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Effect of Once-Yearly Zoledronic Acid Five Milligrams on Fracture Risk and Change in Femoral Neck Bone Mineral Density

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Abstract

Context—In the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly – Pivotal Fracture Trial (HORIZON-PFT), zoledronic acid (ZOL) 5 mg significantly reduced fracture risk.

Objective—The aim of the study was to identify factors associated with greater efficacy during ZOL 5 mg treatment.

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Design, Setting, and Patients—We conducted a subgroup analysis (preplanned and *post hoc*) of a multicenter, double-blind, placebo-controlled, 36-month trial in 7765 women with postmenopausal osteoporosis.

Intervention—A single infusion of ZOL 5 mg or placebo was administered at baseline, 12, and 24 months.

Main Outcome Measures—Primary endpoints were new vertebral fracture and hip fracture. Secondary endpoints were nonvertebral fracture and change in femoral neck bone mineral density (BMD). Baseline risk factor subgroups were age, BMD T-score and vertebral fracture status, total hip BMD, race, weight, geographical region, smoking, height loss, history of falls, physical activity, prior bisphosphonates, creatinine clearance, body mass index, and concomitant osteoporosis medications.

Results—Greater ZOL induced effects on vertebral fracture risk were seen with younger age (treatment-by-subgroup interaction, $P=0.05$), normal creatinine clearance ($P=0.04$), and body mass index   25 kg/m^2 ($P=0.02$). There were no significant treatment–factor interactions for hip or nonvertebral fracture or for change in BMD.

Conclusions—ZOL appeared more effective in preventing vertebral fracture in younger women, overweight/obese women, and women with normal renal function. ZOL had similar effects irrespective of fracture risk factors or femoral neck BMD.

Zoledronic acid is a bisphosphonate that is administered iv for the treatment of postmenopausal osteoporosis; a single dose has been reported to decrease bone turnover and improve bone mineral density (BMD) for at least 12 months after infusion (1). Furthermore, recent data from the HORIZON-PFT (Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly – Pivotal Fracture Trial) showed that a once-yearly infusion of zoledronic acid 5 mg during a 3-yr period significantly reduced the risk of vertebral, hip, and other fractures (2).

A number of risk factors for fracture have been identified, and it is possible that the effect of zoledronic acid differs across categories of these risk factors; there may even be an interaction between these factors and the treatment. Age may affect the response to treatment because older people have faster hip bone loss than younger individuals (3), and the efficacies of risedronate, strontium, and PTH have been evaluated for elderly subjects (4–6). Data from the Hip Intervention Program (HIP) study have been used to suggest that risedronate does not reduce the risk of fracture in women over the age of 80 yr (7). A more likely interpretation, however, is that women were selected for the study based on risk factors for falls. Baseline BMD has also been claimed to be a determinant of response to treatment. The Fracture Intervention Trial 2 showed that in women who have a T-score above −2.5 at the hip without existing vertebral fractures, there is no effect of alendronate on fracture risk (8). Similarly, in the Oral Ibandronate Osteoporosis Vertebral Fracture Trial in North America and Europe, there was no effect of ibandronate on fracture risk in women with a hip T-score above −3.0 and existing vertebral fractures (9). There are other patient characteristics that may have an effect on fracture risk; these effects could interact with treatment, but they have been insufficiently studied. These include race (10), although data from the Women's Health Initiative hormone trials in U.S. women show no evidence of an

interaction between hormone therapy, race (11), and body mass index (BMI), which is a very strong risk factor for fracture (12). In addition to effects of individual demographic parameters on fracture risk, there is also tremendous variability in hip fracture rates worldwide, with the highest rates observed in Northern European countries (13, 14). In contrast, the variability in vertebral fractures is much less. For example, Asian women have low rates of hip fracture but similar rates of vertebral fractures compared with white women (15). Other factors that are known to have an effect on fracture risk include smoking (smokers have an increased risk of fracture that is partially explained by their lower body weight) (16), height loss since age 25 yr (16), occurrence of a fall in the past 12 months (a marker of frailty) (17, 18), leisure-time activity (hours of walking) (19), and renal impairment (creatinine clearance <65 ml/min) (20). It is also possible that previous bisphosphonate use may influence response because prior therapy may have a persistent effect of reducing fracture risk, although the drug has been stopped (21, 22).

We analyzed the effect of zoledronic acid on vertebral fracture, hip fracture, nonvertebral fracture, and femoral neck BMD in patients from HORIZON-PFT divided into subgroups based on baseline risk factors to determine whether these factors were associated with greater treatment efficacy.

Subjects and Methods

Subjects

Full details of the HORIZON-PFT have been published previously (2). Postmenopausal women aged 65–89 yr were eligible for inclusion if they had a femoral neck T-score −2.5 with or without evidence of an existing vertebral fracture, or a T-score −1.5 with radiological evidence of at least two mild or one moderate vertebral fracture(s). Prior oral bisphosphonate use was allowed, with washout duration dependent on previous use (*e.g.* >48 wk of usage required a 2-yr washout). All subjects provided informed consent, and local institutional review board approval was obtained for the protocol. The study was conducted in accordance with good clinical practice and the Declaration of Helsinki.

Subjects were assigned to one of two strata on the basis of whether they were taking allowed osteoporosis medications at baseline. Stratum I was defined as women not taking any osteoporosis medications at the time of randomization, whereas stratum II was defined as those taking an allowed medication at the time of randomization.

Endpoints

The primary endpoints were new vertebral fractures (in stratum I) and hip fracture (in both strata). Secondary efficacy endpoints included any nonvertebral fracture, any clinical vertebral fracture, any clinical fracture (including hip fracture) and change in femoral neck BMD.

BMD

Dual-energy x-ray absorptiometry at the hip was performed at baseline and months 6, 12, 24, and 36. Total hip and femoral neck BMD were used to categorize patients into subgroups

according to their BMD at baseline. Change in femoral neck BMD over 3 yr was also evaluated as an efficacy endpoint. Investigators and coordinators were blinded to comparative results from the individual follow-up scans. Bone loss was monitored centrally, and if it exceeded specified criteria, the site was notified and patient counseling occurred. All BMD measurements were corrected for variations related to machinery and site-related differences in BMD means.

Fractures

Lateral radiographs of the spine were obtained at baseline and at 12, 24, and 36 months (or early termination) for stratum I, and at baseline and 36 months (or early termination) for stratum II. All vertebrae from T4 to L4 were evaluated by quantitative morphometry by an expert reader at a central imaging laboratory (Synarc, Inc., San Francisco, CA) using standard methods (23). Incident morphometric vertebral fractures were defined by any vertebral height reduction from baseline of at least 20% and 4 mm by quantitative morphometry, confirmed by one severity grade or greater increase from baseline by semiquantitative reading (23). Baseline prevalent fractures were defined as those with height ratios at least 3 SD values below the mean height ratio for that specific vertebral level on the quantitative reading.

The present analysis of vertebral fracture focuses only on incidence of vertebral fracture at 3 yr. Patient reports of clinical fractures (including hip fracture) were obtained at each patient contact. Each report of a nonvertebral fracture required central confirmation (University of California, San Francisco Coordinating Center) based on a radiological or surgical procedure report or a copy of the radiograph. Fractures to toes, facial bones, and fingers and those resulting from excessive trauma [as assessed by *a priori* criteria (2)] were excluded. For clinical vertebral fractures, the community-obtained radiograph was compared with the baseline study radiograph by a central reader (Synarc). Evidence of an incident vertebral fracture by semi quantitative criteria was required to confirm a clinical vertebral fracture.

Adverse events

Safety was assessed by the recording of all adverse events and serious adverse events and by physical examination, regular measurement of vital signs, and regular monitoring of hematological, blood chemical, and urinary values. A more detailed description of adverse event reporting has been published previously (2).

Statistical analysis

Analysis of the percentage of subjects with at least one new morphometric vertebral fracture was performed for the modified intent-to-treat population (defined as all randomized subjects who were evaluable for at least one vertebra at baseline and at least one follow-up radiograph). Women in stratum I who had incident vertebral fractures at month 12 and month 24 had their fracture results carried forward to subsequent time points. Logistic regression adjusting for the effects of treatment, number of prevalent baseline vertebral fractures, subgroup, and treatment-by-subgroup interaction was used to report odds ratios and *P* values. For clinical fracture endpoints, Cox proportional hazard models adjusting for the effects of treatment, subgroup, and treatment-by-subgroup interaction were used to

report relative hazard ratios and *P* values. Percentage change from baseline in femoral neck BMD was analyzed using an ANOVA model with treatment, geographic region, subgroup, and treatment-by-subgroup interactions as factors in the models. Treatment-by-subgroup interaction was considered statistically and clinically significant at *P* <0.05, and relevant trends were noted with 0.05 < *P* < 0.2. Categorical subgroup variables were used for all analyses. Because the study was not generally designed to detect difference within and/or across levels of subgroups, the information provided should be interpreted as being descriptive, with the *P* values being used to guide in the interpretation of individual results. All efficacy analyses, other than vertebral fractures, were performed on the complete intent-to-treat population.

In the present subgroup analysis, the preplanned determinants of response considered were: age (<70, 70–74, 75 yr), femoral neck BMD T-score (above or below –2.5) and prevalent vertebral fracture status at baseline (present or absent), race (Caucasian or other), weight (tertiles), region (Europe, Asia, the Americas), past use of bisphosphonates (yes or no), stratum (with or without concomitant osteoporosis medication, including hormone replacement therapy), and creatinine clearance calculated using the Cockcroft-Gault equation (<60 ml/min, 60 ml/min). *Post hoc* determinants of response considered were: total hip BMD by tertile, smoking (current smoker or not), height loss since age 25 yr (by tertile), fall in past 12 months (yes or no), walking duration (by tertile), and BMI (<18, 18–24.9, 25–29.9, and 30 kg/m^2).

Results

Results of the primary and secondary analyses of the HORIZON-PFT have been reported previously (2). Baseline characteristics for women in strata I and II are shown in Table 1, and for stratum I alone in Table 2. Baseline characteristics in the combined strata I and II population were comparable between zoledronic acid and placebo groups, with the exception of BMI and weight. In stratum I, baseline characteristics were comparable between the treatment groups, except for mean BMI and mean weight. A total of 286 patients in the zoledronic acid group and 289 patients in the placebo group were included, although they had a baseline femoral neck T-score above –2.5 and no vertebral fracture and thus deviated from the entry criteria for the study.

Adverse events were not analyzed separately in all the subgroups reported here. However, adverse events in the overall population have been reported previously, where zoledronic acid (5 mg) treatment was generally safe and well tolerated (2).

Changes in fracture risk

Zoledronic acid treatment was associated with significant reductions in the risk of vertebral fractures at 3 yr in all categories (Fig. 1). Zoledronic acid treatment reduced the risk of hip fracture and nonvertebral fracture over 3 yr across all subgroups (hazard ratio <1) except for those treated previously with bisphosphonates (Figs. 2 and 3).

With vertebral fracture risk, significant treatment–factor interactions were observed for age (*P* = 0.05), BMI (*P* = 0.02), and creatinine clearance (*P* = 0.04), with greater effects of

zoledronic acid in younger women (<70 yr), women who were overweight or obese (BMI >30 g/cm^2), and women with creatinine clearance above 60 ml/min (Fig. 1). There were no significant treatment–factor interactions ($P < 0.05$) for hip fractures (Fig. 2) or nonvertebral fractures (Fig. 3).

Changes in femoral neck BMD

There was a significant beneficial effect of zoledronic acid treatment on femoral neck BMD in all subgroups compared with placebo (all $P < 0.0001$) (Table 3). The following subgroup categories had significant treatment-by-subgroup interactions ($P < 0.05$) and were associated with different magnitudes of greater increase in BMD by zoledronic acid relative to placebo: smaller absolute total hip BMD (0.23–0.61 g/cm^2) and BMD T-score below −2.5 with and without prevalent vertebral fractures. However, these results relate to percentage changes in femoral neck BMD. When we calculated the absolute changes in femoral neck BMD, we found that the interaction with smaller absolute total hip BMD (0.23–0.61 g/cm^2) was not significant ($P = 0.06$), and BMD T-score below −2.5 with and without prevalent vertebral fractures was not significant either ($P = 0.5$).

Discussion

In general, this analysis showed that zoledronic acid 5 mg had similar effects on femoral neck BMD, hip and nonvertebral fracture independent of patient demographics, and baseline risk factors for fracture. However, although zoledronic acid showed significant reductions in vertebral fractures across all subgroups, there appeared to be larger reductions in vertebral fractures with zoledronic acid in younger women, women with higher BMI, and women with normal renal function. BMI and renal function have not previously been reported as factors that increase or decrease the efficacy of an anticatabolic treatment for postmenopausal osteoporosis. These interactions would be more compelling had they been consistently significant among fracture types and BMD changes. However, there was little evidence that these factors modified the effect of zoledronic acid for the other endpoints evaluated.

In interpreting the subgroup analyses presented, it is important to consider the well-known statistical limitations of subgroup analyses including the lack of power and violation of model assumptions that occur by including such interaction terms in the statistical model and confound the interpretation of effects within and across levels of subgroups (24). As recommended (24), interpretation of results has primarily been based on tests of interaction, recognizing that a nonsignificant interaction may reflect lack of power and may not demonstrate homogeneity of effect. Also, when interpreting these analyses, we took into account the results from other studies and the consistency of results within ours.

Fracture risk, particularly for hip and vertebral fractures, increases exponentially with age, and it is therefore of paramount importance to establish the efficacy of treatments among those over 75 and over 80 yr. The importance of age as a determinant of responsiveness to treatments for postmenopausal osteoporosis has been considered for alendronate, risedronate, strontium ranelate, and teriparatide, as well as for hormone replacement therapy (4–6, 11, 25, 26) for vertebral and for nonvertebral fractures. Nonvertebral fracture risk

reduction as a result of treatment with bisphosphonates has not been demonstrated in patients over 80. However, the numbers of patients over 80 yr (or over 75 yr) in these studies were limited. In addition, the studies were not specifically designed (or powered) to assess fracture risk reduction in old age. As a result, the number of nonvertebral fracture events in elderly subsets of the trial populations was relatively small, and the confidence limits were relatively wide. This was demonstrated by the effects of risedronate on fracture risk in 8680 women from the HIP and Vertebral Efficacy with Risedronate Therapy (VERT) studies (4). The effect of risedronate on vertebral fracture risk was similar in subjects above and below the age of 80 yr (4). However, the effect of risedronate on nonvertebral fracture risk was only significant in subjects below the age of 80 yr (4). Similarly, the Fracture Intervention Trial (FIT) showed significant reductions in vertebral fracture in the subgroup over age 75 with alendronate treatment. Although the reductions in clinical fractures overall were not statistically significant in those over 75, the treatment-by-age interaction was not significant, supporting a homogeneity of effect across age groups (25). HORIZON-PFT is the first study to show a significant reduction in nonvertebral fractures with bisphosphonates among those over age 75.

In the teriparatide study, which included 1085 women from the fracture prevention study, the effect of teriparatide on vertebral fractures was similar in subjects above and below the age of 75 yr (5). However, the effect on nonvertebral fractures was only significant below the age of 75 yr. Again, the subset of elderly patients was relatively small, as was the number of nonvertebral fractures, limiting the statistical power to address nonvertebral fracture efficacy. The strontium ranelate study prospectively assessed 1488 women over age 80 yr and showed a significant reduction in vertebral and nonvertebral fractures (6). The Women's Health Initiative hormone trials did not find a difference in the effects of hormone replacement therapy on fracture risk according to age (11, 26).

Whether reductions in hip fracture risk with therapy decrease with age has been the subject of some controversy. We found no treatment by age interaction for hip fracture and so cannot claim less efficacy of zoledronic acid in hip fracture risk in the elderly. In the HIP study of risedronate, in the subgroup of women over age 80, the reduction in hip fracture risk was 20% (7) but was not statistically significant. This oldest group of women was recruited based on their age plus an additional risk factor for hip fracture but did not necessarily have low BMD. Whether this lack of reduction was due to the presence of other risk factors (*e.g.* high risk of falling), absence of low BMD, or other factors such as low compliance cannot be determined.

We cannot be certain whether or not there is an attenuation of effect of osteoporosis treatments on fracture risk reduction with increasing age, and this merits further study. It is likely that there is some attenuation because there is a lesser dependency of fracture risk on BMD with age (12).

There have been no analyses of any treatment interaction with renal function, although poor renal function has been associated with greater fracture risk (20). The impact of renal function was attenuated after adjustment for age. We defined our threshold for decreased renal function based on the definition of stage 3 chronic kidney disease, *i.e.* estimated

creatinine clearance between 30 and 59 ml/min, and we limited inclusion of patients to those with creatinine clearance above 30 ml/min measured at two separate occasions before randomization. This level of chronic kidney disease can be associated with the early stages of renal osteodystrophy, such as secondary hyperparathyroidism, and this may attenuate the benefit of the drug (27). However, this is not as likely because there was no treatment-by-BMD interaction in the current study. There is an association between fall risk and renal impairment (20), and so falls may have a more important role in fracture risk in such subjects. More studies are needed to examine for an interaction between renal function and treatment on fracture risk.

The least expected interaction was between BMI and treatment for vertebral fracture in which those with highest BMI had the strongest reduction. There is a similar (nonsignificant) trend for nonvertebral fractures. Low BMI is a strong indicator of risk for all fractures, but the relationship is most evident for hip fractures (13). This effect is mainly mediated through low BMD, and so it might have been expected that women with low BMI would be more responsive to zoledronic acid than overweight women (with high BMI). Falls are considered to be an important risk factor for vertebral fracture (18, 28); it is possible that they are particularly important for slender women because there is insufficient "padding" to protect against a fall. If the trauma of a fall was more important in slender women, then zoledronic acid would not be expected to be as protective as when low BMD is a more important factor. More studies are needed to examine for an interaction between BMI and treatment on fracture risk.

The interactions between risk factors and treatment were not significant for nonvertebral fracture or hip fracture. For both, there was a weak relationship with prior use of bisphosphonates. We appreciate that bisphosphonates such as alendronate may continue to suppress bone turnover and possibly fracture risk for several years after stopping them (21, 22), and this might mean that the effect of a newly introduced treatment might be less effective. This is further supported by the smaller increase in BMD noted with zoledronic acid after prior bisphosphonate use in the current study, although there was no significant treatment-by-prior-use interaction with femoral neck BMD. Several previous studies have noted an interaction between baseline BMD and nonvertebral fracture reduction for bisphosphonates wherein nonvertebral fracture reductions were great among those with lower BMD (7, 9, 29). However, greater efficacy for nonvertebral or hip fractures was not observed with zoledronic acid for those with lower BMD. However, it should be noted that in the current study, women were selected by baseline BMD T-score and vertebral fracture status in such a way that no women with high BMD (T-score >−2.5) without a vertebral fracture were included (2). Therefore, the effect of baseline BMD on reduction of fracture or BMD could not be independently evaluated.

The only significant interaction with treatment and hip BMD was for baseline total hip BMD; there was a larger BMD increase among those with lower BMD. This may relate to the higher bone turnover rate found in women with low BMD. Therefore, higher bone turnover might be expected to be associated with bigger increases in BMD in response to zoledronic acid, because the level of mineralization would be lower at baseline and the remodeling space higher. However, this could be a common variable effect; when we

examined absolute change in BMD, we found that there was no longer a significant interaction with low BMD.

In conclusion, we found that zoledronic acid had similar effects on hip and nonvertebral fracture and change in femoral neck BMD independent of demographics and baseline risk factors for fracture. However, zoledronic acid appeared more effective in preventing vertebral fracture in younger women, women with higher BMI, and women with normal renal function. Overall, in general, even when treatment-by-factor interactions were present, the efficacy of zoledronic acid was positive across the different levels of subgroups, indicative of the robust efficacy profile of zoledronic acid as a once-a-year therapy for the treatment of postmenopausal osteoporosis.

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Abbreviations

BMD   Bone mineral density

BMI   body mass index

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FIG. 1.
Effect of baseline risk factors on reduction in vertebral fracture with zoledronic acid 5 mg at 3 yr in stratum I. OP, Osteoporosis (femoral neck T-score −2.5); VFx, vertebral fracture; BP, bisphosphonate; CrCl, creatinine clearance; ZOL, zoledronic acid; CI, confidence interval. *, Vertebral fracture risk was assessed in the stratum I modified intent-to-treat population.
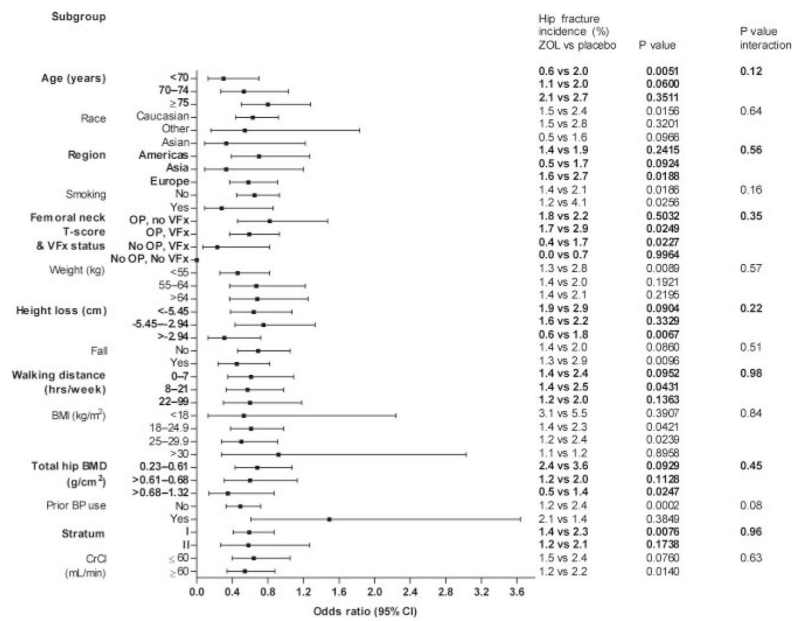
FIG. 2.
Effect of baseline risk factors on reduction in hip fracture with zoledronic acid 5 mg at 3 yr (strata I and II). OP, Osteoporosis (femoral neck T-score −2.5); VFx, vertebral fracture; BP, bisphosphonate; CrCl, creatinine clearance; ZOL, zoledronic acid; CI, confidence interval.
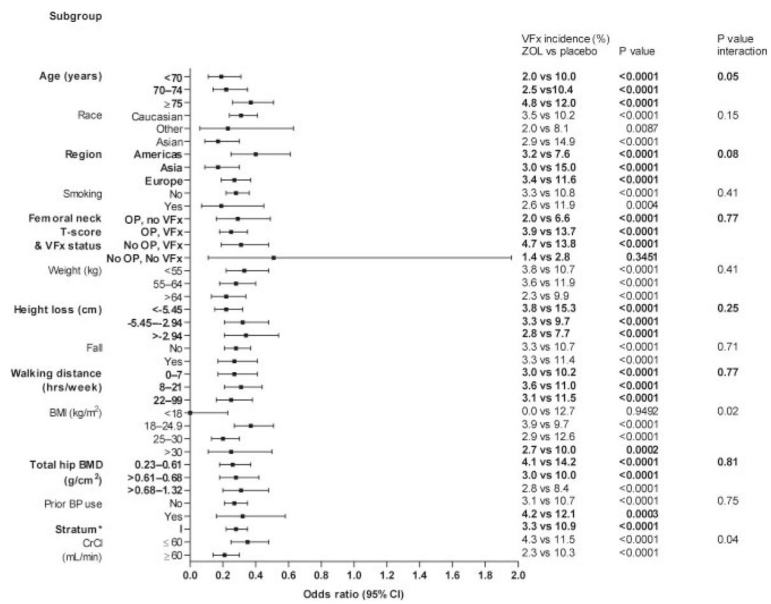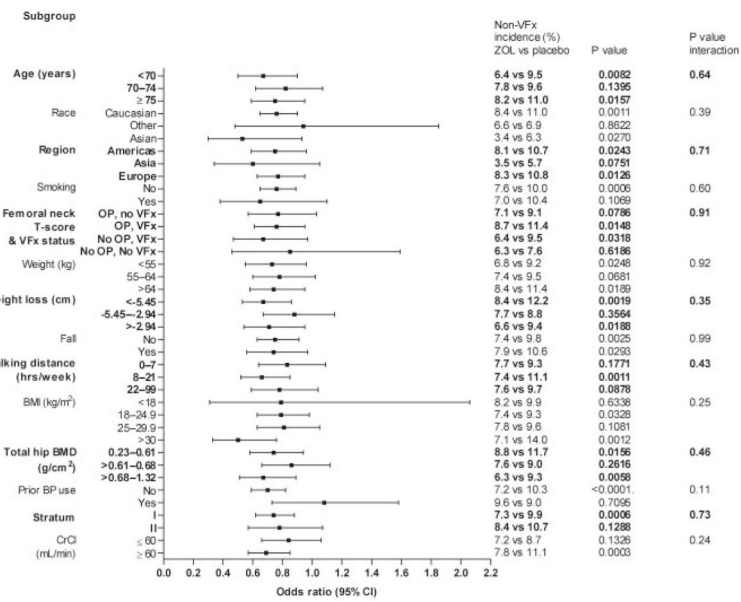
FIG. 3.
Effect of baseline risk factors on reduction in nonvertebral fracture with zoledronic acid 5 mg at 3 yr (strata I and II). OP, Osteoporosis (femoral neck T-score −2.5); VFx, vertebral fracture; BP, bisphosphonate; CrCl, creatinine clearance; ZOL, zoledronic acid; CI, confidence interval.

TABLE 1

Baseline characteristics of subjects in overall population (strata I and II combined)

	Zoledronic acid	Placebo
n	3875	3861
Age (yr)	73.1 ± 5.3	73.0 ± 5.4
Age group		
<70 yr	1140 (29.4)	1174 (30.4)
70–74 yr	1238 (31.9)	1235 (32.0)
75 yr	1497 (38.6)	1452 (37.6)
Age at menopause (yr)	48.0 ± 5.5	47.9 ± 5.5
Stratum		
I	3045 (78.6)	3039 (78.7)
II	830 (21.4)	822 (21.3)
Race		
Caucasian	3054 (78.8)	3055 (79.1)
Asian	562 (14.5)	559 (14.5)
Other	259 (6.7)	247 (6.4)
Region		
Americas	1391 (35.9)	1387 (35.9)
Asia	550 (14.2)	540 (14.0)
Europe	1934 (49.9)	1934 (50.1)
BMI (kg/m^2)[a]	25.1 ± 4.3	25.4 ± 4.3
BMI[a]		
<18 kg/m^2	98 (2.5)	91 (2.4)
18–24.9 kg/m^2	1969 (50.9)	1845 (47.8)
25–29.9 kg/m^2	1333 (34.5)	1420 (36.8)
30 kg/m^2	468 (12.1)	500 (13.0)
Weight (kg)[a]	59.9 ± 11.1	60.6 ± 11.3
Height loss		
<−5.65 cm	1243 (32.9)	1276 (33.8)
−5.65 to −3 cm	1283 (34.0)	1242 (32.9)
>−3 cm	1253 (33.2)	1262 (33.4)
Baseline VFx		
Yes	2416 (62.4)	2477 (64.2)
No	1457 (37.6)	1383 (35.8)
Current smoker		
Yes	344 (8.9)	316 (8.2)
No	3531 (91.1)	3544 (91.8)
History of falls		
Yes	1139 (29.5)	1130 (29.3)
No	2706 (70.0)	2711 (70.3)

	Zoledronic acid	Placebo
Unknown	20 (0.5)	15 (0.4)
Physical activity (hours walking/wk)	19.6 ± 18.0	19.8 ± 17.9
Prior bisphosphonate usage		
Yes	565 (14.6)	557 (14.4)
No	3293 (85.1)	3282 (85.1)
Total hip BMD (g/cm^2)	0.65 ± 0.09	0.65 ± 0.09
Standardized total hip BMD (g/cm^2)		
0.23–0.61	1290 (33.6)	1262 (32.9)
>0.61–0.68	1301 (33.8)	1276 (33.2)
>0.68–1.32	1253 (32.6)	1301 (33.9)
Femoral neck BMD (g/cm^2)	0.53 ± 0.06	0.53 ± 0.06
Femoral neck T-score	−2.8 ± 0.5	−2.7 ± 0.6
Femoral neck T-score		
−2.5	2814 (73.1)	2734 (71.1)
>−2.5	1037 (26.9)	1111 (28.9)
Femoral neck T-score by baseline VFx status		
−2.5 + VFx	1649 (42.8)	1645 (42.8)
−2.5 − VFx	1163 (30.2)	1088 (28.3)
>−2.5 + VFx	751 (19.5)	822 (21.4)
>−2.5 − VFx	286 (7.4)	289 (7.5)
Creatinine clearance		
<60 ml/min	1786 (46.1)	1728 (44.8)
60 ml/min	2089 (53.9)	2133 (55.2)

Data are presented as mean ± SD or number (%). VFx, Vertebral fracture.

[a]Significant difference ($P < 0.05$) between treatment groups (t test for continuous variables; χ^2 test for categorical variables).

TABLE 2

Baseline characteristics for patients in stratum I

	Zoledronic acid	Placebo
n	2822	2853
Age (yr)	73.0 ± 5.2	3.1 ± 5.4
Age group		
<70 yr	832 (29.5)	852 (29.9)
70–74 yr	907 (32.1)	923 (32.4)
75 yr	1083 (38.4)	1078 (37.8)
Age at menopause (yr)	48.2 ± 5.3	48.0 ± 5.4
Race		
Caucasian	2135 (75.7)	2179 (76.4)
Asian	482 (17.1)	477 (16.7)
Other	205 (7.3)	197 (6.9)
Region		
Americas	917 (32.5)	931 (32.6)
Asia	473 (16.8)	461 (16.2)
Europe	1432 (50.7)	1461 (51.2)
BMI (kg/m^2)[a]	25.2 ± 4.2	25.5 ± 4.3
BMI		
<18 kg/m^2	67 (2.4)	63 (2.2)
18–24.9 kg/m^2	1400 (49.7)	1348 (47.3)
25–29.9 kg/m^2	1014 (36.0)	1059 (37.2)
30 kg/m^2	334 (11.9)	379 (13.3)
Weight (kg)[a]	59.9 ± 11.0	60.6 ± 11.4
Height loss		
<−5.65 cm	966 (32.7)	981 (33.0)
−5.65 to −3 cm	1005 (34.0)	969 (32.6)
>−3 cm	985 (33.3)	1021 (34.4)
Baseline VFx		
Yes	1752 (62.1)	1815 (63.6)
No	1070 (37.9)	1038 (36.4)
Current smoker		
Yes	235 (8.3)	218 (7.6)
No	2587 (91.7)	2635 (92.4)
History of falls		
Yes	811 (28.7)	837 (29.3)
No	1998 (70.8)	2006 (70.3)
Unknown	13 (0.5)	10 (0.4)
Physical activity (hours walking/wk)	19.8 ± 17.9	20.0 ± 18.0
Prior bisphosphonate usage		
Yes	335 (11.9)	339 (11.9)

	Zoledronic acid	Placebo
No	2479 (87.8)	2502 (87.7)
Total hip BMD (g/cm^2)	0.65 ± 0.09	0.65 ± 0.09
Standardized total hip BMD (g/cm^2)		
0.23–0.61	931 (33.2)	951 (33.5)
>0.61–0.68	939 (33.5)	939 (33.0)
>0.68–1.32	933 (33.3)	952 (33.5)
Femoral neck BMD (g/cm^2)	0.53 ± 0.06	0.53 ± 0.06
Femoral neck T-score	−2.7 ± 0.5	−2.8 ± 0.5
Femoral neck T-score		
−2.5	2037 (72.7)	2054 (72.3)
>−2.5	766 (27.3)	788 (27.7)
Femoral neck T-score by baseline VFx status		
−2.5 + VFx	1185 (42.3)	1238 (43.6)
−2.5 − VFx	852 (30.4)	816 (28.7)
>−2.5 + VFx	556 (19.8)	571 (20.1)
>−2.5 − VFx	210 (7.5)	217 (7.6)
Creatinine clearance		
<60 ml/min	1289 (45.7)	1274 (44.7)
60 ml/min	1533 (54.3)	1579 (55.3)

Data are presented as mean ± SD or number (%). VFx, Vertebral fracture.

[a]Significant difference ($P < 0.05$) between treatment groups (t test for continuous variables; χ^2 test for categorical variables).

TABLE 3

Effect of factors on mean percentage change from baseline in femoral neck BMD at 3 yr (strata I and II)

Category	n	Mean % change in FN BMD		Least squares mean between-treatment difference (95% CI)	P value within category	P value interaction
		Zoledronic acid	Placebo			
Age (yr)						
<70	959	4.33	−0.76	5.09 (4.55, 5.62)	<0.0001	0.99
70–74	1015	4.09	−0.96	5.05 (4.52, 5.57)	<0.0001	
75	1093	3.90	−1.14	5.04 (4.53, 5.55)	<0.0001	
Race						
Asian	469	4.37	−0.49	4.85 (4.08, 5.63)	<0.0001	0.51
Caucasian	2390	4.08	−0.96	5.04 (4.70, 5.38)	<0.0001	
Other	208	3.71	−1.97	5.68 (4.50, 6.85)	<0.0001	
Region						
Americas	1074	3.5	−1.47	4.98 (4.47, 5.48)	<0.0001	0.70
Asia	459	4.35	−0.48	4.82 (4.04, 5.61)	<0.0001	
Europe	1534	4.44	−0.73	5.17 (4.74, 5.60)	<0.0001	
Smoking						
No	2810	4.17	−0.92	5.08 (4.77, 5.40)	<0.0001	0.58
Yes	257	3.35	−1.42	4.77 (3.70, 5.84)	<0.0001	
Femoral neck T-score and VFx status						
OP, no VFx	953	4.81	−0.56	5.37 (4.82, 5.92)	<0.0001	0.004
OP, VFx	1258	4.44	−0.92	5.36 (4.89, 5.83)	<0.0001	
No OP, no VFx	238	3.21	−1.38	4.59 (3.53, 5.65)	<0.0001	
No OP, VFx	617	2.65	−1.37	4.02 (3.36, 4.68)	<0.0001	
Weight (kg)						
<55	1040	3.92	−1.29	5.21 (4.68, 5.74)	<0.0001	0.77
55–64	1067	3.97	−1.10	5.07 (4.56, 5.58)	<0.0001	
>64	957	4.43	−0.50	4.93 (4.40, 5.46)	<0.0001	
Height loss (cm)						
<−5.65	1015	4.05	−1.48	5.53 (5.00, 6.05)	<0.0001	0.10
−5.65 to −3	1009	4.02	−0.86	4.89 (4.37, 5.41)	<0.0001	

Category	n	Mean % change in FN BMD		Least squares mean between-treatment difference (95% CI)	P value within category	P value interaction
		Zoledronic acid	Placebo			
>−3	972	4.26	−0.53	4.79 (4.26, 5.31)	<0.0001	
BMI (kg/m²)						
<18	74	2.66	−2.42	5.07 (3.07, 7.07)	<0.0001	0.27
18–24.9	1574	3.95	−1.15	5.10 (4.67, 5.53)	<0.0001	
25–29.9	1064	4.39	−0.90	5.29 (4.79, 5.79)	<0.0001	
>30	350	4.22	−0.07	4.28 (3.41, 5.16)	<0.0001	
Total hip BMD (g/cm²)						
0.23–0.61	1035	4.72	−1.27	5.98 (5.46, 6.51)	<0.0001	<0.0001
>0.61–0.68	1019	3.99	−1.06	5.05 (4.52, 5.57)	<0.0001	
>0.68–1.32	1006	3.56	−0.55	4.10 (3.58, 4.63)	<0.0001	
Prior BP use						
No	2604	4.3	−0.86	5.16 (4.84, 5.49)	<0.0001	0.26
Yes	455	2.86	−1.60	4.46 (3.67, 5.26)	<0.0001	
Stratum						
I	2394	4.26	−0.87	5.13 (4.79, 5.47)	<0.0001	0.40
II	673	3.53	−1.29	4.81 (4.16, 5.47)	<0.0001	
CrCl (ml/min)						
<60	1361	3.88	−1.31	5.18 (4.73, 5.64)	<0.0001	0.48
60	1706	4.27	−0.69	4.96 (4.56, 5.37)	<0.0001	

Falls and walking distance had no effect on BMD change by category and so are not listed. CI, Confidence interval; BP, bisphosphonate; FN, femoral neck; OP, osteoporosis (femoral neck T-score −2.5); VFx, vertebral fracture; CrCl, creatinine clearance.