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A decade of FRAX: how has it changed the management of osteoporosis?

John A. Kanis^{1,2} · Nicholas C. Harvey³ · Helena Johansson^{1,2} · Enwu Liu² · Liesbeth Vandenput⁴ · Mattias Lorentzon^{2,4} · William D. Leslie⁵ · Eugene V. McCloskey^{1,6}

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Abstract

The fracture risk assessment tool, FRAX[®], was released in 2008 and provides country-specific algorithms for estimating individualized 10-year probability of hip and major osteoporotic fracture (hip, clinical spine, distal forearm, and proximal humerus). Since its release, 71 models have been made available for 66 countries covering more than 80% of the world population. The website receives approximately 3 million visits annually. Following independent validation, FRAX has been incorporated into more than 80 guidelines worldwide. The application of FRAX in assessment guidelines has been heterogeneous with the adoption of several different approaches in setting intervention thresholds. Whereas most guidelines adopt a case-finding strategy, the case for FRAX-based community screening in the elderly is increasing. The relationship between FRAX and efficacy of intervention has been explored and is expected to influence treatment guidelines in the future.

Keywords FRAX · Fracture probability · Clinical risk factors · Intervention thresholds · Risk assessment · Screening

Introduction

The principal aim of treatments for osteoporosis is to decrease the risk of fragility fractures. Thus, the ability to assess fracture risk is critical in identifying patients who are eligible for intervention [1, 2]. Historically, the gateway to fracture risk assessment has been the assessment of fracture risk by means of bone mineral density (BMD) alone. Indeed, osteoporosis is defined as a femoral neck BMD 2.5 SD or

more below the young adult female mean (T score ≤ -2.5) [3, 4]. Although the WHO diagnostic criteria for osteoporosis were intended primarily for descriptive epidemiology [3, 4], they were soon adopted as inclusion criteria for drug trials and subsequently proposed as intervention thresholds and a basis for health technology assessments.

There are, however, several considerations that make the use of a T score problematic as a universal intervention threshold. These include:

Relatively low sensitivity to detect who will fracture under most reasonable assumptions [3, 5].

Any given T score threshold has a different significance at different ages [6–10].

It is well established that fracture rates vary widely from country to country—much more so than can be explained by variations in BMD [9]. Thus, for any given fracture risk, the T score 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% (as used in Canada and the United States), the femoral neck T score ranges from -4.6 SD in Venezuela, to -2.0 SD in Iceland.

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For these reasons, intervention thresholds based on BMD alone do not optimally target individuals at high fracture risk and provide the rationale for the development of risk engines to improve the assessment of fracture risk [11–13]. Of these, FRAX[®] is the most widely used. The aim of this review is to outline developments in FRAX since its release in 2008 and the way in which this has influenced the management of osteoporosis.

The development of FRAX

In 2008, the World Health Organization (WHO) Collaborating Centre at Sheffield, UK released FRAX—a fracture risk assessment tool for estimating individualized 10-year probability of hip and major osteoporotic fracture (hip, clinical spine, distal forearm, and proximal humerus) [14]. The FRAX tool integrates seven dichotomous clinical risk factors (CRFs: prior fragility fracture, parental hip fracture, smoking, systemic glucocorticoid use, excess alcohol intake, rheumatoid arthritis, and other causes of secondary osteoporosis), which, in addition to age and sex and body mass index (BMI), contribute to a 10-year fracture probability estimate independently of bone mineral density (BMD) [14, 15]. BMD at the femoral neck is an optional input variable.

Fracture probability is computed taking both the risk of fracture and the risk of death into account. This is important, because some of the risk factors affect both these outcomes. Examples include increasing age, low body mass index (BMI), low BMD, glucocorticoids, and smoking. Other risk engines calculate the risk of a clinical event without taking into account the possibility of death over the timeframe considered [12, 13].

New models and uptake of FRAX

Fracture probability differs markedly within and across regions of the world [16, 17], so that FRAX models are calibrated to the epidemiology of fracture and death in individual nations. At the launch of FRAX, models were available for eight countries. 71 models are currently available for 66 countries comprising more than 80% of the world population [18]. FRAX is available in 35 languages and the website (<http://www.shef.ac.uk/FRAX>) receives approximately 3 million visits annually. Usage by country model is available on the website. This underestimates the uptake of FRAX, since the website is not the sole portal for the calculation of fracture probabilities. For example, FRAX is available in BMD equipment, on smartphones, embedded in some healthcare electronic record systems and, in some countries, through hand-held calculators.

With regard to website visits, calculations arose from 173 countries in 2012/13. Uptake was high in North America,

the Antipodes, and most countries of Europe, intermediate in Latin America and the Middle East, and very low in Africa and much of South East Asia. The countries that used FRAX most frequently were the United States, United Kingdom, Canada, Spain, Japan, France, Belgium, Italy, Switzerland, and Turkey. Collectively, these countries undertook more than 80% of all calculations [18]. When uptake was expressed per million of the population, highest usage was seen for Slovenia, Switzerland, US, Belgium, New Zealand, and the UK.

Performance characteristics

For the purpose of risk assessment, the characteristic of major importance is the ability of a technique to predict fractures, traditionally expressed as the increase in hazard ratio per standard deviation (SD) unit increase in risk score—termed the gradient of risk. The gradients of risk for fracture prediction are shown in Table 1 for the use of the clinical risk factors alone, femoral neck BMD alone, and the combination [19]. Overall, the predictive value compares very favourably with other risk engines such as the Gail score for breast cancer [20].

Whereas both BMD and the clinical risk factors alone provide significant gradients of risk, the highest gradients of risk are seen when BMD is co-entered into the FRAX model. It is important to recognise that the impact of the CRFs and BMD are not purely multiplicative as there is some interdependence ($r = -0.25$ for FRAX score without BMD and femoral neck BMD). The importance of this observation is that the selection of patients with FRAX, but without BMD, will preferentially select patients with low BMD, and that the higher the fracture probability, the lower will be the BMD [21, 22]. This finding has obvious significance for case finding in the absence of access to BMD [23].

Validation

The performance characteristics of FRAX have been evaluated in 11 independent cohorts that did not participate in the model synthesis. In all the validation cohorts, the use of clinical risk factors alone or in combination with BMD gave gradients of fracture risk that differed significantly from unity and which were comparable to those in the original cohorts used for model building [19].

Calibration

All FRAX models are calibrated with regard to the epidemiology of hip fracture (preferably from national sources) and mortality (usually UN source). Thus, were the population of each country to be “FRAXed”, the number of hip

Table 1 Gradients of risk (increase in fracture risk per SD change in with 95% confidence intervals) with the use of BMD at the femoral neck, clinical risk factors, or the combination ([19] 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)

fractures and deaths estimated would match that provided from the source data. It follows that the calibration of the FRAX algorithms is only as good as the epidemiology with which the tools are populated. Additionally, any validation exercise will be critically dependent on the representativeness of the population tested for the index country. Several investigators have studied populations that were considered to represent national populations, including the UK, Canada, and Norway [24–27]. In these studies, FRAX appears to be well calibrated.

FRAX and the development of intervention thresholds

The influence of FRAX in clinical practice is highlighted by the many published clinical guidelines and health technology assessments recommending treatment on the basis of 10-year fracture probability. The first was the incorporation of FRAX in the guideline of the US National Osteoporosis Foundation (NOF) [28, 29] followed by the National Osteoporosis Guideline Group (NOGG) in the UK [30, 31]. Since then, FRAX has been incorporated into more than 80 guidelines worldwide [8]. However, the application of FRAX in guidelines has been heterogeneous. Several guidelines have adopted FRAX within pre-existing guidelines. In the US, for example, the gateway to treatment includes either a prior fracture (hip or spine fracture) or a BMD T score of ≤ -2.5 SD [32] irrespective of FRAX. FRAX is reserved for individuals in whom the T score is in the osteopenic range and treatment recommended if the probability of a major fracture or hip fracture lies at 20% or more or 3% or more, respectively. Similarly, in Japan, the use of FRAX is reserved for individuals without a prior fracture and a BMD that lies between a T score of -1.8 and -2.77 SD and treatment

recommended if the probability of a major fracture is 15% or more [33].

In many countries, particularly in Europe and Latin America, age-dependent intervention thresholds have been developed [8, 34]. The first guideline to develop the approach was that of the NOGG in the UK [30, 31], updated in 2017 [35]. Briefly, the NOGG guidance ‘translated’ the preceding Royal College of Physicians (RCP) guideline [36] 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 (as espoused in many guidelines worldwide [8]). The translational logic used was that if a woman with a prior fragility fracture be 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 was set at the age-specific fracture probability equivalent to women with a prior fragility fracture of average BMI [30] and, therefore, rose with age (Fig. 1). In other words, the intervention threshold was set at the age-dependent ‘fracture threshold’.

BMD assessment thresholds

In addition to intervention thresholds, NOGG developed age-dependent assessment thresholds for the UK. The lower assessment threshold was set to exclude a requirement for BMD testing in women with no clinical risk factors as recommended in the RCP and European guidelines prevailing at that time [36, 38]. The upper assessment threshold was set at 1.2 times the intervention threshold, chosen to minimise the probability that a patient characterised to be at high risk on the basis of clinical risk factors alone would be reclassified

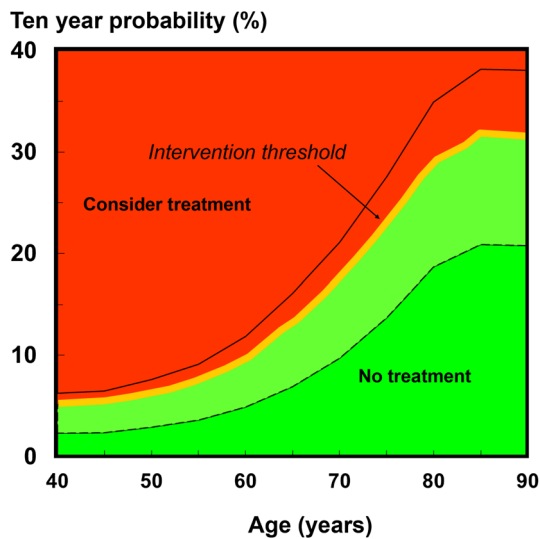


Fig. 1 The 10-year probability (%) of a major osteoporotic fracture by age in women with a prior fracture and no other clinical risk factors in the five major EU countries (weighted average of Spain, France, Germany, Italy, and UK) as determined with FRAX (version 3.5). Body mass index was set to 24 kg/m² without BMD. The line dividing the red and green zones represents the age-dependent intervention threshold or ‘fracture threshold’ Redrawn from [37] with kind permission from Springer Science and Business Media

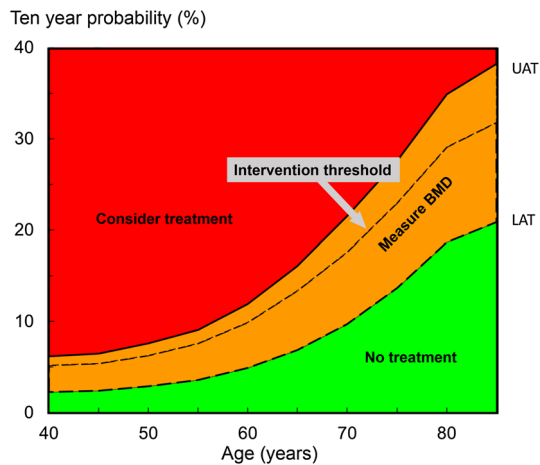


Fig. 2 Assessment guidelines based on the 10-year probability of a major osteoporotic fracture (%). The dotted line denotes the intervention threshold. Where assessment is made in the absence of BMD, a BMD test is recommended for individuals where the probability assessment lies in the orange region between the upper assessment threshold (UAT) and the lower assessment threshold (LAT). The intervention threshold and BMD assessment From [39], with kind permission from Springer Science and Business Media

to be at low risk with additional information on BMD [21]. The assessment thresholds are illustrated in Fig. 2 [39].

The major difference between NOGG-like guidance and the RCP guidance is that the latter predicated treatment on the basis of a BMD test (T score ≤ -2.5), whereas for the

former, FRAX provided the gateway to assessment which, in turn, provided a restricted indication for BMD testing. Compared with the RCP strategy, NOGG identified slightly reduced numbers of women above the respective intervention thresholds (on average 35.7 vs. 34.6%, respectively, depending on age) [40]. 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. This led to a subsequent revision of the NOGG thresholds in older women, to equalise the fracture risk in women with and without prior fracture identified for treatment [41].

A further difference between the two strategies was that more efficient use was made of BMD measurements with no loss in sensitivity for hip fracture [40]. 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. 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 [42].

Case finding

In keeping with 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 in younger individuals or 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 (Fig. 2). 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 considered eligible for treatment. Where BMD is not available, the same intervention threshold can be used. Note that the same intervention threshold is applied to men as in women, since the effectiveness and cost-effectiveness of intervention in men are broadly similar to that in women for equivalent risk [43–45].

The approach outlined above has been incorporated in European and Latin American guidelines [34, 39, 46], which has been well validated [15, 21, 22, 40, 47, 48], and the intervention strategy shown to be cost-effective [40, 49]. Many other approaches have been adopted, but have been less well characterised [8].

Very high risk

In 2020, the International Osteoporosis Foundation (IOF) and the European Society for Clinical and Economic Evaluation of Osteoporosis and Osteoarthritis (ESCEO) published an algorithm for the dichotomisation of high risk into high- and very-high-risk categories [37]. The stimulus arose from the increasing availability of anabolic agents, including new agents such as abaloparatide and romosozumab, or established agents such as teriparatide, which have a demonstrably more rapid and greater fracture risk reductions than antiresorptive treatments [50–52]. These have the potential to revolutionise treatment strategies, particularly in individuals at very-high-fracture risk. Thus, current initial treatment recommendations for women at high risk most usually start with an inhibitor of bone resorption. For example, the UK National Institute for Clinical Excellence (NICE), NOGG and the IOF/ESCEO guidelines recommend oral bisphosphonates [35, 39, 53]. In contrast, women at very high risk might be more suitably treated with an anabolic treatment followed thereafter by an inhibitor of bone resorption [54]. Given that treatments with anabolic agents are limited to 12–24-month duration and that efficacy will wane once treatment is stopped, the real potential of the anabolic treatments is that their greater effect on BMD and fracture can be maintained with the inhibitors of bone turnover once anabolic treatment is stopped [52, 55, 56]. Such regimens save more fractures than inhibitors of bone resorption followed by anabolic agents.

The algorithm follows the guidance of the IOF and ESCEO in the use of age-dependent intervention thresholds with the use of FRAX. In addition to the categories of low and high risk espoused in the current IOF-ESCEO guideline, very high risk can be identified as a fracture probability that exceeds the current intervention threshold by 20% (Fig. 3).

Screening with FRAX

At present, there is no universally accepted policy for population screening in Europe to identify patients with osteoporosis or those at high risk of fracture [3]. In the absence of a screening policy, patients are identified opportunistically using a case-finding strategy on the finding of a previous fragility fracture or the presence of significant risk factors, as

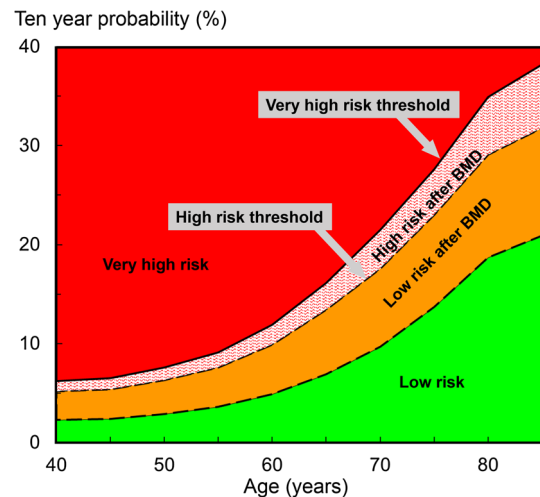


Fig. 3 Assessment guidelines based on the 10-year probability of a major osteoporotic fracture (%). The pattered red area denotes high risk. Very high risk is when FRAX estimates lie in the unpattered red zone

outlined above. With the increasing development of effective agents and price reductions, this view may change, particularly for elderly people [57, 58]. The SCOOP trial (screening of older women for the prevention of fractures) provided strong support for such a strategy [57]. This seven-centre pragmatic randomised-controlled trial with 5-year follow-up included women aged 70–85 years, who were randomised to receive a care algorithm including FRAX and drug targeting ($n = 6233$) or usual primary care for osteoporosis based on opportunistic case finding ($n = 6250$). Women were recruited from 100 UK general practices, and the outcome measures included all osteoporotic, major osteoporotic, and hip fractures. There was no significant effect on all fractures (HR 0.94; 95% CI 0.85–1.03), but screening reduced the incidence of hip fractures (HR 0.72; 95% CI 0.59–0.89; $p = 0.002$). The effect on hip fracture increased significantly with increasing baseline FRAX hip fracture probability [58]. For example, at the 10th percentile of baseline FRAX hip probability (2.6%), hip fractures were not significantly reduced (HR 0.93; 95% CI 0.71–1.23), but at the 90th percentile (16.6%), there was a 33% reduction (HR 0.67; 95% CI 0.53–0.84) (Fig. 4). The screening algorithm resulted in a marked increase in the use of anti-osteoporosis medication, and greater compliance with therapy, over the period of follow-up [59]. These findings strongly support a systematic, community-based screening program of fracture risk in older women. In addition, the strategy appears to be cost-effective [60, 61].

Two further trials of screening with FRAX have subsequently been reported [62, 63] but differed in several respects from SCOOP. In the Risk-stratified Osteoporosis Strategy Evaluation (ROSE) study [62], the entire

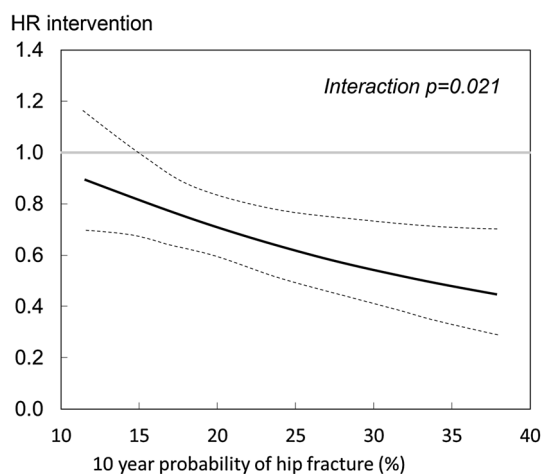


Fig. 4 Impact of screening on hip fracture compared with control arm, expressed as hazard ratio, across range of FRAX 10-year hip fracture probabilities at baseline, calculated without BMD. There was a significant interaction of effectiveness with baseline probability of hip fracture [figure redrawn from 58]

population age 65–80 years at risk was randomised, whereas the SCOOP study randomised those willing and eligible to participate. Screening used in ROSE was the probability of major osteoporotic fracture with a threshold $\geq 15\%$ to designate high risk, whereas SCOOP used hip fracture probability with an age-dependent threshold. The ultimate arbiter of treatment in ROSE was based on a BMD test rather than FRAX with BMD. The treatment strategy based on BMD (lowest T score of two site assessment) weakens the power of FRAX by excluding some high-risk individuals [64]. The ROSE study reported no difference in fracture risk between those randomised to screening or the control arm. When the actual group targeted for treatment (i.e., at high risk) was compared to the control arm in a per protocol analysis, there was a significant reduction in hip fracture (HR 0.71; 95% CI 0.55–0.91), major osteoporotic fracture (HR 0.85; 95% CI 0.76–0.97), and all osteoporotic fractures (HR 0.88; 95% CI 0.79–0.98) which were observed. Interpretation of the latter results requires caution as there was evidence of a healthy selection bias in those in the screening group attending for BMD measurements.

A third trial of screening with FRAX, the SALT Osteoporosis Study (SOS), has recently been published from The Netherlands [63]. In this study, women aged 65–90 years were recruited if they had at least one clinical risk factor associated with osteoporosis or increased fracture risk. Following randomisation, women in the intervention group were offered a screening program, to identify the women with a high fracture risk, whilst women in the control group received usual care. In contrast to SCOOP and ROSE, screening and subsequent treatment had no statistically significant effect on any fracture, osteoporotic fractures,

major osteoporotic fractures, or hip fractures. The trial had a number of shortcomings including low participation, low medication uptake, and adherence in the screening group. Although age-dependent FRAX thresholds were used for screening, the UK FRAX tool was used. Because of the difference in fracture risk between the UK and The Netherlands, a much smaller proportion of individuals would be identified for treatment than with the Dutch FRAX model. Of greater concern, treatment was not targeted by identification of high risk by FRAX alone. Indeed, for those above an age-dependent threshold by FRAX without BMD, treatment initiation also required a BMD T score at the spine or hip of ≤ -2 , a threshold that could lower the actual fracture probability in the identified population [9]. For example, women with a prior fragility fracture at the age of 75 years (the mean age of the screening cohort) have a 10-year probability of a major osteoporotic fracture of 19%. The same individual with a T score of -2 SD has a fracture probability of 14%. The selection of relatively low-risk women is evident in that FRAX probabilities were only marginally higher in the treatment group than in the general population (by 20–50%), whereas probabilities in the equivalent arms of SCOOP were twofold higher. Thus, the choice of the intervention thresholds was unfortunate, to say the least. It is relevant to observe that women at very high risk (because of a recent fracture) showed a significant decrease in hip fracture rate (HR 0.38; 95% CI 0.18–0.79) and for major osteoporotic fracture (HR 0.65; 95% CI 0.44–0.96) reinforcing the view that the screening methodology was wanting.

Efficacy of treatment and FRAX

In addition to the SCOOP study above, several studies have examined the effectiveness of interventions according to baseline fracture probability. Analyses of four phase 3 studies have shown similar efficacy of strontium ranelate [65], teriparatide [66, 67] or raloxifene [68] across a range of fracture probabilities (with greater absolute risk reductions in those at higher risk). In contrast, greater fracture relative risk reduction has been reported at higher fracture probabilities in the case of clodronate [69], bazedoxifene [70], and, in a pre-planned analysis, with denosumab [71].

These results have a number of important implications. First, they mitigate a concern that patients identified on the basis of clinical risk factors with FRAX would not respond to pharmacologic interventions. Indeed, these studies showed that high FRAX probabilities were associated with efficacy, even when BMD was not used to characterise risk. Second, they support the view of the regulatory agencies that treatments should be targeted preferentially to men and women at high fracture risk. Third, the finding of greater efficacy at higher fracture probabilities with

some interventions has important implications for health technology assessments and challenges the current meta-analytic approach. Finally, since treatments directed to high-risk patients improve the budget impact, greater efficacy in the higher risk groups will improve still further the budget impact and the cost-effectiveness of intervention [72].

FRAX for connoisseurs

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 [14, 23]. 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 into account 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, because the relevant information was not available in the source cohorts on which FRAX was based. 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 appears misplaced [73].

To address some of these limitations, relatively simple arithmetic procedures have been proposed which can be applied to the 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 [74];
concurrent data on lumbar spine BMD [75, 76];
information on trabecular bone score (TBS) [77–79];
hip axis length [80];
falls history [81, 82];
immigration status [83];
type 2 diabetes [47, 84];
chronic kidney disease [85];
recency of vertebral fracture [37, 86].

Additionally, FRAX values have been shown to be largely unaffected by socioeconomic status [87], variation in body composition [88], exposure to aromatase inhibitors and concurrent treatment for osteoporosis [73, 89], and the latter at least at a population level.

The most recent FRAX adjustment was related to the recency of vertebral fracture. There is now a substantial

Table 2 10-year probability of major osteoporotic fracture (MOF) for Icelandic women at different ages, categorized by (A) a clinical vertebral fracture within the previous 2 years and (B) a prior fracture of undetermined recency. From [37] with kind permission from Springer Science and Business Media

Age	10-year probability of MOF		Ratio
	(A) Recent vertebral fracture	(B) Prior fracture in adult life	
50	29.0	11.7	2.47
60	36.1	19.4	1.86
70	41.9	27.6	1.52
80	42.5	34.2	1.24
90	34.7	33.3	1.04

BMI set at 25 kg/m²

The right-hand column provides the ratio by which to adjust FRAX probabilities by virtue of a recent clinical vertebral fracture. Probabilities and ratios are derived from the UK

body of evidence that the risk of a subsequent osteoporotic fracture is particularly acute immediately after the index fracture and wanes progressively with time [90–93]. Thus, the incidence of second fracture in those who will sustain a further fracture is particularly high in the first 2 years after the index event [94]. The FRAX tool provides fracture probabilities associated with a prior fracture, irrespective of its recency, and, thus, underestimates fracture probability where the prior fracture occurred within 2 years.

Adjustments have been proposed for a recent vertebral fracture. For example, for a woman at age 70 years, a prior clinical vertebral fracture within the past 2 years is associated with a 1.52-fold higher fracture probability than for a woman of the same age with a prior fragility fracture of uncertain recency [37] (Table 2). Thus, a recent clinical vertebral fracture uplifts the fracture probability from 16 to 24%. Adjustments ratios range from 1.04 to 2.47, depending on age. Adjustment ratios for recent fractures at other sites have yet to be determined.

Compliance with ethical standards

Conflict of interest Professor Kanis led the team that developed FRAX as director of the WHO Collaborating Centre for Metabolic Bone Diseases; he has no financial interest in FRAX. Professors McCloskey, Lorentzon, Harvey, Dr Liu, and Dr Johansson are members of the FRAX team. Professors Kanis, Harvey, and McCloskey are members of the advisory body to the National Osteoporosis Guideline Group.

Human and animal rights This review article reviews studies but does not contain any original studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

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