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POSITION PAPER

European guidance for the diagnosis and management of osteoporosis in postmenopausal women

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Abstract

Summary Guidance is provided in a European setting on the assessment and treatment of postmenopausal women at risk from fractures due to osteoporosis.

Introduction The International Osteoporosis Foundation and European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis published guidance for the diagnosis and management of osteoporosis in 2013. This manuscript updates these in a European setting.

Methods Systematic reviews were updated.

Results The following areas are reviewed: the role of bone mineral density measurement for the diagnosis of osteoporosis and assessment of fracture risk; general and pharmacological management of osteoporosis; monitoring of treatment; assessment of fracture risk; case-finding strategies; investigation of patients; health economics of treatment. The update includes new information on the evaluation of bone microstructure evaluation in facture risk assessment, the role of FRAX® and Fracture Liaison Services in secondary fracture prevention, long-term effects on fracture risk of dietary intakes, and increased fracture risk on stopping drug treatment.

Conclusions A platform is provided on which specific guidelines can be developed for national use.

Keywords Bone mineral density · Diagnosis of osteoporosis · Fracture risk assessment · FRAX · Health economics · Treatment of osteoporosis

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Summary of main recommendations

Diagnosis of osteoporosis

1. The operational definition of osteoporosis is based on the T-score for BMD assessed by DXA at the femoral neck or spine and is defined as a value for BMD 2.5 SD or more below the young female adult mean.
2. For clinical purposes, other sites and techniques can be used for diagnosis.
3. Low bone mass (osteopenia) should not be considered a disease category but is intended solely for purpose of epidemiological description.

Risk factors for fragility fractures

1. Several factors contribute significantly to fracture risk over and above that provided by bone mineral density measurements. These include age, sex, low body mass index,

previous fragility fracture, parental history of hip fracture, glucocorticoid treatment, current smoking, alcohol intake of 3 or more units daily and causes of secondary osteoporosis.
2. Additional risk factors that are of use in case finding include height loss (> 4 cm) and thoracic kyphosis.
3. Bone markers (serum procollagen type I N propeptide (s-PINP) and serum C-terminal cross-linking telopeptide of type I collagen (s-CTX) as markers of bone formation and bone resorption, respectively) have some prognostic significance for fracture in situations where BMD is unavailable.

Assessment of fracture risk

1. Country-specific FRAX® should be used to assess fracture probability in postmenopausal women who have risk factors for fracture. In individuals at intermediate risk, bone mineral density (BMD) measurement should be performed using dual energy X-ray absorptiometry and FRAX fracture probability re-estimated.
2. Where BMD testing is unavailable, FRAX can be used without the input of BMD
3. Trabecular bone score (TBS) may be used as an adjunct to BMD measurements and FRAX.
4. Interpretation of FRAX scores may be influenced by exposure to glucocorticoids, information on lumbar spine BMD, trabecular bone score, hip axis length, falls history, immigration status and type 2 diabetes mellitus.
5. Vertebral fracture assessment should be considered if there is a history of ≥ 4 cm height loss, kyphosis, recent or current long-term oral glucocorticoid therapy or a BMD T-score ≤ − 2.5.

Lifestyle and dietary measures

1. Recommendations should include a daily calcium intake of between 800 and 1200 mg and sufficient dietary protein, ideally achieved through dairy products.
2. A daily dose of 800 IU cholecalciferol should be advised for postmenopausal women at increased risk of fracture.
3. Calcium supplementation is appropriate if the dietary intake is below 800 mg/day, and vitamin D supplementation considered in patients at risk of, or showing evidence of, vitamin D insufficiency.
4. Regular weight-bearing exercise should be advised, tailored to the needs and abilities of the individual patient.
5. A history of falls should be obtained in individuals at increased risk of fracture with further assessment and appropriate measures undertaken in those at increased risk.

Pharmacological intervention in postmenopausal women

1. The oral bisphosphonates (alendronate, risedronate and ibandronate) may be used as initial treatments in the majority of cases. In women intolerant to oral bisphosphonates (or in those for whom they are contraindicated), intravenous bisphosphonates or denosumab provide the most appropriate alternatives, with raloxifene, or menopause hormone therapy as additional options. Teriparatide is preferentially recommended for patients at high risk of fracture.
2. Treatments should be reviewed after 3–5 years treatment with bisphosphonate. Fracture risk should be reassessed after a new fracture, regardless of when it occurs. The risk of new clinical and vertebral fractures increases in patients who stop treatment.
3. Withdrawal of denosumab therapy is associated with a rebound in vertebral fracture rate. Bisphosphonate therapy can be considered after discontinuation of denosumab.
4. There is little evidence to guide decision-making beyond 10 years of treatment and management options in such patients should be considered on an individual basis.

Intervention thresholds for pharmacological intervention

1. The thresholds recommended for decision-making are based on probabilities of major osteoporotic and hip fracture derived from FRAX. These vary in different healthcare systems with variation in 'willingness to pay'.
2. Women aged over 65 years with a prior fragility fracture can be considered for treatment without the need for further assessment; BMD measurement may be felt more appropriate in younger postmenopausal women.
3. Age-dependent intervention thresholds provide clinically appropriate and equitable access to treatment and have been shown to be cost-effective.

Systems of care

1. The utility of age-dependent FRAX thresholds in population screening approach has recently been validated as feasible, effective and health economically viable.
2. Coordinator-based Fracture Liaison Services (FLS) should be used to systematically identify men and women with fragility fracture. Their effectiveness and cost-effectiveness have been established recently.

Introduction

In 1997 The European Foundation for Osteoporosis and Bone Disease (subsequently the International Osteoporosis Foundation; IOF) published guidelines for the diagnosis and management of osteoporosis [1], subsequently updated in 2008 [2] and 2013 [3] by the IOF and European Society for Clinical and Economic Evaluation of Osteoporosis and Osteoarthritis (ESCEO). The scope of the present guideline is to review and update the assessment and diagnosis of

osteoporosis, the therapeutic interventions available and the manner in which these can be used to develop management strategies for the prevention of fragility fracture in postmenopausal women. The guideline is intended for all healthcare professionals involved in the management of osteoporosis. Where available, systematic reviews, meta-analyses and randomised controlled trials have been used to provide the evidence base. The evidence base was updated using PubMed to identify systematic reviews and meta-analyses from January 2008 to December 2017. The recommendations in this guideline were endorsed by the Scientific Advisory Board of ESCEO and the Committee of Scientific Advisors and the Committee of National Societies of the IOF.

The high societal and personal costs of osteoporosis pose challenges to public health and physicians, particularly since most patients with osteoporosis remain untreated. There is a large gap between the number of women who are treated compared to the proportion of the population that could be considered eligible for treatment based on their fracture risk. In the European Union (EU), it is estimated that there are and 18.44 million women who have a fracture probability that equals or exceeds that of a woman with a prior fragility as assessed by FRAX® (i.e. individuals at or above a 'fracture threshold'). On the conservative assumption that treatments are only given to patients at high risk, prescription data suggest that more than 57% of women at high risk do not receive bone-specific treatment [4]. Moreover, uptake of treatments for osteoporosis, particularly the bisphosphonates, has declined in recent years [5, 6]. In patients with fragility fractures, less than 20% of patients with a fragility fracture receive therapy to reduce future fracture within the year following fracture [7–9]. Against this sobering background, the aim of this guidance is to stimulate a cohesive approach to the management of osteoporosis in Europe. The term guidance rather than guidelines is used, to avoid any prescriptive connotations since country- or region-specific guidelines are now widely available in many European countries and continue to evolve. Rather, the guidance can inform the development of new guidelines or the revision of existing guidelines. Whilst focussed on a European perspective and on postmenopausal women, the principles may be of some assistance in other regions of the world and in men.

Osteoporosis in Europe

Osteoporosis is defined as a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture [10]. Although the diagnosis of the disease relies on the quantitative assessment of bone mineral density, which is a major determinant of bone strength, the clinical significance of osteoporosis lies in the fractures that arise. Because a variety of non-skeletal factors contribute to fracture risk [11–13], the diagnosis of osteoporosis by the use of BMD measurements is at the same time an assessment of a risk factor for the clinical outcome of fracture. For these reasons, there is a distinction to be made between the use of BMD for diagnosis and for risk assessment.

Common sites for osteoporotic fracture are the spine, hip, distal forearm and proximal humerus. The remaining lifetime probability in women at the menopause of a fracture at any one of these sites exceeds that of breast cancer (approximately 12%), and the likelihood of a fracture at any of these sites is 40% or more in Western Europe [14] (Table 1), a figure close to the probability of coronary heart disease.

Fragility fractures are a major cause of morbidity in the population. Hip fractures cause acute pain and loss of function, and nearly always lead to hospitalisation. Recovery is slow, and rehabilitation is often incomplete, with many patients permanently institutionalised in nursing homes. Vertebral fractures may cause acute pain and loss of function but may also occur without serious symptoms. Vertebral fractures often recur, however, and the consequent disability increases with the number of fractures. Distal radial fractures also lead to acute pain and loss of function, but functional recovery is usually good or excellent.

In 2010, it was estimated that 22 million women and 5.5 million men in the EU had osteoporosis using the diagnostic criterion of the WHO [4]. The number of new fractures in 2010 in the EU was estimated at 3.5 million, comprising approximately 610,000 hip fractures, 520,000 vertebral fractures, 560,000 forearm fractures and 1,800,000 other fractures (i.e. pelvis, rib, humerus, tibia, fibula, clavicle, scapula, sternum and other femoral fractures). Two thirds of all incident fractures occurred in women. Among people age 50 years or more who were still alive in 2010, 3.3 million individuals had sustained a hip fracture (prevalence of prior hip fracture). The corresponding number of men and women with prior clinical vertebral fractures was estimated at 3.5 million. Due to changes in population demography, the annual number of fragility fractures will rise from 3.5 million in 2010 to 4.5 million in 2025, corresponding to an increase of 28%.

Table 1 Remaining lifetime probability of a major osteoporotic fracture at the age of 50 and 80 years in men and women from Sweden [14], with kind permission from Springer Science and Business Media

	At 50 years		At 80 years	
Site	Men	Women	Men	Women
Forearm	4.6	20.8	1.6	8.9
Hip	10.7	22.9	9.1	49.3
Spine	8.3	15.1	4.7	8.7
Humerus	4.1	12.9	2.5	7.7
Any of these	22.4	46.4	15.3	31.7

It is widely recognised that osteoporosis and the consequent fractures are associated with increased mortality, with the exception of forearm fractures [15]. In the case of hip fracture, most deaths occur in the first 3–6 months following the event, of which 20–30% is causally related to the fracture event itself [16]. In Sweden, the number of deaths that are causally related to hip fracture account for more than 1% of all deaths, somewhat higher than the deaths attributed to pancreatic cancer and somewhat lower than the deaths attributed to breast cancer [16]. In 2010, the number of deaths in the EU that were causally related to fractures was estimated at 43,000. Approximately 50% of fracture-related deaths in women were due to hip fractures, 28% to clinical vertebral and 22% to other fractures. Corresponding proportions for men were 47, 39 and 14%, respectively [4].

The total health burden, measured in terms of lost quality-adjusted life years (QALYs), was estimated at 1,180,000 QALYs for the EU. Twice as many QALYs were lost in women compared to men. The majority of the QALYs lost were a consequence of prior fractures. In Europe, osteoporosis accounted for more disability and life years lost (DALYs) than rheumatoid arthritis, but less than osteoarthritis. With regard to neoplastic diseases, the burden of osteoporosis was greater than for all sites of cancer, with the exception of lung cancers [17].

The cost of osteoporosis, including pharmacological intervention in the EU in 2010, was estimated at €37 billion. Costs of treating incident fractures represented 66% of these costs, pharmacological prevention 5% and long-term fracture care 29%. Excluding cost of pharmacological prevention, hip fractures represented 54% of the costs, 'other fractures' represented 39% and vertebral and forearm fractures represented 5 and 1%, respectively [4]. Assigning a QALY the value of 2xGDP, the total value of QALYs lost in 2010 was estimated at €61.4 billion.

Bone mineral measurements

The objectives of bone mineral measurements are to provide diagnostic criteria, prognostic information on the probability of future fractures, and a baseline on which to monitor the natural history of the treated or untreated patient. Bone mineral density (BMD) is the amount of bone mass per unit volume (volumetric density), or per unit area (areal density), and both can be measured in vivo by densitometric techniques.

A wide variety of techniques is available to assess bone mineral that are reviewed elsewhere [18–21]. The most widely used are based on X-ray absorptiometry in bone, particularly dual energy X-ray absorptiometry (DXA). Other techniques include quantitative ultrasound (QUS), quantitative computed tomography (QCT) applied both to the appendicular skeleton and to the spine, peripheral DXA, digital X-ray radiogrammetry, radiographic absorptiometry and other radiographic techniques. Other important determinants of bone strength for both cortical and trabecular bone include macro- and microarchitecture (e.g. cross-sectional moment of inertia, hip axis length, cortical thickness, finite element analysis, trabecular bone score, cortical porosity) [22–27].

DXA is the most widely used bone densitometric technique. It is versatile in the sense that it can be used to assess bone mineral density/bone mineral content of the whole skeleton as well as specific sites, including those most vulnerable to fracture [18]. Areal density (g/cm^2) rather than a true volumetric density (g/cm^3) is measured since the scan is two dimensional. Areal BMD accounts for about two thirds of the variance of bone strength as determined in vitro on isolated bones, such as the vertebral body or proximal femur. DXA can also be used to visualise lateral images of the spine from T4 to L4 to detect fractures of the vertebral bodies [28–30]. Vertebral fracture assessment (VFA) may improve fracture risk evaluation, since many patients with vertebral fracture may not have a BMD T-score classified as osteoporosis. This procedure involves less radiation and is less expensive than a conventional X-ray examination but performs comparably to traditional radiographs [31].

Whereas whole body bone, fat and lean mass can also be measured using DXA, these measurements are useful for research, but they do not assist in the routine diagnosis or assessment of osteoporosis.

The performance characteristics of many measurement techniques have been well documented [32, 33]. For the purpose of risk assessment and for diagnosis, a characteristic of major importance is the ability of a technique to predict fractures. This is traditionally expressed as the increase in the relative risk of fracture per standard deviation unit decrease in bone mineral measurement—termed the gradient of risk.

Limitations of BMD

There are a number of technical limitations in the general application of DXA for diagnosis, which should be recognised [34, 35]. The presence of osteomalacia, a complication of poor nutrition in the elderly, will underestimate total bone matrix because of decreased mineralisation of bone. Osteoarthrosis or osteoarthritis at the spine or hip are common in the elderly, and contribute to the density measurement, but not necessarily to skeletal strength. Heterogeneity of density due to osteoarthrosis, previous fracture or scoliosis can often be detected on the scan and in some cases excluded from the analysis. Some of these problems can be overcome with adequately trained staff and rigorous quality control.

Diagnosis of osteoporosis

Bone mineral density is most often described as a T-score or Z-score, both of which are units of standard deviation (SD).

The T-score describes the number of SDs by which the BMD in an individual differs from the mean value expected in young healthy individuals. The operational definition of osteoporosis is based on the T-score for BMD [11, 34] assessed at the femoral neck and is defined as a value for BMD 2.5 SD or more below the young female adult mean (T-score less than or equal to − 2.5 SD) [3, 12, 36, 37]. The Z-score describes the number of SDs by which the BMD in an individual differs from the mean value expected for age and sex. It is mostly used in children and adolescents [38].

The reference range recommended by the IOF, ESCEO, ISCD, WHO and NOF for calculating the T-score [3, 12, 36, 37, 39] is the NHANES III reference database for femoral neck measurements in women aged 20–29 years [36]. Note that the diagnostic criteria for men use the same female reference range as that for women. This arises fortuitously because for any age and BMD at the femoral neck, the risk of hip fracture or a major osteoporotic fracture is approximately the same in men and women [40–42]. On GE Healthcare bone densitometers, there is an option for T-scores for men to be given relative to either the male or female reference range in DXA readouts. However, the T-score cannot be used interchangeably with different techniques and at different sites, since the prevalence of osteoporosis and proportion of individuals allocated to any diagnostic category would vary, as does the risk of fracture [39].

These considerations have led to the adoption of the femoral neck as the reference site [39], but do not preclude the use of other sites and technologies in clinical practice, though it should be recognised that the information derived from the T-score will differ from that provided by BMD at the femoral neck.

Measurement of multiple skeletal sites

A number of guidelines favour the concurrent use of BMD at the proximal femur and at the lumbar spine for patient assessment. Patients are defined as having osteoporosis on the basis of the lower of two T-scores [43, 44]. The prediction of fracture is, however, not improved overall using multiple sites [45–47]. Selection of patients on the basis of a minimum value from two or more tests will, however, increase the number of patients selected. The same result can be achieved by less stringent criteria for the definition of osteoporosis, by defining osteoporosis, for example, as a T-score of ≤ -2.0 SD rather than ≤ -2.5 SD. Notwithstanding, the measurement of more than one site can aid in the assessment of individuals (discussed below).

Low bone mass (osteopenia)

It is recommended that diagnostic criteria be reserved for osteoporosis and that low bone mass (osteopenia) should not be considered a disease category.

Prevalence of osteoporosis

Because the distribution of BMD in the young healthy population is normally distributed and bone loss occurs with advancing age, the prevalence of osteoporosis increases with age and thus depends on the demography of the population. The prevalence of osteoporosis in the 27 countries of the EU in men and women is shown in Table 2 [4]. Approximately 21% of women aged 50–84 years are classified as having osteoporosis accounting for more than 22 million women in these countries.

These data assume that the distribution of femoral neck BMD is the same in these index countries. There may be small differences in the age- and sex-specific BMD in different European countries as well as within countries. If so, these differences in BMD are relatively small [48] and insufficient to account for the observed differences in fracture rates (see below).

Risk factors for fracture

BMD

Assessment of BMD has provided a pivotal determinant of fracture risk and many guidelines have used BMD thresholds to determine whether treatments should be recommended. Intervention thresholds have ranged from T-scores of − 3 SD to − 1.5 SD depending on the clinical context, the country or on health economic factors. The use of bone mass measurements for prognosis depends upon accuracy. Accuracy in this context is the ability of the measurement to predict fracture. In general, all densitometric techniques have high specificity but low sensitivity, which varies with the cutoff chosen to designate high risk.

At the age of 50 years, for example, the proportion of women with osteoporosis who will fracture their hip, spine or forearm or proximal humerus in the next 10 years (i.e. positive predictive value) is approximately 45%. Despite this, the overall detection rate for these fractures (sensitivity) is low and 96% of fractures at the spine, hip, forearm or proximal humerus will occur in women without osteoporosis [49]. The low sensitivity is one of the reasons why widespread population-based screening with BMD is not widely recommended in women at the time of the menopause [11].

Many cross-sectional and prospective population studies indicate that the risk for fracture increases by a factor of 1.5 to 3.0 for each standard deviation decrease in bone mineral density [32]. There are, however, significant differences in the performance of different techniques at different skeletal sites. In addition, the performance depends on the type of fracture that one wishes to predict [30, 32, 50]. For example, BMD assessments by DXA to predict hip fracture are more predictive when measurements are made at the hip rather than at the spine or forearm (Table 3). For the

Table 2 Estimated number of men and women with osteoporosis (defined as a T-score of − 2.5 SD or less at the femoral neck) and prevalence in the population aged over 50 years in the EU27, 2010. From [4], with kind permission from Springer Science and Business Media

Age group (years)	Individuals with osteoporosis (000)			Population at risk (000)			Prevalence (%)		
	Women	Men	Total	Women	Men	Total	Women	Men	Total
50–54	1106	429	1535	17,556	17,152	34,708	6.3	2.5	4.4
55–59	1578	547	2125	16,434	15,637	32,071	9.6	3.5	6.6
60–64	2188	826	3014	15,302	14,242	29,544	14.3	5.8	10.2
65–69	2523	818	3341	12,489	11,054	23,543	20.2	7.4	14.2
70–74	3409	777	4186	12,217	9967	22,184	27.9	7.8	18.9
75–79	3876	768	4644	10,335	7459	17,794	37.5	10.3	26.1
80+	7350	1325	8675	15,573	7980	23,553	47.2	16.6	36.8
50+	22,029	5491	27,520	99,906	83,491	183,397	22.1	6.6	15.0

prediction of hip fracture, the gradient of risk provided by hip BMD in a meta-analysis is 2.6 [32]. In other words, the fracture risk increases 2.6-fold for each SD decrease in hip BMD. Thus, an individual with a Z-score of − 3 SD at the hip would have a 2.6^3 or greater than 15-fold higher risk than an individual of the same age with a Z-score of 0. Where the intention is to predict any osteoporotic fracture, the commonly used techniques are comparable: The risk of fracture increases approximately 1.5-fold for each standard deviation decrease in the measurement so that an individual with a measurement of 3 standard deviations below the average value for age would have a 1.5^3 or greater than 3-fold higher risk than an individual with an average BMD. Note that the risk of fracture in individuals with an average BMD is lower than the average fracture risk, since fracture risk is a convex function of BMD.

The performance characteristics of quantitative ultrasound are similar. Most studies suggest that measurements of broadband ultrasound attenuation or speed of sound at the heel are associated with a 1.5- to 2-fold increase in risk for each standard deviation decrease in the measured variable [33, 51]. Comparative studies indicate that these gradients of risk are very similar to those provided by peripheral assessment of bone mineral density at appendicular sites by absorptiometric techniques to predict any osteoporotic fracture [32]. Unlike DXA, however, the long-term predictive value wanes with time [52]. Note also that the WHO criteria for the diagnosis of osteoporosis cannot be applied to ultrasound results.

Clinical risk factors

A large number of risk factors for fracture have been identified [53–55]. For the purposes of improving risk assessment, interest lies in those factors that contribute significantly to fracture risk over and above that provided by bone mineral density measurements or age [56]. A good example is age. For any BMD, fracture risk is much higher in the elderly than in the young [57]. This is because age contributes to risk independently of BMD. At the threshold for osteoporosis (T-score = − 2.5 SD), the 10-year probability of hip fracture ranges 5-fold in women from Sweden depending on age (Fig. 1) [49]. Thus, the consideration of age and BMD together increases the range of risk that can be identified.

Over the past few years, a series of meta-analyses have been undertaken to identify additional clinical risk factors that could be used in case-finding strategies, with or without the use of BMD [12]. There are a number of factors to be considered in the selection of risk factors for case finding. Of particular importance in the setting of primary care is the ease with which they might be used. For a globally applicable tool, the chosen risk factors should also be valid in an international setting and their predictive value documented over time. A further and critical consideration is the reversibility of risk, i.e. is there evidence that the risk identified by a risk factor is amenable to therapeutic intervention (reversibility of risk—*not* reversible risk). Age is an example of an irreversible risk factor, but the risk of fracture identified by age has reversibility. The risk

Table 3 Age-adjusted increase in risk of fracture (with 95% confidence interval) in women for every 1 SD decrease in bone mineral density (by absorptiometry) below the mean value for age [amended from [32], with permission from the BMJ Publishing Group

	Outcome			
Site of measurement	Forearm fracture	Hip fracture	Vertebral fracture	All fractures
Distal radius	1.7 (1.4–2.0)	1.8 (1.4–2.2)	1.7 (1.4–2.1)	1.4 (1.3–1.6)
Femoral neck	1.4 (1.4–1.6)	2.6 (2.0–3.5)	1.8 (1.1–2.7)	1.6 (1.4–1.8)
Lumbar spine	1.5 (1.3–1.8)	1.6 (1.2–2.2)	2.3 (1.9–2.8)	1.5 (1.4–1.7)

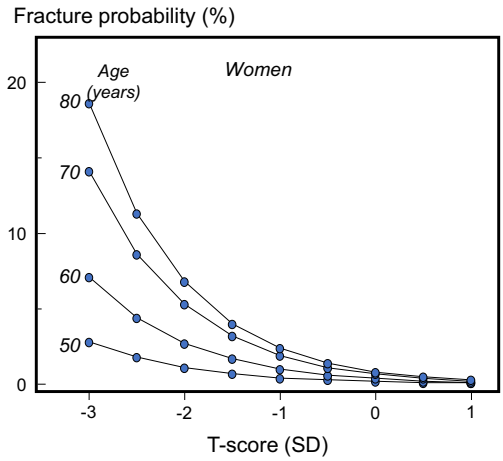

Fig. 1 Ten-year probability of hip fracture in women from Sweden according to age and T-score for femoral neck BMD [49], with kind permission from Springer Science and Business Media

factors that are used for clinical assessment with FRAX are summarised in Table 4 [12, 41, 58–64]. Each of these risk factors has been shown to identify reversibility of risk [65].

In the case of causes of secondary osteoporosis, the increase in fracture risk is presumed to be mediated by low BMD. The exceptions are glucocorticoid exposure and rheumatoid arthritis for which risks have been identified that are independent of BMD. A further candidate is type 2 diabetes mellitus since recent evidence suggests an important independent risk [66–68].

It should be noted that falls risk is not included in Table 4, though it has been used in some risk engines [69, 70], since the risk of fracture that is identified may not be associated with reversibility of risk. For example, patients selected on the basis of risk factors for falling may respond less to agents that preserve bone mass than those selected on the basis of low BMD [71].

Table 4 Clinical risk factors used for the assessment of fracture probability [12] Centre for Metabolic Bone Diseases, University of Sheffield Medical School, UK, University of Sheffield, UK]

Age
Sex
Low body mass index
Previous fragility fracture, particularly of the hip, wrist and spine including morphometric vertebral fracture in adult life
Parental history of hip fracture
Glucocorticoid treatment (≥ 5 mg prednisolone daily or equivalent for 3 months or more)
Current smoking
Alcohol intake 3 or more units daily
Causes of secondary osteoporosis
Rheumatoid arthritis
Untreated hypogonadism in men and women, e.g. premature menopause, bilateral oophorectomy or orchidectomy, anorexia nervosa, chemotherapy for breast cancer, hypopituitarism, androgen deprivation therapy in men with prostate cancer.
Inflammatory bowel disease, e.g. Crohn's disease and ulcerative colitis. It should be noted that the risk is in part dependent on the use of glucocorticoids, but an independent risk remains after adjustment for glucocorticoid exposure.
Prolonged immobility, e.g. spinal cord injury, Parkinson's disease, stroke, muscular dystrophy, ankylosing spondylitis
Organ transplantation
Type 1 and type 2 diabetes
Thyroid disorders, e.g. untreated hyperthyroidism, thyroid hormone suppressive therapy
Chronic obstructive pulmonary disease
HIV infection

Biochemical assessment of fracture risk

Bone markers are increased after the menopause, and in several studies the rate of bone loss varies according to the marker value [72]. Thus, a potential clinical application of biochemical indices of skeletal metabolism is in assessing fracture risk. The IOF and International Federation of clinical Chemistry and Laboratory Medicine (IFCC) have proposed two of several markers as reference analytes in the prediction of fracture risk; serum procollagen type I N propeptide (s-PINP) and serum C-terminal cross-linking telopeptide of type I collagen (s-CTX) as markers of bone formation and bone resorption, respectively [73]. A meta-analysis of prospective studies showed a significant association between s-PINP and the risk of fracture. The hazard ratio per SD increase in s-PINP (gradient of risk; GR) was 1.23 (95% CI 1.09–1.39) for men and women combined unadjusted for bone mineral density. There was also a significant association between s-CTX and risk of fracture GR = 1.18 (95% CI 1.05–1.34) unadjusted for bone mineral density. For the outcome of hip fracture, the association between s-CTX and risk of fracture was slightly higher, 1.23 (95% CI 1.04–1.47) [74]. Thus, there is a modest but significant association between these markers and the future risk of fractures. Currently, there are efforts by IFCC and IOF to harmonise markers of bone turnover, which, if successful, may promote markers of bone turnover for fracture risk prediction [75].

Trabecular bone score

Trabecular bone score (TBS) is a recently developed analytical tool that performs novel grey-level texture measurements on lumbar spine DXA images, and thereby captures information relating to trabecular microarchitecture. Low TBS is consistently associated with an increase in both prevalent and incident fractures that is partly independent of both clinical risk factors and areal BMD at the lumbar spine and proximal femur [23, 76]. It can thus be used as an adjunct to BMD measurements and is a software option for densitometers. Studies including a meta-analysis have shown an incremental improvement in fracture prediction when lumbar spine TBS is used in combination with FRAX variables [77–81]. In the meta-analysis, when additionally adjusted for FRAX 10-year probability of major osteoporotic fracture, TBS remained a significant, independent predictor for fracture (Gradient of risk = 1.32, 95% CI 1.24–1.41) [77]. The

adjustment of FRAX probability for TBS resulted in a small increase in the GR (1.76, 95% CI 1.65–1.87 versus 1.70, 95% CI 1.60–1.81). A smaller change in GR for hip fracture was observed (FRAX® hip fracture probability GR 2.25 vs. 2.22). Thus, TBS is a predictor of fracture risk independently of FRAX and supports the use of TBS to adjust for FRAX probability. Adjustment of FRAX probabilities [77] is available from a dedicated web site (https://www.sheffield.ac.uk/TBS/CalculationTool.aspx) or via the FRAX web site (see Fig. 2).

TBS may also have a role in the assessment of fracture risk in some causes of secondary osteoporosis (e.g. diabetes, hyperparathyroidism and glucocorticoid-induced osteoporosis).

Vertebral fracture assessment

The majority of vertebral fractures do not come to medical attention and thus remain undiagnosed [82]. Moderate or severe vertebral fractures, even when asymptomatic, are strong risk factors for subsequent fracture at the spine and other skeletal sites [83, 84]. Vertebral fracture assessment should therefore be considered in high-risk individuals, using either lateral lumbar and thoracic spine radiographs or lateral spine DXA imaging. Vertebral fracture assessment should be considered in postmenopausal women if there is a history of ≥ 4 cm height loss, kyphosis, recent or current long-term oral glucocorticoid therapy, or a BMD T-score ≤ − 2.5. It should also be considered in individuals with a history of non-vertebral fracture [85].

Assessment of fracture risk

Whereas assessment guidelines have traditionally been based on BMD, its limitations have stimulated the development of risk engines that integrate several risk factors for fracture [86]. These include the Garvan fracture risk calculator [69], QFracture® [70] and FRAX® [12, 87]. Of these, FRAX has been the most extensively used. Since its release in 2008, models have been made available for 64 countries in 34 languages, covering 80% of the world population. The website (http://www.shef.ac.uk/FRAX) receives approximately 6 million visits annually and in 2012–2013 calculations arose from 173 countries [88]. This underestimates considerably the uptake of FRAX because the website is not the sole portal for the calculation of fracture probabilities. For example, FRAX

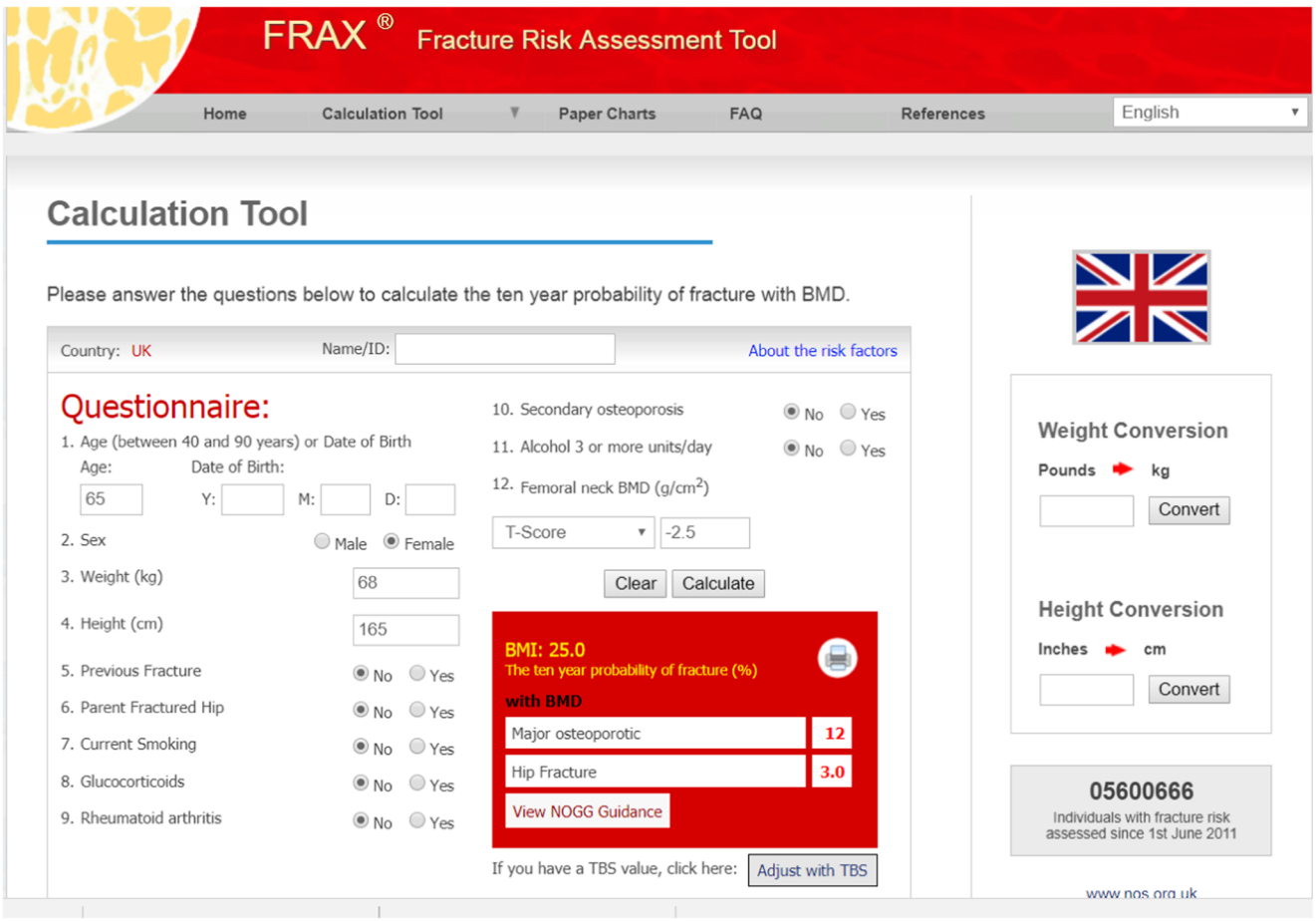

Fig. 2 Screen page for input of data and format of results in the UK version of the FRAX® tool (UK model, version 3.5. http://www.shef.ac.uk/FRAX). [With permission of the Centre for Metabolic Bone Diseases, University of Sheffield Medical School, UK]

is available in BMD equipment, on smartphones, and, in some countries, through hand-held calculators. FRAX has been incorporated into more than 80 guidelines worldwide [89].

Introduction to FRAX

FRAX® is a computer-based algorithm that calculates the 10-year probability of a major fracture (hip, clinical spine, humerus or wrist fracture) and the 10-year probability of hip fracture [12].

Fracture risk is calculated from age, body mass index and dichotomized risk factors comprising prior fragility fracture, parental history of hip fracture, current tobacco smoking, ever use of long-term oral glucocorticoids, rheumatoid arthritis, other causes of secondary osteoporosis and alcohol consumption (Fig. 2). Femoral neck BMD can be optionally input to enhance fracture risk prediction [90]. Fracture probability is computed taking both the risk of fracture and the risk of death into account. The use of clinical risk factors in conjunction with BMD and age improves sensitivity of fracture prediction without adverse effects on specificity [90].

Fracture probability differs markedly in different regions of the world [91]. The heterogeneity in Europe is shown in Fig. 3. For this reason, FRAX is calibrated to those countries where the epidemiology of fracture and death is known (currently 64 countries).

Limitations of FRAX

The limitations of FRAX have been reviewed recently [89]. The FRAX assessment takes no account of dose-responses for several risk factors. For example, two prior fractures carry a much higher risk than a single prior fracture [92]. Dose-responses are also evident for glucocorticoid exposure [93], cigarette smoking [61] and alcohol intake [60]. Since it is not possible to accommodate all such scenarios with the FRAX algorithm, these limitations should temper clinical judgement.

A history of falls is a significant risk factor for fracture but is not incorporated into the FRAX model. Moreover, a significant risk of fracture remains after adjusting for FRAX [94]. However, the incorporation of falls into FRAX is problematic for several reasons. First, at the time of the release of FRAX, existing falls data were not of adequate quality, including the heterogeneous construct of questions on falls. Second, falls risk is inherently taken into account in the algorithm, though not as an input variable [95]. Thus, the fracture probability given for any combination of risk factors assumes that the falls risk is that observed (but not documented) in the cohorts used to construct FRAX. Third, the interrelationship of falls risk with the other FRAX variables has been inadequately explored on an international basis. Fourth, the relationship between the risk variable and mortality needs to be accounted for, but there are no data available. These technical problems aside, risk assessment tools are intended to identify a risk that is amenable to a therapeutic intervention. However, falls as a risk variable do not consistently pass the test of reversibility of risk [71, 96–98], a necessary feature of any risk variable used in tools to direct interventions [12, 65, 99].

To address some of these and other limitations, relatively simple arithmetic adjustments have been proposed, which can be applied to conventional FRAX estimates of probabilities of hip fracture and a major fracture to adjust the probability assessment with knowledge of:

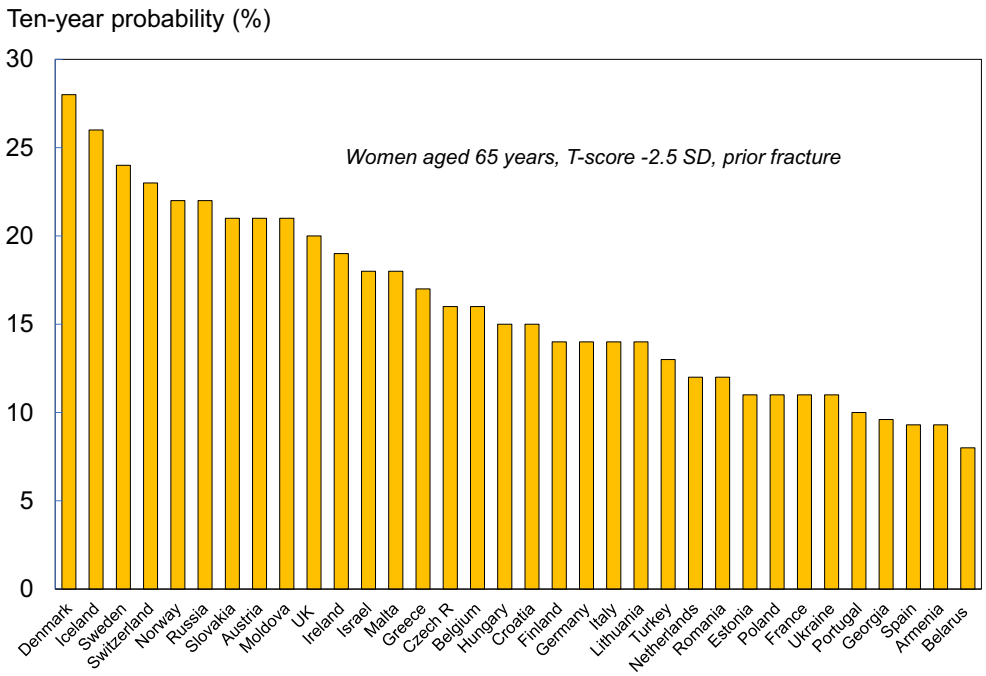

Fig. 3 Ten-year probability (%) of a major osteoporotic fracture in women from different European countries. BMI set to 25 kg/m^2. Data from http://www.shef.ac.uk/FRAX

high, moderate, and low exposure to glucocorticoids [100]—see below
concurrent data on lumbar spine BMD [101, 102]—see below
trabecular bone score [77, 80, 81, 103]
hip axis length [104]
falls history [105]
immigration status [106]
type 2 diabetes [68, 107]

With regard to glucocorticoids, Table 5 summarises the manner in which FRAX estimates of probabilities of hip fracture and a major osteoporotic fracture can be adjusted with knowledge of the dose of glucocorticoids [100]. For example, a woman aged 60 years from the UK taking glucocorticoids for rheumatoid arthritis (no other risk factors and BMI of 24 kg/m^2) has a 10-year probability for a major fracture of 13%. If she is on a higher than average dose of prednisolone (> 7.5 mg daily), then the revised probability should be 15% (13 × 1.15).

Lumbar spine BMD is frequently measured by DXA and indeed is incorporated into several clinical guidelines. It is the site favoured for monitoring treatment and there is thus much interest in the implications for FRAX of measurements at the lumbar spine, since there are situations where there is a large discordance in the T-score at different skeletal sites in individuals for whom the use of this information will enhance the accuracy for the characterisation of risk, particularly if they lie close to an intervention threshold. The impact of spine/femoral neck T-score discordance has been explored in a large BMD-referral population from Manitoba, Canada. There was approximately a 10% change in fracture risk for each unit of T-score discordance [101]. On this basis, the clinician may increase/decrease FRAX estimate for a major fracture by one-tenth for each rounded T-score difference between the lumbar spine and femoral neck.

Additionally, FRAX values have been shown to be largely unaffected by socioeconomic status [108], variation in body composition [109] and a concern that treatment might invalidate the interpretation of FRAX appears misplaced [110].

Assessment of risk

At present there is no universally accepted policy for population screening in Europe to identify patients with osteoporosis or those at high risk of fracture. With the increasing development of effective agents and price reductions, this view may change, particularly for elderly people [111, 112]. In the absence of a screening policy, patients are identified opportunistically using a case-finding strategy on the finding of a previous fragility fracture or the presence of significant risk factors. The risk factors that are used for clinical assessment, summarised in Table 4, may be used but in principle any risk factor that alerts the physician to the possibility of osteoporosis is a candidate. Examples are height loss (> 4 cm) [113], thoracic kyphosis and the many other less well-characterised causes of secondary osteoporosis.

A general approach to risk assessment is shown in Fig. 4 [114]. The process begins with the assessment of fracture probability and the categorisation of fracture risk on the basis of age, sex, BMI and the clinical risk factors. On this information alone, some patients at high risk may be considered for treatment without recourse to BMD testing. For example, many guidelines in Europe [1, 89, 114] recommend treatment in the absence of information on BMD in women with a previous fragility fracture (a prior vertebral or hip fracture in North America) [115, 116]. Many physicians would also perform a BMD test, but frequently this is for reasons other than to decide on intervention, for example, as a baseline to monitor treatment. There will be other instances where the probability is so low that a decision not to treat can be made without BMD. Thus, not all individuals require a BMD test. The size of the intermediate category in Fig. 4 will vary in different countries. In countries that provide reimbursement for DXA, this will be a large category, whereas in a large number of countries with limited or no access to densitometry, the size of the intermediate group will necessarily be small. In other countries (e.g. the UK), where provision for BMD testing is sub-optimal [117], the intermediate category will lie between the two extremes.

Table 5 Average adjustment of 10-year probabilities of a hip fracture or a major osteoporotic fracture in postmenopausal women and older men according to dose of glucocorticoids. [Adapted from [100] with kind permission from Springer Science and Business Media B.V]

Dose	Prednisolone equivalent (mg/day)	Average adjustment over all ages
Hip fracture		
Low	< 2.5	0.65
Medium	2.5–7.5	No adjustment
High	≥ 7.5	1.20
Major osteoporotic fracture		
Low	< 2.5	0.8
Medium	2.5–7.5	No adjustment
High	≥ 7.5	1.15

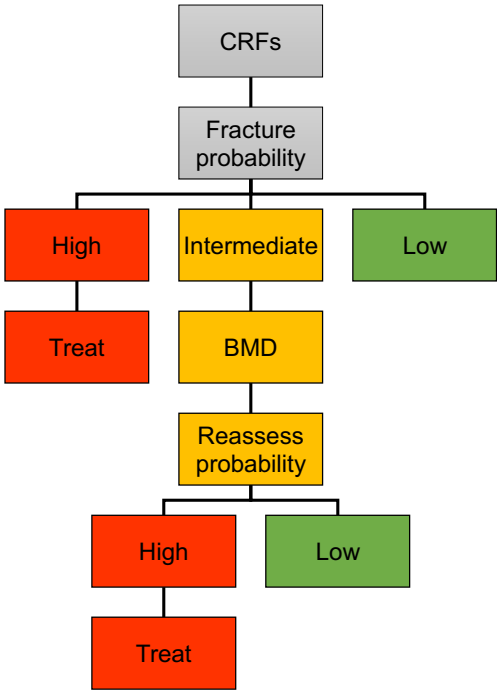

Fig. 4 Management algorithm for the assessment of individuals at risk of fracture [114], with kind permission from Springer Science and Business Media

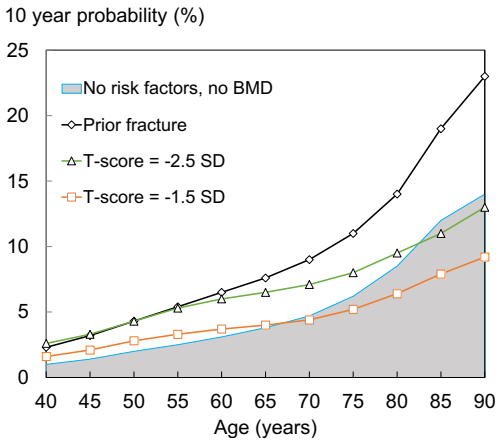

Fig. 5 Ten-year probabilities (%) of a major osteoporotic fracture for women from Kuwait at a T-score of − 2.5 SD (open triangle), − 1.5 SD (open square) and prior fracture (open diamond). The shaded area represents fracture probabilities in women with no clinical risk factors and average BMD. From [120] with kind permission from Springer Science and Business Media

Intervention thresholds

Whereas BMD provides the cornerstone for the diagnosis of osteoporosis, the use of BMD alone is less than optimal as an intervention threshold for several reasons. Firstly, the fracture risk varies markedly in different countries, but the T-score varies only by a small amount. Secondly, the significance of any given T-score to fracture risk in women from any one country depends on age (see Fig. 1) and the presence of clinical risk factors. Intervention thresholds will also be determined in part by the cost and benefits of treatment. In addition, since the T-score for BMD decreases with age, a T-score of, say, − 2.5 SD becomes less significant as a risk indicator with age [118–120]. Thus, with advancing age, the difference in the probability of fracture between the general population and those with a T-score of − 2.5 SD diminishes and indeed, from the age of 78 years in the USA and 81 years onwards in Kuwait, the fracture probability becomes progressively lower than that of the age and sex-matched individuals (Fig. 5). In other words, a T-score of − 2.5 SD becomes a diminishing risk factor with advancing age. In contrast, a prior fragility fracture is a highly significant risk factor at all ages (see Fig. 5).

The use of FRAX in clinical practice demands a consideration of the fracture probability at which to intervene, both for treatment (an intervention threshold) and for BMD testing (assessment thresholds). Many approaches have been used to set intervention thresholds with FRAX [89]. The thresholds used have varied since they depend critically on local factors such as reimbursement issues, health economic assessment, willingness to pay for health care in osteoporosis and access to DXA. For this reason, it is not possible or desirable to recommend a unified intervention strategy. The strategy given below draws on that most commonly applied in Europe in the context of postmenopausal osteoporosis but takes account that access to DXA varies markedly in different European countries [117].

Since many guidelines recommend that women with a prior fragility fracture may be considered for intervention without the necessity for a BMD test (other than to monitor treatment), a prior fracture can be considered to carry a sufficient risk that treatment can be recommended. For this reason, the intervention threshold in women without a prior fracture can be set at the age-specific fracture probability equivalent to women with a prior fragility fracture [114] and therefore rises with age, for example, from a 10-year probability of 8 to 33% in the UK [121]. In other words, the intervention threshold is set at the 'fracture threshold'. This is the approach to intervention thresholds proposed or used in Belgium, Finland, France, Italy, Ireland, Poland, Romania, Russia, Spain, Switzerland and by the National Osteoporosis Guideline Group (NOGG) in the UK [89, 122] and European guidelines for glucocorticoid-induced osteoporosis [123]. Incidentally, the same intervention threshold is applied to men, since the effectiveness and cost-effectiveness of intervention in men is broadly similar to that in women for equivalent risk [42, 121, 124]. The approach used has been well validated and the intervention strategy shown to be cost-effective [114, 125–128].

Using this criterion, the intervention threshold will vary from country to country because the population risks (of fracture and death) vary [91, 129]. The fracture probability in women with a prior fracture in the five major EU countries is shown in Fig. 6. Probabilities are highest in the UK and lowest in Spain. The

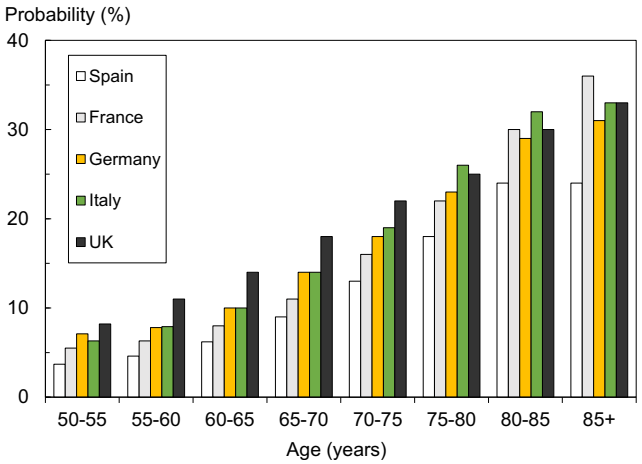

Fig. 6 The 10-year probability of a major osteoporotic fracture by age in women with a prior fracture and no other clinical risk factors in the five major EU countries as determined with FRAX (version 3.5). Body mass index set to 24 kg/m^2 without BMD. From [3], with kind permission from Springer Science and Business Media

difference between countries is most evident at younger ages and becomes progressively less with advancing age.

For the purposes of illustration in this guidance, an aggregate value is chosen. Thus, for the countries shown in Fig. 6, the mean probability of a major fracture in women with a prior fracture is 6.3% between the ages of 50 and 55 years. The mean is weighted for population size in each age interval in each country. The probability rises with age (Table 6) and can be taken as an intervention threshold. Countries with much higher or lower probabilities may wish to develop intervention thresholds based on country-specific risks as has been adopted in several countries in Europe and elsewhere. Note that the example in Table 6 uses the probability of a major osteoporotic fracture to determine an intervention threshold fracture. In addition to the 10-year probability of a major osteoporotic fracture, intervention thresholds can be based on the 10-year probability of hip fracture. Either or both thresholds can be used as recommended in the recent NOGG guidance [85].

Assessment thresholds for BMD testing

The assessment strategy outlined in Fig. 4 requires the determination of assessment thresholds for making recommendations for the measurement of BMD. There are, in principle, two assessment thresholds [114]:

A threshold probability below which neither treatment nor a BMD test should be considered (lower assessment threshold).

A threshold probability above which treatment may be recommended irrespective of BMD (upper assessment threshold).

Most countries adopt a case-finding strategy where individuals with clinical risk factors are identified for further assessment [12]. For this scenario, the lower assessment threshold

Table 6 Intervention thresholds as set by FRAX-based 10-year probability (%) of a major osteoporotic fracture equivalent to women with a previous fracture (no other clinical risk factors, a body mass index of 24 kg/m^2 and without BMD). The lower assessment thresholds set by FRAX is based on the 10-year probability (%) of a major osteoporotic fracture equivalent to women without clinical risk factors (a body mass index of 24 kg/m^2 and without BMD). The upper assessment threshold is set at 1.2 times the intervention threshold. Population weighted mean values for the five major EU countries. From [3], with kind permission from Springer Science and Business Media

	Ten-year fracture probability (%)		
Age range (years)	Intervention threshold	Lower assessment threshold	Upper assessment threshold
40–44	5.2	2.3	6.2
45–49	5.4	2.4	6.5
50–54	6.3	2.9	7.6
55–59	7.6	3.6	9.1
60–64	9.9	4.9	11.9
65–69	13.4	6.9	16.1
70–74	17.6	9.7	21.5
75–79	23.0	13.7	27.6
80–84	29.1	18.7	34.9
85–89	31.8	20.9	38.2
90–94	31.7	20.8	38.0
95–99	32.2	21.1	38.6
100+	32.5	21.3	39.0

can be set to exclude a requirement for BMD testing in women without clinical risk factors, as given in previous European guidelines [1–3, 123]. The probability equivalents are given in Table 6. In a few countries, population-based assessment with BMD is recommended (Germany and France in Europe). In such cases, there would be no lower assessment threshold.

An upper threshold can be chosen to minimise the probability that a patient characterised to be at high risk on the basis of clinical risk factors alone would be reclassified to be at low risk with additional information on BMD [125]. In the UK, the upper assessment threshold was set at 1.2 times the intervention threshold [114]. The rationale is that reclassification of risk with the addition of a BMD test (from high risk to low risk and vice versa) is high when fracture probabilities estimated without BMD are close to the intervention threshold and the likelihood of reclassification decreases the further away the probability estimate is from the intervention threshold [125]. When patients have a fracture probability that is 20% or more than the intervention threshold, almost no individuals will be reclassified (from high to low risk) when probabilities are recomputed with the addition of BMD to FRAX [124, 130–132]. Thus, a quotient of 1.2 is applied to the intervention, illustrated for the European example in Table 6. An attraction of the approach is that efficient use is made of BMD testing.

Application of probability thresholds

The application of these assessment thresholds depends critically on the availability (and reimbursement) of densitometry, which vary from country to country. It has been estimated that the requirements to service osteoporosis amount to approximately 11 DXA units/millions of the general population [117], though this estimate probably requires updating to take account of population demography. The availability of DXA falls above this estimate in a minority of European countries (Fig. 7). The large variation in resources for BMD testing demand the consideration of three assessment scenarios that depend on the access to central densitometry.

Unrestricted access to densitometry

Where resources for BMD testing are adequate, BMD tests can be undertaken in women with any clinical risk factors as shown in Fig. 8. Treatment is recommended where fracture probability exceeds the intervention threshold. Note that the lower assessment threshold is set as equivalent to women without clinical risk factors (see above). In those countries where screening of women without risk factors is recommended, there would be no lower assessment threshold. An additional option is to recommend treatment in women with a prior fragility fracture without recourse to BMD (though BMD might be undertaken to monitor treatment).

The assessment algorithm is summarised in Box 1. BMD tests are recommended in all postmenopausal women with a clinical risk factor.

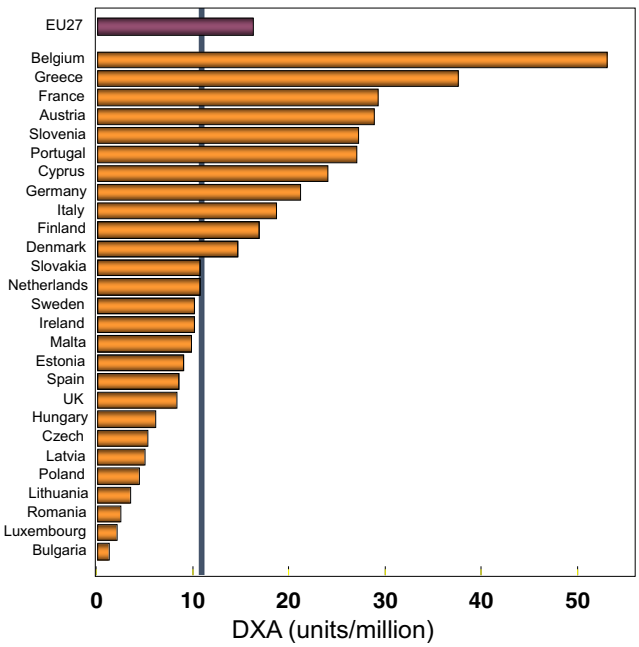

Fig. 7 The density of central DXA equipment (units/million of the general population in the EU countries in 2010 [Kanis JA, data on file]

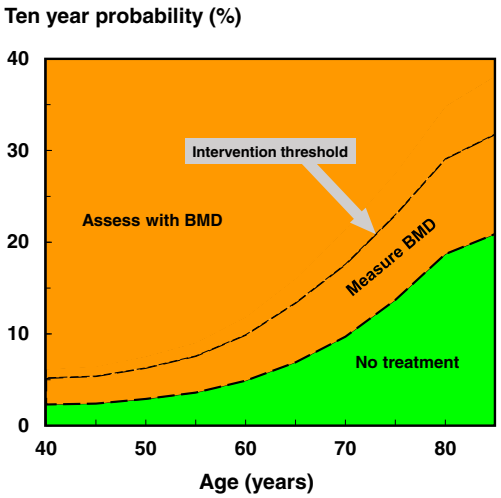

Fig. 8 Assessment of major osteoporotic fracture risk in countries with high access to DXA. DXA is undertaken in women with a clinical risk factor. Assessment with DXA and/or treatment is not recommended where the FRAX probability is lower than the lower assessment threshold (green area). BMD is recommended in other women and treatment recommended where the fracture probability exceeds the intervention threshold (dotted line). The intervention threshold used is that derived from Table 6. From [3], with kind permission from Springer Science and Business Media

Limited access to densitometry

Several countries must take a parsimonious approach to the use of BMD. The guidance recommends that postmenopausal women with a prior fragility fracture may be considered for intervention without the necessity for a BMD test. In women without a fragility fracture but with one or more other CRF, the intervention threshold is set at the age-specific fracture probability equivalent to women with a prior fragility fracture and BMD testing recommended in those in whom fracture probability lies between the upper and lower assessment threshold as described above [114]

BOX 1 Assessment of fracture risk with FRAX with unlimited access to BMD*

- Fracture risk should be assessed in postmenopausal women with one or more clinical risk factor *where assessment would influence management*.
- Women with a prior fragility fracture might be considered for treatment without the need for further risk assessment although BMD measurement may sometimes be appropriate.
- In women without a prior fragility fracture, the 10-year probabilities of a major osteoporotic fracture (clinical spine, hip, forearm or humerus) and hip fracture should be determined using FRAX without BMD. In the absence of other clinical considerations, men and women with probabilities below the assessment threshold can be reassured.
- Those with probabilities above the assessment threshold can be considered for testing with BMD using DXA and their fracture probability reassessed. Thereafter, women with probabilities above the intervention threshold should be considered for treatment.

*From [3], with kind permission from Springer Science and Business Media

This approach, adapted to the common EU thresholds shown in Table 6, is illustrated in Fig. 9.

The assessment algorithm is summarised in Box 2.

No access or patchy access to densitometry

In countries with very limited or no access to DXA, FRAX can be used without BMD. For the purpose of risk assessment, a characteristic of major importance is the ability of a technique to predict fractures, traditionally expressed as the increase in relative risk per standard deviation (SD) unit decrease in risk score—termed the gradient of risk. The gradient of risk with FRAX is shown in Table 7 for the use of the clinical risk factors alone, femoral neck BMD and the combination [90].

The use of clinical risk factors alone provides a GR that lies between 1.4 and 2.1, depending upon age and the type of fracture predicted. These gradients are comparable to the use of BMD alone to predict fractures [32, 41]. For example, for the prediction of any osteoporotic fracture, the GR at the age of 70 years was 1.5 with femoral neck BMD [32]. With peripheral BMD, the gradient of risk is somewhat, though not significantly lower (GR = 1.4/SD; 95% CI = 1.3–1.5/SD). These data suggest that clinical risk factors alone are of value and can be used, therefore, in the many countries where DXA facilities are insufficient (Box 3). The rationale for the use of FRAX in the absence of access to BMD or limited access has been recently reviewed [65, 89]. Briefly, most of the risk factors incorporated within FRAX contribute independently from BMD to fracture risk, but are not totally independent of BMD; thus, higher risk is associated with lower underlying BMD [125, 132].

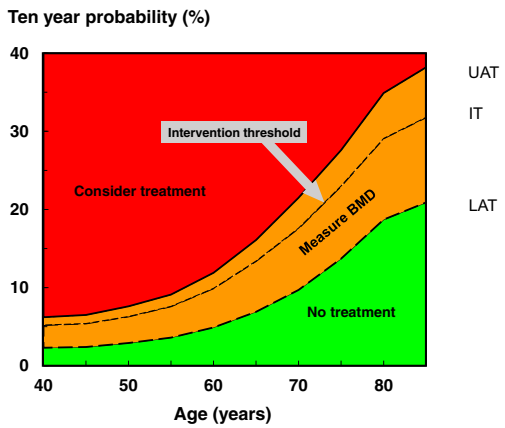

Fig. 9 Assessment guidelines based on the 10-year probability of a major osteoporotic fracture (%). The dotted line denotes the intervention threshold. Where assessment is made in the absence of BMD, a BMD test is recommended for individuals where the probability assessment lies in the orange region. The intervention threshold and BMD assessment thresholds used are those derived from Table 6. From [3], with kind permission from Springer Science and Business Media

BOX 2 Assessment of fracture risk with FRAX with limited access to BMD*

- Fracture risk should be assessed in postmenopausal women with one or more clinical risk factor *where assessment would influence management*.
- Women with a prior fragility fracture should be considered for treatment without the need for further risk assessment although BMD measurement may sometimes be appropriate, particularly in younger postmenopausal women.
- In women without a prior fragility fracture, the 10-year probabilities of a major osteoporotic fracture (clinical spine, hip, forearm or humerus) and hip fracture should be determined using FRAX without BMD. In the absence of other clinical considerations, men and women with probabilities below the lower assessment threshold can be reassured and those with probabilities above the upper assessment threshold can be considered for treatment.
- Those with probabilities above the lower assessment threshold but below the upper assessment threshold can be considered for testing with BMD using DXA and their fracture probability reassessed. Thereafter, women with probabilities above the intervention threshold should be considered for treatment.

*From [3], with kind permission from Springer Science and Business Media

In several countries (Finland, Lebanon, Romania, UK), there is a link between the FRAX web site to an independent site that plots the FRAX output against the intervention thresholds for that country and facilitates treatment decisions. The NOGG web site in the UK is widely used (https://www.sheffield.ac.uk/NOGG/) [133].

Alternative approaches to intervention thresholds

The NOGG guidelines in the UK have recently been revised [134]. The intervention threshold up to age 70 years is set at a risk equivalent to that associated with a prior fracture, in line with current clinical practice, and therefore rises with age. At age 70 years and above, however, a fixed threshold is applied [134]. The alternative thresholds equilibrate fracture risk, particularly hip fracture risk, in those with or without prior fracture selected for treatment and reduce BMD usage at older ages. This modification from the age of 70 years is not necessarily applicable to other countries and would require the impact of changes to be evaluated.

An alternative approach to intervention thresholds has been applied in Germany, which uses a country-specific algorithm to estimate the 10-year incidence (not probability) of fracture [135].

Several guidelines in Europe that use FRAX have recommended that a fixed probability threshold be used as an intervention threshold. Examples include a 20% 10-year probability of a major fracture in several European countries and a 15% probability in Sweden [89]. Many utilise a threshold probability of 20% for a major osteoporotic fracture many of which also mention a hip fracture probability of 3% as an alternative intervention threshold. In nearly all instances, no rationale is provided other than the fact that this was the

Table 7 Gradients of risk (the increase in fracture risk per SD change in risk score) with 95% confidence intervals with the use of BMD at the femoral neck, clinical risk factors or the combination [90], with kind permission from Springer Science and Business Media B.V

	Gradient of risk		
Age (years)	BMD only	Clinical risk factors alone	Clinical risk factors + BMD
(a) Hip fracture			
50	3.68 (2.61–5.19)	2.05 (1.58–2.65)	4.23 (3.12–5.73)
60	3.07 (2.42–3.89)	1.95 (1.63–2.33)	3.51 (2.85–4.33)
70	2.78 (2.39–3.23)	1.84 (1.65–2.05)	2.91 (2.56–3.31)
80	2.28 (2.09–2.50)	1.75 (1.62–1.90)	2.42 (2.18–2.69)
90	1.70 (1.50–1.93)	1.66 (1.47–1.87)	2.02 (1.71–2.38)
(b) Other osteoporotic fractures			
50	1.19 (1.05–1.34)	1.41 (1.28–1.56)	1.44 (1.30–1.59)
60	1.28 (1.18–1.39)	1.48 (1.39–1.58)	1.52 (1.42–1.62)
70	1.39 (1.30–1.48)	1.55 (1.48–1.62)	1.61 (1.54–1.68)
80	1.54 (1.44–1.65)	1.63 (1.54–1.72)	1.71 (1.62–1.80)
90	1.56 (1.40–1.75)	1.72 (1.58–1.88)	1.81 (1.67–1.97)

threshold used by the National Osteoporosis Foundation of the USA [116]. The rationale for a fixed threshold in the USA was based on the fracture probability at which intervention becomes cost-effective in the USA and is, therefore, not relevant for any other country.

The impact of using a fixed intervention threshold is shown in Fig. 10 for postmenopausal women in the UK. At high thresholds e.g. > 20% fracture probability 17% of postmenopausal women would be eligible for treatment. A problem that arises is that very few women under the age of 60 years would ever attain this threshold. On the other hand, if a less stringent threshold were chosen, say 5%, then nearly all women at the age of 50 years and above would exceed this threshold. Both scenarios could be justified on health economic criteria in the UK [128], but both are counterintuitive to clinical practice. Critically, economic criteria should not be used to set intervention thresholds but, more appropriately, to validate the implementation of clinically driven intervention thresholds [136].

BOX 3 Assessment of fracture risk with FRAX without BMD

- Fracture risk should be assessed in postmenopausal women with one or more clinical risk factor where *assessment would influence management*.
- Women with a prior fragility fracture should be considered for treatment without the need for further risk assessment.
- In men, and in women without a prior fragility fracture, the 10-year probabilities of a major osteoporotic fracture (clinical spine, hip, forearm or humerus) and hip fracture should be determined using FRAX without BMD. In the absence of other clinical considerations, men and women with probabilities below the intervention threshold can be reassured.
- Treatment can be considered in those in whom fracture probabilities lie above the intervention threshold.

*From [3], with kind permission from Springer Science and Business Media

Other assessment models

As well as the FRAX tool, other fracture risk calculators are available online which include the Garvan fracture risk calculator and QFracture® [69, 70]. A fundamental difference between these risk models and FRAX is that the parameters of risk differ (incidence vs. probabilities) so that comparative data are not readily interpreted [137] (Fig. 11). In FRAX, fracture probability is computed taking both the risk of fracture and the risk of death into account. This is important because some of the risk factors affect the risk of death as well as the fracture risk. Examples include increasing age, sex, low BMI, low BMD, use of glucocorticoids and smoking.

Effectiveness of risk assessment strategies

Until recently, the effectiveness of risk-assessment strategies in which samples of the general population might be evaluated for risk factors and BMD estimation to derive individual estimates of absolute fracture risk, with targeting of anti-osteoporosis therapy on the basis of these estimates, remained uncertain. The publication of the MRC SCOOP trial (SCreening of Older wOmen for the Prevention of fractures) provides strong support for such a strategy [111]. This seven-centre pragmatic randomised controlled trial with 5-year follow-up included 11,580 women aged 70–85 years, who were randomised to receive a care algorithm including FRAX and drug targeting ($n = 6233$) or usual primary care for osteoporosis based on opportunistic case finding ($n = 6250$). Women were recruited from 100 UK general practices, and the principle outcome measures were major osteoporotic, hip and all fractures. Screening reduced the incidence of hip fractures (0.72, 0.59–0.89,

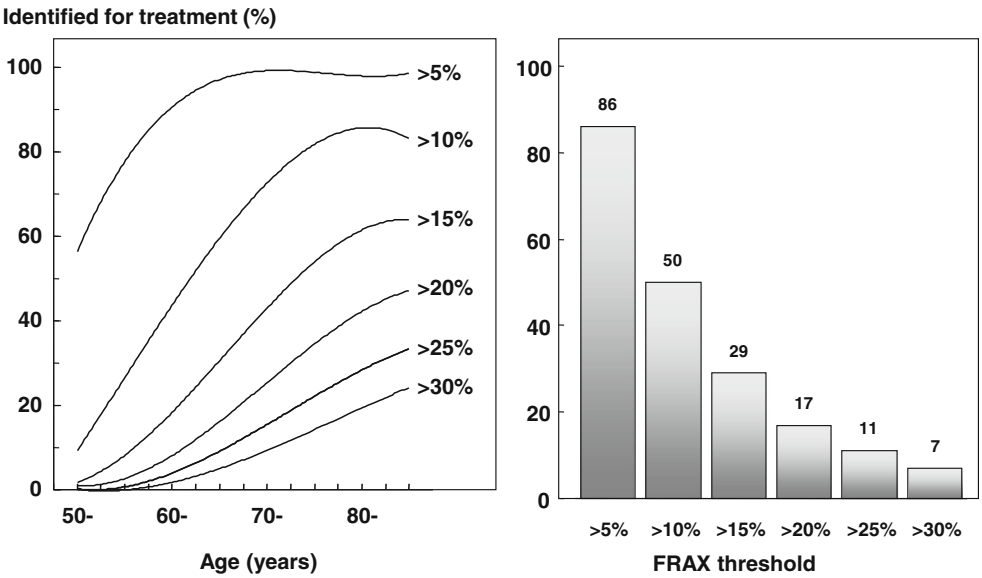

Fig. 10 The impact of a fixed treatment threshold in postmenopausal women in the UK according to threshold values for the probability of a major osteoporotic fracture. The left-hand panel shows the proportion of the postmenopausal population exceeding the threshold shown at each age. The right-hand panel shows the proportion of the total postmenopausal population that exceed a given threshold. From [3], with kind permission from Springer Science and Business Media

$p = 0.002$). The effect on hip fracture increased significantly with baseline FRAX hip fracture probability ($p = 0.021$ for interaction); for example, at the 10th percentile of baseline FRAX hip probability (2.6%), hip fractures were not significantly reduced (HR 0.93, 0.71 to 1.23), but at the 90th percentile (16.6%), there was a 33% reduction (HR 0.67, 0.53 to 0.84) [112]. The screening algorithm resulted in a pronounced increase in the use of anti-osteoporosis medication, and greater compliance with therapy, over the period of follow-up. These findings strongly support a systematic, community-based screening programme of fracture risk in older women. In addition, the strategy appears to be cost-effective [138].

General management

Mobility and falls

Immobilisation causes of bone loss. Immobilised patients when confined to bed may lose as much bone in a week than they would otherwise lose in a year. Weight-bearing exercise forms an integral component of osteoporosis management [139–141]. The amount of weight-bearing exercise that is optimal for skeletal health in patients with osteoporosis is not known. Physiotherapy is an important component of rehabilitation after fracture. At all times, exercises to improve muscle strength and balance may

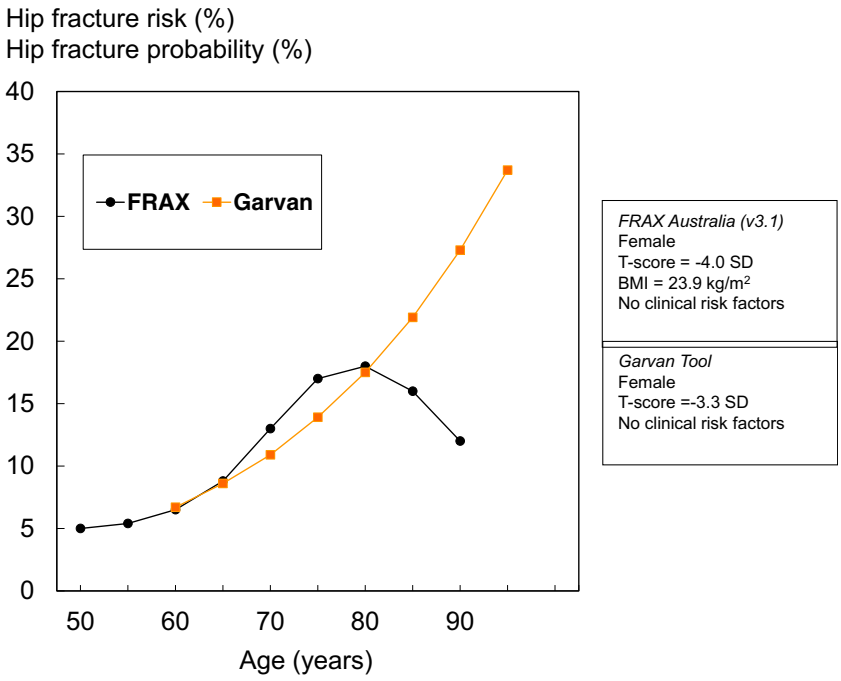

Fig. 11 The risk of hip fracture with age in a model that considers 10-year fracture risk alone (the Garvan tool) and FRAX, which computes the probability of hip fracture from the fracture and death hazards (FRAX). The T-scores are set differently in the two models so that the risks are approximately equal at the age of 60 years. Data are computed from the respective web sites [137]. With kind permission from Springer Science and Business Media

prevent falls by restoring confidence and coordination, and additionally maintain bone mass by stimulating bone formation and decreasing bone resorption.

Such measures can be coupled with a programme to reduce the likelihood of falls in those at high risk [142, 143]. Modifiable factors such as correcting decreased visual acuity, reducing consumption of medication that alters alertness and balance, and improving the home environment (slippery floors, obstacles, insufficient lighting, handrails) are important measures aimed at preventing falls [144]. Fall prevention exercise interventions have been shown to reduce the risk of injurious falls and of fracture [145]. Whole body vibration may be beneficial for falls risk reduction, but without effect on BMD or fracture risk [146]. Some randomised trials have shown that wearing hip protectors can reduce hip fracture risk, particularly in the elderly living in nursing homes. A meta-analysis of well-conducted randomised controlled trials has, however, cast some doubt about the anti-fracture efficacy of this preventive measure [147–150].

Nutrition

At every stage of life, adequate dietary intakes of key bone nutrients such as calcium, vitamin D and protein contribute to bone health and reduce thereby the risk of osteoporosis and of fracture later in life [151]. Dietary sources of calcium are the preferred option and calcium supplementation should only be targeted to those who do not get sufficient calcium from their diet and who are at high risk for osteoporosis. The Recommended Nutrient Intakes are 800–1000 mg of calcium and 800 IU of vitamin D per day in men and women over the age of 50 years [152].

Combined calcium and vitamin D supplements in a daily dose of 0.5–1.2 g and 400–800 IU, respectively, are generally recommended in patients receiving bone protective therapy, since most randomised controlled trial evidence for the efficacy of interventions is based on co-administration of the agent with calcium and vitamin D supplements [153]. Calcium and vitamin D supplements may decrease secondary hyperparathyroidism and reduce the risk of proximal femur fracture, particularly in the elderly living in nursing homes [154, 155]. In six trials included in the meta-analysis [155], hip fracture risk was 0.61 (95% CI 0.46–0.62) with calcium and vitamin D supplementation. In contrast, a recent meta-analysis did not find a reduction in fracture risk in community-dwelling older adults receiving calcium, vitamin D, or the combination [156]. The latter included seven trials, but only three among those analysed in [155]. Adding to the controversies over calcium, a meta-analysis has concluded that calcium supplements without co-administered vitamin D were associated with an increase in the risk of myocardial infarction by around 30% [157]. Cardiovascular outcomes were not primary endpoints in any of the studies and the association remains the subject of some controversy [158–163].

Overall, it can be concluded that (1) calcium and vitamin D supplementation may lead to a modest reduction in fracture risk, although population-level intervention has not been shown to be an effective public health strategy; (2) supplementation with calcium alone does not reduce fracture risk; (3) side effects of calcium supplementation include renal stones and gastrointestinal symptoms; (4) vitamin D supplementation, rather than calcium, may reduce falls risk; and (5) increased cardiovascular risk consequent to calcium supplementation is not convincingly supported by current evidence; (6) calcium and vitamin D supplementation is recommended for patients at high risk of calcium and vitamin D insufficiency, and in those who are receiving treatment for osteoporosis [153]. This approach appears to be cost-effective [164].

Vitamin D supplements alone may reduce the risk of fracture and falls provided the daily dose of vitamin D is greater than 700 IU [165, 166]. In contrast, studies with large annual doses of vitamin D have reported an increased risk of hip fracture and, in one study, and also of falls [167, 168]. The upper limit of vitamin D dose that is beneficial on falls may be lower than previously estimated [169, 170].

Whereas a gradual decline in caloric intake with age can be considered as an appropriate adjustment to the progressive reduction in energy expenditure, a parallel reduction in protein intake may be detrimental for maintaining the integrity and function of several organs or systems, including skeletal muscle and bone. Sufficient protein intakes are necessary to maintain the function of the musculoskeletal system, but they also decrease the complications that occur after an osteoporotic fracture [151, 171]. Correction of poor protein nutrition in patients with a recent hip fracture has been shown to improve the subsequent clinical course by significantly lowering the rate of complications, such as bedsores, severe anaemia and intercurrent lung or renal infection. The duration of hospital stay of elderly patients with hip can thus be shortened [151].

Dairy products are a source of both protein and calcium, since 1 L of milk provides 32 g of protein and 1200 mg of calcium. Dairy products, some being fortified with calcium or vitamin D, decrease circulating PTH, increase IGF-I and decrease bone resorption markers [171–173]. Dairy products are associated with higher bone strength in both men and women [174, 175]. In older US men and women, higher milk consumption is associated with a lower hip fracture risk [176]. Fermented milk products like yogurt or soft cheese may provide larger amounts of these nutrients than the same volume of plain milk because of enrichment with milk powder to make the yogurt matrix denser [177–179]. Thus, calcium and vitamin D fortified dairy products (yogurt, milk) providing at least 40% of the RNI of calcium (400 mg) and 200 IU of vitamin D per portion are valuable options for covering the needs in the oldest old. Cheese consumption is associated with lower

mortality [180]. Several studies have concluded to a favourable cost-effectiveness of dairy products in osteoporosis management [181–184].

Major pharmacological interventions

The most commonly used agents in Europe are raloxifene, the bisphosphonates alendronate, ibandronate, risedronate and zoledronic acid, agents derived from parathyroid hormone and denosumab. They have all been shown to reduce the risk of vertebral fracture. Some have also been shown to reduce the risk of non-vertebral fractures and, in some cases, agents have been shown specifically to decrease fracture risk at the hip (Table 8) [3, 85, 185, 186].

Selective oestrogen receptor modulators

Selective oestrogen receptor modulators (SERMs) are nonsteroidal agents that bind to the oestrogen receptor and act as oestrogen agonists or antagonists, depending on the target tissue. The concept of SERMs was triggered by the observation that tamoxifen, which is an oestrogen antagonist in breast tissue, is a partial agonist on bone, reducing the rate of bone loss in postmenopausal women [187]. Raloxifene is the only SERM widely available for the prevention and treatment of postmenopausal osteoporosis, but several others are in clinical development. Raloxifene prevents bone loss [188] and reduces the risk of vertebral fractures by 30–50% in postmenopausal women with low bone mass, and with osteoporosis with or without prior vertebral fractures as shown in the MORE trial [188]. There was no significant reduction of non-vertebral fractures. In women with severe vertebral fractures at baseline (i.e. at highest risk of subsequent fractures), a post hoc analysis showed a significant reduction of non-vertebral fractures [189].

In the MORE study and its placebo-controlled 4-year follow-up (CORE), the only severe (but rare) adverse event was an increase of deep venous thromboembolism. Hot flushes and lower limb cramps are commonly reported. There was a significant and sustained decrease of the risk of invasive breast cancer (by about 60%) [190], that has been subsequently confirmed in two other large cohorts, including the STAR study that showed similar breast cancer incidences with raloxifene and tamoxifen in high-risk populations [191]. The RUTH study, performed in postmenopausal women at high risk of cardiovascular disease [192], showed that raloxifene had no effect on cardiovascular death, and on the incidence of coronary heart disease and stroke [193]. However, an increased risk of death from stroke has been reported in women with or at risk of coronary heart disease. The efficacy of raloxifene has been shown in women with osteopenia [194] and is not dependent on the level of fracture risk assessed by FRAX [195]. In summary, the overall risk-benefit ratio of raloxifene is favourable and the drug is approved widely for the prevention and treatment of postmenopausal osteoporosis.

Bazedoxifene is a selective oestrogen receptor modulator that has been approved in Europe but is only available in Spain and Germany. In phase 3 clinical trials, bazedoxifene was shown to reduce the risk of new vertebral fracture, with favourable effects on bone mineral density, bone turnover markers and the lipid profile [196, 197]. The phase III study was extended up to 7 years [198]. During this period, the efficacy and safety of bazedoxifene were sustained. Two separate network meta-analyses provided an indirect comparison of the effect of bazedoxifene versus oral bisphosphonates, for the prevention of vertebral [199] and non-vertebral fractures [200], respectively. They concluded that bazedoxifene is expected to have at least a comparable relative risk reduction of vertebral [199] and non-vertebral fracture [200]

Table 8 Anti-fracture efficacy of the most frequently used treatments for postmenopausal osteoporosis when given with calcium and vitamin D, as derived from randomised controlled trials (updated from [3])

	Effect on vertebral fracture risk		Effect on non-vertebral fracture risk	
	Osteoporosis	Established osteoporosis[a]	Osteoporosis	Established osteoporosis[a]
Alendronate	+	+	NA	+ (including hip)
Risedronate	+	+	NA	+ (including hip)
Ibandronate	NA	+	NA	+[b]
Zoledronic acid	+	+	NA	+[c]
HRT	+	+	+	+ (including hip)
Raloxifene	+	+	NA	NA
Teriparatide	NA	+	NA	+
Denosumab	+	+[c]	+ (including hip)	+[c]

NA no evidence available, + effective drug

[a] Women with a prior vertebral fracture

[b] In subsets of patients only (post hoc analysis)

[c] Mixed group of patients with or without prevalent vertebral fractures

as alendronate, ibandronate and risedronate. In a post hoc study in a subgroup of women at increased risk of fracture, bazedoxifene decreased non-vertebral fracture risk. In contrast to raloxifene, the efficacy of bazedoxifene is dependent on the level of fracture risk assessed by FRAX [201]. In common with raloxifene, venous thromboembolic events, primarily deep vein thromboses, leg cramps and hot flushes were more frequently reported in the active treatment groups compared with the placebo group [202].

Bazedoxifene has been combined with conjugated equine oestrogen to create a tissue selective oestrogen complex for the management of vasomotor symptoms and the prevention of osteoporosis associated with menopause [203]. A series of five phase III studies known as the Selective estrogen, Menopause And Response to Therapy (SMART) trials led to the approval, by the US Food and Drug Administration (FDA) and in Europe, of a daily dose of bazedoxifene 20 mg/conjugated equine oestrogen 0.45 mg. This association improved vasomotor symptoms whilst opposing breast and endometrial proliferation, preventing bone resorption and improving lipid profiles [203]. Over 12 months, this combination product improved BMD at the spine and at the hip, reduced markers of bone turnover and significantly improved vasomotor function score in a population of European postmenopausal women without effects on fracture risk [204].

Bisphosphonates

Bisphosphonates are stable analogues of pyrophosphate characterised by a P-C-P bond. A variety of bisphosphonates has been synthesised, the potency of which depends on the length and structure of the side chain [205]. Bisphosphonates have a strong affinity for bone apatite, both in vitro and in vivo, which is the basis for their clinical use. They are potent inhibitors of bone resorption and produce their effect by reducing the recruitment and activity of osteoclasts and increasing their apoptosis. The potency and chemical affinity to bone of bisphosphonates determines their effect to inhibit bone resorption and varies greatly from compound to compound. Potency differences can range 10,000-fold in vitro, so that the doses used clinically also vary. The mechanism of action on osteoclasts includes inhibition of the proton vacuolar adenosine triphosphatase (ATPase) and alteration of the cytoskeleton and the ruffled border. Amino-bisphosphonates also inhibit the farnesyl pyrophosphate synthase step in the mevalonate pathway, thereby modifying the isoprenylation of guanosine triphosphate binding proteins.

Oral bioavailability of bisphosphonates is low, around 1% of the dose ingested, and is impaired by food, calcium, iron, coffee, tea and orange juice. Bisphosphonates are quickly cleared from plasma, about 50% being deposited in bone and the remainder excreted in urine. Their half-life in bone is very prolonged [206].

Alendronate 70 mg once weekly and risedronate 35 mg once weekly are the most commonly used bisphosphonates worldwide. In the Fracture Intervention (FIT) study, alendronate was shown to reduce the incidence of vertebral, wrist and hip fractures by approximately half in women with prevalent vertebral fractures [207–209]. In women without prevalent vertebral fractures, there was no significant decrease in clinical fractures in the overall population, but the reduction was significant in the one third of patients that had a baseline hip BMD T-score lower than − 2.5 SD [210]. In a population of more than 90,000 men and women aged 80 years and older and who had sustained a prior fracture, a case-control analysis revealed that alendronate use was associated with a 34% decrease in hip fracture risk, and a 12% lower mortality risk but with a 58% increase in the risk of mild upper gastrointestinal symptoms [211].

Risedronate has been shown to reduce the incidence of vertebral and non-vertebral fractures by 40–50% and 30–36%, respectively, in women with prevalent vertebral fractures [212, 213]. In a large population of elderly women, risedronate decreased significantly the risk of hip fractures by 30%, an effect that was greater in osteoporotic women age 70–79 years (− 40%), and not significant in women over the age of 80 years without evidence of osteoporosis [71]. A delayed-release formulation of 35 mg risedronate weekly, given before or immediately following breakfast, showed a similar or greater effect on spine and hip BMD than traditional immediate-release 5 mg risedronate daily. This formulation allows osteoporotic patients to take their weekly risedronate dose immediately after breakfast, hence offering a potential for improved adherence and persistence to treatment [214].

Ibandronate given daily (2.5 mg) reduces the risk of vertebral fractures by 50–60%. An effect on non-vertebral fractures was only demonstrated in a post hoc analysis of women with a baseline of BMD T-score below − 3 SD [215–217]. Bridging studies have shown that oral ibandronate 150 mg once monthly is equivalent or superior to daily ibandronate in increasing BMD and decreasing biochemical markers of bone turnover, giving rise to its approval for the prevention of vertebral fracture in postmenopausal osteoporosis [218]. The efficacy and safety of oral monthly ibandronate was confirmed for up to 5 years in women with postmenopausal osteoporosis [218, 219]. Similarly, bridging studies comparing intermittent intravenous ibandronate to daily oral treatment has led to the approval of intravenous ibandronate 3 mg every 3 months for the same indication [220]. A post hoc analysis of pooled individual patient data from the studies assessing the long-term (5 years) efficacy of oral [218] and intravenous [221] ibandronate concluded that for ibandronate regimens with annual cumulative exposure ≥ 10.8 mg, time-to-fracture was significantly longer for all clinical fractures, non-vertebral and clinical vertebral fractures versus placebo and that for all fracture types, the rate of fracture appeared stable up to 5 years [222].

Based on the result of a phase II study [223], a large phase III trial in over 7700 postmenopausal osteoporotic patients assessed the efficacy of yearly infusion of zoledronic acid

5 mg over 3 years. As compared to the placebo group, zoledronic acid was found to reduce the incidence of vertebral fractures by 70% and that of hip fractures by 40% [224] and is now available for the treatment of postmenopausal osteoporosis. Intravenous zoledronic acid has also been shown to decrease the risk of fracture and mortality when given shortly after a first hip fracture [225]. The phase III trial was extended to 6 [226] and 9 [227] years. The overall conclusion was that pursuing treatment beyond 3 years only provided marginal benefits [227]. Some authors even argue that an annual administration of 5 mg zoledronic acid might represent over treatment [228]. A single dose of 5 mg zoledronic acid given to frail elderly women improved spine and total hip BMD over 2 years, compared to placebo but the treated group had an increase in fractures, multiple falls and mortality [229] suggesting that zoledronic acid may not be an appropriate treatment for such patients.

Safety of bisphosphonates

The overall safety profile of bisphosphonates is favourable. Oral bisphosphonates are associated with mild gastrointestinal disturbances, and some amino-bisphosphonates (alendronate and pamidronate) can rarely cause oesophagitis. A network meta-analysis compared the gastrointestinal safety of all oral and injectable bisphosphonates given to osteoporotic patients. It concluded that zoledronic acid has the highest probability of causing gastrointestinal adverse events, possibly related to nausea [230]. Intravenous amino-bisphosphonates can induce a transient acute phase reaction with fever, bone and muscle pain that ameliorates or disappears after subsequent courses [231].

Osteonecrosis of the jaw has been described in cancer patients receiving high doses of intravenous pamidronate or zoledronate. The incidence in osteoporotic patients treated with oral and intravenous bisphosphonates appears to be very rare (in the order of 1/100,000 patient-year), only slightly higher than the incidence in the general population [232, 233]. The risk of osteonecrosis of the jaw is reported to be greater with a longer duration of bisphosphonate therapy [234, 235], but this finding is not consistent [232]. Possible explanations relate to the class of bisphosphonate, differences in potency and route of administration. The time to onset of osteonecrosis of the jaw may be shorter for intravenous zoledronic acid compared to oral alendronate [236] [237].

Concerns have been raised about a possible association between bisphosphonate therapy and atrial fibrillation. Subsequent studies have produced conflicting results, but have not excluded the possibility of such an association in people at increased risk of fracture [238]. Patients to whom zoledronic acid was administered for up to 9 years had a higher risk of cardiac arrhythmias compared to those who discontinued the treatment after 6 years [227].

The possibility that bisphosphonate therapy is associated with increased risk of oesophageal cancer has been raised. Two studies from the General Practice Research Database in the UK have produced conflicting results, one failing to show any association but another concluding that there was an increased risk with extended use over 5 years [239, 240]. Finally, bisphosphonate use may be associated with atypical subtrochanteric fractures [241–243]. Likewise, associations between bisphosphonate exposure and lower risks of mortality and cancer also require further scrutiny [244–247]. The risk-benefit ratio remains favourable for the use of bisphosphonates to prevent fractures [242].

Many authors recommend that patients be reviewed after 3 years (IV) or 5 years (oral) treatment with bisphosphonate [85, 232, 235, 237]. It is appropriate that periodic assessment of fracture risk should use FRAX with femoral neck BMD [85]. Fracture risk should be reassessed after a new fracture, regardless of when it occurs [85]. Although some advocate a ‘drug holiday’, prospective and retrospective analyses report that the risk of new clinical fractures was 20–40% higher in subjects who stopped treatment [248, 249] and vertebral fracture risk was approximately doubled [226, 250].

A substantial body of evidence indicates that some generic formulations of alendronate are more poorly tolerated than the proprietary preparations, which results in significantly poorer adherence and thus effectiveness [251].

Peptides of the parathyroid hormone family

The continuous endogenous production of parathyroid hormone (PTH), as seen in primary or secondary hyperparathyroidism, or its exogenous administration can lead to deleterious consequences for the skeleton, particularly on cortical bone. However, intermittent administration of PTH (e.g. with daily subcutaneous injections) results in an increase of the number and activity of osteoblasts, leading to an increase in bone mass and in an improvement in skeletal architecture at both cancellous and cortical skeletal sites [252].

The 1-34 N-terminal fragment (teriparatide) is used for the management of osteoporosis. The marketing authorisation for the 1 to 84 intact molecule has been withdrawn at the request of the marketing authorisation holder. Treatment with teriparatide has been shown to reduce significantly the risk of vertebral fractures and also non-vertebral fractures. There is no convincing evidence that teriparatide reduces hip fracture, but this may reflect absence of evidence, not evidence of absence. Thus, the recommendation for its use in high-risk people is particularly strong in patients with vertebral fracture. The recommended dose is 20 μg of teriparatide, given as a subcutaneous injection [253]. Treatment with PTH has been studied when given for 18 to 24 months and beneficial effects on non-vertebral fracture with teriparatide have been shown to persist for up to 30 months after stopping teriparatide [254].

The most common reported adverse events in patients treated with PTH or teriparatide are nausea, pain in the limbs, headache and dizziness. In normocalcaemic patients, slight and transient elevations of serum calcium concentrations have been observed following the injection teriparatide. Serum calcium concentrations reach a maximum between 4 and 6 h and return to baseline 16 to 24 h after each dose. The change is small and routine monitoring of serum calcium during therapy is not required. PTH and teriparatide may cause small increases in urine calcium excretion but the incidence of hypercalciuria does not differ from that in placebo-treated patients. However, these agents should be used with caution in patients with active or recent urolithiasis because of their potential to exacerbate the disorder. Isolated episodes of transient orthostatic hypotension are also reported. They typically resolve within minutes to a few hours, and do not preclude continued treatment.

The use of peptides of the PTH family is contraindicated in conditions characterised by abnormally increased bone turnover (e.g. pre-existing hypercalcaemia, metabolic bone diseases other than primary osteoporosis, including hyperparathyroidism and Paget's disease of bone, unexplained elevation of alkaline phosphatase, prior external beam or implant radiation therapy to the skeleton or in patients with malignancies or bone metastasis). Severe renal impairment is also a contraindication. Studies in rats have indicated an increased incidence of osteosarcoma, with long-term administration of very high doses of teriparatide [255, 256]. These findings have not been considered relevant for patients treated with very much smaller doses of teriparatide.

Denosumab

Critical molecules for the differentiation, activation and survival of osteoclasts are the receptor activator of nuclear factor NFkB (RANK), its ligand RANKL, a member of the tumour necrosis factor (TNF) superfamily, and osteoprotegerin (OPG), which acts as a decoy receptor for RANKL. A fully human antibody against RANKL has been developed. This antibody, denosumab, has been shown to specifically bind to RANKL with a very high affinity, preventing its interaction with the receptor RANK [257].

The anti-fracture efficacy of 60 mg denosumab given subcutaneously every 6 months has been evaluated in postmenopausal osteoporotic women. After 3 years, there was a 68% reduction in the incidence of new vertebral fractures. The incidence of clinical vertebral fractures was similarly reduced by 69%. The incidence of non-vertebral fractures was reduced by 20% and of hip fractures by 40% [258]. After completing the first 3 years of the study, women from the denosumab group had 7 more years of denosumab treatment (long-term group) and those from the placebo group had 7 years of denosumab exposure (cross-over group) [259]. The yearly incidence of new vertebral fractures remained low during the extension, whereas non-vertebral fractures further significantly decreased in year 4 [260] and thereafter remained stable (approximately 1.5% per year for both vertebral and non-vertebral fractures) [235, 259]. The incidence of vertebral and non-vertebral fracture observed during the extension was similar to that observed in the denosumab group during the first 3 years and lower than rates projected from a virtual long-term placebo cohort [259].

Discontinuation of denosumab is associated with a rapid offset of action: Markers of bone turnover increased to above baseline levels, which returned to baseline values within 1 to 2 years after stopping treatment [261] and BMD decreased to baseline values by 12–18 months, independently of the duration of treatment [261]. In a sample of 1000 patients who discontinued denosumab during the 3-year pivotal study [258] or its extension [259], the vertebral fracture rate increased to a value similar to that observed in participants who received and then discontinued placebo [262]. The proportion of patients developing multiple vertebral fractures after stopping treatment was higher in the denosumab group than in the placebo group. In addition, the odds of developing multiple vertebral fractures after stopping denosumab was increased in patients with prior vertebral fracture sustained before or during treatment, or in those with the longer exposure to denosumab [262]. No increase in non-vertebral fracture after denosumab cessation was reported. A short duration of bisphosphonate therapy could be considered when discontinuing denosumab to prevent the rebound effect [263]. In women transitioning from oral bisphosphonates to injectable treatments, denosumab was associated with greater BMD increases at all skeletal sites and greater inhibition of bone remodelling, compared with zoledronic acid [235, 264].

The incidence of adverse events for all individuals who received denosumab for 10 years [259] tended to decrease over time whereas serious adverse events were stable. One atypical femoral fracture occurred in each group during the extension. Seven cases of osteonecrosis of the jaw were reported in the long-term group and six cases in the cross-over group [259]. In a meta-analysis of four clinical trials, the relative risk of serious adverse events for the denosumab group compared with the placebo group was 1.33, of serious adverse events related to infection 2.10, of neoplasm 1.11, of study discontinuation due to adverse events 1.10, and of death 0.78. These risks were all non-significant [265].

Summary of effects

The effects of the major pharmacological interventions on vertebral and hip fracture risk are summarised in Table 9.

Combination and sequential treatments

These treatment regimens include the concomitant or sequential use of compounds sharing the same mode of action (e.g. two or more inhibitors of bone resorption) or agents with

Table 9 Study details and anti-fracture efficacy (relative risk (RR and 95% confidence intervals (CI)) of the major pharmacological treatments used for postmenopausal osteoporosis when given with calcium and vitamin D, as derived from randomised controlled trials

Intervention	Study	Entry criteria	Mean age (years)	Number of patients randomised	Fracture incidence (%) over 3 years[a]			
					Placebo	Drug	RR	95% CI
a. Vertebral fracture (high risk population)								
Alendronate 5–10 mg	Black 1996 [207]	Vertebral fractures, BMD ≤ 0.68 g/m^2	71	2027	15.0	8.0	0.53	0.41–0.68
Risedronate 5 mg	Harris 1999 [212]	2 vertebral fractures or 1 vertebral fracture and T-score ≤ − 2.0	69	2458	16.3	11.3	0.59	0.43–0.82
Risedronate 5 mg	Reginster 2000 [213]	2 or more vertebral fractures—no BMD entry criteria	71	1226	29.0	18.0	0.51	0.36–0.73
Raloxifene 60 mg	Ettinger 1999 [188]	Vertebral fractures—no BMD entry criteria	66	7705	21.2	14.7	0.70	0.60–0.90
Teriparatide 20 μg[b]	Neer 2001 [253]	Vertebral fractures and FN or LS T-score ≤ − 1 if less than 2 moderate fractures	69	1637	14.0	5.0	0.35	0.22–0.55
Ibandronate 2.5 mg	Chesnut 2004 [215]	Vertebral fractures and LS − 5 < T-score ≤ − 2.0	69	2946	9.6	4.7	0.38	0.25–0.59
Ibandronate 20 mg	Delmas 2004 [216]	Vertebral fractures and LS − 5 < T-score ≤ − 2.0	70	708	9.6	4.9	0.50	0.34–0.74
Zoledronic acid 5 mg	Black 2007 [224]	FN T-score ≤ − 2.5, ± vertebral fracture, or T-score ≤ − 1.5 and 2+ mild or 1 moderate vertebral fracture	73	7765	10.9	3.3	0.30	0.24–0.38
b. Vertebral fracture (low risk population)								
Alendronate 5–10 mg[c]	Cummings 1998 [210]	FN T-score ≤ − 2	68	4432	3.8	2.1	0.56	0.39–0.80
Ale Alendronate 5–10 mg[c]	Cummings 1998 [210]	Subgroup of women, T-score < 2.5	NA	1631	4.0	2.0	0.50	0.31–0.82
Raloxifene 60 mg	Ettinger 1999 [188]	FN or LS T-score ≤ − 2.5, ± vertebral fractures	66	7705	4.5	2.3	0.50	0.40–0.80
Denosumab 60 mg	Cummings 2009 [258]	TH or LS ≤ − 2.5 and > − 4; 60–90 years	72	7868	7.2	2.3	0.32	0.26–0.41
c. Hip fracture								
Alendronate 5–10 mg	Black 1996 [207]	Vertebral fractures with BMD ≤ 0.68 g/m^2	71	2027	2.2	1.1	0.49	0.23–0.99
Alendronate 5–10 mg[c]	Cummings 1998 [210]	FN T-score ≤ − 2[d]	68	4432	0.8	0.7	0.79	0.43–1.44
Alendronate 5–10 mg[c]	Cummings 1998 [210]	FN T-score ≤ − 2.5[d] (subgroup analysis)	NA	1631	1.6	0.7	0.44	0.18–1.97
Risedronate 2.5 and 5 mg	McClung 2001 [71]	T-score < − 3[d] or < − 2[d] and ≥ 1 non-skeletal risk factor for hip fracture (subgroup analysis osteoporotic patients 70–79 years)	77	9331	3.2	1.9	0.60	0.40–0.90
Raloxifene 60 and 120 mg	Ettinger 1999 [188]	FN or LS T-score ≤ − 2.5, ± vertebral fractures	66	7705	0.7	0.8	1.10	0.60–1.90
Zoledronic acid 5 mg	Black 2007 [224]	FN T-score ≤ − 2.5 or less, ± vertebral fracture, or T-score ≤ − 1.5 and 2+ mild or 1 moderate vertebral fracture	73	7765	1.4	2.5	0.59	0.42–0.83
Denosumab 60 mg	Cummings 2009 [258]	TH or LS ≤ − 2.5 and > − 4; age 60–90 years	72	7868	1.2	0.7	0.60	0.37–0.97

FN femoral neck, *TH* total hip, *LS* lumbar spine, *NA* not available

[a] Except where indicated in column 1

[b] 20-month study

[c] 4.2-year study

[d] BMD adjusted to NHANES population

differing activities (e.g. an inhibitor of resorption plus an anabolic agent). None of the available studies has been powered so far, to assess differences in fracture incidence between combination therapy and monotherapy, but results obtained with BMD, bone histomorphometry, finite element analysis or markers of bone turnover shifted the treatment paradigm towards a greater use of combination or sequential therapies. Whereas the first attempts to combine alendronate and PTH were disappointing [266], combination of teriparatide and denosumab generated greater increments in BMD and calculated bone strength compared to either drug alone [267], supporting further investigation of this combination. Similarly, in alendronate-treated women, 3-month teriparatide cycles followed by 3-month off improve BMD similarly to daily continuous treatment with teriparatide, an observation which was not confirmed in alendronate-naive women [268]. In a controlled comparison of women who switched from alendronate to teriparatide versus those who added teriparatide to ongoing alendronate, the effect on hip BMD and on hip strength was greater with combination therapy. Continuing a potent anti-resorptive agent when starting a bone-forming agent might thus improve hip outcomes [269].

In patients at high risk of fracture, starting treatment with an anabolic agent seems most appropriate to promptly reduce the fracture risk [186]. Given that treatments with anabolic agents are limited to 18–24 months and that efficacy will wane once treatment is stopped, the real potential of the anabolic treatments is whether their greater effect on BMD and fracture can be maintained with the inhibitors of bone turnover once treatment is stopped (Fig. 12) [270]. In the absence of a subsequent prescription of an anti-resorptive agent, the benefits obtained during treatment with teriparatide progressively disappear [271], whereas they are maintained when denosumab [267] is prescribed, as soon as possible after stopping the anabolic intervention.

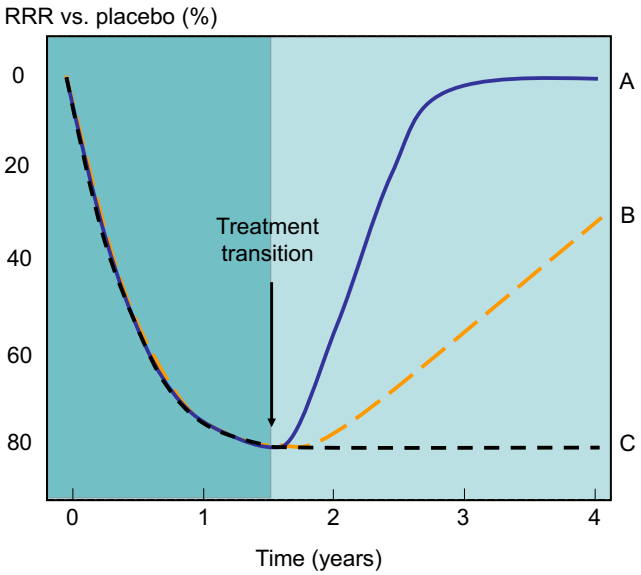

Fig. 12 Schematic diagram showing the effects of a bone-forming agent on the relative fracture risk reduction (RRR) compared with placebo. In scenario A, treatment with a bone-forming agent induces a marked effect on fracture risk over an 18 months exposure compared with placebo. On stopping the bone-forming agent, the effect on fracture wanes off over a similar time interval of 18 months. In scenario C, placebo group remains untreated, whereas the group treated with a bone-forming agent is transitioned to an inhibitor of bone turnover, which maintains the efficacy up to 4 years. In scenario B, both the treatment and the placebo groups are treated after the exposure with an inhibitor of bone turnover [270]. With kind permission from Springer Science and Business Media

Other pharmacological interventions

Menopausal hormone therapy

Oestrogens reduce the accelerated bone turnover induced by the menopause and prevent bone loss at all skeletal sites regardless of age and duration of therapy. Results from observational studies and randomised placebo-controlled trials have shown that estrogens decrease the risk of vertebral and non-vertebral fractures (including hip fracture) by about 30%, regardless of baseline BMD [272, 273]. When hormone replacement therapy is stopped, bone loss resumes at the same rate as after the menopause, but fracture protection may persist arguably for several years [274, 275].

The original analyses of the Women's Health Initiative (WHI) suggested, however, that the long-term risks of menopausal hormone therapy (MHT) outweighed the benefits. In this large cohort of postmenopausal women in their 60s, the combined use of conjugated oestrogen and medroxyprogesterone acetate was originally associated with a 30% increased risk of coronary heart disease (CHD), and breast cancer and with a 40% increase in stroke [276–278]. There was also a slight increase in the risk of dementia [279], and no clinically meaningful effect on health-related quality of life such as sleep disturbance or vasomotor symptoms [280]. In a subsequent analysis, the increase in breast cancer risk was much less in women not previously exposed to MHT [278]. In hysterectomized women receiving conjugates oestrogen alone, there was also an increase in stroke, but not of CHD and breast cancer, suggesting a deleterious effect of medroxyprogesterone acetate [281]. It has been postulated that the benefits of HRT outweigh the risks in younger postmenopausal women [282, 283], but so far there is no placebo-controlled study showing the long-term safety of such approaches. However, in a recent publication, re-assessing the long-term outcomes of the WHI, MHT with conjugated oestrogen and medroxyprogesterone acetate for a median of 5.6 years or with conjugated oestrogen alone for a median of 7.2 years was not associated with an increased risk of all-cause, cardiovascular, or cancer mortality during a cumulative follow-up of 18 years [284]. This may challenge the current recommendation to use HRT only for climacteric symptoms, at a dose as small as possible and for a limited period of time [285].

Vitamin D derivatives

Alfacalcidol is a synthetic analogue of the vitamin D metabolite calcitriol (1,25-dihydroxyvitamin D_3) and it is metabolised to calcitriol by its 25-hydroxylation in the liver. It is somewhat less potent than calcitriol. Both alfacalcidol and calcitriol are used in some countries for the treatment of osteoporosis. Several but not all studies show decreases in vertebral fracture risk [286, 287]. A meta-analysis suggested that combined treatment with alendronate and alfacalcidol prevented all osteoporotic fractures more than alfacalcidol or alendronate alone [288]. The effects on bone mineral density have been less extensively studied. A few reports have suggested that alfacalcidol and calcitriol exert a direct action on muscle strength and decreases the likelihood of falling in elderly subjects [289, 290].

The major problem with the use of the vitamin D derivatives is the risk of hypercalcaemia and hypercalciuria. Adverse effects of prolonged hypercalcaemia include impairment of renal function and nephrocalcinosis. The narrow therapeutic window demands the frequent surveillance of serum and possibly urine calcium in patients exposed to these agents. Calcium supplementation of the diet should be avoided or used with care.

Clodronate

Clodronate is a relatively weak bisphosphonate, but has been shown to decrease the risk of vertebral and non-vertebral fractures in randomised controlled studies [291, 292]. It is widely available for the treatment of neoplastic bone disease but licensed for use in osteoporosis in only a few countries.

Local osteo-enhancement procedure

Local osteo-enhancement procedure (LOEP) is a local treatment, which requires a minimally invasive injection in the femoral neck of a resorbable synthetic bone graft substitute, containing a proprietary triphasic calcium sulphate/calcium phosphate implant [293]. In postmenopausal women with low hip BMD (mean T-score = − 3.1), femoral neck BMD in treated hips increased by 58% compared to contralateral control hips, during 5–7 years of follow-up [293]. X-ray and QCT analyses demonstrated that the implant material was completely resorbed in all patients and replaced with bone that integrated with the surrounding trabecular and cortical bone [294]. QCT scans were used to conduct patient-specific, non-linear finite element analysis to estimate hip strength in simulated sideways fall and stance loading conditions. Femoral strength in sideway fall was 36% higher in treated than control femurs 5–7 years after the procedure [295]. No safety issues were reported during the study [293–295]. Data on fracture outcomes are not yet available.

Vertebroplasty and kyphoplasty

In patients with recent vertebral fracture in whom pain persists for 2 to 3 weeks despite a well-conducted analgesic programme, injection of cement in the fractured vertebral body without (vertebroplasty) or with preceding balloon inflation (kyphoplasty) may lead to reduction of pain and positive functional outcomes [296, 297]. Whether pain relief is related to the cement itself or to local anaesthetic is still unclear [298, 299]. Heterogeneity in treatment recommendations is, in part, explained by an insufficient clinical evidence base for vertebral augmentation and heterogeneity of patients, leading to undue reliance on expert opinion [300, 301]. An increase in new vertebral fracture rates at non-treated levels, especially those adjacent to the treated vertebrae, has been reported [297, 302] but not consistently [303] following both vertebroplasty and kyphoplasty.

Fracture liaison services

Fracture liaison services (FLS), also known as osteoporosis coordinator programmes and care manager programmes, provide a system for the routine assessment and management of postmenopausal women and older men who have sustained a fragility fracture [304–306]. Since the majority of patients presenting with fragility fracture do not receive appropriate assessment and treatment, fracture liaison services address this need through a systematic approach to identify cases, assess risk of further fractures and the need for treatment. Most fracture liaison services are based in secondary care although models in primary care have also been described. A dedicated coordinator, often a nurse, working closely with the patient, primary care physician, orthopaedic and trauma department and osteoporosis and falls service is central to the development of a successful service. An example of the structure of a fracture liaison service is shown in Fig. 13.

The IOF has launched a global campaign ('Capture the fracture®') to promote this approach for the prevention of a second fracture [308, 309]. This initiative aims to set internationally endorsed standards for best practice by facilitating the implementation of fracture liaison services involving best practice frameworks, multidisciplinary models and FLS questionnaires.

The benefits of coordinator-based systems to ensure appropriate management of patients following a fracture are well established [7, 308–315]. Use of a systematic coordinator approach in the Kaiser Permanente Healthy Bones Program was associated with a 40% reduction in hip fractures [314]. Recent studies from the UK [316–318] reported that the initiation of FLS reduced the 30-day and 1-year mortality rates following hip fracture, led to a significant reduction in second fracture rate and increased the utilisation of anti-osteoporosis treatment by 15%. Although the health economic analyses that have been published so far have shown that osteoporosis

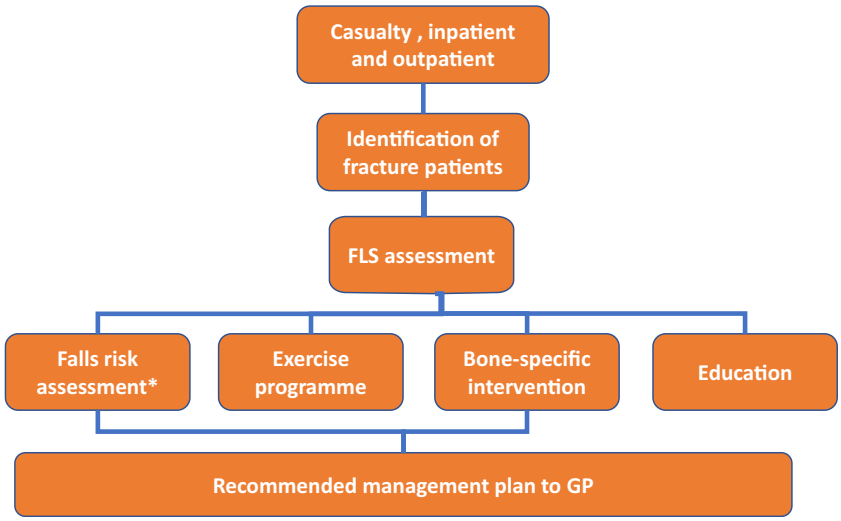

Fig. 13 Schema of a Fracture Liaison Service (FLS) integrated with post-fracture falls risk assessment [after [307]]

management programmes are a cost-effective intervention for the prevention of fractures [314, 315, 319–321], larger and longer-term studies will be needed to further quantify the effect of FLS care on subsequent fracture risk [322].

Adherence and monitoring of treatment

Adherence to treatment

When discussing adherence, there is a need to define the terminology [323], since a wide variety of definitions is used in the literature.

1. Adherence is a general term encompassing the aspects mentioned below.
2. Persistence describes for how long the medication is taken. Persistence could be expressed as number of days until discontinuation or the proportion of the cohort still on the medication after a given time since first prescription. Non-persistence is assumed to be the same as discontinuation if a treatment gap is longer than a set number of days.
3. Compliance denotes the proximity to the treatment recommendation as given in the official product information (SPC). It is often simplified to mean the number of doses taken divided by the number of prescribed doses. This simplification does not include some important aspects of compliance, such as taking medication with food (for the oral bisphosphonates), at the correct time of the day, too large doses to compensate for forgotten doses, pill dumping, etc.
4. Primary non-adherence is when the patient is prescribed a drug and then never fills the prescription.

Non-adherence to medical therapy is a widespread public health problem. It is estimated that only half of the patients comply with long-term therapy of which a substantial minority do not even redeem their prescription. Overcoming non-adherence presents particular challenges in asymptomatic bone diseases and other chronic, asymptomatic conditions. In such settings, the level of perceived threat to health does not motivate the patient to adhere to therapy. In addition, risk of non-adherence with any therapy increases with increased duration of treatment [324].

Poor adherence to medication is associated with adverse effects on outcomes in osteoporosis or osteopenia, and non-adherent patients have smaller decreases in rates of bone turnover, smaller gains in BMD and a significantly greater risk of fracture [325–327]. Partial adherence also has a significant impact on cost-effectiveness [328]. Further research is required to optimise thresholds of compliance and persistence, the impact of gap length, offset times, and fraction of benefit [329].

Improving adherence to osteoporosis therapy requires effective patient/provider communication and close patient monitoring for the early identification of declining adherence. Patients' belief in a medication contributes to better adherence and can be improved by firmly associating treatment with expected benefits such as reduced risk of fracture and thereby an improved quality of life. Patients may be encouraged to adhere when presented with measurements of biochemical markers of bone turnover or their BMD results together with an explanation of how these measures relate to risk reduction. Another primary component of improving adherence is to use simplified or user-friendly treatment programmes [330, 331]. Frequency of dosing is another determinant of adherence [332, 333]. A recent IOF and ECTS taskforce suggested that screening to detect a lack of adherence with oral bisphosphonates should involve the measurement of P1NP and CTX at baseline and 3 months after starting therapy. In the absence of a decrease above the least significant change (i.e. − 38% for P1NP and − 56% for CTX), a low adherence should be suspected [334].

It should be noted that inadequate adherence can also take the form of improper drug administration, even when doses are not missed. An example is the malabsorption of oral

bisphosphonates when taken with food. Such non-adherence poses the potential problems of decreased drug absorption and increased risk of adverse effects [335].

Monitoring of treatment with densitometry

The goal of bone-targeted drug therapy in a patient with osteoporosis is to increase bone strength, in order to decrease the risk of fracture. In untreated men and women, BMD is one of the major determinants of bone strength, and low BMD is an important predictor of fracture. Whether the long-term anti-fracture efficacy of anti-osteoporotic drugs depends on the extent to which treatment can increase or maintain BMD is controversial [336]. Meta-regressions, based on summary statistics, demonstrate a stronger correlation between the change in BMD and fracture risk reduction than results based on the individual patient data [337, 338].

Whereas 16% of vertebral fracture risk reduction after treatment with alendronate was attributed to an increase in BMD at the lumbar spine [339], larger increases in BMD at both the spine and hip, observed with alendronate, were associated with greater reductions in the risk of non-vertebral fractures. However, for patients treated with risedronate or raloxifene, changes in BMD predict even more poorly the degree of reduction in vertebral (raloxifene) or non-vertebral (risedronate) fractures. Twelve percent and 7% of the effects of risedronate to reduce non-vertebral fractures were attributed to changes in the spine and femoral neck BMD, respectively [340]. For raloxifene, the percentage changes in BMD accounted for 4% of the observed vertebral fracture risk reduction [341]. Percent changes in total hip BMD at month 36 explained up to 35% of the effect of denosumab to reduce new or worsening vertebral fractures and up to 84% of the reduction in non-vertebral fracture risk [342]. It is reasonable to conclude, however, that early monitoring of BMD has limited value in the prediction of treatment responses with inhibitors of bone resorption.

For bone-forming agents, increases in BMD account for approximately one third of the vertebral fracture risk reduction with teriparatide [343]. Further data are needed on the role of BMD monitoring patients treated with bone-forming agents but appears to be of greater value than their use with inhibitors of bone resorption.

In postmenopausal osteoporosis, treatment-induced increments in BMD with inhibitors of bone turnover are modest (typically 2% per year) in comparison to the precision error of repeat measurements (typically 1–2%) so that the time interval of repeat estimates must be sufficiently long in order to determine whether any change is real [344]. In the absence of other clinical imperatives, a 5-year interval may be appropriate. For other agents such as and PTH derivatives, the treatment-induced increment is much more rapid and more frequent BMD tests may be considered.

Monitoring of treatment with biochemical markers of bone turnover

The most informative biochemical markers of bone turnover for the monitoring of osteoporosis are procollagen I N-terminal extension peptide (P1NP) for assessing bone formation, and C-telopeptide breakdown products (especially serum CTX) to assess bone resorption [72–74].

Treatment-induced changes in bone markers are more rapid than changes in BMD and are typically measured 3–6 months or so after starting treatment when treatment-induced changes are expected to be most evident. In a research setting, a significant association has been reported between the short-term decrease in markers of bone turnover with the use of anti-resoptive agents and gains in BMD [345, 346]. More importantly, significant associations have been reported between the short-term decrease in markers of bone turnover and the reduction in risk of vertebral and non-vertebral fractures with the use of anti-resorptive agents (raloxifene and bisphosphonates). For the bisphosphonates, a screening strategy has been proposed by the IOF based on the response of P1NP and CTX after 3 months of therapy [334]. If no change is observed, the clinician should reassess the adherence to the treatment and also other potential issues with the drug. More research is required using standardised analytes before robust evidence-based recommendations can be given [73].

Despite limited evidence, failure of treatment may be inferred when two or more incident fractures have occurred during treatment, when serial measurements of bone turnover markers are not suppressed by anti-resorptive therapy and where bone mineral density continues to decrease [347].

Investigation of patients with osteoporosis

Diagnostic work up

The same diagnostic approach should be undertaken in all patients with osteoporosis irrespective of the presence or absence of fragility fractures. However, the range of clinical and biological tests will depend on the severity of the disease, the age at presentation and the presence or absence of vertebral fractures. The aims of the clinical history, physical examination and clinical tests are as follows:

- To exclude a disease which can mimic osteoporosis (e.g. osteomalacia, myelomatosis);
- To elucidate causes of osteoporosis and contributory factors;
- To assess the severity of osteoporosis to determine the prognosis of the disease, i.e. the risk of subsequent fractures;
- To select the most appropriate form of treatment;

- To perform baseline measurements for subsequent monitoring of treatment.

The procedures that may be relevant to the investigation of osteoporosis are shown in Table 10. These investigations may be used to:

- Establish the diagnosis of osteoporosis (e.g. DXA or X-rays);
- Establish the cause (e.g. thyroid function tests for hyperthyroidism, and urinary free cortisol for Cushing syndrome);
- Establish differential diagnosis (e.g. protein electrophoresis for myeloma, and serum calcium and alkaline phosphatase for osteomalacia).

Investigations commonly conducted in secondary care include a full blood count, ESR, serum calcium and phosphate, liver function tests and tests of renal function. Additional measurements include the biochemical indices of bone turnover, serum parathyroid hormone, serum 25-hydroxyvitamin D, serum or urine protein electrophoresis, fasting and 24-h urinary calcium, urinary free cortisol, thyroid function tests, IgA anti-tissue transglutaminase antibody or IgA endomysial antibody, tryptase and (rarely) transiliac bone biopsy. Free testosterone, gonadotrophin and prolactin measurements may be of value in men. Assessment is guided by the clinical findings, and some patients who apparently have primary osteoporosis are subsequently found to have mild hyperparathyroidism or hyperthyroidism, systemic mastocytosis, the late appearance of osteogenesis imperfecta or osteomalacia.

Differential diagnosis of osteoporosis

Osteomalacia and malignancy commonly induce bone loss and fractures. Osteomalacia is characterised by a defect of mineralisation of bone matrix most commonly attributable to impaired intake, production or metabolism of vitamin D.

Table 10 Routine procedures proposed in the investigation of osteoporosis. From [2], with kind permission from Springer Science and Business Media

Routine
History including the FRAX clinical risk factors
Examination including height and weight
Blood cell count, sedimentation rate, serum calcium, albumin, creatinine, phosphate, alkaline phosphatase and liver transaminases
Lateral radiograph of lumbar and thoracic spine
Bone densitometry (dual energy X-ray absorptiometry at hip and spine)
Other procedures
Lateral imaging DXA for vertebral fracture assessment (VFA)
Markers of bone turnover, when available

Other causes include impaired phosphate transport or the chronic use of some drugs such as aluminium salts (and other phosphate binding antacids), high doses of fluoride or etidronate, and the chronic use of some anticonvulsants. In most cases, the diagnosis of osteomalacia is suspected by the clinical history and by abnormalities in biochemical tests such as low values of serum and urinary calcium, serum phosphate and 25-hydroxyvitamin D, and high values for alkaline phosphatase and parathyroid hormone. A transiliac bone biopsy after double tetracycline labelling may be necessary to demonstrate unequivocally a defect in mineralisation.

Diffuse osteoporosis with or without pathological fracture is common in patients with multiple myeloma, a condition suspected by the severity of bone pain, increased sedimentation rate and Bence Jones proteinuria and identified by marrow aspirate, and serum and urine (immuno-) electrophoresis of proteins. Similarly, pathological fractures resulting from metastatic malignancies can mimic osteoporosis and can be excluded by clinical and radiological examination, biological tests such as tumour markers, and scintigraphy or other imaging techniques. Vertebral fractures in osteoporosis should be differentiated from vertebral deformities attributable to other disorders such as scoliosis, osteoarthrosis and Scheuermann's disease.

Health economics

There is an increasing need for management strategies to be placed in an appropriate health economic perspective for guideline development and for reimbursement. The type of evaluation used is principally cost-utility analysis as a measure of cost-effectiveness. In the context of evaluating treatments, this takes account, not only of fractures avoided, but also of any change in morbidity and mortality from both beneficial and unwanted effects. QALYs are the accepted unit of measurement in health economic assessment of interventions using cost-utility analysis. In order to estimate QALYs, each year of life is valued according to its utility to the patient. Values range from 0, the least desirable health state, to 1, or perfect health. The decrement in utility associated with fractures is the cumulative loss of utility over time. There is at present little international consensus as to when treatment can be considered to be cost-effective [348, 349]. One approach is to base the threshold value on a measure of a country's economic performance and a value of about 2 times GDP/capita has been suggested as a threshold that can be applied to Western economies [350]. On this basis, threshold values would be about €32,000 in the UK, close to the recommendation of the National Institute for Health and Clinical Excellence [351]. Although the GDP per capita provides an index of affordability, there is also a marked heterogeneity in the proportion of GDP that countries are willing to devote to health care, and in the proportion of the population at risk from

osteoporotic fracture (i.e. elderly people). In a systematic review, the ratio between WTP per QALY and GDP per capita varies widely from 0.05 to 5.40, depending on scenario outcomes. The average ratio of WTP per QALY and GDP per capita for extending life or saving life was 2.03 [352].

Studies of intervention

There has been a rapid expansion of research in Europe on the cost-utility of interventions in osteoporosis, which has been the subject of several reviews [124, 128, 353–357]. A useful tabular summary of studies up to April 2012 is provided in Brandão et al. [358]. Despite the use of different models, different settings and payer perspectives, analyses suggest that there are cost-effective scenarios that can be found in the context of the management of osteoporosis for all but the most expensive interventions (Table 11) [127]. A pan-European study from 2004 estimated the cost-effectiveness of branded alendronate in nine countries [359]. Alendronate was shown to be cost-saving compared to no treatment in women with osteoporosis (with and without previous vertebral fracture) from the Nordic countries (Norway, Sweden and Denmark). The cost-effectiveness of alendronate compared to no treatment was also within acceptable ranges in Belgium, France, Germany, Italy, Spain, Switzerland and the UK. However, with the markedly decrease in price of generic bisphosphonates, analyses based on a branded drug price have become obsolete. For example, the cost of alendronate (70 mg weekly) assumed in Table 11 was £95 per annum (2007) and in 2017 had fallen to a yearly cost of £8.64 in the UK. NICE have recently reappraised the cost-effectiveness of oral and intravenous bisphosphonates [128]. Treatment with oral bisphosphonates was cost-effective of women with a 10-year probability of a major osteoporotic fracture of 1% or more. For intravenous bisphosphonates, the threshold for cost-effectiveness was a 10-year probability of 10%.

Table 11 Comparison of the cost-effectiveness (£/QALY gained) of alendronate with other interventions in women aged 70 years from the UK [data for treatments other than alendronate from [127], with permission from Elsevier]

Intervention	T-score = − 2.5 SD		No BMD
	No prior fracture	Prior fracture	Prior fracture
Alendronate	6225	4727	6294
Etidronate	12,869	10,098	9093
Ibandronate daily	20,956	14,617	14,694
Ibandronate intermittent	31,154	21,587	21,745
Raloxifene	11,184	10,379	10,808
Raloxifene without breast cancer	34,011	23,544	23,755
Risedronate	18,271	12,659	13,853

The advent of probability-based assessment has prompted the cost-effectiveness of interventions as a function of fracture probability. Several studies have examined the cost-effectiveness of intervention thresholds expressed in terms of fracture probability [123, 127, 130, 360, 361]. In studies from the UK [114, 127], generic alendronate was shown to be cost-effective in the prevention and treatment of fractures in postmenopausal women with a 10-year fracture probability for a major fracture that exceeded 7.5% (Fig. 14). It is interesting that in the different European countries where such studies have been performed, the probabilities of major fractures selected as making generic alendronate a cost-effective intervention are quite similar: 7.5% in the UK [127], 8.8% in Portugal [363], 13.8% in Switzerland [361] and 10–15%, depending on age, in Greece [362]. This is quite remarkable, given the disparities in the clinical and economic epidemiology of factures and, especially, the willingness to pay adopted for each country: the UK €27,786, Switzerland €115,000, Portugal €32,000 and Greece €30,000.

The recent appraisal by NICE [128] indicated that all oral bisphosphonates were cost-effective in women with a 10-year probability of 1% or more. Thus, the all treatment scenarios with alendronate can be considered as cost-effective (see Table 6 and Fig. 9). This raises an important issue in that the health economic thresholds espoused by NICE simply demarcate a level of risk above which the respective oral and IV bisphosphonate treatments are cost-effective but that the thresholds used to decide treatment should be based on clinical appropriateness [136, 364].

A special need for the incorporation of FRAX into health economic models arises from studies that have examined the interaction between FRAX-based probabilities with

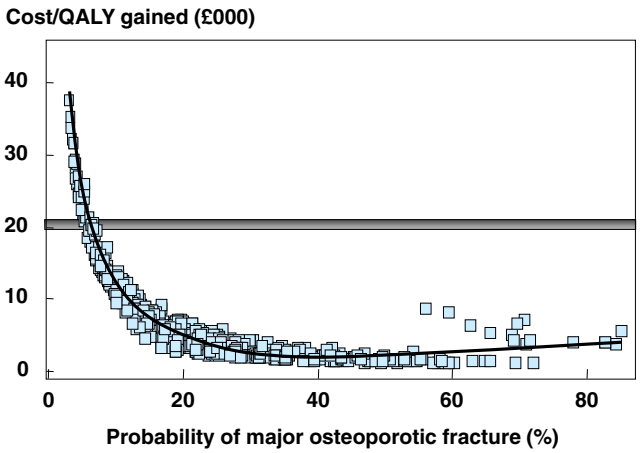

Fig. 14 Correlation between the 10-year probability of a major fracture (calculated with BMD) and cost-effectiveness of generic alendronate at the age of 50 years in women (BMI set to 26 kg/m^2). Each point represents a particular combination of BMD and clinical risk factors (all possible combinations of CRFs at BMD T-scores between 0 and − 3.5 SD in 0.5 SD steps—512 combinations) with a BMI set to 26 kg/m^2. The horizontal line denotes the threshold for cost-effectiveness (a willingness to pay of £20,000/QALY gained). From [114], with kind permission from Springer Science and Business Media

effectiveness. Interventions studied include raloxifene [195, 201], bazedoxifene [201], clodronate [365], daily and weekly teriparatide [366, 367], denosumab [368], alendronate [369], as well as a basket of interventions used by general practitioners in the UK [111]. Most of these were post hoc but, in the case of denosumab, was a pre-planned analysis. In addition, the 'screening for prevention of fractures in older women' (SCOOP) study was a prospective randomised study that demonstrated efficacy for hip fracture in women selected on the basis of hip fracture probability assessed using FRAX [111].

Several of these studies have shown greater efficacy against fracture in individuals at higher risk treated with clodronate, bazedoxifene, denosumab and in the SCOOP study. This FRAX-dependency has marked economic consequences, illustrated when comparing the cost-effectiveness of the two selective oestrogen receptor modulators, raloxifene and bazedoxifene. The overall effectiveness of these two agents on vertebral fracture risk is rather comparable but the efficacy of bazedoxifene increases in women with the higher the baseline fracture probability. In contrast, the relative risk reduction with raloxifene is constant over the range of fracture probabilities studied. As a consequence, raloxifene has better cost-effectiveness at low fracture probabilities whereas bazedoxifene has the better cost-effectiveness at high baseline fracture probabilities [370, 371]. The contrasting effect of FRAX-dependent and FRAX-independent interactions with efficacy on fractures averted is shown in Table 12.

Despite differences in apparent cost-effectiveness, there is, however, no proven difference in efficacy between the majority of treatments shown in Table 11 and head to head comparisons of interventions with fracture outcomes are few and recent [372]. For these reasons, the value of an incremental analysis between the individual treatments is questionable, since any resulting hierarchy of treatments is dependent largely on price, but otherwise meaningless in clinical terms. In addition, the large number of untreated patients makes 'no treatment' a relevant comparator. Notwithstanding, alendronate has been considered as a first line intervention. The view arises, not because of apparent differences in efficacy between treatments, but because of cost. However, the poor effectiveness and side effect profile of many generic formulations challenge this view [251].

The advent of new anabolic agents given for relatively short periods followed by maintenance with sequential inhibitors of bone resorption will offer new challenges for health economic appraisal.

Table 12 Contrasting effects on the number of fractures saved with an intervention, the efficacy of which the relative risk reduction (RRR) is independent or dependent on FRAX (average RRR set at 40%)

	FRAX independent		FRAX dependent	
Fracture probability (%)	RRR (%)	Fractures saved	RRR (%)	Fractures saved
0	40	0	0	0
5	40	2	0.14	1
10	40	4	0.27	3
15	40	6	0.40	6
20	40	8	0.54	11
25	40	10	0.68	17
30	40	12	0.80	24
Total		42		62

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Compliance with ethical standards

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