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Treatment of osteoporosis and osteoarthritis in the oldest old

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Running head

Treatment of osteoporosis & osteoarthritis in the oldest old

Key points

- The numbers of 'The Oldest Old' are set to rise over the coming years, and with this the burden of osteoporosis and osteoarthritis will expand
- At present evidence for treatments for osteoporosis and osteoarthritis is lacking in this age group (with post-hoc analysis playing a major role in demonstrating fracture risk reduction efficacy in anti-osteoporosis medications) and should be the subject of a future research agenda, including clinical trials

Abstract

Osteoporosis and osteoarthritis are key diseases of musculoskeletal ageing and are increasing in prevalence and burden with the progressively ageing population worldwide. These conditions are thus particularly common in 'the oldest old' and there are complexities of managing them within the context of extensive multimorbidity, physical and mental disability and polypharmacy, the rates for all of which are high in this population.

In this narrative review we explore the epidemiology of osteoporosis and osteoarthritis in the oldest old before examining trials and real-world data relating to the pharmacological treatment of these diseases in older adults including anti-resorptives and bone-forming agents in osteoporosis and Symptomatic Slow-acting Drugs for Osteoarthritis (SYSADOAs), paracetamol and NSAIDs in osteoarthritis, recognizing that in most cases the oldest old are excluded from clinical trials.

We then review the potential benefits of nutritional interventions and exercise therapy before highlighting the health economic benefits of interventions for osteoporosis and osteoarthritis.

In conclusion, the high prevalence of risk factors for both disease and adverse events associated with treatment in the oldest old mean that careful attention must be paid to the potential benefits of intervention (including fracture risk reduction and improvements in osteoarthritis pain and function) against the potentials harms and adverse effects. Further direct evidence relating to such interventions is urgently needed from future research.

1. Introduction

Advances in health and social care have led to a global increase in the proportion of individuals surviving into older age.

Osteoarthritis and osteoporosis were previously thought to be mutually exclusive but this relationship has been questioned since, and, further research has some shared associations and co-existence[1]. Both osteoarthritis and osteoporosis are associated with an increasing prevalence with age and so present a particular burden in older adults[2-5]. They cause substantial morbidity for individual patients, and substantial financial burden for the health economy at large[6, 7].

Ageing is associated with alterations in physiology which alter the presentation of diseases and the physiological capacity to respond to interventions. Age-related changes in pharmacokinetics and pharmacodynamics are well-established[8], such that a tailored regulatory approach has been developed for the assessment of new medications in this age-group[9, 10].

Within the cohort of ageing older adults sits a sub-group of 'the oldest old'[11]. The definition of this term is debated, but with the expansion of the ageing population, and the consequent increase in diseases of musculoskeletal ageing, there is a clear need for a robust review of interventions for osteoarthritis and osteoporosis in this group. In order to address this need, The European Society for the Clinical and Health Economic aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Disorders (ESCEO) convened an expert working group in February 2024. This group included patients, geriatricians, rheumatologists, orthopaedic surgeons, researchers, regulatory experts and health economists with oral presentations of the latest literature and discussion to determine a group consensus. This is presented in the following narrative review.

2. Definition of the oldest old population

The phrase 'the oldest old' refers to the oldest subset of older adults and emphasises a group of patients which may have substantial differences in pharmacokinetics, higher concurrent levels of co-morbidity and are often excluded from participating in randomised controlled trials. Chronological age cut-off values for this group vary.

For example, the European Medicines Agency sub-categorises the older adults into 65-74 years for the 'young old', 75-84 years as 'middle old' and ≥85 years as 'oldest old'[12]. The latter is the same as the British Geriatrics Society threshold, however, The American Geriatrics Society and World Health Organisation set a chronological threshold at ≥80 years[13]. Some individual studies choose a higher threshold of ≥90 years[14].

The term ‘the oldest old’ is sometimes used in conjunction with ‘the fourth age’. Old age classically commences at 60-65 years, due to this being a common time for retirement from employment and has been referred to as ‘the third age’[15]. The fourth age marks a move into ‘dependence’ and is thus used in similar context to ‘the oldest old’[15].

When considering clinical practice, clinical practice, in some countries, older adults are admitted to a geriatric unit at the age of 80 years; however, the age of admission to such services has crept up (from≥ 75 years) over the last 10 years and may be more due to stretched geriatric healthcare resources, rather than a clinically meaningful threshold.

Indeed, it is arguable that chronological age is limited in its application to the issue at hand, and that measures of ‘biological age’[16-18] would be more accurate in identifying individuals who display the characteristics which most associate with ‘the oldest old’ (greater morbidity, higher levels of dependence, higher risk of death) but without the bias of ‘ageism’, however, measures of biological age are not available in clinical practice.

It is important to conclude that a universal definition of ‘the oldest old’ is yet to be reached, however, in this review we will investigate the literature relating to those (chronologically) aged 80 years and above, though focusing on as old an age group as possible (within the confines of the currently available evidence).

2.1 Osteoporosis

The operational definition of osteoporosis rests upon the measurement of bone mineral density (via Dual-energy X-ray Absorptiometry (DXA))[19] which varies across the lifecourse, reaching a peak in early adulthood during the fourth decade, plateauing in middle life, and then declining from the age of 50 years. There is an increase in the incidence of all major fracture types (hip, vertebral, distal radial, proximal humerus) with age, with a near exponential increase in hip fracture incidence in men and women beyond 75 years[3], and, indeed, the median age for hip fracture is well above 80 years in many countries[20]. Although in this study, vertebral fracture incidence was not included above the age of 75 years, a similar pattern of increasing incidence is observed for vertebral fractures in other studies[21].

Epidemiological trends for fractures vary according to type of fracture. For example, data from Tottori (Japan) demonstrate an exponential increase in the incidence of fractures of the femoral neck and trochanter with increasing age, reaching an incidence of 700/100,000 person-years for femoral neck fractures and 1700/100,000 person-years for trochanteric fracture in women aged 85-90 years between 2004-2006[22]. The incidence is lower in men; approximately 300/100,000 person-years for

femoral neck and 600/100,000 person-years for trochanteric fracture over the same period[22]. There is variation in the distribution of incidence by age. With trochanteric fractures there is a fairly rapid increase from the age of 75 years, and, for fractures of the femoral neck, a more constant, almost linear increase in incidence from the age of 65 years[22, 23]. A recent extension of this study has demonstrated that the exponential increase in trochanteric fractures continues in the 10th decade of life (those aged between 90-100 years) with an incidence of over 2000/100,000 person-years in women and approximately 1000/100,000 person-years[23]. Fractures are also associated with substantial increases in mortality[24, 25].

Concerningly, given the above epidemiology which emphasises the predilection for fractures in the oldest old, there is recognised undertreatment for those requiring anti-osteoporosis medication in this population[26]. A study from the Newcastle 85+ cohort showed that, of 259 older adults (mean age 85.5 years, all participants were born in 1921) who were identified as requiring treatment for osteoporosis (via fracture risk calculation), only 74 (28.6%) were receiving anti-osteoporosis medication[27]. This represents a treatment gap of 71.4%, higher than the UK national average of 66%, emphasising the neglect that the oldest old are experiencing when it comes to osteoporosis care[28]. The issue of health equity runs deeper than the treatment gap, with a relative paucity of research into osteoporosis in older adults, leading to calls for more evidence from the International Conference on Frailty and Sarcopenia Research (ICFSR) which is echoed by the authors of this article[29].

2.2 Osteoarthritis

Osteoarthritis is a disease of the joint characterised by reduction of cartilage thickness and is associated with pain, loss of function and reduced quality of life. The robust mapping of the epidemiology of osteoarthritis is hampered, in part, by variations in disease definitions [30]. Osteoarthritis can be defined clinically (by the presence of clinician-elicited signs)[31], radiographically (by features on radiograph images)[32] or via patient self-report of prior diagnosis (for example via a questionnaire assessment in a cohort study). It is worth considering that the clinical diagnosis of osteoarthritis includes measures of pain and discomfort and, given that activity levels are lower in the oldest old, the degree of movement-induced pain[33] (or any pain at rest which is precipitated by preceding physical activity) may be less, potentially leading to artificially lower rates of diagnosis in this population.

The epidemiology of osteoarthritis was investigated in the 2021 Global Burden of Disease study which estimated the global prevalence of osteoarthritis at 595 million (95% uncertainty interval 535–656 million) or 7.6% (95% UI 6.8–8.4%) of the global population[2]. The prevalence had grown 132% (130.3–134.1%) since the year 1990 demonstrating a striking upward trajectory with a projected

increase of 60-100% (depending on the site of osteoarthritis) by the year 2050 such that 1 billion people will have some form of osteoarthritis[2]. This is supported by the findings of Belgian Primary Care Registry study which found steady increases in prevalence in all age groups between the years 1996 to 2015[34].

Across the lifecourse, osteoarthritis is more common in women than in men with an age-standardized prevalence of 8,059 per 100,000 (95% CI 7251.9, 8867.9) for women and 5,780 per 100,000 (95% CI 5,217.8, 6,341.2) for men[2]. In terms of the effect of age in this global, osteoarthritis epidemic, the prevalence of osteoarthritis (as a whole) steadily increases from the age of 40 years until the age of 80 years. At this point the prevalence continues to increase, though at a less substantial rate[2]. The age distribution for osteoarthritis differs depending on the site, with hip, hand and 'other' (e.g. shoulder) arthritis increasing constantly from the age of 40 years, but with knee osteoarthritis peaking at the age of 80 years and then decreasing thereafter[2]. This distribution was also observed in osteoarthritis cases in a UK primary care data base study (in the Clinical Practice Research Datalink (CPRD)) [35]. The fact that this was observed in the entire osteoarthritis population may be due to the high prevalence of knee osteoarthritis in this study (over twice that of hip osteoarthritis and over three times that of hand osteoarthritis), or a reduced rate of presentation or diagnosis in this 'oldest old' population or the competing nature of morbidity.

Indeed, an insurance registry study in Canada including nearly 500,000 participants highlighted the high level of co-morbidity in those with osteoarthritis, with 29% having hypertension, 20% depression, 19% Chronic Obstructive Pulmonary Disease (COPD), 10% diabetes and 6% congestive heart failure[36].

To summarise, osteoarthritis and osteoporosis are frequent in the oldest old and, if the number of oldest old individuals increase, the prevalence of these diseases of musculoskeletal ageing will increase. The epidemiology of fractures is mapped for age, gender, geography and time, but the secular trends of osteoarthritis require further research. Further work is also needed to close the treatment gap for osteoporosis in the oldest old.

3. Osteoporosis interventions

As is the common theme throughout this paper, there is a paucity of data relating to osteoporosis interventions in the oldest old, with the majority of (particularly pivotal) trials neglecting to include this population and subsequent reliance on post-hoc analyses (Table 1). There are multiple causes for this underrepresentation of oldest old adults in clinical trials [37], including ageism (i.e. discrimination towards older subjects)[38].

3.1 Anti-resorptive therapy

Anti-resorptive medications, which largely inhibit the activity of osteoclasts, are the most commonly prescribed for the treatment of osteoporosis and have been widely studied for efficacy and safety, though less so in the oldest old age-group.

The efficacy of alendronate was extensively examined in the Fracture Intervention Trials (FIT), with FIT-1 demonstrating fracture risk reduction (with 22 hip fractures in the placebo group and 11 in the treatment group) in postmenopausal women with a history of radiographic vertebral fracture and DXA-defined low bone mineral density (femoral neck BMD (FN-BMD) <0.68 g/cm^2)[39] and FIT-2 in postmenopausal women with DXA-defined low FN-BMD alone (<0.68 g/cm^2).

Women aged 55-80 years were enrolled in FIT-I and randomised to placebo or alendronate (5mg daily for 2 years followed by 10mg daily for a further 1-2.5 years)[40, 41]. A post-hoc analysis (of data from FIT-1 and FIT-2 for participants with an osteoporotic level of BMD) of the relative risk reduction for fracture demonstrated that alendronate reduced the risk of hip fracture by 53% (relative risk (RR) 0.47, 95% CI 0.27, 0.81, p<0.01), vertebral fracture by 45% (RR 0.55, 95% CI 0.37, 0.83, p<0.01), and distal radial fracture by 31% (RR 0.69, 95% CI 0.50, 0.98, p=0.04)[42]. For a composite end point of any hip, vertebral or distal radial fracture, alendronate was associated with a significant risk reduction of 40% (RR 0.60, 95% CI 0.47, 0.77, p<0.01)[42]. The absolute risk reduction (ARR) of this composite end point was examined in age categories which showed increasing absolute risk reduction with increasing age, including up to the age of 85 years (ARR 65 per 10,000 person-years for those aged 55 to <65 years; 161 per 10,000 person-years for those aged 75–85 years) demonstrating the increasing benefit of alendronate versus placebo with age in this group (aged 75 to 85 years). The oldest old were not included in this study and, in order to examine the efficacy of alendronate in this population, we must move to evidence generated from real world data.

A Swedish database of adults who were 80 years or older and had been referred for falls risk assessment was used as a basis for identifying those who had sustained a prior fracture[43]. Those taking alendronate were identified (n=1961) and propensity score matching was used to identify a control group (n=7844) with incident hip fracture as the primary outcome[43]. The mean age of the analysis group was 84.7 years (SD ~4). Cox proportional hazard models demonstrated that alendronate therapy was associated with a reduced hazard of hip fracture in unadjusted models (Hazard Ratio (HR) 0.62, 95% CI 0.49, 0.79, p<0.001) and in those adjusted for confounders (age, sex, weight and height, and previous medication (including glucocorticoids and calcium/vitamin D), secondary osteoporosis, rheumatoid arthritis, alcohol-related diseases, Charlson comorbidity index, time since fracture,

previous vertebral fracture, previous hip fracture, previous hip arthroplasty, number of prior fractures, prior falls injury and prior diagnosis of osteoporosis) (HR 0.66, 95% CI 0.51, 0.86), p<0.01)[43].

In this group of middle/oldest old adults, alendronate treatment was associated with a reduced risk of mortality (HR 0.88, 95% CI 0.82, 0.95) but an increased risk of upper gastrointestinal symptoms (HR 1.58, 95% CI 1.12, 2.24)[43], the latter being common to all age groups taking conventional, oral bisphosphonates[44].

The Hip Intervention Program (HIP) study was a 3-year, randomised, placebo-controlled trial of risedronate (2.5mg or 5mg daily) which included an arm of women 3886 women aged 80 years or more, who had at least one clinical risk factor for fracture or very low FN-BMD (T-score <–4 or T-score <–3 plus a hip-axis length of ≥11.1cm)[45]. Although there was a significant reduction in the risk of hip fracture from taking risedronate in the other, younger (aged 70-79 years) arm of the study (RR 0.6, 95% CI 0.4, 0.9, p=0.009), there was no significant reduction in hip fracture incidence in the ≥80 year arm with an incidence of 4.2% (82 hip fractures) in those taking risedronate (n=2573) and 5.1% (49 hip fractures) in those taking placebo (n=1313) (RR 0.8, 95% CI 0.6, 1.2, p=0.35)[45].

The safety and efficacy of risedronate was examined in an analysis of the oldest old (in this case ≥80 years) from pooled trial data including HIP[45], Vertebral Efficacy with Risedronate Therapy-Multinational (VERT-MN)[46] and VERT-North America (NA)[47]. The population was defined as women aged ≥80 years with a FN-BMD T-score of <-2.5 or at least one prevalent vertebral fracture, with 688 receiving placebo and 704 receiving risedronate (5mg daily). The anti-vertebral fracture efficacy of risedronate in this population was confirmed across the 3 years of study (HR 0.56, 95% CI 0.39, 0.81, p<0.001) but it was particularly striking that the protective effect was observed as early as 12 months after commencing treatment (HR 0.19, 95% CI 0.08, 0.40, p<0.001)[48]. The same, significant protective effect was not observed for non-vertebral fractures. The authors of this pooled analysis concluded that risedronate was “well tolerated, with a safety profile comparable with that of placebo”[48]. This was even the case for those with baseline active gastrointestinal tract disease and those taking NSAIDs, proton pump inhibitors (PPIs) or aspirin.

Zoledronate, an intravenous bisphosphonate, was explored in the HORIZON trial[49] with a post-hoc analysis subsequently performed in a population of postmenopausal women aged ≥75 years with either a prevalent hip or vertebral fracture or an osteoporotic level of FN-BMD and were randomised to zoledronate (5mg per year) or placebo[50]. Zoledronate significantly protected against any clinical fracture as a whole and hip fracture, non-vertebral fracture and clinical vertebral fracture individually at both 1 year and 3 years after commencement with the most impressive reduction in risk for clinical vertebral fracture at 3 years (HR 0.34, 95% CI 0.21, 0.55, p<0.001)[50]. The efficacy of zoledronate to

reduce fracture risk in a group of individuals with a mean age of ~74 years was demonstrated in the HORIZON recurrent fracture trial, in which zoledronate was given to patients within 90 days of a low-trauma hip fracture (resulting in a 35% risk reduction in clinical fracture, 8.6% in the zoledronate group and 13.9% in the placebo group, p=0.001)[51].

The safety profile reported for those ≥75 years in the HORIZON trial was similar for zoledronate and placebo, although adverse events proximal to the infusion (within 3 days of infusion) were more common in those receiving zoledronate (placebo vs zoledronate, 25.7% vs 41.5%, p<0.001), as were pyrexia (4.0% vs 12.1%, p<0.001), chills (0.6% vs 3.5%, p<0.001), influenza-like illness (2.1% vs 5.2%, p<0.001), myalgia (3.1% vs 8.6%, p<0.001) and bone pain (1.5% vs 4.3%, p<0.001)[50]. Interestingly, an increased risk of atrial fibrillation requiring hospitalisation[52], whilst observed in younger populations, was not observed in the older age group.

Denosumab, a monoclonal antibody inhibitor of RANK ligand, was examined in the 'Fracture REduction Evaluation of Denosumab in Osteoporosis every 6 Months' (FREEDOM) trial[53] with those aged ≥75 years accounting for only 31.6% of the trial population[54]. A post-hoc analysis focusing on the efficacy of the intervention in high-risk populations including women aged 75 years or more (mean age 78.2 years). The risk reduction for hip fracture in this group was 62% (p<0.01) and was comparable to the overall trial population[55]. These post-hoc analyses have demonstrated that adverse effects were similar in the older age group compared to the study population as a whole[55], though, in clinical practice, it is important to be aware of the increased risk of hypocalcaemia in older adults and those with severe renal impairment (creatinine clearance <30 mL/min). Monitoring and appropriate replacement of calcium and vitamin D must be ensured in these groups. The risk of rebound vertebral fractures following the discontinuation of denosumab, which appears to increase with greater duration of treatment[56] may be at least partly mitigated with one or more doses of zoledronate. A further post-hoc analysis of the FREEDOM study compared adults above and below a 75 year age threshold and found similar vertebral fracture protection for those ≥75 years (RR 0.36, 95% CI 0.25, 0.53) as for those <75 years (RR 0.30, 95% CI 0.22, 0.41)[57]. Non-vertebral fracture protection was not significant in those ≥75 years (RR 0.84, 95% CI 0.63, 1.12) but was for those <75 years (RR 0.78, 95% CI 0.63, 0.96)[57].

3.2 Bone-forming therapy

Within the panoply of anti-osteoporosis medications, in addition to the anti-resorptive agents discussed above, we have bone-forming, anabolic, bone-remodelling agents which stimulate new bone to form. These comprise recombinant parathyroid hormone (PTH) analogues including teriparatide and abaloparatide and the anti-sclerostin monoclonal antibody, romosozumab. Network

meta-analysis has shown that these bone-forming agents result in greater reduction in the risk of fracture than anti-resorptives [58], and that the fracture reducing efficacy of bone-forming agents is similar for PTH analogues as for anti-sclerostin agents[59].

The Fracture Prevention Trial (FPT) was a randomised, placebo-controlled trial of teriparatide in postmenopausal women (aged 42 to 86 years)[60] which demonstrated the BMD gains and fracture protection which could be accrued via teriparatide. The data from the FPT have been reviewed in a post-hoc analysis to investigate the effect of age with 75 years as the threshold (two groups aged <75 years (n=841) or ≥75 years (n=244))[61]. Although the power of this study was limited by the low number of non-vertebral fractures in the older age group, overall, this study suggested that there wasno significant difference in efficacy between the two groups, and no difference in terms of safety [61].

Abaloparatide differs in structure to teriparatide, sharing 41% of its structure with PTH 1-34 and 76% with PTH-related protein 1-34[62] and showed significant efficacy for reducing the risk of vertebral and non-vertebral fractures[63] in postmenopausal women aged >65 years. A post-hoc analysis investigated the efficacy of abaloparatide in the women who were aged ≥80 years (abaloparatide: n= 51, mean age 81.7 years, placebo: n=43, mean age 81.9 years)[64]. Whilst significant improvements in BMD were observed in those receiving abaloparatide in this age group (3.6% at the femoral neck and 12.1% at the lumbar spine over 18 months) only numerical benefits (and not statistically significant benefits) were observed in terms of vertebral (abaloparatide=0, placebo=2) and non-vertebral fractures (abaloparatide=1, placebo=2) [64]. It should be noted that the power in these analyses may be the limiting factor for the demonstration of a statistically significant effect (for example, there were only 2 vertebral fractures and 3 non-vertebral fractures in this older age sub-group. In terms of safety, there was no clear distinction between the ≥80-year group and the study population as a whole.

Abaloparatide treatment is associated with transient increases in heart rate of mild to moderate severity. These transient increases in heart rate were not associated with an increased number of serious cardiovascular events (MACE) or arrhythmias and no safety signal was identified for cardiovascular events with abaloparatide treatment from the available data including completed and ongoing clinical studies, and approximately 5 years of post-marketing experience data from the United States[65].

A direct comparison of teriparatide against abaloparatide in the real-world data setting of a US claims database demonstrated that (even after 5 months of treatment) there is a lower risk of hip fracture with abaloparatide and there was no significant difference in cardiovascular safety profile between these two bone forming agents, although a higher frequency of cardiovascular events was reported as

compared to those reported in the pivotal ACTIVE study[66]. Of note, the incidence of serious cardiovascular events was similar in abaloparatide- and teriparatide-treated patients with a history of stroke or MI within the year before the index date or those with cardiovascular risk factors representing approximately 75% of patients in this retrospective observational study[65].

One of the pivotal trials of romosozumab, ARCH[67], was a randomised, blinded, alendronate-controlled trial of romosozumab in a population of postmenopausal women (n=4093) treated for 12 months with either romosozumab or alendronate, followed by an open-label period of 12 months treatment with alendronate in both groups. For the purposes of our review of the oldest old, the mean age of participants was 74 years (in both the alendronate and romosozumab arms) with 52% of participants being ≥75 years[67]. At 24 months, the romosozumab group had a clear benefit including a 48% reduction in the risk of vertebral fractures (RR 0.52, 95% CI, 0.40, 0.66, p<0.001), 27% lower risk of clinical fractures (HR 0.73, 95% CI, 0.61, 0.88, p<0.001) and 19% reduced risk of non-vertebral fracture (HR 0.81, 95% CI, 0.66, 0.99, p=0.04). In terms of safety profile, whilst there was no significant difference in osteonecrosis of the jaw (one episode in each group) and atypical femoral fracture (2 events in the romosozumab-alendronate group and 4 events in the alendronate-alendronate group) more serious cardiovascular events were observed in the romosozumab-alendronate group (2.5%) versus the alendronate-alendronate group (1.9%). There is a rationale behind the association between cardiovascular disease and the inhibition of sclerostin[52], however, it has also been argued that the differential rates in cardiovascular events in the romosozumab group compared to the alendronate group is actually driven by the potential cardioprotective effects of alendronate, rather than the deleterious effects of romosozumab. Indeed, in a smaller randomised placebo-controlled study (n=332) of romosozumab (at doses of 70mg, 140mg and 210mg) in a post-operative hip fracture population in which over 60% of participants on romosozumab were ≥75 years there was no significant difference in myocardial infarction or fatal adverse events with romosozumab, although the numbers were numerically higher in the romosozumab groups. [68].

A meta-analysis of the five trials of romosozumab in postmenopausal females including ARCH[67], FRAME[69], STRUCTURE[70], McClung and colleagues[71] and Ishibashi and colleagues[72], and a single study in men, BRIDGE[73], showed no significant impact of romosozumab on single outcomes including myocardial infarction, stroke, cardiovascular death, heart failure or atrial fibrillation or on a composite cardiovascular outcome (stroke, atrial fibrillation, heart failure and coronary artery disease) or 3P-MACE (cardiovascular death, MI, stroke), but did show a significantly adverse effect for romosozumab on 4P-MACE (3P-MACE plus heart failure)[74] (Risk Ratio 1.39, 95% CI 1.01, 1.90). A further Bayesian network meta-analysis of the cardiovascular risk of osteoporosis medications in postmenopausal women alone showed no significant increase in odds of cardiovascular adverse

events including individual and composite outcomes[75]. In this network meta-analysis there was observed to be a cardioprotective effect of abaloparatide.

A subsequent pharmacovigilance study in the US and Japan reporting potential romosozumab-related adverse events demonstrated an increased reporting odds ratio of MACE events with romosozumab in Japan, though not in the US. This may have been due to the older age and the higher proportion of men in the Japanese population[76].

To conclude, there is evidence of a signal for increased cardiovascular risk with romosozumab from trials, real-world data and a meta-analysis; however, the association with MACE is only significant if men are included in the meta-analysis. This does not preclude the use of romosozumab (and in men, new data or analyses may become available), which has clear skeletal benefits in reducing fracture risk but does highlight the need to assess cardiovascular risk in patients prior to commencing therapy. This might take the form of a clinical assessment of cardiovascular risk, perhaps combined with tools used for cardiovascular risk assessment, such as Q-RISK-3[77]. Comorbidity increases with age and will be substantially raised in the oldest old. For this reason, particularly rigorous cardiovascular assessment should be used in women over the age of 75 years.

There are no significant cardiovascular safety concerns for teriparatide and according to currently available post-marketing experience this also seems to be the case for abaloparatide. Taking into account new results from an extension of the observational US claims database, which corroborate the previous finding of no significant difference in the safety profiles of abaloparatide and teriparatide (Reginster and colleagues, submitted for publication), it appears reasonable to limit the cardiovascular assessment prior to prescription of abaloparatide to blood pressure measurements.

3.3 Fracture Liaison Services

So far we have focused on primary prevention of fractures. Although there are clinically effective and health economically efficient models for screening for osteoporosis[78, 79], a substantial treatment gap still remains[80] but secondary prevention still provides an opportunity to reduce the risk of future fractures and may be particularly relevant in the population of the oldest old.

Fracture Liaison Services (FLS) are models of care which systematically identify those who have sustained afracture so that they can be appropriately treated and their risk of future fractures reduced. This framework has been shown to be clinically effective, cost effective with reduced mortality[81-83] and is an important facet of the treatment of osteoporosis in the oldest old.

4. Osteoarthritis interventions

Guidelines for the management of osteoarthritis at the knee, hand, hip and other joints recommend a step-wise approach to treatment, advocating a multimodal approach using a combination of exercise, dietary optimisation and weight management together with pharmacological therapies to benefit patients with the disease[84]. Surgical interventions, including arthroplasty, are associated with significant functional benefits, but the focus of this review will be on the pharmacological and (non-surgical) non-pharmacological interventions for osteoarthritis[85].

4.1 SYSADOAs

Symptomatic Slow-Acting Drugs for Osteoarthritis (SYSADOAs), including glucosamine and chondroitin, are included in the ESCEO knee osteoarthritis algorithm as a step 1 intervention for those patients who are symptomatic[84]. This is based on evidence from the literature, including a systematic review demonstrating benefits in reduced joint space narrowing and increased cartilage volume (glucosamine standard mean difference (SMD) 0.16, 95% CI 0.04, 0.28, chondroitin SMD 0.21, 95% CI 0.10, 0.32) and symptomatic benefit in terms of pain (glucosamine SMD −0.15, 95% CI −0.25, −0.05, chondroitin SMD −0.06, 95% CI −0.15, 0.03), and function (glucosamine SMD −0.17, 95% CI −0.28, −0.07, chondroitin SMD −0.15, 95% CI −0.26, −0.03)[86]. There is variation in the quality of these medications and it is clear that high quality, prescription-grade formulations have a greater clinical effect than over-the-counter [87-89], and also greater [90, 91].

SYSADOAs have a neutral safety profile as seen in the above individual studies[92], but also via meta-analysis[93] and are therefore recommended as long-term therapy in guidelines[84]. Although specific data, including sub-group analysis or de novo studies are required in the oldest old, the current data from other age groups would suggest that this group of medications is safe to use in the oldest old.

4.2 Analgesic medications

4.2.1 Paracetamol

Despite the widespread usage of paracetamol, and particularly in the oldest old who are more likely to have osteoarthritis, there is a distinct paucity of data relating to paracetamol in this population.

In terms of the epidemiology of paracetamol usage, the mean age in osteoarthritis trials is 61-63 years, far below the threshold of the oldest old[94, 95]. Data from the Osteoarthritis Initiative (OAI) in the US show that 14% of patients with knee osteoarthritis used paracetamol, compared to what was found in a Dutch osteoarthritis survey where 13.1% of patients had ever taken paracetamol for their condition if they were only taking one medication, but the majority of patients take it in conjunction with another analgesic (for example NSAIDs and paracetamol were taken by 23% of the study population)[95]. The ‘over the counter’ availability of paracetamol makes it difficult to track consumption via prescription

studies alone. A large study of patients ≥65 years with chronic pain in Taiwan showed that paracetamol use was highly prevalent in those ≥85 years with 76.9% patients taking the medication[96]. An Australian study of hospital patients with a mean age of 83 years showed that falls and osteoarthritis (both of which are associated with quadriceps weakening) were strongly associated with paracetamol usage and, separately, emphasised the extent of multimorbidity and poly-pharmacy which is relevant as we strive to manage osteoarthritis in the oldest old[97].

Efficacy data on paracetamol come via established libraries of evidence including Cochrane review[98] which includes trials with an age range of 55-70 years and network meta-analysis of 122 randomised controlled trials of knee osteoarthritis treatments, but only one study with a mean age >70 years[99]. In a further network meta-analysis including 192 trials of hip and knee osteoarthritis medications only 3% of patients were ≥70 years[100] and, similar proportions of older adults were included in a meta-analysis of osteoarthritis and back pain[101], emphasising once again the paucity of data in the oldest old. In the latter meta-analysis by Machado and colleagues, a significant (though not clinical meaningful) benefit was demonstrated for knee and hip osteoarthritis in terms of pain (Weighted mean difference (WMD) -3.7, 95% CI -5.5, -1.9) and disability (WMD -2.9, 95% CI -4.9, -0.9)[101].

However, learning from young age groups can be extrapolated from these data, including an increased risk of abnormal liver function tests with paracetamol usage (weighted mean difference 3.8, 95% CI 1.9 to 7.4)[101], and that the rate of hospitalisation rises with increasing dose of paracetamol[102]. Indeed, the risk of abnormal liver function tests is likely to be higher in the oldest old, given, for example, the higher prevalence of polypharmacy in older age groups. In terms of cardiovascular adverse events, a Spanish registry case-control study has demonstrated that paracetamol was not associated with increased risk of acute myocardial infarction or stroke[103]. The mean age in this study was 72 years, older than that of the trials in osteoarthritis.

A study investigating paracetamol usage in hospitalised patients with COPD, with a mean age of 85 years, found that, at a dose of 4g per day (over the recommended daily maximum dosage), there was a time-dependent effect on COPD exacerbation risk, with usage for 7 days associated with a lower risk (HR 0.78, 95% CI 0.67, 0.92) and usage for 30 days associated with a higher risk (HR 1.27, 95% CI 1.06, 1.52)[104].

There is potential promise from the ongoing RETHINK trial which is examining the efficacy of analgesics in osteoarthritis specifically recruiting patients from an older age group, in this case ≥65 years[105]; however, at present there is a distinct lack of efficacy and safety data relating to paracetamol usage in the oldest old, particularly in the disease of osteoarthritis. Extrapolation from other disease areas suggest that dose and duration may be important from an efficacy and safety standpoint and

polypharmacy will likely play a substantial role in the pharmacokinetics of paracetamol in the oldest old. There may also be responders and non-responders to this widely used and prescribed medication, which should be an area of future work. In the absence of direct evidence regarding paracetamol in the oldest old, informed clinical practice must centre around current guidance with short-term use only[106, 107].

4.2.2 NSAIDs

Cyclo-oxygenase (COX) has two subtypes: COX-1 which is constitutively expressed and plays a key role in the maintenance of renal homeostasis, protection of the gastric mucosa and regulation of platelet aggregation. COX-2 is induced by cytokines and growth factors as part of a pro-inflammatory response[108]. Non-steroidal anti-inflammatory drugs (NSAIDs) demonstrate a range of COX-selectivity, from those which inhibit both COX-1 and COX-2 to formulations which more selectively target COX-2 [109].

There are particular issues which need to be considered when using NSAIDs in the oldest old. On the one hand, oldest old patients are more likely to have gastric, cardiovascular, cerebrovascular and renal comorbidities which will increase the risk of NSAID-related adverse events[110]. On the other hand, in osteoarthritis populations as a whole, NSAIDs are a useful alterative to opioids for those older adults who are known to have substantial adverse effects (including constipation, reduced appetite, drowsiness, confusion and dependence) [110, 111].

A meta-analysis of 68 trials of NSAIDs in hip and knee osteoarthritis demonstrated that although efficacy (in terms of analgesic effect) may be better with higher dosages, lower doses may still provide some analgesic effect and may be associated with a lower risk of adverse events in an oldest old population[100]. Dose titration is therefore advocated if NSAIDs are used in the oldest old in the absence of relevant comorbidities.

The effect profile of NSAIDs was investigated in a randomised trial of celecoxib, ibuprofen, or naproxen in patients with high cardiovascular risk and either osteoarthritis or rheumatoid arthritis (mean age 63 years, 64% women)[112]. It should be noted that the mean dose of ibuprofen used was over 2g which is higher than the usual recommended clinical dosage but, nevertheless, ibuprofen was associated with higher renal adverse events compared to celecoxib, with celecoxib having significantly lower gastrointestinal adverse events than ibuprofen (but not significantly lower than naproxen)[112]. There was no significant difference in cardiovascular adverse event profile among the three NSAIDs[112].

Cardiovascular risk with NSAIDs was extensively studied via a meta-analysis including 280 trials of NSAIDs vs placebo and 474 trials of NSAID vs NSAID (encompassing over 200,000 person-years of

follow-up). This showed that, compared to placebo, coxibs (cyclooxygenase-2 (COX-2) inhibitors) were associated with an increased risk of MI or coronary heart disease death (RR 1.76, 95% CI 1.31, 2.37), major vascular events (RR 1.37, 95% CI 1.14, 1.66), death (RR 1.22, 95% CI 1.04, 1.44) and particularly heart failure (RR 2.28, 95% CI 1.62, 3.20)[113]. Interestingly, compared to non-selective NSAIDS, coxibs were only associated with a greater risk of MI or coronary heart disease death (RR 2.11, 95% CI 1.44, 3.09) and major vascular events (RR 1.49, 95% CI 1.16, 1.92) when compared to naproxen (and not diclofenac or ibuprofen), emphasising the need to consider cardiovascular risk with coxibs but also with non-selective NSAIDs (perhaps less so with naproxen) [113].

In the same meta-analysis, all NSAIDs were associated with increased upper gastrointestinal complications (coxibs RR 1.81, 95% CI 1.17, 2.81, p=0.0070; diclofenac RR 1.89, 95% CI 1.16, 3.09, p=0.0106; ibuprofen RR 3.97, 95% CI 2.22, 7.10, p<0.0001; and naproxen RR 4.22, 95% CI 2.71, 6.56, p<0.0001)[113]

The absolute impact of adverse events in coxibs was summarised in a meta-analysis of 36 osteoarthritis studies with the risk difference with COX-2 inhibitors (compared to placebo) being 5 more per 1000 patients for upper gastrointestinal adverse events, 9 more per 1000 patients for abdominal pain, 12 more per 1000 patients for hypertension and 7 more per 1000 patients for heart failure and oedema.

As mentioned, the mean age in osteoarthritis trial populations is in the early 60-year bracket and it is likely that the rate of adverse events will rise beyond those quoted above in the oldest old. Real-world data suggest an increased risk of acute kidney injury, in particular, when treating with non-selective NSAIDs[114].

Proton pump inhibitors (PPI) attenuate the upper gastrointestinal adverse effects of non-selective NSAIDs; however, there is evidence to suggest that PPIs do not provide protection from lower gastrointestinal adverse effects, but also that PPIs may exacerbate lower gastrointestinal adverse effects, perhaps via alteration of the microbiome[115, 116].

The above should inform a clinical approach to treating osteoarthritis in the oldest old via both non-selective NSAIDs and coxibs. Careful assessment of cardiovascular, gastrointestinal, haemorrhagic and renal risk should take place prior to commencement of NSAID therapy. Blood pressure should be monitored and gastroprotection provided (whilst bearing in mind the risk to the lower gastrointestinal tract). Diclofenac and rofecoxib should be avoided due to their high cardiovascular risk. Renal toxicity may be lower with celecoxib than non-selective NSAIDs. In general, NSAIDs should be used at the lowest dose for the shortest duration.

5. Diet

The potential impact of diet on both osteoporosis and osteoarthritis has been extensively considered and the impact of quality of diet throughout the lifecourse may come to bear in the oldest old. Nutritional research is limited by issues with randomisation of diet and so robust trials are limited to dietary supplementation.

Nevertheless, there are extensive guidelines for calcium, vitamin D and protein intake within a balanced diet in order to support bone health published by the International Osteoporosis Foundation[117]. This contains specific recommendations for older (including the oldest old) adults including calcium intake recommendations of 1200mg daily for those aged 70+, vitamin D intake of 800 international units daily for those aged 71+ and protein intake ≥0.8g/kg body weight/day (above the recommended daily allowance, and usually in the range of 1.0-1.2 g(kg body weight/day) may be recommended for the oldest old) [117].

Overall, inferences on the effect of nutrition on osteoarthritis and osteoporosis in the oldest old must be drawn from studies in younger cohorts[118].

5.1 Osteoporosis

5.1.1 Macronutrients

Omega-3 fatty acids modulate the activity of osteoclasts and osteoblasts, dampen inflammatory processes and regulate calcium metabolism, working in consort to potentially benefit bone health. However, there is limited evidence regarding prevention and a systematic review of the literature demonstrated no effect of n-3 fatty acids on bone health[119, 120].

For carbohydrate there is a paucity of data, but a single study in postmenopausal women showed that diets with higher glycaemic index increased the risk of osteopenia and osteoporosis, with higher carbohydrate quality index leading to a reduced risk of low BMD[121].

For protein intake there is more data (though not in the oldest old) with a meta-analysis of 12 cohort studies and randomised controlled trials demonstrating a positive trend between higher protein intakes and higher femoral neck and total hip BMD[122]. A meta-analysis of four cohort studies showed that higher protein intakes were associated with a significantly lower risk in of hip fractures (pooled HR 0.89, 95% CI 0.84, 0.94)[122]. This is supported by other meta-analyses[123, 124] and supports the assertion that higher protein intake of 1.2-1.5g/kg body weight/day should be considered for the oldest old[125].

5.1.2 Micronutrients

In terms of micronutrients, excess phosphorus should be avoided, particularly in low-calcium diets and magnesium levels should be replete, derived ideally via diet rather than supplementation[126, 127].

Vitamin intake should be adequate, including B12 vitamins [128], vitamin C [129], and moderate evidence of a similar effect for vitamin E[130]. The data regarding vitamin K is more mixed, with no clear effect[131, 132].

Like bisphosphonates, phytates are analogs of pyrophosphate and a diet rich in phytates (via legumes, cereals, nuts) is associated with better BMD[133].

5.1.3 Foods

When it comes to foods and dietary patterns there are theoretical benefits of dairy products on bone via calcium intake, but meta-analyses of longitudinal studies are largely null[134, 135]. This should not dampen recommendations around dairy intake for protein and calcium intake[136], or indeed fermented dairy products[137, 138] and the potential role of the gut microbiome[139]. Soy, mostly supplemented to provide isoflavones, shows some relationship with BMD[140] and green tea (if intake is at least 5 cups per day) has been associated with small improvements in BMD and reduced fracture risk[141].

5.2 Osteoarthritis

The majority of nutritional studies in osteoarthritis are, quite correctly, centred on obesity. However systematic reviews have shown reduced prevalence of osteoarthritis and improved quality of life in those taking a Mediterranean diet, and reduced progression of symptoms with a prudent diet[142]. Although there are studies examining the effect of alternative, supplemental therapies, many of these only show benefit in symptoms but no disease modification[143]. The gut microbiota is another area of interest and may be a future target for interventions[139, 144].

6. Exercise

Musculoskeletal ageing, including in the oldest old, is associated with mitochondrial dysfunction, hormonal function, neuromuscular impairment, reduced protein turnover, reduced cardiorespiratory function, impaired myogenic capacity and an increasingly pro-inflammatory cytokine milieu[145].

The World Health Organisation provided guidelines on physical activity in 2020[146], with a general rule being ‘start low and go slow’ but ultimately aiming to exercise more than 300 minute per week for everyone who can, and older adults should aim to perform multicomponent activities for strength and balance on at least 3 days per week.

In osteoarthritis there is a graded relationship between average daily energy expenditure and benefits for osteoarthritis. Evidence from the OsteoArthritis Initiative (OAI) suggests that 150 minutes of moderate-vigorous physical activity (MVPA) per week reduces functional decline by 32%[147], but even at lower levels of physical activity (at 55 minutes of Moderate to Vigorous Physical Activity

(MVPA)/week), osteoarthritis patients can maintain disability free status at 4 years[148]. Even if there were no bout of MVPA during the week but physical activity levels increase, then disability can be reduced[149]. Indeed, breaking the habit of sedentary behaviour may be a good aim and target for physical intervention in older adults[150].

Physical activity can take many forms, including household chores, and those participating in <1 hour of household activities (including chores) have a higher risk of hip fracture (HR 1.85, 95% CI 1.01, 3.38) than those participating in >6 hours of household activity[151].

Structured exercise centres around resistance training, functional training, balance training, impact training and aquatic therapy. Exercise prescription for older adults should focus on increasing the speed of movement to counteract the loss of fast twitch muscle fibres, diversifying load direction and applying loads rapidly to reduce falls risk and aiming to progressively overload to improve performance. The muscle groups targeted may be different for osteoarthritis of the knee, where the focus may be on quadriceps muscle strength, compared to osteoporosis, where the focus may be directed to the specific areas most vulnerable to fracture. For example, targeting the lower quarter for those more vulnerable to hip fracture, targeting the core musculature and back for those more vulnerable to vertebral fracture, with all osteoporosis patients advised to perform exercises to improve balance and minimize falls.

Systematic reviews highlight the importance of potentially focusing on single intervention resistance training in the oldest old to improve strength if compliance is an issue with multicomponent approaches[152].

When considering strengthening approaches, to optimise training exercise should be supervised by a physical therapist, with a minimum effort of 40-60% for one repetition and the task should feel moderately hard to perform. The number of repetitions can be a set number (for example 10-15) of ‘good form’ or according to the threshold that the individual should have no more than 3 ‘repetitions in reserve’[153]. Three or more sessions should be performed per week with 24-48 hours rest between sessions. This can lead to a 30% reduction in the pain from knee osteoarthritis.

High-intensity resistance training, progressing gradually over 12 weeks from education to explosive movements, has been shown to benefit older men with osteosarcopenia associated with improvements in lumbar spine BMD (measured via quantitative CT) and skeletal muscle mass index[154]. The Otago Falls Program and GLA:D®[155] international programme are exemplars of programs for improving falls risk and symptoms from osteoarthritis respectively.

Exercise parameters which should be the subject of future work in the oldest old include muscle power (including ballistic exercises), adherence to therapy and adaption.

7. Health economics

Analysis of health economics is vital in the current healthcare environment with rising demands and budgetary constraints. Health Technology Assessment is a broad scientific field that encompasses a multi-disciplinary process incorporating various dimensions of value including effectiveness of an intervention, safety, costs, ethical-social-cultural factors, legal framework and the environment and sustainability[156, 157]. An economic evaluation typically investigates the (societal) costs against the number of Quality Adjusted Life Years (QALY, one QALY corresponding to 1 year in perfect health). When the intervention is associated with more QALY for lower cost, the intervention is said to be dominant. For interventions associated with more QALYs and more costs, the incremental cost-effectiveness ratio (ICER) is investigated. The lower the ICER the more cost-effective the intervention.

7.1 Osteoporosis

The cost-effectiveness of anti-osteoporosis medications has been analysed in multiple studies[81, 158-161], concluding that these interventions are generally cost-effective in men and women with low bone mass and/or fractures over the age of 60 years.

Due to the increased incidence and high costs resulting from fractures in the oldest old, in terms of acute management and long-term care requirements, cost-effectiveness of these medications rises with age[162] and is often dominant in the oldest old (as the cost of the treatment is less than the cost of fractures prevented). There is a reduction in the ICER with increasing age due to higher fracture incidence with increasing age.

7.2 Osteoarthritis

Several studies have investigated cost-effectiveness of interventions for osteoarthritis[163-166]. The cost-effectiveness of these interventions (including pharmacological and non-pharmacological interventions) is heterogeneous, although most studies found interventions to be cost-effective (for specific ICER thresholds). There are very few studies including the oldest old. Mazzei and colleagues included individuals over the age of 50 years and found that most osteoarthritis interventions were cost-effective or dominant[165] and Kunkel and colleagues demonstrated the cost-effectiveness of total hip replacement as a surgical intervention for hip osteoarthritis in patients aged ≥80 years[167].

In summary, treatment strategies for osteoarthritis and osteoporosis, are cost-effective in the oldest old, though there are relatively few analyses incorporating individuals ≥80 years.

8. Conclusions

To conclude, despite osteoarthritis and osteoporosis being highly prevalent in the oldest old, there is a remarkable paucity of data to inform clinical practice in this population.

This evidence gap is particularly wide in trials of osteoarthritis, which generally have a mean age in the early 60s. Real-world data on pharmaceutical interventions in osteoarthritis is hampered by the inability to readily record over-the-counter medicines (such a paracetamol and NSAIDs). In osteoporosis, the evidence for older age groups comes largely from post-hoc analyses of pivotal trials but very rarely include the oldest old. It should also be emphasised that, although the *relative* fracture risk reduction may be similar across age groups, the *absolute* fracture risk reduction is greater in the oldest old.

Medications for osteoarthritis and osteoporosis should be prescribed after a thorough assessment of comorbidity and polypharmacy in each individual patient. It should also be considered that chronological age is a single measure of ageing and substantial biological ageing can occur at younger ages, and the same careful approach should be taken to these 'accelerated ageing' patients.

We finish with a call to fight ageism and for further research (clinical, epidemiological and health economic) focusing on interventions for osteoporosis and osteoarthritis in the oldest old in order to counteract the projected increases in prevalence which will arrive with the ageing epidemic.

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Conflicts of interest

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All authors contributed to the discussion of the subject matter. NF, AL, RR, JYR and NCH wrote the drafted the manuscript. All authors reviewed and commented on the manuscript.

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Table 1: The characteristics and efficacy results for post-hoc analyses focused on older age groups of pivotal trials for anti-osteoporosis medications

Medication	Comparator	n	Age	Fracture site	Effect size
Alendronate[42]	Placebo	3658 (in total)	75-85 years	Any hip, vertebral or distal radial fracture	Hip fracture RR 0.47 (95% CI 0.27,0.81, p < 0.02) Vertebral fracture RR 0.55 (95% CI 0.37, 0.83, p < 0.01) Distal radius RR 0.69 (95% CI 0.50, 0.98) p<0.04)
Zoledronate (HORIZON)[50]	Placebo	Zoledronate=1961, Placebo= 1926	≥75 years	Clinical fracture, Clinical vertebral and non-vertebral fracture	Clinical fracture HR 0.65 (95% CI 0.54, 0.78, p<0.001) Clinical vertebral HR 0.34 (95% CI 0.21, 0.55, p<0.001) Nonvertebral fracture HR 0.73 (95% CI 0.60,0.90, p=0.002)
Risedronate (HIP)[45]	Placebo	3886 (in ≥80 year arm)	≥80 years	Hip	Hip fracture RR 0.8(95% CI 0.6, 1.2, p=0.35)
Denosumab (FREEDOM)[55]	Placebo	2471 (≥75 years)	≥75 years	Hip	Hip fracture RR 0.38 (95% CI 0.18, 0.78, p=0.07)
Teriparatide (FPT)[61]	Placebo	244 (≥75 years)	≥75 years	Vertebral and non-vertebral fracture	Vertebral fracture RR 0.35, (p<0.05) Non-vertebral fracture RR 0.75, (p=0.661)
Abaloparatide (ACTIVE)[64]	Placebo	94 (≥80 years)	≥80 years	Vertebral and non-vertebral fracture	Vertebral fracture (placebo 2, ABL 0) Non-vertebral fracture (placebo 2, ABL 1) Not statistically significant

ABL – abaloparatide, CI – Confidence Interval, HR – Hazard Ratio, NNT – Number Needed to Treat, RR – Relative Risk, ZOL – Zoledronate

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