Article:

Treatment-Related Changes in Bone Turnover and Fracture Risk Reduction in Clinical Trials of Antiresorptive Drugs: Proportion of Treatment Effect Explained

Richard Eastell,[1] Dennis M Black,[2] Li-Yung Lui,[3] Arkadi Chines,[4] Fernando Marin,[5] Sundeep Khosla,[6] Anne E de Papp,[7] Jane A Cauley,[8] Bruce Mitlak,[9] Charles E McCulloch,[2] Eric Vittinghoff,[2] and Douglas C Bauer,,[2,10] for the Foundation for the National Institutes of Health (FNIH) Bone Quality Project

[1]Academic Unit of Bone Metabolism, University of Sheffield, Sheffield, UK
[2]Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA, USA
[3]California Pacific Medical Center, San Francisco, CA, USA
[4]Amgen Inc., Thousand Oaks, CA, USA
[5]Eli Lilly and Company, Lilly Research Centre, Windlesham, UK
[6]Mayo Clinic College of Medicine, Rochester, MN, USA
[7]Merck & Co., Inc., Kenilworth, NJ,, USA
[8]Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA
[9]Radius Health, Waltham, MA, USA
[10]Department of Medicine, University of California, San Francisco, San Francisco, CA, USA

ABSTRACT

Few analyses of antiresorptive (AR) treatment trials relate short-term changes in bone turnover markers (BTMs) to subsequent fracture reduction seeking to estimate the proportion of treatment effect explained (PTE) by BTMs. Pooling such information would be useful to assess new ARs or novel dosing regimens. In the Foundation for the National Institutes of Health (FNIH) Bone Quality project, we analyzed individual-level data from up to 62,000 participants enrolled in 12 bisphosphonate (BP) and four selective estrogen receptor modulator (SERM) placebo-controlled fracture endpoint trials. Using BTM results for two bone formation markers (bone-specific alkaline phosphatase [bone ALP] and pro-collagen I N-propeptide [PINP]) and one bone resorption marker (C-terminal telopeptide of type I collagen [CTX]) and incident fracture outcome data, we estimated the PTE using two different models. Separate analyses were performed for incident morphometric vertebral, nonvertebral, and hip fractures over 1 to 5 years of follow-up. For vertebral fracture, the results showed that changes in all three BTMs at 6 months explained a large proportion of the treatment effect of ARs (57 to >100%), but not for and non-vertebral or hip fracture. We conclude that short-term AR treatment-related changes in bone ALP, PINP, and CTX account for a large proportion of the treatment effect for vertebral fracture. Change in BTMs is a useful surrogate marker to study the anti-fracture efficacy of new AR compounds or novel dosing regiments with approved AR drugs. © 2020 The Authors. *Journal of Bone and Mineral Research* published by American Society for Bone and Mineral Research.

KEY WORDS: BIOCHEMICAL MARKERS OF BONE TURNOVER; BONE MODELING AND REMODELING; DISEASES AND DISORDERS OF/RELATED TO BONE; EPIDEMIOLOGY; OSTEOPOROSIS

Introduction

Bone turnover markers (BTMs) decrease in response to antiresorptive (AR) treatments, and the greater the decrease the greater the apparent reduction in fracture risk, especially vertebral fracture.[1] Guidelines published by International Osteoporosis Foundation (IOF) expert working groups proposed that BTM might be useful in clinical practice as an indication of failure to respond[2] to oral bisphosphonates, especially as a result of poor adherence.[3] These guidelines propose that a decrease beyond the BTM-specific least significant change (LSC), which corresponds to 25% to 30% reductions for serum C-terminal telopeptide of type I collagen (sCTX) and pro-collagen I N-propeptide (PINP), is desirable.

In treatment trials for osteoporosis medications, BTMs are potential surrogate markers for fracture risk reduction. The Food and Drug Administration (FDA) specifies two types of studies in order to evaluate a surrogate marker for qualification.[4] The first approach is a study-level meta-regression analysis, and we have completed such an analysis for BTMs.[1] The other approach, utilized in this analysis, is an individual-level analysis estimating the proportion of treatment effect explained (PTE) by BTMs.

PTEs have been reported in single randomized controlled trials of antiresorptive drugs including risedronate,[5,6] zoledronic acid,[7] raloxifene,[8] and bazedoxifene.[9] These studies were mostly concerned with vertebral fractures, and the point estimates for PTE ranged from 14% to 67%; the one study of nonvertebral fractures reported a PTE of 54% to 77%.[5] There have been no studies of hip fracture. Several BTMs have been evaluated, including those that reflect bone resorption (urine and serum C-telopeptide [CTX] and urine N-telopeptide of collagen [NTX]) and bone formation (bone alkaline phosphatase [ALP], procollagen I N-propeptide [PINP], and osteocalcin [OC]).

The methods used for calculating PTE have differed by study with some using an approach based on the comparison of treatment effects before and after adjustment for the surrogate,[10] and others using an approach combining treatment effects on the surrogate and fracture, as well as the surrogate on fracture.[11] These different approaches may have resulted in different estimates for PTE.

The aim of the present study was to systematically collect individual-level data from existing placebo-controlled trials of AR agents and to estimate PTE for three fracture types (vertebral, nonvertebral, hip) using three BTMs (CTX, PINP, bone ALP). We planned to calculate PTE using both previously described methods (Freedman and colleagues[10] and Li and colleagues[11]). We estimated the BTM level month by month.[12] We also aimed to describe the relationship between change in BTM and fracture risk on treatment or placebo from this individual patient level study to relate the prior estimates of LSC and the mean reduction in fracture risk with antiresorptive drugs.

We faced a challenge in that generally BTMs were only measured on a subset of patients in clinical trials. We addressed this by using the total alkaline phosphatase level to impute missing values. We report the PTE results with and without imputation. We included pure antiresorptive agents (hence, we excluded odanacatib) and did not have access to BTM data on denosumab.

Materials and Methods

This analysis was part of the Foundation of the National Institutes of Health Bone Quality project, which is a public-private partnership with the aim of studying fracture surrogates, including bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA) and quantitative computed tomography (QCT) as well as BTMs. We searched through published literature for placebo-controlled trials of AR medication as we described previously.[1]

The list of studies includes most osteoporosis medication trials (Table 1).[13–28] We used a standard data template. We took a standard approach to the definition of fractures. The assays for serum CTX, PINP, and bone ALP are described in Table 2. We did not include results from OC, urinary NTX, or urinary CTX because these are not used routinely in clinical practice now.

Baseline and follow-up total ALP was measured by autoanalyzer technique and the results were correlated with bone

ALP, PINP, and CTX with correlations between 0.55 to 0.77, allowing imputation for patients with missing BTM results (for all results, see Tables).

Statistical approach

The three-stage approach we used to estimating PTE is given in Supplemental Materials and Methods. The key points to note are: (i) we used all the BTM measurements available to fit a smoothed trajectory for each individual; (ii) when BTM measurements were not available, we imputed the results from the measured level of ALP; (iii) we then adjusted the effect of treatment on fracture risk for the estimated change in BTMs at 6 months and calculated PTE using the methods of Freedman and colleagues[10] or Li and colleagues.[11]

We show the results as graphical summaries showing fracture risk, evaluated at mean values of other covariates, plotted against the 1st to 99th percentile of expected percent change in BTMs in each group. The slope of each line reflects the effect of BTM change on fracture risk, and the vertical offset between lines for active and placebo reflects the direct effect of treatment not mediated by change in the BTMs.

Results

We included 13 AR trials (n = 53,974) that reported 3673 incident vertebral fracture and 15 AR trials (n = 62,064) that reported 5523 nonvertebral and 717 hip fractures (Table 1).

The baseline BTMs differed by study. For example, the range of baseline results for CTX was 0.24 to 0.54 ng/mL. The change in BTMs differed by drug. For example, mean percent decrease between groups in CTX ranging from 18% (raloxifene) to 41% (zoledronic acid) (Table 2).

Change in BTMs explains much of the reduction in vertebral fracture (Table 3). Using the Freedman method, the PTEs varied from 82% to 113% for vertebral fracture. None of the PTEs for nonvertebral or hip fracture were statistically significant. Using the Li method, the PTEs varied from 85% to 109% for vertebral fracture. None of the PTEs for hip fracture and only one of the PTE for nonvertebral fracture (bone ALP) were statistically significant.

We recognized that we might obtain different results if we just analyzed those subjects with BTMs measured directly and not subjects with all imputed data. Thus, we repeated the PTE estimates with just those patients with two or more measurements of BTMs and found high estimates for PTE (Table 3), but the confidence intervals (CI) were much wider than for the original results (Table 3) and several of the estimates exceeded 100%.

The different BTMs differed by the percent change in response to active compared with placebo. These mean differences were 17% reduction for bone ALP, 31% for PINP, and 32% for CTX. The associated reductions in vertebral fracture risk were about 41% (95% CI 37% to 45%).

Finally, we examined the relationship between 6-month change in BTMs and vertebral fracture, and this shows that the greater the reduction in BTMs, the lower the risk of fracture (Fig. 1). The slopes and intercepts of the fitted lines were similar for placebo and active treatment.

Table 1. Characteristics of Placebo (PBO)-Controlled Fracture Endpoint Trials

Study name (year conducted)	Study drug	N	Age (years, mean)/sex (% women)	Mean follow-up (months)	Baseline femoral neck T-score (mean)	Prevalent vertebral fracture at baseline (%)	Fracture outcomes vertebral/non-spine/hip (N)
ALN Phase 3[13] (1995)	Alendronate	994	63.5/100	32.5	−2.15	23.4	Active[a]: −/35/1 PBO: −/33/3
FIT Vertebral Fracture[14] (1996)	Alendronate	2027	70.3/100	35.0	−2.44	100	Active: 78/109/11 PBO: 145/136/22
FIT Clinical Fracture[15] (1998)	Alendronate	4432	67.1/100	51.2	−2.21	0	Active: 43/234/18 PBO: 78/260/23
FOSIT[16] (1999)	Alendronate	1908	62.7/100	11.4	−1.97	–	Active: −/16/2 PBO: −/36/2
Men's Study[17] (2000)	Alendronate	241	62.7/0	22.4	−2.15	50.2	Active: 4/−/− PBO: 7/−/−
Bone[18] (2004)	Ibandronate (oral)	2929	68.7/100	29.9	−2.10	93.6	Active[a]: 87/158/17 PBO: 80/71/4
IBAN IV[19] (2004)	Ibandronate (iv)	2860	67.0/100	34.0	−2.14	98.4	Active[a]: 172/159/13 PBO: 102/84/13
HIP[20] (2001)	Risedronate	9331	78.0/100	24.9	−2.75	31.0	Active[a]: 298/601/123 PBO: 199/312/82
VERT-North America[21] (1999)	Risedronate	1628	68.4/100	27.8	−2.21	78.1	Active: 77/68/9 PBO: 103/89/6
VERT-Multi-national[22] (2000)	Risedronate	814	70.8/100	28.7	−2.40	94.1	Active: 63/47/8 PBO: 103/53/9
HORIZON 2301[23] (2007)	Zoledronic acid (iv)	7736	73.1/100	33.9	−2.71	63.2	Active: 138/292/52 PBO: 397/387/88
HORIZON 2310[24] (2007)	Zoledronic acid (iv)	2127	74.5/76.1	23.6	−2.39	–	Active: −−/79/23 PBO: −−/107/33
Generations[25] (2010)	Arzoxifene[b]	9354	67.4/100	49.3	−1.87	15.2	Active: 110/334/20 PBO: 184/353/26
BZA Phase 3[26] (2008)	Bazedoxifene[b]	5643	66.4/100	28.7	−1.82	56.1	Active[a]: 79/165/13 PBO: 62/93/5
PEARL[27] (2010)	Lasofoxifene[b]	8556	67.4/100	54.9	−2.19	28.2	Active[a]: 345/479/55 PBO: 262/281/35
MORE[28] (1999)	Raloxifene[b]	7705	66.0/100	31.8	−2.30	37.3	Active[a]: 272/437/40 PBO: 231/240/18

[a]Active treatment group combines multiple dosages for study reporting more than one dose.
[b]SERM.
Dashes indicate that no data were available.

Discussion

For AR treatments, BTMs explain a large proportion of the vertebral fracture benefit. The point estimates for vertebral fracture were close to 100%, suggesting that potentially a large proportion of treatment-related fracture risk reduction can be explained by the decrease in BTMs in populations of women with osteoporosis. These estimates are higher than most prior analyses, and this may be attributable to the strength of our novel statistical methodology. BTMs can be variable over time, but this can be addressed by fitting smoothing models to the BTM changes. The PTEs we report are higher than reported for the percent treatment effect explained by LDL cholesterol for subsequent coronary heart disease events of 52%,[29] and yet this marker is commonly used for the registration study of cardiovascular drugs.[30]

The estimate of PTE varied by fracture type. For example, the PTE estimates were lower for nonvertebral and hip fracture and mostly were not statistically significant. For hip fracture, this may be related to number of fracture events as there were 5523 nonvertebral and 717 hip fractures, resulting in a ratio of 8:1. The 95% CI for all BTM are quite wide, and this may relate to the variability of BTM over time.

For vertebral fracture, the greater the reduction in BTM, the greater the reduction in the risk of fracture. This relationship appears to be linear and the line describing placebo similar intercept and slope to the line describing the AR drug, consistent with a PTE estimate close to 100%.

Table 2. Median Expected Total ALP and BTM Baseline (BL) and % Expected Change at 6 Months in Fracture Endpoint Trials

Study name	Study drug	Total ALP BL (IU/L)	% change Active	PBO	Bone ALP BL (ng/mL or IU/L)	% change Active	PBO	PINP BL (ng/mL)	% change Active	PBO	CTX BL (ng/mL)	% change Active	PBO
Overall			−12.1	−3.1		−21.4	−7.3		−39.1	−9.4		−48.0	−12.6
ALN Phase 3 (2000)	Alendronate	51.7	−10.7	0.8	15.1 (1)	−29.4	−5.2	38.4	−41.6	−8.7	0.24	−50.0	−23.7
FIT Vertebral Fracture (2004)	Alendronate	83.4	−9.2	−0.8	13.3 (1)	−22.1	−8.6	47.0 (5)	−39.7	−10.2	0.28 (7)	−48.0	−26.1
FIT Clinical Fracture (2004)	Alendronate	83.3	−9.7	−1.3	13.0 (1)	−21.3	−6.3	48.4 (5)	−40.3	−9.9	0.30 (7)	−48.9	−24.9
FOSIT (1999)	Alendronate	124.0	−19.3	−2.9	11.5 (1)	−40.6	−8.9	57.5	−42.8	−10.2	0.36	−51.4	−25.0
Men's Study (2000)	Alendronate	109.7	−7.8	−0.8	11.6 (1)	−19.8	−2.6	55.0	−39.7	−9.4	0.34	−48.6	−24.3
Bone (2004)	Ibandronate (oral)	71.2	−12.0	−5.8	37.7 (2)	−24.0	−6.5	44.6	−41.7	−11.7	0.28	−50.1	−26.2
IBAN IV (2004), CSR	Ibandronate (iv)	67.4	−3.4	0.0	45.6 (2)	−16.2	−5.3	43.6	−38.8	−9.1	0.27	−47.8	−24.0
HIP (2001)	Risedronate	86.0	−11.1	−4.7	11.8 (1)	−29.6	−10.1	45.7 (5)	−49.3	−15.3	0.29	−49.5	−25.6
VERT-North America (1999, 2003)	Risedronate	76.2	−11.6	−4.2	13.0 (1)	−34.0	−12.6	46.4	−41.4	−10.9	0.29	−49.9	−25.5
VERT-Multi-national (2000, 2003)	Risedronate	75.4	−12.7	−3.5	12.6 (1)	−34.4	−7.5	45.9	−41.8	−10.6	0.28	−50.2	−25.3
HORIZON 2301 (2009)	Zoledronic acid (iv)	76.5	−12.4	−3.4	13.1 (3)	−20.7	−2.3	48.7 (6)	−39.8	−5.6	0.30 (7)	−44.3	−3.1
HORIZON 2310	Zoledronic acid (iv)	104.6	−17.2	−11.8	15.2	−23.7	−8.5	51.6	−42.3	−13.6	0.32	−50.9	−27.9
Generations (2010)	Arzoxifene[a]	81.3	−17.5	−1.1	16.6	−21.3	−7.3	47.9 (5)	−40.1	−10.3	0.54 (7)	−48.7	−8.4
BZA Phase 3 (2008)	Bazedoxifene[a]	76.3	−11.1	−5.5	16.2	−19.3	−8.8	43.5	−24.3	−5.5	0.45 (7)	−50.4	−30.2
PEARL (2012)	Lasofoxifene[a]	90.5	−18.2	−4.6	20.4 (4)	−15.9	−2.1	40.7 (6)	−28.3	−2.7	0.32 (7)	−26.5	−3.2
MORE (2006)	Raloxifene[a]	73.2	−11.9	−2.7	14.8 (1)	−22.0	−10.5	50.9 (5)	−23.1	−6.4	0.38	−28.1	−10.4

BTM = bone turnover marker; PBO = placebo; CSR = case study report.

Italics indicate bone turnover markers were not measured in specific study but imputed.

The references relate to the description of the BTM assays and the numbers in parentheses describe the assay method: Bone ALP, (1) Ostase Tandem IRMA (ng/mL), (2) Wheat germ lectin precipitation (IU/L), (3) Beckman autoanalyzer (ng/mL), (4) Alkphase B ELISA (IU/L). PINP, (5) RIA (Orion) (ng/mL), (6) automated immunoassay analyzer (Roche Elecsys) (ng/mL). CTX, (7) CrossLaps ELISA (Nordic Bioscience).

[a]SERM.

Table 3. Odds Ratio/Hazard Ratio (95% CI) for Overall Treatment Effect on Fracture and Percent of Treatment Effect (95% CI) Explained by 6-Month Change in BTM, Using Freedman and Li Methods

	Bone ALP			PINP			sCTX		
		PTE			PTE			PTE	
	OR/HR	Freedman	Li	OR/HR	Freedman	Li	OR/HR	Freedman	Li
All participants									
Vertebral	0.58 (0.54, 0.62)	89% (48, 130%)	91% (58, 124%)	0.58 (0.54, 0.62)	82% (37, 127%)	85% (47, 123%)	0.59 (0.55, 0.64)	113% (70, 157%)	109% (81, 137%)
(n = 53,974)	$p < 0.0005$	$p < 0.0005$	$p < 0.0005$	$p < 0.0005$	$p < 0.0005$	$p < 0.0005$	$p < 0.0005$	$p < 0.0005$	$p < 0.0005$
Nonvertebral	0.88 (0.84, 0.93)	94% (−2, 191%)	95% (13, 178%)	0.88 (0.84, 0.93)	59% (−42, 161%)	62% (−35, 158%)	0.89 (0.84, 0.94)	57% (−34, 147%)	60% (−27, 148%)
(n = 62,064)	$p < 0.0005$	$p = 0.06$	$p = 0.024$	$p < 0.0005$	$p = 0.25$	$p = 0.21$	$p < 0.0005$	$p = 0.22$	$p = 0.18$
Hip (n = 62,064)	0.78 (0.67, 0.90)	−26% (−162, 109%)	−31% (−191, 129%)	0.78 (0.67, 0.90)	36% (−109, 182%)	38% (−111, 188%)	0.81 (0.70, 0.95)	−6% (−151, 138%)	−7% (−182, 167%)
	$p = 0.001$	$p = 0.70$	$p = 0.70$	$p = 0.001$	$p = 0.62$	$p = 0.62$	$p = 0.008$	$p = 0.93$	$p = 0.93$
Participants with BTM measurements									
Vertebral (n = 10, 476–13,561)	0.59 (0.52, 0.68)	108% (25, 191%)	106% (46, 167%)	0.55 (0.47, 0.64)	154% (70, 238%)	130% (92, 169%)	0.58 (0.49, 0.68)	139% (54, 223%)	124% (79, 170%)
	$p < 0.0005$	$p = 0.01$	$p = 0.001$	$p < 0.0005$	$p < 0.0005$	$p < 0.0005$	$p < 0.0005$	$p = 0.001$	$p < 0.0005$
Nonvertebral (n = 11,093–16,798)	0.87 (0.79, 0.96)	99% (−48, 246%)	99% (−14, 212%)	0.87 (0.78, 0.98)	103% (−95, 300%)	102% (−58, 262%)	0.85 (0.76, 0.95)	7% (−103, 116%)	8% (−122, 138%)
	$p = 0.006$	$p = 0.19$	$p = 0.09$	$p = 0.02$	$p = 0.31$	$p = 0.21$	$p = 0.006$	$p = 0.90$	$p = 0.91$
Hip (n = 11,093–16,797)	0.87 (0.63, 1.19)	−201% (−812, 411%)	−430% (−2416, 1555%)	0.70 (0.49, 1.00)	50% (−145, 245%)	57% (−150, 263%)	0.65 (0.44, 0.96)	−25% (−168, 118%)	−37% (−273, 200%)
	$p = 0.37$	$p = 0.52$	$p = 0.67$	$p = 0.05$	$p = 0.62$	$p = 0.59$	$p = 0.03$	$p = 0.73$	$p = 0.76$

CI = confidence interval; OR = odds ratio; HR = hazard ratio; PTE = proportion of treatment effect explained; BTM = bone turnover marker.
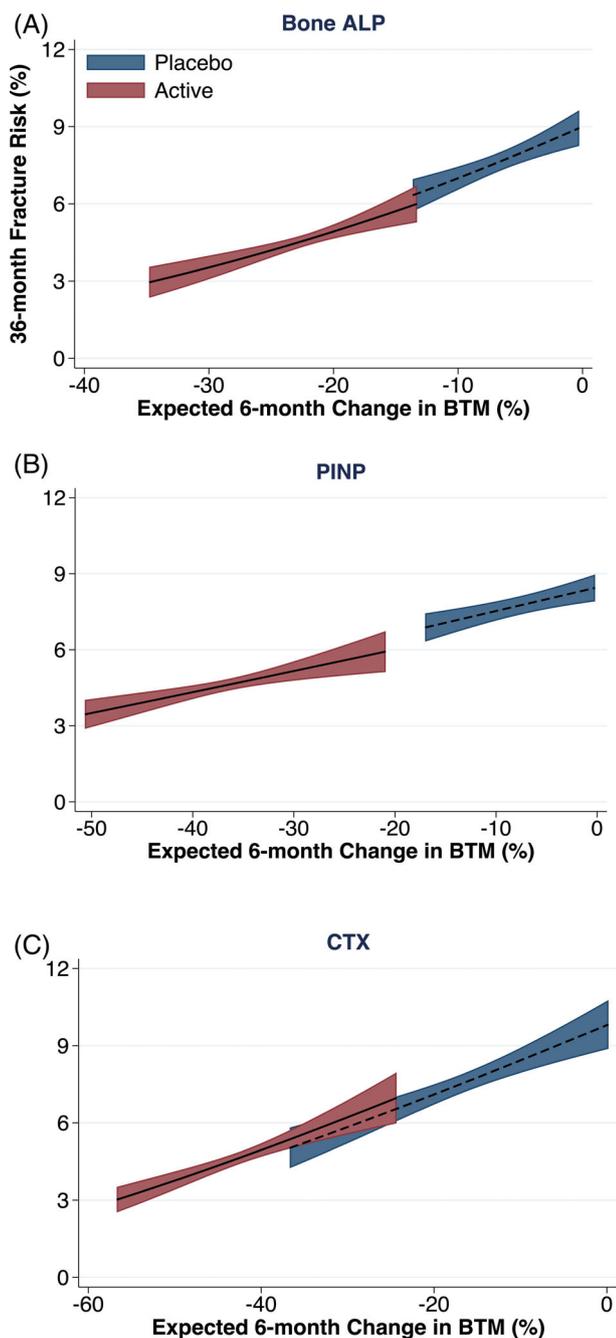
Fig 1. Relationship between reduction in bone turnover markers and vertebral fracture risk. (A) Bone ALP; (B) PINP; (C) CTX.

The main purpose of our analysis is to evaluate BTMs as potential surrogate markers for fracture for future trials and different analyses would be relevant to assessing how this information might be relevant to clinical practice. Nonetheless, our results might further inform the interpretation of BTM when used in clinical practice. First, it is important to know that the change in BTMs is strongly associated with the reduction in the risk of vertebral fracture. Second, a 25% to 30% decrease in CTX or PINP, corresponding to the least significant change, is a threshold sometimes used in clinical practice to define an adequate

response to antiresorptive.[2] We have shown that this value, for grouped studies, is associated with about a 40% reduction in vertebral fracture. This additional information provides insight into the magnitude of vertebral fracture risk reduction associated with this level of change in BTM. Also, this relationship between fracture risk reduction and change in BTM was similar to our published study-level meta-regression. Treatment that reduces PINP by 30% would be expected to reduce vertebral fracture by 42% according to meta-regression analysis[1] and 41% in this individual-level analysis.

The PTE values we report here are high and they are of similar magnitude or greater than PTE estimates based on analyses of change in BMD and AR treatments, which vary from 4% to 72%.[7,9,12,31–35] The 95% CI associated with these PTE estimates are wide and in some cases very wide, extending below 0 and above 100%. Using similar methods as reported here, we are currently conducting a PTE in this database that incorporates both change in BTM and change in DXA BMD. It will be interesting to see how the results compare with the results for BTMs alone and whether the combination of BMD and BTM is even better.

Why is there a stronger relationship between change in BTM and reduction in vertebral fracture risk with AR compared with effects on nonvertebral and hip fracture? The vertebra is rich in cancellous bone and the impact of AR is to increase BMD and to prevent the development of stress risers and plate perforation.[36] At a clinical level, it has been observed that a large increase in bone remodeling is often associated with an increase in vertebral fracture risk (but not always other fractures). Such large increases in remodeling can occur during the third trimester of pregnancy[37] and after stopping denosumab therapy.[38]

Our study has several strengths. It is the first study to combine randomized controlled trials to calculate PTE with improved precision. We have not found such combined studies in any other disease area. We have used individual-level data, so this approach is not dependent upon published analyses. We used a novel imputation approach, which we applied to all data, consistent fracture definition, and PTE methodology.[10] We have reported 95% confidence intervals for PTE. We acknowledge that we report multiple such intervals, so this should be taken into account in interpretation.

Our study does have limitations. We were able to include most but not all major AR RCTs. We did not include anabolic treatment RCTs. We had a problem of significant missing data with a requirement for imputation. We had no control over the specific BTM assays or quality control. We chose to standardize our results using percent change rather than standard deviation (SD) units or absolute units because the assays themselves were not standardized. Imputation of the expected values of the BTMs, rather than random draws from their conditional distribution, could increase apparent precision. The results apply to groups rather than individuals; we plan to work on threshold analyses in the future to address this. The results apply to antiresorptive but not anabolic treatments. The results are applicable to bisphosphonates and SERMs; it is uncertain if and how they might be used for drugs with other mechanisms of action such as anabolic drugs.

In summary, in this large pooled analysis of individual-level data from multiple osteoporosis treatment trials, we found that a substantial part of the reduction in vertebral fracture risk could be explained by the changes in several bone turnover markers.

Disclosures

Acknowledgments

Author Contributions

Richard Eastell: Conceptualization; formal analysis; investigation; methodology; writing-original draft; writing-review and editing. **Dennis Black:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; supervision; validation; visualization; writing-original draft; writing-review and editing. **Li-Yung Lui:** Formal analysis; methodology; software; writing-review and editing. **Arkadi Chines:** Resources; writing-review and editing. **Fernando Marin:** Resources; writing-review and editing. **Sundeep Khosla:** Resources; writing-review and editing. **Anne de Papp:** Resources; writing-review and editing. **Jane Cauley:** Resources; writing-review and editing. **Bruce Mitlak:** Resources; writing-review and editing. **Charles McCulloch:** Formal analysis; investigation; methodology; writing-review and editing. **Eric Vittinghoff:** Formal analysis; methodology; writing-original draft; writing-review and editing. **Douglas Bauer:** Conceptualization; data curation; formal analysis; methodology; visualization; writing-original draft; writing-review and editing.

Peer Review

References

1. Bauer DC, Black DM, Bouxsein ML, et al. Treatment-related changes in bone turnover and fracture risk reduction in clinical trials of antiresorptive drugs: a meta-regression. J Bone Miner Res. 2018;33(4):634–42.
2. Diez-Perez A, Adachi JD, Agnusdei D, et al. Treatment failure in osteoporosis. Osteoporos Int. 2012;23(12):2769–74.
3. Diez-Perez A, Naylor KE, Abrahamsen B, et al. International Osteoporosis Foundation and European Calcified Tissue Society working group. Recommendations for the screening of adherence to oral bisphosphonates. Osteoporos Int. 2017;28(3):767–74.
4. Amur S, LaVange L, Zineh I, Buckman-Garner S, Woodcock J. Biomarker qualification: toward a multiple stakeholder framework for biomarker development, regulatory acceptance, and utilization. Clin Pharmacol Ther. 2015;98(1):34–46.
5. Eastell R, Barton I, Hannon RA, Chines A, Garnero P, Delmas PD. Relationship of early changes in bone resorption to the reduction in fracture risk with risedronate. J Bone Miner Res. 2003;18(6):1051–6.
6. Eastell R, Hannon RA, Garnero P, Campbell MJ, Delmas PD. Relationship of early changes in bone resorption to the reduction in fracture risk with risedronate: review of statistical analysis—response. J Bone Miner Res. 2007;22(11):1656–60.
7. Jacques RM, Boonen S, Cosman F, et al. Relationship of changes in total hip bone mineral density to vertebral and nonvertebral fracture risk in women with postmenopausal osteoporosis treated with once-yearly zoledronic acid 5 mg: the HORIZON-pivotal fracture trial (PFT). J Bone Miner Res. 2012;27(8):1627–34.
8. Sarkar S, Reginster JY, Crans GG, Diez-Perez A, Pinette KV, Delmas PD. Relationship between changes in biochemical markers of bone turnover and BMD to predict vertebral fracture risk. J Bone Miner Res. 2004;19(3):394–401.
9. Bruyere O, Detilleux J, Chines A, Reginster JY. Relationships between changes in bone mineral density or bone turnover markers and vertebral fracture incidence in patients treated with bazedoxifene. Calcif Tissue Int. 2012;91(4):244–9.

10. Freedman LS, Graubard BI, Schatzkin A. Statistical validation of intermediate endpoints for chronic diseases. Stat Med. 1992;11(2):167–78.

11. Li Z, Meredith MP, Hoseyni MS. A method to assess the proportion of treatment effect explained by a surrogate endpoint. Stat Med. 2001; 20(21):3175–88.

12. Austin M, Yang YC, Vittinghoff E, et al. Relationship between bone mineral density changes with denosumab treatment and risk reduction for vertebral and nonvertebral fractures. J Bone Miner Res. 2012; 27(3):687–93.

13. Liberman UA, Weiss SR, Broll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The alendronate phase III osteoporosis treatment study group. N Engl J Med. 1995;333(22):1437–43.

14. Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet. 1996;348 (9041):1535–41.

15. Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA. 1998;280(24):2077–82.

16. Pols HA, Felsenberg D, Hanley DA, et al. Multinational, placebo-controlled, randomized trial of the effects of alendronate on bone density and fracture risk in postmenopausal women with low bone mass: results of the FOSIT study. Fosamax International Trial study group. Osteoporos Int. 1999;9(5):461–8.

17. Orwoll E, Ettinger M, Weiss S, et al. Alendronate for the treatment of osteoporosis in men. N Engl J Med. 2000;343(9):604–10.

18. Chesnut CH 3rd, Skag A, Christiansen C, et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. J Bone Miner Res. 2004;19(8):1241–9.

19. Recker R, Stakkestad JA, Chesnut CH 3rd, et al. Insufficiently dosed intravenous ibandronate injections are associated with suboptimal antifracture efficacy in postmenopausal osteoporosis. Bone. 2004;34(5):890–9.

20. McClung MR, Geusens P, Miller PD, et al. Effect of risedronate on the risk of hip fracture in elderly women Hip Intervention Program Study Group. N Engl J Med. 2001;344(5):333–40.

21. Harris ST, Watts NB, Genant HK, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. JAMA. 1999;282(14):1344–52.

22. Reginster J, Minne HW, Sorensen OH, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Osteoporos Int. 2000;11(1):83–91.

23. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med. 2007;356 (18):1809–22.

24. Lyles KW, Colon-Emeric CS, Magaziner JS, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med. 2007;357(18):1799–809.

25. Cummings SR, McClung M, Reginster JY, et al. Arzoxifene for prevention of fractures and invasive breast cancer in postmenopausal women. J Bone Miner Res. 2011;26(2):397–404.

26. Silverman SL, Christiansen C, Genant HK, et al. Efficacy of bazedoxifene in reducing new vertebral fracture risk in postmenopausal women with osteoporosis: results from a 3-year, randomized, placebo-, and active-controlled clinical trial. J Bone Miner Res. 2008; 23(12):1923–34.

27. Cummings SR, Ensrud K, Delmas PD, et al. Lasofoxifene in postmenopausal women with osteoporosis. N Engl J Med. 2010;362(8): 686–96.

28. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple outcomes of raloxifene evaluation (MORE) investigators. JAMA. 1999; 282(7):637–45.

29. Simes RJ, Marschner IC, Hunt D, et al. Relationship between lipid levels and clinical outcomes in the long-term intervention with pravastatin in ischemic disease (LIPID) trial: to what extent is the reduction in coronary events with pravastatin explained by on-study lipid levels? Circulation. 2002;105(10):1162–9.

30. Yu T, Hsu YJ, Fain KM, Boyd CM, Holbrook JT, Puhan MA. Use of surrogate outcomes in US FDA drug approvals, 2003-2012: a survey. BMJ Open. 2015;5(11):e007960.

31. Cummings SR, Karpf DB, Harris F, et al. Improvement in spine bone density and reduction in risk of vertebral fractures during treatment with antiresorptive drugs. Am J Med. 2002;112(4):281–9.

32. Watts N, Cooper C, Lindsay R, et al. Relationship between changes in bone mineral density and vertebral fracture risk associated with risedronate. J Clin Densitom. 2004;7(3):255–61.

33. Watts NB, Geusens P, Barton IP, Felsenberg D. Relationship between changes in BMD and nonvertebral fracture incidence associated with risedronate: reduction in risk of nonvertebral fracture is not related to change in BMD. J Bone Miner Res. 2005;20 (12):2097–104.

34. Miller PD, Delmas PD, Huss H, et al. Increases in hip and spine bone mineral density are predictive for vertebral antifracture efficacy with ibandronate. Calcif Tissue Int. 2010;87(4):305–13.

35. Sarkar S, Mitlak BH, Wong M, Stock JL, Black DM, Harper KD. Relationships between bone mineral density and incident vertebral fracture risk with raloxifene therapy. J Bone Miner Res. 2002;17(1):1–10.

36. Parfitt AM. Implications of architecture for the pathogenesis and prevention of vertebral fracture. Bone. 1992;13(Suppl 2):S41–7.

37. Naylor KE, Iqbal P, Fledelius C, Fraser RB, Eastell R. The effect of pregnancy on bone density and bone turnover. J Bone Miner Res. 2000;15 (1):129–37.

38. Bone HG, Bolognese MA, Yuen CK, et al. Effects of denosumab treatment and discontinuation on bone mineral density and bone turnover markers in postmenopausal women with low bone mass. J Clin Endocrinol Metab. 2011;96(4):972–80.