Treatment with Denosumab Reduces the Incidence of New Vertebral and Hip Fractures in Postmenopausal Women at High Risk

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Context: The FREEDOM (Fracture REduction Evaluation of Denosumab in Osteoporosis every 6 Months) trial showed denosumab significantly reduced the risk of fractures in postmenopausal women with osteoporosis.

Objective: We evaluated the effect of denosumab on the incidence of new vertebral and hip fractures in subgroups of women at higher risk for these fractures.

Design: FREEDOM was a 3-yr, randomized, double-blind, placebo-controlled, phase 3 trial.

Participants and Setting: Postmenopausal women (N = 7808) with osteoporosis were enrolled at 213 study sites worldwide.

Interventions: Subjects received sc denosumab (60 mg) or placebo every 6 months and daily supplements of calcium (≥1000 mg) and vitamin D (≥400 IU).

Main Outcome Measures: This *post hoc* analysis evaluated fracture incidence in women with known risk factors for fractures including multiple and/or moderate or severe prevalent vertebral fractures, aged 75 yr or older, and/or femoral neck bone mineral density T-score of −2.5 or less.

Results: Compared with placebo, denosumab significantly reduced the risk of new vertebral fractures in women with multiple and/or severe prevalent vertebral fractures (16.6% placebo *vs.* 7.5% denosumab; $P < 0.001$). Similarly, denosumab significantly reduced the risk of hip fractures in subjects aged 75 yr or older (2.3% placebo *vs.* 0.9% denosumab; $P < 0.01$) or with a baseline femoral neck bone mineral density T-score of −2.5 or less (2.8% placebo *vs.* 1.4% denosumab; $P = 0.02$). These risk reductions in higher-risk individuals were consistent with those seen in patients at lower risk of fracture.

Conclusions: Denosumab reduced the incidence of new vertebral and hip fractures in postmenopausal women with osteoporosis at higher risk for fracture. These results highlight the consistent antifracture efficacy of denosumab in patients with varying degrees of fracture risk. **(*J Clin Endocrinol Metab* 96: 1727–1736, 2011)**

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Abbreviations: AE, Adverse events; BMD, bone mineral density; FREEDOM, Fracture REduction Evaluation of Denosumab in Osteoporosis every 6 Months; NNT, number needed to treat.

Osteoporosis is characterized by a deterioration of skeletal microarchitecture and decreased bone density and strength predisposing a person to an increased risk of fracture (1). Osteoporotic fractures of the spine and hip are common at an older age and are associated with greater economic impact, mortality, and morbidity (2–9).

Denosumab (Prolia) is a fully human monoclonal antibody against receptor activator of nuclear factor-κB ligand, an essential mediator of osteoclast development, function, and survival (10–12). In phase 2 and 3 trials, denosumab rapidly decreased bone resorption markers and increased bone mineral density (BMD) at all skeletal sites measured compared with placebo (13–16). In the registrational Fracture REduction Evaluation of Denosumab in Osteoporosis every 6 Months (FREEDOM) trial, treatment with denosumab for 3 yr significantly reduced the risk of new vertebral, nonvertebral, and hip fractures in postmenopausal women with osteoporosis (17).

The pivotal phase 3 fracture trials of the various therapeutic agents for the treatment of osteoporosis have enrolled subjects across a spectrum of fracture risk, as indicated by the difference in fracture incidence observed in the placebo groups for these trials (18–22). Participants in the FREEDOM trial had a somewhat lower risk of fractures than participants enrolled in other trials. At baseline, less than one quarter of postmenopausal women enrolled in FREEDOM had a prevalent vertebral fracture and only about one third had a femoral neck BMD T-score of −2.5 or less. As a consequence, the 3-yr new vertebral fracture incidence in subjects who received placebo was lower in FREEDOM (7.2%) than in either the Fracture Intervention Trial-I (FIT-I) of alendronate (15.0%) or the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) trial of zoledronic acid (10.9%). The 3-yr hip fracture incidence in subjects who received placebo also was lower in FREEDOM (1.2%) than in either the Fracture Intervention Trial-I (2.2%) or the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly trials (2.5%) (18, 19).

The aim of the current analysis was to further characterize the fracture risk reduction observed with denosumab in subgroups of subjects who were more likely to develop new vertebral and hip fractures. These subset analyses were based on well-documented risk factors for fractures, including low bone density, number and degree of severity of existing vertebral deformities, and advanced age.

Materials and Methods

Study population

The FREEDOM study (17) enrolled 7808 postmenopausal women with osteoporosis. Subjects were randomized to receive either a sc injection of denosumab (60 mg) or placebo every 6 months; all received daily calcium and vitamin D supplements. Ambulatory postmenopausal women with a BMD T-score less than −2.5 at the lumbar spine or total hip but not less than −4.0 at either site were eligible to enroll in this study. Women with two or more vertebral deformities could be eligible, as long as there were no severe vertebral deformities and at most two moderate vertebral deformities. The primary end point was the incidence of new vertebral fractures over 3 yr. The study design and key end points have been reported previously (17).

For new vertebral fractures the higher-risk subgroups included women with the following: 1) two or more preexisting vertebral fractures of any degree of deformity, or one or more vertebral fracture of moderate or severe deformity, or both (prevalent vertebral fracture status); 2) a femoral neck BMD T-score of −2.5 or less; or 3) both multiple and/or moderate or severe vertebral deformities and a femoral neck BMD T-score of −2.5 or less. For hip fractures the higher-risk subgroups included women: 1) 75 yr old or older; 2) with a femoral neck BMD T-score of −2.5 or less; or 3) 75 yr old or older and with a femoral neck BMD T-score of −2.5 or less. Women who did not have the risk factor(s) specified were included in the lower-risk subgroups. All analyses were done *post hoc* except for the analysis of new vertebral fractures in women with a femoral neck BMD T-score of −2.5 or less.

Assessment of fractures

Lateral spine x-rays (thoracic and lumbar, T4 through L4) were taken at the baseline visit and month 12, 24, and 36 visits and additionally at unscheduled visits when a subject presented with acute back pain and occurrence of a symptomatic vertebral fracture was suspected. Information about any new on-study fractures was recorded at each visit. Only those fractures confirmed by the central imaging vendor (Synarc, San Francisco, CA) were included in the analyses. All clinical fractures reported by the investigators were considered adverse events, whereas morphometric vertebral fractures noted only by Synarc were not reported as adverse events.

Prevalent vertebral fractures at baseline and incident vertebral fractures were assessed by Synarc using the Genant SQ scoring method (23). A prevalent vertebral fracture was defined as a vertebra (T4 to L4) with a deformity of Genant grade 1 or greater at baseline. Adjudication of lateral spine films by Synarc identified a small number of enrolled subjects who had a severe vertebral fracture (SQ3) at baseline. A new vertebral fracture was defined as an increase of one grade or greater from the previous grade of 0 in any vertebra between T4 and L4 (includes morphometric and clinical vertebral fractures).

Hip fractures were also confirmed by Synarc and included fractures of femur neck, femur intertrochanter, and femur subtrochanter. Fractures associated with high trauma or those categorized as pathologic fractures were excluded from the analyses.

Additional end points evaluated

Additional analyses were done to assess the number of subjects who would need to be treated to prevent one new vertebral or hip fracture. The number needed to treat (NNT) was calculated as the reciprocal of the absolute risk reduction for the fracture of interest.

Statistical analyses

The incidence of new vertebral fractures was analyzed within each higher- or lower-risk subgroup. The risk ratio and the corresponding 95% confidence interval for denosumab as compared with placebo were summarized. The treatment compari-

son within each higher- or lower-risk subgroup was based on a score test from a logistic regression. The quantitative treatment-by-risk subgroup interaction, which assesses whether the treatment effect varies in magnitude between subgroups, was tested using a logistic regression model including treatment, age strata (60–64, 65–69, 70–74, and 75 yr old or older per stratification at randomization), individual risk subgroup, and treatment-by-risk subgroup interaction. The age stratification variable is omitted from the model when the risk subgroup is age related (*e.g.* age 75 yr old or older). If the quantitative *P* value of the interaction term was 0.05 or greater, the treatment-by-risk subgroup interaction was considered not significant. If the quantitative treatment-by-risk subgroup interaction was significant, Gail and Simon test (24) was used to test for qualitative interaction, evaluating whether the treatment effect changes direction between subgroups.

The cumulative incidence of hip fractures within each higher- or lower-risk subgroup was based on the Kaplan-Meier estimate. The hazard ratio and the corresponding 95% confidence interval relative to placebo were based on a stratified Cox proportional hazards model adjusting for age strata. The treatment response and the quantitative treatment-by-risk subgroup interaction were based on the score test. The significance level for each subgroup analysis was set at 5% without adjusting for multiplicity.

The log-rank test was used to calculate the *P* values for overall adverse events (AE) and serious AE between the treatment groups within each risk subgroup. The score test from the Cox proportional hazard model, adjusting for baseline cardiovascular risk score, was used to calculate the *P* values for fatal AE between the treatment groups and the treatment-by-risk subgroup interaction.

Results

Baseline characteristics

Body mass index, lumbar spine BMD T-score, and the percentage of subjects with a history of parental hip fracture (not shown) were similar among the various risk subgroups (Table 1). There were differences in the other baseline characteristics, including age and number and severity of prevalent vertebral fractures, between the higher-risk and lower-risk subgroups mainly due to the definitions of the risk subgroups.

Review of the baseline lateral spine x-rays by the central imaging vendor identified 58 subjects who had a severe vertebral deformity (Table 1) and an additional seven subjects who had more than two moderate vertebral deformities. The number of protocol violations related to the number or severity of vertebral deformities was less than 1% of the enrolled study population.

New vertebral fractures

Denosumab treatment over 3 yr was equally effective at reducing the risk of new vertebral fractures in subjects both at higher risk and lower risk for these types of fractures with no significant treatment-by-subgroup interactions based on any of the three higher-risk subgroups investigated ($P \geq 0.18$). For each of the higher- and lower-risk subgroups, approximately one third of new vertebral fractures were clinically apparent, whereas the remaining two thirds were morphometrically detected. This is similar to that reported for the overall FREEDOM population (17).

The higher fracture incidence observed in the higher-risk placebo subgroups confirmed that the selected risk criteria appropriately identified subjects at higher risk for new vertebral fractures. As compared with placebo, treatment with denosumab significantly reduced the incidence of new vertebral fractures among subgroups at higher risk because of prevalent vertebral fracture status (16.6% placebo *vs.* 7.5% denosumab; absolute risk reduction 9.2%; $P < 0.001$), a baseline femoral neck BMD T-score of −2.5

TABLE 1. Baseline demographics of subjects at higher-risk of new vertebral or hip fracture

		Prevalent vertebral fracture status		Femoral neck BMD T-score		Age	
	Overall FREEDOM population (N = 7808)	≥2 and/or ≥1 moderate or severe deformity, or both (N = 759)	<2 and no moderate or severe deformity (N = 6803)	≤−2.5 (N = 2790)	>−2.5 (N = 4979)	≥75 yr (N = 2471)	<75 yr (N = 5337)
Age (yr), mean (SD)	72.3 (5.2)	73.7 (5.2)	72.1 (5.2)	74.1 (5.3)	71.4 (4.9)	78.2 (3.1)	69.6 (3.5)
BMD T-score, mean (SD)							
Lumbar spine	−2.8 (0.7)	−2.9 (0.7)	−2.8 (0.7)	−2.8 (0.8)	−2.8 (0.6)	−2.7 (0.8)	−2.9 (0.6)
Total hip	−1.9 (0.8)	−2.1 (0.8)	−1.9 (0.8)	−2.6 (0.6)	−1.5 (0.7)	−2.2 (0.8)	−1.8 (0.8)
Femoral neck	−2.2 (0.7)	−2.4 (0.7)	−2.1 (0.7)	−2.9 (0.3)	−1.8 (0.5)	−2.4 (0.7)	−2.1 (0.7)
Subjects with prevalent vertebral fracture, n (%)	1844 (23.6%)	759 (100.0%)	1085 (15.9%)	793 (28.4%)	1039 (20.9%)	692 (28.0%)	1152 (21.6%)
Prevalent vertebral fracture							
Number[a]							
0	5718 (73.2%)	0 (0.0%)	5718 (84.1%)	1893 (67.8%)	3801 (76.3%)	1664 (67.3%)	4054 (76.0%)
1	1314 (16.8%)	229 (30.2%)	1085 (15.9%)	538 (14.3%)	769 (15.4%)	486 (19.7%)	828 (15.5%)
≥2	530 (6.8%)	530 (69.8%)	0 (0.0%)	255 (9.1%)	270 (5.4%)	206 (8.3%)	324 (6.1%)
Severity[a]							
Normal	5718 (73.2%)	0 (0.0%)	5718 (84.1%)	1893 (67.8%)	3801 (76.3%)	1664 (67.3%)	4054 (76.0%)
Mild	1415 (18.1%)	330 (43.5%)	1085 (15.9%)	584 (20.9%)	823 (16.5%)	500 (20.2%)	915 (17.1%)
Moderate	371 (4.8%)	371 (48.9%)	0 (0.0%)	183 (6.6%)	185 (3.7%)	158 (6.4%)	213 (4.0%)
Severe	58 (0.7%)	58 (7.6%)	0 (0.0%)	26 (0.9%)	31 (0.6%)	34 (1.4%)	24 (0.4%)

N, Number of randomized subjects.

[a] Percentages may not total 100% due to missing x-rays.

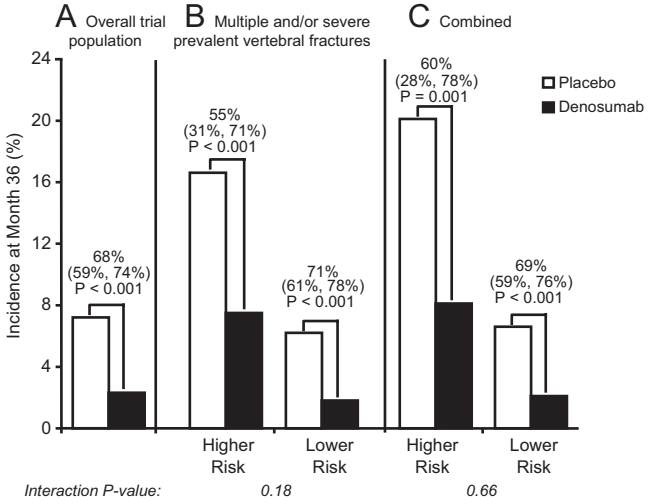

FIG. 1. Relative risk reduction in new vertebral fractures over 36 months with denosumab treatment in higher-risk and lower-risk subgroups. The numbers of subjects experiencing a new vertebral fracture in each subgroup are shown; A, Overall FREEDOM trial population (17): placebo = 264 of 3691 and denosumab = 86 of 3702. B, Multiple prevalent vertebral fractures and/or moderate or severe vertebral deformity are shown: higher-risk placebo subgroup = 57 of 343 and higher-risk denosumab subgroup = 27 of 359; lower-risk placebo subgroup = 202 of 3237 and lower-risk denosumab subgroup = 59 of 3251. C, Combined group includes subjects with multiple prevalent vertebral fractures and/or moderate or severe vertebral deformity and a baseline femoral neck BMD T-score of −2.5 or less: higher-risk placebo subgroup = 31 of 154 and higher-risk denosumab subgroup = 14 of 172; lower-risk placebo subgroup = 230 of 3497 and lower-risk denosumab subgroup = 72 of 3480.

or less (9.9% placebo *vs.* 3.1% denosumab; absolute risk reduction 6.8%; $P < 0.001$) as well as the subgroup with both of these risk factors (20.1% placebo *vs.* 8.1% denosumab; absolute risk reduction 12.3%; $P = 0.001$) (Fig. 1). The NNT to prevent one new vertebral fracture for each of these higher-risk subgroups is 11 (prevalent vertebral fracture status), 15 (low baseline femoral neck BMD), and 9 (both risk factors), respectively.

Similar results were also observed for the lower-risk subgroups. Treatment with denosumab *vs.* placebo significantly reduced the incidence of new vertebral fractures over 3 yr in all of the lower-risk subgroups: absent of prevalent vertebral fracture: 6.2% placebo *vs.* 1.8% denosumab; absolute risk reduction 4.4%; baseline femoral neck BMD T-score greater than −2.5: 5.6% placebo *vs.* 1.9% denosumab; absolute risk reduction 3.7%; and subjects without one or both of these risk factors: 6.6% placebo *vs.* 2.1% denosumab; absolute risk reduction 4.5%; $P < 0.001$ for all lower-risk subgroups (Fig. 1).

After initiation of denosumab treatment, a significant reduction in new vertebral fractures was observed as soon as 12 months in the subgroup at higher risk because of a baseline femoral neck T-score of −2.5 or less ($P = 0.001$) and at 24 months in the subgroups at higher risk because of prevalent vertebral fracture status ($P < 0.001$) or with

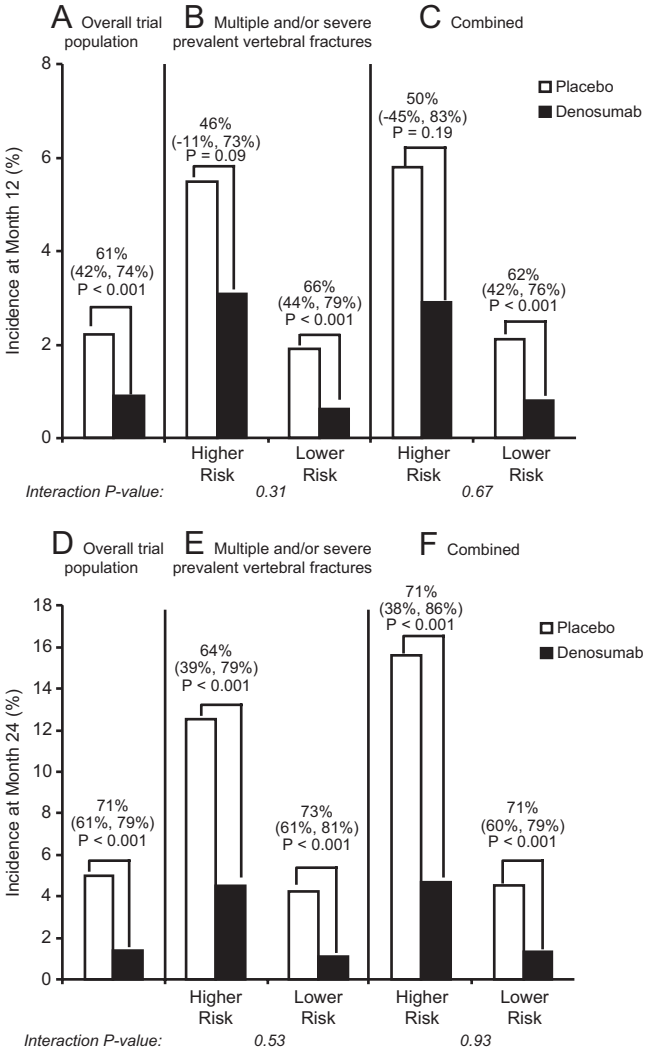

FIG. 2. Relative risk reduction in new vertebral fractures over 12 and 24 months with denosumab treatment in higher-risk and lower-risk subgroups. The numbers of subjects experiencing a new vertebral fracture in each subgroup over 12 months are shown; A, Overall FREEDOM trial population: placebo = 82 of 3691 and denosumab = 32 of 3702. B, Multiple prevalent vertebral fractures and/or moderate or severe vertebral deformity: higher-risk placebo subgroup = 19 of 343 and higher-risk denosumab subgroup = 11 of 359; lower-risk placebo subgroup = 61 of 3237 and lower-risk denosumab subgroup = 21 of 3251. C, Combined group includes subjects with multiple prevalent vertebral fractures and/or moderate or severe vertebral deformity and a baseline femoral neck BMD T-score of −2.5 or less: higher-risk placebo subgroup = nine of 154 and higher-risk denosumab subgroup = five of 172; lower-risk placebo subgroup = 72 of 3497 and lower-risk denosumab subgroup = 27 of 3480. The numbers of subjects experiencing a new vertebral fracture in each subgroup over 24 months are shown; D, Overall FREEDOM trial population: placebo = 183 of 3691 and denosumab = 53 of 3702. E, Multiple prevalent vertebral fractures and/or moderate or severe vertebral deformity: higher-risk placebo subgroup = 43 of 343 and higher-risk denosumab subgroup = 16 of 359; lower-risk placebo subgroup = 136 of 3237 and lower-risk denosumab subgroup = 37 of 3251. F, Combined group includes subjects with multiple prevalent vertebral fractures and/or moderate or severe vertebral deformity and a baseline femoral neck BMD T-score of −2.5 or less: higher-risk placebo subgroup = 24 of 154 and higher-risk denosumab subgroup = eight of 172; lower-risk placebo subgroup = 157 of 3497 and lower-risk denosumab subgroup = 45 of 3480.

both risk factors ($P < 0.001$) (Fig. 2). In all lower-risk subgroups, a significant reduction in new vertebral fractures was observed as soon as 12 months after the initiation of the denosumab treatment ($P < 0.001$). The small size of the higher-risk subgroups and the low number of fractures during the first year likely explain the inability to detect a significant reduction in new vertebral fractures at 12 months in two of the higher-risk subgroups. More importantly, because the fracture reduction was similar between the respective higher- and lower-risk subgroups at 12 months (treatment-by-subgroup interaction $P > 0.30$), this suggests that the risk reduction in new vertebral fractures at 12 months in either risk subgroup can be best described based on that reported for the overall FREEDOM population ($P < 0.001$) (17). Thus, the subgroup results over 3 yr are consistent with the reduction in new vertebral fractures reported for the overall FREEDOM population (17).

Hip fractures

The antifracture efficacy of denosumab against hip fracture was consistent across subjects with different levels of risk; no significant treatment-by-subgroup interaction was demonstrated based on any of the three higher-risk subgroups investigated ($P \geq 0.07$).

The greater hip fracture incidence observed in the higher-risk placebo subgroups confirmed that both advanced age and low femoral neck BMD appropriately identified subjects at higher risk for hip fractures. Compared with placebo, denosumab treatment significantly reduced the incidence of hip fracture among subjects aged 75 yr old or older (2.3% placebo *vs.* 0.9% denosumab; absolute risk reduction 1.4%; $P < 0.01$); subjects with a baseline femoral neck BMD T-score of −2.5 or less (2.8% placebo *vs.* 1.4% denosumab; absolute risk reduction 1.4%; $P = 0.02$); and subjects with both risk factors (4.1% placebo *vs.* 1.7% denosumab; absolute risk reduction 2.4%; $P = 0.02$; Fig. 3). This reduction was significant as early as 12 months after denosumab treatment was initiated (Fig. 4). The NNT to prevent one new hip fracture for each of these higher risk subgroups is 71 (aged 75 yr old or older), 73 (baseline femoral neck BMD T-score of −2.5 or less), and 42 (both risk factors), respectively.

The incidence of hip fractures in the placebo arm was quite low in subjects younger than 75 yr old, those with a baseline femoral neck BMD T-score greater than −2.5, and those without one or both of these risk factors (Fig. 2). Absolute risk and consequently absolute risk reduction were low, and the difference was not statistically significant for any of these lower-risk subgroups: younger than 75 yr old (0.7% placebo *vs.* 0.6% denosumab; absolute risk reduction 0.1%), baseline femoral neck BMD T-score

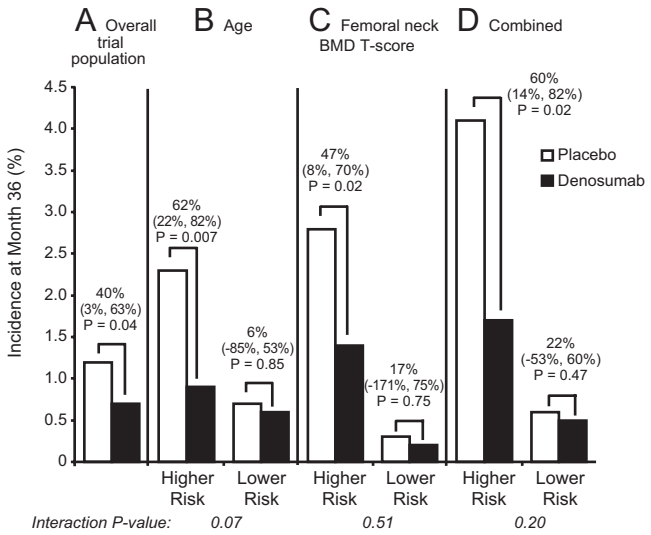

FIG. 3. Relative risk reduction in hip fractures with denosumab treatment for 36 months in higher-risk and lower-risk subgroups. The numbers of subjects experiencing a hip fracture in each subgroup are shown; A, Overall FREEDOM trial population (17): placebo = 43 of 3906 and denosumab = 26 of 3902. B, Age (subjects 75 yr old or older): higher-risk placebo subgroup = 26 of 1236 and higher-risk denosumab subgroup = 10 of 1235; lower-risk placebo subgroup = 17 of 2670 and lower-risk denosumab subgroup = 16 of 2667. C, Baseline femoral neck BMD T-score of −2.5 or less: higher-risk placebo subgroup = 36 of 1406 and higher-risk denosumab subgroup = 19 of 1384; lower-risk placebo subgroup = six of 2484 and lower-risk denosumab subgroup = five of 2492. D, Combined group includes subjects 75 yr old or older and with a baseline femoral neck BMD T-score of −2.5 or less: higher-risk placebo subgroup = 23 of 629 and higher-risk denosumab subgroup = nine of 602; lower-risk placebo subgroup = 19 of 3261 and lower-risk denosumab subgroup = 15 of 3277.

greater than −2.5 (0.3% placebo *vs.* 0.2% denosumab; absolute risk reduction 0%), or younger than 75 yr old and/or with a baseline femoral neck BMD T-score greater than −2.5 (0.6% placebo *vs.* 0.5% denosumab; absolute risk reduction 0.2%).

In summary, the subgroup results are consistent with the reduction in hip fractures reported for the overall FREEDOM population (17).

Safety

The AE incidences were not statistically different between the treatment groups within any of the higher- and lower-risk subgroups investigated (data not shown) and were consistent with the AE incidences for the overall FREEDOM trial (17). Because AE may occur more frequently in elderly patients, the AE reported for subjects 75 yr old or older were evaluated in more detail (Table 2); the AE incidences were similar to those reported for the overall FREEDOM population (17).

For the subgroups, as well as the overall FREEDOM population, there were fewer fatal AE among subjects treated with denosumab *vs.* placebo. Mortality was numerically lower but did not reach statistical significance in

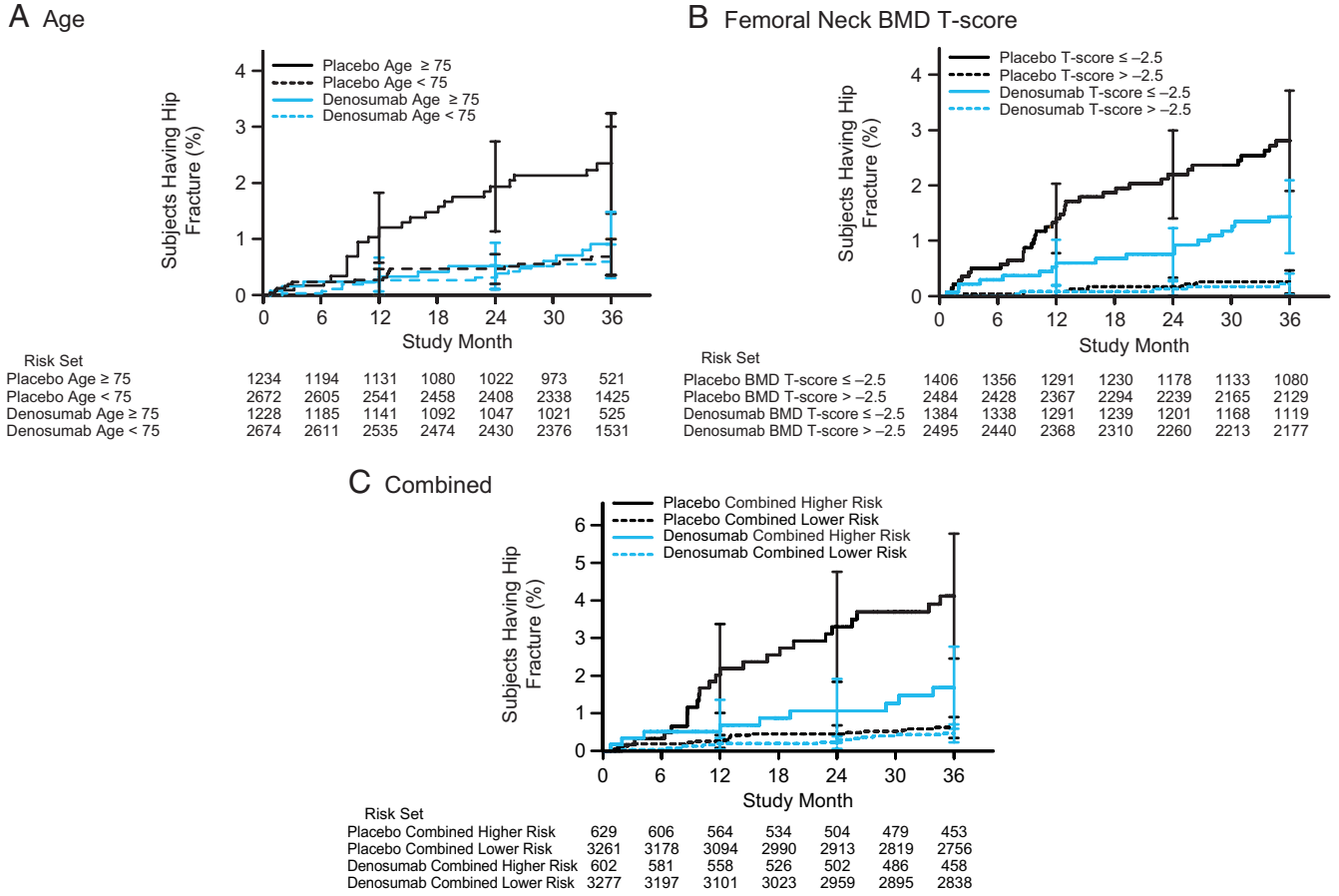

FIG. 4. Time to first hip fracture over 36 months among subjects in the higher-risk and lower-risk subgroups. Values shown are absolute risk reduction [95% confidence interval (CI)]. A 95% CI that does not include 0 indicates a significant risk difference between groups. A, The absolute risk reductions (95% CI) by denosumab treatment within the higher-risk and lower-risk subgroups: month 12: 0.9 (0.2, 1.6) for subjects 75 yr old or older and 0.0 (−0.3, 0.3) for subjects younger than 75 yr; month 24: 1.4 (0.5, 2.3) for subjects 75 yr old or older and 0.2 (−0.2, 0.5) for subjects younger than 75 yr; and month 36: 1.4 (0.4, 2.5) for subjects 75 yr old or older and 0.1 (−0.4, 0.5) for subjects younger than 75 yr. B, The absolute risk reduction (95% CI) by denosumab treatment within the higher-risk and lower-risk subgroups: month 12: 0.8 (0.1, 1.6) for subjects with baseline femoral neck BMD T-score of −2.5 or less and 0.0 (−0.2, 0.2) for subjects with baseline femoral neck BMD T-score greater than −2.5; month 24: 1.4 (0.5, 2.4) for subjects with baseline femoral neck BMD T-score of −2.5 or less and 0.0 (−0.2, 0.3) for subjects with baseline femoral neck BMD T-score greater than −2.5; and month 36: 1.4 (0.3, 2.5) for subjects with baseline femoral neck BMD T-score of −2.5 or less and 0.0 (−0.2, 0.3) for subjects with baseline femoral neck BMD T-score greater than −2.5. C, The absolute risk reduction (95% CI) by denosumab treatment within the higher-risk and lower-risk subgroups: month 12: 1.5 (0.1, 2.9) for subjects 75 yr old or older and with baseline femoral neck BMD T-score of −2.5 or less and 0.1 (−0.2, 0.2) for subjects younger than 75 yr and/or with baseline femoral neck BMD T-score greater than −2.5; month 24: 2.2 (0.5, 3.9) for subjects 75 yr old or older and with baseline femoral neck BMD T-score of −2.5 or less and 0.2 (−0.1, 0.5) for subjects younger than 75 yr and/or with baseline femoral neck BMD T-score greater than −2.5; and month 36: 2.4 (0.4, 4.4) for subjects 75 yr old or older and with baseline femoral neck BMD T-score of −2.5 or less and 0.2 (−0.2, 0.5) for subjects younger than 75 yr and/or with baseline femoral neck BMD T-score greater than −2.5.

most subgroups (data not shown). However, a significant difference in fatal AE between treatment groups was noted for subjects at higher risk of new vertebral fractures based on prevalent vertebral fracture status (4.9% placebo *vs.* 1.8% denosumab; $P = 0.02$) and in those at higher risk based on both prevalent vertebral fracture status and low femoral neck BMD (7.1% placebo and 1.6% denosumab; $P = 0.01$). The observed significance difference in the

TABLE 2. Adverse events in subjects 75 yr old or older and younger than 75 yr of age

	Subjects ≥75 yr			Subjects <75 yr		
AE	Placebo (N = 1229)	Denosumab (N = 1225)	*P* value[a]	Placebo (N = 2647)	Denosumab (N = 2661)	*P* value[a]
All	1143 (93.0%)	1144 (93.4%)	0.86	2464 (93.1%)	2461 (92.5%)	0.78
Serious	371 (30.2%)	368 (30.0%)	0.76	601 (22.7%)	636 (23.9%)	0.39
Fatal	51 (4.1%)	39 (3.2%)	0.18	39 (1.5%)	31 (1.2%)	0.32

N, Number of subjects who received at least one dose of investigational product. Values are N (%).

[a] *P* values are based on log-rank test (all AE and serious AE) or score test from the Cox proportional hazard model (fatal AE).

higher-risk subgroup based on prevalent vertebral fracture status was not statistically different from the difference observed in the corresponding lower-risk subgroup (treatment-by-subgroup interaction $P = 0.07$). However, the difference in mortality observed in the higher-risk subgroup based on both prevalent vertebral fractures and a low femoral neck BMD was statistically different from that observed in the lower-risk subgroup, [treatment-by-subgroup interaction, $P = 0.03$; Gail and Simon test, $P = 0.5$]. This result indicates a potentially greater impact of treatment on mortality risk in subjects in this combined higher-risk category compared with that observed in the combined lower-risk category.

Discussion

Prevalent vertebral fractures, low BMD, and advanced age are the three most important risk factors for future fractures (25, 26). The present analysis evaluated the effect of denosumab on the risk of new vertebral and hip fractures in patients at higher risk for fractures, defined by prevalent vertebral fracture status, low femoral neck BMD, or age 75 yr or older by investigating subgroups of patients enrolled in the FREEDOM trial. For prevalent vertebral fractures, both the number and severity of the existing deformities contribute to subsequent fracture risk (18, 26–30). Similarly, the risk of hip and spine fractures progressively increases as femoral neck BMD decreases (31). Independent of these two important risk factors, advancing age increases the risk of fractures. Although this effect is a continuous phenomenon affecting all osteoporotic fractures, the increase is most striking for hip fractures after the age of 75 yr (32, 33). The data presented in this manuscript reinforce these findings and reveal marked increases in the observed risk for both new vertebral and hip fractures in the placebo groups of the various higher-risk subgroups investigated in this analysis.

Vertebral fractures are among the most common osteoporotic fractures and may lead to adverse health outcomes, including back pain, height loss, kyphosis, declines in physical performance and loss of independence, long-term decrease in quality of life, and increased mortality (34–38). In the current analyses, a consistent reduction in new vertebral fractures was observed across all the higher-risk and lower-risk subgroups evaluated. The robust effect of denosumab treatment for 3 yr on new vertebral fracture incidence in subjects with multiple and/or moderate/severe vertebral deformities and in subjects with osteoporotic BMD T-scores at the femoral neck suggests that denosumab is effective in reducing new vertebral fractures across a broad range of disease severity.

Hip fracture is among the most devastating consequences of osteoporosis. It is associated with significant excess risk of mortality, which endures for several years after the index fracture (39). In those who do survive the fracture, some 20% will have to be institutionalized because of functional consequences (40). In subjects at higher risk for hip fractures, due to a low femoral neck BMD or an age of 75 yr old or older, denosumab treatment for 3 yr reduced the risk of hip fractures, such that these subjects fractured at rates observed in lower-risk populations, in which hip fractures uncommonly occurred. In higher-risk subjects, the treatment benefit of denosumab for hip fracture was significant as early as 12 months (Fig. 3). This early onset of action at the hip has not been documented with any other antiresorptive drug (22, 41–44) and is consistent with the rapid increase in BMD (seen as early as 1 month) and decrease in bone turnover markers observed soon after denosumab treatment in previous trials (13, 15).

In denosumab-treated subjects aged younger than 75 yr or those with a BMD T-score greater than −2.5 at the femoral neck, in which hip fractures occurred with low incidence, there was a trend toward a reduced rate of hip fractures, which, however, was not statistically significant. Due to the low number of events in the subjects younger than 75 yr and/or with a femoral neck BMD T-score greater than −2.5, the confidence limits of the point estimates were wide. Although the relative risk reduction showed numerical differences between higher- and lower-risk subgroups, treatment-by-subgroup interactions were not statistically significant for any of the subgroups at higher-risk or lower-risk for hip fracture, supporting the consistent efficacy of denosumab across subjects with various degrees of fracture risk.

The criteria used to select the higher-risk populations in the FREEDOM trial identified subjects with the greater absolute risk for fracture. In light of the observed consistent antifracture efficacy, subjects at higher risk for fracture would be expected to experience a greater absolute benefit from treatment, and this is indeed reflected in the NNT estimated for the higher-risk subgroups treated with denosumab.

As previously described, denosumab treatment was well tolerated by subjects in the FREEDOM trial (17). In general, no significant differences were noted in the safety profile between placebo-treated and denosumab-treated subjects in the various higher-risk and lower-risk subgroups, including subjects who were 75 yr old or older.

The rate of mortality was greater in the higher-risk placebo subgroups than in the lower-risk placebo subgroups. Among denosumab-treated subjects, the mortality rate was found to be numerically lower in the overall popula-

tion and significantly lower among two subgroups at higher risk for new vertebral fracture: 1) those with multiple and/or moderate or severe prevalent vertebral fractures and, 2) those who had both multiple and/or moderate or severe vertebral fractures and a femoral neck BMD T-score of −2.5 or less. These results are based on exploratory subset analyses and have to be interpreted with caution. Nevertheless, our findings are in agreement with previous reports that found that patients with a history of vertebral fracture had an increased risk of mortality (2, 5). Moreover, although this manuscript did not address the potential cause of a decrease in mortality observed with denosumab in the combined higher-risk group, this effect is consistent with recent findings demonstrating a reduction of mortality with osteoporotic therapy in patients at higher risk of fractures (45, 46).

The study design contributed to the limitations of this analysis. The study was not designed to detect treatment differences in the subgroups with sufficient power. Although it may appear that there were not statistically significant differences in efficacy in the lower-risk subgroups, this may be misleading because of the very small number of hip fractures in those groups, as indicated by the wide confidence intervals. Second, the enrollment criteria of the FREEDOM trial excluded patients with the most severe osteoporosis (BMD T-score less than −4.0 and/or multiple vertebral fractures). Thus, we could not assess the effect of denosumab in extremely high-risk patients.

The strengths of these analyses were that they were done within the framework of a large, well-designed, pivotal fracture trial. In addition, for the *post hoc* analyses we evaluated risk factors and subgroups that are established and clinically relevant. Furthermore, the findings for the subgroups analyses were consistent with the findings of the overall trial analysis with no significant interactions.

In summary, our analyses highlight the consistency of the antifracture efficacy of denosumab across subjects with differences in a variety of major risk factors for fractures at baseline. Our analyses suggest that denosumab reduces both new vertebral and hip fractures, regardless of the underlying risk and that the higher absolute fracture risk observed in the higher-risk subgroups is associated with greater absolute risk reduction. These analyses add to the evidence that denosumab is an effective option for the treatment of postmenopausal osteoporosis.

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