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A report prepared for the National Osteoporosis Guideline Group
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Abstract

In most assessment guidelines, treatment for osteoporosis is recommended in individuals with prior fragility fractures, especially fractures at spine and hip. However, for those without prior fractures, the intervention thresholds can be derived using different methods. The aim of this report was to undertake a systematic review of the available information on the use of FRAX® in assessment guidelines, in particular the setting of thresholds and their validation. We identified 120 guidelines or academic papers that incorporated FRAX of which 38 provided no clear statement on how the fracture probabilities derived are to be used in decision-making in clinical practice. The remainder recommended a fixed intervention threshold (n=58), most commonly as a component of more complex guidance (e.g. bone mineral density (BMD) thresholds) or an age-dependent threshold (n=22). Two guidelines have adopted both age-dependent and fixed thresholds. Fixed probability thresholds have ranged from 4 to 20 % for a major fracture and 1.3-5 % for hip fracture. More than one half (39) of the 58 publications identified utilized a threshold probability of 20 % for a major osteoporotic fracture, many of which also mention a hip fracture probability of 3 % as an alternative intervention threshold. In nearly all instances, no rationale is provided other than that this was the threshold used by the National Osteoporosis Foundation of the US. Where undertaken, fixed probability thresholds have been determined from tests of discrimination (Hong Kong), health economic assessment (US, Switzerland), to match the prevalence of osteoporosis (China) or to align with pre-existing guidelines or reimbursement criteria (Japan, Poland). Age-dependent intervention thresholds, first developed by the National Osteoporosis Guideline Group (NOGG), are based on the rationale that if a woman with a prior

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fragility fracture is eligible for treatment, then, at any given age, a man or woman with the same fracture probability but in the absence of a previous fracture (i.e. at the 'fracture threshold') should also be eligible. Under current NOGG guidelines, based on age-dependent probability thresholds, inequalities in access to therapy arise especially at older ages (70 years) depending on the presence or absence of a prior fracture. An alternative threshold using a hybrid model reduces this disparity. The use of FRAX (fixed or age-dependent thresholds) as the gateway to assessment identifies individuals at high risk more effectively than the use of BMD. However, the setting of intervention thresholds need to be country-specific.

Keywords

Introduction

Osteoporosis is a major health problem, particularly in the elderly because of the fractures that arise as a consequence of the decreasing bone mineral density with age. Common sites of fragility fracture are at the hip, spine and wrist. The incidence of these and other fragility fractures rises markedly with age. The most serious fracture in terms of morbidity, mortality and health care costs is hip fracture. As populations expand and life expectancy improves, the number of fractures is set to increase. The demographics of world populations are set to change with more elderly living in developing countries [1]. In Europe in 2010, 22 million women and 5.5 million men were estimated to have osteoporosis; and 3.5 million new fragility fractures were sustained, comprising 610,000 hip fractures, 520,000 vertebral fractures, 560,000 forearm fractures and 1,800,000 other fractures (i.e. fractures of the pelvis, rib, humerus, tibia, fibula, clavicle, scapula, sternum and other femoral fractures). The economic burden of incident and prior fragility fractures was estimated at €37 billion. Incident fractures represented 66 % of this cost, long-term fracture care 29 % and pharmacological prevention 5 % [2].

A significant advance over the past 15 years has been the development of medical interventions that have been shown to decrease the risk of fragility fractures in high quality randomised controlled trials [2, 3]. Unfortunately, only a minority of men and women receives treatment even after sustaining a fragility fracture [2, 4]. The reason for this large treatment gap (the difference between the number of individuals at high risk and the proportion of the population that receives treatment) is complex and multifactorial. One of the reasons is, however, is limitations in the assessment of fracture risk.

Although the diagnosis of osteoporosis relies on the quantitative assessment of bone mineral density, which is a major determinant of bone strength, the clinical significance of osteoporosis lies in the fractures that arise. The causation of fractures is, however multifactorial. In this respect, there are some analogies with other multifactorial chronic diseases. For example, hypertension is diagnosed on the basis of blood pressure whereas an important clinical consequence of hypertension is stroke.

Assessment of bone mineral density (BMD) provides a crucial determinant of fracture risk and many guidelines have used BMD thresholds to determine whether treatments should be recommended. However, the multifactorial nature of fracture risk means that BMD does not capture non-skeletal determinants of fracture risk such as liability to fall. A number of risk factors for fracture has been identified that contribute significantly to fracture risk over and above that provided by BMD [5]. A good example is age. The same BMD has a different significance at different ages, such that fracture risk is much higher in the elderly than in the young [6, 7]. This is because age contributes to risk independently of BMD. Over the past few years a series of meta-analyses has been undertaken to identify additional clinical risk factors that could be used in case finding strategies, with or without the use of BMD. This gave rise to the development of FRAX®, a tool that integrates the information derived from clinical risk factors and BMD [8].

As well as the FRAX tool, other fracture risk calculators are available online which include the Garvan fracture risk calculator and QFracture® [9, 10]. Both QFracture and FRAX have been approved by the National Institute for Health and Care Excellence (NICE) for use in the UK [11]. Their comparative features are summarised in Table 1. The QFracture tool is based on a UK prospective open cohort study of routinely collected data from 357 General Practices on over 2 million men and women aged 30–85 years (www.qfracture.org). Like the FRAX tool, it takes into account history of smoking, alcohol, glucocorticoid use, parental history (of hip fracture or osteoporosis) and multiple secondary causes of osteoporosis. Unlike FRAX, it also includes a history of falls (yes/no only over an unspecified time frame). It has been internally validated (i.e. from a stratum of the same population) and also externally validated, but only from GP records in the UK [12].

FRAX calculates fracture probability in individuals from age, body mass index and dichotomized risk factors comprising prior fragility fracture, parental history of hip fracture, current tobacco smoking, ever use of long-term oral glucocorticoids, rheumatoid arthritis, other causes of secondary osteoporosis and alcohol consumption [8]. Femoral neck BMD can be optionally input to enhance fracture risk prediction. Fracture probability is computed taking both the risk of fracture and the risk of death into account. The use of clinical risk factors in conjunction with BMD and age improves sensitivity of fracture prediction without adverse effects on specificity [14]. Even if the performance of FRAX is enhanced by the use of BMD tests, it should be recognised that FRAX without BMD has a predictive value for fractures that is comparable to the use of BMD alone [15]. The availability and access to densitometry in many countries is low [16], so that a major advantage of FRAX is the ability to assess fracture risk where BMD is unavailable.

Fracture probability varies markedly in different regions of the world [17]. Thus, the FRAX® models need to be calibrated to those countries where the epidemiology of fracture and death is known. Models are currently available for 58 countries across the world: for Argentina, Armenia (surrogate), Austria, Australia, Belgium, Brazil, Canada, Chile, Czech, China (revised 2013), Colombia, Croatia, Denmark, Ecuador, Estonia, France, Finland, Germany, Greece, Hong Kong, Hungary, Iceland, India (surrogate), Indonesia, Ireland, Israel, Italy, Japan, Jordan (updated), S Korea, Kuwait, Lebanon, Lithuania, Malta, Mexico, Morocco, Netherlands, New Zealand, Norway, Palestine (surrogate), Philippines, Poland,

Portugal, Romania, Russia, Singapore, Slovakia, Sri Lanka (surrogate), Spain, Sweden, Switzerland, Taiwan, Thailand, Tunisia, Turkey, UK, US, Venezuela. The model is available in 27 languages: Arabic, Bengali, Chinese (traditional and simplified), Czech, Danish, Dutch, English, Finnish, French, German, Greek, Icelandic, Indonesian, Italian Japanese, Korean, Lithuanian, Norwegian, Polish, Portuguese, Romanian, Russian, Slovak, Spanish, Swedish, Thai and Turkish.

FRAX has been widely used for the assessment of fracture risk since the launch of the website in 2008 and currently processes approximately 225,000 calculations per month. Following regulatory review by the US Food and Drug Administration, FRAX was incorporated into DXA scanners to provide FRAX probabilities at the time of DXA scanning. For those without internet access, hand-held calculators and an application for Apple and Android smartphones have been developed by the IOF (http://itunes.apple.com/us/app/frax/id370146412?mt=8; https://play.google.com/store/apps/details?id=com.inkrypt.clients.iof.drfrax). A paper-based FRAX pad allows patients to document risk variables prior to medical consultation and is available from the IOF (www.iofbonehealth.org) in several languages.

The limitations of FRAX have been reviewed recently [18, 19]. In order to overcome some of these, relatively simple arithmetic procedures have been proposed which can be applied to conventional FRAX estimates of probabilities of hip fracture and a major fracture to adjust the probability assessment with knowledge of:

> High, moderate and low exposure to glucocorticoids [20]
>
> Concurrent data on lumbar spine BMD [21, 22]
>
> Information on trabecular bone score (TBS) [23–25]
>
> Hip axis length [26]
>
> Falls history [27]

The use of FRAX in clinical practice demands consideration of the fracture probability at which to recommend treatment – termed the intervention threshold. Many different approaches have been used to set intervention thresholds with FRAX. 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. The aim of the present report, supported by a systematic review, was to review the available information on the use of FRAX in assessment guidelines, in particular the setting of thresholds and their rationale. In addition, the performance characteristics of FRAX are reviewed to better inform the future developments of probability-based guidance.

Research questions

The National Osteoporosis Guideline Group aims to update its guidance on risk assessment. In so doing, three research questions were posed:

How is the FRAX calculator used in guidelines for fracture risk assessment?

What intervention thresholds are used in such guidelines, and what is the rationale for these thresholds?

How have the performance and implementation of guidelines/thresholds been assessed, and what are the findings?

Methods

Design

We undertook a systematic review of evidence to address the research questions, following the methods recommended by the Centre for Reviews and Dissemination (CRD), University of York (http://www.york.ac.uk/inst/crd/). Since quantitative synthesis of the data was inappropriate, we undertook a narrative review. The review protocol was registered with the International Prospective Register of systematic Reviews (Prospero; registration number: CRD42015027880)

Outcomes

Treatment intervention thresholds using FRAX for major osteoporotic fracture and hip fracture

Incidence of major osteoporotic or hip fracture

Health-economic benefit

Inclusion criteria

Studies and guidelines relating to risk assessment in the prevention of osteoporotic fracture using the FRAX calculator

Studies of intervention thresholds using the FRAX calculator including validation of thresholds

All studies which contributed relevant information were included, regardless of the setting. However, the setting was noted as part of data abstraction and was used in narrative synthesis. Studies were not excluded on the basis of publication date. There was no language restriction.

Exclusion criteria

Studies were excluded if they did not address human populations. We also excluded paediatric guidelines as the primary aim was to assess adult fracture prevention.

Search strategy for identification of studies

The search strategy was informed by initial scoping exercises (NCH, EM). We searched electronic databases including PubMed, Web of Science and Google Scholar, from their inception until 13th October 2015. Additionally, to reduce publication bias and to identify grey literature, we searched the abstracts of conference proceedings of the American Society for Bone and Mineral Research, European Calcified Tissue Society and World Congress of

Osteoporosis, and the web sites of the 200+ National Societies affiliated to the International Osteoporosis Foundation (http://www.iofbonehealth.org/societies-country-index-view/all). We hand-searched the reference lists of publications and also web pages of national and international scientific societies related to the management of osteoporosis, and agencies that develop guidelines.

Search terms included:

1. FRAX

2. guideline

3. guidance

4. recommendation

5. 1 AND 2

6. 1 AND 3

7. 1 AND 4

We made an additional search to identify assessment guidelines from government agencies and non-governmental organisations where guideline collections were documented:

Obstetrics and gynecology guidelines Geneva Foundation for Medical Education and Research http://www.gfmer.ch/Guidelines/Osteoporosis/Osteoporosis.htm

US Department of Health and Human Services. National Guideline Clearing House http://www.gfmer.ch/Guidelines/Osteoporosis/Osteoporosis.htm

IOF http://www.iofbonehealth.org/national-regional-osteoporosis-guidelines

Screening of abstracts

When applying inclusion criteria, all abstracts, guidelines and potentially relevant papers were assessed by JAK, with independent parallel review by NCH, and decisions shown to be reproducible. Disagreements over inclusion were resolved through consensus and, where necessary, following discussion with a third member of the review team (EM).

Data extraction and quality assessment

Data extraction was carried out in the same way as the abstract assessment. We undertook the quality assessment of studies using approaches specific to the study type, that is whether it was a guideline, or an assessment of a threshold/guideline. With regard to the former, the assessment focused on the degree to which a guideline was developed on the basis of a rigorous evidence base versus expert consensus, with recognition that the majority would be a combination of these two approaches. Where several editions of guidelines were available, the most recent was retained unless otherwise specified. Where guidelines were abstracted or reviewed, the original guideline was retained unless further insight was available on the rationale for the setting of intervention thresholds with FRAX. With regard to assessments of thresholds or guidelines, we focused on elements of study design (appropriate adult

population, outcome definition, fracture and/or health economic assessment, threshold definition). Given the nature of the studies, it was judged inappropriate to give a formal quality score. However, an appropriate critique was applied to characterise study quality.

Data synthesis

Owing to the nature of the review and the included studies, meta-analysis was not appropriate. We therefore undertook a narrative data synthesis in the presentation of the systematic review results.

Results

The initial search revealed 228 citations, with a further 198 identified from websites and other sources (Figure 1). After initial assessment for relevance 307 were retained for full appraisal and 231 were included in the narrative synthesis. Redundant or irrelevant articles (77) are provided in the appendix.

In reviewing FRAX-based intervention thresholds, it is important to recognise that the vast majority of assessment guidelines recommend that men and women with prior fractures are eligible for treatment [28]. In some countries, treatment is recommended in patients with fractures at the spine and hip e.g. Canada [29], the US [30], Japan [31] and Scotland [32]. Thus, with few exceptions, the place for FRAX resides in those patients without prior fractures (or without prior spine or hip fracture). The aim of this review was not to focus on the adequacy of this gateway for patient assessment but, rather, the subsequent triage with FRAX.

FRAX was launched in 2008. It is to be expected that there be a time-delay between the availability of new technologies and in its clinical acceptance, particularly given the long cycle between guideline development and their updates. In addition, the incorporation of FRAX-specific thresholds into guidance is commonly preceded by academic research to provide the rationale. However, the widespread availability of FRAX, during a time of transition, has resulted in the inclusion of FRAX in many with no clear statement on how the fracture probabilities derived are to be used for decision-making in clinical practice. We identified 38 guidelines or academic papers that fell into this category (Table 2).

Where guidance on intervention thresholds has been provided, three broad approaches have been adopted. The first was to determine a *fixed threshold* that could be applied to men and women, irrespective of age. This could be applied either alone or as a component of other thresholds (e.g. BMD, parental history of fracture etc.). A second approach was to use *age-dependent thresholds* where the fracture probability at which treatment was recommended was age specific. Finally a study from the UK and a guideline from Lebanon have used both fixed and age-dependent thresholds – termed *hybrid thresholds*. These three approaches are reviewed in turn.

The use of a fixed FRAX intervention threshold

Several guidelines that use FRAX have recommended that a fixed probability threshold be used as an intervention threshold. Examples include a 20 % ten-year probability of a major

fracture in Canada and the US, and a 15 % probability in Japan and Sweden [29, 31, 67, 68]. Other examples are given in Table 3.

More than one half (39) of the 58 publications reviewed utilize a threshold probability of 20 % for a major osteoporotic fracture, many of which also mention a hip fracture probability of 3 % as an alternative intervention threshold. This is understandable in those guidelines arising from the US (see below) but in 25 other countries, in nearly all instances, no rationale is provided other than the fact that this was the threshold used by the National Osteoporosis Foundation of the US.

The minority of papers that provide some logic for the manner by which thresholds were set are those from the US, Japan, Poland, Hong Kong and Switzerland, which are each briefly reviewed. Although the SIGN guidance in Scotland gave no rationale for the chosen threshold [32], this is also included because of its similarity to that of the US Preventive Services Task Force] [112] and because its impact has been assessed [13]. Additionally, the Taiwanese guidelines are reviewed as this is the sole guideline developed that uses FRAX as the exclusive gateway to treatment.

National Osteoporosis Foundation (NOF), US—Apart from recommending treatment in individuals with a prior hip or vertebral fracture, the primary gateway for patient assessment under the NOF guidance is the assessment of BMD [111]. Treatment is recommended for those with BMD defined osteoporosis at the femoral neck, total hip, or lumbar spine by DXA. FRAX is reserved for men and women with low bone mass (T-score between −1.0 and −2.5, osteopenia) at the femoral neck, total hip, or lumbar spine. For osteopenic subjects, a fixed intervention threshold is recommended for all ages and for both sexes set at 20 % for a major osteoporotic fractures and 3 % for hip fracture probability [30]. The intervention thresholds were based on an economic analysis [124] (see Health economic approach to intervention thresholds with FRAX).

The impact of the introduction of FRAX to the NOF guidelines has been assessed in women from the population-based Framingham study [125]. At all ages, the proportion of women meeting treatment criteria was slightly less when the 2008 guidelines, including FRAX as above, were applied (41.1 %) compared with the 2003 guidelines (47.8 %). However, the impact was age-dependent. The proportion of women under the age 65 years meeting treatment criteria was markedly less when applying 2008 Guidelines (8.3 % vs. 23.1 % in 200 (USPSTF8 and 2003, respectively), whereas the proportion of women at or over age 75 years increased slightly (86.0 % vs. 78.3 %).

An analysis of the National Health and Nutrition Examination Survey III [126] estimated a higher proportion of the women eligible for treatment under the 2003 guidance than in the Framingham study (53% vs. 48%, respectively) but overall the 2008 guidance decreased the percentage of eligible women to 41%. Also, the guideline revision directed intervention more to the elderly at high risk and less to younger women with osteopenia but at low risk. Overall, approximately 20 million men and women in the US would be eligible for treatment [126].

The US Preventive Services Task Force—Like the NOF, the US Preventive Services Task Force (USPSTF) recommends BMD testing in all women age 65 years or older. For younger women age 50-65 years, FRAX is recommended as a screening tool for BMD testing. A BMD test is recommended in younger women whose fracture probability is equal to or greater than that of a 65-year-old white woman who has no additional risk factors [112]. With the U.S. FRAX tool, a 65-year-old white woman of average BMI (25 kg/m^2) with no other risk factors has a 9.3 % 10-year probability for a major osteoporotic fracture. In women age 50-65 years who exceed this threshold, a BMD test is indicated and treatment recommended in those in whom BMD is in the range for osteoporosis.

The probability threshold of 9.3 % used by the USPSTF appears logical, but is inappropriate in the sense that "The objective of screening is to identify postmenopausal women with T-scores of -2.5 SD or lower" [127]. In such a case it is more appropriate to use tools that detect osteoporosis rather than a tool to assess fracture risk [128]. Appropriate tools include the Osteoporosis Self-Assessment Tool (OST) and Simple Calculated Osteoporosis Risk Estimation Tool (SCORE) [129, 130]. OST is calculated from weight and age, whereas SCORE uses 6 clinical risk factors (race, rheumatoid arthritis, history of non-traumatic fracture, age, prior oestrogen therapy, and weight). As might be expected, Crandall et al [127] showed that the FRAX based (USPSTF) strategy had a somewhat higher specificity but much lower sensitivity than SCORE or OST for the identification of individuals with a femoral neck T-score of -2.5 SD (Table 4). The low sensitivity with the FRAX cut-off means that two thirds of women with a BMD in the range of osteoporosis would be missed. Similar findings have been reported in an independent cohort [131].

Had the intention of screening been to identify women at high fracture risk, then a fracture risk assessment algorithm is the appropriate tool. In this context FRAX outperforms OST or SCORE for fracture prediction [8].

American College of Rheumatology—The most recent (2010) recommendations from the American College of Rheumatology (ACR) provide guidance for patients exposed to glucocorticoids [113]. Recommendations are stratified by glucocorticoid dose and fracture risk based on FRAX calculations. They recommend that low- and medium-risk patients (FRAX <10 and 10–20 % probability of a major fracture, respectively) should be treated if their glucocorticoid dose is greater than or equal to 7.5 mg/day. High-risk patients (FRAX >20 %) should be treated if they receive glucocorticoids at any dose for >1 month or if they are on 5 mg/day prednisolone equivalent even for <1 month [113]. The 10 % threshold is lower than the generally accepted 20 % threshold for postmenopausal osteoporosis in use in North America [132]. The rationale for the two thresholds is the established exposure-dependent association of glucocorticoids and fracture risk [133]. The 20 % threshold was chosen to match that of the National Osteoporosis Foundation though there are no details provided on how the 10 % threshold was derived. The same thresholds have been adopted in Finland [78].

Japanese National Guidelines—In 2012, the Japan Osteoporosis Society, Japanese Society for Bone and Mineral Research (JSBMR) and Japan Osteoporosis Foundation updated the guidance of the JSBMR issued ten years previously, [31]. As is the case for most

assessment guidelines, treatment is offered to individuals with a prior vertebral or hip fracture. In common with the NOF guidelines, testing with BMD provides the gateway thereafter in the assessment algorithm (Figure 2). The BMD thresholds used are unique to Japan; intervention is based on BMD expressed as a % of young adult mean values (YAM). These diagnostic (and intervention) thresholds were derived by maximising sensitivity and specificity for fracture detection with several technologies at several skeletal sites [134]. Intervention thresholds using YAM were set at 70 % and 80 %. For BMD at the femoral neck with DXA, a YAM of 70 % and 80 % are equivalent to a T-score of −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 (the international T-score referent used in FRAX).

After the FRAX tool became available, probabilities of a major osteoporotic fracture were calculated that were equivalent to the existing intervention thresholds based on YAM [135]. Thresholds of equivalence varied with age, ranging from 5 % at an age of 50 years to more than 20 % at the age of 80 years. Although equivalent probabilities were age-dependent, the guideline revision recommended a fixed intervention threshold of 15 % for major osteoporotic fracture for men and women with no fracture history and a YAM between 80 and 70 % (the Japanese equivalent to osteopenia) [31].

Poland—A study of a convenience sample of 1,608 women age 40-89 years in the region of Bialystok, Poland recommended an intervention threshold set at 18 % probability of a major osteoporotic fracture or a 9 % probability of a hip fracture [91]. These values approximated the mean fracture probabilities in women with a prior fragility fracture.

A subsequent approach to the development of FRAX-based intervention thresholds in Poland was, as in Japan, to determine the fracture probabilities that were equivalent to intervention thresholds that pre-existed the development of FRAX. At that time, intervention was recommended in individuals with a BMD T-score of   -2.5 SD or a prior fragility fracture. Badurski [89] explored FRAX-based intervention thresholds in 1608 postmenopausal women from Białystok, Poland using the UK FRAX model that were equivalent to a T-score of -2.5 SD and a prior fragility fracture. The mean 10 year probability of a major osteoporotic fracture was 11.6 % with BMD included in the FRAX model in women with a T-score of -2.5 SD or less. In women with a prior fragility fracture, the mean probability was 17.4 %. Note that these thresholds were based on the UK version of FRAX and subsequently, a Polish-specific model became available (June 2011).

The authors concluded that age specific intervention thresholds were more clinically appropriate than a fixed probability threshold for all ages (see Age-dependent thresholds in other countries below). Notwithstanding, Polish guidelines subsequently recommended (expert opinion) a fixed intervention threshold of 10 % for a major osteoporotic fracture [92].

Hong Kong—Fixed FRAX thresholds were explored in a convenience sample of 2,266 postmenopausal Chinese women from Hong Kong followed for an average of 4.5 years to determine the incidence of new fractures [81]. One hundred and six new major osteoporotic fractures were reported. The sensitivity and specificity of two FRAX-based strategies were

explored. The first was to determine the operating characteristics in women where the threshold probability was set to the age-specific fracture probability equal to that of a woman with a prior fracture. The second was to determine the 'optimal' fixed FRAX threshold.

Where the threshold probability was set to the age-specific fracture probability equal to that of a woman with a prior fracture (FRAX, with BMD), the sensitivity and specificity was 47 % and 83 %, respectively. Unsurprisingly, the use of a fixed threshold across all ages yielded higher sensitivity. The optimal cut-off point for the 10-year probability of a major fracture as 9.95 % was identified with a sensitivity of 62.3 %, a specificity of 73.5 %) and a positive predictive value of 10.3 %. The current guidance of the Osteoporosis Society of Hong Kong mentions the 20 % fixed threshold of NOF but gives no practical guidance on the use of FRAX in Hong Kong [45].

China—In China, intervention thresholds were set at 4 % for the 10-year probability of major osteoporotic fracture and 1.3 % for hip fracture. In a series of postmenopausal women, 37.5 % were found to have osteoporosis calculated with BMD. The FRAX-based thresholds were set at the 62.5 (100-37.5) percentile of the FRAX distribution i.e. to match the prevalence of osteoporosis [75].

Switzerland—In Switzerland, a FRAX intervention threshold of 15% probability of a major osteoporotic fractures was set, based on a cost-utility analysis. The age-dependent variations around these mean values were judged to be modest [105]. Treatment was recommended in men age 55 years or above and women age 60 years or above with prior fractures. In those without a prior fracture, treatment was recommended where the probability of major osteoporotic fracture was 15% or above. The same paper explored the NOGG approach in order to compare the results with the economic analysis (see Health economic approach to intervention thresholds with FRAX).

Scottish Intercollegiate Guidelines Network (SIGN)—The Scottish Intercollegiate Guidelines Network (SIGN) issued guidance on the management of osteoporosis and the prevention of fragility fractures [32]. These represent a departure from their earlier guidelines following the endorsement of risk assessment algorithms by National Institute for Health and Care Excellence (NICE) in the UK [11].

The SIGN guidance utilises a 10% fixed intervention threshold but gives no explanation for the choice. However the threshold is similar to that used in the USPTF guidance and is deployed in much the same way [112] (see The US Preventive Services Task Force above).

The assessment algorithm is summarised in Figure 3. In brief, there are different pathways for patients with a prior fragility fracture and those with other clinical risk factors for fracture. Patients with a prior fragility fracture are assessed by DXA (at the spine or hip) and treatment considered in patients with a T-score diagnosis of osteoporosis. There is an exception for a prior vertebral fracture (not defined) or prior hip fracture where BMD testing is left to the physician's discretion. In the case of men and women aged 50 years or more without a prior fracture, individuals are screened using other clinical risk factors. In the

presence of clinical risk factors, fracture risk is assessed either with QFracture® or FRAX® (but preferentially the former). Where the cumulative 10-year incidence of major osteoporotic fracture (10-year probability in the case of FRAX) equals or exceeds 10 %, then a BMD test is recommended and treatment considered in patients with a T-score diagnosis of osteoporosis.

Apart from individuals with a prior fracture where BMD is usually recommended, the FRAX threshold (10 % probability of a major fracture) is used to determine the eligibility of individuals to have a BMD test to detect the presence of absence of osteoporosis. However, the FRAX assessment does not thereafter influence the interpretation of the BMD test. In other words, FRAX (and QFracture) are used as a screening tools for the detection of densitometric osteoporosis. Thus, the SIGN guidance firmly entrenches a T-score threshold of -2.5 SD as an intervention threshold, reminiscent of European and UK guidance nearly 20 years ago [136, 137].

The SIGN guidance does not distinguish the output from FRAX and QFracture. In other words, the 10 % threshold is used irrespective of the assessment tool that is used. Since the units of measurement differ (cumulative incidence for QFracture and probability for FRAX) together with the problems of calibration [13], clinical decisions will also differ.

This makes an assessment of the impact of the guidelines problematic. Indeed, independent research indicated that the number of women eligible for testing in Scotland was 275,600 if FRAX were used as a screening tool but only 26,500 with the use of QFracture (28 % and 3 % of the total population, respectively). The number of women eligible for treatment (i.e. with osteoporosis) was 81,700 with the use of FRAX and 12,300 with QFracture representing 8.2 % and 1.2 % of the total population, respectively [13].

Taiwan—The most purist application of the fixed threshold is seen in the guidelines from Taiwan [138]. The Taiwanese guidelines adopt a 20 % threshold for a major osteoporotic fracture and a 3 % threshold for hip fracture probability as in the NOF guidelines but extend its application in that the FRAX thresholds are the sole gateway to treatment (Figure 4). Thus, the Taiwanese guidelines do not differentiate between those with osteoporosis or osteopenia, or on prior fracture status.

To our knowledge, this is the only guideline that does not give 'preferential' treatment to individuals with a prior fragility fracture. The use of a fixed threshold in this way is likely to outperform the age-dependent algorithms. A small comparative study applied to a Hong Kong cohort compared the Taiwan guidelines to the Hong Kong equivalent of the NOGG guidance [81]. A total of 2266 women (mean age 61 years) were followed for 4.5 years (range 1-14.6). More women were selected under the Taiwan guideline than by NOGG (25.4 % vs 15.5 %, respectively) but the crude incidence in women eligible for treatment was similar (10.9 vs. 10.3 %). This suggests a higher sensitivity in the Taiwanese guidelines. The study suffers from the low number of fractures recorded; during the follow-up period; 106 (4.7 %) women sustained a new fracture at the proximal humerus, hip, clinical spine or forearm. Additionally, the categorisation of women was incorrectly applied to those triaged

using the Taiwan guidelines in that individuals with prior fracture were allocated to treatment.

Age dependent intervention thresholds using FRAX

Principles of derivation—The launch of FRAX in April 2008 was shortly followed by the National Osteoporosis Guideline Group (NOGG) thresholds, with an easy-to-use link via the FRAX UK calculator website [139]. Briefly, the NOGG guidance 'translated' the preceding Royal College of Physicians guideline [137] which indicated that women with a prior fragility fracture may be considered for intervention without the necessity for a BMD test for the purpose of making the treatment decision. The translational logic used is that if a woman with a prior fragility fracture is eligible for treatment, then a woman with the same fracture probability but, in the absence of a previous fracture, should also be eligible. For this reason, the intervention threshold in women without a prior fracture at any given age can be set at the age-specific fracture probability equivalent to women with a prior fragility fracture [140] and, therefore, rises with age (Figure 5). In other words, the intervention threshold is set at the age-dependent 'fracture threshold'.

Management algorithm—A general approach to risk assessment is shown in Figure 6 [140]. The 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 considered for treatment without recourse to BMD testing. For example, many guidelines recommend treatment in the absence of information on BMD in women with a previous fragility fracture (a prior vertebral or hip fracture in some countries).

Conversely low risk individuals would not normally be eligible for further assessment. The intermediate category in Figure 6 will vary in different countries. In countries that encourage screening (the US) or that provide reimbursement for DXA, this will be a large category, whereas in the many 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-optimal [16], the intermediate category will lie between the two extremes.

National Osteoporosis Guideline Group (NOGG), UK—NOGG developed age-dependent intervention thresholds for the UK shortly after the first release of FRAX in 2008 [141] with an update in 2013 [139]. The lower assessment threshold was set to exclude a requirement for BMD testing in women with no clinical risk factors, as given in the prevailing RCP and European guidelines [136, 137]. 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 re-classified to be at low risk with additional information on BMD [142]. The upper assessment threshold was set at 1.2 times the intervention threshold.

In keeping the majority of guidelines worldwide, individuals with a prior fragility fracture can be considered for treatment without the need for further risk assessment although BMD measurement may be appropriate to monitor treatment.

In those without prior fragility fracture but other clinical risk factors, the 10-year probability of a major osteoporotic fracture (clinical spine, hip, forearm or humerus) is determined using FRAX. Men and women with probabilities below the lower assessment threshold can be reassured (Figure 7). Those with probabilities above the lower assessment threshold but below the upper assessment threshold can be considered for testing with BMD using DXA and their fracture probability reassessed. NOGG also developed intervention thresholds based on hip fracture probability. Men and women with probabilities above the intervention threshold for major osteoporotic fracture OR for hip fracture are deemed eligible for treatment. Note that the same intervention threshold is applied to men as in women, since the effectiveness Kanis 2011a] and cost-effectiveness of intervention in men are broadly similar to that in women for equivalent risk [105,124, 143].

Without computer access, colour coded charts are available that give average fracture probabilities according to BMI and the number of clinical risk factors. There is, however, a link from the FRAX web site to the NOGG web site (www.shef.ac.uk/NOGG) and the probability of both hip fracture and major osteoporotic fracture can be automatically displayed (Figure 8).

Uptake and impact of NOGG—The linkage of FRAX to the NOGG web site can facilitate treatment decisions and appears to be well used [109]. Between 1st July 2013 and 30th June 2014, there were 348,964 sessions (a user interaction with the website) from UK-based users on the FRAX web site. Over the same time, 253,530 sessions were recorded on the NOGG website and the vast majority (82 %) arose from users in the UK, of which almost all (95.7 %) arose from calculations passing from the FRAX site to NOGG.

The NOGG approach to assessment has been compared with previous guidance issued by the Royal College of Physicians, London (RCP) [144]. Compared with the RCP strategy, NOGG identified slightly reduced numbers of women above the respective intervention threshold (average 34.6 % vs. 35.7 % across all ages). The proportion of women in the UK potentially eligible for treatment using NOGG rises from 20 % to 40 % with age [140]. At older ages (75+ years), NOGG recommended treatment in fewer patients without prior fracture but these were at higher risk than those identified by RCP. For example, at age 80 years the expected incidence was 28.6 % in those identified by RCP but was 40 % in those identified by NOGG. A further difference between the two strategies was that more efficient use was made of BMD measurements in younger women with no loss in sensitivity for hip fracture (Table 5). For example, at the age of 55 years, nine BMD scans were required to identify a single case of future hip fracture in women in the RCP strategy, whereas only two BMD scans were required in the NOGG approach. The lower number of BMD tests means that the acquisition costs for identifying a hip fracture case and the total costs (acquisition and treatment) per hip fracture averted were also lower. The economic dividend is discussed below (see Health economic approach to intervention thresholds with FRAX; Table 8). A reduction in the use of BMD tests was also reported in a comparison between NOGG and the NOF guidance applied to a Spanish cohort [145].

Age-dependent thresholds in other countries—The age-dependent approach to intervention threshold adopted by NOGG has been explored or adopted in several countries

and in European guidance for postmenopausal osteoporosis and glucocorticoid-induced osteoporosis (Table 6). Independent web sites similar to the NOGG site have been developed for Finland, Lebanon and Romania (available via the FRAX website).

The majority of publications adopt an identical approach to NOGG. Two exceptions are hybrid models adopted in Lebanon [84] and being explored in the UK [109]. The impact of guidelines has been explored in Belgium which showed that adoption of the age-dependent guidance, compared with current reimbursement guidelines, would have a marked beneficial effect on the budget impact by the more accurate targeting to high risk patients and the avoidance of intervention in those at low risk [159].

Using the same criteria, the intervention threshold will vary from country to country because the population risks (of fracture and death) vary [17]. The fracture probability in women with a prior fracture in the five major EU countries is shown in Figure 9. Probabilities are highest in the UK and lowest in Spain. The difference between countries is most evident at younger ages and becomes progressively less with advancing age [3]. In Europe, the proportion of men and women age 50 years and older above this threshold varies little from 11-13% [2].

Several independent research studies have examined age-dependent intervention thresholds with the use of FRAX and these are briefly reviewed.

Poland—A comparison of a fixed and age-specific intervention thresholds was explored in 1608 unselected postmenopausal women from Białystok, Poland using the UK version of FRAX [89]. Intervention thresholds were set at fracture probability equal to that of women with a BMD T score of −2.5 standard deviations irrespective of age (fixed threshold), women with a prior fracture (fixed threshold), the combination (fixed threshold) or an age-dependent threshold. As expected, all scenarios were more efficient than no threshold (Table 7). Compared to the fixed threshold, the age-dependent threshold identified fewer women but at higher risk thereby increasing the dividends of intervention. The Polish Multidisciplinary Osteoporotic Forum, however, elected to use a fixed probability threshold of 10 % a [92], close to the threshold derived from a fixed BMD T-score of -2.5 SD (11.6 % [89].

Australia—An age-dependent threshold has been explored in Australia using a large cohort of men and women who were randomly selected participants from the database of Australia's universal health insurance provider (Medicare Australia) [146]. A comparison was made of the number of men and women who would be eligible for treatment following the NOGG approach (i.e. age-dependent thresholds using the Australian FRAX model), the NOF thresholds (>3 % or >20 % probability of hip and major fracture, respectively) and the current guidelines. The authors suggested that too few men and women fell above these intervention thresholds and proposed age-dependent thresholds based on hip fracture probability. They were set at 3% for men and women age 50–69 years, 5 % for 70–79 years and 7 % for 80 years. No rationale was offered for the choice other than the alternatives "did not work well in the Australian population".

There was a number of limitations in the assessment. The FRAX tool used was a simplified version based on the number of clinical risk factors. A prior history of fracture that was used in the analysis comprised fracture in the previous five years. This would have markedly underestimated the prevalence of a past history of fragility fracture. Thus, a large number of individuals, eligible for treatment under the NOGG or NOF guidelines, would have been missed. The comparison with the NOF guidelines was unfair in that eligibility for treatment on the basis of FRAX was reserved for individuals with osteopenia and not the whole population over the age of 50 years.

Hong Kong—In Hong Kong, the NOF, NOGG and Taiwanese guidelines were compared in a cohort of community-dwelling, ambulatory, postmenopausal women age 40 years or more (mean age 62 years) and comprised 2261 women followed on average for 4.5 years [81]. During the follow-up period, only 106 women sustained a new fracture at the proximal humerus, hip, clinical spine or forearm so that the relative performance characteristics were difficult to compare. In addition, FRAX was calculated using locally derived T-scores which would bias the findings differently in each guideline. Overall, the clinical utility index (the product of positive concordance rate and positive predictive value) for the three guidelines was low. In line with the findings from the UK [160], the requirement for BMD testing was lowest for the NOGG approach.

Japan—As previously discussed, the revision of the Japanese guidelines by the Japan Osteoporosis Society, Japanese Society for Bone and Mineral Research, and Japan Osteoporosis Foundation opted to use a probability of FRAX for major osteoporotic fracture of 15 % in those subjects without other additional factors, such as low BMD and prior fracture (see Figure2) [31]. However, thresholds of equivalence to BMD- based intervention thresholds also varied with age, ranging from 5 % at the age of 50 years to more than 20 % at the age of 80 years (Figure 10) [135]. Thus, the 15 % fixed threshold was a compromise, possibly driven by the need for simplicity.

Hybrid intervention thresholds using FRAX

The hybrid model for intervention adopts both fixed and age-dependent thresholds. To date, two such models have been explored that differ substantially in their approach. The one from Lebanon uses a fixed threshold up to the age of 70 years and an age-dependent threshold over the age of 70 years [84]. The other from the UK uses an age- dependent threshold up to the age of 70 years and fixed threshold over this age [109].

Lebanon—For the determination of an intervention threshold, both a fixed (20% ten-year probability of a major fracture) and an age-dependent (NOGG-like) intervention threshold model were considered, and a hybrid model finally adopted [84]. It was considered that application of the NOGG model at the fracture threshold for Lebanon would result in over-treating a large proportion of women at low risk for fractures (below 10 %) up to the age of 70 years. It also would be too taxing financially at the public health level, as it would treat 25-30 % of postmenopausal women, a treatment that is also not without its risks when started at such a young age. The authors did not define overtreatment.

Treatment is recommended with a history of fragility fracture at the spine or hip or the presence of two or more fragility fractures at other sites. For subjects who have not experienced any fragility fracture, the intervention threshold is set at 10 % for the 10-year probability of a major fracture for individuals up to age 70 years. For individuals above age 70 years, the threshold increases with age: 15% at 75 years, 21% at 80 years, 27% at 85 years, and 30% at 90 years (Figure 11).

Of note is that a BMD T-score -2.5 SD, in the absence of additional risk factors, is no longer an indication for treatment in itself due to the very low estimated 10-year probability of fracture in such clinical scenarios (the 10-year overall risk of fractures is less than 10 %, both in women up to age 70 years, and men up to age 90 years).

UK—Although NOGG has become well accepted, some anomalies arise from the starting premise that individuals with a prior fragility fracture should be eligible for treatment without the requirement for a BMD test. Although not a prerequisite for the eligibility for treatment, many primary care practitioners undertake a BMD test – sometimes as a baseline to monitor treatment. When fracture probability is reassessed this may lie below the treatment threshold in some patients (for example in women with a higher than average age-specific BMD). This may be a source of confusion. The obverse is also true; namely that those eligible for treatment without a prior fracture have on average higher probabilities than those eligible on the basis of a previous fragility fracture. This inequity, results in a lower sensitivity of the algorithm for individuals without a prior fracture, as previously noted [160]. The inequity is most apparent in the elderly. As a mechanism of compensation, it was proposed that a fixed intervention threshold be used at the age of 70 years or more [109].

The analysis was based on a simulated population of 50,633 women aged 50-90 years in the UK, with a distribution of risk factors similar to that in the European FRAX derivation cohorts and a UK-matched age distribution. The 5th percentile of major osteoporotic fracture probability in UK women aged 75 years or older with prior fracture was 19.2%. This value approximated the mean value of major osteoporotic fracture probability at the age of 70 years (20.3%) so that for ease of translation, a fixed threshold at 20% was chosen from the age of 70 years. The assessment thresholds for BMD testing were also fixed from the age of 70 years (Figure 12). The corresponding threshold for intervention based on hip fracture probability was 5.4% at 70 years and was applied to women age 70 years or above.

In the case of major osteoporotic fracture probability, women in the UK at the age of 70 years or more with a prior fracture had an average 10-year probability of 25.5% using the NOGG algorithm. This was lower than the probability in women selected without prior fracture (30.8%). For hip fracture probability, the inequity was more marked (average probability 11.3% and 19.7%). With the use of a fixed intervention threshold set at a 20% probability for a major osteoporotic fracture, the differences in average probability all but disappeared (Figure 13). The same phenomenon was seen for hip fracture probabilities (Figure 14). Another feature of the hybrid model was that the need for BMD testing in the elderly was reduced, particularly at older ages (>80 years). The number of BMD tests would be decreased by approximately half.

Figures 13 and 14 also show the proportions of women eligible for treatment. Amongst women age 70 years or more the use of the alternate hybrid model would increase the proportion of women assessed over the age of 70 years without a prior fracture from 7.4 % to 15.4 %.

Health economic approach to intervention thresholds with FRAX

The National Clinical Guideline Centre (UK) did not identify economic studies that examined the cost-effectiveness of measures that used FRAX for targeting people at high fracture risk [161]. The deficit is being addressed in the SCOOP (screening of older women for prevention of fracture study) [162]. SCOOP is a randomised controlled trial designed to test screening for risk of fracture for women aged 70 to 85 years with the use of FRAX. Women in this age group recruited to the study will either be screened or managed as usual. Those screened and considered at high risk will be offered treatment by their GPs. The study will have a follow-up of 5 years and it is hoped that screening will reduce the number of fractures by around 25 %. The study has a health-economics component and is due to report its findings later this year.

Cost effectiveness of intervention based on FRAX—There are several appraisals that have assessed the cost-utility of interventions that used the probability of fracture. Indeed, models have been developed that incorporate the FRAX algorithms [163, 164]. The approach has generally been to determine the fracture probability at which interventions became cost-effective (i.e. an economic threshold). Economic thresholds have been variously used to set intervention thresholds or to validate the use of clinically driven intervention thresholds

National Osteoporosis Guideline Group: The NOGG age-dependent thresholds were driven by clinical considerations. At the same time NOGG wished to determine whether the strategy was cost-effective. The relationship between fracture probability and cost-utility were derived from all of the possible combinations of CRFs and BMD and age. This approach has been explored for the use of alendronate [105–165], risedronate [166], denosumab [164, 167], raloxifene, [168], strontium [169] and bazedoxifene [163, 170]. The major intervention in the UK and many other countries is alendronate [2]. In the case of generic alendronate treatment compared to no treatment was found to be cost-effective at a 10-year probability of a major fracture of 5.6 % (95% credibility interval; 4.8-6.8 %) in women from the UK at the age of 50 years (Figure 15) [14]. The economic threshold varied little by age and the mean threshold was 6.9 % with the range of 95 % credibility intervals between 4.2 and 9.6 %. In this analysis, the cost of alendronate was set at £95 per year, which is now a conservative figure since the current price has subsequently fallen to £12. Given that NOGG-based intervention thresholds range from 7.5 % at the age of 50 years to 30 % in the elderly [140], NOGG concluded that treatment with alendronate under the NOGG strategy was cost-effective.

The threshold probability at which treatment became cost-effective was higher with treatments other than alendronate, related in large part to the higher cost of intervention. For example, with willingness to pay set at £20,000 per QALY, treatment in the UK with

risedronate was cost-effective at a probability threshold of 17% at the age of 50 years [166]compared with a threshold of 7% with generic alendronate. Other studies have examined strontium ranelate, bazedoxifene and denosumab in this way [167, , 169, 170]. However, the cost-effectiveness of different interventions will vary between countries due to differences in drug costs, fracture risk, costs of treating fractures, utility estimates and willingness to pay.

The cost of the NOGG strategy has also been determined and compared with the RCP guidelines [160]. The identification costs and costs per averted hip fracture for the RCP and NOGG strategies are shown in Table 8. The NOGG strategy resulted in a lower cost per identified or averted fracture across all ages. As a consequence of the larger number of scans required, the costs of identification of incident hip fractures were somewhat higher, particularly at younger ages, using the RCP strategy. For example, at the age of 60 years, the cost per hip fracture identified was almost 1.5-fold higher for the RCP approach (£407 vs. £278). The differences in costs between the two strategies were less marked at older ages (Table 8).

Switzerland: In Switzerland, FRAX intervention thresholds of 13.8 % (for major osteoporotic fractures) or above (range, 10.8 to 15.0 %) and 15.1 % (range, 9.9 to 19.9 %) for women and men, respectively, were reported to be cost-effective using branded alendronate as the intervention [105]. The willingness to pay was set at 2 X GDP/capita. In addition to women age 60 years or above and men age 55 years or above with prior fractures, treatment was recommended for rest of the population at risk who had FRAX (for major osteoporotic fracture) probabilities of 15 % or above. If a NOGG approach to intervention thresholds were applied to the Swiss population, the vast majority of intervention scenarios would be cost-effective (Figure 16). Subsequent Swiss guidelines abandoned this approach in favour of age-dependent thresholds [157].

National Osteoporosis Foundation: The NOF set a 3% probability of hip fracture and a 20% 10-year probability of a major fracture as intervention thresholds in women with osteopenia in their clinical practice guidelines of 2008 [132]. The basis of this was a health economic analysis that examined the cost-effectiveness of pharmaceutical intervention [124]. A Markov cohort model of annual US 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/year drug cost for 5 years with 35 % fracture reduction). A 5-year course of treatment with a bisphosphonate-like therapy was modelled. 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 (optimistically) a 10-year hip fracture probability of 3 % as an intervention threshold. A 20 % probability of a major osteoporotic fracture was chosen as being equivalent to a hip fracture probability of 3 %.

The adoption of the 20 % fixed intervention threshold has had an enormous impact on the setting of thresholds in many countries worldwide for no better reason than this was the threshold adopted by the US (see Table 3). It is relevant then to draw attention to some limitations in the interpretation of the findings. The first relates to the threshold for hip

fracture probability that was chosen by the NOF since the analyses consistently showed that at this threshold, intervention was cost-ineffective as noted above. Secondly, the relationship between hip fracture probability and that for major fracture is not straightforward. Whereas there is a correlation between the probability of hip fracture and the probability of a major fracture, this is of poor predictive value (Figure 17) [140]. Indeed, the predicted probability of a major osteoporotic fracture derived from the probability of hip fracture could lie anywhere between 5 and 25%. Thirdly, the economic analysis was undertaken 8 years ago and many of the underlying assumptions will have changed in the interval.

A fixed threshold was also evaluated in a Spanish population and compared with the use of BMD as a gateway to treatment [171]. The use of a 7.5% threshold for a major osteoporotic fracture decreased markedly the requirements for BMD testing and the cost/fracture averted.

National Institute for Health and Care Excellence (NICE): Although the FRAX algorithm was used in early appraisals by NICE, the output was to determine the cost-effectiveness of individual agents according to clinical characteristics (T-score at -2.5 SD, prior fracture etc. [172–174]. The resulting guidance was complex and not without some controversy [175]. More recently a draft appraisal from NICE has been released for consultation [108] that incorporates fracture probability as an output variable. For the bisphosphonates alendronate and risedronate, the incremental net benefit with a willingness to pay of £20,000/QALY gained was positive over the range of fracture probabilities that were studied.

Hybrid thresholds (UK): There has been no formal health economic assessment of the UK hybrid variant where an age-dependent intervention threshold is used up to the age of 70 years and, thereafter, a fixed threshold is employed. Up to the age of 70 years, the threshold is identical to that used by NOGG. In the economic analysis from NOGG, intervention with generic alendronate was cost-effective at fracture probabilities for a major osteoporotic fracture that exceeded 7-8 % [140], significantly far removed from the 20 % threshold provided in the hybrid model. A similar analysis with risedronate, which cost £264 at the time, showed cost-effectiveness at a probability threshold of 18 % [166], close to the alternative intervention threshold studied in this paper. The 8-fold reduction in the cost of alendronic acid since then and the more recent availability of cheap generic forms of other osteoporosis agents including risedronate, ibandronic acid and zoledronic acid support the notion that the fixed intervention threshold comfortably represent cost-effective scenarios.

Greece: In a health economic assessment from Greece [80] proposed a biphasic intervention threshold based on cost-utility derived from on a previously developed state transition Markov cohort model developed for the International Osteoporosis Foundation [176]. The model was used to determine fracture probabilities at which intervention became cost-effective. The model was used in the Greek healthcare setting and economic thresholds determined employing the FRAX tool, recently calibrated for Greece. A bisphosphonate-like intervention for 5 years was modelled using the weighted average cost of treatments offered in Greece. From the results (Table 9) a "biphasic" economic probability threshold was proposed using 10-year probabilities for hip and major osteoporotic fractures of 2.5 and 10 %, respectively, under the age of 75 years, and 5 and 15 %, respectively from age of

75 years. The authors indicate that the proposed thresholds are consistent with the present guidelines for Greece which recommend treatment based on BMD defined osteoporosis or a prior fragility fracture [79].

Discrimination of FRAX

Discrimination is the ability to distinguish people at high risk from people at low risk. The performance characteristics of FRAX were validated prior to its launch by comparing the increase in fracture risk per SD of change in the risk score (termed the gradient of risk) [14]. The gradients of risk in the nine cohorts used to construct FRAX were compared with those determined in 11 validation cohorts comprising 230,486 men and women studied for 1,208,528 person years. During follow-up, there were 18,543 osteoporotic fractures, 3360 of which were hip fractures. Gradients of risk did not differ from the original cohorts used for model building (Table 10). Whereas both BMD and the clinical risk factors alone provide significant gradients of risk for fracture, the highest gradients of risk are seen when BMD is co-entered into the FRAX model. These data give some credence to the view that the original algorithms may be widely applicable, though further validation is required in men and in ethnic groups not covered in these analyses. An important observation was that gradients of risk were markedly age-dependent making cross-comparison not possible with studies that do not adjust for age.

In this context, there was a rash of so-called validation studies between 2009 and 2012, that reported the performance characteristics of FRAX using ROC curves [177–188] to give but a few. Other examples are given elsewhere [189]. Some of these were summarised and reported by the National Clinical Guideline Centre [161] though, for unknown reasons, the validation studies in Table 10 were omitted. The same paper reported sensitivities and specificities at a fixed but inappropriate threshold. For a variety of reasons, it is inappropriate to compare performance characteristics using ROC curves across studies [190]. Reasons include the variable follow up of different cohorts and the need to standardise by age [14]. Fewer such analyses have been reported recently although those listed above regrettably still appear in systematic reviews [161, 191, 192]. For the reasons given above, we prefer the use of gradients of risk as given in Table 10.

Comparing cohort-specific models with FRAX—Omission of CRFs from fracture prediction models has been suggested in a number of publications, since alternative and simpler models discriminate as well as or better than FRAX [178– 184]. The attraction for the deletion of CRFs is either to convert a complex model into a simpler tool that is easier to use in routine clinical practice, or to have a more accurate tool for a local population. The argument runs that the application of an independent 'home grown' model to an index cohort with fewer risk factors gives the same or better discrimination of cases and controls than does the more complex FRAX model. Irrespective of the reasoning, the logic is faulty as are the methodological approaches [193]. An internal model will almost invariably provide higher gradients of risk (or fracture discrimination) than models that are derived externally. This arises because the internal model is constructed to best fit the data within the index cohort, whereas an external model is necessarily derived from other sources. It follows that any assessment of predictive value within a single cohort will not necessarily be

identical to the predictive value for the future. In the context of fracture risk prediction, the internal model is un-validated and only of retrospective value to the population studied.

The fallacy of comparing internal with external models is shown in a report by Bolland and colleagues [180] who studied a cohort of healthy women from New Zealand enrolled in a 5-year trial of calcium supplements, and followed on average for 8.8 years. The area under the curve (AUC) for receiver operating characteristic curves (ROC) curve for hip fracture was 0.69-0.70 with FRAX. The AUC was similar in the cohort –specific model that only used age.

Calibration of FRAX

Several sources have reported that there are limited studies of the calibration available for FRAX [161, 192]. However, the view is somewhat misplaced in that each FRAX model goes through an *internal* calibration step [8]. Thus, if the whole population of a country were to be FRAXed with the country-specific model, the number of deaths and hip fractures would match those predicted by FRAX. The calibration is, however, dependent on the accuracy of the fracture hazard and death hazard for each country or ethnicity. For this reason, where possible, FRAX models are built on national data.

Additionally any validation exercise will be critically dependent on the representativeness of the population tested for the index country. There are several studies that have studied populations that represent national populations.

England—The first was based on a UK prospective open cohort study of routinely collected data from 357 general practices on over 2 million men and women aged 30-85 years. The area under the ROC curve for the FRAX algorithm in hip fracture prediction was 0.85 for women and 0.82 for men. Given the small differences in the incidence of hip fracture assumed by FRAX and that observed in the cohort, FRAX appears well calibrated for hip fracture in the UK. The calibration of major osteoporotic fractures differs markedly when compared with Q fracture [9] (Figure 18), which has been attributed to a greater accuracy of QFracture compared with FRAX [11, 32]. However, the available evidence indicates that the converse is more likely, and that QFracture is poorly calibrated for this fracture outcome, probably because of the low quality of computerised general practitioner records [13].

Canada—The second study was from Canada [194]. Observed ten-year fracture incidence from men and women in the CaMos study (n = 1,919 and 4,778, respectively) was compared with fracture probabilities based on the Canadian FRAX tool (both without and with BMD). FRAX-estimated 10-year probabilities for a major osteoporotic fracture were similar to the incidence rates in men (5.4 % vs. 6.4 %, respectively) and in women (10.8% vs. 12.0%). Similar findings were reported for hip fracture risk. Comparable findings were also reported in a large Canadian BMD referral population from Manitoba [195] (Figure 19). Note however, that incidence is compared with probability so that, as expected, incidence values are higher than probability values. In a subsequent analysis in untreated women, FRAX estimates of fracture probability were very closely matched with those observed when adjusted for competing mortality; for hip fracture, the mean predicted probability was 1.9%

and that observed was 1.9%. For major fractures, the respective values were 10.9% and 10.0% (95% CI, 8.8-11.2) [197]. Thus, FRAX appears well calibrated for Canada. A strength of these studies is that fracture incidence was collected over 10 years and only the first major fracture taken into account.

Denmark—A registry linkage study (Danish National Register of social security numbers) was undertaken to determine FRAX-based probabilities using baseline questionnaire data derived from a structured questionnaire [197]. From a random sample of 5000 women, complete information was available for 3,636 women. FRAX hip fracture probabilities were calculated without BMD using the Swedish tool. Predicted and observed risks estimates incorporated adjustment for 10-year survival rates. The predicted 10-year hip fracture risk was 7.6 % overall with observed risk also 7.6 %, ranging from 0.3 % at the age of 41–50 years (observed risk 0.4 %) to 25.0 % at the age of 81–90 years (observed risk 24.0 %). There were no significant differences overall or by decade of age. For the closely related Scandinavian countries of Sweden and Denmark, a single FRAX tool may be sufficient.

Kuopio Osteoporosis Risk Factor and Prevention (OSTPRE) study—The most thoughtful and revealing calibration study was undertaken in Finland using information from the Kuopio Osteoporosis Risk Factor and Prevention (OSTPRE) study cohort of postmenopausal women from the Kuopio Region of Finland. OSTPRE was one of the 12 cohorts used in the risk factor evaluation of osteoporotic fractures during the development of FRAX. The population included 13,917 women who were still alive after a 10-year follow-up, and excluded women who had sustained a previous hip fracture. Observed hip fracture outcomes were compared with hip fractures expected using the Finnish FRAX model [198]. The Finnish FRAX model (version 3.6) was based on the national incidence of the first hip fracture for 2002 to 2006 [199] and national mortality data supplied by the WHO. FRAX without BMD was calculated in 11,182 women and femoral neck BMD information was available in a subset of 2,755 women for the calculation of hip fracture probability with BMD.

The relationship between the FRAX probability of a hip fracture and the 10-year period prevalence of a hip fracture was examined by quintiles of hip fracture probability. The average predicted probability of a hip fracture during a 10-year period was 0.80 % (95 % CI: 0.78–0.81) when calculated without BMD and the same for the subset of women with BMD measurement. The similarity of predictions with and without BMD indicates that the subgroup studied was not preferentially enriched by women with low (or high) BMD for age. The 10-year period prevalence was lower than predicted (0.71 %), was even lower in women in whom FRAX without BMD had been calculated (0.66 %) and lowest in those in whom FRAX with BMD had been calculated (0.61 %).

The relatively moderate calibration might lead one to the view that the use of the Finnish FRAX model results in misleading information as a result of errors in accuracy. Errors of accuracy in the FRAX model may, in principle, reside in the fracture hazards or the death hazards, both of which contribute to fracture probability but the model used national data and there is no reason to question the validity of these hazards, especially because it is known that regional variation in hip fracture incidence is small in Finland [200].

However, these findings also showed that the 10-year period prevalence of the hip fracture (and thereby hip fracture incidence) varied according to observation status. Thus the likely reason for poor calibration is the selection bias between those who did and did not respond. Women who had reported enough information for the calculation of a FRAX probability had a tendency for a lower risk of hip fracture than women who did not respond; that is, many women with a high risk for a hip fracture may have been missing from the calibration calculations. This occurred in spite of the relatively high response rate of 84–88 % in each of the OSTPRE enquiries used. Thus, such bias is likely to be present in most of the corresponding study cohorts: not only do they not represent the whole population, but the people with the highest risks are missing.

As an aside, self-reports missed 38 % of all hip fractures in the national register in women who responded and missed about 45 % of hip fractures in women who had a FRAX estimate.

Difficulties in calibration of FRAX—The considerations above highlight intrinsic difficulties with sampling bias and incomplete fracture acquisition. There are several additional problems to be faced with the external calibration of FRAX models.

Difficulties arise when FRAX probabilities are compared with observed incidences [177, 179–182, 184–186, 188, 201, 202]. Other examples are listed in Leslie and Lix [189]. In the case of FRAX, the algorithm computes a fracture probability (i.e. a metric that incorporates the death hazard), which is not synonymous with simple fracture incidence. As a result, the comparison is largely invalid, particularly at older ages, and it is wrong to conclude that a FRAX tool or comparator tool is ill-calibrated.

One of the ways of checking bias is to compare calibration with and without the inclusion of BMD. Because of the internal calibration of FRAX, fracture probabilities (particularly for hip fracture) will be the same in a sample representative of the national population. The several studies that report differences in fracture probabilities with and without BMD [182], [181, 182, 184, 202–206] should be treated with suspicion with regard to calibration.

Cohorts used for validation should be representative of the population because fracture and death rates may vary within countries. For fracture risk, this may vary more than two-fold [18] so that the interpretation of non-representative cohorts is difficult.

In addition to geographic variation reported in the incidence of hip fracture within countries, the age-and sex-specific incidence of fracture is changing in several countries. This has been well characterised for hip fracture, but also noted at other sites of fracture [207, 208]. Estimates of incidence trends have varied widely and variously reported as an increase, plateau, and decrease, in age-adjusted incidence rates for hip fracture among both men and women. In contrast, the mortality hazard has continued to decrease in most regions of the world. FRAX is based on cohorts studied years prior to the launch of FRAX in 2008, so that there may 10+ years between the FRAX model and the cohort testing the calibration. As noted above, the calibration of the FRAX algorithms is only as good as the epidemiology

with which the tools are populated. Indeed the FRAX models have been updated where more recent or higher quality data have become available (e.g. Turkey and the US).

Regardless of the difficulties to be faced with calibration, it should be noted that any systematic errors have little impact on the rank order of fracture probabilities produced by the FRAX tool. For example, the FRAX tool for the United States was revised to take into account changes in hip fracture and mortality risks [209]. Importantly, the revisions have little impact on the stratification of fracture probabilities because the revisions do not change the rank order of fracture probability in any population. In the US revision, the correlation coefficients between versions 2.0 and 3.0 probabilities exceeded 0.99, so that the one can be accurately predicted from the other. In other words, an individual at the 90th percentile of risk would still be at the 90th percentile of risk using the revised FRAX tool, though the probability of a major fracture that was 53 % in the original version was 44 % in the revision. Thus, the consequences of improving accuracy reside in the absolute number generated and not in the rank order of risk so that the consequences of inaccurate epidemiological data are of minor consequence to daily clinical practice. An exception arises when fracture probabilities are used in health-economic analysis to inform practice guidelines where accuracy becomes a matter of importance.

Other determinants of accuracy—A number of studies have investigated potential errors of accuracy within populations. The accuracy of FRAX does not appear to be affected by socioeconomic status – at least in Canada [210]. A much smaller study from Australia suggested no association of FRAX with socioeconomic status in women with a history of prior fracture but surprisingly, a significant effect in women without a prior fracture [197].

It has been suggested that FRAX should not be used in patients taking medication for osteoporosis. In a large study that addressed the question [211], the impact of compliance to bisphosphonates on calibration was very modest and non-significant. The study reported good concordance between observed and predicted major osteoporotic fractures in patients with high compliance, suggesting that FRAX is not invalid in patients exposed to treatment (observed/predicted ratio 0.92, 95 % CI 0.78-1.06). Only in the highest risk tertile of women highly adherent to at least 5 years of bisphosphonate treatment was the observed hip fracture risk significantly less than predicted.

A factor that appears to affect calibration is immigrant status. The incidence of hip fracture in Sweden was reported to be substantially lower in immigrants than in the population native to Sweden [212]. Although there was a small rise in age- and sex-specific incidence after immigration, the incidence remained markedly lower than that observed in Swedish-born individuals even after 20 or more years. Thus, the use of a FRAX model for Sweden will overestimate the risk of fracture for foreign-born individuals living in Sweden. Sweden has one of the highest hip fracture rates worldwide and, if the findings in Sweden are replicated in other countries (with a lower indigenous fracture risk), the quantum of effect may be more modest.

Reclassification—The guidelines developed by NOGG and adopted in several other countries has the characteristic that individuals may be eligible or otherwise without a BMD

test. Rather, the use of BMD is restricted to individuals that lie close to the age-dependent intervention threshold. In turn decision rules are required to determine a threshold probability below which neither treatment nor a BMD test should be considered (lower assessment threshold) and a threshold probability above which treatment may be recommended irrespective of BMD (upper assessment threshold). The attraction of the approach is that efficient use is made of BMD testing. The justification of these assessment thresholds depends on reclassification rates when FRAX is calculated with and without BMD.

An example of such an approach is shown in Table 11, which shows the distribution of fracture probability in a random sample of women aged 75 years or more drawn from the general population of Sheffield [142]. With an arbitrary treatment threshold set at a probability of any fracture of 35 % (note, all fractures and not just a major fracture- this was a forerunner of FRAX), approximately 17 % of the 2113 women were classified at high risk when assessed in the absence of BMD. When all women were reassessed with the inclusion of BMD, a total of 319 women (15 %) were reclassified from high risk to low risk and vice versa. However reclassification was most frequent at probabilities close to the intervention threshold. Indeed 96 % (305 of 319) of women reclassified had probabilities without BMD within 10 % of the treatment threshold (see Table 11). In other words, if BMD testing was confined to those with a probability between 25 and 45 % then almost no cases would be missed that would otherwise (using probabilities with BMD) have been detected. Importantly, a BMD test would only be required in about 50 % of the population. In practice, the NOGG upper assessment threshold is 20 % higher than the intervention threshold, so that almost all relevant cases are appropriately stratified.

Broadly similar conclusions have recently been reported in a large Canadian referral population [213] and in the UK, an analysis, using the finalised FRAX algorithm, to examine hip fracture outcomes [214]. These various studies examined reclassification rates within a single assessment algorithm; several publications have compared concordance or discordance following different guidelines.

Comparison of guidelines—It is axiomatic that different intervention thresholds will identify different patients at different risk. However, empirical data examining the degree of concordance between high risk and low risk classification based upon FRAX probability estimates and thresholds based on BMD suggest that discordance rates are low [195, 215]. Indeed, a large majority (85 %) of individuals designated by FRAX as high risk, when BMD was not used in the calculation, had a T-score in the osteoporotic range at one or more BMD measurement sites (Table 12). Conversely, there were extremely few individuals (<1 %) who were at high risk of major osteoporotic or hip fracture with normal T-scores at any BMD measurement sites. Similar patterns were seen for hip fracture probability, when data were stratified by sex and age.

Further examples of different strategies are given in Table 13 based on the National Health and Nutrition Examination Survey (NHANES) 2005–2008 [215]. The application of FRAX used the US model for Caucasian men and women. Not surprisingly all examples select individuals at high risk. It is of interest that the guideline of the US National Osteoporosis

Foundation (scenario F in Table 13) selects the greatest number of patients eligible for treatment and that the application of an age-specific FRAX threshold with (D) or without prior fracture (C) identifies a smaller proportion of the population but at higher risk. Also of relevance is that a fixed FRAX threshold set according to the NOF guidelines (but applied to the whole cohort) (scenario B) identifies men and women at lower fracture risk than the use of an age-dependent intervention threshold (C).

Net Reclassification Improvement (NRI)—As reviewed above, there has been some debate regarding the value of complex fracture risk assessment tools over simpler more intuitive tools. Indeed, the Canadian clinical practice guidelines go so far as to endorse both complex (WHO FRAX) and simple (Canadian Association of Radiologists and Osteoporosis Canada (CAROC) tools [29]. CAROC uses age, sex, femoral neck BMD and two clinical risk factors (prior fracture and prolonged glucocorticoid use) to assign semi-quantitative 10-year probabilities (low: 10 %, moderate: 10-20 %, high: >20 %). The net incremental benefit of using the complete FRAX tool vs CAROC tool was explored using Net Reclassification Improvement (NRI) to quantify the differences between FRAX vs CAROC [217].

The study population included 54,493 women and men with a mean age of 67 years, of whom 4,508 (8.3 %) had sustained an incident major osteoporotic fracture during a mean follow up of 6 years. FRAX and CAROC both provided good risk stratification and calibration with identical risk categorisation in 82.3 % (FRAX higher 6.7 %, CAROC higher 11. 0 %). NRI for FRAX vs CAROC was no different in those who experienced an incident major osteoporotic fracture (-0.7 %, p=0.23) but it was significantly greater for those who did not (+4.6 %, p<0.001) as well as for the entire cohort (+3.9 %, p<0.001). The NNF ("Number Needed to FRAX") to improve fracture prediction was 26 overall and 7 in those with a prior fracture. Thus, both FRAX and CAROC provide good risk stratification and are well calibrated to the Canadian population, but FRAX provides a more accurate quantitative assessment of risk, particularly in those with prior fracture, compared with more parsimonious semi-quantitative systems.

Discussion

The use of FRAX in assessment guidelines has grown progressively since its launch in 2008. At the time of writing, FRAX had been incorporated variously into 120 guidelines developed by government agencies or learned societies. Of these 82 provide intervention thresholds. As might be expected for a new technology, its uptake and application is heterogeneous. The present review identifies two broad approaches to the implementation of FRAX in assessment guidelines (Figure 20):

> The use of a fixed FRAX intervention threshold either alone or as a component of other thresholds (e.g. BMD, parental history of fracture etc.). Fixed thresholds have been variously used to screen for osteoporosis (BMD testing threshold) or as an intervention threshold.

> Age-dependent intervention thresholds using FRAX as a principal gateway to assessment.

In some instances, economic thresholds based on cost-effectiveness of intervention have been used to set either approach.

Use of fixed thresholds

The use of a fixed FRAX threshold has some intuitive appeal in that it directs intervention in an equitable manner and is more readily used in clinical practice than more complex approaches inherent in the application of age-dependent thresholds. There is, however only one poorly validated guideline that directs intervention solely on this basis (Taiwan). An important precedent is that the vast majority of guidelines worldwide recommend that individuals with a prior fragility fracture should be offered treatment. Irrespective of the merits of this approach, this sets up an immediate problem of consistency in that the fracture probability in men and women with a prior fracture is age dependent (Figure 21). Thus, the setting of a fixed threshold, say at 15 %, would mean that few individuals with a prior fracture would be eligible for treatment below the age of 65 years.

A further problem with the use of fixed thresholds alone arises in the proportion of the population eligible for treatment. The impact of using different intervention thresholds is shown in Figure 22 for postmenopausal women in the UK [3]. Very similar findings are reported from Japan [218]. At high thresholds e.g. >20 % fracture probability, 20.5 % of postmenopausal women would be eligible for treatment. A problem that arises is that very few women under the age of 60 years would ever attain this threshold (less than 1 %). On the other hand, if a less stringent threshold were chosen, say 10 %, then approximately 5 % of women at the age of 50 years would exceed this threshold, and a majority of women over the age of 65 years would be eligible and the treatment threshold would be exceeded in 50 % of all postmenopausal women. Both scenarios are counterintuitive to clinical practice [81, 218].

The problem of consistency with the use of a fixed FRAX threshold is not unique to FRAX. The same problem arises with fixed BMD thresholds in that the fracture probability in men and women with a fixed T-score is also age dependent (see Figure 21).

These considerations support the avoidance of the use of a fixed FRAX intervention threshold as the principal gateway to fracture risk assessment. This is one of the reasons why fixed thresholds form but one component of more complex assessment models. The prime examples are in the US and Japan where the use of FRAX is confined to individuals with osteopenia [30, 31]. A second reason is that, where there have been established guidelines for many years, there has been a reluctance to disturb historical precedent with potential consequences for regulatory approval or reimbursement. Rather, FRAX has been fitted into the historical guidelines.

Although fixed thresholds are not used as the principal gateway to treatment, FRAX (without the inclusion of BMD) is recommended as a screening tool to direct the use of subsequent BMD testing by the ACR and SIGN [32, 113], as well as in an academic paper from Japan [83]. Since the detection of osteoporosis is the goal, then it is inappropriate to use FRAX, which is designed for the prediction of fracture but not osteoporosis [13]. Indeed there are more appropriate tools available for the detection of osteoporosis [8,192]. In one

study, for example, the sensitivity of FRAX (i.e. the detection rate for osteoporosis) at a similar probability threshold as used by SIGN and the US Preventive Services Task Force (10 and 9.3 %, respectively) was 33.3 % whereas the Osteoporosis Self-Assessment Tool (OST) [130] had, in the same population, a sensitivity of 79.3 % [127, 128]. Sensitivities in the order of 90 % or more are reported in other populations [8]. Moreover these instruments are easier to administer than FRAX; OST is calculated only from weight and age. If the intention of screening had been to identify women at a high risk, then a fracture risk assessment algorithm would the appropriate tool. In this context, it is worth noting that FRAX outperforms OST for fracture prediction [8].

Setting fixed FRAX thresholds

A variety of approaches has been used to set intervention thresholds. Relatively few publications provide an explanation of the manner in which they have been derived. Those noted in this review are summarised in Table 14. Apart from the US Preventive Services Task Force thresholds that are used for screening, there are nine relevant publications which provide a rationale for the intervention threshold. Notably, only two of these have been incorporated in official guidelines (Lebanon and NOF).

The most influential thresholds are those derived from the National Osteoporosis Foundation in the US. Treatment is recommended when the 10-year probability of a major fracture is 20 % or above, or where the probability of a hip fracture exceeds 3 %. It should be noted that these fixed thresholds are not used in isolation and are reserved for patients with low bone mass (osteopenia). As reviewed in this report, the basis on which these are derived may no longer be appropriate. Reasons include that the thresholds are derived from cost-effectiveness in 2008 and the cost of intervention has changed since then; the threshold was derived from hip fracture probabilities and their transformation to MOF equivalents is not straightforward. Thus, the thresholds may have to be revisited.

This apart, the thresholds are relevant only to the US and are inappropriate for use elsewhere because of differences in the importance of osteoporosis, the heath care budget allocated, current practice guidelines, reimbursement and health economic considerations. Although this states the obvious, the majority of guidelines that use a fixed threshold have chosen a 20 % fracture probability without any justification other than its use in North America.

Additionally, within Europe, the proportion of the population aged 50 years or more with a FRAX probability of a major fracture >20 % varies from 2 % (Romania) to 19 % (Denmark) [28] (Figure 23). This variation in risk needs to be balanced against the health care spend (4.5 % of gross domestic product in Romania and 10.8 % in Denmark, equivalent to €309 and €4759/per capita per year, respectively [2]. In Europe, the 20 % threshold has been recommended in Austria, Greece, Hungary, Slovenia and Sweden (see Table 3), which in turn will have a marked effect on the population eligible for treatment. Given also that the cost of intervention varies little between countries, no one fixed FRAX threshold is applicable to all countries, and if fixed thresholds are to be used, they need to be country-specific [219].

Consequences of a 20% threshold

The use of the 20% threshold without economic justification has important implications for clinical practice. The proportion of the population at risk varies according to the distribution of fracture probabilities. Since there are marked international differences in the death and fracture hazards, so too are there differences in the proportion of the population who would be deemed at high risk. Figure 23 shows the proportion of the population (aged 50-85 years) above the 20% threshold value in countries of the European Union [3] with a 10-fold variation. Of these countries, the 20% threshold has been recommended in Austria, Greece, Hungary, Slovenia and Sweden (see Table 3), which in turn will have a marked effect on the population eligible for treatment.

Another way of looking at this is to determine the T-score that is equivalent to a probability threshold of 20 %. Given that fracture rates vary widely from country to country – much more so than can be explained by variations in BMD for any given fracture risk [220], the T-score threshold will vary from country to country. For example, when an intervention threshold is set at a 10-year probability of a major fracture of 20 %, the femoral neck T-score ranges widely in different countries. Figure 24 illustrates this for women aged 65 years, prior fracture and a BMI of 24 kg/m^2 using the FRAX tool. For this clinical scenario, a 10-year fracture probability of 20 % is equivalent to a T-score of -4.6 SD in Venezuela whereas the equivalent T-score in women from Iceland is -2.0 SD. In the absence of a prior fracture the T-score ranges from -3 to -5 SD.

This argues strongly that intervention thresholds need to be determined on a country-by-country basis.

Economic thresholds

Health economic assessment in the context of intervention thresholds and guideline development has used two approaches with FRAX. The first has been to set a FRAX intervention threshold at the point at which intervention becomes cost-effective. This is the approach that historically has been used by the National Institute for Health and Care Excellence in the UK [173, 174]. Other examples, reviewed in this report, include the development of the 20 % thresholds used in the NOF guidelines of the United States [124]. The fracture probabilities at which intervention becomes cost-effective have been explored for the use of alendronate [105, 165], risedronate [166], denosumab [167], raloxifene [168], strontium [169] and bazedoxifene [163, 170]. As would be expected, analysis of each intervention produces different thresholds. Moreover, a threshold determined for one country cannot inform a threshold in another. This poses problems in the application of the guidance to primary care if intervention thresholds are drug-specific. This has led to analyses being based on a basket of interventions, an approach that has been resisted by NICE [108]. This in turn raises additional problems of management. Imagine, for example, Mrs x aged 56 years with a prior vertebral fracture whose probability of a major osteoporotic fracture is 10 %, well above the threshold where treatment with alendronate is reimbursed. She is given alendronate, which is poorly tolerated, but she cannot be offered an alternative treatment (e.g. risedronate) until her fracture probability has increased to 18 %, because the agent-specific threshold had not been reached. In this example a wait of 11 years is required, all

other things being equal. Such guidance is cumbersome and cannot be readily used in the primary care setting. Moreover, thresholds produced in this way are very sensitive in that even a modest change in the cost of intervention will invalidate the threshold.

The second and alternative approach, adopted by NOGG was to devise intervention thresholds based on clinical imperatives, always provided that the strategy proves to be cost-effective [139]. In the former scenario, health technology assessment sets intervention thresholds and in the latter, intervention thresholds are validated by economic analysis. The major intervention in the UK and many other countries is alendronate [2]. In the case of generic alendronate treatment compared to no treatment was found to be cost-effective at a 10-year probability of a major fracture of approximately 7 % indicating that the use of NOGG thresholds were cost-effective [165].

Age-dependent intervention thresholds

Prior to the advent of FRAX, many guidelines in Europe, North America and elsewhere recommended treatment in women with a previous fragility fracture (a prior vertebral or hip fracture in some countries) in the absence of information on BMD. This gave rise to the view that intervention thresholds in women without a prior fracture could be set at the age-specific fracture probability equivalent to women with a prior fragility fracture and therefore rises with age. In other words, the intervention threshold is set at the 'fracture threshold'. This approach to intervention thresholds, first adopted by the National Osteoporosis Guideline Group (NOGG) for the UK [140, 141] is now used in two European guidelines (one for postmenopausal osteoporosis [3] and the other for glucocorticoid-induced osteoporosis [149], 12 practice guidelines and explored in 10 another research papers (see Table 6). The same intervention threshold is applied to men, since the effectiveness and cost-effectiveness of intervention in men are broadly similar to that in women for equivalent risk.

The present review has identified several merits of the use of FRAX and, in particular, age-specific thresholds that are summarised in Table 15. They include the wide availability of well-calibrated models which can be applied to a large segment of the world population. Indeed the 62 FRAX models in 57 countries that are available to date, cover approximately 80 % of the world population [221]. With regard to the strategy itself, there are several features which indicate that the performance characteristics are significantly better than the UK or European guidance that it replaces. Of strategic importance, the use of age-dependent thresholds has been demonstrated to be more effective than fixed thresholds in identifying populations at high risk. In the UK, there appears to be high concordance between clinician-determined treatment interventions to reduce fracture risk compared with FRAX-NOGG output data. The predominant reason for differences in opinion was the use of lumbar spine BMD to help assess fracture risk by clinicians [222].

Limitations of FRAX

No risk assessment engine is perfect. The introduction of FRAX, particularly with BMD has increased the sensitivity of fracture risk prediction. In the case of FRAX without BMD included the gradient of risk for a major osteoporotic fracture is approximately equal to that of BMD alone [14]. Despite the step change in prognostic value, sensitivity remains low.

Thus FRAX should not be viewed through rose tinted spectacles but considered as a reference platform to aid but not replace decision-making. The rapid and widespread uptake of FRAX has made it the subject of great scrutiny and the limitations have been widely articulated. In some instances concerns have been raised over FRAX in general or its use in assessment guidelines (Table 16), which are reviewed briefly.

Well established limitations of FRAX—The limitations of FRAX have been extensively reviewed [8, 18] and are only briefly mentioned. The risk factors included in FRAX were chosen carefully to limit the number and complexity, for ease of input, and to include only well-recognised, independent contributors to fracture risk. In addition, it was important that the factors used identified a risk that was amenable to an intervention [8, 15]. The FRAX tool has been appreciated for its simplicity for use in primary care but criticised for the same reason because it does not take account of exposure response. For example, the risk of fracture increases with exposure to glucocorticoids, but FRAX only accommodates a yes/no response to the relevant question. Other well-researched examples of 'dose–response' include the number of prior fractures and the consumption of alcohol. Other concerns are the lack of provision for lumbar spine BMD which is commonly recommended in treatment guidelines, and the absence of measurements of the material or structural properties of bone. A concern that treatment might invalidate the interpretation of FRAX is misplaced [196].

If FRAX is to be made more accurate by the inclusion of different degrees of exposure, then information is required not only on the risk of fracture associated with these exposures but also on their dependence on the other risk variables in FRAX and their independent effect on the death hazard. This demands the collection of new population cohorts that include such information as well as the other FRAX variables in sufficient numbers and with wide geographical representation.

In order to overcome some of these demands, relatively simple arithmetic procedures have been formulated which can be applied to conventional FRAX estimates of probabilities of hip fracture and a major fracture to adjust the probability assessment with knowledge of:

> High, moderate and low exposure to glucocorticoids [20]
>
> Concurrent data on lumbar spine BMD [21, 22]
>
> Information on trabecular bone score (TBS) 23-25]
>
> Hip axis length [26]
>
> Falls history [27]

Such analyses can inform the clinician how to temper clinical judgement on the existing output of the FRAX models.

The most frequent concern, however, is the omission of falls as a risk variable in the FRAX model, particularly as this is included in other risk assessment tools. Indeed, a Task Force of the ISCD recommended that falls should be incorporated into FRAX [27]. Whereas this view is a sound academic conclusion from the literature on falls risk, the incorporation into FRAX is problematic for several reasons. First, at the time of the release of FRAX, existing

falls data were not of adequate quality, including the heterogeneous construct of questions on falls. Second, falls risk is inherently taken into account in the algorithm, though not as an input variable. Thus, the fracture probability given for any combination of risk factors assumes that the falls risk is that observed (but not documented) in the cohorts used to construct FRAX. Third, the interrelationship of falls risk with the other FRAX variables has been inadequately explored on an international basis. Fourth, the relationship between the risk variable and mortality needs to be accounted for, but there are no data available.

These technical problems aside, FRAX is intended to identify a risk that is amenable to a therapeutic intervention. In a single study, a post hoc analysis of a community-based intervention study with clodronate in elderly women [224] showed that fracture reduction was similar in women with or without recent multiple falls or in those with impaired ability in rising from a chair. This finding suggests that falls or falls risk may identify a risk amenable to intervention. In contrast, in the phase III trial of risedronate, where hip fracture was the primary end point, hip fracture risk was not significantly decreased in women over the age of 80 years, the majority of whom were purportedly selected on the basis of falls risk [225]. Thus, falls as a risk variable does not consistently pass the test of reversibility of risk, a necessary feature of any risk variable used in FRAX [8, 15]. More recently, both FRAX and past falls were shown to be associated with falls on follow-up in elderly men. Whereas past falls were a significant predictor of incident falls, even after adjustment for FRAX, the hazard ratio decreased markedly with increasing follow-up time [226] and an analysis in the same cohort, only available as a meeting abstract, indicated the predictive value of falls for fracture also waned significantly with time [227]. If the phenomenon is replicated more generally, then this would call into question the utility of falls history in the long term (e.g. 10-year) assessment of fracture risk. Thus a useful role of falls history in fracture risk assessment remains *sub judice*.

Reliance on computer access—The vast majority of FRAX calculations are undertaken through the FRAX website so that there is a reliance on access to computers. In this context a link from the FRAX website to a site that plots the result on a country specific chart allows easy interpretation of result according to the relevant guideline. Such links are available for the models of Finland, Lebanon, Romania and the UK. A recent audit from the UK indicated a high uptake of this facility [223] and the approach could usefully be adopted in all countries for which a FRAX model and a guideline are available.

In countries with limited electronic access in primary care, downloadable country-specific charts are available through the FRAX website. These provide a simplified assessment, relying on the number of clinical risk factors rather than on their independent weights. They are used in Belgium, Japan, Mexico, Poland and Russia The web site is not the sole portal for the calculation of fracture probabilities. FRAX is also available in most BMD equipment that measures the femoral neck. Versions for use on smartphones, tablets and computer driven versions that do not rely on internet connection are available through the International Osteoporosis Foundation.

Not all countries have FRAX models—The creation of a FRAX model requires high quality (preferably national) data on fracture risk and mortality. At present, there are

upwards of 60 models available but this number will increase at a rate that depends on the generation of new data. Thus, the options are to use a surrogate model from another country where the fracture risk is judged to be similar to the index country. Indeed the UK model was used for several years in Poland before a Polish model became available. At present, approximately 15-20 % of FRAX visits to the UK web site arise from outside the UK. In this regard, it may be recalled that the categorisation of risk will be very similar irrespective of the model used [209]. A more satisfactory solution is to adopt a surrogate country but to incorporate the death hazard of the index country, as recommended by the International Society for Clinical Densitometry [228]. This type of surrogate model is available for Armenia, India, Sri Lanka and Palestine.

Efficacy in patients selected without BMD—A concern that is raised with the NOGG guidelines is that treatment is offered to patients in whom BMD is unknown, since BMD is tested in a minority of patients [32, 173, 174, 229]. For example, the SIGN guidance states "that the beneficial effects (of treatment) on fracture risk is restricted to patients with osteoporosis as defined by the presence of pre-existing vertebral fractures and or those with BMD values that lie within or close to the osteoporotic range." The concern is misplaced in that the use of FRAX (without BMD) preferentially selects individuals with low BMD [15, 142, 216, 230].

For example, in a population sample of approximately 2000 older women (aged 75 years or more), those characterized at higher fracture probability (by a precursor of FRAX but not FRAX) without the inclusion of BMD had progressively lower mean femoral neck BMD values (Figure 25). In women above an arbitrary risk threshold (e.g. 30 % 10-year fracture probability), mean femoral neck BMD was approximately 1 SD lower than in women below the threshold [142].

Similar findings were reported in a large referral population from Manitoba, Canada [231]. 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 categorised 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 (10-20% probability), the T-score was -2.2 SD, and in those at high risk (> 20% probability) was -2.8 SD.

Low BMD values are also noted when the NOGG strategy is applied to a simulated UK population (Table 17).

These data indicate that FRAX without BMD identifies individuals with low BMD. The reason is that several of the FRAX input variables are weakly correlated with BMD (though of statistical significance) such as age, prior fracture and glucocorticoid exposure. The conclusion is also supported by NICE [161] which made two recommendations of relevance in this regard.

> *Recommendation 6.* Do not routinely measure BMD to assess fracture risk without prior assessment using FRAX (without a BMD value) or QFracture.

> *Recommendation 7.* Following risk assessment with FRAX (without a BMD value) or QFracture, consider measuring BMD with DXA in people whose fracture risk is in the region of an intervention threshold for a proposed treatment, and recalculate absolute risk using FRAX with the BMD value.

Both recommendations support the parsimonious use of BMD and the strategy intrinsic to NOGG.

Controlled trials—There is no conclusive evidence that providing treatment on the basis of risk assessment will result in better clinical and cost-effective care. However, the NOGG strategy is less costly than the RCP strategy that it replaces [144], and intervention with alendronate is cost-effective over all intervention scenarios [140]. It is relevant to note that no trials have been undertaken with guidelines that are currently used to identify high risk patients. There is an ongoing trial in which the efficacy of treatment in individuals identified by FRAX as being at high risk of fracture is being investigated (the SCOOP study) which will include a health economic appraisal [162].

Age-dependent thresholds are ageist—It has been said that the NOGG approach discriminates by age and is one of the reasons cited for avoiding this method of threshold-setting [44]. This is somewhat ironic given that under the DVO guidelines in Germany, eligibility for testing is age and sex dependent. For example, a woman with a parental history of hip fracture is not eligible for assessment between the ages of 50 and 60 years, but becomes eligible for assessment from the age of 60 years. The corresponding age-dependent thresholds for men are 60–70 years and >70 years, respectively. Notwithstanding, the intervention threshold used In NOGG is overtly age-dependent but so too is the use of the T-score (see Figure 21) or probability fixed thresholds (see Figure 22), both of which 'discriminate' by age, though somewhat more covertly.

Inequity across countries—The merit of the NOGG approach (age-dependent thresholds) is that it can be readily applied to all countries and is more allied to a fracture threshold. Given the heterogeneity of mortality and fracture risk in different countries, the intervention threshold (i.e. the fracture threshold) will also differ. An example is shown in Figure 26 in women age 65-70 years for countries of the European Union [2]. This means that fracture thresholds need to be tailored individually on a country-by-country basis. This is a straightforward process but leaves the unsatisfactory position that a woman aged 72 years with a fracture probability of, say 15 %, would be eligible for treatment in Slovakia but not in Slovenia (see Figure 26). In Europe, the proportion of men and women above the age-dependent threshold varies little from 11-13 % across countries [2]. Although age-dependent thresholds seem to offer several advantages over fixed thresholds, problems of equality remain in that that the probability at which treatment is recommended is country-specific, though varies little in the western world.

A limitation of country-specific thresholds that are set at the fracture threshold is that, assuming a constant efficacy, there will be a much larger number of patients treated to prevent one fracture in countries with lower FRAX probabilities (e.g. China) compared to those counties with higher FRAX scores (e.g. Sweden). There is of course no obligation to

use the fracture threshold as the route to age dependency. In countries with a more conservative approach or low fracture probabilities, the threshold can be uplifted, say by 10 or 20 %. Conversely, an intervention threshold can be downward-adjusted where a more liberal approach is desired.

Sensitivity of NOGG in subgroups—The concept that women without fracture merit treatment if their risk of fracture is similar to or exceeds that of an average woman with a prior fracture is a concept that attempts to embrace fairness and equity of access to treatment.

Within a country, it would seem desirable that at any given age, the selection criteria for intervention results in equitable access to therapy for patients with the same age-specific absolute probability of fracture.

It is apparent that, following the NOGG guidance, this goal is not realised, particularly at older ages in that that those eligible for treatment without a prior fracture have on average higher probabilities than those eligible on the basis of a previous fragility fracture. This inequity results in a lower sensitivity of the algorithm for individuals without a prior fracture [109, 144].

This appears to be resolved with the UK hybrid model [109]. This uses an age-dependent intervention up to the age of 70 years, and thereafter a fixed threshold of 20 % probability of a major osteoporotic fracture. It must be emphasised, however, that the identification of a threshold for major osteoporotic fracture at or around 20 % is not a validation of this threshold on a global scale, but rather represents a chance occurrence. Fortuitously, this is the probability at the age of 70 years in a woman with a prior fracture in the UK, but will differ if the same approach is taken to determine fracture thresholds in other populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Abbreviations

AACE	American Association of Clinical Endocrinologists
ACR	American College of Rheumatology
AUC	Area Under the receiver operating characteristic (ROC) Curve

BMD	Bone mineral density
BMI	Body mass index
CAROC	Canadian Association of Radiologists and Osteoporosis Canada
CI	Confidence interval
CRF	Clinical risk factor
DXA	Dual-energy X-ray absorptiometry
ECTS	European Calcified Tissue Society
EFPIA	European Federation of Pharmaceutical Industry Associations
ESCEO	European Society for Clinical and Economic Aspects of Osteoporosis
FRAX	WHO fracture risk assessment tool
HF	Hip fracture
HSOO	Hungarian Society for Osteoporosis and Osteoarthrology
IOF	International Osteoporosis Foundation
ISCD	International Society of Clinical Densitometry
JSBMR	Japanese Society for Bone and Mineral Research
MOF	Major osteoporotic fracture
NCGC	National Clinical Guideline Centre
NCGC	National Clinical Guideline Centre
NICE	National Institute for health and Clinical Excellence
NNF	Number Needed to FRAX
NNS	Number needed to scan
NOF	National Osteoporosis Foundation, US
NOFSA	National Osteoporosis Foundation of South Africa
NOGG	National Osteoporosis Guideline Group, UK
NRI	Net reclassification improvement (I)
OST	Osteoporosis Self-Assessment Tool
OSTPRE	Kuopio Osteoporosis Risk Factor and Prevention - study
PSTF	US Preventive Services Task Force
QALY	Quality-adjusted life year

QALY	Quality-adjusted life year
QFracture	A fracture risk assessment tool
RCP	Royal College of Physicians, London
ROC	Receiver operating characteristics
SCOOP	Screening of older women for prevention of fracture - study
SCORE	Simple Calculated Osteoporosis Risk Estimation Tool
SD	Standard deviation
SIGN	Scottish Intercollegiate Guidelines Network
SIOMMMS	Società Italiana dell'Osteoporosi, del Metabolismo Minerale e delle Malattie dello Scheletro
TBS	Trabecular bone score
THIN	The Health Improvement Network
T-score	The number of SD units that BMD differs from the young healthy reference population
WHO	World Health Organization
YAM	Young adult mean values for BMD

Age-dependent threshold
Intervention or assessment threshold of fracture probability that varies with age

Assessment threshold
The fracture probability at which further assessment id recommended (usually BMD)

Fixed threshold
Intervention or assessment threshold of fracture probability that is fixed over all ages

Fracture threshold
The average probability of fracture for a specific age

Hybrid threshold
Intervention or assessment threshold of fracture probability that partly varies with age and is partly fixed

Intervention threshold
For this report, the fracture probability at which treatment is recommended

Major osteoporotic fracture
Fracture of hip, spine (clinical), distal forearm or humerus.

NOGG strategy

The strategy that describes intervention or assessment threshold of fracture probability that varies with age

Osteopenia

In this report, BMD defined : a T-score of between -1 and -2.5

Osteoporosis

In this report, BMD defined : a T-score of   -2.5

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231. Leslie WD, Morin S, Lix LM, et al. Fracture risk assessment without bone density measurement in routine clinical practice. Osteoporos Int. 2012; 23:75–85. [PubMed: 21850546]

Executive summary

1. According to most current guidelines, treatment for osteoporosis is recommended in individuals with prior fragility fractures, especially fractures at spine and hip. However, for those without prior fractures, the intervention thresholds can be derived using different methods.

2. FRAX is a tool designed for primary care and developed by the WHO for the calculation of the 10-year probability of hip fracture and a major osteoporotic fracture from readily assessed clinical risk factors. Bone mineral density can be optionally entered to improve its accuracy.

3. The general aims of this report were to review the available information on the use of FRAX in assessment guidelines, in particular the setting of thresholds and their validation.

4. A systematic search identified 435 citations from which 307 full publications were read and from which 231 were included in this report.

5. The widespread uptake and availability of FRAX, during a time of transition since its launch in 2008, has resulted its inclusion in many guidelines. We identified 120 guidelines or academic papers that included FRAX. However, 38 provided no clear statement on how the fracture probabilities derived are to be used in decision-making in clinical practice.

6. Two broad approaches have been used to develop intervention thresholds with FRAX. The first was to determine a *fixed threshold* probability that could be applied to men and women, irrespective of age. The second approach was to use *age-dependent thresholds* where the fracture probability at which treatment was recommended was age specific. Also, two guidelines have used both fixed and age-dependent thresholds – termed *hybrid thresholds*.

7. Fixed probability thresholds have ranged from 4 to 20 % for a major fracture and 1.3-5 % for hip fracture. More than one half (39) of the 58 publications identified utilized a threshold probability of 20 % for a major osteoporotic fracture, many of which also mention a hip fracture probability of 3 % as an alternative intervention threshold. In nearly all instances, no rationale is provided other than that this was the threshold used by the National Osteoporosis Foundation of the US.

8. Where undertaken, fixed probability thresholds have been determined from tests of discrimination (Hong Kong), health economic assessment (US, Switzerland), to match the prevalence of osteoporosis (China) or to align with pre-existing guidelines or reimbursement criteria (Japan, Poland).

9.	Fixed thresholds for a major osteoporotic fracture have been recommended by the US Preventive Services Task Force and the Scottish Intercollegiate Guidelines Network (9.3 % and 10 %, respectively) as a screening tool for osteoporosis (but not fracture risk). Both guidelines perform badly because of poor sensitivity. Several other guidelines in the US have adopted the 9.3 % threshold.
10.	The impact of the use of fixed thresholds has been determined only in the US and Hong Kong for the 20 % major osteoporotic fracture and 3 % hip fracture probability.
11.	The National Osteoporosis Guideline Group (NOGG) in the UK was the architect of the development of age-dependent intervention thresholds. The rationale was that if a woman with a prior fragility fracture is eligible for treatment, then, at any given age, a man or woman with the same fracture probability but in the absence of a previous fracture (i.e. at the 'fracture threshold') should also be eligible. The fracture threshold increases with age. Additionally, NOGG devised assessment thresholds to determine the efficient use of bone densitometry.
12.	Linkage of the FRAX web site to the NOGG web site facilitates treatment decisions and is widely used. Similar country-specific linkages are used in Finland, Lebanon and Romania.
13.	The NOGG approach has been compared with previous guidance issued by the Royal College of Physicians, London (RCP). Compared with the RCP strategy, NOGG identified slightly reduced numbers of women without prior fractures above the respective intervention thresholds but these were at higher risk than those identified by the RCP strategy. A major benefit was the reduction in the number of BMD tests required using the NOGG guidance, and this was associated with significant economic dividends.
14.	Proposed and established intervention thresholds using age-specific fracture probabilities were found in 24 guidelines, including European guidance for postmenopausal osteoporosis and for glucocorticoid-induced osteoporosis.
15.	Comparisons of age-dependent thresholds with fixed thresholds (Belgium, Poland, US) showed the former were associated with higher dividends on budget impact (Belgium), cost/fracture identified (UK) and improved sensitivity (US, Poland).
16.	Under current NOGG guidelines, based on age-dependent probability thresholds, inequalities in access to therapy arise especially at older ages (70 years) depending on the presence or absence of a prior fracture. An alternative threshold using a hybrid model reduces this

disparity, increases treatment access and decreases still further the need for bone densitometry.

17. No randomised studies were identified that examined the cost-effectiveness of strategies that used FRAX for targeting people at high fracture risk, though one is near completion.

18. There are several appraisals that have determined the fracture probability at which interventions became cost-effective (i.e. an economic threshold). Economic thresholds have been variously used to set intervention thresholds or, more appropriately, to validate the use of clinically driven intervention thresholds. For alendronate in the UK and Switzerland, all treatment scenarios using the NOGG approach were cost-effective.

19. Consistent discriminative performance of FRAX has been shown worldwide.

20. All FRAX models are internally calibrated. Comparison with external calibration using samples representative of the national population are few (Canada, Denmark, Finland, and UK) but are concordant.

21. Calibration within a country does not appear to be affected by concurrent treatment or socioeconomic status (Canada), but is affected by immigrant status (Sweden).

22. In individuals in whom FRAX is calculated without BMD, subsequent reclassification rates by the inclusion of BMD were low (UK, Canada) and confined to individuals close to an intervention threshold.

23. Net reclassification improvement was reported comparing a fixed intervention threshold using FRAX and a more parsimonious model (Canadian Association of Radiologists and Osteoporosis Canada; CAROC).

Conclusions and recommendations

24. The use of a fixed FRAX threshold has some intuitive appeal in that it directs intervention in an equitable manner and is more readily used in clinical practice than more complex approaches inherent in the application of age-dependent thresholds. There is, however only one guideline that directs intervention solely on this basis (Taiwan) but documentation of its impact is wanting.

25. The use of guidelines that use BMD as the principal gateway and incorporate fixed FRAX thresholds as a component identifies individuals at high risk less effectively than the use of age-dependent thresholds (US National Osteoporosis Foundation).

| 26.	The use of FRAX as a screening tool for subsequent measurement of BMD for the detection of osteoporosis is not recommended because of low sensitivity of FRAX for the detection of osteoporosis.
27.	We recommend the avoidance of the use of a fixed FRAX intervention threshold as the principal gateway to fracture risk assessment. This view may change with further research.
28.	Fixed intervention thresholds may be used usefully as a component of pre-existing guidelines e.g. confined to individuals with low bone mass in Japan and the US. However, where used, country-specific thresholds need to be determined.
29.	The use of economic thresholds is problematic as analysis of each intervention produces different thresholds; they are sensitive to changes in cost and are not relevant to other countries
30.	We recommend that intervention thresholds be based on clinical imperatives, always provided that the strategy proves to be cost-effective.
31.	The present review has identified several merits of the use of age-specific thresholds. The algorithm can be readily used in all countries where a FRAX model is available.
32.	Concerns that the selection of individuals without measurement of BMD may have normal BMD and not respond to pharmaceutical intervention is misplaced in that the use of FRAX (without BMD) preferentially selects individuals with low BMD.
33.	It is apparent that, following the NOGG guidance, particularly at older ages, those eligible for treatment without a prior fracture have on average higher probabilities than those eligible on the basis of a previous fragility fracture. This appears to be remedied with the hybrid modification.
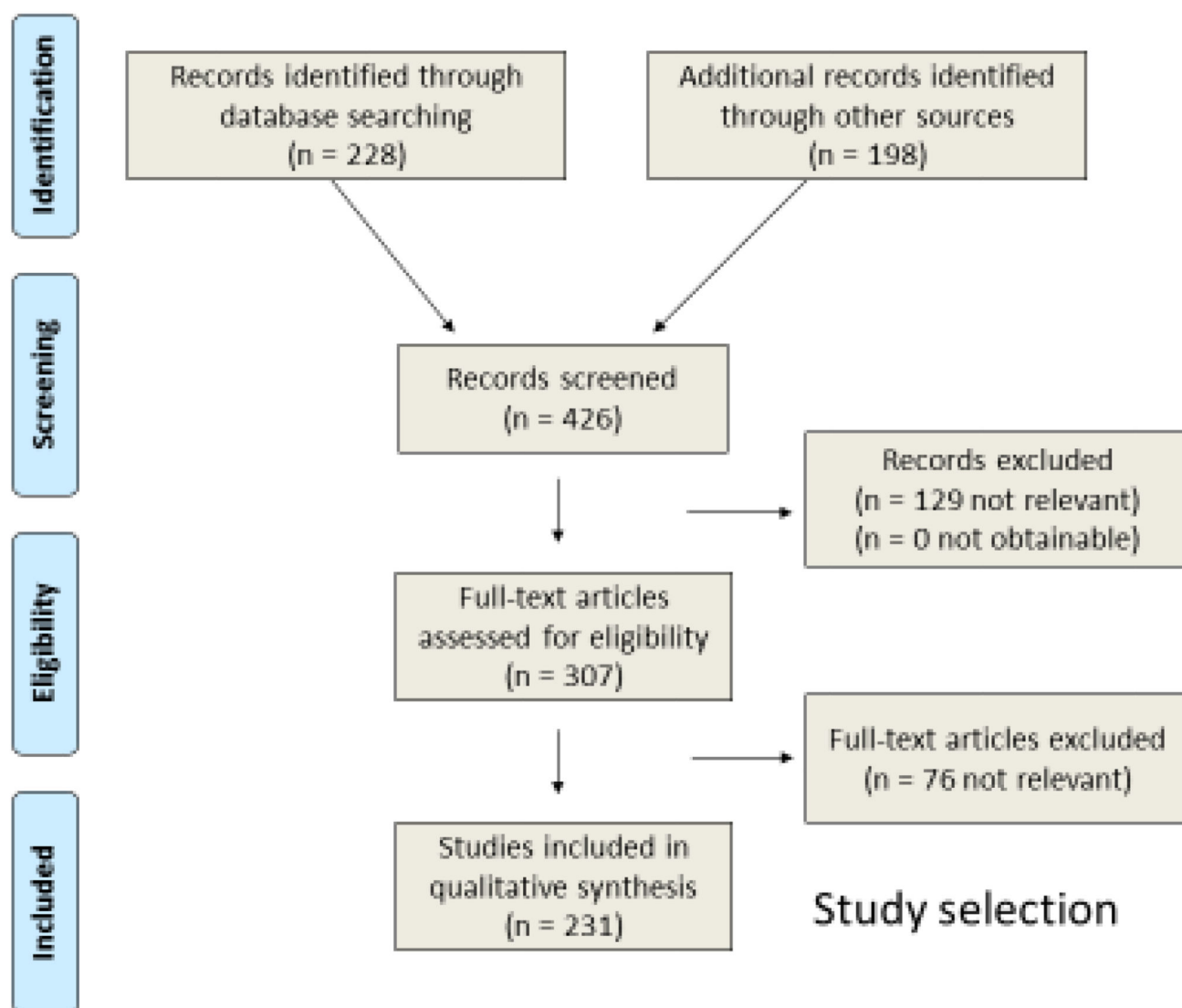
Figure 1.
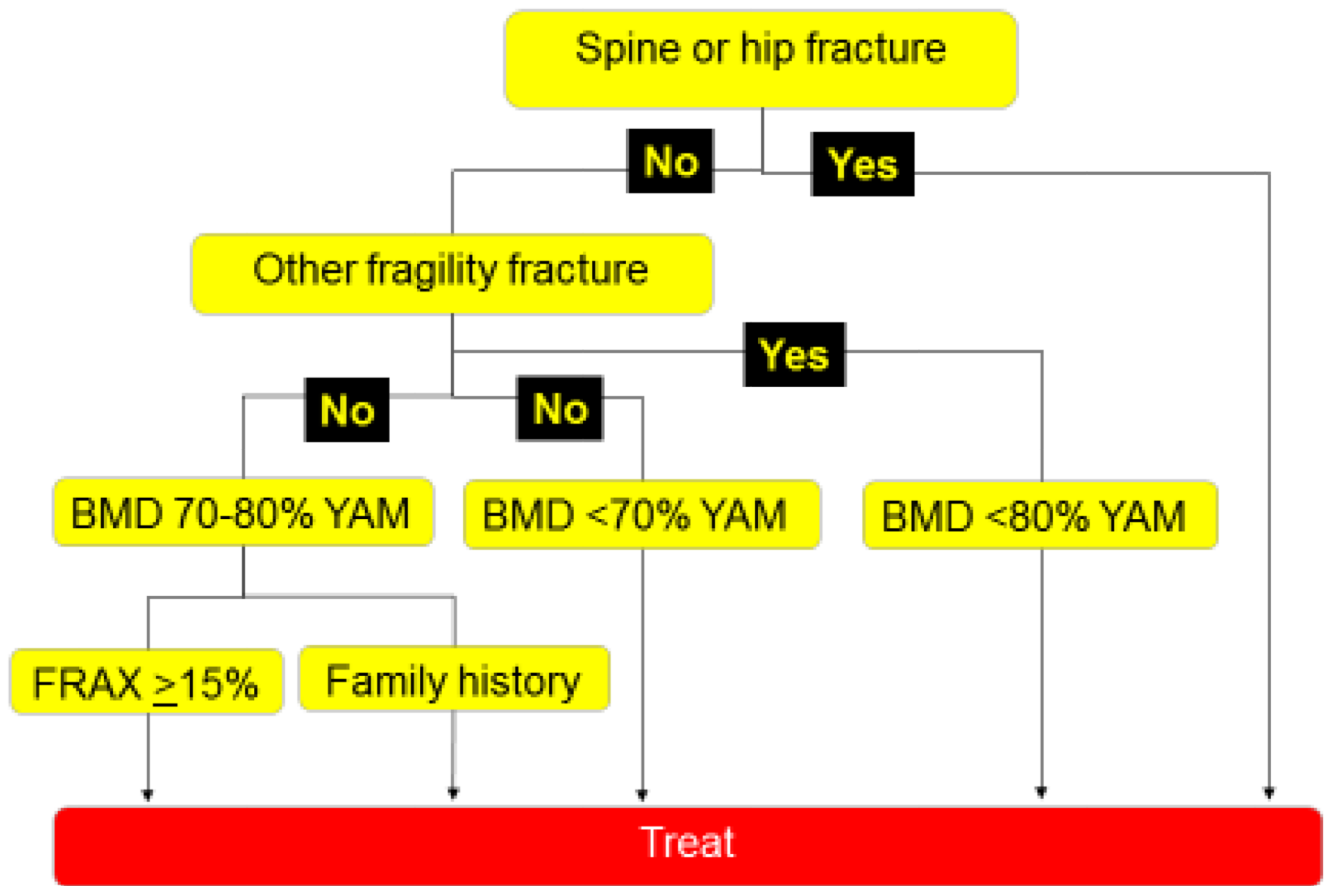Flow diagram demonstrating study identification and selection.

Figure 2.
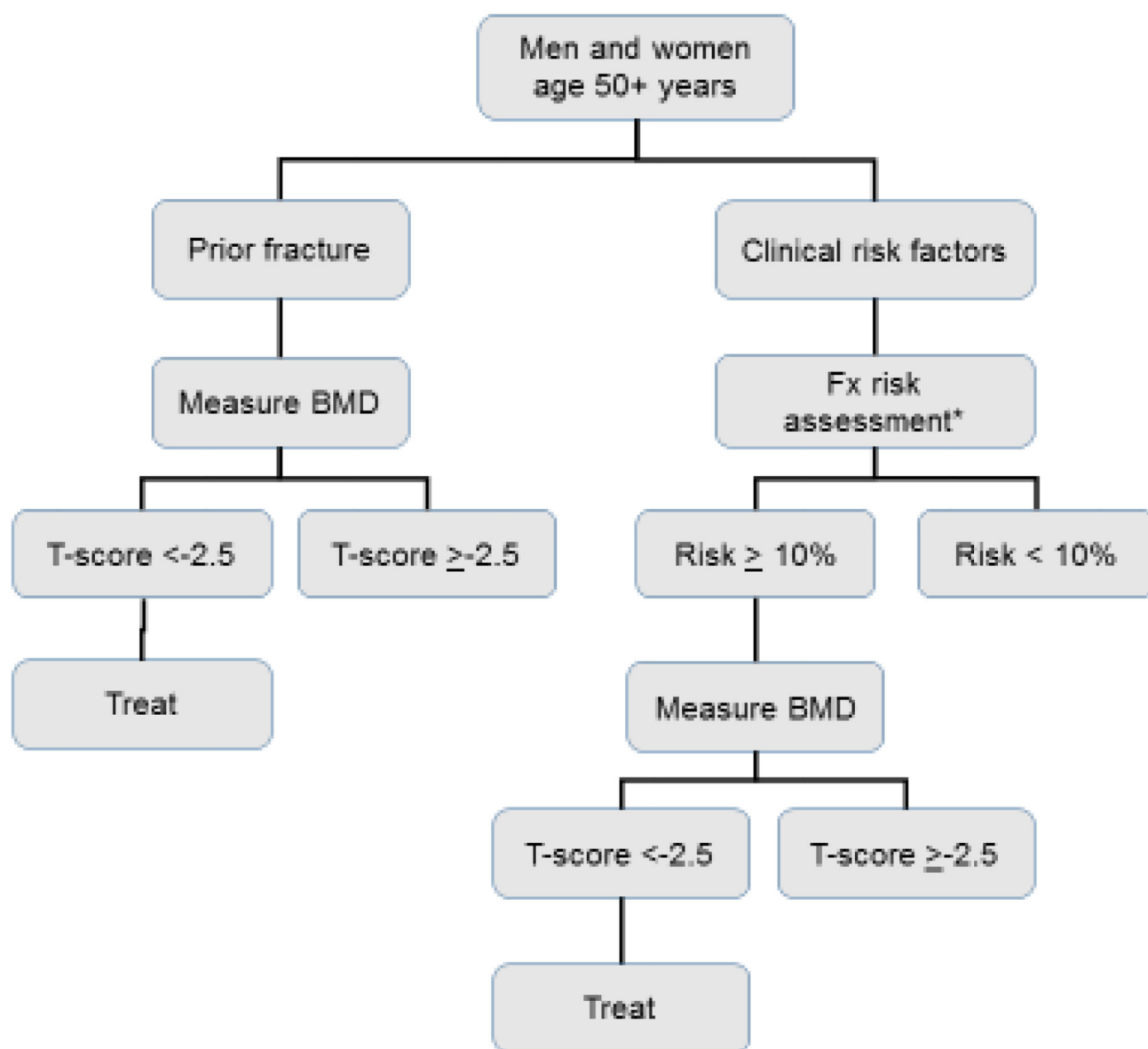Flow chart for the assessment of osteoporosis in Japan.

Figure 3.
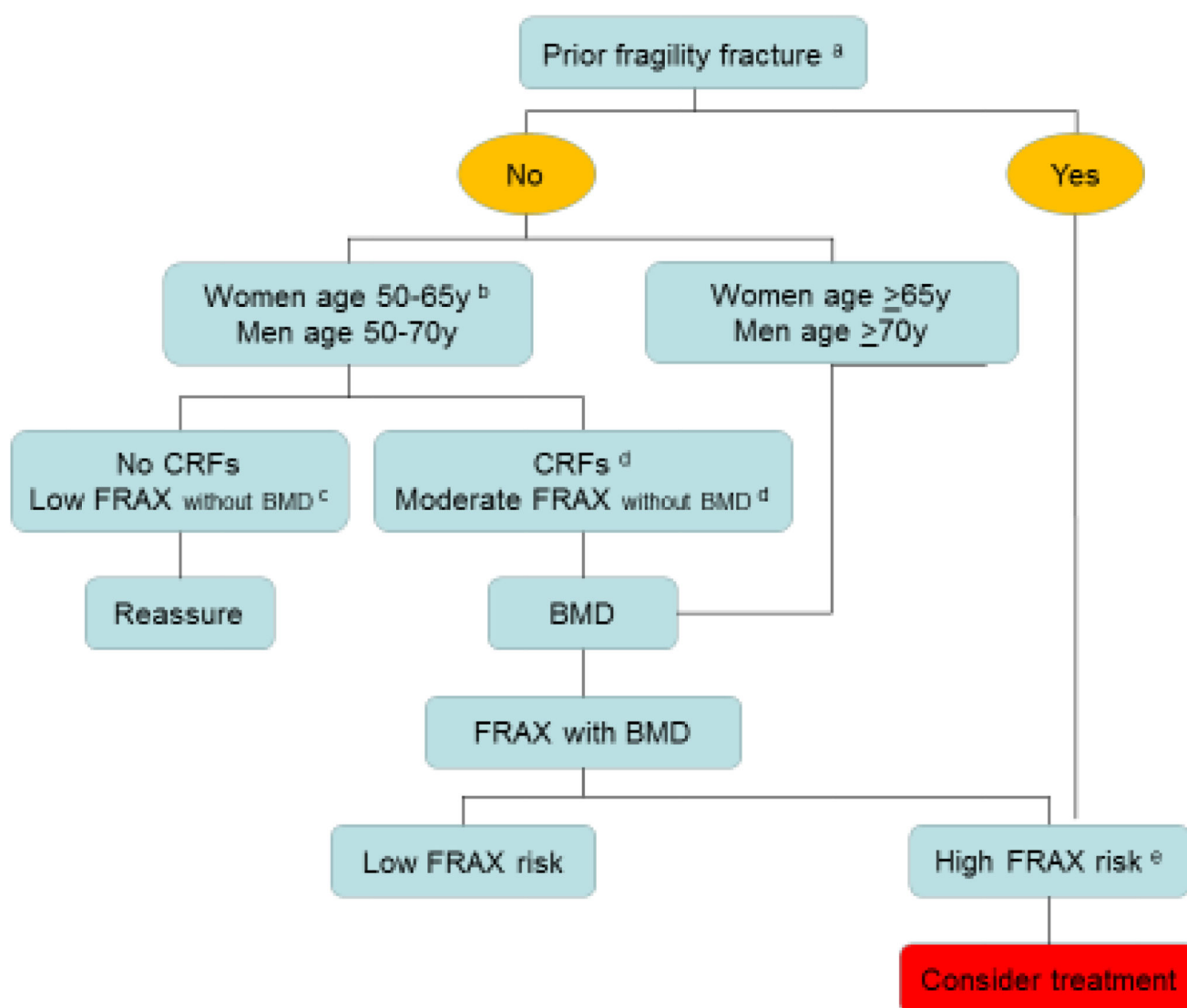Summary of assessment algorithm in the SIGN guidance

Figure 4.

Algorithm for the assessment of fracture risk in men and postmenopausal women from Taiwan [138].

CRFs, clinical risk factors. MOF, major osteoporotic fracture.

[a] Prior fragility from the age of 50 years

[b] Postmenopausal women age 50-65 years

[c] Low FRAX risk; probability of MOF or hip fracture <10 % and <1.5 %, respectively

[d] Moderate FRAX risk; hip fracture probability 1.5 % and <3 % or MOF probability >10 % and <20 %

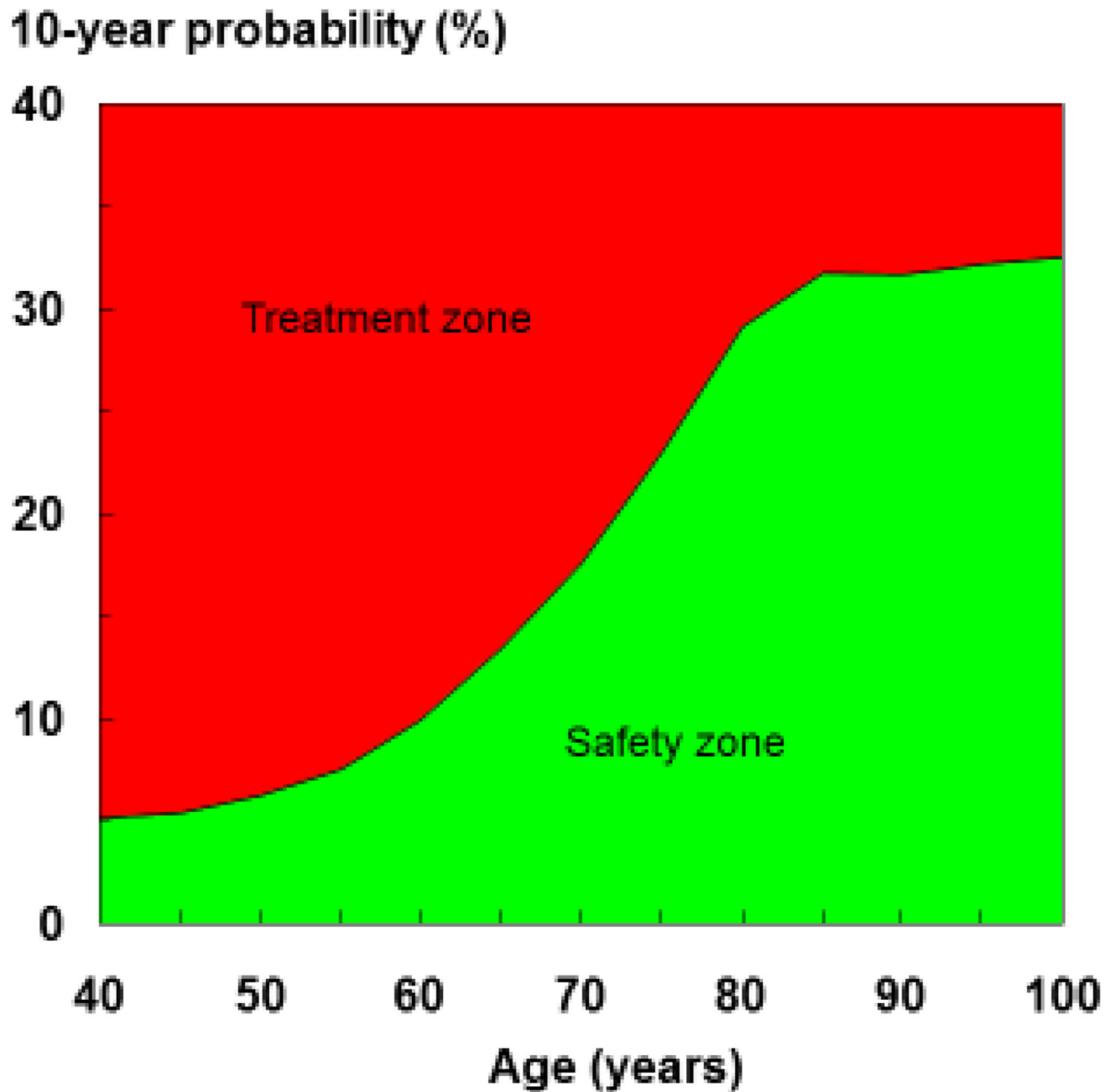[e] High FRAX risk; hip fracture probability 3 % or MOF probability 20 %

Figure 5.
The 10-year probability (%) of a major osteoporotic fracture by age in women with a prior fracture and no other clinical risk factors in the five major EU countries (weighted average of Spain, France, Germany, Italy and UK) as determined with FRAX (version 3.5). Body mass index was set to 24 kg/m^2 without BMD. The line dividing the red and green zones represents the age-dependent intervention threshold or 'fracture threshold'. (Extracted from [28] with kind permission from Springer Science and Business Media.
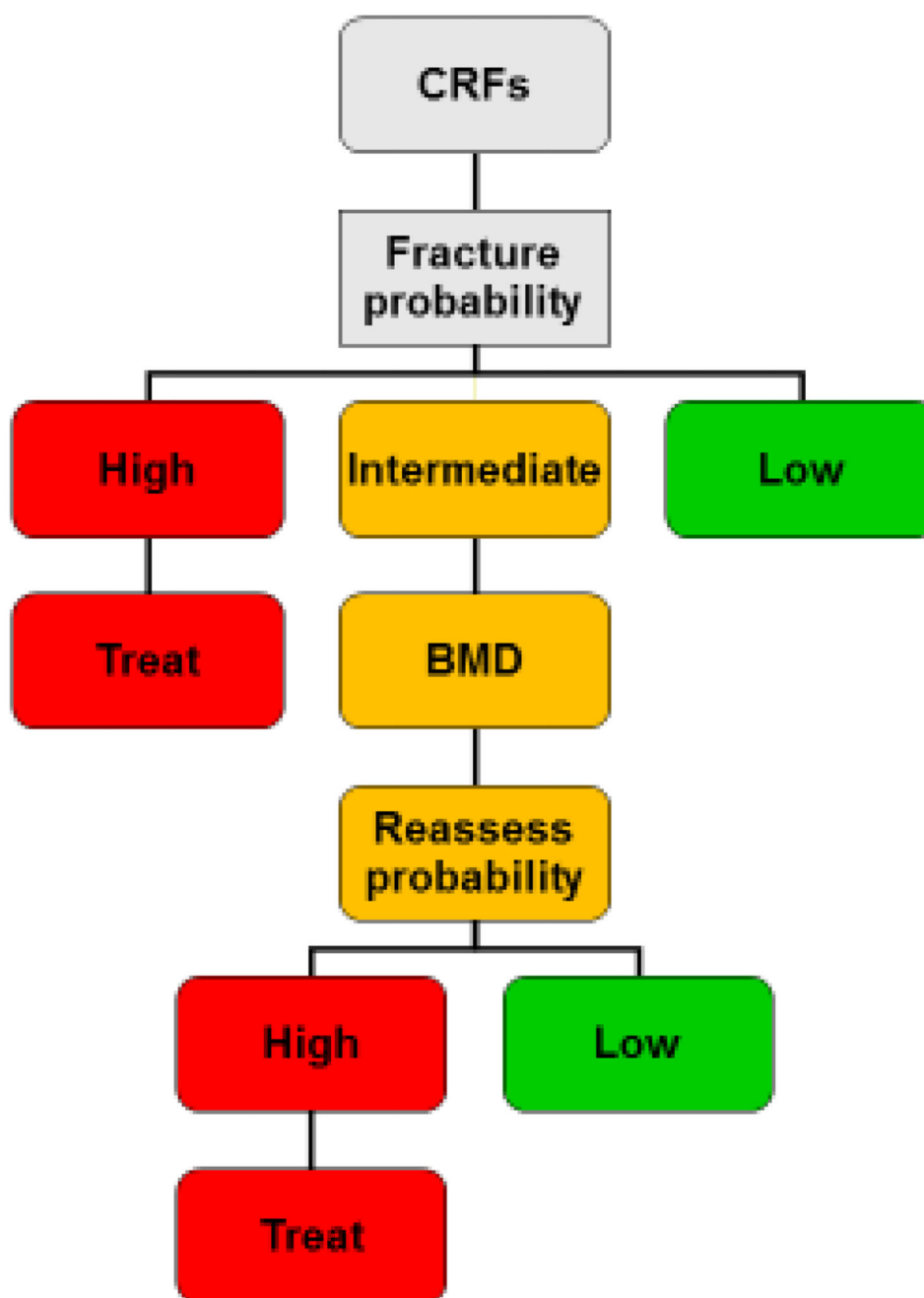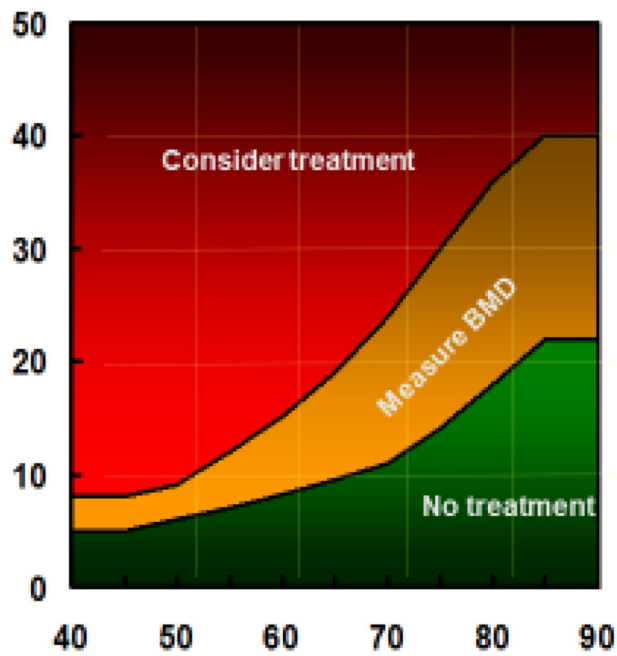
Figure 6.
Management algorithm for the assessment of individuals at risk of fracture [140], with kind permission from Springer Science and Business Media.

Assessment without BMD

10 year fracture probability (%)

Assessment with BMD
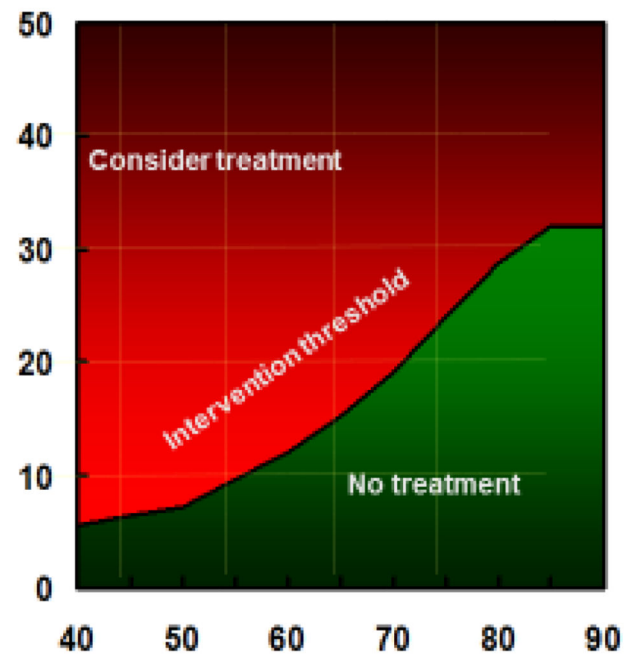
Figure 7.
Assessment and treatment thresholds in the absence of a BMD test (left) and with a BMD test to compute fracture probability (right) for men and women. Redrawn from [141]
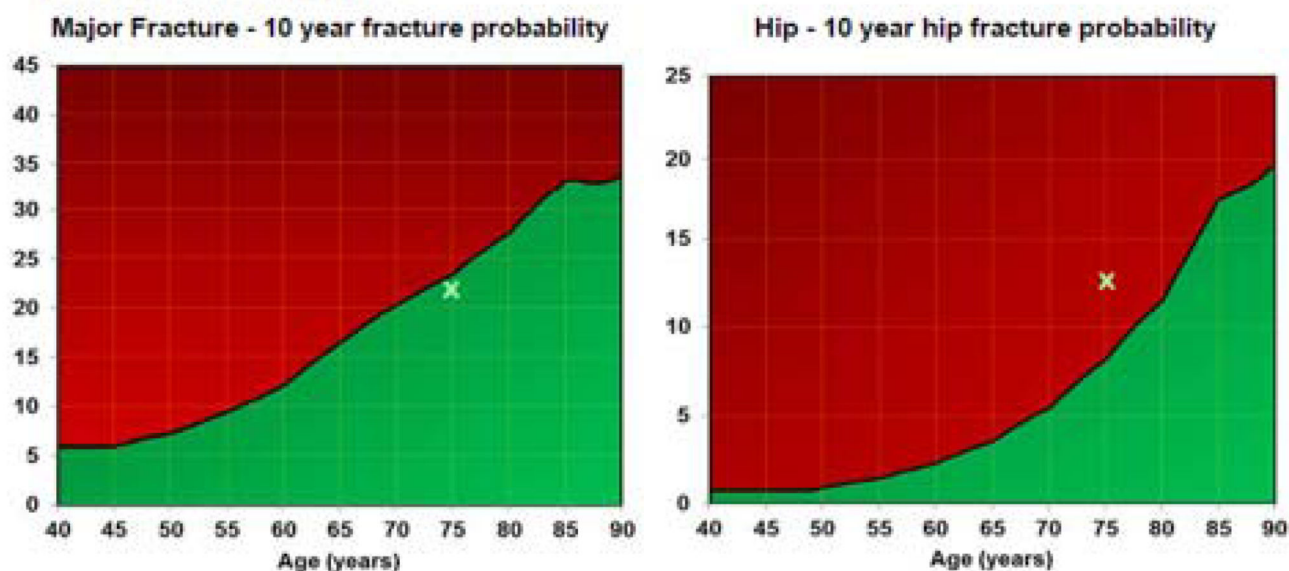
Figure 8.
NOGG web page plotting the results of a FRAX measurement (Female age 75 years with a BMD T-score of -2.0 SD and a parental history of hip fracture). In the example, treatment is recommended since the hip fracture probability exceeds the intervention threshold (www.shef.ac.uk/NOGG).
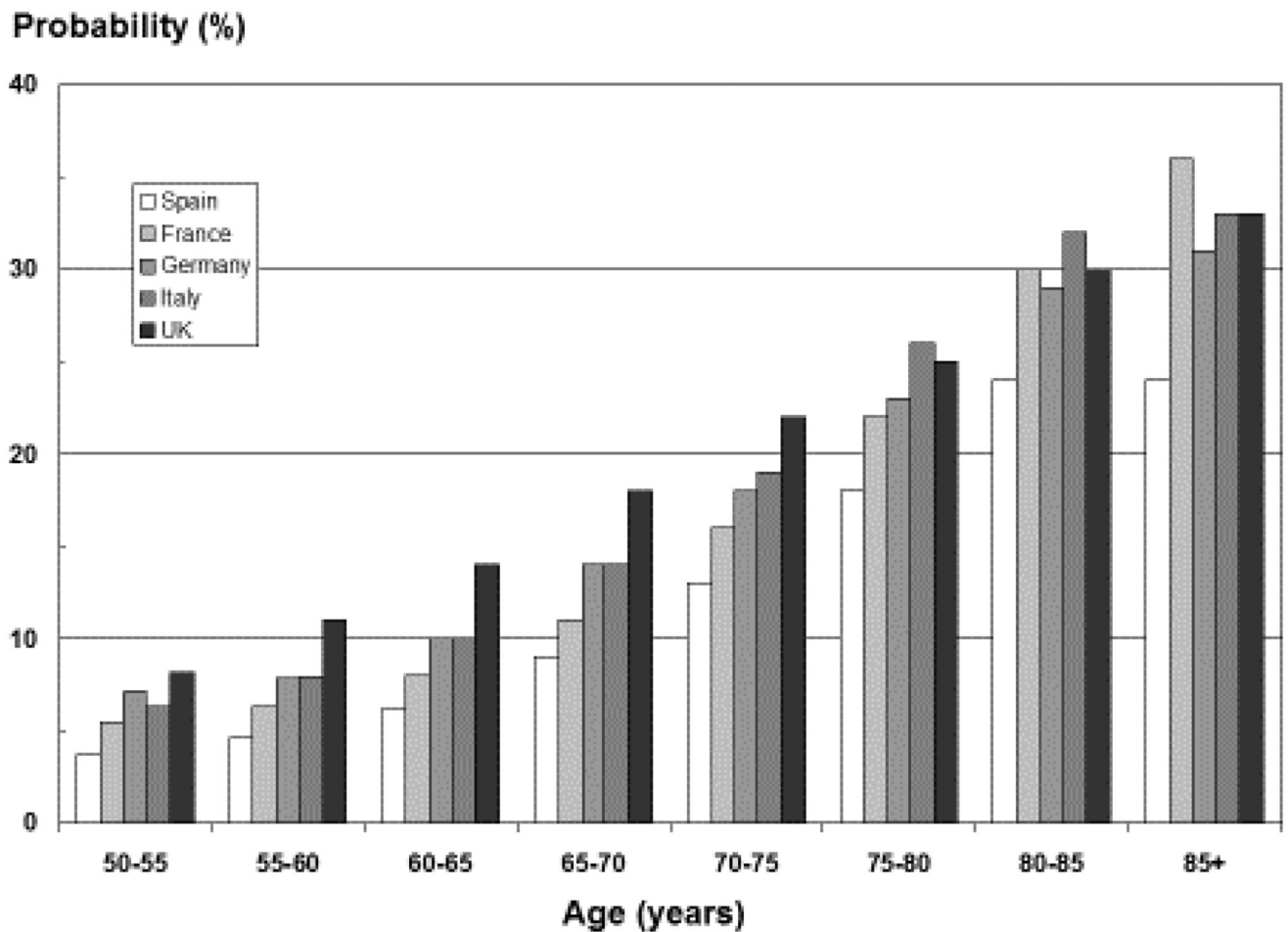
Probability (%)

Figure 9.
The 10-year probability of a major osteoporotic fracture by age in women with a prior fracture and no other clinical risk factors in the five major EU countries as determined with FRAX (version 3.5). Body mass index was set to 24 kg/m^2 without BMD [3], with kind permission from Springer Science and Business Media.

10-year fracture* probability (%)
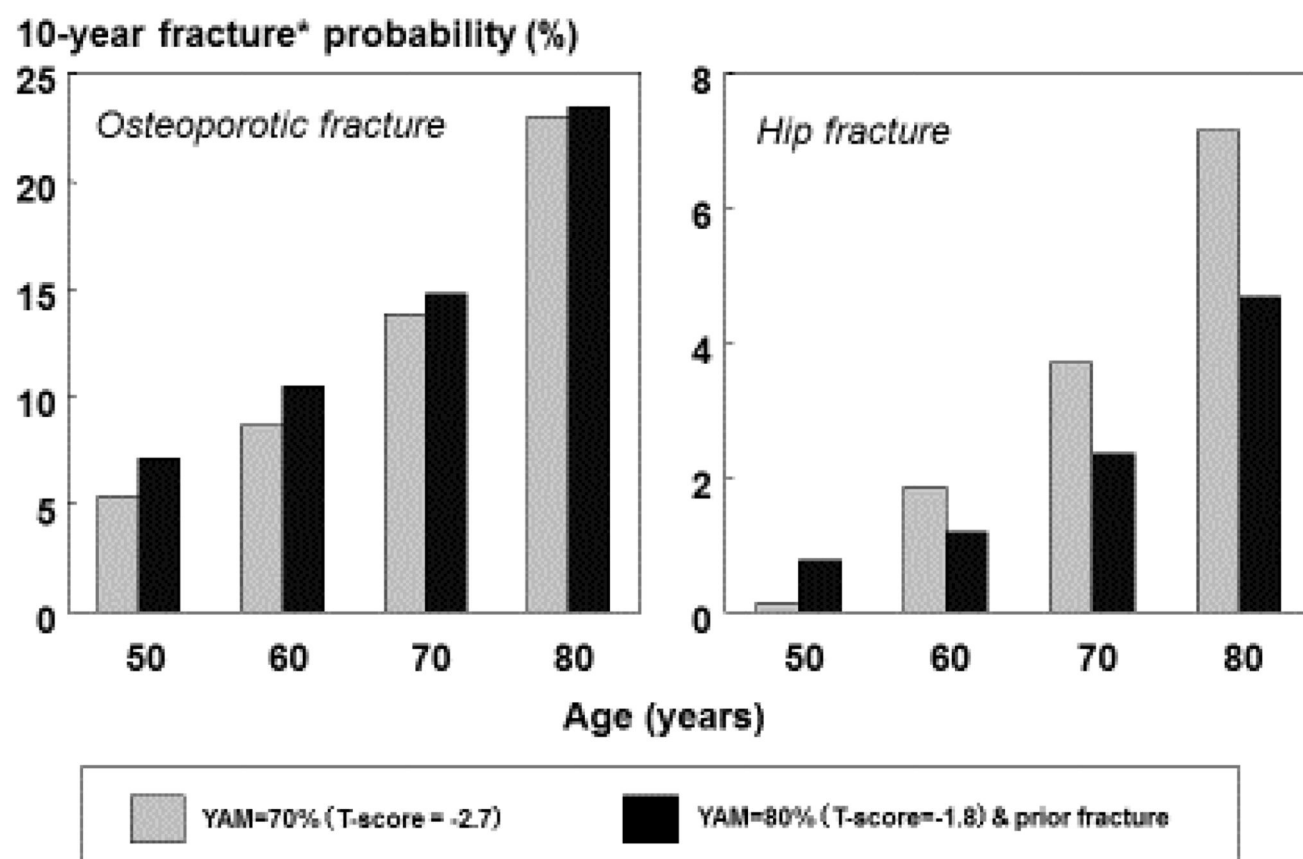
Figure 10.
Ten-year probability of osteoporotic (hip, clinical spine, humerus or forearm) and hip fracture based on women at the threshold for the diagnosis of osteoporosis using the criteria of the Japanese Bone Mineral Metabolism Association. From [135] with kind permission from Springer Science and Business Media.
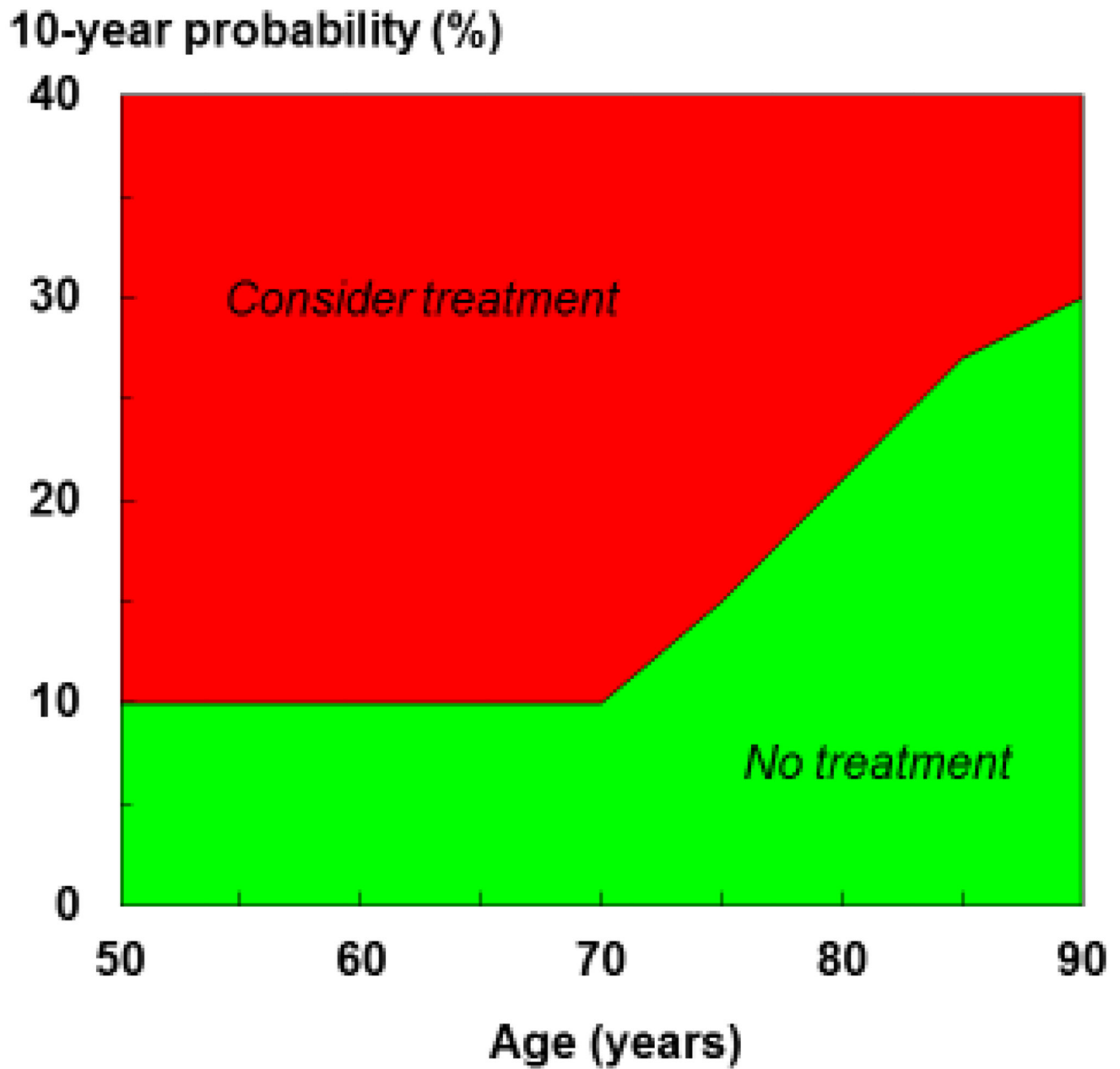
Figure 11.
Intervention thresholds in Lebanon that use a fixed threshold up to the age of 70 years and thereafter an age-dependent threshold.

10-year probability of major osteoporotic fracture (%)
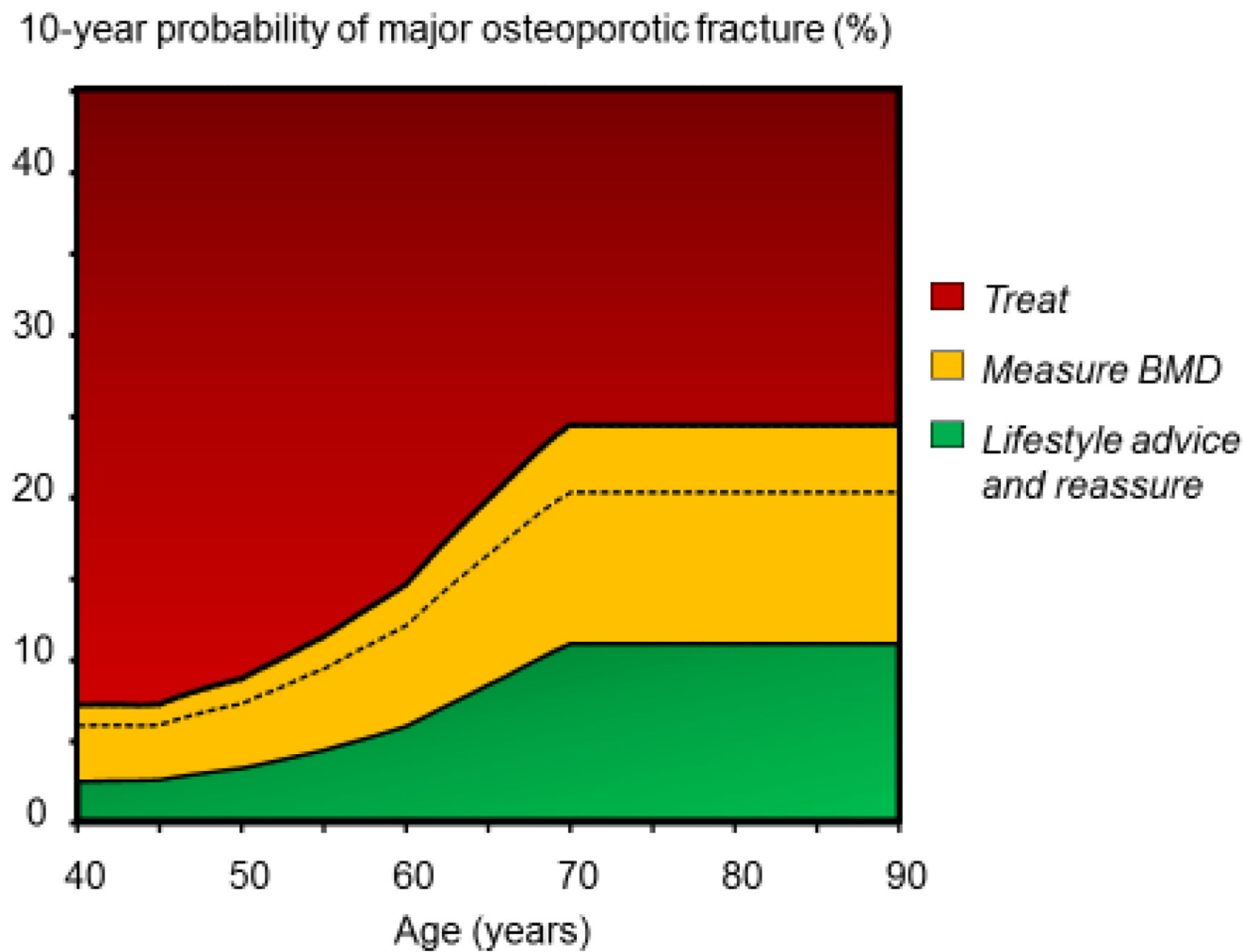
Figure 12.
Graph of intervention and assessment thresholds showing the alternative thresholds in the hybrid model. The dotted line represents the intervention threshold and the assessment thresholds enclose the amber area. From [109] with kind permission from Springer Science and Business Media.

10-year probability MOF (%)
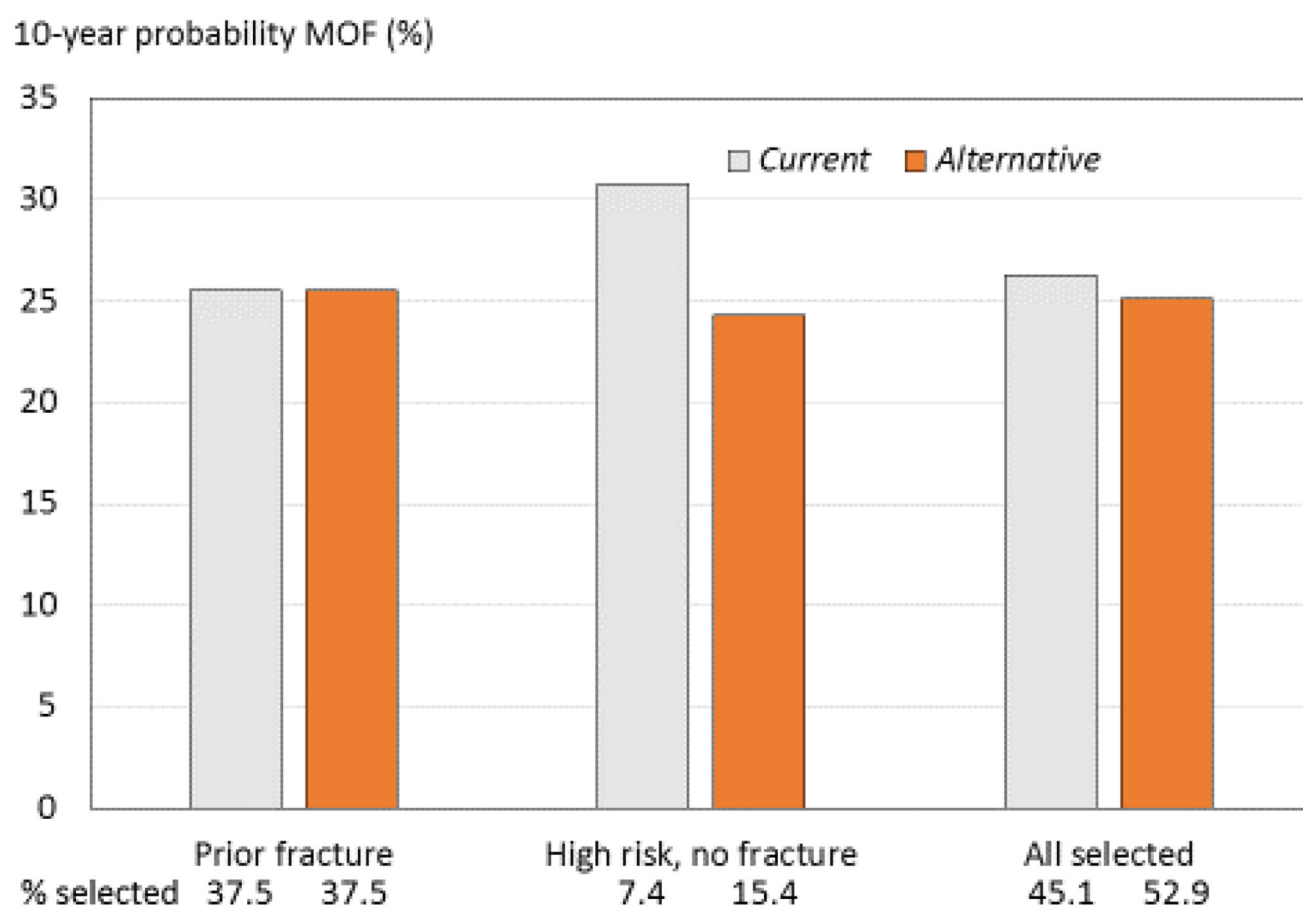
Figure 13.
Mean probability of major osteoporotic fracture (MOF, %) in patients age 70 years or more
identified for consideration of treatment under the current thresholds (light bars) and the
alternative thresholds (shaded bars). Data extracted from [109].
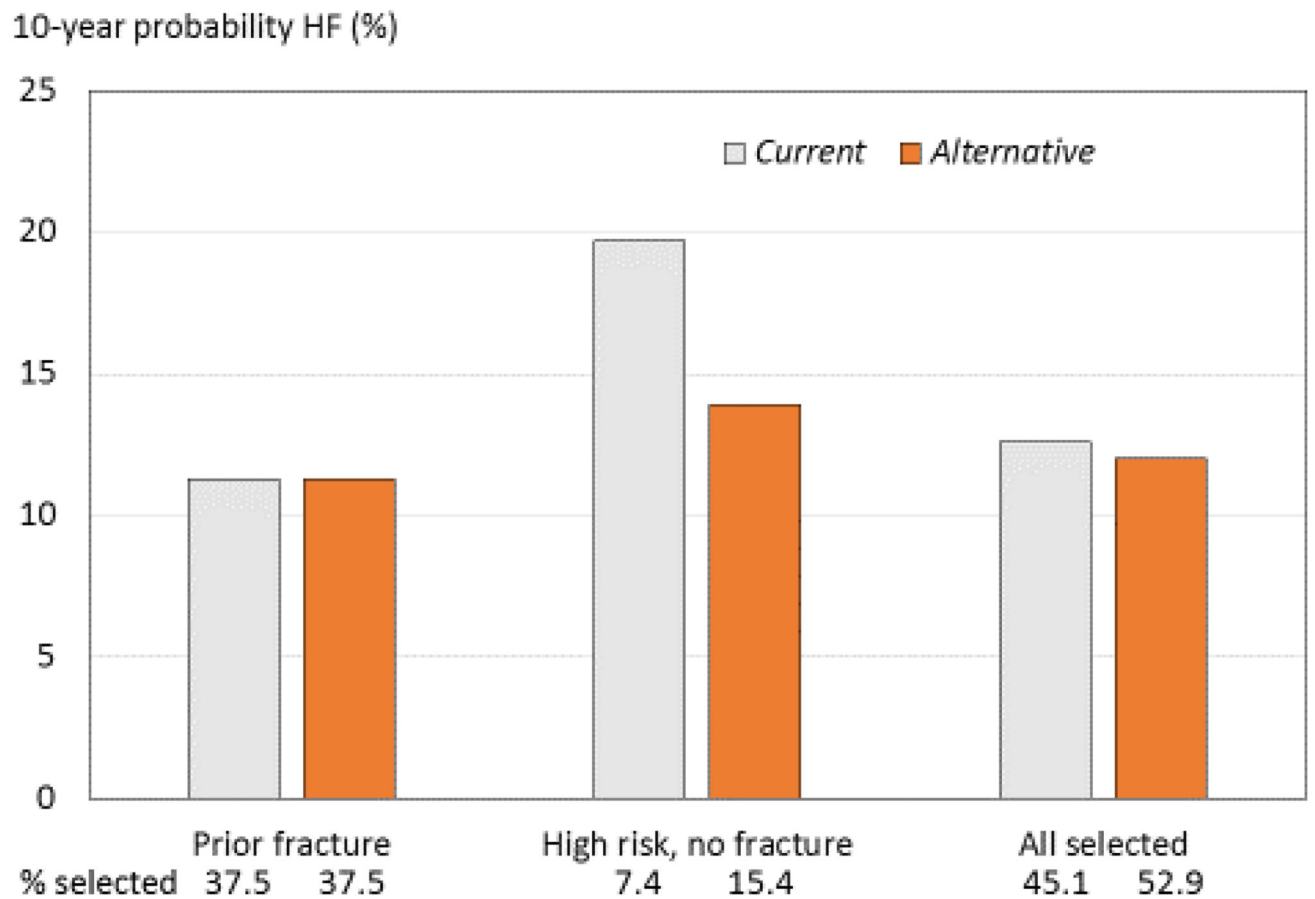
Figure 14.
Mean probability of hip fracture (HF, %) in patients age 70 years or more identified for consideration of treatment under the current thresholds (light bars) and the alternative thresholds (shaded bars). Data extracted from [109].
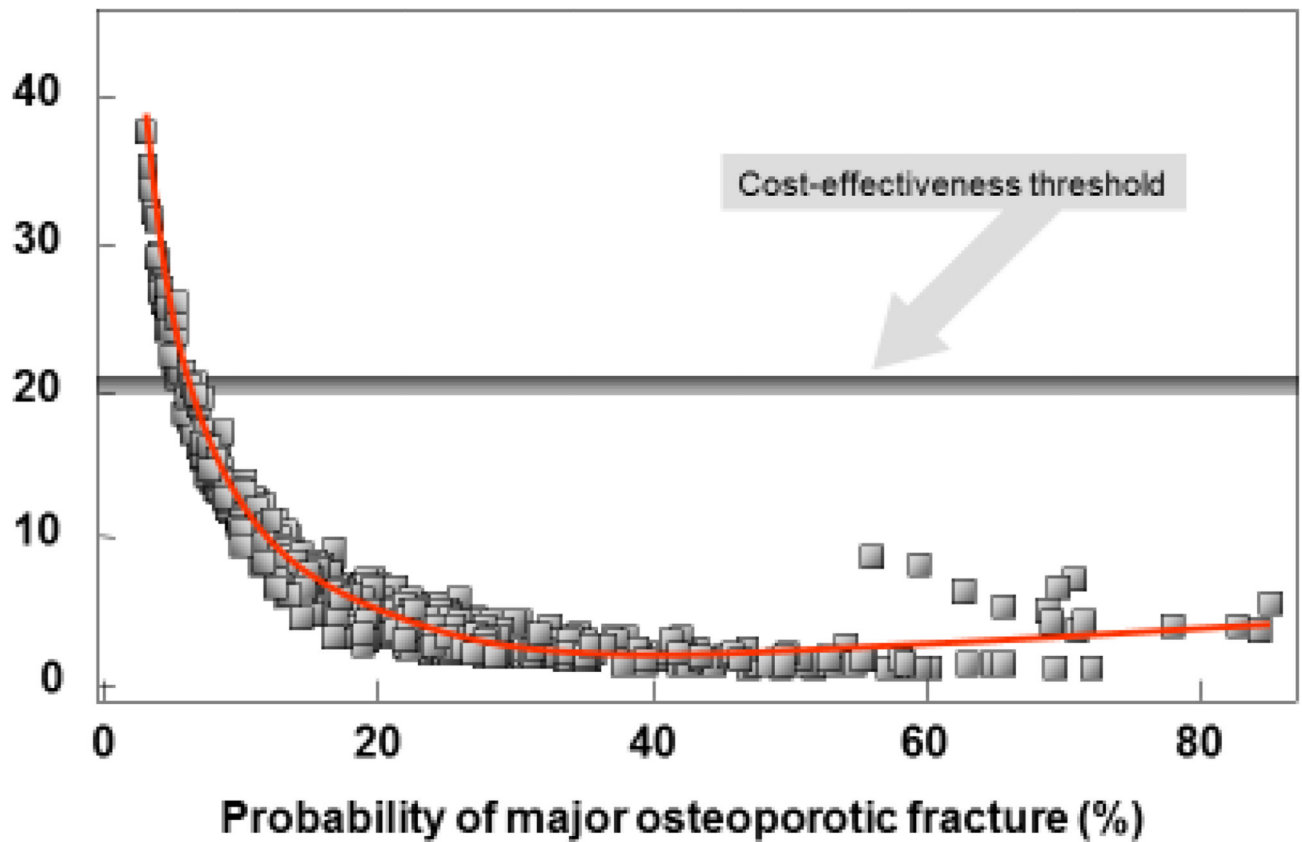
Figure 15.
Correlation between the probability of a major osteoporotic fracture and cost-effectiveness of generic alendronate at the age of 50 years in women from the UK (BMI set to 26 kg/m^2). The line indicates the willingness to pay set at £20,000/QALY gained. Each point represents a particular combination of BMD and clinical risk factors. Taken from [140] with kind permission from Springer Science and Business Media.
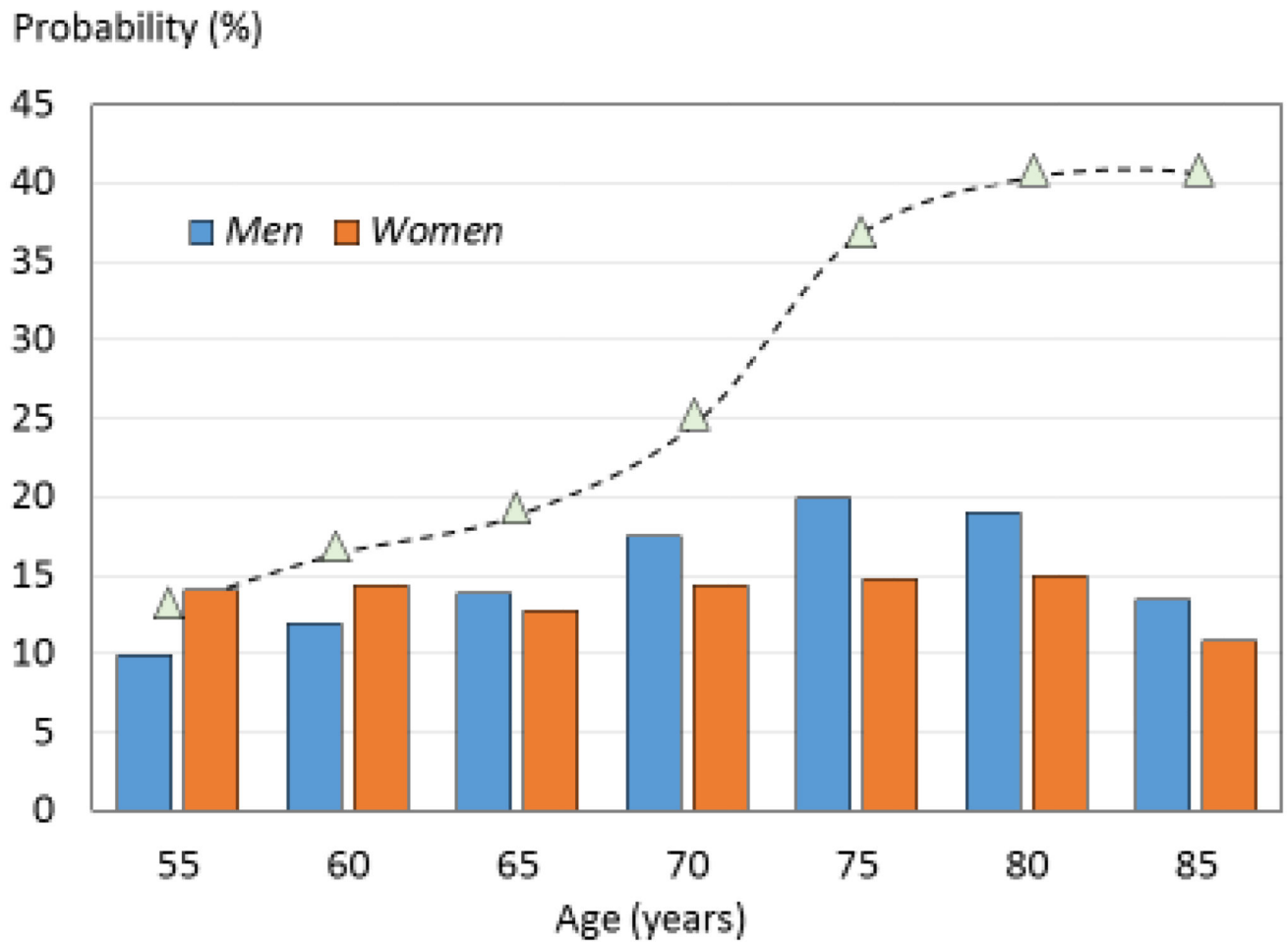
Figure 16.
Fracture probabilities at which treatment with alendronate becomes cost-effective in men and women from Switzerland. The dotted line denotes the fracture probability at the fracture threshold (i.e. the probability equivalent to a woman with a prior fracture by age). Adapted from [105].

10 year probability of a major osteoporotic fracture (%)
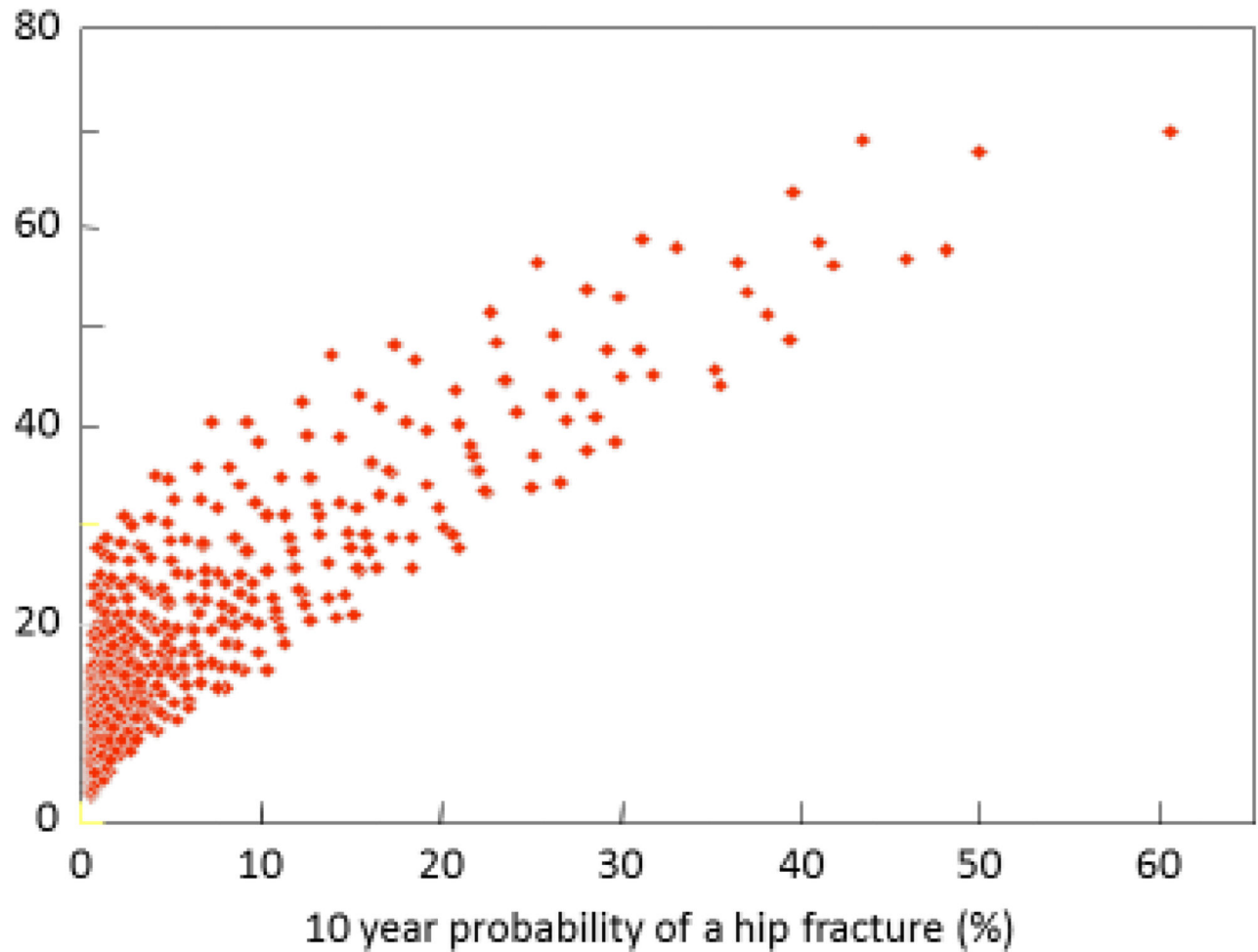
Figure 17.
Relation between the 10-year probability of a major osteoporotic fracture and the 10-year probability of a hip fracture in women aged 50 years from the UK. Each point represents a particular combination of BMD and clinical risk factors. From [140] with kind permission from Springer Science and Business Media.

FRAX probability (%)

QFracture incidence (%)
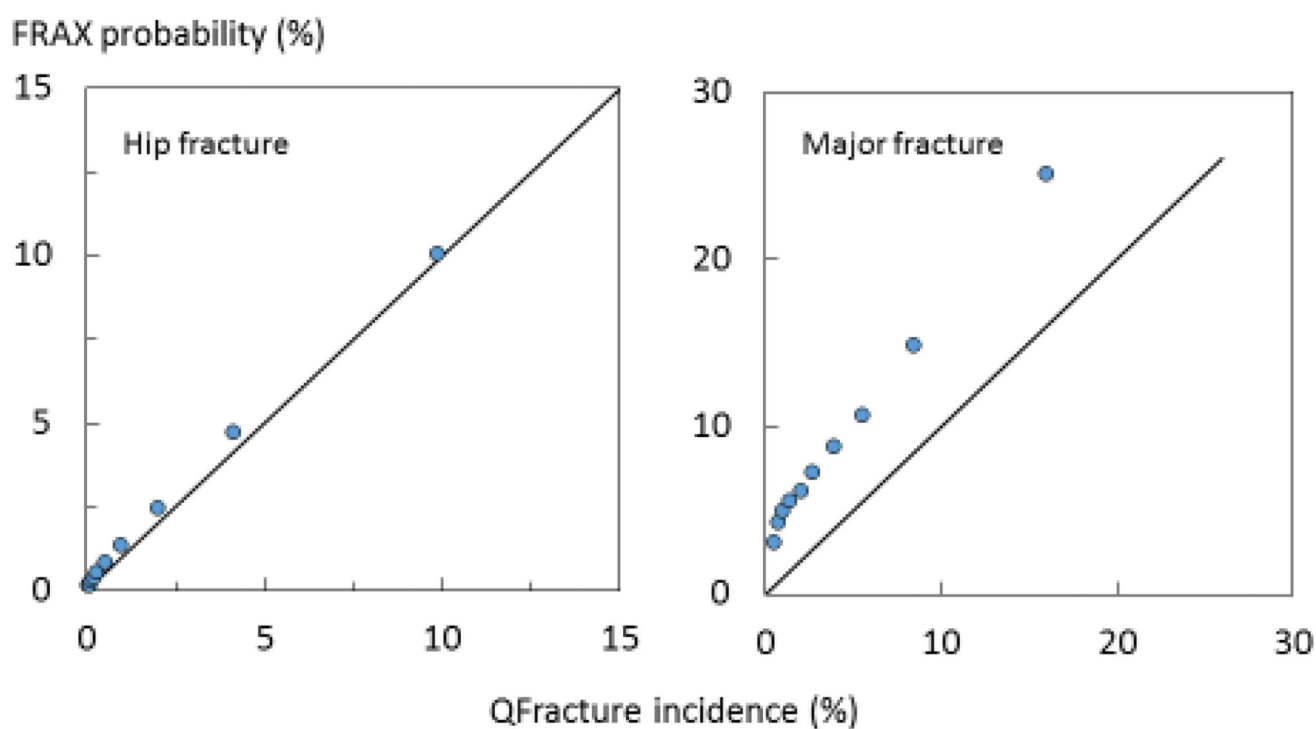
Figure 18.
Comparison of the distribution of FRAX and QFracture (QF) model output by decile of risk in women for hip fracture (left panel) and major fracture (right panel). The diagonal line shows the line of identity. From [13] with kind permission from Springer Science and Business Media.
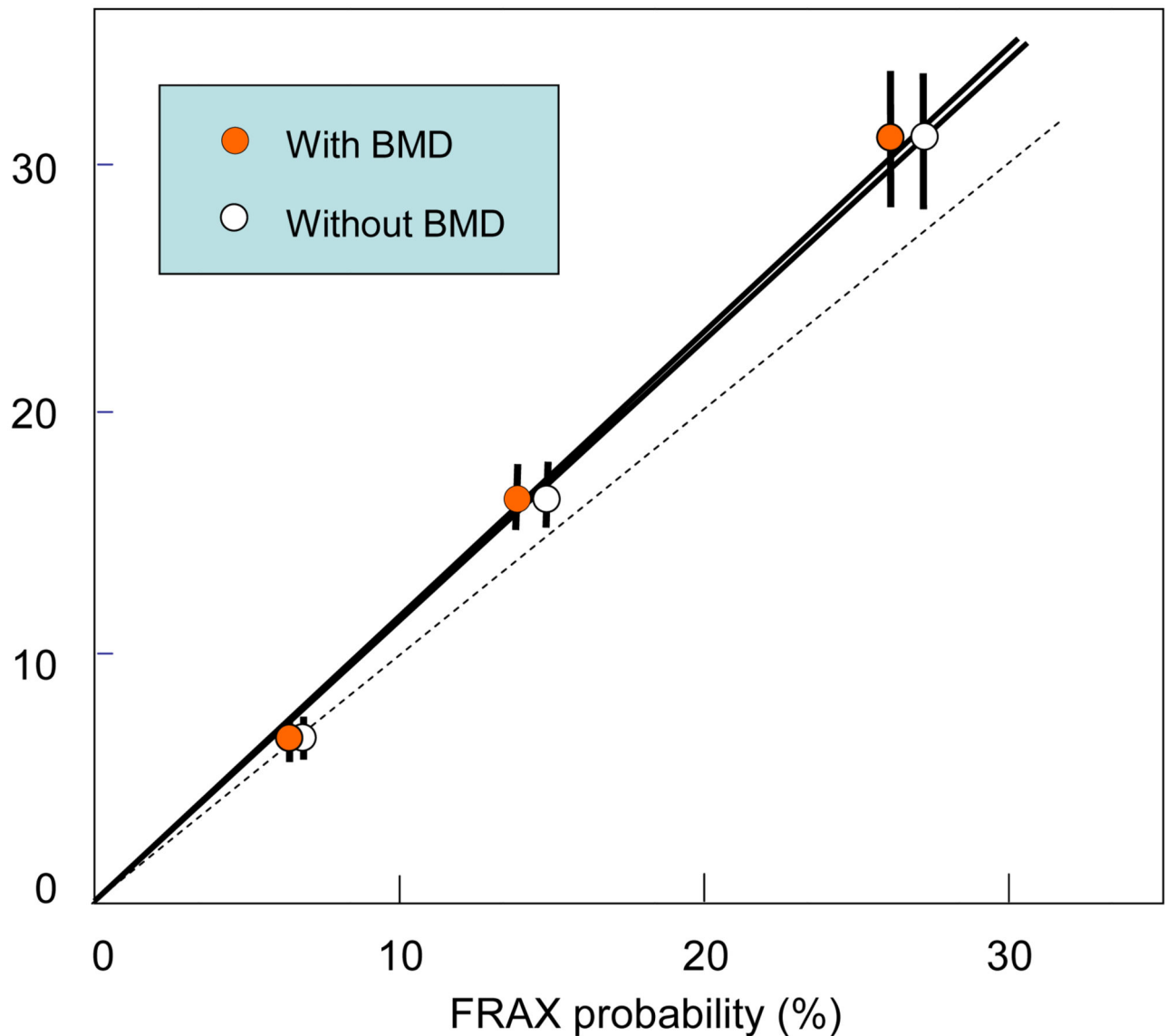
Figure 19.
10-year fracture probability for a major fracture derived from the Canadian FRAX tool with and without BMD versus observed 10 year fracture rates (95 % confidence interval) by risk category (low, less than 10 %; moderate, 10-20 %; high, greater than 20 %) with BMD (solid line) and without BMD (dashed line). The dashed line depicts the line of identity. Redrawn from [195].
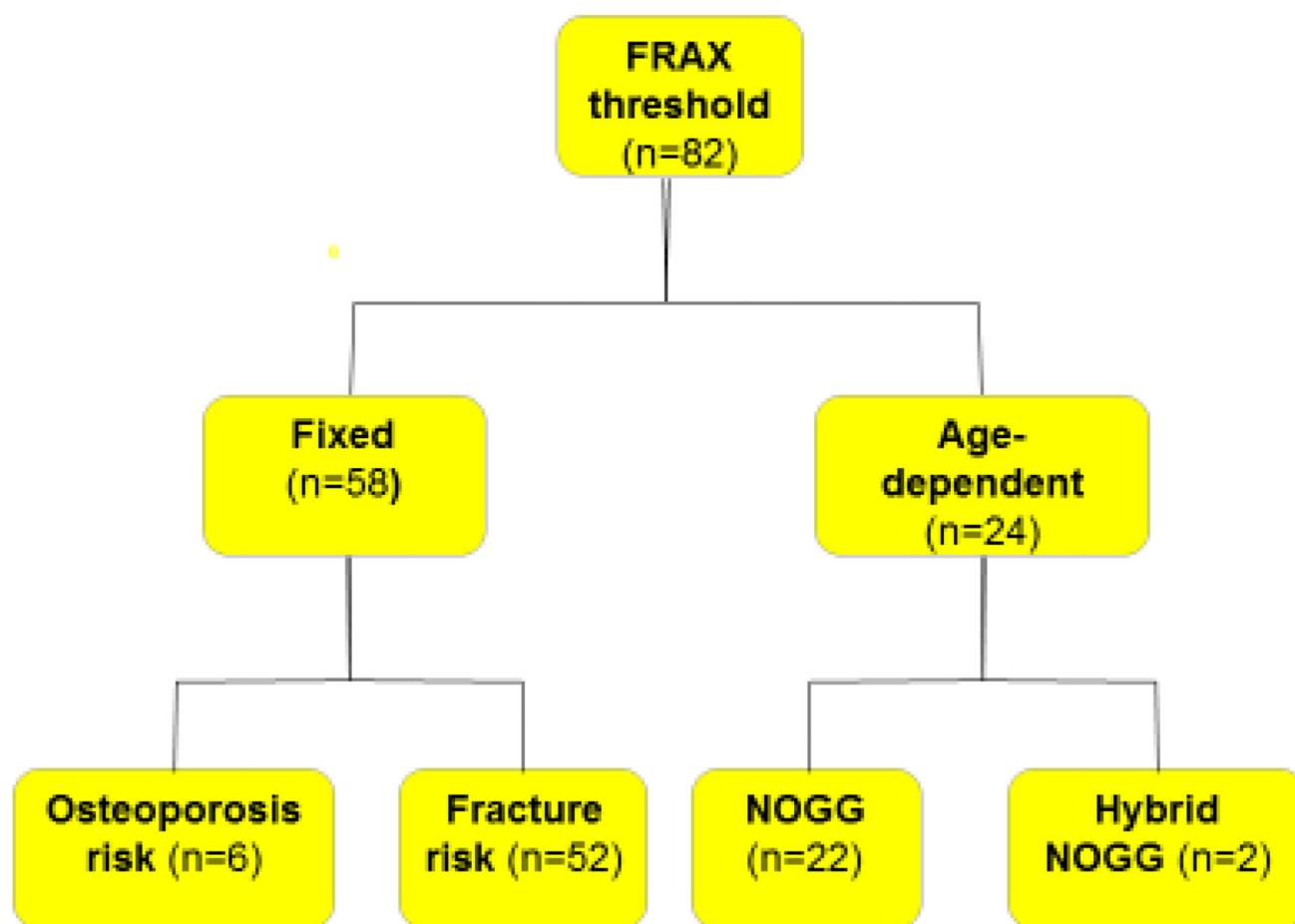
Figure 20.
The various ways in which FRAX has been used to set thresholds.
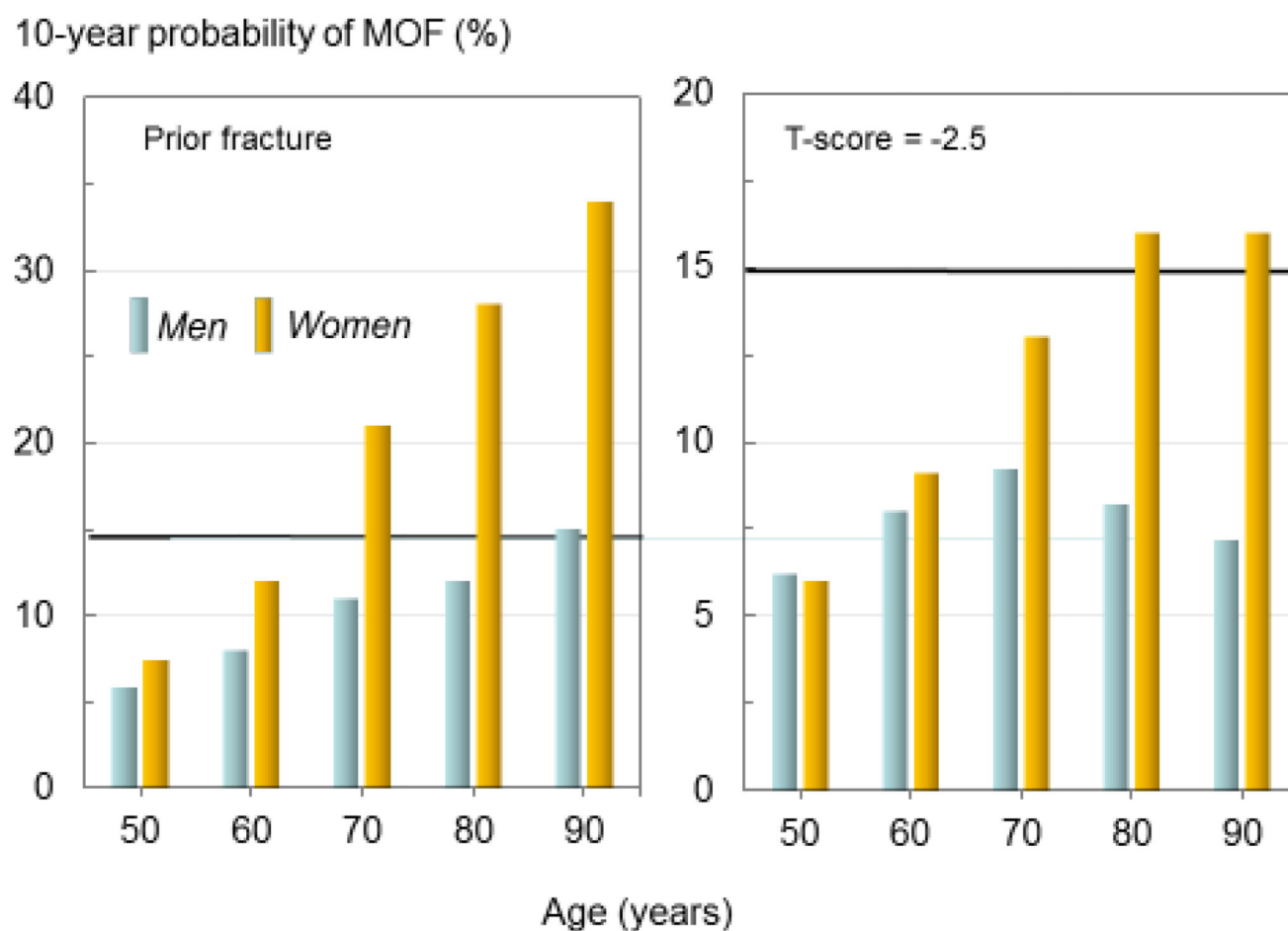
Figure 21.
The probability of a major osteoporotic fracture (MOF) in men and women from the UK by age. The horizontal line depicts an arbitrary intervention threshold set at 15 %. The left panel gives probabilities in the presence of a prior fracture and the right panel, probabilities with a T-score of -2.5 SD (BMI set to 23 kg/m^2, no other clinical risk factors). [http://www.shef.ac.uk/FRAX]
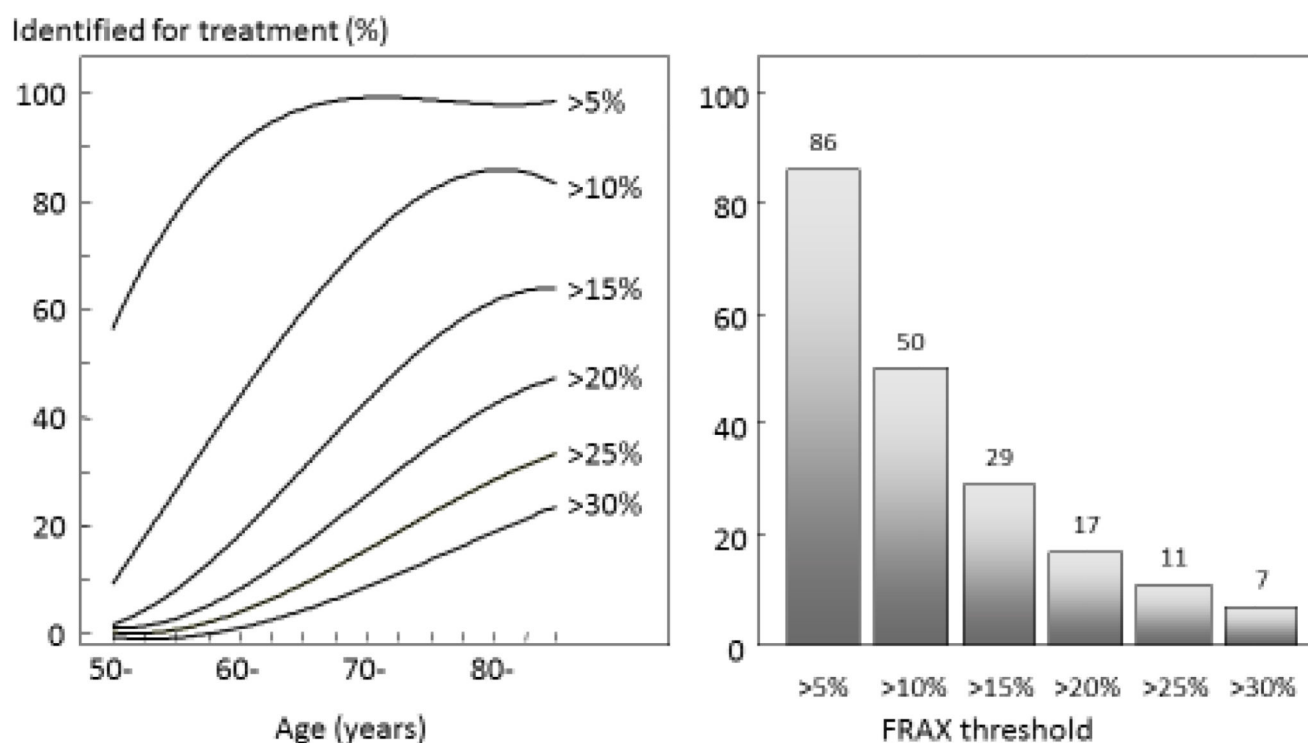
Figure 22.
The impact of a fixed treatment threshold in postmenopausal women in the UK according to threshold values for the probability of a major osteoporotic fracture. The left hand panel shows the proportion of the postmenopausal population exceeding the threshold shown at each age. The right hand panel shows the proportion of the total postmenopausal population that exceed a given threshold. From [3] with kind permission from Springer Science and Business Media.

Men and women aged 50-89 years (%)
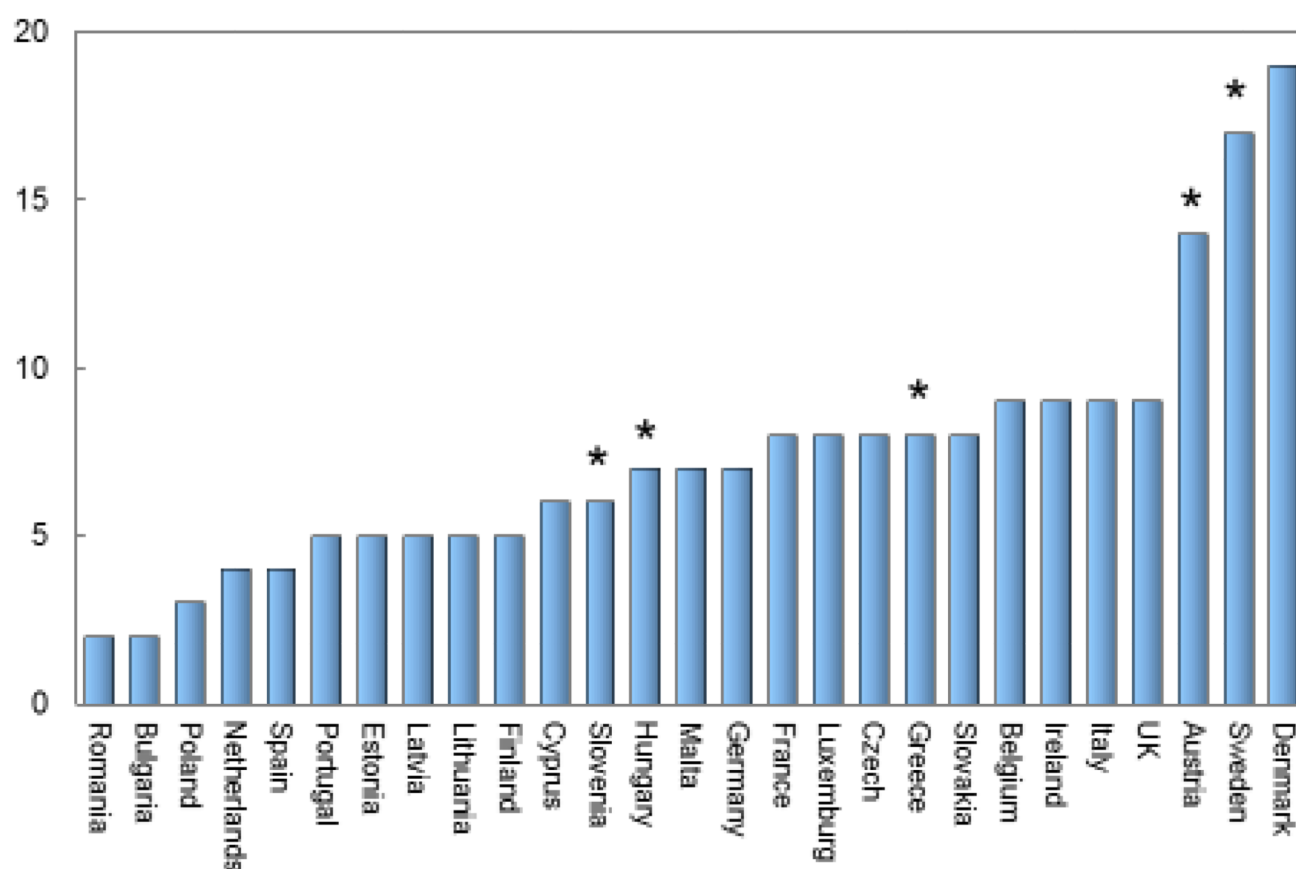
Figure 23.
Proportion of men and women (%) aged 50–89 years with a 10-year probability of a major fracture that is more than 20 % in different countries of the European Union. Those marked with an asterisk utilise a 20 % intervention threshold for a major osteoporotic fracture. Adapted from [3].
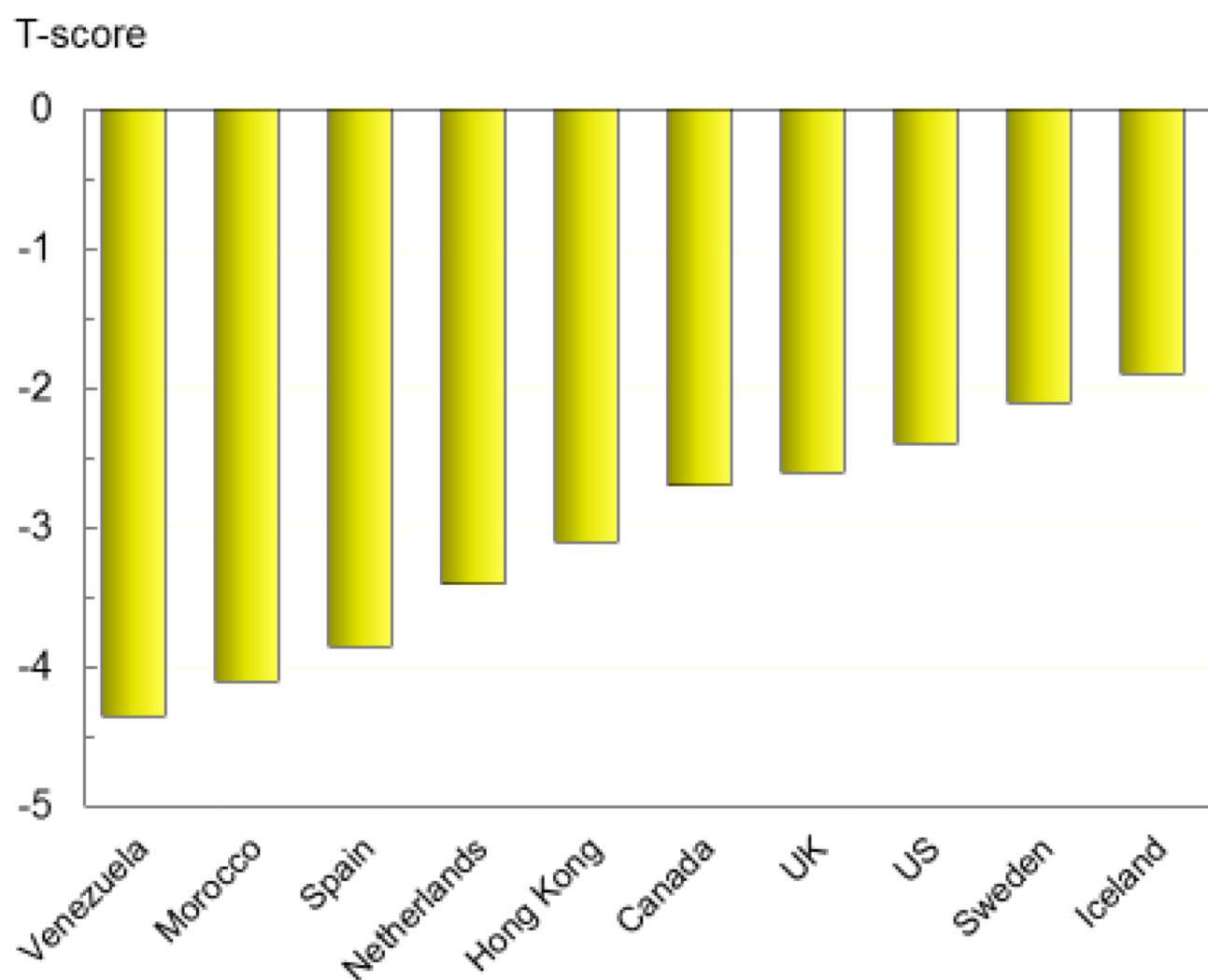
Figure 24.
T-scores in selected countries that are equivalent to a 20% 10-year probability of a major fracture (women aged 65 years, prior fracture and a BMI of 24kg/m^2) From [216] with permission from John Wiley and Sons.
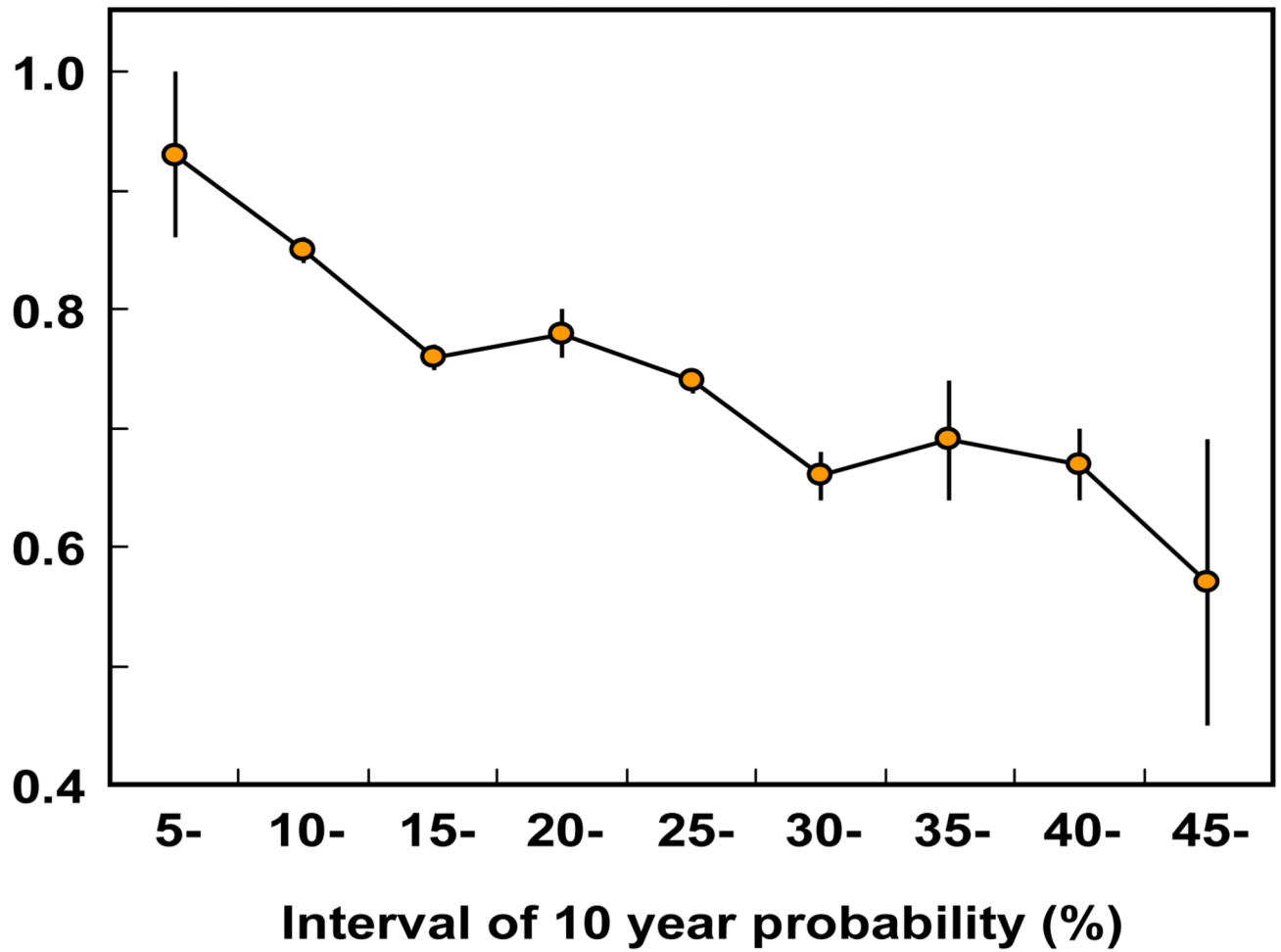
Figure 25.
Mean BMD at the femoral neck (with 95 % confidence intervals) in randomly selected women aged 75 years or more according to their 10-year probability of a major fracture calculated without BMD. Figure derived from data in [142].

10-year probability of MOF (%)
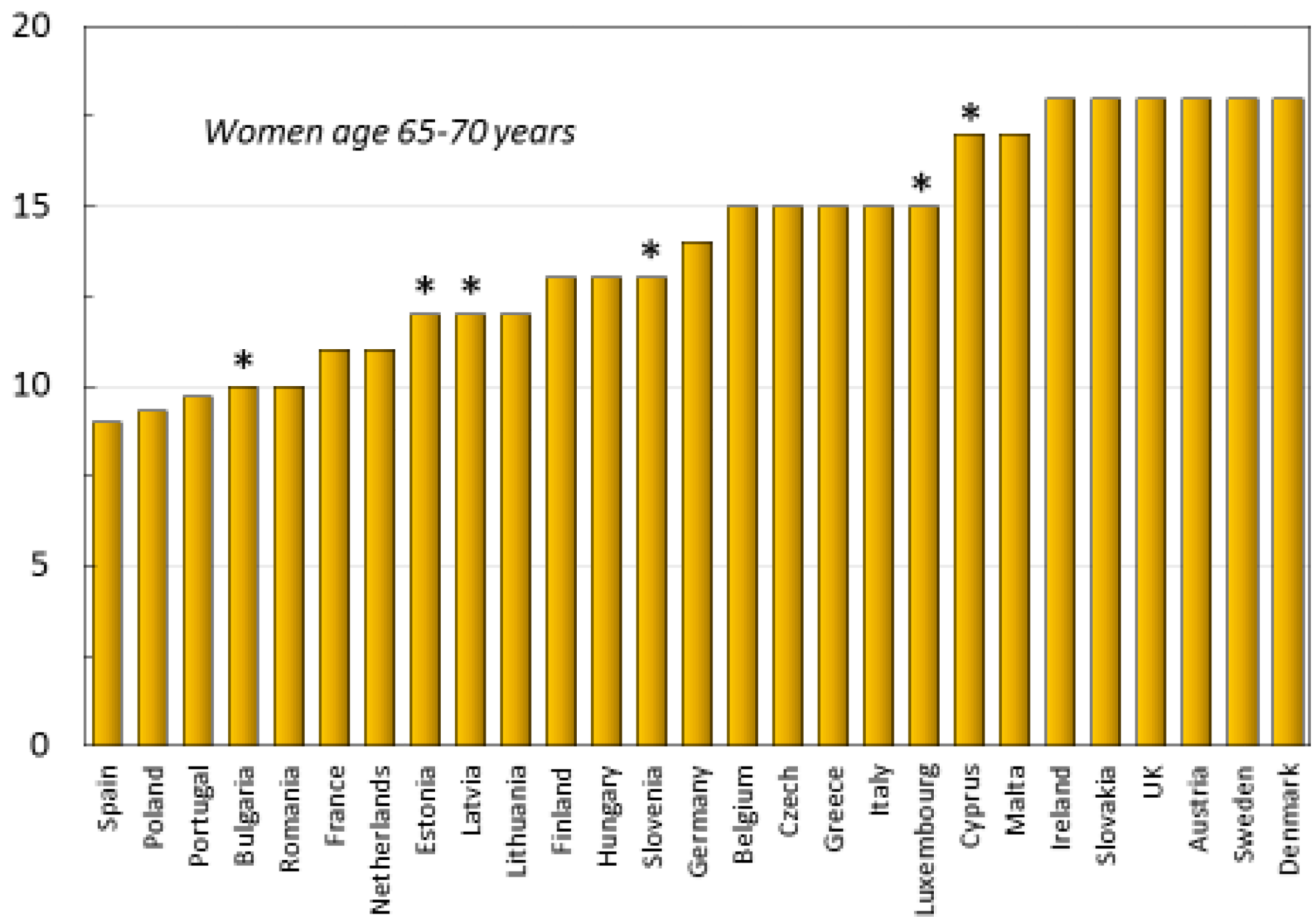
Figure 26.
FRAX 10-year probability (%) of a major osteoporotic fracture (MOF) in women between the ages of 65 and 70 years from the European Union with a previous fracture (no other clinical risk factors, BMI of 24 kg/m^2 and without BMD) representing the age-specific intervention threshold under the NOGG approach. Note that FRAX models were not available for Bulgaria, Cyprus, Estonia, Latvia, Luxembourg and Slovenia (labelled above with an asterisk). For these countries surrogate FRAX models were used. Extracted from [2].

Table 1

Comparative features of QFracture and FRAX. Source [13] with kind permission from Springer Science and Business Media.

	QFracture	**FRAX**
Externally validated	Yes (UK only)	Yes, internationally
Calibrated	Yes (hip only)	Yes
Applicability	UK	57 countries
Falls as an input variable	Yes	No
BMD as an input variable	No	Yes
Prior fracture as an input variable	Yes	Yes
Family history as an input variable	Yes	Yes
Outcome	Hip, forearm, spine, shoulder	Hip, forearm, spine, humerus
Outcome metric	Incidence	Probability

Table 2

Guidelines or academic research papers providing information on FRAX without defining intervention thresholds.

Country/region	Sponsor/source	Footnote	Reference
Argentina	Academia		[33]
Asia Pacific	International Society of Clinical Densitometry		[34]
Brazil	Brazilian Society of Rheumatology and others	a	[35]
Bulgaria	Ministry of Health; Bulgarian Societies of Endocrinology and Rheumatology		[36]
Canada	Expert group	b	[37]
China	Chinese Gerontological Society		[38]
Croatia	Croatian Society for Rheumatology		[39]
Czech Republic	International Osteoporosis Foundation		[3]
Denmark	International Osteoporosis Foundation		[3]
Europe	European Society for Medical Oncology	c	[40]
Europe	European Menopause and Andropause Society		[41]
Europe	European League Against Rheumatism	a	[42]
France	Expert group	d	[43]
Germany	Dachverband Osteologie e.V	e	[44]
Hong Kong	Osteoporosis Society of Hong Kong		[45]
India	Indian Menopause Society	f	[46]
International	International Society of Clinical Densitometry		[47]
Ireland	Irish Osteoporosis Society		[48]
Italy	Società Italiana dell'Osteoporosi, del Metabolismo Minerale e delle Malattie dello Scheletro		[49]
Lebanon	Ministry of Public Health		[50]
Latin America	Iberoamerican Society of Osteology and Mineral Metabolism		[51]
Latvia	Latvian Osteoporosis and Metabolic Diseases Association		[52]
Lithuania	International Osteoporosis Foundation		[3]
Luxembourg	Conseil Scientifique, Domaine de la Santé		[53]
Malta	International Osteoporosis Foundation		[3]
Mexico	Mexican association for postmenopausal osteoporosis (AMMOM)		[54]
Netherlands	Dutch Institute for Healthcare Improvement (CBO)		[55]
Romania	Ministry of Health		[56]
Poland	Polish Osteoarthrology Society and Polish Foundation of Osteoporosis		[57]
Saudi Arabia	Saudi Osteoporosis Society		[58]
Slovakia	Ministry of Health		[59]
Spain	International Osteoporosis Foundation		[3]
Singapore	Ministry of Health		[60]
UK	National Institute for Health and Care Excellence		[61]
US	American Association of Clinical Endocrinologists		[62]
US	Academy of Orthopaedic Surgeons		[63]
US	American College of Physicians		[64]
US	American College of Preventive Medicine)		[65]

[a] Guidelines for glucocorticoid induced osteoporosis

[b] Guideline for coeliac disease

[c] Guidelines for bone health in cancer

[d] Guideline for prostate cancer

[e] Uses an alternative risk assessment tool

[f] Guidance given in an accompanying editorial [66]

Table 3

Intervention thresholds explored or adopted using a fixed FRAX probability for a major osteoporotic fracture (MOF) or hip fracture (HF).

Country/region	Source	Reference	Threshold (%)	
			MOF	HF
__[a]	Academia	[69]	20	3
Austria	Pharmig, Verband der pharmazeutischen Industrie Österreichs	[70]	20	
Belgium [b]	Academia	[71]	20	3
Canada	Osteoporosis Canada.	[29]	20	
Canada	Ministry of Health, British Columbia	[73]	20	
Canada	Society of Obstetricians and Gynaecologists of Canada	[74]	20	
China	Academia	[75]	4	1.3
Czech [c]	Academia	[76]		3
Europe [b]	European Society for Clinical and Economic Aspects of Osteoporosis	[77]	20	3
Finland [d]	National	[78]	10, 20	
Greece	Greek National Medicine Agency	[79]	20	3
Greece [e]	Academia	[80]	10 15	2.5 5
Hong Kong	Academia	[81]	9.95	
Hungary	Hungarian Society for Osteoporosis and Osteoarthrology	[82]	20	3
Japan	Japan Osteoporosis Society; Japanese Society for Bone and Mineral Research; Japan Osteoporosis Foundation	[31]	15	
Japan	Academia	[83]	10	5
Lebanon [f]	Ministry of Public Health and multiple societies	[84]	10	
Malaysia	Ministry of Health, Malaysia	[85]	20	
Malaysia	Malaysian Osteoporosis Society	[86]	20	3
Mexico	Colegio Mexicano de Ortopedia y Traumatología	[87]	20	3
Philippines	Osteoporosis Society of the Philippines and Philippine Orthopedic Association	[88]	20	3
Poland	Academia	[89]	11.6, 17.4	
Poland	Multiple societies	[90]	20	
Poland	Academia	[91]	18	9
Poland	Multidisciplinary Osteoporotic Forum	[92]	10	
Portugal	Academia	[93]	20	3
Saudi Arabia	Academia	[94]	20	3
Scotland	Scottish Intercollegiate Guidelines Network	[32]	10 [j]	
Slovakia	Academia	[95]	20	
Slovenia	Endocrine Society	[96]	20	
Slovenia	Reimbursement agency	[97]	10-20	
South Africa	National Osteoporosis Foundation of South Africa (NOFSA)	[98]		3-5
South Korea	Academia	[99]	20 or 10	3
Spain	Spanish Society of Rheumatology	[100]	20	

Country/region	Source	Reference	Threshold (%)	
			MOF	HF
Spain	Sociedad Española de Cirugía Ortopédica y Traumatología [k]	[101]	20	3
Spain	Sociedad Española de Endocrinilogia y Nutricion	[102]	20	3
Sri Lanka	Ministry of Health	[103]	11	3-5
Sweden [g]	Socialstyrelsen	[68, 104]	15, 20	
Switzerland	Academia	[105]	15	
Taiwan	Taiwanese Osteoporosis Association	[106]	20	3
Thailand	Royal College of Orthopaedic Surgeons of Thailand and the Thai Osteoporosis Foundation	[107]	20	3
UK	National Institute for Health and Care Excellence	[108]	Various [k]	
UK [f]	Academia	[109]	20	
UK [h]	Academia	[110]	20	5
US	National Osteoporosis Foundation	[67, 111]	20	3
US	US Preventive Services Task Force	[112]	9.3 [j]	
US [d]	American College of Rheumatology	[113]	10 20	
US	Endocrine Society	[114]	20	3
US [i]	Academia	[115]	20	
US	Michigan Quality Improvement Consortium	116]	9.3 [j]	
US	American College of Obstetricians and Gynecologists	[117]	20	3
US	North American Menopause Society	[118]	20	3
US	Family practice	[119]	20	3
US	Academia	[120]	20	3
US	National Comprehensive Cancer Network (NCCN)	[121]	20	3
US	American Academy of Family Physicians	[122]	9.3 [j]	
US	Institute for Clinical Systems Improvement	[123]	9.3 [j]	
US	Institute for Clinical Systems Improvement	[72]	20	3

[a] Guideline for chronic obstructive pulmonary disease

[b] Guidance for women treated with aromatase inhibitors for breast cancer

[c] Guidelines for glucocorticoid induced osteoporosis.

[d] Guidelines for glucocorticoid induced osteoporosis. Thresholds dependent on dose and duration of exposure

[e] Higher thresholds at age 75 years or more.

[f] Hybrid model, also uses an age-dependent threshold at some ages (see Hybrid intervention thresholds using FRAX)

[g] 15 % =investigation threshold; 20-30 % = treatment threshold

[h] Guideline for Parkinson disease

[i] Endogenous hypercortisolism

[j] Assessment threshold for subsequent testing with BMD

kIntervention threshold set where treatment becomes cost-effective

Table 4

Sensitivity, specificity (%) and area under the receiver operating characteristic curve (AUC) using three assessment tools for the identification of individuals with femoral neck T-score ≤ -2.5 SD (extracted from [127]).

Tool	Cut off	Sensitivity	Specificity	AUC
FRAX	9.4 %	33.3	86.4	0.60
SCORE	>7	74.1	70.8	0.72
OST	<2	79.3	70.1	0.75

Table 5

Comparison of the number of patients selected for treatment/1000 and hip fractures identified by the RCP and NOGG strategies in all women, by age. The number selected is the number fulfilling requirements for treatment under the strategies. Hip fracture is the expected numbers of hip fractures in those selected for treatment. NNS is the number needed to scan to identify one hip fracture case. From [144], with kind permission from Springer Science+Business Media B.V.

Age (y)	RCP			NOGG		
	N selected[*]	Hip fractures	NNS	N selected[*]	Hip fractures	NNS
50	218	17	13.9	230	18	3.5
55	254	25	8.7	252	25	1.9
60	295	36	5.4	288	35	1.7
65	328	60	3.0	341	62	2.1
70	371	84	2.0	365	83	1.7
75	422	101	1.5	395	95	0.9
80	468	128	1.0	434	120	0.6
85	503	142	0.8	462	133	0.4

[*] includes women identified for therapy on the basis of prior fracture alone

Table 6

Proposed and established intervention strategies using age-specific fracture probabilities

Country	Source	Reference
Australia	Academia	[146]
Belgium	Academia	[147]
Brazil	Academia	[148]
Europe	European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis; International Osteoporosis Foundation	[28]
Europe [a]	International Osteoporosis Foundation; European Calcified Tissue Society	[149]
Finland	Finnish Medical Society (Duodecim), Finnish Endocrine Society and Finnish Gynaecological Association	[150]
France	French Society for Rheumatology and Groupe de Recherche et d'Information sur les Ostéoporoses (GRIO),	[151]
Hong Kong	Academia	[81]
India	Indian menopause society	[66]
Ireland	Academia	[152]
Japan	Academia	[135]
Lebanon [b]	Ministry of Public Health and multiple societies	[84]
Mexico	Ministry of Health	[d]
Poland	Academia	[89]
Romania	Ministry of Health	[56]
Romania	Academia	[153]
Russia	Academia	[154]
Russia	Russian Association on Osteoporosis	[155]
Spain	Sociedad Española de Cirugía Ortopédica y Traumatología [c]	[101]
Sri Lanka	Ministry of Health	[103, 156]
Switzerland	Association Suisse contre l'Ostéoporose	[105,157]
UK	NOGG	[141]
UK	Nottinghamshire	[158]
UK [b]	Academia	[109]

[a] Glucocorticoid-induced osteoporosis

[b] Hybrid model, also uses a fixed threshold at some ages (see Hybrid intervention thresholds using FRAX)

[c] Also recommend fixed thresholds

[d] P Clark, personal communication October 2015

Table 7

The effect of two different intervention thresholds in postmenopausal women aged 50 years or older. The fixed threshold was the average fracture probability in women with a prior fracture (17.5 % probability of a major fracture). The age-specific threshold was set to be equal to that of a woman of the same age with a prior fragility fracture (4-33 % depending on age). Adapted from [89].

Eligible women	No threshold	Fixed threshold Prior fracture	Age-dependent Prior fracture[a]
% identified	100	38.5	15.5
Fracture probability, %[c]	12.3	18.4	23.7
Expected number of fracture patients in 10 years/1000[b]	123	184	237
Fractures saved by treatment [c]	36	21	11
Number needed to treat	27	18	14

[a] age-dependent thresholds

[bc] in those eligible for treatment

[c] 30 % efficacy (relative risk = 0.7)

Table 8

Comparison of the identification and total costs (identification and treatment) per hip fracture averted for the RCP and NOGG strategies. From [160] with kind permission from Springer Science and Business Media.

Age (years)	Cost per hip fracture identified (£)		Total cost per hip fracture averted (£)*	
	RCP	**NOGG**	**RCP**	**NOGG**
50	891	506	6,211	4,797
55	597	352	4,607	3,678
60	407	278	3,505	3,020
65	243	216	2,256	2,144
70	176	171	1,765	1,716
75	145	132	1,609	1,537
80	114	102	1,371	1,306
85	103	89	1,306	1,231

*The cost of treatment was set at £100 equivalent to 5 years of therapy with generic alendronate (approximately £19 per annum [p.a.]) on the assumption that 5 years of treatment would confer a 10-year fracture benefit with a relative risk reduction of 35 %,

Table 9

Probability thresholds at which treatment in men and women from Greece became cost effective determined for the 10-year probability of hip fracture or a major osteoporotic fracture (MOF). Data extracted from [80].

Age (years)	Women		Men	
	Threshold	Range	Threshold	Range
MOF				
50-54	13	8.9-20	20	11-34
55-64	8.5	7.8-9.1	9.5	9.3-9.6
65-74	8.9	8.5-9.2	9.5	8.9-10
75	15	13-16	11	10-11
Hip fracture				
50-54	1.2	0.9-1.	1.4	1.0-1.8
55-64	1.2	1.0-1.5	1.2	1.2-1.5
65-74	2.2	1.8-2.6	2.3	2.3-2.4
75	6.5	4.7-7.8	5.7	4.5-6.6

Table 10

Gradients of risk (RR per SD change in with 95 % confidence intervals) in men and women with the use of BMD at the femoral neck, clinical risk factors or the combination. Source [14] with kind permission from Springer Science+Business Media B.V]

Age (years)	Gradient of risk		
	BMD only	**Clinical risk factors alone**	**Clinical risk factors + BMD**
(a) Hip fracture			
50	3.68 (2.61–5.19)	2.05 (1.58–2.65)	4.23 (3.12–5.73)
60	3.07 (2.42–3.89)	1.95 (1.63–2.33)	3.51 (2.85–4.33)
70	2.78 (2.39–3.23)	1.84 (1.65–2.05)	2.91 (2.56–3.31)
80	2.28 (2.09–2.50)	1.75 (1.62–1.90)	2.42 (2.18–2.69)
90	1.70 (1.50–1.93)	1.66 (1.47–1.87)	2.02 (1.71–2.38)
(b) Other osteoporotic fractures			
50	1.19 (1.05–1.34)	1.41 (1.28–1.56)	1.44 (1.30–1.59)
60	1.28 (1.18–1.39)	1.48 (1.39–1.58)	1.52 (1.42–1.62)
70	1.39 (1.30–1.48)	1.55 (1.48–1.62)	1.61 (1.54–1.68)
80	1.54 (1.44–1.65)	1.63 (1.54–1.72)	1.71 (1.62–1.80)
90	1.56 (1.40–1.75)	1.72 (1.58–1.88)	1.81 (1.67–1.97)

Table 11

Distribution of 10-year probabilities of a major fracture in 2113 elderly women assessed with and without BMD measurements. From [142], with kind permission from Springer Science and Business Media.

Fracture probability (%)	Number of women categorised		Number reclassified	% reclassified[a]
	Without BMD	With BMD		
5-10	0	9	0	0
10-15	15	76	0	0
15-20	302	349	1	0.05
20-25	621	502	9	0.43
25-30	312	399	36	1.70
30-35	509	323	164	7.69
35-40	245	218	99	4.64
40-45	55	126	8	0.38
45-50	45	59	2	0.09
50-55	9	35	0	0
55-60	0	10	0	0
60-65	0	6	0	0
70-75	0	1	0	0
Totals			319	14.98

[a]% of all women

Table 12

Number (percentage) of men and women predicted to have a low, intermediate and high risk of major osteoporotic fracture assessed by FRAX without the use of BMD (Canadian model, version 3.1) according to diagnostic category based on the T-score. From [195] with kind permission from Springer Science+Business Media B.V.

Lowest T-score	N	Low	Moderate	High
		FRAX risk calculated with BMD		
Normal	8,248	7721 (33.4)	517 (4.2)	10 (0.1)
Low bone mass	19,465	12651 (54.7)	6177 (50.4)	637 (15.1)
Osteoporosis	11,890	2765 (12.0)	5552 (45.3)	3573 (84.7)
Totals	39,603	23137 (100)	12246 (100)	4220 (100)
		FRAX risk calculated without BMD		
Normal	8,248	6665 (29.5)	1358 (11.7)	225 (4.2)
Low bone mass	19,465	12019 (53.2)	5617 (48.3)	1829 (34.0)
Osteoporosis	11,890	3915 (17.3)	4655 (40.0)	3320 (61.8)
Totals	39,603	22599 (100)	11630 (100)	5374 (100)

Table 13

Number selected as being above the intervention threshold and the proportion who will fracture over 10 years (mean 10-year fracture probability of major osteoporotic fracture (MOF) and hip fracture) in men and women aged 50 years or more from the NHANES cohort according to different intervention thresholds. From [216] with permission from John Wiley and Sons.

	men			women		
		% who fracture			% who fracture	
Selection	N	MOF	Hip	N	MOF	Hip
A None	1959	6.0	1.5	1649	10.2	2.4
B FRAX fixed thresholds[a]	266	13.5	6.3	387	21.2	7.9
C FRAX at fracture threshold[b]	54	16.3	4.0	144	26.0	9.7
D FRAX fixed thresholds + prior fracture[c]	326	12.3	5.3	414	20.5	7.5
E FRAX at fracture threshold + prior fracture[c]	121	11.9	2.9	179	23.4	8.2
F NOF[d]	330	11.7	4.9	511	17.7	6.2
G Prior fracture[c]	71	8.9	2.1	57	19.0	6.1
H T-score -2.5[e]	79	11.2	5.4	298	17.3	6.7
I Prior fracture & T-score -2.5[e]	148	9.9	3.6	335	17	6.4

[a] FRAX with 20 % and 3 % probability thresholds for major fracture and hip fracture, respectively

[b] FRAX with age-specific thresholds plus prior fracture

[c] Prior hip or spine fracture

[d] National Osteoporosis Foundation Guidelines

[e] T-score at proximal femur or lumbar spine

Table 14

Intervention thresholds explored or adopted using a fixed FRAX probability for a major osteoporotic fracture (MOF) or hip fracture (HF).

Country	Source	Reference	Threshold (%)		Adoption
			MOF	HF	
Greece [a]	Academia	[80]	10, 15	2.5, 5	No
China	Academia	[75]	4	1.3	No
Hong Kong	Academia	[81]	9.95		No [e]
Lebanon [b]	Ministry of Public Health	[84]	10		Yes
Poland	Academia	[89]	11.6, 17.4		No [e]
Switzerland	Academia	[105]	15		No [e]
UK	National Institute for Health and Care Excellence	[108]	Various [c]		No [d]
UK [b]	Academia	[109]	20		No [d]
US	National Osteoporosis Foundation	[124]	20	3	Yes
US	Preventive Services Task Force	[112]	9.3		Yes

[a] Higher thresholds at age 75 years or more.

[b] Hybrid model, also uses an age-dependent threshold at some ages (see Hybrid intervention thresholds using FRAX)

[c] Intervention threshold set where treatment becomes cost-effective

[d] Appraisal in the consultation process

[e] Guidance recommends age-dependent thresholds

Table 15

Strengths of FRAX and the age-dependent NOGG approach

	Country	Reference
FRAX		
Models internally calibrated	All models	[8]
Well calibrated externally	UK Canada Finland Denmark	[13] [194] [198] [197]
Extensively validated	Worldwide	[8]
Readily administered in primary care	UK	[223]
Attuned to clinical practice	UK	[222]
Can be applied to all countries with a FRAX model or a surrogate	80 % of world	[221]
Multimedia availability including densitometers	Worldwide	
More accurate than simpler models	Canada	[217]
Age-dependent thresholds		
Strategy is cost-effective	UK Switzerland	[140] [105]
Lower costs per fracture case identified than RCP guidelines	UK	[144]
More economic use of BMD tests than RCP or NOF guidelines	UK	[144] [145]
Treatment decisions not wholly based on BMD		[140]
Fewer but higher risk patients identified than RCP guidelines	UK	[144]
Fewer but higher risk patients identified than NOF guidelines	US	[216]
More effective than fixed thresholds	US Poland	[216] [89]

Table 16

Limitations of FRAX – real and perceived

FRAX in general

        Reliance on computer access

        Not all countries have FRAX models

        Efficacy in patients selected without BMD

FRAX in guideline development

        No controlled trials

        Age-dependent thresholds are ageist

        Inequity across countries

        Sensitivity of NOGG in subgroups

Table 17

NOGG strategy applied to women from without prior fracture, by age (/1000) [144] with kind permission from Springer Science+Business Media B.V.

Age (years)	Number scanned	Number selected	Expected hip fractures	Expected MOF	Mean FN T-score
50	63	22	2	52	-1.78
55	48	16	2	27	-2.28
60	59	14	2	17	-2.67
65	131	38	7	48	-2.58
70	140	29	8	38	-2.91
75	89	18	6	23	-3.35
80	69	15	6	16	-3.60
85	50	15	7	20	-3.66
			40	241	

FN femoral neck

MOF major osteoporotic fracture (hip, clinical spine, forearm, proximal humerus)