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Salmeterol and Fluticasone Propionate and Survival in Chronic Obstructive Pulmonary Disease

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ABSTRACT

BACKGROUND

Long-acting beta-agonists and inhaled corticosteroids are used to treat chronic obstructive pulmonary disease (COPD), but their effect on survival is unknown.

METHODS

We conducted a randomized, double-blind trial comparing salmeterol at a dose of 50 μg plus fluticasone propionate at a dose of 500 μg twice daily (combination regimen), administered with a single inhaler, with placebo, salmeterol alone, or fluticasone propionate alone for a period of 3 years. The primary outcome was death from any cause for the comparison between the combination regimen and placebo; the frequency of exacerbations, health status, and spirometric values were also assessed.

RESULTS

Of 6112 patients in the efficacy population, 875 died within 3 years after the start of the study treatment. All-cause mortality rates were 12.6% in the combination-therapy group, 15.2% in the placebo group, 13.5% in the salmeterol group, and 16.0% in the fluticasone group. The hazard ratio for death in the combination-therapy group, as compared with the placebo group, was 0.825 (95% confidence interval [CI], 0.681 to 1.002; P=0.052, adjusted for the interim analyses), corresponding to a difference of 2.6 percentage points or a reduction in the risk of death of 17.5%. The mortality rate for salmeterol alone or fluticasone propionate alone did not differ significantly from that for placebo. As compared with placebo, the combination regimen reduced the annual rate of exacerbations from 1.13 to 0.85 and improved health status and spirometric values (P<0.001 for all comparisons with placebo). There was no difference in the incidence of ocular or bone side effects. The probability of having pneumonia reported as an adverse event was higher among patients receiving medications containing fluticasone propionate (19.6% in the combination-therapy group and 18.3% in the fluticasone group) than in the placebo group (12.3%, P<0.001 for comparisons between these treatments and placebo).

CONCLUSIONS

The reduction in death from all causes among patients with COPD in the combination-therapy group did not reach the predetermined level of statistical significance. There were significant benefits in all other outcomes among these patients. (ClinicalTrials.gov number, NCT00268216.)

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Chronic obstructive pulmonary disease (COPD) is a major cause of illness, death, and the use of health care resources globally.[1-3] The disease causes approximately 2.75 million deaths annually, and the number is projected to increase.[2] Treatment for COPD is focused on minimizing risk factors, improving symptoms, and preventing exacerbations.[3] With the exception of smoking-cessation programs for patients with early disease,[4] home oxygen treatment for persistent hypoxemia,[5,6] and lung-reduction surgery for selected patients with emphysema,[7] no treatment has been shown to reduce mortality.

Pulmonary inflammation is prominent in COPD.[8] Antiinflammatory drugs such as inhaled corticosteroids have little or no effect on the rate of decline of lung function[9,10] but may reduce the frequency of exacerbations,[9] especially when combined with an inhaled long-acting beta-agonist.[11] Retrospective analyses suggest that inhaled corticosteroids reduce the mortality rate among patients with COPD[12] and that adding a long-acting beta-agonist might increase this effect.[13] We hypothesized that the combination of the long-acting beta-agonist salmeterol and the inhaled corticosteroid fluticasone propionate would reduce mortality among patients with COPD, as compared with usual care. To test this hypothesis, we undertook the Towards a Revolution in COPD Health (TORCH) trial, a double-blind, placebo-controlled, randomized, parallel-group study comparing salmeterol plus fluticasone propionate (the combination regimen) with each of the components alone and with placebo over a 3-year period.

Methods

Details of the study design and the analysis plan were published previously.[14] The complete study protocol is in Supplementary Appendix 1, available with the full text of this article at www.nejm.org.

Patients

We recruited patients who were current or former smokers with at least a 10-pack-year history. Eligible patients were 40 to 80 years of age and had received a diagnosis of COPD, with a prebronchodilator forced expiratory volume in 1 second (FEV_1) of less than 60% of the predicted value,[15] an increase of FEV_1 with the use of 400 μg of albuterol of less than 10% of the predicted value for that patient, and a ratio of prebronchodilator FEV_1 to forced vital capacity (FVC) equal to or less than 0.70. For the exclusion criteria, see Table 1 in Supplementary Appendix 2. All patients gave written informed consent. The study was approved by local ethics review committees and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Study Design

This double-blind study was conducted at 444 centers in 42 countries; center and data auditing ensured the integrity of the data (see the study protocol in Supplementary Appendix 1). After a 2-week run-in period, eligible patients were randomly assigned, in permuted blocks with stratification according to country and smoking status, to treatment with the combination of salmeterol at a dose of 50 μg and fluticasone propionate at a dose of 500 μg (Advair Diskus, Seretide, GlaxoSmithKline) or salmeterol (Serevent, GlaxoSmithKline) alone at a dose of 50 μg, fluticasone propionate (Flovent Diskus, Flixotide, GlaxoSmithKline) alone at a dose of 500 μg, or placebo, all taken in the morning and the evening for 3 years. Study medications were administered as a dry powder with the use of an inhaler (Diskus, Accuhaler, GlaxoSmithKline). Inhalers were collected every 12 weeks, and the number of doses remaining in each inhaler was recorded to check adherence to the study regimen. Before the run-in period, all use of corticosteroids and inhaled long-acting bronchodilators was stopped, but patients could continue other medications for COPD.

After randomization, patients were seen every 12 weeks to confirm vital status, record any unscheduled visits to a health care provider, and note the occurrence of any adverse events. Postbronchodilator spirometry was performed and health status was assessed every 24 weeks. An independent safety and efficacy data monitoring committee performed safety reviews every 6 months, and two interim efficacy analyses were performed, the first after the first 358 deaths had occurred and the second after a total of 680 deaths had occurred.

Outcome Measurements

Vital status was assessed until 3 years after treatment had begun, regardless of whether the patients continued to take study medication. The

primary end point was the time to death from any cause by 3 years. An independent clinical end point committee, whose members were unaware of the treatment assignments, determined the primary cause of death and whether death was related to COPD. The committee used information obtained from investigators, medical records, and other data, as available.

Secondary end points were the frequency of exacerbations, defined as a symptomatic deterioration requiring treatment with antibiotic agents, systemic corticosteroids, hospitalization, or a combination of these, and health status, as assessed according to scores on the St. George's Respiratory Questionnaire.[16] Scores are based on a scale of 0 to 100, with lower scores indicating better functioning; a change of 4 units is generally considered clinically relevant. The questionnaire was administered in the 28 countries where a validated translation was available. Lung function was assessed with the use of postbronchodilator spirometry. For patients who withdrew from the study prematurely, all data on exacerbations, health status, and lung function available at the time of a patient's withdrawal from the study were included in the analysis.

SAFETY EVALUATION

Adverse events and medications were reviewed at each study visit. Additional information was collected about any fractures, classified as either traumatic or nontraumatic, with nontraumatic fractures considered to be caused by falls from less than standing height or falls occurring spontaneously. Dual-energy x-ray absorptiometry at the hip and lumbar spine and slit-lamp examinations were performed on patients' entry into the study and annually thereafter in a safety substudy conducted in the United States and involving 658 patients.

STATISTICAL ANALYSIS

All reported data analyses were prespecified. Assuming a 17% mortality rate in the placebo group at 3 years,[17] we estimated that 1510 patients would be needed for each study group to detect a reduction in mortality of 4.3 percentage points in the combination-therapy group, as compared with the placebo group (hazard ratio for death, 0.728), at a two-sided alpha level of 0.05 with 90% power. Two interim analyses of death from any cause were planned to assess whether there was overwhelming evidence of a benefit from the combination regimen, as compared with placebo, or of harm in any study group; these analyses were performed by the independent safety and efficacy data monitoring committee according to the method of Whitehead.[18] As a consequence, the P value for the primary comparison between the combination regimen and placebo was adjusted upward to conserve an overall significance level of 0.050.

The difference in times to death from any cause between the combination-therapy group and the placebo group was analyzed with the use of the log-rank test (with stratification according to smoking status) and expressed as a hazard ratio. We used a Cox proportional-hazards model as a supportive secondary analysis.

The frequency of exacerbations was analyzed with the use of a generalized linear model (assuming a negative binomial distribution, which accounts for variability among patients in the number and frequency of exacerbations), with the number of exacerbations as the outcome and the logarithm of time during which treatment was received as an offset variable. Total scores on the St. George's Respiratory Questionnaire and postbronchodilator FEV_1 were analyzed as changes from baseline values with the use of repeated-measures analysis of covariance (ANCOVA). Estimated differences between treatments at each visit were averaged with equal weights to determine the overall treatment effect during the 3-year study period. All efficacy analyses were performed according to the intention-to-treat principle. Comparisons other than those between the combination regimen and placebo and between the combination regimen and salmeterol alone were exploratory.

Times to the first fracture, eye disorder, and pneumonia were compared among the study groups in the safety population with the use of Kaplan–Meier estimates and the log-rank test, with stratification according to smoking status. In the safety substudy, bone mineral density for the total hip and lumbar spine was analyzed by repeated measures of ANCOVA, and the development of cataracts was analyzed with the use of logistic regression. (For details of the statistical analysis, see Supplementary Appendixes 1 and 2.)

The steering committee, made up of six academic investigators and two employees of the sponsor, developed the design and concept of the study, approved the statistical plan, had full access

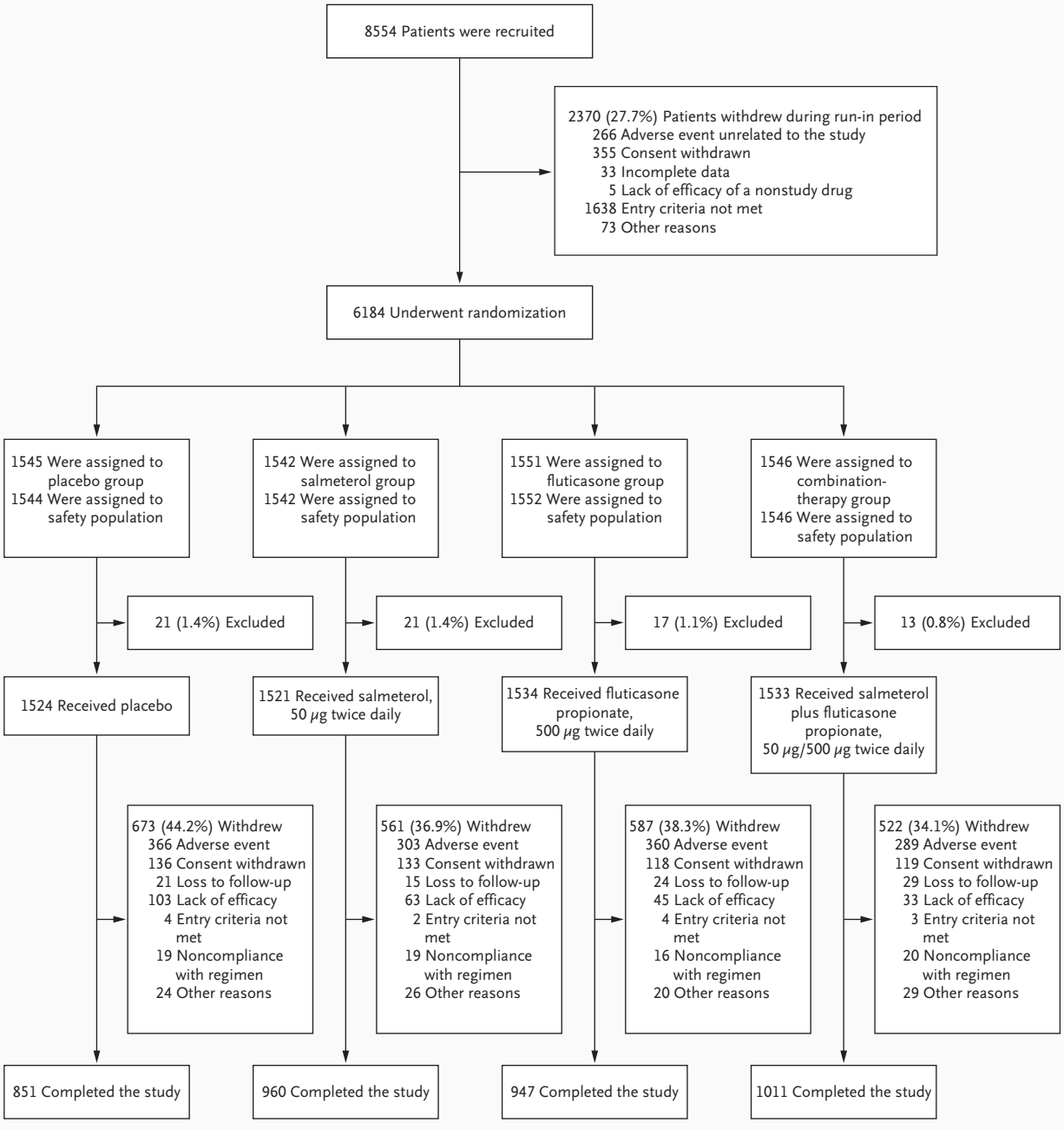

Figure 1. Enrollment of Patients and Completion of the Study.

Adverse events included death during the study period but may not have included deaths occurring after patients withdrew from the study. The number of patients who underwent randomization and the number of those included in the safety population differ in the placebo group and the fluticasone group, because one patient who was assigned to placebo received fluticasone propionate for more than half the study period; this patient was therefore included in the safety population of the fluticasone group and in the efficacy population of the placebo group. In each study group, patients were excluded from the efficacy analysis because during routine site visits and data audits, data from centers at which there were unacceptable research practices were excluded (see Supplementary Appendix 2). Vital status for patients included in the efficacy analysis was established at the end of the study, except for one patient in the combination-therapy group whose data were censored at the last point at which he was known to be alive (day 792).

Table 1. Demographic and Baseline Clinical Characteristics of Patients in the Efficacy Population.*

Variable	Placebo Group (N=1524)	Salmeterol Group (N=1521)	Fluticasone Group (N=1534)	Combination-Therapy Group (N=1533)
Age at enrollment — yr	65.0±8.2	65.1±8.2	65.0±8.4	65.0±8.3
Male sex — no. (%)	1163 (76)	1160 (76)	1157 (75)	1151 (75)
Body-mass index†	25.4±5.2	25.4±5.2	25.4±5.1	25.4±5.3
Geographic region — no. (%)				
United States	345 (23)	346 (23)	348 (23)	349 (23)
Asia–Pacific	188 (12)	189 (12)	193 (13)	188 (12)
Eastern Europe	290 (19)	289 (19)	287 (19)	288 (19)
Western Europe	476 (31)	475 (31)	481 (31)	476 (31)
Other	225 (15)	222 (15)	225 (15)	232 (15)
Current smoker — no. (%)	658 (43)	651 (43)	661 (43)	660 (43)
Pack-years — no.	48.6±26.9	49.3±27.7	49.2±28.6	47.0±26.5
Previous treatment — no. (%)‡				
Inhaled corticosteroid	338 (22)	273 (18)	306 (20)	292 (19)
Long-acting beta-agonist	118 (8)	137 (9)	130 (8)	137 (9)
Inhaled corticosteroid plus long-acting beta-agonist	449 (29)	413 (27)	414 (27)	435 (28)
Exacerbation — no.‡				
Requiring antibiotics or oral corticosteroids	1.0±1.4	1.0±1.4	1.0±1.4	1.0±1.3
Requiring hospitalization	0.2±0.7	0.2±0.6	0.2±0.6	0.2±0.6
Lung function§				
Prebronchodilator FEV_1 — liters	1.12±0.40	1.10±0.39	1.12±0.39	1.12±0.40
Postbronchodilator FEV_1 — liters	1.22±0.42	1.21±0.41	1.22±0.41	1.22±0.42
FEV_1 — % of predicted	44.1±12.3	43.6±12.6	44.1±12.3	44.3±12.3
Reversibility — % of predicted FEV_1¶	3.7±3.7	3.7±3.9	3.7±3.7	3.6±3.6
Prebronchodilator FEV_1:FVC (%)	48.6±10.9	48.7±10.8	48.5±10.7	48.7±10.8
Total score at baseline on St. George's Respiratory Questionnaire‖	49.0±17.4	49.9±16.6	49.5±17.1	48.9±17.4

* Plus–minus values are means ±SD.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Exacerbations during the 12 months before screening were self-reported.
§ Clinical data are from visit 1 (the screening visit). FEV_1 denotes forced expiratory volume in 1 second, and FVC forced vital capacity.
¶ Reversibility denotes the change in the FEV_1 after the administration of 400 μg of albuterol to less than 10% of the predicted value for the patient.
‖ Scores on the St. George's Respiratory Questionnaire are based on a scale of 0 to 100, with lower scores indicating better functioning; a change of 4 units is considered clinically relevant. Data are given for the centers at which the questionnaire was administered.

to and interpreted the data, wrote the manuscript, and was responsible for the decision to publish the manuscript. An academic author wrote a draft of the manuscript; an employee of the sponsor performed the statistical analysis. The academic authors vouch for the veracity and completeness of the data and the data analysis. The sponsor did not place any restrictions on the academic authors regarding statements made in the final manuscript.

RESULTS

STUDY POPULATION

Of 8554 patients recruited, 6184 underwent randomization (Fig. 1). Of these, 72 patients at five

sites were excluded from the efficacy analysis because these sites failed to meet the standards of the study for Good Clinical Practice and ethical practices and were closed before the study ended (see Supplementary Appendix 2). These 72 patients were included in the safety analysis, and a total of 6112 patients were included in the efficacy population.

Demographic and baseline clinical characteristics of the efficacy population are shown in Table 1. The mean age was 65 years, and the mean value of postbronchodilator FEV_1 was 44% of the predicted value. During the year before entry into the study, more than half the patients had used inhaled corticosteroids, a long-acting beta-agonist, or both, and 57% of the patients had reported an exacerbation. The proportion of patients who withdrew from the study was significantly higher in the placebo group (44%) than in the three other groups, and the proportion was lowest in the combination-therapy group (34%) (Fig. 2A). The total number of years of exposure to the study drugs was 3678 in the combination-therapy group, 3238 in the placebo group, 3499 in the salmeterol group, and 3532 in the fluticasone group. The rate of adherence to treatment was similar in all groups, ranging from 88% to 89% of the prescribed doses taken.

MORTALITY

Vital status was known at 3 years for 6111 of the 6112 patients included in the efficacy population. There were 875 deaths within 3 years after randomization. The proportions of deaths from any cause at 3 years were 12.6% in the combination-therapy group, 15.2% in the placebo group, 13.5% in the salmeterol group, and 16.0% in the fluticasone group. The absolute risk reduction for death in the combination-therapy group as compared with the placebo group was 2.6%, and the hazard ratio was 0.825 (95% confidence interval [CI], 0.681 to 1.002; P=0.052), corresponding to a reduction in the risk of death at any time in the 3 years of 17.5% (95% CI, −0.2 to 31.9) (all adjusted for the interim analyses) (Fig. 2B and Table 2).

Prespecified secondary analyses for mortality were also performed: Cox proportional-hazards testing yielded a hazard ratio of 0.811 (95% CI, 0.670 to 0.982; P=0.03) (Table 2); log-rank testing, stratified according to smoking status and country of residence, yielded a hazard ratio of 0.815 (95% CI, 0.673 to 0.987; P=0.04) (see Table 2 in Supplementary Appendix 2). There was no interaction between treatment and age, sex, region of country, baseline FEV_1 categorized by disease stage according to the Global Initiative for Chronic Obstructive Lung Disease, body-mass index, or smoking status. Adjusting for exposure to smoking (pack-years) did not affect the results.

The risk of death in the salmeterol group and in the fluticasone group did not differ significantly from that in the placebo group (Table 2). The risk was similar among patients who died

Figure 2 (facing page). Outcomes.

In the combination regimen, salmeterol was administered at a dose of 50 μg and fluticasone propionate at a dose of 500 μg twice daily. Salmeterol alone was administered at a dose of 50 μg twice daily, and fluticasone propionate alone was administered at a dose of 500 μg twice daily. Cumulative incidences of discontinuation of a study drug at 3 years were 43.5% in the placebo group, 36.4% in the salmeterol group, 38.1% in the fluticasone group, and 33.7% in the group receiving the combination of salmeterol plus fluticasone propionate (Panel A). Intergroup comparisons yielded the following hazard ratios for the discontinuation of a study medication: 0.69 (95% CI, 0.62 to 0.78, P<0.001) for the combination-therapy group versus the placebo group; 0.89 (95% CI, 0.79 to 0.999; P<0.05) for the combination-therapy group versus the salmeterol group; 0.86 (95% CI, 0.76 to 0.96; P=0.010) for the combination-therapy group versus the fluticasone group; 0.78 (95% CI, 0.70 to 0.86; P<0.001) for the salmeterol group versus the placebo group; and 0.81 (95% CI, 0.72 to 0.90; P<0.001) for the fluticasone group versus the placebo group. Patients discontinuing a study medication were included in the mortality analysis at 3 years but could receive any treatment. In the analysis for the primary end point of the probability of death from any cause at 3 years, the risk of death in the placebo group was 15.2%, as compared with 12.6% in the combination-therapy group. Salmeterol and fluticasone propionate in combination reduced the risk of death at any time during the 3-year study period by 17.5% (P=0.052) (Panel B). The probability of COPD-related death at 3 years was 6.0% in the placebo group, 6.1% in the salmeterol group, 6.9% in the fluticasone group, and 4.7% in the combination-therapy group (Panel C). The effect of each study medication on health status (assessed according to changes in patients' total scores on the St. George's Respiratory Questionnaire) and FEV_1 during the 3-year study period are shown in Panels D and E, respectively. Values in the tables below the graphs represent the numbers of patients alive (Panel B), the numbers of of patients alive or dead from non–COPD-related causes (Panel C), or the number of patients remaining in the study (Panels A, D, and E). I bars represent standard errors (at approximately 1, 2, and 3 years in Panels A, B, and C). HR denotes hazard ratio.

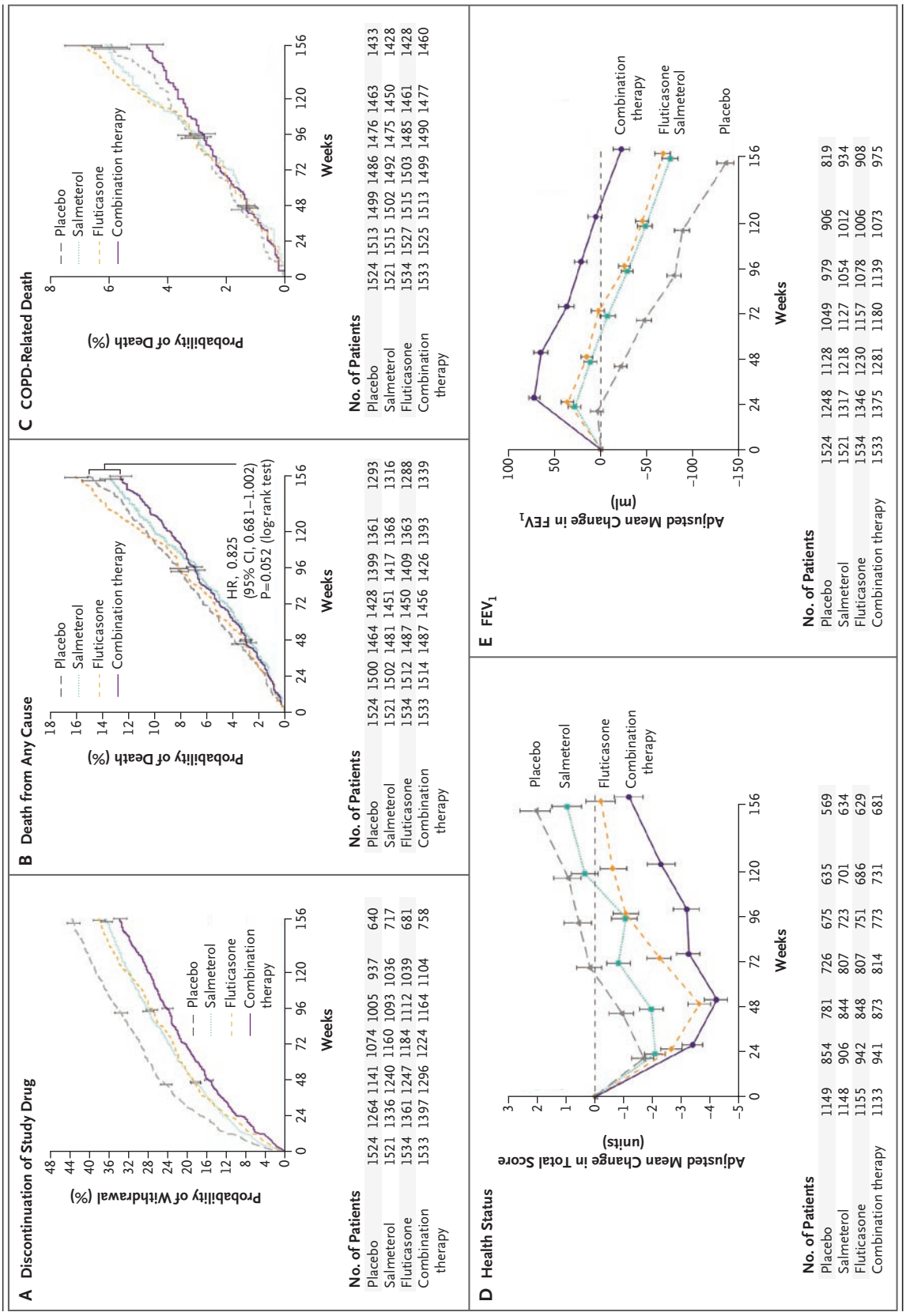

Table 2. Results of the Mortality Analysis and the Efficacy Analysis for Exacerbation.

Variable	Placebo Group (N=1524)	Salmeterol Group (N=1521)	Fluticasone Group (N=1534)	Combination-Therapy Group (N=1533)	Comparison	Hazard Ratio (95% CI)	P Value
Mortality analysis							
No. of deaths from any cause	231	205	246	193			
Probability of death at 3 yr — %	15.2	13.5	16.0	12.6	Combination therapy vs. placebo (adjusted)*	0.825 (0.681–1.002)	0.052
					Combination therapy vs. placebo (unadjusted)	0.820 (0.677–0.993)	0.04
					Combination therapy vs. salmeterol	0.932 (0.765–1.134)	0.48
					Combination therapy vs. fluticasone propionate	0.774 (0.641–0.934)	0.007
					Salmeterol vs. placebo	0.879 (0.729–1.061)	0.18
					Fluticasone propionate vs. placebo	1.060 (0.886–1.268)	0.53
Adjusted probability of death at 3 yr — %†	12.6	10.9	13.3	10.3	Combination therapy vs. placebo	0.811 (0.670–0.982)	0.03
					Combination therapy vs. salmeterol	0.946 (0.777–1.151)	0.58
					Combination therapy vs. fluticasone propionate	0.768 (0.636–0.927)	0.006
					Salmeterol vs. placebo	0.857 (0.710–1.035)	0.11
					Fluticasone propionate vs. placebo	1.056 (0.883–1.264)	0.55
COPD-related deaths‡							
No. of deaths	91	93	106	72			
Probability of death at 3 yr — %	6.0	6.1	6.9	4.7	Combination therapy vs. placebo	0.78 (0.57–1.06)	0.11
					Combination therapy vs. salmeterol	0.77 (0.56–1.04)	0.09
					Combination therapy vs. fluticasone propionate	0.67 (0.50–0.90)	0.008
					Salmeterol vs. placebo	1.01 (0.76–1.35)	0.93
					Fluticasone propionate vs. placebo	1.16 (0.88–1.53)	0.30

Primary cause of death up to 3 yr — no. (%)							
Cardiovascular	71 (5)	45 (3)	61 (4)	60 (4)			
Pulmonary	74 (5)	80 (5)	91 (6)	61 (4)			
Cancer	45 (3)	44 (3)	51 (3)	44 (3)			
Other	23 (2)	22 (1)	30 (2)	11 (1)			
Unknown	18 (1)	14 (1)	13 (1)	17 (1)			
Efficacy analysis for exacerbation						**Rate Ratio (95% CI)**	
Annual rate							
Moderate or severe	1.13	0.97	0.93	0.85	Combination therapy vs. placebo	0.75 (0.69–0.81)	<0.001
					Combination therapy vs. salmeterol	0.88 (0.81–0.95)	0.002
					Combination therapy vs. fluticasone propionate	0.91 (0.84–0.99)	0.02
					Salmeterol vs. placebo	0.85 (0.78–0.93)	<0.001
					Fluticasone propionate vs. placebo	0.82 (0.76–0.89)	<0.001
Requiring systemic corticosteroids	0.80	0.64	0.52	0.46	Combination therapy vs. placebo	0.57 (0.51–0.64)	<0.001
					Combination therapy vs. salmeterol	0.71 (0.63–0.79)	<0.001
					Combination therapy vs. fluticasone propionate	0.87 (0.78–0.98)	0.02
					Salmeterol vs. placebo	0.80 (0.72–0.90)	<0.001
					Fluticasone propionate vs. placebo	0.65 (0.58–0.73)	<0.001
Severe (requiring hospitalization)	0.19	0.16	0.17	0.16	Combination therapy vs. placebo	0.83 (0.71–0.98)	0.03
					Combination therapy vs. salmeterol	1.02 (0.87–1.20)	0.79
					Combination therapy vs. fluticasone propionate	0.95 (0.82–1.12)	0.56
					Salmeterol vs. placebo	0.82 (0.69–0.96)	0.02
					Fluticasone propionate vs. placebo	0.88 (0.74–1.03)	0.10

* Only the primary comparison was adjusted because interim analyses were performed. Unadjusted data for the primary end point are provided for comparison.
† The adjusted probability of death was calculated with the use of a Cox proportional-hazards model.
‡ Cause of death was adjudicated by the clinical end-point committee.

while receiving a study medication (data not shown) and those who died from COPD-related causes (Fig. 2C). The risk of death in the combination-therapy group did not differ significantly from that in the salmeterol group, but patients receiving the combination regimen were less likely to die than those receiving fluticasone propionate (hazard ratio for death, 0.774 [95% CI, 0.641 to 0.934]; P=0.007). Overall, 27% of the deaths were adjudicated as due to cardiovascular causes, 35% to pulmonary causes, and 21% to cancer (for other causes of death, see Table 3 in Supplementary Appendix 2).

EXACERBATIONS, HEALTH STATUS, AND LUNG FUNCTION

According to our statistical models, the annual rate of exacerbations was 0.85 (95% CI, 0.80 to 0.90) in the combination-therapy group and 1.13 (95% CI, 1.07 to 1.20) in the placebo group, resulting in a rate ratio for exacerbations of 0.75 (95% CI, 0.69 to 0.81; P<0.001), which is a reduction of 25% and corresponds to a number needed to treat of four to prevent one exacerbation in 1 year. Annual rates of exacerbations in the salmeterol group and the fluticasone group were significantly lower than in the placebo group (Table 2). Overall, 26% of the patients were hospitalized at least once during the 3-year study period. Annual admission rates were 17% lower in the combination-therapy and salmeterol groups than in the placebo group (P≤0.03) (Table 2), corresponding to a number needed to treat of 32 to prevent one hospitalization in 1 year.

Total scores on the St. George's Respiratory Questionnaire initially improved from baseline in all groups, with the greatest changes occurring in the combination-therapy group (mean score at baseline, 48.7, with a mean reduction of 3.0 units averaged over 3 years), as compared with the placebo group (a mean score of 48.4 at baseline, with an increase of 0.2 unit in the placebo group) (Fig. 2D and Table 3). Similarly, for lung function, the mean baseline FEV_1 in the combination-therapy group was 1.236 liters with an average increase of 0.029 liter, whereas in the placebo group, the mean baseline FEV_1 was 1.257 liters and a decrease of 0.062 liter. Averaged over 3 years, the health status (a reduction of 3.1 units in the score for the St. George's Respiratory Questionnaire) and spirometric measurements (an increase in FEV_1 of 0.092 liter) in the combination-therapy group were significantly better than in the groups receiving placebo, salmeterol alone, or fluticasone propionate alone (Fig. 2E and Table 3).

ADVERSE EVENTS AND SAFETY

Adverse events were reported by 90% of the patients in the study, and serious adverse events were reported by 41% of the patients (Table 4). (For mortality data for the safety population, see Fig. 1 and Table 4 in Supplementary Appendix 2.) The most frequently reported adverse event was an exacerbation of COPD. The probability of having pneumonia reported as an adverse event during the 3-year study period was significantly greater among patients receiving a study medication containing fluticasone propionate: the probability was 19.6% in the combination-therapy group, 12.3% in the placebo group, 13.3% in the salmeterol group, and 18.3% in the fluticasone group (P<0.001 for the comparison between both the combination-therapy and fluticasone groups and the placebo group). Among patients receiving study medications, there were 8 deaths from pneumonia in the combination-therapy group, 7 in the placebo group, 9 in the salmeterol group, and 13 in the fluticasone group. There was no significant difference in the probability of fractures among the groups (6.3% in the combination-therapy group, 5.1% in the placebo group, 5.1% in the salmeterol group, and 5.4% in the fluticasone group). There was no excess of cardiac disorders among patients treated with the combination regimen or salmeterol alone (reported event rates per study year, 0.087 in the combination-therapy group, 0.113 in the placebo group, 0.114 in the salmeterol group, and 0.102 in the fluticasone group). In the safety substudy, there were no significant differences in bone mineral density or in the numbers of patients in whom cataracts developed between the groups receiving active study drugs and the placebo group (Table 4).

DISCUSSION

In this trial, the reduction in mortality from any cause in the combination-therapy group, as compared with the placebo group, did not meet the predetermined level of statistical significance. During the 3 years of the study, treatment with the combination regimen resulted in significantly fewer exacerbations and improved health status and lung function, as compared with placebo.

Table 3. Other Efficacy Outcomes.*

Variable	Placebo Group (N=1524)	Salmeterol Group (N=1521)	Fluticasone Group (N=1534)	Combination-Therapy Group (N=1533)	Comparison	Difference (95% CI)	P Value
St. George's Respiratory Questionnaire*							
No. of patients completing a validated questionnaire	1231	1232	1248	1240			
No. of patients included in the analysis†	924	980	1005	1002			
Mean baseline score	48.4	49.4	49.5	48.7			
Adjusted mean change in score averaged over 3 yr (units)	+0.2	−0.8	−1.8	−3.0	Combination therapy vs. placebo	−3.1 (−4.1 to −2.1)	<0.001
					Combination therapy vs. salmeterol	−2.2 (−3.1 to −1.2)	<0.001
					Combination therapy vs. fluticasone propionate	−1.2 (−2.1 to −0.2)	0.02
					Salmeterol vs. placebo	−1.0 (−2.0 to 0)	0.06
					Fluticasone propionate vs. placebo	−2.0 (−2.9 to −1.0)	<0.001
Postbronchodilator FEV_1							
No. of patients included in the analysis†	1261	1334	1356	1392			
Mean baseline FEV_1 (liters)‡	1.26	1.23	1.23	1.24			
Adjusted mean change in FEV_1 averaged over 3 yr (liters)	−0.062	−0.021	−0.015	+0.029	Combination therapy vs. placebo	0.092 (0.075 to 0.108)	<0.001
					Combination therapy vs. salmeterol	0.050 (0.034 to 0.067)	<0.001
					Combination therapy vs. fluticasone propionate	0.044 (0.028 to 0.061)	<0.001
					Salmeterol vs. placebo	0.042 (0.025 to 0.058)	<0.001
					Fluticasone propionate vs. placebo	0.047 (0.031 to 0.064)	<0.001

* Scores on the St. George's Respiratory Questionnaire are based on a scale of 0 to 100, with lower scores indicating better functioning; a change of 4 units is generally considered clinically relevant.
† Patients for whom at least one measurement was obtained after baseline were included in the analysis.
‡ Patients included in the analysis were those for whom data on the change from baseline FEV_1 were available.

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There are two possible reasons why the reduction in mortality in the combination-therapy group, as compared with the placebo group, did not achieve statistical significance. The first is that there is no effect of salmeterol plus fluticasone propionate on survival. In this scenario, the data would suggest that the observed symptomatic and functional improvement derives from mechanisms other than those that prolong life. It could be that mortality is influenced mainly by factors that are currently unidentified and unresponsive to therapy with salmeterol plus fluticasone propionate.

The second possible reason, which we believe is the more likely one, is that salmeterol plus fluticasone propionate does have an effect on mortality but that our study was underpowered to detect this effect. Our power calculations were based on the Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) study, and there were fewer deaths in the placebo group than anticipated.[14,17] The TORCH study was designed to have 90% power to detect an effect of 4.3 percentage points on overall mortality; in practice, we identified a reduction of 2.6 percentage points. In addition, there was a high withdrawal rate, which was highest among patients in the placebo group, who were free to receive active therapy subsequently. Furthermore, performing the second interim analysis so close to the final analysis increased the threshold required for significance. More studies are needed to determine whether either of these explanations or another explanation accounts for the primary finding.

Our data on the secondary outcomes are consistent with and extend previous observations in studies using combinations of inhaled corticosteroids and long-acting beta-agonists[19-21] in showing that the combination regimen reduced exacerbations significantly, as compared with placebo, including those exacerbations requiring hospitalization. The combination regimen was also significantly better than each of its components alone in preventing exacerbations, and these benefits were accompanied by sustained improvements in health status and FEV_1; the values for both were better at the end of the trial than at baseline. Unlike previous studies in which reductions in exacerbations and improvements in health status have also been reported,[19,21] in our study there was no requirement of exacerbations during the year before entry into the trial. Furthermore, the greater number of patients withdrawing from the placebo group is likely to have resulted in an underestimation of the effect of the combination regimen on all the secondary outcomes. Nevertheless, the number needed to treat to prevent an exacerbation in 1 year was 4, and the number needed to treat to prevent a hospitalization was 32.

An important safety finding, identified because the size of the study was sufficient to detect infrequent events, was the excess of patients who received a diagnosis of pneumonia among those receiving study medications containing fluticasone propionate. This finding had not been previously reported in studies involving the use of inhaled corticosteroids by patients with COPD. Since the finding was unexpected, there was no prospective definition of pneumonia in the study protocol (e.g., confirmation on chest radiography). However, this finding was observed in the different subgroups, which suggests that it may be an important signal whose mechanism is currently unclear and requires further study. The increase in pneumonia did not appear to represent an increase in the number of deaths. As determined by the independent clinical end-point committee, among deaths attributed to pneumonia in patients in the safety population while they were receiving a study medication, there was one more death in the combination-therapy group and six more in the fluticasone group than in the placebo group.

The increase in oropharyngeal side effects among patients receiving fluticasone propionate or the combination regimen was expected, but there was no evidence of excess cardiac events among those receiving salmeterol alone or the combination regimen. The total number of fractures, including those associated with minimal trauma or none, did not differ significantly among the four groups. This finding was in keeping with the absence of a significant difference among the groups in bone mineral density among patients in the U.S. substudy. The prevalence of cataracts at baseline in all the study groups was high, but it was not influenced by treatment during the course of the study. However, exposure to the study medications for 3 years may not be long enough to detect differences in the occurrence of fractures and eye disorders.

The TORCH study recruited patients with COPD from around the world, and we think that our findings can therefore be generalized. The par-

Table 4. Adverse Events among 6184 Patients in the Safety Population and 658 Patients in the Substudy of Bone Mineral Density.

Adverse Event	Placebo Group (N=1544)	Salmeterol Group (N=1542)	Fluticasone Group (N=1552)	Combination-Therapy Group (N=1546)
Reported during treatment — % of patients				
Any event	90	90	90	89
Serious event	41	40	42	43
Drug-related event	13	12	19	18
Event resulting in withdrawal or discontinuation of study medication	24	20	23	18
Total exposure to study medication — yr	3278	3531	3555	3700
Most commonly reported event during treatment — rate per yr				
COPD exacerbation	0.92	0.76	0.78	0.67
Upper respiratory tract infection	0.10	0.08	0.09	0.11
Nasopharyngitis	0.09	0.09	0.10	0.10
Pneumonia	0.04	0.04	0.07	0.07
Bronchitis	0.05	0.05	0.05	0.05
Headache	0.08	0.06	0.06	0.05
Back pain	0.04	0.04	0.04	0.04
Sinusitis	0.03	0.03	0.04	0.04
Cough	0.03	0.03	0.04	0.03
Hypertension	0.03	0.03	0.03	0.02
Additional events associated with the use of corticosteroids — rate per yr				
Candidiasis	0.02	0.02	0.09	0.07
Dysphonia	0.004	0.005	0.017	0.028
Of specific interest during treatment — % of patients*				
Pneumonia	12.3	13.3	18.3†	19.6‡
Fractures				
Total	5.1	5.1	5.4	6.3
Nontraumatic	1.8	2.5	1.7	1.7
Eye disorders	3.6	4.3	4.1	5.2
Safety substudy				
Cataracts§				
None at baseline — no. of patients/total no.	47/164	41/166	47/163	52/165
Developed during treatment — no. of patients/total no. (%)	10/47 (21)	6/41 (15)	8/47 (17)	14/52 (27)
Bone mineral density¶				
Hip — no. of patients/total no.	52/164	78/166	65/163	82/165
Change from baseline — %‖	–3.1	–1.7	–2.9	–3.2
Lumbar spine — no. of patients/total no.	50/164	76/166	63/163	81/165
Change from baseline — %‖	0	1.5	–0.3	–0.3

* Probability was calculated by the Kaplan–Meier method.
† P<0.001 for the comparison between the fluticasone group and the placebo group.
‡ P<0.001 for the comparisons between the group receiving salmeterol plus fluticasone propionate and the placebo group and between the combination-therapy group and the salmeterol group.
§ Patients who had cataracts at baseline were not included in the subsequent analysis.
¶ Patients included in the analysis were those for whom measurements of bone mineral density at baseline and at 158 weeks were available.
‖ The percentage of change was calculated as [(ratio of bone mineral density at week 158 to the value at baseline) – 1] multiplied by 100.

ticular strengths of the study are the virtually complete survival data to 3 years and the independent adjudication of causes of death, which eliminated between-country variation in death certification. Although the TORCH study is a large COPD trial, as compared with studies of mortality associated with other major chronic illnesses such as cardiovascular disease,[22-24] its size is modest. The results of our mortality analysis should be viewed in this context. The potential for a reduction in the risk of death of 2.6 percentage points among patients treated with salmeterol plus fluticasone propionate, as compared with placebo, and the 17.5% reduction in the risk of death that was identified in the study clearly merit further investigation in future large, prospective trials. Until such trials are completed, our data support the use of salmeterol plus fluticasone propionate in the clinical management of COPD.

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APPENDIX

For a complete list of investigators of the Towards a Revolution in COPD Health (TORCH) study, see Supplementary Appendix 2. Committee members were as follows: **Steering Committee:** P.M.A. Calverley (chair), Liverpool, United Kingdom; J.A. Anderson, Greenford, United Kingdom; B. Celli, Boston; G.T. Ferguson, Livonia, MI; C. Jenkins, Sydney; P.W. Jones, London; K. Knobil, J.C. Yates, Research Triangle Park, NC; J. Vestbo, Manchester, United Kingdom. **Safety and Efficacy Data Monitoring Committee:** R. Cherniack, Denver; T. Similowski, Paris; J. Cleland, Hull, United Kingdom; A. Whitehead, Reading, United Kingdom. **Clinical End Point Committee:** R. Wise, Baltimore; L. McGarvey, Belfast, Northern Ireland; M. John, Berlin.

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Eagle Owl

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