**Identification of patient profile for treatment**

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**Abstract: 140 words**

The WHO clinical definition of osteoporosis, based on a measurement of bone mineral density (BMD) by Dual Energy X-ray Absorptiometry, has been used globally since the mid-1990s. However, although this definition identifies those at greatest individual risk of fracture, in the population overall a greater total number of fractures occur in individuals with BMD values above the osteoporosis threshold. The inclusion of clinical risk factors, with or without BMD, in fracture prediction algorithms can improve the identification of individuals at high fracture risk; thus a number of web-based tools have been developed, the most commonly used globally being FRAX®. In this review, we will discuss the epidemiology of osteoporosis, clinical risk factors for fragility fracture, and how this knowledge is being used to aid risk stratification. Importantly, research is on-going to demonstrate the clinical efficacy and cost-effectiveness of such case-finding strategies.

**Key words**

Osteoporosis, fracture, epidemiology, bone mineral density, FRAX, Garvan, QFracture, probability

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# Introduction

Osteoporosis is characterised by low bone mass and microarchitectural deterioration of bone tissue. The result is bone fragility, and increased risk of the major clinical consequence, fracture. Since a histological definition is of limited utility in such a widespread condition, a clinical definition was devised, in the mid-1990s, by the World Health Organisation. This is based on bone mineral density (BMD) measured at the femoral neck by Dual Energy X-ray Absorptiometry (DXA). Independent of age and sex, individual BMD is related to data from a reference population comprised of healthy young adult females to generate a standard deviate “T-score”. A BMD that is 2.5 standard deviations or more below the young adult female mean defines osteoporosis; a T-score between -1 and -2.5 SDS as osteopenia[[1](#_ENREF_1)]. Although this definition has proved to be valuable for the identification of those individuals at high individual risk of fracture, it is clear that BMD alone does not encompass all factors that are associated with increased fracture risk. Understanding the epidemiology of osteoporosis and osteoporotic fracture is therefore important to identifying patients who are at greatest risk. This has led to the development of fracture probability tools that can be used to guide health care providers in deciding when to implement therapies aimed at primary and secondary fracture prevention. In this review, we will describe the epidemiology of, and risk factors for, osteoporotic fractures, and the tools available with which to undertake risk stratification.

# Global Burden of Osteoporosis

Osteoporosis is common: a recent report estimated that in 2010, 6.6% of men and 22.1% of women aged over 50 years living in the European Union (EU) had osteoporosis, and that there were 3.5 million fragility fractures [[2](#_ENREF_2)]. The annual direct costs attributable to fracture treatment in the EU equate to approximately €24 billion. However inclusion of the indirect costs of osteoporosis, such as fracture prevention therapies and long-term post-fracture care, which account for 29% and 5% of the total costs, raises this figure to €37 billion per year [[2](#_ENREF_2)]. Although historically it has been thought that hip fractures contribute the vast majority of this burden, recent data suggest that this is not the case: thus approximately half (54%) of these costs are attributable to hip fractures. Non-hip, non-wrist and non-spine fractures account for 39% of the economic burden, with vertebral and wrist fractures contributing 5% and 2%, respectively [[2](#_ENREF_2)].

Globally, there is marked heterogeneity in annual age-standardised hip fracture rates: the highest rates are observed in Scandinavia (Denmark 439/100,000 person-years; Norway 420/100,000 person-years; Sweden 401/100,000 person-years) and the lowest in Tunisia (50/100,000 person-years), Ecuador (55/100,000 person-years) and Morocco (69/100,000 person-years) [[3](#_ENREF_3) [4](#_ENREF_4)]. This is illustrated in figure 1 [[3](#_ENREF_3)], which demonstrates that the highest incidence of hip fracture is generally observed in countries furthest from the equator and in countries in which extensive skin covering due to religious or cultural practices is the norm. Although the exact mechanisms underlying this variation remain to be elucidated, the geographic distribution would suggest that vitamin D status might be an important factor. Worldwide, the number of hip fractures is increasing due to improvements in life expectancy and an aging population; in 1990 there were estimated to be 1.7 million hip fractures worldwide, but this is predicted to reach 6.3 million annually by 2050 [[5](#_ENREF_5)]. These estimates assume a constant age-specific hip fracture incidence, yet varying secular changes in fracture rates across the globe have been observed. Whilst age and sex-specific hip fracture rates increased in Europe and North America until the late 20th century, with subsequent plateauing or even a decline, there is evidence to suggest that fracture rates are continuing to rise in developing countries (Figure 2) [[6](#_ENREF_6) [7](#_ENREF_7)]. As such, the economic burden of osteoporotic fracture in developing countries is likely to increase markedly.

Importantly, the burden of fragility fracture extends beyond the economic costs: mortality is elevated for most fracture types, although it is highest for hip fracture [[8](#_ENREF_8)]. Mortality risk is elevated by 5-8 times in the first three months following a hip fracture [[9](#_ENREF_9)], and whilst this risk does decrease with time, at 10 years post-fracture it still remains above baseline [[9](#_ENREF_9) [10](#_ENREF_10)]. Although hip fractures are more common in women than men, short-term mortality is greater in men [[9](#_ENREF_9) [10](#_ENREF_10)], which might result from greater prevalence of co-morbidities at fracture in men and more frequent perioperative complications, including infection [[11](#_ENREF_11)] and cardiovascular events [[12](#_ENREF_12)]. Poorer quality of life [[13](#_ENREF_13)] and functional decline are also common following an osteoporotic fracture, particularly after hip, pelvis and vertebral fractures [[13](#_ENREF_13)]. Fewer than 40% of individuals who sustain a hip fracture will regain their pre-fracture ambulatory status within two years of the fracture, and poorer post-fracture function is more likely in those who have an underlying malignancy or cognitive impairment [[14](#_ENREF_14)]. Furthermore, rates of admission to nursing home following a hip fracture exceed those observed in non-fracturing age and sex-matched controls [[15](#_ENREF_15)].

Future fracture risk is also increased following a fracture. A prior history of any fracture has been shown to increase the risk of an osteoporotic fracture by approximately two fold [[16-18](#_ENREF_16)], with the greatest predictive power for fractures at the same site. For example, a fourfold increase in vertebral fracture incidence is observed in women with a history of vertebral fracture [[17](#_ENREF_17)]. Additionally, in women, the incidence of fracture rises further with increasing numbers of prior fractures since the age of 45 years [[18](#_ENREF_18)]. This highlights the need for both primary and secondary prevention strategies.

# Risk factors for Osteoporosis and Fragility Fracture

Spontaneous fractures in osteoporosis are rare, and an impact, even if the force is low, is usually required for a fracture to occur. The epidemiology of osteoporosis and fragility fracture therefore reflects both influences on architectural changes to bone structure, and clinical risk factors that increase the likelihood of an impact force occurring. Other than for vertebral fracture, in most cases a fracture is the result of a fall [[19](#_ENREF_19)].

## Age and Gender

The prevalence of osteoporosis rises steeply after 50 years of age, and there is a similar rise in fragility fracture incidence, demonstrated in figure 3 [[20](#_ENREF_20)]. In childhood and early adulthood, fracture rates are higher in males than females [[21](#_ENREF_21) [22](#_ENREF_22)], however, after the age of 50 years, this pattern is reversed, and the overall fracture incidence in women is three times higher than that observed in men [[22](#_ENREF_22)]. Forearm fractures display a marked sex disparity after 50 years of age due to a substantial increase in the incidence in women without a corresponding increase in men [[22](#_ENREF_22)]. Sex differences in bone geometric structure and microarchitecture that confer greater bone strength are observed from early childhood and persist through to later life; these include greater bone cross-sectional area, thicker cortices, and greater trabecular number and thickness in males [[23](#_ENREF_23) [24](#_ENREF_24)]. These factors contribute to the differences in incidence of fragility fracture in men and women, but the steep rise in older women is also partly attributable to post-menopausal oestrogen withdrawal. After the female menopause, there is an accelerated reduction in bone mass, decreased trabecular connectivity [[25](#_ENREF_25)] and increasing cortical porosity and thinning [[23](#_ENREF_23) [26](#_ENREF_26)]. Women who experience an early menopause are therefore at greater risk of osteoporosis and fracture [[27](#_ENREF_27)].

The increasing risk of falls with advancing age also contributes to the rise in fragility fracture incidence in later life. Falls are four times more common in 90 year olds compared to 60 year olds, and twice as common in women than men [[28](#_ENREF_28)]. Sarcopenia, poor functional mobility, visual impairment, balance disturbances, neurocognitive dysfunction, cardiovascular instability and sedative medications all increase falls risk [[28](#_ENREF_28)], and their prevalence increases with aging.

## Ethnicity

The incidence of hip fracture differs with ethnicity. In the USA, the highest frequencies are observed in white women and the lowest in Black-American women [[29](#_ENREF_29)]. Hip fracture rates in women of Hispanic and Asian ethnicity living in the USA are lower than those observed in white women, but higher than Black women [[29](#_ENREF_29)]. These differences likely reflect a combination of ethnic differences in BMD, skeletal size and microarchitecture; African-American women have higher areal BMD [[30](#_ENREF_30)], greater bone area [[31](#_ENREF_31)], increased trabecular thickness, cortical area and cortical thickness compared to Caucasian women [[31](#_ENREF_31)], all of which will confer greater bone strength and resistance to fracture.

## Stature and Obesity

In post-menopausal women, tall stature and low body mass index are established risk factors for some fracture types [[32-34](#_ENREF_32)]. Traditionally, obesity was considered to be a protective against fragility fracture due to the higher BMD in obese individuals from greater mechanical loading, and protective cushioning in the event of a fall. However findings of the Global Longitudinal study of Osteoporosis in Women (GLOW), which included over 46000 women from 10 countries, suggested that overall fracture rates did not differ between normal weight and obese women, but differences across fracture sites were observed [[35](#_ENREF_35)]. Indeed higher frequencies of ankle and lower leg fractures were seen in obese compared with normal weight women, but obese women had lower rates of wrist, hip and pelvic fractures [[35](#_ENREF_35)]. A recent meta-analysis of prospective data from nearly 400,000 women similarly reported a lower risk of forearm and hip fractures in obese compared to healthy weight women, but a higher incidence of humeral fractures [[34](#_ENREF_34)]. The mechanisms underlying these differences in site-specific fracture rates are not fully understood, but could relate to size and direction of loading and/or dissipation of forces by adipose tissue in the event of a fall. Furthermore, although in crude analyses the hazard ratio for fracture at a BMI of 35 kg/m2 compared with 25 kg/m2 was 0.87 (95%CI: 0.85-0.90), when this relationship was adjusted for the effect of BMD, the hazard ratio was 1.16 (95%CI: 1.09-1.23); taken with the site-specificity of BMI-fracture associations, the relationships between BMI, BMD and fracture risk are clearly complex, and the implications of these findings for risk stratification require further clarification.

## Heritable influences

Fragility fracture has a large heritable component, and fracture risk certainly is higher in individuals who have a parent with a history of fragility fracture [[36](#_ENREF_36)]. However, it is likely that this reflects intrauterine and shared environmental factors in addition to genetic inheritance. Twin and family studies have suggested that a large proportion of the variance in BMD is heritable, although this does vary by skeletal site, with lumbar spine BMD displaying greater heritability than that at the wrist [[37](#_ENREF_37)]. However, to date, polymorphisms identified by genome-wide association studies can account for only 1-3% of the variance in BMD, suggesting that further genetic signals remain to be discovered from newer approaches such as deep sequencing, and that shared environmental factors also contribute to the heritable component. This is supported by finding that the inherited component of BMD is lower in post-menopausal than pre-menopausal women [[37](#_ENREF_37) [38](#_ENREF_38)]. Furthermore it is increasingly recognised that environmental factors can influence gene expression, for example, the observed interaction between vitamin D receptor genotype and birth weight in determining lumbar spine BMD [[39](#_ENREF_39)], and the observation that polymorphisms in the interleukin-6 promoter gene were only associated with hip BMD in women who were not using oestrogen replacement [[40](#_ENREF_40)]. Indeed, in twin studies, intrapair differences in birthweight correlated with adult BMC[[41](#_ENREF_41) [42](#_ENREF_42)], with one investigation demonstrating greater intrapair differences in both birthweight and adult BMC in monozygotic than dizygotic twins[[41](#_ENREF_41)], consistent with the notion that differential placentation may lead to long-term alterations to postnatal growth, despite identical genetic make-up. Additionally, the role of epigenetic processes in mediating gene expression and repression is becoming increasingly recognised [[43](#_ENREF_43)], and understanding of their role in the development of osteoporosis is likely to evolve in subsequent years. Finally, it is likely that genetic determinants of bone turnover, age at menopause, hip geometry and muscle strength, in addition to BMD, contribute to the susceptibility to fragility fracture.

## Medications

Glucocorticoid exposure may lead to one of the most common forms of secondary osteoporosis, and is associated with an increased risk of fracture [[44-46](#_ENREF_44)]. Using the General Practice Research Database (GPRD), it was shown that the increased risk is greatest for vertebral fractures, for which the risk is increased even with low dose steroids (<2.5mg/day). Moderate and high dose steroids were associated with increased risk of hip and forearm fractures [[46](#_ENREF_46)]. Continuous rather than intermittent dosing schedules and prolonged duration of exposure may further increase associated fracture risk [[44](#_ENREF_44) [45](#_ENREF_45)]. Fracture rates increase dramatically in the first 3 months of steroid treatment and then remain stable during prolonged use. Cessation of steroid treatment is associated with a rapid reversal of risk, even if steroids have been used continuously for over 6 months [[46](#_ENREF_46)]. The mechanisms responsible for the increased fracture risk in patients requiring steroid therapy are poorly understood: Whilst there is evidence for a reduction in BMD with steroid exposure, a meta-analysis of 42500 individuals from 8 different cohort studies suggested the increased fracture risk was independent of BMD [[47](#_ENREF_47)], and post-menopausal women treated with glucocorticoids sustain vertebral fractures at a higher BMD than do women who have not received steroids [[48](#_ENREF_48)]. Thus, other factors appear to contribute to the increased fracture risk, and bone quality might be important. Indeed, there is evidence that corticosteroid exposure reduces activity of osteoblasts and osteocytes, and stimulates osteoclastic bone resorption, with effects on the RANK/ RANKL pathway [[49](#_ENREF_49)]. Histomorphometric studies have identified a reduction in trabecular thickness and greater trabecular separation in women with glucocorticoid-induced osteoporosis compared to postmenopausal osteoporosis [[50](#_ENREF_50)]. Case-control and longitudinal studies using advanced micro-imaging techniques are now required to further understand such observations.

A number of other medications have also been linked to higher fracture risk, including proton pump inhibitors [[51](#_ENREF_51)], thiazolidinediones [[52](#_ENREF_52) [53](#_ENREF_53)], anti-depressants[[54](#_ENREF_54)], and anti-epileptic drugs [[55](#_ENREF_55)], with varying degrees of certainty in terms of causation and biological mechanism.

## Co-morbid medical conditions

Individual studies have examined particular comorbidities, and recent analysis of data from 60393 participants of the GLOW study, of whom 6.1% sustained a fracture over the two year follow-up period, demonstrated that a number of co-morbid medical conditions were associated with increased fracture incidence [[56](#_ENREF_56)]. This included cardiovascular disease, asthma, chronic obstructive pulmonary disease, osteoarthritis, rheumatoid arthritis, stroke, inflammatory bowel disease, Parkinson’s disease, multiple sclerosis and type 1 diabetes mellitus. In this study, hypertension and malignancy were not associated with an excess fracture risk [[56](#_ENREF_56)]. It is likely that the cause for the increased fracture incidence observed in these medical conditions is multifactorial, including steroid usage, low grade chronic inflammation, lifestyle factors, BMI, poor mobility and increased falls.

## Smoking and Alcohol Consumption

Smoking is a well-established risk factor for osteoporotic fracture. The risk is highest in current smokers, but remains elevated in those with a history of smoking compared to non-smokers [[57](#_ENREF_57)]. This is partly mediated through a negative association of smoking with BMD and through differences in BMI [[57](#_ENREF_57)]. High, but not moderate, alcohol consumption is also associated with increased fracture incidence [[58](#_ENREF_58)].

# D. Patient identification

Osteoporosis is a silent disease until a fracture occurs. Patient perception of fracture risk is often underestimated [[59](#_ENREF_59) [60](#_ENREF_60)], and therefore initiation of primary prevention is usually reliant on health care practitioners. It is unsurprising that secondary prevention, that is identifying individuals for treatment on the basis of a fracture occurring, is the approach most often taken as the starting point for fracture prevention.

*Approaches to secondary fracture prevention*

A detailed description of the various approaches to secondary fracture prevention is beyond the scope of this review, but the key issue is how to achieve risk stratification and treatment, if appropriate, following attendance with a new fragility fracture. Several methods have been explored, both staff and IT-based and the most successful systems usually focus on a multi-disciplinary Fracture Liaison Service[[61](#_ENREF_61)], incorporating orthogeriatricians who can ensure that medical management of orthopaedic patients is optimised, both whilst in hospital, and for future fracture prevention. The International Osteoporosis Foundation has recently instituted “a global campaign to facilitate the implementation of coordinated, multi-disciplinary models of care for secondary fracture prevention.”  (http://www.capturethefracture.org). The “Capture the Fracture” initiative has provided guidance on secondary fracture prevention, and also a global map, with a quality grading scheme, on which, subject to application, secondary fracture prevention services can be documented [[62](#_ENREF_62)]. There is currently huge variation, not only between, but also within countries, and in the availability, scope and quality of secondary prevention facilities. This kind of initiative, aimed at raising quality and population coverage, should provide a valuable contribution to service improvement.

*Approaches to primary fracture prevention*

In any non-communicable chronic disease such as osteoporosis there is clearly a balance between the benefits of widespread treatment, with associated increased cost and risk of side-effects consequent on a systematic screening approach, and the danger of under-treatment attendant on a case-finding strategy focused on those at greatest individual risk. Although in the US, DXA screening is standard at the age of 65 years, in the majority of countries, population screening is not judged to be cost-effective and primary prevention is focused more on opportunistic case-finding, triggered by the presence of clinical risk factors. Incentives for more systematic identification of those at highest risk, such as those generated by the UK Quality Outcome Framework, may also be used. Again, space does not permit a detailed overview of national approaches to primary prevention, but these policies are often readily available online (for example: US: <http://nof.org/files/nof/public/content/file/2237/upload/878.pdf>; UK: <http://guidance.nice.org.uk/CG146>) and as position papers[[63-65](#_ENREF_63)].

**Approaches to risk stratification**

## *i. BMD alone*

The traditional WHO definition of osteoporosis is based on a measurement of BMD, and there is evidence that fracture risk approximately doubles for every standard deviation decrease in BMD [[66](#_ENREF_66)]. However, over recent years, it has been increasingly recognised that low BMD should be viewed as a risk factor for fragility fracture rather than as a disease in itself. Furthermore, bone geometric and microarchitectural properties, which cannot be assessed by DXA, and other clinical risk factors, clearly contribute to fracture risk, effects that may be independent of DXA-derived BMD. A small proportion of the population is identified by a T-score of -2.5 or below, and in terms of total numbers, more fractures in later life may occur in individuals who have a BMD in the normal or osteopenic range. For example, Wainwright et al prospectively studied 8065 post-menopausal women in the USA. 243 women experienced a hip fracture over the 5 year study period, and only 46% of these women had an osteoporotic T-score at baseline screening [[67](#_ENREF_67)]. As such, if BMD alone is used to determine treatment thresholds, then many women at risk of fracture will not be offered intervention. Newer techniques including peripheral quantitative computed tomography and HR-pQCT can provide a more detailed assessment of bone structure, but their use in clinical practice is limited by availability of instruments, a lack of population-based reference data and, indeed, any convincing evidence of their superiority, in terms of risk stratification, over traditional densitometry.

## *ii. Fracture risk assessment tools encompassing BMD and clinical risk factors*

The use of clinical risk factors (CRFs) in addition to BMD measurement has been demonstrated to increase the accuracy of hip and major osteoporotic fracture risk assessment [[68](#_ENREF_68)]. As such, a number of tools have been developed to calculate an individual’s risk of fracture, either based on clinical risk factors alone, or in combination with BMD measurement. The three most widely used instruments are the WHO Fracture Risk Assessment Tool, FRAX® ([www.shef.ac.uk/FRAX](http://www.shef.ac.uk/FRAX)) [[69](#_ENREF_69)], Garvan Fracture Risk Calculator (www.garvan.org.au/bone-fracture-risk) and QFracture ([www.qfracture.org](http://www.qfracture.org)) [[70](#_ENREF_70)] (Table 1).

*iia. FRAX*®

The most comprehensively developed risk assessment tool is FRAX®, produced by the Centre for Metabolic Bone Diseases at the University of Sheffield [[69](#_ENREF_69)]. It estimates 10-year major osteoporotic (vertebral, hip, forearm and proximal humerus) and hip fracture probability, either with or without inclusion of BMD measurement. The CRFs were chosen on the basis of intuitive linkage to fracture risk and ready clinical availability following a series of meta-analyses of prospective cohort studies from Europe, North America, Asia and Australia including nearly 45000 individuals, and have subsequently been validated in other cohorts. A unique feature of the FRAX algorithm is the integration of risk of death with risk of fracture, to yield a 10-year probability of fracture, which incorporates not just fracture risk, but also the competing hazard of death. Fifty-eight population-specific FRAX calculators for use in fifty-three countries have since been developed to account for geographical variations in fracture incidence and mortality [[71](#_ENREF_71)]. Importantly an internet-based calculator (Figure 4) allows rapid use and implementation in the primary care setting, and models that do not require BMD assessment [[72](#_ENREF_72) [73](#_ENREF_73)] are likely to be helpful in identifying high-risk patients in low resource settings where availability of DXA is limited. Recent data suggest that in 2013 nearly 2.4million FRAX calculations were performed in 173 different countries [[71](#_ENREF_71)].

As with all risk assessment tools, it is clear that not all CRFs for osteoporotic fracture are included in the FRAX algorithm (this being limited by which data were available globally in population-based cohorts), and many of the included CRFs have a dose-response element that is not incorporated into the algorithm. For example, only current smoking is considered, whereas a past history of smoking also increases fracture risk above that of a lifetime non-smoker [[57](#_ENREF_57)], and the calculator assumes an average daily consumption for all current smokers. Similarly, details of glucocorticoid exposure (e.g. dose, duration) were not available in the original FRAX cohorts so that the relationship again assumes an average exposure; this will lead to an underestimation of fracture risk for recipients of higher daily doses of steroids, and overestimation for low daily doses [[45](#_ENREF_45)]. Based on the assumption that the average exposure in the FRAX cohorts probably lay within the range of 2-5-7.5mg daily, an adjustment to the calculated fracture risk has been proposed based on the relative fracture risks according to steroid dose, as shown in table 2 [[74](#_ENREF_74)][[75](#_ENREF_75)], and a recent paper has described how to use FRAX optimally in clinical practice, incorporating methods to interpret the output where dose response considerations are present [[76](#_ENREF_76)]. Furthermore, although like all risk assessment tools FRAX has not been validated in patients who have received anti-osteoporotic treatment, there is some evidence that it may still provide a useful guide in terms of continuation or cessation of therapy [[77](#_ENREF_77)].

*iib: Garvan Fracture Risk Calculator and QFracture*

The Garvan Fracture Risk Calculator and QFracture provide country specific (Australia and UK) alternatives to FRAX. It is important to understand that there are fundamental differences in these algorithms, and that resulting absolute fracture risks/ probabilities, even over the same time span of 10 years, will differ and thus necessitate the derivation of tool-specific intervention thresholds. The Garvan calculator was derived using the Australian Dubbo cohort of around 2000 individuals and includes men and women [[78](#_ENREF_78)]. It yields absolute fracture risk as a percentage over 5 or 10 years for osteoporotic fracture or hip fracture, based on age, sex, prior fracture, falls and bone mineral density. A 5-year fracture risk may be felt to be useful at older ages, and like QFracture, this algorithm does not incorporate the competing hazard of death. This approach has been used in other cohorts, although it lacks the wider generalizability and local calibration of the FRAX calculator. QFracture takes a different approach, with a statistically driven identification of multiple clinical risk factors (30 in total, and including falls), which are ostensibly readily available from the General Practice record [[70](#_ENREF_70) [79](#_ENREF_79)]. Although the first version of QFracture was validated in an independent UK cohort [[79](#_ENREF_79)], the second version, (which now includes prior fracture) has only been tested and validated in random subsets of the same overall cohort [[70](#_ENREF_70) [80](#_ENREF_80)]. A further consideration is the definition of osteoporotic fracture, which differs from that employed by FRAX (with the definition in the Garvan calculator differing again), meaning that the 10-year fracture risk percentage may differ markedly between the three calculators. Overall, Garvan and QFracture risk calculators may find most favour with those managing the oldest old, where clinicians may have a preference for inclusion of falls as a risk factor (although falling does not directly identify a risk amenable to pharmacologic treatment), and estimation of risk over shorter time periods may be felt to be an advantage (the inclusion of the death hazard in FRAX also addresses this issue). However, the limitations of both QFracture and the Garvan calculator in relation to generalizability, death hazard and national treatment thresholds must be considered when used more generally in clinical practice.

## *iii. Intervention thresholds*

It is important to appreciate that a high fracture probability is not a diagnosis of future fracture: If an individual with a high fracture probability does not sustain a broken bone, it is thus not necessarily due to failure of the prediction model. Similarly, a proportion of individuals predicted to be at low probability will still experience an incident fracture. Furthermore, neither FRAX itself, nor the Garvan calculator or QFracture, inform treatment decisions by themselves. The threshold risk/ probability at which treatment may be given to reduce the risk of future fracture will depend on many considerations, not just at the level of the individual, but critically in terms of cost-benefit and how much an individual country is prepared to pay for each year of quality adjusted life saved.

There are a number of country-specific treatment threshold guidelines available, many of which advocate the use of fracture prediction models (usually FRAX) for case-finding approaches [[81](#_ENREF_81)]. Even between the USA and UK guidance, there is marked heterogeneity. The National Osteoporosis Foundation in the USA suggests BMD assessment for women over 65 years and men over 70 years, in addition to younger post-menopausal women at sufficiently high risk based on CRFs. Treatment is recommended for those with a history of vertebral or hip fracture, osteoporosis on BMD assessment, or osteopenia and a 10-year FRAX-calculated probability of a hip fracture >3% or major osteoporotic fracture >20% [[82](#_ENREF_82)]. Conversely, the UK National Osteoporosis Guideline Group (NOGG) recommends the use of FRAX as the first step in risk assessment, with prior fragility fracture usually a sufficient basis for treatment regardless of other risk factors. Where a 10-year probability has been generated by FRAX, threshold graphs are subsequently used to guide appropriate intervention: patient reassurance with further risk calculation at a later date (low risk), BMD assessment (intermediate risk), or immediate treatment without the need for BMD assessment (high risk) (Figure 4B) [[83](#_ENREF_83)]. Once BMD has been performed, the 10-year probability of fracture is plotted by age, either above or below a single treatment threshold, which is set at the 10-year fracture probability conferred by having had a previous fragility fracture, corresponding to older UK national guidance. The treatment threshold thus increases with age, but even so, the proportion of women potentially eligible for treatment rises from 20% to 40% across the age range assessed. Differences in access to health care, cost of medications, willingness to pay for quality adjusted life years saved, fracture epidemiology, other disease burdens, and the implications of fracture at the individual and societal level within different countries will reflect the threshold and overall strategy employed, and direct translation of an approach from one country to another may well not be appropriate. Recognising this, the International Osteoporosis Foundation has published guidance relating to osteoporosis and corticosteroid-induced osteoporosis, which can be readily modified to reflect national priorities and subsequent treatment thresholds[[63-65](#_ENREF_63)].

At present, there have been few randomised controlled trials (RCT) to investigate the efficacy and cost-effectiveness of fracture prediction algorithms. However, a trial of clodronate compared to placebo for fracture prevention in post-menopausal women, demonstrated that clodronate was effective at reducing fracture incidence in women with a high fracture risk assessed by FRAX without BMD measurement [[84](#_ENREF_84)], therefore supporting the NOGG guideline than BMD measurement is not necessary for patients characterised as high risk by FRAX. Similarly, greater fracture reduction with denosumab was demonstrated in osteoporotic women with a moderate to high fracture risk assessed by FRAX [[85](#_ENREF_85)], but there is heterogeneity across therapies as a whole [[86](#_ENREF_86)]. The SCOOP (Screening of Older Women for Prevention of Fracture) study has been designed to assess the effectiveness and cost effectiveness of community based screening using FRAX to reduce fracture incidence [[87](#_ENREF_87)]. This multicentre study in the UK has recruited over 11000 women aged 70 to 85 years. Women randomised to the intervention arm had their 10-year fracture probability assessed by FRAX. Those deemed to be above an age-dependent threshold had an assessment of BMD by DXA, and the fracture probability recalculated by FRAX. Women who had a probability above a treatment threshold were subsequently advised to discuss their treatment options with the general practitioner. The control group received usual primary health care. Both groups are being followed-up for 5 years for incident fracture, and an early qualitative study in this trial population demonstrated that these screening approaches are acceptable to patients and general practitioners [[88](#_ENREF_88)].

# E. Summary

Osteoporosis and associated fragility fracture are globally common conditions, and contribute significantly to morbidity, mortality and healthcare spending. Although there is some evidence for a plateauing of fracture incidence in the developed world, an aging population and adoption of westernised lifestyles in transitioning populations will lead to an increasing burden of osteoporosis globally. The clinical definition of osteoporosis has been based solely on BMD, but the prediction of fracture at the individual level has been improved by incorporation of clinical risk factors, derived from a greater understanding of the epidemiology of osteoporosis. Although fracture prediction tools are now available, which can be used to stratify risk and guide treatment, studies are required to demonstrate cost-effectiveness and clinical efficacy of these approaches.

**Practice Points**

* Osteoporosis has been defined as a T-score of <-2.5 at the femoral neck, but this definition does not encompass other determinants of fracture risk including bone quality and clinical risk factors.
* Female sex, older age, white ethnicity, smoking, high alcohol consumption, steroid exposure, past fracture, and a family history of osteoporotic fracture are all risk factors for future fracture.
* The use of clinical risk factors in addition to BMD can improve fracture prediction.
* A number of fracture probability tools have been developed to encompass clinical risk factors and BMD in stratifying fracture risk, with FRAX® the most widely validated and utilized.
* A high fracture risk does not equate to a definite fracture, and some individuals with a low fracture probability will also sustain fractures.

**Research agenda**

* The burden of fragility fracture, and associated secular trends, in the developing world, particularly in African and South American countries, is yet to be fully described.
* Future work needs to elucidate the impact of clinical risk factors, for example smoking and alcohol consumption, on bone microarchitecture and quality.
* The use of fracture probability tools for case identification and/or treatment stratification needs to be examined in randomised controlled trials.

**Figure 1**: Hip fracture rates for men and women combined in different countries of the world categorised by risk. Where estimates are available, countries are colour coded red (annual incidence >250/100,000), orange (150–250/100,000) or green (<150/100,000). Reprinted from Kanis et al., Osteoporosis International 2012 [[3](#_ENREF_3)]. With permission from Springer Science and Business Media.

**Figure 2**: Secular trends in hip fracture incidence. Reprinted from Cooper C et al., Osteoporosis International 2011 [[6](#_ENREF_6)]. With permission from Springer Science and Business Media.

**Figure 3:** Hip, wrist and radiographic vertebral fracture incidence by age and gender.Reprinted from The Lancet, Vol 367 (9527), P Sambrook & C Cooper, Osteoporosis, Pages 2010-18., Copyright 2011, with permission from Elsevier [[20](#_ENREF_20)].

**Figure 4: (A)** A screen shot from the FRAX® calculator website ([www.shef.ac.uk/FRAX](http://www.shef.ac.uk/FRAX)). Data from a hypothetical female patient, aged 72 with a history of current steroid exposure and a parental history of fracture, in whom BMD assessment has not been performed, has been entered into the calculator. This patient has a 10-year probability of major osteoporotic fracture and hip fracture of 25% and 12%, respectively. **(B)** The UK FRAX® calculator provides a link to the National Osteoporosis Guideline Group (NOGG) treatment threshold graphs, which can be used by health care practitioners to guide treatment decisions. Based on the same patient, these graphs recommend assessment of BMD by DXA, unless the patient was receiving >7.5mg prednisolone per day, when treatment without BMD assessment would be recommended.

**Table 1**: Comparison of fracture probability calculators.

**Table 2**: Percentage adjustment of 10 year probabilities of a hip fracture or a major osteoporotic fracture by age according to dose of glucocorticoids. Reproduced with permission from Kanis et al., Osteoporosis Int 2011 [[75](#_ENREF_75)]. With permission from Springer Science and Business Media.

1. Consensus development conference: diagnosis, prophylaxis, and treatment of osteoporosis. Am J Med 1993;**94**(6):646-50

2. Hernlund E, Svedbom A, Ivergard M, et al. Osteoporosis in the European Union: medical management, epidemiology and economic burden : A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Archives of osteoporosis 2013;**8**(1-2):136 doi: 10.1007/s11657-013-0136-1[published Online First: Epub Date]|.

3. Kanis JA, Oden A, McCloskey EV, et al. A systematic review of hip fracture incidence and probability of fracture worldwide. Osteoporos Int 2012;**23**(9):2239-56 doi: 10.1007/s00198-012-1964-3[published Online First: Epub Date]|.

4. Litwic A, Edwards M, Cooper C, et al. Geographic differences in fractures among women. Women's health (London, England) 2012;**8**(6):673-84 doi: 10.2217/whe.12.54[published Online First: Epub Date]|.

5. Cooper C, Campion G, Melton LJ, 3rd. Hip fractures in the elderly: a world-wide projection. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 1992;**2**(6):285-9

6. Cooper C, Cole ZA, Holroyd CR, et al. Secular trends in the incidence of hip and other osteoporotic fractures. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 2011;**22**(5):1277-88 doi: 10.1007/s00198-011-1601-6[published Online First: Epub Date]|.

7. Morin SN, Lix LM, Majumdar SR, et al. Temporal Trends in the Incidence of Osteoporotic Fractures. Current osteoporosis reports 2013 doi: 10.1007/s11914-013-0168-x[published Online First: Epub Date]|.

8. Bliuc D, Nguyen ND, Milch VE, et al. Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. JAMA 2009;**301**(5):513-21

9. Haentjens P, Magaziner J, Colon-Emeric CS, et al. Meta-analysis: excess mortality after hip fracture among older women and men. Annals of internal medicine 2010;**152**(6):380-90 doi: 10.7326/0003-4819-152-6-201003160-00008[published Online First: Epub Date]|.

10. Abrahamsen B, van Staa T, Ariely R, et al. Excess mortality following hip fracture: a systematic epidemiological review. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 2009;**20**(10):1633-50 doi: 10.1007/s00198-009-0920-3[published Online First: Epub Date]|.

11. Wehren LE, Hawkes WG, Orwig DL, et al. Gender differences in mortality after hip fracture: the role of infection. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2003;**18**(12):2231-7 doi: 10.1359/jbmr.2003.18.12.2231[published Online First: Epub Date]|.

12. Roche JJ, Wenn RT, Sahota O, et al. Effect of comorbidities and postoperative complications on mortality after hip fracture in elderly people: prospective observational cohort study. Bmj 2005;**331**(7529):1374 doi: 10.1136/bmj.38643.663843.55[published Online First: Epub Date]|.

13. Adachi JD, Adami S, Gehlbach S, et al. Impact of prevalent fractures on quality of life: baseline results from the global longitudinal study of osteoporosis in women. Mayo Clinic proceedings. Mayo Clinic 2010;**85**(9):806-13 doi: 10.4065/mcp.2010.0082[published Online First: Epub Date]|.

14. Kim SM, Moon YW, Lim SJ, et al. Prediction of survival, second fracture, and functional recovery following the first hip fracture surgery in elderly patients. Bone 2012;**50**(6):1343-50 doi: 10.1016/j.bone.2012.02.633[published Online First: Epub Date]|.

15. Leibson CL, Tosteson AN, Gabriel SE, et al. Mortality, disability, and nursing home use for persons with and without hip fracture: a population-based study. Journal of the American Geriatrics Society 2002;**50**(10):1644-50

16. Kanis JA, Johnell O, De Laet C, et al. A meta-analysis of previous fracture and subsequent fracture risk. Bone 2004;**35**(2):375-82 doi: 10.1016/j.bone.2004.03.024[published Online First: Epub Date]|.

17. Klotzbuecher CM, Ross PD, Landsman PB, et al. Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2000;**15**(4):721-39 doi: 10.1359/jbmr.2000.15.4.721[published Online First: Epub Date]|.

18. Gehlbach S, Saag KG, Adachi JD, et al. Previous fractures at multiple sites increase the risk for subsequent fractures: the Global Longitudinal Study of Osteoporosis in Women. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2012;**27**(3):645-53 doi: 10.1002/jbmr.1476[published Online First: Epub Date]|.

19. Costa AG, Wyman A, Siris ES, et al. When, Where and How Osteoporosis-Associated Fractures Occur: An Analysis from the Global Longitudinal Study of Osteoporosis in Women (GLOW). PloS one 2013;**8**(12):e83306 doi: 10.1371/journal.pone.0083306[published Online First: Epub Date]|.

20. Sambrook P, Cooper C. Osteoporosis. Lancet 2006;**367**(9527):2010-8 doi: 10.1016/s0140-6736(06)68891-0[published Online First: Epub Date]|.

21. Cooper C, Dennison EM, Leufkens HG, et al. Epidemiology of childhood fractures in Britain: a study using the general practice research database. J.Bone Miner.Res. 2004;**19**(12):1976-81 doi: 10.1359/JBMR.040902 [doi][published Online First: Epub Date]|.

22. van Staa TP, Dennison EM, Leufkens HG, et al. Epidemiology of fractures in England and Wales. Bone 2001;**29**(6):517-22

23. Hansen S, Shanbhogue V, Folkestad L, et al. Bone Microarchitecture and Estimated Strength in 499 Adult Danish Women and Men: A Cross-Sectional, Population-Based High-Resolution Peripheral Quantitative Computed Tomographic Study on Peak Bone Structure. Calcified tissue international 2013 doi: 10.1007/s00223-013-9808-5[published Online First: Epub Date]|.

24. Macdonald HM, Nishiyama KK, Kang J, et al. Age-related patterns of trabecular and cortical bone loss differ between sexes and skeletal sites: a population-based HR-pQCT study. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2011;**26**(1):50-62 doi: 10.1002/jbmr.171[published Online First: Epub Date]|.

25. Seeman E. Bone quality: the material and structural basis of bone strength. Journal of bone and mineral metabolism 2008;**26**(1):1-8 doi: 10.1007/s00774-007-0793-5[published Online First: Epub Date]|.

26. Zebaze RM, Ghasem-Zadeh A, Bohte A, et al. Intracortical remodelling and porosity in the distal radius and post-mortem femurs of women: a cross-sectional study. Lancet 2010;**375**(9727):1729-36 doi: 10.1016/s0140-6736(10)60320-0[published Online First: Epub Date]|.

27. Svejme O, Ahlborg HG, Nilsson JA, et al. Early menopause and risk of osteoporosis, fracture and mortality: a 34-year prospective observational study in 390 women. BJOG : an international journal of obstetrics and gynaecology 2012;**119**(7):810-6 doi: 10.1111/j.1471-0528.2012.03324.x[published Online First: Epub Date]|.

28. Stenhagen M, Ekstrom H, Nordell E, et al. Falls in the general elderly population: a 3- and 6- year prospective study of risk factors using data from the longitudinal population study 'Good ageing in Skane'. BMC geriatrics 2013;**13**:81 doi: 10.1186/1471-2318-13-81[published Online First: Epub Date]|.

29. Wright NC, Saag KG, Curtis JR, et al. Recent trends in hip fracture rates by race/ethnicity among older US adults. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2012;**27**(11):2325-32 doi: 10.1002/jbmr.1684[published Online First: Epub Date]|.

30. Looker AC, Melton LJ, 3rd, Harris TB, et al. Prevalence and trends in low femur bone density among older US adults: NHANES 2005-2006 compared with NHANES III. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2010;**25**(1):64-71 doi: 10.1359/jbmr.090706[published Online First: Epub Date]|.

31. Putman MS, Yu EW, Lee H, et al. Differences in skeletal microarchitecture and strength in African-American and white women. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2013;**28**(10):2177-85 doi: 10.1002/jbmr.1953[published Online First: Epub Date]|.

32. Benetou V, Orfanos P, Benetos IS, et al. Anthropometry, physical activity and hip fractures in the elderly. Injury 2011;**42**(2):188-93 doi: 10.1016/j.injury.2010.08.022[published Online First: Epub Date]|.

33. De Laet C, Kanis JA, Oden A, et al. Body mass index as a predictor of fracture risk: a meta-analysis. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 2005;**16**(11):1330-8 doi: 10.1007/s00198-005-1863-y[published Online First: Epub Date]|.

34. Johansson H, Kanis JA, Oden A, et al. A meta-analysis of the association of fracture risk and body mass index in women. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2014;**29**(1):223-33 doi: 10.1002/jbmr.2017[published Online First: Epub Date]|.

35. Compston JE, Watts NB, Chapurlat R, et al. Obesity is not protective against fracture in postmenopausal women: GLOW. The American journal of medicine 2011;**124**(11):1043-50 doi: 10.1016/j.amjmed.2011.06.013[published Online First: Epub Date]|.

36. Cummings SR, Nevitt MC, Browner WS, et al. Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. The New England journal of medicine 1995;**332**(12):767-73 doi: 10.1056/nejm199503233321202[published Online First: Epub Date]|.

37. Slemenda CW, Christian JC, Williams CJ, et al. Genetic determinants of bone mass in adult women: a reevaluation of the twin model and the potential importance of gene interaction on heritability estimates. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 1991;**6**(6):561-7 doi: 10.1002/jbmr.5650060606[published Online First: Epub Date]|.

38. Pocock NA, Eisman JA, Hopper JL, et al. Genetic determinants of bone mass in adults. A twin study. The Journal of clinical investigation 1987;**80**(3):706-10 doi: 10.1172/jci113125[published Online First: Epub Date]|.

39. Dennison EM, Arden NK, Keen RW, et al. Birthweight, vitamin D receptor genotype and the programming of osteoporosis. Paediatric and perinatal epidemiology 2001;**15**(3):211-9

40. Ferrari SL, Karasik D, Liu J, et al. Interactions of interleukin-6 promoter polymorphisms with dietary and lifestyle factors and their association with bone mass in men and women from the Framingham Osteoporosis Study. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2004;**19**(4):552-9 doi: 10.1359/jbmr.040103[published Online First: Epub Date]|.

41. Antoniades L, MacGregor AJ, Andrew T, et al. Association of birth weight with osteoporosis and osteoarthritis in adult twins. Rheumatology (Oxford) JID - 100883501 2003;**42**(6):791-96

42. Frost M, Petersen I, Andersen TL, et al. Birth weight and adult bone metabolism are unrelated: results from birth weight-discordant monozygotic twins. J Bone Miner Res 2013;**28**(12):2561-9 doi: 10.1002/jbmr.1995[published Online First: Epub Date]|.

43. Holroyd C, Harvey N, Dennison E, et al. Epigenetic influences in the developmental origins of osteoporosis. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 2012;**23**(2):401-10 doi: 10.1007/s00198-011-1671-5[published Online First: Epub Date]|.

44. Steinbuch M, Youket T, Cohen S. Oral glucocorticoid use is associated with an increased risk of fracture. Osteoporosis International 2004;**15**(4):323-28 doi: 10.1007/s00198-003-1548-3[published Online First: Epub Date]|.

45. van Staa TP, Leufkens HG, Abenhaim L, et al. Oral corticosteroids and fracture risk: relationship to daily and cumulative doses. Rheumatology (Oxford, England) 2000;**39**(12):1383-9

46. Van Staa TP, Leufkens HG, Abenhaim L, et al. Use of oral corticosteroids and risk of fractures. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2000;**15**(6):993-1000 doi: 10.1359/jbmr.2000.15.6.993[published Online First: Epub Date]|.

47. Kanis JA, Johansson H, Oden A, et al. A meta-analysis of prior corticosteroid use and fracture risk. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2004;**19**(6):893-9 doi: 10.1359/jbmr.040134[published Online First: Epub Date]|.

48. Van Staa TP, Laan RF, Barton IP, et al. Bone density threshold and other predictors of vertebral fracture in patients receiving oral glucocorticoid therapy. Arthritis and rheumatism 2003;**48**(11):3224-9 doi: 10.1002/art.11283[published Online First: Epub Date]|.

49. Manolagas SC. Steroids and osteoporosis: the quest for mechanisms. J Clin Invest 2013;**123**(5):1919-21 doi: 10.1172/jci68062[published Online First: Epub Date]|.

50. Dalle Carbonare L, Arlot ME, Chavassieux PM, et al. Comparison of trabecular bone microarchitecture and remodeling in glucocorticoid-induced and postmenopausal osteoporosis. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2001;**16**(1):97-103 doi: 10.1359/jbmr.2001.16.1.97[published Online First: Epub Date]|.

51. Khalili H, Huang ES, Jacobson BC, et al. Use of proton pump inhibitors and risk of hip fracture in relation to dietary and lifestyle factors: a prospective cohort study. Bmj 2012;**344**:e372 doi: 10.1136/bmj.e372[published Online First: Epub Date]|.

52. Bazelier MT, de Vries F, Vestergaard P, et al. Risk of fracture with thiazolidinediones: an individual patient data meta-analysis. Frontiers in endocrinology 2013;**4**:11 doi: 10.3389/fendo.2013.00011[published Online First: Epub Date]|.

53. Loke YK, Singh S, Furberg CD. Long-term use of thiazolidinediones and fractures in type 2 diabetes: a meta-analysis. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 2009;**180**(1):32-9 doi: 10.1503/cmaj.080486[published Online First: Epub Date]|.

54. Rizzoli R, Cooper C, Reginster JY, et al. Antidepressant medications and osteoporosis. Bone 2012;**51**(3):606-13 doi: 10.1016/j.bone.2012.05.018[published Online First: Epub Date]|.

55. Nicholas JM, Ridsdale L, Richardson MP, et al. Fracture risk with use of liver enzyme inducing antiepileptic drugs in people with active epilepsy: cohort study using the general practice research database. Seizure : the journal of the British Epilepsy Association 2013;**22**(1):37-42 doi: 10.1016/j.seizure.2012.10.002[published Online First: Epub Date]|.

56. Dennison EM, Compston JE, Flahive J, et al. Effect of co-morbidities on fracture risk: findings from the Global Longitudinal Study of Osteoporosis in Women (GLOW). Bone 2012;**50**(6):1288-93 doi: 10.1016/j.bone.2012.02.639[published Online First: Epub Date]|.

57. Kanis JA, Johnell O, Oden A, et al. Smoking and fracture risk: a meta-analysis. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 2005;**16**(2):155-62 doi: 10.1007/s00198-004-1640-3[published Online First: Epub Date]|.

58. Kanis JA, Johansson H, Johnell O, et al. Alcohol intake as a risk factor for fracture. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 2005;**16**(7):737-42 doi: 10.1007/s00198-004-1734-y[published Online First: Epub Date]|.

59. Grover ML, Edwards FD, Chang YH, et al. Fracture risk perception study: patient self-perceptions of bone health often disagree with calculated fracture risk. Women's health issues : official publication of the Jacobs Institute of Women's Health 2014;**24**(1):e69-75 doi: 10.1016/j.whi.2013.11.007[published Online First: Epub Date]|.

60. Gregson CL, Dennison EM, Compston JE, et al. Disease-specific perception of fracture risk and incident fracture rates: GLOW cohort study. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 2014;**25**(1):85-95 doi: 10.1007/s00198-013-2438-y[published Online First: Epub Date]|.

61. Eisman JA, Bogoch ER, Dell R, et al. Making the first fracture the last fracture: ASBMR task force report on secondary fracture prevention. J Bone Miner Res 2012;**27**(10):2039-46 doi: 10.1002/jbmr.1698[published Online First: Epub Date]|.

62. Akesson K, Marsh D, Mitchell PJ, et al. Capture the Fracture: a Best Practice Framework and global campaign to break the fragility fracture cycle. Osteoporos Int 2013;**24**(8):2135-52 doi: 10.1007/s00198-013-2348-z[published Online First: Epub Date]|.

63. Kanis JA, McCloskey EV, Johansson H, et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int 2013;**24**(1):23-57 doi: 10.1007/s00198-012-2074-y[published Online First: Epub Date]|.

64. Lekamwasam S, Adachi JD, Agnusdei D, et al. A framework for the development of guidelines for the management of glucocorticoid-induced osteoporosis. Osteoporos Int 2012;**23**(9):2257-76 doi: 10.1007/s00198-012-1958-1[published Online First: Epub Date]|.

65. Lekamwasam S, Adachi JD, Agnusdei D, et al. An appendix to the 2012 IOF-ECTS guidelines for the management of glucocorticoid-induced osteoporosis. Archives of osteoporosis 2012;**7**(1-2):25-30 doi: 10.1007/s11657-012-0070-7[published Online First: Epub Date]|.

66. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ 1996;**312**(7041):1254-59

67. Wainwright SA, Marshall LM, Ensrud KE, et al. Hip fracture in women without osteoporosis. The Journal of clinical endocrinology and metabolism 2005;**90**(5):2787-93 doi: 10.1210/jc.2004-1568[published Online First: Epub Date]|.

68. Kanis JA, Oden A, Johnell O, et al. The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women. Osteoporos Int 2007;**18**(8):1033-46 doi: 10.1007/s00198-007-0343-y[published Online First: Epub Date]|.

69. Kanis JA, Johnell O, Oden A, et al. FRAX and the assessment of fracture probability in men and women from the UK. Osteoporos Int 2008;**19**(4):385-97 doi: 10.1007/s00198-007-0543-5[published Online First: Epub Date]|.

70. Hippisley-Cox J, Coupland C. Derivation and validation of updated QFracture algorithm to predict risk of osteoporotic fracture in primary care in the United Kingdom: prospective open cohort study. Bmj 2012;**344**:e3427 doi: 10.1136/bmj.e3427[published Online First: Epub Date]|.

71. Kanis JA, Johansson H, Oden A, et al. Worldwide uptake of FRAX. Archives of osteoporosis 2014;**9**(1):166 doi: 10.1007/s11657-013-0166-8[published Online First: Epub Date]|.

72. Leslie WD, Morin S, Lix LM, et al. Fracture risk assessment without bone density measurement in routine clinical practice. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 2012;**23**(1):75-85 doi: 10.1007/s00198-011-1747-2[published Online First: Epub Date]|.

73. Olmez Sarikaya N, Kapar Yavasi S, Tan G, et al. Agreement between FRAX scores calculated with and without bone mineral density in women with osteopenia in Turkey. Clinical rheumatology 2014 doi: 10.1007/s10067-014-2491-8[published Online First: Epub Date]|.

74. van Staa TP, Leufkens HG, Abenhaim L, et al. Use of oral corticosteroids and risk of fractures. J Bone Miner Res JID - 8610640 2000;**15**(6):993-1000

75. Kanis JA, Johansson H, Oden A, et al. Guidance for the adjustment of FRAX according to the dose of glucocorticoids. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 2011;**22**(3):809-16 doi: 10.1007/s00198-010-1524-7[published Online First: Epub Date]|.

76. Kanis JA, Hans D, Cooper C, et al. Interpretation and use of FRAX in clinical practice. Osteoporos.Int. 2011;**22**(9):2395-411

77. Leslie WD, Lix LM, Johansson H, et al. Does osteoporosis therapy invalidate FRAX for fracture prediction? J Bone Miner Res 2012;**27**(6):1243-51 doi: 10.1002/jbmr.1582[published Online First: Epub Date]|.

78. Nguyen ND, Frost SA, Center JR, et al. Development of prognostic nomograms for individualizing 5-year and 10-year fracture risks. Osteoporos Int 2008;**19**(10):1431-44 doi: 10.1007/s00198-008-0588-0[published Online First: Epub Date]|.

79. Hippisley-Cox J, Coupland C. Predicting risk of osteoporotic fracture in men and women in England and Wales: prospective derivation and validation of QFractureScores. BMJ 2009;**339**:b4229

80. Cooper C, Harvey NC. Osteoporosis risk assessment. BMJ 2012;**344**:e4191 doi: 10.1136/bmj.e4191[published Online First: Epub Date]|.

81. Leslie WD, Schousboe JT. A review of osteoporosis diagnosis and treatment options in new and recently updated guidelines on case finding around the world. Current osteoporosis reports 2011;**9**(3):129-40 doi: 10.1007/s11914-011-0060-5[published Online First: Epub Date]|.

82. National Osteoporosis Foundation. Clinician's Guide to the Prevention and Treatment of Osteoporosis. Washington DC: National Osteoporosis Foundation, 2013.

83. Compston J, Bowring C, Cooper A, et al. Diagnosis and management of osteoporosis in postmenopausal women and older men in the UK: National Osteoporosis Guideline Group (NOGG) update 2013. Maturitas 2013 doi: 10.1016/j.maturitas.2013.05.013[published Online First: Epub Date]|.

84. McCloskey EV, Johansson H, Oden A, et al. Ten-year fracture probability identifies women who will benefit from clodronate therapy--additional results from a double-blind, placebo-controlled randomised study. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 2009;**20**(5):811-7 doi: 10.1007/s00198-008-0786-9[published Online First: Epub Date]|.

85. McCloskey EV, Johansson H, Oden A, et al. Denosumab reduces the risk of osteoporotic fractures in postmenopausal women, particularly in those with moderate to high fracture risk as assessed with FRAX. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2012;**27**(7):1480-6 doi: 10.1002/jbmr.1606[published Online First: Epub Date]|.

86. Fiore CE, Gaudio A. When the FRAX((R)) test is applied to controlled clinical trials. Clinical cases in mineral and bone metabolism : the official journal of the Italian Society of Osteoporosis, Mineral Metabolism, and Skeletal Diseases 2012;**9**(3):135-7

87. Shepstone L, Fordham R, Lenaghan E, et al. A pragmatic randomised controlled trial of the effectiveness and cost-effectiveness of screening older women for the prevention of fractures: rationale, design and methods for the SCOOP study. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 2012;**23**(10):2507-15 doi: 10.1007/s00198-011-1876-7[published Online First: Epub Date]|.

88. Emmett CL, Redmond NM, Peters TJ, et al. Acceptability of screening to prevent osteoporotic fractures: a qualitative study with older women. Family practice 2012;**29**(2):235-42 doi: 10.1093/fampra/cmr069[published Online First: Epub Date]|.