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# IOF World Congress on Osteoporosis & 10th European Congress on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis

## Oral Communication Abstracts

### OC1 - HOW DOES 10-YEAR ABSOLUTE FRACTURE RISK AFFECT WOMEN'S ATTITUDES TOWARD FRACTURE PREVENTION AND OSTEOPOROSIS TREATMENT?

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**Aims:** Current osteoporosis treatment guidelines use absolute 10-year fracture risks, but it is not known if these risks are meaningful to patients. We assessed the impact of absolute risk information on fracture prevention attitudes using a web-based decision tool. We also estimated the minimum acceptable absolute risk reduction women demand of osteoporosis treatment.
**Methods:** Our study included a clinical group with t-score<-1.0 and an internet group with high fracture risk visiting the "YourDiseaseRisk" website. We report data for untreated women with estimated 10-year absolute fracture risks >10%. Each rated fracture prevention importance on a Likert scale (unimportant to very important) before and after seeing her 10-year absolute fracture risk depicted graphically alongside the 10-year risk for a typical woman her age. To identify the minimum fracture risk reduction that women required to initiate osteoporosis treatment, absolute fracture risk was shown both with and without treatment in side-by-side 100-face pictograms. Relative treatment benefit was systematically improved in successive scenarios. Proportions, means, and 95% confidence intervals (CI) were estimated to characterize the impact of absolute risk information on perceived importance of fracture prevention and minimum demanded risk reduction.
**Results:** Among 967 participants (101 clinical, 866 internet; mean age 63), 71% gave fracture prevention the highest importance rating at study entry (n= 690). For these women, provision of personalized risks lowered importance ratings among 10.1% (CI: 7.9-12.4) with none rating prevention as unimportant. For the remaining women (n=277), importance ratings increased among 17.3% (CI: 12.9-21.8) with most giving prevention the highest rating; ratings decreased among 7.6% (CI: 4.4-10.7) with prevention rated as unimportant among fewer than 5%. 693 women completed the demanded risk reduction exercise. The mean demanded absolute risk reduction was 6.9% (CI: 6.6-7.3). A minority (16.3%, n=111/693) would not take medication at any level of benefit and 24.5% (170/693) required an 80% or greater risk reduction with a mean absolute risk reduction of 11.9% (CI:11.4-12.5) before indicating they would initiate treatment.
**Conclusions:** Individualized estimates of 10-year absolute fracture risk affect fracture prevention attitudes. Many women require fracture risk reductions that exceed the benefits of most currently available treatments.

**Disclosure of Interest**: None Declared

### OC2 - EPIDEMIOLOGY OF FALLS AMONG 11009 ELDERLY MEN – THE MR OS STUDY

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**Aims:** Most peripheral fractures are preceded by a fall and many of the same risk factors account for falling and fractures. Given the relatively low frequency of fractures, number of falls is often used as a surrogate endpoint for fracture. However, there exist few reports that directly compare differences in the epidemiology of falls in diverse populations with different incidence of hip fractures. The aim of this study was to evaluate fall epidemiology in elderly men.
**Methods:** Included were elderly men in Hong Kong (n=2000, ages 65-92 years), United States (n=5995, ages 64-100 years) and

Sweden (n=3014, ages 69-81 years), who comprised the MrOS International Study (n=11009). At baseline epidemiology of falls during the preceding year was evaluated by a questionnaire.
**Results:** During one year, 1207 men (11.0%) fell one time and 863 (7.8%) two or several times. In this report we evaluate the men in 5-year classes. Fall frequency increased significantly with advancing age so that the annual incidence of falls ranged from 16.5% in ages 64-69 years, to 43.2% in ages >90 years (groups comparisons p<0.001). There was no difference in the proportion of frequent fallers in the different 5 year classes, the annual incidence varying between 38.3%>51.2%, p=0.14).

The proportion of fallers was in most ages highest in US, intermediate in Sweden and lowest in Hong Kong (in age group 70-74 years the proportions were 18.6%, 15.4% and 14.4%, respectively; p=0.01). The proportion of frequent fallers showed a different pattern, being highest in Sweden, intermediate in US and lowest in Hong Kong (in age group 70-74 years the proportions were 50.8%, 44.3% and 20.6%, respectively; p<0.001). The fall epidemiology did not differ when comparing Asian men living in Hong Kong or US whereas white men living in Sweden had a higher frequency of one or more falls than white men living in US, in age group 75-79 years with the proportions 22.2% and 17.2%, p<0.001).
**Conclusions:** These findings indicate that among older men, the risk for any fall increases with advancing age; however the risk of frequent falls is not significantly different across age groups. Risk of falls is different in different geographic regions. When using falls as surrogate endpoint for fractures, we must take into account both number of fallers and the proportion of frequent fallers. In addition, this survey indirect indicates that both ethnicity and environmental factors may influence the fall risk.

**Disclosure of Interest**: None Declared

## OC3 - THE RELATIONSHIP BETWEEN INTRAUTERINE GROWTH AND POSTNATAL SKELETAL DEVELOPMENT

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**Aims:** To relate intrauterine growth assessed by high resolution ultrasound scanning to postnatal bone mineral measurements at birth and 4 years.
**Methods:** 435 subjects were recruited from the Southampton Women's Survey. Fetal abdominal circumference (AC) was measured at 11,19 and 34 weeks gestation. Offspring underwent DXA at birth(Lunar DPXL) and 4 years(Hologic Discovery) [whole body minus head bone area (BA), bone mineral content (BMC), bone mineral density (BMD)]. Royston models were fitted to fetal measurements to create Z-scores for size and conditional growth velocity from 11-19 and 19-34 weeks.
**Results:** Conditional change in AC from 11 to 19 weeks and from 19 to 34 weeks predicted BA (r=0.17, p=0.007; r=0.45, p<0.001, respectively), BMC (r=0.17, p=0.009; r=0.44, p<0.001), aBMD (r=0.04, p=0.56; r=0.15, p=0.02). Associations were stronger for late than for early growth. Conversely bone indices at 4 years were more strongly associated with early compared with late AC growth. Thus Pearson correlations for 11-19 week and 19-34 week growth respectively with bone indices at 4 years: BA (r=0.19, p=0.001; r=-0.01, p=0.93), BMC (r=0.24, p<0.001; r=0.07, p=0.21), aBMD (r=0.24, p<0.001; r=0.13, p=0.03).
**Conclusions:** Bone mineral at birth is predicted by rate of abdominal circumference growth in late pregnancy more strongly than by growth in early pregnancy. By 4 years old the pattern is reversed. This suggests that the child reverts to the early growth trajectory during the first few years of postnatal life. Further work is needed to elucidate the extent to which perturbations of growth in later pregnancy may alter this natural pattern.

**Disclosure of Interest**: None Declared

## OC4 - IN HEALTHY 15-YEAR OLD BOYS PREVIOUS FRACTURES ARE ASSOCIATED WITH PREFERENTIAL TRABECULAR BONE DEFICIT AT WEIGHT-BEARING SKELETAL SITES

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**Aims:** Traumatic fractures affect nearly one out of two healthy children, with a maximal incidence concomitant to peak height velocity (PHV). It has been hypothesized that bone fragility at that time results from a transient deficit in bone mineral accrual relative to bone size. The influence of fracture history on bone mineral density, cortical and trabecular microstructure was studied in a cohort of 176 healthy young boys aged 15.2±0.5 (±SD) yrs and prospectively followed from age 7.5±0.5 yrs.
**Results:** 156 fractures were recorded in 87/176 boys with peak incidence between 10 and 14 yrs. Most common fractures were localized in forearm and wrist (40%), followed by hand/fingers (18%) and arm/shoulder (14%). 20% affected the lower limb (including foot, ankle, tibia, femur) and 8% others sites. 38 boys reported multiple fractures (2 to 5), accounting for 2/3 of all fractures; in this case the upper limb was always affected. Whereas no significant difference was observed at the distal radius for aBMD as well as for the volumetric and microstructure parameters, subjects with a positive fracture history (n=87) had lower femoral neck (0.847±0.116 vs. 0.901±0.133 g/cm$^2$, P=0.005) and total hip aBMD (936±133 vs. 992±139 g/cm$^2$, P=0.007) as compared to boys without fractures (n=89), corresponding to a delta Z-score of -0.45 at the femoral neck. Boys with a fracture history displayed at the distal tibia lower trabecular vBMD (196±27 vs. 205±27 mg HA /cm$^3$, corresponding to a delta Z-score of -0.34, P=0.029) and number (2.04±0.26 vs. 2.13±0.31 mm$^{-1}$, P=0.040) and greater trabecular spacing (418±60 vs. 398±62 mm, P=0.028). The statistical significance of these differences remained similar after adjustment for standing height, body weight, calcium and protein intakes, physical activity, pubertal stage, calcium supplement or placebo randomization between age 7.5 and 8.5 yrs, as well as after exclusion of 7 boys with major lower limb fractures.
**Conclusions:** In healthy adolescent boys fracture history was associated with lower aBMD and trabecular vBMD at weight-bear-

ing skeletal sites. These deficits may explain the increased incidence of fractures occurring during childhood and adolescence.

**Disclosure of Interest**: None Declared

## OC5 - RISEDRONATE REDUCES MICRO-STRUCTURAL DETERIORATION OF CORTICAL BONE ACCOMPANYING MENOPAUSE

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**Aims:** Increased remodeling with its negative bone balance contributes to structural deterioration of the skeleton after menopause. While accelerated trabecular bone loss contributes to bone fragility, cortical bone is a neglected determinant of bone strength even though it comprises 80% of the skeleton. Risedronate (RIS) is effective in reducing the risk for non-vertebral and hip fracture and reduces intra-cortical porosity assessed in iliac crest biopsies[1]. To better understand the structural basis of the anti-fracture efficacy of risedronate, we conducted a 12 month double-blind pilot study among 159 women aged 45-55 years within 36 months since menopause and with osteopenia as determined densitometrically.

**Methods:** Participants were assigned to oral RIS 35mg/week or placebo (PLB) in a 2:1 randomization. Using high resolution pQCT (XtremeCT, Scanco, ~100 μm resolution), microstructural parameters were measured at baseline and 12 months at distal tibia (DT) and distal radius (DR).

**Results:** In the PLB group, total and cortical but not trabecular vBMD decreased in DT relative to baseline. Cortical thickness also decreased from baseline in the PLB group. No treatment differences were detected in trabecular vBMD, BV/TV or other trabecular bone indices in DT or DR. RIS prevented the decline in cortical vBMD in DT (p=0.03, Table). Similar but less significant (p>0.05) observations were made for cortical thickness at DT and for cortical vBMD and thickness at DR. RIS decreased P1NP (-44.1%) and sCTX (-39.4%) and increased aBMD in the lumbar spine (1.4%) and proximal femur (0.5%) from baseline.

**Conclusions:** Consistent with the reduction of remodeling, these data support the hypothesis that treatment with risedronate reduces the deterioration of cortical microstructure, likely due to the reduction of intra-cortical porosity and may therefore, protect against developing bone fragility in postmenopausal women.

**References:** [1]B Borah et.al., JBMR 2010

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## OC6 - RANKL UPREGULATES MOUSE RANK GENE TRANSCRIPTION THROUGH THE NFAT BINDING SITE OF RANK GENE PROMOTER

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**Aims:** Receptor Activator of NF-κB (RANK) expressed on osteoclasts and their precursors is a receptor for RANK Ligand (RANKL). Signals transduced by RANKL-RANK interaction induce genes essential for the differentiation and function of osteoclasts partly through the direct binding of NFATc1 to target gene promoters. We have cloned a 6-kb fragment containing the 5'-flanking region of the mouse RANK gene and found the three putative NFAT binding sites (-370, -550 and -720). Here, we examined the regulatory mechanism of the RANK gene by RANKL signaling through NFATc1 binding.

Table 1: Mean % Change (95% CI) of Cortical Parameters at Month 12

| | PLB (n=49) | RIS (n=110) | Difference | P-value |
|---|---|---|---|---|
| DT vBMD | -0.78 (-1.34, -0.23)* | -0.10 ( -0.48, 0.27) | 0.68 (0.05, 1.30\) | 0.03 |
| DT Cort. Thickness | -1.30 (-2.40, -0.20)* | -0.32 (-1.07, 0.43) | 0.98 (-0.26, 2.23) | 0.12 |
| DR vBMD | -0.77 (-1.34, -0.21)* | -0.31 (-0.68, 0.07) | 0.47 (-0.17, 1.11) | 0.15 |
| DR Cort. Thickness | -3.47 (-4.93, -2.01)* | -2.44 (-3.42, -1.45)* | 1.03 (-0.61, 2.67) | 0.21 |

*Statistically significant change from baseline

**Methods:** RAW264 cells were subjected to RT-PCR and transfection experiments. The 1kb from the transcription start site of the mouse RANK gene was ligated into a pGL3 Basic vector. Three putative NFAT binding sites (-373/-368, -556/-550, -722/-717) were analyzed by site-specific mutagenesis study. The siRNA against NFATc1 Exon 4 and Exon 8 were used for knockdown experiment. For gel shift assay, NFAT binding sites of the mouse RANK gene promoter and consensus NFAT sequence of the mouse IL-2 gene promoter were used.
**Results:** In vitro RANKL treatment of RAW264 cells increased RANK expression, and transfection of an NFATc1-expression vector also increased RANK and TRACP mRNA expression. Furthermore, NFATc1 knockdown by siRNA nullified the inducible effect of RANKL on RANK expression. By EMSA, an oligonucleotide (-388/-353) showed specific DNA protein binding, whereas no specific DNA protein binding was observed in nucleotides (-569/-537) and (-735/-704). Co-transfection with an NFATc1-expression vector and the promoter constructs showed that NFATc1 increased RANK promoter activity 2-fold in RAW cells. Mutagenesis of the putative NFAT site (-370) nullified the inducible effect of NFATc1 on promoter activity; mutagenesis of sites (-550) and (-720) revealed no change in the inducible effect of NFATc1.
**Conclusions:** Taken together, these results indicate that RANK transcription is positively regulated by RANKL signal through the direct binding of NFATc1 to its specific binding site of the RANK gene promoter, suggesting the presence of a positive feedback mechanism of gene expression that promotes differentiation of RANK-positive committed precursors to mature osteoclasts.
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**Disclosure of Interest**: None Declared

## OC7 - USE OF DEPOT MEDROXYPROGESTERONE ACETATE AND FRACTURE RISK

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**Aims:** Depot medroxyprogesterone acetate (MPA) is used by more than 9 million women worldwide and has a high usage among teenagers in Europe and the US. Use of MPA is associated with impaired bone mineral acquisition during adolescence and accelerated bone loss later in life, mainly in younger women with lower estradiol levels. Studies investigating the association between MPA use and fracture risk are limited. Therefore, we aimed to evaluate the relationship between long-term use of MPA and other hormonal contraceptives and the risk of fractures.
**Methods:** We conducted a case-control analysis using the UK-based General Practice Research Database. We identified female cases with an incident fracture diagnosis between 1995 and 2007. Four controls were matched to each case on age, sex, general practice, calendar time, and years of history in the database. We used conditional logistic regression to assess odds ratios [OR] with 95% confidence intervals [CI] of incident fracture in relation to previous exposure to hormonal contraceptives or postmenopausal estrogen replacement therapy, stratified by exposure timing (current=last prescription <180 days prior to the index date, past=thereafter), and duration (1-2, 3-9, 10 prescriptions). We adjusted the ORs for smoking, BMI, and additional potential confounders.
**Results:** We identified 71,089 incident fracture cases and 274,520 control patients. Compared to non-use, current use of 3-9 or 10 prescriptions for MPA alone yielded adjusted ORs of 1.24 (95% CI 1.05-1.45) and of 1.54 (95% CI 1.35-1.77), respectively. For use of MPA in combination with estrogens and other estrogens opposed and unopposed the fracture risk was decreased. Stratification by age yielded ORs for current long-term use of MPA alone of 1.69 (95% CI 1.46-1.96) for <50 years and 0.82 (95% CI 0.55-1.21) for 50 years.
**Conclusions:** In women below 50 years of age, longer-term use of MPA alone but not in combination with estrogens is associated with an increased risk of fracture.

**Disclosure of Interest**: None Declared

## OC8 - ALTERATIONS OF BONE MICROARCHITECTURE IN YOUNG PATIENTS WITH INFLAMMATORY BOWEL DISEASES ARE ASSOCIATED WITH FRACTURE RISK DURING GROWTH

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**Aims:** Inflammatory bowel diseases (IBD) appearing during childhood and adolescence compromise peak bone mass acquisition and increase fracture risk. The structural determinants of bone fragility in IBD however remain unknown.
**Methods:** We investigated volumetric bone mineral density (vBMD), trabecular and cortical bone microstructure at distal radius and tibia by high-resolution pQCT (XtremeCT, Scanco, Switzerland), aBMD at distal radius, hip and spine and vertebral fracture assessment (VFA) by DXA in 107 young patients (mean age 22.8 yrs, range 12.2-33.7 yrs; 62 females and 45 males) with Crohn's disease (n=75), ulcerative colitis (n=25), undetermined colitis (n=2), and no definitive diagnosis (n=5), and in 389 healthy young individuals.
**Results:** Mean disease duration was 6.1 yrs, 89/107 IBD patients received corticosteroids, 83 other immunomodulators, and 59 vitamin D. Clinical fractures were reported by 38 patients (mean age at 1st fracture, 12.6 yrs), the vast majority of the forearm, arm or hand; 5 had vertebral crush fractures (Grade 1 or 2) and 11 had multiple fractures. As compared to healthy controls (matched 2:1 for age, sex, height and fracture history), the 102 patients with established IBD had similar weight but significantly lower aBMD

at all sites, lower trabecular (Tb) BV/TV and number, and greater Tb separation and inhomogeneous Tb distribution (1/SD TbN) at both distal radius and tibia, lower tibia cortical thickness (CTh), but no differences in cortical vBMD nor bone perimeter. Among IBD's, aBMD was not associated with fractures (by logistic regression adjusted for age, age square, sex, height, weight and protein intake). However, radius and tibia Tb BV/TV, thickness and SD 1/TbN, as well as radius Tb separation and perimeter, were significantly associated with fracture risk (fully adjusted as above), whereas cortical vBMD and CTh were not. After adjustment for aBMD at radius, respectively at femur neck, radius SD 1/TbN and tibia BV/TV, TbTh and perimeter remained independently associated with fracture risk.

**Conclusions:** Young subjects with IBD have low bone mass and poor bone microarchitecture compared to healthy controls. Alterations of bone microarchitecture, particularly in the trabecular bone compartment, are specifically associated with increased fracture risk during growth.

**Acknowledgement:** The Crohn's and Colitis Foundation of America (CCFA) for funding this study

**Disclosure of Interest**: None Declared

## OC9 - INFLUENCE OF 25-HYDROXYVITAMIN D STATUS ON SERUM PARATHYROID HORMONE LEVELS VARIES WITH KDOQI CLASSIFICATION OF RENAL FUNCTION AND IS INDEPENDENT OF 1,25 DIHYDROXYVITAMIN D CONCENTRATIONS

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**Aims:** Vitamin D status is an important determinant of serum parathyroid hormone (PTH) secretion. There is little knowledge, however, to what extent renal function modulates the interaction between 25-hydroxyvitamin D (25OHD) or 1,25 dihydroxyvitamin D [1,25(OH)2D] and PTH secretion.

**Methods:** We analyzed this relationship in 3252 male and female patients who participated in a long-term follow-up study (LURIC study) designed to evaluate the impact of genetic polymorphisms and plasma biomarkers on cardiovascular health. Two-thirds of the study population were male and two thirds were found to have significant coronary artery disease. Based on their renal function patients were categorized into KDOQI categories 1 (creatinine clearance >90ml/min/1.73m2; N=1044), KDOQI 2 (60-89 ml; N=1849) and KDOQI 3 (30-59.9 ml; N=359). Serum levels of 25OHD were assayed using a radioimmunoassay (DiaSorin).

**Results:** Age of patients in the respective categories was 56±10, 64±9 and 69±8 years, respectively. There was a rather small, yet significant difference in 25OHD levels across the 3 KDOQI categories 17.1±9.0, 17.8±9.3 and 15.4±9.1 ng/ml. We formed quartiles (QU) of 25OHD levels and the absolute values of 25OHD (median and interquartile range) were: 7.1 (5.8-8.7), 12.8 (11.5-14.3), 19.0 (17.2-20.9) and 30.1 (25.1-33.3) ng/ml and performed an ANCOVA adjusting for age, sex, BMI, average daily physical activity, pro-NT BNP levels, diabetes mellitus, and blood pressure. With decreasing 25OHD QU (QU4 to QU1) there was a proportionally higher increase in PTH levels with declining renal function: 25.7% (KDOQI1), 32.0% (KDOQI2) and 60.8% (KDOQI3), respectively (all $P<0.001$). Further adjustment for 1,25(OH)2D and serum phosphate levels did not influence this relationship noticeably.

**Conclusions:** We conclude that PTH secretion over a large eGFR range (30 to 120 ml/min/1.73 $m^2$) is almost exclusively regulated by 25OHD and not by 1,25(OH)2D levels as is commonly believed. In addition, a decline in renal function independently of 1,25(OH)2D and serum phosphate levels led to a considerably larger increase in PTH secretion for a given level of 25OHD.

**Disclosure of Interest**: None Declared

## OC10 - GENETIC VARIATION IN THE RANKL/RANK/OPG SIGNALLING PATHWAY IS ASSOCIATED WITH RADIUS GEOMETRY AND VOLUMETRIC BONE MINERAL DENSITY IN MEN

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**Aims:** The aim of this study was to determine if single nucleotide polymorphisms (SNPs) in *RANKL*, *RANK* and *OPG* influence volumetric bone mineral density ($BMD_v$) or bone geometry in men.

**Methods:** Pair-wise tag SNPs ($r^2 \geq 0.8$) were selected for *OPG*, *RANKL* and *RANK* and their 10 kb flanking regions. The SNPs were genotyped in men aged 40-79 years recruited for participation in a population-based study of male aging, the European Male Ageing Study (EMAS). Peripheral quantitative computed tomography (pQCT) measurements were made at the distal (4%) and midshaft (50%) radius in men from two EMAS centres (Manchester, UK and Leuven, Belgium). Total and trabecular $BMD_v$ ($mg/mm^3$), and bone cross sectional area ($mm^2$) were measured at the distal radius. Cortical $BMD_v$ ($mg/mm^3$); total, cortical and medullary area ($mm^2$); and cortical thickness (mm) were measured at the midshaft radius. Linear regression was used to test the association between SNPs and bone phenotypes under an additive genetic model adjusting for centre. Results are reported as mean change in the outcomes for each copy of the minor allele.

**Results:** Seventy-four SNPs (*RANKL*: 8, *RANK*: 44 and *OPG*: 22) and 589 subjects were included in the analysis. We identified

a number of SNPs in *RANKL*, *RANK* and *OPG* associated with $BMD_v$ including rs2073617 in *OPG* associated with total $BMD_v$ (β=9.00; 95% CI=1.73, 16.27; p=0.016) and rs4524035 in *RANK* associated with trabecular $BMD_v$ both at the distal radius (β= -8.59; 95% CI=-16.3, -0.87; p=0.030), and rs10505348 in *OPG* associated with cortical $BMD_v$ at the midshaft radius (β=5.50; 95% CI=0.94, 10.06; p=0.019). The SNP rs10505348 was also associated with higher cortical thickness (β=0.06; 95% CI=0.01, 0.11; p=0.026) and smaller medullary area (β= -2.33; 95% CI=-4.45, -0.21; p=0.031) at the midshaft radius. There were four other SNPs in *RANKL* associated with medullary area at the midshaft radius including rs633137 (β=4.74; 95% CI=1.13, 8.35; p=0.010). We also identified four SNPs in *RANK* associated with the distal radius cross sectional area including rs8083511 (β=10.39; 95% CI=2.05, 18.73; p=0.015).

**Conclusions:** Our findings suggest that genetic variation in the *RANKL/RANK/OPG* signalling pathway influences radius geometry and $BMD_v$ (cortical, trabecular and total) in men with some SNPs influencing both.

**Disclosure of Interest**: None Declared

## OC11 - QUALITY OF LIFE REDUCTION OF VERTEBRAL FRACTURES – THE DIFFERENCE BETWEEN HOSPITALIZED AND NON-HOSPITALIZED PATIENTS

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**Aims:** To present an interim analysis of the International Costs and Utilities Related to Osteoporotic fractures Study (ICUROS) of the quality of life impact of vertebral fractures during the first twelve months after sustaining the fracture and any difference in quality of life (QoL) between hospitalized and non-hospitalized patients in Austria, France, Italy and Russia.

**Methods:** Patients were enrolled from 23 study centers in Austria, France, Italy, and Russia. Patients were asked about their QoL before (recollected), directly after the fracture (within two weeks after fracture), at four months and 12 months after the fracture. The QoL was measured by the EQ-5D questionnaire.

**Results:** A data extraction in January 2010 resulted in a dataset of 253 patients with a vertebral fracture, out of which 21.3% had been hospitalized in connection to this event, however varying markedly between countries (in Russia 11.5% and Austria 51.2%). 85% were women with a mean age of 69 at the time of fracture. There was no significant difference in QoL before fracture between the two patient groups. The result presented in Figure 1 indicates that the effect on quality of life was larger for hospitalized patients compared to non-hospitalized. The effect sustained one year after the fracture. The average QoL loss the first year was estimated at 18.6% and 33.9% for non-hospitalized and hospitalized patients, respectively.

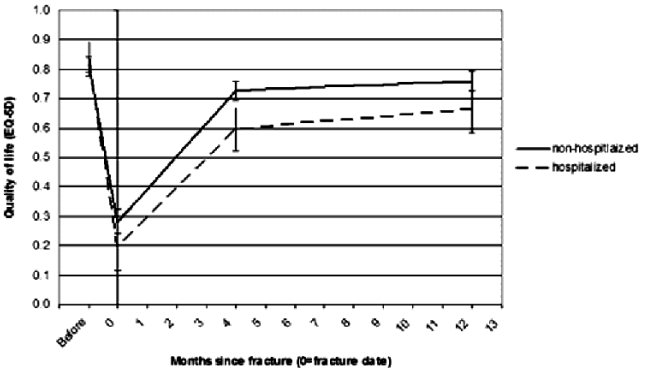


Figure 1. Quality of life after sustaining a vertebral fracture (95% Cl)

**Conclusions:** Patients who were hospitalized following a vertebral fracture had a larger absolute and relative health related quality of life decrement than non-hospitalized patients.

**Disclosure of Interest**: None Declared

## OC12 - COMPARISON OF PREDICTION MODELS FOR TEN-YEAR RISK OF OSTEOPOROTIC FRACTURES WITH FRAX®: THE JAPANESE POPULATION-BASED OSTEOPOROSIS (JPOS) COHORT STUDY

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**Aims:** The objective was to evaluate the ability of the Japanese version of FRAX®, a WHO fracture risk assessment tool, to predict the 10-year probability of osteoporotic fractures.

**Methods:** Major (hip, clinical vertebral, forearm, and proximal humeral) and hip osteoporotic fracture event was ascertained in the 10-year follow-up survey. The subjects for the analysis were 831 women aged 40-74 years at the baseline survey. The ratio of the observed events to the events estimated from FRAX® (O/E ratio) was obtained. The area under the curve (AUC) from receiver operating characteristic curve analysis was obtained for FRAX® and multiple logistic regression models using age, body weight, and femoral neck bone mineral density (FN BMD).

**Results:** There were no significant differences between any probabilities of observed events and probabilities obtained using FRAX® with or without FN BMD regarding major (O/E ratio, 0.87 with P=0.544; O/E ratio, 0.87 with P=0.568), or hip (O/E ratio, 0.47 with P=0.314; O/E ratio, 0.44 with P=0.210) fractures. AUC values from FRAX® with BMD were similar to those of models using age and FN BMD (Table).

**Conclusions:** The Japanese version of FRAX® estimated the 10-year probability of osteoporotic fractures in this population, although it was not superior to models that used only age and FN BMD.

Table. Ability of FRAX® and multiple logistic regression models to predict 10-year probability of osteoporotic fracture in the JPOS Cohort Study, 1996-2006 (N=831).

| Model | RR/SD (95%CI) | AUC (95%CI) |
|---|---|---|
| Major osteoporotic fracture | | |
| Age | 1.83 (1.39-2.40) | 0.69 (0.61-0.76) |
| FN BMD | 1.67 (1.32-2.11) | 0.64 (0.57-0.72) |
| Age + FN BMD | 1.97 (1.50-2.59) | 0.69 (0.62-0.77) |
| Age + BW + FN BMD | 1.89 (1.50-2.37) | 0.71 (0.63-0.78) |
| FRAX® with FN BMD | 1.71 (1.37-2.12) | 0.69 (0.62-0.77) |
| FRAX® without FN BMD | 1.55 (1.24-1.94) | 0.67 (0.60-0.75) |
| Hip fracture | | |
| Age | 1.91 (1.34-2.71) | 0.87 (0.74-1.00) |
| FN BMD | 1.49 (0.94-2.39) | 0.82 (0.68-0.96) |
| Age + FN BMD | 1.64 (1.19-2.27) | 0.89 (0.77-1.01) |
| Age + BW + FN BMD | 1.65 (1.22-2.22) | 0.89 (0.78-1.01) |
| FRAX® with FN BMD | 1.70 (1.28-2.24) | 0.87 (0.74-1.00) |
| FRAX® without FN BMD | 2.01 (1.45-2.77) | 0.85 (0.70-1.01) |

RR/SD: Relative risk per 1 SD-increase. 95%CI: 95% Confidence Interval. AUC: Area under the curve.

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**Disclosure of Interest**: None Declared

## OC13 - PROXIMAL FEMORAL STRENGTH FOR PREDICTING HIP FRACTURE IN MEN AND WOMEN: THE AGES-REYKJAVIK STUDY

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**Aims:** Hip fracture risk depends on fall risk and hip bone strength. Finite element (FE) models explicitly account for bone density/property distribution and bone geometry, the determinants of hip bone strength. The study goal was to evaluate FE-computed hip strength as a predictor of hip fracture in elderly men and women.

**Methods:** 5500 subjects from the AGES-Reykjavik study age 65-90 years had quantitative CT (QCT) scans of the hip (Siemens Somatom 4, 120 kVp, 150 mAs, 3-mm-thick slices). During 5 to 7 years follow-up, 27 men and 52 women sustained hip fractures. For each fracture subject, roughly 2 sex- and age-matched control subjects (57 men, 104 women) were randomly selected. FE models of the left proximal femur of each subject were created and analyzed under single-limb stance loading. These models used nonlinear material properties and computed the fracture load (FL); analogous models for fall loading are not yet available. Proximal femur areal bone mineral density (BMD) was computed from the CT scans. Logistic regression was used to identify hip fracture predictors separately in men and women, and odds ratios (OR) per standard deviation were computed with adjustment for age, height and weight.

**Results:** FL was significantly associated with hip fracture in both men and women ($p<0.002$), and OR values increased after controlling for age, height and weight (Table). OR values for FL were greater than those for areal BMD but not statistically greater. Both sexes had nearly identical correlations between FL and BMD (r=0.86-0.87). Even so, when FL and BMD were combined in the same prediction model while controlling for age, height and weight, FL (OR=4.15, p=0.04), but not BMD (OR=1.22, p=0.72), was significantly associated with fracture in men, but neither FL (OR=1.76, p=0.21) nor BMD (OR=1.50, p=0.30) remained associated with fracture in women. OR values for FL tended to be greater in men than in women.

Table. Odds Ratios (OR) per Standard Deviation

| Predictor | Men - OR (95% CI) | Women - OR (95% CI) |
|---|---|---|
| FL | 3.8 (1.7-8.2) | 2.2 (1.4-3.7) |
| FL \| Age, Height, Weight | 5.0 (2.0-12.4) | 2.5 (1.3-4.6) |
| BMD | 3.1 (1.6-5.8) | 2.2 (1.4-3.4) |

**Conclusions:** FE-computed hip FL predicts hip fracture in both men and women. FL appears to be a stronger predictor of hip fracture in men than in women, perhaps due to the inherently lower bone strength in women regardless of fracture status. These results imply that an additional factor, such as propensity for falling, may be important for assessing fracture risk in women.

**References:** This work was presented previously at the 2009 meeting of the ASBMR. Keyak et al., J Bone Miner Res 24 (Suppl 1). Available at http://www.asbmr.org/Meetings/AnnualMeeting/Abstracts09.aspx

**Acknowledgement:** Funded by NIA/NIH.

**Disclosure of Interest**: None Declared

## OC14 - IN VIVO DISCRIMINATION OF HIP FRACTURE WITH VOLUMETRIC QUANTITATIVE COMPUTED TOMOGRAPHY (QCT): RESULTS FROM THE PROSPECTIVE EUROPEAN FEMUR FRACTURE STUDY (EFFECT)

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**Aims:** The aim of the EFFECT study was the discrimination of osteoporotic hip fractures. This in vivo case-control study had 3 objectives: (1) to evaluate the power of QCT using a dedicated 3D image analysis tool (MIAF-Femur) to predict hip fracture; (2) to determine the main risk predictors of fractures; (3) to compare QCT to DXA.

**Methods:** 107 women were enrolled, 47 women with fresh hip fractures (mean age, 81.6 years) and 60 female controls (mean age, 73.4 years). In 24 cases, the fracture was cervical, in 23 cases, trochanteric. Bone mineral density (BMD) and geometric variables of cortical and trabecular bone in the femoral head, neck, trochanteric, intertrochanteric and proximal shaft volumes of interest (VOI) were assessed using QCT. The analysis was performed by MIAF-Femur. Areal BMD was assessed using DXA. In the 47 fractured women measurements were performed of the non-fractured hip; in the controls the left hip was investigated. Between groups difference of anthropometric, densitometric and geometric variables were compared by Student's t-tests. For multivariate analysis stepwise logistic regressions were employed.
**Results:** Apart from age there were no group differences for anthropometric, densitometric or geometric variables. After age adjustment in the most significant model predictors for all fractures were integral head BMD and cortical thickness of the proximal shaft (AUC=0.843). Combinations of integral head BMD and cortical neck thickness (AUC=0.824) or trabecular trochanteric BMD and cortical thickness of the proximal shaft (AUC=0.835) were almost as strong. For cervical fractures only trabecular BMD of the femoral head remained (AUC=0.81; p=0.005). The best prediction of trochanteric fractures was obtained by combining trabecular BMD and cortical thickness of the trochanter (AUC=0.88). The predictive power of QCT was not significantly different from that of DXA.
**Conclusions:** Trochanteric fractures were best predicted by trochanter measurements, whereas for all and cervical hip fractures BMD of the head and cortical thickness of the shaft played a dominant role. QCT of the hip is the method of choice to differentiate these different compartments. With advanced analysis software such as MIAF-Femur the head and proximal shaft VOIs can be assessed in addition to the neck, trochanter and intertrochanteric VOIs, however, in our population the prediction of hip fractures by DXA was not significantly inferior compared to that by QCT.

**Disclosure of Interest**: None Declared

## OC15 - BASELINE RANKL:OPG RATIO AND MARKERS OF BONE AND CARTILAGE DEGRADATION PREDICT ANNUAL RADIOLOGICAL PROGRESSION OVER 11 YEARS IN RHEUMATOID ARTHRITIS

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**Aims:** Traditional predictors of radiological progression in rheumatoid arthritis (RA) are mostly markers of inflammation. We investigated to what extent baseline measurements of the ratio of receptor activator of nuclear factor κB ligand (RANKL) / osteoprotegerin (OPG) and C-terminal cross linking of type-I and type-II (CTX I and CTX-II) in addition to traditional markers of disease severity, could predict annual radiological progression.
**Methods:** A cohort of 155 early, active, untreated RA patients that participated in the COBRA trial was followed for 11 years. Urine was sampled at baseline and after 3 months from start of treatment and analyzed for CTX-I and CTX-II. Baseline serum samples were analyzed for RANKL and OPG. Available traditional markers of disease severity included baseline measurements of erythrocyte sedimentation rate, rheumatoid factor and baseline radiological damage. A digital database of frequent radiographs was available, scored according to the Sharp/van der Heijde method. Individual annual progression rates were calculated and used as outcome variable. Multiple linear regression analyses identified the strongest predictors of annual radiological progression.
**Results:** In multivariable analyses the RANKL:OPG ratio and CTX-I or CTX-II proved to be independent predictors of annual radiological damage over 11 years. The prediction of annual radiological progression was strongest when the RANKL:OPG ratio and CTX1 or CTX2 were evaluated in the same model (36-39% explained variance). Adding the effect of treatment at 3 months to the baseline models improved the predictive ability of the models up to 44-46%.
**Conclusions:** Unfavorable baseline levels of the RANKL:OPG-ratio as well as CTX-I (markers of bone resorption) and CTX-II (a marker of predominantly cartilage degradation) in patients with early, active, untreated RA are strong independent predictors of rapid and persistent damage progression over 11 years follow up. Early improvement in bone markers on treatment predicts a better outcome.

**Disclosure of Interest**: None Declared

## OC16 - EVALUATION OF HEALTH-RELATED QUALITY OF LIFE IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS WHO PARTICIPATED IN THE FREEDOM TRIAL

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**Aims:** Denosumab (DMAb) is a fully human antibody that inhibits RANKL, an essential mediator of osteoclast formation, function, and survival. In the FREEDOM trial, DMAb significantly reduced the risk of fractures.[1] In fracture trials with other osteoporosis therapies, no difference between treatment groups in health-related quality of life (HRQoL) was observed.[2,3] Here we evaluate the effect of DMAb on HRQoL, and the association of all incident clinical fractures, regardless of treatment group, with HRQoL, in the women who participated in the FREEDOM trial.
**Methods:** The FREEDOM trial enrolled 7,868 women aged 60-90 years with a total hip and/or lumbar spine DXA T-score <–2.5 and not <–4.0 at either site. Women were randomized to receive DMAb 60 mg sc every 6 months or placebo, in addition to daily

calcium and vitamin D. HRQoL was assessed with the Osteoporosis Assessment Questionnaire-Short Version (OPAQ-SV) at baseline and every 6 months for 3 years. The OPAQ-SV has 34 disease-specific questions in 3 HRQoL dimensions of physical function, emotional status, and back pain. Higher scores represent better health status.

**Results:** OPAQ-SV completion rates at year 3 were 83%. There were no significant differences between treatment groups in HRQoL measures when comparing baseline to year 3. However, compared with women without any fractures, women with incident clinical fractures, regardless of treatment group, reported declines in OPAQ-SV physical function and emotional status dimensions at year 3 ($P$<0.0001; Table).

**Table: OPAQ-SV Changes From Baseline to Year 3[†]**

| | With Incident Clinical Fracture[††] (N=670) | | Without Any Incident Fracture (N=6821) | |
|---|---|---|---|---|
| | n | Mean (95% CI) | n | Mean (95% CI) |
| OPAQ-SV: Physical function | 567 | −4.1 (−5.7, −2.6)* | 5585 | −0.5 (−0.9, −0.1) |
| OPAQ-SV: Emotional status | 566 | −5.0 (−6.6, −3.5)* | 5588 | −0.8 (−1.2, −0.4) |
| OPAQ-SV: Back pain | 567 | 1.6 (−0.4, 3.7)* | 5597 | 4.6 (4.0, 5.2) |

[†]Subjects with only morphometric vertebral fractures were not included in the analysis. [††]Includes all subjects with clinical fractures regardless of trauma severity (excluding skull, facial, finger, and toe fractures). *P≤0.0001 compared with the group without any incident fracture; based on an ANCOVA model, adjusting for age and the respective OPAQ-SV baseline score.

**Conclusions:** As observed in similar studies with other osteoporosis therapies, statistically significant differences in mean change in HRQoL from baseline to end of study were not found when comparing treatment groups. However, incident clinical fractures were associated with significant decreases in HRQoL at year 3, as assessed by the OPAQ-SV. Future analyses will incorporate the effects of time elapsed since fracture.

**References:** [1]Cummings SR et al., N Engl J Med 2009;361:756; [2]Silverman SL et al., Arthritis Rheum 2001;44:2611; [3]Oglesby AK et al., J Rheumatol 2003;30:1579

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## OC17 - SUSTAINED EFFICACY OF BAZEDOXIFENE IN PREVENTING FRACTURES IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS: RESULTS OF A 5-YEAR, RANDOMIZED, PLACEBO-CONTROLLED STUDY

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**Aims:** In a pivotal 3-year phase 3 study, bazedoxifene (BZA) was shown to significantly reduce new vertebral fracture risk in postmenopausal women with osteoporosis, and in a subgroup of women at higher fracture risk, to decrease the risk of nonvertebral fracture (NVF). Here we describe the efficacy of BZA in preventing fractures over 5 years of therapy.

**Methods:** The core study enrolled generally healthy postmenopausal women aged 55 to 85 years (N=7,492; mean age, 66.4 y) with osteoporosis, defined as lumbar spine (LS) or femoral neck (FN) T-scores ≤-2.5 and no prevalent vertebral fracture or LS and FN T-scores ≥-4.0 with prevalent vertebral fracture. Eligible subjects were randomized to daily treatment with BZA 20 or 40 mg, raloxifene (RLX) 60 mg, or placebo; subjects received supplemental elemental calcium (1,000-1,200 mg/d) and vitamin D (400-800 IU/d). A total of 4,216 subjects were enrolled in the extension study (Years 4 and 5). The RLX 60-mg treatment arm was discontinued in the fourth year and subjects receiving BZA 40 mg were transitioned to BZA 20 mg (BZA 40/20 mg) after 4 years. Findings at 5 years are reported for BZA 20 mg, BZA 40/20 mg, and placebo only. The primary endpoint was the incidence of new vertebral fractures; the incidence of NVFs was a secondary endpoint.

**Results:** At 5 years, Kaplan-Meier estimates of the incidence of new vertebral fractures in the intent-to-treat population was significantly reduced with BZA 20 mg (4.5%) and BZA 40/20 mg (3.9%) compared with placebo (6.8%), corresponding to relative risk reductions of 35% ($P$=0.014) and 40% ($P$=0.005), respective-

ly. There was no difference in NVF rates among subjects treated with BZA 20 mg (9.5%), BZA 40/20 mg (7.6%), or placebo (9.0%) in the overall population. An analysis of a higher-risk subgroup (femoral neck T-score ≤-3.0 and/or ≥1 moderate or ≥2 mild vertebral fractures; n=1324) showed a 37% ($P$=0.06) and 31% ($P$=0.16) reduction in NVF rates with BZA 20 mg and BZA 40/20 mg, respectively, relative to placebo. Overall, BZA showed a favorable safety and tolerability profile over 5 years of treatment.
**Conclusions:** Overall findings at 5 years were similar to those observed at 3 years, and support a sustained anti-fracture effect of BZA 20 mg on new vertebral fractures in postmenopausal women with osteoporosis and on NVFs in a subgroup of women at higher risk for fracture.

**Disclosure of Interest**: A. Chines Employee of: Pfizer Inc, J. Zanchetta Consultant / Speaker's bureau / Advisory activities with: Amgen, Lilly, Pfizer, Servier, H. Genant Consultant / Speaker's bureau / Advisory activities with: GSK, Roche, Wyeth, Novartis, Lilly, Amgen, Servier, Merck, Synarc, Stock ownership or royalties of: Synarc, D. Kendler Grant / Research Support from: Amgen, Lilly, Novartis, Merck, P&G, Wyeth, Pfizer, BioSante, GSK, Zelos, Consultant / Speaker's bureau / Advisory activities with: Amgen, Lilly, Novartis, Merck, P&G, Wyeth, Pfizer, BioSante, GSK, Zelos, F. Rio de la Loza: None Declared, A. Kung: None Declared, G. Constantine Employee of: Pfizer Inc, J. Adachi Grant / Research Support from: Amgen, Lilly, GSK, Merck, Novartis, Pfizer, P&G, sanofi-aventis, Roche, Wyeth, Bristol-Myers Squibb, Consultant / Speaker's bureau / Advisory activities with: Amgen, AstraZeneca, Lilly, GSK, Merck, Novartis, Nycomed, Pfizer, P&G, Roche, sanofi-aventis, Servier, Wyeth, Bristol-Myers Squibb, S. Silverman Grant / Research Support from: Wyeth, Lilly, Consultant / Speaker's bureau / Advisory activities with: Lilly

## OC18 - SKELETAL EFFECTS OF A SCLEROSTIN ANTIBODY ALONE OR IN COMBINATION WITH AN ANTI-RESORPTIVE AGENT IN OVARIECTOMIZED RATS PRETREATED WITH AN ANTI-RESORPTIVE AGENT

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**Aims:** Inhibition of sclerostin by treatment with a sclerostin antibody (Scl-Ab) has been shown to increase bone formation and restore bone mass and bone strength in ovariectomized (OVX) rats with established osteopenia. In the current study, we examined whether pretreatment with the anti-resorptive agent alendronate (ALN) would result in a blunting of the bone anabolic effects induced by Scl-Ab in OVX rats.
**Methods:** Ten-month-old OVX rats (3.5 months post-OVX) were treated with ALN (0.028 mg/kg, SC, 2x/week) for 6 weeks and then transitioned to Scl-Ab (25 mg/kg, SC, 1x/week) alone, or to a combination of Scl-Ab plus ALN (n=10/group) for an another 6 weeks. As additional controls for the study, a separate set of OVX rats were treated with vehicle for 6 weeks and then transitioned to Scl-Ab alone, or to vehicle for another 6 weeks (n=10/group).
**Results:** Histomorphometric analysis of the 3rd lumbar vertebral bodies revealed that 6 weeks of ALN treatment significantly reduced trabecular mineralizing surface (MS/BS), mineral apposition rate (MAR) and bone formation rate (BFR/BS) in OVX rats. Transition to Scl-Ab from ALN or vehicle was equally effective at restoring trabecular bone volume (BV/TV) and increasing trabecular thickness (Tb.Th), indicating that ALN pretreatment did not blunt the bone restorative effects of Scl-Ab in OVX rats. Consistent with these findings, dynamic histomorphometric analysis showed that transition to Scl-Ab from ALN or vehicle was equally effective at increasing trabecular MS/BS, MAR, and BFR/BS at lumbar vertebrae. Similar findings for MS/BS, MAR, and BFR/BS were observed on both the periosteal and the endocortical surfaces of the tibial shaft. Transition to Scl-Ab from ALN or vehicle was equally effective at increasing serum osteocalcin, a marker of bone formation. Furthermore, BV/TV, Tb.Th, trabecular and cortical bone formation parameters, and serum osteocalcin did not differ significantly between Scl-Ab alone and the combination of Scl-Ab plus ALN in OVX rats pretreated with ALN.
**Conclusions:** The increases in bone formation and bone mass resulting from treatment with a sclerostin antibody, with or without alendronate co-administration, were not blunted by pretreatment with alendronate in OVX rats. These data suggest that the anabolic effects of sclerostin antibody are independent from activation of bone resorption.

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## OC19 - RONACALERET, A CALCIUM-SENSING RECEPTOR ANTAGONIST, FAILS TO INCREASE BMD

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**Aims:** The calcium-sensing receptor in parathyroid cells regulates PTH secretion. Antagonism of this receptor was anticipated to stimulate PTH release and increase BMD.
**Methods:** In a phase II, dose-ranging, placebo-(PBO) controlled study, 569 postmenopausal women with osteoporosis were enrolled into open-label teriparatide (TER), or randomized to PBO, one of 4 doses of ronacaleret (RON, 100, 200, 300, and 400 mg) or alendronate (ALN, 70 mg weekly). The primary endpoint was the % change in lumbar spine (LS) BMD at 12 months.
**Results:** Following an interim analysis at 6 months, the trial was phased out due to lack of efficacy; patients returned for their fi-

nal visit between months 10-12. RON (200, 300, and 400 mg) increased LS BMD more than PBO (1.4-1.9%); ALN and TER increased LS BMD 4.7% and 9.2%, respectively. RON (200-400 mg) caused small but statistically significant decreases in total hip (TH) BMD. ALN and TER increased TH BMD by 2.8% and 2.6%, respectively. Median increases in serum CTx were >20% on RON (200-400 mg) at month 6, reaching a maximum of 58% at month 10. In comparison, TER produced a median increase of 57% at month 3 and reached a maximum of 103% at month 10. P1NP had a median increase over baseline up to 38% in the RON groups (200, 300, 400 mg) at week 4 vs. a median increase of 98% for TER. P1NP reached a maximal median increase up to 148% in the RON groups at month 10 as compared to the maximal median increases of 151% for TER at month 6. Serum calcium showed dose-dependent elevations at pre- and post-dose in the RON groups as early as week 1. Pharmacokinetic data revealed that PTH(1-84) AUC was larger in the RON groups compared to historical data with TER. We hypothesized that RON induced a mild sustained hyperparathyroidism. An observational extension study followed subjects off study for 6-12 months. LS BMD changed from the month 10-12 endpoint in the PBO group by -1.5%. Changes in the RON 100, 200, 300, and 400 mg and ALN groups were 1.4%, 0.1%, -0.9%, 1.3%, 0% respectively. At the TH, changes were minimal for the PBO, RON 100, 200, 300, and 400 mg and ALN groups, respectively: -1.2%, +0.2%, -0.1%, -0.6, +0.1%, and -1.7%.

**Conclusions:** These findings are consistent with the hypothesis that ronacaleret, due to a prolonged pharmacodynamic effect, induced a mild primary hyperparathyroidism and did not produce therapeutically promising effects on bone density.

**Disclosure of Interest**: L. Fitzpatrick Employee of: GlaxoSmithKline, C. Dabrowski Employee of: GlaxoSmithKline, G. Cicconetti Employee of: GlaxoSmithKline, S. Papapoulos Consultant / Speaker's bureau / Advisory activities with: GlaxoSmithKline, Roche, H. Bone Grant / Research Support from: Amgen, Merck, Lilly, Zelos, Consultant / Speaker's bureau / Advisory activities with: Amgen, Merck,GlaxoSmithKline, Zelos, Novartis, J. Bilezikian Consultant / Speaker's bureau / Advisory activities with: GlaxoSmithKline, Merck, Lilly, Novartis, Alliance for Better Bone Health

## OC20 - EFFICACY OF DENOSUMAB RELATIVE TO OTHER OSTEOPOROSIS THERAPIES FOR PREVENTION OF FRACTURES IN POSTMENOPAUSAL OSTEOPOROSIS: RESULTS OF AN ADJUSTED INDIRECT AND MIXED TREATMENT COMPARISON

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**Aims:** Denosumab has been shown to significantly reduce three of the most prevalent types of fractures (vertebral, hip, non-vertebral) compared to placebo (FREEDOM, 2009[1]). This analysis assesses the efficacy of denosumab versus other osteoporosis therapies in reducing fracture risk in postmenopausal women with osteoporosis.

**Methods:** A systematic review used the National Collaborating Centre for Nursing & Supportive Care methods (National Institute for Clinical Excellence, 2008[2]) to identify blinded randomized clinical trials which evaluated fracture efficacy of osteoporosis therapies in postmenopausal women. A meta-analysis was conducted with random effect models using relative risks (RR) based on raw events for the number of patients with a fracture during follow-up. Treatment effect was measured using RR for adjusted indirect comparisons (Bucher et al.,1997[3]) and using odds ratios (OR) for mixed treatment comparison (combination of evidence from direct and indirect comparisons to incorporate all available evidence). All analyses were carried out in SAS® v9.1 or above.

**Results:** The systematic review identified 211 studies, of which 34 met inclusion criteria for evaluation. Results of random effects meta-analysis, adjusted indirect comparison and mixed treatment comparison in reducing fracture risk are summarized in Table 1.

**Table 1: Random Effects Meta-Analysis, Adjusted Indirect Comparison, & Mixed Treatment Comparison***

| Fracture type<br>Intervention | Random Effects Meta-Analysis & Adjusted Indirect Comparison<br>RR; 95% CI | Mixed Treatment Comparison<br>OR; 95% CI; P value |
|---|---|---|
| **New Vertebral**[§] | | |
| Denosumab vs Placebo | **0.325 (0.256, 0.412)** | **0.311 (0.236, 0.409; P<.0001)** |
| Denosumab vs. Oral BPs | **0.565 (0.429, 0.743)** | **0.567 (0.408, 0.788; P=0.003)** |
| **Non-Vertebral** | | |
| Denosumab vs. Placebo | **0.813 (0.689, 0.959)** | **0.801 (0.650, 0.987; P=0.04)** |
| Denosumab vs. Oral BPs | 0.961 (0.790, 1.169) | 0.987 (0.779, 1.250;P=0.899) |
| **Hip** | | |
| Denosumab vs. Placebo | **0.605 (0.373, 0.983)** | **0.603 (0.365, 0.996; P=0.049)** |
| Denosumab vs. Oral BPs | 0.832 (0.491, 1.411) | 0.841 (0.486, 1.455; P=0.455) |

[§]Fractures that are identified radiographically are termed radiographic or morphometric, and include both symptomatic and asymptomatic fractures.
*Bold type refers to significant results at 5% level. RR: relative risk; OR: odds ratio; CI: confidence interval; BP: bisphosphonate

**Conclusions:** Denosumab therapy was associated with significantly improved reductions in all fracture types evaluated (new vertebral, non-vertebral and hip) compared to placebo. Denosumab was significantly more effective in preventing new vertebral fractures than the current standard of care, oral bisphosphonates.

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Advisory activities with: Amgen, C. Cooper Grant / Research Support from: Project was funded by Amgen, Consultant / Speaker's bureau / Advisory activities with: Servier, Procter & Gamble/ Alliance, Eli Lilly, Merck Sharpe & Dohme, GSK/Roche, Amgen, Novartis, H. Man Employee of: Amgen UK, Stock ownership or royalties of: May own stock or stock options in Amgen, S. Shepherd Employee of: Amgen UK , Stock ownership or royalties of: May own stock or stock options in Amgen, E. Badamgarav Employee of: Amgen Inc., Stock ownership or royalties of: May own stock or stock options in Amgen, M. Gitlin Employee of: Amgen (Europe) GmbH, Stock ownership or royalties of: May own stock or stock options in Amgen, C. Roux Grant / Research Support from: Project was funded by Amgen, Consultant / Speaker's bureau / Advisory activities with: Amgen, Alliance, MSD, Novartis, Roche, Servier

## OC21 - REASONS FOR STOPPING ANTI-OSTEOPOROSIS MEDICATIONS AMONG POSTMENOPAUSAL WOMEN: THE GLOBAL LONGITUDINAL STUDY OF OSTEOPOROSIS IN WOMEN

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**Aims:** Women on prescription anti-osteoporosis medications often fail to continue their therapy, with some switching and others discontinuing treatment. We assessed discontinuation of such medications and factors associated with stopping treatment in a large international study.

**Methods:** GLOW is an observational study of non-institutionalized women 55+ recruited by 723 primary physician practices (10 countries). Women visiting practices in prior 2 years were eligible. Self-administered questionnaires were mailed (baseline, 12 months). We collected data on demographics; medical history; risk factors for fracture; fracture occurrence; self-report of prevention, diagnosis & treatment. Women were asked if they had stopped taking any of 10 anti-osteoporosis medications: alendronate, etidronate, ibandronate, pamidronate, risedronate (bisphosphonates), calcitonin, raloxifene, strontium ranelate, teriparatide, tibolone (non-bisphosphonates).

**Results:** 1-year data were available for 32,457 (54%) women. 5321 had been on an anti-osteoporosis medication at baseline; 1029 (19%) reported stopping it around 1 year later. Prevalence of prior fracture, perception of risk, and concomitant use of calcium/vit D did not differ between the 2 populations. Number of concomitant medicines was not a determinant of stopping. Most frequent reasons for stopping were doctor's advice, side effects, & concern about long-term risks (Table). Side effects or long-term risk was the reason cited by 37%. Similar percentages of women stopped taking non-bisphosphonates as bisphosphonates (20% vs. 18%). More women who stopped bisphosphonates cited difficulty taking the medicine vs. those stopping non-bisphosphonates (7.8% vs. 2.7% p=0.01). When comparing reasons for stopping monthly (N=350) vs. weekly (N=4692) bisphosphonates, more monthly users stopped due to side effects than did weekly users (31% vs. 21%, p=0.046).

Table Reasons for stopping anti-osteoporosis medication at 1 year (N=32,457)
*Alendronate, etidronate, ibandronate, pamidronate, risedronate

| | Any anti-osteoporosis medication (n=5321) N (%) | Bisphosphonate* (n=5042) N (%) | Non-bisphosphonate (n=1028) N (%) |
|---|---|---|---|
| Stopped taking bone medication at 1 year | 1029 (19) | 835 (18) | 185 (20) |
| Didn't feel it was helping | 43 (4.2) | 30 (3.6) | 12 (6.5) |
| Side effects | 224 (22) | 183 (22) | 40 (22) |
| Difficult to take as directed | 70 (6.8) | 65 (7.8) | 5 (2.7) |
| Concern about long term risks | 196 (19) | 158 (19) | 37 (20) |
| Side effect or concern over long term risk | 384 (37) | 314 (38) | 68 (37) |
| Too expensive | 71 (6.9) | 58 (6.9) | 13 (7.0) |
| Doctor's advice | 386 (37) | 303 (36) | 80 (43) |
| Taking too many other medicines | 49 (4.8) | 44 (5.3) | 4 (2.2) |
| Other reason | 156 (15) | 126 (15) | 27 (14) |

**Conclusions:** The most frequently cited reasons for stopping treatment at 1 year were doctor's advice, side effects and concern over long-term risks. Over twice the percentage of bisphosphonate users who stopped taking medication cited difficulty taking the medicine vs. users of other anti-osteoporosis medications.

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/ Advisory activities with: Amgen, sanofi-aventis, GlaxoSmithKline, Roche, Lilly Deutschland, Orion Pharma, Merck Sharp and Dohme, Merckle, Nycomed, Procter & Gamble, Novartis, Roche, TEVA, Other: GE LUNAR, G. Nika: None Declared, S. Gehlbach Grant / Research Support from: The Alliance for Better Bone Health (sanofi-aventis and Warner Chilcott)

## OC22 - BISPHOSPHONATES AND GLUCOCORTICOID OSTEOPOROSIS IN MEN: RESULTS OF A RANDOMIZED CONTROLLED TRIAL COMPARING ZOLEDRONIC ACID WITH RISEDRONATE

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**Aims:** There are limited data available on the effect of bisphosphonates in men receiving glucocorticoid therapy. We studied 265 men, mean age 56.4 yrs (range 18-83), among the patients enrolled in two arms of a double-blind, double dummy, 1-year study comparing the effects of Zoledronic acid (ZOL) *vs.* Risedronate (RIS) in patients either commencing glucocorticoid treatment at a dose of at least 7.5 mg per day of prednisone or equivalent (prevention arm, $n$=88) or continuing long-term treatment of glucocorticoid at that dose (treatment arm, $n$=177).
**Methods:** Patients received either ZOL 5 mg infusion at study entry or RIS 5 mg daily, along with calcium and vitamin D supplementation (1000 mg and 400-1200 IU respectively). The primary endpoint was difference in bone mineral density (BMD) at the lumbar spine (LS) at 12 months. Secondary endpoints included changes in BMD at other sites such as total hip and femoral neck, changes in biochemical markers of bone turnover (β-C-terminal telopeptides of type 1 collagen [β-CTx] and procollagen type 1 aminoterminal propeptide [PINP]), and overall safety.
**Results:** In the treatment arm, ZOL increased LS BMD by 4.7% compared with 3.3% for RIS and at the total hip the changes were 1.8% *vs.* 0.2%, respectively. In the prevention arm, bone loss was prevented by both treatments. At the LS the changes were 2.5% *vs.* -0.2% for ZOL *vs.* RIS and at the total hip the changes were 1.1% *vs.* -0.4%, respectively. The differences between ZOL and RIS were significant at the LS in the treatment ($p$<0.025) and prevention ($p$<0.0025) arms as well as at the total hip ($p$=0.0004 and $p$<0.025 for treatment and prevention, respectively). In the treatment sub-group, ZOL demonstrated a significantly greater reduction in serum β-CTx and PINP relative to RIS at all time-points. In the prevention sub-group, ZOL demonstrated a significantly greater reduction in β-CTx at all time-points, and in PINP at Month 3 ($p$=0.0297) only. Both treatments were well tolerated in men, albeit with a higher incidence of influenza-like illness and pyrexia events post-infusion with ZOL.
**Conclusions:** Once yearly treatment with ZOL preserves or increases bone density within 1 year to a greater extent than daily treatment with RIS in men receiving glucocorticoid therapy.

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## OC23 - MORTALITY RISK FOR OPERATED AND NON-OPERATED VERTEBRAL FRACTURE PATIENTS IN THE U.S. MEDICARE POPULATION

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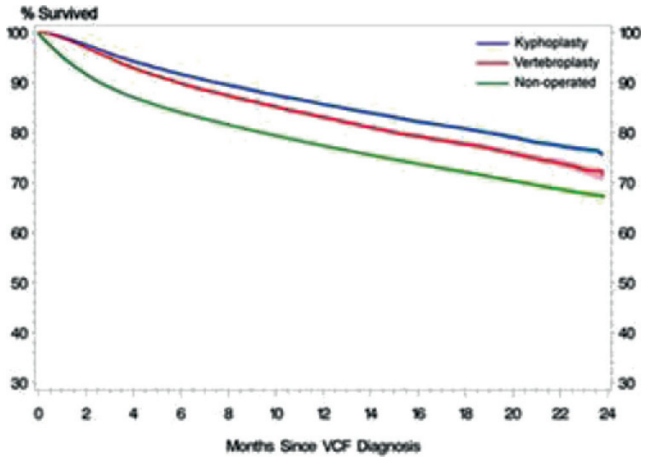
**Aims:** Mortality risk has been shown to increase following the onset of vertebral compression fractures (VCFs). However, the difference in survival for VCF patients following non-operative and operative (kyphoplasty or vertebroplasty) treatments has not been examined.
**Methods:** Operated and non-operated VCF patients were identified from the 100% Medicare national sample in 2006 and 2007 and followed for up to 24 months. Patients with previously diagnosed pathological and traumatic VCFs in the prior year were excluded. The mortality rate associated with VCF was evaluated by determining the date of death from the annual Medicare "denominator" file. Overall survival was estimated by the Kaplan-Meier method, and the differences in mortality rates (operated vs. non-operated; vertebroplasty vs. kyphoplasty) were assessed by Cox regression, which were adjusted for patient demographics and various comorbidities. These comorbidities included arterial disease, chronic obstructive pulmonary disease, cancer, diabetes, hip fracture, hypertension, ischemic heart disease, other heart disease (e.g., conduction disorders), pneumonia, pulmonary heart disease, stroke and wrist fracture.

**Results:** 81,662 patients that underwent vertebroplasty or kyphoplasty had a higher survival rate of 74.8% at 24 months following VCF diagnosis compared to 67.4% for the 329,303 non-operated patients. Vertebroplasty or kyphoplasty patients were 44% less likely to die than non-operated VCF patients (adjusted OR=0.56; p<0.0001). The survival rates for VCF patients following vertebroplasty or kyphoplasty were 72.3% and 76.2% at 24 months, respectively (Fig. 1). The adjusted risk of mortality for the 53,820 kyphoplasty patients was 12.5% lower than that for the 27,842 vertebroplasty patients (adjusted OR=0.87; p<0.0001). Patients with COPD, cancer, other heart diseases, and pneumonia were consistently associated with greater mortality risk, while those with diabetes, stroke, hypertension, and wrist fracture were generally associated with lower mortality risk.

**Image:**




**Conclusions:** We measured the risk of mortality at short-term follow-up to be significantly higher for patients treated non-operatively following VCF diagnosis, as well as for those treated with vertebroplasty compared to kyphoplasty. VCF represents a significant health burden to elderly patients.

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## OC24 - DEVELOPMENT AND VALIDATION OF AN EPIDEMIOLOGICAL MODEL TO ESTIMATE THE BURDEN OF POST-MENOPAUSAL OSTEOPOROSIS

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**Aims:** To develop and validate a disease model to estimate the clinical burden of post-menopausal osteoporosis (PMO) in terms of prevalence (women with low bone mineral density [BMD] and/or a history of fracture), fracture incidence and attributable mortality up to 2020.

**Methods:** The model was validated using Swedish data (where epidemiology of osteoporosis is particularly well documented) and provided estimates from 1990. The "incident cohort" (defined as women experiencing a first osteoporotic fracture), was estimated for each year throughout the study period and processed through a Markov model of 1-year cycles until 2020. Health states were based on the number of fractures (1, 2, 3+) and death. Fracture by site (hip, vertebral, non-hip non-vertebral (NHNV)) was tracked for each health state. Transition probabilities reflected site-specific risk of death and subsequent fractures. BMD was included as a model output reflecting the difference between women with and without a history of fracture. Model inputs included population and life tables from 1970 to 2020, incidence of fracture, relative risk of subsequent fractures based on prior fracture, relative risk of death following a fracture by site, and BMD by age (mean and standard deviation).

**Results:** Model predictions averaged across age groups estimated the incidence of hip, vertebral and other osteoporotic fractures within a 5% margin of error compared to published data (hip, 4%; vertebral, 1% and NHNV, 5%). Between 2009 and 2020, the number of women aged 50+ years is expected to increase by 10.1%. The number of osteoporotic fractures is expected to increase by 11.5%, while the prevalence of established osteoporosis (BMD T-score <-2.5 SD and history of fracture) is predicted to increase by 17.6%. Vertebral fractures are expected to increase the most (+13.8%) compared to other sites (hip: +7.7% and NHNV: +12.5%).

**Conclusions:** A PMO disease model was developed and validated against Swedish data. Based on our assumptions, the number of osteoporotic fractures is expected to rise by 11.5% between 2009 and 2020 in Sweden and the prevalence of established osteoporosis is predicted to rise by 17.6%. This model can be easily adapted to other countries as local specificities are captured via demographic and epidemiological model inputs. This model provides the opportunity to assess the burden of osteoporosis in different settings and countries, using a consistent approach.

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## OC25 - EFFECT OF CALCIUM SUPPLEMENTS ON THE RISK OF MYOCARDIAL INFARCTION AND CARDIOVASCULAR EVENTS: A META-ANALYSIS

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**Aims:** Calcium supplements are commonly prescribed for skeletal health, but have recently been associated with increased cardiovascular events in people with renal failure and in a clinical trial in healthy, older women. Therefore, we investigated whether calcium supplements increase the risk of cardiovascular events.
**Methods:** MEDLINE, EMBASE, and Cochrane CENTRAL (1966-Nov. 2007), reference lists of meta-analyses, and 2 clinical trial registries were searched for studies of calcium supplements. Eligible studies were randomised, placebo-controlled trials of calcium supplements (≥500 mg/day) with ≥100 participants, mean age >40y and duration >1y. Trials in which co-administered calcium and vitamin D was compared with a placebo comparator, or calcium was administered as dietary modification were excluded.

15 trials were eligible for inclusion, with patient-level data available for 5 studies, and trial-level data for 11 studies. 4 studies had no available data. Data were supplied by the lead authors of eligible trials. Cardiovascular outcomes were obtained from self-reports, hospital admissions and death certificates.

Patient-level analyses were performed using Cox proportional hazards models, and trial-level data were pooled using fixed-effects models.
**Results:** In 5 studies contributing patient-level data from 8151 participants with median follow-up of 3.6y (IQR: 2.7-4.3y), 143 people allocated to calcium had a myocardial infarction compared with 111 allocated to placebo (HR 1.31, 95%CI 1.02-1.67, P=0.035). There were non-significant increases in incidence of stroke (HR 1.20, 95%CI 0.96-1.50, P=0.11), the composite endpoint of myocardial infarction, stroke or sudden death (HR 1.18, 95%CI 1.00-1.39, P=0.057), and death (HR 1.09, 95%CI 0.96-1.23, P=0.18). The meta-analysis of trial-level data (11,921 participants, 11 trials, mean duration 4.0y) showed similar results: 296 people had a myocardial infarction (166 allocated to calcium, 130 to placebo), with an increased incidence of myocardial infarction in those allocated to calcium (pooled RR 1.27, 95%CI 1.01-1.59, P=0.038)
**Conclusions:** Calcium supplements (without co-administration of vitamin D) are associated with an increased risk of myocardial infarction. As calcium supplements are widely used, these modest increases in risk of cardiovascular disease might translate into a large burden of disease in the population. A reassessment of the role of calcium supplements in the management of osteoporosis is warranted.

**Disclosure of Interest**: None Declared

## OC26 - A RANDOMIZED TRIAL OF BALLOON KYPHOPLASTY AND NON SURGICAL CARE FOR PATIENTS WITH ACUTE VERTEBRAL COMPRESSION FRACTURES: TWO YEAR RESULTS

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**Aims:** Balloon kyphoplasty is a minimally invasive treatment for acute vertebral fractures that aims to reduce and correct vertebral deformity by inserting expandable balloon tamps and then stabilize the body by filling it with bone cement.
**Methods:** Patients with up to 3 non-traumatic acute vertebral compression fractures were enrolled within 3 months of diagnosis, randomly assigned to receive either balloon kyphoplasty (N=149) or usual nonsurgical care (N=151) and assessed through 24 months of follow-up.
**Results:** The mean SF-36 physical component summary (PCS) score improved 5.1 points (95%CI, 2.8-7.4; p<0.0001) more in the kyphoplasty than the nonsurgical group at one month, the primary endpoint of the study.

Kyphoplasty improved the PCS score by an average of 3.0 points (95%CI, 1.6-5.4; p=0.002) during the 2-year follow-up. Comparisons at individual time points indicate that the differences in improvement between groups were 3.9 (95%CI, 1.5-6.2; p=0.001), 3.1 (95%CI, 0.8-5.5; p=0.009), 1.4 (95%CI, -1.0–3.8; p=0.25) and 1.4 (95%CI, -1.0–3.8; p=0.26) at 3, 6, 12 and 24 months.

Overall, patients assigned to kyphoplasty also had statistically significant improvements in global quality of life; the Euroquol-5D (EQ-5D) improved an average of 0.13 (95% CI, 0.04-0.22; p=0.004) points more than nonsurgical care over the two years of follow-up. Kyphoplasty resulted in more pain relief on a 0 to 10-point numeric rating scale (1.5 points; 95% CI 1.0-1.9; p<0.0001), less Roland-Morris back disability (2.9 points; 95% CI, 1.6-4.1; p<0.0001) and 2.2 (95% CI 1.1-3.7; p=0.0008) fewer days of limited activity (within a two-week period) when averaged over 2 years.

There was no significant difference in the number of patients with adverse events or serious adverse events in the kyphoplasty and nonsurgical groups. Three patients had serious adverse events attributed to kyphoplasty; a patient with a soft tissue hematoma, a patient with a post-operative urinary tract infection with subsequent spondylitis at the treated level, and a patient with re-collapse of an index fracture with anterior cement migration. New radiographically detected vertebral fractures were not statistically different between groups at 3, 12 or 24 months
**Conclusions:** Compared to nonsurgical care, balloon kyphoplasty improved quality of life and reduced back pain and disability and did not increase adverse events including the risk of vertebral fracture over 2 years.

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## OC27 - BONE MINERAL QUALITY IS MAINTAINED IN OSTEOPOROTIC WOMEN TREATED UP TO 60 MONTHS WITH STRONTIUM RANELATE

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**Aims:** Strontium ranelate, has demonstrated its early and sustained antifracture efficacy at the vertebral and nonvertebral levels *(1,2)*. The aim is to evaluate bone quality and to extend up to 60 months the analyses of the distribution and content of strontium (Sr) in bone and its effect on mineralization.
**Methods:** 32 iliac bone biopsies were taken from postmenopausal osteoporotic (PMOP) women after 2, 12, 24, 36, 48 and 60 months of treatment with strontium ranelate (2 g/day; *1,2,3*). Samples were investigated both by X-ray microanalysis *(4,5)* for focal bone Sr uptake and distribution, and by quantitative microradiography *(6)* for the degree of mineralization of bone (DMB). On 10 of the samples, global Sr distribution was analyzed by X-ray cartography on the whole sample surface and the % of surface containing Sr was calculated *(4)*.
**Results:** Sr was heterogeneously distributed into bone tissue and exclusively present in newly formed bone, what corresponded to the bone formation activity during the treatment period. The surfaces of bone containing Sr increased from 2 months (2%) to 36 months of treatment (35%), followed by a smaller increment until 60 months (48%). This evolution was more marked in cancellous (4, 44, 88%, respectively) than in cortical bone (1, 29, 44%, respectively). However, focal bone Sr content remained constant in the new bone from 2 to 60 months of treatment (mean: 0.41±0.12 atomic %). DMB was maintained and its distribution was heterogeneous in cortical, cancellous or total bone, independently of treatment duration.
**Conclusions:** Even after a prolonged treatment with strontium ranelate (up to 60 months), the distribution of Sr corresponded only to formation activity and the quality of bone mineral was preserved, supporting the safety of this treatment at bone tissue level.
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## OC28 - FRAX® AND THE EFFECT OF RALOXIFENE ON VERTEBRAL AND NON-VERTEBRAL FRACTURE

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**Aims:** The Multiple Outcomes of Raloxifene Evaluation (MORE) study, a placebo controlled phase III trial of raloxifene in postmenopausal osteoporosis, showed that both doses tested (60 mg and 120 mg daily) reduced the risk of vertebral fracture. There was no significant effect on non-vertebral fracture. The aim of the present study was to evaluate the distribution of fracture risk assessed at baseline using the FRAX® tool in MORE and to determine the efficacy of raloxifene as a function of baseline fracture risk.
**Methods:** The effects of raloxifene (60 and 120 mg daily combined) compared to placebo on the risk of all clinical fractures as well as the risk of morphometric vertebral fracture were examined as a function of baseline fracture risk. Baseline clinical risk factors and BMD were entered in country specific FRAX® models to compute the 10-year probability of major osteoporotic fractures. No information was available on parental history of hip fracture and this variable was simulated. The interaction between fracture probability and treatment efficacy was examined by Poisson regression.
**Results:** The mean±SD 10-year probability of major osteoporotic fractures (with BMD) was 21±11% (range 0.9-77.2%). Treatment with raloxifene was associated with an 18% decrease in all clinical fractures compared to placebo treatment (hazard ratio HR=0.82; 95% CI=0.71-0.95; p=0.0063) and a 42% decrease in incident morphometric vertebral fractures (HR=0.58; 95% CI=0.48-0.69; p<0.001). Efficacy was shown over the whole range of fracture probability and the interaction between fracture probability and treatment was not significant. The efficacy or raloxifene on vertebral fracture risk was significantly greater at lower ages. At the 90$^{th}$ percentile of age (75 years) vertebral fracture risk was reduced by 31% irrespective of FRAX® probabilities. In contrast at younger ages, efficacy was higher and increased further still with decreasing fracture probability.
**Conclusions:** Raloxifene (60 and 120 mg doses combined) significantly decreased the risk of all clinical fractures and morphometric fractures in women. Overall, there was no significant interaction between efficacy and fracture probability. In the case of morphometric vertebral fractures efficacy decreased significantly with increasing age.
**Acknowledgement:** Research support from Lilly

**Disclosure of Interest**: None Declared

## OC29 - SUBTROCHANTERIC FRACTURES: RESULTS FROM THE HORIZON-RECURRENT FRACTURE TRIAL

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**Aims:** To identify the risk factors for subtrochanteric fractures in osteoporotic patients treated in HORIZON-Recurrent Fracture Trial (RFT).

**Methods:** The HORIZON-RFT was a double-blind, randomized, placebo-controlled trial assessing the efficacy of once-yearly i.v. infusion of zoledronic acid (ZOL) 5 mg in 2127 men and women aged ≥50 years who had undergone surgical repair of a low-trauma hip fracture in the preceding 90 days. We conducted a post-hoc analysis of the baseline and post-treatment characteristics of patients with subtrochanteric fractures *versus* incident hip fracture.

**Results:** A total of 106/2127 (5.0%) patients had sustained subtrochanteric fractures (ZOL, *n*=50; placebo, *n*=56) at baseline. The mean age, age distribution, sex distribution and BMI were similar between groups. Femoral neck and total hip BMD, and distribution of femoral neck BMD were similar between groups. There were no clinically relevant differences in concomitant medications (glucocorticoids, anticonvulsants or psychoactive drugs) and comorbidities between groups. Health status as measured by EQ-5D (total score and all domains) between groups was also similar (Table 1). The post-treatment hip fracture rate in overall study population was 2.0% (*n*=23) in the ZOL group and 3.5% (*n*=33) in the placebo group, a nonsignificant 30% risk reduction with ZOL. The number of patients with a recurrent subtrochanteric hip fracture were too few to be able to draw any conclusions.

**Table 1. Patient baseline characteristics by hip fracture type**

| Characteristics | Subtrochanteric hip fracture (*n*=106) | | Other hip fracture (*n*=2021) | |
|---|---|---|---|---|
| **Age** (years), mean (SD) | 73.9 (9.3) | | 74.5 (9.7) | |
| <65 years | 21 (19.8) | | 343 (17.0) | |
| 65–74 years | 27 (25.5) | | 549 (27.2) | |
| 75–84 years | 48 (45.3) | | 847 (41.9) | |
| ≥85 years | 10 (9.4) | | 282 (14.0) | |
| **Sex**, *n* (%) | | | | |
| Male | 30 (28.3) | | 478 (23.7) | |
| Female | 76 (71.1) | | 1543 (76.3) | |
| **BMI** (kg/cm$^2$), mean (SD) | 24.6 (4.2) | | 24.8 (4.4) | |
| **Patients receiving** | | | | |
| Concomitant osteoporosis therapy, *n* (%) | 5 (4.7) | | 103 (5.1) | |
| Glucocorticoids, *n* (%) | 2 (1.9) | | 63 (3.1) | |
| Anticonvulsants, *n* (%) | 4 (3.8) | | 62 (3.1) | |
| Psychoactive medications, *n* (%) | 0 | | 2 (0.1) | |
| **EQ-5D, mean total score (SD)** | 0.55 (0.31) | | 0.57 (0.30) | |
| Thermometer (VA scale); mean (SD) | 67.7 (16.75) | | 65.7 (17.97) | |
| | With P/EP | With EP | With P/EP | With EP |
| Mobility, *n* (%) | 83 (82.2) | 10 (9.9) | 1497 (77.1) | 91 (4.7) |
| Self care, *n* (%) | 54 (54.0) | 6 (6.0) | 1049 (54.1) | 134 (6.9) |
| Activities, *n* (%) | 71 (71.7) | 19 (19.2) | 1398 (72.6) | 387 (20.1) |
| Pain, *n* (%) | 60 (59.4) | 5 (5.0) | 1242 (64.1) | 55 (2.8) |
| Anxiety/depression, *n* (%) | 39 (39.4) | 2 (2.0) | 755 (39.0) | 72 (3.7) |

VA: visual analogue; P: problem; EP: extreme problem.

**Conclusions:** Our analysis showed that subtrochanteric fractures are not uncommon and do occur in bisphosphonate-naive patients, though it failed to show factors that would identify those at greater risk for subtrochanteric fracture. The incidence of subtrochanteric fractures after zoledronic acid treatment was rare and too small to draw any meaningful conclusion.

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## OC30 - EFFECTS OF ARZOXIFENE ON FRACTURE INCIDENCE IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS OR WITH LOW BONE MASS

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**Aims:** To assess the effect of arzoxifene, a benzothiophene SERM, on the incidences of new vertebral fracture and invasive breast cancer in postmenopausal women (PMW) with low bone mass or osteoporosis.

**Methods:** GENERATIONS was a phase 3, multicenter, placebo-controlled, double-blind, 60-month randomized trial of 9354 PMW with osteoporosis (N=5252) or low bone mass (N=4102), defined by bone mineral density (BMD) at screening. Participants were randomly assigned to arzoxifene 20mg/d (N=4678) or placebo (N=4676). The primary endpoints were the incidence of radiographic vertebral fracture in the osteoporotic population (at 36 months) and invasive breast cancer in all study participants (after all participants had completed 48 months of treatment). The incidence of nonvertebral fractures was assessed in all women. BMD and serum bone biomarkers (CTX and PINP) were measured in a subset of women (n=1022).

**Results:** Baseline characteristics were well matched between treatment groups for age, BMD and T-scores. Compared to placebo, arzoxifene reduced the risk of vertebral fracture after 3 years in participants with osteoporosis (5.6% vs. 3.3%, Risk Ratio [95%CI]:0.59 [0.45, 0.77], p<0.001) but not nonvertebral fracture (8.0% vs.7.7%, Hazard Ratio [95%CI]: 0.92 [0.71, 1.19], p=0.71). Results were similar in participants with low bone mass. At 12 months, women in the arzoxifene group had a 42.1% (95% CI -46.1, -38.3) reduction in CTX and a 33.5% (95% CI -36.5, -30.5) reduction in P1NP compared with placebo. Arzoxifene resulted in 3-year increases in BMD of 2.6% at the total hip, 2.8% at the femoral neck and 2.9% at the lumbar spine (p<0.001). Arzoxifene reduced the incidence of invasive breast cancer by 56% after 4 years of treatment (p=0.002). Arzoxifene was associated with a significant increase in venous thromboembolism, gall bladder disease, pulmonary obstructive/infective disorders, hot flushes, muscle cramps and gynecological-related events.

**Conclusions:** Arzoxifene reduced the incidence of vertebral fracture as well as invasive breast cancer. Because there was no significant effect on the incidence of nonvertebral fractures and there was an increase in certain adverse events, this trial did not support further development of arzoxifene as a meaningful advance in the treatment of osteoporosis.

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