T-Score as an Indicator of Fracture Risk During Treatment With Romosozumab or Alendronate in the ARCH Trial

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ABSTRACT

In the Active-Controlled Fracture Study in Postmenopausal Women With Osteoporosis at High Risk (ARCH) clinical trial (NCT01631214), 1 year of romosozumab followed by alendronate reduced the risk of vertebral and nonvertebral fractures compared to alendronate alone in women with prevalent fracture. We performed post hoc analyses of data from patients in ARCH (romosozumab, n = 1739; alendronate, n = 1726) who had a baseline BMD measurement and received at least one open-label alendronate dose. We evaluated 1-year mean BMD and corresponding T-score changes; proportions of patients achieving T-scores > −2.5 at the total hip (TH), femoral neck (FN), and lumbar spine (LS); and group differences in fracture rates after 12 months, while all participants were on alendronate. Subsequently, we investigated the relationship between T-scores achieved at the TH, FN, and LS at 12 months and subsequent fracture incidence. At 1 year, mean change from baseline in TH BMD was 6.3% (T-score change 0.31) with romosozumab versus 2.9% (T-score change 0.15) with alendronate (p < .001). The proportion of patients with TH T-score > −2.5 increased from 34% at baseline to 55% after 1 year of romosozumab and from 32% at baseline to 44% after 1 year of alendronate. Compared with patients receiving alendronate in year 1, those receiving romosozumab had a 75% reduction in new or worsening vertebral fracture (p < .001) in year 2, and a 19% reduction in nonvertebral fracture (p = .120) and 40% reduction in hip fracture (p = .041) during the open-label period. TH and FN T-scores achieved at month 12 were associated with subsequent nonvertebral and vertebral fracture rates and the relationships were independent of treatment received. LS T-score at 12 months was associated with vertebral but not nonvertebral fracture risk. We conclude that 1 year of romosozumab leads to larger BMD gains versus alendronate, and that the T-score achieved with either therapy is related to subsequent fracture risk. These data support the use of T-score as a therapeutic target for patients with osteoporosis. © 2020 The Authors. Journal of Bone and Mineral Research published by American Society for Bone and Mineral Research.

KEY WORDS: ALENDRONATE; BONE MINERAL DENSITY; POSTMENOPAUSAL OSTEOPOROSIS; ROMOSOZUMAB; T-SCORE

Introduction

BMD is a strong predictor of fracture risk in untreated patients.[1,2] Extension studies of large clinical trials show a relationship between attained hip BMD on antiresorptive therapy and subsequent fracture incidence.[3–5] In postmenopausal women with low BMD who received daily alendronate for 5 years in the Fracture Intervention Trial (FIT) trial and were then randomized to placebo in the study extension (FIT Long-Term Extension [FLEX]),[3] hip BMD attained at 5 years was

associated with subsequent fracture risk over 5 additional years. Similarly, in another study of postmenopausal women with osteoporosis who received zoledronic acid for 3 years and were then randomized to placebo,[4] hip BMD achieved at 3 years was a predictor of subsequent fracture risk over 3 years. In the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) study in which women received denosumab for up to 10 years,[5] higher hip BMD achieved at any time during treatment was associated with lower subsequent nonvertebral and vertebral fracture incidence. A large meta-regression study of 38 placebo-controlled trials, evaluating 19 therapeutic agents, concluded that total hip (TH) BMD gain on treatment is associated with fracture risk reduction.[6] These studies suggest that TH *T*-score achieved on therapy could be considered as a target to help guide osteoporosis treatment; however, such a *T*-score is likely to vary depending on patient risk factors, such as age, prior fracture history, or susceptibility to falls.[5]

Romosozumab is a bone-forming agent with the dual effect of increasing bone formation and decreasing bone resorption.[7,8] Romosozumab 210 mg administered s.c. monthly for 12 months produced large increases in lumbar spine (LS) and TH BMD,[7,9] reduced the risk of new vertebral and clinical fractures compared with placebo,[10] and reduced the risk of vertebral, clinical, nonvertebral, and hip fractures compared with alendronate over a median treatment period of 33 months.[11]

In the Fracture Study in Postmenopausal Women With Osteoporosis (FRAME),[10] the large BMD increases with an initial 1 year of romosozumab treatment were associated with a rapid reduction in fracture risk. This benefit extended into years 2[10] and 3,[12] when all participants received denosumab. Quantitative analyses of the relationship between *T*-scores achieved with romosozumab and fracture risk reduction could not be evaluated in the FRAME study because of the small number of fractures observed.[13]

In the Active-Controlled Fracture Study in Postmenopausal Women With Osteoporosis at High Risk (ARCH),[11] treatment with romosozumab followed by alendronate produced larger BMD gains and greater fracture risk reduction compared to treatment with alendronate alone. In ARCH, all patients had a prior fracture and the numbers of on-study vertebral and nonvertebral fractures observed in this high-risk population were sufficient to allow further evaluation of the relationships between *T*-scores achieved and fracture risk reduction. Additionally, the two treatment groups in ARCH were on active therapy for an equal duration (1 year of romosozumab followed by alendronate or 1 year of alendronate followed by continued alendronate throughout the study period).

In the post hoc analyses of the ARCH study reported here, we evaluated whether *T*-scores achieved at the TH, femoral neck (FN), and LS after 1 year of treatment with romosozumab or alendronate were related to subsequent risk of vertebral and nonvertebral fracture.

Patients and Methods

Study design and patient population

This post hoc analysis was based on ARCH (Clinical Trial NCT01631214), a phase 3, multicenter, international, randomized, active-controlled, double-blind study in postmenopausal women with osteoporosis. Details of the ARCH study have been previously published.[11] Briefly, patients were randomized 1:1 to receive monthly s.c. romosozumab 210 mg or weekly oral alendronate 70 mg for 12 months (Supplemental Fig. 1). After completion of the double-blind study period, all patients received open-label weekly oral alendronate 70 mg through end of study, blinded to initial treatment assignment. Patients received daily calcium and vitamin D as previously described.[11]

Primary endpoints for ARCH were incidence of new vertebral fracture through 24 months and clinical fracture at primary analysis (event-driven upon ≥330 clinical fractures and all patients had completed the month 24 visit), and secondary endpoints included incidence of nonvertebral and hip fractures at primary analysis, results of which have been previously published.[11] This report is focused on results from the post hoc analyses that evaluated mean BMD and corresponding mean *T*-score changes, and the relationships between *T*-scores after 1 year of romosozumab or alendronate and subsequent fracture incidence.

Outcome measures

We determined mean BMD percentage change from baseline, mean *T*-score change from baseline, *T*-scores achieved at the TH, FN, and LS at month 12, and the proportion of patients who achieved *T*-scores > −2.5 and > −2.0 at the three skeletal sites at month 12. We then evaluated the effects of romosozumab versus alendronate for 1 year on incidence of new or worsening vertebral fracture in year 2 and incidence of nonvertebral and hip fractures during the open-label period.

Our primary objective was to determine the relationships between TH, FN, and LS *T*-scores achieved at month 12 and subsequent fracture incidence (nonvertebral and new or worsening vertebral fractures) across the treatment groups. Because BMD continues to increase between 12 and 24 months, we also assessed relationships between *T*-scores achieved at each of the three skeletal sites at month 24 with subsequent fracture incidence (nonvertebral and new or worsening vertebral fractures). Because BMD increases very rapidly with romosozumab, we also sought to determine if these rapid increments at this very early time point were associated with subsequent risk of fracture. To accomplish this, we imputed 6-month *T*-scores for the population using a model based on the subset of patients who had 6-month measurements (*n* = 143), and then determined if the 6-month *T*-score level was also associated with subsequent risk of fracture. Our approach is similar to the approach used in FREEDOM,[5] except that we estimated *T*-score at 6 months only, whereas *T*-score was estimated for every fracture time point in FREEDOM.

Statistical analysis

The post hoc analyses included all patients who had a baseline TH or FN BMD *T*-score measurement and had received at least one open-label alendronate dose. Means and 95% CIs are reported for BMD percentage change from baseline, and least squares means and 95% CIs are reported for *T*-score change from baseline and *T*-score achieved. For BMD percentage change, *T*-score change, and *T*-score achieved, treatment comparisons were based on an analysis of covariance (ANCOVA) model adjusting for treatment, age strata (<75 versus ≥75 years), presence of severe vertebral fracture at baseline, baseline BMD value or *T*-score, machine type, and baseline BMD value or *T*-score-by-machine-type interaction. For proportions of patients with *T*-scores of > −2.5 and > −2.0, *p* values were based on a logistic regression model adjusting for treatment, age strata, presence of

severe vertebral fracture at baseline, and baseline *T*-score. Missing values were imputed by carrying forward the last nonmissing postbaseline value prior to the missing value and within the treatment period.

Fracture efficacy focused on the relative risk reductions in year 2 for new or worsening vertebral fracture (given all patients had a baseline and spine X-ray at 24 months allowing for this assessment) and during the full open-label period for nonvertebral and hip fracture, when all patients were receiving alendronate. For new or worsening vertebral fracture, the analysis set included all randomized patients who received at least one open-label alendronate dose and had a spine X-ray evaluation for vertebral fracture at baseline, month 12, and at or before month 24. Risk ratios were determined by means of the Mantel-Haenszel method with treatment comparison assessed with the use of the logistic regression model adjusting for age strata (<75 versus ≥75 years), baseline TH *T*-score, and presence of severe vertebral fracture at baseline. For nonvertebral and hip fractures, the analysis set included all randomized patients who had received at least one open-label alendronate dose. Treatment groups were compared based on the Cox proportional hazards model adjusting for age strata (<75 versus ≥75 years), baseline TH *T*-score, and presence of severe vertebral fracture at baseline. Because these were post hoc analyses, no multiplicity adjustments were performed.

Analyses for the relationships between TH, FN, or LS *T*-scores achieved at month 12 and subsequent nonvertebral and new or worsening vertebral fracture incidence were based on the Cox proportional hazards model with time to fracture as the response and *T*-score at month 12 as a covariate. The relationships between TH, FN, or LS *T*-scores achieved at month 24 and subsequent nonvertebral and new or worsening vertebral fracture incidence in the open-label period were based on the Cox proportional hazards model with time to fracture as the response and *T*-score at month 24 as a covariate. Robustness of the

relationships was evaluated by the likelihood ratio test. The dependence of the relationships on treatment was evaluated by the interaction test in Cox proportional hazards models, by testing the interaction term between treatment and BMD *T*-scores.

For patients with no month 6 BMD measurements, month 6 BMD *T*-scores were estimated using all observed postbaseline *T*-scores based on a mixed-effect model adjusting for baseline BMD, age strata, and presence of severe vertebral fracture at baseline. The estimated month 6 *T*-scores were then used to evaluate the association of subsequent nonvertebral and new or worsening vertebral fracture incidence (after month 6) based on the Cox proportional hazards model with time to fracture as the response and *T*-score at month 6 as a covariate.

Results

Patients and baseline demographics

ARCH enrolled 4093 patients (romosozumab, *n* = 2046; alendronate, *n* = 2047). Median (quartile 1 [Q1], quartile 3 [Q3]) follow-up time through the primary analysis (double-blind period plus open-label period) was 2.7 (2.2, 3.3) years. The post hoc analyses reported here (in patients who had a month 12 BMD measurement and at least one open-label alendronate dose) included 3465 patients (romosozumab, *n* = 1739; alendronate, *n* = 1726), with a median (Q1, Q3) follow-up time of 2.9 (2.4, 3.4) years through the primary analysis, 1.9 (1.4, 2.4) years for the open-label period only, and 0.9 (0.4, 1.4) years after month 24. Demographic characteristics for the treatment groups in the post hoc analyses were similar to those of the full ARCH cohort[11] and did not differ significantly from each other (Table 1). Mean baseline *T*-scores were −2.78 at the TH, −2.89 at the FN, and −2.97 at the LS.

BMD and *T*-score changes

Mean BMD changes after 1 year of romosozumab were all significantly higher than those seen after 1 year of alendronate (6.3% at the TH, 5.0% at the FN, and 13.9% at the LS, compared with 2.9%, 1.7%, and 5.1%, respectively; Table 2). Corresponding *T*-score changes and mean *T*-scores achieved were all significantly higher at all three skeletal sites in patients who received romosozumab compared with those who received alendronate (*p* < .001 for all comparisons) (Table 2). Mean BMD percentage changes from baseline, *T*-score changes, and *T*-scores achieved at the TH, FN, and LS at month 24 (after all patients had transitioned to alendronate for 12 months) were also all significantly higher in patients who received romosozumab during the first year than in patients who received alendronate (Supplemental Table 1).

Proportion of patients who achieved *T*-scores > −2.5 and > −2.0 at the three skeletal sites

The proportion of patients who achieved *T*-scores of > −2.5 and > −2.0 was larger with romosozumab than with alendronate at all time points. With romosozumab, the proportion of patients who achieved TH *T*-scores > −2.5 increased from 34% at baseline to 55% at 1 year (Fig. 1*A*). After 1 year of alendronate, the proportion of patients with TH *T*-scores > −2.5 increased from 32% at baseline to 44%. Similar results were observed at the FN (Fig. 1*B*) and LS (Fig. 1*C*); with *p* < .001 for all group comparisons at the three skeletal sites. Mean *T*-scores at each skeletal site

Table 1. Baseline Demographic and Clinical Characteristics for Patients Included in Post Hoc Analyses

Characteristic	Romosozumab (*n* = 1739)	Alendronate (*n* = 1726)
Age (years), mean ± SD	74.1 ± 7.5	74.0 ± 7.4
BMD *T*-score, mean ± SD		
Total hip	−2.77 ± 0.67	−2.80 ± 0.65
Femoral neck	−2.88 ± 0.47	−2.90 ± 0.50
Lumbar spine	−2.95 ± 1.23	−3.00 ± 1.22
Previous osteoporotic fracture at ≥45 years of age, *n* (%)	1718 (98.8)	1709 (99.0)
Prevalent vertebral fracture, *n* (%)	1671 (96.1)	1651 (95.7)
Moderate	450 (25.9)	476 (27.6)
Severe	1165 (67.0)	1112 (64.4)
Previous nonvertebral fracture at ≥45 years of age, *n* (%)	645 (37.1)	657 (38.1)
Previous hip fracture, *n* (%)	152 (8.7)	155 (9.0)

n = number of patients randomized to the 12-month double-blind period and who had a baseline value and received at least one open-label alendronate dose. Previous osteoporotic fractures include both nonvertebral and prevalent vertebral fractures, excluding high trauma and pathologic fractures. Previous nonvertebral and hip fracture excludes pathologic or high-trauma hip fractures.

Table 2. Mean BMD Percentage Changes From Baseline, Mean BMD *T*-Score Changes From Baseline, and Mean BMD *T*-Scores Achieved at the Total Hip, Femoral Neck, and Lumbar Spine at Month 12

	Romosozumab (n = 1739[a])			Alendronate (n = 1726[a])		
Parameter	Mean BMD percentage change	Mean *T*-score change	Mean *T*-score achieved	Mean BMD percentage change	Mean *T*-score change	Mean *T*-score achieved
Total hip	6.3 (6.1–6.5)	0.31 (0.30–0.33)	−2.46 (−2.48 to −2.45)	2.9 (2.7–3.1)	0.15 (0.14–0.16)	−2.63 (−2.64 to −2.62)
Femoral neck	5.0 (4.7–5.3)	0.23 (0.22–0.24)	−2.66 (−2.67 to −2.65)	1.7 (1.5–2.0)	0.09 (0.08–0.10)	−2.80 (−2.81 to −2.79)
Lumbar spine	13.9 (13.6–14.3)	0.90 (0.88–0.92)	−2.07 (−2.09 to −2.05)	5.1 (4.8–5.3)	0.34 (0.32–0.35)	−2.64 (−2.65 to −2.62)

For BMD percentage change, data are mean % (95% CI). For *T*-score change and *T*-score achieved, data are least squares mean (95% CI) based on an ANCOVA model adjusting for treatment, age strata (<75 versus ≥75 years), presence of severe vertebral fracture at baseline, baseline BMD value or *T*-score, machine type, and baseline BMD value or *T*-score-by-machine-type interaction.

ANCOVA = analysis of covariance; *n* = number of patients with BMD values at baseline and at least one open-label alendronate dose.

[a]*n* values shown are for total hip and femoral neck; for lumbar spine, *n* = 1665 for romosozumab and *n* = 1647 for alendronate. Missing values were imputed by carrying forward the last nonmissing postbaseline value prior to the missing value and within the treatment period. *P* < .001 for difference between romosozumab and alendronate for all comparisons at the three skeletal sites.

increased similarly from month 12 to month 24 when patients in both groups received alendronate (Supplemental Fig. 2).

Effect of romosozumab versus alendronate treatment on subsequent fracture incidence

Compared with alendronate, romosozumab treatment for 1 year lowered subsequent fracture incidence (Fig. 2). In year 2, while all patients were on alendronate, patients who had received romosozumab in year 1 had a 75% lower risk of new or worsening vertebral fracture than those who had received alendronate alone for 2 years (risk ratio 0.25; 95% CI, 0.15 to 0.41; *p* < .001). During the open-label period, patients who had received romosozumab in year 1 had a 19% lower risk of nonvertebral fracture (risk ratio 0.81; 95% CI, 0.63 to 1.05; *p* = .120) and a 40% lower risk of hip fracture (risk ratio 0.60; 95% CI, 0.37 to 0.99; *p* = .041) compared with patients who had received alendronate alone.

Relationship between *T*-scores achieved at month 12 and incidence of subsequent fracture

Fig. 3 illustrates the relationships between TH, FN, and LS *T*-scores achieved at month 12 and subsequent nonvertebral and new or worsening vertebral fracture incidence for both treatment groups combined. Results analyzed by each treatment group alone were consistent with findings for the treatment groups combined (data not shown). A relationship was observed between month 12 TH *T*-score and incidence of subsequent nonvertebral fracture (Fig. 3*A*; with a likelihood ratio test of *p* < .001), and new or worsening fracture (Fig. 3*B*; *p* = .004). Similarly, a relationship was observed between month 12 FN *T*-score and incidence of subsequent nonvertebral fracture (Fig. 3*C*; *p* < .001) and new or worsening vertebral fracture (Fig. 3*D*; *p* = .005). For LS, a relationship was observed between month 12 *T*-score and incidence of subsequent new or worsening vertebral fracture (Fig. 3*F*; *p* < .001) but not incidence of subsequent nonvertebral fracture (Fig. 3*E*; *p* = .666).

Relationship between *T*-scores achieved at other time points and incidence of subsequent fracture

Relationships were also observed between month 24 TH *T*-score and incidence of subsequent nonvertebral fracture (Fig. 4*A*;

p = .003) and new or worsening vertebral fracture (Fig. 4*B*; *p* = .006). For FN, a relationship was observed between month 24 *T*-score and incidence of subsequent new or worsening vertebral fracture (Fig. 4*D*; *p* = .020) but not incidence of nonvertebral fracture (Fig. 4*C*; *p* = .107). Similarly, for the 24-month LS *T*-score, there was a relationship with incidence of subsequent new or worsening vertebral fracture (Fig. 4*F*; *p* < .001) but not with incidence of nonvertebral fracture (Fig. 4*E*; *p* = .934).

Additionally, modeled data indicated relationships between month 6 TH *T*-score and incidence of subsequent nonvertebral fracture (Fig. 5*A*; *p* < .001) and new or worsening vertebral fracture (Fig. 5*B*; *p* < .001). Similar results were observed for FN (nonvertebral fracture, *p* = .006; and new or worsening fracture, *p* < .001; Fig. 5*C,D*). The modeled 6-month LS *T*-score analyses also reflected those seen for 12-month and 24-month actual LS *T*-scores, showing an association with new or worsening vertebral fracture (Fig. 5*F*; *p* < .001), but not with nonvertebral fracture (Fig. 5*E*; *p* = .748).

Discussion

Results from the analyses we report here support prior observations with antiresorptive therapies indicating that on-treatment *T*-scores can serve as a predictor of fracture risk and reflect the potential benefit to patients from rapidly increasing BMD to reduce fracture risk. Mean BMD gains after 1 year of romosozumab were more than twice those seen with alendronate at the TH, FN, and LS. These BMD changes resulted in a larger proportion of patients who achieved *T*-scores above osteoporosis level at each of the skeletal sites after 1 year of therapy. Fewer fractures occurred during the second year and the entire open-label period among patients who had received romosozumab first compared with those who had received alendronate. TH and FN *T*-scores achieved on treatment at 12 months were related to subsequent vertebral and nonvertebral fracture rates and the relationships were independent of treatment received. The relationships were most robust for the TH; at the LS, *T*-scores were associated with vertebral but not nonvertebral fracture risk. *T*-scores achieved as early as 6 months were predictive of subsequent fracture risk. *T*-scores achieved at the TH after 24 months with sequential romosozumab followed by alendronate or alendronate alone for 24 months remained predictive of subsequent
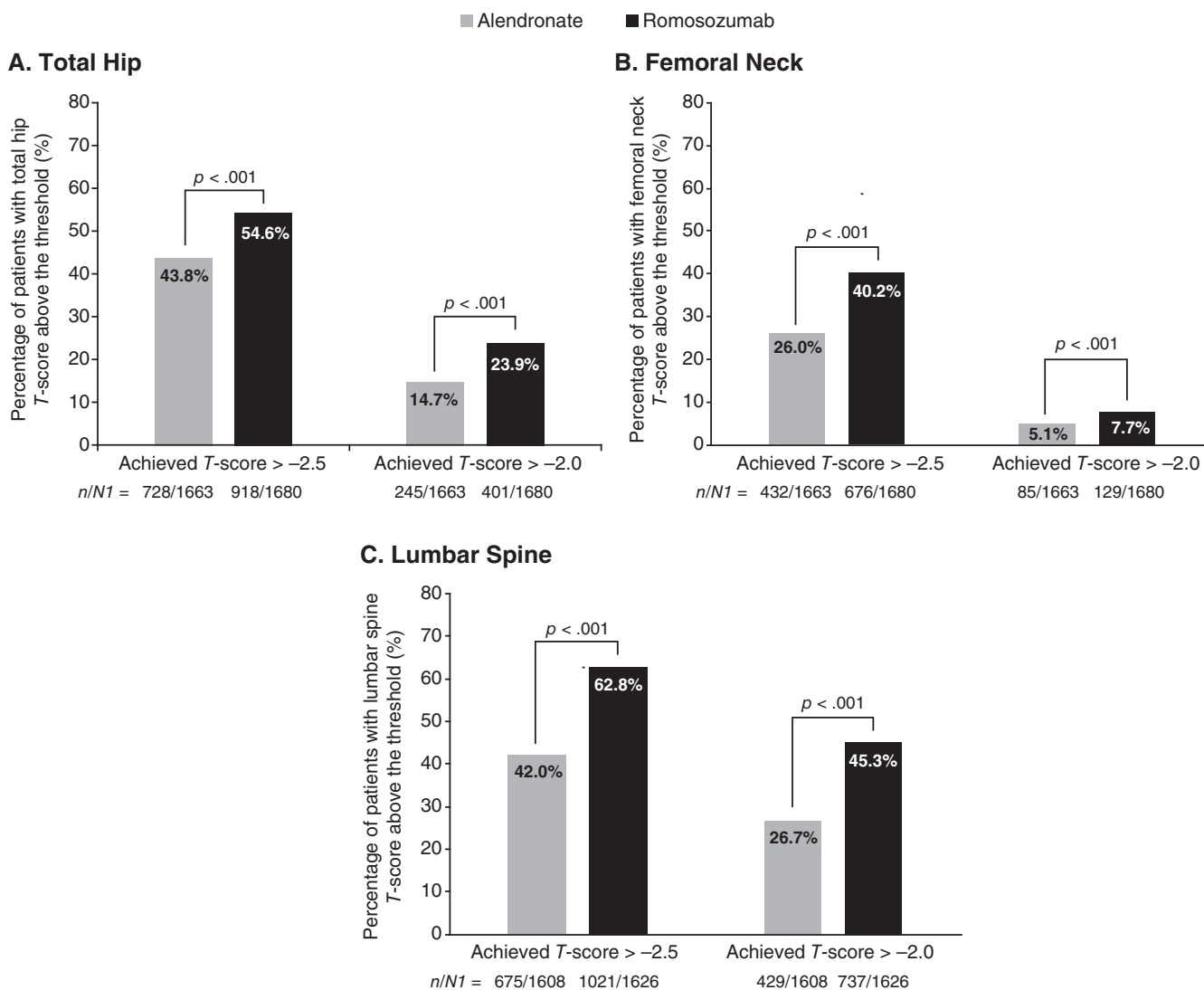
Fig. 1. Percentage of patients with achieved T-scores > −2.5 and > −2.0 at the total hip (*A*), femoral neck (*B*), and lumbar spine (*C*) at month 12. The analysis included patients with BMD values at baseline and at least one open-label alendronate dose. *p* values were based on a logistic regression model adjusting for treatment, age strata (<75 versus ≥75 years), presence of severe vertebral fracture at baseline, and baseline T-score. Missing values were imputed by carrying forward the last nonmissing postbaseline value prior to the missing value and within the treatment period. *n/N1* = number of patients with T-score change above the threshold/number of patients with an evaluation at that time point.

fracture risk. Our findings suggest that TH *T*-score on treatment can be used to monitor if osteoporosis treatment goals have been achieved, to minimize future fracture risk. This suggests that in clinical practice, use of an osteoporosis treatment goal for individual patients could minimize future fracture risk.

The findings from our study are similar to the results from the post hoc analyses performed for the FRAME study,[10,13] in which patients who had received romosozumab 210 mg monthly for 12 months had fewer fractures in year 2 compared with patients who had received placebo. Most patients who were treated with romosozumab in FRAME had substantial BMD and corresponding *T*-score gains at the TH and LS.[13] Observations from our current study, as well as from the FRAME study, suggest that achieving a higher BMD with treatment within 1 year not only quickly reduces fracture risk but also leads to a persistent benefit when transitioning to antiresorptive therapy. Furthermore,

results from our analyses are consistent with results from an analysis of the relationship between TH *T*-score and incidence of nonvertebral fracture in women who received up to 10 years of continued denosumab therapy in the FREEDOM and FREEDOM Extension studies[5] where TH *T*-scores above −2.0 were associated with minimized risk of future fracture.

There may be several explanations for the TH being a better skeletal site for a *T*-score target than the FN or LS. The TH is a peripheral site that is similarly defined by major DXA manufacturers, represents a large area of interest with cortical and trabecular bone, and has good precision error.[14–16] The FN, on the other hand, is not consistently defined by different densitometry manufacturers and is a site with a smaller area and greater precision error than the TH.[14–16] The LS (L$_1$–L$_4$) has a larger area and usually has better precision than TH and is more responsive to changes with therapy than the TH, due to higher cancellous

■ Alendronate after 12 months of alendronate   ■ Alendronate after 12 months of romosozumab
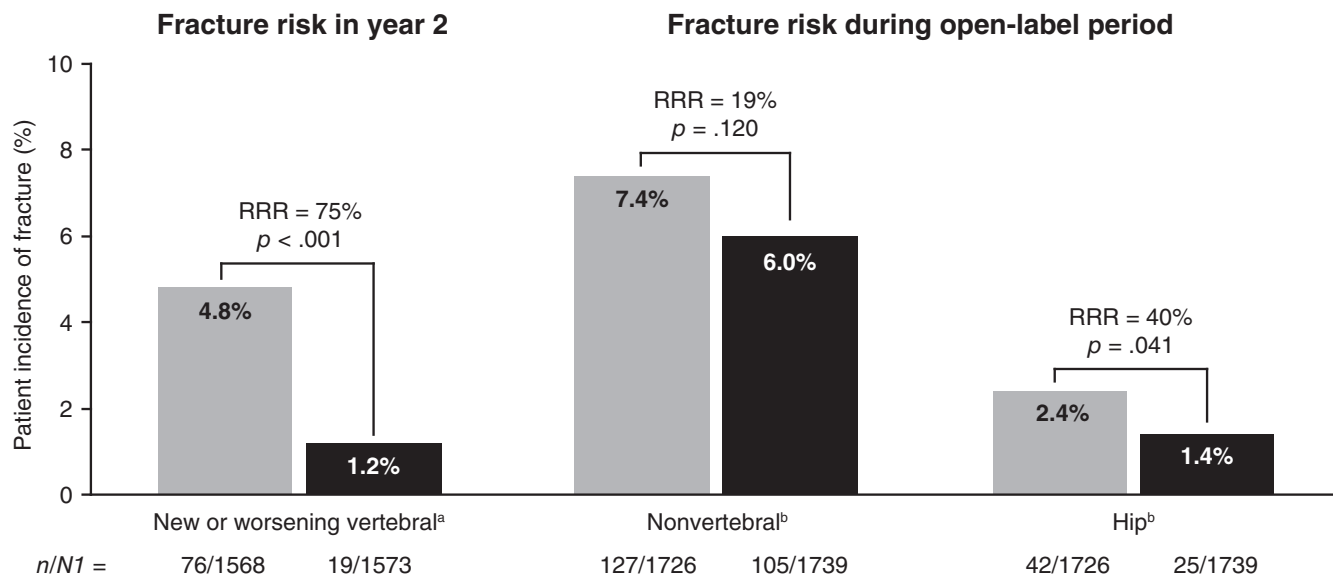
Fracture risk in year 2   **Fracture risk during open-label period**

Patient incidence of fracture (%)

RRR = 19%
p = .120

RRR = 75%
p < .001

7.4%

6.0%

4.8%

RRR = 40%
p = .041

2.4%

1.4%

1.2%

New or worsening vertebral[a]   Nonvertebral[b]   Hip[b]

n/N1 =   76/1568   19/1573   127/1726   105/1739   42/1726   25/1739

Fig. 2. Incidence of fracture during the post-romosozumab open-label alendronate period. [a]Analysis set included all randomized patients who received at least one open-label alendronate dose and had an evaluation of vertebral fracture at month 12 and at or before month 24; analysis was based on the Mantel-Haenszel method adjusting for age strata, baseline total hip BMD *T*-score, and presence of severe vertebral fracture at baseline, without multiplicity adjustment. [b]Analysis set included all randomized patients who had received at least one open-label alendronate dose; analysis was based on the Cox proportional hazards model adjusting for age strata, baseline total hip BMD *T*-score, and presence of severe vertebral fracture at baseline, without multiplicity adjustment. *n/N1* = number of patients with fractures/number of patients in the efficacy analysis set; RRR = relative risk reduction.

bone content; however, measurement in older patients is often confounded by degenerative changes and other artifacts that increase *T*-score without increasing bone strength.[17] Furthermore, the LS does not predict nonvertebral fractures as well as the TH or FN in untreated women, also perhaps because of the lower cortical bone content.

The strengths of our current study include the high incidence of fractures observed in the population evaluated in the ARCH study, which allowed for evaluation of the relationship between *T*-score achieved with treatment and future fracture risk reduction. Furthermore, the study provided for patients in both groups to receive active therapy for a similar duration, allowing assessment of BMD changes over a continuous treatment period in both groups. However, a number of limitations must also be considered. First, these were post hoc analyses with no adjustments for multiple comparisons, a fact discounted by the consistency and robustness of the associations. Second, BMD was only assessed in yearly intervals in the total study population and relationships between 6-month BMD changes and subsequent fractures were modeled based on the much smaller subset of patients who had 6-month measurements. The number of fracture events after month 24 was lower than that after month 12, leading to loss of statistical power for assessing the relationship between month 24 *T*-score and subsequent incidence of fracture. Last, our analyses do not consider mechanisms of action beyond BMD increases as contributors to bone strength, such as improvement in bone microarchitecture or reduction in bone turnover, although the association between *T*-scores achieved on therapy and subsequent fracture risk reductions was similar for romosozumab and alendronate. This underscores the importance and major impact of bone density over other variables influencing bone strength.

Our data show that 1 year of romosozumab leads to larger BMD gains compared with alendronate and results in a greater likelihood of osteoporosis resolution. The *T*-score achieved with either therapy, as early as 6 months and as late as 24 months, is related to subsequent fracture risk. The findings support the concept of treat-to-target for osteoporosis and are consistent with the results of other studies showing the correlation between *T*-score achieved with many osteoporosis treatments and reduction in fracture risk. We conclude that *T*-scores may be a clinically useful target for postmenopausal women treated with romosozumab. The large BMD gains seen with romosozumab suggest it could have an important role in treating patients with osteoporosis who are at high risk for fracture.

Disclosures

Total Hip

A. Nonvertebral

Likelihood ratio test *p* < .001

B. New or Worsening Vertebral

Likelihood ratio test *p* = .004

Femoral Neck

C. Nonvertebral

Likelihood ratio test *p* < .001

D. New or Worsening Vertebral

Likelihood ratio test *p* = .005

Lumbar Spine

E. Nonvertebral

Likelihood ratio test *p* = .666

F. New or Worsening Vertebral

Likelihood ratio test *p* < .001

Fig. 3. Month 12 total hip (*A,B*), femoral neck (*C,D*), and lumbar spine (*E,F*) *T*-scores and subsequent nonvertebral and new or worsening vertebral fracture incidence. The analysis included patients who had a month 12 total hip or femoral neck BMD *T*-score and had at least one open-label alendronate dose (3342 patients [romosozumab, 1679; alendronate, 1663] for both total hip and femoral neck and 3232 patients [romosozumab, 1625; alendronate, 1607] for lumbar spine) and was based on the Cox proportional hazards model with time to fracture as the response and total hip *T*-score at month 12 as a covariate. Dashed lines indicate upper and lower 95% CIs. *P*-values were based on the likelihood ratio test.
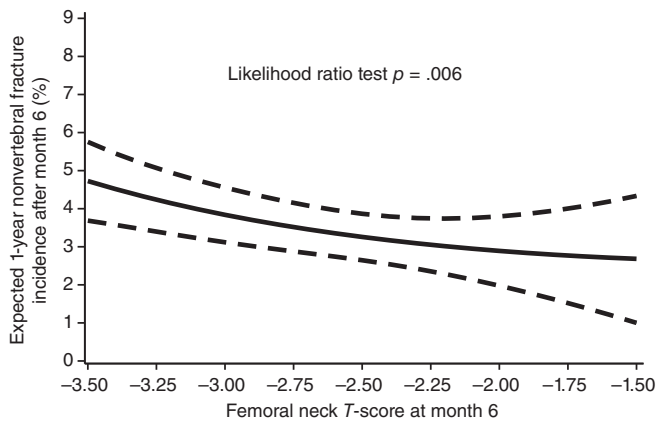
Total Hip
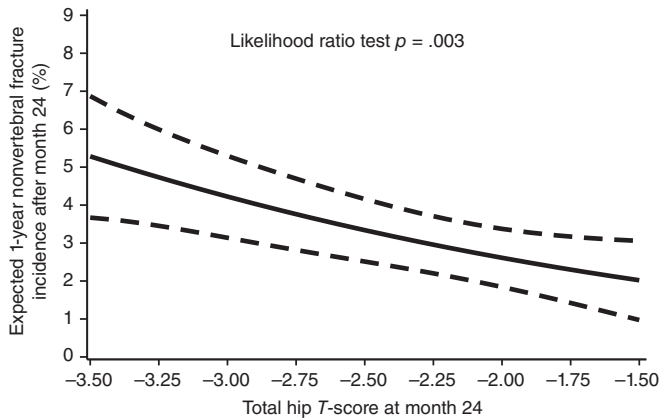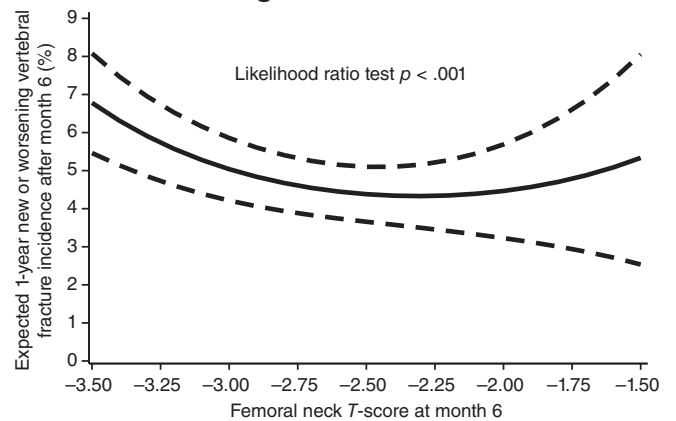
A. Nonvertebral

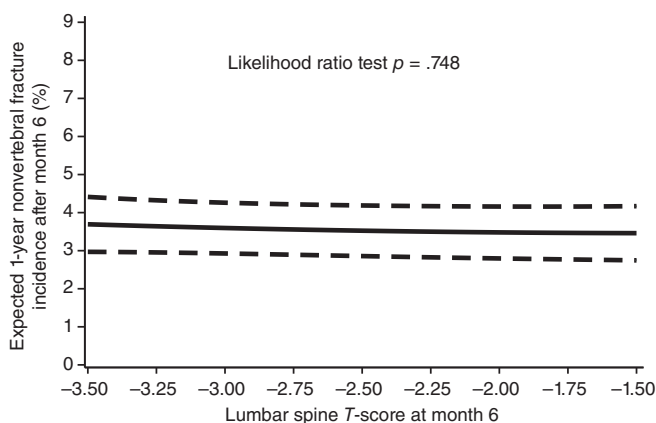## B. New or Worsening Vertebral
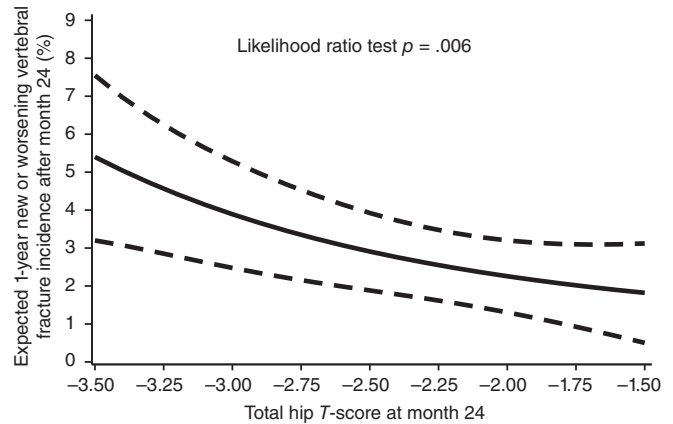
Femoral Neck
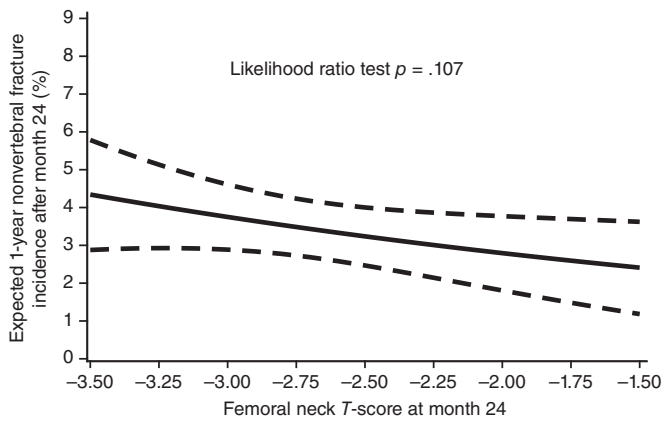
C. Nonvertebral

D. New or Worsening Vertebral
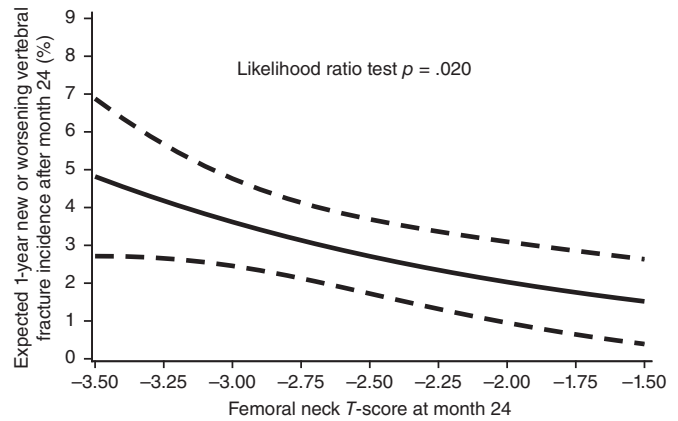
Lumbar Spine
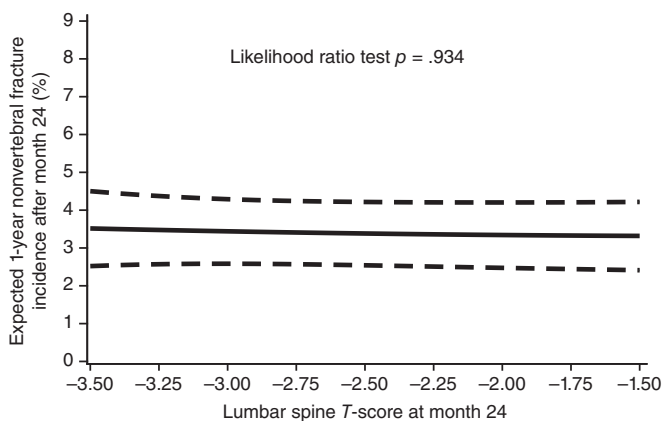
E. Nonvertebral
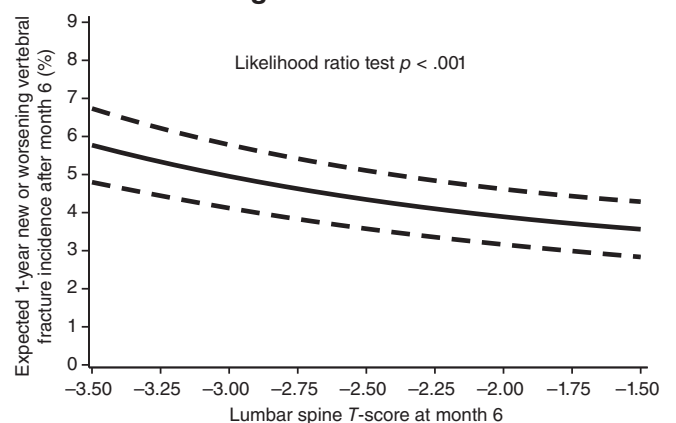

F. New or Worsening Vertebral
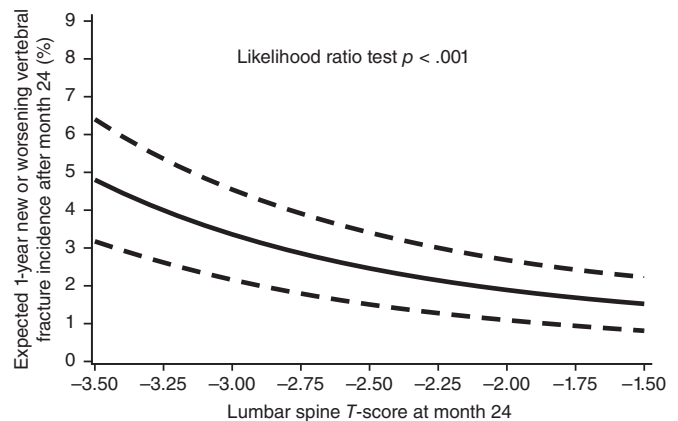
Fig. 4. Month 24 total hip (*A,B*), femoral neck (*C,D*), and lumbar spine (*E,F*) *T*-scores and subsequent nonvertebral and new or worsening vertebral fracture incidence. The analysis included patients who had a month 24 total hip or femoral neck BMD T-score and at least one open-label alendronate dose (3243 patients [romosozumab, 1619; alendronate, 1624] for both total hip and femoral neck and 3142 patients [romosozumab, 1568; alendronate, 1574] for lumbar spine) and was based on the Cox proportional hazards model with time to fracture as the response and total hip *T*-score at month 24 as a covariate. Dashed lines indicate upper and lower 95% CIs. *P*-values were based on the likelihood ratio test.

Total Hip
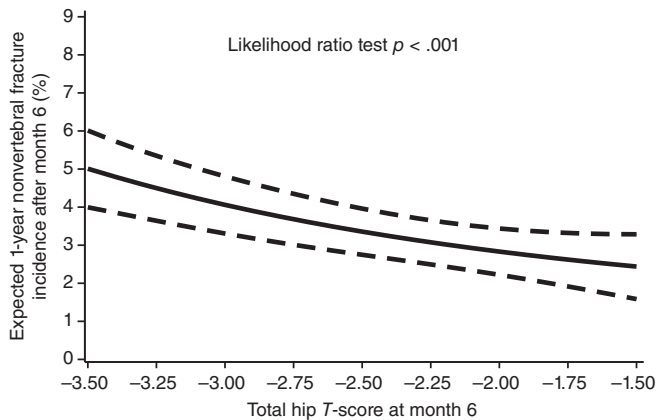
A. Nonvertebral
B. New or Worsening Vertebral
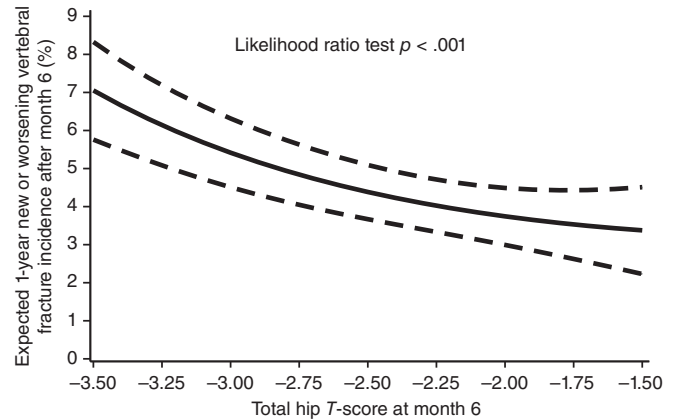
Femoral Neck

C. Nonvertebral
D. New or Worsening Vertebral

Lumbar Spine

E. Nonvertebral
F. New or Worsening Vertebral

Fig. 5. Modeled month 6 total hip (*A,B*), femoral neck (*C,D*), and lumbar spine (*E,F*) *T*-scores and subsequent nonvertebral and new or worsening vertebral fracture incidence. All observed postbaseline BMD *T*-scores were used to predict month 6 BMD *T*-scores using the mixed-effect model adjusting for baseline BMD, age strata, and presence of severe vertebral fracture at baseline. Then the predicted month 6 BMD *T*-scores were used to determine the relationship between month 6 total hip *T*-score and subsequent nonvertebral and new or worsening vertebral fracture incidence after month 6. The analysis included patients who had an observed BMD *T*-score at baseline and at least one observed postbaseline BMD *T*-score (4092 patients [romosozumab, 2046; alendronate, 2046] for both total hip and femoral neck and 3896 patients [romosozumab, 1950; alendronate, 1946] for lumbar spine) and was based on the Cox proportional hazards model with time to fracture as the response and total hip *T*-score at month 6 as a covariate. Dashed lines indicate upper and lower 95% CIs. *P*-values were based on the likelihood ratio test.

Acknowledgments

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