NEW HORIZONS

New horizons in fracture risk assessment

TERRY J. ASPRAY1,2

1The Bone Clinic, Musculoskeletal Unit, Freeman Hospital, NE7 7DN Newcastle upon Tyne, UK
2Institute for Ageing and Health, Newcastle University, Newcastle upon Tyne, UK

Address correspondence to: T. J. Aspray. Tel: (+44) 01912137975; Fax: (+44) 01912231159. Email: t.j.aspray@newcastle.ac.uk

Abstract

Fracture is the clinical outcome of concern in osteoporosis, a disease variably defined over the last 30 years, mostly in terms of bone mineral density (BMD). However, an ‘osseocentric’ view of the condition may have hampered our understanding of how best to identify patients at the greatest risk of fragility fracture. More recently, the identification of a number of clinical risk factors for fragility fracture and the creation of fracture risk assessment tools, such as FRAX®, QFracture and Garvan have helped in a move towards clinically useful definitions, using the common currency of 10-year major osteoporotic and 10-year hip fracture risks. However, there are a large number of available fracture risk assessment tools and there remain few validation studies comparing their performance. The National Institute for Health and Clinical Excellence has recently advocated the use of these methods in case finding and studies are underway in their clinical application. It seems likely that the operational definition of osteoporosis must now include fracture risk, which will never replace fracture incidence as a measure of clinical efficacy but may be used in future studies to define patient groups likely to benefit from intervention. We still need to understand more about the performance of these tools, particularly in the context of specific patient groups, such as those with vertebral osteoporosis, the frail, those who fall and patients with secondary osteoporosis.

Keywords: osteoporosis, fracture, FRAX, QFracture, guideline

The origins of fracture risk assessment

In 1984, the US National Institute for Health (NIH) defined osteoporosis as ‘an age-related disorder characterized by decreased bone mass and increased susceptibility to fractures in the absence of other recognizable causes of bone loss’ [1]. By 2000, the definition had simplified to ‘a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture’ [2]. Meanwhile, the International Consensus Development Conference in 1990 defined osteoporosis as ‘a disease characterized by low bone mass and micro-architectural deterioration of bone tissue, enhanced bone fragility and an increase in fracture risk’ [3]. These definitions incorporate three important factors. Firstly, low bone mineral density (BMD), now measured using dual energy X-ray absorptiometry (DXA), is a determinant of osteoporosis. Secondly, bone quality and strength are important but the third and most important clinical feature is an association of osteoporosis with so-called ‘fragility fractures’.

However, such ‘osseocentric’ reflections cannot completely explain the epidemiology of osteoporotic fractures, with more than half of older women who fracture having normal BMD on DXA scan [4, 5], and it has long been recognised that other factors such as falls risk and poor vision may contribute to fracture risk [3, 6]. In 1994, a WHO study group reported its evaluation of available methods for the assessment of fracture risk and their suitability for screening for osteoporosis [7]. Although the report recognised the ‘heterogeneity of skeletal and extraskeletal factors in the causation of fractures’, BMD alone was used in defining clinical fracture risk, which possibly reflected an interest in the latest developments in densitometry and the need to define easily measurable levels of fracture risk to justify pharmacological interventions. Consideration was given in the report to the use of standard deviation from the mean (Z-scores) for BMD and it was suggested that thresholds for treatment might be set at a level of BMD below the normal for the population or thresholds for BMD set above that of patients sustaining a fracture. For example, either BMD more than a defined level below the mean for the normal population or a BMD less than a defined level above the mean for fracture patients could define a group at higher fracture risk. A third suggested approach was to generate a lifetime risk of fragility fracture based on BMD with perhaps a doubling...
of mean fracture risk for younger age defining a treatment threshold.

The 1994 report concluded that a T-score should be used, based on the BMD results of ‘normal’ healthy women at the age they achieve peak bone mass. A threshold for considering treatment was set at 2.5 SD below that mean, defining osteoporosis. This results in the thresholds for diagnosis we still use today of normal (T-score >−1.0), osteopenia (T-score ≤−1.0 but >−2.5), osteoporosis (T-score ≤−2.5) and severe osteoporosis (T-score ≤−2.5 and a fragility fracture). These thresholds represented a potentially useful method for the identification of a population at risk of fracture. In developing such a tool, justification on how to assess risk, with some evidence on who to assess and when to assess is needed. A valid method will allow us to identify those who may benefit from treatment and this should be informed by clinical trials with a decrease in fracture incidence as the only logical outcome. The final component, for which there appears to be scant evidence still, is the choice of treatment, based on superior clinical efficacy and health economic analysis (Figure 1). We certainly owe a lot to the WHO report from 1994, which helped to standardise a diagnostic approach in osteoporosis, and it is easy to criticise in retrospect, but confusion of fracture risk assessment and identification of treatment thresholds was already present in the 1994 document. However, it was probably unduly influenced by the already established use of BMD in early clinical trials of osteoporosis treatments [8], which showed measurable changes: initially, for hormone replacement therapy in postmenopausal women and subsequently with bisphosphonates [9, 10]. The use of BMD as a proxy for fracture risk has also driven the clinical research agenda to focus on a diagnostic threshold primarily based on BMD at the age of peak bone mass (the T-score). However, using this approach, a third of 70 year olds and more than half of 80 year olds have osteoporosis, since the average T-score at this age is <−2.5 [11]. Moreover, there are a number of high-risk groups such as patients on glucocorticoids [12], and patients about to commence androgen deprivation therapy [13] or anti-oestrogens [14] in whom fracture risk may be greater than suggested by BMD alone or for whom treatment may be offered to decrease risk of other complications such as bony metastasis.

Clinical risk factors

As already mentioned, there are a number of skeletal and non-skeletal clinical risk factors (CRFs) which predict fracture risk. The most conspicuous skeletal risk factor remains low BMD [15], but other measures such as aspects of bone geometry, including hip axis length, may also be relevant and partially explain genetic and racial differences in fracture risk [16, 17]. Some extra-skeletal risk factors may represent causes of secondary osteoporosis such as hypogonadism or other risks associated with bone quality, such as chronic kidney disease [18]. However, some factors may be truly extra-skeletal, for example, reflecting an increased risk of frailty and falling with associated fracture. Recognition that CRFs are important has led to the development of more complex fracture risk assessment tools. Early work, by Kanis et al. found that BMD predicted hip fracture in previously studied populations, with a gradient of risk (GR, presented as risk ratio/SD change in risk score) of 3.7/SD. The inclusion of CRFs with BMD was associated with a higher GR of 4.2/SD, whereas CRFs alone had a lower GR of 2.1/SD [19]. With the backing of the WHO, refinement of the methodology has resulted in FRAX®, which was launched in 2008 [20]. However, at least 12 fracture risk assessment tools have now been evaluated and they include up to 31 different CRFs [21]. The use of 10-year fracture risk (rather than a densitometric diagnosis of osteoporosis) is one important outcome of this approach.

Alternative fracture risk assessment tools

FRAX® [22] and QFracture [23] are the most commonly used tools for assessing fracture risk in the UK. Both use CRFs to estimate a 10-year risk of major osteoporotic fracture and hip fracture, with FRAX® using data derived from epidemiological studies and the results of placebo-controlled arms of clinical studies to estimate fracture risk. Whereas QFracture uses routine clinical data from British general practice surgeries, on more than 5 million British patients attending their own GPs [24]. Both tools were recently recommended by the National Institute for Health and Clinical Excellence (NICE) in England and Wales for the assessment of fragility fracture risk [25]. A comparison of FRAX® and QFracture is presented in Table 1. However, the Garvan tool has also been included as it may be of particular interest to geriatricians, as it is very simple with only five CRFs, including a history of falls (unlike FRAX®), and is aimed at assessing fracture risk in patients who are older.

Only three tools are presented here but there are many used to assess fracture risk (as well as predicting low BMD), which have been comprehensively reviewed by Rubin et al. [21]. Overall, there is no evidence for superiority of any one tool over another; nor is there evidence that complex tools with multiple CRFs are superior to simpler tools or (most importantly) is there yet any evidence of the clinical effectiveness of tools in preventing fractures. Methods of development, validation and transparency relating to comparable risk assessment tools have also been critically reviewed, and there is clearly more work to be done in identifying which methods work the best in which populations [21, 26].

Figure 1. The place of fracture risk assessment in providing a tool for treatment choice.
NICE technology appraisals and fracture risk assessment

In England and Wales, NICE issued revised guidance on the primary and secondary prevention of osteoporotic fracture in postmenopausal women in 2010 and 2011 [27–29], incorporating aspects of fracture risk assessment, osteoporosis treatment thresholds and treatment choices (see Figure 1). The appraisal committee considered the evaluation of 10-year fracture risk, and FRAX® in particular, but stated that ‘recommendations about treatment should [not] be based on absolute risk as calculated using FRAX®.’ The committee did not agree that all CRFs used in FRAX® were appropriate and also said that absolute fracture risk was not directly related to cost effectiveness, since ‘different fracture sites have different impacts on quality of life, costs and mortality’ [27]. The resultant Technology Appraisals in England and Wales have proved difficult to implement. They require a DXA scan diagnosis of osteoporosis (T-score ≤−2.5), although this is not considered necessary in women aged 75 years or older, in whom osteoporosis ‘may be assumed’ if the clinician thinks DXA scan is ‘inappropriate or unfeasible’. The resultant guidance set differing treatment thresholds, based on health economic analysis. For the patient intolerant of alendronate, a lower BMD is required together with more CRFs in most cases, before she is allowed to take an alternative bisphosphonate or strontium ranelate. The guidance specifically does not apply to (primary or secondary) fracture prevention in patients on glucocorticoids; nor is there reference made to other patients at risk of secondary osteoporosis, due to conditions such as diabetes mellitus [30], chronic liver disease or thyroid disorder.

The National Osteoporosis Guideline Group

Partly in response to difficulties in implementing NICE guidance, 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 and are supported by a number of agencies, including the British Geriatrics Society, Royal College of Physicians and National Osteoporosis Society [31]. The essentials of NOGG are that:

(i) A history of a fragility fracture in a postmenopausal woman should prompt consideration for treatment (irrespective of BMD);

(ii) 10-year fracture risk should be estimated in

(a) Men aged 50 years or more with at least one CRF (derived from FRAX®) or BMI <19 kg/m²;

(b) Postmenopausal women without fracture but with at least one CRF (derived from FRAX®) or BMI <19 kg/m².

Table 1. Comparison of some commonly used fracture risk assessment tools

<table>
<thead>
<tr>
<th>Experience with the tool</th>
<th>QFracture</th>
<th>FRAX®</th>
<th>Garvan</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMD</td>
<td>Cannot use BMD</td>
<td>With/without BMD or weight required</td>
<td>BMD or weight required</td>
<td>BMD is variably (but not consistently) reported to improve the performance of FRAX® [33,48,49]. Garvan requires either BMD (unspecified site on web page) or weight. However, BMD cannot be interpreted with QFracture.</td>
</tr>
<tr>
<td>Age range</td>
<td>30 to 99 years</td>
<td>40 to 90 years</td>
<td>60 to 96 years</td>
<td>QFracture applies to a wide age range; FRAX® excludes the very old and (less significantly, perhaps) the young (&lt;40 years); but Garvan has been developed in an old population</td>
</tr>
<tr>
<td>Fracture risk estimate</td>
<td>available yearly to 10-year</td>
<td>10-year only</td>
<td>5-year and 10-year</td>
<td>FRAX® uses data from clinical trials identifying incident fractures; QFracture data are from routine GP records. Historically, fragility fracture records have been poor in UK general practice. Garvan is derived from the Dubbo Epidemiological Study, Australia with good fracture ascertainment</td>
</tr>
<tr>
<td>Risk factors</td>
<td>n = 31, dose response on most variables</td>
<td>n = 11, simple clinical data with no dose response</td>
<td>n = 5, very simple clinical data with dose response for falls</td>
<td>A dose response is included for most variables in QFracture but not for FRAX®. The FRAX® website advises that estimates are influenced by, for example, number of cigarettes or glucocorticoid dose, for which guidance on dose response has recently been published [42]. Fewer data are required for FRAX® (or Garvan) than for QFracture, while, data on variables such as parental fracture are seldom collected in routine GP practice. More risk factors contribute to QFracture and Garvan probably works best with DXA scan. For the geriatrician, these tools may be of particular interest as ‘falls’ (and for QFracture ‘dementia’) are included</td>
</tr>
</tbody>
</table>
The resultant 10-year fracture risk estimate can then be plotted against age. In Figure 2a, the upper (red) zone corresponds to a recommendation for treatment, the lower (green) zone for lifestyle advice and reassurance. If the risk falls between the two in the middle (amber) zone DXA scanning is recommended to refine the risk estimate. The refined estimate should be plotted on Figure 2b to prompt a decision about treatment: patients in the green zone have a fracture risk estimate less than the average risk associated with a fragility fracture at that age. Those in the red zone have a fracture risk greater than expected for a patient with a fragility fracture at that age.

NOGG is commonly used in clinical practice. It starts with recognition that an incident fragility fracture is a risk for further fragility fracture and warrants treatment. In the absence of a fragility fracture, 10-year fracture risk can be interpreted in the context of age to decide who should be considered for a DXA scan and who should then be considered for treatment. It is counter-intuitive that the threshold for treatment increases so steeply with age and it is not commonly realised that this threshold 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.

**NICE short clinical guideline**

NICE first started looking at risk assessment for osteoporosis in 2010 and, by Spring 2011, a considerable amount of work had been done in scoping the project to evaluate fracture risk assessment tools. The short clinical guideline CG146 Osteoporosis: assessing the risk of fragility fracture was published in August 2012 [32]. It focuses on: who to assess, how to assess them and when to re-assess their fracture risk. For those aged 40–50 years of age fracture risk assessment is not advocated, unless patients have major risk factors, which comprise: glucocorticoid therapy, untreated premature menopause or previous fragility fracture.

**Who?**

The guideline suggests that fracture risk is assessed in women aged over 64 years and men over 74 years. For patients aged over 50 years, the presence of CRFs should prompt an assessment of fracture risk. The CRFs comprise previous fragility fracture, glucocorticoid treatment, a history of falls, a family history of hip fracture, other secondary causes (with an extensive list), low BMI (<18.5 kg/m²), smoking or alcohol (more than 14 units per week for women and more than 21 units per week for men).

**How?**

FRAX® or QFracture should be used to estimate absolute risk when assessing risk of fracture and this should be done using either FRAX® (without BMD) or QFracture to calculate 10 year predicted absolute fracture risk. However, we should recognise underestimation of fracture risk, including the clinical contexts 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 be recalculated after a minimum of 2 years if the original risk was close to an intervention threshold for a proposed treatment or when there has been a change in the person’s risk factors (e.g. fracture).

**Does DXA help?**

The NICE clinical guidelines discourage routinely measurement of BMD without prior assessment using FRAX® or QFracture and argue against routine DXA scanning as there appears to be little evidence that BMD significantly improves performance, even added to FRAX®, as reclassification rarely moves individuals from high to low risk or vice versa [33]. However, there is some evidence that DXA scanning does help refine estimates of fracture risk [34–36].

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Figure 2. The National Osteoporosis Guideline Group (NOGG) interpretation of fracture risk. [Figures reproduced with permission of National Osteoporosis Guideline Group (NOGG, with thanks to Prof. Eugene McCloskey)].
evidence of refined fracture risk with DXA may support the approach used in the NOGG algorithm where that threshold is set as the expected subsequent fracture risk after an index fragility fracture. One disadvantage of the QFracture tool is that it 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. However, BMD may contribute to treatment decisions and current NICE TAs for osteoporosis treatment include thresholds for BMD (at least for postmenopausal women aged under 75 years). CG146 recommends that BMD measurement should be considered ‘if fracture risk is in the region of an intervention threshold for a proposed treatment’ or ‘before starting treatments that may have a rapid adverse effect on bone density (for example, sex hormone deprivation for treatment for breast or prostate cancer)’ and the guideline also highlights that the evaluation of fracture risk in younger people is more difficult and recommends expert opinion, probably with DXA.

Horizon scanning

This has been a slightly historical review and current summary of where we are with regard to fracture risk assessment. There are some gaps in our knowledge but perhaps we can anticipate where we might be going in the future. One current problem is the application of the evidence base. Since the 1994 WHO densitometry criteria have been so influential, virtually all evidence of treatment benefit is based on randomised clinical trials recruiting using BMD T-score criteria. One study has shown that high fracture risk, estimated using FRAX®, was associated with the greatest fracture risk reduction in response to treatment with clodronate [37]. Another clinical trial (SCOOP) is currently underway, screening a large UK population of women aged 70–85 years, using FRAX® (with BMD). The intervention arm will have prescription of bone protective therapy recommended for participants above an age-defined threshold of fracture probability. The control arm will receive ‘usual care’. While ‘contamination’ of the control arm resulting in treatment is likely, this study will contribute to the necessary evidence base on the value of CRFs in prioritising treatment.

Continued work to clarify the role of BMD measurement in assessing fracture risk is needed. For example, although spinal BMD measurements are not considered in FRAX®, vertebral fractures are a significant source of morbidity [38] and an independent predictor of fracture risk [39]. Attempts have been made to adjust fracture risk estimates, where there is a considerable disparity in BMD between the spine and the hip [40], and we certainly see a number of patients with spinal osteoporosis with or without vertebral fractures, who should be considered for treatment, irrespective of the hip BMD. Similarly, fracture risk assessment tools vary in their performance across a number of subgroups, which have already been highlighted by the NICE guidance CG146. Such patients include the frail, those who fall, older people living in care homes, those on glucocorticoids and those treated with androgen deprivation therapy or anti-oestrogens. For some, fracture risk assessment may fail to consider competing risks of mortality [41]; whereas for others, current BMD may contribute to an under-estimate of fracture risk, as seen with anti-oestrogens and anti-androgens, used in cancer treatment [42–45]. A similar effect is evident in the case of glucocorticoids therapy, which is complicated further by a significant dose effect, for which a further weighting has been suggested (i.e. estimated fracture risk to be decreased or increased according to the dose [42]) and the latest version of the NOGG guidelines incorporates a dose–response element, with three points now appearing on the graph corresponding to low, medium and high dose therapy [46]. The updated NOGG guideline focuses on fracture risk assessment, including the interpretation of 10-year fracture risks derived using FRAX®. However, it also moves on a little from fracture risk assessment, acknowledging newer information on the balance of benefits with risks of treatment, including vitamin D, calcium and other anti-resorptive therapies and the role of the ‘drug holiday’ [46] Ultimately, no predictor of fracture risk can identify all patients before they sustain a fragility fracture. However, we have come a long way in 30 years from a primarily anatomical diagnosis of osteoporosis ‘associated with decreased bone mass [and] an increased susceptibility to fractures’[1] to clinically relevant case finding strategies, supported by effective agents, which can decrease the risk of future fragility fracture.

Key points

- Fracture is the primary clinical outcome of concern in osteoporosis.
- Although BMD has been an important tool for a number of years, increasingly CRFs are being used to refine estimates of fracture risk.
- Fracture risk assessment tools commonly used include FRAX®, QFracture and Garvan.
- The National Institute for Health and Clinical Excellence (NICE) has recently advocated the use of these methods in case finding and studies are underway in their clinical application.
- The operational definition of osteoporosis must now include fracture risk, which may be used in future studies to define patient groups likely to benefit from intervention.
- We need to understand more about these tools, particularly in specific patient groups, such as those with vertebral osteoporosis, the frail, those who fall and patients with secondary osteoporosis.

Conflicts of interest

None declared.

References

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