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Assessment of fracture risk with FRAX and FRAXplus

*Teck H.A. Tan,[1,2] Helena Johansson,[3,4] Nicholas C. Harvey,[5,6] Mattias Lorentzon,[3,4] John A. Kanis,[4,7] Eugene McCloskey,[7,8] and Marian Schini[7,8]**

[1]Fast and Chronic Programmes Alexandra Hospital Singapore; [2]Division of Endocrinology Department of Medicine National University Health System Singapore; [3]Sahlgrenska Osteoporosis Centre Department of Internal Medicine and Clinical Nutrition Institute of Medicine Sahlgrenska Academy University of Gothenburg Gothenburg Sweden; [4]Mary McKillop Institute for Health Research Australian Catholic University Melbourne Australia; [5]MRC Lifecourse Epidemiology Centre University of Southampton Southampton United Kingdom; [6]National Institute for Health and Care Research Southampton Biomedical Research Centre University of Southampton and University Hospital Southampton NHS Foundation Trust Southampton United Kingdom; [7]Centre for Metabolic Bone Diseases University of Sheffield Sheffield United Kingdom; [8]Division of Clinical Medicine School of Medicine and Population Health University of Sheffield Sheffield United Kingdom

Abstract

FRAX®, a risk calculator that provides individualized 10-year probabilities of hip and major osteoporotic fracture, has been widely used for fracture risk assessment since its launch in 2008. It is now incorporated into very many guidelines worldwide to inform osteoporosis management. In this review, we explore the development of FRAX and how it enhances fracture risk prediction as compared to use of bone mineral density alone, as well as approaches to utilizing FRAX in determining intervention and assessment thresholds. We also discuss the limitations of FRAX and the arithmetic adjustments that have been proposed to address these. The introduction of FRAXplus® includes these adjustments on a web-based platform for ease of application to enhance treatment decisions in osteoporosis.

KEYWORDS: *FRAX. FRAXplus. Osteoporosis. Fracture probability. Risk assessment. Epidemiology.*

Evaluación del riesgo de fractura con FRAX y FRAXplus

Resumen

El FRAX® es una calculadora de riesgo que estima de forma individual las probabilidades de riesgo de fractura a 10 años de la fractura de cadera y las fracturas mayores por osteoporosis. Que ha sido ampliamente utilizado desde 2008 cuando fue lanzado. Se encuentra incorporado a muchas guías de manejo y tratamiento en el mundo. En esta revisión, nosotros exploramos el desarrollo del FRAX® y como mejora la predicción del riesgo comparado con el uso de la densidad mineral ósea, así como diferentes formas de utilizar el FRAX® para determinar las intervenciones y los umbrales de evaluación. También discutimos las limitaciones del FRAX® y los ajustes matemáticos que se han propuesto para mejorar estas limitaciones. La introducción del FRAXplus® incluye estos ajustes en una plataforma de aplicación fácil que permite el mejorar las decisiones del tratamiento en la osteoporosis.

PALABRAS CLAVE: *FRAX. FRAXplus. Osteoporosis. Probabildad de fractura. Evaluación de riesgos. Epidemiología.*

***Correspondence:**
Marian Schini
E-mail: m.schini@sheffield.ac.uk

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Introduction

Osteoporosis is defined as a disease characterized by low bone mass and microarchitectural deterioration of bone tissue leading to enhanced bone fragility, and a consequent increase in fracture risk[1]. Since 1994, the diagnosis of osteoporosis has been based on bone mineral density (BMD) - defined as a BMD that is 2.5 standard deviations (SD) or more below the mean value of young women, that is, T-score ≤ −2.5 SD[2]. The reference range for calculating the T-score in both men and women is the Third National Health and Nutrition Examination Survey III database for femoral neck (FN) measurements in white women aged 20-29 years in the United States, as recommended by the international osteoporosis foundation (IOF), the national osteoporosis foundation, and the international society of clinical densitometry (ISCD)[3,4]. The use of BMD-based diagnostic thresholds was widely adopted as inclusion criteria for intervention trials in osteoporosis[5], and subsequently seen as intervention thresholds. While BMD forms a central component of fracture risk assessment, the accuracy of risk prediction is improved when other indices of fracture risk, particularly those that add information beyond that provided by BMD, are considered. Several risk prediction models have been developed, and the most widely used is the fracture risk assessment tool FRAX®. In this review, we discuss the role of FRAX in osteoporosis management, as well as recent developments to incorporate additional risk factors in its use.

Development of FRAX

FRAX is a computer-based algorithm first released in 2008 by the then World Health Organization Collaborating Center for Metabolic Bone Diseases in Sheffield, United Kingdom (UK)[6,7]. It estimates the 10-year probability of hip and major osteoporotic fracture (MOF: hip, clinical spine, distal forearm, or proximal humerus fracture) in postmenopausal women and men age 40 years or more. The algorithm integrates age, sex, body mass index (BMI), and seven dichotomized clinical risk factors (CRFs) comprising prior fragility fracture, parental history of hip fracture, current tobacco smoking, oral glucocorticoid use (> 3 months), rheumatoid arthritis (RA), excessive alcohol consumption (3 or more units per day), and other causes of secondary osteoporosis, to generate an average 10-year fracture probability. FN BMD can be optionally input to improve fracture prediction. Both the risk of fracture and risk of death are taken into account in generating fracture probability. This is important as individuals with a high risk of death have a lower fracture probability than those with a longer life expectancy; also, some of the risk factors affect both the risk of fracture and the risk of death, such as increasing age, low BMI, low BMD, glucocorticoid use, and smoking. Thus, in the elderly, the 10-year probability is in effect the remaining lifetime probability.

The performance of a risk assessment tool can be assessed by the gradient of risk - in the case of FRAX, as the increase in fracture risk per SD unit increase in risk score. Table 1 shows the gradients of risk for fracture prediction with the use of CRFs alone, FN BMD alone, and the combination. The use of CRFs in conjunction with BMD and age improves sensitivity of fracture prediction without adversely affecting specificity[8]. Overall, the predictive value of FRAX compares favorably with other risk engines such as the Gail score for breast cancer[9].

The use of CRFs alone provides comparable gradients of risk (1.4-2.1) to the use of BMD alone, but the best performance (highest gradients of risk) is observed when the combination is used, particularly in hip fracture prediction (Table 1). Importantly, there is a weak but significant correlation (r = −0.25) between the FRAX score without BMD and FN BMD, meaning that individuals with high fracture probabilities based on CRFs alone tend to have lower BMD[8,10]. By way of illustration, women aged ≥ 75 years with MOF probabilities above a threshold of 35% based on CRFs alone have a BMD 1 SD lower than those below the threshold[11]. This has obvious significance for case finding in the absence of access to BMD.

Validation and calibration of FRAX

FRAX has been validated in 11 independent cohorts that did not participate in the model synthesis. The use of CRFs alone or in combination with BMD gave gradients of risk that differed significantly from unity in all the validation cohorts, and were comparable to those in the original cohorts used for model building[8].

As age-specific rates of fracture and death differ within and across regions of the world[12,13], FRAX models are usually calibrated to the epidemiology of hip fracture (preferably from national sources; other MOF sites

Table 1. Gradients of risk with the use of femoral neck BMD, CRFs, or the combination

Age (years)	Gradient of risk		
	Femoral neck BMD alone	CRFs alone	CRFs + 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)

Data presented as relative risk per standard deviation change (95% confidence interval)[8]. Table reproduced with kind permission from Springer Science and Business Media.
BMD: bone mineral density; CRFs: clinical risk factors.

can be used if data are available) and mortality (usually derived from United Nations data) in individual countries, with models currently available for 84 countries/territories, covering well over 80% of the world population. The tool appears well-calibrated when examined in studies considered to include representative national populations, including the UK, Norway, Israel, Japan, Taiwan, and Canada[14-20].

The FRAX tool is currently available in 35 languages and is readily accessible through two websites (https://frax.shef.ac.uk/FRAX and https://www.fraxplus.org), as well as other technologies such as BMD equipment, smartphone applications and, in some countries, through hand-held calculators.

The use of FRAX in intervention and assessment

An important objective of fracture risk assessment is for interventions to be targeted appropriately to those at high fracture risk. The use of BMD T-score as the sole threshold for intervention is less than optimal as it has low sensitivity but high specificity for identifying individuals at high fracture risk, with the majority of fragility fractures occurring in those with BMD values above the osteoporosis threshold[19]. In addition, the same T-score threshold has a smaller impact on fracture probability with increasing age, due to increasing competing risk of death and decreasing BMD with age[20]. In contrast, a prior fragility fracture is a highly significant risk factor at all ages. Finally, fracture rates differ widely from country to country, much more so than can be explained by variations in BMD - a T-score corresponding to a 65 year-old woman with a 10-year MOF probability of 20% varies from −4.6 in Venezuela to −2.0 in Iceland[21]. When intervention thresholds are based on T-scores alone, individuals at high fracture risk but not meeting the densitometric definition of osteoporosis are denied appropriate treatment. This problem is exacerbated further in some health-care systems which limit reimbursement of treatment costs according to densitometric criteria[22,23], and/or the relative lack of access to DXA resources.

To address these limitations, intervention thresholds based on FRAX probabilities have been incorporated into more than 80 guidelines worldwide[24], though its application has been heterogeneous. Fixed intervention thresholds of 10-year probability of 20% or greater for MOF, or 3% or greater for hip fracture, based on a now-outdated economic analysis[25], are utilized in several guidelines, initiated originally by National Osteoporosis Foundation in the USA (now the Bone Health and Osteoporosis Foundation)[26,27]. However, this approach is problematic in the proportion of the population eligible for treatment, as illustrated by a study in Japanese postmenopausal women: < 1% of women under 60 years would ever attain a fracture probability threshold of ≥ 20%, while the use of a less stringent threshold of 10% would result in a majority of women over the age of 65 years, and more than 50% of all postmenopausal women, being eligible[28]. Thresholds based on cost-effective analyses are also time- and health-care system-dependent - costs of treatment change with time, and factors such as fracture risk, cost of fracture, and willingness to pay, among others, will vary across health-care systems.

The UK national osteoporosis guideline group (NOGG) was the first to develop guidelines incorporating age-dependent intervention thresholds[29,30]. Since women with a fragility fracture can be recommended treatment without requiring a BMD for the purpose of making a decision to treat, this "fracture threshold" - the age-specific fracture probability equivalent to women of average BMI with a prior fragility fracture - was set as the intervention threshold. This threshold rises with age, is independent of cost-effectiveness approaches to threshold setting but has been shown to be cost-effective in a UK setting[31]. The same age-dependent thresholds are also applied to men, since the effectiveness and cost-effectiveness of interventions in men are broadly similar to that in women for equivalent risk[32]. This approach to intervention thresholds has since been incorporated into guidelines across Europe, Eurasia, Middle East, and Latin America[33-40]. The NOGG thresholds were subsequently revised to flatten the threshold from the age of 70 years, as the previous thresholds required a higher risk of fracture, particularly hip fracture, for treatment to be indicated in women aged ≥ 70 years without a prior fracture, than those qualifying on the basis of fracture alone[41]. This resulted in a hybrid of both age-dependent and fixed thresholds for intervention (Fig. 1)[42].

The NOGG guideline also provides an example of the use of FRAX as a gateway to assessment: by delineating an upper assessment threshold (UAT), above which the patient is deemed at sufficiently high risk of fracture to be considered for treatment without recourse to BMD; and a lower assessment threshold (LAT), below which the patient is at low enough risk that a decision not to treat could be made without BMD. This focuses the use of BMD in the intermediate category to guide treatment - after the inclusion of BMD, patients with fracture probabilities exceeding the intervention threshold would merit treatment (Fig. 1). Approaches to defining the assessment thresholds differ according to availability (and reimbursement) of densitometry, and approach to diagnosing osteoporosis (e.g., a case-finding approach, compared to population-based screening). In the case of the NOGG Guidelines, the UAT has been set at 1.2 times the intervention threshold, as this was found to be the threshold above which almost no individuals will be reclassified from high to low risk with the addition of BMD to FRAX[29]. Based on a case-finding approach where assessment is targeted at individuals with CRFs, the LAT was set at the age-specific

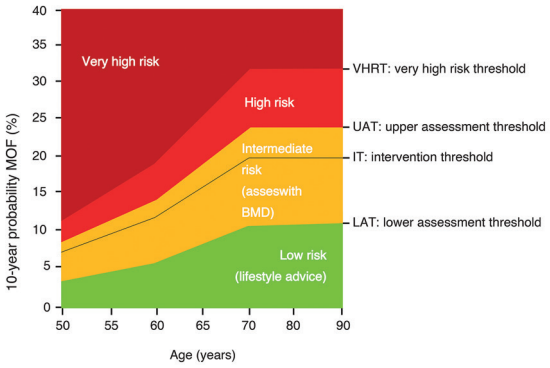

Figure 1. *National osteoporosis guideline group assessment, intervention, and risk thresholds for major osteoporotic fracture probability in the United Kingdom based on FRAX. Where assessment is made in the absence of bone mineral density (BMD), BMD assessment is recommended for individuals whose fracture probability falls between the upper assessment threshold and lower assessment threshold - intervention is recommended if the resultant probability lies above the intervention threshold. Treatment is recommended for individuals in the high risk and very high risk categories, with first-line anabolic therapies recommended for those at very high risk (see text)[42]. Reproduced with kind permission from Springer Science and Business Media.*

fracture probabilities of women of average BMI with no CRF. In countries with very limited or no access to DXA, FRAX can be used without BMD[43], since the use of CRFs alone provides gradients of risk comparable to those with the use of BMD alone.

Identifying those at very high risk

More recently, evidence demonstrating more rapid and greater fracture risk reduction with anabolic compared to antiresorptive treatment[44,45], as well as recognition that the risk of a subsequent osteoporotic fracture is particularly acute immediately after an index fracture and wanes progressively over time (termed "imminent risk")[46,47], led to the stratification of high risk to delineate a very high risk category[48], where the use of first-line anabolic treatment can be considered[49]. The approach to defining this very high-risk threshold varies - for example, the NOGG guidelines have set it at 1.6 times the age-specific intervention threshold (Fig. 1)[42,50], and the IOF-ESCEO guidelines at the UAT (1.2 times the intervention threshold)[33]. The American Association of Clinical Endocrinologists/American College of Endocrinology set the very high-risk threshold at 1.5 times the intervention threshold, that is, a hip fracture probability of 4.5% or a MOF probability of 30%[26]. In contrast, the

definition adopted by the US Endocrine Society guidelines is the presence of multiple vertebral fractures and hip or spine BMD T-score of −2.5 SD or below[51].

Screening with FRAX

The role of FRAX in population-screening has been examined in three large randomized prospective studies of potential population screening strategies[52-54], although with important differences in study design and approaches to intervention thresholds. The use of FRAX-based screening to identify and treat individuals at high fracture risk was observed to achieve a reduction in hip fractures in the screening for prevention of fractures in older women (SCOOP) trial in the UK and the risk-stratified osteoporosis strategy evaluation study in Denmark[52,53], while no significant difference in fracture rates was seen in the SALT osteoporosis study in the Netherlands[54]. A meta-analysis of all three studies showed a 20% reduction in hip fractures, and smaller but significant reductions in MOF and all osteoporotic fractures, despite treatment being targeted to only 11-18% of those in the screening arms[55]. In addition, the approach utilized in the SCOOP trial has been shown to be highly cost-effective and/or cost-saving[56,57]. These findings provide evidence that population screening of fracture risk is effective to reduce fractures.

Efficacy of intervention stratified by baseline fracture risk

FRAX has been applied in predominantly *post hoc* analyses of several phase 3 studies of osteoporosis therapies to determine the enrolment characteristics of study participants, and whether treatment efficacy varies according to baseline fracture risk. Strontium ranelate[58], teriparatide[59,60], abaloparatide[61], zoledronate[62], menopausal hormonal therapy,[63] and raloxifene displayed similar efficacy across a range of fracture probabilities[64], while clodronate[65], denosumab[66], romosozumab[67], and bazedoxifene had greater relative fracture risk reduction at higher baseline fracture probabilities[68]. Importantly, these results imply that pharmacological intervention, traditionally based on BMD thresholds in intervention trials, is equally effective in patients targeted based on FRAX on the basis of CRFs alone, without BMD. They also support the view of the regulatory agencies that treatments should be targeted preferentially to men and women at high fracture risk; utilizing treatments that show greater efficacy with higher baseline fracture risk improves the budget impact and cost-effectiveness of intervention. Finally, the findings of greater efficacy at higher fracture probabilities with some interventions have important implications for health technology assessments and challenges the current meta-analytic approach.

Addressing the limitations of FRAX - introduction to FRAXplus®

FRAX was intended for use in the primary care setting; hence, the CRFs included were carefully chosen to limit their number and complexity, for ease of input, and to include only well-validated, independent contributors to fracture risk. Furthermore, it was important that the factors identified a risk that was amenable to intervention - termed reversibility of risk[8]. While appreciated for its simplicity, an important limitation for which FRAX has been criticized is several of the CRFs identified do not take into account exposure response, such as the increase in fracture risk with increasing dose and duration of oral glucocorticoids, number of prior fractures, and magnitude of tobacco and alcohol exposure[24]. Concerns regarding the lack of provision for lumbar spine (LS) BMD (commonly recommended in treatment guidelines), and the absence of measurements of the material or structural properties of bone have also been highlighted. To address some of these limitations, a number of exploratory analyses have been conducted in population cohorts to examine the impact of factors outside of those included in FRAX, with access to these adjustments now being provided through the FRAXplus web-based platform (https://www.fraxplus.org). Importantly, FRAX probabilities have been shown to be largely unaffected by socioeconomic status[69], variation in body composition[70], exposure to aromatase inhibitors[71], and concurrent treatment for osteoporosis[72].

Recent fragility fracture

The risk of a subsequent osteoporotic fracture has been shown to be particularly acute immediately after an index fracture, and wanes progressively with time[73-75]. This “imminent risk” has also been found to be

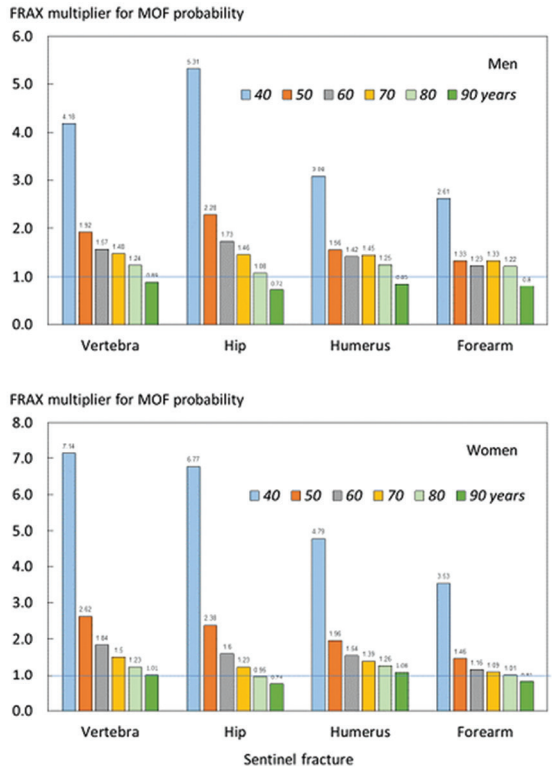

Figure 2. *Ratio of 10-year probabilities of a major osteoporotic fracture by age in men (top panel) and women (lower panel). The ratio is the 10-year probability of a major osteoporotic fracture for a recent fracture (within 2 years) at the sites shown divided by 10-year probability at any site irrespective of its recency[47]. Reproduced with kind permission from Springer Science and Business Media.*

age-dependent[46]. Analysis of a population-based cohort from Reykjavik, Iceland, provided a method for adjusting conventional FRAX estimates of fracture probability, derived using a prior fracture of uncertain recency, to take account of the impact of a known recent fracture within a 2-year interval[47]. The effect of recency is also site-dependent, as well as more marked in younger men and women (Fig. 2). In the elderly, a downward adjustment in fracture probabilities with a recent fracture can be seen, due to the incremental death hazard immediately following a recent fracture competing with the incremental fracture hazard. Importantly, even where the probability ratios fall below unity, those with a recent fracture still have a higher fracture probability than those without a prior fracture.

Number of prior fractures

Further, examination of the Reykjavik cohort also provided data for adjustment of fracture probabilities according to the number of prior fractures - as expected, the probabilities of both major osteoporotic and hip fracture increase with the number of past fractures[76]. Ten-year probabilities of hip fracture and MOF were determined according to the number of prior osteoporotic fractures over a 20-year interval from the hazards of death and fracture, and probability ratios derived by comparison to the probability calculated for prior fracture irrespective of the number of previous fractures. The ratios again provided adjustments to conventional FRAX estimates of fracture. Mean probability ratios according to the number of prior fractures for all scenarios were 0.95, 1.08, 1.21, and 1.35, for 1, 2, 3, and 4 or more prior fractures, respectively[76]. The increment in fracture probabilities with number of recent fractures diminished with increasing age, but was unaffected by sex.

Dose of oral glucocorticoids

The impact of oral glucocorticoid intake on fracture probabilities in FRAX assumes exposure to an average dose of oral glucocorticoids, though in reality, the risk of fracture is dependent on both dose and duration of exposure[77,78]. In an analysis of the general practice research database from the UK, comparisons were made between exposure to low dose (< 2.5 mg/day prednisolone or equivalent dose), medium dose (2.5 mg-7.5 mg/day), and high dose (> 7.5 mg/day) oral glucocorticoids, where medium dose was taken as the average exposure[79]. Exposure to higher doses of glucocorticoids was associated with increased risk of fracture. An assumption was made that higher doses of glucocorticoids were likely to be associated with a higher risk of mortality, either directly or as a consequence of the severity of underlying disease needing high-dose therapy. Hence, the increment in fracture probability was less than would be predicted only from the hazard ratio of fracture. The results from this study provided the basis for a simple arithmetic adjustment to conventional FRAX estimates of fracture probability in individuals exposed to high-dose oral glucocorticoids - an upward revision of 15% for MOF probability and 20% for that of hip fracture (i.e., multiplying the output probability by 1.15 and 1.20, respectively)[79].

Type 2 diabetes mellitus (T2DM)

T2DM is a risk factor for osteoporotic fracture despite being associated with higher BMD, and FRAX

underestimates this risk[80,81]. To address this, several methods have been proposed to improve the performance of FRAX for those with T2DM. These are as follows: using the RA input to FRAX as a proxy for the effect of T2DM; using the trabecular bone score (TBS) adjustment to the FRAX score; reducing the FN T-score input to FRAX by 0.5 SD in patients with diabetes; or increasing the age input to FRAX by 10 years in patients with diabetes. While no single method was optimal for all fracture outcomes and durations of diabetes, the use of the RA input was shown to be fairly effective in improving FRAX performance for prediction of both MOF and hip fractures[82], and is the simplest method for clinical application. FRAX probabilities can also be adjusted for duration of T2DM, with longer duration of disease associated with higher fracture risk[82].

Falls history

A history of falls was not incorporated into the FRAX model at the time of its development for several reasons - a lack of uniformly reliable data on falls history[83], insufficient evidence to support the contribution of falls risk to fracture risk prediction[84-86], as well as concerns that the fracture risk attributable to falls risk might not be amenable to pharmacological treatment[87]. Since then, assessment of falls risk has been shown to improve fracture prediction in addition to FRAX CRFs and BMD, irrespective of sex[88,89]. Several bone-targeted interventions have also been shown to lower increased fracture risk in patients with a history of falls[62,63,90,91]. A previous report from the ISCD and IOF Task Force suggested the application of a multiplication factor of 1.3 to the FRAX probability of hip fracture for each past fall (up to 5 falls)[83]. Analysis of the Manitoba cohort provided data for the adjustment of FRAX probabilities according to number of falls in the preceding year and age (Table 2)[92].

Concurrent data on LS BMD

As discussed above, the inclusion of FN BMD in the calculation of FRAX improves fracture risk prediction above that provided by CRFs alone. The preferential use of FN BMD over measurements from other sites relates principally to its wide availability in the development cohorts for FRAX. In addition, FN BMD is associated with a higher gradient of risk for hip fracture than BMD measurements at other skeletal sites, with similar or better prediction of MOF when appropriate adjustment is made[93,94]. However, there are instances when a large discordance in the T-scores at FN versus LS may occur, and the accuracy of risk prediction can be improved by accounting for this[95-97]. Analysis of multiple international cohorts found that discordance in FN and LS BMD T-scores contributes to fracture risk independently of FRAX probabilities that incorporate FN BMD alone[98]. In general, where the LS BMD T-score is lower than the FN BMD T-score by 1-2 SDs, and 2-3 SDs, the MOF probability is increased by 10% and 20%, respectively, with a corresponding decrease in MOF probability where the LS BMD T-score is greater than that of the FN. A more refined adjustment of the differences in BMD is included in FRAXplus.

TBS

TBS is an analytical tool that performs novel gray-level texture measurements on LS DXA images, thereby capturing information relating to trabecular microarchitecture[99]. A low TBS score is a predictor of fracture risk independently of FRAX and FN BMD[100,101]. Data from the Manitoba cohort have been used to derive an adjustment factor for FRAX probabilities when accounting for TBS[102]. The validity of this adjustment to FRAX was, further, explored in a meta-analysis of 14 cohorts (excluding Manitoba), with TBS shown to be a significant, independent predictor for fracture[103]. A recent review confirms the independent contribution of TBS to fracture prediction[99].

Hip axis length (HAL)

HAL, defined as the distance from the base of the greater trochanter to the inner pelvic brim, can be obtained from DXA reports. Longer-than-average HAL is associated with increased hip fracture risk irrespective of gender, with data from the Manitoba cohort showing a relative increase in hip fracture probability by 4.7% and decrease by 3.8% for every millimeter that HAL is above and below the sex-specific average, respectively[104].

Concomitant chronic medical conditions

The performance of FRAX has also been examined in cohorts with other chronic diseases known to influence fracture risk - chronic kidney disease[105], primary hyperparathyroidism[106], multiple sclerosis[107], and Parkinson's disease[108].

Table 2. Probability ratios for a MOF and HF in men and women by age according to the number of reported falls in the absence of BMD input into FRAX and when BMD is entered into FRAX

Age	No fall		1 fall		2 falls		≥ 3 falls	
	MOF	HF	MOF	HF	MOF	HF	MOF	HF
(a) In the absence of BMD								
40	0.90	0.89	1.23	1.28	1.54	1.71	2.02	2.57
45	0.90	0.89	1.23	1.28	1.53	1.70	2.01	2.56
50	0.90	0.89	1.23	1.27	1.51	1.67	1.96	2.51
55	0.91	0.89	1.22	1.27	1.48	1.64	1.91	2.43
60	0.91	0.90	1.21	1.26	1.43	1.58	1.83	2.32
65	0.91	0.90	1.20	1.25	1.36	1.51	1.71	2.18
70	0.92	0.90	1.19	1.24	1.30	1.40	1.63	1.95
75	0.92	0.91	1.18	1.21	1.22	1.28	1.52	1.72
80	0.93	0.92	1.16	1.19	1.15	1.20	1.41	1.56
85	0.93	0.93	1.15	1.17	1.10	1.13	1.33	1.43
90	0.94	0.93	1.14	1.16	1.10	1.13	1.32	1.41
(b) When BMD is entered								
40	0.92	0.91	1.19	1.21	1.46	1.54	1.88	2.24
45	0.92	0.90	1.20	1.22	1.47	1.55	1.91	2.28
50	0.92	0.90	1.20	1.22	1.45	1.54	1.88	2.26
55	0.92	0.90	1.19	1.22	1.43	1.52	1.84	2.22
60	0.92	0.91	1.19	1.21	1.39	1.48	1.77	2.15
65	0.92	0.91	1.18	1.22	1.34	1.44	1.68	2.06
70	0.92	0.91	1.18	1.20	1.29	1.35	1.62	1.90
75	0.92	0.91	1.18	1.19	1.23	1.27	1.54	1.74
80	0.92	0.92	1.17	1.19	1.17	1.20	1.45	1.62
85	0.93	0.92	1.17	1.18	1.12	1.14	1.38	1.51
90	0.93	0.92	1.17	1.18	1.12	1.15	1.39	1.52

From[92], reproduced with kind permission from springer science and business media. MOF: major osteoporotic fracture; HF: hip fracture; BMD: bone mineral density.

FRAXplus

While some of the arithmetic adjustments for conventional FRAX estimates of fracture probability as described above have been simplified for ease of clinical application, web-based algorithms allow for these adjustments to be performed more accurately and with ease. FRAXplus (https://www.fraxplus.org) allows for modulation of FRAX output for recency of osteoporotic fracture, high exposure to oral glucocorticoids, duration of T2DM, number of falls in the previous year, and concurrent information on LS, TBS, and HAL. At a population level, application of these adjustments could result in reclassification of individuals in relation to thresholds for intervention including reclassification between high and very high risk, thus affecting treatment decisions. An important caveat to the use of FRAXplus is that there is no evidence base available to inform on the accuracy of multiple adjustments, and a pragmatic approach would be to select the most dominant factor, that is, that which is likely to have the greatest clinical relevance for the estimated probability.

Update of FRAX

A planned update to FRAX has identified 64 eligible cohorts, comprising 2,138,428 participants (69% women) followed for approximately 20 million person-years, with 116,117 documented MOFs[109]. The larger analysis population, increased representation of men, and longer follow-up time will increase the general applicability of the tool and improve characterization of existing and novel CRFs for fracture, with exploration of sex-dependent differences, time-dependent effects, ethnicity effects where possible, and interaction terms. Two meta-analyses have been completed and others are in progress[110,111].

Conclusion

The FRAX fracture risk assessment tool provides country-specific algorithms for estimating individualized 10-year probability of MOF and hip fractures based on CRFs and BMD and improves decision-making in osteoporosis management over the use of BMD alone. The relationship between FRAX probabilities and treatment

efficacy is now well established and is expected to further influence treatment guidelines in the future. The FRAXplus website facilitates consideration of important clinical scenarios where adjustments in FRAX probabilities will affect assessment and treatment decisions.

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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

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