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ORIGINAL ARTICLE

Ten-year fracture probability identifies women who will benefit from clodronate therapy—additional results from a double-blind, placebo-controlled randomised study

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Abstract
Summary Fracture risk prediction can be enhanced by the concurrent assessment of other clinical risk factors. This study demonstrates that the estimation of an individual's 10-year probability of fracture by the FRAX® algorithm identifies patients at high risk of fracture who will respond to bisphosphonate therapy.

Introduction Treatments for osteoporosis are targeted largely to patients with low bone density (BMD) or a prior fragility fracture. Fracture risk prediction can be enhanced by the concurrent assessment of other clinical risk factors, but it is important to determine whether the risk so identified can be reduced by intervention. We determined the effect of a bisphosphonate on fracture rates when risk was calculated using a new risk algorithm (FRAX®).
Methods Women aged 75 years or more were recruited to a randomised, double-blind controlled trial of 800 mg oral clodronate (Bonefos®) daily over 3 years. Baseline clinical risk factors were entered in the FRAX® model to compute the 10-year probability of major osteoporotic fractures with or without input of femoral neck BMD. The interaction between fracture probability and treatment efficacy was examined by Poisson regression.
Results In 3,974 women, the interaction between fracture probability and treatment efficacy was significant when probability was assessed without BMD ($p=0.043$), but not when BMD was included ($p=0.10$). Efficacy was more evident in those deemed at highest risk. For example women lying at the 75th percentile of fracture probability in the absence of BMD (10-year probability 24%) treatment reduced fracture risk by 27% (HR 0.73, 95%CI 0.58–0.92). In those with a fracture probability of 30% (90th percentile), the fracture risk reduction was 38% (HR 0.62, 0.46–0.84).
Conclusions The estimation of an individual's 10-year probability of fracture by the FRAX® algorithm identifies patients at high risk of fracture who will respond to bisphosphonate therapy.

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Keywords Bisphosphonate · BMD · Clodronate · Efficacy · Fractures · Fracture probability · Osteoporosis · Risk factors

Introduction

Bisphosphonates have been demonstrated to significantly reduce fracture risk by decreasing bone turnover and maintaining or increasing bone mineral density (BMD) [1–7]. To date, most studies with bisphosphonates have reported on their use in individuals selected to be at high risk for fracture usually by the presence of low BMD or a prior fragility fracture, most commonly at the spine. An analysis of the effect of alendronate 10 mg daily on clinical (largely non-vertebral) fractures suggested that clinical and/or hip fracture risk reduction is largely confined to those women whose BMD values meet the criterion for osteoporosis[5]. The failure of risedronate to reduce non-vertebral and hip fracture risk in a subgroup of elderly women recruited on the basis of risk factors largely related to falls risk [7] was interpreted by some as supporting the hypothesis that bisphosphonates are only effective in the presence of low BMD measured by dual X-ray absorptiometry (DXA). It is clear, however, that at least half of hip fractures and a larger proportion of clinical fractures occur in individuals with osteopenia rather than osteoporosis [8, 9]. The poor sensitivity of the BMD osteoporosis threshold for fracture has led to the development of several fracture prediction tools that attempt to integrate other clinical risk factors with BMD to enhance fracture prediction [10–12]. The World Health Organization has recently developed a highly sophisticated algorithm for the estimation of 10-year fracture probability of individuals that has been validated in several population cohorts [13]. This algorithm (the FRAX® tool; www.shef.ac.uk/FRAX) computes fracture probabilities with or without the input of femoral neck BMD, but its clinical utility, like that of all other clinical risk algorithms, will be dependent on the efficacy of treatments, predominantly bisphosphonates, in those identified to be at high risk. We have previously shown that the bisphosphonate clodronate decreases clinical and osteoporotic fracture risk in elderly women unselected for osteoporosis [14]. In this analysis, we wished to examine the interaction between treatment efficacy and fracture probability determined by the WHO algorithm.

Materials and methods

The study was a double-blind, prospective, randomised, placebo-controlled single-centre study in elderly community-dwelling women aged 75 years or more. The study details have been published previously [14]. In brief, in addition to examining the efficacy of clodronate, the study was also designed to determine risk factors for fracture in elderly women in the UK. Participants were therefore recruited randomly from general practice lists and did not need to have proven osteoporosis nor any other known risk factors for fracture. Exclusion criteria comprised concurrent treatment for a malignancy, concurrent medication likely to influence skeletal metabolism (other than calcium supplements ≤500 mg daily), bilateral hip arthroplasty, known malabsorptive states, illness that would impede informed consent or adherence to the study, significant impairment of renal or hepatic function and serum biochemistry consistent with underlying metabolic bone disease (e.g. osteomalacia) or calcium disorders other than primary hyperparathyroidism.

The current analysis was conducted in a cohort comprising 3,974 out of 5,212 women (76.2%) recruited to the main part of the study in whom complete data on clinical risk factors required for the computation of 10-year fracture probability were available.

Baseline assessments and WHO algorithm

All of the baseline assessments were carried out during a single clinic visit with recruitment occurring between 1996 and 1999. All follow-up visits thereafter were conducted in the community by a team of study nurses at 6-month intervals to undertake collection of fracture data, adverse events and hospitalisations as well as to collect and dispense study medication.

Each participant underwent a detailed and comprehensive assessment of their general health, fracture history and a number of measurements of bone density, muscle strength and postural stability. Bone mineral density was measured by DXA at the hip using a Hologic QDR4500 Acclaim densitometer. None of the results of the baseline assessments of fracture risk, including bone density values, were communicated to the participants.

The following clinical variables were used to compute the 10-year probability of a major osteoporotic fracture (hip, clinical vertebral, wrist or humerus) by the WHO algorithm: age, body mass index (BMI), history of prior fragility fracture after the age of 50 years, maternal history of hip fracture (father's history of hip fracture was not documented), rheumatoid arthritis (yes, if patient self-reported ever being told they probably had or did have rheumatoid arthritis), oral glucocorticoid use (yes, if ever used) and smoking (yes, if current). Information on alcohol intake was not captured in the study. The 10-year probability was calculated with and without input of femoral neck BMD.

Incident fracture

All reported incident fractures were confirmed by hospital notes, discharge/GP letters, copies of radiographic reports or review of radiographs if necessary. Only verified

fractures were included in statistical analyses and were defined as "clinical fractures", as they had presented symptomatically and triggered radiological investigation. The current analysis is confined to incident osteoporotic clinical fractures (excludes high trauma fractures and those of the skull, nose, face, hand, finger, feet, toe, ankle and patella fractures regardless of trauma level) [15]. Incident fracture ascertainment was shown to be greater than 98.3%.

Study treatment

Following randomisation, the women received either clodronate 800 mg daily (two Bonefos® 400 mg tablets once daily or one tablet twice daily) or an identical placebo. Women were randomised 1:1 in each group using the SAS®/PLAN procedure for one site, two treatments and a block size of ten. Study medication was taken on an empty stomach with a drink of water at least 1 h before breakfast. It could also be taken in the middle of the night if desired by the women after fasting for approximately 5–6 h. The intervention was continued for 3 years. Concomitant calcium and vitamin D supplementation was not given.

Statistical analysis

All analyses were undertaken on an intent-to-treat basis so that all osteoporotic fractures were included in the analyses regardless of whether the women were taking study medication or not.

The principal aim of the analysis was to examine whether clodronate had greater or lesser efficacy in relation to 10-year fracture probability determined by FRAX®. Poisson regression [16] was used to examine the interaction between calculated 10-year fracture probability, determined with and without input of femoral neck BMD, and clodronate treatment (zero/one variable). In addition to the interaction term, further covariates in the model included age, the time since baseline, treatment and the calculated 10-year probability of fracture. The hazard function for fracture was assumed to be $\exp(\beta_0 + \beta_1 \times$ current time from baseline $+ \beta_2 \cdot \times$ current age $+ \beta_3 \cdot \times$ 10-year probability $+ \beta_4 \cdot \times$ treatment $+ \beta_5 \cdot \times$ 10-year probability$\cdot \times$ treatment). The beta coefficients reflect the importance of the variables as in a logistic or Cox model, and a coefficient of 0 denotes that the corresponding variable does not contribute to fracture risk. Thus, a beta coefficient of zero for the interaction (β_5) means that the efficacy of clodronate is the same independently of the calculated probability.

Results

The baseline characteristics of the 3,974 women included in this analysis are shown in Table 1. Compared to those women excluded because of missing risk factor data, the participants were slightly younger (mean±SD; 79.7±3.7 vs. 81.0±4.5 years) with similar BMI (mean±SD; 26.9±4.6 vs. 26.5±4.8 kg/m^2) and a slightly higher femoral neck BMD (mean±SD; 0.65±0.12 vs. 0.63±0.12 g/cm^2; *T* scores −1.73±0.98 vs. −1.89±0.97, respectively). However, the characteristics of women randomly assigned to clodronate treatment were similar to those in the placebo group (Table 1). The prevalence of clinical risk factors ranged from 2% for rheumatoid arthritis to 24% for prior low trauma fracture, with a total of 39% having one or more clinical risk factors and 6% having two or more in both groups.

Table 1 Baseline characteristics, including prevalence of risk factors, for the women assigned to the clodronate and placebo groups included in the present analysis (*N*=3,974)

	Clodronate (*N*=2,016)	Placebo (*N*=1,958)
Age (years)	79.8±3.7	79.7±3.7
Height (cm)	156.1±6.0	156.1±5.9
Weight (kg)	65.3±11.8	65.7±12.1
BMI (kg/m^2)	26.8±4.4	27.0±4.7
Femoral neck BMD (g/cm^2)	0.65±0.12	0.65±0.12
Femoral neck BMD *T* score	−1.74±0.98	−1.72±0.99
Previous fracture (%)	22	24
Family history (%)	5	6
Current smoking (%)	6	6
Corticosteroids (%)	9	10
Rheumatoid arthritis (%)	2	2

Efficacy of clodronate to reduce the risk of osteoporotic fracture

During the 3-year intervention period, 305 women sustained an incident osteoporotic fracture, including 54 hip fractures. The effect of clodronate to reduce osteoporotic fractures was similar in these 3,974 women (HR 0.77, 95% CI 0.61–0.97, p=0.024) to that observed in the complete study population of 5,212 women (HR 0.76, 95%CI 0.63–0.93, p=0.006; Fig. 1). Treatment was associated with a reduction in fracture risk by 1 year (HR 0.79, 95% CI 0.64–0.99), but the interaction between treatment efficacy and the duration in the study was not statistically significant (p>0.30).

The mean±SD 10-year probability of a major osteoporotic fracture calculated by clinical risk factors alone was 20±7% (range 7.3–72.8%). The additional input of femoral neck BMD resulted in a mean 10-year probability of 18±9% (range 1–73%). The observed incidence of osteoporotic fractures increased as the estimated 10-year probability of fracture using the WHO algorithm increased. For example, in the placebo arm of the study, those lying in the highest quintile of probability estimated by clinical risk factors in

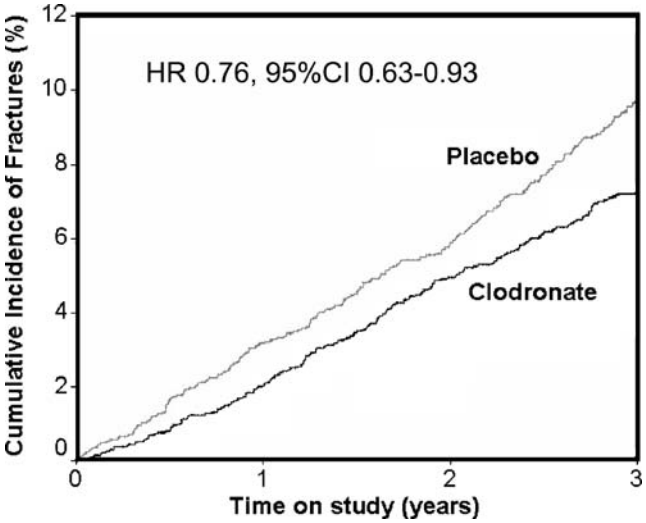

Fig. 1 Impact of clodronate on the incidence of osteoporotic fractures over 3 years of treatment in the 3,974 women included in this analysis

the absence of BMD (median 10-year probability 30%) had an incidence of fracture over 3 years of 5.4 in 100 person-years of follow-up compared to 1.5 in 100 person-years in those in the lowest quintile (median 10-year probability 13%; Fig. 2). A similar pattern was observed when femoral neck BMD was included in the estimation of 10-year probability (Fig. 2) with those in the highest quintile having a sevenfold higher incidence of fractures than those in the lowest quintile (6.2 vs. 0.9/100 person-years).

The effects of clodronate to reduce fracture incidence at various 10-year probabilities of fracture, calculated with and without femoral neck BMD, are shown in Figs. 3 and 4. In the absence of BMD, there was a statistically significant interaction (β_5 coefficient −0.0261, SD 0.0129, p=0.043)

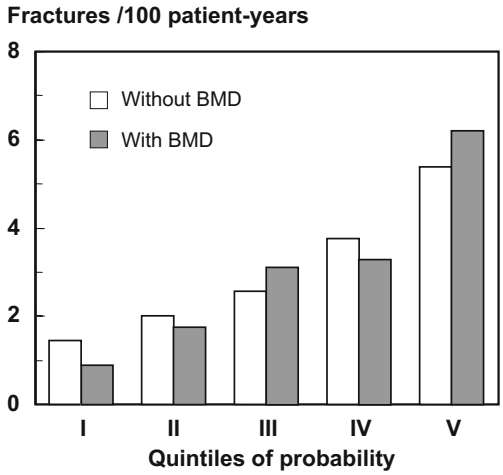

Fig. 2 Relationship in women assigned to the placebo arm of the study between 10-year probabilities of fracture (as quintiles) and observed fracture incidence (fractures/100 person-years) over 3 years with femoral neck excluded from (i.e. clinical risk factors alone) or included in the calculation of fracture probability

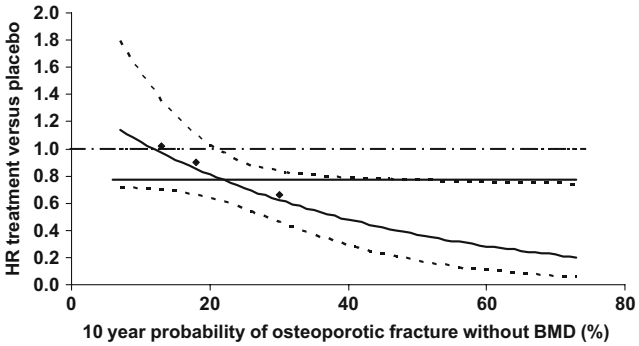

Fig. 3 Relationship between 10-year probabilities of major osteoporotic fracture, calculated with clinical risk factors alone (i.e. without femoral neck BMD) and the efficacy of clodronate to reduce fracture risk (hazard ratio with 95% confidence intervals). The *solid horizontal line* represents the overall treatment efficacy (HR 0.77) and the *dashed horizontal line* a hazard ratio of 1. The *diamonds* correspond to the 10th, 50th and 90th percentiles of probability in the population studied

with a better effect of clodronate at higher probabilities (Fig. 3). For example, at a probability of 15% (25th percentile), the relative risk for fracture was reduced by 8% with clodronate (RR 0.92, 0.69–1.24), whereas at a probability of 24% (75th percentile), the reduction was 27% (RR 0.73, 0.58–0.92). The interaction between efficacy and probability of fracture was not statistically significant when BMD was used in the calculation of probability (β_5 coefficient −0.0164, SD 0.0100, p=0.10), but the pattern of efficacy was very similar with more evident fracture reductions at higher probabilities of fracture (Fig. 4).

Impact of risk factors on reversibility of risk by clodronate

A number of analyses were conducted to examine the interaction between clodronate efficacy and the individual risk variables included in the algorithm to estimate 10-year

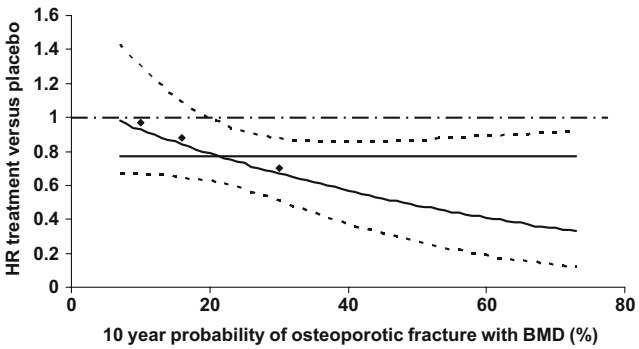

Fig. 4 Relationship between 10-year probabilities of fracture, calculated with clinical risk factors combined with femoral neck BMD, and the efficacy of clodronate to reduce fracture risk (hazard ratio with 95% confidence intervals). The *solid horizontal line* represents the overall treatment efficacy (HR 0.77) and the *dashed horizontal line* a hazard ratio of 1. The *diamonds* correspond to the 10th, 50th and 90th percentiles of probability in the population studied

probabilities. There was no significant interaction between treatment efficacy and age across the age range in the study ($p>0.30$). For example, at 80 years, clodronate was associated with a fracture risk reduction of 21% (HR 0.79, 95%CI 0.63–0.98) and at 90 years with a reduction of 32% (HR 0.68, 95%CI 0.46–1.01). As demonstrated previously [14], there was no significant interaction between treatment efficacy and femoral neck BMD in the current subgroup or in the total study population. In contrast, there was a significant interaction between treatment efficacy and BMI at entry to the study (coefficient 0.0441, SD 0.0224, $p=0.049$; Fig. 5). Thus, in women with a BMI of 30 kg/m^2 (the 75th percentile), the reduction in fractures was only 10% (HR 0.90, 0.69–1.17), whereas at a BMI of 26 (median BMI), the reduction was 25% (HR 0.75, 0.62–0.92), and at a BMI of 21 (the 10th percentile), treatment with clodronate reduced fracture risk by 40% (HR 0.60, 0.45–0.81). The efficacy of clodronate to reduce fracture risk was not affected by the inclusion or exclusion of the bivariate risk factors (e.g. prior fracture, maternal history of hip fracture, current smoking, ever glucocorticoid use or rheumatoid arthritis) in the analyses, confirming that BMI was the only significant moderator of treatment efficacy.

Discussion

A critical question in proposing the use of clinical risk factors alone for patient assessment relates to the reversibility by pharmacological intervention of the risk so identified. The present analysis suggests that those individuals identified at higher risk of fracture by the FRAX™ tool are responsive to treatment with an inhibitor of bone resorption, the bisphosphonate clodronate. Moreover, effectiveness of the bisphosphonate was evident in women characterised at high risk with the FRAX tool even in the absence of information on BMD. This finding, if confirmed in studies with other agents, is likely to change the management of individuals with osteoporosis in that treatment will be directed on the basis of fracture risk as assessed by the clinical risk factors rather than predominantly on the basis of BMD.

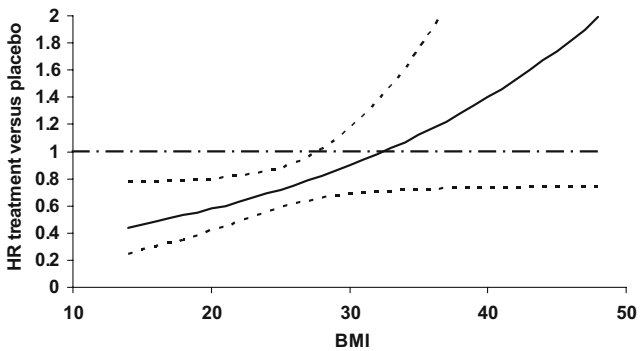

Fig. 5 Relationship between the treatment efficacy of clodronate (hazard ratio with 95% confidence intervals) and BMI at entry to the study. The *dashed horizontal line* represents a hazard ratio of 1. The significant interaction suggests a stronger treatment effect in those women with lower BMI at entry

The efficacy of inhibitors of bone resorption has been well characterised in individuals with low bone mass, such that the BMD thresholds published by the WHO in 1994 [17] are widely accepted as both a diagnostic and an intervention threshold. Indeed, low BMD is recommended as an entry criterion for the development of pharmaceutical interventions in osteoporosis, and drugs are usually licensed for use in patients below a given BMD threshold. The implication of these development programmes is that BMD should be assessed before treatment is considered, and this has been reflected in clinical guidelines [18, 19]. Many recent studies indicate, however, that pharmacological interventions have efficacy in patients with osteopenia or in whom BMD was not assessed [20–24]. A further problem with the use of BMD to direct interventions is that BMD alone is not optimal for the detection of individuals at high risk of fracture. Indeed, the majority of osteoporotic fractures will occur in individuals without osteoporosis [8, 9].

In the past decade, other factors have been identified that contribute to fracture risk, partially or wholly independent of BMD, which improve fracture prediction and the selection of individuals at high risk for treatment [10, 12, 25–27]. A series of meta-analyses using individualised data from 12 global population cohorts [28–35] has identified clinical risk factors for use in the assessment of fracture risk with or without the use of BMD. The adequacy of the risk factors has been validated in a further 12 independent population-based cohorts [13]. The risk factors identified formed the basis for the development of the WHO algorithms that calculate fracture probability in an individual, expressed as the 10-year fracture probability (FRAX®) [13]. Unlike many previous algorithms, the FRAX® tool takes into account the relationship between individual risk factors and both fracture and death hazards [13]. The risk factors in the FRAX® tool include age, sex, glucocorticoid use, secondary osteoporosis, parental history of hip fracture, prior fragility fracture, low BMI, current smoking, excess alcohol consumption (three or more units daily) and femoral neck BMD. These were selected on the basis of their international validity and evidence that the identified risk was likely to be modified by subsequent intervention (modifiable risk). Modifiable risk was validated from clinical trials (BMD, prior fracture, glucocorticoid use, secondary osteoporosis) or partially validated by excluding interactions of risk factors on therapeutic efficacy in large randomised intervention studies (e.g. smoking, family

history, BMI) [36]. It is important to note that risk factors for falling were not considered for inclusion in the FRAX® tool, since there is some concern that the risk identified would not be modified by a pharmaceutical intervention targeted at the skeleton [7]. It is notable that in this latter study, the precise criteria for inclusion were not documented, and further work is required to determine whether risk factors for falls or a history of falls would identify a risk that was modifiable by pharmacological intervention.

The present study indicates that the clinical risk factors alone identify a modifiable risk and so raises the question whether BMD tests are needed to identify candidates for treatment. The case for including a BMD test is that the predictive value is higher than the use of the FRAX tool without BMD [13]. It has been argued that a BMD test is mandatory since treatment is only effective in patients with low BMD. The present study and several additional studies, as noted above [20–24], contradict this view. Moreover, the FRAX tool without including BMD identifies women with low BMD, and in the placebo arm of the present study, we have previously demonstrated that in women characterised by significant risk factors without reference to BMD, mean BMD values decreased with increasing 10-year probability of fracture [37]. In women above an arbitrary risk threshold, 10-year probability was approximately 1 SD lower than in women below the threshold.

The current study has limitations. No data were collected at baseline on the paternal history of hip fracture or alcohol intake of three or more units daily. The prevalence of both is relatively low in elderly female populations, and it is unlikely that they would have impacted significantly on the outcome. For example, in women of similar age recruited to the cohorts used by WHO to derive FRAX®, alcohol intake as defined was reported by 3.5%, whilst a paternal history of hip fracture was reported by 8.2% (H. Johansson, personal communication). Oral clodronate is not licensed for use in osteoporosis, but despite differences in intracellular targets to the more widely used nitrogen-containing bisphosphonates, clinical data suggest that there are more similarities than differences in the anti-fracture efficacy of these agents [1, 4–6, 14]. The design of the current study is unique, as it examined the efficacy of a bisphosphonate, clodronate, in a population cohort of elderly women, randomly selected from general practice lists, regardless of underlying osteoporosis or fracture risk. If anything, this would mitigate against the observation of a treatment effect, as much larger numbers of participants would be required to confidently demonstrate efficacy in individuals at lower risk. This effect is compounded by a healthy selection bias that is frequently observed in such studies [14]. This design is, however, also the study's major strength in that it permitted us to examine the efficacy of treatment across a much wider range of risk than that usually observed in osteoporosis trials. It is essential, however, that similar analyses are conducted within different clinical trial populations with other agents.

Relatively little is known about the determinants of anti-fracture efficacy in bisphosphonate users. We have observed a significant interaction between treatment efficacy and probability of fracture when BMD was not included in the estimate, with greater fracture reduction in those deemed at highest risk. Further analysis suggests that BMI is the major driver of this interaction with greater clodronate efficacy in women with lower BMI. The potential mechanism(s) underlying this interaction remain unclear but include a possible volume of distribution effect or an effect of underlying bone mass or bone turnover. The interaction is similar but no longer statistically significant when femoral neck BMD is included in the calculation of fracture risk, suggesting that at least part of the effect of BMI may be mediated by a relatively weak effect of BMD. The weakness of this effect has been reported in a previous univariate analysis where we observed a lack of interaction with hip BMD and treatment efficacy in the same population [14]. Interestingly, analyses of the pivotal fracture studies with alendronate have suggested that baseline BMD or biochemical markers of bone turnover interact significantly with treatment efficacy [5, 38], both of which are known to correlate with BMI. Further analyses of other fracture studies are required to better understand these potential interactions.

The availability of the FRAX tool for predicting fracture risk will lead to major changes in the management of patients. This study is a critical addition to the body of evidence required for such changes, as it demonstrates, for the first time, that patients deemed to be at highest risk of fracture by FRAX are responsive to anti-resorptive therapy. Recently developed European guidelines for the evaluation of drugs in osteoporosis recognise the importance of global risk assessments. It is likely that further data will become available from current and future clinical trials of other agents.

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Conflicts of interest None.

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