-related death have suggested that LABAs are associated with a higher risk of death than are non-LABA medications.[10,19,20] However, the concomitant use of inhaled glucocorticoids was not a consistently controlled variable in these studies. In the meta-analysis conducted by Weatherall et al.,[10] investigators who compared

salmeterol with non-LABA treatments found an increased risk of asthma-related death only when salmeterol was dispensed as monotherapy and not necessarily when an inhaled glucocorticoid was used as concomitant therapy. Of the 35 deaths included in that meta-analysis, 30 (86%) were observed in the SNS and SMART trials.[10] With a combined enrollment of more than 50,000 patients in these trials,[7,8] they contributed heavily to the data in all the meta-analyses. Thus, further clinical trials that specifically addressed the use of LABAs plus concurrent inhaled glucocorticoids, as compared with inhaled glucocorticoids alone, were warranted, particularly because standards of care for asthma have changed since the time that earlier trials were conducted and because the use of inhaled glucocorticoids was not controlled in the earlier trials. No patients who were treated with fluticasone–salmeterol or fluticasone alone in our trial died from asthma-related causes, which provides further evidence that the use of fluticasone–salmeterol does not increase the risk of asthma-related death.

In our trial, the risk of asthma-related hospitalization was low, approximately 1 per 100 patient-years, and corresponds to low incidences that were observed in other studies involving similar populations.[9,18,21,22] Since the patients in our trial were at high risk for asthma-related events, the low incidence of serious asthma-related events suggests that treatment adherence may be key to controlling asthma. The association between these events and fluticasone–salmeterol that we observed is consistent with that in a nested case–control analysis of inhaled glucocorticoids plus LABAs, as compared with inhaled glucocorticoids alone, in which the rate ratio for asthma-related hospitalization among patients receiving inhaled glucocorticoids plus LABAs, as compared with those receiving inhaled glucocorticoids alone, was 1.14 (95% CI, 0.93 to 1.41).[23]

Studies and reviews that have evaluated the safety of SABAs and LABAs have included a discussion of possible causes of the observed increase in the risk of asthma-related death and have noted a concern about whether the risk was greater among specific age or racial groups.[1,8,10,18-20,24-26] Data from our trial do not support hypotheses that specific age or racial groups are at greater risk when beta-agonists are used concurrently with inhaled glucocorticoids.

Another important finding in our trial is that the risk of a severe asthma exacerbation was 21% lower among patients who were treated with fluticasone–salmeterol than among those treated with fluticasone alone. The difference was most prominent among adolescents, in whom the risk was 35% lower. Among patients in whom asthma was well controlled on a previous regimen of inhaled glucocorticoids plus LABAs, the risk of a severe asthma exacerbation was 24% lower in the fluticasone–salmeterol group than in the fluticasone-only group. These effect sizes are consistent with a previous meta-analysis that compared fluticasone–salmeterol with fluticasone alone[18] and with other trials in which patients were included only if they had a history of a severe exacerbation in the 12 months before randomization.[24,27]

Studies have shown that routine use of SABAs or LABAs without inhaled glucocorticoids increases the risk of serious and potentially fatal outcomes among patients with asthma.[1-5,7-9] The frequent use of SABAs is the hallmark of uncontrolled asthma, and escalation in therapy with antiinflammatory agents such as inhaled glucocorticoids is recommended.[12] In addition, LABA monotherapy may mask underlying disease by providing a temporary reduction in symptoms but ultimately placing patients at risk for serious exacerbations.[28] However, the risks appear to be mitigated when beta-agonists are reliably used with concomitant inhaled glucocorticoids, including with the fixed-dose combination of fluticasone–salmeterol.[7,9,10,18]

Limitations of this trial include its relatively short duration of 26 weeks and the infrequent occurrence of serious asthma-related events. Also, we enrolled patients with moderate-to-severe asthma, and the results may not be applicable to all patients with asthma. For example, since patients with a history of life-threatening or unstable asthma were excluded from the study, our results cannot be extrapolated to such patients. The study was designed with FDA guidance, and we assessed a composite end point of serious asthma-related events to help address the infrequent occurrence of asthma-related death and intubation. In addition, although we designed

the trial as a "real world" analysis, adherence was high, which may not always occur in real-world clinical practice. The extent of underlying inflammatory disease in each patient was not measured, a factor that may have influenced the results; the prespecified efficacy subgroups were included to partly counterbalance this limitation.

In conclusion, we found that among patients with moderate-to-severe asthma, serious asthma-related events occurred with similar frequency among those receiving 26 weeks of treatment with fluticasone–salmeterol and those receiving fluticasone alone, which showed the noninferiority of the fixed-dose combination to fluticasone alone. The clinical benefits of fluticasone–salmeterol were significant, with a 21% lower risk of a severe asthma exacerbation among patients who received that therapy than among those who received fluticasone alone.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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