

The Prevention of Chronic Obstructive Pulmonary Disease Exacerbations by Salmeterol/Fluticasone Propionate or Tiotropium Bromide

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Rationale: Exacerbations are key drivers of morbidity and mortality in chronic obstructive pulmonary disease (COPD).

Objectives: We compared the relative efficacy of the long-acting inhaled bronchodilator/antiinflammatory combination (salmeterol/fluticasone propionate) 50/500 µg twice daily and the long-acting bronchodilator (tiotropium) 18 µg once daily in preventing exacerbations and related outcomes in severe and very severe COPD.

Methods: A total of 1,323 patients (mean age, 64 yr, post-bronchodilator FEV₁, 39% predicted) were randomized in this 2-year, double-blind, double-dummy parallel study.

Measurements and Main Results: Primary endpoint was health care utilization exacerbation rate. Other endpoints included health status measured by St. George's Respiratory Questionnaire (SGRQ), mortality, adverse events, and study withdrawal. Probability of withdrawing from the study was 29% greater with tiotropium than salmeterol/fluticasone propionate ($P = 0.005$). The modeled annual exacerbation rate was 1.28 in the salmeterol/fluticasone propionate group and 1.32 in the tiotropium group (rate ratio, 0.967; 95% confidence interval [CI], 0.836–1.119; $P = 0.656$). The SGRQ total score was statistically significantly lower at 2 years on salmeterol/fluticasone propionate versus tiotropium (difference 2.1 units; 95% CI, 0.1–4.0; $P = 0.038$). Mortality was significantly lower in the salmeterol/fluticasone propionate group; 21 (3%) of patients in this group died compared with 38 (6%) in the tiotropium group ($P = 0.032$). More pneumonias were reported in the salmeterol/fluticasone propionate group relative to tiotropium ($P = 0.008$).

Conclusions: We found no difference in exacerbation rate between salmeterol/fluticasone propionate and tiotropium. More patients failed to complete the study while receiving tiotropium. A small statistically significant beneficial effect was found on health status, with an unexpected finding of lower deaths in salmeterol/fluticasone propionate-treated patients.

Clinical trial registered with www.clinicaltrials.gov (NCT 00361959).

Keywords: chronic obstructive pulmonary disease; exacerbations; mortality; health status

Chronic obstructive pulmonary disease (COPD) is a major cause of poor health and death worldwide (1) and contributes significantly to health care costs and comorbidity (2, 3). Many patients with COPD experience periodic worsening of their

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

A variety of treatments, including salmeterol, tiotropium, and inhaled corticosteroids have been shown to prevent COPD exacerbations. However, the efficacy of a combination of inhaled corticosteroids with salmeterol versus tiotropium has not been tested.

What This Study Adds to the Field

The study shows no difference in reduction of exacerbations between salmeterol/fluticasone propionate and tiotropium, although patients receiving the salmeterol/fluticasone combination were less likely to withdraw, had better health status, and had better survival.

symptoms, reflecting an acute deterioration in lung mechanics (4) and airway inflammation secondary to viral and/or bacterial infection (5, 6). These exacerbations contribute to impaired health status (7, 8) and increased hospitalization costs (9), and predict mortality (10).

A variety of COPD treatments have been shown to prevent exacerbations (11). These include long-acting inhaled bronchodilators, such as salmeterol (12) and tiotropium (13), as well as inhaled corticosteroids (ICS) alone (14) or when combined with long-acting β -agonists (LABAs) (15, 16). The efficacy of an ICS/LABA combination or of a long-acting anticholinergic in preventing exacerbations has not been directly compared nor has the effect of these treatments on lung function or health status been tested over an extended period.

The aim of the INSPIRE (Investigating New Standards for Prophylaxis in Reducing Exacerbations) study, therefore, was to compare the effect of the antiinflammatory/bronchodilator combination of salmeterol/fluticasone propionate (SFC) with the bronchodilator tiotropium bromide on the rate of moderate and/or severe exacerbations during a 2-year treatment period, and secondarily on outcomes that might relate to exacerbations. In this article, exacerbation rates were defined by health care resource utilization.

METHODS

Patients were recruited between June 2003 and February 2004 in 179 centers from 20 countries. Full details of the study methodology are given in Reference 17 and a list of participating investigators is provided in Table E1 of the online supplement. We recruited patients aged 40 to 80 years, with a smoking history of 10 or more pack-years, a clinical history of COPD exacerbations, a post-bronchodilator FEV₁

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of less than 50% predicted, reversibility to 400 μg salbutamol 10% or less of predicted FEV₁, and a score of 2 or more on the Modified Medical Research Council dyspnea scale. We excluded patients with any respiratory disorder other than COPD or who required daily long-term oxygen therapy (≥ 12 h/d). All patients gave written, informed consent, and the protocol was approved by the appropriate institutional review boards and conducted in accordance with good clinical practice guidelines and the 1996 version of the Declaration of Helsinki.

Study Design

INSPIRE was a 2-year multicenter, randomized, double-blind, double-dummy controlled trial. Patients entered a 2-week run-in period during which they discontinued all existing COPD maintenance medications and received oral prednisolone 30 mg/day and inhaled salmeterol 50 μg twice daily to standardize their clinical condition before randomization, an approach described previously in COPD studies (18). Patients were then randomized to inhaled salmeterol 50 μg plus fluticasone propionate 500 μg combination (SFC) twice daily by Diskus/Accuhaler (GlaxoSmithKline, Ware, UK) or tiotropium bromide 18 μg once daily by Handihaler (Boehringer Ingelheim, Ingelheim, Germany). Subjects randomized to SFC received a once daily placebo inhalation by Handihaler and subjects randomized to tiotropium received a twice-daily placebo inhalation by Diskus/Accuhaler. Treatment compliance was assessed at each study visit by recording the number of doses remaining in each returned inhaler.

After randomization, in addition to study medication, patients were allowed short-acting inhaled β -agonists for relief therapy and standardized short courses of oral systemic corticosteroids and/or antibiotics where indicated for treatment of COPD exacerbations.

Patients were randomized using a predefined, computer-generated, central randomization list and a telephone-based interactive voice response system. Treatment allocation was stratified by center and smoking status on a 1:1 basis, in line with current guidelines (19). The block size used was four.

Postrandomization, patients were reviewed at Weeks 2 and 8, and every 12 weeks thereafter to record details of any COPD exacerbations, unscheduled health care visits and adverse events. Postdose FEV₁ and other respiratory parameters were measured at Weeks 2 and 8, and every 24 weeks thereafter with St. George's Respiratory Questionnaire (SGRQ) measurement at Weeks 32, 56, 80, and 104.

Outcome Measurements

The primary efficacy endpoint was the rate of health care utilization (HCU) exacerbations, defined as those that required treatment with oral corticosteroids and/or antibiotics or required hospitalization. Predefined secondary endpoints included health status measured by the SGRQ, postdose FEV₁ (measured 2 h after inhalation of study medication), and study withdrawal rate. All-cause mortality was an efficacy and safety endpoint.

Safety was assessed by documenting all adverse events together with an oropharyngeal examination for evidence of candidiasis and inspection of the volar aspect of the forearm for spontaneous bruises. Electrocardiograms were performed at Weeks 0, 56, and 104.

Statistical Analysis

On the basis of previous studies of long-acting bronchodilators (20, 21), we expected an exacerbation rate of 1.7 per patient per year in the tiotropium group and a 20% study withdrawal rate. We estimated that 635 patients per treatment group would detect a reduction in exacerbations of at least 15% (equal to 1.445 exacerbations per subject per year) in the SFC group at a two-sided significance level of $\alpha = 0.05$ with 90% power. An independent data safety monitoring committee monitored all deaths and reviewed the unblinded data after the first 15 deaths and from then at 6-month intervals to ensure the safety of study participants. No interim efficacy analyses were conducted.

All reported data analyses were prespecified except for further *post hoc* safety analyses identified below and were conducted by the sponsor under the direction of the steering committee. Exacerbation rates were analyzed using a generalized linear model (assuming the negative binomial distribution) (22) with number of exacerbations as the outcome and the log of time on treatment as an offset variable, with

covariates of baseline smoking status, disease severity (% predicted FEV₁ at baseline), body mass index (BMI), number of exacerbations reported in the 12 months before screening, age, gender, and country. Adjusted mean rates per year and pairwise treatment ratios with *P* values and confidence intervals (CIs) were calculated. The incidence of exacerbations requiring hospitalization was compared between treatments using Fisher's exact test. Postdose FEV₁ was compared between treatments at each visit during treatment using a mixed model repeated measures analysis with covariates of baseline value, baseline smoking status, disease severity, age, gender, and country. SGRQ score was compared between treatments at Weeks 32, 56, 80, and 104 in the same manner. Time to withdrawal from start of treatment was analyzed using the Cox proportional hazards model with covariates of baseline smoking status, disease severity (% predicted FEV₁ at baseline), age, gender, and country. The *a priori* comparison of total number of reported deaths in each treatment group was done with the Fisher's exact test. Additional *post hoc* analyses were performed for time to death on treatment (including deaths up to 2 wk post-treatment cessation) and time to first pneumonia using the Cox proportional hazards model with covariates for time to withdrawal.

To investigate the clinical relevance of health status effects, SGRQ changes at each visit were classified as "improvement" (change of -4 points or less from baseline), "no change" (change of more than -4 and less than 4), or "deterioration" (change of 4 or more). For visits in which a change in SGRQ total score could not be calculated (withdrawal or other nonresponse), the classification from the previous visit was retained unless any of the following criteria were met, in which case change in health status was classed as deterioration: death, withdrawal due to respiratory adverse event or lack of efficacy, health care utilization exacerbation that started in the previous 28 days, or initiation of long-term oxygen therapy. Treatments were compared using a proportional odds model, with covariates as for time to withdrawal.

All efficacy and safety analyses used the intent-to-treat population, defined as all randomized patients who received at least one dose of study medication. The study was designed to show superiority of either treatment group and used a two-sided test at the 5% level of significance.

RESULTS

Of 1,499 patients screened, 1,323 were randomized and comprised the intent-to-treat population. Details of patient disposition and reasons for patient discontinuation are shown in Figure 1, and patients' baseline characteristics are shown in Table 1. Baseline characteristics of patients who completed or who withdrew from the study are shown in Table 2. Details of patients' concurrent disorders and medication taken for COPD at study entry are found in Tables E2 and E3. Median adherence to treatment was more than 99% in both groups. Patients randomized to tiotropium were significantly more likely to withdraw from the study than those randomized to SFC (the Kaplan-Meier estimated probability of withdrawing before Week 104 was 34.5% in the SFC group and 41.7% in the tiotropium group; hazard ratio for tiotropium vs. SFC was 1.29; 95% CI, 1.08–1.54; *P* = 0.005) (Figure 2). This withdrawal differential was evident by Week 13, increased to Week 52, and was maintained thereafter. Withdrawing from the study after receiving tiotropium was unrelated to the subjects' prior use of ICS (used by 25% of those withdrawing and 26% of those completing). As a result of this study dropout, the mean patient days of study drug exposure was 561 days with the SFC group and 519 days with the tiotropium group. The main reasons for withdrawal are shown in Figure 1.

Exacerbations

Over 2 years, 62% of the SFC group and 59% of the tiotropium group had at least one exacerbation requiring therapeutic intervention. The estimated overall rates of exacerbations were 1.28 per year for SFC and 1.32 per year for tiotropium, with

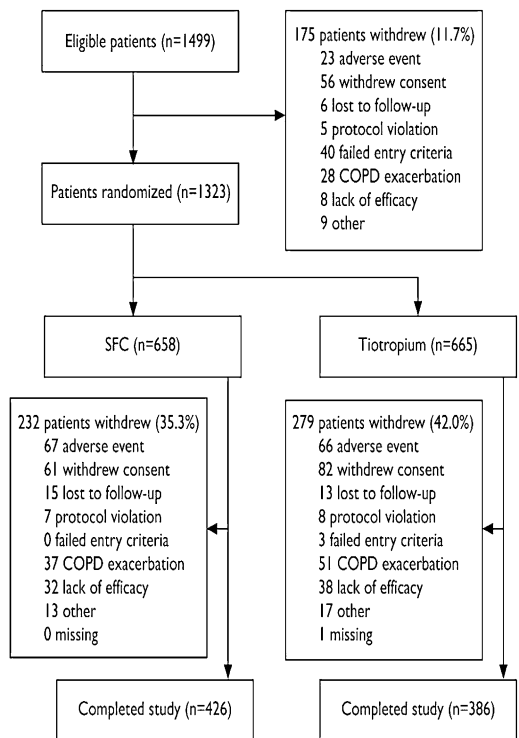


Figure 1. Patient disposition and reasons for discontinuation for the salmeterol 50 µg + fluticasone propionate 500 µg (SFC) and tiotropium (18 µg) treatment groups. COPD = chronic obstructive pulmonary disease.

a ratio of rates of 0.967 (95% CI, 0.836–1.119) indicating no difference between rates ($P = 0.656$). Exacerbations requiring antibiotics occurred more frequently in patients treated with SFC (SFC, 0.97/yr; tiotropium, 0.82/yr) ($P = 0.028$) but those requiring systemic corticosteroids were less frequent than in the tiotropium-treated patients (SFC, 0.69/yr; tiotropium, 0.85/yr) ($P = 0.039$) (Table 3). The incidence of exacerbations requiring hospitalizations was 16% for SFC and 13% for tiotropium ($P = 0.085$).

TABLE 1. PATIENT CHARACTERISTICS

Parameter	SFC (n = 658)	Tiotropium (n = 665)
Age, yr, mean	64	65
Males, %	81	84
Post-bronchodilator FEV ₁ , L, mean	1.11	1.13
Post-bronchodilator FEV ₁ , % predicted, mean	39.1	39.4
Reversibility, % predicted, mean	2.34	2.63
≥1 Exacerbation in the 12 mo before study start, %	85	88
Prebronchodilator FEV ₁ , L, mean		
All patients	1.05	1.06
GOLD stage III (≥30 to <50% predicted)	1.09 (n = 540)	1.11 (n = 537)
GOLD stage IV (<30% predicted)	0.73 (n = 100)	0.71 (n = 101)
Current smokers, %	38	38
Smoking history, pack-years, mean	41.3	39.5
SGRQ score at baseline,* mean	48.6	49.1
Patients discontinuing ICS at entry, n (%)	319 (48)	340 (51)

Definition of abbreviations: GOLD = Global Initiative for Chronic Obstructive Lung Disease; ICS = inhaled corticosteroids; SFC = salmeterol + fluticasone propionate; SGRQ = St. George’s Respiratory Questionnaire.

* Baseline following treatment intensification period.

TABLE 2. COMPARISON OF CHARACTERISTICS FOR PATIENTS WHO COMPLETED OR WITHDREW FROM THE STUDY

	SFC (n = 658)	Tiotropium (n = 665)
Completers, n	426	386
Post-bronchodilator FEV ₁ , L, mean	1.15	1.18
Post-bronchodilator FEV ₁ , %predicted, mean	39.8	40.5
SGRQ score at baseline,* mean	48.1	48.0
Patients discontinuing ICS at entry, n (%)	193 (45)	174 (45)
Withdrawals, n	232	279
Post-bronchodilator FEV ₁ , L, mean	1.05	1.07
Post-bronchodilator FEV ₁ , %predicted, mean	37.8	37.9
SGRQ score at baseline*, mean	49.7	50.5
Patients discontinuing ICS at entry, n (%)	126 (54)	166 (59)

Definition of abbreviations: ICS = inhaled corticosteroids; SFC = salmeterol + fluticasone propionate; SGRQ = St. George’s Respiratory Questionnaire.

* Baseline = following intensification run-in period.

Additional Outcomes

Mean SGRQ total score values at screening were 50.3 units for the SFC and 52.3 for the tiotropium treatment groups and improved after run-in treatment with systemic steroids and salmeterol to 48.0 and 48.2 units at baseline, respectively. The total SGRQ was significantly lower in the SFC group compared with the tiotropium group at Weeks 32, 56, 80, and 104 (Figure 3A), although this difference did not reach the minimum clinically important difference. At Week 104, the adjusted mean treatment difference for SFC versus tiotropium was –2.1 units (95% CI, –4.0 to –0.1 units; $P = 0.038$). The improvement in total score was reflected by improvements in the impacts domain with an adjusted mean treatment difference for SFC versus tiotropium of –3.2 units (95% CI, –5.4 to –0.1 units; $P = 0.004$) and to a lesser extent in the symptoms domain (Table 3). Figure 3B shows the mean SGRQ according to when the patient withdrew from treatment. Patients whose last SGRQ measurement was at 32 weeks or 56 weeks had deteriorated by more than 4 units from baseline before withdrawal. The proportion of patients achieving a clinically significant improvement in SGRQ at 2 years was greater in the SFC (32%) group than in the tiotropium group (27%). The odds ratio for a patient in the SFC group

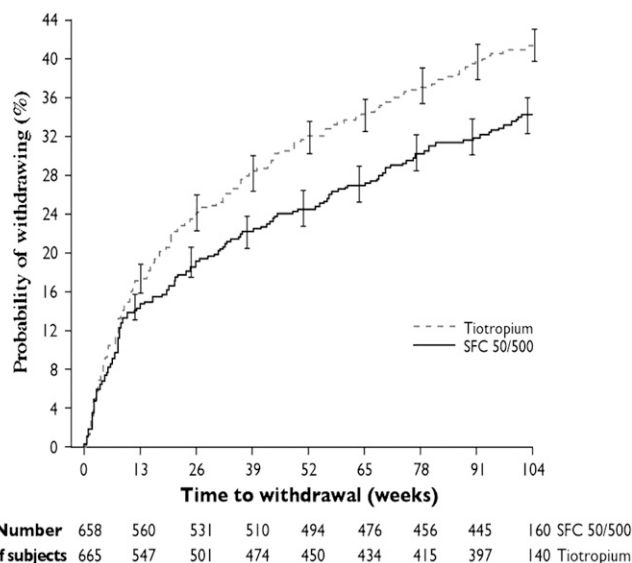


Figure 2. Time to withdrawal on treatment in the salmeterol + fluticasone propionate (SFC) and tiotropium treatment groups.

TABLE 3. SUMMARY OF EFFICACY RESULTS

Variable	SFC 50/500 (n = 658)	Tiotropium (n = 665)	Rate Ratio*	95% CI	P Value
Exacerbations (mean no./yr)					
HCU	1.28	1.32	0.97	0.84 to 1.12	0.656
Requiring oral corticosteroids	0.69	0.85	0.81	0.67 to 0.99	0.039
Requiring antibiotics	0.97	0.82	1.19	1.02 to 1.38	0.028
SGRQ (adjusted mean change at 2 yr [units])					
			Treatment Difference (units)*		
Total score	-1.70	0.37	-2.07	-4.02 to -0.12	0.038
Activity score	-0.38	-0.18	-0.56	-2.67 to 1.56	0.605
Impact score	-2.65	0.56	-3.20	-5.36 to -1.05	0.004
Symptom score	-2.94	-0.57	-2.37	-5.02 to 0.28	0.080
SGRQ (no. of patients [%] with a change from baseline ≥4 units)					
			Odds Ratio*		
Week 32	211 (35%)	190 (30%)	1.24	1.01 to 1.54	0.045
Week 56	194 (32%)	180 (29%)	1.29	1.04 to 1.60	0.021
Week 80	198 (33%)	171 (27%)	1.34	1.08 to 1.67	0.008
Week 104	193 (32%)	169 (27%)	1.29	1.04 to 1.60	0.021
Post-bronchodilator FEV ₁ (adjusted mean change over 2 yr [L])					
			Treatment Difference (L)*		
Adjusted mean change	-0.01	0.01	-0.02	-0.06 to 0.01	0.218

Definition of abbreviations: CI = confidence interval; HCU = health care utilization; SFC = salmeterol + fluticasone propionate; SGRQ = St. George's Respiratory Questionnaire.

* SFC versus tiotropium.

being at least one category of change higher than those in the tiotropium group at Week 104 was 1.30 for SFC versus tiotropium (95% CI,1.05–1.61; *P* = 0.018; Table 3).

At the end of the study, both treatments largely maintained the improvement in FEV₁ achieved during the run-in period. There was no evidence of a difference in adjusted mean FEV₁ postdose between the treatments at 2 years (Table 3). There was, however, a small statistically significant difference between tiotropium and SFC between Week 44 and 80 (Table E4).

Safety

Mortality was significantly lower in the SFC treatment group; 21 (3%) of SFC patients and 38 (6%) of those in the tiotropium group died (*P* = 0.032) during the study period. In addition, using the Cox proportional hazards model to analyze time to death on treatment (excluding seven deaths that occurred more than 2 wk after cessation of treatment), the hazard ratio for SFC versus tiotropium was 0.48 (95% CI, 0.27–0.85; *P* = 0.012) (Figure 4), which represents an estimated 52% reduction in the

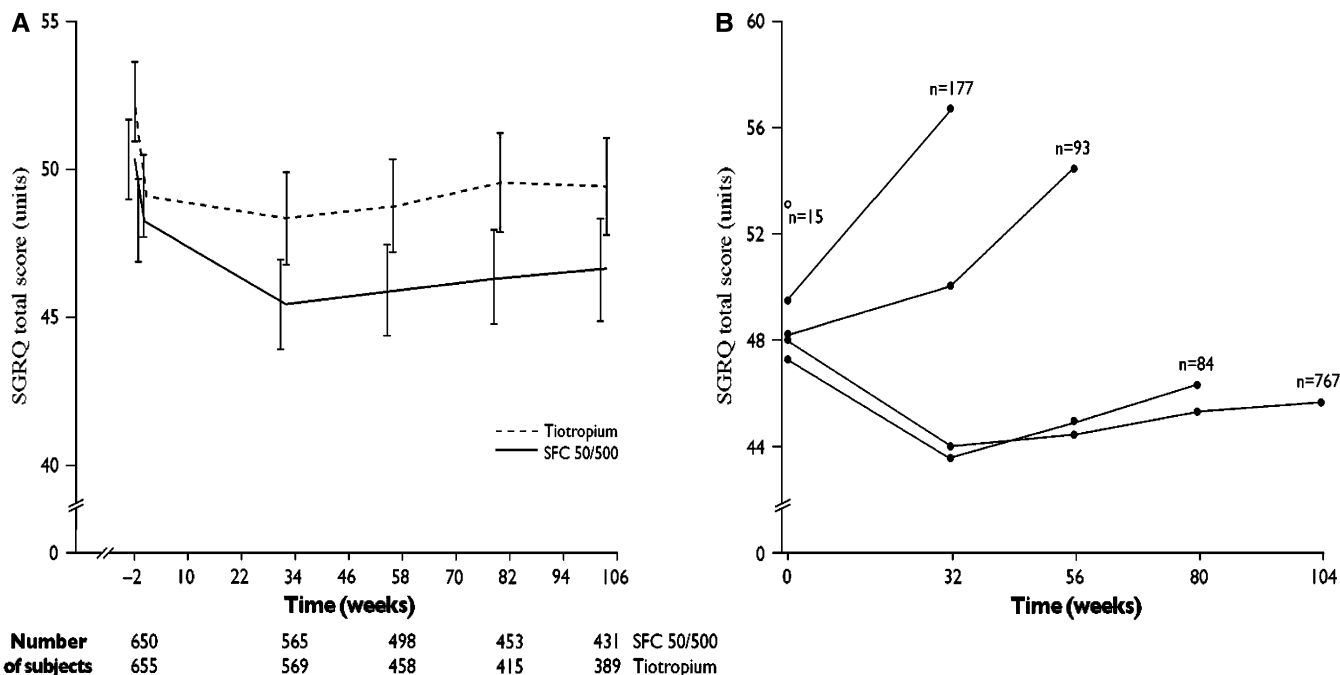


Figure 3. Total St. George's Respiratory Questionnaire (SGRQ) score over 2 years (A) and at the time of withdrawal from the study for those patients who withdrew during treatment (B).

risk of on-therapy all-cause mortality at any time during the 2-year period with SFC compared with tiotropium. Cardiac disorders recorded by the investigator were associated with death in 9 (1%) SFC-treated and 19 (3%) tiotropium-treated patients (Table 4). Among those with concurrent medical disorders, there were 15 (3%) deaths on treatment among patients randomized to SFC and 27 (6%) among patients randomized to tiotropium. In those subjects with baseline cardiovascular disease, there were 9 deaths (3%) in SFC patients and 24 (8%) for tiotropium patients. No more than 2% of patients in either treatment group had clinically significant ECG abnormalities at any time point in the study.

The frequency of adverse events is reported in Table 4, with 66% of patients on SFC and 62% of those receiving tiotropium reporting some adverse event, the most frequent of which was a COPD exacerbation. The diagnosis of pneumonia was based on clinical judgment, with radiologic confirmation not necessarily obtained even in episodes reported as lobar or bronchopneumonia. Pneumonia was reported during treatment in 8 and 4% of patients, respectively, and the hazard ratio for time to reported pneumonia was 1.94 (95% CI, 1.19–3.17; $P = 0.008$) for SFC compared with tiotropium over the 2 years. The number of reported pneumonias that overlapped with an exacerbation treated with antibiotics was 55% in the SFC group and 48% in the tiotropium group (i.e., the other episodes were not given antibiotic treatment despite the report of pneumonia). A total of 14 patients were withdrawn from the study due to pneumonia (9 SFC, 5 tiotropium).

Serious adverse events were reported during treatment by 30% of SFC-treated and 24% of tiotropium-treated patients. Other adverse events (e.g., fractures, bruising, candidiasis) were infrequent (Table 4).

DISCUSSION

INSPIRE is the first large-scale trial to evaluate the impact of two different treatment approaches—bronchodilatation with a long-acting inhaled anticholinergic agent or the combination of bronchodilatation using an LABA and antiinflammatory therapy with an ICS—on COPD exacerbations over a 2-year period. We found no difference in the overall rate of exacerbations between treatment groups (suggesting that both treatments reduced exacerbations frequency by a similar magnitude).

However, SFC treatment was associated with better health status, fewer patient withdrawals, and a lower mortality rate than occurred during tiotropium therapy. Conversely, there was a small but significant increase in reported pneumonia in the SFC-treated group; however, despite this there was still a mortality reduction benefit in favor of SFC.

The strengths of the INSPIRE trial include its size, long duration, and the inclusion of a large number of patients with severe and very severe COPD, all of which allowed more exacerbation events to be identified. COPD exacerbations in clinical trials are usually defined by the need for additional treatment (23). Exacerbations are intermittent events, however, and not all patients experience an exacerbation even during a 3-year trial (14). We recruited patients who had a history of exacerbations; we expected these patients to experience an exacerbation during the study due to the severity of their disease and because a previous exacerbation is one of the most important risk factors for consecutive exacerbations (7). Overall, 39% of the patients in INSPIRE did not have an exacerbation. The best way to analyze the exacerbation data has been controversial (24), and we have addressed these concerns by using a negative binomial analysis, which accommodates for different individual variation in the event rate. The event rates in our study were comparable to those reported previously in populations with a prior exacerbation history on therapy (13, 15, 18). The overall exacerbation rate did not differ between treatments. There were fewer episodes requiring oral corticosteroid treatment in the SFC group compared with the tiotropium group but relatively more patients were treated with antibiotics in the SFC group. This provides indirect evidence that these treatments affect apparently similar patients in different ways that affect clinical judgment. This difference warrants further study to determine the factors that influence therapeutic choice. The number of patients who had a report of pneumonia that overlapped with an exacerbation treated with antibiotics was nevertheless similar between the treatment groups.

More patients failed to complete the study while receiving tiotropium. The differential withdrawal rate was evident from Week 13 and persisted to Week 104. This differential withdrawal from the study may have led to a healthy survivor effect as seen in other studies (16), and suggests that the disease severity in the two limbs was not entirely comparable during the trial as patients whose well-being was deteriorating more rapidly withdrew sooner (see Figure 3B). The differential withdrawal rate is in itself an indirect marker of treatment efficacy.

A placebo arm was not included in this study as all patients had severe to very severe disease and it was deemed unethical to withhold known effective therapies. Previous data have shown that patients experience an exacerbation within 8 weeks after regular ICS treatment has been discontinued (25). The withdrawal rate with tiotropium was similar to that observed in placebo-treated patients in previous studies in which ICS were permitted (20, 21), suggesting that the differential withdrawal rate was not due to steroid removal in the tiotropium arm.

We used a short treatment intensification regime during the run-in period before randomization as used in previous studies (18). This treatment intensification helps differentiate between the improvement in health status due to the increased medical attention at the start of a clinical study from the improvement derived from the study interventions. The short-term beneficial effects of treatment intensification on health status are not maintained without subsequent maintenance therapy (26).

Patients showed an improvement in the SGRO total score during the 2 weeks of treatment intensification. After treatment intensification, patients receiving tiotropium maintained this initial level of improvement, but there was a further statistically

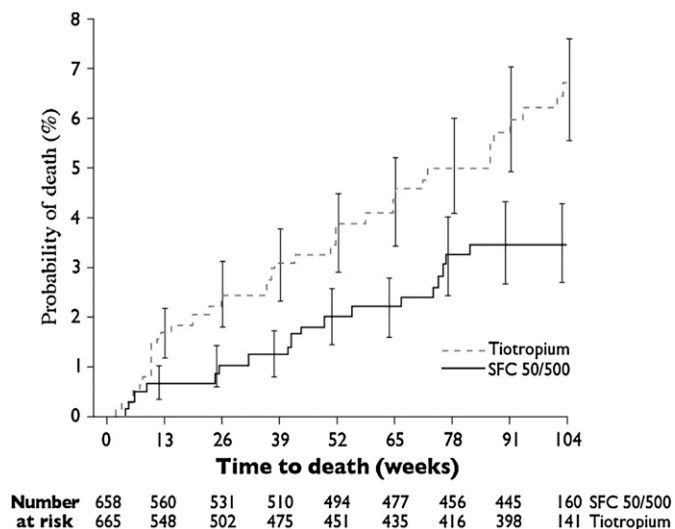


Figure 4. Time to death on treatment in the salmeterol + fluticasone propionate (SFC) and tiotropium treatment groups.

TABLE 4. SUMMARY OF SAFETY RESULTS

Variable	SFC 50/500 (n = 658)	Tiotropium (n = 665)
All-cause mortality		
Deaths, n (%)	21 (3)	38 (6)
During treatment	18 (3)	34 (5)
Events (grouped by body system) associated with death*, n (%)		
Cardiac disorders	9 (1)	19 (3)
Respiratory, thoracic and mediastinal disorders	5 (<1)	6 (<1)
Neoplasms benign, malignant and unspecified	2 (<1)	7 (1)
General disorders and administration site conditions	5 (<1)	2 (<1)
Infections and infestations	4 (<1)	0
Nervous system disorders	1 (<1)	2 (<1)
Vascular disorders	2 (<1)	0
Gastrointestinal disorders	0	1 (<1)
Hepatobiliary disorders	1 (<1)	0
Top 5 most commonly reported AEs that began during treatment, n (%)		
All events	435 (66)	414 (62)
COPD	122 (19)	104 (16)
Nasopharyngitis	115 (17)	98 (15)
Pneumonia [†]	50 (8)	24 (4)
Headache	48 (7)	60 (9)
Pharyngolaryngeal pain	34 (5)	26 (4)
Other AEs of interest, n (%)		
Bone disorders	17 (3)	12 (2)
Eye disorders	2 (< 1)	3 (< 1)
Candidiasis [‡]	40 (6)	20 (3)
Contusions	8 (1)	2 (< 1)
Top 5 most commonly reported SAEs (grouped by body system) that began during treatment, n (%)		
All events	199 (30)	162 (24)
Respiratory, thoracic and mediastinal disorders	111 (17)	87 (13)
Infections and infestations	63 (10)	28 (4)
Cardiac disorders	23 (3)	34 (5)
Neoplasms benign, malignant, and unspecified	18 (3)	15 (2)
Gastrointestinal disorders	10 (2)	14 (2)

Definition of abbreviations: AE = adverse event; COPD = chronic obstructive pulmonary disease; SAE = serious adverse event; SFC = salmeterol/fluticasone propionate combination.

* Deaths can be associated with more than one adverse event.

[†] Includes events of pneumonia, lobar pneumonia, and bronchopneumonia.

[‡] Includes events of candidiasis, oral candidiasis, and oropharyngeal candidiasis.

significant 2-unit improvement in the SFC arm during treatment. However, a 4-unit change in the SGRQ has been traditionally used as the minimally clinically important difference (27). We therefore present a responder analysis to clarify the clinical significance of this finding, which shows that a significantly greater number of patients receiving SFC had a greater than 4 point change from baseline than patients receiving tiotropium.

The improvement in the total SGRQ score in the SFC treatment group was largely driven by changes in the impacts and symptom score, which may help to explain the differential withdrawal rate between the groups. Interestingly, the increase after the intensification period in the SFC group was not related to a parallel improvement in lung function and exacerbations, suggesting it relates to as yet undetermined benefits.

COPD is a condition partly defined by an abnormal inflammatory response to noxious fumes (28). Inflammation in COPD predates the appearance of symptoms and is elevated during exacerbations (29). The differences in outcomes we observed could be due to antiinflammatory properties in SFC. Tiotropium has been shown to reduce exacerbations in the absence of any antiinflammatory activity (30), whereas it has previously been demonstrated that SFC has airway antiinflammatory effects (31, 32), which may contribute to its beneficial effect on health status and exacerbations in COPD.

The difference in lung function between treatments was modestly in favor of tiotropium-treated patients between Weeks 44 and 80. This transient difference was small and likely due to the

differential withdrawal rate and to an unequal FEV₁ at randomization.

Despite similar exacerbation rates between treatment groups, and although the trial was not powered to detect a difference in mortality as it was not the primary outcome, a statistically significant difference was seen in favor of SFC. The difference was present when all known deaths were considered or if mortality was restricted to death on treatment (including 2-wk post-treatment cessation). Mortality data was not collected after patients withdrew from therapy as in the TORCH (Toward a Revolution in COPD Health) study (16). Because there were no differences in comorbid illnesses at baseline, the difference in the all-cause mortality cannot be the result of such an imbalance. The difference between groups in the reporting of fatal events was largest in those associated with cardiovascular causes. There are several possible explanations for this difference. It could be that tiotropium increases mortality, although this cannot be determined from our data in the absence of a placebo arm. A recent meta-analysis involving 8,002 patients reported that tiotropium was shown to have no influence on all-cause mortality when compared with placebo (33). Therefore, there is no evidence to support an increase in mortality with tiotropium. Alternatively, it could be that SFC improves survival. This has recently been suggested by the TORCH study in which a 17.5% reduction in all-cause mortality (although not statistically significant; $P = 0.052$) was observed in patients treated with SFC (16). The presumed reduction in mortality

seen in INSPIRE supports that seen in TORCH but further studies powered on mortality will be required to confirm this finding.

We observed more episodes of reported pneumonia in the SFC-treated patients. The TORCH trial also reported more pneumonia in patients receiving inhaled steroids (16). In both TORCH and INSPIRE, the increased incidence of pneumonia was not reflected by an overall worsening in health status or mortality in the SFC-treated group. The exact nature of these episodes and why they should occur is being evaluated further and remains to be determined.

Our study raises several important questions: Why is there a difference in the nature of the exacerbations between the two treatments? What is the biological basis of the differential effect on exacerbations and is it related to the difference in mortality between the two treatments? Finally, there may be potential advantages from combining SFC and tiotropium and this should be formally tested in adequately powered trials against other active comparators. A recently reported study has compared the effects of tiotropium combined with SFC with tiotropium alone and tiotropium and salmeterol combined and found no benefit of the tiotropium–SFC combination on the percentage of patients who experienced an exacerbation compared with the other therapies (34). However, the statistical power to identify differences in treatment was limited, in part by the differential withdrawal from the non–steroid treatment limb as we saw in INSPIRE. Despite powering issues, the authors reported improvement in lung function, health status, and hospitalization rates of patients randomized to the SFC and tiotropium arm. Further studies are needed to address the effect of pharmacologic therapy combination on exacerbation rates and other outcomes.

In summary, this is the first study to directly compare an ICS/LABA combination (SFC) and a long-acting anticholinergic (tiotropium) in severe COPD. Both treatments had a similar impact on COPD exacerbation rate, but the ICS/LABA combination reduced the perceived need for systemic corticosteroids and improved health status compared with anticholinergic therapy. Antibiotics were prescribed more frequently and clinician-diagnosed pneumonia was more common in the ICS/LABA group compared with anticholinergic therapy. INSPIRE is also the first study to show a statistically significant difference in the relative risk of all-cause mortality between two established treatments for COPD, SFC and tiotropium.

Treatment with SFC and tiotropium achieved similar exacerbation rates with different mechanisms (as evidenced by the difference in use of oral corticosteroids and antibiotics to treat HCU exacerbations), and this resulted in different outcomes. We believe that this has important implications for the choice of therapy in the management of COPD.

Conflict of Interest Statement: J.A.W. has received research funding in the last 3 years from GlaxoSmithKline (\$400,000 for the ECLIPSE study), Boehringer Ingelheim (\$600,000 for a study on inflammatory markers and exacerbations) and AstraZeneca (\$500,000 for a study of immunological mechanism and exacerbations), honoraria for participation in advisory boards from GlaxoSmithKline (\$3,000) and Novartis (\$2,500 in 2007) and for lectures from GlaxoSmithKline (\$8,000), Boehringer Ingelheim (\$4,000 from 2005–2006 and \$2,000 from 2006–2007), AstraZeneca (\$8,000 from 2005–2006) and Novartis (\$2,500). P.M.A.C. has received funding from GlaxoSmithKline (\$8,000 paid to the University of Liverpool for consultancy on the TORCH study; \$300,000 for the ECLIPSE study), Altana (\$50,000 for the HERO study), and Chiesi (\$50,000), honoraria for participation to advisory boards from GlaxoSmithKline (\$4,500 from 2005–2006) and Pfizer (\$3,000 in 2006), and for lectures from GlaxoSmithKline (\$10,000 in 2006) and Altana (\$3,000 from 2005–2006). T.A.S. does not have a financial relationship with commercial entity that has an interest in the subject of this manuscript. G.H. has been an employee of the sponsor, GlaxoSmithKline, since 1996 and holds stock options in different formats. Z.A. was employed by GlaxoSmithKline between October 2002 and November 2006 as a full-time employee. R.A.S. has received industry-sponsored grants from AstraZeneca (£30,000 in 2006), Talecris (£317,000 in 2006), and honoraria for participation in advisory boards from GlaxoSmithKline (£3,000), Roche (£1,000), and Merck Sharp & Dohme (£1,000).

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References

1. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease, NHLBI/WHO workshop report. Updated 2005 [Internet]. Bethesda (MD): National Heart, Lung, and Blood Institute; 1998 Apr [updated 2005 Sep; accessed 21 Jul 2006]. Available from: <http://www.goldcopd.com>
2. Lopez AD, Shibuya K, Rao C, Mathers CD, Hansell AL, Held LS, Schmid V, Buist S. Chronic obstructive pulmonary disease: current burden and future projections. *Eur Respir J* 2006;27:397–412.
3. Chapman KR, Mannino DM, Soriano JB, Vermeire PA, Buist AS, Thun MJ, Connell C, Jemal A, Lee TA, Miravittles M, et al. Epidemiology and costs of chronic obstructive pulmonary disease. *Eur Respir J* 2006; 27:188–207.
4. Stevenson NJ, Walker PP, Costello RW, Calverley PM. Lung mechanics and dyspnea during exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006;172:1510–1516.
5. Wilkinson TMA, Hurst JR, Perera WR, Wilks M, Donaldson GC, Wedzicha JA. Interactions between lower airway bacterial and rhinoviral infection at exacerbations of chronic obstructive pulmonary disease. *Chest* 2006;129:317–324.
6. Sethi S, Maloney J, Grove L, Wrona C, Berenson CS. Airway inflammation and bronchial bacterial colonization in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006;173:991–998.
7. Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;157:1418–1422.
8. Spencer S, Calverley PM, Burge PS, Jones PW. Impact of preventing exacerbations on deterioration of health status in COPD. *Eur Respir J* 2004;23:698–702.
9. Andersson F, Borg S, Jansson SA, Jonsson AC, Ericsson A, Prutz C, Ronmark E, Lundback B. The costs of exacerbations in chronic obstructive pulmonary disease. *Respir Med* 2002;96:700–708.
10. Soler-Cataluna JJ, Martinez-Garcia MA, Roman Sanchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax* 2005;60: 925–931.
11. Scott S, Walker P, Calverley PM. COPD exacerbations—4: prevention. *Thorax* 2006;61:440–447.
12. Mahler DA, Donohue JF, Barbee RA, Goldman MD, Gross NJ, Wisniewski ME, Yancey SW, Zakes BA, Rickard KA, Anderson WH. Efficacy of salmeterol xinafoate in the treatment of COPD. *Chest* 1999;115:957–965.
13. Niewoehner DE, Rice K, Cote C, Paulson D, Cooper JA, Kordecki L, Cassino C, Kesten S. Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator: a randomized trial. *Ann Intern Med* 2005;143:317–326.
14. Burge PS, Calverley PM, Jones PW, Spencer S, Anderson J, Maslen TK. Randomized, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ* 2000;320:1297–1303.
15. Calverley PM, Pauwels R, Vestbo J, Pride N, Gulsvick A, Anderson J, Maden C; TRial of Inhaled STeroids ANd long-acting beta2 agonists study group. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2003;361:1660. Erratum for: *Lancet* 2003;361:449–456.
16. Calverley PMA, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, Yates JC, Vestbo J; TORCH Investigators. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007;356:775–789.
17. Seemungal T, Stockley R, Calverley PM, Hagan G, Wedzicha JA. Investigating New Standards for Prophylaxis In Reduction of Exacerbations: the INSPIRE study methodology. *COPD* 2007;4:177–183.
18. Calverley PM, Boonsawat W, Cseke Z, Zhong N, Peterson S, Olsson H. Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. *Eur Respir J* 2003;22:912–919.
19. Committee for Proprietary Medical Products. Points to consider on clinical investigation of medicinal products in the chronic treatment of patients with chronic obstructive pulmonary disease (COPD) [Inter-

- net]. London: European Medicines Agency (EMA); [accessed 21 July 2006]. 1999. Available from: <http://www.emea.eu.int/pdfs/human/ewp/056298en.pdf>
20. Vincken W, van Noord JA, Greefhorst AP, Bantje TA, Kesten S, Korducki L, Cornelissen PJ. Improved health outcomes in patients with COPD during 1 year's treatment with tiotropium. *Eur Respir J* 2002;19:209–216.
 21. Casaburi R, Mahler DA, Jones PW, Wanner A, San PG, ZuWallack RL, Manjoge SS, Serby CW, Witek T. A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. *Eur Respir J* 2002;19:217–224.
 22. Keene ON, Jones MRK, Lane PW, Anderson J. Analysis of exacerbation rates in asthma and chronic obstructive pulmonary disease: example from the TRISTAN study. *Pharm Stat* 2007;6:89–97.
 23. Rodriguez-Roisin R. Toward a consensus definition for COPD exacerbations. *Chest* 2000;117:398S–401S.
 24. Suissa S. Statistical treatment of exacerbations in therapeutic trials of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006;173:842–846.
 25. Jarad NA, Wedzicha JA, Burge PS, Calverley PM. An observational study of inhaled corticosteroid withdrawal in stable chronic obstructive pulmonary disease. ISOLDE Study Group. *Respir Med* 1999;93:161–166.
 26. Jones PW, Stahl E. Budesonide/formoterol sustains clinically relevant improvements in health status in COPD [abstract]. *Eur Respir J* 2005;26(Suppl 49):208s.
 27. Jones PW. Health status measurement in chronic obstructive pulmonary disease. *Thorax* 2001;56:880–887.
 28. Hogg JC, Chu F, Utokaparch S, Woods R, Elliott WM, Buzatu L, Cherniack RM, Rogers RM, Sciurba FC, Coxson HO, *et al.* The nature of small airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med* 2004;350:2645–2653.
 29. Sethi S, Muscarella K, Evans N, Klingman KL, Grant BJ, Murphy TF. Airway inflammation and etiology of acute exacerbations of chronic bronchitis. *Chest* 2000;118:1557–1565.
 30. Powrie DJ, Wilkinson TMA, Donaldson GC, Jones P, Scrine K, Viel K, Kesten S, Wedzicha JA. Effect of tiotropium on sputum and serum inflammatory markers and exacerbations in chronic obstructive pulmonary disease. *Eur Respir J* 2007;30:472–478.
 31. Bourbeau J, Christodoulouopoulos P, Maltais F, Yamauchi Y, Olivenstein R, Hamid Q. Effect of salmeterol/fluticasone propionate on airway inflammation in COPD: a randomized controlled trial. *Thorax* 2007;62:938–943.
 32. Jeffery P. Anti-inflammatory effects of inhaled corticosteroids in chronic obstructive pulmonary disease: similarities and differences to asthma. *Expert Opin Investig Drugs* 2005;14:619–632.
 33. Barr RG, Bourbeau J, Camargo CA, Ram FS. Tiotropium for stable chronic obstructive pulmonary disease: A meta-analysis. *Thorax* 2006;61:854–862.
 34. Aaron SD, Vandemheen KL, Fergusson D, Maltais F, Bourbeau J, Goldstein R, Balter M, O'Donnell D, McIvor A, Sharma S, *et al.*; Canadian Thoracic Society/Canadian Respiratory Clinical Research Consortium. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med* 2007;146:545–555.