FRAX® and its applications to clinical practice


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Abstract

The introduction of the WHO FRAX® algorithms has facilitated the assessment of fracture risk on the basis of fracture probability. FRAX® integrates the influence of several well validated risk factors for fracture with or without the use of BMD. Its use in fracture risk prediction poses challenges for patient assessment, the development of practice guidelines, the evaluation of drug efficacy and reimbursement, as well as for health economics which are the topics outlined in this review.

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Introduction

FRAX® is a computer based algorithm (http://www.shef.ac.uk/FRAX) that provides models for the assessment of fracture probability in men and women [1–3]. The approach uses easily obtained clinical risk factors (CRFs) to estimate 10-year fracture probability. The estimate can be used alone or with femoral neck bone mineral density (BMD) to enhance fracture risk prediction. In addition, FRAX® uses Poisson regression to derive hazard functions of death as well as fracture. These hazard functions are continuous as a function of time which permit the calculation of the 10-year probability of a major osteoporotic fracture (hip, clinical spine, humerus or wrist fracture) and the 10-year probability of hip fracture. Some of the risk factors affect the risk of death as well as the fracture risk. Examples include increasing age, low body mass index (BMI), low BMD and smoking. Other risk engines calculate the probability of a clinical event (e.g. a myocardial infarct) without taking into account the possibility of death from other causes. In addition, the FRAX® model can be calibrated for different countries [1–3]. Probability of fracture is calculated in men or women from age, body mass index (BMI) computed from height and weight, and dichotomised risk variables that comprise;

- a prior fragility fracture,
- parental history of hip fracture,
- current tobacco smoking,
- ever long-term use of oral glucocorticoids,
- rheumatoid arthritis,
other causes of secondary osteoporosis, daily alcohol consumption of 3 or more units daily.

These variables are entered onto the web site. Femoral neck BMD can additionally be entered as a T-score derived from the NHANES III database for female Caucasians aged 20–29 years [4]. When entered, calculations give the 10-year probabilities as defined above with the inclusion of BMD (Fig. 1).

The relationships between risk factors and fracture risk incorporated within FRAX® have been constructed using information derived from the primary data of nine population based cohorts from around the world, including centres from North America, Europe, Asia and Australia and has been validated in 11 independent cohorts (mainly women) with a similar geographic distribution with in excess of 1 million patient years [5]. The use of primary data for the model construct permits the determination of the predictive importance in a multivariable context of each of the risk factors, as well as interactions between risk factors, and thereby optimises the accuracy by which fracture probability can be computed. The large sample permits the examination of the general relationship of each risk factor by age, sex, duration of follow up and, for continuous variables (BMD and BMI), the relationship of risk with the variable itself in a manner hitherto not possible. The use of primary data also eliminates the risk of publication bias.

In addition to the clinical risk factors, fracture probability varies markedly in different regions of the world [6]. Thus the FRAX® models need to be calibrated to those countries where the epidemiology of fracture and death is known. At present FRAX® models are available for Austria, China, Germany, France, Italy, Japan, Spain, Sweden, Switzerland, Turkey, and the UK and US. Other models are being developed, but there are relatively few other countries with sufficient information to construct FRAX® models [3], and these are listed below according to categories of hip fracture risk.

(a) Very high risk (e.g. Denmark, Iceland, Norway, Sweden, United States).

(b) High risk (e.g. Australia, Austria, Canada, Finland, Germany, Greece, Hungary, Italy, Kuwait, Netherlands, Portugal, Singapore, Switzerland, Taiwan, UK).

(c) Moderate risk (e.g. Argentina, China, France, Hungary, Hong Kong, Japan, Spain).

(d) Low risk (e.g. Cameroon, Chile, Korea, Turkey, Venezuela).

Each category of risk has been represented in the FRAX® models currently available (in italics, above). Thus 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.

The obvious application of FRAX® is in the assessment of individuals to identify those who would be candidates for pharmacological intervention, and it has been widely used since the launch of the web site, currently receiving on average 55,000 hits daily. But FRAX® should not be used in the clinic without an appreciation of its limitations as well as its strengths. There are also challenges to be faced in the construct of new clinical guidelines, the assessment of pharmacologic agents for drug registration (in Europe) and in health economics. These applications are the focus of this review.

Assessment of patients

Rationale for use

Until recently, the majority of clinical guidelines for the management of osteoporosis have made recommendations for intervention based predominantly on the basis of the T-score for BMD [3]. In the UK, for example, guidance for the identification of individuals at high fracture risk was provided until recently, by the Royal College of Physicians (RCP) [7–9]. The guidance was based on an opportunistic case finding strategy where physicians are alerted to the possibility of osteoporosis and high fracture risk by the presence of clinical risk factors (CRFs) associated with fracture. This provides a trigger for the measurement of BMD, and treatment was considered in those with a BMD value that lies in the range of osteoporosis as defined by the

![Fig. 1. Chart for input of data and format of results in the UK version of the FRAX® tool. (With permission of the World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield Medical School, UK.)](image)
World Health Organization (WHO). Treatment was, however, also recommended for women with a prior fragility fracture without necessarily measuring BMD. A similar approach has been used in many European countries [10–12]. The National Osteoporosis Foundation (US) adopted a similar approach, though used a less stringent T-score [13].

Since the development of such guidelines, it has become apparent that the presence of several of the risk factors used to trigger a BMD test is associated with a fracture risk greater than can be accounted for by BMD alone [14]. Thus, the assessment of fracture risk should take account of specific risk factors that contribute to fracture risk in addition to BMD, since this would increase the sensitivity for fracture prediction (i.e. detection rate of individuals who would fracture) [15]. The most obvious example is age which confers a risk greater than that accounted for by BMD. For example, from the known relationship of BMD and fracture risk, it might be expected that hip fracture risk would increase approximately 4-fold between the age of 55 and 85 years in women because of the age-related decrease in bone mass.

In practice, hip fracture risk in many countries increases 40-fold [16]. Thus, over this age range, the impact of increasing age is 11-fold greater than the impact of decreasing BMD. The interaction of age and BMD has been formalized in several studies [16,17]. In the case of DXA at the femoral neck, the risk of fracture by age varies markedly at the threshold of osteoporosis, i.e. with a T-score of exactly −2.5 SD. Thus, at the age of 50 years the 10-year hip fracture probability is approximately 2% in women but at the age of 80 years it is 12% for the same T-score (Fig. 2). For any major osteoporotic fracture (hip, forearm, shoulder or clinical spine fracture), the 10-year probability in women with a T-score of −2.5 SD ranges from 11% at the age of 50 years to 26% at the age of 80 years [16].

This simple example illustrates that fracture risk can be more accurately assessed from age and BMD than by BMD alone. Similar considerations pertain to the other clinical risk factors used in FRAX®, which each make an independent contribution to fracture risk as illustrated in Fig. 3.

Limitations

Experts in the care of patients with osteoporosis are used to integrating information derived from multiple risk factors. If a physician is prepared to treat a patient with a T-score of say, −2.5 SD, then intuitively the fact that a patient is additionally taking oral glucocorticoids would lead him to intervene at a higher T-score. By contrast, primary care physicians in most countries have little expert knowledge and it is this constituency for which FRAX® is primarily designed.

The use of FRAX® with the generation of a number does not, however, replace clinical judgment. For example, several of the clinical risk factors identified take no account of dose–response, but give risk ratios for an average dose or exposure. By contrast, there is good evidence that the risk associated with excess alcohol consumption, cigarette smoking and the use of glucocorticoids is dose-responsive [18–20]. In addition, the risk of fracture increases progressively with the number of prior fractures [21,22]. These limitations should be recognised when interpreting the FRAX® result in the clinic.

It should also be acknowledged that there are many other risk factors for fracture that are not incorporated into assessment algorithms. Examples include the biochemical markers of bone turnover,
risk factors for falls and previous exposure to pharmacologic intervention. The reason for not including such risk factors in FRAX® relates to the paucity of large international data bases, but the clinician may wish to take such information into account.

At present the FRAX® tool limits BMD to that measured at the femoral neck. This is because of the wealth of data available for this site. It has the advantage that for any given age and BMD, the fracture risk is approximately the same in men and women [23]. Because of this, the T-score is derived from a single reference standard (the NHANES III database for female Caucasians aged 20–29 years) as widely recommended [3, 24]. There are, however, other bone measurements that provide information on fracture risk [3]. These include BMD at other skeletal sites [25], quantitative ultrasound [26] or computed tomography [27] and the biochemical indices of bone turnover [28]. The available information was too sparse to provide a meta-analytic framework for the present version of FRAX®, but other assessment tools should be incorporated into risk assessment algorithms when they are more adequately characterised.

 Provision is made for the inclusion of many secondary causes of osteoporosis. A distinction is made between rheumatoid arthritis and other secondary causes. There is good evidence that rheumatoid arthritis carries a fracture risk over and above that provided by BMD [29]. Whereas this may hold true for other secondary causes of osteoporosis, the evidence base is weak. For this reason, the other secondary causes of osteoporosis are conservatively assumed to mediate fracture risk as a result of low BMD. It is assumed that they increase fracture risk in a manner similar to patients with rheumatoid arthritis. However, when BMD is entered into the FRAX® equations, no weight is accorded by these other secondary causes [1].

 For these reasons, the FRAX® tool should not be considered by physicians as a gold standard, but rather as a platform technology on which to build as new validated risk indicators become available. Nevertheless, the present model provides an aid to enhance patient assessment by the integration of clinical risk factors alone and/or in combination with BMD.

Clinical guidelines

The application of this methodology to 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). These have been developed for Europe, Canada, Germany, Japan, the UK and US [11, 30–34]. There have been two approaches to the development of guidelines based on fracture probability. The first is to ‘translate’ current practice in the light of FRAX®, and the second has been to determine the threshold fracture probability at which intervention becomes cost-effective. The latter approach is discussed in the section on health economic use of FRAX®.

The UK guidance for the identification of individuals at high fracture risk developed by the National Osteoporosis Guideline Group (NOGG) is an example of the translation of existing guidance provided by the Royal College of Physicians (RCP) [7–9] into probability based assessment [35]. As with the RCP guidance, the strategy is based on opportunistic case finding where physicians are alerted to the possibility of increased fracture risk by the presence of clinical risk factors (CRFs). The clinical risk factors used differ somewhat from those of the RCP, and comprised those used in the FRAX® algorithms together with low BMI (<19 kg/m²).

The RCP guidance indicates that women with a prior fragility fracture may be considered for intervention without the necessity for a BMD test, and the management of women over the age of 50 years on this basis has been shown to be cost-effective [36]. For this reason, the intervention threshold set by NOGG was at the fracture probability equivalent to women with a prior fragility fracture without knowledge of BMD [35]. The same intervention threshold was applied to men, since the effectiveness of intervention in men is broadly similar to that in women for equivalent risk [37].

In addition to an intervention threshold, assessment thresholds for the use of BMD testing were devised. The concept of assessment thresholds is illustrated in the management algorithm given in Fig. 4 [3]. The management process begins with the assessment of fracture probability and the categorization of fracture risk on the basis of age, sex, BMI and the clinical risk factors. On this information alone, some patients at high risk may be offered treatment without recourse to BMD testing. As noted, many guidelines [7–13] recommend treatment in the absence of information on BMD in women with a previous fragility fracture. Many physicians would also perform a BMD test, but frequently this is for reasons other than to decide on intervention 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 Fig. 4 will vary in different countries, but a pragmatic strategy was used by NOGG because of the limited facilities for BMD testing in the UK [38].

The NOGG management strategy requires consideration of two additional thresholds.

- 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)

The lower assessment threshold was set to exclude a requirement for BMD testing in women of average BMI (24 kg/m²) with weak or no clinical risk factors, as given in the RCP and European guidelines [7–12]. The upper threshold was chosen to minimise the probability that a patient characterised to be at high risk on the basis of clinical risk factors alone would be reclassified to be at low risk with additional information on BMD [39]. The upper assessment threshold was set at 1.2 times the intervention threshold. The value 1.2 is arbitrary and determines the number of men and women who would be eligible for a BMD test. With this value, BMD tests would be undertaken in 15–30% of individuals depending on age (excluding those with a prior fracture) [35]. Scanning this proportion of the population maximises the positive predictive value of the assessment, at least with respect to hip fracture [40].

Fig. 4. Management algorithm for the assessment of individuals at risk of fracture [3, with permission of the World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield Medical School, UK].
The management algorithm is shown in Fig. 5 and summarised below [35]:

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

The transformation of these recommendations into a format that is readily usable by primary care physicians is not straightforward, given that intervention and assessment thresholds vary by age, and are ideally based on the probability of a hip fracture and a major fracture. The most accurate approach is a computer program and is available through http://www.shef.ac.uk/NOGG/index.htm or directly from the FRAX® site (http://www.shef.ac.uk/FRAX/index.htm). Simplified paper charts are also available [41].

Women potentially eligible for treatment using the NOGG algorithm include those with a prior fracture (irrespective of fracture probability) and those with a CRF in whom fracture probability lay above the intervention threshold for age. The numbers eligible for treatment are shown in Table 1. The proportion of the female population potentially treated varied from 24% to 47%, depending on age. The proportion of women potentially eligible for treatment increased with age, despite the apparently more stringent intervention threshold. More women with a prior fracture would be treated than women with any other CRF [35].

A similar approach has been developed in Europe by the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO), and indeed the same intervention threshold is used. The difference lies in the upper assessment threshold in that it is recommended that all patients with probabilities above the lower assessment threshold should receive a BMD test [11].

A translational approach to guideline development has also been examined in Japan [31]. In Japan, the criteria for the diagnosis of osteoporosis prepared by the Japanese Society for Bone and Mineral Research [42] are based on BMD measurements expressed as a percentages of the young adult mean (YAM) for women. In patients with no prior fragility fracture a diagnosis of osteoporosis is made and treatment recommended where the BMD is less than 70% of YAM. In patients with a previous fracture, osteoporosis is diagnosed and treatment recommended where the BMD is less than 80% of YAM. In order to compare intervention thresholds using YAM with probabilities derived from the FRAX® algorithm, T-score equivalents were used. The T-score equivalent to 70% and 80% of YAM for Japanese people is −2.7 SD and −1.8 SD respectively, using the NHANES III reference for BMD at the femoral neck in Caucasian women aged 20–29 years [4]. The probabilities equivalent to the

![Fig. 5.](http://www.shef.ac.uk/NOGG/index.htm)

**Table 1**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Intervention threshold (%)</th>
<th>Prior fracture</th>
<th>&gt;1 CRFa</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>50–54</td>
<td>7.5</td>
<td>17.1</td>
<td>6.5</td>
<td>23.6</td>
</tr>
<tr>
<td>55–59</td>
<td>10</td>
<td>21.8</td>
<td>7.0</td>
<td>28.8</td>
</tr>
<tr>
<td>60–64</td>
<td>12.5</td>
<td>26.9</td>
<td>9.3</td>
<td>35.3</td>
</tr>
<tr>
<td>65–69</td>
<td>15</td>
<td>29.0</td>
<td>9.2</td>
<td>38.2</td>
</tr>
<tr>
<td>70–74</td>
<td>20</td>
<td>30.8</td>
<td>7.0</td>
<td>37.8</td>
</tr>
<tr>
<td>75–79</td>
<td>25</td>
<td>35.9</td>
<td>5.5</td>
<td>41.1</td>
</tr>
<tr>
<td>80–84</td>
<td>30</td>
<td>41.3</td>
<td>5.2</td>
<td>46.5</td>
</tr>
</tbody>
</table>

*Excluding prior fracture and probability above the intervention threshold after testing with BMD.
current intervention thresholds vary with age and are shown in Fig. 6 against the backdrop of the European and UK intervention thresholds and show a high degree of concordance with intervention thresholds developed for the UK and Europe. Other countries that have developed or are developing translational approaches include Canada [33], Poland [43], Hong Kong [44], Switzerland [45] and Germany [30].

These translational approaches from existing treatment guidelines are characterised by an intervention threshold that increases progressively with age. The major reason for this is that the source guidelines took little or no account of age. In the UK, for example, intervention is recommended in women with a prior fragility fracture, irrespective of age. Since age is an important independent determinant of fracture probability, the fracture probability of an individual with a prior fracture is higher at the age of 70 years than at the age of 50 years. This age-dependent increase in the intervention threshold is not found when intervention thresholds are derived from health economic analyses and are discussed in the section on the health economic use of FRAX®.

Assessment of drug efficacy

Revised guidelines on the evaluation of medicinal products in the treatment of primary osteoporosis have been developed by the Committee for Medicinal Products for Human Use (CHMP) and came into effect at the end of May 2007 [46]. A major departure from previous guidance is that there is no longer any distinction between prevention and treatment, but an emphasis on the study of patients at risk from fracture. The preferred metric for expressing risk is the ten-year probability of fracture, in line with the recommendations of the WHO [2,3]. Suggested probabilities as inclusion criteria into phase III trials are given as 15–20% for spine fracture, 5–7.5% for hip fracture and 10–15% for major non-vertebral fractures. These are intended to approximate the fracture risks in previous phase III studies.

As a consequence FRAX® has been applied to several phase III studies in order to determine the enrolment characteristics of patients. A development has been to examine whether patients characterised on the basis of fracture probability respond to treatment. An example is provided in a 3-year prospective, randomized, placebo-controlled trial of oral clodronate [47]. Women aged 75 years or more living in the general community, identified from general practice registers, were given 800 mg oral clodronate or matching placebo daily over three years. Baseline risk factors, including age, BMI, prior fracture, glucocorticoid use, rheumatoid arthritis or other secondary causes of osteoporosis, smoking and maternal history of hip fracture, were used to compute the 10-year probability of a major osteoporotic fracture. Femoral neck BMD was also measured at entry. The main outcome of this analysis was the interaction between fracture probability and treatment efficacy examined by Poisson regression. Greater fracture reduction was seen at higher fracture probabilities, with or without the use of BMD [47]. Efficacy was evident at fracture probabilities that exceeded 20%. The effect was seen irrespective of whether BMD was used in the calculation of fracture probability.

Similar findings have been found for bazedoxifene [48] and other classes of agent [49]. In the phase III study of bazedoxifene, the agent significantly decreased the risk of vertebral fractures in postmenopausal women [50]. No significant effect was noted on the risk of clinical fractures, but fracture risk reduction was reported in a post hoc subgroup analysis in a high risk group categorised on the basis of BMD and prior fracture. The characterisation of the enrolled population with FRAX® permitted the re-evaluation of the efficacy of baze-
doxifene on fracture outcomes avoiding subgroup analysis by examining the efficacy of intervention as a function of fracture risk. As in the case of clodronate, hazard ratios for the effect of bazedoxifene on all clinical fractures decreased with increasing fracture probability (Fig. 8). In patients with 10-year fracture probabilities at or above 16%, bazedoxifene was associated with a significant decrease in the risk of all clinical fractures. Hazard ratios for the effect of bazedoxifene on morphometric vertebral fractures also decreased with increasing fracture probability (see Fig. 8). In patients with 10-year fracture probabilities above 6.9%, bazedoxifene was associated with a significant decrease in the risk of morphometric vertebral fractures. At equivalent fracture probability percentiles, the treatment effect of bazedoxifene was greater on vertebral fracture risk than on the risk of all clinical fractures. For example, at the 90th percentile of FRAX® probability, bazedoxifene was associated with a relative risk reduction of 33% (95% CI=7–51%) for all clinical fractures and 51% reduction (95% CI=21–69%) for morphometric vertebral fractures [48].

These results, if confirmed in other clinical settings, have a number of important implications. First, they dispel a minority view that patients identified on the basis of clinical risk factors with FRAX® would not respond to pharmacologic interventions. Indeed both studies showed that high FRAX® probabilities were associated with efficacy, even when BMD was not used to characterise risk. Second, they support the views of the European regulatory agency that treatments should be developed preferentially to men and women at high fracture risk. Third, the finding of greater efficacy at higher fracture probabilities has important implications for health technology assessments and challenges the current meta-analytic approach. Finally, since treatments directed to high risk patients

**Table 2**

Cost-effectiveness analysis by age, sex and race for men and women at average risk and relative risk thresholds in the United States [Data extracted from Table 2 of reference 60, with permission from Springer]

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>General population</th>
<th>Threshold for cost-effectiveness</th>
<th>General population</th>
<th>Threshold for cost-effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fracture probability</td>
<td>ICER ($000/QALY)</td>
<td>Relative risk</td>
<td>Fracture probability</td>
<td>ICER ($000/QALY)</td>
</tr>
<tr>
<td>White female</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>0.72</td>
<td>380.7</td>
<td>3.5</td>
<td>2.5</td>
</tr>
<tr>
<td>55</td>
<td>1.18</td>
<td>222.8</td>
<td>2.3</td>
<td>2.8</td>
</tr>
<tr>
<td>60</td>
<td>1.79</td>
<td>139.6</td>
<td>1.6</td>
<td>3.0</td>
</tr>
<tr>
<td>65</td>
<td>2.24</td>
<td>88.4</td>
<td>1.3</td>
<td>2.8</td>
</tr>
<tr>
<td>70</td>
<td>4.66</td>
<td>44.2</td>
<td>0.9</td>
<td>4.0</td>
</tr>
<tr>
<td>75</td>
<td>9.80</td>
<td>cs</td>
<td>0.4</td>
<td>4.4</td>
</tr>
<tr>
<td>80</td>
<td>13.52</td>
<td>cs</td>
<td>0.3</td>
<td>3.3</td>
</tr>
<tr>
<td>85</td>
<td>12.96</td>
<td>cs</td>
<td>0.3</td>
<td>3.3</td>
</tr>
<tr>
<td>Average</td>
<td>3.4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Black female | | | | | |
| 50          | 0.31                | 932.3                        | 8.1                 | 2.5                             | 0.18    | 1552.3                    | 13.1                    | 2.4 |
| 55          | 0.5                | 576.2                        | 5.4                 | 2.7                             | 0.26    | 1282.8                    | 11.5                    | 3.0 |
| 60          | 0.75                | 392.8                        | 3.8                 | 2.9                             | 0.59    | 790.9                     | 6.5                     | 3.8 |
| 65          | 0.92                | 268.1                        | 2.9                 | 2.7                             | 0.75    | 425.7                     | 4.3                     | 3.3 |
| 70          | 1.90                | 166.7                        | 2.0                 | 3.8                             | 1.25    | 306.9                     | 3.5                     | 4.4 |
| 75          | 4.08                | 63.1                         | 1.0                 | 4.2                             | 1.96    | 138.5                     | 1.9                     | 3.6 |
| 80          | 5.85                | 28.6                         | 0.7                 | 4.0                             | 2.72    | 92.1                      | 1.4                     | 3.7 |
| 85          | 5.81                | 22.2                         | 0.6                 | 3.4                             | 3.68    | 44.6                      | 0.8                     | 3.0 |
| Average     | 3.3                 |                               |                     |                                 | 3.4     |                             |                         |     |

cs, cost saving; ICER, incremental cost effectiveness ratio.

a Average 10-year probability of hip fracture (%) in the general population.
b Cost-effectiveness of treating individuals at average risk.
c The relative risk for hip fracture at which intervention becomes cost-effective.
d 10-year probability of hip fracture (%) at which intervention becomes cost-effective.

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Fig. 8. Hazard ratio between treatments (bazedoxifene versus placebo) with 95% confidence intervals according to values of 10-year probability of a major osteoporotic fracture calculated with BMD [48, with permission from Elsevier].
This is equivalent to about £30,000/QALY and close to that used by NICE and others in most appraisals in the UK [53–55]. In the context of prevention of osteoporosis, NICE used a £20,000/QALY threshold [55].

Several studies have examined intervention thresholds in terms of fracture probability [35,56–60]. The majority have expressed results as the 10-year probability of hip fracture at which treatment is cost-effective, i.e. using hip fracture as a metric to measure the impact of all fracture outcomes. The most recent assessment using this approach has come from the National Osteoporosis Foundation (NOF) who have updated pre-existing clinical practice guidelines with a further health economic analysis [60] to reflect the growing international consensus that intervention thresholds for osteoporosis treatment should be determined on the basis of fracture probability [2,3,24].

A Markov-cohort model of annual United States age-specific incidence of hip, wrist, clinical spine and other fractures, costs (2005 US dollars), and quality-adjusted life years (QALYs) was used to assess the cost-effectiveness of osteoporosis treatment ($600/yr drug cost for 5 years with 35% fracture reduction). A five-year course of treatment with a bisphosphonate-like therapy was modelled. Randomized clinical trial evidence for the effectiveness of treatment in reducing fracture risk varies by fracture site and the population studied [61]. For comparability with other studies, a fracture reduction of 35% (relative risk [RR] = 0.65) was assumed [57–59]. Treatment effectiveness was assumed to wane when treatment was stopped with an offset time of 5 years as recommended elsewhere [62]. The threshold for cost-effectiveness was set at $60,000 per QALY gained.

The cost-effectiveness analysis of treatment relative to no intervention among the population at average risk populations ranged from over $380,000 per QALY gained in 50-year-old white women to being cost-saving in 75-year-old white women (Table 2). Cost-effectiveness was poorer in white men, and poorer still in black women and men due to the lower risk of fracture in these populations. Although relative risks differed between race groups for each gender, the intervention thresholds by race and sex were relatively constant (see Table 2). In white men and women, treatment became cost-effective at a hip fracture probability of 3.4% and 3.8%, respectively. The corresponding probabilities in blacks were 3.3% and 3.4%. On this basis, the NOF chose a 10-year hip fracture probability of 3% as an intervention threshold.

A somewhat different approach has been used in the UK. Fracture probabilities were computed using the FRAX® tool calibrated to the epidemiology of fracture and death in the UK [1]. The cost effectiveness of generic alendronate in the UK was taken from an independent paper [36]. The cost of alendronate was set at £95 per year, which is now a conservative figure since the current price has subsequently fallen to £24.

In order to determine whether to express intervention thresholds as the 10-year probability of hip fracture or of a major osteoporotic fracture, the relationship between fracture probabilities expressed using either outcome and the cost-effectiveness were examined for all

Table 3

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>10-year probability of osteoporotic fracture with BMD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
</tr>
<tr>
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<tr>
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<td>80</td>
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</table>
possible combinations of CRFs at BMD T-scores between 0 and −3.5 SD in 0.5 SD steps (512 combinations) with a BMI set to 26 kg/m² [35]. Thus, this was not a population simulation, but a display of all possible combinations.

The relationship of the two probability outputs to cost-effectiveness are shown in Fig. 9. It is evident that a threshold value for hip fracture probability (say 2%) would encompass a very wide range of cost-effectiveness. The relationship of cost-effectiveness with major osteoporotic fracture probability is, however, more favourable since, at probability values that might be appropriate as a threshold, the range of cost-effectiveness was much less than in the case of hip fracture probability. For this reason, the major index used to assess intervention thresholds in the UK has been the 10-year probability of a major osteoporotic fracture.

The point estimates for the correlations shown in Fig. 9 permit an estimate of the mean fracture probability for any willingness to pay as shown in Table 3 for a WTP of £20,000 [35]. There was rather little difference in the threshold at different ages with a mean value of 7.0%. At a WTP of £10,000 the mean probability threshold was 11.7% and at a WTP of £30,000 was 3.6%. Thus, with a WTP of £20,000, any recommendations for intervention should ensure that individuals have a fracture probability that exceeds 7%. As can be seen from Fig. 5, all treatment scenarios developed for postmenopausal women or men aged 50 years or more in the UK were cost-effective.

The low cost of generic alendronate, and the improvement in the point estimate for the correlations shown in Fig. 9 permit an estimate of the mean fracture probability for any willingness to pay as shown in Table 3 for a WTP of £20,000 [35]. There was rather little difference in the threshold at different ages with a mean value of 7.0%. At a WTP of £10,000 the mean probability threshold was 11.7% and at a WTP of £30,000 was 3.6%. Thus, with a WTP of £20,000, any recommendations for intervention should ensure that individuals have a fracture probability that exceeds 7%. As can be seen from Fig. 5, all treatment scenarios developed for postmenopausal women or men aged 50 years or more in the UK were cost-effective.

The low cost of generic alendronate, and the improvement in cost-effectiveness derived thereby, allowed an assessment of the cost-effectiveness of clinical guidelines, whereas intervention thresholds in the UK were limited by cost-effectiveness. The same is not true of more expensive interventions. An example is provided in Table 4 for risedronate [63]. At a WTP of £20,000 per QALY, treatment with risedronate was cost-effective at a probability threshold of 19% compared with a threshold of 7% with generic alendronate.

Comparison of intervention thresholds based on cost-effectiveness and those derived from the translational approach from existing guidelines show important differences. Whereas the intervention threshold rises steeply with age in the latter approach, there is no marked effect of age in thresholds derived from health economic analysis (see Tables 3 and 4). The difference arises because health economic analysis takes account of the age-dependent fracture risk, whereas many established guidelines based on clinical imperatives do not. There is no right or wrong methodological approach and the approach used is dependent on the socioeconomic setting. In the US for example, screening of men and women (at the ages of 70 and 65 years, respectively) with BMD is recommended. In the UK, BMD tests are reserved for individuals with clinical risk factors for fracture. In addition, intervention costs are much lower than in the US. An intervention threshold based on cost-utility alone in the UK would permit intervention in very many individuals in whom this was considered clinically inappropriate, and many more than would be deemed eligible in the US.

Because intervention thresholds are in part based on cost-effectiveness, and in part on clinical considerations, the examples above are not necessarily applicable to other countries, where the WTP and/or the costs of osteoporosis or intervention may differ. Notwithstanding, a health economic analysis in a ‘European setting’ [11] suggests that similar thresholds could apply to several European countries. In the event, intervention thresholds need to be determined on a country by country basis.

References


