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REVIEW

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

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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

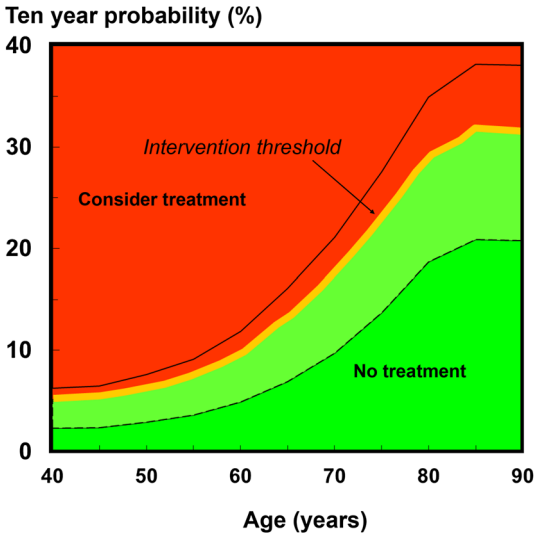

Fig. 1 The 10-year probability (%) of a major osteoporotic fracture by age in women with a prior fracture and no other clinical risk factors in the five major EU countries (weighted average of Spain, France, Germany, Italy, and UK) as determined with FRAX (version 3.5). Body mass index was set to 24 kg/m^2 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

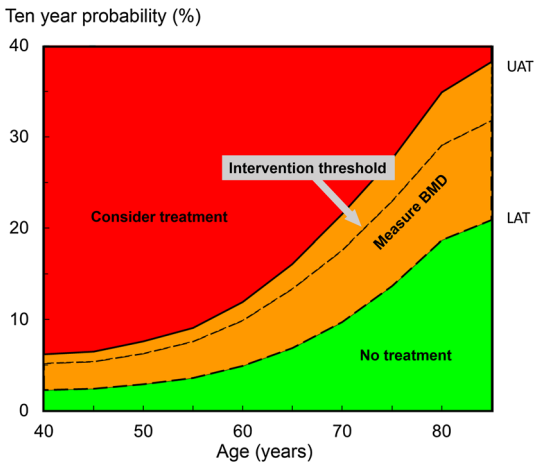

Fig. 2 Assessment guidelines based on the 10-year probability of a major osteoporotic fracture (%). The dotted line denotes the intervention threshold. Where assessment is made in the absence of BMD, a BMD test is recommended for individuals where the probability assessment lies in the orange region 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

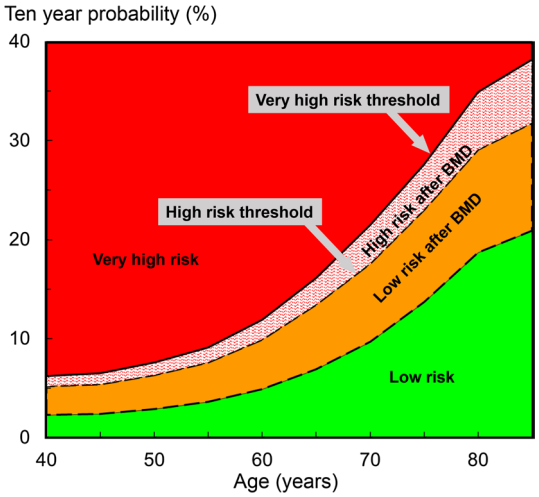

Fig. 3 Assessment guidelines based on the 10-year probability of a major osteoporotic fracture (%). The patterned red area denotes high risk. Very high risk is when FRAX estimates lie in the unpatterned red zone

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

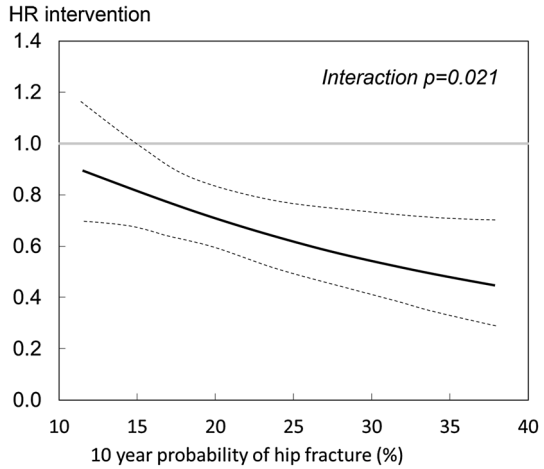

Fig. 4 Impact of screening on hip fracture compared with control arm, expressed as hazard ratio, across range of FRAX 10-year hip fracture probabilities at baseline, calculated without BMD. There was a significant interaction of effectiveness with baseline probability of hip fracture [figure redrawn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

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/m^2

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

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.

References

1. Kanis JA, Oden A, Johnell O et al (2001) The burden of osteoporotic fractures: a method for setting intervention thresholds. Osteoporos Int 12:417–427
2. Kanis JA, Borgstrom F, De Laet C, Johansson H et al (2005) Assessment of fracture risk. Osteoporos Int 16:581–589
3. World Health Organisation (1994) Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. WHO Technical Report Series 843. WHO, Geneva
4. Kanis J, McCloskey EV, Johansson H et al (2008) A reference standard for the description of osteoporosis. Bone 42:467–475
5. Cranney A, Jamal SA, Tsang JF et al (2007) Low bone mineral density and fracture burden in postmenopausal women. CMAJ 177:575–580
6. Kanis JA, Johnell O, Oden A et al (2000) Risk of hip fracture according to World Health Organization criteria for osteoporosis and osteopenia. Bone 27:585–590
7. Grigorie D, Sucaliuc A, Johansson H et al (2013) Incidence of hip fracture in Romania and the development of a Romanian FRAX model. Calcif Tissue Int 92:429–436
8. Kanis JA, Harvey NC, Cyrus Cooper C et al (2016) A systematic review of intervention thresholds based on FRAX. A report prepared for the National Osteoporosis Guideline Group and the International Osteoporosis Foundation. Arch Osteoporos 11:25. https://doi.org/10.1007/s11657-016-0278-z
9. Kanis JA, McCloskey EV, Harvey NC et al (2015) Intervention thresholds and the diagnosis of osteoporosis. J Bone Miner Res 30:1747–1753
10. Johansson H, Azizieh F, Harvey NC et al (2017) FRAX- vs. T-score-based intervention thresholds for osteoporosis. Osteoporos Int 28:3099–3105
11. Kanis JA, Harvey NC, Johansson H et al (2017) Overview of fracture prediction tools. J Clin Densitom 20:360–367
12. Nguyen ND, Frost SA, Center JR et al (2008) Development of prognostic nomograms for individualizing 5-year and 10-year fracture risks. Osteoporos Int 19:1431–1444
13. Hippisley-Cox J, Coupland C (2012) Derivation and validation of updated QFracture algorithm to predict risk of osteoporotic fracture in primary care in the United Kingdom: prospective open cohort study. BMJ. https://doi.org/10.1136/bmj.e3427
14. Kanis JA on behalf of the World Health Organization Scientific Group (2008) Assessment of osteoporosis at the primary healthcare level. Technical Report. WHO Collaborating Centre, University of Sheffield, UK. http://www.shef.ac.uk/FRAX/index.htm. Accessed 26 Sept 2019
15. Kanis JA, Johnell O, Oden A et al (2008) FRAX™ and the assessment of fracture probability in men and women from the UK. Osteoporos Int 19:385–397
16. Kanis JA, Odén A, McCloskey EV et al (2012) A systematic review of hip fracture incidence and probability of fracture worldwide. Osteoporos Int 23:2239–2256
17. Cauley JA, Chalhoub D, Kassem AM et al (2014) Geographic and ethnic disparities in osteoporotic fractures. Nat Rev Endocrinol 10:338–351
18. Kanis JA, Johansson H, Oden A et al (2014) Worldwide uptake of FRAX. Arch Osteoporos 9:166. https://doi.org/10.1007/s11657-013-0166-8
19. Kanis JA, Oden A, Johnell O et al (2007) The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women. Osteoporos Int 18:1033–1046
20. Chlebowski RT, Anderson GL, Lane DS et al (2007) Predicting risk of breast cancer in postmenopausal women by hormone receptor status. J Natl Cancer Inst 99:1695–1705
21. Johansson H, Oden A, Johnell O et al (2004) Optimisation of BMD measurements to identify high risk groups for treatment—a test analysis. J Bone Miner Res 19:906–913
22. Leslie WD, Majumdar SR, Lix L et al (2012) High fracture probability with FRAX usually indicates densitometric osteoporosis: implications for clinical practice. Osteoporos Int 23:391–397
23. Kanis JA, McCloskey E, Johansson H et al (2012) FRAX with and without BMD. Calcif Tissue Int 90:1–13
24. Hippisley-Cox J, Coupland C (2009) Predicting risk of osteoporotic fracture in men and women in England and Wales: prospective derivation and validation of QFractures Scores. Br Med J 339:b4229
25. Hoff M, Meyer HE, Skurtveit S et al (2017) Validation of FRAX and the impact of self-reported falls among elderly in a general population: the HUNT study, Norway. Osteoporos Int 28:2935–2944
26. Fraser L-A, Langsetmo L, Berger C et al (2011) Fracture prediction and calibration of a Canadian FRAX® tool: a population-based report from CaMos. Osteoporos Int 22:829–837
27. Leslie WD, Lix LM, Johansson H et al (2010) Manitoba bone density program. Independent clinical validation of a Canadian FRAX((R)) tool: fracture prediction and model calibration. J Bone Miner Res 25:2350–2358
28. Dawson-Hughes B, Tosteson AN, Melton LJ 3rd et al (2008) Implications of absolute fracture risk assessment for osteoporosis practice guidelines in the USA. Osteoporos Int 19:449–458
29. Dawson-Hughes B (2008) A revised clinician's guide to the prevention and treatment of osteoporosis. J Clin Endocrinol Metab 93:2463–2465
30. Kanis JA, McCloskey EV, Johansson H et al (2008) Case finding for the management of osteoporosis with FRAX®—assessment and intervention thresholds for the UK. Osteoporos Int 19:1395–1408 (Erratum Osteoporos Int 2009;20:499-502)
31. Compston J, Cooper A, Cooper C et al (2009) Guidelines for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK. Maturitas 62:105–108
32. Cosman F, de Beur SJ, LeBoff MS et al (2014) Clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int 25:2359–2381 (Erratum Osteoporos Int 2015;26:2045-7)
33. Orimo H, Nakamura T, Hosoi T et al (2012) Japanese 2011 Guidelines for prevention and treatment of osteoporosis—executive summary. A report of the committee for developing guidelines for prevention and treatment of osteoporosis: Japan Osteoporosis Society, Japanese Society for Bone and Mineral Research, and Japan Osteoporosis Foundation. Arch Osteoporos 7:3–20
34. Clark P, Denova-Gutiérrez E, Zerbini C et al (2018) FRAX-based intervention and assessment thresholds in seven Latin American countries. Osteoporos Int 29:707–715
35. Compston J, Cooper A, Cooper C et al (2017) UK clinical guideline for the prevention and treatment of osteoporosis. Arch Osteoporos 12:43
36. Royal College of Physicians (1999) Osteoporosis: clinical guidelines for the prevention and treatment. RCP, London
37. Kanis JA, Harvey NC, McCloskey E et al (2020) Algorithm for the management of patients at low/middle/high risk of osteoporotic fracture: a global perspective. Osteoporos Int 31:1–12. https://doi.org/10.1007/s00198-019-05176-3
38. Kanis JA, Delmas P, Burckhardt P et al (1997) Guidelines for diagnosis and management of osteoporosis. Osteoporos Int 7:390–406
39. Kanis JA, Cooper C, Rizzoli R et al (2019) European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int 30:3–44

40. Johansson H, Kanis JA, Oden A et al (2012) A comparison of case-finding strategies in the UK for the management of hip fractures. Osteoporos Int 23:907–915
41. McCloskey E, Kanis JA, Johansson H et al (2015) FRAX-based assessment and intervention thresholds—an exploration of thresholds in women aged 50 years and older in the UK. Osteoporos Int 26:2091–2099
42. Yriakos G, Vidal-Casariego A, Fernández-Martínez MN et al (2015) Impact of the NOGG and NOF guidelines on the indication of bone mineral density in routine clinical practice. J Clin Densitom 18:533–538
43. Kanis JA, Stevenson M, McCloskey EV et al (2007) Glucocorticoid-induced osteoporosis: a systematic review and cost-utility analysis. Health Technol Assess 11:1–256
44. Lippuner K, Johansson H, Borgström F et al (2012) Cost-effective intervention thresholds against osteoporotic fractures based on FRAX® in Switzerland. Osteoporos Int 23:2579–2589
45. Tosteson AN, Melton LJ 3rd, Dawson-Hughes B et al (2008) Cost-effective osteoporosis treatment thresholds: the United States perspective. Osteoporos Int 19:437–447
46. Lekamwasam S, Adachi JD, Agnusdei D et al (2012) A framework for the development of guidelines for the management of glucocorticoid-induced osteoporosis. Osteoporos Int 23:2257–2276
47. Leslie WD, Rubin MR et al (2012) Perspective: diabetes and bone. J Bone Miner Res 27:2231–2237
48. Johansson H, Kanis JA, Oden A et al (2009) BMD, clinical risk factors and their combination for hip fracture prevention. Osteoporos Int 20:1675–1682
49. Kanis JA, Adams J, Borgstrom F et al (2008) The cost-effectiveness of alendronate in the management of osteoporosis. Bone 42:4–15
50. Cosman F, Nieves JW, Dempster DW (2017) Treatment sequence matters: anabolic and antiresorptive therapy for osteoporosis. J Bone Miner Res 32:198–202
51. Kendler DL, Marin F, Zerbini CAF et al (2018) Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial. Lancet 391:230–240 (Erratum Lancet 2018; 392: 2352)
52. Saag KG, Petersen J, Brandi ML et al (2017) Romosozumab or alendronate for fracture prevention in women with osteoporosis. N Engl J Med 377:1417–1427
53. National Institute for Health and Care Excellence (NICE) (2017) Bisphosphonates for treating osteoporosis. Technology appraisal guidance, vol 464. National Institute for Health and Care Excellence, London
54. Kanis JA, Rizzoli R, Cooper C et al (2014) Challenges for the development of bone forming agents in Europe. Calcif Tissue Int 94:469–473
55. Leder BZ, Tsai JN, Neer RM et al (2016) Response to therapy with teriparatide, denosumab, or both in postmenopausal women in the DATA (Denosumab and Teriparatide Administration) study randomized controlled trial. J Clin Densitom 19:346–351
56. Bone HG, Cosman F, Miller PD et al (2018) ACTIVExtend: 24 months of alendronate after 18 months of abaloparatide or placebo for postmenopausal osteoporosis. J Clin Endocrinol Metab 103:2949–2957
57. Shepstone L, Lenaghan E, Cooper C et al (2018) Screening in the community to reduce fractures in older women (SCOOP): a randomised controlled trial. Lancet 391:741–747
58. McCloskey E, Johansson H, Harvey NC et al (2018) Management of patients with high baseline hip fracture risk by FRAX reduces hip fractures—a post hoc analysis from the SCOOP Study. J Bone Miner Res 33:1020–1026
59. Parsons C, Harvey N, Shepstone L et al (2020) Systematic screening using FRAX® leads to increased use of, and adherence to, anti-osteoporosis medications: an analysis of the UK SCOOP Trial. Osteoporos Int 31:67–75. https://doi.org/10.1007/s00198-019-05142-z
60. Turner DA, Khioe RFS, Shepstone L et al (2018) The cost-effectiveness of screening in the community to reduce osteoporotic fractures in older women in the UK: economic evaluation of the SCOOP study. J Bone Miner Res 33:845–851
61. Borgström F, Jonsson E, Harvey N et al (2018) Cost-effectiveness evaluation of a screening programme for fracture risk in UK. J Bone Miner Res 33(Suppl 1):398
62. Rubin KH, Rothmann MJ, Holmberg T (2018) Effectiveness of a two-step population-based osteoporosis screening program using FRAX: the randomized Risk-stratified Osteoporosis Strategy Evaluation (ROSE) study. Osteoporos Int 29:567–578
63. Merlijn T, Swart KM, van Schoor NM et al (2019) The effect of a screening and treatment program for the prevention of fractures in older women: a randomized pragmatic trial. J Bone Miner Res 34:1993–2000. https://doi.org/10.1002/jbmr.3815
64. Kanis JA, Seeman E, Johnell O et al (2005) The perspective of the International Osteoporosis Foundation on the Official Positions of the International Society for Clinical Densitometry. Osteoporos Int 16:456–459
65. Kanis JA, Johansson H, Odén A et al (2011) A meta-analysis of the effect of strontium ranelate on the risk of vertebral and non-vertebral fracture in postmenopausal osteoporosis and the interaction with FRAX®. Osteoporos Int 22:2347–2355 (with erratum Osteoporos Int. 22: 2357-2358)
66. Harvey NC, Kanis JA, Odén A et al (2015) FRAX and the effect of teriparatide on vertebral and non-vertebral fracture. Osteoporos Int 26:2677–2684
67. Harvey NC, Kanis JA, Odén A et al (2015) Efficacy of weekly teriparatide does not vary by baseline fracture probability calculated using FRAX. Osteoporos Int 26:2347–2353
68. Kanis JA, Johansson H, Oden A et al (2010) A meta-analysis of the efficacy of raloxifene on all clinical and vertebral fractures and its dependency on FRAX. Bone 47:729–735
69. McCloskey EV, Johansson H, Oden A et al (2009) Ten-year fracture probability identifies women who will benefit from clodronate therapy—additional results from a double blind, placebo controlled randomised study. Osteoporos Int 20:811–818
70. Kanis JA, Johansson H, Oden A et al (2009) Bazedoxifene reduces vertebral and clinical fractures in postmenopausal women at high risk assessed with FRAX. Bone 44:1049–1054
71. McCloskey EV, Johansson H, Oden A et al (2012) Denosumab reduces the risk of all osteoporotic fractures in postmenopausal women, particularly in those with moderate to high fracture risk as assessed with FRAX®. J Bone Miner Res 27:1480–1486
72. Kanis JA, Harvey NC, Johansson H et al (2017) FRAX update. J Clin Densitom 20:360–367
73. Leslie WD, Lix LM, Johansson H et al (2012) Does osteoporosis therapy invalidate FRAX for fracture prediction? J Bone Miner Res 27:1243–1251
74. Kanis JA, Johansson H, Oden A et al (2011) Guidance for the adjustment of FRAX according to the dose of glucocorticoids. Osteoporos Int 22:809–816
75. Leslie WD, Lix LM, Johansson H et al (2011) Spine-hip discordance and fracture risk assessment: a physician-friendly FRAX enhancement. Osteoporos Int 22:839–847
76. Johansson H, Kanis JA, Oden A et al (2014) Impact of femoral neck and lumbar spine BMD discordances on FRAX probabilities in women: a meta-analysis of international cohorts. Calc Tiss Int 95:428–435
77. Leslie WD, Johansson H, Kanis JA et al (2014) Lumbar spine texture enhances ten-year fracture probability assessment. Osteoporos Int 25:2271–2277

78. McCloskey EV, Odén A, Harvey NC et al (2015) Adjusting fracture probability by trabecular bone score. Calcif Tiss Int 96:500–509
79. McCloskey EV, Odén A, Harvey NC et al (2016) A meta-analysis of trabecular bone score in fracture risk prediction and its dependence on FRAX. J Bone Miner Res 31:940–948
80. Leslie WD, Lix LM, Morin SM et al (2015) Adjusting hip fracture probability in men and women using hip axis length: the Manitoba Bone Density Database. J Clin Densitom 19:326–331
81. Masud T, Binkley N, Boonen S, Hannan MT et al (2011) Can falls and frailty be used in FRAX? J Clin Densitom 14:194–204
82. Leslie WD, Morin SN, Lix LM et al (2019) Fracture prediction from self-reported falls in routine clinical practice: a registry-based cohort study. Osteoporos Int 30:2195–2203
83. Johansson H, Odén A, Lorentzon M et al (2015) Is the Swedish FRAX model appropriate for immigrants to Sweden? Osteoporos Int 26:2617–2622
84. Leslie WD, Johansson H, McCloskey EV et al (2018) Comparison of methods for improving fracture risk assessment in diabetes: the Manitoba BMD Registry. J Bone Miner Res 33:1923–1930
85. Whitlock R, Leslie WD, Shaw J et al (2019) The Fracture Risk Assessment Tool (FRAX®) predicts fracture risk in patients with chronic kidney disease. Kidney Int 95:447–454
86. Johansson H, Siggeirsdóttir K, Harvey NC et al (2017) Imminent risk of fracture after fracture. Osteoporos Int 28:775–780
87. Brennan SL, Leslie WD, Lix LM et al (2014) FRAX provides robust fracture prediction regardless of socioeconomic status. Osteoporos Int 25:61–69
88. Leslie WD, Orwoll ES, Nielson CM et al (2014) Estimated lean mass and fat mass differentially affect femoral bone density and strength index but are not FRAX independent risk factors for fracture. J Bone Miner Res 29:2511–2519
89. Leslie WD, Morin SN, Lix LM et al (2019) Performance of FRAX® in women with breast cancer initiating aromatase inhibitor therapy: a registry-based cohort study. J Bone Miner Res 34:1428–1435
90. Giangregorio LM, Leslie WD (2010) Manitoba Bone Density Program. Time since prior fracture is a risk modifier for 10-year osteoporotic fractures. J Bone Miner Res 25:1400–1405
91. Balasubramanian A, Zhang J, Chen L et al (2019) Risk of subsequent fracture after prior fracture among older women. Osteoporos Int 30:79–92
92. Johnell O, Oden A, Caulin F et al (2001) Acute and long-term increase in fracture risk after hospitalization for vertebral fracture. Osteoporos Int 12:207–214
93. Johnell O, Kanis JA, Oden A et al (2004) Fracture risk following an osteoporotic fracture. Osteoporos Int 15:175–179
94. Kanis JA, Johansson H, Odén A et al (2018) Characteristics of recurrent fractures. Osteoporos Int 29:1747–1757