

Development and use of FRAX® in osteoporosis

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Abstract This paper reviews briefly the development and clinical use of FRAX® in the development of assessment guidelines for osteoporosis.

Fractures are the clinical consequence of osteoporosis and are a major cause of morbidity and mortality worldwide. Several treatments are available that have been shown to decrease the risk of fracture, but problems arise in identifying individuals at high fracture risk so that treatments can be effectively targeted. Case finding can be enhanced by the consideration of clinical risk factors that provide information on fracture risk over and above that provided by bone mineral density measurements. The FRAX tool integrates information on fracture risk from clinical risk factors with or without the use of BMD and can be used to improve the targeting of individuals at high fracture risk.

Keywords Case finding · Clinical guidelines · Fracture probability · FRAX · Intervention threshold

Introduction

Fractures due to osteoporosis are an important cause of mortality and morbidity in the Western world [1]. Common

sites of fracture are the hip, spine, distal forearm and proximal humerus. In Sweden, the remaining lifetime risk of a fracture at one of these sites at the age of 50 years is 22% and 46% in men and women, respectively [2], which is similar to that for coronary heart disease. Osteoporotic fractures are also major contributors to a loss of independence in older individuals [1, 3].

A wide variety of agents is available for the treatment of osteoporosis. Many have been shown to decrease the risk of vertebral fracture in well-designed prospective controlled studies. Some have been shown to also reduce the risk of non-vertebral fractures, in some cases specifically at the hip [4, 5]. The application of these treatments is however more problematic. There is no international consensus on who to treat. The problems arise because osteoporosis (a T-score of -2.5 SD or less) has a quite different clinical significance in different regions of the world, given the marked heterogeneity in fracture risk worldwide that is largely independent of variations in bone mineral density (BMD) [1]. The problem is compounded by differing clinical practices, the availability of BMD machines, and willingness to pay for health care [1]. Thus, health care policies need to take account of local health care priorities, which will differ in different regions of the world.

Case-finding algorithms are available in many countries [1] but, for the reasons given above, differ markedly in approach. Recent developments in fracture risk assessment include the availability of the FRAX® tool that integrates the weight of clinical risk factors for fracture risk with or without information on BMD and computes the 10-year probability of fracture. The tool provides new opportunities to improve management but requires a reappraisal of clinical guidelines. This review discusses the development of the FRAX tool and the manner in which it is being applied to clinical guidelines.

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Assessment of fracture risk

Although bone mass is an important component of the risk of fracture, other abnormalities in the skeleton contribute to fragility. In addition, a variety of non-skeletal factors, such as the liability to fall and force of impact, contribute to fracture risk. Since BMD forms but one component of fracture risk, accurate assessment of fracture risk should ideally take into account other readily measured indices of fracture risk that add information to that provided by BMD [6].

The performance characteristics of the test are improved by the concurrent consideration of risk factors that operate independently of BMD. A good example is age. The same T-score with the same technique at any one site has a different significance at different ages. For any given BMD, fracture risk is much higher in the elderly than in the young [7]. In other words, age contributes to risk independently of BMD. At the threshold for osteoporosis (T-score = -2.5 SD), the probability of hip fracture ranges from 1.4% to 10.5% in men and women from Sweden depending on age [8]. Thus, the consideration of both age and BMD together permits risk to be stratified more accurately.

There are, however, additional risk factors identified [9] that provide information on fracture risk independently of both age and BMD. These are summarised below in Table 1.

In the following papers of this supplement, the authors will present the importance of several risk parameters:

- Age, as discussed above
- Severity of the disease, taking into account the level of BMD and previous fragility fractures
- Other risk factors for fracture demonstrated in clinical trials

Fracture probability

The absolute risk of fracture depends upon age and life expectancy as well as the current relative risk. The IOF and the WHO recommend that risk of fracture should be expressed as a short-term absolute risk, i.e., probability over a 10-year interval [10]. Probability estimates standardise the output from the multiple techniques and sites used for assessment and incorporate the additional information derived from age and the clinical risk factors.

Algorithms that integrate the weight of clinical risk factors for fracture risk with or without information on BMD have been developed by the WHO Collaborating Centre for Metabolic Bone Diseases at Sheffield, UK. The algorithm is based on a series of meta-analyses [9, 11–16] using information derived from the primary data of nine population based cohorts from around the world, includ-

Table 1 Clinical risk factors used for opportunistic case finding [1]^a

Age
Sex
Low body mass index
Previous fragility fracture, particularly of the hip, wrist and spine including morphometric vertebral fracture
Parental history of hip fracture
Glucocorticoid treatment (>5 mg prednisolone daily for 3 months or more)
Current smoking
Alcohol intake, three or more units daily
Rheumatoid arthritis
Other secondary causes of osteoporosis
•Untreated hypogonadism in men and women, e.g., premature menopause, bilateral oophorectomy or orchidectomy, anorexia nervosa, chemotherapy for breast cancer, hypopituitarism
•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 I diabetes
•Thyroid disorders, e.g., untreated hyperthyroidism, over-treated hypothyroidism
•Chronic obstructive pulmonary disease

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ing centres from North America, Europe, Asia and Australia and has been validated in 11 independent cohorts with a similar geographic distribution within excess of 1 million patient years [17]. The use of primary data for the model construct permits the determination of the predictive importance in a multivariable context of each of the risk factors, as well as interaction between risk factors, and thereby to optimise the accuracy whereby fracture probability can be computed. The FRAX[®] tool (www.shef.ac.uk/FRAX) stratifies fracture risk more accurately than is possible with the use of BMD alone [17]. FRAX[®] computes the 10-year probability of hip fracture or a major osteoporotic fracture, the latter comprising a clinical spine, hip, forearm or humerus fracture. The risks of fracture and death vary in different regions of the world [18] so that the tool needs to be calibrated to the epidemiology of the region [1, 19]. Models are currently available for Argentina, Austria, Belgium, China, Finland, France, Germany, Hong Kong, Italy, Japan, Lebanon, New Zealand, Spain, Sweden, Switzerland, the UK and the USA. Others are being developed. Where a country is not represented (because of the lack of epidemiological data) a surrogate can be chosen.

Probability-based assessment

In men and in women, management strategy can be based on the assessment of the 10-year probability. The risk factors, given in Table 1, are entered as shown in Fig. 1. Femoral neck BMD can additionally be entered as a machine specific BMD or as a T-score derived from the NHANES III database for female Caucasians aged 20–29 years.

The availability of fracture probabilities derived from FRAX[®] raises the question: when is the risk unacceptably high so that intervention should be offered? This is a complex question that depends on local circumstances including the risk of fracture and death and willingness to pay for treatment. In many countries, treatment of osteoporosis has to compete with other health care priorities, which is usually based on a health economic argument. In the UK, for example, a treatment that costs £20,000–30,000 per quality of life year gained is considered to be cost-effective. Using this criterion, a 10-year probability of a major osteoporotic fracture of about 7% or more provides a cost-effective threshold for men and women in the UK, though this varies slightly by age [20].

Clinical guidelines based on fracture probability

The application of fracture probability to clinical practise demands a consideration of the thresholds at which to intervene, both for treatment (an intervention threshold), and if BMD access is limited, for BMD testing (assessment

thresholds). These have been developed for Europe, Canada, Germany, Japan, Sweden, the UK and USA [20–26]. There have been several approaches to the development of guidelines based on fracture probability. A method commonly used is to ‘translate’ current practise in the light of FRAX[®].

The UK guidance for the identification of individuals at high fracture risk developed by the National Osteoporosis Guideline Group (NOGG) is an example of the translation of existing guidance provided by the Royal College of Physicians (RCP) [27–29] into probability-based assessment [20]. As with the RCP guidance, the strategy is based on opportunistic case finding where physicians are alerted to the possibility of increased fracture risk by the presence of clinical risk factors. The clinical risk factors used differ somewhat from those of the RCP and comprise those used in the FRAX[®] algorithms together with low BMI (<19 kg/m²).

The RCP guidance indicates that women with a prior fragility fracture may be considered for intervention without the necessity for a BMD test, and the management of women over the age of 50 years on this basis has been shown to be cost-effective [30]. For this reason, the intervention threshold set by NOGG was at the fracture probability equivalent to women with a prior fragility fracture without knowledge of BMD [20]. The same intervention threshold was applied to men, since the effectiveness of intervention in men is broadly similar to that in women for equivalent risk [31].

In addition to an intervention threshold, assessment thresholds for the use of BMD testing were devised. The

Fig. 1 Chart for input of data and format of results in the UK version of the FRAX[®] tool. [With permission of the World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield Medical School, UK] [08ca032]

FRAX WHO Fracture Risk Assessment Tool

HOME | CALCULATION TOOL | FAQ | REFERENCE

Your Country : **UK** Name / ID : Patient [About the risk factors](#)

Questionnaire:

- Age (between 40-90 years) or Date of birth
Age: Date of birth: Y: M: D:
- Sex Male Female
- Weight (kg)
- Height (cm)
- Previous fracture No Yes
- Parent fractured hip No Yes
- Current smoking No Yes
- Glucocorticoids No Yes
- Rheumatoid arthritis No Yes
- Secondary osteoporosis No Yes
- Alcohol 3 more units per day No Yes
- Femoral neck BMD
T-score:

Clear Calculate

BMI: 24

The ten year probability of fracture (%) with BMD

Major osteoporotic fracture	23.9
Hip fracture:	8.0

concept of assessment thresholds is illustrated in the management algorithm given in Fig. 2 [1]. The management process begins with the assessment of fracture probability and the categorization 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 offered treatment without recourse to BMD testing. As noted, many guidelines [1] recommend treatment in the absence of information on BMD in women with a previous fragility fracture. Many physicians would also perform a BMD test, but frequently this is for reasons other than to decide on intervention. There will be other instances where the probability will be so low that a decision not to treat can be made without BMD. An example might well be the woman at menopause with no clinical risk factors. Thus, not all individuals require a BMD test. The size of the intermediate category in Fig. 2 will vary in different countries, but a pragmatic strategy was used by NOGG because of the limited facilities for BMD testing in the UK [32].

The management algorithm is shown in Fig. 3 and summarised below [20, 33]. Note that the algorithm is intended to be applied to men aged 50 years or more and to women at or after the menopause. Provision is given to calculating probability from the age of 40 years to accommodate premature menopause.

The NOGG guideline states that:

1. Postmenopausal women with a prior fragility fracture should be considered for treatment; BMD measurement may sometimes be appropriate, particularly in younger postmenopausal women. Men with a prior fragility fracture should be referred for BMD.

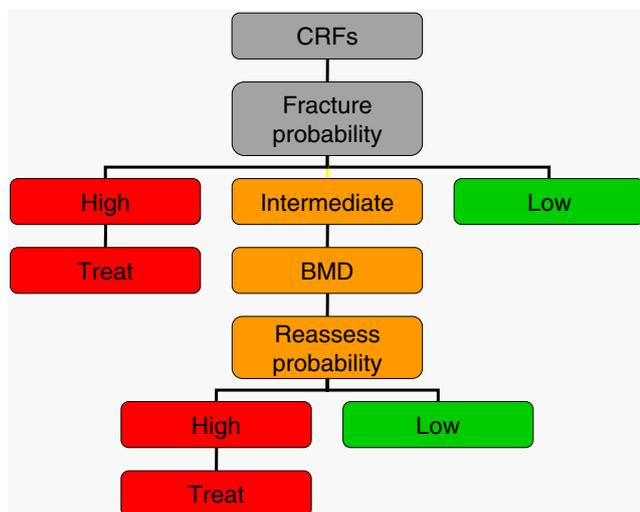


Fig. 2 Management algorithm for the assessment of individuals at risk of fracture by the use of clinical risk factors (CRFs) and bone mineral density (BMD) [1], with permission of the World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield Medical School, UK [05ca092]

Ten year probability of a major osteoporotic fracture (%)

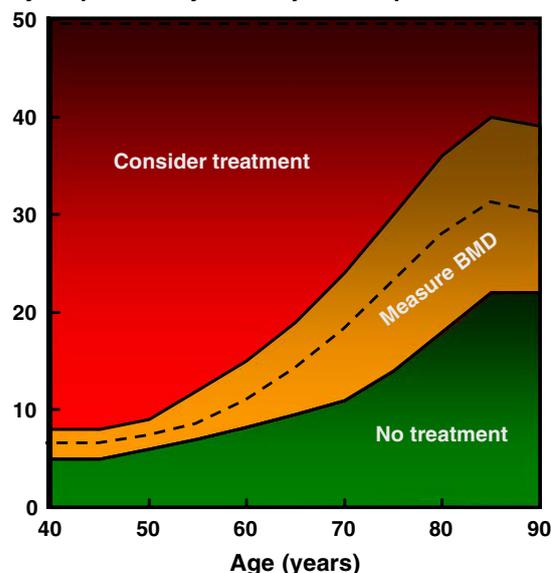


Fig. 3 Management chart for osteoporosis. The *dotted line* shows the intervention threshold, i.e., the probability at which intervention is recommended. The *orange shaded area* shows the limits of fracture probabilities for the assessment of BMD (BMD assessment thresholds). Reproduced with permission of the World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield Medical School, UK [09ca135]

2. Men aged 50 years or more and all postmenopausal women with a WHO risk factor or a BMI < 19 kg/m² should have fracture probability assessed using the FRAX[®] tool.
3. Individuals with probabilities of a major osteoporotic fracture below the lower BMD assessment threshold given in Fig. 3 can be reassured. A further assessment is recommended in 5 years or less depending on the clinical context.
4. Individuals with probabilities of a major osteoporotic fracture above the upper BMD assessment threshold given in Fig. 3 or with probabilities of a hip fracture above the intervention threshold (not shown) can be treated without recourse to BMD testing.
5. Individuals with probabilities of a major osteoporotic fracture within the limits of the assessment thresholds given in Fig. 3 and with probabilities of a hip fracture below the intervention threshold (not shown) should have a BMD test and probabilities recomputed. If recomputed probabilities exceed the treatment threshold, intervention should be considered. Where probabilities fall below the treatment threshold, a further assessment is recommended in 5 years or less depending on the clinical context.

The transformation of these recommendations into a format that is readily useable by primary care physicians is

available through <http://www.shef.ac.uk/NOGG/index.htm> or directly from the FRAX[®] site (<http://www.shef.ac.uk/FRAX/index.htm>).

The proportion of the female population potentially treated varied from 24% to 47%, depending on age [20] and has been shown to be cost-effective [20].

A similar approach has been developed in Europe by the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis, and indeed, the same intervention threshold is used. The difference lies in the upper assessment threshold in that it is recommended that all patients with probabilities above the lower assessment threshold should receive a BMD test [4]. Other countries that have developed or are developing translational approaches include Canada [21], Germany [23], Hong Kong [34], Japan [22], Lebanon, Poland [35], Sweden [26], Switzerland [36], Belgium [37] and the USA [24].

In the USA, the guidelines of the National Osteoporosis Foundation have been amended recently to accommodate in part the incorporation of fracture probability [38]. Patients with a prior hip or vertebral fracture (clinical or morphometric) are recommended for treatment as are men and women with a T-score for BMD of -2.5 SD or below. Conversely, no treatment recommendation is provided for those with a T-score of -1.0 SD or above. In the remainder, recommendations for intervention are guided by fracture probabilities that are based on a health economic analysis [39] and treatment recommended when FRAX[®] probabilities are 20% or greater for major osteoporotic fractures or 3% or greater for hip fracture in untreated patients with low bone mass (osteopenia) at the hip or spine and without a history of low trauma fractures of either the hip or spine (clinical or morphometric) [38].

Assessment of drug efficacy

Probability-based assessment has also had an effect on drug development. Guidelines on the evaluation of medicinal products in the treatment of primary osteoporosis have been developed by the Committee for Medicinal Products for Human Use and came into effect at the end of May 2007 [40]. A major departure from previous guidance is that there is no longer any distinction between prevention and treatment, but an emphasis on the study of patients at risk from fracture. Suggested probabilities as inclusion criteria into phase III trials are given as 15–20% for spine fracture, 5–7.5% for hip fracture and 10–15% for major non-vertebral fractures. These are intended to approximate the fracture risks in previous phase III studies.

As a consequence, FRAX[®] has been applied to several phase III studies in order to determine the enrolment characteristics of patients. A development has been to examine whether patients characterised on the basis of

fracture probability respond to treatment. An example is provided in a 3-year prospective, randomised, placebo-controlled trial of oral clodronate [41]. Women aged 75 years or more living in the general community, identified from general practise registers, were orally given 800 mg clodronate or matching placebo daily over 3 years. Baseline risk factors were used to compute the 10-year probability of a major osteoporotic fracture. Femoral neck BMD was also measured at entry. The main outcome of this analysis was the interaction between fracture probability and treatment efficacy examined by Poisson regression. Greater fracture reduction was seen at higher fracture probabilities. Similar findings have been found for bazedoxifene [42].

These results, if confirmed in other clinical settings, have a number of important implications for therapeutics. First, they dispel a minority view that patients identified on the basis of clinical risk factors with FRAX[®] would not respond to pharmacologic interventions. Second, they support the views of the European regulatory agency that treatments should be developed preferentially to men and women at high fracture risk. Third, the finding of greater efficacy at higher fracture probabilities has important implications for health technology assessments and challenges the current meta-analytic approach. Finally, since treatments directed to high risk patients improve the budget impact, greater efficacy in the higher risk groups will improve still further the budget impact and the cost-effectiveness of intervention.

Conclusions

In the absence of validated global or population screening strategies, a case-finding strategy is recommended based on the assessment of fracture probability utilising clinical risk factors, and where appropriate, additional testing such as BMD. Recent revisions of the US, European and UK guidance provide case-finding strategies that have been validated from a health economic perspective. Because of the multiple techniques available for fracture risk assessment, and the multiple fracture outcomes, the desirable measurement to determine who to treat is the 10-year probability of fracture.

Conflicts of interest None.

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