Denosumab and teriparatide transitions in postmenopausal osteoporosis (the DATA-Switch study): extension of a randomised controlled trial

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Summary

Background Unlike most chronic diseases, osteoporosis treatments are generally limited to a single drug at a fixed dose and frequency. Nonetheless, no approved therapy is able to restore skeletal integrity in most osteoporotic patients and the long-term use of osteoporosis drugs is controversial. Thus, many patients are treated with the sequential use of two or more therapies. The DATA study showed that combined teriparatide and denosumab increased bone mineral density more than either drug alone. Discontinuing teriparatide and denosumab, however, results in rapidly declining bone mineral density. In this DATA-Switch study, we aimed to assess the changes in bone mineral density in postmenopausal osteoporotic women who transitioned between treatments.

Methods This randomised controlled trial (DATA-Switch) is a preplanned extension of the denosumab and teriparatide administration study (DATA), in which 94 postmenopausal osteoporotic women were randomly assigned to receive 24 months of teriparatide (20 mg daily), denosumab (60 mg every 6 months), or both drugs. In DATA-Switch, women originally assigned to teriparatide received denosumab (teriparatide to denosumab group), those originally assigned to denosumab received teriparatide (denosumab to teriparatide group), and those originally assigned to both received an additional 24 months of denosumab alone (combination to denosumab group). Bone mineral density at the spine, hip, and wrist were measured 6 months, 12 months, 18 months, and 24 months after the drug transitions as were biochemical markers of bone turnover. The primary endpoint was the percent change in posterior-anterior spine bone mineral density over 4 years. Between-group changes were assessed by one-way analysis of variance in our modified intention-to-treat population. This study is registered with ClinicalTrials.gov, number NCT00926380.

Findings Between Sept 27, 2011, and Jan 28, 2013, eligible women from the DATA study were enrolled into DATA-Switch. Of 83 potential enrollees from the DATA study, 77 completed at least one post-baseline visit. After 48 months, the primary outcome of mean spine bone mineral density increased by 18·3% (95% CI 14·9–21·8) in 27 women in the teriparatide to denosumab group, 14·0% (10·9–17·2) in 27 women the denosumab to teriparatide group, and 16·0% (14·0–18·0) in 23 women in the combination to denosumab group, although this increase did not differ significantly between groups (for between-group comparisons, p=0·13 for the teriparatide to denosumab group *vs* the denosumab to teriparatide group, p=0·30 for the teriparatide to denosumab group *vs* the combination to denosumab group, and p=0·41 for the denosumab to teriparatide group *vs* the combination to denosumab group). For the bone mineral density secondary outcomes, total hip bone mineral density increased more in the teriparatide to denosumab group (6·6% [95% CI 5·3–7·9]) than in the denosumab to teriparatide group (2·8% [1·3–4·2], p=0·0002), but had the greatest increase in the combination to denosumab group (8·6% [7·1–10·0]; p=0·0446 *vs* the teriparatide to denosumab group, p<0·0001 *vs* the denosumab to teriparatide group). Similarly, femoral neck bone mineral density increased more in the teriparatide to denosumab group (8·3% [95% CI 6·1–10·5]) and the combination to denosumab group (9·1% [6·1–12·0]) than in the denosumab to teriparatide group (4·9% [2·2–7·5]; p=0·0447 for teriparatide to denosumab *vs* denosumab to teriparatide, p=0·0336 for combination to denosumab *vs* denosumab to teriparatide). Differences between the combination to denosumab group and the teriparatide to denosumab group did not differ significantly (p=0·67). After 48 months, radius bone mineral density was unchanged in the teriparatide to denosumab group (0·0% [95% CI –1·3 to 1·4]), whereas it decreased by –1·8% (–5·0 to 1·3) in the denosumab to teriparatide group, and increased by 2·8% (1·2–4·4) in the combination to denosumab group (p=0·0075 for the teriparatide to denosumab group *vs* the combination to denosumab group; p=0·0099 for the denosumab to teriparatide group *vs* the combination to denosumab group). One participant in the denosumab to teriparatide group had nephrolithiasis, classified as being possibly related to treatment.

Interpretation In postmenopausal osteoporotic women switching from teriparatide to denosumab, bone mineral density continued to increase, whereas switching from denosumab to teriparatide results in progressive or transient bone loss. These results should be considered when choosing the initial and subsequent management of postmenopausal osteoporotic patients.

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Research in context

Evidence before this study

We searched PubMed with the terms "anabolic", antiresorptive", "osteoporosis", "combination therapy", "sequential therapy", "denosumab", "bisphosphonates", and "teriparatide". No parameters were set for language or date of publication. We reviewed all randomised controlled trials and accompanying editorials, when available, and animal studies published in peer-reviewed journals. Several high-quality randomised controlled trials have been done addressing the issue of sequential anabolic and bisphosphonate osteoporosis therapy, but none have addressed the sequential use of denosumab and teriparatide.

Added value of this study

In our current study, we report that in osteoporotic women treated with denosumab for 2 years, switching to teriparatide resulted in transient decreases in bone mineral density of the hip and spine, and progressive bone loss at the distal radius. Conversely, we show that the initial use of teriparatide or combined teriparatide plus denosumab followed by denosumab results in the largest 4-year increases in spine and hip bone mineral density reported in any clinical trial so far. As the first study addressing the issue of sequential therapy with denosumab and teriparatide, these results provide a framework by which physicians can make informed decisions when initiating osteoporosis therapy or transitioning from one drug to another.

Implications of all the evidence

These results, along with previous studies performed with other antiresorptive drugs, indicate that physicians should strongly consider the initial use of anabolic therapy (or combined denosumab and teriparatide) in patients with established osteoporosis. Moreover, these findings provide the scientific rationale for the support of this approach by those responsible for the allocation of health-care resources, especially in patients with severe disease. Future research should focus on the efficacy of these interventions in fracture reduction and the cost-effectiveness of combined and sequential use of denosumab and teriparatide in diverse populations.

Introduction

Osteoporotic fractures, more than 75% of which occur in women, are a major cause of death, disability, and worldwide health-care expenditure.[1,2] Unlike most chronic diseases, approved treatments for osteoporosis are generally limited to the use of one drug at a fixed dose and dosing frequency. Although the therapeutic options in osteoporosis treatment have expanded greatly in the past two decades, no currently approved therapy is able to restore skeletal integrity in most patients with established disease.

Current medications approved to treat postmenopausal osteoporosis can be separated into two categories. The most commonly used drugs are the antiresorptive drugs, a class that includes the nitrogen-containing bisphosphonates and the receptor activator of nuclear factor κB ligand (RANKL) inhibitor, denosumab. Less commonly used and generally reserved for patients with severe and established osteoporosis, is the anabolic drug teriparatide (PTH-1-34). In view of the fact that current recommendations question the long-term use of potent antiresorptive osteoporotic drugs and that use of teriparatide is limited to 18–24 months by regulatory bodies,[3,4] the treatment of patients with established or severe osteoporosis often requires the sequential use of several drugs.

Although denosumab and teriparatide are two of the most potent therapies currently available to physicians,[5] both are associated with abrupt and rapid bone loss when discontinued.[6,7] Whether switching from denosumab to teriparatide or from teriparatide to denosumab can prevent this decline in bone mineral density or further increase bone mass is unknown. In the denosumab and teriparatide administration study of postmenopausal osteoporotic women (DATA), we reported that concurrent denosumab and teriparatide administration increases spine and hip bone mineral density more than either drug alone and to a greater degree than has been achieved with any currently available drug.[8,9] Less positive results have been reported for combinations of teriparatide and bisphosphonates.[10–12] We now test the hypothesis that the transition from teriparatide or combined teriparatide plus denosumab to denosumab monotherapy and the transition from denosumab to teriparatide monotherapy will further increase bone mineral density in postmenopausal osteoporotic women. In so doing, we aimed to provide physicians with the evidence necessary to formulate a rational approach to the sequential and combined use of these medications.

Methods

Study design and participants

In the prospectively planned DATA-Switch study, postmenopausal women aged 45 years or older were recruited through targeted mailings, advertisements, and physician referrals. Participants were required to be at least 36 months beyond their last menses (or 36 months after hysterectomy with a concentration of follicle-stimulating hormone in serum of 40 IU/L or higher) and at high fracture risk. High fracture risk was defined as a bone mineral density T score ≤–2·5 at the spine, hip, or femoral neck; T score ≤–2·0 with at least one bone mineral density independent risk factor (fracture after age 50 years, parental hip fracture after age 50 years, previous hyperthyroidism, inability to rise from a chair with arms elevated, or current smoking),[13] or T score ≤–1·0 with a history of a fragility fracture. Participants were excluded if they had evidence of hyperparathyroidism, vitamin D deficiency (serum level <20 ng/mL), other congenital or acquired bone disease, history of malignancy (with the

exception of non-melanoma skin cancer), history of ionising radiation therapy, significant cardiopulmonary, liver, or renal disease, major psychiatric disease, or excessive alcohol intake. Participants were also excluded if they had ever taken parenteral bisphosphonates, teriparatide, or strontium ranelate. Additionally, participants were excluded if they had taken glucocorticoids or oral bisphosphonates within 6 months of enrolment or if they had taken oestrogen, selective oestrogen receptor modulators, or calcitonin within 3 months of enrolment. All provided written informed consent. The study was approved by the Partners Healthcare Institutional Review Board.

Randomisation and masking

In the DATA study, patients were originally randomly assigned (1:1:1) to receive teriparatide, denosumab, or both. Randomisation was done in random blocks of three or six created with a computer algorithm. Before randomisation, women were stratified for age (younger than 65 years *vs* 65 years or older) and previous bisphosphonate use. Physicians interpreting bone mineral density assessments and assessing all serum markers were masked to treatment group.

Procedures

In the original DATA study, participants received teriparatide 20 µg subcutaneously daily (Forteo, Eli Lilly Inc, Indianapolis, IN, USA), denosumab 60 mg subcutaneously every 6 months (Prolia, Amgen Inc, Thousand Oaks, CA, USA), or both drugs. Participants who completed the 24-month trial were then offered enrolment in the DATA-Switch study as long they continued to meet one of the following three criteria: 1) dual x-ray absorptiometry spine or hip T score <–1·5; 2) dual x-ray absorptiometry spine or hip T score <–1·0 plus one or more of the following risk factors for fracture: fracture after age 50 years, parental hip fracture after age 50 years, previous hyperthyroidism, inability to rise from a chair with one's arms elevated, current tobacco smoker; or 3) history of more than one adult low-trauma fracture with any bone mineral density (low-trauma fracture is defined as a fracture after no trauma or fracture after falling <6 inches when stationary or moving slower than a run).

In DATA-Switch, women originally assigned to 24 months of teriparatide received 24 months of denosumab, whereas those participants who were originally randomised to 24 months of denosumab received 24 months of teriparatide. Participants who originally received both drugs, received an additional 24 months of denosumab alone (figure 1). After the drug transition, participants were seen 1 month later (month 25), and then again at months 30, 36, 42, and 48. At the 25-month visit, participants underwent blood sampling only, whereas at all the other visits blood sampling and dual energy x-ray absorptiometry were done. All blood sampling was done before teriparatide administration (ie, 24 h after the last teriparatide dose) and physicians interpreting bone mineral density assessments were masked to treatment group. All participants were given calcium carbonate and vitamin D supplements if needed to achieve a total daily intake of 1200 mg of elemental calcium and to maintain a serum 25-hydroxyvitamin D level of at least 20 ng/mL. Adherence to teriparatide was assessed by medication diary.

Areal bone mineral density of the posterior-anterior lumbar spine, total hip, femoral neck, and distal 1/3 radius shaft was measured by dual x-ray absorptiometry with a Hologic QDR 4500A densitometer (Hologic, Waltham, MA, USA). All scans of an individual participant were done on the same densitometer. Quality control measurements were done daily with a Hologic anthropomorphic spine phantom. Our standard deviations of in-vivo same-day reproducibility are 0·005 g/cm², 0·006 g/cm², and 0·007 g/cm² for posterior-anterior spine, total hip, and femoral neck bone mineral density measurements, respectively.

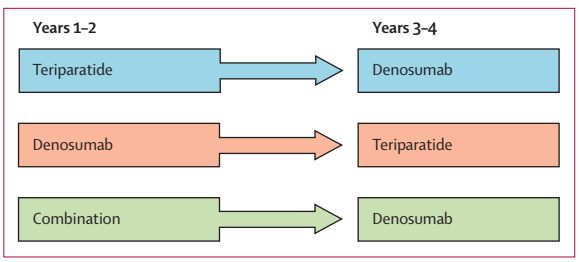

Figure 1: **DATA-Switch study design**

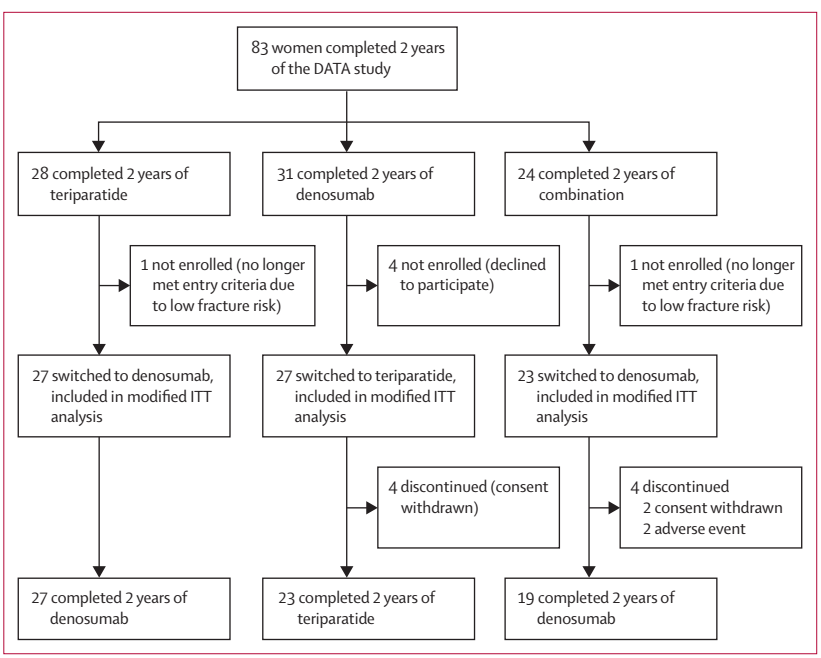

Figure 2: **Trial profile**
ITT=intention to treat.

Fasting morning blood samples (collected 24 h after last injection if taking teriparatide) were obtained at every visit. Serum osteocalcin, a marker of bone formation, was measured via electrochemiluminescent immunoassay (Meso Scale Discovery, Rockville, MD, USA) with interassay and intra-assay coefficients of variation of 10% and 8%, respectively. Serum β-C-terminal telopeptide of type I collagen (C-telopeptide), a marker of bone resorption, was measured via a fully automated electrochemiluminescent immunoassay (Roche Diagnostics, Indianapolis, IN, USA) with an interassay coefficient of variation of less than 5%. The limit of detection for serum C-telopeptide was 0·01 ng/mL and the reportable range was 0·01–5·99 ng/mL. Biochemical markers of bone turnover were only measured in participants completing 48 months of therapy. For every marker, all blood samples from a participant were analysed together in the same assay run.

Study physicians assessed the safety and tolerability of the medications at each visit. At the time of reporting, a study physician also determined whether each adverse event was related to the study drug.

Outcomes

The predetermined primary endpoint was the percent change in posterior-anterior spine bone mineral density over 4 years. Secondary endpoints included the percent change in total hip, femoral neck, and radius shaft bone mineral density and the percent change in serum osteocalcin and C-telopeptide concentrations.

Statistical analysis

For the **WHO Fracture Risk Assessment Tool** see https://www.shef.ac.uk/FRAX/index.aspx

Sample size considerations were reported previously for the 94 participants enrolled in the DATA study.[9] Between-group baseline characteristics of DATA-Switch participants were compared by one-way analysis of variance (ANOVA). For bone mineral density, we used a modified intention-to-treat analysis, which included all data from participants completing at least one additional bone density measurement after switching therapies (month 30). Between-group differences in the mean change in bone mineral density from baseline to 48 months were examined by one-way ANOVA and subsequent between-group differences confirmed by independent samples *t* test. Between-group differences in the percent change in bone mineral density from 24 months to 48 months were also examined by one-way ANOVA and if significant by subsequent between-group differences confirmed by independent samples *t* test. Biochemical markers of bone turnover measurements were restricted to participants who completed all visits (valid completers). Because the changes in these markers were not normally distributed, the medians and 25th–75th percentiles were used for data summary and the between-group differences in each marker at each timepoint was examined by Wilcoxon's rank sum test. Two-sided $p \leq 0 \cdot 05$ was considered statistically significant. Statistical analysis was done with SAS version 9.2.

This study is registered with ClinicalTrials.gov, number NCT00926380.

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or the writing of the report. BZL had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Sept 27, 2011, and Jan 28, 2013, 77 participants who completed the DATA study were enrolled into DATA-Switch, of whom 27 women originally assigned to 24 months of teriparatide received 24 months of denosumab, 27 women originally randomised to 24 months of denosumab received 24 months of teriparatide, and 23 women who originally received both drugs received an additional 24 months of denosumab alone. 77 participants completed at least one post-baseline visit (modified intention-to-treat population) and 69 completed all visits through to 48 months (figure 2).

Baseline demographic and clinical characteristics did not differ significantly between the three treatment groups (table 1). Additionally, no significant differences in the baseline characteristics of women in the DATA-Switch cohort compared with those in the original DATA population (either within each group or the population as a whole) were noted (data not shown). The entry criteria resulted in mean 10-year fracture risks (based on the WHO Fracture Risk Assessment Tool) of 14·4% and 2·6% for major osteoporotic fracture and hip fracture, respectively. 59% of participants had at least one T score of ≤–2·5.

	Teriparatide to denosumab (N=27)	Denosumab to teriparatide (N=27)	Combination to denosumab (N=23)
Age (years)	66·1 (7·9)	65·1 (6·2)	65·3 (8·0)
Body-mass index (kg/m²)	25·5 (3·7)	23·8 (4·1)	25·9 (5·2)
White, non-Hispanic	27 (100%)	24 (89%)	20 (87%)
Clinical fracture at age >45 years (%)	14 (52%)	10 (37%)	8 (35%)
Previous oral bisphosphonate use (%)	12 (44%)	9 (33%)	9 (39%)
Duration of use (months)	45 (23)	45 (26)	25 (21)
Time since discontinuation (months)	27 (20)	35 (24)	41 (18)
Serum 25-hydroxyvitamin D concentration (ng/mL)	32·2 (8·5)	35·9 (11·0)	34·8 (12·8)
Osteocalcin (ng/mL)	46·3 (26·1)	43·9 (20·2)	55·0 (32·6)
C-terminal telopeptide (ng/mL)	0·34 (0·15)	0·41 (0·22)	0·44 (0·17)
DXA bone mineral density (g/cm²)			
Posterior-anterior spine	0·815 (0·109)	0·863 (0·096)	0·847 (0·130)
Femoral neck	0·642 (0·064)	0·639 (0·090)	0·638 (0·054)
Total hip	0·756 (0·072)	0·759 (0·102)	0·750 (0·068)
One-third radius	0·618 (0·072)	0·608 (0·088)	0·614 (0·072)

Data are mean (SD), unless otherwise noted. DXA=dual x-ray absorptiometry.

Table 1: **Baseline demographic and clinical characteristics**

As reported previously, after 24 months of the originally assigned drugs, mean lumbar spine bone mineral density had increased significantly in all treatment groups relative to baseline with the greatest increases in women treated with both drugs together.[8] In women switching from teriparatide to denosumab, mean (SD) lumbar spine bone mineral density continued to increase resulting in 48-month increases of 18·3% (8·5). In women switching from combination therapy to denosumab, the net 48-month increase in bone mineral density was 16·0% (4·1; figure 3, table 2). Conversely, in women who after 24 months of denosumab were treated with 24-month teriparatide, lumbar spine bone mineral density decreased over the first 6 months followed by increases resulting in a mean net 48-month increase of 14·0% (6·7). There was no significant difference in the 48-month increase in lumbar spine bone mineral density between any of the treatment groups (primary endpoint): p=0·13 for the teriparatide to denosumab group versus the denosumab to teriparatide group, p=0·30 for the teriparatide to denosumab group versus the combination to denosumab group, and p=0·41 for the denosumab to teriparatide group versus the combination to denosumab group. Bone mineral density increased more after the treatment transition (between months 24 and 48) in the teriparatide to denosumab group (8·6 [SD 5·0]) than in either the denosumab to teriparatide group (4·8 [5·6]; between group p=0·0203) or the combination to denosumab group (3·4 [3·5]; between-group p=0·0005).

Also as reported previously, after 24 months of the originally assigned therapy, mean total hip bone mineral density increased significantly in all treatment groups relative to baseline with the greatest increases in women treated with both drugs.[8] In women switching from teriparatide to denosumab, total hip bone mineral density continued to increase, resulting in 48-month increases of 6·6% (SD 3·3). In women switching from combination therapy to denosumab, total hip bone mineral density also increased. resulting in 48-month net increases of 8·6% (SD 3·0). Conversely, in women who were treated with 24 months of denosumab followed by 24 months of teriparatide, total hip bone mineral density progressively decreased from 24 months to 36 months before beginning to increase between 36 months and 42 months. At the conclusion of DATA-Switch (month 48), total hip bone mineral density had increased more in the combination to denosumab group than in either the teriparatide to denosumab group (between-group

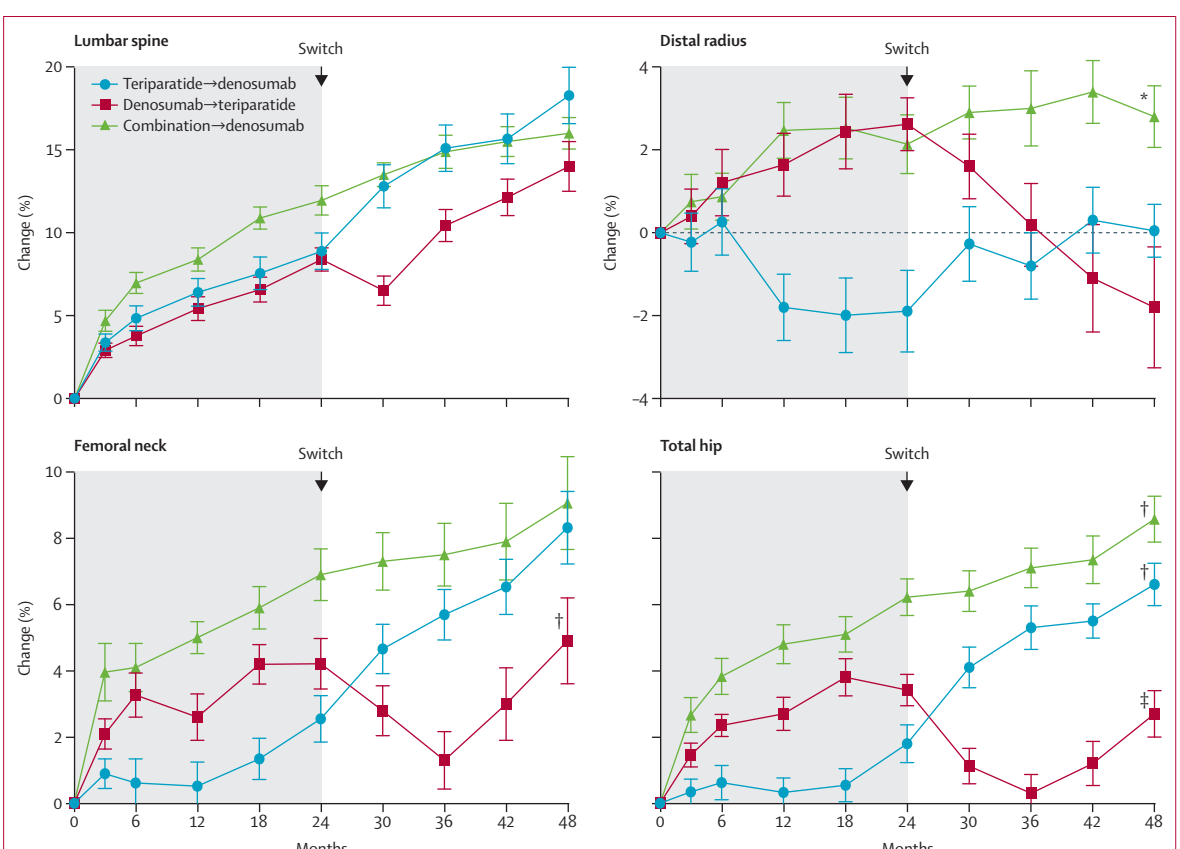

Figure 3: **Mean percent change (SEM; error bars) in bone mineral density from baseline to 48 months in the lumbar spine, 1/3 distal radius, femoral neck, and total hip**

*p<0·01 versus both other groups. †p<0·05 versus both other groups. ‡p<0·0005 versus both other groups.

p=0·0446) or the denosumab to teriparatide group (between-group p<0·0001). At the conclusion of DATA-Switch, total hip bone mineral density also increased more in the teriparatide to denosumab group than in the denosumab to teriparatide group (between-group p=0·0002). When the analysis was restricted to changes occurring after the treatment transitions (months 24–48), total hip bone mineral density increased more in the teriparatide to denosumab group (4·7% [SD 2·6]) than in both the combination to denosumab group (2·2% [1·8]; p=0·0008) and the denosumab to teriparatide group (–0·7% [3·1]; p<0·0001).

Changes in femoral neck bone mineral density after 24 months of the originally assigned therapy showed a pattern similar to total hip, with similar transient bone loss occurring between months 24–36 in women treated with denosumab followed by teriparatide. From 0–48 months, femoral neck bone mineral density increased by 8·3% (SD 5·6) in the teriparatide to denosumab group, 4·9% (6·0) in the denosumab to teriparatide group, and 9·1% (6·1) in the combination to denosumab group (denosumab to teriparatide *vs* teriparatide to denosumab p=0·0447; denosumab to teriparatide *vs* combination to denosumab p=0·0336). However, when the analysis was restricted to changes occurring after the treatment transitions (months 24–48), the increases in the teriparatide to denosumab group

	Teriparatide to denosumab group	Denosumab to teriparatide group	Combination to denosumab group
Percent change 0–48 months			
Lumbar spine	18·3 (14·9 to 21·8)	14·0 (10·9 to 17·2)	16·0 (14·0 to 18·0)
Femoral neck	8·3 (6·1 to 10·5)	4·9 (2·2 to 7·5)	9·1 (6·1 to 12·0)
Total hip	6·6 (5·3 to 7·9)	2·8 (1·3 to 4·2)	8·6 (7·1 to 10·0)
Distal radius	0·0 (–1·3 to 1·4)	–1·8 (–5·0 to 1·3)	2·8 (1·2 to 4·4)
Percent change 24–48 months			
Lumbar spine	8·6 (6·6 to 10·6)	4·8 (2·2 to 7·4)	3·4 (1·7 to 5·2)
Femoral neck	5·6 (3·9 to 7·2)	1·2 (–1·0 to 3·4)	2·1 (–0·2 to 4·5)
Total hip	4·7 (3·7 to 5·8)	–0·7 (–2·0 to 0·7)	2·2 (1·3 to 3·1)
Distal radius	2·3 (0·5 to 4·1)	–5·0 (–7·5 to –2·6)	0·5 (–0·6 to 1·6)

Data are % change (95% CIs).

Table 2: **Mean change in bone mineral density between 0–48 months and 24–48 months**

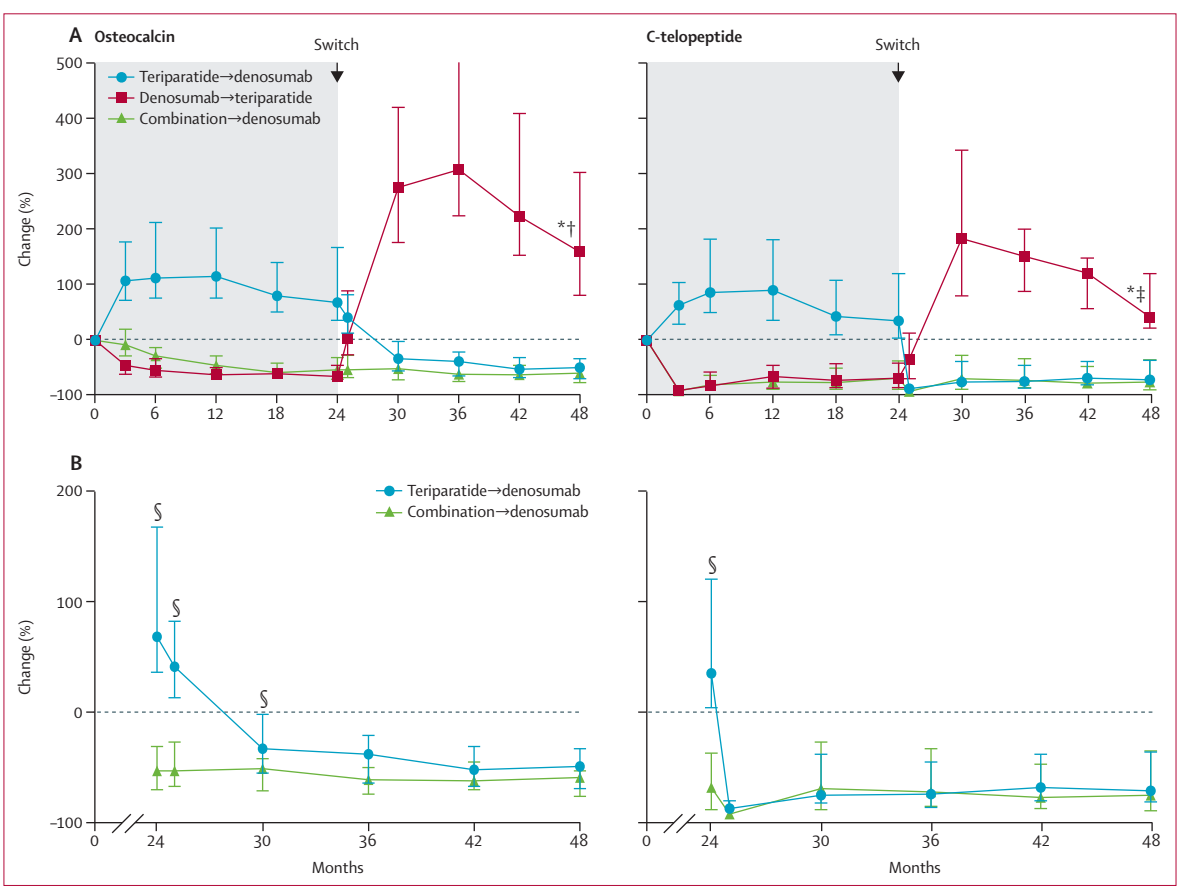

Figure 4: **Median percent change (IQR; error bars) in osteocalcin and C-telopeptide from baseline to 48 months (A) and baseline to 24–48 months in the teriparatide to denosumab group and combination to denosumab group (B)**

*p<0·0001 versus combination to denosumab at months 24, 25, 30, 36, 42, and 48. †p<0·0001 versus teriparatide to denosumab at months 24, 30, 36, 42, and 48; p=0·41 at month 25. ‡p<0·0001 versus teriparatide to denosumab at months 25, 30, 36, 42, and 48; p=0·36 at month 24. §p<0·05 compared with combination to denosumab at the indicated timepoints.

(5·6% [SD 4·5]) were larger than in either the combination to denosumab group (2·1% [4·9]; p=0·0156) or the denosumab to teriparatide group (1·2% [4·9]; p=0·0019).

After 24 months of the originally assigned therapy, mean bone mineral density at the distal radius had increased in the denosumab and combination groups, whereas it decreased in the teriparatide group.[8] When patients originally treated with denosumab switched to teriparatide, radius bone mineral density progressively decreased resulting in net 0–48-month decrease of –1·8% (SD 5·9). At the conclusion of DATA-Switch, radius shaft bone mineral density had increased by 2·8% (SD 3·2) in the combination to denosumab group and reverted to the original baseline in the teriparatide to denosumab group (0·0% [2·9]). The 0–48-month bone mineral density increases at the distal 1/3 radius in the combination to denosumab group were significantly larger than those either in the teriparatide to denosumab group (p=0·0075) or the denosumab to teriparatide group (p=0·0099).

In women treated with denosumab followed by teriparatide, median osteocalcin increased by 275% (IQR 176–410) above the original baseline after 6 months of teriparatide (month 30) and remained 159% (81–302) over the original baseline even after 24 months of teriparatide (month 48; figure 4A, B). In these same women, C-telopeptide concentrations increased by 183% (IQR 80–343) at month 30 and were 42% (22–120) above baseline at month 48. In women treated with teriparatide followed by denosumab, the changes in bone resorption and formation showed different patterns. Bone resorption (C-telopeptide) was maximally suppressed after 1 month of denosumab, whereas bone formation (osteocalcin) was not maximally suppressed until 12–24 months of denosumab treatment. In women treated with combination therapy followed by denosumab monotherapy, however, both markers were maximally suppressed at all post-switch timepoints. When comparing women in the teriparatide to denosumab group with women in the combination to denosumab group (both of which are receiving the same treatment from month 24–48), serum osteocalcin was significantly higher in those switching from teriparatide monotherapy to denosumab monotherapy than in those switching from combination therapy to denosumab monotherapy at 1 months and 6 months after the transition (months 25 and 30; p<0·0001 at month 25 and p<0·0023 at month 30). Conversely, C-telopeptide in these two groups did not differ at any timepoint after the treatment transitions.

Significant hypercalcaemia (blood calcium >10·8 mg/dL confirmed on repeat testing) was identified in one patient during months 24–48 (denosumab to teriparatide group). Serious adverse events were reported in six participants in the teriparatide to denosumab group (ductal carcinoma in situ of the breast, syncope, chronic obstructive pulmonary disease exacerbation, elective cervical laminectomy, fundoplication procedure, and non-ST elevation myocardial infarction), four participants in the denosumab to teriparatide group (appendicitis, laryngitis or pharyngitis, nephrolithiasis without hypercalcaemia, and anaemia due to a gastric ulcer), and three participants in the combination to denosumab group (breast cancer, atrial fibrillation, and atrial fibrillation with stroke). With the exception of the patient with nephrolithiasis, which was classified as possibly related to treatment (teriparatide), the other serious adverse events were classified as unrelated to therapy by the study investigators and an independent safety monitoring board.

Discussion

In this study, we have shown that in postmenopausal osteoporosis, switching therapy from teriparatide to denosumab further increases bone mineral density at all measured sites, whereas switching therapy from denosumab to teriparatide results in transient bone loss at the hip and spine and progressive bone loss at the radius shaft. Additionally, we have shown that 24 months of combined therapy followed by 24 months of denosumab alone is associated with largest cumulative bone mineral density increases at the hip and radius, increases that are greater than have been reported with any currently available therapy taken for a similar duration.[14–17]

These findings have several important clinical ramifications. First, this study shows the importance of the order of anabolic versus antiresorptive therapy with denosumab. The bone loss that occurs in patients switching from denosumab to teriparatide was an unexpected finding. Studies investigating the effects of teriparatide after bisphosphonates report further increases in bone mineral density, although generally smaller increases than those observed when teriparatide is given to a patient who has not received previous bisphosphonate therapy.[18–23] It was postulated that because bisphosphonates are present in the bone matrix for years after administration,[24] teriparatide-induced increases in bone turnover were being inhibited in a manner similar to that noted when bisphosphonates are given concurrently with teriparatide or parathyroid hormone.[10–12] If this hypothesis had been correct, one might have expected that the administration of teriparatide after denosumab would not be associated with this blunting and would allow for the full anabolic effect of teriparatide to proceed. Indeed, our data do show that there is no blunting of teriparatide-induced stimulation of bone turnover after denosumab therapy. By contrast, bone resorption and formation increased more after switching from denosumab to teriparatide than when the DATA patients were treated with teriparatide de novo. Bone resorption, as measured by median C-telopeptide, increased by 183% during the original baseline 6 months after switching from denosumab to teriparatide and bone formation, as measured by median osteocalcin, increased by 275%. Notably, this degree of stimulation of bone metabolism is much greater than in the same women

treated with teriparatide de novo, who in the DATA study had a 6-month median C-telopeptide increase of 86% and a 6-month median osteocalcin increase of 112% (figure 4B). It is also significantly greater than the magnitude of the reported so-called overshoot in bone turnover noted in patients stopping denosumab after 24 months of treatment.[7]

The mechanism by which teriparatide exerts such a large effect on bone metabolism in patients discontinuing denosumab is unknown, but could relate to teriparatide stimulating a large pool of dormant osteoclast precursors in patients in whom RANKL inhibition has been sustained for 2 years.

The substantial increase in bone mineral density in women switching from teriparatide to denosumab is consistent with studies reporting that bisphosphonates further increase bone mineral density when given after parathyroid hormone or teriparatide.[25,26] In this study, it should be noted that the increases in bone mineral density in women treated with teriparatide monotherapy followed by denosumab were even greater than in those treated with combination teriparatide plus denosumab therapy followed by denosumab alone. The mechanism underlying the greater 24–48-month increases in the teriparatide to denosumab group could relate to the changed relation between bone formation and bone resorption in these patients. Specifically, bone resorption, as measured by C-telopeptide, is more quickly suppressed after transitioning from teriparatide to denosumab than is bone formation, as measured by osteocalcin. This discrepancy probably allows for a several month period of relative unlinking of bone formation and resorption, which favours the accrual of bone mass. It is, notably, a very similar unlinking that we hypothesised mechanistically explains the larger increases in bone mineral density achieved by combination teriparatide–denosumab therapy in the initial 12 months of osteoporosis treatment.[9] It is also notable that despite the so-called catch up in bone mineral density gains achieved in women transitioning from teriparatide to denosumab, women treated initially with combined therapy followed by denosumab had the most favourable 48-month bone mineral density changes at the total hip and distal radius, the two measured sites with the highest proportion of cortical bone. In view of the importance of cortical bone mass in maintaining skeletal integrity, the noted persistent benefit at these anatomic sites would be expected to confer significantly greater bone strength to these patients.[27,28] Moreover, although studies undertaken in different populations cannot be precisely compared, it is notable that the total bone mineral density increases achieved in both the combination to denosumab and teriparatide to denosumab groups are larger than those noted with any one drug given for a similar period of treatment. Specifically, the reported 4-year bone mineral density gains with either denosumab or zoledronic acid are less than 12% at the spine and less than 6% at the femoral neck.[16,17]

Our study has several limitations. First, the size of the study precludes an assessment of the relative safety or antifracture efficacy of the three assigned treatment regimens. Bone mineral density, however, has proven to be a reliable, although imperfect, predictor of antifracture efficacy in patients treated with osteoporosis drugs, including denosumab and teriparatide.[29,30] Additionally, the specific clinical impact of the transient bone loss that occurs in women switching from denosumab to teriparatide cannot be precisely estimated. It is notable, however, that several studies have reported that both elevated markers of bone turnover and increased rates of bone loss are associated with increased fracture risk.[31–35] Consistent with these studies, it has also been reported that postmenopausal women who discontinue oestrogen (and hence have increased bone turnover) have an increased risk of hip fracture than do women who never used oestrogen.[36] Thus, even without specific fracture data, we feel that the practising physician must consider these factors before recommending drug changes or initiating therapy in their osteoporotic patients.

The open-label design is a potential limitation. The potential for bias is limited, however, in that the physicians interpreting the dual x-ray absorptiometry measurements and the laboratory who did the bone marker assays were masked to treatment assignment. Additionally, the women who entered the DATA-Switch were only a subset of those originally randomised in the parent DATA study. That said, our retention in this 24-month extension of a 24-month randomised controlled trial is quite strong and no significant differences were noted in any demographic or clinical parameter between those participants who participated in DATA-Switch and the original DATA cohort. Finally, our study population is at somewhat lower risk of fracture than those for whom this type of intensive therapy might be recommended and thus should be considered as a proof-of-concept study, supporting a more definitive trial with a fracture-reduction endpoint.

In postmenopausal osteoporosis, the order in which denosumab and teriparatide are used has a significant effect on overall treatment effectiveness. Specifically, teriparatide does not adequately prevent bone loss after denosumab, whereas denosumab stabilises and further increases bone mineral density when used after teriparatide or combination therapy. Furthermore, the largest increases in bone mineral density at the hip and wrist, and the largest bone mineral density increases possible in any clinical context, are achieved in women treated with 24 months of combined teriparatide plus denosumab followed by 24 months of denosumab monotherapy. These results should influence the approach to the initial and sequential treatment of osteoporotic women, particularly those with established disease who are at an acutely high risk of fragility fracture.

Contributors
BZL, JNT, AVU, S-AMB-B, RMN, and HL conceived and designed the study. BZL, JNT, AVU, S-AMB-B, HL, and PMW collected, analysed, and interpreted the data. BZL, JNT, and PMW drafted the report. BZL, JNT, AVU, S-AMB-B, RMN, HL, and PMW critically revised the report for important intellectual content. HL did the statistical analysis. BZL obtained the funding.

Declaration of interests
BZL serves as a consultant for Eli Lilly, Amgen, Merck, and Radius Health and receives research support from Lilly and Amgen. RMN is a consultant to Eli Lilly and Radius Health Inc. All other authors declare no competing interests.

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ORIGINAL ARTICLE

Cost-effective osteoporosis treatment thresholds in Greece

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Abstract
Summary A Greek-specific cost-effectiveness analysis determined the FRAX-based intervention thresholds. Assuming a willingness to pay of 30,000 €, osteoporosis treatment is cost-effective in subjects under the age of 75 with 10-year probabilities for hip and major osteoporotic fractures of 2.5 and 10 %, respectively, while for older patients, the same thresholds are raised to 5 and 15 %.
Introduction The purpose of this study was to determine the FRAX calculated fracture probabilities at which therapeutic intervention can be considered as cost-effective in the Greek setting.
Methods A Markov cohort model was populated with Greek data, and quality-adjusted life years (QALYs) were used to calculate the cost-effective thresholds for an annual medication cost of 733.7 € by gender and age. Average FRAX-based 10-year probabilities for both major osteoporotic and hip fractures were multiplied by the model-derived relative risk at which a cost of 30,000 € for each QALY gained was observed for treatment versus to no intervention.
Results A biphasic intervention threshold model is supported by our findings. Osteoporosis treatment becomes cost-effective when absolute 10-year probabilities for hip and major osteoporotic fractures reach 2.5 and 10 %, respectively, among both men and women under the age of 75. For older subjects, the proposed intervention thresholds are raised to 5 and 15 % 10-year probability for hip and major osteoporotic fractures, respectively.
Conclusions Cost-effective osteoporosis treatment may be facilitated in Greece if FRAX algorithm is used to identify subjects with 10-year probabilities for hip and major osteoporotic fractures of 2.5 and 10 %, under the age of 75, while for older patients, the relevant thresholds are 5 and 15 %, respectively.

Keywords FRAX · Greece · Intervention thresholds · Osteoporosis · Ten-year fracture probability

Introduction

Osteoporosis is a chronic disease with a high economic burden on Western countries mainly through the complications of fractures. However, it is frequently underdiagnosed and undertreated, and even patients with major fractures at the spine, hip, proximal humerus, and distal forearm receive treatment at a rate of <10–20 % within the first year following the event [1]. According to the overall sex- and age-specific incidence rate of fractures, especially those of hip, Greece appears within the high-risk countries such as those in Northern Europe (Iceland, Ireland, Norway, and Sweden) [2], while the economic burden of incident and previous fragility fractures was estimated at 680 million € in 2010 and is expected to increase by 20 % in 2025 [3]. The proportion of patients aged 50 or above who received treatment increased from 1.67 % in 2001 to 9.1 % in 2009 but subsequently declined to 8.2 % in

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2011; in addition, a substantial minority of women at high fracture risk were not administered active treatment for osteoporosis [3].

Up to 2011, the therapeutic intervention in osteoporosis in Greece was mainly based on the T-score of individuals, and reimbursement of treatment was most of the times not feasible if a score of>−2.5 SD existed. However, it is well known that a large proportion of fragility fractures occur in patients with a BMD score above the traditional −2.5 SD [4, 5]. In the current era of osteoporosis treatment, several fracture risk algorithms have been developed integrating various risk factors, with the FRAX tool being the most extensively used worldwide. The FRAX assessment algorithm (http://www.shef.ac.uk/FRAX/tool.aspx) has been recently calibrated for Greek-specific fracture risk and life expectancy and is incorporated in the national guidelines for the diagnosis and treatment of osteoporosis [6]. As in many other approaches using FRAX intervention thresholds [7–16], the Greek guidelines aimed also to identify individuals at high fracture risk who on the basis of BMD measurement would be ineligible for treatment.

Cost-effective intervention thresholds based on fracture risk assessment tools should be ideally country-specific. In the USA, a 3 % probability of hip fracture and/or a 20 % probability of major osteoporotic fracture is considered as cost-effective intervention thresholds [17], whereas a 15 % and a 7 % risk of major osteoporotic fracture is recommended to permit a cost-effective access to therapy in Switzerland and UK, respectively [12, 15]. The Greek guidelines incorporated the US FRAX thresholds for cost-effective intervention due to the lack of a country-specific analysis. However, there exists a large epidemiological and economical variability between the two countries especially after the recent economic recession period of Greece and its significant impact on national health expenses.

In this study, we aimed to undertake a health economic analysis in order to estimate the 10-year major osteoporotic and hip fracture probability in the Greek setting at which the currently prescribed treatment could be considered as cost-effective.

Materials and methods

Model structure

The model used was based on a previously developed state transition Markov cohort model [18] in order to estimate the cost-effective intervention thresholds of osteoporotic therapy employing the FRAX® tool, recently calibrated for the Greek healthcare setting.

FRAX calculates fracture risk individually for each patient integrating significant clinical risk factors (age, body mass index fragility fracture, parental history of hip fracture, smoking status, long-term use of glucocorticoids, rheumatoid arthritis, secondary osteoporosis, alcohol consumption) and optionally femoral neck bone mineral density (BMD), in order to enhance risk prediction [19]. As already mentioned, the Markov model that we used was based on a previous one that has been described in 2007 and can calculate the relative risk (RR) that should be multiplied with the baseline risk of fractures (hip, vertebral, forearm) for the treatment to become cost-effective in every defined population. However, and in order to allow direct comparison with previously published national reports, we herein present intervention thresholds on the basis of absolute 10-year hip and major fracture risk. The FRAX cost-effective intervention threshold was calculated by multiplying the derived, by the Markov model, RR with the corresponding average 10-year hip and major fracture risk at each age group, as previously described [9]. As an example, in our analysis, a RR of 1.33 must be applied to the baseline risk of each fracture type (hip, vertebral, forearm) in order for the treatment to become cost-effective for the 65-year old female Greek population. The same population, with a BMI set at 25 kg/m^2, has an average FRAX 10-year fracture risk of 6.6 % for major osteoporotic fractures and 1.4 % for hip fractures. These results translate into absolute 10-year probabilities of 8.7 % for major osteoporotic fractures (6.6 % multiplied by RR of 1.33) and 1.8 % for hip fractures (1.4 % multiplied by RR of 1.33) as cost-effective treatment intervention thresholds.

The cycle length of the model was 1 year, and patients aged 50 years or above were followed through the model for a lifelong time span of time. All patients included in the model, commenced in the "well" health state. At each cycle, a patient had a probability of remaining in the well state, experiencing a fracture or die. If the patient had a fracture, he/she will move to the "wrist fracture," "vertebral fracture," "hip fracture," or "other osteoporotic fracture" health state, depending on the fracture type. After 1 year in that health state, the patient could incur another fracture, move to the "postvertebral fracture," "posthip fracture" states, or die, except for patients who had a "wrist" or other osteoporotic fractures. These could experience another fracture or move back to the well state. Patients in the postvertebral fracture state would therefore remain in the same state and have another vertebral or hip fracture or move to the "dead" state, unlike patients in the posthip fracture state, who could only have a hip fracture, that remain in that state or die. Once a patient has moved to the dead state, then he/she would remain there for the rest of the simulation (Fig. 1).

Model inputs included treatment efficacy, incidence of fractures, mortality, quality of life, and costs.

In order to test the robustness of our model and the model outcomes, a validation procedure was performed, as described under the general principles for model transparency and validation by the International Society for Pharmacoeconomics and Outcomes Research and the Society for Medical Decision

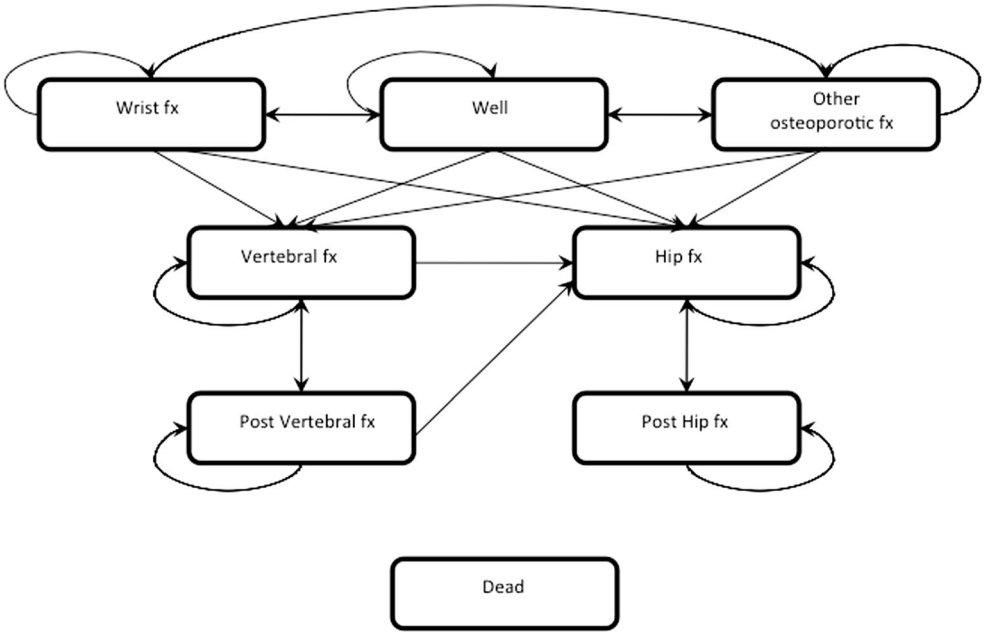

Fig. 1 Structure of the Markov model. Influenced by Zethraeus et al. [18]. *fx* fracture

Making (ISPOR-SMDM) Modeling Good Research Practices Task Force [20]. Face validity of the model (model structure, data sources, problem formulation, and results) was reviewed and approved by persons with clinical expertise (members of the team of authors, as well as external experts). Validation for external consistency followed the cross-validation methodology, using the Zethreus et al. [18] model as the basis for comparisons (as per its initial purpose). Running both models on similar baseline populations provided corresponding results.

Treatment efficacy

A bisphosphonate-like intervention for 5 years is modeled as in previous similar studies [9, 12]. Full persistence is assumed, while the model accepts that the intervention reduces by 35 % (RR=0.65) the risk of all fractures for any individual therapeutic modality and in each considered population group during the treatment period; the remaining effect wanes linearly for the next 5 years following discontinuation of treatment until fully offset [18]. The intervention is compared with standard treatment (calcium and vitamin D), and both the "generalized" fracture reduction of 35 % and the optimistic hypothesis of 100 % persistence over the 5-year treatment period are assumed in order to maintain comparability between our analysis and previous studies addressing treatment intervention thresholds based on economic evaluation.

Incidence of fractures

Data on the incidence of fractures in Greece were indispensable in order to populate the model and calculate the cost-effective intervention thresholds. These were available through a previously published report, describing the epidemiology, burden, and treatment of osteoporosis in Greece [3]. Based on the incidences of fractures, the age-specific annual fracture risks for Greek females and males were derived and input in the model. We herein comprehensively provide the incidence of fractures per 100,000 person-years by age and by gender, in the population aged 50 years and over, for 2010 (Table 1), as previously described [3]. Incidence of fractures increased with age and was generally higher for women compared to men, some exceptions apart.

Mortality

The age-specific incidence rates of deaths related to fractures were also available through the aforementioned report presenting epidemiological data of osteoporosis in Greece [3]. With the exemptions of hip and vertebral fractures, no excess mortality was assumed following all other fractures. Along with previous reports taking into account comorbidities [21–23] and the model's structure, 30 % of the excess mortality following a hip or a vertebral fracture was associated with the fracture event; the incidence of causally related deaths in Greece within the first year after fracture was calculated per 100,000 [3]. Contrary to the incidence of fractures, men's mortality rates were higher compared to those of women and increased with age (Table 2).

Costs

Cost inputs included fracture and treatment costs. As no specific data concerning fracture costs were available for Greece, they were estimated using information from other countries,

Table 1 Incidence per 100,000 person-years of hip, clinical vertebral, forearm, and "other" fractures in Greece by age

Fracture at the				
Age (years)	Hip	Vertebra	Forearm	Other
Women				
50–54	2	5	12	12
55–59	61	170	469	537
60–64	120	213	455	464
65–69	198	288	480	675
70–74	436	614	783	1235
75–79	707	688	690	1488
80–84	1281	805	802	2178
85+	1855	872	792	3116
Men				
50–54	21	55	20	94
55–59	45	79	69	420
60–64	69	165	130	678
65–69	102	161	154	660
70–74	220	336	141	1132
75–79	363	418	103	968
80–84	725	503	141	1927
85+	1087	730	199	3148

From Svedbom A. et al. [3]

Table 2 Incidence (per 100,000) of causally related deaths in Greece within the first year after fracture (adjusted for comorbidities), 2010

Age (years)	Hip	Clinical vertebral	Other fracture
Women			
50–54	409	531	11
55–59	607	746	18
60–64	867	1007	28
65–69	1162	1273	44
70–74	1431	1476	65
75–79	2138	2066	134
80–84	2753	2436	307
85–89	4702	3655	824
90+	9119	5142	3170
Men			
50–54	1656	1986	26
55–59	2139	2431	44
60–64	2267	2438	61
65–69	2986	3029	107
70–74	3214	3060	145
75–79	4243	3763	252
80–84	5128	4165	431
85–89	7278	5320	786
90+	17,298	11,257	2164

From Svedbom A. et al. [3]

such as Italy and Bulgaria, by adjusting for differences in health care price levels, as extensively described in the study cited above [3, 24]. As a result, the first year cost of hip fracture (acute phase) was calculated at 12,550 €, of clinical vertebral fracture at 2,776 €, while the cost of other fractures was computed at 6,624 € (in 2010). According to the same report, the annual nursing home costs, constituting long-term disability costs, were estimated at 13,271 € (in 2010) [24]. The annual cost of a BMD measurement (60 €) and a physician visit (10 €) were also included in the cost assumptions.

It was assumed that expenditures for osteoporosis treatment would be the same for each patient and this involved the annual drug cost per patient as derived from data on the pharmaceutical consumption available from the National Organization For Health Care Services Provision (NOHCSP) [25] and the latest official price list of August 2013 [26] (Table 3). Annual medication cost was derived from the actual cost of the total annual drug consumption provided by NOHCSP divided by the estimated number of treated patients, in order to include the real current prescribing policy for osteoporosis medications in Greece. In specific, the number of medicinal packages sold of each active substance, including calcium and vitamin D supplementation, was multiplied by the corresponding price, considering that generics accounted for 18 % of the total consumption, while brand names for the remaining 82 % [27]. The number of treated patients was also calculated from the number of medicinal packages sold assuming a 100 % persistence (Table 4); as an example, 12 packages containing four tabs of weekly alendronate corresponded to one treated patient, while one patient was

Table 3 Annual drug costs per patient in Greece, 2013

Medication	Annual drug cost (€)
Alendronate	192.9
Risedronate	135.6
Ibandronate	659.8
Zoledronic acid	150.3
Raloxifene	131.8
Strontium ranelate	278.5
Parathyroid hormone	3191.2
Teriparatide	3271.3
Alfacalcidol	72.2
Alendronate/Cholecalciferol	131.8
Calcium	50.3
Calcium/Cholecalciferol	53.9
Bazedoxifene	229.3
Denosumab	325.5

Prices correspond to the National Health System contribution for each medication and not to the commercial value. National Health System covers the 100 % of medication costs for inpatients and the 75 % of cost for outpatients

Table 4 Osteoporosis medications use according to gender, 2013

Medication	Men	Women	N/A[a]	Total drug use
Total number/(%) of patients receiving treatment				
Alendronate	3278 (29 %)	76,917 (30.8 %)	2160 (36.7 %)	82,355 (31 %)
Risedronate	2786 (24.6 %)	53,974 (21.6 %)	1206 (20.5 %)	57,966 (21.8 %)
Ibandronate	1076 (9.6 %)	24,934 (10 %)	488 (8.3 %)	26,498 (9.9 %)
Zoledronic acid	310 (2.7 %)	274 (0.1 %)	162 (2.7 %)	746 (0.3 %)
Raloxifene	–	5638 (2.2 %)	161 (2.7 %)	5799 (2.1 %)
Strontium ranelate	618 (5.6 %)	15,625 (6.2 %)	302 (5.1 %)	16,545 (6.2 %)
Parathyroid hormone	–	7 (0.0 %)	1 (0.0 %)	8 (0.0 %)
Teriparatide	224 (2 %)	2946 (1.1 %)	34 (0.5 %)	3204 (1.2 %)
Bazedoxifene	–	736 (0.2 %)	17 (0.3 %)	753 (0.3 %)
Alendronate/Cholecalciferol	1366 (12 %)	24,764 (9.9 %)	518 (8.8 %)	26,648 (10 %)
Denosumab	1649 (14.5 %)	45,365 (18.2 %)	830 (14.1 %)	47,844 (18 %)
Alfacalcidol	4855	46,493	1408	52,756
Calcium	3480	47,811	2118	55,954
Calcium/cholecalciferol	361	4235	51	4647
Total[b]	11,307	248,180	5879	265,366

[a] N/A: Information regarding gender not available

[b] Calcium and vitamin D supplementations are not added in the totals, as they are mainly used concomitantly with the remaining medication

assigned to each package of i.v. zoledronic acid 5 mg. During 2013, a total number of 265,366 was estimated as receiving osteoporosis treatment with the women/men ratio being 22:1. Bisphosphonates were used for the treatment of the 73 % of all patients, and this was more or less the case in both genders (women 78 %, men 72 %). Denosumab was the second most frequently used medication accounting for the 18 % of all treated cases (women 18 %, men 14.5 %). The remaining patients were treated with strontium ranelate (6 % of all cases; women 6.5 %, men 5.5 %), selective estrogen receptor modulators (SERMs) (2 % of all cases; women 2.5 %), and teriparatide (1 % of all cases; women 1 %, men 2 %) (Table 4). Annual medication cost was 733.7 € in the base case analysis although it ranged from 3271.3 € (teriparatide) to 131.8 € (alendronate/cholecalciferol) (Table 3). Indirect costs such as fracture-related productivity losses were not included.

Cost-effectiveness analysis

The present study intended to determine the fracture probability at which intervention becomes cost-effective. The analysis was undertaken from a third-party payer perspective, assuming a willingness to pay (WTP) an incremental cost-effectiveness ratio (ICER) of 30,000 € per each gained quality-adjusted year of life (QALY) as cost-effective. This almost corresponds to a WTP a value of two times the gross domestic product (GDP) per capita (GDP/capita for Greece in 2014 16,398 €) [28].

The cost-effectiveness of treatment was compared to no intervention in a Greek setting by simulating costs and outcomes among women and men aged ≥50 years at variable probabilities of major and hip fracture. For each sex and each age (50–85 years) and with a BMI set at 25 kg/m^2, intervention thresholds were calculated by multiplying the average FRAX 10-year fracture risk of each age group with the relevant RR of the model that yielded a 30,000 € cost per QALY; all possible combinations of RR between 1 and 20.0 were tested in 0.01 steps.

Results

Ten-year probability of a major osteoporotic fracture

The 10-year major osteoporotic fracture probability at which treatment could be cost-effective seemed to generally increase with age, in both sexes, and there was a fair relationship with the ICER throughout the age range. More specifically, drug intervention was found to be cost-effective at/or above 13.2 % (range 8.9–20.4 %) for women and 20.0 % (range 11.5–34.2 %) for men aged from 50 to 54 years. When considering women and men aged between 55 and 64 years, the threshold was estimated at/or above 8.5 % (range 7.8–9.1 %) and 9.5 % (range 9.3–9.6 %), respectively. The cost-effective intervention thresholds were computed at/or above 8.9 % (range 8.5–9.2 %) for women aged 65–74 years and 9.5 % (range 8.9–10 %) for men, whereas for women and men over 75 years old, they were calculated at/or above 15.0 % (range 13.0–16.0 %) and 11.0 % (range 10.6–11.2 %) accordingly (Table 5). Minor age variations were generally noticed, except for the age range of 50–55 probably due to the low incidence of fractures at this particular age group and especially among men.

Table 5 Comparison of cost-effective FRAX 10-year probabilities for hip and major osteoporotic fractures according to gender and age with the corresponding FRAX probabilities of subjects with a prior fragility fracture or with a femoral neck BMD score of −2.5

Age	Women							Men						
	RR	"Cost effect" Major	"Cost effect" Hip	Prior Fx Major	Prior Fx Hip	−2.5 Major	−2.5 Hip	RR	"Cost effect" Major	"Cost effect" Hip	Prior Fx Major	Prior Fx Hip	−2.5 Major	−2.5 Hip
50	8.5	20.4	1.7	5.2	0.8	4.8	1.5	18	34.2	1.8	4.1	0.5	5.2	2.3
55	2.38	7.8	0.95	7.0	1.3	6.2	2.0	4	9.6	0.8	5.0	0.8	6.3	2.9
60	1.93	9.1	1.5	9.9	2.2	8.1	2.6	3	9.3	1.5	6.5	1.4	7.6	3.5
65	1.33	8.7	1.8	13	3.5	10	3.3	2.5	10	2.25	8.0	2.1	8.7	4.0
70	1	9.2	2.6	17	5.6	12	4.2	1.75	8.9	2.4	9.7	3.3	9.8	4.7
75	1	13	4.7	22	8.5	14	5.6	1.6	10.56	4.48	12	5.0	11	5.6
80	1	16	7.1	25	11	15	6.5	1.4	11.2	5.9	13	6.4	11	5.9
85	1	16	7.8	26	12	14	5.8	1.37	11.23	6.57	13	7.3	9.1	5.0

Major 10-year probability for major osteoporotic fractures, *Hip* 10-year probability for hip fracture, *RR* relative risk, *Fx* fracture

Ten-year probability of a hip fracture

As for the major osteoporotic fractures, when considering hip fractures, an increase in the 10-year probability rates with age in both sexes was observed, some exceptions apart. In Greece, the drug intervention aiming at reducing the fracture risk was found to be cost-effective with a 10-year probability for a hip fracture at/or above 1.2 % (range 0.9–1.7 %) for women and 1.4 % (range 1.0–1.8 %) for men aged from 50 to 54 years. For the next age group of 55–64, the threshold was calculated at/or above 1.2 % for both women and men (range 1.0–1.5 and 0.8–1.5 %, respectively). Taking into consideration women aged between 65 and 74 years, the 10-year probability for a hip fracture was computed at/or above 2.2 % (range 1.8–2.6 %), for the intervention to be cost-effective, while the corresponding figure for men was at/or above 2.3 % (range 2.3–2.4 %). Finally, for patients over 75 years, it was calculated at/or above 6.5 % (range 4.7–7.8 %) for women and 5.7 % (range 4.5–6.6 %) for men (Table 5). Significant age variations were generally not noticed.

Sensitivity analysis

The cost-effective intervention thresholds in relation to WTP of around 2.0 (30,000 €), 1.0 (15,000 €), and 1.5 (22,500 €) GDP per capita are presented in Table 6. The cost-effective intervention thresholds proportionally increase with decreasing WTP, as expected. Notably, the suggested as cost-effective 10-year probabilities for hip and major osteoporotic fractures of 2.5 and 10 % under the age of 75 and 5 and 15 % for older subjects seem applicable even in the scenario of a WTP of 1.5 GDP per capita, especially among women.

Discussion

Our report identifies the absolute 10-year major osteoporotic and hip fracture risk at which osteoporosis treatment could be considered as "cost-effective" in the Greek setting. Due to the increasing probability for both major osteoporotic and hip fractures with age, especially after 75 years in both sexes, and in combination with life expectancy, a biphasic intervention threshold model is supported by our findings. In specific and with an anticipated decrease in osteoporosis treatment cost, mainly due to the continuous increase of generic bisphosphonates use, our analysis suggests absolute 10-year probabilities of 2.5 and 10 % for hip and major osteoporotic fractures, respectively, among both men and women under the age of 75. For older subjects, the proposed intervention threshold is raised to 5 and 15 % 10-year probability for hip and major osteoporotic fracture, respectively. The increase in fracture risk intervention thresholds among older subjects is not unexpected as mortality from other causes competes with the probability of fracture in these age groups.

According to the Greek guidelines [6], subjects with a prior fragility fracture as well as individuals with a T-score≤−2.5 should be considered for treatment. When comparing the 10-year probability of major osteoporotic and hip fracture for the two above states with the cost-effective intervention thresholds (Table 5), a close relationship is observed between the "prior fracture" probabilities and the cost-effective thresholds

Table 6 Cost-effective intervention thresholds in relation to WTP cutoffs of 2.0 (30,000 €), 1.0 (15,000 €), and 1.5 (22,500 €) GDP per capita

Age	Women									Men								
	2×GDP			1×GDP			1.5×GDP			2×GDP			1×GDP			1.5×GDP		
	RR	Major	Hip	RR	Major	Hip	RR	Major	Hip	RR	Major	Hip	RR	Major	Hip	RR	Major	Hip
50	8.5	20.4	1.7	17.3	41.5	3.46	11.5	27.6	2.3	18	34.2	1.8	2.0	38	2	20	38	2
55	2.38	7.8	0.95	4.28	14.12	1.7	3.0	10	1.22	4.0	9.6	0.8	7.36	17.67	1.47	5.25	12.6	1.05
60	1.93	9.1	1.5	3.46	16.6	2.76	2.48	11.9	1.98	3.0	9.3	1.5	5.25	16.27	2.62	3.8	11.4	1.9
65	1.33	8.7	1.8	2.3	15.1	3.2	1.68	11.08	2.35	2.5	10	2.25	4.4	17.6	3.96	3.2	12.8	2.88
70	1	9.2	2.6	1.54	14.16	4.0	1.17	10.76	3.0	1.75	8.9	2.4	2.94	15.0	4.7	2.2	11.22	3.52
75	1	13	4.7	1.42	18.46	6.67	1.1	14.3	5.17	1.6	10.56	4.48	2.57	16.96	7.2	2	13.13	5.57
80	1	16	7.1	1.25	20	8.87	1	16	7.1	1.4	11.2	5.9	2.12	16.96	8.9	1.7	13.6	7.14
85	1	16	7.8	1.25	20	9.75	1	16	7.8	1.37	11.23	6.57	1.96	16.07	9.4	1.62	13.28	7.77

WTP willingness to pay, *GDP* gross domestic product, *Major* 10-year probability for major osteoporotic fractures, *Hip* 10-year probability for hip fracture, *RR* relative risk

(especially for major osteoporotic fractures) among women ≤65 years old. In addition, similarity is obvious between the cost-effective thresholds and the major osteoporotic and hip fracture probabilities of female individuals at all ages with a T-score≤−2.5; notably, the major osteoporotic fracture probabilities at this instance are almost identical with the cost-effective thresholds. Among men, the cost-effective thresholds for major osteoporotic fracture exhibit a close relationship with the corresponding 10-year probabilities of individuals with either a prior fragility fracture or with a T-score≤−2.5. In addition, the cost-effective thresholds for hip fracture in men are almost identical with those derived among male subjects with a prior fragility fracture at all ages, while they are quite similar with those of males ≥75 years old with a T-score≤−2.5. Therefore and according to these comparisons, it seems that the intervention thresholds that our analysis propose as cost-effective are quite close to the clinical "reality" of the Greek setting and they will hopefully contribute to an effective and realistic management of the growing osteoporosis problem. Additionally, as Greece has the second larger number of DXA machines in the European Union (37.5 machines per million inhabitants) [3] and measurement is offered in a wide age spectrum [6], there exists a significant number of subjects with a radiological diagnosis of osteopenia but without a prior fragility fracture in whom a cost-effective therapeutic decision was difficult to be made up to now based on Greek data.

There have been several advancements in the cost-effectiveness models for osteoporosis treatment, while some of them have integrated FRAX algorithm in the model structure [29, 30]. However, our model calculates the cost-effective RR, and the corresponding FRAX probability is then calculated, as previously described [9]. It is of note that the calculated cost-effective RR for females ≥70 years old was 1 corresponding to FRAX thresholds >9 and >2.5 % for major osteoporotic and hip fractures, respectively (Table 5). This could be interpreted as suggesting osteoporosis treatment to every female subject after the age of 70 since this appears as cost-effective according to our analysis. However, this is not probably the case in the proposed management of osteoporosis in Greece. As already mentioned, a DXA measurement is suggested to every subject after the age of 65 [6], and these measurements should be used for an accurate estimation of FRAX thresholds. As an example, a 75-year-old woman with a BMI of 25 kg/m^2, with a total hip T-score of −2.0 and without any other risk factors, would not be eligible for treatment according to the present analysis, as her FRAX probabilities (11.2 % for major osteoporotic and 3.6 % for hip fracture) do not exceed the proposed cost-effective thresholds for her age (15 % for major osteoporotic fracture; 5 % for hip fracture).

Another remarkable finding of our analysis is the relatively high FRAX thresholds found solely among both male and female subjects of 50 years old (Table 5). This could be probably attributed to the quite small number of fractures in this specific age group (Table 1), while the thresholds normalize thereafter following an age-dependent increasing trend (Table 5).

Our results may serve as an example of a country with a relatively low WTP, derived by its low GDP, however with a low quota of generics use and treatment guidelines permitting the use of osteoporosis medication in a cost-independent manner [6], as physicians can choose the preferred medication irrespective from the drug's cost. Although the mean cost-effective intervention thresholds increase with decreasing WTP, the suggested thresholds for major osteoporotic fractures of our study are similar with the Swiss ones [16] in older subjects and significantly lower than the USA [9] and Swiss [16] intervention thresholds for younger subjects, in spite of the fact that these two countries used a greater WTP in their analysis than Greece (USA 46,300 €; Switzerland 115,000 €;

Greece 30,000 €/based on currency rates on September 2014). In addition, the estimated annual medication cost was higher in Greece though hospitalization and rehabilitation costs were significantly lower than the two countries above. It appears that the relatively low average FRAX 10-year fracture risk of the Greek population counterbalanced the impact of low WTP resulting in relatively low intervention thresholds. As an example, the average FRAX 10-year risk for major osteoporotic fractures for the 65-year-old female Greek population is 6.6 %, while it is 9.6 and 9.4 % for the same Swiss and US (white) female population, respectively. This is one more proof that cost-effective intervention thresholds based on fracture risk assessment tools should be always country-specific.

Our study has several limitations and strengths. Notably, both the major limitation and strength of this analysis rely on the report of the actual number of osteoporosis medications consumed in Greece during 2013. Therefore, the model includes the real total cost of osteoporosis treatment, while for the first time, the exact quota of the medications used is reported in the Greek setting. However, the number of treated patients has been estimated based on the model's assumption of a 100 % persistence, which is probably not the case in a real setting. Nevertheless, it is quite possible that the actual number of patients receiving treatment in Greece is bigger than the reported one, thus decreasing the real annual medication cost per patient which is already anticipated to decrease with an increasing use of generics. In addition, a 35 % efficacy in reduction of all fracture types does not correspond to the profile of any agent. However, this reduction is within an accepted range for bisphosphonate and denosumab treatment that constitute the 90 % of all medications used, while it allows comparison with previous similar reports. A third limitation of our study is that the analysis was restricted to a single WTP threshold. However, we believe that the WTP of 30,000 € is quite realistic for Greece with its economic status struggling to stabilize after several years of recession. A fourth major limitation is the fact that the 10-year FRAX-derived fracture probabilities systematically underestimate the 10-year fracture probability in the general population as it is assumed that the prevalence of clinical risk factors in this population is zero. However, the FRAX clinical risk factors such as smoking, alcohol consumption, and glucocorticoids' use are prevalent in the Greek general population, although this was not included in our estimations due to the lack of the relevant data. Therefore, it can be speculated that the cost-effective intervention thresholds might be underestimated, as well. Furthermore, the gender of the 2.2 % of all treated patients was not available being reported as N/A in Table 4. The women/men ratio of the rest patients was applied to this small percentage of patients, as well. Finally, the model we used is limited by restrictive assumptions about transitions between states; as an example, patients with a prior hip fracture cannot experience any future non-hip fracture.

In conclusion, among both men and women under the age of 75, absolute 10-year probabilities calculated with the Greek-specific FRAX algorithm of 2.5 and 10 % for hip and major osteoporotic fractures, respectively, are indicative for a cost-effective intervention aiming to decrease fracture risk. For older subjects, the proposed intervention thresholds are raised to 5 and 15 % 10-year probabilities for hip and major osteoporotic fractures, respectively. The above thresholds may allow access to treatment in subjects with a relatively high fracture risk who would not be eligible to therapy up to now, thereby contributing in the management of the growing problem of osteoporosis in Greece. In all cases, clinical judgment cannot be replaced by any health economic modeling results, which should be only used ancillary in the final clinical decision based on the special clinical characteristics of each patient.

Conflicts of interest P. Makras has received lecture fees and research grants from Amgen and lecture fees from Pfizer, Leo, Genesis, ELPEN, UniPharma, VIANEX. A.D. Anastasilakis has received lecture fees from Amgen. G.P. Lyritis has received lecture fees from Amgen, Servier, Merck, Eli Lilly. K. Athanasakis, N. Boubouchairopoulou, J. Kyriopoulos, and S. Rizou have nothing to disclose.

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Bone Material Strength as Measured by Microindentation In Vivo Is Decreased in Patients With Fragility Fractures Independently of Bone Mineral Density

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Context: Bone mineral density (BMD) does not fully capture fracture risk as the majority of fractures occur in patients with osteopenia, suggesting that altered bone material properties and changes in microarchitecture may contribute to fracture risk.

Objective: This study aimed to evaluate the relationship between bone material strength (BMS), measured by microindentation in vivo, and fracture in patients with low bone mass.

Methods: BMS was measured in 90 patients (mean age, 61.0 y; range, 40.4–85.5 y) with low bone mass with or without a fragility fracture. Sixty-three patients had sustained one or more fragility fractures.

Results: There was a significant negative correlation between age and BMS ($r = -0.539$; $P < .001$) and with the 10-year fracture probability with and without inclusion of femoral neck BMD as calculated by FRAX ($r = -0.383$; $P < .001$ and $r = -0.426$; $P < .001$, respectively). BMS values were lower in patients with a fragility fracture compared with nonfracture patients (79.9 ± 0.6 vs 82.4 ± 1.0; $P = .032$) despite similar BMD. BMS was comparable in patients with a fragility fracture whether they had osteopenia or osteoporosis (79.8 ± 0.8 vs 78.7 ± 1.1; $P = .456$). In patients with osteopenia, BMS was significantly lower in fracture patients than in nonfracture patients (80.3 ± 0.7 vs 83.9 ± 1.2; $P = .015$).

Conclusion: These data suggest that patients with fractures have altered material properties of bone that are not captured by BMD. Additional studies are required to establish the value of BMS in the prediction of fracture risk, especially in patients with osteopenia. **(*J Clin Endocrinol Metab* 100: 2039–2045, 2015)**

Osteoporotic fractures are common and their incidence increases with age, regardless of sex (1–3). All fractures represent a significant cause of morbidity and decreased quality of life, but fractures have also been shown to be associated with increased mortality (4, 5). There is mounting evidence that bone mineral density (BMD) measurements using dual-energy x-ray absorptiometry (DXA) only partially capture fracture risk, given that a majority of fragility fractures have been shown to occur in patients with osteopenia (6, 7). This strongly suggests that determinants of bone strength other than bone mass may contribute to bone fragility in these patients. Such determinants would include changes in microarchitecture and of material properties of bone. Up until recently this hypothesis was, however, difficult to test in humans due to lack of appropriate techniques for evaluation of these determinants of bone strength.

Recent studies examining structural changes of bone in patients with fractures demonstrated a deterioration in bone microarchitecture (8, 9), as well as an association

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Abbreviations: BMD, bone mineral density; BMI, body mass index; BMS, bone material strength; DXA, dual-energy x-ray absorptiometry; FN, femoral neck; FRAX, 10-year fracture probability; IDI, indentation distance increase; PMMA, polymethylmethacrylate.

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between increased cortical porosity and distal forearm fractures in patients with osteopenia (10). Reference point indentation is a new tool that permits in vivo measurements of bone material properties in humans. This technique has been extensively validated in animal models (11–13). Diez-Perez et al (14) were the first to report data on microindentation in vivo in humans, showing a significantly higher indentation distance increase (IDI) in patients with osteoporotic fractures compared with nonfracture controls. Further development of the technique has led to the introduction of a handheld device to measure bone material strength (BMS), a parameter derived from the ratio of the mean IDI between the calibration phantom and bone, as a quantifiable parameter of the ability of bone to resist microindentation (15). This device is inserted in the skin of the tibia until it reaches the bone surface and indents it. Using this technique, Farr et al (16) recently reported that postmenopausal women with type 2 diabetes mellitus had lower BMS compared with age-matched nondiabetic controls, and suggested that this may contribute to the increased bone fragility observed in these patients.

The main objective of our study was to evaluate the relationship between BMS, as assessed by the microindentation in vivo technique, and fracture in patients with low bone mass.

Patients and Methods

Study design

This was a cross-sectional study evaluating BMS using the microindentation in vivo technique in men and women attending the outpatient clinic of the Center for Bone Quality or the regional Fracture Liaison Service of the Leiden University Medical Center between July 2013 and August 2014.

Patients

Patients were sequentially invited to take part in the study. Details of the recruitment process are shown in Supplemental Figure 1. Inclusion criteria included age between 40 and 85 years, low bone mass (osteopenia or osteoporosis as diagnosed by DXA), and willingness to be investigated using the microindentation in vivo technique. Exclusion criteria were a metabolic bone disorder other than osteoporosis, serum 25-OH vitamin D concentrations less than 25 nmol/L, pathological fractures, severe liver or kidney impairment (chronic kidney disease stage IV or V), current use of glucocorticoids, aromatase inhibitors, androgen deprivation therapy, or chemotherapy, and previous or current use of bone-acting agents (bisphosphonates, denosumab, selective estrogen receptor modulators, strontium ranelate, recombinant PTH), immobilization, local infection of the tibia at the site of examination, bilateral hip replacement, participation in other research studies, and inability to provide informed consent. Past use of glucocorticoids (>3 mo ago) was not an exclusion criterion as fracture risk has been shown to reverse quickly after discontinuation of treatment (17, 18). The Medical Ethics Committee of the Leiden University Medical Center approved the study and informed consent was obtained from all patients.

Methods

A full medical history including data on menopausal status, clinical risk factors for fractures for the calculation of the 10-year fracture probability (FRAX), a detailed fracture history with documentation of site and date of occurrence of the fracture, and information regarding use of medication were obtained from all patients. A fragility fracture was defined as any low-energy fracture, excluding those of the hands, feet, and skull. The FRAX probability for a major osteoporotic fracture and for a hip fracture was calculated using reference values for the Dutch population (19). Both fracture probabilities were computed with and without the inclusion of femoral neck BMD in the calculation. Fractures sustained less than 12 months before the investigation were not included as a previous fracture in the calculation of the FRAX (20–22).

Serum biochemistry

Blood samples were collected for the measurement of serum calcium, phosphate, albumin, creatinine, and liver enzymes using semiautomated techniques; serum 25-hydroxyvitamin D was measured using the 25-OH-vitamin D TOTAL assay (DiaSorin D.A./N.V., Brussels, Belgium) and plasma Intact PTH was measured by the immulite 2500 (Siemens Diagnostics).

Bone mineral density

Areal BMD was measured at the lumbar spine (L1–L4) and at both femoral necks using DXA with the Hologic QDR 4500 (Hologic Inc). Average values of the left and right femoral neck (FN) were used for analysis. T-scores were calculated using reference values of the National Health and Nutrition Examination Survey (NHANES) III and osteopenia and osteoporosis were diagnosed according to World Health Organization criteria.

Radiographs of the spine

Lateral radiographs of the thoracic and lumbar spine were performed for the detection of vertebral deformities. All radiographs were independently evaluated by two of the authors using the semiquantitative method of Genant (23).

Bone material strength

BMS was evaluated by microindentation in vivo using the Osteoprobe, a Reference Point Indenter (kindly provided by Active Life Scientific Inc) (11, 14, 15). After local anesthesia using a solution of 1% Lidocaïne, the hand-held Osteoprobe is inserted in the skin of the midshaft of the right tibia (mean distance between distal apex of the patella and medial malleolus) until it reaches the bone surface, which is indented upon activation of the instrument. During measurements, the Osteoprobe is maintained perpendicular to the surface of bone at the site of investigation. A minimum of five and up to 25 measurements were performed at the same site. During the procedure, the operator

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classified the sequential measurements as poorly, adequately, or well performed before checking the obtained data, to avoid reporter bias in the interpretation of results. After at least five adequate measurements in each subject, five additional measurements are performed on a polymethylmethacrylate (PMMA) plastic calibration phantom. BMS is calculated as 100 times the ratio of the mean indentation distance increase from impact into the PMMA calibration phantom divided by the indentation distance increase from impact into bone. The probe induces a microfracture as it indents the surface of the cortical bone of the tibia. The more easily this occurs, the deeper the probe indents the bone, and thus the lower the BMS (15). Coefficient of variation of the method was less than 10% for different levels of BMS.

Statistical analysis

All analyses were performed using the SPSS software for Windows (Version 20.0; SPSS Inc). All data are expressed as mean ± SD unless otherwise stated. Normality assumptions were checked by normality plots and by inspection of histograms of residuals from the various regression models. Between-group differences in baseline characteristics were assessed using a Student *t* test, a χ^2 test, or a Mann-Whitney *U* test for nonnormally distributed variables. Pearson's correlations were used to assess correlations between patients' parameters and BMS. Spearman's correlations were used to assess correlations between parameters that were not normally distributed and BMS values. ANOVA models with BMS as outcome variable, adjusted for covariates, were used to compare BMS values between groups. Binary logistic regression analysis was used to assess the separate contributions of BMS and femoral neck BMD (variables) to fracture (outcome). A probability level of random difference of .05 was considered significant.

Results

Ninety of 125 eligible patients with low bone mass agreed to take part and were included in the study (Supplemental Figure 1). Forty-nine of them, all with fractures, were recruited from the Fracture Liaison Service whereas 41, with or without fractures, were attending the outpatient clinic. Patients' characteristics and laboratory values are shown in Table 1. These were 53 women and 37 men; mean age, 61.0 years; range, 40.4–85.5 years; 61% of whom had osteopenia. Sixty-three patients (24 men) had sustained a low-energy fracture (vertebral n = 8; hip n = 10; nonhip/nonvertebral n = 45), in 43 of whom the fracture was recent. Microindentation was performed at a median time of 4.0 months after a fracture. Patients without history of a clinical fracture had also no radiological evidence for vertebral deformities on spinal radiographs.

BMS was significantly inversely related with age ($r = -0.539$; $P < .001$; Figure 1) and with the 10-year fracture probability with and without inclusion of femoral neck BMD in the calculation of FRAX ($r = -0.383$; $P < .001$ and $r = -0.426$; $P < .001$, respectively). BMS values were inversely and significantly related with age and with the 10-year fracture probability in both sexes (age: women, $r = -0.422$, $P = .001$; men, $r = -0.570$, $P < .001$; FRAX: women, $r = -0.286$, $P = .038$; men, $r = -0.393$, $P = .016$). Because of the relationship between BMS and age all further reported values of BMS were adjusted for age. Unadjusted values are shown in Supplemental Table 1.

Table 1. Characteristics of 90 Patients With Low Bone Mass

Characteristic	Fracture (n = 63)	No Fracture (n = 27)	*P* Value
n	63	27	
Age, y	62.6 ± 9.6	57.1 ± 9.5	.015
Male/female	24/39	13/14	.374
BMI, kg/m^2	24.3 ± 3.5	25.3 ± 4.7	.725
Parental hip fracture, n (%)	9 (14%)	4 (15%)	.948
Smoking, n (%)	14 (22%)	2 (7%)	.092
Alcohol use >3 IU/d, n (%)	14 (22%)	1 (4%)	.031
Glucocorticoids, n (%)	4 (6%)	6 (22%)	.028
FRAX probability			
Major fracture, %	6.9 ± 1.0	4.0 ± 0.8	.001
Hip fracture, %	2.0 ± 0.8	1.0 ± 0.3	.003
PTH[a], pmol/L	3.8 ± 1.9	3.5 ± 1.5	.570
Calcium[b], mmol/L	2.41 ± 0.08	2.41 ± 0.10	.826
25-OH D, nmol/L	67.4 ± 28.6	79.6 ± 26.5	.062
Creatinine[c], μmol/L	73.5 ± 13.1	78.4 ± 15.0	.163
LS BMD, g/cm^2	0.87 ± 0.13	0.86 ± 0.12	.402
T-score LS	−1.7 ± 1.2	−1.9 ± 1.1	.431
FN BMD, g/cm^2	0.67 ± 0.09	0.69 ± 0.08	.303
T-score FN	−1.8 ± 0.7	−1.6 ± 0.6	.329

Abbreviation: LS, lumbar spine. Values are expressed as mean ± SD FRAX is expressed as median ± SEM.

[a] PTH reference range, 0.7–8.0 pmol/L.

[b] Calcium reference range, 2.15–2.55 mmol/L.

[c] Creatinine reference range, 64–104 μmol/L for males; 49–90 μmol/L for females.

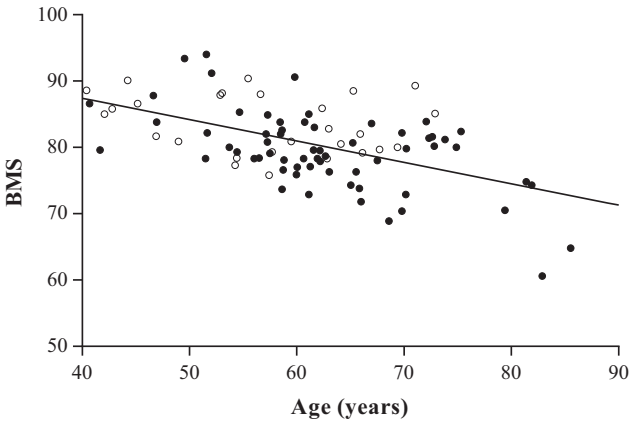

Figure 1. Relationship between age and BMS in 90 patients with osteoporosis or osteopenia. Closed circles represent patients with fragility fractures, open circles represent patients without fragility fractures. $r = -0.539$; $P < .001$.

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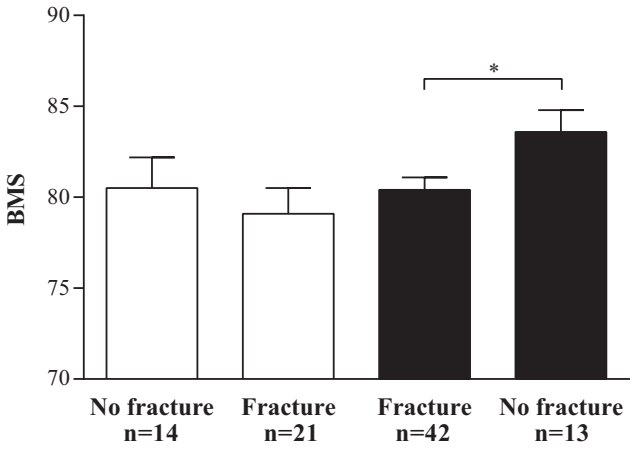

Figure 2. BMS in patients with osteoporosis (open bars) and osteopenia (closed bars), with and without fragility fractures. Mean ± SEM are shown. *, $P = .015$.

BMS values did not differ between women and men (80.0 ± 0.7 vs 81.6 ± 0.8; $P = .147$). There was no significant relationship between BMS and BMD (lumbar spine, r = 0.129, $P = .157$; femoral neck, r = 0.134, $P = .143$), body mass index (BMI; r = 0.075, $P = .413$) or any of the biochemical parameters measured.

BMS in patients with low bone mass

BMS was comparable in patients with osteoporosis and those with osteopenia (79.9 ± 0.8 vs 81.2 ± 0.7; $P = .230$). Patients with osteoporosis were predominantly women, had significantly lower BMI and significantly lower lumbar spine and femoral neck BMD than patients with osteopenia.

Patients with osteoporosis and a history of fragility fracture (n = 21) were significantly older than those without a fragility fracture (n = 14) (65.8 ± 10.5 y vs 53.7 ± 10.0 y; $P = .002$) and were more likely to be active smokers and/or to consume more than 3 units of alcohol per day (29% vs 0%; $P = .028$ for either). All other measured parameters, including BMS (79.3 ± 1.3 vs 80.7 ± 1.6, $P = .540$) did not differ between the two groups; Figure 2.

In patients with osteopenia, there was no significant difference in clinical characteristics, serum biochemistry, or BMD between fracture (n = 42) and nonfracture (n = 13) patients. However, BMS values were significantly lower in patients with fragility fractures compared with those without a fragility fracture (80.3 ± 0.7 vs 83.9 ± 1.2; $P = .015$; Figure 2). This difference remained significant also after exclusion of patients with a hip fracture (80.4 ± 0.8 vs 83.8 ± 1.2; $P = .027$).

BMS in patients with fragility fractures

BMS values were significantly lower in patients with fragility fractures compared with those who had never sustained a fracture (79.9 ± 0.6 vs 82.4 ± 1.0, $P = .032$), despite similar lumbar spine and femoral neck BMD values between the two groups; Figure 3. A lower BMS was associated with a higher odds for fractures (odds ratio, 1.15 [95% confidence interval 1.05–1.27], $P = .004$) whereas this was not the case for femoral neck BMD (odds ratio, 6.17 [95% confidence interval 0.02–2124.51], $P = .542$).

Among patients with a fragility fracture (n = 63), 42 had osteopenia and 21 osteoporosis; details shown in Table 2. BMS values were comparable in all patients with fragility fractures whether they had osteopenia or osteoporosis (79.8 ± 0.8 vs 78.7 ± 1.1; $P = .456$); Figure 2. There was no significant difference in BMS between pa-

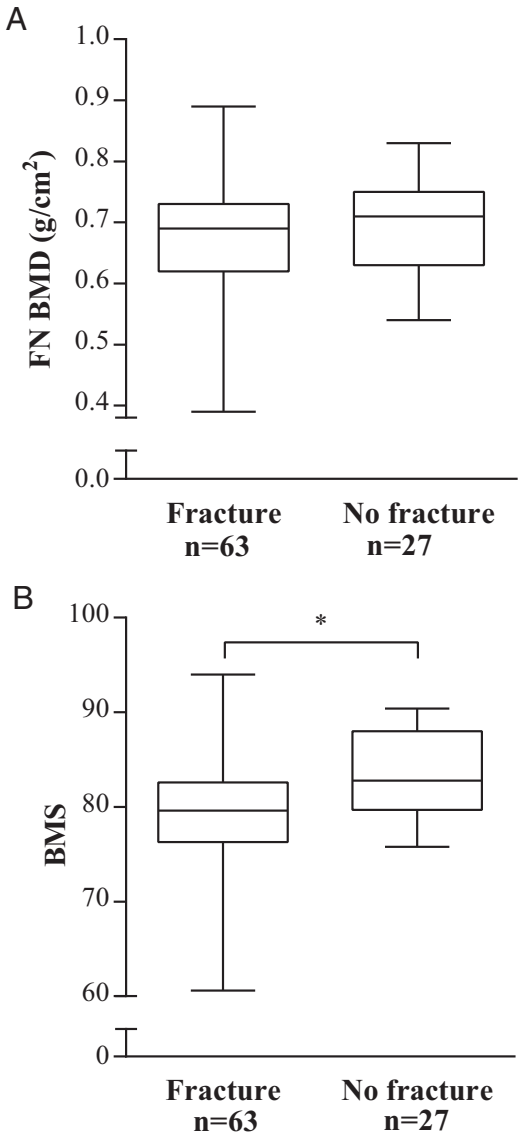

Figure 3. A, FN BMD; and B, BMS in patients with and without fragility fractures. Data are shown in box-whisker plots and statistical differences are displayed for BMS. Boxes indicate median and interquantile range. Bars indicate minimum and maximum values. *, $P = .032$.

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Table 2. Characteristics of 63 Patients With Fragility Fractures

Characteristic	Osteopenia (n = 42)	Osteoporosis (n = 21)	*P* Value
n	42	21	
Age, y	61.0 ± 8.8	65.8 ± 10.5	.058
Male/female	20/22	4/17	.028
BMI, kg/m^2	25.0 ± 3.2	22.8 ± 3.8	.046
Parental hip fracture, n (%)	6 (14%)	3 (14%)	1.000
Smoking, n (%)	8 (19%)	6 (29%)	.391
Alcohol use >3 IU/d, n (%)	8 (19%)	6 (29%)	.391
Glucocorticoids, n (%)	3 (7%)	1 (5%)	.715
FRAX probability			
Major fracture, %	6.5 ± 0.6	9.8 ± 2.6	.004
Hip fracture, %	1.4 ± 0.4	4.0 ± 2.2	.001
PTH, pmol/L	3.8 ± 1.8	3.9 ± 2.2	.913
Calcium, mmol/L	2.41 ± 0.08	2.41 ± 0.09	.975
25-OH D, nmol/L	69.2 ± 29.3	63.7 ± 27.5	.474
Creatinine, μmol/L	74.6 ± 12.1	71.5 ± 14.9	.159
LS BMD, g/cm^2	0.92 ± 0.12	0.77 ± 0.09	<.001
T-score LS	−1.3 ± 1.1	−2.6 ± 0.9	<.001
FN BMD, g/cm^2	0.71 ± 0.07	0.60 ± 0.09	<.001
T-score FN	−1.5 ± 0.5	−2.3 ± 0.8	<.001

Abbreviation: LS, lumbar spine. Values are expressed as mean ± SD. FRAX is expressed as median ± SEM.

tients who had sustained a leg fracture of the ipsilateral side of the measurement (n = 8) compared with those with a fracture of the contralateral side (n = 10) (77.6 ± 1.8 vs 78.3 ± 1.6; $P = .777$). Compared with patients with osteoporosis, patients with osteopenia comprised relatively more men and had higher BMI and BMD and lower 10-year fracture probability. All other clinical characteristics and biochemical measurements were similar between the two groups.

Discussion

We show here that patients who had sustained a fragility fracture demonstrate a significantly lower BMS, as measured by the microindentation in vivo technique, compared with patients who did not fracture. More importantly, our data also demonstrate that there was no difference in BMS in patients with fragility fractures whether they had osteopenia or osteoporosis. Our findings thus suggest that bone material properties are altered in patients with a fragility fracture and that the microindentation in vivo–derived BMS measurement captures elements of bone fragility independently of BMD. Analysis of data on bone turnover markers, which may also be associated with an increase in fracture risk independently of BMD (24), were not undertaken in this study because reliable interpretation of the data was precluded by the large number of patients with a recent fracture and the influence of this on serum levels of these markers.

Microindentation in vivo is a new technique, designed to measure the resistance of bone to fracture by separating mineralized collagen microfibers and thus, locally inducing microcracks. In the first human studies, the material properties of bone were quantified by total indentation distance, indentation distance increase (IDI), and creep indentation distance (14, 25). Of these parameters, IDI differentiated best between bone that was easily susceptible to fracture and bone that did not easily fracture, and the parameter was found to correlate best with toughness of bone (11, 13). This has led to the development of the derived parameter of BMS, which is calculated by the ratio of the IDI of the calibration material PMMA to the IDI of bone (15).

In our study, we found a strong relationship between BMS and age, which may play an important role in the increased fracture risk observed in elderly patients, in whom deteriorated bone microarchitecture has also been demonstrated (8). Several ex vivo studies have shown an inverse relationship between age and toughness of bone (26, 27). Bone toughness is best predicted by the Indentation Distance Increase and thus by BMS (13). As bone strength is inversely correlated with the density of microcracks in bone tissue, the observed alteration in bone material properties in the elderly might well be explained by the previously demonstrated age-related accumulation of microcracks (26, 27).

Having established that BMS reflected bone fragility independently of BMD, we went on to test the association between BMS and the clinical risk factors used in the FRAX algorithm without inclusion of BMD measurements in the calculation. We found a significant relationship between BMS and the 10-year fracture probability calculated by FRAX without BMD, probably reflecting the lack of correlation between BMS and BMD values. These observations suggest that microindentation in vivo is able to capture an element of the contribution of clinical risk factors used in the FRAX algorithm to altered material properties of bone, and thus to increased fracture risk.

Our data complement and extend those of Diez-Perez et al (14), who, using the microindentation technique, showed that bone material properties, as measured by IDI, were poorer in 27 postmenopausal women who had sustained mainly a hip fracture (n = 25) or vertebral fracture (n = 2), compared with age-matched controls who had not sustained a fracture, with the caveat that women in the control group had a higher BMD than the fracture patients.

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Postmenopausal women have altered bone microarchitecture, and more recent data showed that osteopenic women who sustained a fracture had worse bone microarchitecture than nonfracture controls (8, 9). Increased cortical porosity has also been suggested to contribute to the risk of distal forearm fractures in postmenopausal women with osteopenia (10). Our data provide evidence that bone material properties are altered in patients with osteopenia who have sustained a fracture, most whom are currently not being offered treatment with bone-modifying agents.

Our study has strengths as well as limitations. We sequentially investigated patients of both sexes with a wide age range and low bone mass reflecting everyday clinical practice. The frequency of osteopenia and osteoporosis within the group of patients with a fragility fracture is further consistent with previous reports in fracture patients (6, 7) and all measurements were performed by two dedicated operators. Furthermore, age and sex of patients enrolled onto the study did not differ from those who were not investigated. A limitation of our study is that, whereas the main source of the fragility fracture patients included in the study was our regional Fracture Liaison Service, the nonfragility fracture controls were recruited from patients routinely attending our outpatient clinic, in whom BMD measurements were requested at the discretion of the treating physician, possibly creating a selection bias.

In conclusion we demonstrate in this study that BMS, as measured by the microindentation in vivo technique, captures elements of bone fragility such as the effect of aging and that of the cumulative effect of clinical risk factors as calculated by the FRAX algorithm, independently of BMD. Furthermore, we demonstrate that BMS is comparable in patients with a fragility fracture, whether they have osteoporosis or osteopenia. These data suggest an aspect of altered bone quality contributing to bone fragility which is not captured by BMD. Additional studies are required to establish the value of BMS as a predictor of fracture risk, especially in patients with osteopenia.

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Disclosure Summary: The authors have nothing to disclose.

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CLINICAL TRIAL

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A Randomized, Double-Blind Phase 2 Clinical Trial of Blosozumab, a Sclerostin Antibody, in Postmenopausal Women with Low Bone Mineral Density

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ABSTRACT

Sclerostin, a *SOST* protein secreted by osteocytes, negatively regulates formation of mineralized bone matrix and bone mass. We report the results of a randomized, double-blind, placebo-controlled multicenter phase 2 clinical trial of blosozumab, a humanized monoclonal antibody targeted against sclerostin, in postmenopausal women with low bone mineral density (BMD). Postmenopausal women with a lumbar spine *T*-score −2.0 to −3.5, inclusive, were randomized to subcutaneous blosozumab 180 mg every 4 weeks (Q4W), 180 mg every 2 weeks (Q2W), 270 mg Q2W, or matching placebo for 1 year, with calcium and vitamin D. Serial measurements of spine and hip BMD and biochemical markers of bone turnover were performed. Overall, 120 women were enrolled in the study (mean age 65.8 years, mean lumbar spine *T*-score −2.8). Blosozumab treatment resulted in statistically significant dose-related increases in spine, femoral neck, and total hip BMD as compared with placebo. In the highest dose group, BMD increases from baseline reached 17.7% at the spine, and 6.2% at the total hip. Biochemical markers of bone formation increased rapidly during blosozumab treatment, and trended toward pretreatment levels by study end. However, bone specific alkaline phosphatase remained higher than placebo at study end in the highest-dose group. CTx, a biochemical marker of bone resorption, decreased early in blosozumab treatment to a concentration less than that of the placebo group by 2 weeks, and remained reduced throughout blosozumab treatment. Mild injection site reactions were reported more frequently with blosozumab than placebo. In conclusion, treatment of postmenopausal women with an antibody targeted against sclerostin resulted in substantial increases in spine and hip BMD. These results support further study of blosozumab as a potential anabolic therapy for osteoporosis. © 2014 American Society for Bone and Mineral Research.

KEY WORDS: BLOSOZUMAB; SCLEROSTIN ANTIBODY; ANABOLICS; BONE MINERAL DENSITY; OSTEOPOROSIS TREATMENT

Introduction

An estimated 200 million people worldwide are affected by osteoporosis.[1] This condition is characterized by bone fragility and susceptibility to fracture resulting from low bone mineral density (BMD), altered bone microarchitecture, and decreased bone strength.[2–5] Sclerostin, a *SOST* gene protein secreted by osteocytes, is a negative regulator of mineralized bone matrix formation and bone mass.[5–10] An antibody targeted toward sclerostin increased bone mass and strength in animals[11,12] and resulted in dose-related increases in BMD in healthy postmenopausal women.[13–18] This report summarizes the results of a randomized, double-blind, placebo-controlled phase 2 clinical trial of blosozumab, a humanized monoclonal antibody targeted to sclerostin, in the treatment of postmenopausal women with low BMD.

Subjects and Methods

Study design

This study evaluated the efficacy and safety of blosozumab in ambulatory postmenopausal women between 45 and 85 years of age, with a lumbar spine BMD *T*-score of −2.0 to −3.5, inclusive. The primary objective was to evaluate the dose-response of blosozumab on lumbar spine BMD measured by dual-energy

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Additional Supporting Information may be found in the online version of this article.
[a]At the time of this study, SM was an employee of Eli Lilly and Company. He is now retired from the company.
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X-ray absorptiometry (DXA). This study included a 1-year treatment period and a 3-month follow-up period. The study was conducted at 13 sites in five countries in accordance with the ethical principles of the Declaration of Helsinki,[19] The International Conference on Harmonization Guideline for Good Clinical Practices,[20] and governing laws and regulations. Ethical Review Board approval was obtained at each clinical site. All study participants provided written informed consent prior to study enrollment. This clinical trial, NCT01144377, was sponsored by Eli Lilly and Company.[21]

The study also evaluated the effect of blosozumab on change from baseline in BMD of the hip and wrist (distal radius); total body mineral content; and biochemical markers of bone metabolism, including serum procollagen type 1 N propeptide (P1NP), osteocalcin, bone-specific alkaline phosphatase, and serum carboxy-terminal cross-linking telopeptide of type 1 collagen (CTx). The study was not designed or powered to evaluate fracture efficacy.

Patients were excluded if they had a history of the following: osteoporotic fracture; recent or long-term oral bisphosphonate treatment (defined as treatment within the last year if the previous duration was less than 1 year, or treatment within the last 3 years if previous total treatment duration exceeded 1 year); intravenous bisphosphonate treatment; treatment with therapeutic doses of systemic corticosteroids, fluoride, strontium, or parathyroid hormone (PTH); a metabolic bone disease other than primary osteoporosis; a history of Bell's palsy or other cranial nerve damage; a diagnosis of cancer within the previous 5 years, except for excised superficial basal cell or squamous cell cancers; or a known allergy to a monoclonal antibody.

At study enrollment, each patient was provided oral calcium (approximately 1000 mg/day) and vitamin D (approximately 1000 IU/day) for 4 to 8 weeks before receiving the study drug and continuing through study end. Patients meeting all enrollment criteria were randomized to double-blind treatment groups by a computer-generated random sequence interactive voice response system. Patients, investigators, study site personnel, and the sponsor study team in contact with the study sites remained blinded during the treatment phase and follow-up period, with the exception of pharmacy personnel preparing and dispensing study medication.

A medical history and physical examination were performed at baseline. Measures of vital signs and clinical assessments, including electrocardiograms and recording of adverse events, were continued throughout the study. Laboratory tests of serum calcium, 25-hydroxyvitamin D, 1, 25-dihydroxyvitamin D, intact PTH, and biochemical markers of bone turnover were performed at baseline and regular intervals throughout the study. Auditory-evoked potentials were obtained for a subset of patients at baseline and at treatment end. For all primary efficacy and safety measures, a central laboratory and reading facility maintained consistency of methods and data collection across sites.

Blosozumab was administered by subcutaneous (s.c.) injections delivering 180 mg every 4 weeks (Q4W), 180 mg every 2 weeks (Q2W), or 270 mg every 2 weeks (Q2W) (Fig. 1). Matching placebo injections were administered every 2 weeks such that all study patients, regardless of treatment arm, received three subcutaneous injections at their study visit every 2 weeks. Each injection totaled 1.5 mL in volume. These injections were administered in the lower abdomen and outer thigh by clinical study personnel. A fifth s.c. treatment arm, blosozumab 270 mg every 12 weeks, was later added through protocol addendum, and is not included in this report.

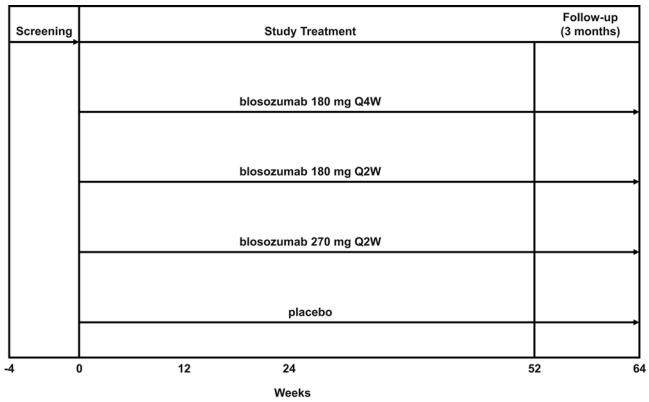

Fig. 1. Study design of the randomized, double-blind, placebo-controlled, multicenter phase 2 clinical trial of blosozumab in postmenopausal women with low bone mineral density.

The sample size was determined based on simulations to achieve a greater than 90% power in detecting a change of 0.05 g/cm^2 in lumbar spine BMD between blosozumab and placebo at week 52. Data from the phase 3 trial of an approved anabolic, teriparatide,[22,23] and data observed in a phase 1 multiple-dose study of blosozumab,[13] were used for simulations. Increases in lumbar spine BMD of 0.03 g/cm^2 at week 12, 0.05 g/cm^2 at week 24, and 0.06 g/cm^2 at week 52 with blosozumab treatment were assumed, corresponding to increases of 3.78%, 6.22%, and 8.26%, respectively. With placebo, increases in lumbar spine BMD of 0 g/cm^2 at week 12, 0.01 g/cm^2 at week 24, and 0.01 g/cm^2 at week 52 were assumed. In addition, a common SD of 0.04 g/cm^2 for lumbar spine BMD and a compound symmetry variance-covariance structure with a correlation of 0.5 were used in the mixed-effects repeated measures model. With at least 20 evaluable patients per treatment group, the study has 93% power in detecting a difference in lumbar spine BMD between blosozumab and placebo at week 52 (two-sided 0.05 significance level). Assuming a dropout rate of 30%, approximately 30 patients per treatment group were randomized.

The active treatment in this study, blosozumab, a humanized monoclonal antibody targeted to sclerostin, is regulated and restricted for distribution by the U.S. Food and Drug Administration (FDA) under an Investigational New Drug Application (IND), and is proprietary property of Eli Lilly and Company. Both the screening assay and neutralizing assay used in immunogenicity analyses were developed by Eli Lilly and Company. These assays are not commercially available and are proprietary property of Eli Lilly and Company. Therefore, access to both blosozumab and the immunogenicity assays used in the conduct of this trial is restricted.

Statistical analysis

Efficacy and safety analyses were conducted according to a prespecified statistical analysis plan, using the full analysis set of study data, which included all data from all randomized patients receiving at least one dose of the assigned treatment. Missing data were not imputed.

All tests of treatment effect were conducted at a two-sided alpha level of 0.05, unless otherwise stated, using SAS™ version 9 (SAS Institute, Cary, NC, USA) or later.

The primary efficacy analysis of change from baseline in lumbar spine BMD at week 52 compared with placebo was performed using a mixed-effects repeated measures model analysis of covariance. Mixed-effects repeated measures takes into account within-subject and between-subject variability, and is appropriate for longitudinal data.[24] Factors in the model included treatment, time, and the interaction of treatment-by-time as fixed effects, with baseline lumbar spine BMD as a covariate. Pairwise comparisons of the difference in lumbar spine BMD changes (two-sided 0.05 significance level, Dunnett's multiplicity-adjusted for multiple treatment arms) between the blosozumab regimens and placebo were constructed and analyzed for the week 52 primary endpoint. Additional time points were evaluated as secondary analyses without multiplicity adjustment among the different times. However, within each time point, the comparisons among multiple treatment arms were multiplicity-adjusted. Analyses of percent changes of lumbar spine and hip BMD were also performed.

The change from baseline for laboratory parameters and vital signs was evaluated using a mixed-effects repeated measures model.[24] Comparisons of treatment groups were made based on least squares means at each visit.[25]

Interim analyses were conducted by an assessment committee independent of the study team, in accordance with the study protocol and the prespecified statistical analysis plan. Adverse events were evaluated by blinded investigators to determine if they were treatment-emergent adverse events and categorized by severity level using the lowest-level term from *The Medical Dictionary for Regulatory Activities*.[20] The proportion of patients experiencing treatment-emergent adverse events was compared among all treatments groups and pairwise using Fisher's exact test.

Results

Study patients

Overall, 120 postmenopausal women enrolled and 106 patients completed the primary treatment phase; 1 additional patient discontinued during follow-up (Fig. 2). There were no statistically significant differences between the treatment groups in the number of patients who discontinued the study. The baseline characteristics of the study population were similar across treatment groups (Table 1).

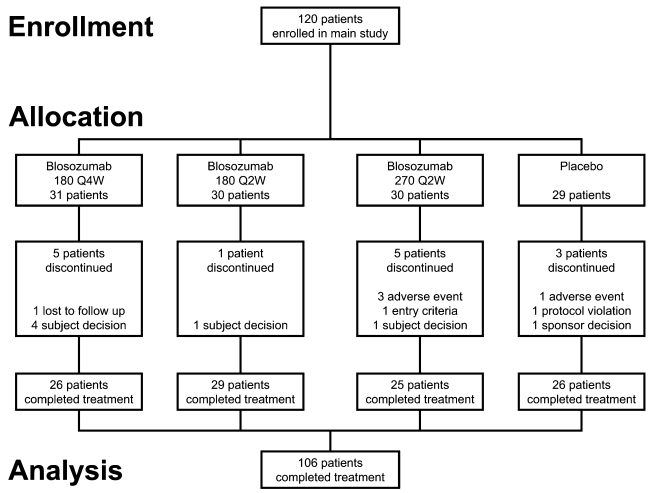

Fig. 2. Enrollment of the study patients through 52 weeks of treatment.

Efficacy

Blosozumab treatment resulted in statistically significant dose-related increases in lumbar spine BMD. The changes were apparent after 12 weeks of treatment, and the mean increase after 52 weeks of treatment at the primary study endpoint was 8.4% above baseline in women assigned to blosozumab 180 mg Q4W, 14.9% above baseline with blosozumab 180 mg Q2W, and 17.7% above baseline with blosozumab 270 mg Q2W (Fig. 3). When compared with placebo, these mean increases in lumbar spine BMD from baseline to week 52 were statistically significant for all blosozumab treatment groups ($p < 0.001$). In women receiving placebo, lumbar spine BMD declined from baseline to week 52 by a mean of 1.6%.

There were also statistically significant dose-related increases in total hip and femoral neck BMD. At 52 weeks of treatment, total hip BMD increased from baseline by a mean of 2.1% in women assigned to blosozumab 180 mg Q4W, 4.5% for women assigned to blosozumab 180 mg Q2W, and 6.7% for women

Table 1. Baseline Characteristics for All Study Patients

	Placebo	Blosozumab 180 mg Q4W	Blosozumab 180 mg Q2W	Blosozumab 270 mg Q2W
n	29	31	30	30
Age, years (mean ± SD)	66.0 ± 9.2	66.8 ± 9.0	64.2 ± 8.2	66.1 ± 7.7
Race, *n* (%)				
White	16 (55.2)	17 (54.8)	17 (56.7)	17 (56.7)
Black	1 (3.4)	0	0	0
Asian, Japanese	12 (41.4)	14 (45.2)	13 (43.3)	13 (43.3)
BMI, kg/m^2 (mean ± SD)	23.8 ± 5.6	23.1 ± 3.7	23.7 ± 3.8	24.6 ± 4.7
LS *T*-score (mean ± SD)	−2.8 ± 0.5	−2.8 ± 0.5	−2.8 ± 0.4	−2.7 ± 0.5
FN *T*-score (mean ± SD)	−2.1 ± 1.0	−2.2 ± 0.7	−2.1 ± 0.9	−1.9 ± 0.6
25-hydroxyvitamin D, nmol/L (mean ± SD)	67.8 ± 15.9	68.9 ± 24.2	68.6 ± 18.8	68.4 ± 23.9
1,25-dihydroxyvitamin D, pmol/L (mean ± SD)	161.9 ± 68.2	156.3 ± 55.9	189.2 ± 63.4	160.9 ± 56.3

Q4W = every 4 weeks; Q2W = every 2 weeks; BMI = body mass index; LS = lumbar spine; FN = femoral neck.

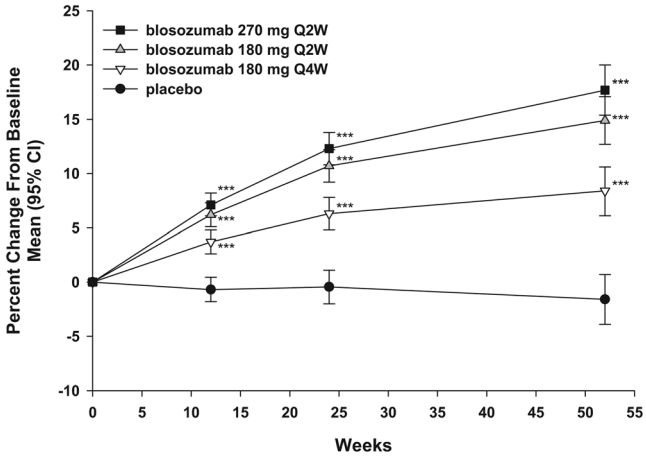

Fig. 3. Percent change (mean, 95% CI) in bone mineral density of the lumbar spine from baseline to week 52 for all study patients according to study group. The least squares mean percent change (mean, 95% CI) in bone mineral density of the lumbar spine from baseline to week 52 is shown. Asterisks (*) indicate statistically significant differences ($^{*}p < 0.050$, $^{**}p < 0.010$, $^{***}p < 0.001$) for each study group as compared with placebo.

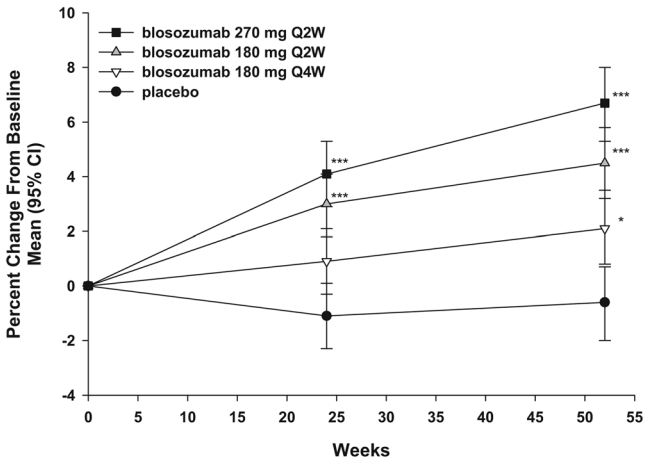

Fig. 4. Percent change (mean, 95% CI) in bone mineral density of the total hip from baseline to week 52 for all study patients according to study group. The least squares mean percent change (mean, 95% CI) in bone mineral density of the total hip from baseline to week 52 is shown. Asterisks (*) indicate statistically significant differences ($^{*}p < 0.050$, $^{**}p < 0.010$, $^{***}p < 0.001$) for each study group as compared with placebo.

assigned to blosozumab 270 mg Q2W (Fig. 4). Femoral neck BMD increased from baseline by a mean of 2.7% in women assigned to blosozumab 180 mg Q4W, 3.9% in women assigned to blosozumab 180 mg Q2W, and 6.3% for women receiving blosozumab 270 mg Q2W. When compared with placebo, the mean increases in total hip BMD from baseline to week 52 were statistically significant for all blosozumab treatment groups. However, when compared with placebo, the mean increases in femoral neck BMD from baseline to week 52 were statistically significant only for patients receiving blosozumab 180 mg Q2W and 270 mg Q2W. In women receiving placebo, total hip and femoral neck BMD decreased from baseline to week 52 by a mean of 0.7% and 0.6%, respectively.

There were no statistically significant changes in wrist BMD observed in the study treatment groups. At the one-third radius, mean 1.5% and 1.9% decreases in BMD were observed for the two blosozumab 180 mg treatment groups at week 52. However, in the blosozumab 270 mg Q2W treatment group, a 0.9% mean increase from baseline was observed at week 52, which was not statistically significant when compared with placebo ($p = 0.11$). A mean 1.4% decrease in one-third radius BMD from baseline was observed at the end of the treatment period for the placebo group.

At baseline, 95.6% of the women randomized to blosozumab treatment had a lumbar spine *T*-score less than or equal to −2.0. At the end of treatment, a positive shift in the lumbar spine *T*-score to greater than −2.0 was observed in 72.4% of the women receiving blosozumab 180 mg Q2W, and 88.5% of the women receiving blosozumab 270 mg Q2W.

Total body bone mineral content

Total body bone mineral content (BMC), a measure of treatment effect on the skeleton, increased from baseline to week 52 by a mean of 1.7%, 4.2%, and 7.3% in women assigned to blosozumab 180 mg Q4W, 180 mg Q2W, and 270 mg Q2W, respectively. For women randomized to placebo, total body BMC declined from baseline by a mean of 1.9% over 52 weeks of treatment. The corresponding mean percent changes from baseline in BMC of the head (skull) subregion were an increase of 1.6%, 1.4%, and 4.0% in women assigned to blosozumab 180 mg Q4W, 180 mg Q2W, and 270 mg Q2W, respectively. The changes in BMC of the head for women randomized to placebo were a mean decrease of 2.2% from baseline during 52 weeks of treatment.

Biochemical markers of bone turnover

Treatment with blosozumab resulted in increased serum concentrations of biochemical markers of bone formation, including serum P1NP, osteocalcin, and bone-specific alkaline phosphatase, measured prior to dose of study drug. Serum concentrations of P1NP increased toward a peak level within 4 weeks of blosozumab treatment, remained significantly above baseline through 24 weeks for all but one blosozumab treatment group, as compared with placebo, and then trended toward pretreatment concentrations by study end (Fig. 5). Osteocalcin and serum bone-specific alkaline phosphatase concentrations increased early and significantly from baseline during blosozumab treatment, as compared with placebo, and were approaching baseline by study end (Fig. 5). However, the blosozumab 270 mg Q2W group maintained an increase in bone-specific alkaline phosphatase concentration significantly greater than placebo through week 52 (Fig. 5). Serum concentrations of CTx, a biochemical marker of bone resorption, decreased from baseline during blosozumab treatment, with a trough concentration less than placebo occurring by 2 weeks, a concentration similar to placebo at 12 weeks, and a concentration less than placebo at study end (Fig. 5).

Safety

Other than mild injection site reactions reported more frequently with blosozumab than placebo, the frequency of adverse events

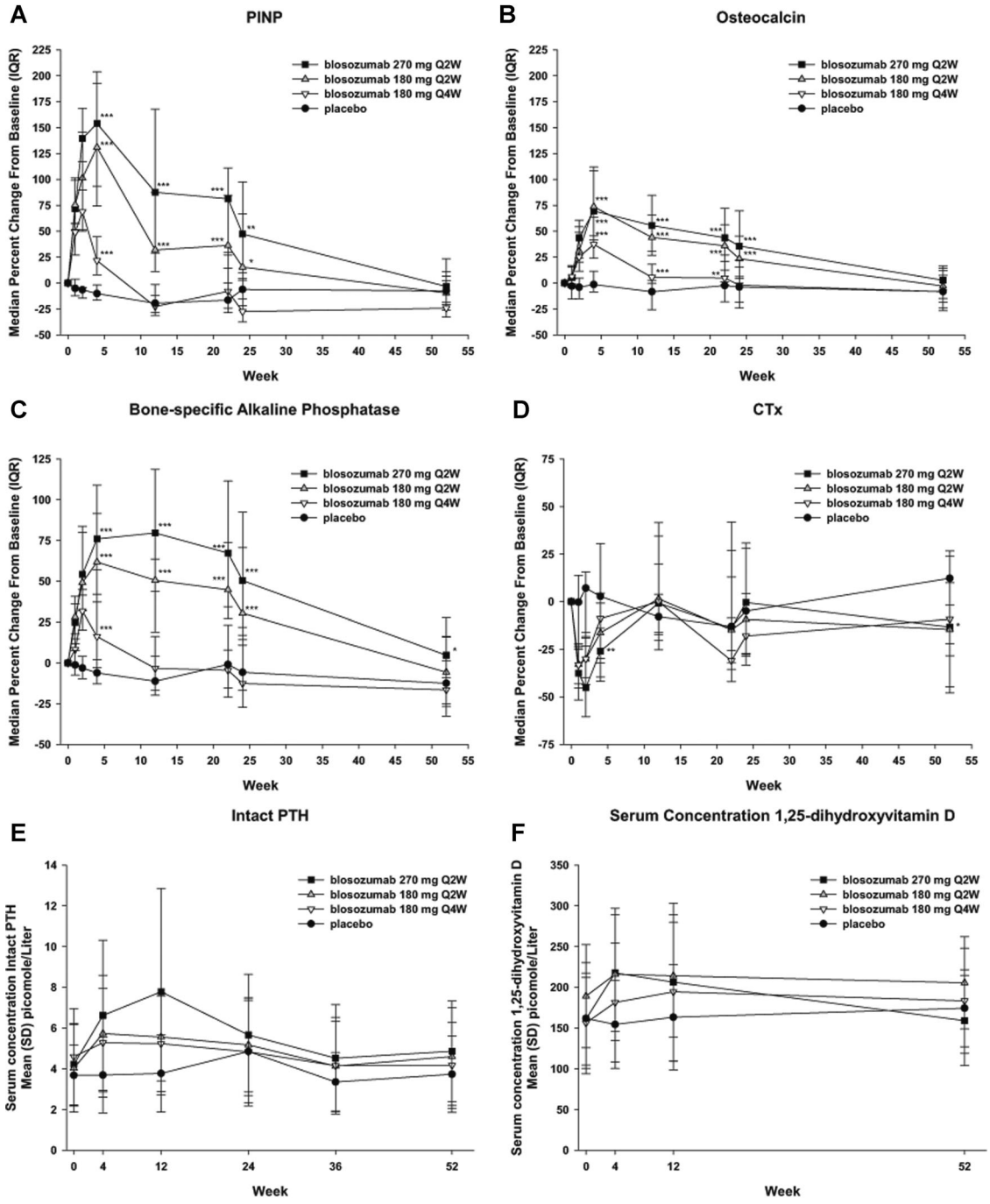

Fig. 5. Median percent change (IQR) in biochemical markers of bone turnover from baseline to week 52 and serum concentration of intact PTH and 1,25-dihydroxyvitamin D from baseline to week 52. Median percent change (IQR) in predose serum concentrations of biochemical markers of bone turnover from baseline to week 52 for all study patients: serum P1NP (*A*); osteocalcin (*B*); bone-specific alkaline phosphatase (*C*); and serum CTx (*D*). Asterisks (*) indicate statistically significant differences ($^{*}p < 0.050$, $^{**}p < 0.010$, $^{***}p < 0.001$) for each study group as compared with placebo. In *A*, in addition to designations of statistical significance provided on the figure, all values for median percent change from baseline in P1NP at weeks 1 and 2 are statistically significant at $p < 0.001$ as compared with placebo. In *B*, in addition to designations of statistical significance provided on the figure, all values for median percent change from baseline in osteocalcin at week 1 are statistically significant at $p < 0.050$ as compared with placebo, and $p < 0.001$ at week 2 as compared with placebo. In *C*, in addition to designations of statistical significance provided on the figure, the values at week 1 for median percent change from baseline in bone-specific alkaline phosphatase are statistically significant at $p < 0.050$ for blosozumab 180 mg Q4W as compared with placebo, and $p < 0.001$ for blosozumab 180 mg Q2W and blosozumab 270 mg Q2W. At week 2, all values for median percent change from baseline in bone-specific alkaline phosphatase are statistically significant at $p < 0.001$ for blosozumab as compared with placebo. In *D*, in addition to designations of statistical significance provided on the figure, all values for median percent change from baseline in CTx are statistically significant at $p < 0.001$ as compared with placebo at weeks 1 and 2. In (E), approximately one-half of the patients in each treatment group had an iPTH assessment at week 24. IQR = interquartile range; P1NP = procollagen type 1 N propeptide; CTx = carboxy-terminal cross-linking telopeptide of type 1 collagen.

during treatment and the 3-month follow-up period was similar across all treatment groups. Mild injection-site reactions, including pruritus, swelling, erythema, bruising, and pain, were reported by 22.6% to 40.0% of women receiving blosozumab and 10.3% of women receiving placebo, and were not associated with the development of anti-drug antibodies. A complete table of treatment-emergent adverse events is included as Supporting Table 1.

There were no patient deaths during the study. Nine patients reported serious adverse events during the treatment period, with only 1 evaluated by a blinded investigator as possibly related to the study drug. This patient, randomized to placebo, experienced a cerebral infarction after 3 weeks of treatment. Breast cancer was reported in 4 women receiving blosozumab: 2 women (270 mg Q2W group) within 3 months of initiating blosozumab treatment, 1 woman (180 mg Q2W group) 3 months after the last dose of blosozumab, and 1 woman (180 mg Q4W group) approximately 1 year after the last dose of blosozumab. All 4 women were Japanese and enrolled in two study sites in Japan. A retrospective exploration of these 4 patients' medical histories provided additional information. One patient, with bone metastases detected at the time of the breast cancer diagnosis, had a mammogram report indicating microcalcifications prior to study enrollment. Two patients had not had a screening mammogram for over 4 years prior to the study, and 1 patient had never had a mammogram. The tumors were heterogeneous with respect to histopathology, receptor status, and stage. None of the investigators considered this serious adverse event to be related to blosozumab treatment.

There was a slight initial decrease in serum calcium (0.01 to 0.05 mmol/L, equivalent to 0.04 to 0.20 mg/dL) in the blosozumab treatment groups that was notable at week 4, with the maximum decrease occurring by week 12. Thereafter, serum calcium fluctuated around baseline for the duration of the study and follow-up period in all treatment groups. As expected with the decrease in serum calcium concentrations, there was a corresponding increase in intact PTH concentrations (0.61 to 3.57 pmol/L, equivalent to 5.8 to 34.0 pg/mL) (Fig. 5E) The increase was noted at week 4 and continued through week 24, returning to normal levels by week 36 and remaining normal through the follow-up period. These observed changes in calcium concentrations were likely a result of rapid bone mineral increase associated with blosozumab treatment, and the changes in PTH were a physiological response to changes in serum calcium concentrations. There were no adverse events associated with the changes in calcium or PTH.

An increase in 1,25-dihydroxyvitamin D concentration was observed in patients during the treatment period. The increase in 1,25-dihydroxyvitamin D concentration appeared to be dose-related in the blosozumab groups, with the peak mean increase of 56.8 pmol/L occurring in the blosozumab 270 mg Q2W group at week 4 (Fig. 5F). At week 12, mean increases in serum concentration of 1,25-dihydroxyvitamin D were 32.0 to 32.7 pmol/L from baseline in the blosozumab 180 mg groups, and 45.4 pmol/L in the blosozumab 270 mg Q2W group. Mean serum concentrations of 1,25-dihydroxyvitamin D declined toward baseline at the end of treatment, with the blosozumab 270 mg Q2W group essentially reaching the level of pretreatment concentration at week 52.

Serum concentration of 25-hydroxyvitamin D was measured at baseline (Table 1) and at the end of the treatment phase. An increase in serum concentration of 25-hydroxyvitamin D was observed in all groups during the treatment period. At the end of treatment, a mean increase from baseline of 2.1 to 12.2 nmol/L was observed in the blosozumab treatment groups, whereas a mean increase from baseline of 10.0 nmol/L was seen in the placebo group. There were no adverse events associated with these changes in vitamin D metabolites.

There were no clinically relevant changes in systolic or diastolic blood pressure, heart rate, or any electrocardiogram parameter at any blosozumab dose during treatment or during the follow-up period.

Thirty-two patients (35%) developed anti-drug antibodies after exposure to blosozumab. The highest incidence was noted in the blosozumab 180 mg Q4W and 180 mg Q2W groups, with increasing occurrence observed over the course of treatment. The development of anti-blosozumab antibodies appeared to be inversely dependent on dose and dose frequency. Only 1 patient (180 mg Q2W group) developed anti-blosozumab antibodies that had an effect on blosozumab exposure and efficacy. Briefly, the treatment-emergent anti-drug antibody was first detected at week 24 with blosozumab serum concentration more than 10-fold lower than the expected level. Based on a validated screening assay, the anti-drug antibody titer reached its maximal level ($>$1:160000) at the end of the treatment, when blosozumab could no longer be detected in serum. The anti-drug antibodies in this patient were found to be neutralizing to blosozumab using a validated neutralizing assay. The BMD responses at the end of treatment were relatively small in this patient, with increases from baseline of approximately 3.2% and 0.2% in lumbar spine BMD and total hip BMD, respectively. There were no adverse events associated with the development of anti-drug antibodies in any of the patients, including the 1 patient with reduced blosozumab exposure.

Pretreatment and posttreatment brainstem auditory-evoked potential testing was performed in a subset of 44 patients. One woman in the blosozumab 180 mg Q2W group began the study with a normal auditory-evoked potential and ended with an observed abnormality. This abnormality was described as probable conductive loss, thought to be secondary to a technical effect, such as ear wax blocking the auditory canal. The results of auditory-evoked potential testing were otherwise unremarkable, as judged by a blinded expert clinician.

Discussion

The dose-related increases in lumbar spine BMD observed at 52 weeks of treatment with blosozumab met the primary objective of the study. Injection of blosozumab, a humanized IgG4 monoclonal antibody designed to neutralize sclerostin, at doses of 180 mg Q4W, 180 mg Q2W, and 270 mg Q2W, increased BMD up to 17.7% at the lumbar spine, and up to 6.7% at the total hip, compared with pretreatment levels. In this patient population at risk for osteoporotic fracture, based on baseline BMD, 72% to 89% of women assigned to one of the every 2 weeks-dosing blosozumab treatment groups experienced an increase in spine BMD to within the range observed in young adult women (*T*-score greater than –2.0). Significant increases in BMD at both the lumbar spine and total hip were clearly shown in the higher dose groups.

Observed increases in total body BMC suggest a net increase in bone at skeletal sites without a disproportionate effect of treatment on the head (skull). Cranial nerve function testing using brainstem auditory-evoked potentials did not detect clinically significant abnormalities. This testing was performed because

compression of the VII and VIII cranial nerves by bone overgrowth is observed in individuals with sclerosteosis and van Buchem disease who have complete loss or deficiency of sclerostin.[26,27] Hence, this finding formed the basis for excluding patients with Bell's palsy or other cranial nerve damage from study enrollment, because preexisting cranial nerve damage might confound the interpretation of safety data in this study.

The serum concentration of P1NP, a biochemical marker of bone formation, increased rapidly during the first 4 weeks of blosozumab treatment, while concurrently the serum concentration of CTx, a biochemical marker of bone resorption, decreased rapidly within the first 2 weeks of treatment to a concentration below that observed with placebo. Although P1NP concentration later trended toward pretreatment levels, CTx concentration remained reduced to study end. The changes in biochemical markers of bone turnover observed with blosozumab treatment, namely increases in biochemical markers of bone formation and the decrease in biochemical marker of bone resorption, are consistent with a skeletal anabolic response to blosozumab therapy. The reasons for transient changes in biochemical markers of bone formation during treatment are unclear. Sampling of marker concentrations occurred predose, during trough concentrations of blosozumab, with no measure of marker concentrations between dosing. The trend in bone formation markers toward baseline later during treatment might be a result of new bone formation in the skeleton reducing stresses and strains within the skeleton, thereby reducing a positive signal for bone formation. In addition, negative counter-regulation of bone formation by molecules such as Dickkopf-related protein 1 (DKK-1) might reduce bone formation.[3] The significant decrease in biochemical markers of bone resorption observed with blosozumab treatment may be related to an inhibitory effect on the RANK-L-RANK osteoclastogenic signaling pathway. In osteoblasts and osteocytes, Wnt-β-catenin signaling is required for expression of the RANK-L decoy receptor osteoprotegerin (OPG).[28] Additionally, sclerostin may upregulate the expression of RANK-L.[29] It is plausible that blosozumab, as an antibody targeted to sclerostin, may decrease RANK-L and increase OPG, with a reduction in the RANK-L to OPG ratio, decreasing bone resorption.[3,29–31]

Observed changes in laboratory assessments are consistent with physiologic efflux of calcium into mineralizing new bone, and were not associated with patient symptoms or adverse events. Further evaluation of the cardiovascular safety of drugs targeting sclerostin, specifically vascular calcification, has been suggested in the literature.[32] The authors cite increasing recognition of Wnt signaling in vascular pathophysiology, and raise the question of whether sclerostin directly affects vascular calcification. However, toxicology studies conducted for the blosozumab development program showed no effect on the vasculature and no effect on cardiovascular risk. A review of patients with sclerosteosis and van Buchem disease does not reveal increased cardiovascular risk factors.[26,27] There have been no reports of vascular calcification in *SOST* knockout mice.[33] The role of Wnt signaling in vascular pathophysiology is an emerging area of exploration, and data from larger phase 3 study populations and increased patient-years of exposure to sclerostin antibodies may provide insight.

Changes in serum concentrations of intact PTH (iPTH) and vitamin D metabolites among patients treated with blosozumab are consistent with the observed physiologic movement of calcium from blood to bone during bone mineralization. This pattern of iPTH response to blosozumab is similar to the dose-related trend reported in the blosozumab phase 1 study by McColm and colleagues.[13] Linking the observed increase in iPTH with the anabolic effect of blosozumab requires consideration of physiologic variables in calcium movement and intricacies of Wnt signaling, and will require further study.

The imbalance in breast cancer cases reported in patients receiving blosozumab has been extensively explored. Screening mammography was not included in the protocol, and is not routinely obtained in some study site locations. Based on timing of the breast cancer diagnosis and size of the tumors, the investigators determined the breast cancers were likely preexisting. Preclinical rat and monkey toxicity studies of blosozumab have not shown an effect on mammary gland histology or increased cell proliferation. Sclerostin mRNA does not appear to be widely expressed in human breast cancer tissue,[34] but additional investigation is ongoing. In addition, in one report of 63 patients with sclerosteosis followed for 38 years, there was no evidence of an increased risk of cancer in general or breast cancer in particular.[35]

Anti-drug antibodies have been noted to occur with low-dose therapy of therapeutic antibodies,[36] a finding in the present study. However, the occurrence of anti-drug antibodies was not associated with adverse events and, in all but 1 anti-drug antibody–positive patient, it did not appear to affect blosozumab exposure or anabolic bone activity of blosozumab.

The findings that blosozumab increases bone formation, decreases bone resorption, and increases spine and total hip BMD are consistent with a recently published report of an antibody targeted to sclerostin.[18] Although blosozumab and romosozumab are both sclerostin antibodies, they are structurally diverse, and indirect comparisons must be made with caution. While there have been no direct comparisons, the blosozumab trial explored high doses, achieved large increases in BMD at the lumbar spine and hip, and included measures of total body and skull BMC. The potential significance of the findings we report herein is the substantial anabolic effects on the skeleton achieved with blosozumab treatment, supporting further investigation of blosozumab as a potential therapy for osteoporosis. Further study of blosozumab will continue to assess the efficacy and safety of blosozumab in the treatment of osteoporosis.

In conclusion, injections of blosozumab for 1 year resulted in substantial anabolic effects on the skeleton and were well tolerated. These findings support further investigation of blosozumab as a potential therapy for osteoporosis.

Disclosures

RRR received consulting fees for protocol design related to the submitted work, consultancy and grants with Merck outside the submitted work, and consultancy with Novartis outside the submitted work. TM received consultant fees or honorarium and travel support to meetings for the study related to the submitted work, and reports board membership, consultancy, and payment for lectures including speakers bureaus outside the submitted work for Eli Lilly and Company. MB has no disclosures to report. CB, DB, JA, AYC, LH, JHK, HS, BM, and SM are employees of Eli Lilly and Company and stockholders in the company, which is the sponsor of the submitted work.

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RESEARCH ARTICLE

Comparison of Bone Mineral Density in Lumbar Spine and Fracture Rate among Eight Drugs in Treatments of Osteoporosis in Men: A Network Meta-Analysis

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Abstract

Context

The preferred treatment for osteoporosis in men is debated, and pairwise meta-analysis cannot obtain hierarchies of these treatments.

Objective

The objective of this study was to integrate the evidence and provide hierarchies of eight drugs based on their effect on the bone mineral density in the lumbar spine (BMD in LS) and the fracture rate.

Data Sources

Eligible studies were identified by searching Amed, British Nursing Index, EMBASE, PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), Google Scholar, SIGLE, the National Technical Information Service, the National Research Register (UK), and the Current Controlled Trials databases.

Study Selection

RCTs or quasi-RCTs reporting at least two drugs (two active drugs or one active drug and a placebo) used to treat osteoporosis in men were selected by two authors.

Data Extraction

Two authors independently extracted the data.

Data Synthesis

Thirteen studies involving 3647 patients were included. Compared with placebo therapy, zoledronate (SMDs 13.48, 95% credible intervals 11.88-15.08) yielded the most significant effect on increasing the BMD in LS, followed by alendronate (11.04, 9.68-12.41), teriparatide (20mcg) + risedronate (10.98, 8.55-13.48), risedronate (10.33, 8.68-12.01), teriparatide (20mcg) (9.33, 6.87-11.76), strontium ranelate (8.88, 7.51-10.24), ibandronate (5.49, 3.82-7.16), parathyroid hormone (1-84) (4.89, 3.12-6.62) and alfacalcidol (3.42, 1.7-5.2). Placebo therapy had a significantly higher fracture rate in contrast to risedronate (OR 2.51, 95% CrI 1.23-4.24) or zoledronate (2.92, 1.29-5.62) or teriparatide (20mcg) (4.04, 1.36-8.49) or teriparatide (40mcg) (3.5, 1.14-8.34). Zoledronate ranked first for increasing the BMD in LS, and teriparatide (20mg) was ranked first for decreasing the fracture rate.

Conclusions

Zoledronate might be the best choice to increase the BMD in LS and teriparatide (20mg) might lead to the lowest fracture rate.

Introduction

Osteoporosis is a common disease that impairs bone mass and bone microarchitecture and is a major cause of fragility fracture [1]. The fracture rate varies in different countries, and there has been a trend for the occurrence of fractures to decline in recent years [2]. Studies with a long follow-up duration, demonstrate that osteoporotic fractures lead to an increase in death, destitution and debility [3]. Several cohort studies indicate that improvement in the bone mineral density (BMD) reduces the osteoporotic fracture rate, although discrepancies in the literature also exist [4, 5].

Anti-resorptive drugs and bone-anabolic drugs are two main classes of the drugs to treat osteoporosis. Anti-resorptive drugs mainly include bisphosphonates, raloxifene and strontium ranelate, and the latter two are suggested for use in women with postmenopausal osteoporosis. Bisphosphonates (e.g., alendronate, risedronate, ibandronate and zoledronate) are widely used in postmenopausal women, men, and those with steroid-induced osteoporosis or with as Paget's disease because of their high affinity for bone, low costs and safety [6, 7]. Parathyroid hormone (PTH 1–84) and teriparatide (PTH 1–34) belong to the bone-anabolic drug class as they can build up new bone, and the duration of their use is limited to 24 months due to the safety concerns [7–9]. Some randomized controlled trials (RCTs) have proved that alfacalcidol which is an active form of vitamin D is an effective and safe drug to treat osteoporosis [10, 11]. However, debates exist as to which therapy should be used first.

We aimed to compare the BMD in the lumbar spine (LS) and the fracture rate in osteoporotic men being treated with eight drugs (alfacalcidol, alendronate, ibandronate, risedronate, zoledronate, strontium ranelate, teriparatide and parathyroid hormone). Our intention was to provide hierarchies of the comparative BMD in LS and the fracture rate of the drugs. Therefore, a network meta-analysis was performed.

Methods

Criteria for considering studies

Studies were considered acceptable for inclusion in the meta-analysis if they met the following criteria: (1) Participants: Men with primary or idiopathic osteoporosis. For some studies

including hypogonadal men, considering the number of these patients was small which had limited effect on the results, we also included these studies; (2) Interventions and comparisons: Therapy regimens that included two of the following drugs or one drug and a placebo: alfacalcidol, alendronate, ibandronate, risedronate, zoledronate, strontium ranelate, teriparatide and parathyroid hormone; (3) Outcomes: the BMD in LS (we chose the BMD in LS because the number of the studies reported LS was the largest. With the largest number of included patients, the results based on LS was more reliable than the results from the other sites) and the fracture rate; (4) Study design: randomized controlled trials (RCTs) or quasi-RCTs.

Trials were excluded if: (1) they were abstracts, letters, or meeting proceedings; (2) they contained repeated data or did not report the outcomes of interest; or (3) the duration of follow-up was $<$ 12 months.

Search methods and study selection

We searched Amed (from 1985 to May 2014), British Nursing Index (from 1985 to May 2014), EMBASE (from 1974 to May 2014), PubMed (from 1966 to May 2014), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, most recent issue), Google scholar, SIGLE (System for Information on Grey Literature in Europe) and clinicaltrials.gov. Keywords and MeSH terms including "alfacalcidol", "alendronate", "ibandronate", "risedronate", "zoledronate", "strontium ranelate", "teriparatide", "parathyroid hormone", "men or male" and "osteoporosis" were used in the search strategy. We performed a primary search pertaining to vitamin D and osteoporosis in PubMed and found no relevant RCT involving vitamin D and osteoporosis in men except for alfacalcidol. So we searched other databases for studies using alfacalcidol. We also viewed the reference list of the included studies for any additional papers. We included only articles written in English.

Two authors independently made the selection based on the title and abstract. Any disagreement between the two authors was resolved by a discussion. If there was no consensus, a third reviewer (Feng) was consulted.

Data extraction and assessment for risk of bias

Information including trial name, sample size, comparators, country, clinical setting and maximum follow-up time were extracted by the two authors for each included study. Dichotomous data were used for reporting the fracture rate. The fracture rate was referred to as the incidence of new vertebral fractures, which was determined by radiograph of the vertebral column. The fracture rate was reported as odds ratios (ORs) with a 95% confidence interval (CI) for direct comparisons or 95% credible intervals (CrI) for indirect comparisons. For continuous data (e.g., BMD in LS), the standardized mean differences (SMDs) with a 95% CI for direct comparisons or CrI for indirect comparisons were used. We contacted the first or corresponding author of the included trials to obtain any missing information. We used the Cochrane risk of bias tool to assess the risk bias of the included studies [12]. The tool included seven domains that included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias (funding and baseline imbalance). The judgment for each domain was a low risk of bias (sufficient information to describe the right methods), a high risk of bias (sufficient information to describe the wrong methods), or an unclear risk of bias (insufficient information to describe the methods) and two authors independently evaluated the risk of the studies.

Data synthesis and analysis

Two outcomes (BMD in LS and fracture rate) were analyzed. To evaluate whether there was inconsistency between direct and indirect evidence, we compared the pooled ORs or SMDs calculated from the network meta-analysis with the corresponding effect size from pair-wise meta-analysis. At first, we made pairwise meta-analyses for studies that directly compared different treatments using Stata software (version 12.0, StataCorp, College Station, TX). The DerSimonian and Laird random effects model was used. Chi-square tests and I-square tests were used for testing heterogeneity between studies. For publication bias, we would use the funnel plots if the number of included studies in one pair of comparison was larger than 10. Then, network meta-analysis was performed using WinBUGS (version 1.4.3, MRC Biostatistics Unit, Cambridge, UK) with random effects models developed by Chaimani (downloaded from www.mtm.uoi.gr). For the network meta-analysis, the posterior parameters were calculated by Markov chain Monte Carlo methods. Non-informative uniform and normal prior distributions were performed to fit the model [13]. An automatically generated starting value was used to fit the model [13]. For each analysis, we used 300,000 iterations after an initial burn-in of 50,000 [14]. To rank the treatments, we used the surface under the cumulative ranking probabilities (SUCRA) to indicate which treatment was the best one [15]. Finally, the robustness of the model was tested by calculating the posterior mean residual deviance [16] with R (version 3.1.1, R Foundation for Statistical Computing, Vienna, Austria). When the posterior mean residual deviance approximated the data points, the model fit the data well. Sensitivity analyses were performed by excluding studies with a high risk of bias.

There was no protocol.

Results

Study selection and characteristics of included studies

The PRISMA flow diagram of studies is depicted in Fig 1. The last electronic search was performed on May 25th, 2014 and identified 836 related references in the primary search and 47 through other sources. After removal of 231 duplicate references, 652 records were screened. Twenty-seven publications were eligible for inclusion criteria, whereas others were not selected for various reasons (e.g., studies without a control group or that included non-osteoporotic patients). A total of 13 studies were included in the qualitative synthesis, and data from these studies were included in the meta-analysis [17–29]. Fourteen studies were excluded: 2 studies due to a follow up time of less than 12 months [30, 31] and 12 studies due to not reporting the outcomes of interest [32–43].

Table 1 provides a summary of the studies included in the review. A total of 3647 participants were included in this meta-analysis. The study sample size ranged from 23 to 1199. These studies were published between 2000 and 2013.

Risk of bias in included studies

Fig 2 shows the risk of bias in all 13 studies. Six studies described random sequence generation. Only one study described adequate allocation concealment. Seven studies described blinding of participants and personnel. Four studies did not blind to participants and personnel. Three studies described blinding of outcome assessment. One study had a high risk of bias in blinding of outcome assessment. Nine studies had a low risk of incomplete outcome data. One study was considered as a high risk of incomplete outcome data. Ten studies had a low risk of selectively reporting results.

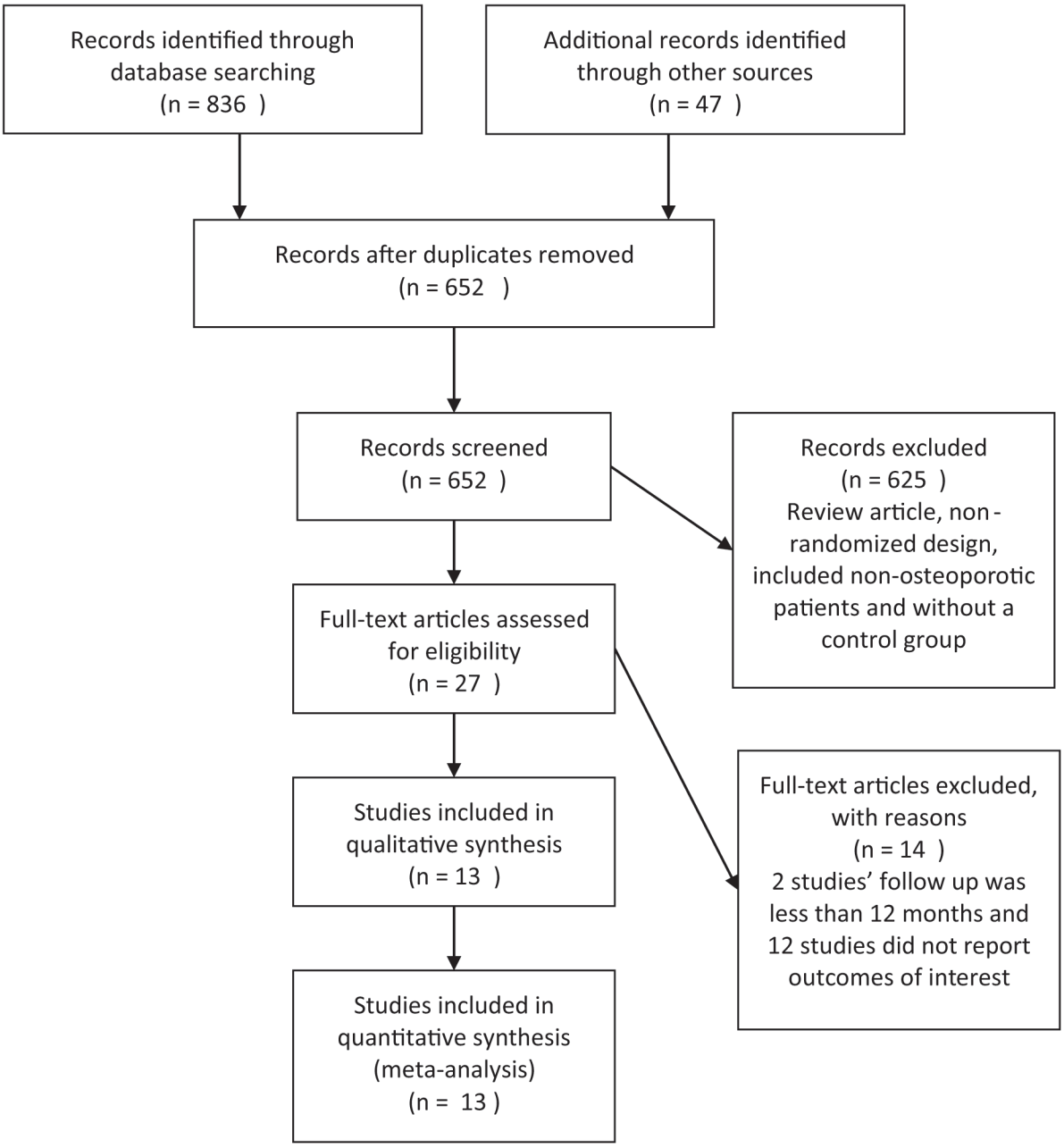

Fig 1. PRISMA flow diagram.

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BMD in LS

The network of comparisons on the BMD in LS is shown in Fig 3A. A total of 916 patients were assigned to placebo therapy, 588 to zoledronate therapy, 335 to alendronate therapy, 237 to strontium ranelate therapy, 198 to risedronate therapy, 132 to alfacalcidol therapy, 85 to ibandronate therapy, 13 to parathyroid hormone (1–84) therapy, 10 to teriparatide (20mcg) + risedronate therapy and 9 to teriparatide (20mcg) therapy.

Compared with placebo therapy, zoledronate (SMDs 13.48, 95%CrI 11.88–15.08) yielded the most significant effect on increasing the BMD in LS, followed by alendronate (11.04, 9.68–

Table 1. Study Characteristics.

Trial	Sample size	Comparators	Country	Follow-up	Clinical setting
2000,Orwoll	241	ALE v PLA	Multicenter	24 months	PO
2001,Ringe	134	ALE v ALF	Germany	24 months	PO
2004,Ringe	134	ALE v ALF	Germany	36 months	PO
2009,Boonen	284	RIS v PLA	Multicenter	24 months	PO
2010,Orwoll	135	IBA v PLA	USA	12 months	PO;IO;HO
2010,Orwoll	302	ZOL v ALE	Multicenter	24 months	PO;HO
2012,Boonen	1199	ZOL v PLA	Multicenter	24 months	PO;HO
2010,Ringe	152	STR v ALE	Germany	12 months	PO
2013,Kaufman	261	STR v PLA	Multicenter	24 months	PO
2005,Kaufman	437	TER(20μg) v TER(40μg) v PLA	Multicenter	48 months	IO;HO
2013,Walker	29	RIS v TER(20μg) v Both	USA	18 months	IO
2009,Ringe	316	RIS v PLA	Germany	24 months	PO
2000,Kurland	23	PTH v PLA	USA	18 months	IO

ALE: Alendronate; PLA: Placebo; ALF: Alfacalcidol; RIS: Risedronate; IBA: Ibandronate; ZOL: Zoledronic Acid; STR: Strontium Ranelate; TER: Teriparatide; PTH: Parathyroid Hormone; PO: Primary Osteoporosis; IO: Idiopathic Osteoporosis; HO: Hypogonadal Osteoporosis

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12.41), teriparatide (20mcg) + risedronate (10.98, 8.55–13.48), risedronate (10.33, 8.68–12.01), teriparatide (20mcg) (9.33, 6.87–11.76), strontium ranelate (8.88, 7.51–10.24), ibandronate (5.49, 3.82–7.16), parathyroid hormone (4.89, 3.12–6.62) and alfacalcidol (3.42, 1.7–5.2). Except for teriparatide (20mcg) + risedronate therapy (2.5, -0.41–5.47), zoledronate therapy was better than other active therapies: 2.44 (0.36–4.55) for alendronate, 10.06 (7.66–12.46) for alfacalcidol, 3.14 (0.83–5.49) for risedronate, 7.98 (5.73–10.28) for ibandronate, 4.6 (2.51–6.72) for strontium ranelate, 4.15 (1.23–7.11) for teriparatide (20mcg) and 8.58 (6.27–10.93) for parathyroid hormone (1–84). Details pertaining to other comparisons are listed in S1 Table. The result of the model test showed that the posterior mean residual deviance (23.73) approximated the data points (21), which confirmed the fitness of the model.

Fracture rate

The network of comparisons on the fracture rate is shown in Fig 3B. A total of 1142 patients were assigned to placebo therapy, 707 to zoledronate therapy, 506 to alendronate therapy, 353 to risedronate therapy, 196 to strontium ranelate therapy, 132 to alfacalcidol therapy, 101 to teriparatide (20mcg) therapy, 86 to ibandronate therapy, 84 to teriparatide (40mcg) therapy, 10 to parathyroid hormone (1–84) therapy and 10 to teriparatide (20mcg) + risedronate therapy.

The use of placebo therapy resulted in a significantly higher fracture rate in contrast to risedronate (OR 2.51, 95% CrI 1.23–4.24) or zoledronate (2.92, 1.29–5.62) or teriparatide (20mcg) (4.04, 1.36–8.49) or teriparatide (40mcg) (3.5, 1.14–8.34). Alfacalcidol therapy significantly increased the fracture rate compared with risedronate (7.66, 1.74–19.27) or zoledronate (8.41, 2.12–20.03) or strontium ranelate (5.21, 1.32–11.88) or teriparatide (20mcg) (12.12, 2.17–33.84) or teriparatide (40mcg) (10.49, 1.83–30.47). There were no significant differences between other therapies. The details of other comparisons are listed in S2 Table. The result of the model test showed a posterior mean residual deviance (26.23) that approximated the data points (28), which confirmed the fitness of the model.

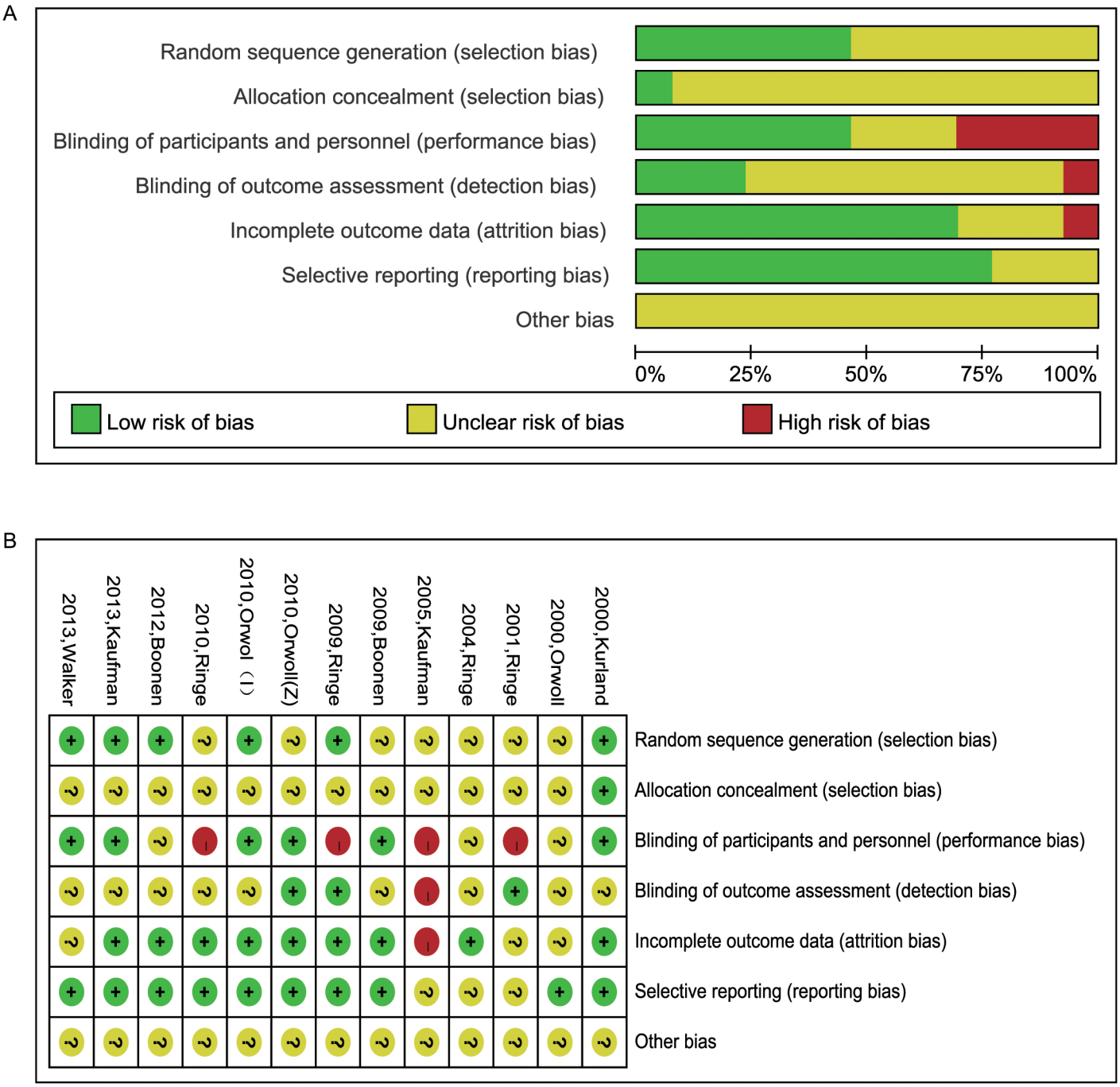

Fig 2. Risk of bias graph and summary. Panel A: Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies. Panel B: Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

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Comparisons between traditional pairwise and Bayesian network meta-analyses

The results of the pairwise and Bayesian network meta-analysis are shown in Fig 4 and S1 Fig. The CI from the pairwise meta-analyses and the CrI from the Bayesian network meta-analyses

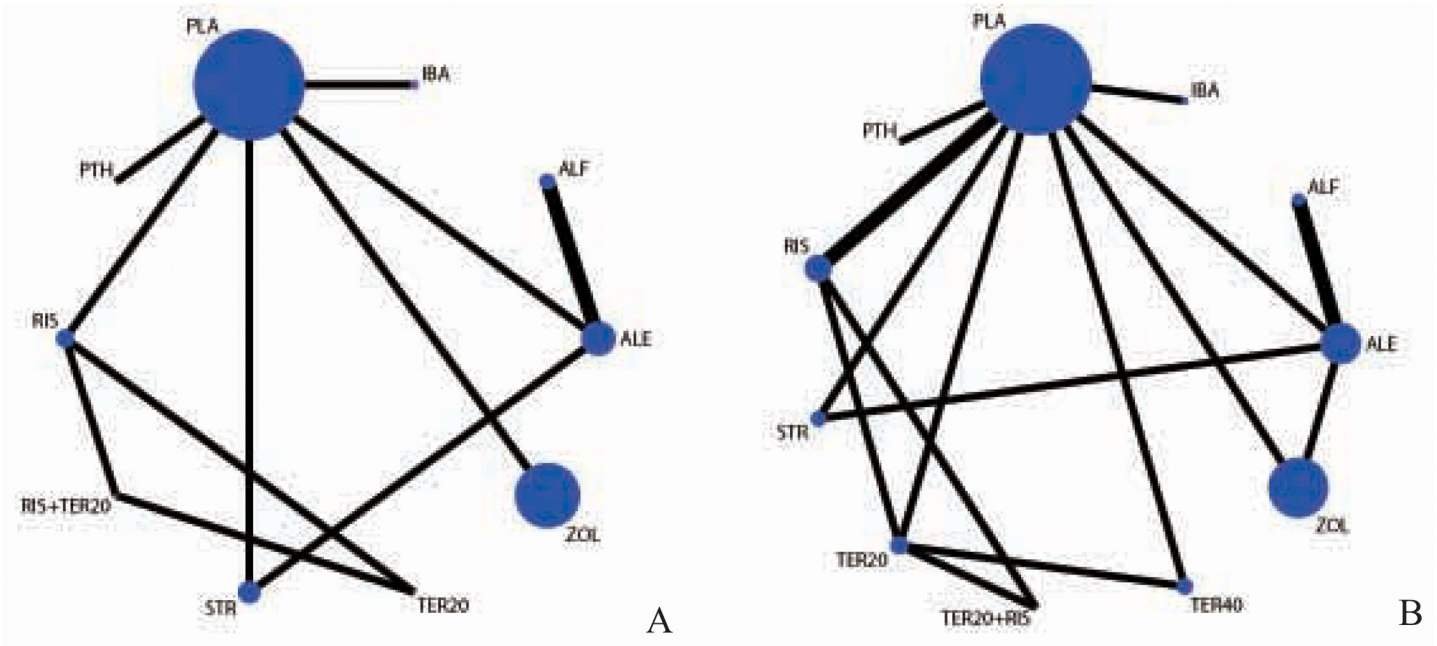

Fig 3. Network of treatment comparisons. The size of the nodes represents the total sample size of treatments. The lines' thickness corresponds to the number of trials that compare each other. Panel A: Network of treatment comparisons for the BMD in LS. Panel B: Network of treatment comparisons for the fracture rate. ALE: Alendronate; PLA: Placebo; ALF: Alfacalcidol; RIS: Risedronate; IBA: Ibandronate; ZOL: Zoledronate; STR: Strontium Ranelate; TER: Teriparatide; PTH: Parathyroid Hormone.

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almost overlapped, which indicated that there were no inconsistencies between direct and indirect comparisons.

Ranking of treatments

In Fig 5, we summarized the ranking of eight drugs for eleven treatment strategies in terms of the BMD in LS and fracture rate—with details supplied in S3 Table. For increasing the BMD in LS, zoledronate might be the best therapy and placebo most likely the worst. For decreasing the fracture rate, teriparatide (20mcg) might be the best option, and alfacalcidol ranked the lowest.

Publication bias and sensitivity analyses

The funnel plots were not performed because the number of included studies in one comparison was less than 10. Overall, the sensitivity analyses (S4 Table and S5 Table) did not change the results.

Discussion

Summary of main results

The network meta-analysis provided hierarchies for the BMD in LS and the fracture rate of the different therapies in men with osteoporosis. The meta-analysis indicated that: For increasing the BMD in LS, zoledronate might be the best therapy and placebo might be the worst one. For decreasing the fracture rate, teriparatide (20mcg) might be the best option and alfacalcidol might the worst one.

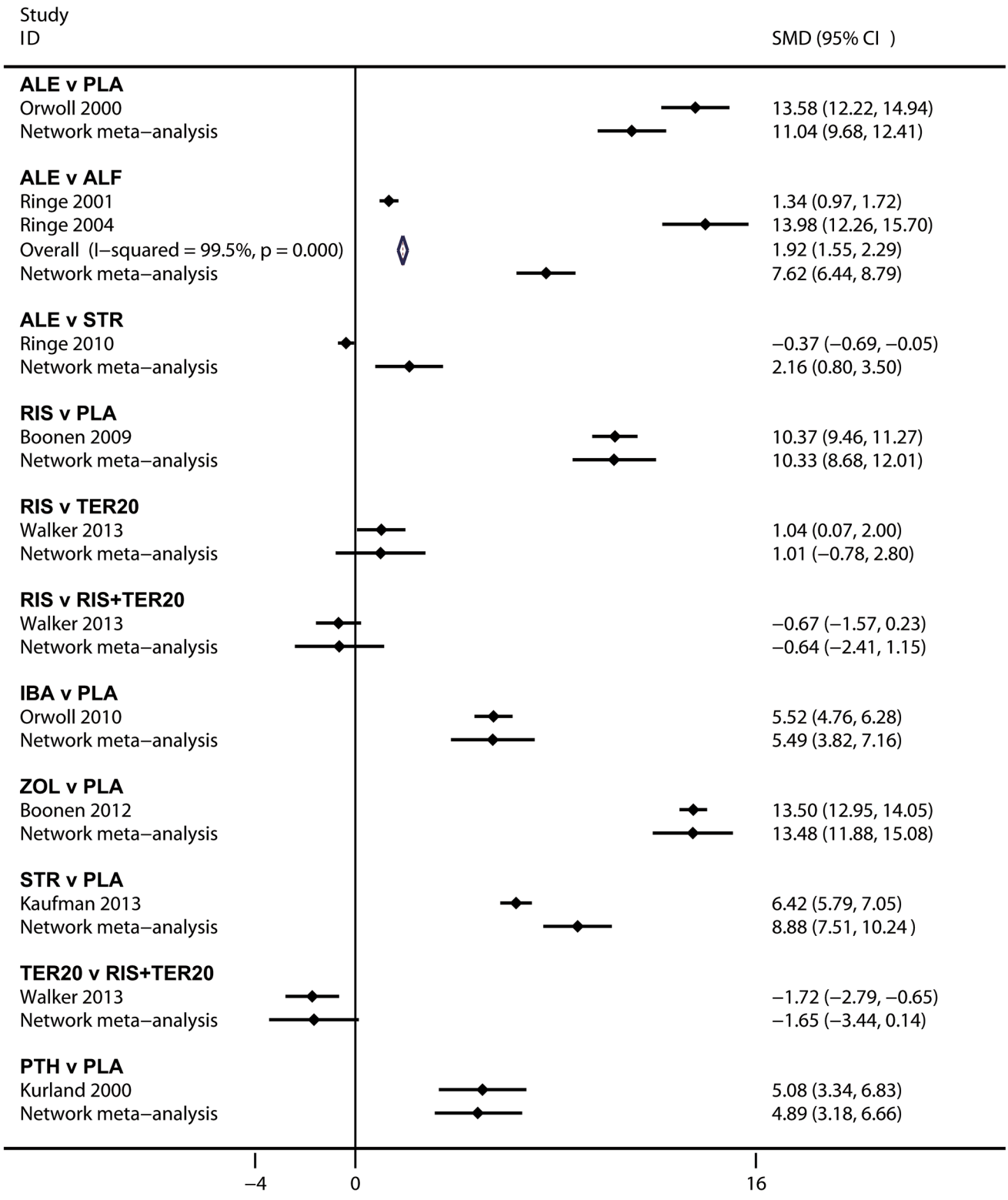

Fig 4. Pooled SMD for the BMD in LS by Bayesian network meta-analysis and traditional meta-analysis. ALE: Alendronate; PLA: Placebo; ALF: Alfacalcidol; RIS: Risedronate; IBA: Ibandronate; ZOL: Zoledronate; STR: Strontium Ranelate; TER: Teriparatide; PTH: Parathyroid Hormone.

doi:10.1371/journal.pone.0128032.g004

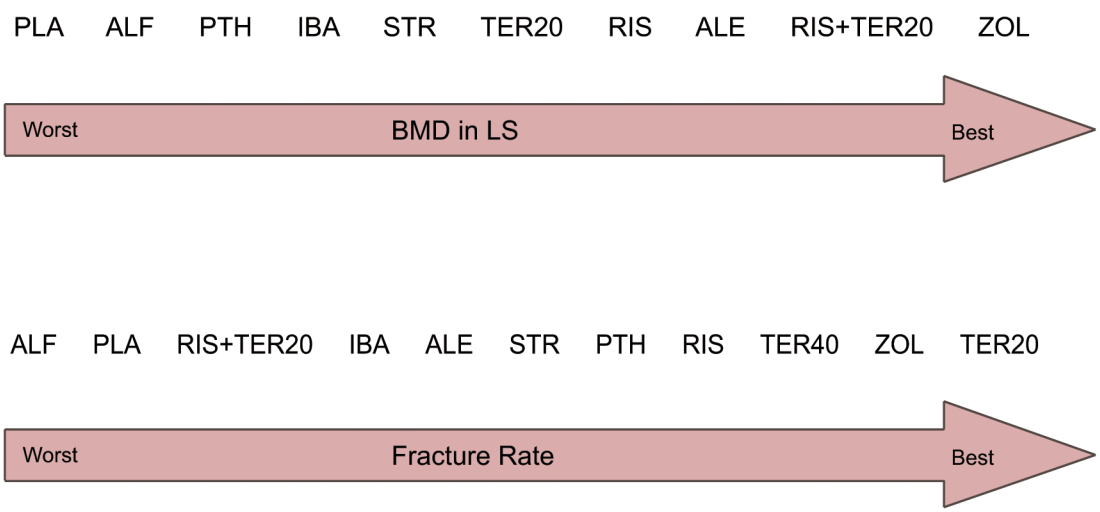

Fig 5. Ranking of treatments in terms of the BMD in LS and fracture rate. ALE: Alendronate; PLA: Placebo; ALF: Alfacalcidol; RIS: Risedronate; IBA: Ibandronate; ZOL: Zoledronate; STR: Strontium Ranelate; TER: Teriparatide; PTH: Parathyroid Hormone.

doi:10.1371/journal.pone.0128032.g005

Strengths and weaknesses

There are some strengths in this paper: (1) we used a comprehensive search strategy to minimize the possibility of publication bias, (2) we included the result of direct comparisons and indirect comparisons, and (3) we tested the fitness of the model. However, the result of the review should be interpreted under some limitations. First, both the number of the included studies and the sample size were small, which might affect the outcome. For the BMD in LS, zoledronate, ibandronate, teriparatide (20mcg), parathyroid hormone (1–84) and teriparatide (20mcg) + risedronate were analyzed in only one study. Moreover, the sample size for the latter four drugs was less than 100. For the fracture rate, ibandronate, parathyroid hormone (1–84) and teriparatide (20mcg) + risedronate were mentioned in one study and their sample size was less than 100. Therefore, the results presented in this meta-analysis need to be carefully interpreted. Second, some study characteristics such as performance bias and detection bias might be potential interferences for our study. Third, there was substantial heterogeneity due to the inconformity regarding the duration of follow-up. Fourth, most of included studies (61.53%) were placebo-controlled trials that might overestimate the beneficial effect of the active therapies. Fifth, for the studies where the fracture rate was a secondary outcome, the number of measuring time point was insufficient which might underestimate the fracture rate. For example, in one study performed by Ringe et al, the BMD was measured at baseline and at 6, 12, 18, 24 months. The definitive fracture was measured at baseline and at 12, 24 months. Therefore, some fracture events might be missed due to the healing of fracture in 6 months. We should cautiously interpret the results due to the underestimate of the fracture rate to some extent. Sixth, our article used summary data instead of individual patient data, which might lead to the loss of some covariates at the individual patient level. Seventh, due to some hypogonadal men [Two of included studies mentioned the detailed number of the patients and the number of hypogonadal men is small (7.9%, 24/302 in Orwoll 2011; 0.25%, 3/1199 in Boonen 2012)] were including in our article, some potential biases were introduced to our results. The sensitivity analysis by excluding the hypogonadal men could not be performed due to the relevant data could not be extracted. Finally, because four studies had a high risk of bias in blinding of participants and personnel, one study did not blind to outcome assessment and one study had a high

risk of bias in incomplete outcome data, the performance, detection and attribution bias might affect the results.

Agreements and disagreements in the current literature

Prior meta-analyses have mainly focused on postmenopausal osteoporosis or osteoporosis in both males and females; however, less is known about osteoporosis in men. Although previous studies have mixed combinations, the rank methods are relatively rough and their including drugs are not comprehensive [44–46]. Therefore, we performed this network meta-analysis. Only one previous meta-analysis included men with osteoporosis and its results showed that both antiresorptive treatments (alendronate, risedronate, ibandronate, nasal miacalcic and zoledronate) and anabolic treatments (teriparatide) significantly increased spine BMD. For reducing the incidence of fractures, the results are inconclusive [47]. Overall, our results agree with previous research. In addition, our article supports current guidelines to use bisphosphonates (alendronate, risedronate, ibandronate and zoledronate), teriparatide and alfacalcidol in patients with osteoporosis [48, 49] and makes hierarchies of these drugs that previous reviews did not include.

Currently, one RCT for parathyroid hormone has been completed, but data pertaining to this RCT has not been published. Results from this RCT might add new evidence for treating osteoporosis in men [50]. Moreover, data from a completed cohort study with a maximum follow-up duration of 17 years is waiting to be analyzed, and this study investigated the long-term efficacy and tolerability of different treatments in men with osteoporosis (however, no detailed drugs were mentioned) [51].

Conclusions

This meta-analysis provides evidence that zoledronate might be the best choice to increase the BMD in LS and teriparatide (20mcg) might lead to the lowest fracture rate. Placebo and alfacalcidol might the worst option in increasing the BMD in LS and decreasing the fracture rate, respectively. Higher quality RCTs and direct head to head trials are needed to confirm these results.

Supporting Information

S1 Fig. Pooled odds ratio for fracture rate by Bayesian network meta-analysis and traditional meta-analysis.
(EPS)

S1 File. A list of full-text excluded articles.
(DOC)

S1 PRISMA Checklist. PRISMA Checklist for this meta-analysis.
(DOC)

S1 Table. The BMD in LS for different treatments.
(DOC)

S2 Table. The fracture rate for different treatments.
(DOC)

S3 Table. The SUCRA of different therapies in different outcomes.
(DOC)

S4 Table. Sensitivity analysis: the BMD in LS for different treatments (exclude trials with a high risk of bias).
(DOC)

S5 Table. Sensitivity analysis: the fracture rate for different treatments (exclude trials with a high risk of bias).
(DOC)

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Xiao-bo Wang and Yong Zhou have contribution in extracting the data.

Author Contributions

Conceived and designed the experiments: LXC SQF. Performed the experiments: LXC YLL. Analyzed the data: ZRZ GZN. Contributed reagents/materials/analysis tools: TSZ DZ. Wrote the paper: LXC.

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Increased Risk of Sudden Sensorineural Hearing Loss in Patients With Osteoporosis: A Population-based, Propensity Score-matched, Longitudinal Follow-Up Study

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Context: Previous studies have reported an increased prevalence of sudden sensorineural hearing loss (SSNHL) in osteoporotic patients. However, the risk of SSNHL in this population remains unclear.

Objective: This study investigated the risk of SSNHL in osteoporotic patients.

Setting: Taiwan launched a single-payer National Health Insurance (NHI) program on March 1, 1995. NHI covers nearly all of Taiwan's residents.

Design: Using randomized representative sample of one million individuals from Taiwan's National Health Insurance claims database, we compared the data of 10 660 patients with newly diagnosed osteoporosis from 1998–2008 and with 31 980 patients without osteoporosis. All patients were tracked until SSNHL was diagnosed, death, or the end of 2011. Osteoporosis was identified based on a primary diagnosis of osteoporosis (ICD-9-CM code 7330) by dual-energy x-ray absorptiometry.

Intervention: Identified the diagnosis of osteoporosis and SSNHL by ICD-9CM code.

Main Outcome Measure: The identification of patients with newly diagnosed SSNHL by ICD-9CM code.

Results: The incidence rates of SSNHL in the osteoporosis cohort and comparison group were 10.43 and 5.93 per 10 000 person years. Patients with osteoporosis were at 1.76 times the risk of developing SSNHL than patients without osteoporosis. The incidence rate ratio (IRR) for SSNHL was significantly greater in older (50–64 y and ≥65 y), and female patients, and borderline greater in hypertensive patients with osteoporosis than the controls, IRRs being 1.50, 2.33, 1.87, and 1.59.

Conclusions: Patients with osteoporosis are at significantly greater risk of developing SSNHL. **(*J Clin Endocrinol Metab* 100: 2413–2419, 2015)**

Osteoporosis is a common skeletal condition characterized by systemic impairment of bone mass, strength, and microarchitecture, resulting in skeletal fragility and increased risk of fractures (1). The World Health Organization defines osteoporosis as a bone mineral density (BMD) T-score less than −2.5 measured by dual-emis-

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Abbreviations: BMD, bone mineral density; CAD, coronary artery disease; CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; IRR, incidence rate ratio; LHID2000, Longitudinal Health Insurance Database 2000; NF-κB, nuclear factor-κB; NHI, National Health Insurance; PY, person years; SSNHL, sudden sensorineural hearing loss.

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sion x-ray absorptiometry. A growing body of evidence is showing a correlation between skeletal disease and systemic inflammatory responses and endothelial dysfunctions. One cross-sectional study reported severe bone loss to be an independent risk factor for brain infarction (2). Another study suggested that lower BMD may be associated with increased risk of myocardial infarction (3). Therefore, osteoporosis is very probably a systemic disease rather than a disease affecting the bones only.

There are three types of hearing loss: sensorineural, conductive, and mixed. Conductive hearing loss involves the middle and outer ear whereas sensorineural hearing loss involves the inner ear, cochlea, or the auditory nerve (4). Sudden sensorineural hearing loss (SSNHL) is an acute, unexplained loss of hearing. The U.S. National Institute on Deafness and other Communication Disorders defined SSNHL as a loss of greater than 30 dB in three contiguous frequencies in less than 3 days. Most cases of SSNHL are idiopathic. There are several possible etiologies of SSNHL, including local vascular abnormalities, viral infection, immune-mediated mechanisms, chronic inflammation, and abnormalities of the inner ear (5–8). Previous studies have also shown that SSNHL increases the risk of subsequent stroke and myocardial infarction (9, 10).

Although osteoporosis and SSNHL are complex and heterogeneous disorders and are related to cerebrovascular and cardiovascular disease, the relationship between the two diseases remains undetermined. One study mentioned a possible association between idiopathic osteoporosis and decreased hearing function (11). Another study proposed an association between lower femoral neck bone mass and SSNHL (12). However, one study investigating 120 postmenopausal women, showed no statistical significance at low frequencies, irrespective of BMD values (13). These previous studies were of small sample sizes or cross-sectional designs and their results were inconclusive. Therefore, we used a nationwide population-based insurance dataset to conduct a follow-up study investigating the risk of SSNHL in 10 660 patients with osteoporosis compared with 31 980 age-matched unaffected individuals in Taiwan by propensity-score matching for underlying comorbidities.

Materials and Methods

Data sources

Taiwan launched a single-payer National Health Insurance (NHI) program on March 1, 1995. NHI claims database, which covers nearly all of Taiwan's residents (coverage rate >98% in 2009), is one of the largest and most complete population-based datasets in the world. Data used in this study were obtained from NHI's Longitudinal Health Insurance Database 2000 (LHID2000), a subdataset of NHI database, which contains all claims data (from 1996–2011) of one million beneficiaries who were systemic-randomly selected in 2000. There is no significant difference in age, sex, and health care costs between the sample group and all enrollees. The LHID2000 provides encrypted patient identification numbers, sex, date of birth, dates of admission and discharge, the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes of diagnoses and procedures, details of prescriptions, registry of catastrophic illness patient database, and costs covered and paid for by NHI. The institutional review board of Chi Mei Medical Center approved the study and waived the requirement of informed consent because the datasets we analyzed were devoid of identifiable personal information.

Study sample

A retrospective cohort study was conducted with two study groups—a newly onset osteoporosis group and a matched nonosteoporosis (comparison) group recruited 1999–2008. Osteoporosis was identified in patients with claims data containing a primary diagnosis of osteoporosis (ICD-9-CM code 7330) by dual-energy x-ray absorptiometry. In Taiwan, osteoporosis is defined as a T-score of −2.5 SD or less at the spine, hip, or forearm. Patients who were diagnosed as having osteoporosis before 1999 were excluded. Patients who were diagnosed as having SSNHL (ICD-9-CM code 388.2) before osteoporosis were also excluded.

From the same dataset, we randomly selected control patients (three per osteoporosis patient) who were not diagnosed with osteoporosis. They were matched using a propensity score by age, sex, area, income and comorbid diabetes mellitus (DM), hypertension, chronic kidney disease, and coronary artery disease (CAD) status. Propensity-score matching was used to reduce selection bias because it can be used to bundle many confounding covariates that may be present in an observational study with this number of variables. Propensity scores were computed by modeling a logistic regression model with the dependent variable as the odds of diagnosis of osteoporosis, and the independent variables as the age at which DM was diagnosed (±30 d), sex, and selected comorbidities, area, and income. Then, a SAS matching macro "%OneToManyMTCH" was used following a recommendation proposed in the proceedings of the 29th SAS Users Group International (14). This macro matching allows propensity score matching from 1-to-1 to 1-to-N based on specifications from the user. The macro makes "best" matches first and "next-best" matches next, in a hierarchical sequence until no more matches can be made. Each control is selected at most once. The final matched-pair samples contain both closely matched individual pairs and balanced case and control groups. We also recorded claims data on comorbid disorders, including DM (250), hypertension (401–405), chronic kidney disease (582, 583, 585, 586, 588), and CAD (410–414) status. We counted these comorbid conditions if they were diagnosed in either an inpatient setting or in three or more ambulatory care claims coded 1 year before the index medical care date. Person years (PY) of follow-up time were calculated for each person until SSNHL was diagnosed, death, or the end of 2011. Information that identified patients with SSNHL was based on a minimum of three visits and a corresponding diagnosis provided by referral teaching hospitals and tertiary referral medical centers.

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Table 1. Demographic Data for Patients with Osteoporosis and Controls (n = 42 640)

Category	Osteoporosis, n (%)	Controls, n (%)	Standardized Difference
N	10 660	31 980	
Age, y			
0∼49	1029 (9.653)	3062 (9.57)	0.003
50∼64	4883 (45.81)	14 910 (46.62)	0.016
≥65	4748 (44.54)	14 008 (43.80)	0.015
Female	9542 (89.51)	28 745 (89.88)	0.012
Comorbidity			
DM	1568 (14.71)	4775 (14.93)	0.006
HTN	3220 (30.21)	9777 (30.57)	0.008
CKD	230 (2.16)	622 (1.94)	0.016
CAD	1177 (11.04)	3445 (10.77)	0.009
Area			
North	5211 (48.88)	15 594 (48.76)	0.002
Center	1505 (14.12)	4442 (13.89)	0.007
South	3722 (34.92)	11 284 (35.28)	0.008
East	222 (2.08)	660 (2.06)	0.001
Income			
NT<15 840	6346 (59.53)	18 998 (59.41)	0.002
NT 15 841approximately 25 000	3117 (29.24)	9277 (29.01)	0.005
NT>25 001	1197 (11.23)	3705 (11.59)	0.011

Abbreviations: CKD, chronic kidney disease; HTN, hypertension.

Statistical analyses

All statistical operations were performed using the SAS 9.3 statistical package (SAS Institute, Inc). We used standardized difference, which was proposed by Ho (35), to assess the balance of measured variables between osteoporosis and nonosteoporosis subjects in the matched sample, because assessment of balance in baseline variables between treated and untreated cases should use methods that are not influenced by sample size and that are sample specific and do not refer to a hypothetical population (15). A standardized difference of 0.1 or more was considered indicative of imbalance (16). All following analyses were performed in the matched sample, using methods appropriate for the analysis of matched data in estimating the outcome effect. The incidence rate was calculated as the number of SSNHL cases during the followup divided by the total PY for each group by sex, age, and selected comorbidities. The risk of SSNHL between the osteoporotic subjects and matched controls was compared by estimating the incidence rate ratio (IRR) with conditional Poisson regression. Moreover, Cox proportional hazard regression was performed to compute the risk of SSNHL between the osteoporotic subjects and control groups after taking pair matching into account. To assess the effect of specific antiosteoporotic therapy on the association between SSNHL and osteoporosis, Cox proportional hazard regression was also performed to analyze osteoporotic patients who had received bisphosphonate therapy and without bisphosphonate therapy, which was used as a surrogate marker for severity of osteoporosis. In Taiwan, antiosteoporotic therapy, such as bisphosphonate, is covered by National Health Insurance only in the osteoporotic patients (T-score ≤ -2.5), who have at least one spine or hip fracture. The SAS procedures GENMOD (for conditional Poisson regression) and PHREG (for Cox proportional hazards regression on the matched pairs) can be used to analyze matched-pair cohort data. A Kaplan-Meier survival curve was estimated in both groups and stratified log-rank test was used to compare the difference between two cohorts by a test described by Klein and Moeschberger (17). A two-sided $P < .05$ was considered significant.

Results

Table 1 is a summary of the baseline characteristics and comorbid medical disorders in the study and comparison group. In total, we recruited 10 660 patients with osteoporosis and 31 980 controls matched by age, sex, baseline comorbidities (including DM, hypertension, chronic kidney disease, and CAD), resident area, and monthly income. Most of the enrolled subjects were female (89.51%) and more than 50 years old (91%), and 89% of patients with osteoporosis had a monthly income less than 25 000 NT dollars (USD 806).

The osteoporotic group had a significantly higher incidence of SSNHL than the control group (Table 2). A total of 91 of the 10 660 osteoporotic patients were diagnosed as having SSNHL during the follow-up period (10.43 per 10 000 PY). One hundred fifty-five of 31 980 of the controls developed SSNHL during the follow-up period (5.93 per 10 000 PY), making the incidence rate ratio (IRR) of 1.76 (95% confidence interval [CI], 1.36–2.28; $P < .0001$). Patients with osteoporosis aged 50 years or older were at higher risk of SSNHL, and the incidence rate ratio was 1.50 in those between 50 and 64 years old and 2.33 in those 65 years or older, respectively. Women with osteoporosis were at higher risk of SSNHL than those without osteoporosis (IRR = 1.87; 95% CI, 1.42–2.45; $P < .0001$). This tendency was not observed in men. Al-

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Table 2. Risk of SSNHL for Osteoporotic Patients and Controls

	Osteoporosis				Controls					
Characteristics	**N**	**SSNHL**	**No. PY**	**Rate[a]**	**N**	**SSNHL**	**No. PY**	**Rate[a]**	**IRR (95% CI)**	***P* Value**
All	10 660	91	87 260.85	10.43	31 980	155	261 519.33	5.93	1.76 (1.36–2.28)	<.0001
Age, y										
0∼49	1029	6	9006.52	6.66	3062	13	26 687.96	4.87	1.36 (0.52–3.56)	.5274
50∼64	4883	46	42 348.17	10.86	14 910	92	127 603.31	7.21	1.50 (1.06–2.14)	.0234
≥65	4748	39	35 906.16	10.86	14 008	50	107 228.06	4.66	2.33 (1.53–3.55)	<.0001
Sex										
Male	1118	6	7687.67	7.80	3235	19	23 704.87	8.02	0.97 (0.39–2.44)	.9500
Female	9542	85	79 573.17	10.68	28 745	136	237 814.46	5.72	1.87 (1.42–2.45)	<.0001
Comorbidity										
DM	1568	12	12 765.92	9.40	4775	34	37 026.28	9.18	1.02 (0.52–1.99)	.9532
HTN	3220	28	24 517.73	11.42	9777	53	73 927.61	7.17	1.59 (1.01–2.51)	.0465
CKD	230	0	1524.66	—	655	5	4037.66	12.38	—	—
CAD	1177	10	8890.43	11.25	3445	26	26 011.82	10.00	1.13 (0.55–2.33)	.7445

Abbreviations: CKD, chronic kidney disease; HTN, hypertension.

[a] Rate per 10 000 PY.

though hypertensive patients with osteoporosis seemed to have higher risk of SSNHL than hypertensive patients without osteoporosis (IRR = 1.59; 95% CI, 1.01–2.51; $P = .0465$), the lower bound of the CI was essentially 1 and the *P* value was on the borderline of statistical significance.

In Table 3 we divided female patients into four groups by decades of age. We found an increasing trend in the IRR accompanying increases in age. Patients with osteoporosis aged 60 years or older were at higher risk of SSNHL. The IRR was 2.38 (95% CI, 1.50–3.75; $P = .0002$) in those between 60–70 years old and 2.59 (95% CI, 1.42–4.70; $P = .0018$) in those 70 years or older.

Table 4, the results of our Cox proportional hazard regressions, shows that the hazard ratio (HR) for SSNHL in patients with osteoporosis was 1.76, compared with those without osteoporosis (95% CI, 1.33∼2.34; $P < .0001$). To examine the effect of antiosteoporotic therapy on the association between osteoporosis and SSNHL, we also analyzed the effect of bisphosphonate therapy in Table 4. The HR for SSNHL in osteoporotic patients who has received bisphosphonate therapy was 2.46, compared with control group (95% CI, 1.52–3.99; $P = .0005$) and the HR for SSNHL in osteoporotic patients who had not received bisphosphonate therapy was 1.64, compared with control group (95% CI, 1.24–2.17; $P = .0003$). As can be seen in Figure 1, the Kaplan-Meier analysis revealed that patients with osteoporosis had a higher incidence of SSNHL than the control group (log-rank test $P < .0001$).

Discussion

This study found an approximately 1.76-fold increase in the incidence of SSNHL for patients with osteoporosis compared with the comparison group. The risk of SSNHL associated with osteoporosis remained high even after controlling for age, sex, medical comorbidities, geographical area, and monthly income. To the best of our knowledge, this is the first and largest population-based study to evaluate the risk of SSNHL in a national cohort of Asian patients with osteoporosis.

Several studies have suggested the risk factors for SSNHL include traditional cardiovascular risk factors, such as CAD, hypertension, chronic kidney disease, and DM (18, 19). In our study, hypertensive patients with osteoporosis had borderline higher risk of SSNHL than hypertensive pa-

Table 3. Risk of SSNHL for Osteoporotic Patients and Controls in Females

	Osteoporosis				Controls					
Characteristics	**N**	**SSNHL**	**No. PY**	**Rate[a]**	**N**	**SSNHL**	**No. PY**	**Rate[a]**	**IRR (95% CI)**	***P* Value**
Age										
0∼49	924	5	8176.83	6.11	2795	12	24 635.45	4.87	1.25 (0.44–3.54)	0.6680
50∼60	3239	27	28 289.6	9.54	9947	60	85 613.41	7.01	1.36 (0.86–2.13)	0.1844
60∼70	2721	33	23 461.34	14.07	8266	41	69 019.97	5.94	2.38 (1.50–3.75)	0.0002
≥70	2658	20	19 645.41	10.18	7737	23	58 545.63	3.93	2.59 (1.42–4.70)	0.0018

Abbreviation: CKD, chronic kidney disease.

[a] Rate per 10 000 PY.

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Table 4. Cox Proportional Hazard Regressions and 95% confidence interval Stratified on the Matched Pairs for the Development of SSNHL for Study Cohorts

	HR	95% CI	*P*-Value
Controls	1.00		
Osteoporosis	1.76	1.33–2.34	<.0001
Osteoporosis without bisphosphonate therapy	1.64	1.24–2.17	.0003
Osteoporosis with bisphosphonate therapy	2.46	1.52–3.99	.0005

Adjusted by age group, sex, diabetes, hypertension, CAD, chronic kidney disease, income, and area.

tients without osteoporosis. The results should be interpreted with caution given that the lower bound of the CI was essentially 1. Additional studies are needed to clarify these results. One possible explanation for the association between osteoporosis and SSNHL is that osteoporosis contributes to the development of SSNHL via the effects of cardiovascular disease and risk factors. However, there remained a significant relationship between osteoporosis and SSNHL in our patients matched for these comorbidities after adjustment in our analysis. Therefore, cardiovascular disease and risk factors do not exclusively explain the relationship between osteoporosis and SSNHL.

Although the underlying mechanism contributing to the association between osteoporosis and SSNHL is likely complex, there are some possible explanations for our findings. One study concluded that dysfunction of cochlear capsule in osteoporotic patients might play a role in the development of SSNHL (20). One radiologic study of Paget's disease reported a significant association between demineralization of the cochlear capsule and the development of SSNHL (21). Demineralization of cochlear capsule was found to be correlated with hearing loss in patients with metabolic bone disorders such as Paget's disease and osteogenesis imperfecta. Hearing loss might also be caused by internal auditory canal invasion and compression of the cochlear division of the cranial nerve (22, 23). Similar mechanisms might also underlie the relationship between osteoporosis and SSNHL. One study found an inverse association between BMD of the femoral neck and sensorineural hearing loss (12). They hypothesized that the bone mass of the femoral neck might reflect bone mass of the petrous temporal bone. Because osteoporosis is possibly a systemic metabolic disease with demineralization of skeletal system, it is reasonable to hypothesize that systemic demineralization may not spare the temporal bone, which contains the cochlea capsule and the conductive system.

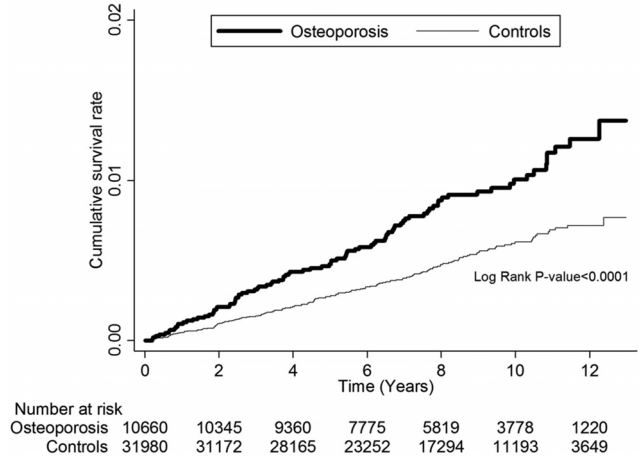

Figure 1. The cumulative incidence rate for SSNHL for patients with osteoporosis and without osteoporosis (log-rank $P < .0001$).

There is a close link between inflammation and bone destruction. One study reported an increased level of inflammatory mediators such as interleukin IL-6, TNF-α, C-reactive protein (CRP), and soluble receptors (IL-2 sR, IL-6 sR, TNF sR1, and TNF sR2) in patients with osteoporosis (24). Cytokines play an important role in inflammatory bone destruction by up-regulating the receptor activator of nuclear factor-κB (NF-κB) ligand (25). There is also a close association between systemic inflammation and SSNHL. One study discovered that NF-κB activation in the cochlea can cause severe SSNHL, and the NF-κB activation can be induced by decreased natural killer cell activity, increased neutrophil count, and increased IL-6 level (26). Several studies have found increased systemic inflammation, represented by higher levels of mediators such as white cell count, neutrophil count, CRP or IL-6, to be associated with SSNHL (27, 28). Another recent study has proposed the markers of the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio values can be used for the diagnosis and prognosis of SSNHL. Endothelial dysfunction might play a role in SSNHL and is associated with microvascular disturbances and inflammatory processes (29). Both osteoporosis and SSNHL are complex disorders and may be caused by multiple mechanisms, such as cardiovascular risk factors, bone demineralization, inflammation, and endothelial dysfunction.

This study found an association between osteoporosis and SSNHL in female but not male patients. It also found that osteoporotic patients aged 50 years or older were at higher risk of SSNHL, a tendency not found in those younger than 50 years. We subanalyzed the association between the onset of osteoporosis and SSNHL in women by decades of age. The association between osteoporosis and SSNHL was obvious in women age 60 years or older. Although the exact mechanism is not known, we speculate that estrogen may play a role in the development of SSNHL, however, in older women the lack of estrogen does not seem to be essentially connected with bone demineralization (30). Therefore, there might be other factors affecting

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this relationship in women, such as genetic factors, aging, or lifestyle pattern. Additional studies investigating fine clinical details are needed to explore the possibilities.

It is worth noting that osteoporotic patients with antiosteoporotic therapy had higher HR. In Taiwan, antiosteoporotic therapy is covered by NHI only in the osteoporotic patients who have had at least one spine or hip fracture, and thus antiosteoporotic therapy is supported by NHI for severe osteoporotic patients only. Patients with more severe osteoporosis may have a higher risk of SSNHL than patients with osteoporosis of milder severity.

Our study has some limitations. One limitation was that the identification of osteoporosis and SSNHL diagnoses were based on diagnoses listed in an administrative database which may be less accurate. However, the Bureau of the NHI has formed different audit committees that randomly sample the claims data from every hospital and review charts on a regular basis to verify the diagnostic validity and quality of care. The NHI Research Database has acceptable validity for epidemiologic investigations (31). To further maximize case ascertainment, we selected only patients who fulfilled the dual-emission x-ray absorptiometry criteria for osteoporosis. Patients who had at least three ambulatory medical care visits and a principle diagnosis of SSNHL provided by an otolaryngologist in the referral teaching hospitals and tertiary referral medical centers to validate the diagnosis, which might be expected to provide adequate diagnostic accuracy. This method of identifying these diseases has been used extensively in various studies of Taiwan National Health Insurance Research Database, and many articles have been published (32–34). Another limitation is the difficulty in documenting the finer clinical details, such as cigarette smoking, alcohol consumption, family history, noise exposure, and changes in BMD in the analysis. Such data are not available in the NHI Research Database. Additional study is needed to clarify the effects of these factors.

In summary, this large population-based study reveals that patients with osteoporosis are at significantly increased risk of developing SSNHL. Additional studies should be performed to confirm our findings and determine the mechanism of the association between osteoporosis and SSNHL.

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