CHEST

Original Research

COPD

Prevalence and Progression of Osteoporosis in Patients With COPD

Results From the Towards a Revolution in COPD Health Study

Gary T. Ferguson, MD, FCCP; Peter M. A. Calverley, MD; Julie A. Anderson, MA; Christine R. Jenkins, MD; Paul W. Jones, MD; Lisa R. Willits, MSc; Julie C. Yates, BS; Jørgen Vestbo, MD; and Bartolome Celli, MD, FCCP

Background: **Osteoporosis is common in patients with COPD, but its prevalence and progression are not well characterized. Concerns have been raised over the possible deleterious effect of long-term therapy with inhaled corticosteroids (ICSs) on bone density in this population. Here, we investigated the long-term effects of therapy with fluticasone propionate (FP) alone, salmeterol (SAL) alone, and a SAL/FP combination (SFC) on bone mineral density (BMD) and bone fractures in patients with moderate-to-severe COPD in the TOwards a Revolution in COPD Health (TORCH) study.**

Methods: **A randomized, double-blind, parallel-group, placebo-controlled study conducted at 88 US centers involving 658 patients (a subset of 6,184 international subjects in TORCH). Therapy with placebo, SAL (50 μg), FP (500 μg), or SFC (SAL 50 μg/FP 500 μg) twice daily was administered for 3 years. Baseline and yearly measurements of BMD at the hip and lumbar spine were performed. The incidence of traumatic and nontraumatic bone fractures was recorded.**

Results: **At baseline, 18% of men and 30% of women had osteoporosis, and 42% of men and 41% of women had osteopenia based on BMD assessments. Forty-three percent of subjects completed all testing. The changes in BMD at the hip and lumbar spine over 3 years were small. No significant differences were observed between treatment arms (adjusted mean percent change from baseline at hip was −3.1% for placebo, −1.7% for SAL, −2.9% for FP, and −3.2% for SFC therapy, respectively; while, the corresponding changes for the lumbar spine were 0, 1.5%, −0.3%, and −0.3% for placebo, respectively, SAL, FP, and SFC therapy). The incidence of fractures was low and was similar for all treatments (5.1% to 6.3%).**

Conclusions: **Osteoporosis is highly prevalent in patients with COPD, irrespective of gender. In the TORCH study, no significant effect on BMD was detected for ICS therapy compared with placebo.**

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Abbreviations: BMD = bone mineral density; DEXA = dual-energy x-ray absorption; FP = fluticasone propionate; ICS = inhaled corticosteroid; LABA = long-acting β-agonist; OCS = oral corticosteroid; SAL = salmeterol; SCS = systemic corticosteroid; SFC = salmeterol/fluticasone propionate combination; SGRQ = St. George Respiratory Questionnaire; TORCH = TOwards a Revolution in COPD Health

COPD is a lung disease that is thought to result from chronic inflammation that may affect other organ systems.[1] Evidence[2,3] suggests that the prevalence of osteoporosis in patients with COPD is high and potentially important. It is unknown whether osteoporosis in COPD patients is due to its systemic nature, to physical limitations imposed by the disease, or to the COPD therapies received. In particular, the association between oral corticosteroid (OCS) usage and osteoporosis[4] has raised concerns over the potential risk of osteoporosis in patients with COPD who use inhaled corticosteroids (ICSs) regularly.[5]

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The authors of observational,[6,7] randomized, placebo-controlled,[8] and systematic review[9] studies have reported that ICS therapy is associated with an increased risk of osteoporosis. However, the authors of other randomized, placebo-controlled studies[10–12] have found no such association. The limitations of these studies include small numbers of patients assessed for bone mineral density (BMD), a predominance of milder and younger patients, and a lack of detailed information about specific bone complications. In addition, the ICSs utilized in these trials have been different. The long-term effects of therapy with long-acting bronchodilators alone on BMD in COPD patients are also not known.

We prospectively evaluated BMD and fracture rates in patients with moderate-to-severe COPD before and during 3 years of treatment with a salmeterol/fluticasone propionate combination (SFC), fluticasone propionate (FP), and salmeterol (SAL), compared with placebo in a large subset of patients recruited in the United States as a part of the TOwards a Revolution in COPD Health (TORCH) study.[13] We also determined whether changes in BMD were associated with baseline factors and evaluated whether the incidence of fractures in the BMD population was similar to that observed in the overall safety population from the TORCH study.[13]

Materials and Methods

Design Overview, Setting, and Participants

Details of the TORCH study design and analyses have been published in detail elsewhere.[13,14] The authors of the TORCH study evaluated outpatients with moderate-to-severe COPD in 444 centers across 42 countries. The BMD study was conducted in 88 of these centers in the United States. Patients requiring OCS or long-term oxygen therapy at study entry were excluded. All patients gave written informed consent prior to participation in the study, which was approved by local ethical review boards, and was conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines.

Randomization and Interventions

TORCH was a multicenter, randomized, double-blind, parallel-group, placebo-controlled study. Eligible patients were randomly assigned to receive placebo, SAL (50 μg), FP (500 μg), or SFC (SAL, 50 μg/FP, 500 μg) inhaled twice daily via an inhaler (Diskus; GlaxoSmithKline; London, UK) for 3 years.

Baseline Information

On study enrollment, detailed information about the medical history was obtained, including requesting outside medical records if available and specific detail about medication usage (ICS, OCS, and long-acting β-agonists [LABAs]) at any time in the prior year. Information on all other medications taken at study initiation was also collected. Patient activity levels were estimated using the St. George Respiratory Questionnaire (SGRQ) activity score.[15]

Outcomes and Follow-up

In this analysis, the primary outcome was BMD measurements of the total hip by using dual-energy x-ray absorption (DEXA). BMD measurements of the total hip and the L1 to L4 regions of the spine were made at baseline and after 1, 2, and 3 years of treatment. All DEXA scans were conducted by qualified technicians and sent electronically for centralized analysis by a clinical services company (Bio-Imaging; Newtown, PA). Quality assurance and calibration of DEXA equipment and densitometric measurements were monitored by this facility to control for site-to-site variability in BMD measurements. Yearly calibration with a phantom was performed at all testing sites to ensure standardized calibration and analysis from all BMD machines used throughout the study. The t scores and Z scores were provided by the manufacturers from a proprietary database for each individual BMD scanner. Osteoporosis was defined as a t score of ≤ -2.5, and osteopenia was defined as a t score between -1.0 and -2.5.[16,17] At any time during the study, if a t score was ≤ -2.0 or if there was a significant decrease in BMD (defined as $\geq 8\%$ after 1 year or $\geq 10\%$ after 2 years) the study site was notified by fax and referred for consultation.

Patients were questioned about fractures throughout the study. If a fracture was reported, additional details, including specific bone location and whether or not the investigator considered the event traumatic or nontraumatic were captured. A nontraumatic bone fracture was defined as a fracture caused by a fall from less than standing height. These data were available for both the BMD study population (n = 658) and the overall TORCH safety population (n = 6,184) [includes all patients who were randomly assigned and received at least one dose of study medication]. Detailed information on medication usage was recorded throughout the trial.

Statistical Analysis

The BMD study population size was powered on information from earlier long-term ICS trials.[8] Assuming an SD of the change in hip BMD of 0.035 g/cm^2, 150 patients per arm would give a

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Affiliations: From the Pulmonary Research Institute of Southeast Michigan (Dr. Ferguson), Livonia, MI; the Department of Medicine (Dr. Calverley), University Hospital Aintree, Liverpool, UK; the Respiratory Medicines Centre (Ms. Anderson and Ms. Willits), GlaxoSmithKline, Middlesex, UK; Woolcock Institute of Medical Research (Dr. Jenkins), Camperdown, NSW, Australia; the Division of Cardiac and Vascular Science (Dr. Jones), St. George's, University of London, London, UK; the Respiratory Medicines Centre (Ms. Yates), GlaxoSmithKline, Triangle Park, NC; the Department of Cardiology and Respiratory Medicine (Dr. Vestbo), Hvidovre Hospital, Hvidovre, Denmark; the North West Lung Centre (Dr. Vestbo), Wythenshawe Hospital, Manchester, UK; and the Pulmonary and Critical Care Division (Dr. Celli), Caritas St. Elizabeth's Medical Center, Tufts University School of Medicine, Boston, MA.
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Correspondence to: Gary T. Ferguson, MD, FCCP, Pulmonary Research Institute of Southeast Michigan, 28815 Eight Mile Rd, Suite 103, Livonia, MI 48152; e-mail: garytferguson@msn.com

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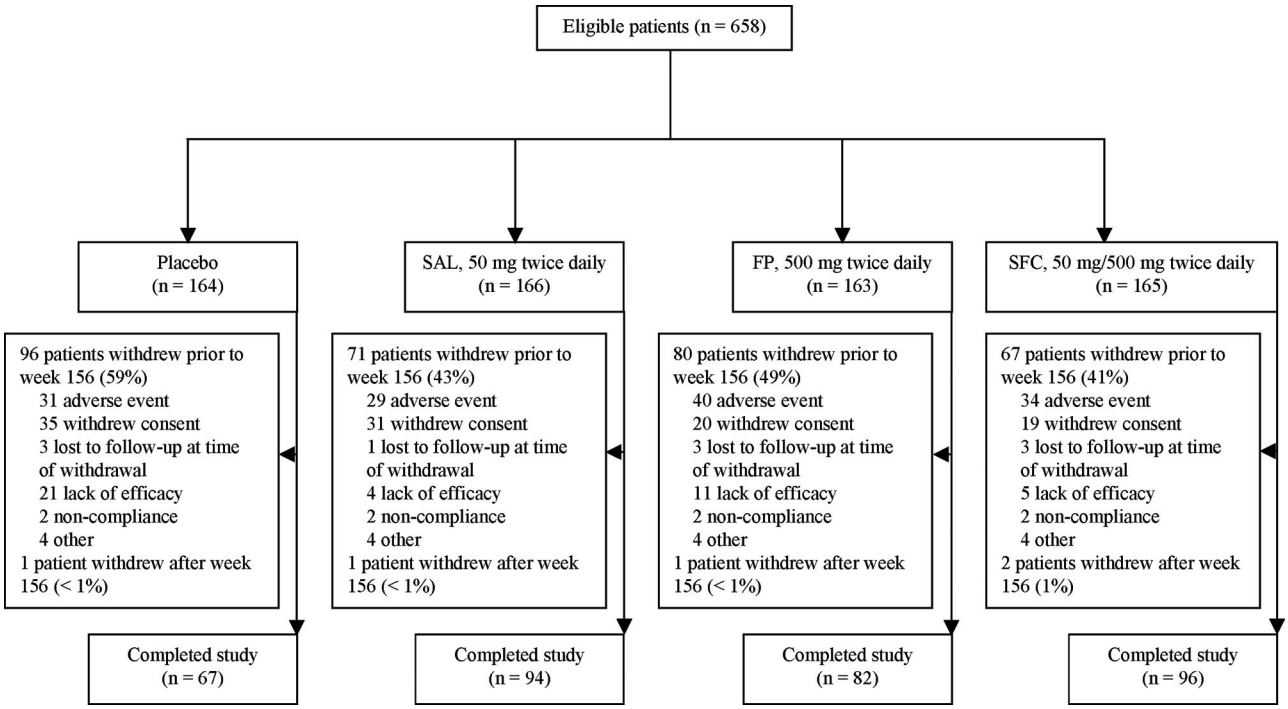

FIGURE 1. Enrollment of patients in the bone density study.

> 95% power to detect a difference of 0.015 g/cm^2. Assuming the baseline total hip density was 0.800 g/cm^2, this would be 0.015/0.800 = 1.9% difference in BMD at 3 years.

BMD at the total hip and lumbar spine was expressed as a log-transformed ratio to baseline, and prespecified analyses were performed by using repeated measures analysis of covariance, where treatment group was fitted as the explanatory variable, and terms for age, gender, smoking status, log baseline BMD, BMI (fitted as a continuous term), baseline BMD therapy, and visit were fitted as covariates. A supportive analysis was performed on the absolute change from baseline BMD at the total hip assessment, using the same analysis of covariance model.

Fracture rates were expressed per 1,000 treatment years by dividing the total number of events by the total time receiving treatment in years, then multiplying by 1,000. Time to first bone fracture was compared between treatment groups using Kaplan-Meier estimates and the log-rank test, stratified by smoking status. A Cox proportional hazards model was performed as a supporting analysis including covariates of baseline FEV_1, BMI, region, smoking status, age, and gender. All analyses were performed by using a statistical software package (SAS, version 8.2 for UNIX; SAS Institute; Cary, NC; UNIX platform).

RESULTS

The bone density study population comprised 658 patients (47% of all US patients) [Fig 1]. All treatment groups were similar with respect to age, gender, FEV_1, BMI, and the number of exacerbations treated with antibiotics and/or OCSs or requiring hospitalization in the prior year. Patient activity levels, as estimated by SGRQ activity score, and the number of patients receiving ICSs, OCSs, bisphosphonates, or other BMD medications (calcium, vitamin D, or hormone replacement therapy) recorded at baseline were also similar. Overall, approximately half of the patients received systemic corticosteroids (SCSs) during treatment (Table 1). Forty-three percent of subjects completed all follow-up testing.

Prevalence of Osteoporosis and Osteopenia

At baseline, the overall prevalence of osteoporosis and osteopenia was high (65%). More women (30%) than men (18%) had osteoporosis. In contrast, the prevalence of osteopenia was comparable between men (42%) and women (41%) [Table 2].

Total Hip BMD

Baseline BMD values at the hip were similar in all treatment groups (Table 2). Over the course of the study, changes in BMD were small. No significant differences were observed when comparing changes in BMD over time between any of the active treatment groups and placebo at 3 years (Table 3, Fig 2*A*). The exclusion of subjects who were known to have received therapy with bisphosphonates at any time during the study did not change these results. Analysis of only those subjects who completed all 3 years of the study, eliminating any effect of dropouts and providing a full 3 years of drug exposure, again revealed no significant differences in BMD over time between any of the active treatment groups and placebo (Fig 2*B*).

Table 1—*Demographic and Baseline Characteristics of the BMD Study Population*

Characteristics	Placebo Group (n = 164)	SAL Group (n = 166)	FP Group (n = 163)	SFC Group (n = 165)	Total (n = 658)
Age, yr*	65 (8)	65 (8)	66 (8)	65 (9)	65 (8)
Male gender†	86 (52)	99 (60)	89 (55)	108 (65)	382 (58)
Current smoker†	69 (42)	71 (43)	71 (44)	66 (40)	277 (42)
Baseline post-bronchodilator therapy FEV_1, L*	1.20 (0.49)	1.22 (0.43)	1.15 (0.39)	1.23 (0.47)	1.20 (0.45)
Post-bronchodilator therapy FEV_1, % predicted	44 (14)	45 (14)	44 (13)	44 (13)	44 (13)
BMI, kg/m^2*	26.2 (6.6)	27.2 (6.2)	26.8 (5.7)	26.8 (6.3)	26.7 (6.2)
Patients having an exacerbation in past year†	81 (49)	76 (46)	84 (52)	74 (45)	315 (48)
SGRQ activity score*	64.8 (21.1)	64.6 (17.9)	67.5 (21.4)	65.7 (19.6)	65.7 (20.0)
ICS received†‡	98 (60)	81 (49)	77 (47)	81 (49)	337 (51)
OCS received†‡	47 (29)	43 (26)	52 (32)	49 (30)	191 (29)
SCS received during study					
Subjects receiving SCS†	84 (51)	87 (52)	82 (50)	76 (46)	329 (50)
Courses of therapy, Total No.	226	217	234	185	862
Cumulative duration*§	46 (72)	52 (121)	43 (60)	60 (118)	50 (96)
Bisphosphonate received prior to study†	17 (10)	8 (5)	13 (8)	9 (5)	47 (7)
Male	3 (3)	1 (1)	3 (3)	3 (3)	10 (3)
Female	14 (18)	7 (10)	10 (14)	6 (11)	37 (13)
Other BMD medication received prior to study†	42 (26)	38 (23)	37 (23)	34 (21)	151 (23)
Male	8 (9)	12 (12)	8 (9)	4 (4)	32 (8)
Female	34 (44)	26 (39)	29 (39)	30 (53)	119 (43)
Bisphosphonate therapy started during study†	14 (9)	17 (10)	23 (14)	21 (13)	75 (11)
Male	6 (7)	7 (7)	9 (10)	9 (8)	31 (8)
Female	8 (10)	10 (15)	14 (19)	12 (21)	44 (16)
Other BMD medication therapy started during study†	13 (8)	17 (10)	12 (7)	16 (10)	58 (9)
Male	6 (7)	7 (7)	3 (3)	6 (6)	22 (6)
Female	7 (9)	10 (15)	9 (12)	10 (18)	36 (13)

*Values are given as the mean (SD).
†Values are given as No. (%).
‡Exposure in the 12 months prior to study entry.
§For subjects taking at least one course of medication.

Lumbar Spine BMD

BMD values for the lumbar spine at baseline were similar in all groups. Again, changes in BMD over time were small, and no differences were found between any of the active treatment groups and the placebo group at 3 years (Table 2, Fig 3*A*). As with the hip, the exclusion of subjects known to receive therapy with bisphosphonates at any time during the study and the analysis of only those subjects completing all 3 years of the study (Fig 3*B*) did not change these results.

Table 2—*BMD at Baseline in the BMD Study Population*

Baseline BMD Values	Placebo Group (n = 164)	SAL Group (n = 166)	FP Group (n = 163)	SFC Group (n = 165)	Total (n = 658)
Hip, g/cm^2*	0.85 (0.17)	0.89 (0.17)	0.85 (0.17)	0.91 (0.19)	0.88 (0.17)
Spine, g/cm^2*	1.00 (0.19)	1.04 (0.22)	0.99 (0.20)	1.03 (0.23)	1.02 (0.21)
Hip, *t* score*	−1.26 (1.23)	−0.98 (1.25)	−1.26 (1.14)	−0.92 (1.28)	−1.08 (1.23)
Spine, *t* score	−1.10 (1.56)	−0.77 (1.81)	−1.19 (1.57)	−0.77 (1.84)	−0.96 (1.70)
Osteoporosis, BMD *t* score < -2.5 for hip or spine†	37 (23)	35 (21)	44 (28)	31 (19)	147 (23)
Male	11 (13)	17 (18)	20 (23)	18 (17)	66 (18)
Female	26 (33)	18 (27)	24 (34)	13 (23)	81 (30)
Osteopenia, *t* score < -1.0 and ≥ -2.5 for hip or spine†	73 (45)	63 (39)	68 (43)	68 (41)	272 (42)
Male	43 (51)	39 (40)	39 (44)	39 (36)	160 (42)
Female	30 (38)	24 (36)	29 (41)	29 (51)	112 (41)
Osteoporosis or osteopenia, BMD *t* score < -1.0 for hip or spine†	110 (67)	98 (60)	112 (70)	99 (60)	419 (65)
Male	54 (64)	56 (58)	59 (67)	57 (53)	226 (60)
Female	56 (72)	42 (64)	53 (75)	42 (74)	193 (71)

*Values are given as the mean (SD).
†Values are given as No. (%).

Table 3—*Change in BMD Over 3 Years in the BMD Study Population*

Changes in BMD	Placebo Group (n = 164)	SAL Group (n = 166)	FP Group (n = 163)	SFC Group (n = 165)
Hip				
Subjects in analysis, No.*	94	115	119	131
Adjusted mean change in hip BMD at 3 yr, g/cm^2	−0.026	−0.014	−0.025	−0.025
Adjusted % change in hip BMD at 3 yr	−3.1	−1.7	−2.9	−3.2
Difference between active treatment and placebo (difference in percentage change)		1.4	0.2	−0.1
95% CI		−0.4 to 3.2	−1.7 to 2.0	−1.9 to 1.7
p Value		0.134	0.853	0.885
Spine				
Subjects in analysis, No.*	94	114	117	131
Adjusted mean change in spine BMD at 3 yr, g/cm^2	0.001	0.017	−0.004	−0.003
Adjusted % change in spine BMD at 3 yr	0.0	1.5	−0.3	−0.3
Difference between active treatment and placebo (difference in percentage change)		1.5	−0.3	−0.3
95% CI		−0.2 to 3.2	−2.0 to 1.4	−1.9 to 1.3
p Value		0.084	0.685	0.711

Repeated measures analysis of covariance was adjusted for smoking status, age, gender, BMI, baseline BMD therapy, log baseline BMD, visit, log baseline BMD by visit, treatment, and treatment by visit.
*Includes all subjects with baseline and one on-treatment assessment.

Analysis of Treatment Interactions With Baseline Factors

No significant interactions of treatment with age, smoking status, percent predicted FEV_1, gender, BMI, and baseline BMD for change in BMD at the total hip or the lumbar spine were found.

Pooled Analysis

Since no differences were found between the treatment arms, overall or within specific subgroups, data from all treatment arms were combined to further assess the relationship between the change in hip BMD and several potential predictive variables. Patients receiving treatment for osteoporosis with medications known to improve BMD had significant improvements in their BMD over time, with BMD being 4% higher at 3 years compared with those patients not receiving specific BMD-improving therapy. While unadjusted data analysis suggested that a larger BMI and a higher baseline BMD resulted in smaller declines in BMD over time, these differences were not statistically significant after adjustment for differences in other baseline factors, including age and sex. No significant relationship was found between the change in BMD and smoking status, age, sex, baseline percent predicted FEV_1, SGRQ activity score, history of exacerbations, or use of OCSs or ICSs in the year prior to the study, when all baseline factors were taken into account.

Incidence of Fractures

Baseline characteristics of the overall TORCH safety population are described in Table 4, and the incidence, type, and location of bone fractures experienced during the study in the safety population are summarized in Table 5. Few patients experienced one or more fractures (range, 5.1% to 6.3%), with population risk rates and mean fracture event rates being similar across treatment groups. There were fewer nontraumatic fractures than traumatic fractures for all treatment groups. No major differences in fracture type were seen between treatment groups. Fractures of the spine were the most common nontraumatic events, whereas fractures of the hands, feet, or limbs constituted the majority of the "other" locations for traumatic fractures. Log-rank analysis showed no difference between any of the treatment groups in the time to first bone fracture or first nontraumatic or traumatic bone fractures (Table 5). Similar results were obtained by using the Cox proportional hazards model.

The number of patients with fractures in the bone density study was small. The proportion of patients with fractures and types of fractures in the bone density study population was similar to the results observed in the overall TORCH safety population.

Treatment of Osteoporosis and Osteopenia

Prior to study initiation, 7% of patients in the BMD study were receiving a bisphosphonate to treat BMD loss and 23% were receiving other BMD medications, with a higher proportion of women receiving BMD treatment compared with men (Table 1). During the study, an additional 11% of patients were started on therapy with bisphosphonate and 9% were

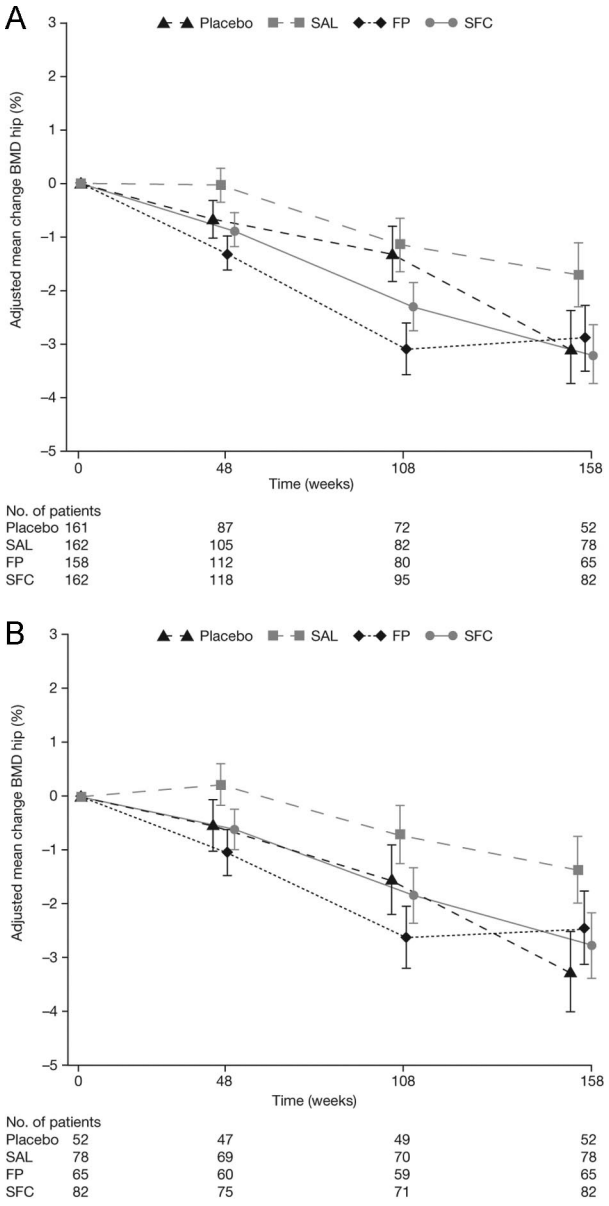

FIGURE 2. Adjusted mean percent change in BMD at the total hip (*A*) in all patients over the course of the study and (*B*) in patients who completed all 3 years of therapy. Vertical bars represent SEs.

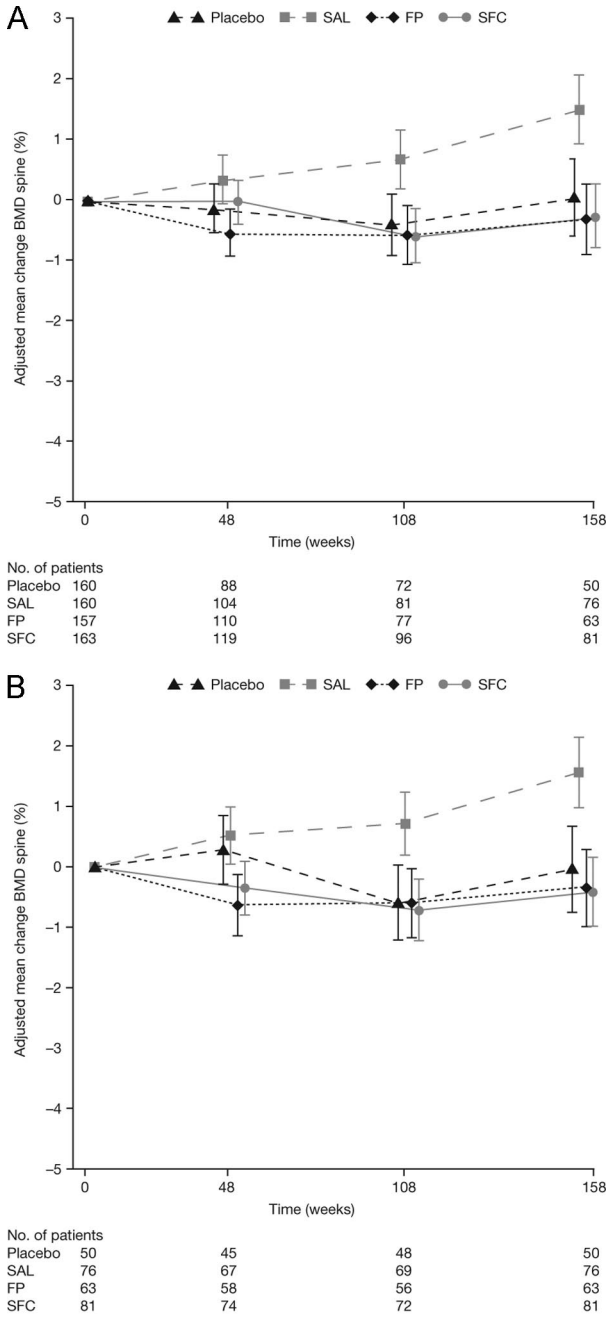

FIGURE 3. Adjusted mean percent change in BMD at the lumbar spine (*A*) in all patients over the course of the study and (*B*) in patients who completed all 3 years of therapy. Vertical bars represent SEs.

started therapy with other BMD medications, again with a higher rate of treatment in women compared with men (Table 1).

In the global safety population, only 2% of patients were receiving therapy with a bisphosphonate, whereas 8% were receiving other BMD medications prior to the start of the study. During the study, an additional 3% of patients were started on therapy with a bisphosphonate and 4% were started on therapy with other BMD medications (Table 4). Again, the proportions of women receiving bisphosphonate and other BMD medications were much greater than those for men (Table 4). No differences in bisphosphonate or other BMD therapies were found between individual treatment arms for the BMD or the safety population.

DISCUSSION

The TORCH study is the first to prospectively investigate the long-term safety of therapy with an

Table 4—*Demographic and Baseline Characteristics of the TORCH Safety Population*

Characteristics	Placebo Group (n = 1,544)	SAL Group (n = 1,542)	FP Group (n = 1,552)	SFC Group (n = 1,546)	Total (n = 6,184)
Age, yr*	65 (8)	65 (8)	65 (8)	65 (8)	65 (8)
Male gender†	1,175 (76)	1,176 (76)	1,169 (75)	1,164 (75)	4,684 (76)
Current smoker†	664 (43)	657 (43)	666 (43)	667 (43)	2,654 (43)
Baseline post-bronchodilator therapy FEV_1, L*	1.23 (0.45)	1.21 (0.43)	1.23 (0.44)	1.23 (0.46)	1.23 (0.44)
Post-bronchodilator therapy FEV_1, % predicted*	44 (12)	44 (13)	45 (13)	45 (14)	44 (13)
BMI, kg/m^2*	25.5 (5.2)	25.4 (5.2)	25.3 (5.1)	25.4 (5.3)	25.4 (5.2)
Patients having an exacerbation in past year†	887 (57)	865 (56)	897 (58)	866 (56)	3515 (57)
SGRQ activity score*‡	62.3 (20.6)	63.6 (19.5)	63.5 (20.0)	62.7 (19.9)	63.0 (19.9)
ICS received†§	815 (53)	712 (46)	739 (48)	745 (48)	3,011 (49)
OCS received†§	332 (22)	303 (20)	313 (20)	321 (21)	1,269 (21)
Bisphosphonate prior to study†	36 (2)	31 (2)	35 (2)	28 (2)	130 (2)
Male	6 (1)	8 (1)	9 (1)	5 (< 1)	28 (1)
Female	30 (8)	23 (6)	26 (7)	23 (6)	102 (7)
Other BMD medication prior to study†	112 (7)	115 (7)	113 (7)	131 (8)	471 (8)
Male	19 (2)	23 (2)	20 (2)	21 (2)	83 (2)
Female	93 (25)	92 (25)	93 (24)	110 (29)	388 (26)
Bisphosphonate started during study†	38 (2)	50 (3)	48 (3)	58 (4)	194 (3)
Male	13 (1)	18 (2)	19 (2)	28 (2)	78 (2)
Female	25 (7)	32 (9)	29 (8)	30 (8)	116 (8)
Other BMD medication started during study†	57 (4)	56 (4)	59 (4)	68 (4)	240 (4)
Male	26 (2)	24 (2)	20 (2)	31 (3)	101 (2)
Female	31 (8)	32 (9)	39 (10)	37 (10)	139 (9)

*Values are given as the mean (SD).
†Values are given as No. (%).
‡Health outcomes population as follows: placebo group, n = 1,183; SAL group, n = 1,181; FP group, n = 1,186; SFC group, n = 1,174; and total, n = 4,724.
§Exposure in the 12 months prior to study entry.

ICS in combination with an inhaled LABA and either component alone with respect to BMD in patients with COPD. There were three important findings in the study. First, the prevalence of osteoporosis and osteopenia in patients with COPD is very high, irrespective of gender. Second, no statistically or clinically significant differences in BMD or fractures were observed between placebo and any of the therapies during the 3 years of the study. Third, the rate of identification and treatment of patients with osteopenia and osteoporosis was low, even though these patients were participating in a BMD clinical trial.

COPD and BMD

The authors of the TORCH study documented a higher prevalence of osteoporosis and osteopenia at baseline than that reported by authors of epidemiologic studies evaluating patients with COPD.[2,3] In addition, in these patients with spirometrically confirmed COPD there was no association between FEV_1 impairment and BMD when adjusted by age and gender. This differs from cross-sectional studies[3,18,19] in which the authors have suggested an association between the prevalence of osteoporosis and the severity of COPD. Methodological differences may account for the differences in results, with epidemiologic studies using data obtained from population-based surveys and relying on clinical information and not on spirometry to define COPD severity. On the other hand, this could be due to the lack of patients with mild stages of COPD in our study. Importantly, adjustments for confounding factors were not performed in the epidemiologic database studies.

In the TORCH study, ICS therapy alone, or in combination with a LABA, had no significant impact on BMD over 3 years time compared with placebo.[13] Previous long-term trials investigating BMD in patients with COPD have produced conflicting results. In the Lung Health Study II,[8] the use of inhaled triamcinolone was associated with a small (2%) reduction in BMD at the femoral neck over 3 years compared with placebo. On the other hand, no significant differences in femoral or lumbar BMD were found following 3 years of therapy with inhaled budesonide compared with placebo in the European Respiratory Society Study on COPD (or EUROSCOP) trial.[12] The authors of a metaanalysis[20] of 14 studies of long-term use of ICSs in patients with COPD and asthma reported no effects of ICSs on BMD. Our data from over 3 years in a carefully defined patient population support this conclusion.

Table 5—*Bone Fractures Identified in the Overall TORCH Safety Population Over Time*

Fractures	Placebo Group (n = 1,544)	SAL Group (n = 1,542)	FP Group (n = 1,552)	SFC Group (n = 1,546)
All fractures				
Patients with fractures	57 (4)	61 (4)	65 (4)	78 (5)
Fractures, total No.	61	72	72	83
Rate of fracture per 1,000 treatment years	19	20	20	22
Probability of a fracture by 3 yr, % (HR; p value)*	5.1	5.1 (0.995; 0.98)†	5.4 (1.056; 0.77)†	6.3 (1.223; 0.25)†
Nontraumatic fractures				
Patients with fractures	20 (1)	29 (2)	21 (1)	21 (1)
Fractures, total No.	20	34	23	22
Probability of a fracture by 3 yr, % (HR; p value)*	1.8	2.5 (1.353; 0.30)†	1.7 (0.969; 0.92)†	1.7 (0.931; 0.82)†
Site of fracture‡				
Hip	0	2 (0.1)	2 (0.1)	0
Wrist	2 (0.1)	2 (0.1)	0	1 (0.1)
Spine	7 (0.5)	12 (0.8)	7 (0.5)	7 (0.5)
Rib	6 (0.4)	8 (0.5)	4 (0.3)	3 (0.2)
Other	5 (0.3)	7 (0.5)	9 (0.6)	10 (0.6)
Traumatic fractures				
Patients with fractures	39 (3)	37 (2)	45 (3)	58 (4)
Fractures, total No.	41	38	49	61
Probability of a fracture by 3 yr, % (HR)*	3.5	3.1 (0.878; 0.57)†	3.7 (1.068; 0.76)†	4.7 (1.328; 0.17)†
Site of fracture‡				
Hip	5 (0.3)	6 (0.4)	8 (0.5)	7 (0.5)
Wrist	5 (0.3)	2 (0.1)	11 (0.7)	3 (0.2)
Spine	1 (0.1)	4 (0.4)	2 (0.1)	5 (0.3)
Rib	9 (0.6)	8 (0.5)	10 (0.6)	15 (1.0)
Other	21 (1.4)	17 (1.1)	17 (1.1)	30 (1.9)

Values are given as No. (%), unless otherwise indicated. HR = hazard ratio.
*Kaplan-Meier probability.
†HR vs placebo, for time to first event (HR < 1 indicates lower probability of a fracture for the active arm).
‡Patients could have more than one fracture site.

Differences between the results in the TORCH trial and the Lung Health Study II may relate to methodology. Lung Health Study II[21] used a fluorinated corticosteroid, which is more likely to produce systemic effects. Additionally, the authors of the TORCH study reported BMD outcomes in all patients irrespective of whether the patients had completed all 3 years of follow-up, while the Lung Health Study II only reported data from those patients who completed the study. Analysis of data for completers in the TORCH trial did not change our results.

The TORCH study revealed a strong association between the change in BMD over time and the use of bisphosphonates to treat osteoporosis. Despite the high prevalence of osteoporosis and the benefit of appropriate osteoporosis therapy, only a small proportion of patients with osteoporosis were receiving bisphosphonate or other BMD medications for the treatment of osteoporosis at baseline or had therapy initiated during the course of the study. This indicates a need to raise awareness of the high prevalence and importance of osteoporosis diagnosis and treatment in patients with COPD.

COPD and Bone Fractures

Long-term SCS use is associated with an increased risk of bone fractures due to osteoporosis and reductions in BMD.[4,22] These fractures are important, with the 1-year mortality rate for hip fractures in the elderly exceeding 25%.[23]

The association between ICS use and bone fractures remains unclear. The authors of several observational and cross-sectional studies have reported an association in patients with respiratory diseases,[7] with some authors[24] suggesting a dose-response relationship, even after adjustment for SCS usage. However, the authors of other studies[11,25] have not confirmed this relationship, especially when corrected for the use of SCSs or other comorbid conditions. Indeed, a systematic review[26] of studies involving patients with asthma or COPD revealed no evidence for any effect on vertebral fracture from ICSs administered at conventional doses for 2 or 3 years.

The data from the TORCH study revealed no significant increase in the incidence of total fractures, nontraumatic fractures, or nonvertebral fractures with ICS, either alone or in combination with a

LABA. These results are in line with those of other prospective trials[27–29] in which the authors have compared therapy with an ICS, with or without a LABA, with placebo. Nevertheless, in a population such as that recruited for the TORCH trial, the risk of fracture may relate more to the incidence of trauma than to alterations in BMD.[30]

Potential Study Limitations

Our BMD study was specifically powered to assess changes in BMD over time based on the Lung Health Study II.[8] Since only 43% of our subjects completed all study procedures, study dropouts could have potentially limited our power to detect significant differences in BMD over the 3 years. It is also possible that different withdrawal rates in the study treatment arms could have impacted our results. However, patients dropped out of the study for reasons other than bone-related problems, making it less likely that a therapy-induced bone problem accounted for our results. In addition, analysis adjusting for factors that might influence the results (*eg*, age or disease severity) and analysis of those subjects who completed the study suggest that the study dropouts might not have changed the results. Another potential limitation could be the use of investigator-reported adverse events as the identifier for fractures in the safety population. Indeed, it is likely that vertebral fractures were underreported throughout the study as no systematic radiologic assessments were performed and subclinical vertebral fractures are common. Attempts were made to minimize this problem by identifying fractures as adverse events of special interest in the study and obtaining detailed information about fractures on a regular basis. Although absolute numbers of vertebral fractures would likely have been higher for all treatment arms if more detailed surveillance radiograph monitoring were performed, the lack of differences in fractures between treatment arms in the study is likely to have not changed. It is acknowledged that the extrapolation of data from the BMD study population in the United States to the international population for the TORCH study may be limited by differences between these populations, including a higher percentage of women and a greater use of osteoporosis therapies in the BMD study population. Nevertheless, similarities in the majority of the demographic features and in the bone study population and overall TORCH study safety cohort (Table 1) suggest that these data are relevant to the larger population. Finally, our data are for only 3 years of therapy. It is possible that BMD changes could be observed if evaluated over a longer time period.

Conclusions

We observed a high prevalence of osteopenia and osteoporosis in men and women with COPD. It is important to remain aware of these potentially treatable conditions. Although safety concerns remain paramount in the care of patients with COPD, the results of the TORCH study are reassuring as we did not detect that either SFC or its individual components had a significant effect on BMD compared with placebo over 3 years.

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