Treatment-Related Changes in Bone Turnover and Fracture Risk Reduction in Clinical Trials of Anti-Resorptive Drugs: A Meta-Regression

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Abstract

Few pooled analyses of anti-resorptive (AR) treatment trials are available that relate short-term changes in bone turnover markers (BTMs) to fracture reduction. Such information would be useful to assess new ARs or novel dosing regimens.

In the FNIH Bone Quality project, we received and analysed individual-level data from 28,000 participants enrolled in 11 bisphosphonate (BP) and 3 selective estrogen receptor modulator (SERM) placebo-controlled fracture endpoint trials. Using BTM results for 2 bone formation markers (bone specific alkaline phosphatase [bone ALP] and pro-collagen I N-propeptide [PINP]) and 2 bone resorption markers (N- and C-terminal telopeptide of type I collagen) and incident fracture outcome data, we performed a meta-regression relating the mean net effect of treatment on change in bone turnover (active minus placebo percent difference after 3-12 mo.) to the log of studywide fracture risk reduction, and used linear regression to plot the best fitting line. Separate analyses were performed for incident morphometric vertebral, non-vertebral and hip fractures over 1-4 yr. of follow-up.

Change in bone ALP and PINP were available for over 16,000 and 10,000 participants, respectively. For vertebral fracture, the results showed a strong relationship between treatment-related bone ALP or PINP changes and vertebral fracture risk reduction [r^2=0.82 ($p<0.001$) and 0.75 ($p=0.011$), respectively] Relationships were weaker and no longer statistically significant for non-vertebral [r^2=0.33 ($p=0.053$) and 0.53 ($p=0.065$), respectively] and hip fracture [r^2=0.17 ($p=0.24$) and 0.43 ($p=0.11$), respectively] outcomes. Analyses limited to BP trials gave similar results. For all fracture types, relationships were weaker and non-significant for bone resorption markers.

We conclude that short-term AR treatment-related changes in bone ALP and PINP strongly predict vertebral fracture treatment efficacy, but not non-vertebral or hip fracture treatment efficacy. Change in bone formation markers might be useful to predict the anti-vertebral fracture efficacy of new AR compounds or novel dosing regiments with approved AR drugs.

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Introduction

Short term changes in bone turnover markers (BTM) are typically assessed in randomised controlled trials of drugs being developed for osteoporosis. In the early phases of clinical trial development, they may be useful in selecting the optimal dose to take forward to Phase III and once the dose and dosing regime is established they provide insight into the mechanism of action of the drug. The commonest mechanism of action for therapies for osteoporosis is to inhibit bone resorption ('anti-resorptive', AR) and so these drugs result in decreases in bone resorption markers. They reduce the rate of bone remodelling and as the process of bone formation is coupled to bone resorption then, after a delay of about a month, there is a reduction in bone formation markers. The lowering of levels of BTMs to levels found in healthy young women (or below) is believed to be one mechanism whereby anti-resorptive therapy reduce the risk of fracture[1, 2].

Different anti-resorptive drugs reduce bone turnover markers to different extents. Within clinical trials, there is some evidence that the greater the reduction in bone turnover within an individual, the greater the reduction in fracture risk[3]. Such evidence is available for selective oestrogen receptor modulators (SERMs)[4,5,6] and bisphosphonates administered orally[7,8] or intravenously[9,10]. Only one analysis[11] has pooled multiple AR treatment trials to establish a more robust relationship between short-term changes in BTM and fracture reduction. If strong and reproducible relationships between change in BTMs and fracture outcomes exist, prior to initiating large and expensive fracture endpoint trials for new ARs, or when assessing novel AR dosing regiments for established ARs, it might be useful to assess the effects of treatment on BTMs to predict the likely fracture outcome and select the optimal dose.

A 2002 meta-regression[11] that pooled the published results from 18 AR trials found that a 50% reduction in various bone formation markers (vs. placebo) predicted a 44% risk reduction in non-vertebral fracture over 2-5 years, but vertebral and hip fractures were not assessed. Further, in that meta-regression the specific BTMs and analytic approach varied between studies. Since 2002 additional large trials with other BPs (zoledronic acid[12], ibandronate[13] and SERMS (basedoxifene[14], lasofoxifene[15], arzoxifene[16]) have been completed.

To determine the relationship between short-term treatment-related changes in bone turnover markers and study-level fracture risk reduction, we systematically collected individual level data from existing placebo-controlled trials of AR agents (both bisphosphonates and SERMs) to perform a meta-regression. The goal of such a meta-regression, which plots the average short-term treatment-related changes in BTM against the

observed study-level reduction in fractures, is to determine how well short-term changes in BTMs predict fracture outcomes.

Methods

Study data

A systematic search through published literature was made to identify any study that met the following criteria: placebo-controlled randomized trial of osteoporosis medication with a fracture endpoint. Studies targeting specific medical conditions (e.g. rheumatoid arthritis) and treatments (e.g., corticosteroid users) were excluded. We then attempted to collect the complete data files, including individual subject-level data, from the study sponsors. Within each sponsor, we attempted to identify an individual who was knowledgeable about the study. In many cases, the medications have now become available as generics or the companies had merged with others, making contact more difficult. Once a contact was established, we established a contract for transfer of the data and a data use agreement. We also sought data documentation including study protocol, data specifications, clinical study reports and annotated forms.

The list of studies for which we could acquire data that included BTM's is shown in Table 1 and includes most osteoporosis medication studies including drugs that were eventually approved as well as others for which regulatory approval was not sought or received. As our original intention was to include all anti-resorptive agents, we requested densoumab data from the sponsor, but due to the low number of patients with serial bone marker samples in the densoumab fracture trial (n=80 per group)[17] a meaningful analysis was not considered possible.

Conversion of studies to standard data template

A standard data template was established into which all studies were converted. In brief, this data template included a file for each of the following types of data: baseline demographics, bone turnover markers, DXA, QCT/finite element, clinical fractures and vertebral fractures. Each study was converted to the standard format. Some data sought (e.g., parental history of hip fracture) was available in some, but not all, studies.

Fracture outcomes

The study focused on creating a standardized definition for fracture outcomes. If possible given the data, we excluded fractures due to major trauma (i.e., trauma sufficient to case a fracture in a young, normal individual). For some of the studies, only the predefined categories for that study were available so that some

of these subcategories could not be defined. The time to first non-vertebral fracture of each type was calculated. For vertebral fractures, we used the individual study definitions based on a comparison of a baseline with one or more follow-up lateral spine radiographs. Definitions of an incident vertebral fracture varied somewhat across studies. These definitions are either based on quantitative morphometry (QM), semi-quantitative assessment (SQ)[18] or a combination of these criteria. For studies that assessed morphometric vertebral fracture on more than one occasion, we used the fracture data from the final study evaluation. Based upon the available study data, we then used the fracture outcomes in each trial to define the relative hazard (RH) for non-vertebral and hip fracture in treatment vs. placebo and the odds ratio (OR) for incident morphometric vertebral fracture. Note that in some cases, for various reasons the RH or OR varies slightly from the original published results.

Assays for bone turnover markers

The assays made on blood samples (bone ALP, PINP, and sCTX) all used serum, not plasma. Different assays were used to measure the bone formation markers (bone ALP and PINP) and the bone resorption markers (NTX/Cr, sCTX) as described in Table 2. The assays for bone ALP included an immunoradiometric assay (Ostase, Hybritech, La Jolla, CA), a wheat-germ lectin precipitation assay[19], an autoanalyser method (Beckman-Coulter Inc, San Diego, CA) and the Alkphase B ELISA assay (Metra Biosystems Inc, Mountain View, CA). The assay for PINP included a radioimmunoassay (Orion Diagnostica, Espoo, Finland) and an automated immunoassay analyser method (Roche Elecsys 2010, Penzburg, Germany). The assays for urine NTX included an ELISA (Osteomark, Ostex International Inc, Seattle WA) and an automated immunoassay analyser method (Vitros ECi, Ortho Clinical Inc, Rochester, NY). The urine collections were generally made as second morning voids and the NTX result was expressed as a ratio to the creatinine concentration (NTX/Cr). The assays for sCTX included an ELISA (CrossLaps, Nordic Bioscience Diagnostics AS, Herlev, Denmark) and an automated immunoassay analyser (Roche Elecsys 2010, Penzburg, Germany). Other bone turnover measurements were made in a few of the trials, but are not included here, and these included osteocalcin, urinary sCTX and deoxypyridinoline. We chose not to include these markers as they did not include the two markers recommended by the International Osteoporosis Foundation and International Federation of Clinical Chemistry[3] or else they had fewer studies in which they were measured.

Data analysis

Our overall goal of this analysis is to assess the relationship, across studies, between short-term net change in bone turnover marker and longer-term fracture reduction. For most studies, we analyzed the change in

marker from baseline to 3 months. For 4 studies for which 3 month BTM values were not available, we used 12 month values (Table 2). For the HORIZON PFT study of Zoledronic acid where BTM's change over time after infusion, we used the 6 month BTM value. For each BTM we calculated the median percent change from baseline to the follow-up value (as the data were not normally distributed). For studies reporting multiple doses, the active treatment groups were combined regardless of dose. We used Cox and logistic models to estimate the effect of assignment to active treatment on clinical and vertebral fractures, respectively. Both the BTMs and fractures were analysed by ITT, ignoring adherence to treatment.

We then plotted the log hazard or odds ratio for the 3 primary types of fractures (vertebral, non-vertebral, hip) against the net median % change in BTM (treatment minus the placebo group). Each study was plotted as a circle with the size proportional to the inverse of the variance of the log of the hazard or odds-ratio. Thus, larger circles represent studies with more fractures.

Next, we used a linear model to estimate the effect of the median % change in the BTM on the log hazard or odds ratio for each study, again weighted by the inverse of the variance of each outcome. Finally, we added a line interpolating the exponentiated fitted values to the plot described above. From these regressions we also calculated the r^2 with 95% confidence intervals, and for those with statistically significant relationships, estimated the calculated net change in BTM and associated fracture risk reductions defined by the smallest and largest net effects on change in each BTM.

Results

Characteristics of included trials

Patient level data was successfully collected for 14 randomized trials, including 11 bisphosphonate (5 alendronate, 3 risedronate, 2 ibandronate and 1 zoledronic acid) and 3 SERM studies (raloxifene, arzoxifene and lasofoxifene, 1 each) (Table 1). Parenteral study medication or placebo was given every 3-12 months in 2 BP trials. Trial size ranged from 240 to over 9300 participants and trial duration ranges from 1 to 4 years of follow-up. Most of the trials enrolled postmenopausal women (13) and 1 trial only enrolled men.

Treatment-related changes in BTMs

After pooling individual trials we had paired measurements for bone ALP and PINP in 16,087 and 10,335 subjects, respectively. We had measurements for urinary NTX/Cr and serum sCTX in 6,722 and 8,006, respectively (Table 3). Studies varied as to which subset of participants had BTM assessments and which

BTM's were measured, and therefore the various BTM and fracture analyses reported here are not necessarily among the same studies or the same study participants.

BTM percent changes in the active treatment groups were larger for some markers than others; for example, the maximum reduction in bone ALP was 39% but for sCTX it was 69% (Table 2). Reductions in BTMs were also observed in the placebo-treated participants.

In general, the greater the net reduction in BTMs the greater the reduction in the risk of fractures, and this was more striking for bone formation (Figure 1) than bone resorption markers (Figure 2).

Extrapolating from observed effects on change in BTM and vertebral fracture risk reduction (Figure 3), we found that a 12% net reduction in bone ALP would predict a 33% reduction in vertebral fracture risk, while a 30% net reduction in bone ALP would predict a 65% reduction in fracture risk. Similarly, a 22% net reduction in PINP would predict a 30% reduction in vertebral fracture risk, while a 50% net reduction in bone ALP would predict a 62% reduction in fracture risk.

Meta-regression results

The overall meta-regression results, quantified by variance explained (r^2) with 95% confidence intervals and statistical significance are shown in Table 4. The point estimates for r^2 were higher for bone ALP and PINP but the confidence intervals are wide. The associations for non-vertebral and hip fracture were not statistically significant, again with wide confidence intervals, but for vertebral fracture both bone formation markers were associated significantly.

We further tested whether the higher r^2values seen with bone formation markers was due to older vs. more recent trials by taking the 5 contemporary trials that included both PINP and sCTX. In a meta-regression limited to those 5 contemporary trials, the R-squared values for vertebral, non-vertebral and hip fracture for PINP were 0.74 ($p=0.06$), 0.44 and 0.54 (both $p>0.15$), respectively, whereas the values for sCTX were 0.62, 0.47 and 0.20, respectively (all $p>0.05$).

Sensitivity analyses

We performed several sensitivity analyses to test the robustness of our results. Analyses limited to a single Bone ALP assay (Ostase Tandem IRMA) and a single NTX/Cr assay (Ostemark ELISA) gave similar results to

those that pooled several different assays (Table 4). Similarly, analyses limited to just bisphosphonates generated results similar to analyses conducted for all AR trials (data not shown).

Discussion

In this pooled meta-regression of individual level data collected from 14 AR trials, greater short-term treatment-related reductions in two formation BTMs, bone ALP and PINP, were associated with greater reductions in vertebral fracture during follow-up. We found no significant relationship between short term changes in NTX/Cr or sCTX and any fracture outcome. None of the BTMs were significantly associated with non-vertebral or hip fracture risk.

Bone ALP was available on the largest number of trial participants. The robust relationship between changes in bone ALP and incident vertebral fractures might be useful for future AR drug development or assessment of novel dosing regiments for existing ARs. For example, as shown in Figure 3 if a hypothetical new AR reduced bone ALP by 30% it would be expected to reduce vertebral fractures by 65%, while a new AR that only reduced bone ALP by 12% would be expected to reduce vertebral fractures by 33%.

It was notable that bone formation markers appeared to be at least as good as bone resorption, according to the magnitude of the r^2 value (Table 4). Of course, the anti-resorptives work by the inhibition of bone resorption, but bone formation subsequently decreases due to the phenomenon of coupling. The reasons why there are stronger relationships with the bone formation markers is that these tend to be less variable and less affected by meal times and circadian rhythm than bone resorption markers[3]. However, the bone formation markers were measured in more subjects than the bone resorption markers which may also be partially responsible for the stronger relationship for formation markers. Similarly, compared to vertebral fracture outcomes, changes in bone turnover markers were less strongly associated with both non-spine and hip fractures, perhaps making a significant correlation more difficult to observe as a result of the generally lower risk reductions for these outcomes.

It should be noted that these findings only relate to anti-resorptive treatments. Anabolic treatments such as teriparatide increase bone formation markers (and sometimes bone resorption markers) and so observed relationship are likely to be different. Unlike anti-resorptive and anabolic therapies, formation sparing resorption inhibitors[20] such as odanacatib result in a long-term decrease in bone resorption but not bone formation, and yet odanacatib treatment reduces the risk of both vertebral and non-vertebral fractures[21].

We recognise that our study has several additional limitations. Not all subjects had bone turnover markers measured and a different set of studies had data for each BTM. Not all trials included all bone turnover markers and studies with men were available. The assays for the bone turnover markers differed; we were unable to find any study that compared two assays for the same marker for the treatments we have reported here. Also the timing of sampling during the trials differed, varying from 3 to 12 months on treatment. The sample for sCTX was not always obtained in the fasting state; this is important as CTX has a circadian rhythm with the lowest values in the afternoon. Lastly, there were too few denosumab BTM and fracture data to include in our analyses.

The findings from this study-level meta-regression are broadly consistent with observations made in individual anti-resorptive trials of the relationship between short term change in BTM and fracture risk reduction in a single participant. These studies have included trials of selective estrogen receptor modulators (SERMs)[4,5,6] and bisphosphonates administered orally[7,8] or intravenously[9,10]. To better determine the clinical utility of serial BTM measurements for a specific patient, we are currently using this large dataset to conduct analyses that examine pooled individual level BTM data and fracture outcomes. These analyses utilize analytic approaches, such as the proportion of treatment effect explained (or PTE), that better reflect the relationship between short term treatment-related BTM changes and subsequent fractures in individuals. In addition, it will be interesting to determine through future analyses if these relationships are strengthened or differ for drugs with different mechanisms of action from that of the anti-resorptives.

In summary, in this pooled meta-regression of multiple anti-resorptive trials we found that greater short term reductions in two bone formation markers were strongly associated with subsequent vertebral fracture outcomes. We believe that our meta-regression results may be helpful in the future development of anti-resorptive drugs for osteoporosis, particularly in choosing the dose and treatment schedule. They may allow prediction of the fracture risk reduction from small, short term randomised clinical trials and this might encourage the development of additional effective drugs for fracture prevention.

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Table 1. Characteristics of Placebo-Controlled Fracture Endpoint Trials Included in Meta-Regression.

Study Name (Year of trial report)	Study Drug	N Total	Age (mean)/ gender (% women)	Mean Follow-up (months)	Baseline Femoral Neck T-score (mean)	Prevalent Vertebral Fracture at Baseline (%)	Fracture Outcomes (N) Vertebral/ Non-Vertebral/Hip
ALN PHASE 3 (1995 [22])	Alendronate	994	63.5/100	32.5	-2.15	23.4	--/68/4
FIT VERTEBRAL FRACTURE (1996 [23])	Alendronate	2027	70.3/100	35.0	-2.44	100	223/245/33
FIT CLINICAL FRACTURE (1998 [24])	Alendronate	4432	67.1/100	51.2	-2.21	0	121/494/41
FOSIT (1999 [25])	Alendronate	1908	62.7/100	11.4	-1.97	--	--/52/4
MEN'S STUDY (2000 [26])	Alendronate	241	62.7/0	22.4	-2.15	50.2	11/--/--
BONE (2004 [13])	Ibandronate (oral)	2929	68.7/100	29.9	-2.10	93.6	167/229/21
IBAN IV (2004 [27])	Ibandronate (i.v.)	2860	67.0/100	34.0	-2.14	98.4	274/243/26
HIP (2001[28])	Risedronate	9331	78.0/100	24.9	-2.75	31.0	497/913/205
VERT-NORTH AMERICA (1999 [29])	Risedronate	1628	68.4/100	27.8	-2.21	78.1	180/157/15
VERT-MULTI-NATIONAL (2000 [30])	Risedronate	814	70.8/100	28.7	-2.40	94.1	166/100/17

HORIZON 2301 (2007 [12])	Zoledronic acid (i.v.)	7736	73.1/100	33.9	-2.71	63.2	535/679/140
MORE (1999 [31])	Raloxifene*	7705	66.0/100	31.8	-2.30	37.3	503/677/58
GENERATIONS (2010 [16])	Arzoxifene*	9354	67.4/100	49.3	-1.87	15.2	294/687/46
PEARL (2010 [15])	Lasofoxifene*	8556	67.4/100	54.9	-2.19	28.2	607/760/90

*Selective Estrogen Receptor Modulator (SERM)
Dashes indicate that no data was available.

Table 2. Median BTM Baseline (BL) and % Change in Fracture Endpoint Trials. The references relate to the description of the BTM assays and the numbers in parentheses describe the assay method (see footnote).

Study Name (Year BTM assay reported)	Study Drug	BTM timing, months	Bone ALP			PINP			NTX/Cr			sCTX		
			BL, ng/mL or IU/L	% Change		BL, ng/mL	% Change		BL, nmol/mmol Cr	% Change		BL, ng/mL	% Change	
				Active	PBO		Active	PBO		Active	PBO		Active	PBO
ALN PHASE 3 (2000 [32])	Alendronate	3	17.0 (1)	-38.7	-12.1	--	--	--	66.0 (7)	-66.3	-24.3	--	--	--
FIT VERTEBRAL FRACTURE (2004 [7], 2004 [33])	Alendronate	12	13.2 (1)	-37.3	-13.6	47.6 (5)	-62.0	-15.6	56.9 (7)	-64.0	-29.1	0.29 (9)	-69.7	-40.9
FIT CLINICAL FRACTURE (2004 [7], 2004 [33])	Alendronate	12	12.9 (1)	-35.4	-10.6	49.1 (5)	-63.1	-16.3	58.0 (7)	-61.5	-26.8	0.31 (9)	-71.1	-40.9
FOSIT (1999 [25])	Alendronate	3	12.3 (1)	-38.9	-9.7	--	--	--	54.8 (7)	-69.0	-18.1	--	--	--
MEN'S STUDY (2000 [26])	Alendronate	3	12.1 (1)	-26.8	-4.1	--	--	--	33.0 (7)	-49.0	-2.9	--	--	--
BONE (2004 [13])	Ibandronate (oral)	3	40.0 (2)	-25.7	-7.7	--	--	--	57.0 (7)	-46.7	-22.7	--	--	--
IBAN IV	Ibandronate (i.v.)	3	51.0 (2)	-25.5	-14.3	--	--	--	68.0 (7)	-35.7	-30.2	--	--	--

(2004 [27]), CSR (b)														
HIP	Risedronate	3	11.9 (1)	-21.7	-9.8	47.9 (5)	-41.3	-16.0	56.9 (8)	-50.9	-21.9	--	--	--
VERT-NORTH AMERICA (1999 [29], 2003 [8])	Risedronate	3	13.3 (1)	-28.5	-13.6	--	--	--	63.6 (8)	-50.8	-22.0	--	--	--
VERT-MULTI-NATIONAL (2000 [30], 2003 [8])	Risedronate	3	12.4 (1)	-22.4	-2.5	--	--	--	75.6 (8)	-48.1	-19.6	--	--	--
HORIZON 2301 (2009 [9])	Zoledronic acid (i.v.)	6/12 (a)	13.2 (3)	-36.8	-6.6	49.4 (6)	-61.6	-11.6	--	--	--	0.37 (6)	-73.9	-13.4
MORE (2006 [5])	Raloxifene*	6/12 (a)	15.8 (1)	-28.6	-15.5	50.3 (5)	-40.8	-11.0	--	--	--	--	--	--
GENERATIONS (2010 [16])	Arzoxifene*	3	--	--	--	48.9 (5)	-30.2	-8.0	--	--	--	0.57 (9)	-38.8	-1.5
PEARL (2012[34])	Lasofoxifene*	3	22.6 (4)	-19.4	-8.4	48.7 (6)	-34.9	-9.3	--	--	--	0.42 (6)	-45.2	-4.9

*Selective Estrogen Receptor Modulator (SERM)

Assays:
Bone ALP, (1) Ostase Tandem IRMA (ng/mL), (2) Wheat germ lectin precipitation (IU/L), (3) Beckman autoanalyser (ng/mL), (4) Alkphase B ELISA (IU/L).
PINP, (5) RIA (Orion) (ng/mL), (6) automated immunoassay analyser (Roche Elecsys) (ng/mL)
NTX/Cr, (7) Osteomark ELISA (nmol BCE/mmol creatinine), (8) Ortho Clinical ECI automated immunoassay (nmol BCE/mmol creatinine)
sCTX, (9) CrossLaps ELISA (Nordic Bioscience), (6) automated immunoassay analyser (Roche Elecsys) (ng/mL)

a, all assays done at 6 months except PINP which was done at 12 months
b, CSR, case study report.

Table 3. Short-Term Changes in BTMs and Fracture Outcomes.

Study Name	Study Drug	Treatment-Placebo % Change Median Difference (N with BTM)				Treatment vs Placebo RR		
		Bone ALP	PINP	NTX/Cr	sCTX	Vertebral	Non-Vertebral	Hip
ALN PHASE 3	Alendronate	-26.6 (874)	--	-42.0 (859)	--	--	0.70	0.22
FIT VERTEBRAL FRACTURE	Alendronate	-23.6 (1664)	-46.4 (1519)	-34.8 (270)	-28.7 (1657)	0.49	0.78	0.49
FIT CLINICAL FRACTURE	Alendronate	-24.8 (3859)	-46.8 (3453)	-34.8 (587)	-30.2 (3845)	0.55	0.90	0.78
FOSIT	Alendronate	-29.2 (1747)	--	-50.9 (1735)	--	--	0.46	1.04
MEN'S STUDY	Alendronate	-22.8 (237)	--	-46.1 (235)	--	0.36	--	--
BONE	Ibandronate (oral)	-18.0 (627)	--	-23.9 (601)	--	0.52	1.09	2.08
IBAN IV	Ibandronate (i.v.)	-11.2 (584)	--	-5.5 (574)	--	0.82	0.95	0.50
HIP	Risedronate	-11.8 (1437)	-25.3 (1255)	-29.0 (1194)	--	0.74	0.99	0.76
VERT-NORTH AMERICA	Risedronate	-14.9 (460)	--	-28.8 (320)	--	0.69	0.72	1.45
VERT-MULTI-NATIONAL	Risedronate	-19.9 (399)	--	-28.5 (347)	--	0.54	0.87	0.88
HORIZON 2301	Zoledronic acid (i.v.)	-30.2 (582)	-50.0 (1132)	--	-60.5 (484)	0.32	0.75	0.59
MORE	Raloxifene*	-13.0 (2553)	-29.8 (956)	--	--	0.57	0.91	1.08
GENERATIONS	Arzoxifene*	--	-22.2 (952)	--	-37.3 (952)	0.59	0.95	0.77
PEARL	Lasofoxifene*	-11.0 (1064)	-25.6 (1068)	--	-40.3 (1068)	0.64	0.84	0.78

*Selective Estrogen Receptor Modulator (SERM)

Table 4. Meta-regression Summary for Short-term Changes in BTM and Fracture Risk Reduction

	Vertebral			Non-Vertebral			Hip		
	number of studies (N fracture)	**r^2 (95% CI)**	**p value**	**number of studies (N fracture)**	**r^2 (95% CI)**	**p value**	**number of studies (N fracture)**	**r^2 (95% CI)**	**p value**
Bone ALP	11 (3284)	0.82 (0.50, 0.88)	<0.001	12 (4615)	0.33 (0.00, 0.57)	0.053	12 (653)	0.17 (0.00, 0.47)	0.24
PINP	7 (2780)	0.75 (0.17, 0.85)	0.011	7 (4454)	0.53 (0.00, 0.73)	0.065	7 (612)	0.43 (0.00, 0.67)	0.11
NTX/Cr	8 (1639)	0.38 (0.00, 0.64)	0.10	9 (2500)	0.25 (0.00, 0.54)	0.17	9 (366)	0.03 (0.00, 0.34)	0.73
sCTX	5 (1780)	0.62 (0.00, 0.78)	0.11	5 (2865)	0.47 (0.00, 0.71)	0.20	5 (350)	0.20 (0.00, 0.56)	0.45

For Bone ALP Ostase Tandem IRMA Assay and NTX/Cr with Osteomark ELISA Assay:

	Vertebral			Non-Vertebral			Hip		
	number of studies (N fracture)	**r^2 (95% CI)**	**p value**	**number of studies (N fracture)**	**r^2 (95% CI)**	**p value**	**number of studies (N fracture)**	**r^2 (95% CI)**	**p value**
Bone ALP	7 (1701)	0.52 (0.00, 0.72)	0.066	8 (2704)	0.33 (0.00, 0.61)	0.13	8 (376)	0.10 (0.00, 0.47)	0.53
NTX/Cr	6 (1293)	0.41 (0.00, 0.67)	0.17	7 (2244)	0.31 (0.00, 0.60)	0.20	7 (334)	0.03 (0.00, 0.38)	0.78

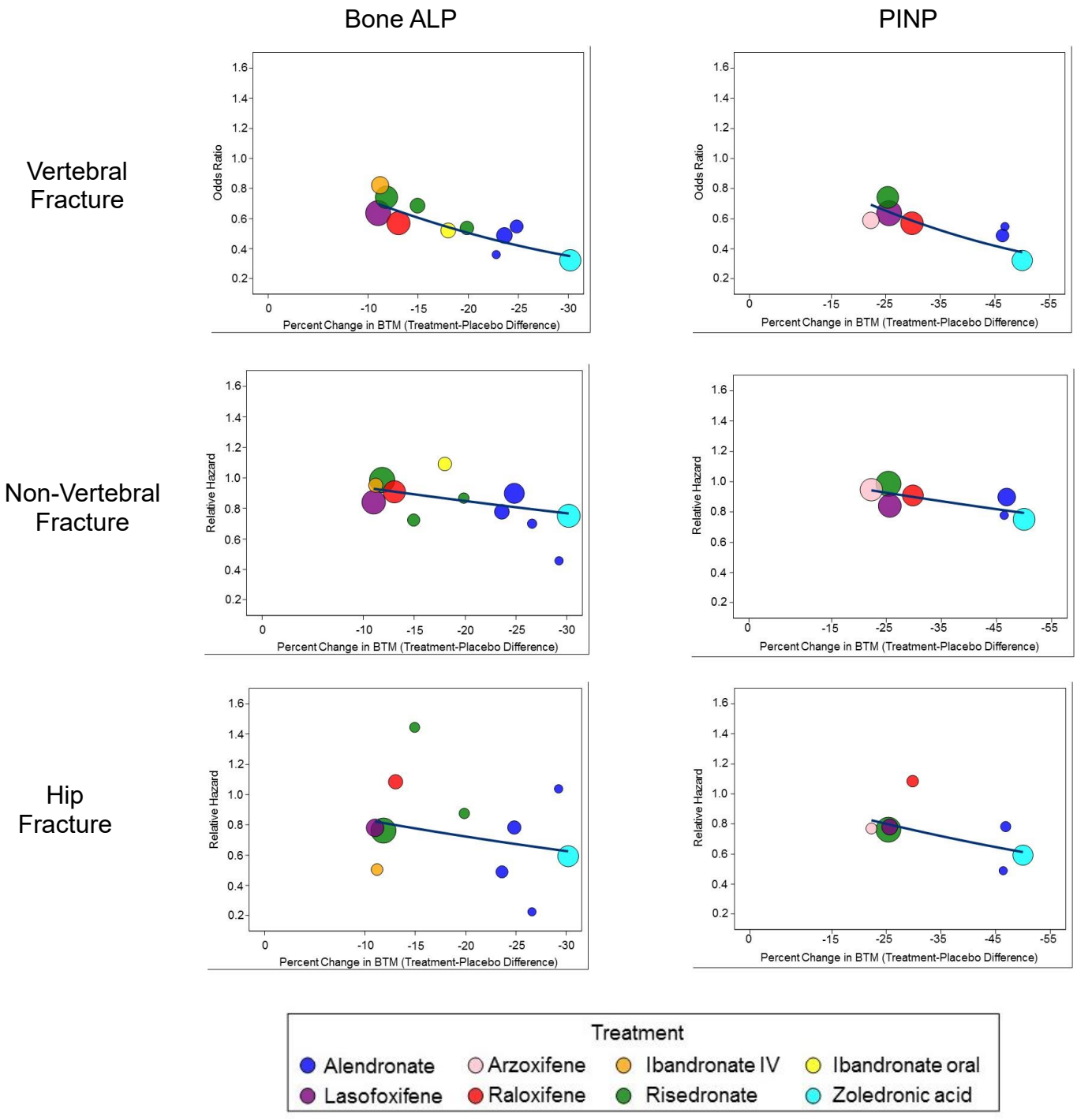


Figure 1. The relationship between the odds ratio (for vertebral fracture) or the relative hazard (for non-vertebral and hip fracture) and the difference between treatment and placebo group in percentage change in BTM for the two bone formation markers. Larger circles indicate studies with more fractures, and the line represents log relative risk plotted against percent change.

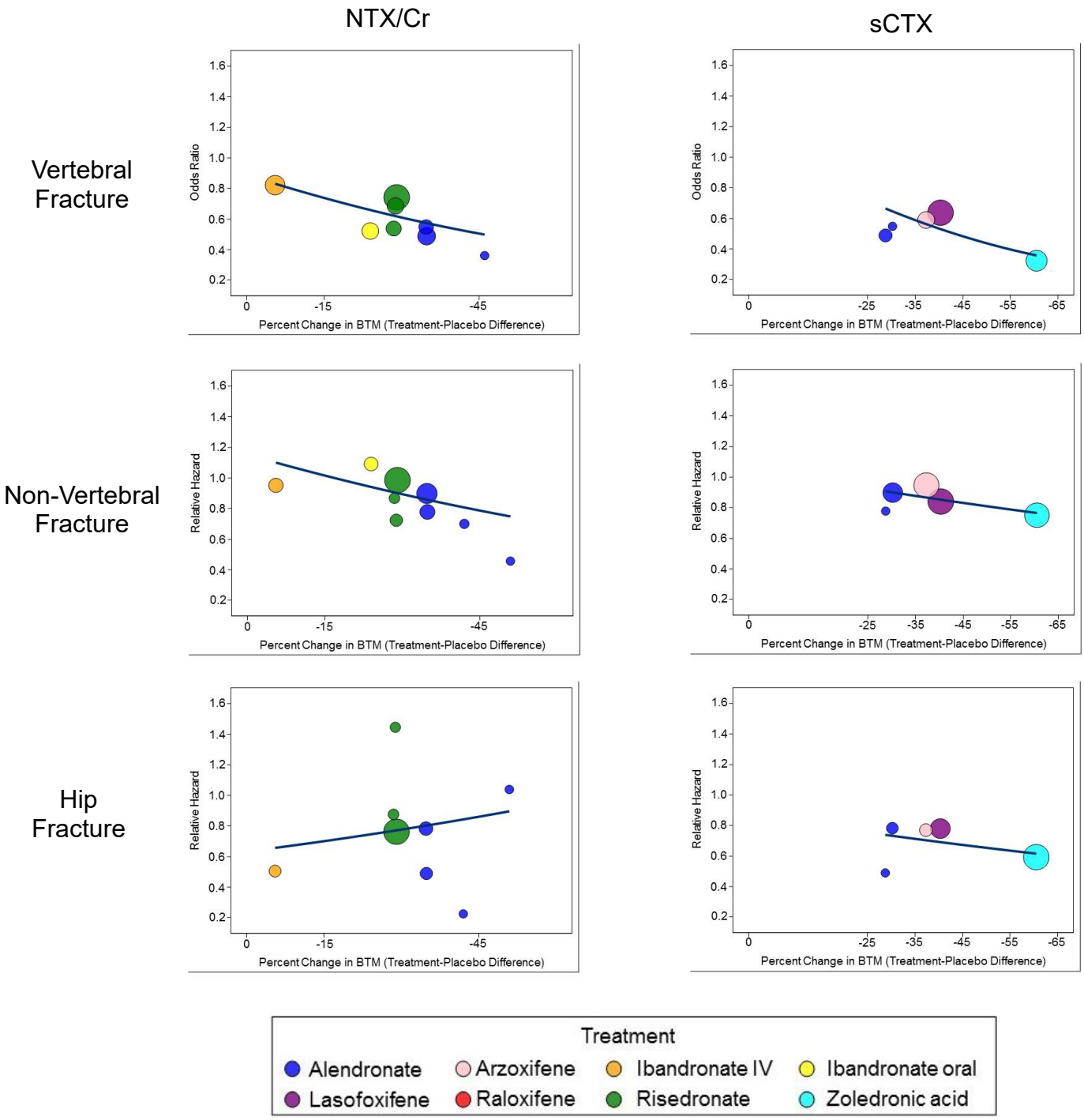
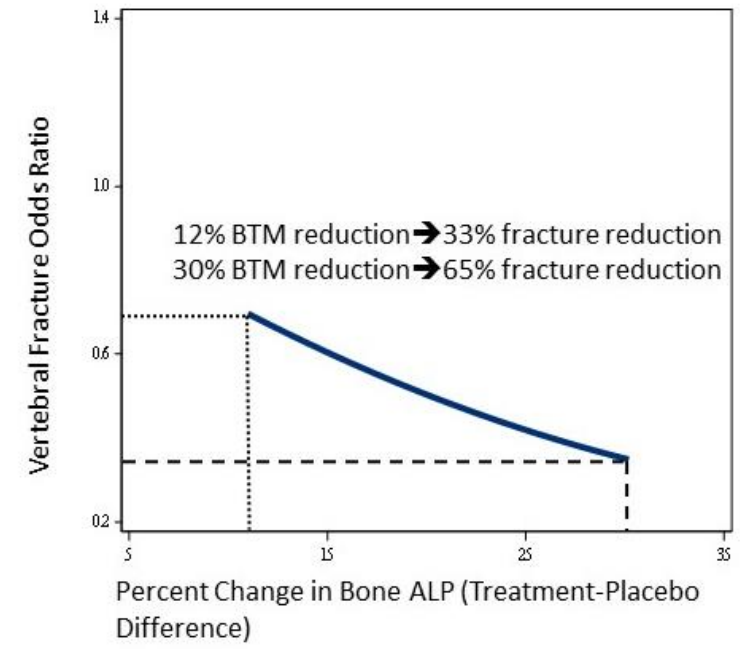


Figure 2. The relationship between the odds ratio (for vertebral fracture) or the relative hazard (for non-vertebral and hip fracture) and the difference between treatment and placebo group in percentage change in BTM for the two bone resorption markers. Larger circles indicate studies with more fractures, and the line represents log relative risk plotted against percent change.



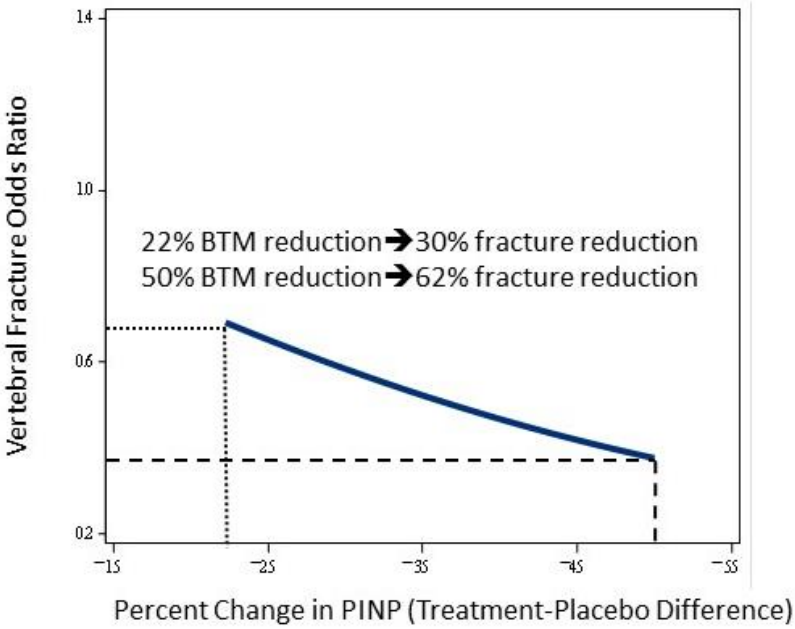


Figure 3. Estimated vertebral fracture risk reduction associated with small and large short-term changes in formation BTMs (data derived from Figure 1)