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**Relationship of Changes in Total Hip Bone Mineral Density to Vertebral and Non-Vertebral Fracture Risk in Women with Postmenopausal Osteoporosis Treated with Once-Yearly Zoledronic Acid 5 mg: the HORIZON-Pivotal Fracture Trial (PFT)**

**Authors:** Richard M Jacques<sup>1</sup>, Steven Boonen<sup>2</sup>, Felicia Cosman<sup>3</sup>, Ian R Reid<sup>4</sup>, Douglas C Bauer<sup>5</sup>, Dennis M Black<sup>5</sup>, Richard Eastell<sup>6</sup>

**Affiliations:**

<sup>1</sup>School of Health and Related Research, University of Sheffield, Sheffield, UK

<sup>2</sup>Division of Geriatric Medicine, Leuven University, Leuven, Belgium

<sup>3</sup>Helen Hayes Hospital, West Haverstraw, NY, USA

<sup>4</sup>University of Auckland, Auckland, New Zealand

<sup>5</sup>University of California, San Francisco, CA, USA

<sup>6</sup>Sheffield NIHR Bone Biomedical Research Unit, University of Sheffield and Sheffield Teaching Hospitals Foundation Trust, UK

**Authors' email addresses:**

r.jacques@sheffield.ac.uk

steven.boonen@uz.kuleuven.be

cosmanf@helenhayeshosp.org

i.reid@auckland.ac.nz

dbauer@psg.ucsf.edu

dblack@psg.ucsf.edu

r.eastell@sheffield.ac.uk

**Running title:** Zoledronic Acid Percent Treatment Effect Explained

**Address for Correspondence:**

Professor Richard Eastell  
Bone Biomedical Research Unit  
Centre for Biomedical Research,  
Northern General Hospital,  
Herries Road,  
Sheffield, S5 7AU,  
UK.

Telephone: +44 (114) 271 4705

Fax: +44 (114) 261 8775

Email: r.eastell@sheffield.ac.uk

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- I.R. Reid: consulting or advisory board fees from Merck, Amgen, Novartis; lecture fees from Amgen, Merck, Novartis; and grant support from Amgen, Novartis, Procter & Gamble and Merck
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## **Abstract**

Measurements of change in bone mineral density (BMD) are thought to be weak predictors of treatment effect on the reduction of fracture risk. In this study we report an alternative year-on-year approach for the estimation of treatment effect explained by BMD in which we examine the relationship between fracture risk and the most recent change in BMD.

We studied 7736 postmenopausal women (ages 65 to 89 years) who were participants in the HORIZON Pivotal Fracture Trial and were randomized to either intravenous administration of zoledronic acid or placebo. The percentage of treatment effect explained by change in total hip BMD was estimated using the alternative year-on-year approach and the standard approach of looking at change over 3 years. We also studied a subset of 1132 women in whom procollagen type 1 amino-terminal propeptide (PINP) was measured at baseline and 12 months, to estimate the percentage of treatment effect explained by change in PINP.

Regardless of the method used, the change in total hip BMD explained a large percentage of the effect of zoledronic acid in reducing new vertebral fracture risk (40% [95% CI: 30% to 54%] for the 3 year analysis). The treatment effects for non-vertebral fracture were not statistically significant for the year-on-year analysis but 3-year change in BMD explained 61% (95% CI: 24% to 156%) of treatment effect. Change in PINP explained 58% (95% CI: 15% to 222%) of the effect of zoledronic acid in reducing new vertebral fracture risk.

We conclude that our estimates of the percentage of treatment effect explained may be higher than in previous studies because of high compliance with zoledronic acid (due to its once-yearly intravenous administration). Previous studies may have underestimated the relationship between BMD change and the effect of treatment on fracture risk.

**Key Words:** zoledronic acid; bone mineral density; PINP; fracture; surrogate; percent of treatment effect explained

## **Introduction**

It is well recognised that there is a strong association between bone mineral density (BMD) and the risk of fracture (1). However, it has been suggested that change in BMD in response to osteoporosis therapies is a poor predictor of future fracture.

The analysis most commonly performed at the individual patient level is the association between the incidence of fracture and the change in BMD over three years (2-6). The percentage of fracture risk reduction explained by change in BMD appears small for existing therapies. However, the apparently low contribution of change in BMD may be due to the way that the data are analysed. A more appropriate approach might be to analyse the relationship between fracture risk and the most recent change in BMD. If a fracture occurs 9 months into the trial for example, then the risk of this fracture may relate more closely to the 1-year change in BMD than the 3-year change. This approach would also allow the analysis of data from trial participants who might subsequently withdraw or be withdrawn before the end of the study.

Zoledronic acid is a bisphosphonate given as an annual intravenous infusion. In the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Pivotal Fracture Trial (7), zoledronic acid reduced the risk of vertebral fractures by 70% ( $p < 0.001$ ) and non-vertebral fractures by 25% ( $p < 0.001$ ). The aim of this study was to investigate the usefulness of measuring change in total hip BMD and procollagen type 1 amino-terminal propeptide (PINP) for the assessment of fracture risk during zoledronic acid treatment. We planned to determine whether fracture risk was explained by changes in total hip BMD or PINP, and whether the timing of BMD measurement in relation to the time of fracture, influences the magnitude of reduction in fracture risk. We also planned to determine whether

the changes in total hip BMD and PINP are independent when they act as surrogates for fracture risk reduction.

## **Methods**

### **Study design and subjects**

We analysed data from the HORIZON Pivotal Fracture Trial. Details of the study design have been reported previously (7). Briefly this was a prospective, randomized, double-blind, placebo-controlled multi-national trial of 7736 postmenopausal women (ages 65 to 89 years). All women had a femoral neck BMD T-score of -2.5 or less, with or without existing vertebral fracture, or a T-score of -1.5 or less, with radiological evidence of at least two mild vertebral fractures or one moderate vertebral fracture. Prior oral bisphosphonate use was allowed, with washout duration dependent on previous use (e.g. >48 weeks of usage required a 2-year washout). Subjects were randomly assigned to receive either an intravenous administration of zoledronic acid or placebo at baseline, 12 and 24 months. All subjects received oral daily calcium (1000 to 1500 mg) and vitamin D (400 to 1200 IU). Subjects were assigned to one of two strata. Subjects in stratum 1 were not taking any osteoporosis medications at the time of randomisation, whereas subjects in stratum 2 were all taking a permitted medication. The 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.

### **Measurements**

Lateral spinal radiographs were obtained at baseline and at 12, 24 and 36 months or early termination for patients in stratum 1 and at baseline and 36 months or early termination for patients in stratum 2. Vertebrae from T4 to L4 were evaluated at a central imaging laboratory



(Synarc, San Francisco, USA) with quantitative morphometry and standard methods. Incident morphometric vertebral fractures were defined as a reduction in vertebral height of at least 20% and 4 mm by quantitative morphometry, confirmed by an increase of one severity grade or more on semi-quantitative analysis (8). Prevalent fracture at baseline was defined by a height ratio at least 3 SD below the vertebra-specific mean height ratio on quantitative reading, with semiquantitative confirmation (9, 10). Clinical fracture reports were obtained from patients at each contact. Non-vertebral fracture reports required central confirmation, which was performed at the University of California at San Francisco (UCSF) Coordinating Centre. For clinical vertebral fractures, community obtained radiographs were compared with the baseline study radiograph by a central reader at Synarc and semiquantitative confirmation was required.

Dual-energy x-ray absorptiometry of the hip was performed at baseline and at months 6, 12, 24 and 36. Measurements of BMD were corrected for site variations. Spine BMD was not used in these analyses because it was only available in a small subset of patients.

PINP was measured in a subgroup of the clinical trial centres. Measurements were made using the Elecsys 2010 Immunoassay System (Roche) in 1132 subjects at baseline and one year. Delmas et al. have reported on changes in PINP in the HORIZON Trial (11).

### **Statistical analysis**

To examine the relationship between total hip BMD and fracture, we used a logistic regression model with new fracture as the dependent response variable, and randomised treatment, previous vertebral fracture, stratum and change in total hip BMD from baseline as covariates. We fitted four separate models to estimate the percentage of treatment effect

explained for four different time periods. As shown in Figure 1, year 1 analysis examined the change in BMD from baseline to 12 months and fractures in the first year. Year 2 analysis examined the change in BMD from baseline to 24 months and fractures in the second year. Year 3 analysis examined the change in BMD from baseline to 36 months and fractures in the third year, and finally, the 3-year analysis examined the change in BMD from baseline to 36 months and fractures in all three years.

To examine the relationship between PINP and fracture, we used a logistic regression model with new fracture as the dependent response variable, and randomised treatment, previous vertebral fracture, stratum, and 12 month change in PINP as covariates. We also fitted a model adding 12 month change in total hip BMD to see if PINP and BMD act independently of each other as surrogates for fracture risk reduction. Measurements of PINP at baseline and 12 months were log-transformed prior to analysis.

We estimated the percentage of treatment effect explained using the method of Li et al. (12) and 95% confidence intervals for these point estimates were calculated using the delta method (13). The interaction between BMD change and treatment was assessed for all models. If the interaction was not significant then the interaction was excluded from the summaries of the model. When using Li's method to estimate the percentage of treatment effect explained, it is possible for the point estimate and the confidence interval to be greater than 100%. If treatment is not statistically significant when fitted in a model with change in BMD, then the confidence interval will exceed 100%.

We explored the relationship between change in BMD and the incidence of new vertebral and non-vertebral fracture in the zoledronic acid treatment group using logistic regression. Using

a similar analysis to Watts et al. (5), we constructed three subgroups based on 3-year change in BMD: patients who had a decrease in BMD (i.e. change in BMD < 0), patients who had an increase in BMD but not more than the median increase (i.e. change in BMD from 0 to < median) and patients who gained at least the median (i.e. change in BMD  $\geq$  median). We then fitted models to calculate the odds ratio of new vertebral or non-vertebral fracture in patients with increased BMD compared to patients with decreased BMD. Previous vertebral fracture and strata were fitted as covariates in the model.

Statistical analysis was implemented using the computing package R (<http://www.R-project.org>). Fracture probability plots were created using the ggplot2 library (14).

## **Results**

### **Baseline Characteristics**

Baseline patient characteristics are listed in Table 1. The proportion of patients in each stratum, age, body mass index (BMI), femoral neck and total hip BMD, femoral neck BMD T-score and history of prevalent vertebral fracture were similar between the placebo and zoledronic acid groups.

### **Fracture Incidence**

The bar charts in Figure 2 show the incidence of (a) new vertebral fracture and (b) non-vertebral fracture in the placebo and zoledronic acid groups for those participants remaining in the trial at the end of each 12-month interval. Women with both baseline and 36-month BMD measurements were included in the 3-year analysis. The number of subjects for analysis in the placebo and zoledronic acid groups decreased over time because a) anyone who fractured in each 12-month period was not included in any subsequent analysis or b)

subjects withdrew or were withdrawn from the trial for other reasons. There was a larger incidence of new vertebral fracture in the placebo than in the zoledronic acid group at every time point.

### **Relationship between change in total hip BMD and new vertebral fracture**

We examined the reduction in vertebral fracture risk and percentage of treatment effect explained at each time point of the analysis (Table 2). We observed a statistically significant reduction in the odds of new vertebral fracture for each of the analyses (all p-values < 0.001). For the yearly analyses, change in total hip BMD explained between 39% and 42% of the reduction in risk of new vertebral fracture. In the 3-year analysis total hip BMD explained 40% (95% CI: 30% to 54%) of the fracture risk reduction.

Figure 3 shows the relationship between change in total hip BMD and the probability of new vertebral fracture for each of the four different analyses. For both the zoledronic acid and placebo groups, the probability of fracture decreased as total hip BMD increased. On testing for an interaction between treatment and change in total hip BMD, we found no statistically significant difference between the gradients of the slopes of the curves.

We examined the relationship between 3-year change in total hip BMD and new vertebral fracture in the zoledronic acid treatment group (Table 3). Among those patients whose 3-year BMD decreased from baseline, the estimated incidence of new vertebral fracture was 7.5%. Zoledronic acid-treated patients in whom BMD decreased were at a significantly greater risk ( $p < 0.001$ ) of sustaining a vertebral fracture than patients with increased BMD. Among those patients with 3-year increases in BMD between 0 and the median of 0.032 g/cm<sup>2</sup>, the incidence of new vertebral fracture was 3.5%, with patients in this group 0.48

times as likely to fracture than those with a decrease in BMD (odds ratio: 0.48, 95% CI: 0.29 to 0.78). Among patients with 3-year increases in BMD  $\geq$  median of 0.032 g/cm<sup>2</sup>, the incidence of new vertebral fracture was 2.0%, with patients in this group 0.27 times as likely to fracture than those with a decrease in BMD (odds ratio 0.27, 95% CI: 0.16 to 0.47). When we compared the fracture incidence in the subgroup of zoledronic acid-treated patients with increases in BMD  $<$  median, with that in the subgroup of patients with increases in BMD  $\geq$  median, we found a significant difference in the risk of fracture ( $p = 0.025$ ).

### **Relationship between change in total hip BMD and non-vertebral fracture**

We examined the reduction in risk of non-vertebral fractures and the percentage of treatment effect explained at each time point of the analysis (Table 2). We found that the reduction in the odds of non-vertebral fracture was not statistically significant for the analysis based on individual years. For the 3-year analysis we observed a statistically significant odds ratio of 0.79 (95% CI: 0.66 to 0.95). As the fracture risk reduction was not statistically significant for the yearly analyses, we did not calculate the percentage of treatment effect explained. In the 3-year analysis, change in BMD explained 61% (95% CI: 24% to 156%) of the treatment effect.

Figure 4 shows the relationship between change in total hip BMD and the probability of non-vertebral fracture for the 3-year analysis. For both the zoledronic acid and placebo groups, the probability of fracture decreased as total hip BMD increased. On testing for an interaction between treatment and change in total hip BMD, we found no statistically significant difference between the gradients of the slopes of the curves.

We examined the relationship between 3-year change in total hip BMD and non-vertebral fracture in the zoledronic acid treatment group (Table 3). When we compared the fracture incidence in the subgroups of patients with decreases or increases in BMD, we found that the reduction in the odds of fracture were similar ( $p = 0.096$ ).

### **Relationship between PINP and fracture**

We examined the reduction in the risk of new vertebral or non-vertebral fractures and the percentage of treatment effect explained by 12-month change in log PINP in the subset of patients with bone marker measurements (Table 4). We observed a statistically significant reduction in the odds of new vertebral fracture, and the change in log PINP explained 58% (95% CI: 15% to 222%) of the reduction. The reduction in odds did not change much when adjusting for total hip BMD and the percentage of treatment effect explained was 57% (95% CI: 14% to 231%). The reduction in odds for non-vertebral fracture was not significant for this subset of patients and therefore the percentage of treatment effect explained was not calculated.

Figure 5 shows the relationship between 12-month change in log PINP and the probability of vertebral fracture. For both the zoledronic acid and placebo groups, the probability of fracture decreased as log PINP decreased. On testing for an interaction between treatment and change in log PINP we found no statistically significant difference between the gradients of the slopes of the curves.

We examined the relationship between 12-month change in log PINP and new vertebral fracture in the zoledronic acid treatment group. Zoledronic acid-treated patients in whom log PINP decreased were at a significantly lower risk (odds ratio: 0.22, 95% CI: 0.05 to 0.88) of

sustaining a vertebral fracture than patients with increased log PINP. When we compared the fracture incidence in the subgroup of zoledronic acid-treated patients with decreases in log PINP < median decrease of 1.02 ng/mL, with that in the subgroup of patients with decrease in log PINP  $\geq$  median decrease we did not find a significant difference in the risk of new vertebral fracture ( $p = 0.268$ ).

## **Discussion**

In this analysis we have shown that for the reduction in risk of non-vertebral fractures by zoledronic acid, the percentage of treatment effect explained by change in total hip BMD was 61%, and for new vertebral fractures it ranged from 39% to 42%. These estimates are higher than those observed in previous studies of alendronate (15) and risedronate (5, 6, 12). For ibandronate, the proportion of treatment effect explained for reduction in the risk of all fractures was 37% in the BONE study (16), and was similar for denosumab for reduction in the risk of vertebral fractures (23% to 51%) and non-vertebral fractures (35% to 89%) in the FREEDOM trial (17).

Our estimate of the percentage of treatment effect explained may be higher than in other studies as (due to the intravenous infusion) compliance tends to be higher with zoledronic acid than with the bisphosphonates which are administered orally on a daily or weekly basis. However, a previous head to head study comparing once yearly intravenous infusion of zoledronic acid and once-weekly oral alendronate in men (18) found similar percentage change in total hip BMD at 6, 12 and 24 months which may suggest that compliance is not a factor.

In the subgroup analysis of zoledronic acid-treated patients, we found that those with decreased BMD were at significantly greater risk ( $p < 0.001$ ) of sustaining a vertebral fracture than patients with increased BMD. In addition, when we compared zoledronic acid-treated patients with  $<$  and  $\geq$  median increases in BMD, we found a significant difference in the risk of fracture ( $p = 0.025$ ). This suggests that larger increases in BMD are significantly associated with greater reduction in new vertebral fracture risk. These results contrast with those of a previous study of risedronate (6) in which greater percentage increases in BMD did not necessarily predict greater decreases in fracture risk.

We observed that 58% (95% CI: 15% to 222%) of the vertebral fracture treatment effect of zoledronic acid was explained by change in PINP. This estimate is similar in magnitude to estimates for the bone resorption markers NTX (49%) and CTX (55%) in a previous study of risedronate (19). When adjusting for change in total hip BMD, we found that there was little change in the percentage of treatment effect explained by change in PINP. Additionally, we found that change in BMD was not statistically significant when it was added to the logistic regression model with change in PINP, and that the Pearson correlation coefficient between change in total hip BMD and change in PINP was -0.42 ( $p$ -value  $< 0.001$ ). This suggests that changes in total hip BMD and PINP are not independent when they act as surrogates for fracture risk reduction.

This study has several strengths: it involved a large number of patients with baseline and follow-up assessments, used individual subject data, and evaluated the relationship between BMD changes and fracture in a year-by-year analysis as well as the standard endpoint approach used by others.



The limitations of our study are the absence of active comparator data in the same trial, the enrollment of only untreated patients at baseline, and the fact that only hip BMD was measured annually in all subjects. As a result, we could not make direct comparisons of our results to those of other studies; the results for lumbar spine BMD may differ, and it is not known if these relationships apply to the BMD gains observed with zoledronic acid. The precision for the estimate of the percentage of treatment effect explained is low, particularly for PINP which was only measured in a subset of patients, leading to large confidence intervals. Additionally, the analyses in this study included all fractures and did not exclude fractures that occurred before the measurement of the endpoint BMD, as in some previous analyses. The assessment of change in BMD after fracture could be influenced by the loss of mobility or increased bed rest after fracture, which could potentially bias the assessment of the relationship between changes in BMD and fracture risk. We did not have any data on ambulatory status to adjust for this in our logistic regression models.

In summary, we found that change in total hip BMD and PINP explain a large proportion of the fracture risk reductions observed with zoledronic acid. Our estimates for BMD may be higher than in previous studies because of high compliance with zoledronic acid. Previous studies may have underestimated the relationship between BMD change and the influence of treatment effect on fracture risk.

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This ancillary study was developed by the authors and approved by the Steering Committee of the HORIZON Study, chaired by Dr Dennis Black. The data was transferred to the University of Sheffield (RE, RJ) where it was analysed. The manuscript was written by RJ and was approved by the Steering Committee and all authors. The sponsor had

representation of the steering committee but the majority of committee members are not employed by the sponsor.

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## Figure Legend

**Fig 1:** The BMD and fracture data used in each analysis. BMD data is represented by the solid lines and fracture data is represented by the dashed lines.

**Fig 2:** Incidence of (a) new vertebral fracture and (b) non-vertebral fractures in the placebo and zoledronic acid groups at the end of each year. Women who had a baseline and 36-month BMD measurement were included in the 3-year analysis: zol, zoledronic acid; fx, fracture

**Fig 3:** Relationship between probability of new vertebral fracture and change in total hip BMD for each analysis. Placebo is represented by the solid line and zoledronic acid by the dashed lines. Shaded regions show 95% confidence bands.

**Fig 4:** Relationship between probability of non-vertebral fracture and change in total hip BMD for the 3-year analysis. Placebo is represented by the solid line and zoledronic acid by the dashed lines. Shaded regions show 95% confidence bands.

**Fig 5:** Relationship between probability of non-vertebral fracture and 12-month change in log PINP. Placebo is represented by the solid line and zoledronic acid by the dashed lines. Shaded regions show 95% confidence bands.

**Table 1:** Baseline characteristics

	<b>Total Population</b>		<b>BTM Population</b>	
	<b>Placebo (N = 3861)</b>	<b>Zoledronic Acid (N = 3875)</b>	<b>Placebo (N = 578)</b>	<b>Zoledronic Acid (N = 554)</b>
<b>Stratum, n (%)</b>				
<b>1</b>	3039 (78.7%)	3045 (78.6%)	388 (67.1%)	365 (65.9%)
<b>2</b>	822 (21.3%)	830 (21.4%)	190 (32.9%)	189 (34.1%)
<b>Age (yr)</b>	73.0 ± 5.4 (3861)	73.0 ± 5.3 (3875)	73.5 ± 5.7 (578)	73.6 ± 5.5 (554)
<b>Body Mass Index (kg/m<sup>2</sup>)</b>	25.4 ± 4.3 (3856)	25.1 ± 4.3 (3868)	25.7 ± 4.5 (576)	25.3 ± 4.3 (553)
<b>Femoral Neck BMD (g/cm<sup>2</sup>)</b>	0.53 ± 0.06 (3845)	0.53 ± 0.06 (3851)	0.54 ± 0.06 (577)	0.54 ± 0.06 (554)
<b>Femoral Neck T- Score, n (%)</b>				
T-Score ≤ -2.5	2734 (70.8%)	2814 (72.6%)	420 (72.7%)	424 (76.5%)
-2.5 < T-Score ≤ -1.5	1073 (27.8%)	1002 (25.9%)	148 (25.6%)	125 (22.6%)
T-Score > -1.5	38 (1.0%)	35 (0.9%)	9 (1.6%)	5 (0.9%)
Missing	16 (0.4%)	24 (0.6%)	1 (0.1%)	0 (0%)
<b>Total Hip BMD (g/cm<sup>2</sup>)</b>	0.65 ± 0.09 (3839)	0.65 ± 0.09 (3844)	0.66 ± 0.08 (577)	0.66 ± 0.08 (554)
<b>Prevalent Vertebral Fx, n (%)</b>				
<b>No</b>	1383 (35.8%)	1457 (37.6%)	242 (41.9%)	226 (40.8%)
<b>Yes</b>	2477 (64.2%)	2416 (62.3%)	335 (58.0%)	328 (59.2%)

BTM = Bone Turnover Marker

Values are means±SD (n) unless otherwise stated

**Table 2:** Odds ratio of new vertebral and non-vertebral fracture in women treated with zoledronic acid compared with those treated with placebo and percentage of treatment effect explained by change in total hip BMD

	New Vertebral Fracture		Non-Vertebral Fracture	
	Odds Ratio (95% CI)	% Treatment Effect Explained (95% CI)	Odds Ratio (95% CI)	% Treatment Effect Explained (95% CI)
<b>Year 1</b>	0.40 (0.28,0.57)	42 (29, 61)	0.87 (0.66, 1.13)	*
<b>Year 2</b>	0.19 (0.12, 0.31)	39 (28, 54)	0.77 (0.57, 1.03)	*
<b>Year 3</b>	0.35 (0.25, 0.49)	42 (28, 63)	0.76 (0.55, 1.05)	*
<b>3 Year Analysis</b>	0.30 (0.24, 0.38)	40 (30, 54)	0.79 (0.66, 0.95)	61 (24, 156)

\* Percentage of treatment effect explained is not calculated when odds ratios are not significant.

**Table 3:** Number and percent of new vertebral fractures and non-vertebral fractures in women treated with zoledronic acid by subgroup of three-year change in total hip BMD

Change in Total Hip BMD Subgroup	New Vertebral Fracture		Non-Vertebral Fracture	
	Fracture Incidence (estimate ± SE)	Odds Ratio (95% CI)	Fracture Incidence (estimate ± SE)	Odds Ratio (95% CI)
< 0 (decrease in BMD)	7.5 ± 1.3%	-	9.6 ± 1.6%	-
0 to < median increase in BMD	3.5 ± 0.5%	0.48 (0.29, 0.78)	7.1 ± 0.7%	0.74 (0.49, 1.10)
≥ median increase in BMD	2.0 ± 0.4%	0.27 (0.16, 0.47)	6.9 ± 0.7%	0.72 (0.49, 1.08)
≥ 0 Increase in BMD	2.7 ± 0.3%	0.37 (0.24, 0.59)	7.0 ± 0.5%	0.73 (0.50, 1.06)

Median increase in BMD = 0.032 g/cm<sup>2</sup>



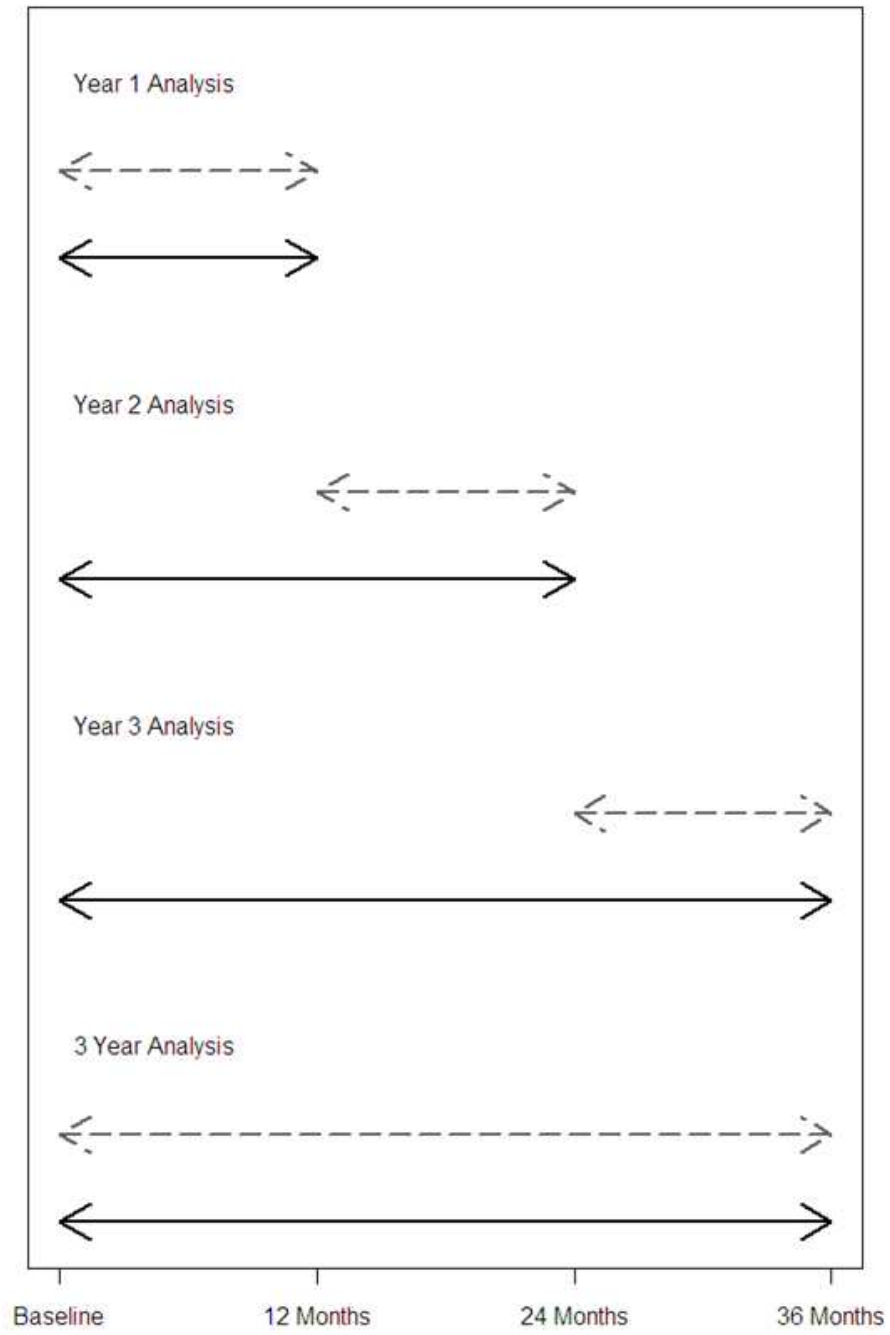
**Table 4:** Odds ratio of new vertebral and non-vertebral fracture in women treated with zoledronic acid compared with those treated with placebo and percentage of treatment effect explained by change in log PINP

	New Vertebral Fracture		Non-Vertebral Fracture	
	Odds Ratio (95% CI)	% Treatment Effect Explained (95% CI)	Odds Ratio (95% CI)	% Treatment Effect Explained (95% CI)
<b>Unadjusted</b>	0.33 (0.17, 0.65)	58 (15, 222)	0.72 (0.47, 1.10)	*
<b>Adjusted for change in BMD</b>	0.38 (0.18, 0.78)	57 (14, 231)	0.76 (0.49, 1.20)	*

\* Percentage of treatment effect explained is not calculated when odds ratios are not significant.

Estimates are adjusted and unadjusted for change in total hip BMD

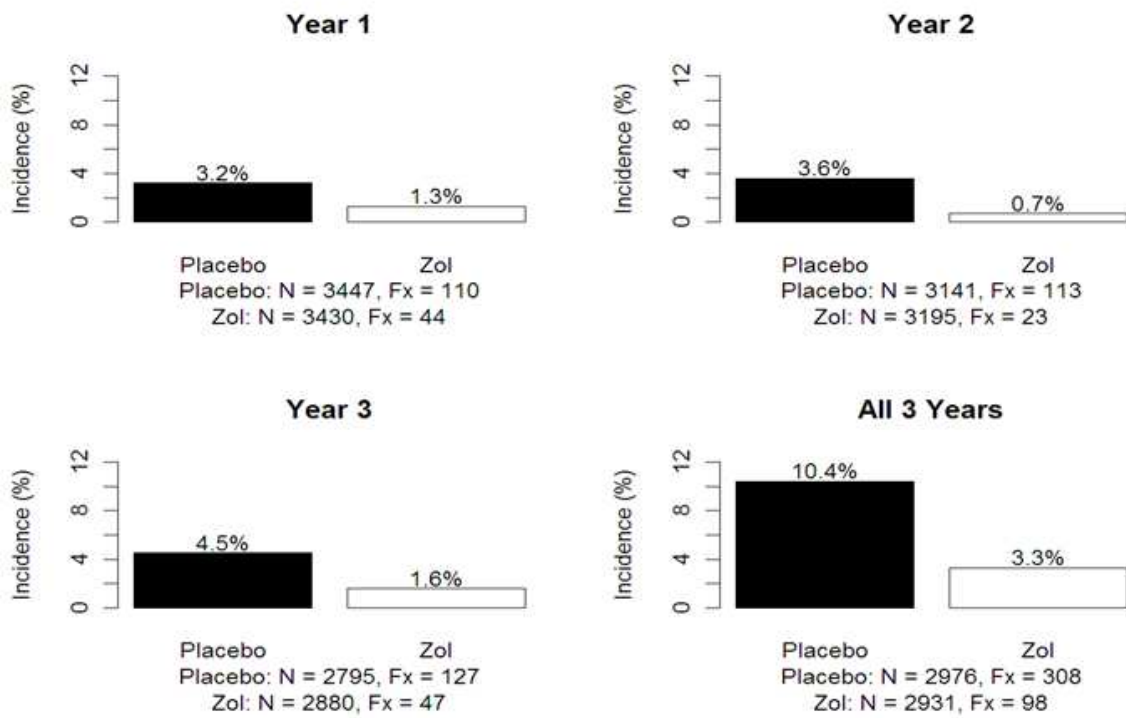
**Fig.1**



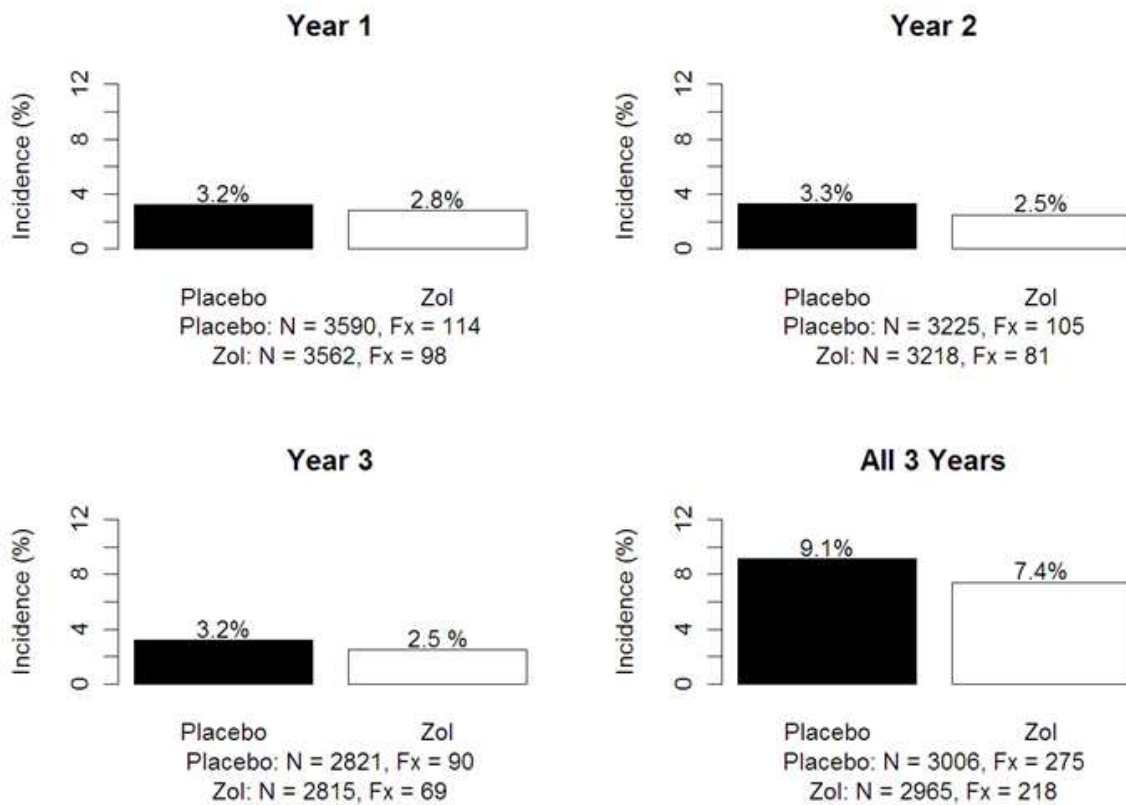
**Fig. 2**

Figure 2

**(a) New Vertebral Fractures**

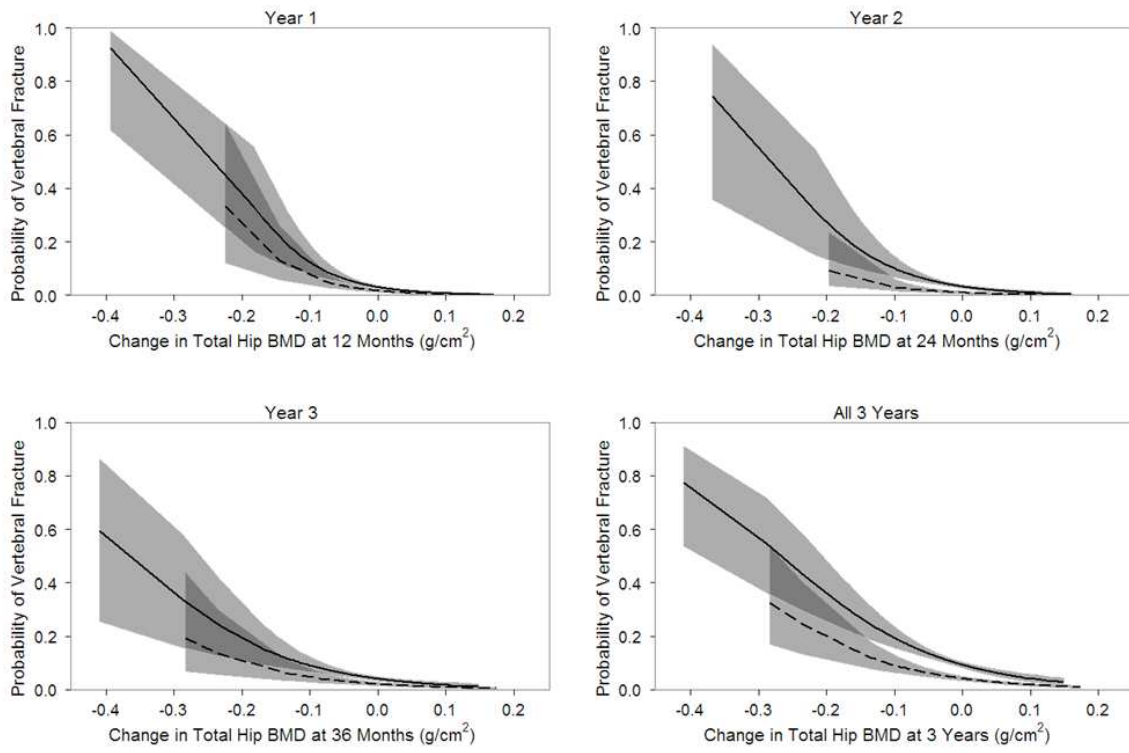


**(b) Non-Vertebral Fractures**



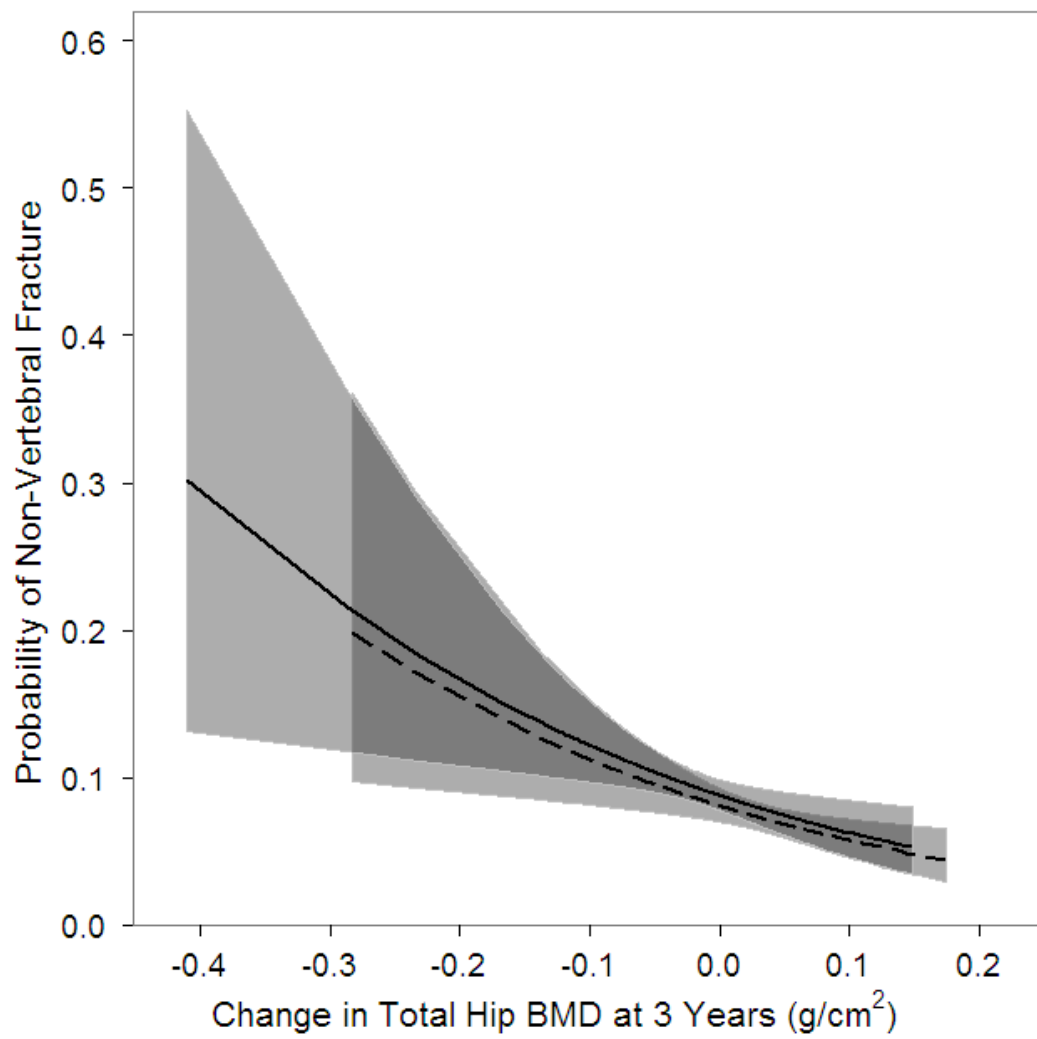
**Fig. 3**

Figure 3



**Fig. 4**

Figure 4



**Fig. 5**

Figure 5

