

Effects of Teriparatide Compared with Risedronate on the Risk of Fractures in Subgroups of Postmenopausal Women with Severe Osteoporosis: The VERO Trial

Piet Geusens,¹ Fernando Marin,² David L Kendler,³ Luis A Russo,⁴ Cristiano AF Zerbini,⁵ Salvatore Minisola,⁶ Jean Jacques Body,⁷ Eric Lespessailles,⁸ Susan L Greenspan,⁹ Alicia Bagur,¹⁰ Jan J Stepan,¹¹ Péter Lakatos,¹² Enrique Casado,¹³ Rüdiger Moericke,¹⁴ Pedro López-Romero,² and Astrid Fahrleitner-Pammer¹⁵

¹Maastricht University Medical Center, Maastricht, The Netherlands

²Lilly Research Center Europe, Madrid, Spain

³University of British Columbia, Vancouver, Canada

⁴CCBR Brasil Centro de Análises e Pesquisas Clínicas, Rio de Janeiro, Brazil

⁵Centro Paulista de Investigaçao Clínica, Sao Paulo, Brazil

⁶"Sapienza" Rome University, Rome, Italy

⁷CHU Brugmann, ULB, Brussels, Belgium

⁸Regional Hospital of Orléans, Orléans, France

⁹Osteoporosis Center, University of Pittsburgh, Pittsburgh, PA, USA

¹⁰Centro de Osteopatías Comlit, Buenos Aires, Argentina

¹¹Institute of Rheumatology and Faculty of Medicine 1, Charles University, Prague, Czech Republic

¹²Semmelweis University Medical School, Budapest, Hungary

¹³University Hospital Parc Taulí Sabadell (UAB), Barcelona, Spain

¹⁴Institut Präventive Medizin & Klinische Forschung, Magdeburg, Germany

¹⁵Division of Endocrinology and Diabetes, Medical University of Graz, Graz, Austria

ABSTRACT

The 2-year, randomized, double-blind, active-controlled fracture endpoint VERO study included postmenopausal women with established osteoporosis, who had at least 2 moderate or 1 severe baseline vertebral fractures (VFX), and bone mineral density (BMD) T -score ≤ -1.5 . Patients were treated with either s.c. daily teriparatide 20 μ g or oral weekly risedronate 35 mg. As previously reported, the risk of new VFX and clinical fractures (a composite of clinical VFX and nonvertebral fragility fractures [NVFFx]) was statistically significantly reduced with teriparatide compared with risedronate. Here we present the prospectively planned subgroup analyses of fracture data across subgroups, which were predefined by the following baseline characteristics: age, number and severity of prevalent VFX, prevalent nonvertebral fractures (NVFX), glucocorticoid use, prior osteoporosis drugs, recent bisphosphonate use, clinical VFX in the year before study entry, and baseline BMD. Heterogeneity of the treatment effect on the primary endpoint (new VFX), and the four key secondary endpoints (including clinical fractures and NVFFx) were investigated by logistic and Cox proportional hazards regression models. A total of 1360 women were randomized and treated (680 per group). Mean age was 72.1 years, mean (SD) number of prevalent VFX was 2.7 (2.1), 55.4% had a BMD T -score < -2.5 , 36.5% had a recent clinical VFX, 28.3% had a prior major NVFX, 43.2% were osteoporosis drug-naïve, 39.3% were recent bisphosphonate users, and 9.3% were taking glucocorticoids at a prednisone-equivalent dose of >5 mg/d. For most fracture endpoints, the risk reduction of teriparatide versus risedronate did not significantly differ in any of the subgroups analyzed (treatment-by-subgroup interaction $p > 0.1$), with most subgroups mirroring results from the total study population. In conclusion, in postmenopausal women with severe osteoporosis, the antifracture efficacy of teriparatide compared with risedronate was consistent in a wide range of patient settings, including treatment-naïve and previously treated patients. © 2018 The Authors. *Journal of Bone and Mineral Research* Published by Wiley Periodicals Inc.

KEY WORDS: TERIPARATIDE; VERTEBRAL FRACTURES; POSTMENOPAUSAL OSTEOPOROSIS; BISPHOSPHONATES; SUBGROUP ANALYSIS

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

Received in original form October 20, 2017; revised form December 19, 2017; accepted December 28, 2017. Accepted manuscript online January 12, 2018. Address correspondence to: Piet Geusens, MD, Department of Internal Medicine, Subdivision of Rheumatology, Maastricht University Medical Center, 6202-Maastricht, The Netherlands. E-mail: drpgeusens@gmail.com

Journal of Bone and Mineral Research, Vol. 33, No. xx, Month 2018, pp 1–12

DOI: 10.1002/jbmr.3384

© 2018 The Authors. *Journal of Bone and Mineral Research* Published by Wiley Periodicals, Inc.

Introduction

The choice of the drug treatment for secondary prevention of fragility fractures in patients with osteoporosis is a controversial topic. Most osteoporosis guidelines consider oral bisphosphonates as a first-line therapy, whereas other anti-resorptives such as zoledronate or denosumab or the bone-forming agent teriparatide are recommended as second-line therapies. We have recently reported the “VERtebral fracture treatment comparisons in Osteoporotic women” (VERO) trial,⁽¹⁾ the first active-controlled clinical trial adequately designed to show superiority in the incidence of new vertebral fractures (VFX) as the primary endpoint, comparing teriparatide with risedronate, an oral bisphosphonate that has shown significant antifracture efficacy results in postmenopausal women with low bone mass and prevalent VFX.^(2–5) In the VERO trial, 24-month treatment with teriparatide significantly reduced the incidence of VFX and clinical fractures (a composite of clinical VFX and nonvertebral fragility fractures [NVFFx]) compared with risedronate by 56% and 52%, respectively, in postmenopausal women with established osteoporosis.⁽¹⁾

Several major risk factors for osteoporotic fractures are recognized, including age, bone mineral density (BMD), glucocorticoid use, or a prior fracture.^(6–8) These factors may influence the treatment effect of the anti-osteoporosis drugs. Using the data from the VERO trial, we examined whether the treatment effect on the incidence of new fractures observed in the entire population as reported by Kendler and colleagues⁽¹⁾ was heterogeneous across predefined subgroups by clinically relevant baseline characteristics. Similar subgroup analyses have been reported previously for alendronate,⁽⁹⁾ risedronate,⁽⁴⁾ zoledronic acid,⁽¹⁰⁾ denosumab,⁽¹¹⁾ and abaloparatide⁽¹²⁾ in the population of patients enrolled in the phase 3 trials but using placebo as the comparator, instead of an active comparator as utilized in the present study.

Materials and Methods

Study design

In this double-blind, multinational, multicenter trial, postmenopausal women with at least 2 moderate or 1 severe VFX, according to the classification of Genant and colleagues,⁽¹³⁾ and a BMD *T*-score of ≤ -1.5 were enrolled. After their eligibility was confirmed, 1360 women were randomized to receive either 20 μ g of s.c. teriparatide once daily plus oral weekly placebo (680 treated patients) or 35 mg of oral risedronate once weekly plus daily injections of placebo (680 treated patients) for up to 24 months. The primary study outcome was the incidence of new radiographic VFX. A new VFX was defined as a vertebral body height loss of at least 20% (and 4 mm) of a vertebra that was unfractured at baseline, based on a 6-point placement of the vertebral bodies from T₄ to L₄, and confirmed by an increase by one or more severity grades according to the semiquantitative grading (SQ) scale by Genant and colleagues.⁽¹³⁾ Key secondary outcomes included the incidence of pooled new and worsened VFX, clinical fractures (a composite of clinical VFX and NVFFx), NVFFx (excluding pathologic fractures and fractures of the skull, face, fingers, metacarpals, and toes), and a subgroup of major NVFFx (hip, radius, humerus, rib, pelvis, tibia, and femur) per the European Medicines Agency definition.⁽¹⁴⁾ Worsening of a

baseline preexisting spine fracture was diagnosed if the decrease in vertebral height was at least one severity grade in the SQ assessment. A clinical VFX was defined as an episode associated with signs and symptoms highly suggestive of a VFX, such as severe back pain of acute onset; pain with little or no exertion; pain localized to specific vertebra and associated with limited back mobility; pain relieved by bed rest; worsened when upright, coughing, sneezing; limited back flexion; or paravertebral muscle tenderness secondary to spasms, confirmed with the detection of a new or worsened radiographic VFX by the centralized X-ray imaging readers. Analyses of nonvertebral and pooled clinical fractures were based on all randomized patients who received at least 1 dose of investigational product (full analysis set) and analyses of VFX on all patients with a baseline and at least 1 post-baseline spinal radiograph evaluable to assess the VFX status after 24 months (modified full analysis set). Further study design, entry criteria, and methodology details are described by Kendler and colleagues⁽¹⁾ in their article summarizing the trial's main efficacy and safety results.

Subgroup analyses

Subgroup analyses were prospectively planned and performed primarily to examine if the treatment effect differs across the different predefined subgroups and, therefore, consistent with the results observed in the entire population. A second aim was to explore the treatment effect within specific subgroups that were considered to be clinically relevant and that have not previously been reported in clinical trials. Subgroup analyses were exploratory and were done for the primary and the key secondary fracture endpoints as defined in the statistical analysis plan of the study that was approved before study unblinding.⁽¹⁾ The following subgroups were prespecified and analyzed: 1) by number of prevalent fragility VFX; 2) by severity of prevalent VFX using the classification by Genant and colleagues;⁽¹³⁾ 3) by prevalent major NVFFx, where major NVFFx included fractures of the hip, radius, humerus, ribs, pelvis, tibia, and femur (excluding pathologic fractures); 4) by use of significant glucocorticoid treatment, defined as >5 mg/d of prednisone-equivalent dose at the baseline visit or during post-baseline visits, regardless of treatment duration; 5) by prior use of osteoporosis drugs using 3 different mutually exclusive categories: prior bisphosphonates users, prior users of osteoporosis medication other than a bisphosphonate, and osteoporosis treatment-naïve patients. The category of prior bisphosphonate users included those patients who had received ≥ 3 months of oral (risedronate, alendronate, ibandronate, etidronate, neridronate), i.m. (clodronate) or i.v. (ibandronate, pamidronate, clodronate) bisphosphonates, or ≥ 1 dose of i.v. zoledronic acid. The category of nonbisphosphonate users included those patients who had received ≥ 3 months of any nonbisphosphonate antiresorptive (excepting denosumab) or ≥ 1 dose of s.c. denosumab. Osteoporosis treatment-naïve patients included patients who had not received any osteoporosis medication, or <3 months of the antiresorptive drugs listed above. Calcium and vitamin D supplements were not considered osteoporosis medications; 6) by the lowest baseline *T*-score (< -2.5 or ≥ -2.5 SDs) measured at the spine and the proximal femur; 7) by age categorized by tertiles; 8) by recent bisphosphonate use, where recent use was defined as a total of 6 or more months of treatment with any oral bisphosphonate—either intermittently

Table 1. Number of Patients per Subgroup (Full Analysis Set and Modified Full Analysis Set)

	No. (%) of patients			
	Full analysis set		Modified full analysis set	
	Teriparatide (N = 680)	Risedronate (N = 680)	Teriparatide (N = 516)	Risedronate (N = 533)
Prevalent VFx (number) ^a				
1	231 (34.0)	240 (35.3)	180 (34.9)	191 (35.8)
2	178 (26.2)	174 (25.6)	132 (25.6)	135 (25.3)
3	104 (15.3)	101 (14.9)	86 (16.7)	82 (15.4)
>3	166 (24.4)	164 (24.1)	118 (22.9)	125 (23.5)
Prevalent VFx (severity) ^a				
SQ2	73 (10.7)	67 (9.9)	59 (11.4)	57 (10.7)
SQ3	606 (89.1)	612 (90.0)	457 (88.6)	476 (89.3)
Prior major nonvertebral fracture ^b				
No	481 (70.7)	494 (72.6)	355 (68.8)	385 (72.2)
Yes	199 (29.3)	186 (27.4)	161 (31.2)	148 (27.8)
Glucocorticoid use ^c				
No	609 (89.6)	624 (91.8)	466 (90.3)	491 (92.1)
Yes	71 (10.4)	56 (8.2)	50 (9.7)	42 (7.9)
Prior osteoporosis drugs ^d				
Bisphosphonate	359 (52.8)	356 (52.4)	280 (54.3)	281 (52.7)
Nonbisphosphonate	26 (3.8)	31 (4.6)	23 (4.5)	25 (4.7)
Treatment-naïve	295 (43.4)	293 (43.1)	213 (41.3)	227 (42.6)
Lowest BMD T-score				
<−2.5	371 (54.6)	382 (56.2)	270 (52.3)	297 (55.7)
≥−2.5	309 (45.4)	298 (43.8)	246 (47.7)	236 (44.3)
Age, years (tertiles)				
<68.7 years	217 (31.9)	236 (34.7)	184 (35.7)	202 (37.9)
≥68.7 and <76.8 years	213 (31.3)	241 (35.4)	152 (29.5)	192 (36.0)
≥76.8 years	250 (36.8)	203 (29.9)	180 (34.9)	139 (26.1)
Recent bisphosphonate use				
No	414 (60.9)	412 (60.6)	309 (59.9)	324 (60.8)
Yes	266 (39.1)	268 (39.4)	207 (40.1)	209 (39.2)
Recent clinical VFx				
No	428 (62.9)	436 (64.1)	319 (61.8)	341 (64.0)
Yes	252 (37.1)	244 (35.9)	197 (38.2)	192 (36.0)

VFx = vertebral fractures; SQ = semiquantitative grading; BMD = bone mineral density.

Note: The full analysis set (FAS) included all randomized patients who received ≥1 dose of investigational product, and the modified full analysis set included all FAS patients who had ≥1 post-baseline spine X-ray available to assess their fracture status during 24 months.

^aExcept for 2 patients, all patients in the FAS had at least 1 vertebral fracture (according to the central assessment) at baseline as per entry criteria. For these 2 patients, central fracture adjudication was not available, which was considered a major protocol violation.

^bHip, radius, humerus, ribs, pelvis, tibia, and femur (excluding pathologic fractures).

^cPrednisone-equivalent doses of >5 mg/d at the baseline or any post-baseline visit.

^dBisphosphonate: ≥3 months of bisphosphonates (ie, risedronate, alendronate, ibandronate, etidronate, neridronate, clodronate, or pamidronate) or ≥1 dose of i.v. zoledronic acid; nonbisphosphonate: ≥3 months of any nonbisphosphonate antiresorptive (except denosumab) or ≥1 dose of denosumab; treatment-naïve: no osteoporosis medication or who received <3 months of the antiresorptive drugs listed above. Calcium and vitamin D supplements were not considered osteoporosis medications.

or continuously—within 3 years before screening, or i.v. zoledronic acid at any dose within 2 years of screening, or i.v. ibandronate or pamidronate at any dose within 12 months before screening; and 9) by antecedent of recent clinical VFx within 12 months before screening. Because 97.3% of the patients in this study were white, analyses by the predefined ethnicity subgroups of whites versus non-whites were not considered feasible.

Statistical analyses

Fracture endpoints in subgroups were analyzed following the same prespecified statistical methods applied in the main analysis of the VERO trial.⁽¹⁾ Cochran-Mantel-Haenszel tests,

adjusted for the two stratification factors used at randomization (ie, the antecedent of recent clinical VFx and recent bisphosphonate use) were employed to estimate the overall treatment effect between teriparatide and risedronate for the primary and secondary analyses of the morphometric (radiographic) VFx endpoints. For the subgroup analysis of the morphometric (radiographic) VFx endpoints, a logistic regression analysis with the adjusting factors treatment, subgroup, treatment-by-subgroup interaction, and the two stratification factors was fitted. These analyses were implemented in the modified full analysis set that included all randomized patients who received ≥1 dose of either investigational product and who had ≥1 post-baseline spine X-ray available to assess their fracture status during 24 months.

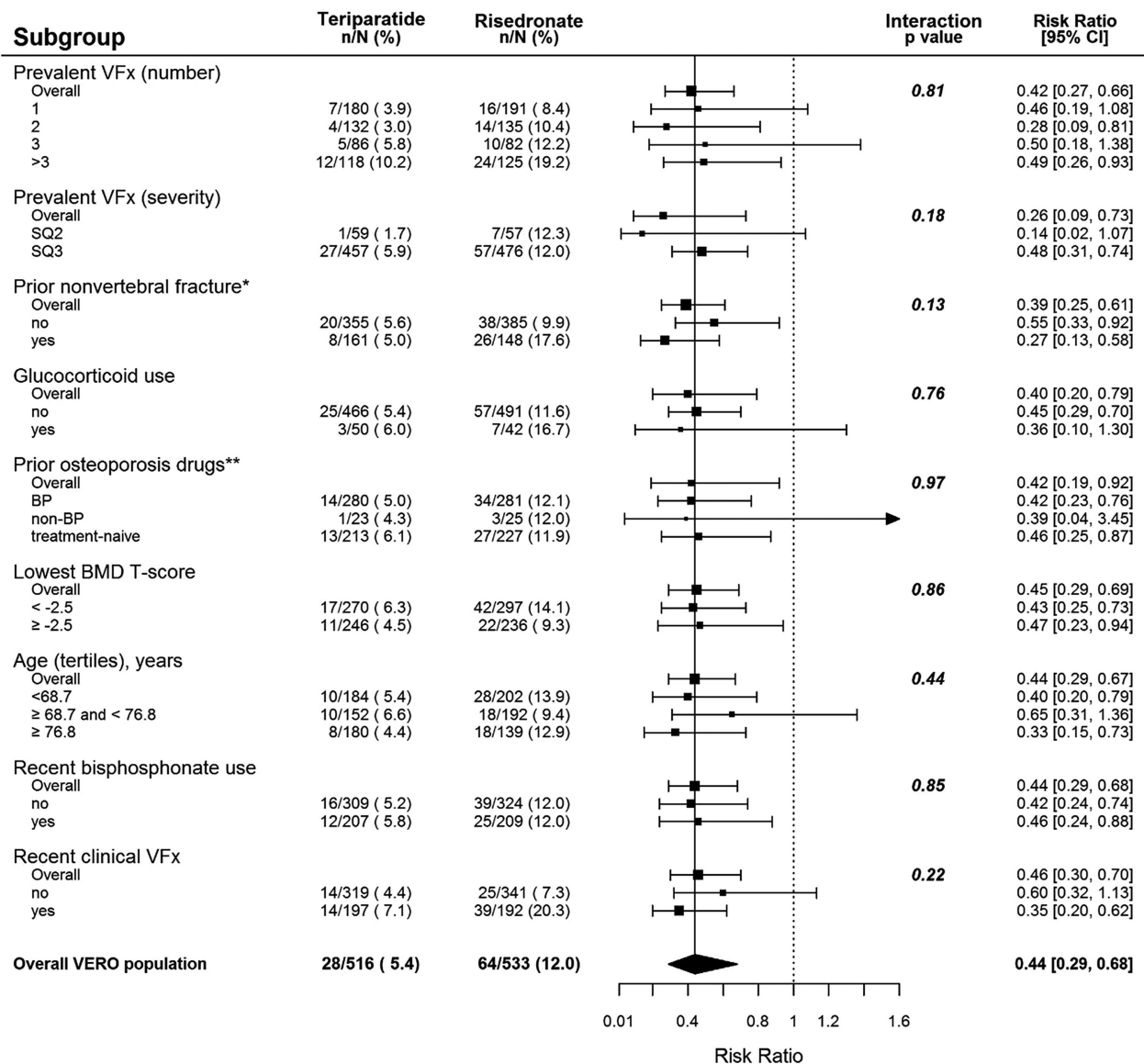


Fig. 1. Relative risk ratio for new vertebral fractures by prespecified subgroups (modified full analysis set). BP = bisphosphonates; *N* = total number of patients; *n* = number of patients in the specified category; SQ = semiquantitative grading; VFX = vertebral fracture. *Major nonvertebral fractures: hip, radius, humerus, ribs, pelvis, tibia, and femur (excluding pathologic fractures). **Nonbisphosphonates include strontium ranelate, denosumab, calcitonin, fluoride, and vitamin D active metabolites.

Stratified log-rank tests, adjusted for the two stratification factors, were employed for the analyses of the clinical fracture endpoints (NVFX and clinical VFX). The overall hazard ratio to estimate the treatment effect of teriparatide versus risedronate was obtained as part of the stratified log-rank test calculations. The corresponding subgroup analyses of the clinical fracture endpoints were performed using a Cox proportional hazards regression model with the same factors as specified above for the logistic regression model. These analyses were conducted in the full analysis set that included all randomized patients who received ≥ 1 dose of either investigational product.

The relative risk ratios (for VFX) or the hazard ratios (for clinical fractures) with the associated 95% CIs and *p* values for teriparatide versus risedronate at each level of the subgroup factor and overall were presented in forest plots, together with

the incidence rates per treatment group within subgroup and the treatment-by-subgroup interaction *p* value. A treatment-by-subgroup interaction *p* value < 0.1 was considered as evidence for the corresponding subgroup acting as an effect modifier, ie, the treatment effect of teriparatide versus risedronate would differ depending on the category of the subgroup.

Results

Baseline characteristics

A total of 1360 patients were randomized and treated, 680 in each treatment group; 74.2% of patients overall completed the trial. Baseline demographics and clinical characteristics were similar between groups and have been described previously in

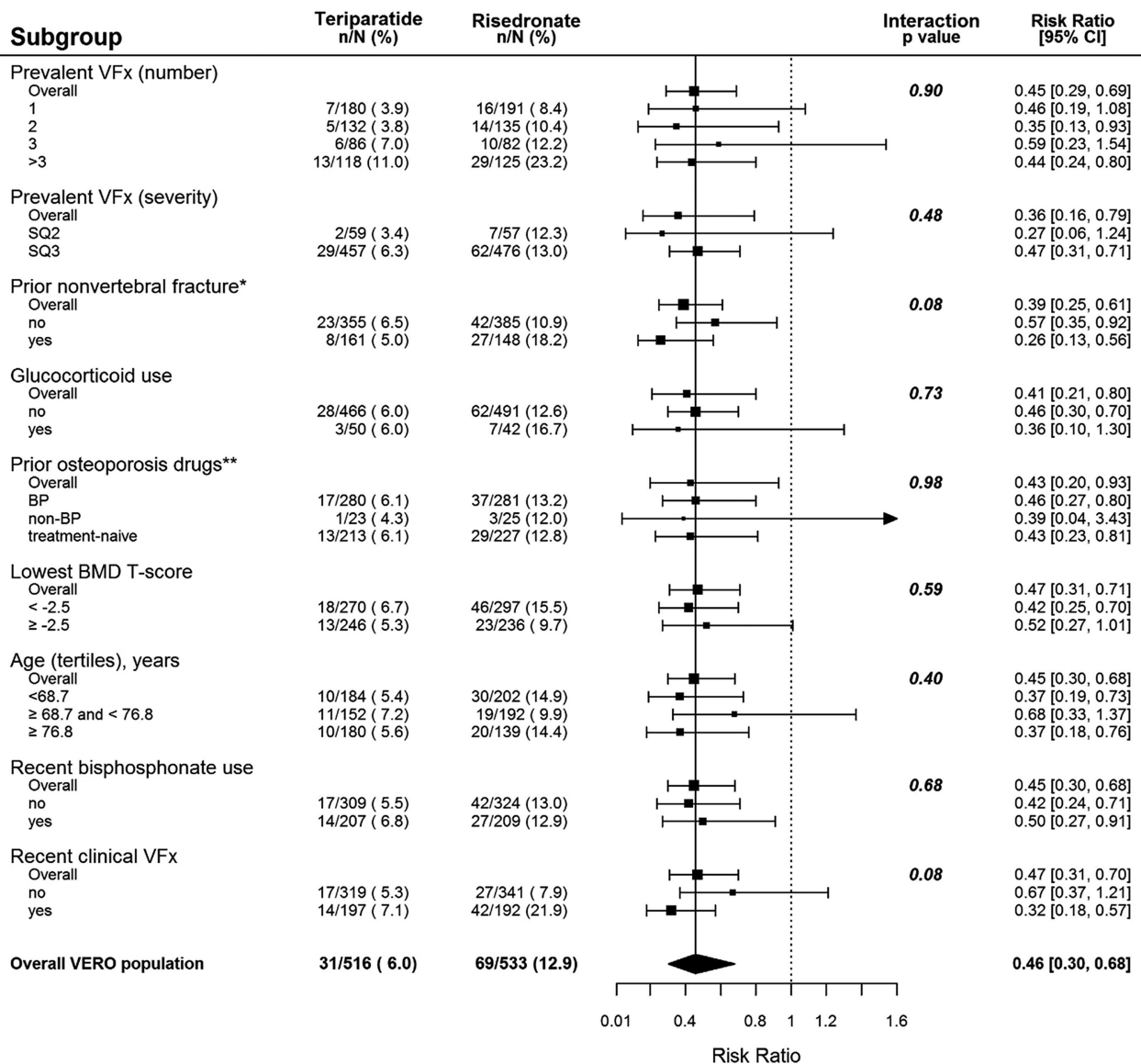


Fig. 2. Relative risk ratio for pooled new and worsened vertebral fractures by prespecified subgroups (modified full analysis set). BP = bisphosphonates; N = total number of patients; n = number of patients in the specified category; SQ = semiquantitative grading; VFX = vertebral fractures. *Major nonvertebral fractures: hip, radius, humerus, ribs, pelvis, tibia, and femur (excluding pathologic fractures). **Nonbisphosphonates include strontium ranelate, denosumab, calcitonin, fluoride, and vitamin D active metabolites.

detail by Kendler and colleagues.⁽¹⁾ The numbers of patients per subgroup were balanced between treatment groups in the two analyzed data sets (Table 1). The overall mean age was 72.1 years and 97.3% of patients were white. The mean (SD) number of prevalent VFX was 2.7 (2.1), with 1218 patients (89.6%) having ≥1 severe (SQ3) VFX at baseline. In the full analysis set, 496 patients (36.5%) had a clinical VFX within the 12 months before entering the study, 385 (28.3%) had a prior major NVFX, and 753 (55.4%) had a lowest BMD T-score of <-2.5 (Table 1). Furthermore, 588 patients (43.2%) were naïve to osteoporosis medication, 534 (39.3%) had been recently treated with bisphosphonates (as per protocol definition), and 127 patients (9.3%) were taking glucocorticoids at a prednisone-equivalent dose of >5 mg/d.

Subgroup analysis results for new vertebral fractures

The forest plot in Fig. 1 illustrates the relative risk ratios between teriparatide and risedronate for the incidence of new VFX, the primary study endpoint, at 24 months within each subgroup as well as overall. The treatment effect found in the entire study population, with an incident rate of new VFX of 5.4% in the teriparatide group compared with 12.0% in the risedronate group (risk ratio 0.44; 95% confidence interval [CI] 0.29–0.68; $p=0.000094$ [Fig. 1; see Kendler and colleagues⁽¹⁾ for details]), was homogeneous across all subgroups, ie, the treatment-by-subgroup interactions were not statistically significant ($p \geq 0.1$) for any of the subgroups. Although none of the subgroups analyzed acted as an effect modifier, the significant treatment

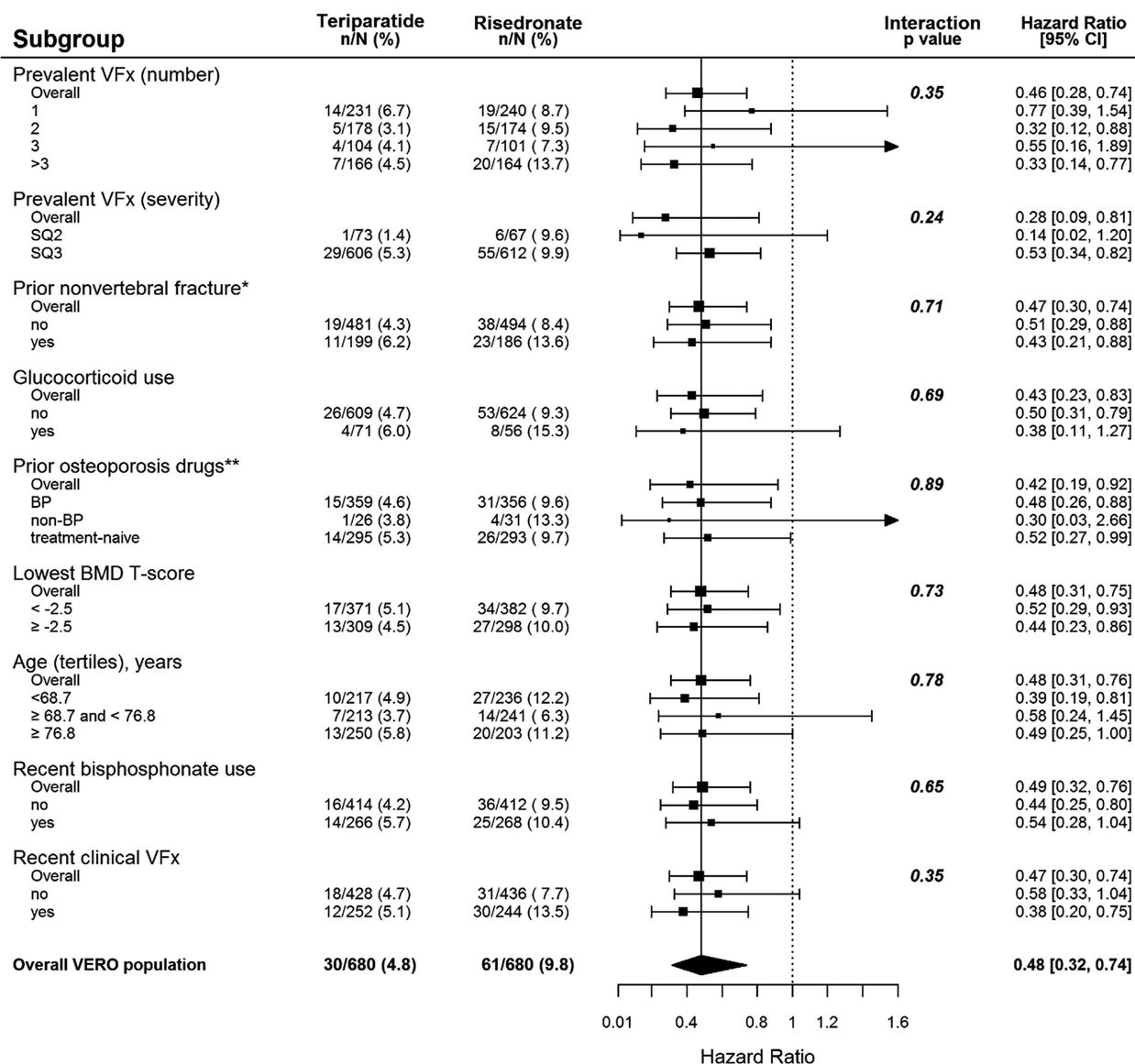


Fig. 3. Hazard ratio for pooled clinical fractures (clinical vertebral and nonvertebral fragility fractures) by prespecified subgroups (full analysis set). BP = bisphosphonates; *N* = total number of patients; *n* = number of patients in the specified category; SQ = semiquantitative grading; VFx = vertebral fractures. Percentages indicate the cumulative incidence of fractures based on Kaplan-Meier methodology. *Major nonvertebral fractures: hip, radius, humerus, ribs, pelvis, tibia, and femur (excluding pathologic fractures). **Nonbisphosphonates include strontium ranelate, denosumab, calcitonin, fluoride, and vitamin D active metabolites.

effect in favor of teriparatide found in the entire population was numerically greater in the subgroups of patients with 2 prevalent VFx (risk ratio 0.28; 95% CI 0.09–0.81), patients with a prior major NVFx (risk ratio 0.27; 95% CI 0.13–0.58), the oldest patient group (aged ≥76.8 years) (risk ratio 0.33; 95% CI 0.15–0.73), and patients with a recent clinical VFx within the 12 months before entering the study (risk ratio 0.35; 95% CI 0.20–0.62) (Fig. 1). Of note, the recent use of bisphosphonates did not influence the overall efficacy results with an almost identical, statistically significant, relative fracture risk reduction in patients with (risk ratio 0.46; 95% CI 0.24–0.88) or without (risk ratio 0.42; 95% CI 0.24–0.74) recent bisphosphonate use (treatment-by-subgroup *p* = 0.85) (Fig. 1). The relative VFx risk reduction was also very similar and statistically significant in the patients with <−2.5 or ≥−2.5 of

the lowest BMD *T*-score value (risk ratio 0.43 and 0.47, respectively, treatment-by-subgroup *p* = 0.86) (Fig. 1).

Subgroup analysis results for pooled new and worsened vertebral fractures

As illustrated in the forest plot for the incidence of pooled new and worsened VFx (Fig. 2), the treatment effect found overall (risk ratio 0.46; 95% CI 0.30–0.68; *p* = 0.000075 [see Kendler and colleagues⁽¹⁾ for details]) was homogeneous across subgroups, with all but two treatment-by-subgroup interactions not being statistically significant (*p* ≥ 0.1). Statistically significant treatment-by-subgroup interactions were observed for the subgroups by prior major NVFx and by recent clinical fragility VFx (treatment-by-subgroup

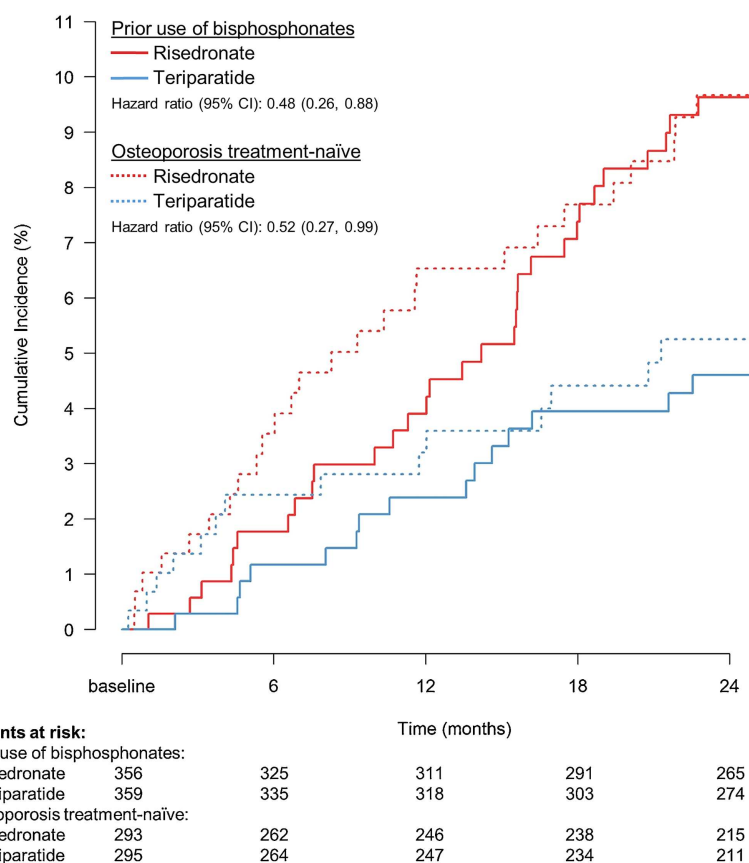


Fig. 4. Cumulative incidence of the first clinical fracture (pooled clinical vertebral and nonvertebral fragility fractures) by prior use of osteoporosis drugs (full analysis set). Hazard ratios for treatment-naïve patients and prior bisphosphonate users were both in favor of teriparatide.

$p = 0.08$ each). The risk ratio within the group of patients with a prior major NVFx was 0.26 (95% CI 0.13–0.56), whereas in the group of patients without prior major NVFx, it was 0.57 (95% CI 0.35–0.92), suggesting a statistically larger reduction in new and worsened VFx incidence for teriparatide in patients with a prior NVFx. Similarly, within patients with a recent clinical fragility VFx, the risk ratio was 0.32 (95% CI 0.18–0.57), whereas in patients without a recent fragility VFx, it was 0.67 (95% CI 0.37–1.21).

Subgroup analysis results for pooled clinical fractures (clinical vertebral and nonvertebral fragility fractures)

The overall treatment effect for the occurrence of new clinical fractures was statistically in favor of teriparatide with a cumulative incidence of 4.8% in the teriparatide group compared with 9.8% in the risedronate group, corresponding to a hazard ratio between teriparatide and risedronate of 0.48 (95% CI 0.32–0.74; $p = 0.000869$ [Fig. 3; see Kendler and colleagues⁽¹⁾ for details]). The treatment effect in favor of teriparatide was homogeneous across subgroups. The treatment-by-subgroup interaction was not statistically significant ($p \geq 0.1$) for any of the subgroups. Treatment effects within subgroups showed similar patterns as described above for the primary and first key secondary endpoints, with numerically greater treatment effects in favor of teriparatide observed for patients with 2 (hazard ratio 0.32; 95% CI 0.12–0.88) or more than 3 prevalent VFx (hazard ratio: 0.33; 95% CI 0.14, 0.77), and

patients with recent clinical VFx (hazard ratio 0.38; 95% CI 0.20–0.75) (Fig. 3). The reduction in the risk of clinical fractures was statistically significant and very similar to the overall population in those patients who had received bisphosphonates as prior osteoporosis drugs (hazard ratio 0.48; 95% CI 0.26–0.88) or had a BMD T -score < -2.5 (hazard ratio 0.52; 95% CI 0.29–0.93). Fig. 4 shows the Kaplan-Meier curves of the cumulative incidence of clinical fractures observed within the groups of osteoporosis treatment-naïve patients and prior bisphosphonate users.

Subgroup analysis results for nonvertebral fragility fractures

As illustrated in Fig. 5 for the VERO study population, the overall estimate of the hazard ratio for the incidence of NVFFx at 24 months between teriparatide and risedronate was 0.66 (95% CI 0.39–1.10; $p = 0.0990$ [Fig. 5; see Kendler and colleagues⁽¹⁾ for details]). The treatment-by-subgroup interactions were not statistically significant ($p \geq 0.1$) for any of the subgroups analyzed. In all subgroups, the treatment difference was not statistically significant. The point estimates of the hazard ratios of all the analyzed subgroups were very similar to the overall estimate of the hazard ratio and numerically in favor of teriparatide, with the exception of the patients with 1 prevalent VFx (hazard ratio 1.06; 95% CI 0.49–2.29) (Fig. 5). We did not observe any increase in the risk of NVFFx fractures in patients with antecedent of prior bisphosphonate use,

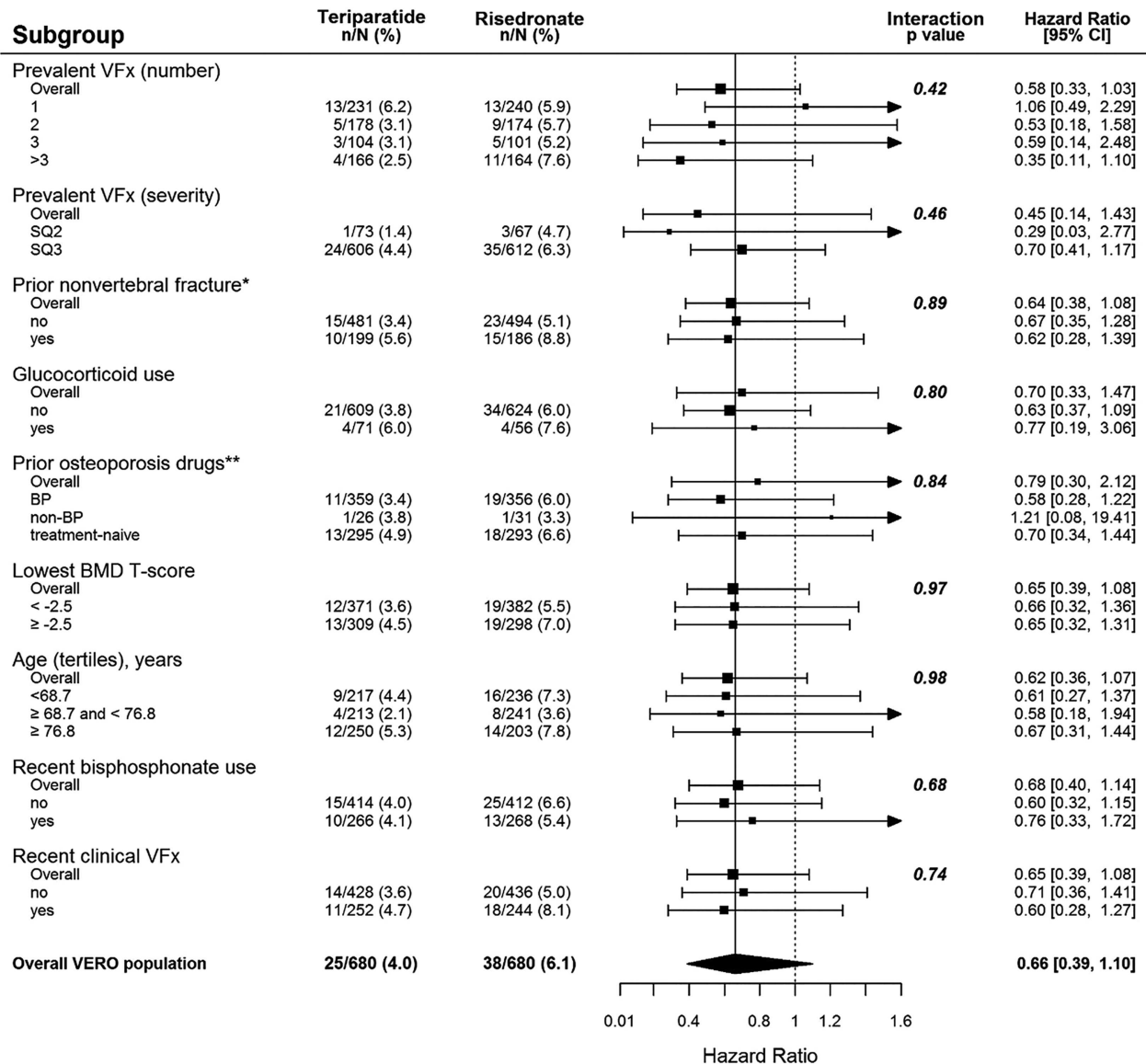


Fig. 5. Hazard ratio for nonvertebral fragility fractures by prespecified subgroups (full analysis set). BP = bisphosphonates; *N* = total number of patients; *n* = number of patients in the specified category; SQ = semiquantitative grading; VFx = vertebral fractures. Percentages indicate the cumulative incidence of fractures based on Kaplan-Meier methodology. *Major nonvertebral fractures: hip, radius, humerus, ribs, pelvis, tibia, and femur (excluding pathologic fractures). **Nonbisphosphonates include strontium ranelate, denosumab, calcitonin, fluoride, and vitamin D active metabolites.

including those with recent bisphosphonate treatment. On the contrary, the statistically nonsignificant risk reduction in the prior bisphosphonate-treated patients was numerically similar to that in the bisphosphonate-naïve group (Figs. 5 and 6A).

Subgroup analysis results for major nonvertebral fragility fractures

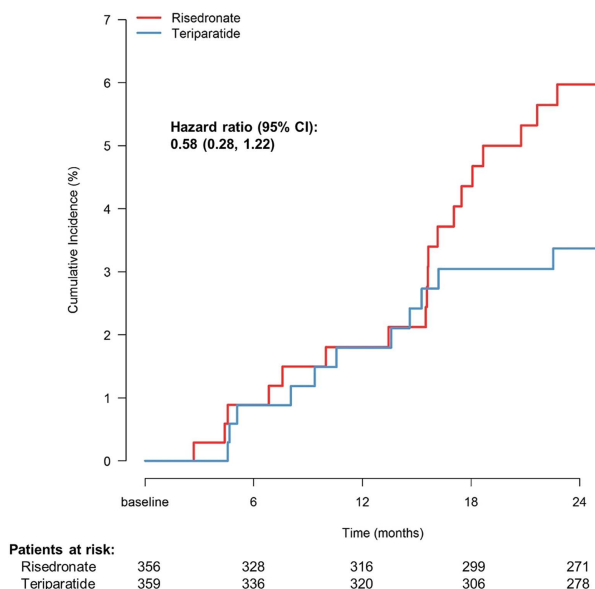
Similar to the results for all NVFFx, albeit numerically in favor of teriparatide, no statistically significant between-treatment difference for the incidence of major NVFFx was found (hazard ratio 0.58; 95% CI 0.32–1.05; $p = 0.0624$ [Fig. 7; see Kendler and colleagues⁽¹⁾ for details]). This nonsignificant treatment effect was homogeneous across subgroups. All treatment-by-subgroup interactions were not statistically significant ($p \geq 0.1$).

Among prior bisphosphonate-treated patients, the statistically nonsignificant risk reduction was numerically similar to that in the bisphosphonate-naïve group (Figs. 6B and 7).

Discussion

Our findings show that the overall treatment effects of teriparatide on the reduction of VFx and clinical fractures that were observed in the entire population of the VERO clinical trial were also consistently observed across all prespecified subgroups analyzed. The treatment-by-subgroup interaction terms were mostly not statistically significant ($p \geq 0.1$), indicating lack of evidence in the data to conclude that the treatment effect was heterogeneous across the different categories of the subgroups.

A) NVFFx



B) Major NVFFx^a

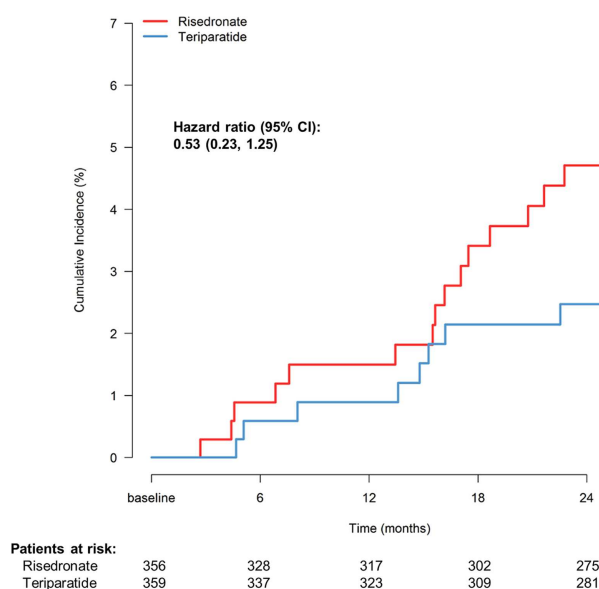


Fig. 6. Cumulative incidence of the first nonvertebral fragility fractures (A) and major nonvertebral fragility fractures (B) in prior bisphosphonate users (full analysis set). NVFFx = nonvertebral fragility fracture. ^aHip, radius, humerus, ribs, pelvis, tibia, and femur (excluding pathologic fractures).

These results support and complement the subgroup analyses by baseline BMD, age, and number of prevalent VFx performed in the patient cohort included in a pivotal phase 3 placebo-controlled clinical trial,⁽¹⁵⁾ where no interactions were observed.

Subgroup analyses of large clinical trials are useful because the beneficial treatment effects of osteoporosis drugs may vary across different categories of relevant risk factors, as has been found before in clinical trials with hip fracture as the study endpoint in patients treated with risedronate⁽⁵⁾ or strontium ranelate.⁽¹⁶⁾ For instance, there is a lack of previous data from randomized clinical trials on fracture outcomes in patients receiving teriparatide who were pretreated with bisphosphonates. Earlier studies analyzing the effects of switching from long-term treatment with a bisphosphonate to teriparatide on BMD and biochemical markers of bone turnover have suggested a “blunted” or “delayed” effect of subsequent teriparatide, at least during the early treatment period.^(17–20) Most recently, the STRUCTURE study randomized patients previously on long-term alendronate to either teriparatide or romosozumab, a monoclonal antibody against sclerostin. At 12 months, both total hip BMD and estimated hip strength significantly increased with romosozumab but declined with teriparatide, although no differences in fracture outcomes, analyzed as adverse events, between the two treatment groups were detected.⁽²¹⁾ Our subgroup data show similar antifracture efficacy with teriparatide in bisphosphonate pretreated and treatment-naïve patients, even in those patients with recent bisphosphonate treatment. This suggests that the antifracture efficacy may differ from that which the bone strength surrogate endpoints indicate, especially with agents differing in mechanism of action, and that the observed early decrease in BMD in cortical-rich bones, such as the forearm and the hip in patients switching to teriparatide from antiresorptives, does not seem to be associated with an increased risk of any type of fracture, including NVFFx. These

findings are of clinical importance because they are obtained from an active-controlled trial with risedronate, a bisphosphonate that has shown significant reduction in NVFFx and hip fractures in two clinical trials that have analyzed patients with established osteoporosis at high risk of fracture, similar to the patients enrolled in the VERO study.^(2,5) As long as a direct comparison of fracture risk is not available between romosozumab and teriparatide after bisphosphonate use, it remains speculative whether the differences in changes in hip BMD and calculated bone strength between these two drugs as reported in the STRUCTURE study⁽²¹⁾ reflect differences in fracture risk during the early treatment after switching from bisphosphonates. On the other hand, the recently reported phase 3 trial of abaloparatide, a parathyroid hormone-related protein analog, in postmenopausal women with osteoporosis excluded patients on previous recent antiresorptive therapy;⁽²²⁾ thus, no conclusions on the fracture efficacy of abaloparatide in the clinical setting of prior bisphosphonate use can be drawn from this study.

Of particular importance is the residual burden of fracture risk in patients on risedronate in the VERO study. Thus, 12% of the patients treated with risedronate had a new VFx during the 24 months of follow-up and 9.8% a new clinical fracture. We have demonstrated that teriparatide can effectively reduce this residual fracture burden in these severely osteoporotic patients, with an absolute risk reduction in new VFx of 6.6% after 24 months of treatment and a consistent effect over the wide range of subgroups analyzed. These results confirm previous findings from two double-dummy, active-controlled trials that included the comparison of the fracture incidence between groups as secondary or exploratory endpoints. Thus, Hadji and colleagues showed a significant 5.0% absolute risk reduction in new VFx with teriparatide compared with risedronate in a randomized, double-blind, 18-month duration clinical trial in

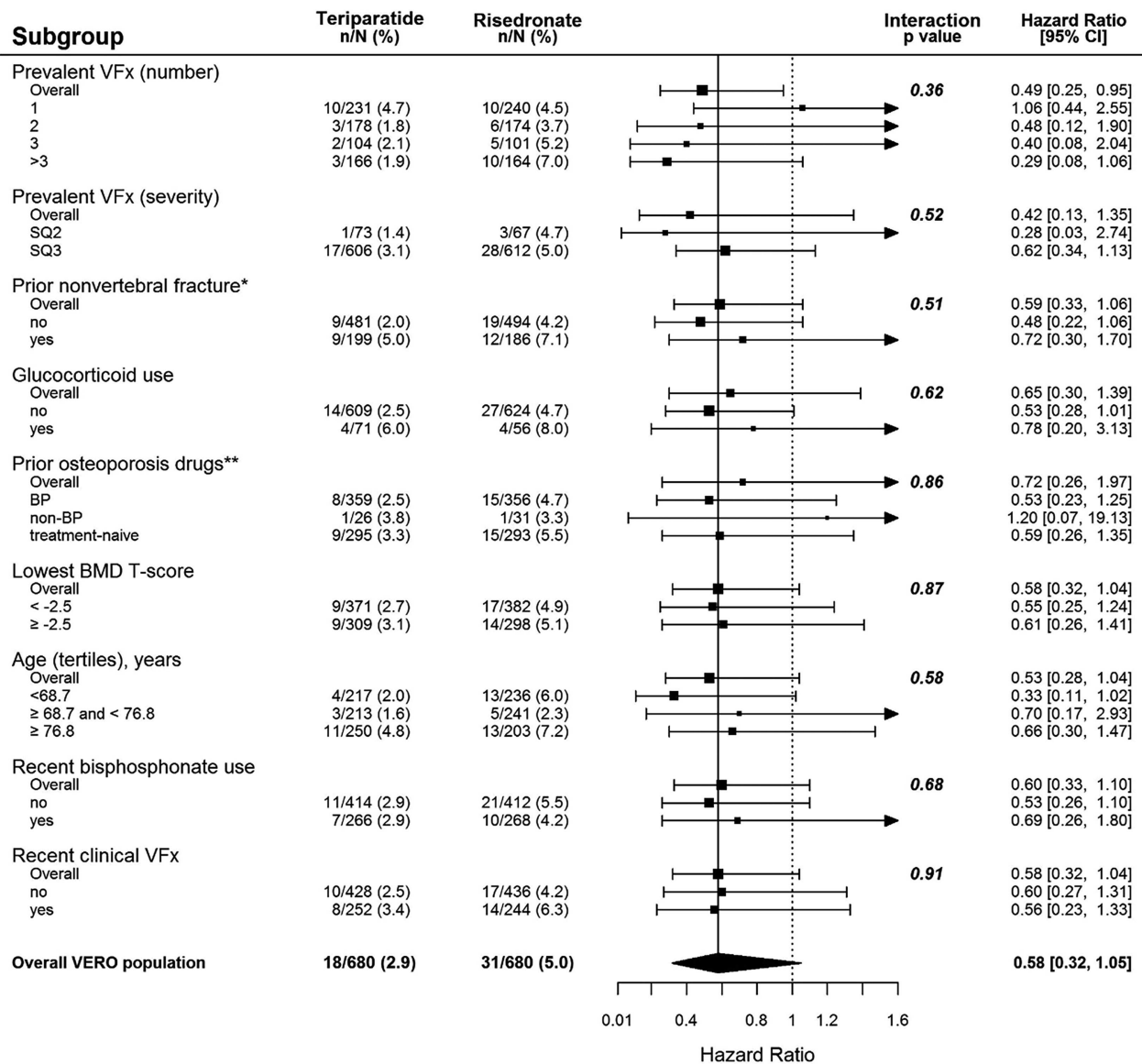


Fig. 7. Hazard ratio for major nonvertebral fragility fractures by prespecified subgroups (full analysis set). BP = bisphosphonates; *N* = total number of patients; *n* = number of patients in the specified category; SQ = semiquantitative grading; VFX = vertebral fractures. Percentages indicate the cumulative incidence of fractures based on Kaplan-Meier methodology. *Major nonvertebral fractures: hip, radius, humerus, ribs, pelvis, tibia, and femur (excluding pathologic fractures). **Nonbisphosphonates include strontium ranelate, denosumab, calcitonin, fluoride, and vitamin D active metabolites.

postmenopausal women with back pain and spine fractures.⁽²³⁾ In the study reported by Saag and colleagues, patients with glucocorticoid-induced osteoporosis treated with teriparatide had an absolute risk reduction of 5.5% in VFX compared with alendronate after the same treatment duration.⁽²⁴⁾

The VERO study also provides new information about antifracture efficacy in patients with near-term fracture risk (or imminent fracture risk) who are at the highest risk of subsequent fractures (ie, the patients with a prior clinical VFX in the year before entering the study). According to our results, the near-term 2-year new VFX, new and worsened VFX, and clinical fracture risks in these patients were still high in the risedronate-treated group, but the fracture risks were significantly reduced with teriparatide by 65%, 68%, and 62% for new VFX, new and

worsened VFX, and clinical fractures, respectively (Figs. 1–3). The reduction of NVFX remained not statistically significant in this subgroup (hazard ratio 0.60; 95% CI 0.28–1.27).

Also of special clinical and pharmacoeconomic interest is the finding that teriparatide was superior to risedronate in the reduction of clinical fractures, regardless of history of a prevalent major NVFX, with a relative risk reduction of 57% after 24 months of treatment in patients with a prior NVFX. This risk reduction in the VERO trial is similar to the 55% reduction in clinical fractures observed in the 3-year Fracture Intervention Trial (FIT) I trial, where alendronate was compared with placebo in a study cohort with similar clinical characteristics, including the presence of baseline VFX.⁽²⁵⁾ In the preplanned subgroup analyses of the phase 3 denosumab and abaloparatide trials, no

significant antifracture effects of those two drugs on NVFx in patients with a history of this type of fracture were found.^(11,12) The analysis by baseline NVFx was not considered in the zoledronic acid subgroup analysis.⁽¹⁰⁾ Clinical fractures were analyzed as secondary fracture endpoints in the zoledronic acid and abaloparatide phase 3 trials,^(22,26) but they were not reported in the subgroup analyses.^(10,12)

Our presented analysis has several limitations common to other subgroup study reports, including the limited power to detect interactions. The VERO study was primarily designed to detect a treatment effect difference between teriparatide and risedronate for the primary endpoint of new VFx, and therefore the detection of treatment-by-subgroup interactions would have required a significantly larger sample size. As a consequence, the possibility of a true differential treatment effect for some of the subgroups cannot be fully ruled out because of the inherent lack of power of the study to detect such effect in statistical tests. Additionally, some subgroups included very few patients, such as the glucocorticoid users (less than 10% of the entire population) or the prior nonbisphosphonate users (less than 5% of the entire population), or had very few fracture events. As a result, the CIs for the treatment effect estimated in these subgroups are considerably wider than the corresponding CI estimated using the overall population. Finally, the statistical significance was considered without adjustment for multiple comparisons. As another limitation, surrogate markers of bone quality such as BMD and biochemical markers of bone turnover were not measured as study endpoints.

The strengths of the study include the enrollment of patients with a high fracture risk, normally considered for osteoanabolic therapy, and numerous clinically relevant prespecified subgroups—including prior osteoporosis therapy, a recent clinical VFx, and number and severity of VFx at baseline—that have not previously been analyzed in subgroup analyses and that increase the clinical relevance to many patients that may be candidates for bone anabolic therapy. This is the first randomized clinical trial that assesses fractures as efficacy endpoints in a substantial subgroup of patients pretreated with bisphosphonates. We also included the analysis of relevant clinical outcomes, such as clinical fractures, that have not been reported before in subgroup analyses.

In conclusion, in postmenopausal women with severe osteoporosis, the antifracture efficacy of teriparatide compared with risedronate was consistent within the various predefined subgroups. There was no evidence of heterogeneity in treatment effect across the different categories of the subgroups in reducing the risk of new VFx or clinical fractures. Teriparatide antifracture efficacy is similarly superior to risedronate in both osteoporosis treatment-naïve and prior bisphosphonate-treated patients. Data for the first time indicate the additional fracture benefit of using an anabolic compared with an antiresorptive across multiple patient clinical scenarios. This information should aid in positioning teriparatide bone anabolic therapy for reduction of residual fracture burden in patients at high fracture risk who are either treatment-naïve or on bisphosphonate treatment.

Disclosures

PG: Research support, consultant and/or speaker fees from Pfizer, Abbott, Lilly, Amgen, MSD, Roche, UCB, BMS, and Novartis. FM: Employee of Lilly. DLK: Honoraria, research grants,

and/or consultant fees from Amgen, Lilly, AstraZeneca, Astellas, UCB. LAR: None. CAFZ: Research support from Lilly. SLG: Research support from Lilly. SM: Speaker and/or consultant fees from Abiogen, Amgen, DiaSorin, Lilly, Italfarmaco, Fujii, MSD, Takeda. AB: None. PL: None. EC: Speaker fees from Amgen and Lilly. AF-P: Speaker fees from Amgen, Alexion, BMS, Lilly, and Fresenius. JJS: None. EL: Speaker and consultant fees from Amgen, Expanscience, Lilly, MSD; research grants from Abbvie, Amgen, Lilly, MSD, and UCB. RM: None. JJB: Speaker fee from Amgen; research support from Lilly. PL-R: Employee of Lilly.

Acknowledgments

We are indebted to Anja Gentzel-Jorczyk (clinical trial coordinator) and Estrella Crespo and Laura Briones (data management) for their contribution to the study; to Ansgar Dressler from Trilogy Writing and Consulting for editorial assistance; to the members of the investigational teams at the study centers; and to the women who participated in the study. This study's identifier at ClinicalTrials.gov is NCT01709110 and EudraCT number is 2012-000123-41.

The following investigators randomized at least 1 patient into the VERO study: Argentina: A Alvarisqueta, A Bagur, C Gómez, L Maffei, F Massari; Austria: E Boschitz, A Fahrleitner-Pammer, G Höfle, H Koller, C Muschitz, E Preisinger; Belgium: I Beyer, JJ Body, K de Vlam, V Gangji, P Geusens, E Gielen, S Goemare, M Leon, J-Y Reginster, M Van den Berghe, R Witvrouw; Brazil: J Borges, M Castro, LA Russo, CA Zerbini; Canada: J Adachi, JP Brown, A Cheung, S Kaiser, A Karaplis, DL Kendler, F Morin, W Olszynski, S Seigel; Czech Republic: E Dokoupilova, M Ladova, R Pikner, J Stepan, V Zikan; France: R Chapurlat, J Fulpin, C Marcelli, M Laroche, E Lespessailles, T Thomas; Germany: G Dahmen, J Fakler, I Frieling, P Hadji, R Möricke, F Thomasius, L Unger, V Ziller; Greece: M Daniilidis, E Fouloulas, G Ioannidis, M Kita, I Kyrkos, I Panagiotopoulos, S Pnevmticos; Hungary: E Kanakaridu, K Kudlak, P Lakatos, K Nagy, P Somogyi, P Suranyi, Z Valkusz; Italy: G Bianchi, ML Brandi, S Giannini, G Isaia, S Minisola, G Osella, M Rossini; Poland: T Blicharski, J Brzezicki, P Leszczynski, M Mazurek, M Rell-Bakalarska, J Supronik; Spain: MJ Amerigo, M Bernad, E Casado, N Chozas, M Díaz-Curiel, J Malouf-Serra, JA Román, FJ Tarazona; USA and Puerto Rico: N Binkley, M Bolognese, P Bressler, M Carroll, A Chang, D Cox, A de la Llana, A Dulgeroff, H El-Kadi, M Goldberg, S Greenspan, H Kenney, A Kivitz, ME Lewiecki, M Lilliestol, P Miller, A Myers, P Norwood, M Perini, S Rao, RR Recker, CP Recknor, H Rodríguez, KG Saag, R Sachson, C Shuhart, O Soto-Raíces, M Spiegel.

Authors' roles: Study design: FM and PL-R; study conduct: all authors; data collection: PG, DK, LR, CZ, SM, JJB, EL, SG, AB, JS, PL, EC, RM, and AF-P; data interpretation: all authors; drafting manuscript: PG and FM; revising manuscript content: all authors; approving final version of manuscript: all authors. PG and PL-R take responsibility for the integrity of the data analysis.

References

1. Kendler DL, Marin F, Zerbini CAF, et al. Effects of teriparatide and risedronate on new fractures in postmenopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial. *Lancet*. 2018; 391:230–40.
2. Harris ST, Watts NB, Genant HK, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. *Vertebral Efficacy*

- with Risedronate Therapy (VERT) Study Group. *JAMA*. 1999; 282(14):1344–52.
3. Reginster J, Minne HW, Sorensen OH, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. *Osteoporos Int*. 2000;11(1):83–91.
 4. Watts NB, Josse RG, Hamdy RC, et al. Risedronate prevents new vertebral fractures in postmenopausal women at high risk. *J Clin Endocrinol Metab*. 2003;88(2):542–49.
 5. McClung MR, Geusens P, Miller PD, et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. *N Engl J Med*. 2001;344(5):333–40.
 6. Kanis JA, Oden A, Johnell O, et al. The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women. *Osteoporos Int*. 2007;18(8):1033–46.
 7. Robbins J, Aragaki AK, Kooperberg C, et al. Factors associated with 5-year risk of hip fracture in postmenopausal women. *JAMA*. 2007;298(20):2389–98.
 8. Nguyen ND, Frost SA, Center JR, et al. Development of prognostic nomograms for individualizing 5-year and 10-year fracture risks. *Osteoporos Int*. 2008;19(10):1431–44.
 9. Ensrud KE, Black DM, Palermo L, et al. Treatment with alendronate prevents fractures in women at highest risk: results from the Fracture Intervention Trial. *Arch Intern Med*. 1997;157(22):2617–24.
 10. Eastell R, Black DM, Boonen S, et al. Effect of once-yearly zoledronic acid five milligrams on fracture risk and change in femoral neck bone mineral density. *J Clin Endocrinol Metab*. 2009;94(9):3215–25.
 11. McClung MR, Boonen S, Törring O, et al. Effect of denosumab treatment on the risk of fractures in subgroups of women with postmenopausal osteoporosis. *J Bone Miner Res*. 2012;27(1):211–8.
 12. Cosman F, Hattersley G, Hu MY, et al. Effects of abaloparatide-SC on fractures and bone mineral density in subgroups of postmenopausal women with osteoporosis and varying baseline risk factors. *J Bone Miner Res*. 2017;32(1):17–23.
 13. Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. *J Bone Miner Res*. 1993;8(9):1137–48.
 14. European Medicines Agency (EMA) – Committee for Medicinal Products for Human Use (CHMP). Guideline on the evaluation of medicinal products in the treatment of primary osteoporosis (CPMP/EWP/552/95 Rev. 2). London; November 16, 2006. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003405.pdf. Accessed August 27, 2017.
 15. Marcus R, Wang O, Satterwhite J, Mitlak B. The skeletal response to teriparatide is largely independent of age, initial bone mineral density, and prevalent vertebral fractures in postmenopausal women with osteoporosis. *J Bone Miner Res*. 2003;18(1):18–23.
 16. Reginster JY, Seeman E, De Vernejoul MC, et al. Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) study. *J Clin Endocrinol Metab*. 2005;90(5):2816–22.
 17. Ettinger B, San Martin J, Crans G, Pavo I. Differential effects of teriparatide on BMD after treatment with raloxifene or alendronate. *J Bone Miner Res*. 2004;19(5):745–51.
 18. Obermayer-Pietsch BM, Marin F, McCloskey EV, et al. Effects of two years of daily teriparatide treatment on BMD in postmenopausal women with severe osteoporosis with and without prior anti-resorptive treatment. *J Bone Miner Res*. 2008;23(10):1591–600.
 19. Boonen S, Marin F, Obermayer-Pietsch B, et al. Effects of previous antiresorptive therapy on the bone mineral density response to two years of teriparatide treatment in postmenopausal women with osteoporosis. *J Clin Endocrinol Metab*. 2008;93(3):852–60.
 20. Cosman F, Wermers RA, Recknor C, et al. Effects of teriparatide in postmenopausal women with osteoporosis on prior alendronate or raloxifene: differences between stopping and continuing the antiresorptive agent. *J Clin Endocrinol Metab*. 2009;94(10):3772–80.
 21. Langdahl BL, Libanati C, Crittenden DB, et al. Romosozumab (sclerostin monoclonal antibody) versus teriparatide in postmenopausal women with osteoporosis transitioning from oral bisphosphonate therapy: a randomised, open-label, phase 3 trial. *Lancet*. 2017;6736(17):31613–6.
 22. Miller PD, Hattersley G, Riis BJ, et al. Effect of abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis: a randomized clinical trial. *JAMA*. 2016;316(7):722–33.
 23. Hadji P, Zanchetta JR, Russo L, et al. The effect of teriparatide compared with risedronate on reduction of back pain in postmenopausal women with osteoporotic vertebral fractures. *Osteoporos Int*. 2012;23(8):2141–50.
 24. Saag KG, Shane E, Boonen S, et al. Teriparatide or alendronate in glucocorticoid-induced osteoporosis. *N Engl J Med*. 2007; 357(20):2028–39.
 25. Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. *Lancet*. 1996;348(9041):1535–41.
 26. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med*. 2007; 356(18):1809–22.