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REVIEW

Management of osteoporosis of the oldest old

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Abstract
Summary This consensus article reviews the diagnosis and treatment of osteoporosis in geriatric populations. Specifically, it reviews the risk assessment and intervention thresholds, the impact of nutritional deficiencies, fall prevention strategies, pharmacological treatments and their safety considerations, the risks of sub-optimal treatment adherence and strategies for its improvement.

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Introduction This consensus article reviews the therapeutic strategies and management options for the treatment of osteoporosis of the oldest old. This vulnerable segment (persons over 80 years of age) stands to gain substantially from effective anti-osteoporosis treatment, but the under-prescription of these treatments is frequent.
Methods This report is the result of an ESCEO (European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis) expert working group, which explores some of the reasons for this and presents the arguments to counter these beliefs. The risk assessment of older individuals is briefly reviewed along with the differences between some intervention guidelines. The current evidence on the impact of nutritional deficiencies (i.e. calcium, protein and vitamin D) is presented, as are strategies to prevent falls. One possible reason for the under-prescription of pharmacological treatments for osteoporosis in the oldest old is the perception that anti-fracture efficacy requires long-term treatment. However, a review of the data shows convincing anti-fracture efficacy already by 12 months.
Results The safety profiles of these pharmacological agents are generally satisfactory in this patient segment provided a few precautions are followed.
Conclusion These patients should be considered for particular consultation/follow-up procedures in the effort to convince on the benefits of treatment and to allay fears of adverse drug reactions, since poor adherence is a major problem for the success of a strategy for osteoporosis and limits cost-effectiveness.

Keywords Ageing · Drug adherence · Fracture risk · Frailty · Malnutrition · Muscle weakness · Osteoporosis · Review

Introduction

In view of the progressive ageing of most of the world's populations, it can be expected that the incidence of age-related conditions will grow and therefore the treatment and management of these individuals will gain increasing priority.

Osteoporosis and frailty, which together greatly increase the risk of fracture, are of particular concern. Hip fractures are the most serious osteoporotic fractures, with high risk of mortality. A large proportion of patients (more than 50 %) admitted to hospital with hip fracture are over 80 years old [1]. The survivors have a high risk of sustaining another major fracture and face deterioration in their quality of life and risk of dependency. Whilst the prevalence of osteoporotic facture is higher in women than men, it is clear that the risk in men is not negligible and ageing men have a greater risk of mortality and morbidity following hip fracture than do women [2].

With a focus on osteoporosis, this review builds on previous review [3] to examine new evidence and guidance for diagnosis and treatment options for the oldest old (80 years and older). The efficacy and safety information on the oldest group is sparse since this age group is rarely included in randomised controlled trials (RCT). But this is beginning to change and more subgroup analyses in older patients are also being published. Of particular interest are new data concerning nutritional supplementation as well as new efficacy studies of pharmacological agents. Although a number of effective treatments for osteoporosis exist, only a small proportion of older individuals receive them, even after major fracture.

An expert working group of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) convened to discuss the current management strategies for older patients in the context of pharmacological and non-pharmacological interventions.

Ageing and age-related changes to the body

The average life expectancy of persons in the countries belonging to the Organisation for Economic Co-operation and Development (OECD) is now 79.5 years [4]. Over the last 50 years, these countries have gained about 11 years in life expectancy, with several (notably South Korea, China, Indonesia and Turkey) gaining over 25 years. In Europe, mean life expectancy at birth for women is 82.6 years (2009 figures) and for men is 76.7 years [5]. In the USA, the segment of the population over 85 years old comprises 5.7 million persons at present (1.8 %) and is expected to rise to 14.1 million by 2040 [6].

As the world's population ages, then the numbers of individuals who will face the problem of increased fracture risk will increase inexorably. The 12 months cumulative mortality following hip fracture is about 30 % [7, 8]. Mortality risk is higher in men (about double) as compared to women [2, 7, 8] and men appear more likely to suffer from markedly muscle loss after hip fracture [9]. In addition to the strong sex-difference in survival following an initial hip fracture, risk of a second hip fracture is increased in the patients that do survive and this carries with a strongly elevated 1-year mortality risk [10]. Thus by proactively treating older individuals who are at high risk of osteoporotic fracture, it might be possible to improve markedly their long-term outcome. Those who do survive have high probability of acquiring co-morbid disease and disability; thus putting a strain on healthcare systems and reducing the quality of life of the oldest old [11].

Another major problem in the older individuals is the decline in muscle function. This is an age-dependent condition, but it is often exacerbated by reduced mobility (caused for instance by osteoarthritis or obesity) and/or by poor nutrition. Reduced muscle function or weakness is one component of the frailty syndrome, which also includes unintended

weight loss, self-reported exhaustion, slow walking speed and low physical activity [12], as proposed by Fried and colleagues [12]. Greater evidence of a "frail phenotype" is associated with a substantially higher risk of recurrent falls and fractures and this risk is largely independent of age [13].

The SHARE frailty instrument, developed for the SHARE study (Survey of Health, Ageing and Retirement in Europe), is based on the criteria of Fried and colleagues has been validated and is predictive of all-cause mortality [14, 15]. An online version is provided as a simple tool for practitioners to obtain an indication of the frail and pre-frail status of individuals. In a non-institutionalised population aged 50 years and older (N=31,115) in the SHARE study, the percentage of frail women was 7.3 % and of frail men was 3.1 % [16].

Osteoporosis in older individuals

A definition of osteoporosis

The operational definition of osteoporosis (endorsed by the World Health Organization [WHO]) is a bone mineral density (BMD) T-score of −2.5 or lower (i.e. at least 2.5 standard deviations below average bone mineral density of healthy young individuals), where BMD assessed by dual X-ray absorptiometry (DXA) at spine or hip. The same definition is applied to men and women, with the same reference population used for both (the NHANES III survey of women aged 20–29 years). It is clear however that the mechanisms of bone loss differ between men and women [17–19].

During the diagnosis of osteoporosis it is, of course, important to determine if the patient has primary osteoporosis (age-related bone loss) or secondary osteoporosis, caused by underlying diseases, amenable to interventions, such as metabolic disease, nutritional deficiencies, or medication (particularly glucocorticoids). Secondary osteoporosis, especially in older men, can be quite frequent [20]. For further information concerning the diagnostic workup, the reader is directed to the articles by Kanis and co-workers [21, 22].

The risk of fracture for an individual is therefore related to BMD, but is also dependent on a number of factors and most particularly age, with the result that T-score alone is not sufficient in defining fracture probability and who should be treated [23, 24].

Fracture risk and age

The risk of sustaining a major fragility fracture increases progressively with age, irrespective of BMD T-score (Fig. 1). The apparent decrease in risk seen in the oldest old segment is due to the competing effect of mortality (i.e. an integration of two hazards: fracture risk and risk of death).

In the general population without apparent clinical risk factors for osteoporosis (the grey filled area in Fig. 1), fracture risk increases with age. From the age of about 75 years and more, the fracture risk is higher than in women with a T-score of −2.5 SD. This is because, after the age of 75 years, the average T-score in the general population falls below −2.5 SD. Thus, a T-score of −2.5 SD is protective since, on average, women at this age have a lower T-score [23].

When prior fracture is integrated into the BMD-based risk score model (the profiles with the thicker lines in Fig. 2), the 10-year risk estimate profiles according to age, more closely match the epidemiological data (grey area).

The objective of the risk calculation is therefore to identify the individuals at higher fracture risk, whether younger or older, and to provide treatment accordingly. If it were decided to treat everyone with a risk of over 5 %, then virtually the whole population over the age of about 60–65 years would be treated, whereas if the threshold was 20 %, a proportion of predominantly older individuals would be treated. The proportions of the population according to age who might be treated according to different risk probabilities are illustrated in Fig. 3 (in Japan for this example).

The intervention thresholds for osteoporosis depend on regional treatment and reimbursement policies and these are increasingly guided by economic evaluations to determine cost-effective intervention thresholds [26]. Figure 4 shows the proportion of the population aged between 50 and 89 years old that have a probability of 20 % or more (darker portion of bars), or 10 % or more (total height of bars) for major fracture. Some countries, such as Romania and Bulgaria, have very low risk, whereas others, such as Denmark, have much higher risk.

Of the various risk assessment tools developed in osteoporosis, the FRAX® model, endorsed by the WHO, is the most widely used. FRAX is designed to predict the probability over

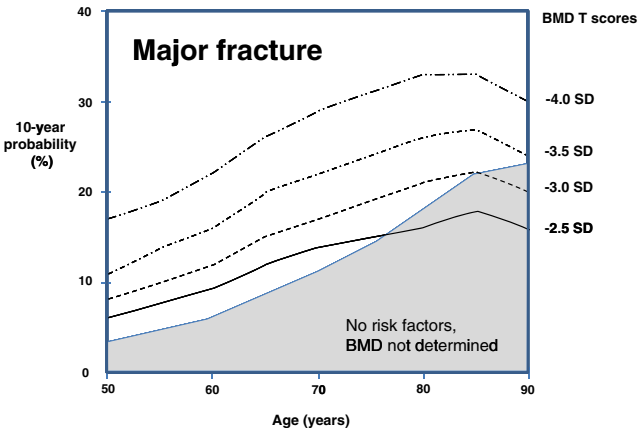

Fig. 1 Risk profiles for British women by age, according to BMD T-score (calculated using FRAX). The *grey area* represents the risk in the general female population having no apparent clinical risk factors for osteoporosis

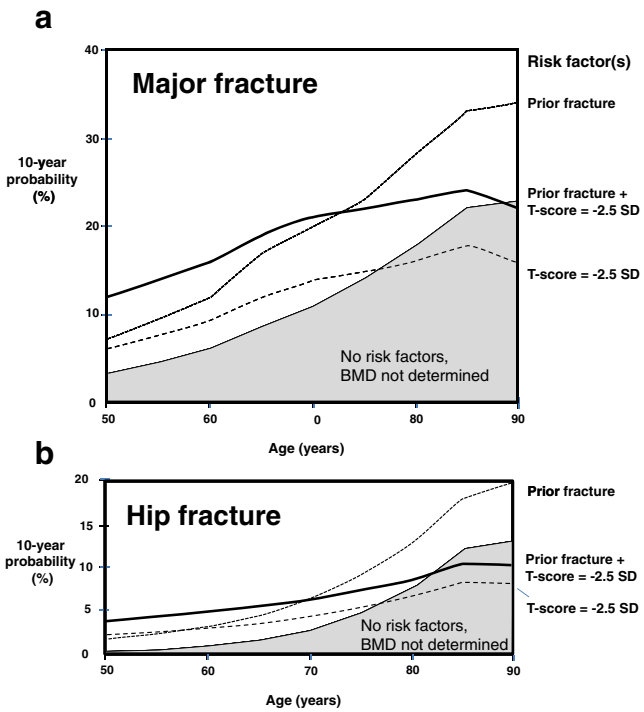

Fig. 2 Risk profiles for British women by age, according to either history of prior fracture, or BMD T-score, or an integration of these two risk factors (calculated using FRAX). **a** Major osteoporosis fracture risk. **b** Hip fracture risk. The *grey area* represents the risk in the general female population having no apparent clinical risk factors for osteoporosis

10 years of a major (i.e. hip, spine, wrist or humerus) osteoporotic fracture [28]. It adjusts the result in very old patients for the competing hazard of death—which is known to be a source of inaccuracy in risk estimates for geriatric studies [29]. It has been updated since its first release, particularly by taking into account glucocorticoid dose.

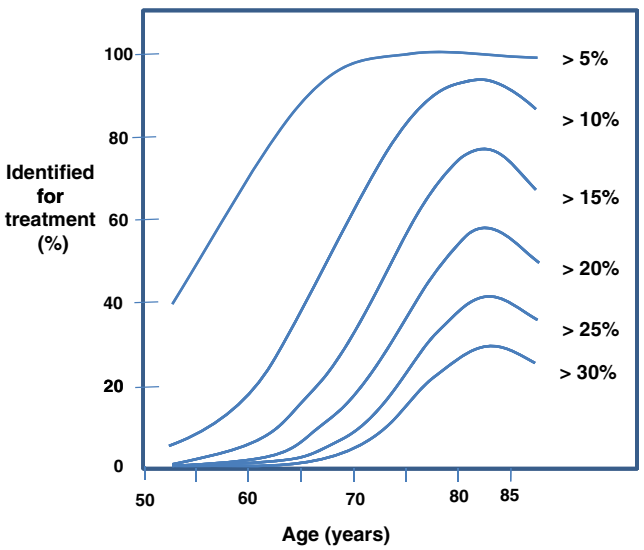

Fig. 3 The proportions of Japanese women by age, who should be treated for osteoporosis, according to their 10-year risk estimate for major fragility fracture (calculated using FRAX) (adapted from Kanis et al. [25])

Diagnosis guidelines

Several clinical groups are involved in the diagnosis and recommendations concerning the treatment of osteoporosis. Two of these, the National Osteoporosis Foundation (NOF) in the USA and the National Osteoporosis Guideline Group (NOGG) in the UK, have recently updated their guidelines and these provide an interesting contrast in views with respect to their use of FRAX as a tool for decisions on intervention (Table 1). Whereas NOF suggests that a FRAX calculation is warranted when the BMD indicates elevated fracture risk, the decision to treat rests mainly on BMD; NOGG suggests that FRAX should be used in a case-finding exercise and the BMD should be performed in cases where the risk estimate is in a borderline zone.

In cases where the diagnostic threshold is crossed (i.e. elevated risk), additional clinical data might be sought to determine whether treatment should be initiated. This could be BMD (as suggested by NOGG), if not already done. Biomarker analysis might also be of potential interest, since high levels of bone turnover markers are associated with increased fracture risk in post-menopausal women [32].

One of the goals of this risk analysis exercise is to improve the targeting of anti-osteoporosis medication to ensure that the individuals who need to be treated are identified and presented with their therapeutic options.

The guidance of NOF concerning the intervention thresholds for treatment (whilst focusing on men and women 50 years and older) is to treat if T-score ≤ -2.5 at femoral neck; or, if the T-score is between -1.0 and -2.5 and the 10-year probability of fracture (on FRAX) is ≥ 3 % for hip or ≥ 20 % for a major fragility fracture. The guidance of NOGG is to treat when the age-related fracture probability exceeds the intervention threshold given by FRAX (where the FRAX threshold is the risk equivalent to a woman with a prior fragility fracture). The age-dependent intervention threshold favoured by NOGG is designed to avoid under-prescription of treatment in eligible younger patients as well as the over-prescription in older age groups that could arise from a fixed threshold.

The FRAX defined intervention threshold therefore corresponds to "severe osteoporosis", i.e. the presence of at least one fragility fracture [33]. Other definitions of severe osteoporosis or high-risk patients could include that used in the GLOW study (Global Longitudinal Study of Osteoporosis in Women) [34], of patients having an age ≥ 65 years and a prior fracture or at least 2 other FRAX risk factors (parental hip fracture, current smoker, less than or equal to three alcoholic drinks/day, rheumatoid arthritis, current corticosteroid use, body mass index (BMI)<20 kg/m^2, or secondary osteoporosis).

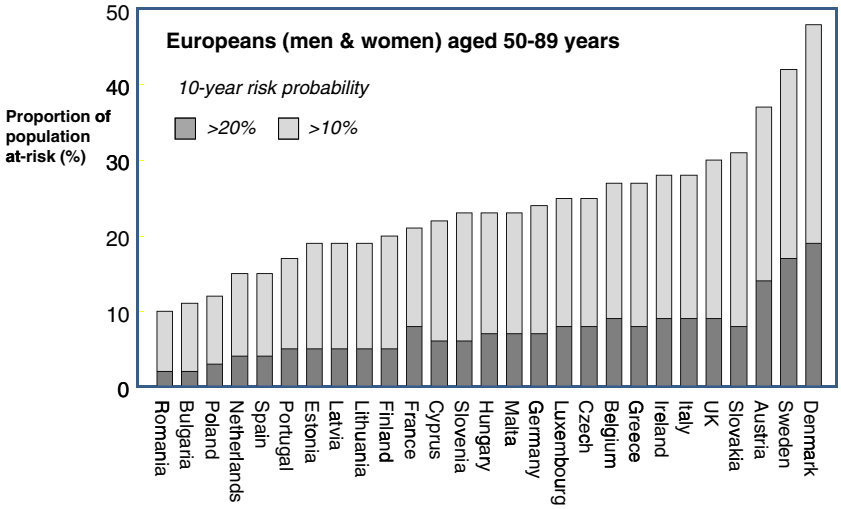

Fig. 4 The proportions of Europeans in each country who should be treated for osteoporosis, according to their 10-year probability estimate (FRAX) for major fragility fracture using either a 10 or 20 % treatment threshold (>10 % whole column height; >20 % dark shaded column height) (adapted from Kanis et al. [27])

Costs

Given a rational strategy of patient identification, a pharmaceutical anti-osteoporosis treatment can change from being cost-effective to being cost-saving in the oldest old [26]. Using a Markov cohort modelling analysis, Lippuner and colleagues [35] estimated the costs associated with the treatment of patients in Switzerland whose fracture risk was estimated using 2 FRAX-based approaches, with the willingness-to-pay threshold for one Quality-adjusted Life-Year (QALY) was set at twice the gross domestic product (GDP) per capita and a first-line treatment with alendronate (original molecule). The analysis found that treatment was cost-effective in women having a 10-year risk for a major osteoporotic fracture of 13.8 % or more, whereas for men the risk estimate should exceed 15 %. Using a translational approach, i.e. the equivalence to a prevalent spine or hip fracture, it was found that in individuals having a previous fragility fracture, treatment was cost-effective in women aged over 60 years and in men aged over 55 years, and cost-saving above the age of 75 years.

Therapeutic approaches to osteoporosis: nutritional supplementation and vitamin D

Vitamin D plays an essential role in the maintenance of bone strength and muscle function. This nutrient/cofactor is involved in the intestinal absorption of calcium and phosphorus, for the mineralization of bone and maintenance of muscle quality as well as a variety of beneficial effects on other organ systems (see review by Boucher [36]).

Vitamin D is synthesised in skin during sun exposure as well as ingested as part of a balanced diet. Older individuals synthesise lower amounts of vitamin D in skin (they also tend

Table 1 Intervention guidelines for osteoporosis, with a focus on older individuals

	NOF	NOGG
BMD testing	Women aged ≥65 years Men aged ≥70 years Initiate therapy in those with T-scores ≤2.5 (at femoral neck, total hip or lumbar spine)	If suggested by FRAX case-finding analysis
Vertebral imaging	Women aged ≥70 years Men aged ≥80 years	Not mentioned
FRAX	Its use is warranted in patients with low femoral neck BMD. Noted that using FRAX in patients with low BMD at the lumbar spine with relatively normal levels at the femoral neck leads to an underestimation of fracture risk.	Case-finding using FRAX in all post-menopausal women and men aged ≥50 years. Initiate therapy following discussion of risk with patient

NOF National Osteoporosis Foundation (USA) [30]

NOGG National Osteoporosis Guideline Group (UK) [31]

to expose their skin less than younger adults) and they frequently have nutritionally impoverished diets. Thus many older people suffer from hypovitaminosis D [36].

A large number of clinical studies have tested the effects of vitamin D supplementation (often in combination with calcium) on fracture risk in older and/or osteoporotic population samples; these have yielded surprisingly varied results and even the meta-analyses have returned equivocal results. It may be, as suggested recently [37], that many of these studies were poorly designed from a methodological viewpoint, in that tests of a causal relationship between a nutrient and a metabolic endpoint (or fracture risk) are fundamentally fraught, because the baseline status of the nutrient may vary widely between individuals and the typical, sigmoid response functions seen for nutrients are very steep.

In a pooled analysis of 11 trials (N=31,000) a lower fracture risk was associated with patients having a plasma concentration of 25-hydroxy-vitamin D (25-OH-D) of at least 60 nmol/L at baseline as compared with those having levels below 30 nmol/L [38]. In a recent analysis of a cohort from the NHANES survey, both major osteoporotic fracture risk and hip fracture risk were significantly related to serum 25-OH-D levels within a period of up to 10 years follow-up. Interestingly, the relationship was linear for major fractures and quadratic for hip fracture, suggesting skeletal site specificities and/or interactions with muscle strength or balance [39]. Indeed there is growing evidence to suggest that vitamin D supplementation has beneficial effects beyond a direct effect on bone health. Bischoff-Ferrari [40] showed in a meta-analysis that raising the levels of 25-OH-D decreased the incidence of falls in older persons by 19 %. A possible mechanism that underlies this effect is the beneficial influence of vitamin D on muscle function, which in turn helps maintain postural stability [41]. Other studies and meta-analyses on vitamin D supplementation have concluded that it is associated with a reduction in all-cause mortality. Whilst several studies and meta-analyses have shown a relatively robust effect on reducing mortality, a recent meta-analysis [42], has given a more muted endorsement. In the group of trials that randomised participants to vitamin D with or without calcium (n=35,116), the risk of death was reduced by 7 % (after adjustment) during the 3 years of follow-up [42]. However, the authors noted that the studies that investigated the effect of vitamin D supplementation with calcium had lower mortality rates than in the studies investigating vitamin D supplementation without calcium (4.4 vs 9.7 %, respectively in the placebo/untreated participants). They found that risk of death in older persons was reduced if vitamin D was given with calcium (hazard ratio, 0.91; 95 % CI, 0.84–0.98) but not if vitamin D alone. In a recent prospective study [43] in 5,292 older persons (85 % women) who were randomised to daily vitamin D3 (800 IU), calcium (1,000 mg), both, or placebo, and followed-up for 3 years, found however no effect on mortality.

Most of the evidence therefore seems to support the beneficial effects of daily vitamin D supplementation. Moreover, it would appear that sufficient levels of vitamin D are a prerequisite for the efficacy of osteoporosis medication [44]. The recommendation of a dose of 800 IU/day (20 μg/day) in older adults (>70 years) has been adopted by most European bodies, as well as the International Osteoporosis Foundation (IOF) and the Institute of Medicine (IOM) and was also advised in a recent ESCEO consensus paper [45–47].

The ESCEO guideline also provided some target thresholds for plasma 25-OH-D levels (Table 2) and whilst most of the background data which was evaluated to produce these threshold was in women (and mostly middle-aged or older and having osteoporosis), they are applicable in both men and women. The NHANES cohort and the MrOS Sweden study, evidenced in men the associations between serum 25-OH-D levels and fracture risk [39] or all-cause mortality [48], respectively.

There is probably no strong necessity to measure circulating levels of 25-OH-D in older patients with suspected high fracture risk and indeed the present cost of testing far exceeds that of supplementation [36]. Vitamin D supplementation should be started de facto, and this should precede any bisphosphonate therapy [44, 47].

Table 2 Threshold levels of 25-hydroxy-vitamin D in the serum and their impact on bone health

Serum 25-OH-D level	Definition	Impact on bone health
< 25 nmol/L (<10 ng/L)	Vitamin D deficiency	Mineralization defects
< 50 nmol/L (<20 ng/L)	Vitamin D insufficiency	Increased bone turnover and/or PTH
50–75 nmol/L (20–30 ng/L)	Vitamin D sufficiency	Neutral effect (bone turnover and PTH normalised), desirable benefits on fracture, falls and mortality
> 75 nmol/L (>30 ng/L)		Desirable target in the fragile individuals or oldest old due to the optimal benefits on fracture, falls and mortality
125 nmol/L (50 ng/L)	Upper limit of adequacy	Possibility of adverse effects above this level

Adapted from Rizzoli et al. [47]

Adverse effects with vitamin D supplementation

Vitamin D supplementation is safe, but caution is advised immediately after treatment initiation in case of nausea, vomiting, gastrointestinal (GI) reflux or excessive thirst, since these symptoms could indicate undiagnosed hyperparathyroidism or overdosage of vitamin D. It should be noted that hyperparathyroidism becomes more common with age, especially in women. The adverse effects of hypercalcemia/hypercalciuria and nephrolithiasis are more frequently associated with high serum 25-OH-D levels (>125 nmol/L), which has been set as the potential upper limit of adequacy [47].

Calcium supplementation

It is important to ensure the sufficient calcium intake through a balanced diet. It appears that an intake of more than 1000 mg/d is sufficient for bone health [49, 50]. A recent meta-analysis [51] which concluded that calcium supplementation (without coadministered vitamin D), might increase the risk of myocardial infarction (MI) has provoked much debate in the professional press. This study appears to present numerous shortcomings that call into question is true validity [52], not least the fact that most of the data come from bisphosphonate-treated osteoporosis patients and a recent epidemiological study of this patient profile has concluded that bisphosphonate usage reduced MI risk [53].

Dietary protein intake

Nutritional insufficiency and malnutrition are frequent in older people [54] and both can result in deficits in essential nutrients. Malnutrition and particularly the protein-energy malnutrition seen in many older people is a major risk factor for sarcopenia and frailty [55, 56]. In a small prospective study of hip fracture patients in Australia (72 % women), 58 % of patients admitted to hospital were undernourished and 55 % had a vitamin D deficiency [57]. Raynaud-Simon and colleagues [58] put the incidences of protein-energy malnutrition as 4–10 % of elderly persons living at home, 15–38 % of those in institutional care, and 30–70 % of hospitalized elderly patients. Questionnaires such as the Mini Nutritional Assessment (MNA) or the SNAQ65+, which have been validated in older persons [59, 60] are useful in this respect to assess nutritional status.

The importance of adequate nutrition for bone health may be appreciated by studies that have assessed plasma levels of insulin-like growth factor-I (IGF-I) in older patients. This important trophic hormone, which mediates the effects of growth hormone (GH), has growth-promoting effects on almost every cell in the body and especially skeletal muscle, cartilage and bone. It regulates phosphate reabsorption in the kidney and has a stimulatory effect on the active uptake of Ca^{2+} and phosphate (PO_4^{2-}) from the intestine via the renal synthesis of calcitriol. Its production in the liver may be severely inhibited in conditions of poor nutrition (see Fig. 5).

The plasma IGF-I concentration has utility as a nutritional biomarker under a range of conditions and may be taken into account in a nutritional assessment [61]. Protein supplementation can lead to a rapid normalisation of IGF-I levels in frail older adults and in recent hip fracture patients (Fig. 6a, b respectively). The 2002 IOM guidelines recommended a protein intake of 0.80 g/kg body weight per day and the 2005 US guidelines maintain this RDA in persons aged over 70 years [64]. Other clinical experts argue however that in view of the impaired protein assimilation of older individuals, the RDA should be increased to 1.0 or 1.2 g/kg per day in this older age group [65–67].

Strategies to prevent falls in older individuals

The elderly are prone to falling [13]. Some of the risk factors are modifiable and should be addressed where possible. Patients who have recovered from a major fracture are significantly more likely to fall, probably because of the combination of muscle loss during the

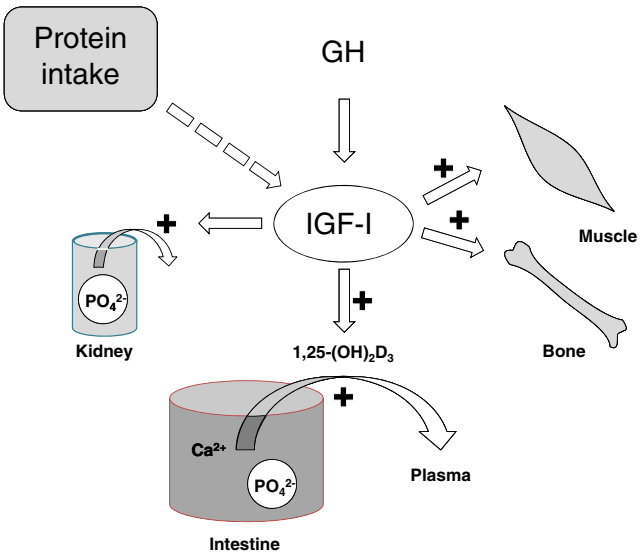

Fig. 5 A schematic diagram showing the central role of IGF-I in bone and muscle health. The production of IGF-I in the liver and other tissues is regulated by growth hormone (GH) secreted by the hypothalamus; this production is also influenced by the nutritional status. IGF-I has trophic effects on skeletal muscle and bone, and regulates phosphate reuptake in the kidney proximal tubules. Via a stimulatory effect the kidney (along with that of parathyroid hormone) IGF-1 raises the plasma level of the calcitriol ($1,25(OH)_2D_3$) form of vitamin D, and so enhances the active uptake of Ca^{2+} and phosphate (PO_4^{2-}) from the intestine

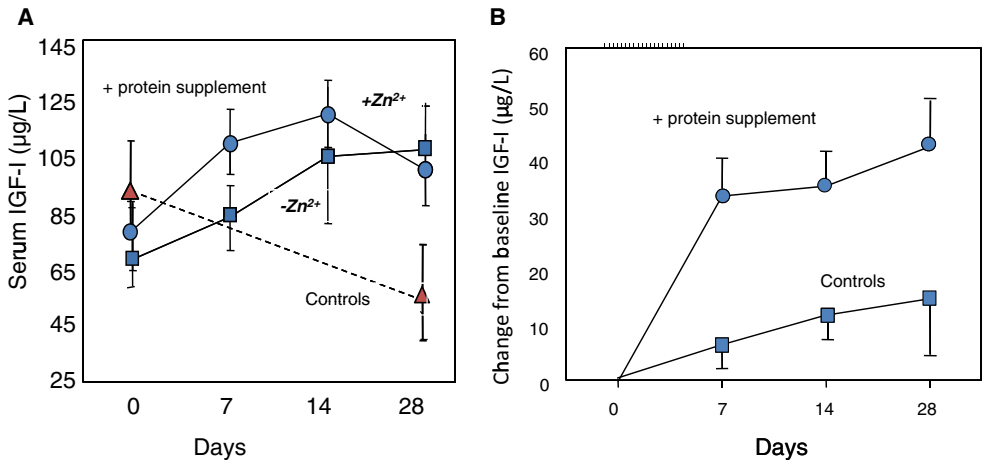

Fig. 6 **a** Serum IGF-I concentrations in frail older adults following protein supplementation (*solid lines*) or no change to diet (*dashed line*). Additional supplementation with zinc enhances the rapidity of the IGF-1 normalisation. **b** Mean change in serum IGF-I concentrations in older women with recent hip fracture following protein supplementation (*upper line*) or controls (*lower line*). References: Panel **a** adapted from Rodondi et al. [62]; panel **b** adapted from Chevalley et al. [63]

convalescent period and balance impairment [68]. In a study of older women (65–75 years) with previous fracture history, the balance was found to be inferior to that of older women with no fracture and younger women with a fracture history. Without corrective measures, this situation can persists for up to 10 years [69]. Other (intrinsic) risk factors include, gait deficits, dizziness and orthostasis, visual impairment, depression, functional and cognitive impairment, low body mass index, urinary incontinence, chronic musculoskeletal pain, female sex, and being 80 years and older [70]. In men, a further association has been found between increased risk of fracture and erectile dysfunction, presumably in relation to frailty or hypogonadism [71]. In a prospective epidemiological study, older frail women (according to the Fried frailty phenotype) had a significantly greater risk of recurrent fall than robust women and in the age group of least 80 years, this risk was almost doubled [72].

Although a number of risk factors for falling are not modifiable, such as age and concomitant diseases that respond poorly to treatment (e.g. neurological impairments, neuromuscular and musculoskeletal diseases), others are, to some extent, modifiable. Whatever the medical history, individuals should be assessed for their level of frailty. Frailty and low muscle strength are associated with a higher risk of falling [73, 74]. Modifiable factors include correcting decreased visual acuity, reducing or stopping medications that can diminish awareness and/or balance, and encouraging modifications to the home environment (correcting slippery floors and mats, improving lighting, fitting handrails in bathroom etc.) [75]. The prescription of certain exercise programs, such as those that focus on gait, co-ordination and functional tasks, as well as strengthening exercises seem to improve clinical balance outcomes in older people [76]. Although various types of exercise training have been assessed in clinical trials in elderly patients, no consensus seems to be apparent as to the most suitable method to be applied in the oldest old. In a systematic review with meta-analysis of 44 studies, including 28 with a patient population aged ≥75 years, Sherrington and colleagues [77] pinpointed the salient aspects of effective programs being balance training, total exercise dose and the prescription of exercises other than walking. Balance training such as Tai Chi in a group setting or at home appeared to be particularly effective [78], as does the practice of Jaques-Dalcroze eurhythmics (a music-based multitask program) [79]. The total exercise dose should preferably be at least weekly over 6 months [77]. An explanation for the greater efficacy of programs without a substantial walking component maybe that the latter diverts too much time from balance training [77]. Weight-bearing activity does however have other health benefits even in the oldest old [68, 80, 81]. Whilst a positive effect of exercise on muscle strength, balance or gait etc. does not automatically translate into a reduction of fracture incidence, it would appear that these improvements do positively impact the physical functioning domain of Quality of Life and are is therefore of clinical benefit [82].

Concomitant medication to be avoided in older adults has been addressed in the updated Beers criteria from the American Geriatrics Society [83]. It might be noted that antiepileptic drug therapy is associated with lower BMD and increased nontraumatic fracture risk [84].

Therapeutic approaches to osteoporosis: pharmacological strategies

Efficacy of osteoporosis drugs

The efficacy of the available pharmacological agents for the treatment of osteoporosis in increasing bone strength and reducing osteoporotic fracture risk is well established, although this evidence is generally better for the prevention of vertebral fractures than that for non-vertebral and hip fractures. Figure 7 presents the efficacy results (forest plots: estimates of treatment effect versus placebo, with the 95 % confidence intervals) in post-menopausal osteoporosis (PMO) for the major pivotal studies on the analyses of vertebral, non-vertebral and hip fractures, respectively. For some of the osteoporosis agents, the beneficial effect of treatment has also been demonstrated on hip fractures (for strontium ranelate, hip fracture analysis was post hoc).

Agents that have been approved for the treatment of osteoporosis in men include the bisphosphonates (alendronate, risedronate and zoledronic acid), teriparatide denosumab, and strontium ranelate (although the availability of the 2 latter agents is more restricted geographically). Except for zoledronic acid, which has been shown to reduce vertebral fracture risk in osteoporotic men [98], the regulatory studies for these agents were bridging studies that relied on changes in BMD and biomarkers, to provide evidence that the changes were essentially the same as observed in women.

The bulk of the evidence of efficacy rests on RCTs in post-menopausal women between the ages of 50 and 80 years and the evidence of anti-osteoporotic efficacy in the oldest old has come primarily from subgroup analyses. A few major studies did however specifically include older post-menopausal women and had prespecified analyses of fracture endpoints: the HIP study on risedronate [90], a clodronate study [99], the TROPOS and SOTI studies on strontium ranelate [97, 100], the HORIZON study on zoledronic acid [101] and the FREEDOM study on denosumab [103] (Table 3). All of these studies showed relatively convincing results on fracture endpoints after 3 years of treatment.

Additional evidence of efficacy in older populations has been provided by the following references:

Alendronate

A post hoc analysis of the Fracture Intervention Trial (FIT)-I of the patients aged ≥75 years, showed that there

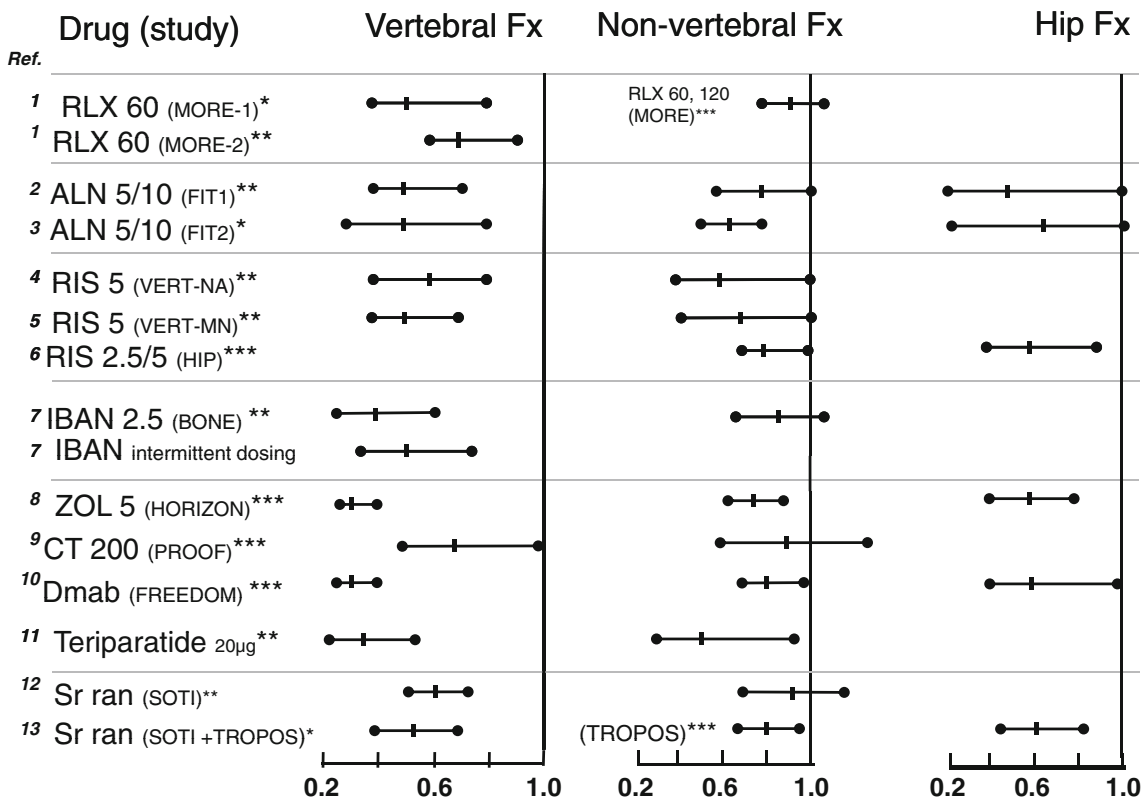

Fig. 7 Forest plots of the treatment effect versus placebo, for the major regulatory studies in post-menopausal osteoporosis, with estimates (with the 95 % confidence intervals) for the relative risk of vertebral fracture (Fx), non-vertebral fracture and hip fractures. References: *1* [85]; *2* [86]; *3* [87]; *4* [88]; *5* [89]; *6* [90]; *7* [91]; *8* [92]; *9* [93]; *10* [94]; *11* [95]; *12* [96]; *13* [97]. With respect to prevalent vertebral fractures, patients were included: without (*), with (**) or irrespectively (***). *RLX* raloxifene, *ALN* alendronate, *RIS* risedronate, *IBAN* ibandronate, *ZOL* zoledronic acid, *CT 200* calcitonin 200 IU, *Dmab* denosumab, *Sr ran* strontium ranelate, *Fx* fracture. The *numbers* refer to doses and (name) to the study

Table 3 Major studies that included significant numbers of older post-menopausal women and had analyses of fracture endpoints

Anti-osteoporosis Drug Study (reference)	Main patient selection criteria (number included)	Cumulative fracture rate over 3 years of treatment duration	Treatment effect versus placebo (p value)
Risedronate			
HIP: 1st pop.[a]	70–79 yr BMD T-score −4 or (−3 plus risk factor) (n=5,445)	Hip fracture: 1.9 vs 3.2 %	RR: 0.6 (p=0.009)
HIP: 2nd pop.[a]	≥80 yr plus risk factor (n=3,886)	Hip fracture: 4.2 vs 5.1 %	RR: 0.8 (p=0.35)
Clodronate[b]	≥75 yr, but no proven osteoporosis (n=5,579)	Hip fracture: 2.0 vs 2.1 %	RR: 1.02 (n.s.)
		Any clinical fracture: 9.5 vs 12.1 %	RR: 0.80
		Non-hip fracture: 5.2 vs 7.4 %	RR: 0.71 (p=0.001)
Strontium ranelate			
TROPOS[c]	≥74 yr BMD T-score −3.0 (n=1977)	Hip fracture: 4.3 vs 6.4 %	RR: 0.67 (p=0.046)
SOTI/TROPOS[d]	≥80 yr subgroup (SOTI inclusion criteria: previous vertebral fracture) (n=1,488)	Vertebral fracture: 19.1 vs 26.5 %	RR: 0.67 (p=0.013)
		Non-vert fracture: 14.2 vs 19.7 %	RR: 0.69 (p=0.011)
		Hip fracture: 5.2 vs 7.4 %	RR: 0.68 (p=0.12)
Zoledronic acid	≥75 yr, M/F, with repaired hip fracture (n=2,127)	Vert fracture 1.1 vs 3.7 %	RR: 0.34 (p=0.001)
HORIZON recurrent fracture[e]		Non-vert fracture 9.9 vs 3.7 %	RR: 0.73 (p=0.002)
		Hip fracture: 2.0 vs 3.5 %	RR: 0.70 (p=0.18)
Denosumab		Vert fracture 3.1 vs 8.6 %	RR: 0.36 (significant)
FREEDOM[f,g]	≥75 yr subgroup (n=2,471)	Non-vert fracture 7.9 vs 9.0 %	RR: 0.84 (n.s.)
		Hip fracture 0.9 vs 2.3 %	RR: 0.39 (p=0.01)
Teriparatide FPT[h]	≥75 yr subgroup (n=244)	Vert fracture 5.2 vs 15.1 %	RR: 0.35 (p<0.05)
		Non-vert fracture 3.2 vs 4.2 %	RR: 0.75 (p=0.66)

n.s. not significant, *pop* population, *vert* vertebral, *vs* versus, *RR* risk ratio; *yr* year

[a] McClung et al. [90]

[b] McCloskey et al. [99]

[c] Reginster et al. [97]

[d] Seeman et al. [100]

[e] Lyles et al. [101]

[f] McClung et al. [103]

[g] Boonen et al. [102]

[h] Boonen et al. [109]

was a significant reduction in risk of new vertebral fracture versus placebo of 38 % [104]. Pooled data from the FIT trials (I and II) with restrictive "documented" osteoporosis inclusion criteria, were used to calculate age-specific fracture rates by treatment group [105]. The relative risk reductions in new fractures (spine, hip or wrist)—in favour of alendronate—were fairly constant across the age groups (5-year intervals from 55 to 85 years) for each site. Finally, in a small study in women in long-term care (mean age 78 years, range 60–91; T-score < −2 at lumbar spine or total hip; n=327), BMD was found to be increased at 2 years by alendronate versus placebo with between-group differences of +4.4 % for spine and +3.4 % at femoral neck [106].

Risedronate

A post hoc analysis of the pooled data from the pivotal studies, Hip Intervention Program (HIP), Vertebral Efficacy with Risedronate Therapy-Multinational (VERT-MN), and VERT-North America (NA) (mean age 83 years, range 80–98; T-score lower than −2.5, or ≥ 1 prevalent vertebral fracture; n=1,392), showed that after 3 years follow-up, the incidence of new vertebral fractures was 18.2 % in the risedronate group versus 24.6 % in the placebo group; an estimated reduction in risk of 44 % [107].

Zoledronic acid

A post hoc subgroup analysis of the pooled data from Health Outcome and Reduced Incidence with Zoledronic Acid One Yearly (HORIZON) and the HORIZON Recurrent Fracture Trial (age≥75 years, T-score ≤ −2.5 at femoral neck or ≥1 prevalent vertebral or hip fracture; n= 3,887) showed that at 3 years follow-up, the hazard ratio for any clinical fracture (versus placebo) was 0.65; for

any vertebral fracture was 0.34; and for non-vertebral fracture was 0.73. All results were statistically significant in favour of zoledronic acid [108].

Teriparatide

In a subgroup analysis of the Fracture Prevention Trial (age ≥75 years in post-menopausal women with ≥ 1 moderate, or ≥ 2 mild, atraumatic vertebral fracture(s); n=244; 1.9 years follow-up), treatment with teriparatide (20 μg by daily self-injection) was associated with a 65 % risk reduction (versus placebo) for new vertebral fracture and a 25 % reduction for new non-vertebral fragility fractures. Teriparatide treatment was associated with a 9.2 % increase in lumbar spine and a 1.9 % increase at the femoral neck BMD [109].

The onset of anti-fracture efficacy

Osteoporosis treatments are frequently found to be under-prescribed, including in women who have sustained an osteoporotic fracture. One reason for this could be a reluctance of clinicians to prescribe treatment because of doubts they might have over the effectiveness of treatment in a short period of time [107]. However, as shown in Table 4, a number of RCTs have demonstrated clinically significant benefits in terms of fracture reduction within the first year of treatment. Thus, even in an oldest old patient population, it would seem that starting treatment with an anti-osteoporosis would, by and large, have time to exert a beneficial effect on bone.

Safety of anti-osteoporotic drugs

In general, the safety margins of anti-osteoporotic drugs are very good. Over the long-term, osteoporosis treatments seem to maintain effectiveness and remain safe [114]. The guidelines, erring on the side of precaution, recommend treatment re-evaluation every 3–5 years [30, 31]. For some patients, a "drug-holiday" might be advocated [115]. The main issues concerning drug therapy in the oldest old include reduced intestinal absorption (thus lower bioavailability of oral treatments), metabolism (slower metabolic rate), excretion (impaired renal function), tissue sensitivity (skin effects), concomitant deficiencies (e.g., reduced endocrine responses to GH and PTH), and concomitant treatments (invoking interactions for drug metabolism as well as target organ effects).

The large RCTs and meta-analyses have shown that under relatively stringent conditions, the adverse events tend to be mild to moderate and reversible. The main adverse events and their approximate incidences are presented in Table 5. As to how these events distribute in the oldest old is less clear. A few pharmacovigilance reports have associated some anti-

Table 4 The beneficial effect of an anti-osteoporotic treatment in older populations is generally seen after the first year of treatment

	Type of vertebral fracture	% risk reduction	1 year fracture rates (treated vs placebo)	RR (95 % CI)
Alendronate[a]	Symptomatic	59	n.a.	0.41 (n.a.)
Risedronate[b]	Symptomatic	69	n.a.	0.31 (0.12–0.78)
Risedronate[c]	Morphometric	81	2.5 vs 10.9 %	0.19 (0.09–0.40)
Zoledronic acid[d]	Morphometric	60	1.5 vs 3.7 %	0.41 (n.a.)
Zoledronic acid (men)[e]	Morphometric	68	0.9 vs 2.8 %	0.32 (0.12–0.88)
Clodronate[f]	Morphometric	46	23.3 vs 12.7 %	0.54 (0.37–0.80)
Raloxifene[g]	Symptomatic	68	0.3 vs 0.8 %	0.32 (n.a.)
Strontium ranelate[h]	Symptomatic	52	3.1 vs 6.4 %	0.48 (0.29–0.80)
Denosumab[i]	Morphometric	61	0.8 vs 2.2 %	0.39 (n.a.)

n.a. not available

[a] [110]

[b] [111]

[c] [107]

[d] [92]

[e] [112]

[f] [99]

[e] [113]

[g] [96]

[i] [94]

Table 5 Summary of adverse drug reactions by frequency according to class of anti-osteoporosis treatment

	Very common ~1/10	Common ≥1/100	Uncommon <1/100 to ≥1/1,000	Rare and very rare <1/1,000 and <1/10,000
Bisphosphonates	-GI effects (oral formulations)	–Musculoskeletal pain –Acute-phase reactions (IV formulations)		–Atrial fibrillation –Atypical fracture/delayed fracture healing –Osteonecrosis of the jaw –Renal impairment –Cutaneous hypersensitivity reactions
Denosumab		–Infection –Rash –Pain in extremity	–Cutaneous effects –Cellulitis	–Osteonecrosis of the jaw –Hypersensitivity reactions
Raloxifene	–Hot flushes –GI effects –Flu syndrome –Increased blood pressure	–Leg cramps –Headache –Rash –Mild breast symptoms –Peripheral oedema	–Venous thrombo embolism	–Stroke –Endometrial effects
Strontium ranelate		–Headache, nausea, and diarrhoea –Venous thromboembolism –Myocardial infarction –Cutaneous effects		–Hypersensitivity reactions
Teriparatide or PTH (1–84)	–Limb pain	–Headache, nausea, dizziness, vertigo –Depression –Palpitations –Sweating increased –Dyspnoea, fatigue	–Myalgia, arthralgia –Urinary incontinence, polyuria, mephrolithiasis	–Renal failure –Allergic reactions

References: Adapted from Rizzoli et al. [116] and the relevant Summaries of Product Characteristics (SmPCs)

osteoporotic agents with rare but severe events (for in-depth reviews see [116, 117]).

Gastrointestinal effects

The problems of upper GI events with oral bisphosphonates, including irritation of the oesophagus, difficulty swallowing, pain on swallowing and heartburn, are well known [118]. The risk of upper GI events is lower when the drug intake instructions are properly followed (including an appropriate quantity of water and post-dosing postural positioning) [119]. In placebo-controlled trials, the reported rates of upper GI events in the active and control arms are often very similar. For example, in the FIT trial, such an event was reported by 47.5 % in the alendronate (10 mg/day) group and 46.2 % of the placebo group [120]. In this trial and many others involving bisphosphonates, women with active ulcers or other GI symptoms requiring daily treatment were excluded and it is likely that the dosing instructions were well explained. Patients with pre-existing upper GI disorders, such as oesophageal stricture, achalasia, or poorly controlled gastroesophageal reflux disease, should preferably, not be treated with oral bisphosphonates.

Generic versions of bisphosphonates are associated with higher rates of GI events and greater risk of treatment discontinuation and this is probably mainly due to their faster disintegration times [121]. Branded formulations allowing weekly or monthly dosing are associated with lower rates of upper GI effects than daily dosing for the same agent. Of potential interest for the oldest old, is the development of an alendronate formulation in a gel form that is easier to swallow [122].

Acute upper gastrointestinal bleeding (UGIB) may be a problem in older patients, but it is not clear that this is exacerbated by bisphosphonates. In a Canadian population-based nested cohort study [123] in patients aged ≥65 years (n=26,223), an incidence rate of 0.4 % of acute UGIB within 120 days of treatment start was found, with 60 % of cases being in patients aged over 80 years. Although relatively few of the affected older patients had a past history of gastric ulcers, serious GI bleeding, or were concurrent NSAID users, it was concluded that the rate was concordant with the prevalence of UGIB (from any cause) in the general population. Indeed, advanced age has consistently been identified as a risk factor for UGIB and is likely related comorbidity and the use of multiple medications [123].

Diarrhoea and nausea is reported as common with strontium ranelate; nausea, vomiting and gastroesophageal reflux

disease are common with teriparatide. For strontium ranelate, these are very rarely severe and more frequently observed at the beginning of treatment [97].

Vascular effects

The use of selective estrogen receptor modulators (SERMs), such as raloxifene or basedoxifene, has been associated with cutaneous flushing, particularly in the face and upper body ('hot flushes'), sweating and leg cramps [124, 125]. In the pivotal regulatory study of raloxifene (MORE)—a PMO population aged 31–80 years (mean age 65 years; 36 month of treatment), "hot flashes" (same as hot flushes) was the most frequently reported non-serious adverse event (almost 10 %) [85]. The incidence of these events appears to be lower in women aged over 55 years, than in a younger age group [124].

The most well-known serious adverse drug reaction with SERMs is venous thromboembolic events (VTE), including deep vein thrombophlebitis and pulmonary embolism. In MORE, the incidence rates of VTE were about 8–12/1,000 in the treated arms (RR vs placebo: 3.1) [85]. A meta-analysis [126] has estimated a 62 % increase in risk of VTE with raloxifene versus placebo. This effect of raloxifene is likely due to the estrogenic effects of on the blood clotting system. Higher risk of VTE has been observed with strontium ranelate than in placebo, without clear explanation [127]. In an analysis of the UK General Practice Research Database (GPRD) database, Breart and colleagues [127] reported annualised VTE rates of 7/1,000 for women (mean age 74 years) treated with strontium ranelate, at a similar rate as in patients receiving alendronate. In that study and another large-scale population-based cohort study [128], the underlying condition itself (i.e., osteoporosis) appeared to be responsible for an increased risk of VTE (possibly due to co-morbid conditions such as previous fracture, or immobilization during hospitalization). In the Breart et al. study, the untreated osteoporotic patients had a rate of VTE of 5.6/1,000 and an age-matched non-osteoporotic cohort 3.2/1,000. In the Vestergaard et al. study [128], the analysis showed an increased risk of VTE with 3 different bisphosphonates compared to the general population and only a borderline effect for raloxifene. It is well established that the risk of VTE increases with age (along with surgery and trauma) [129, 130]. The additional risk of an anti-osteoporosis treatment, in terms of VTE, in the oldest old is therefore very difficult to estimate.

Musculoskeletal pain

Chronic bone pain, as well as joint and muscle pain, have been frequently associated with bisphosphonates, both oral and IV (about 5–10 % of patients) and also to some extent with raloxifene and teriparatide. Intravenous bisphosphonates are associated with the highest rates with some severe cases reported [131]. In 2008, the American Food and Drug Administration (FDA) issued an alert on cases of severe pain which can occur within days, months, or even years after starting bisphosphonates [132]. When initiating once-weekly dosage regimens of alendronate or risedronate, it has been suggested that starting with lower daily dosages for about 2 weeks before switching to the more convenient, once-weekly posology can avoid muscle pain [131].

Limb pain is a commonly reported adverse reaction with teriparatide and, to a slightly lesser extent, back and joint pain. In a placebo-controlled study in elderly women however [109], the incidences of these events was not found greater in the active arm as compared to placebo.

Immune reactions

The administration of intravenous bisphosphonates has been associated with transient flu-like symptoms (myalgia, arthralgia, headache and fever), collectively called an acute-phase reaction (APR). In a study with ibandronate, the incidence of APR with the IV form was 4.9 versus 1.1 % for the oral form. Higher rates of fever have been reported post-dosing with zoledronic acid (around 30 %) [133]. The symptoms of APR, which seem to be related by the release of pro-inflammatory cytokines from circulating gamma-delta T cells, generally appear 24–48 h after administration and resolve, for some patients, within 48 h. The likelihood of having an APR after an IV bisphosphonate, which is mostly observed after the first administration, may be reduced by administration of acetaminophen (paracetamol) prior to dosing.

Cutaneous hypersensitivity reactions are also reported with several anti-osteoporosis drugs [134] although these remain very rare. These events can be serious, with cases of Stevens-Johnson syndrome and toxic epidermal necrolysis reported for bisphosphonates; drug rash with eosinophilia and systemic symptoms (DRESS) in patients receiving strontium ranelate [134, 135]. They require prompt and permanent drug withdrawal and treatment with corticosteroids. The prognosis is good when treated rapidly.

Denosumab has been associated with higher rates of skin infections and eczema [136]. Meta-analysis now indicates that the increased risk is only borderline [136]. Denosumab is a human monoclonal antibody that specifically binds and neutralizes RANKL (receptor activator of nuclear factor-κB ligand), a signalling protein involved in osteoclast formation and function, but is also expressed by activated T lymphocytes, B cells, and dendritic cells. In the FREEDOM trial, the incidence of (serious) cellulitis (including erysipelas) was significantly higher in the active arm (0.3 versus <0.1 %) [94]. The increase rates of eczema and allergic skin reactions, including dermatitis and rashes, seen in denosumab studies are put down to "suboptimal tissue specificity" since RANKL is also expressed in keratinocytes and Langerhans cells [136].

The SmPC for teriparatide notes that this agent is rarely associated with possible allergic events soon after injection, but may include facial oedema, generalised urticarial and acute dyspnoea.

Nervous system effects

Headache is commonly reported with strontium ranelate. The event rate in the oldest old (>80 years) was 3.3 versus 1.7 % on placebo. For teriparatide the rate of headaches in older patients (>75 years) was 6 versus 5 % on placebo (lower than in younger patients); the rate of dizziness was 9 versus 8 % (the same as in younger patients) [109].

Rare cases of seizure have been reported in patients treated with zoledronic acid and it has been hypothesised that the transient hypocalcemia sometimes caused by this bisphosphonate might alter the set point for seizure induction [137].

Teriparatide treatment has been associated with headache, vertigo and depression (SmPC).

Cancer

Rare cases of oesophageal cancer have been reported in patients exposed to alendronate or other oral bisphosphonates, but the results from epidemiological studies on prescription databases have been conflicting. The FDA reports of oesophageal cancer in patients who had received oral bisphosphonates, were after a relatively short treatment times (median time to diagnosis of 2.1 years), thus minimising any probable causative effect. The most recent analysis performed on the UK GPRD [138] concluded that there was a small but significant increased risk of oesophageal cancer in women. Of the 4,442 annually reported cases of upper gastrointestinal cancer, 95 could be linked to bisphosphonate use (Odds Ratio of 1.34 for bisphosphonates). However, an analysis run by another group on the same database concluded there was no significant association [139].

Raloxifene is associated with significantly lower rates of breast cancer as compared to placebo or alendronate treated patients [85, 140].

Teriparatide has been associated with osteosarcoma in experimental animals. However, there is no evidence of any causal association between teriparatide treatment and osteosarcoma in humans according to a long-term surveillance study in the USA [141].

Cardiac effects

An increased risk of atrial fibrillation (AF) has been observed in the pivotal HORIZON study with zoledronic acid. The incidence of AF was 1.3 % in the active arm of zoledronate trial in PMO, versus 0.5 % on placebo ($p<0.001$) [92]. Post hoc analyses of other bisphosphonate trials and several large population-based studies have, however, been inconsistent in their findings, with no conclusive evidence that AF risk is increased. Screening for AF in the older patient may be however important since it is known that the prevalence of AF increases with age, roughly doubling every decade, so that in individuals aged over 85 years the rate is about 10 % [142].

The recent update of the notice for strontium ranelate notes a signal of increased myocardial infarction incidence (1.7 versus 1.1 % in placebo) with a relative risk of 1.6.

No increase in risk of cardiovascular mortality with use of bisphosphonates is reported and indeed a decrease in myocardial infarction has been associated with bisphosphonate use in patients with rheumatoid arthritis [53].

Impaired fracture healing and induced bone weakening

Regarding fracture healing, data from large clinical trials with bisphosphonates indicate no evidence to support stopping therapy whilst a fracture heals.

On the other hand, rare cases of osteonecrosis of the jaw (ONJ) have been reported in recent years. These involve exposed bone in the maxillofacial region that show negligible healing of over a period of 8 weeks. They are mostly (about 95 %) reported in cancer patients receiving high-dose IV bisphosphonates for the prevention or treatment of cancer-related bone disease and in these cases treatment should be stopped. No cases of ONJ have been prospectively identified the major RCTs of bisphosphonates (>60,000 patient-years of exposure) [143]. There have been a few reports of denosumab-related ONJ in the literature, but the incidence rates seem be similar to those of zoledronic acid [136].

Case reports of atypical subtrochanteric, low-trauma, femur fractures in bisphosphonate-treated patients have been published and some have noted prodromal thigh pain in the preceding period. Although some epidemiological evidence suggests there may be an association between these events with duration of BP use, such atypical fractures can occasionally be observed in untreated patients [144–146]. It remains a duration of BP exposure beyond 5 years may constitute a risk factor [147].

Renal safety

Renal insufficiency is common in older patients and therefore causes concern for various drug treatments, including bisphosphonates, because of their primary elimination via the kidney [148]. Therefore, as a precautionary measure, these products (both oral and IV forms) are not recommended in patients with severe renal impairment (creatinine clearance <30–35 mL/min). There have been rare reports of IV forms being associated with nephrotoxicity, but these have been in cancer patients with high treatment doses. Post hoc analyses

of clinical trial data indicate however preserved anti-fracture efficacy and are generally associated with stable serum creatinine levels, suggesting that there is no evidence to suggest that the oral forms confer any increased risk in patients with chronic kidney disease (stage 1, 2 or 3) [148].

Pain management

The management of chronic pain can be a challenge in older patients in view of likely poly-medication, age-related metabolic changes and declining function [149].

Chronic pain is often the result of fractured vertebrae impinging on a nerve root. The use of surgical techniques, such as vertebroplasty (an injection of a cement into the vertebral body) or kyphoplasty (a similar procedure, but with the inflation a small balloon in the bone cavity in an attempt to restore the original height and form of the compressed vertebra), are still debated in the oldest old [150].

Treatment with opioids can be of help, but a careful selection should be made to minimise potential adverse events (notably CNS and gastrointestinal effects) that can be serious. Slow dose titration is advised and doses should remain reduced as compared with younger adults, with a longer time intervals between doses, and regular creatinine clearance monitoring. Buprenorphine shows a distinct benefit in improving neuropathic pain symptoms and it has a half-life of drug activity that is not increased in older patients or in those with renal dysfunction [151].

Optimising therapeutic adherence in osteoporosis

Non-adherence with drug therapy in chronic asymptomatic diseases is widespread [152] and this is also the case for osteoporosis [153, 154]. Whilst different studies in osteoporosis vary substantially in terms of methodology and patient demographics [153], the results indicate yearly persistence rates from 26 to 56 % for daily anti-osteoporosis regimens and from 36 to 70 % for weekly regimens. Estimates of compliance (MPR; see text box) ranged from 46 to 64 % and 58 to 76 %, respectively, and thus also influenced by the dosing interval. The epidemiological study by Rabenda and colleagues [155] noted that the MPR at 12 months was higher among patients receiving weekly as compared to daily alendronate (70.5 versus 58.6 %; $p<0.001$): similar results were found by Cramer et al [153]. It has been noted that compliance tends to diminish with increasing follow-up duration and the drop is particularly rapid over the first 2 years of treatment [153]. In contrast, a recent post-marketing survey has shown an excellent adherence to daily strontium ranelate of 80 % at 1 year, 68 % at 2 years, and 64 % at 32 months [156].

Adherence, compliance and persistence: defining drug usage

The term *adherence* as used by WHO is "the extent to which a person's behaviour—taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider"; where it seems the word "agreed" is important. The term *compliance* is sometimes used to describe more narrowly the behaviour of patients in their respect of drug prescription dose and interval of dosing; whilst the term *persistence* refers to the time from initiation to discontinuation of therapy. Thus, WHO uses "adherence" as a term that encompasses both compliance and persistence. Patients may however be persistent without being particularly compliant, so having the two terms is valuable.

In observational studies, compliance is usually defined as the *medication possession ratio* (MPR), which is the number of days' supply of medication received divided by the period up to prescription refill. Persistence is usually evaluated as the longest period of treatment without a gap (or only a minimal gap) before prescription refill.

The clinical consequence of poor adherence is increased risk of fracture. Siris and colleagues [157] observed that overall fracture rate declined with improved MPR in women aged ≥65 years ($n=175{,}022$): fracture rate was 5.1 % in patients with MPR <50 % whereas it was 3.8 % in those with MPR ≥80 %. In a meta-analysis of six studies (171,063 patients), Imaz and colleagues [158] estimated that the increase in fracture risk for non-compliant patients (1–2.5 years of follow-up) was 28 % for hip fractures and 43 % for clinical vertebral fractures, and a further meta-analysis by Ross and colleagues (0.8–4.2 years of follow-up; $n=698{,}631$) estimated the increase in fracture risk for non-compliance at 30 % and for non-adherence at 30–40 % [159].

Hiligsmann and colleagues, using a 3-year horizon (follow-up) modelled optimal adherence and "real-world adherence" [160]. In the real-world scenario, only 57 % of fractures were prevented and the QALY gain was only 56 % of that expected with full adherence. They concluded that an intervention could be an efficient use of resources if it improved adherence by 25 % and cost less than 100 euros per patient-year.

Adherence to prescribed medication regimens is difficult for all patients and particularly challenging for the elderly. They can be more forgetful, but this can be counteracted by electronic and other reminders to prompt the patient or their carer. However, it appears that about 70 % of non-adherence is intentional, i.e. an active decision by the patient. Many patients seem to perform an implicit risk/benefit analysis once given a prescription for a new treatment and during their treatment, which determines their subsequent behaviour [161–163]. Furthermore, non-adherers are frequently "selectively non-adherent", i.e. whilst they might receive several different treatments for different illnesses, they might be compliant for some treatments, but not for others. As older patients are more likely

to have a number of co-morbid conditions, this selective non-adherence is particularly apparent in this age group.

The reasons for not initiating treatment, and poor medication persistence, were assessed in a large cohort of US adults [163]. The main reason underlying non-adherence was the financial hardship of paying for the treatment (about 50 % of respondents), followed by fear or experience of side-effects (about 40 %), concerns about pharmacological treatments in general (about 28 %) and lack of perceived need for the treatment (about 24 %); with other possible reasons playing more minor roles (see Table 6). The lack of a perceived need for treatment in many patients arises from the fact that they may not experience any symptoms directly from their osteoporosis. Moreover, given the rather wide range of side-effects outlined earlier, many patients are likely to believe that the negative effects of anti-osteoporosis medication outweigh any possible benefits.

In older individuals (without cognitive dysfunction), the main medication difficulties, which give rise to non-adherence, appear to centre around misunderstandings about their disease and health in general, worries concerning adverse effects and polypharmacy, and factors surrounding the patient-provider relationship (and, in some cases, logistical barriers to obtaining medications) [164].

The beliefs and misunderstandings about osteoporosis can be quite varied. In patients with fragility fractures, it has been reported that there may be failure to appreciate or even possible denial of the idea that their facture was related to bone health. Such patients seem to reject the term "fragility" fracture as not being strong enough to reflect their trauma [165]. In addition, whilst patients may have a good understanding of what osteoporosis is, they may not always understand how their treatment can help [166].

The challenge is, therefore, to understand and anticipate these motivations by identifying potential "non-adherers" in the clinic. Predictors of medication non-adherence include specific disease states, such as cardiovascular diseases and depression [167]. A variety of interventions designed to improve treatment compliance have been tested in the clinic, which have been the subject of Cochrane reviews [168, 169] and a further systematic review assessed osteoporosis medications in particular [170]. In general, the periodic follow-up visits between patients and health professionals are beneficial, but few intervention strategies were clearly efficacious. Patient coaching (e.g. a discussion with a nurse just before the consultation that encourages the patient to ask questions), as opposed to the distribution of written material, seems to produce an increase in patient satisfaction with only a small increase in consultation length. Since non-adherence is due to a range of intentional (e.g. negative beliefs) and unintentional (e.g. forgetting) factors, a simple "one size fits all" approach to improving adherence is no longer tenable. Many current adherence programs lack assessment and personalisation around intentional and non-intentional adherence factors, which limits their effectiveness.

During follow-up visits, patients should be questioned as to their adherence, but not by using a closed-ended interrogative approach. Instead, patients should be asked to describe how they take their medicines in a non-threatening manner avoiding any notion of judgment [167]. Assessment tools for older adults may help for these interviews [171–173].

Table 6 Predictors of non-adherence: overview of evidence

Factors that may affect medication taking behaviour	Level of evidence
Gender, income, age, race, personality	Weak
Cognitive ability, depression, social support, self-efficacy, health literacy, number of medicines, disease seriousness beliefs, symptom experience, trust in HCP, HCP-patient concordance.	Moderate
Concerns about treatment, beliefs about illness (cause, timelines), cost of therapy, necessity (perceived need) for treatment, perceived drug efficacy	Strong

HCP Healthcare provider (adapted from McHorney et al. [163])

Conclusions on goals and challenges of osteoporosis treatment in the oldest old

The risk of osteoporotic fractures in the geriatric (≥75 years) and especially the oldest old (≥85 years) continues to be a major healthcare concern. The impact of a major fracture on patients' lives is immense, often heralding the transition to frailty and dependence. The costs borne by society are also significant, both in terms of immediate care and rehabilitation and over the longer term if dependence begins to take hold. The fact that many older people—at high risk of fracture—receive no treatment or highly inadequate treatment is unacceptable. There is now sufficient evidence of the relatively short-term benefits of treatment and of the long-term safety profile of osteoporosis treatments. There is clear evidence that many older people are under-nourished and vitamin D-insufficient—a situation that needs to be rectified quickly and before starting any pharmacological therapy. Because of the widespread levels of poor adherence to treatment, this needs to be addressed in order to ensure that the benefits of treatment can be fully realized.

Whilst information on the relative efficacy of the available osteoporosis treatment is lacking, analytical methods do permit indirect comparison using data from published trials and these are beginning to provide some perspective [174, 175]. In the treatment of the oldest old, however, safety and dosing considerations might possibly outweigh minor efficacy differences. In an interesting new development, it might be noted that combined teriparatide and denosumab treatments in PMO women (mean age 66 years) has shown particularly

impressive results on hip and vertebral BMD after 3, 6 and 12 months of treatment [176].

An awareness of age-related osteoporosis risk, both among healthcare professionals and potential patients, is making slow progress and the laudable communication campaigns on National and International levels have helped to make some headway. In 2012, the IOF launched the *Capture the Fracture Campaign* with the aim of reducing the incidence of secondary fractures by the creation of effective standard of care procedures [177]. The idea is built around the adoption of Fracture Liaison Services that provide comprehensive follow-up of patients after an initial fragility fracture and it proposes to establish a Best Practice Framework that will provide regular updates [178], The year 2012 also saw the launch of *2Million2Many* campaign by the US National Bone Health Alliance (NBHA) which was designed to promote public and professional awareness that 2 million bone breaks occur every year in the USA [179]. The NBHA aims to reduce this number by 20 % by the year 2020 and, to achieve this, it promotes the implantation of the Fracture Liaison Services model of care and provides online resources to healthcare professionals [180]. It might also be noted that OsteoLink (a partnership IOF and the Division of Bone Diseases at the Faculty of Medicine, University of Geneva) is a program that is just getting started, which sets up healthcare social networks to support the osteoporosis community on a national basis [181]. Although none of these programs specifically targets the oldest old, it may be hoped that they reach a wide audience that will make intuitive associations.

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The golden rules of osteoporosis treatment

- Correct or prevent vitamin D insufficiency (≥800 IU/day)
- Ensure dietary calcium intake ~1000 mg/day
- Ensure adequate dietary protein intake ≥ 1 g/kg body wt/day
- Promote weight-bearing physical exercise
- Treat any disease that might be causing bone loss
- Reduce the risk of falls
- Reduce consequences of fall (hip protectors)
- Prescribe pharmaceutical treatment when indicated by risk assessment
- Provide adequate counselling and treatment explanation
- Follow-up patients with enquiries of persistence
- Re-evaluate therapeutic options after 3 years

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