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Assessment of Individual Fracture Risk: FRAX and Beyond

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Abstract The World Health Organization fracture risk assessment tool (FRAX) and the Garvan fracture risk calculator are both widely available tools for individualized fracture risk prediction in daily practice. The FRAX model is implemented in several guidelines and most widely used at present. However, clinicians should take into account the differences between the models, especially with regard to the effect of the number of falls, number and clustering of previous fractures, and the number of clinical risk factors on the outcome of predicted fracture risk. Further development will be needed for optimal integration of bone- and fall-related risks, clustering of fractures, and dosing of risk factors to validate the models in different populations and to validate the ability to select patients who will achieve fracture risk reduction with anti-osteoporosis therapy. FRAX may be used as the primary model, and in patients with recurrent fractures and falls the use of the Garvan model may be of additional value.

Keywords Osteoporosis · Fractures · FRAX · Garvan · Timing of fractures · Risk factors

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Introduction

Osteoporotic fractures are an important cause of morbidity [1] and are linked with significant risk for subsequent fracture and mortality, in both women and men. Epidemiologic studies from North America have estimated the remaining lifetime risk of common fragility fractures in white women 50 years of age to be 17.5% for hip fracture, 15.6% for clinically diagnosed vertebral fracture, and 16.0% for distal forearm fracture. Corresponding risks among men are 6%, 5%, and 3%, respectively [2].

Data from the General Practice Research Database in the United Kingdom (UK, which includes 6% of the UK population) have indicated that the risk is similar in the UK. The lifetime risk of any fracture was found to be 53.2% at 50 years of age in women, and 20.7% at the same age in men. Thus, one in two women and one in five men who are 50 years of age will have an osteoporotic fracture in their remaining lifetime [3]. Among women, the 10-year risk of any fracture increased from 9.8% at 50 years of age to

21.7% at 80 years of age, whereas among men the 10-year risk remained fairly stable with advancing age with a 10-year risk of any fractures of 7.1% at 50 years to 8.0% at 80 years.[3] The health burden of osteoporotic fractures is likely to rise, which is partly due to an increased life expectancy and to changes in lifestyle (eg, less exercises/mobility, less calcium intake). Therefore, understanding the epidemiology of this disease is essential in trying to develop strategies to target individuals at high risk for fracture.

Assessment of Fracture Risk

Bone Mineral Density Measurement

In 1994, the World Health Organization published diagnostic criteria for osteoporosis defined in terms of bone mineral density (BMD) measurement with dual-energy X-ray absorptiometry as a T-score ≤−2.5 standard deviation (SD) below the young mean [4]. Recently, it was proposed that the reference standard should be based on BMD measurement made at the femoral neck because this site has been the most extensively validated, and provides a gradient of fracture risk as high as or higher than that of many other techniques [5].

In prospective and cross-sectional epidemiologic studies it has been shown that there is an inverse relationship between bone mass and fracture. The risk of osteoporotic fracture increases continuously as BMD declines, resulting in a 1.5- to threefold increase in risk of fracture for each SD decrease in BMD [6]. Advanced age and low BMD are strongly associated with higher fracture risk in postmenopausal women [7], and data from multiple randomized controlled trials provide evidence for fracture prevention in individual patients with osteoporosis [8]. Up to now, many guidelines recommend the assessment of BMD in patients with clinical risk factors (CRFs) as a selection for whom to treat. Using T-scores has many benefits, because T-scores are simple and widely used, have a good correlation with fracture risk, and can detect some high-risk patients. However, the majority of fractures occur in the large group of older women without osteoporosis, but with BMD in the osteopenic range [9]. Furthermore, several other independent risk factors for fractures, over and above that reflected by BMD, have been identified [10, 11]. Thus, BMD will not reliably predict all individuals who will sustain a fracture from those who will not.

Assessment of High-Risk Patients

The Fracture Risk Assessment Tool

Given the increasing evidence now suggesting that T-scores alone are not optimal predictors of fracture risk, the World Health Organization Metabolic Bone Disease Group recently developed other ways to assess fracture risk. In 2008 the fracture risk assessment tool (FRAX) was released using CRFs with and without BMD for fracture risk predication in men and women [1, 12]. The development of the FRAX tool has been supported by organizations including the International Osteoporosis Foundation, National Osteoporosis Foundation (NOF), the American Society for Bone and Mineral Research, and the International Society for Clinical Densitometry. The FRAX tool (http://www.shef.ac.uk/FRAX) computes the 10-year probability of hip fracture or a major osteoporotic fracture. A major osteoporotic fracture is defined as a clinical spine, hip, forearm, and humerus fracture. An estimation of the 10-year fracture probability is calculated in men or women using age, body mass index, and CRFs (Table 1) [13–22]. The 10-year risk of fractures can be calculated with or without femoral neck BMD in the model.

Probability models need to be calibrated to the epidemiology of fracture and death for any particular region or country, because of considerable variations in fracture probability and mortality in different regions of the world [7, 23]. Therefore, FRAX models have been developed from study cohorts from Europe, North America, Asia, and Australia. Additionally, in a Poisson regression model, mortality is taken into account as a competing risk [24]. In the absence of a FRAX model for a particular country, a surrogate country should be chosen, based on the likelihood that it is representative of the index country.

In recently updated guidelines, FRAX is included as a tool for case finding for identifying postmenopausal women at high risk for fractures, for selecting subjects who would need a BMD measurement, and for treatment decisions (NOF) in the United States [25] and (National Osteoporosis Guideline Group [NOGG]), in collaboration with many Societies) in the UK [26, 27]. It is expected that FRAX will also be helpful in designing fracture prevention studies and in reimbursement issues, as patients at increased probability of fracture can be identified beyond currently accepted reimbursement thresholds for BMD [28].

In spite of its strengths, FRAX also has limitations. First, the model has not been validated in randomized clinical intervention trials focusing on the prevention of fractures in patients who are included based on FRAX data that are available. In post hoc analyses of intervention studies with clodronate and bazedoxifene, the estimation of an individual's 10-year probability of fracture by the FRAX algorithm identified patients at high risk for fracture who will respond to antiresorptive therapy, irrespective of BMD results [29, 30, 31•, 32].However, once femoral neck BMD and age are known, the eight additional risk factors in FRAX did not significantly improve the prediction of vertebral fracture in post hoc analyses of the alendronate studies. A combination

Table 1 Comparison of risk factors and predicted fracture risk between the FRAX and Garvan fracture risk calculator

FRAX tool	Garvan nomogram
Risk factors	*Risk factors*
Age	Age
Sex	Sex
Body weight	Body weight[a]
Femoral neck BMD	Femoral neck BMD[a]
History of prior fractures[b]	History of prior fractures after age 50 y[c]
Height	History of falls in the previous 12 mo
Parent with hip fracture	
Current smoking	
Glucocorticoid exposure >3 mo ≥5 mg/d	
Rheumatoid arthritis	
Secondary osteoporosis[d]	
Alcohol ≥3 units/d	
Predicted fractures (10-y probability)	*Predicted fractures (5- and 10-y probability)*
Hip	Hip
Spine	Clinical spine
Wrist	Wrist
Humerus	Humerus
	Pelvis
	Rib
	Sternum
	Distal femur
	Proximal tibia/fibula
	Distal tibia/fibula
	Patella
	Hands and feet (not digits)

BMD bone mineral density, *FRAX* fracture risk assessment tool

[a] Either body weight or BMD is used in the Garvan nomogram.

[b] A previous fracture in adult life occurring spontaneously, or a fracture arising from trauma that, in a healthy individual, would not have resulted in a fracture.

[c] Excluding major fractures.

[d] These include untreated hypogonadism in men and women (eg, premature menopause, bilateral oophorectomy or orchidectomy), anorexia nervosa, chemotherapy for breast cancer, hypopituitarism, inflammatory bowel disease (eg, Crohn's disease and ulcerative colitis), prolonged immobility (eg, spinal cord injury, Parkinson's disease, stroke, muscular dystrophy), ankylosing spondylitis, organ transplantation, type 1 diabetes, thyroid disorders (eg, untreated hyperthyroidism, overtreated hypothyroidism), chronic obstructive pulmonary disease, osteogenesis imperfecta in adults, chronic malnutrition, or malabsorption and chronic liver disease

of baseline radiographic vertebral fracture, femoral neck BMD, and age was found to be the strongest predictor of future vertebral fracture [33]. Further studies will be needed to validate the efficacy of treatment in terms of fracture risk reduction when subjects at high risk for fractures are being treated based on FRAX in the absence of a morphometric vertebral fracture, hip fracture, or a low BMD, which is the case in most patients presenting with a nonvertebral fracture. Second, FRAX can only be used in untreated patients. Third, the increased subsequent fracture risk after an initial fracture is considered constant over time in FRAX, so the calculation by FRAX over a 10-year period does not take into account the clustering in time of subsequent fracture risk after an initial fracture. However, subsequent fracture risk fluctuates over time and is highest within the first years after an initial fracture, as has been shown for repeat vertebral, nonvertebral, and hip fractures [34–36, 37•]. Fourth, fall-related risks were explicitly excluded from the FRAX calculations. Reasons were the lack of standardized evaluation methods and the lack of fracture prevention data with fall prevention measures, which decrease the risk of falls (FRAX). However, fall risks were recognized as a risk for fractures independently of bone-related risks, especially for nonvertebral fractures, including hip fractures [8, 38, 39]. Kayan et al. [32] reported that fall risk does not significantly impact on the antifracture efficacy of clodronate, suggesting that after confirmation with other agents, fall risk may be incorporated into risk assessment tools designed to target skeletal therapies. Given this observation, it would be an additional value to take fall risk into account in the assessment of fracture risk. Finally, FRAX does not include several additional risk factors for fractures, such as the number of causes of secondary osteoporosis, the dose and duration of glucocorticoid use [40], characteristics of previous fractures (location, number, and severity) [41], and vitamin D deficiency [42].

The Garvan Fracture Risk Calculator

In 2007, another prognostic nomogram for individualizing the risk of hip fracture was developed based on the Dubbo Osteoporosis Epidemiology Study data [43]. In a subsequent study, the model was extended for prediction of the 5- and 10-year risk of any fragility fracture [44•]. The model uses CRFs such as history of prior fracture (1, 2, or more than 2), history of fall during the past 12 months (1, 2, or more than 2), age, and BMD (Table 1). The authors developed two models, one with weight and one with BMD. The difference in predictive accuracy between the model with BMD and the model with weight is only modest, and therefore, if BMD is not available, the model with weight can be used in clinical practice [44]. The Garvan tool takes into account the history and number of recent falls (1, 2, and >2) and the number of previous fractures (1, 2, and >2). It also predicts more types of fractures than FRAX. The Garvan tool allows 5- and 10-year fracture calculations, whereas the FRAX calculates the 10-year fracture risk [44]. A limitation of the Garvan tool is

that it does not include other risk factors as in FRAX, and therefore, might underestimate fracture risk when many CRFs are present. Another limitation is its availability only in subjects older than 60 years of age and that it is based on an Australian population only, in contrast to FRAX.

When comparing the FRAX and Garvan tool on a theoretic basis, the outcome of the fracture probability of both tools differs depending upon the risk profile of patients. In patients without CRFs, the fracture risk calculation is higher with the Garvan tool than with FRAX, since the number of fractures predicted by Garvan is higher than by FRAX [45]. Also, when using the Garvan tool, calculated fracture risk increases according to the number of previous fractures after 50 years of age and the number of falls in the last 12 months, in contrast to FRAX (Fig. 1). Conversely, calculated fracture risk increases with the number of CRFs with FRAX, whereas Garvan does not take additional CRFs into account (Fig. 2) [45]. In a recent Australian cohort analysis, both approaches were reasonably accurate in women, but FRAX discriminated fracture risk poorly in men [46]. However, it there is no available Australian database for FRAX, and UK and US databases were used instead in this study. In another recent study, in which a comparison is made between both models in a population of 2,012 Polish women, the mean conformity for any fracture risk was 79.1% and for hip fracture 79.5%; however, it appeared that for prediction of hip fractures, the cumulative role of falls and multiple previous fractures was stronger than other CRFs [38].

The Use of FRAX in Guidelines

Until recently, the majority of clinical guidelines for the management of osteoporosis have made recommendations for intervention based on BMD T-scores [1]. In 2008 the NOGG in collaboration with many Societies in the UK recommended an approach for decision making based on fracture probabilities derived from FRAX that can be applied to men and women. The NOGG provided intervention thresholds (the fracture probability at which intervention is recommended) and assessment thresholds (the fracture probabilities at which a BMD test might or might not be recommended). Probabilities of a major osteoporotic and hip fracture can be plotted at the NOGG website (http://www.shef.ac.uk/NOGG) available through FRAX, showing whether the patients should be reassured, need a BMD measurement, or can be considered for treatment. The intervention threshold at each age is set at a risk equivalent to that associated with a prior fracture and therefore rises with age [27]. Men and women with 10-year major fracture probabilities below the lower assessment threshold can be reassured. Men and women with probabilities above the upper assessment threshold can be considered for treatment. Men and women with probabilities between the upper and lower assessment threshold should be referred for BMD measurements and their fracture probability reassessed.

The NOF recommends using FRAX when the decision to treat or not to treat is uncertain. It is primarily intended for postmenopausal women and men 50 years of age and older who have T-scores between −1.0 SD and −2.5 SD and who are not on treatment, and who have not had spine or hip fractures. The guideline recommends drug treatment if the FRAX 10-year probability exceeds 20% for four major fractures or 3% risk for hip fracture based on economic models suggesting cost-effectiveness of osteoporosis treatment above these percentages [25, 47, 48].

The use of FRAX as intended in both guidelines changes current clinical management and may be difficult to

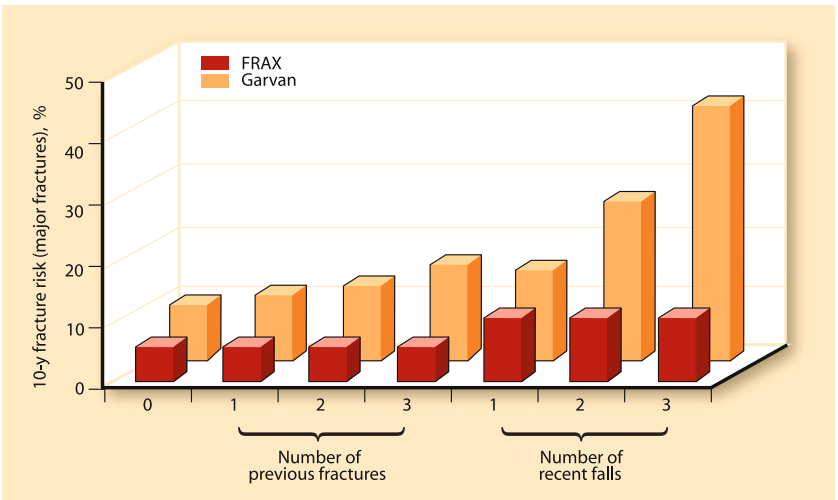

Fig. 1 Ten-year calculated risk of osteoporotic fractures according to the fracture risk assessment tool (FRAX) (UK) and Garvan tool based on the number of recent falls (the last 12 months) and previous fractures after 50 years of age (women, 60 years, 70 kg, 170 cm, no bone mineral density measurement)

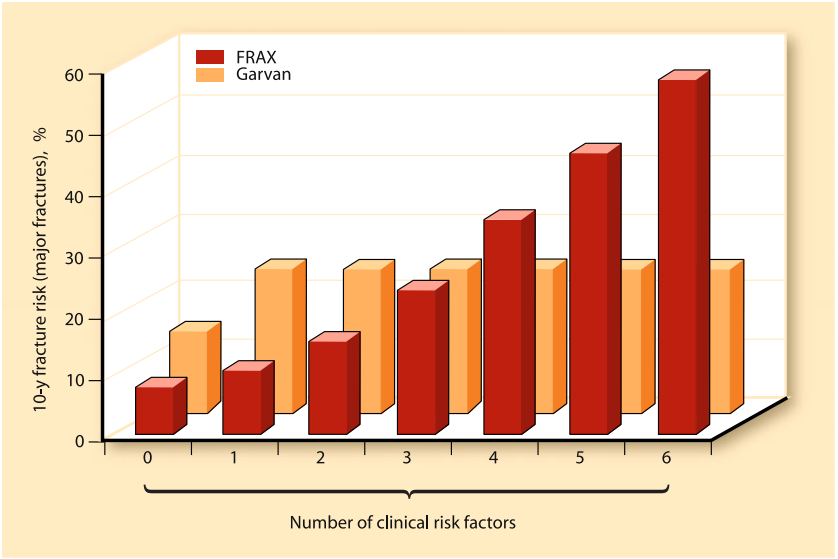

Fig. 2 Ten-year calculated risk of osteoporotic fractures according to the fracture risk assessment tool (FRAX) (UK) and Garvan tool based on the number of clinical risk factors (women, 60 years, 60 kg, 170 cm, T-score femoral neck=−2.5)

interpret for clinicians. For example, there are patients with one CRF who should be referred for a BMD measurement according to the NOGG guide, and when having osteoporosis (T-score ≤−2.5) should not be treated according to the reassessed FRAX probability because it is too low to justify treatment according to the NOGG. In contrast, according to NOF guidelines, patients with osteopenia who have a 10-year major fracture risk greater than 20% based on the presence of CRFs would be treated despite the fact that they do not have osteoporosis.

Additional interpretation issues may arise because a discrepancy may exist between BMD values at the lumbar spine and femoral neck, especially among women around 50 years of age who may have low lumbar spine BMD with normal femoral neck BMD. It is anticipated that FRAX will be incorporated into bone density software in the United States in the near future, so that BMD results will be combined with the FRAX 10-year fracture probability. Patients and physicians will be routinely provided with information on fracture risk that adds to that derived from BMD alone [49]. Physicians should be aware of the fact that BMD is a risk factor for fracture, and the association between BMD and risk is a continuous one despite the T-score cutoff of −2.5 SD that is used for the clinical diagnosis of osteoporosis [50]. Conversely, they also need to be educated about the strengths and limitations of FRAX and how calculated risks can be used in clinical practice for individual patients. Whether to add FRAX to a BMD result in the report to the physician is thus still a matter of debate [39, 49].

The FRAX tool may be inappropriate in a number of situations, most notably when osteoporosis treatment is clearly needed (eg, in the presence of a vertebral fracture), but may be very useful for convincing patients who have low 10-year fracture risks that osteoporosis treatment is unnecessary even when the BMD values are in the lower range and to show patients that fracture risk increases with the occurrence of additional risk factors (eg, smoking, recent insufficiency fracture, or glucocorticoid therapy) regardless of BMD. In patients with high fall risk, a recent previous fracture, and/or multiple previous fractures, the 10-year fracture risks may be underestimated by FRAX, as shown with the use of the Garvan algorithm in such cases.

Conclusions

In daily practice, there is an urgent need for clinicians to have a model that estimates the absolute fracture risk in their patients, since decisions about whether or not to treat patients with anti-osteoporotic drugs should be based on the efficacy of these drugs, but also on the fracture risk. The FRAX and the Garvan fracture risk calculator are both widely available tools for individualized fracture risk prediction in daily practice. The FRAX model is implemented in the NOF, National Osteoporosis Society, and NOGG guidelines and most widely used at present. Its advantage is that it is easy to use in clinical practice for selecting patients at high risk for fractures, thus it is useful for clinical decision making, case finding and is a valuable tool for patient education. Clinicians should take into account the differences between the models especially with respect to the effect of the number of falls and fractures on fracture risk that is implemented in the Garvan model but not in FRAX and the effect of the number of CRFs on fracture risk in the FRAX, not in the Garvan model; they also need to be aware of possible limitations of the models when using them for individual patient management. Both

models still need to be validated in different populations before they can be generalized to other populations and further studies will be needed to validate their contribution in selecting patients who will achieve fracture risk reduction with anti-osteoporosis therapy. Further studies will be needed to develop a case-finding algorithm that integrates bone- and fall-related risks, the clustering of fractures, and the dosing of risk factors (eg, number and severity of previous fractures, dose of glucocorticoids, timing, and number of falls). With the current available algorithms, a possible clinical application may be to use FRAX as the primary model and to consider using Garvan in patients with recurrent fractures and falls.

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