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**AUTHOR QUERIES**

No Queries
FRAX and fracture prediction without bone mineral density

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ABSTRACT
The major application of FRAX in osteoporosis is to direct pharmacological interventions to those at high risk of fracture. Whereas the efficacy of osteoporosis treatment, with the possible exception of alendronate, is largely independent of baseline bone mineral density (BMD), it remains a widely held perception that osteoporosis therapies are only effective in the presence of low BMD. Thus, the use of FRAX in the absence of BMD to identify individuals requiring therapy remains the subject of some debate and is the focus of this review. The clinical risk factors used in FRAX have high evidence-based validity to identify a risk responsive to intervention. The selection of high-risk individuals with FRAX, without knowledge of BMD, preferentially selects for low BMD and identifies a risk that is responsive to pharmacological intervention. The prediction of fractures with the use of clinical risk factors alone in FRAX is comparable to the use of BMD alone to predict fractures and is suitable, therefore, in the many countries where facilities for BMD testing are sparse. In countries where access to BMD is greater, FRAX can be used without BMD in the majority of cases and BMD tests reserved for those close to a probability-based intervention threshold. Thus concerns surrounding the use of FRAX in clinical practice without information on BMD are largely misplaced.

Introduction
The aim of treatments for osteoporosis is to decrease the risk of fragility fractures. Thus, the ability to assess fracture risk is critical in identifying patients who are eligible for intervention1,2. In 2008, the World Health Organization (WHO) Collaborating Centre at Sheffield, UK released FRAX® – the fracture risk assessment tool for estimating individualized 10-year probability of hip and major osteoporotic fracture (hip, clinical spine, distal forearm, and proximal humerus)3. The FRAX tool integrates eight clinical risk factors (CRFs: prior fragility fracture, parental hip fracture, smoking, systemic glucocorticoid use, excess alcohol intake, body mass index, rheumatoid arthritis, and other causes of secondary osteoporosis), which, in addition to age and sex, contribute to a 10-year fracture risk estimate independently of bone mineral density (BMD)2,4. BMD from the femoral neck is an optional input variable when FRAX is used to calculate 10-year fracture probability5.

Fracture probability is computed taking both the risk of fracture and the risk of death into account. This is important because some of the risk factors affect both these outcomes. Examples include increasing age, low body mass index (BMI), low BMD, glucocorticoids and smoking. Other risk engines calculate the risk of a clinical event without taking into account the possibility of death from other causes6,7.

Fracture probability differs markedly in different regions of the world8 and FRAX models are calibrated to the epidemiology of fracture and death in different countries. Models are currently available for 57 countries comprising 79% of the world population9. The model is available in 27 languages and the website (http://www.shef.ac.uk/FRAX) receives approximately 3 million visits annually. The importance of this tool in clinical practice is highlighted by the many published clinical guidelines and health technology assessments recommending treatment on the basis of 10-year fracture probability10–24.

Despite the wide acceptance of FRAX, there has been controversy surrounding its use in clinical practice without information on BMD25–28. The argument runs that efficacy for agents to reduce fracture risk has not been tested in patients selected on the basis of FRAX probabilities. Rather, the entry criteria for most clinical trials of primary prevention in osteoporosis have been based upon the presence of a reduced BMD. Moreover, it has been suggested that such agents do not work in...
patients not selected on the basis of BMD\textsuperscript{29,30}. Thus, with some exceptions (e.g. a prior hip or spine fracture), it is argued that FRAX should not be used in the absence of information on BMD. The view is sufficiently pervasive that the National Osteoporosis Foundation and the International Society for Clinical Densitometry called on the manufacturers of BMD equipment in 2009 to introduce a ‘FRAX filter’ in the US that, by default, suppressed the output of fracture probabilities on the densitometry report in patients with a T-score of -1 SD or greater\textsuperscript{25,31}. The effect of this is to undermine confidence in the use of FRAX (and indeed any treatment) in the absence of a BMD measurement. This paper briefly reviews the evidence for and against this view. A fuller account is presented elsewhere\textsuperscript{32}. Other uses of FRAX, for example, in guideline development, drug registration and health economic applications are reviewed elsewhere\textsuperscript{13–37}.

The notion that treatment should not be recommended in the absence of a BMD test demands a consideration of current treatment guidelines that use FRAX without BMD, the identification of susceptible risk, the performance characteristics of FRAX, and the clinical justification for undertaking a BMD test in the presence of FRAX.

Risk factors and reversibility of risk

There are a number of factors to be considered in the selection of risk factors for case-finding\textsuperscript{32}. An important consideration is the reversibility of risk, i.e. is there evidence that the risk identified by a risk factor is amenable to therapeutic intervention? It is important to draw the distinction between reversible risk and reversibility of risk. An example of the latter ad absurdum, is the high risk of fracture when jumping to the ground from a high-rise building. Although the fracture risk is high, there is little reason to believe that a pharmacological intervention would in any way affect the risk. It would be inappropriate, therefore, to identify such populations in a case-finding strategy. Age is an example of an irreversible risk factor, but the risk of fracture identified by age has reversibility in that interventions induce reductions in fracture risk irrespective of age. The risk factor that is best evaluated in this way is BMD. In recent years, other trials have recruited patients on the basis of age, sex, a prior vertebral fracture, and current exposure to glucocorticoids irrespective of BMD, and have shown therapeutic effects similar to those noted in randomized, controlled trials (RCTs) based on BMD selection\textsuperscript{38–44}. For other risk factors, comparable data are lacking. In the absence of such data, an alternative approach is to demonstrate that the presence (or absence) of a risk factor does not adversely influence therapeutic efficacy against fractures. Systematic studies of RCTs have shown no or limited significant interactions between response to treatment and the presence or absence of any of the risk factors used in FRAX, including age, height, family history of fracture, low body weight or BMI, smoking, alcohol intake, or prior non-vertebral fracture\textsuperscript{12,44–52}. In contrast, some commonly used risk factors\textsuperscript{6,7} may be associated with less reversibility of risk. For example, patients selected on the basis of risk factors for falling may respond less completely to agents that preserve bone mass than those selected on the basis of low BMD\textsuperscript{30}.

Evidence for reversibility of risk is also available from the phase 3 of RCTs in which FRAX-based probabilities were calculated in \textit{post hoc} analyses. These studies examined the interaction between FRAX-based probabilities (rather than the FRAX risk factors) with effectiveness. Two of these re-analyses of clinical trial data have shown greater efficacy against fracture in individuals at higher risk treated with clodronate or ibandronate\textsuperscript{48,53,54} whereas others have shown benefit of strontium ranelate, teriparatide or raloxifene across the range of fracture probabilities (with greater absolute risk reductions in those at higher risk\textsuperscript{55–58}). In a further pre-planned analysis of the FREEDOM trial, greater efficacy against fracture was shown in individuals at higher risk treated with denosumab\textsuperscript{49}. These RCT data strongly suggest that FRAX (with and without BMD) identifies high-risk patients who respond to pharmaceutical interventions.

A second consideration relates to the effects of treatment in patients in whom BMD is unknown or who have normal BMD. It might be argued that treatment will be ineffective in those patients with normal BMD, but at high risk when assessed by FRAX in the absence of BMD. There are several lines of evidence that suggest that responses to treatment are independent of BMD. First, many studies have shown no significant interaction between response to treatment and the baseline BMD. The lack of an interaction with BMD has been shown for risedronate\textsuperscript{44,59,60}, raloxifene\textsuperscript{46,52,55}, ibandronate\textsuperscript{54} and denosumab\textsuperscript{49,62}. It is relevant to note that several of these studies preferentially enrolled patients with low BMD (e.g. a T-score of -2.0 standard deviations (SD) or less), but one trial enrolled patients with osteopenia in which efficacy for raloxifene was demonstrated for vertebral fracture risk\textsuperscript{46} and another was a random population sample in which efficacy for clodronate was shown for non-vertebral fracture risk\textsuperscript{48}. One study, the FIT II study with alendronate, suggested in a \textit{post hoc} analysis that...
treatment efficacy was BMD-dependent. In another sub-group analysis, efficacy of denosumab on non-vertebral fracture risk was confined to patients with osteoporosis at the femoral neck, findings that were not reproduced when BMD was considered as a continuous variable. Moreover, the efficacy of denosumab in breast cancer patients on aromatase inhibitors was similar over the entire range of BMD. This large body of data on a wide variety of interventions indicates that treatment effects, with the possible exception of alendronate, are not dependent on baseline BMD.

Supporting evidence for this conclusion is that intervention in the general population or populations not selected on the basis of low BMD induces therapeutic results similar to those expected in individuals selected to be at high risk.

These data indicate that efficacy is not downgraded when patients are allocated to treatment on the basis of FRAX CRFs.

**BMD in patients selected by FRAX without BMD**

The CRFs used in FRAX are not totally independent of BMD. Indeed there is a weak but significant correlation between the clinical risk factor score for hip fracture (assessed without BMD) and BMD at the femoral neck ($r = -0.25$). This indicates that the selection of individuals with the use of FRAX, without knowledge of BMD, will preferentially select those with low BMD; and that the higher the fracture probability, the lower will be the BMD.

This inference has been addressed in a randomly drawn sample of elderly women (aged 75 years or more) from Sheffield, UK. Approximately 2000 women were assessed at baseline for risk factors for fracture, had a baseline BMD test performed at the femoral neck and were followed up monthly to record fractures and deaths for 6700 patient-years. In women characterized by fracture probability (a precursor of FRAX but not FRAX itself) without the inclusion of BMD in the model, mean BMD values were progressively lower with increasing 10-year probability of a major fracture (Figure 1). In women above an arbitrary risk threshold (30% 10-year fracture probability in Figure 1), the mean BMD was approximately 1 SD lower than in women below the threshold.

Similar finding were reported in a large referral population from Manitoba, Canada. In this study, the minimum T-score (of measurements at the femoral neck, total hip, trochanter or lumbar spine) decreased progressively with increasing FRAX probability measured without BMD. Thus, in patients categorized at low risk using FRAX without BMD (<10% probability of a major fracture), the mean minimum T-score was $-1.5$ SD. In those at intermediate risk (10–19% probability), the T-score was $-2.2$ SD, and in those at high risk (≥20% probability) it was $-2.8$ SD.

These findings consistently indicate that the categorization of patients at high risk on the basis of FRAX without BMD selects patients with low BMD, and the higher the probability, the lower the BMD.

**Performance of FRAX without BMD**

For the purpose of risk assessment diagnosis, a characteristic of major importance is the ability of a technique to predict fractures. This is traditionally expressed as the increase in relative risk per SD unit decrease in risk score – termed the gradient of risk. The performance characteristics of FRAX have been determined using information derived from the primary data of nine population-based cohorts from around the world and validated in many independent cohorts with a similar geographic distribution with in excess of 1 million patient-years. The gradient of risk is shown in Table 1 for the use of the clinical risk factors alone, femoral neck BMD and the combination.

The principal finding is that the use of clinical risk factors alone provides some discriminative value in the categorization of fracture risk. The use of clinical risk factors alone provided a gradient of risk that lay between 1.4 and 2.1, depending upon age and the type of fracture predicted. These gradients are comparable to the use of BMD alone to predict fractures. These data suggest that clinical risk factors alone are of value and
might be used, therefore, in the many countries where DXA facilities are sparse70.

**Case finding with FRAX**

The use of FRAX in clinical practice demands a consideration of the fracture probability at which to intervene, both for treatment (an intervention threshold) and for BMD testing (assessment thresholds). Many approaches have been used to set intervention thresholds with FRAX11,12,14,17,18,20,22–24,71–77. The thresholds used have varied since they depend critically on local factors such as reimbursement issues, health economic assessment, willingness to pay for health care in osteoporosis and access to DXA. For this reason, it is not possible or desirable to recommend a unified intervention strategy.

A general approach is shown in Figure 2. 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. Many guidelines15,28,77–81 recommend treatment in the absence of information on BMD in women with a previous fragility fracture (a prior vertebral or hip fracture in North America). Many physicians would also perform a BMD test, but frequently this is for reasons other than to decide on intervention, for example, as a baseline to monitor treatment. 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 be the well woman at menopause with no clinical risk factors. Thus, not all individuals require a BMD test. The size of the intermediate category in Figure 3 will vary in different countries. In the US, this will be a large category, whereas, in a large number of countries with limited or no access to densitometry, the size of the intermediate group will necessarily be small. In other countries (e.g. the UK), where provision for BMD testing is sub-optimal70, the intermediate category will lie between the two extremes. It has been conservatively estimated that a minimum of 10 DXA units are required per million of the population and such provision is available for less than 20 countries world-wide70.

**Use of FRAX without BMD**

As noted above, many guidelines recommend that women with a prior fragility fracture may be considered for intervention without the necessity for a BMD test (other than to monitor treatment). Since a prior fracture can be considered to carry a sufficient risk that treatment can be recommended, the intervention threshold in women without a prior fracture can be set at the age-specific fracture probability equivalent to women with a prior fragility fracture74 and therefore rises with age from 10-year probability of 8 to 33% in the UK. In other words, the intervention threshold is set at the ‘fracture threshold’. This is the approach to intervention thresholds used in France, Switzerland and by the National Osteoporosis Guideline Group (NOGG) for the UK10,11,75. Incidentally, the same intervention threshold is applied to men, since the effectiveness and cost-effectiveness of intervention in men are broadly similar to those in women for equivalent risk82–84. The approach used has

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**Table 1. Gradients of risk per standard deviation change in risk score (with 95% confidence intervals) with the use of bone mineral density (BMD) at the femoral neck, clinical risk factors or the combination**

<table>
<thead>
<tr>
<th>Age (years)</th>
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<th>Clinical risk factors alone</th>
<th>Clinical risk factors + BMD</th>
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<tr>
<td>Hip fracture</td>
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<td></td>
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<tr>
<td>50</td>
<td>3.68 (2.61–5.19)</td>
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<tr>
<td>60</td>
<td>3.07 (2.42–3.89)</td>
<td>1.95 (1.63–2.33)</td>
<td>3.51 (2.85–4.33)</td>
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<tr>
<td>70</td>
<td>2.78 (2.39–3.23)</td>
<td>1.84 (1.65–2.05)</td>
<td>2.91 (2.56–3.31)</td>
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<tr>
<td>80</td>
<td>2.28 (2.09–2.50)</td>
<td>1.75 (1.62–1.90)</td>
<td>2.42 (2.18–2.69)</td>
</tr>
<tr>
<td>90</td>
<td>1.70 (1.50–1.93)</td>
<td>1.66 (1.47–1.87)</td>
<td>2.02 (1.71–2.38)</td>
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Other osteoporotic fractures

<table>
<thead>
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<th>Age (years)</th>
<th>BMD only</th>
<th>Clinical risk factors alone</th>
<th>Clinical risk factors + BMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>1.19 (1.05–1.34)</td>
<td>1.41 (1.28–1.56)</td>
<td>1.44 (1.30–1.59)</td>
</tr>
<tr>
<td>60</td>
<td>1.28 (1.18–1.39)</td>
<td>1.48 (1.39–1.58)</td>
<td>1.52 (1.42–1.62)</td>
</tr>
<tr>
<td>70</td>
<td>1.39 (1.30–1.48)</td>
<td>1.55 (1.48–1.62)</td>
<td>1.61 (1.54–1.68)</td>
</tr>
<tr>
<td>80</td>
<td>1.54 (1.44–1.65)</td>
<td>1.63 (1.54–1.72)</td>
<td>1.71 (1.62–1.80)</td>
</tr>
<tr>
<td>90</td>
<td>1.56 (1.40–1.75)</td>
<td>1.72 (1.58–1.88)</td>
<td>1.81 (1.67–1.97)</td>
</tr>
</tbody>
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**Figure 2. Management algorithm for the assessment of individuals at risk of fracture. CRF, clinical risk factor; BMD, bone mineral density. Adapted from reference 74 with kind permission from Springer Science and Business Media.**

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been well validated and the intervention strategy shown to be cost-effective.\textsuperscript{65,66,74,85–87}

Using the same criteria, the intervention threshold will vary from country to country because the population risks (of fracture and death) vary\textsuperscript{8} (Figure 4).

The UK guidance of the NOGG is a good example of treatment decisions only partly dependent on BMD testing\textsuperscript{11,74}. As above, women with a prior fragility fracture may be considered for intervention without the necessity for a BMD test. In women without a fragility fracture, the intervention threshold set by NOGG is also set at the age-specific fracture probability equivalent to women with a prior fragility fracture.

The management strategy considers two additional thresholds (Figure 3)\textsuperscript{15}.

- A threshold probability below which neither treatment nor a BMD test should be considered (lower assessment threshold);
- A threshold probability above which treatment may be recommended irrespective of BMD (upper assessment threshold).

In other words, some patients at high risk may be offered treatment without recourse to BMD testing. Conversely, some patients at low risk will appropriately be denied treatment without a BMD test. The attraction of the approach is that efficient use is made of BMD testing. For example, the NOGG strategy requires only 3.5 scans at the age of 50 years to identify one case of hip fracture, whereas the former guidelines of the Royal College of Physicians required 13.9\textsuperscript{86}.

The justification for this parsimonious approach derives from the fact that reclassification of patients from high risk to low risk (and from low risk to high risk) very rarely occurs in individuals that are above the upper assessment threshold (and vice versa)\textsuperscript{65,66}.

Conclusions

The use of clinical risk factors alone in FRAX provides some discriminative value in the categorization of fracture, providing a gradient of risk that lies between 1.4 and 2.1, depending upon age and the type of fracture predicted. These gradients are comparable to...
the use of BMD alone to predict fractures and suggest
that clinical risk factors alone are of value and might be
used, therefore, in the many countries where DXA
facilities are sparse.

The risk factors chosen for incorporation into FRAX
have been shown to identify a risk that is responsive to
pharmaceutical intervention. Moreover, efficacy has
been demonstrated in patients with high FRAX prob-
abilities enrolled into RCTs in post hoc analyses and a
pre-planned analysis.

A large body of data, a wide variety of interventions
indicates that treatment effects, with the possible
exception of alendronate, are not dependent on base-
line BMD. Moreover, the use of FRAX, without knowl-
dge of BMD, preferentially selects individuals with low
BMD; the higher the fracture probability, the lower the
BMD. These data strongly suggest that FRAX identifies
high-risk patients that respond to pharmaceutical
interventions.

Controversy surrounding the use of FRAX in clinical
practice without information on BMD is largely spurious.
Whereas the efficacy for agents to reduce fracture risk has
not been tested prospectively in RCTs in patients selected
on the basis of FRAX probabilities, there is compelling
evidence that FRAX with or without the use of BMD
provides a well-validated instrument for targeting
patients most likely to benefit from an intervention.

Declaration of interest

John A. Kanis led the team that developed FRAX as Director of
the WHO Collaborating Centre for Metabolic Bone Diseases; he
has no financial interest in FRAX.

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