

# Fragility fracture: recent developments in risk assessment

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**Abstract:** More than half of older women who sustain a fragility fracture do not have osteoporosis by World Health Organization (WHO) bone mineral density (BMD) criteria; and, while BMD has been used to assess fracture risk for over 30 years, a range of other skeletal and nonskeletal clinical risk factors (CRFs) for fracture have been recognized. More than 30 assessment tools using CRFs have been developed, some predicting fracture risk and others low BMD alone. Recent systematic reviews have reported that many tools have not been validated against fracture incidence, and that the complexity of tools and the number of CRFs included do not ensure best performance with poor assessment of (internal or comparative) validity. Internationally, FRAX<sup>®</sup> is the most commonly recommended tool, in addition to QFracture in the UK, The Canadian Association of Radiologists and Osteoporosis Canada (CAROC) tool in Canada and Garvan in Australia. All tools estimate standard 10-year risk of major osteoporotic and 10-year risk of hip fracture: FRAX<sup>®</sup> is able to estimate fracture risk either with or without BMD, but CAROC and Garvan both require BMD and QFracture does not. The best evidence for the utility of these tools is in case finding but there may be future prospects for the use of 10-year fracture risk as a common *currency* with reference to the benefits of treatment, whether pharmacological or lifestyle. The use of this metric is important in supporting health economic analyses. However, further calibration studies will be needed to prove that the tools are robust and that their estimates can be used in supporting treatment decisions, independent of BMD.

**Keywords:** fracture risk assessment, FRAX<sup>®</sup>, Garvan, osteoporosis, postmenopausal women, QFracture

## Introduction

The NIH Consensus Development Conference defined osteoporosis as ‘a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture’ [NIH Consensus Development Panel, 2001]. This definition incorporates three important factors:

- low bone mineral density (BMD);
- compromise to bone quality and strength;
- fracture risk.

The measurement of BMD in screening for osteoporosis and assessing fracture risk has dominated practice for more than 20 years [World Health Organization, 1994] and BMD has provided a useful proxy measure for efficacy in clinical trials [Stevenson *et al.* 1990]. However, using these

criteria, a third of 70-year-old and more than half of 80-year-old persons have osteoporosis [Kanis *et al.* 1994], although more than half of older women who fracture do not have osteoporosis by BMD criteria [Greenspan *et al.* 2001; Davis *et al.* 2011]. There are many other factors, including risk of falls and poor vision, which may increase fracture risk [NIH Consensus Development Panel, 1991; Lips, 1997]; and for a number of high-risk groups such as patients commencing glucocorticoids [Royal College of Physicians, 2002], androgen deprivation therapy [Higano, 2004], anti-oestrogens [Reid *et al.* 2008], or suffering from chronic kidney disease [Miller, 2014] BMD alone is not a good predictor of fracture risk.

Both skeletal factors (particularly BMD) and nonskeletal clinical risk factors (CRFs) predict

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fracture risk [Kanis *et al.* 2005] and both were evaluated in their prediction of fractures incidence over 4 years for 46,340 subjects. The resultant tools were subsequently validated in 11 cohorts, where 3360 hip fractures occurred in 230,486 subjects over 1,208,528 person-years. Using the gradient of hip fracture risk (GR, risk ratio/standard deviation [SD] change in risk score), BMD alone was a better predictor than CRFs (GR for BMD was 3.7/SD; for CRFs it was 2.1/SD). However, the GR was highest at 4.2/SD for CRFs combined with BMD [Kanis *et al.* 2007]. This work contributed to the development of the best known and most widely used fracture risk assessment tool (FRAX<sup>®</sup>) which was launched by the WHO in 2008 [McCloskey and Kanis, 2012]. However, many fracture risk assessment tools have now been developed including up to 31 different CRFs [Rubin *et al.* 2013].

The use of 10-year fracture risk, rather than diagnosis of osteoporosis using dual-energy X-ray absorptiometry (DXA), offers a common *currency* for fracture risk assessment. This was recently recognized by a committee of North American clinicians reporting to the National Bone Health Alliance, as they proposed a diagnosis of osteoporosis should be conferred by ‘hip fracture; osteopenia-associated vertebral, proximal humerus, pelvis, or some wrist fractures; or FRAX<sup>®</sup> scores with  $\geq 3\%$  (hip) or 20% (major) 10-year fracture’ [Siris *et al.* 2014]. However, the value of fracture risk assessment is not universally recognized and various criticisms have been made, including its dependence on access to the internet, assumptions made by the tool about fracture risk, body mass index (BMI) and mortality across racial and ethnic groups, the exclusion of variables such as falls and the lack of adjustment for dose–response relationships [Silverman and Calderon, 2010].

#### Alternative fracture risk assessment tools

In their very timely systematic review of risk assessment tools, Rubin and colleagues [Rubin *et al.* 2013] comment that ‘Far from all [tools] have been validated in external studies [and] more of them have absence of methodological and transparent evidence’. They found 48 tools of which only 20 were externally validated and 6 had been tested more than once in a population-based setting with acceptable methodological quality. None of the tools performed consistently better than the others and they found no evidence that complex tools were superior to simple ones.

However, the lack of head-to-head comparisons in similar populations makes it difficult to come to a firm conclusion on comparison. Another recent systematic review highlighted the lack of evaluation of performance and the failure to calibrate osteoporosis fracture risk assessment instruments across different risk categories and in populations separate from their development cohorts [Nayak *et al.* 2014]. Methods of development, validation and transparency relating to comparable risk assessment tools have also been critically reviewed, with only three fracture risk assessment tools identified which have been validated at least once in a population-based setting (Garvan, FRAX<sup>®</sup> and QFracture). There is clearly more work to be done in identifying which methods work the best in which populations [Collins and Michaelsson, 2012; Rubin *et al.* 2013].

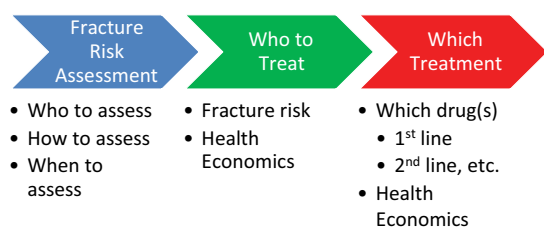
#### Fracture risk assessment in practice

##### *From case finding to decisions about treatment*

Fracture risk assessment can be seen as the first of three stages in evaluating osteoporosis risk and treatment (see Figure 1) [Aspray, 2013]. First, CRFs may be used to assess fracture risk for case finding to identify those most likely to benefit from treatment. Subsequently, it is necessary to define those who warrant pharmacological therapies and subsequently prioritize the choice of different treatments informed by their effect (usually estimated as absolute fracture risk reduction). Historically, the randomized controlled trial has been the means of estimating these effects and criteria based on low BMD and age have often been used for study recruitment. However, fracture risk derived from CRFs (with or without BMD) has potential, but has not been validated in randomized controlled trials of pharmacological treatments for osteoporosis, and so BMD criteria have been incorporated into clinical guidelines. In practice, the adoption of fracture risk assessment has been variable, as outlined in the following national case studies. Various tools are used, with FRAX<sup>®</sup> adopted in most countries. However, while these approaches are based on some evidence, local preference and previous national assessment tool development have also had a considerable impact.

##### *The United Kingdom*

Rubin and colleagues highlight the fact that national guidelines do not generally include



**Figure 1.** The place of fracture risk assessment in providing a tool for treatment choice.

fracture risk assessment tools, although FRAX<sup>®</sup> [Kanis *et al.* 2008] and QFracture [Hippisley-Cox and Coupland, 2012] have been recommended by the National Institute for Health and Care Excellence (NICE) in England and Wales for the assessment of fragility fracture risk [Rabar *et al.* 2012]. Both tools use CRFs to estimate 10-year risk of major osteoporotic fracture and hip fracture. FRAX<sup>®</sup> uses data derived from cohort studies, whereas QFracture uses routine clinical data from British general practice surgeries on approximately 5 million British patients [Hippisley-Cox *et al.* 2007]. The main differences between FRAX<sup>®</sup> and QFracture have been summarized elsewhere [Aspray, 2013], which comprise:

- FRAX<sup>®</sup> has been used in a number of countries; QFracture was developed in the UK;
- the age range for FRAX<sup>®</sup> is 40–90 years and for QFracture 30–99 years;
- both tools estimate 10-year fracture risk; QFracture also estimates an annualized risk;
- FRAX<sup>®</sup> (but not QFracture) can give fracture risk based on CRFs with BMD;
- QFracture uses a wider range of CRFs;
- FRAX<sup>®</sup> uses binary data for all variables other than age, weight, height and BMD (e.g. glucocorticoid therapy/no glucocorticoid therapy, smoker/non-smoker), whereas QFracture includes ‘dose response’ for some variables (e.g. non/ex/light/heavy/moderate smoker).

Perhaps the most comprehensive attempt to implement a strategy for fracture risk assessment has been in England and Wales, where NICE developed its Short Clinical Guideline on Osteoporosis: Assessing the Risk of Fragility Fracture (Clinical Guideline 146, [Rabar *et al.* 2012]). The guideline is comprehensive in its recommendations on: who to assess, how to assess them and when to re-assess their fracture risk.

*Who?* The guideline recommends fracture risk assessment in women aged over 65 years and men over 75 years. For patients aged over 50 years, the presence of CRFs should prompt an assessment of fracture risk. These CRFs comprise: previous fragility fracture, glucocorticoid treatment, a history of falls, a family history of hip fracture, other causes of secondary osteoporosis, low BMI (<18.5 kg/m<sup>2</sup>), smoking (>10 per day) or alcohol (>4 units per day). For those aged 40–50 years of age fracture risk assessment is only advocated for patients with major risk factors: glucocorticoid therapy, untreated premature menopause or previous fragility fracture.

*How?* FRAX<sup>®</sup> (without BMD) or QFracture should be used to calculate 10-year predicted absolute fracture risk. However, we should recognize underestimation of fracture risk in the case of: multiple fractures, high alcohol intake, obesity, heavy smoking, high-dose oral glucocorticoid therapy and in some secondary causes of osteoporosis.

*When?* Fracture risk should not be recalculated within 2 years unless the original risk was close to an intervention threshold for a proposed treatment or there has been a change in the person’s risk factors (e.g. fracture).

Although these guidelines are clear and implementable, NICE technology appraisals for treatments [National Institute for Health and Care Excellence, 2010, 2011a, 2011b] had previously rejected the use of 10-year fracture risk to support treatment decisions, stating that ‘recommendations about treatment should [not] be based on absolute risk as calculated using FRAX<sup>®</sup>’. Instead, the technology appraisals use a DXA scan diagnosis of osteoporosis (*T*-score less than –2.5) as their starting point for decisions about treatment (although in women aged 75 years or older, osteoporosis ‘may be assumed’ if the clinician thinks DXA scan is ‘inappropriate or unfeasible’). In addition to low BMD, CRFs analogous to but not the same as those used in FRAX<sup>®</sup> or QFracture have been included and the cost-effectiveness calculations prioritize more expensive treatment with lower BMD or multiple fractures. Implementation of the technology appraisals has been problematic and it is notable that they specifically do not apply to men, premenopausal women, patients on glucocorticoids or cases of secondary osteoporosis, due to conditions such as diabetes mellitus [Giangregorio *et al.* 2012], chronic liver disease or thyroid disorder.

In Scotland, NICE Guidance does not apply. The Scottish Intercollegiate Guidelines Network (SIGN) Osteoporosis Guideline was published in 2004 and makes a number of evidence-based recommendations, including [Scottish Intercollegiate Guidelines Network, 2004]:

- patients who have suffered one or more fragility fractures should be priority targets for investigation and treatment of osteoporosis;
- use of family history in assessing risk of osteoporosis should include maternal, paternal and sister history;
- family history should include not only a given diagnosis of osteoporosis but also kyphosis and low trauma fracture after age 50;
- smokers should be considered at greater risk of osteoporosis than nonsmokers, and advised to stop, for this and other reasons;
- the possibility of osteoporosis should be considered in patients with specific conditions, i.e. anorexia nervosa, chronic liver disease, coeliac disease, hyperparathyroidism, inflammatory bowel disease, male hypogonadism, renal disease, rheumatoid arthritis, long-term glucocorticoid use and vitamin D deficiency.

However, SIGN concludes that available risk scores for osteoporosis are 'not of satisfactory quality and have not been validated'. An update of the SIGN guidance is awaited.

*Does DXA help?* There is inconsistent evidence that BMD significantly improves the performance of FRAX® [Kanis *et al.* 2005, 2007], with little reclassification of subjects from high to low risk or vice versa [Leslie *et al.* 2012]. However, it has been argued that DXA scanning does help refine estimates of fracture risk [Johansson *et al.* 2009; Leslie *et al.* 2010; Bow *et al.* 2011]. The NICE guideline on fracture risk assessment specifically suggests that BMD should be used in assessing fracture risk in younger people at risk of osteoporotic fracture. It should also be noted that QFracture cannot be interpreted in the context of BMD, so that, if fracture risk is to be presented in the context of BMD, FRAX® CRFs must be used.

*The National Osteoporosis Guideline Group.* Partly in response to difficulties in implementing NICE technology appraisals, further developments in the UK have included the work of the National Osteoporosis Guideline Group (NOGG), whose

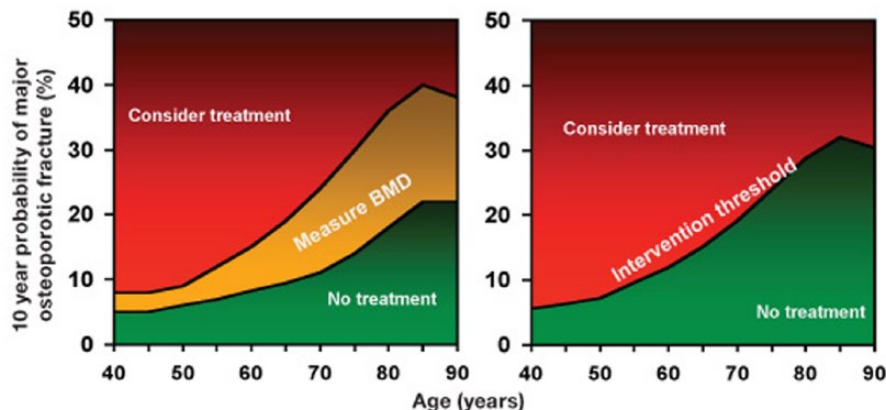
clinical guidelines apply to both men and women at high fracture risk [National Osteoporosis Guideline Group *et al.* 2008]. The essentials of NOGG are that:

- a history of a fragility fracture in a post-menopausal woman should prompt consideration for treatment;
- 10-year fracture risk should be estimated in
  - men aged 50 years or more with at least one CRF (derived from FRAX®) or BMI less than 19 kg/m<sup>2</sup>;
  - postmenopausal women without fracture but with at least one CRF (derived from FRAX®) or BMI less than 19 kg/m<sup>2</sup>.

The resultant 10-year fracture risk estimate can then be plotted against age (see Figure 2) and the output includes an area of risk (shaded amber) for which DXA scanning is advocated, to refine the risk estimate. The refined estimate should be re-plotted on the right-hand panel to prompt a decision about treatment: the green zone recommending lifestyle advice; red zone recommending that pharmacological intervention is considered. The threshold for treatment merely reflects the mean fracture risk associated with a history of fragility fracture at that age. Thus, there may be an argument for setting the threshold higher at younger ages and lower at older age or using a single threshold for all ages, as used by the North Americans [National Osteoporosis Foundation, 2010].

#### Canada

In Canada, a similar process to that seen in England and Wales has been undertaken, with the Osteoporosis Canada 2010 Guidelines recommending two alternative fracture risk assessment tools [Papaioannou *et al.* 2010]: The Canadian Association of Radiologists and Osteoporosis Canada tool (CAROC) and FRAX®. However, CAROC incorporates age, sex, prior fragility fracture, and systemic glucocorticoid use, together with bone mineral density [Leslie *et al.* 2010]. The output for each tool gives a 10-year risk of major osteoporotic fracture, and is associated with thresholds of risk: low (<10%), intermediate (10-20%) or high (>20%). There are calibration data for CAROC and FRAX®, which show good results, when used in a Canadian population, and a low rate of reclassification between low, intermediate and high fracture risk groups [Leslie *et al.* 2011].



**Figure 2.** The National Osteoporosis Guideline Group (NOGG) interpretation of fracture risk.

### Australia

In Australia, FRAX<sup>®</sup> (with BMD) and Garvan are recommended by the Royal Australian College of General Practitioners [The Royal Australian College of General Practitioners, 2010]. The latter is a tool validated in an Australian population and incorporates gender, age, falls and BMD. Both tools incorporate DXA results and the guideline acknowledges that there has been no calibration of the results of the tests. However, more recent studies have shown a similar area under the curve (AUC) for these two methods in Australian [Nguyen *et al.* 2013], but not in New Zealand populations [Bolland *et al.* 2011], suggesting that calculators should be validated in local cohorts before clinical use.

### USA

The National Osteoporosis Federation of America has included some recommendations on case finding and the role of fracture risk assessment in its comprehensive Clinician's Guideline [National Osteoporosis Foundation, 2010]. Lists of risk factors, which should influence the clinician to consider osteoporosis and fracture risk, are tabulated. These include conditions, diseases and medications which contribute to osteoporosis and fracture risk as well as risk factors for falls and a summary of the FRAX<sup>®</sup> risk factors. However, the guide (rather ambitiously) recommends that all postmenopausal women and all men aged 50 years and older should be evaluated clinically for osteoporosis risk. This should include 10-year estimated fracture risk 'where appropriate', although details of when such an assessment is warranted are not clear. The guide also uses thresholds of 10-year fracture probability derived

from health economic evaluations, recommending treatment for patients with a BMD in the osteopenic range, where hip fracture probability is  $\geq 3\%$  or major osteoporosis-related fracture probability  $\geq 20\%$  [Tosteson *et al.* 2008].

### Europe

The variability in fracture risk assessment methodologies, their development, validation and implementation has been widely recognized. Here we have presented four national approaches which vary in their conclusions with regard to the best tools and thresholds for diagnosis. They have also used fracture risk assessment for case finding and making treatment decisions. The International Osteoporosis Foundation (IOF) and European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) have also reviewed the assessment and treatment of post-menopausal osteoporosis [Kanis *et al.* 2013]. Within their review of fracture risk and case-finding strategies, the potential of FRAX<sup>®</sup> to assess fracture risk, develop treatment thresholds and guide access to densitometry are considered in some detail as well as briefer coverage of the Garvan and QFracture tools, highlighting the fact that these both include falls as risk factors. A further innovation of guideline development has taken place in collaboration with IOF-ECTS, who have issued guidelines for the management of glucocorticoid-induced osteoporosis, which can be incorporated into the FRAX<sup>®</sup> output. For example, lower dose therapy (equivalent to prednisolone  $< 2.5$  mg/day) is associated with a 35% lower risk and higher dose (prednisolone  $> 7.5$  mg/day) associated with a 20% greater risk of hip fracture [Lekamwasam *et al.* 2012].



### Clinical implications

The availability of a 10-year fracture risk estimate offers a new currency for osteoporosis and a means to target fracture risk reduction, which aids communication with patients, as it is more intuitive than the WHO diagnostic criteria for osteoporosis. The clinical significance of a femoral neck *T*-score of  $-2.5$  differs between men and women, young and old and those with or without CRF comorbidities. Whereas 10-year risk of hip fracture means the same thing for all and has the potential to be estimated for any interventions, whether targeting bone or falls prevention, using pharmacological or lifestyle modifications. However, although clinical trials have used fracture incidence to measure clinical outcomes, we are a long way from understanding the potential benefit of treatment using fracture risk. Calibration studies are few and focus on the natural history of fracture and not the relation of fracture risk estimates to fracture incidence in response to interventions.

BMD (and biochemical markers of bone turnover) remain important biomarkers and are attractive outcomes for studies to compare treatment effects, as the least significant change is easily established, allowing the design of trials which can be 'powered' to deliver predetermined clinically and statistically significant benefit [Baim *et al.* 2005; Baxter *et al.* 2013]. However, the clinical role of DXA needs clarification and the feasibility of fracture risk estimation using QFracture or FRAX<sup>®</sup> without access to BMD requires some evidence. Vertebral fractures are a significant source of morbidity [Francis *et al.* 2008] and an independent predictor of fracture risk [McCloskey *et al.* 2008] but only femoral neck BMD contributes to FRAX<sup>®</sup>, so the adjustment of fracture risk estimates in patients for spinal BMD is a welcome development, which may help in future clinical practice [Leslie *et al.* 2011]. However, spinal osteoporosis should be considered as a separate clinical entity, with vertebral osteoporotic fractures associated with at least a threefold increased risk of further vertebral fracture [Lunt *et al.* 2003].

### The future

The 1994 WHO densitometry criteria for the diagnosis of osteoporosis have been extremely influential in forming our ideas on clinical osteoporosis, but CRFs can improve our understanding of fracture risk. High fracture risk is associated with the greatest benefit from treatment [McCloskey *et al.*

2009] and a clinical trial assessing the effect of bisphosphonates on fracture incidence is currently underway, following 11,580 older women for 5 years. Treatment decisions are based on estimated fracture probability, using FRAX<sup>®</sup> (with BMD). While fracture incidence is the primary outcome, this will be supplemented by an economic analysis to assess the cost-effectiveness of screening [Shepstone *et al.* 2012]. Such a study will help to fill gaps in our knowledge of the relationship between estimated fracture risk, fracture incidence and the impact of pharmacological therapy on both.

We need to know more about the performance of available fracture risk assessment tools across populations. There are few calibration studies, so we cannot say how consistent most tools are at predicting fracture incidence or how they compare with one another when used in the same population. There is particularly poor evidence for patients who are frail, those who fall, in the oldest old and in care home residents, as well as for those treated with glucocorticoids and the need for future research in these areas has been identified [Rabar *et al.* 2012]. For some patients, fracture risk assessment may fail to consider competing risks of mortality [Leslie *et al.* 2013]; whereas for others BMD may contribute to an underestimate of fracture risk, as seen with glucocorticoids, anti-oestrogens and anti-androgens [Neubecker *et al.* 2011; Hadji *et al.* 2012; Lekamwasam *et al.* 2012; Rizzoli *et al.* 2012]. BMD remains an effective way to diagnose osteoporosis, with more than 30 years' experience of the tool and a wealth of evidence from randomised clinical trials [NIH Consensus Development Panel, 1984]. However, CRFs are valuable in case finding and are most useful at a population level, where mass screening using DXA is not going to be cost-effective. In principle, estimated fracture risk should be a better predictor than BMD, as it targets a hard clinical outcome (fracture) and it can be used both to compare treatments and inform health economic analyses. The utility of fracture risk derived from CRFs (particularly without DXA) still requires more research evidence, so we still need DXA to supporting decisions to treat unless and until a new evidence base is created.

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### Conflict of interest statement

The author declares no conflict of interest in preparing this article.

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