ORIGINAL ARTICLE

Combined Analysis of Asthma Safety Trials of Long-Acting β_2-Agonists

William W. Busse, M.D., Eric D. Bateman, M.B., Ch.B., M.D., Arthur L. Caplan, Ph.D., H. William Kelly, Pharm.D., Paul M. O'Byrne, M.B., Klaus F. Rabe, M.D., Ph.D., and Vernon M. Chinchilli, Ph.D.

ABSTRACT

BACKGROUND

Safety concerns regarding long-acting β_2-agonists (LABAs) in asthma management were initially identified in a large postmarketing trial in which the risk of death was increased. In 2010, the Food and Drug Administration (FDA) mandated that the four companies marketing LABAs for asthma perform prospective, randomized, controlled trials comparing the safety of combination therapy with a LABA plus an inhaled glucocorticoid with that of an inhaled glucocorticoid alone in adolescents (12 to 17 years of age) and adults. In conjunction with the FDA, the manufacturers harmonized their trial methods to allow an independent joint oversight committee to provide a final combined analysis of the four trials.

METHODS

As members of the joint oversight committee, we performed a combined analysis of the four trials comparing an inhaled glucocorticoid plus a LABA (combination therapy) with an inhaled glucocorticoid alone. The primary outcome was a composite of asthma-related intubation or death. Post hoc secondary outcomes included serious asthma-related events and asthma exacerbations.

RESULTS

Among the 36,010 patients in the intention-to-treat study, there were three asthma-related intubations (two in the inhaled-glucocorticoid group and one in the combination-therapy group) and two asthma-related deaths (both in the combination-therapy group) in 4 patients. In the secondary analysis of serious asthma-related events (a composite of hospitalization, intubation, or death), 108 of 18,006 patients (0.60%) in the inhaled-glucocorticoid group and 119 of 18,004 patients (0.66%) in the combination-therapy group had at least one composite event (relative risk in the combination-therapy group, 1.09; 95% confidence interval [CI], 0.83 to 1.43; P=0.55); 2100 patients in the inhaled-glucocorticoid group (11.7%) and 1768 in the combination-therapy group (9.8%) had at least one asthma exacerbation (relative risk, 0.83; 95% CI, 0.78 to 0.89; P<0.001).

CONCLUSIONS

Combination therapy with a LABA plus an inhaled glucocorticoid did not result in a significantly higher risk of serious asthma-related events than treatment with an inhaled glucocorticoid alone but resulted in significantly fewer asthma exacerbations.

From the Department of Medicine, Division of Allergy, Pulmonary and Critical Care Medicine, University of Wisconsin School of Medicine and Public Health, Madison (W.W.B.); the Pulmonary Division, Department of Medicine, University of Cape Town, Cape Town, South Africa (E.D.B.); the Division of Medical Ethics, Department of Population Health, New York University School of Medicine, New York (A.L.C.); the Department of Pediatrics, University of New Mexico Health Sciences Center, Albuquerque (H.W.K.); the Department of Medicine, McMaster University, Hamilton, ON, Canada (P.M.O.); LungenClinic Grosshansdorf and Christian Albrechts University Kiel, Kiel, and Airway Research Center North, German Center for Lung Research, Grosshansdorf — both in Germany (K.F.R.); and the Department of Public Health Sciences, Penn State College of Medicine, Hershey, PA (V.M.C.). Address reprint requests to Dr. Busse at the University of Wisconsin Hospitals and Clinics, 600 Highland Ave., Madison, WI 53792, or at wwb@medicine.wisc.edu.

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Because of concerns about the safety of long-acting β_2-agonists (LABAs) in asthma management,[1-4] the Food and Drug Administration (FDA) in 2010 issued a public health advisory stating that LABAs should not be used as first-line therapy for asthma, and a boxed warning was required for all products containing a LABA. In a meta-analysis conducted by the FDA, there was no noted increase in the risk of serious asthma-related events in study subgroups that included inhaled glucocorticoids as part of the assigned therapy, with the medication delivered in either the same inhaler or different inhalers.[4] However, the FDA stated that the small numbers of patients who were enrolled in these studies prevented a definitive conclusion regarding mitigation of serious asthma-related events with the addition of inhaled glucocorticoids.[4]

In other meta-analyses, investigators reported findings that both supported and contradicted the FDA's findings, which furthered the debate on the safety of LABA use in asthma.[5-10] Consequently, in 2010, the FDA mandated that the four companies marketing LABAs for asthma (AstraZeneca, GlaxoSmithKline, Merck, and Novartis) perform prospective, randomized, controlled trials comparing the safety of combination therapy with a LABA plus an inhaled glucocorticoid with that of an inhaled glucocorticoid alone.[11] In conjunction with the FDA, the manufacturers harmonized their trial methods to allow an independent joint oversight committee to perform a final combined analysis of the four trials to specifically assess the relatively rare severe events (endotracheal intubation or death) as the primary outcome and to analyze the frequency of serious asthma-related events (endotracheal intubation, hospitalization, or death) as a secondary outcome. Our report provides the final combined analysis of these four trials.

Methods

Study Design

Overviews of the individual trial designs are provided at www.clinicaltrials.gov (identifier numbers, NCT01444430, NCT01475721, NCT01471340, and NCT01845025). Each of the four trials targeted an enrollment of 11,664 adolescents (12 to 17 years of age) and adults with persistent asthma into a 26-week, multicenter, parallel, randomized, double-blind, noninferiority trial with a power of 90% to rule out a doubling in the risk (or a hazard ratio of 2.0) of a serious asthma-related event (a composite of hospitalization, intubation, or death), as estimated with the use of Cox proportional-hazards models.[12-14] In each trial, patients were randomly assigned to receive an inhaled glucocorticoid plus a LABA (combination therapy) or an inhaled glucocorticoid alone; the unblinded administration of an as-needed short-acting β_2-agonist was allowed.

The trials that were conducted by representatives of AstraZeneca, GlaxoSmithKline, and Merck incorporated the inhaled glucocorticoids and LABA medications into one inhaler device, whereas the Novartis trial required a separate inhaler for each drug. Three of the sponsors (AstraZeneca, GlaxoSmithKline, and Merck) completed the trials and reported the results,[12-14] whereas the remaining sponsor (Novartis) terminated its trial (not for safety reasons) at an early stage on October 15, 2015, when the company removed its drug from the market in the United States.

Our analyses are based on the intention-to-treat analysis of data from 36,010 patients enrolled in the four trials: 11,693 in the AstraZeneca trial,[13] 11,750 in the GlaxoSmithKline trial,[12] 11,744 in the Merck trial,[14] and 823 in the Novartis trial. These sample sizes are slightly higher than those reported by representatives of GlaxoSmithKline (11,679), Merck (11,729), and Novartis (820), who applied stricter criteria than those used in the intention-to-treat analysis.

Study Outcomes

In this analysis, the prespecified primary outcome was a composite of asthma-related intubation or death. For each serious asthma-related event that was identified, a joint adjudication committee whose members were unaware of study-group assignments made the determination as to whether the event was asthma-related or had another cause. These determinations were followed by a review of the findings by a joint data and safety monitoring committee. We also performed post hoc secondary combined analyses of data from a modified intention-to-treat population, which included all the patients who had undergone randomization and received at least one dose of a blinded trial drug. In these sec-

ondary analyses, we evaluated serious asthma-related events (a composite of hospitalization, intubation, or death), including an analysis of each of the three individual components. We also analyzed subgroups of patients who might be at increased risk for serious asthma-related events (on the basis of age, race, smoking history, or obesity level) and asthma exacerbations (i.e., events that were associated with the use of systemic glucocorticoids for ≥3 outpatient days or an emergency department visit or hospitalization associated with the use of systemic glucocorticoids). The obesity level was categorized according to body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) as follows: normal weight or underweight (<25.0), overweight (25.0 to 29.9), obesity class I (30.0 to 34.9), obesity class II (35.0 to 39.9), or obesity class III (≥40.0).

STATISTICAL ANALYSIS

Before the initiation of the study, we anticipated that few events would result in either asthma-related intubation or death (the primary outcome), so the statistical analysis plan included an exact stratified Mantel–Haenszel analysis in which the trial that was performed by each manufacturer served as a stratum. The primary summary statistic was the overall relative risk of intubation or death with an inhaled glucocorticoid plus a LABA as compared with an inhaled glucocorticoid alone, with an associated 95% confidence interval and P value. Before the analysis was initiated, an exact Mantel–Haenszel test of the heterogeneity of the trial strata was performed. If the test for heterogeneity was significant (P<0.10), the analytic results would not be reported. All the results for risk ratios are displayed in the form of forest plots.

RESULTS

PRIMARY AND SECONDARY OUTCOMES

The demographic and clinical characteristics of the 36,010 patients were similar across the four trials (Table 1). In the intention-to-treat analysis, there were three asthma-related intubations (two in the inhaled-glucocorticoid group and one in the combination-therapy group) and two asthma-related deaths (both in the combination-therapy group) in 4 patients (Table 2). Thus, the secondary analysis of serious asthma-related events provided more robust results and was based primarily on asthma-related hospitalizations.

Serious asthma-related events occurred in 108 of 18,006 patients (0.60%) in the inhaled-glucocorticoid group and in 119 of 18,004 patients (0.66%) in the combination-therapy group (relative risk, 1.09; 95% confidence interval [CI], 0.83 to 1.43; P=0.55) (Table 2 and Fig. 1A). The results from analyses of serious asthma-related events in the modified intention-to-treat population (relative risk, 1.24; 95% CI, 0.94 to 1.65; P=0.13) were very similar to the findings in the intention-to-treat population (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

At least one asthma exacerbation occurred in 2100 patients (11.7%) in the inhaled-glucocorticoid group and in 1768 patients (9.8%) in the combination-therapy group (relative risk, 0.83; 95% CI, 0.78 to 0.89; P<0.001). The lower risk of exacerbation among patients in the combination-therapy group than in the inhaled-glucocorticoid group was consistent across the four individual trials (Fig. 2A).

SUBGROUP ANALYSES

Secondary analyses of serious asthma-related events and asthma exacerbations were conducted in subgroups of patients who were thought to be at higher risk than those in the overall population (Figs. 1B and 2B). There was no significant increase in the relative risk of serious asthma-related events among 3608 adolescents between the ages of 12 and 17 years (relative risk, 0.92; 95% CI, 0.31 to 2.70), among 3419 black patients (relative risk, 1.08; 95% CI, 0.58 to 2.01), among 3058 Asian patients (relative risk, 1.60; 95% CI, 0.68 to 3.95), or among 3188 patients with class II obesity (relative risk, 0.60; 95% CI, 0.28 to 1.28) and 2269 patients with class III obesity (relative risk, 1.10; 95% CI, 0.49 to 2.09). The risk of asthma exacerbations among patients in the combination-therapy group, as compared with the inhaled-glucocorticoid group, was not significantly different among adolescents (relative risk, 0.87; 95% CI, 0.70 to 1.09), among black patients (relative risk, 0.83; 95% CI, 0.69 to 1.01), among Asian patients (relative risk, 0.87; 95% CI, 0.69 to 1.09), or among patients with class II obesity (relative risk, 0.93; 95% CI,

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	AstraZeneca Trial (N=11,693)		GlaxoSmithKline Trial (N=11,750)		Merck Trial (N=11,744)		Novartis Trial (N=823)†		Combined Analysis (N=36,010)	
	ICS (N=5847)	ICS+LABA (N=5846)	ICS (N=5876)	ICS+LABA (N=5874)	ICS (N=5872)	ICS+LABA (N=5872)	ICS (N=411)	ICS+LABA (N=412)	ICS (N=18,006)	ICS+LABA (N=18,004)
	number of patients (percent)									
Age — yr										
12–17	636 (11)	632 (11)	618 (11)	617 (11)	545 (9)	490 (8)	33 (8)	37 (9)	1,832 (10)	1,776 (10)
18–64	4568 (78)	4572 (78)	4632 (79)	4608 (78)	4527 (77)	4579 (78)	320 (78)	328 (80)	14,047 (78)	14,087 (78)
65–91	643 (11)	642 (11)	626 (11)	649 (11)	799 (14)	801 (14)	58 (14)	47 (11)	2,126 (12)	2,139 (12)
Missing data	0	0	0	0	1 (<1)	2 (<1)	0	0	1 (<1)	2 (<1)
Sex										
Female	3820 (65)	3849 (66)	3921 (67)	3876 (66)	3883 (66)	3845 (65)	274 (67)	285 (69)	11,898 (66)	11,855 (66)
Male	2027 (35)	1997 (34)	1955 (33)	1998 (34)	1989 (34)	2027 (35)	137 (33)	127 (31)	6,108 (34)	6,149 (34)
Race or ethnic group‡										
White	4003 (68)	4050 (69)	4433 (75)	4403 (75)	4544 (77)	4519 (77)	286 (70)	305 (74)	13,266 (74)	13,277 (74)
Black	401 (7)	396 (7)	860 (15)	877 (15)	319 (5)	388 (7)	98 (24)	80 (19)	1,678 (9)	1,741 (10)
Asian	907 (16)	848 (15)	363 (6)	370 (6)	268 (5)	287 (5)	10 (2)	5 (1)	1,548 (9)	1,510 (8)
Hawaiian or Pacific Islander	3 (<1)	3 (<1)	10 (<1)	8 (<1)	3 (<1)	6 (<1)	1 (<1)	1 (<1)	17 (<1)	18 (<1)
American Indian or Alaskan Native	207 (4)	225 (4)	116 (2)	110 (2)	222 (4)	218 (4)	1 (<1)	2 (<1)	546 (3)	555 (3)
Mixed	326 (6)	324 (6)	91 (2)	103 (2)	516 (9)	453 (8)	15 (4)	19 (5)	948 (5)	899 (5)
Missing data	0	0	3 (<1)	3 (<1)	0	1 (<1)	0	0	3 (<1)	4 (<1)
Body-mass index§										
<25.0	2178 (37)	2095 (36)	1863 (32)	1849 (31)	2006 (34)	2010 (34)	74 (18)	82 (20)	6,121 (34)	6,036 (34)
25.0–29.9	1892 (32)	1886 (32)	1800 (31)	1766 (30)	1873 (32)	1877 (32)	106 (26)	121 (29)	5,671 (31)	5,650 (31)
30.0–34.9	1043 (18)	1097 (19)	1193 (20)	1169 (20)	1181 (20)	1139 (19)	112 (27)	99 (24)	3,529 (20)	3,504 (19)
35.0–39.9	438 (7)	459 (8)	563 (10)	612 (10)	489 (8)	503 (9)	63 (15)	61 (15)	1,553 (9)	1,635 (9)
≥40.0	286 (5)	307 (5)	454 (8)	470 (8)	311 (5)	336 (6)	56 (14)	49 (12)	1,107 (6)	1,162 (6)
Missing data	10 (<1)	2 (<1)	3 (<1)	8 (<1)	12 (<1)	7 (<1)	0	0	25 (<1)	17 (<1)

Tobacco use										
Never	4921 (84)	4941 (85)	4679 (80)	4696 (80)	4734 (81)	4742 (81)	318 (77)	326 (79)	14,652 (81)	14,705 (82)
Past	746 (13)	719 (12)	904 (15)	883 (15)	910 (15)	937 (16)	84 (20)	71 (17)	2,644 (15)	2,610 (14)
Current	180 (3)	186 (3)	292 (5)	294 (5)	228 (4)	193 (3)	9 (2)	15 (4)	709 (4)	688 (4)
Missing data	0	0	1 (<1)	1 (<1)	0	0	0	0	1 (<1)	1 (<1)

* Percentages may not total 100 because of rounding. ICS denotes inhaled glucocorticoid, and LABA long-acting β_2-agonist.
† Enrollment in the Novartis trial was discontinued early (on October 15, 2015), when the company removed its drug from the market in the United States.
‡ Race or ethnic group was reported by the patients.
§ The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters. The patients were categorized as having a BMI indicating a normal weight or underweight (<25.0), overweight (25.0 to 29.9), obesity class I (30.0 to 34.9), obesity class II (35.0 to 39.9), or obesity class III (≥40.0).

0.77 to 1.13) or class III obesity (relative risk, 0.85; 95% CI, 0.70 to 1.04). Smoking status did not appear to influence the safety or efficacy of combination therapy as compared with therapy with an inhaled glucocorticoid alone.

DISCUSSION

In our combined analysis of four large, harmonized, postmarketing safety trials, we did not find a higher risk of the most severe asthma-related outcomes (endotracheal intubation or death) among patients who received combination therapy with a LABA plus an inhaled glucocorticoid than among those receiving an inhaled glucocorticoid alone. Event rates were lower than those on which the calculations of statistical power were based, which indicated a risk of less than 0.0075 in the two study groups in this large cohort. Although the intention-to-treat population was smaller than planned owing to the discontinuation of one of the trials, the observed event rates make it improbable that a lack of difference can be attributed to this change in study design. Our analysis points to a risk of about 1 in 7200 exposures for these events among patients in the two study groups.

On the basis of previously reported meta-analyses performed by the FDA, the anticipated asthma-related rate of death was 0.06% over the 6-month duration of the trials,[4] an estimate that was heavily influenced by the results of SMART (Salmeterol Multicenter Asthma Research Trial), in which the continued use of inhaled glucocorticoids was neither required nor supervised.[1] Event rates that were reported in the wider global literature were considerably lower.[10,15] Our findings are in agreement with this lower estimate of risk and support the individual trial findings that combination therapy with a LABA plus an inhaled glucocorticoid was noninferior to an inhaled glucocorticoid alone with respect to the risk of asthma-related intubation or death.

The post hoc secondary analysis of serious asthma-related events was performed to examine the effect of the receipt of combination therapy with a LABA plus an inhaled glucocorticoid on the frequency of hospitalization for such events, since such results might obscure increases in the more rare, but more severe, events of intubation or death.[15] However, as in the findings of the individual trials, we found no significant be-

Table 2. Asthma-Related Deaths and Other Outcomes (Intention-to-Treat Population).*

Variable	AstraZeneca Trial	GlaxoSmithKline Trial	Merck Trial	Novartis Trial	Combined Analysis
Asthma-related death					
In ICS group — no./total no.	0/5847	0/5876	0/5872	0/411	0/18,006
In ICS+LABA group — no./total no.	2/5846	0/5874	0/5872	0/412	2/18,004
Asthma-related intubation					
In ICS group — no./total no.	0/5847	2/5876	0/5872	0/411	2/18,006
In ICS+LABA group — no./total no.	1/5846	0/5874	0/5872	0/412	1/18,004
Asthma-related hospitalization					
In ICS group — no./total no. (%)	40/5847 (0.68)	33/5876 (0.56)	32/5872 (0.54)	3/411 (0.73)	108/18,006 (0.60)
In ICS+LABA group — no./total no. (%)	42/5846 (0.72)	34/5874 (0.58)	39/5872 (0.66)	3/412 (0.73)	118/18,004 (0.66)
Relative risk (95% CI) for ICS+LABA vs. ICS	1.04 (0.66–1.64)	1.02 (0.61–1.69)	1.20 (0.73–1.98)	1.02 (0.14–7.62)	1.08 (0.82–1.41)
P value for between-group difference	0.91	>0.99	0.48	0.99	0.60
P value for interaction	NA	NA	NA	NA	0.96
Serious asthma-related event					
In ICS group — no./total no. (%)	40/5847 (0.68)	33/5876 (0.56)	32/5872 (0.54)	3/411 (0.73)	108/18,006 (0.60)
In ICS+LABA group — no./total no. (%)	43/5846 (0.74)	34/5874 (0.58)	39/5872 (0.66)	3/412 (0.73)	119/18,004 (0.66)
Relative risk (95% CI) in ICS+LABA group vs. ICS group	1.06 (0.67–1.68)	1.02 (0.61–1.69)	1.20 (0.73–1.98)	1.02 (0.14–7.62)	1.09 (0.83–1.43)
P value for between-group difference	0.83	>0.99	0.48	>0.99	0.55
P value for interaction	NA	NA	NA	NA	0.96
Asthma exacerbation					
In ICS group — no./total no. (%)	636/5847 (10.9)	624/5876 (10.6)	779/5872 (13.3)	61/411 (14.8)	2100/18,006 (11.7)
In ICS+LABA group — no./total no. (%)	539/5846 (9.2)	497/5874 (8.5)	688/5872 (11.7)	44/412 (10.7)	1768/18,004 (9.8)
Relative risk (95% CI) for ICS+LABA group vs. ICS group	0.84 (0.75–0.94)	0.79 (0.70–0.89)	0.87 (0.78–0.96)	0.74 (0.49–1.10)	0.83 (0.78–0.89)
P value for between-group difference	0.002	<0.001	0.008	0.14	<0.001
P value for interaction	NA	NA	NA	NA	0.58

* CI denotes confidence interval, ICS inhaled glucocorticoid, LABA long-acting β_2-agonist, and NA not applicable.

tween-group differences in the frequency of serious asthma-related events, despite having a sufficient number of events. In the results from the individual sponsored trials (which differ slightly from our findings because the sponsors performed their analyses in a modified intention-to-treat population), the hazard ratio for serious asthma-related events was previously reported as 1.03 (95% CI, 0.64 to 1.66) in the GlaxoSmithKline trial,[12] 1.07 (95% CI, 0.70 to 1.65) in the AstraZeneca study,[13] and 1.22 (95% CI, 0.76 to 1.94) in the Merck study,[14] as compared with 1.09 (95% CI, 0.83 to 1.43) in our combined analysis (Table 2). There also was no significant between-group difference in the time until the first exacerbation in our analysis[12-14] (Figs. S1 through S4 in the Supplementary Appendix).

Our analysis also confirmed a lower relative risk of asthma exacerbations of 17% with combination therapy than with an inhaled glucocorticoid alone. This finding corresponds to the lower relative rates of asthma exacerbations that were reported in the sponsored individual trials: by 21% in the GlaxoSmithKline trial (hazard ratio, 0.79; 95% CI, 0.70 to 0.89),[12] by 16% in the AstraZeneca trial (hazard ratio, 0.84; 95% CI, 0.74 to 0.94),[13] and by 11% in the Merck trial (hazard ratio, 0.89; 95% CI, 0.80 to 0.98).[14] Our findings also parallel the results of clinical studies and meta-analyses of the beneficial effect of

combination therapy with a LABA plus an inhaled glucocorticoid on asthma exacerbations, as compared with an equivalent or higher dose of an inhaled glucocorticoid.[16-18]

There is interest in the possibility that subgroups of patients may have a worse response to combination therapy than to an inhaled glucocorticoid alone[12,19,20] or may be at greater risk for adverse outcomes.[1,21-24] Although a subgroup analysis was not a prespecified objective in our analysis plan, the large sample size of the combined studies, with minimal heterogeneity, provided an opportunity to perform such a post hoc analysis. We found no increased risk of serious asthma-related events, or of the individual components of these events, associated with combination therapy in the subgroups that we evaluated, although our findings cannot be considered to be clinically directive. However, differences emerged to suggest that there were fewer reductions in asthma exacerbations associated with combination therapy among adolescents, black and Asian patients, and those with obesity classes II and III. Conversely, smoking status and an age of more than 64 years did not influence this outcome. These observations may have been affected by the lower numbers of patients in the subgroups, which produced wider confidence intervals with similar point estimates, but these findings provide equipoise for further clinical investigation.

The obvious strengths of our analysis are its size, variety of treatments, and global reach. (The numbers of patients from various regions are provided in Table S2 in the Supplementary Appendix.) The sample size of 36,010 patients provided a treatment exposure of more than 8000 patient-years for each treatment, which made our analysis a very large prospective, randomized safety study in asthma. Harmonization of the individual protocols for the four trials resulted in similar baseline population characteristics in each individual trial, and the representation of ages and racial and ethnic backgrounds was wide and provided sufficient numbers to assess trends. More than 3600 patients (10%) were adolescents, more than 3400 were black, and more than 3000 were of Asian origin. Among the trial patients, the risk of exacerbation was substantial, since 98% of the patients had received systemic glucocorticoids and more

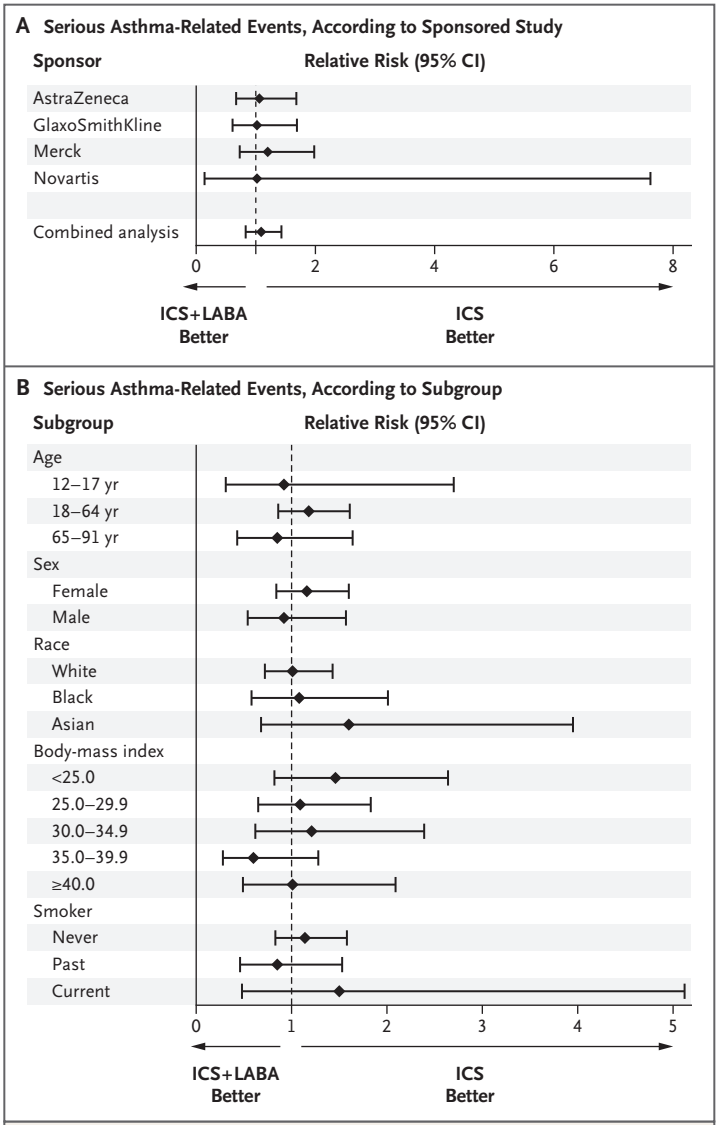

Figure 1. Serious Asthma-Related Events, According to Sponsored Trial and Subgroup.

Shown are forest plots of the relative risk of a composite of serious asthma-related events (intubation, hospitalization, or death) among patients who were assigned to receive combination therapy with an inhaled glucocorticoid (ICS) plus a long-acting β_2-agonist (LABA) as compared with those assigned to receive an inhaled glucocorticoid alone in each of the four sponsored trials (Panel A) and according to subgroup (Panel B). The composite outcome occurred in 108 of 18,006 patients (0.60%) in the inhaled-glucocorticoid group and in 119 of 18,004 patients in the combination group (0.66%) (relative risk in the combination group, 1.09; 95% confidence interval, 0.83 to 1.43; P=0.55). The 95% confidence interval for the Novartis trial is wider than that for the other trials because it was discontinued early (on October 15, 2015), when the company removed its drug from the market in the United States. Race was reported by the patients. The body-mass index is the weight in kilograms divided by the square of the height in meters.

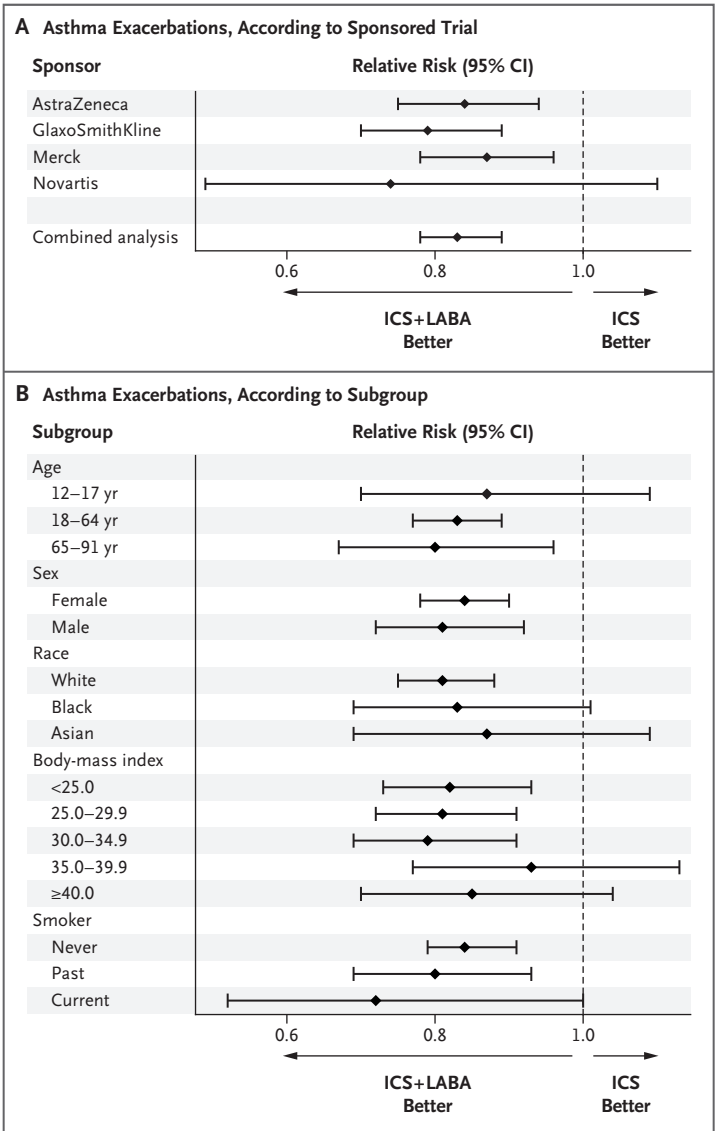

Figure 2. Asthma Exacerbations, According to Sponsored Trial and Subgroup.

Shown are forest plots of the relative risk of an asthma exacerbation among patients who were assigned to receive combination therapy with an inhaled glucocorticoid (ICS) plus a long-acting β_2-agonist (LABA) as compared with those assigned to receive an inhaled glucocorticoid alone in each of the four sponsored trials (Panel A) and according to subgroup (Panel B). At least one asthma exacerbation occurred in 2100 of 18,006 patients in the inhaled-glucocorticoid group (11.7%) and in 1768 of 18,004 patients in the combination-therapy group (9.8%) (relative risk, 0.83; 95% CI, 0.78 to 0.89; P<0.001).

than 12% had been hospitalized for asthma during the preceding year. Of note, two thirds of the patients were overweight (BMI, 25.0 to 29.9) or obese (BMI, ≥30), an additional risk factor for severe asthma events. Furthermore, the generalizability of our results is supported by the fact that several different drugs and formulations were administered, along with a wide range of doses of inhaled glucocorticoids on the basis of disease severity (three doses in the GlaxoSmithKline and Novartis trials and two doses in the AstraZeneca and Merck trials).[12-14]

The four trials and our combined analysis of them have several limitations. First, in the Novartis trial, investigators used separate inhalers for the delivery of LABAs and inhaled glucocorticoids, which could potentially result in preferential use of the LABA inhaler and nonadherence to the inhaled glucocorticoid, a factor that may have contributed to the increased morbidity seen in SMART.[1] However, the numerically lower rate of exacerbations in the combination-therapy group than in the inhaled-glucocorticoid group in the Novartis trial and in our combined analysis argues against this possibility. Second, the reluctance of patients to take part in a trial investigating a potential risk of death associated with a drug may have influenced or biased recruitment, and the drug manufacturers reported that this factor differed according to region. Third, since the conduct of the trials was motivated by signals of increased mortality associated with LABA use in the United States, it could be argued that results from a global study might not address the question of appropriate use of LABAs in individual countries. Fourth, the heterogeneity of products provides data with respect to class effects but does not address the relative safety of different products and doses of inhaled glucocorticoids. However, the absence of events argues in favor of the safety of all the products that were tested. Fifth, a major issue with respect to safety concerns is that patients with a history of life-threatening asthma events, including intubation, were excluded from enrollment. Thus, the comparative safety aspects of LABA use in combination with inhaled glucocorticoids in this small group of extremely high-risk patients with asthma remains to be defined.

In conclusion, our analysis of four trials suggests that the risk of asthma-related death or intubation is unlikely to be estimated with precision in prospective studies. Our data provide support for the treatment guidelines of both the Global Initiative for Asthma[25] and the Expert Panel Report 3 of the National Asthma Education and Prevention Program,[26] which recommend the use of a low-dose glucocorticoid (step 3) and a medium-dose glucocorticoid (step 4), plus a LABA, with the caution that LABAs should not

be used as monotherapy in asthma; the convenience and safety of a combination inhaler is a likely plus.[27] Finally, our combined analysis data provide strong evidence to support the recent FDA decision to remove the boxed safety warning for combination therapy with a LABA plus an inhaled glucocorticoid for asthma treatment.[28]

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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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