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POSITION PAPER

Interpretation and use of FRAX in clinical practice

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Abstract
Summary The introduction of the WHO FRAX® algorithms has facilitated the assessment of fracture risk on the basis of fracture probability. Its use in fracture risk prediction has strengths, but also limitations of which the clinician should be aware and are the focus of this review
Introduction The International Osteoporosis Foundation (IOF) and the International Society for Clinical Densitometry (ISCD) appointed a joint Task Force to develop resource

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documents in order to make recommendations on how to improve FRAX and better inform clinicians who use FRAX. The Task Force met in November 2010 for 3 days to discuss these topics which form the focus of this review.
Methods This study reviews the resource documents and joint position statements of ISCD and IOF.
Results Details on the clinical risk factors currently used in FRAX are provided, and the reasons for the exclusion of others are provided. Recommendations are made for the development of surrogate models where country-specific FRAX models are not available.
Conclusions The wish list of clinicians for the modulation of FRAX is large, but in many instances, these wishes cannot presently be fulfilled; however, an explanation and understanding of the reasons may be helpful in translating the information provided by FRAX into clinical practice.

Keywords Bone mineral density · Clinical risk factors · Fracture probability · Risk assessment

Preamble

In October 2009, the International Osteoporosis Foundation (IOF) and the International Society for Clinical Densitometry (ISCD) agreed to appoint a joint task force to review the strengths and limitations of FRAX under the flag of 'the FRAX initiative'. Several Task Forces were formed to develop resource documents based on literature reviews to answer specific queries on the use of clinical risk factors, the application of bone mineral measurements to FRAX and the epidemiological basis for its international development. In November 2010, the IOF and the ISCD held a joint meeting that invited the Task Force members, an independent panel of experts and an audience to debate the findings of the Task Force. The objective was to make recommendations to improve FRAX and better inform clinicians who use this tool. An outcome of the conference was a position development paper, endorsed by both organisations and published in the *Journal of Clinical Densitometry* [1] and the clinical review in this paper. Papers to support the position statements and a selection of the resource documents are to be published in the *Journal of Clinical Densitometry* and *Archives of Osteoporosis*, respectively. The Task Force membership and Expert Panel are listed at the end of this manuscript.

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Introduction

FRAX® is a computer-based algorithm (http://www.shef.ac.uk/FRAX) developed by the World Health Organization Collaborating Centre for Metabolic Bone Diseases and first released in 2008. The algorithm, intended for primary care, calculates fracture probability from easily obtained clinical risk factors (CRFs) in men and women [2–4]. The output of FRAX is the 10-year probability of a major osteoporotic fracture (hip, clinical spine, humerus or wrist fracture) and the 10-year probability of hip fracture.

Probability is calculated from age, sex, body mass index (BMI) and dichotomized risk factors comprising prior fragility fracture, parental history of hip fracture, current tobacco smoking, ever use of long-term oral glucocorticoid use, rheumatoid arthritis, other causes of secondary osteoporosis and high alcohol consumption (Fig. 1). Femoral neck bone mineral density (BMD) can be optionally input to enhance fracture risk prediction [5]. 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 the risk of death as well as the fracture risk. Examples include increasing age, sex, low BMI, low BMD, use of glucocorticoids and smoking. Other risk algorithms calculate the probability of a clinical event without taking into account the possibility of death from other causes [6, 7]. In addition, the FRAX® models are calibrated for different countries using country-specific fracture and mortality rates.

The relationships between risk factors and fracture probability have been constructed using information derived from the primary data of nine population-based cohorts from around the world, including centres from North America, Europe, Asia and Australia. Clinical risk factors for fracture were identified that provided independent information on fracture risk based on a series of meta-analyses. The FRAX algorithm has been validated in 11 independent cohorts with a similar geographic distribution with in excess of 1 million

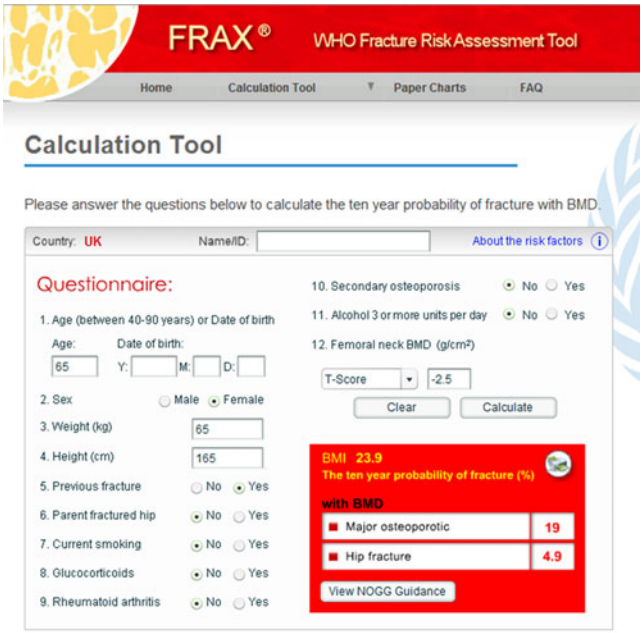

Fig. 1 Screen page for the input of FRAX variables (UK model, version 3.2. http://www.shef.ac.uk/FRAX)

patient-years [5]. The use of primary data for the model construct permits the determination of the predictive importance in a multivariable context of each of the risk factors, as well as interactions between risk factors, and thereby optimises the accuracy by which fracture probability can be computed [8, 9].

Fracture probability varies markedly in different regions of the world [10]. Thus, the FRAX® models need to be calibrated to those countries where the epidemiology of fracture and death is known. Models are currently available for 31 countries across the world: Argentina, Australia, Austria, Belgium, Canada, China, Denmark, Taiwan, Colombia, Finland, France, Germany, Hong Kong, Hungary, Italy, Japan, Jordan, Lebanon, Malta, Mexico, the Netherlands, New Zealand, Philippines, Singapore, South Korea, Spain, Sweden, Switzerland, Turkey, the UK and the USA. The model is available in 13 languages: Arabic, English, traditional and simplified Chinese, Danish, Finnish, French, German, Japanese, Polish, Russian, Spanish, Swedish and Turkish.

The obvious application of FRAX is in the assessment of individuals to identify those who would be candidates for BMD screening or pharmacological intervention. Other uses of FRAX, for guideline development, drug registration and health economic applications, are reviewed elsewhere [11, 12]. It has been widely used for the assessment of patients since the launch of the website in 2008 and currently receives about 200,000 hits per working day. Following regulatory review by the US Food and Drug Administration, FRAX was incorporated into DXA scanners to provide FRAX probabilities at the time of DXA scanning. For those without internet access, handheld calculators and an application for the iPhone® and iPad® have been developed by the IOF (http://itunes.apple.com/us/app/frax/id370146412?mt=8). The FRAX pad allows patients to input risk variables prior to medical consultation and is available from the IOF (www.iofbonehealth.org) in several languages.

FRAX is now, or is in the process of being, incorporated in many clinical guidelines [13–27]. Despite the wide acceptance of the tool, FRAX should not be considered as a gold standard in patient assessment, but rather as a reference platform. The same argument applies to BMD testing. Thus, the fracture risk estimates derived from FRAX (or BMD alone) should not be uncritically used in the management of patients without an appreciation of its limitations as well as its strengths (Table 1). In some instances, limitations (e.g. to experts in bone disease) are perceived as strengths to others (e.g. primary care physicians). Several of these limitations (perceived and real) were considered by the IOF–ISCD Task Forces and are discussed below.

Clinical risk factors currently used in FRAX

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 [3].

The FRAX tool has been appreciated for its simplicity for use in primary care but criticised for the same reason because it does not take account of exposure response. For example, the risk of fracture increases with exposure to glucocorticoids, but FRAX only accommodates a yes/no response to the relevant question. Other well-researched examples of ‘dose–response’ include the number of prior fractures and the consumption of alcohol. If FRAX is to be made more accurate by the inclusion of different degrees of exposure, then information is required not only on the risk of fracture associated with these exposures but also on their dependence on the other risk variables in FRAX and their independent effect on the death hazard. This demands the collection of new population cohorts that include such information as well as the other FRAX variables in sufficient numbers and with wide geographical representation. In the meanwhile, the available research information can inform the clinician how to temper clinical judgement on the existing output of the FRAX models.

Prior fragility fracture

The FRAX tool inputs a history of a prior fragility fracture asking for a yes/no response. There is, however, good evidence that the risk of fracture depends on the number of

Table 1 Strengths and limitations of FRAX

Perceived strengths	Perceived limitations
Derives a probability of fracture, i.e. accounts for life expectancy	
Can be used with or without BMD	Absence of low BMD may influence therapeutic response
Applicable to men (aged 50 years+) as well as postmenopausal women	Not suitable for young men and women with secondary causes of osteoporosis
Constructed from meta-analyses of CRFs in prospective population-based cohorts worldwide	Important risk variables not included
Readily administered in primary care	Does not take account of exposure effect (e.g. dose of glucocorticoids, number of prior fractures)
Simple to administer	Simpler models do just as well
Multiple access (web, iPhone, paper charts, hand held calculators, densitometry equipment, FRAX pad for patients)	These technologies not universally available
31 country-specific models	Not all countries available due to limitations in epidemiology
Designed for primary care	Not all CRFs are included, e.g. falls, markers of bone turnover, prior treatment
Worldwide validation	Not validated in all countries
BMD input based on a well-validated site (femoral neck) that can be standardised across manufacturers	Does not incorporate other bone mineral assessments, e.g. QUS, lumbar spine
Ethnic-specific models available for the USA and Singapore	Does not take account of geographic variation within countries
Models can be updated with new fracture and death risks	The models become outdated because of new information
Stimulates new epidemiological research	
Informs practice guidelines	Global intervention thresholds cannot be derived
Informs drug development and registration	Must be incorporated in new drug development (in the EU)
Can be used in cost-effectiveness analyses	Complicates health technology assessment
Leaves room for clinical judgement	Leaves room for clinical judgement
Identifies a risk amenable to a therapeutic intervention (HT, raloxifene, bazedoxifene, risedronate, clodronate, strontium ranelate, denosumab)	Reversibility of risk challenged in the case of alendronate

QUS quantitative ultrasonography, *HT* hormone therapy

prior vertebral fractures (Table 2). Indeed, both the number and severity of vertebral fractures add information to future fracture risk assessment [28–32]. The evidence is less clear that the number of prior fractures at other sites is a determinant of fracture risk, though there is good evidence that past vertebral, humeral and hip fractures are more

Table 2 Risk ratio for fracture according to the number of prior morphometric vertebral fractures

	Outcome fracture	Number of fractures[a]	Sex	Number of prior fractures				Setting
				0	1	2	3+	
Black [28]	Vertebral	389	F	1.0	3.2	5.4	10.6	Population base
Lunt [29]	Vertebral	679	M+F	1.0	3.2	9.8	23.3	Population base
Delmas [30]	Vertebral	157	F	1.0	3.1	4.4	8.4	RCT
Siris [31]	Vertebral	217	F	1.0	3.1	5.5	8.6	RCT[c]
Puisto [32]	Hip	182	M+F	1.0	1.2	1.5		Population base
Black [28]	Non-vertebral	2433	F	1.0	1.6	1.9	2.2	Population base
Black [28]	Hip	464	F	1.0	2.0	2.2	2.8	Population base
Delmas [30]	Non-vertebral	31	F	1.0	1.3[b]	1.8[b]	1.4[b]	RCT
Black [28]	Forearm	574	F	1.0	1.4	1.5	1.4[b]	Population base

[a] Number of incident fractures

[b] Not significant

[c] Includes patients in Delmas et al. [30]

predictive of future fractures than are fractures at other sites [33].

For the reasons noted above, there are insufficient data available for the adjustment of the current FRAX models to include information on the number, site and severity of past fractures. With regard to the number of prior fractures, it should also be recognised that the cohorts used to build FRAX included individuals with a prior fracture irrespective of their number (which was inconsistently documented). Thus, the probability assessment is based on the risk associated with a single, two and more than two previous fractures. Since the ratios of men and women with these characteristics are not known, this further complicates any adjustment of FRAX. In the absence of quantitative information, the clinician should recognise that fracture probabilities should be upward revised in patients with a history of multiple prior fractures (i.e. more than average) and greater weight accorded to a prior vertebral, hip or humeral fracture than to fractures at other sites.

Long-term use of oral glucocorticoids

Ever use of systemic glucocorticoids is a dichotomous risk factor (yes/no) in FRAX and does not therefore take account of the dose of glucocorticoids. Neither does it take account of the duration of its use, except that exposures of less than 3 months should not be taken into account [34]. For longer-term use, FRAX assumes an average risk, providing hazard ratios for an average dose and duration of exposure to glucocorticoids [35]. The most extensive assessment of dose–response effects of glucocorticoids on fracture risk is found in the studies of van Staa et al [36–38] which examined the general practitioner records of the UK using the General Practice Research Database (GPRD). As might be expected, higher than medium daily doses of oral glucocorticoids (2.5–7.5 mg prednisolone or equivalent) were associated with higher risks of fracture and vice versa (Table 3).

Kanis et al. have recently explored the possible impact of different doses of glucocorticoids on fracture probability using the UK FRAX model and the fracture risks reported in GPRD [39]. Relatively simple arithmetic procedures were formulated which can be applied to conventional FRAX estimates of probabilities of hip fracture and a major osteoporotic fracture to modulate the probability assessment with knowledge of dose of glucocorticoids (Table 4).

As expected, probabilities were dose dependent with higher probabilities associated with the high dose and vice versa. At medium doses (2.5–7.5 mg daily or equivalent), the unadjusted FRAX value can be used. For low-dose exposure (<2.5 mg daily of prednisolone or equivalent), the probability of a major fracture was decreased by about 20% depending on age. For high doses (>7.5 mg daily), probabilities can be upward revised by about 15%. Conversion factors were also determined for the adjustment of hip fracture probability. It is important to note that the adjustments to FRAX in Table 4 were derived from the UK version of FRAX and dose–responses (also from the UK) in an independent study without the possibility of examining the impact of different doses on all other FRAX risk factors. This and a large number of other assumptions were made so that caution should be exercised on the use of the adjustment factors until they are independently validated.

This caveat aside, it is important to note that the increment in fracture probability was less than would be predicted only from the hazard ratio of fracture. For example, the hazard ratio for hip fracture between the medium and high dose (hazard ratio=1.28) would predict a 28% higher hip fracture probability with the high dose, whereas the calculated increment was 18% (rounded to 15% in Table 4). Conversely, fracture probabilities were reduced with the low dose compared to the medium dose but by less than that expected from the hazard ratio for fracture. The reason is that glucocorticoid exposure increases the risk of death as well as for fracture and both compete, therefore in the calculation of fracture probability.

FRAX does not take account of the duration of exposure to glucocorticoids. There is evidence that higher cumulative doses impart a higher fracture risk [36, 37]. Intermittent use of glucocorticoids will also increase fracture risk with higher doses and more frequent use leading to greater risk [34]. Because of the variability in dose and schedule of dosing, quantification of this risk is not possible. Low doses of inhaled glucocorticoids, most commonly given for chronic obstructive pulmonary disease (COPD) or asthma, are not associated with an increase in fracture risk [34]. By contrast, a meta-analysis suggests that inhaled doses of

Table 3 Adjusted relative risk (95% CI) of fracture compared to controls according to dose of oral glucocorticoids [36] (with permission)

Fracture outcome	Low dose (n=50,649)	Medium dose (n=104,833)	High dose (n=87,949)
Non-vertebral	1.17 (1.10–1.25)	1.36 (1.28–1.43)	1.64 (1.54–1.76)
Forearm	1.10 (0.96–1.25)	1.04 (0.93–1.17)	1.19 (1.02–1.39)
Hip	0.99 (0.82–1.20)	1.77 (1.55–2.02)	2.27 (1.94–2.66)
Vertebral	1.55 (1.20–2.01)	2.59 (2.16–3.10)	5.18 (4.25–6.31)

Table 4 Percentage adjustment of 10-year probabilities of a hip fracture or a major osteoporotic fracture by age according to dose of glucocorticoids [39] (with kind permission from Springer Science+Business Media B.V.)

Dose	Prednisolone equivalent (mg/day)	Age (years)						All ages
		40	50	60	70	80	90	
Hip fracture								
Low	<2.5	−40	−40	−40	−40	−30	−30	−35
Medium[a]	2.5–7.5							
High	≥7.5	+25	+25	+25	+20	+10	+10	+20
Major osteoporotic fracture								
Low	<2.5	−20	−20	−15	−20	−20	−20	−20
Medium[a]	2.5–7.5							
High	≥7.5	+20	+20	+15	+15	+10	+10	+15

[a] No adjustment

beclomethasone above 800 μg/day are associated with a small increase in fracture risk [40]. The relative risks for any fracture and hip fractures were 1.30 (95% confidence interval (CI)=1.07–1.58) and 1.32 (95% CI=0.90–1.92), respectively. It should be noted that COPD itself is a risk factor for fracture, so that the association may not be causal [41]

Consumption of alcohol

The input to FRAX asks for a positive entry if the patient takes three or more units of alcohol daily. A unit of alcohol varies slightly in different countries from 8 to 10 g of alcohol. This is equivalent to a standard glass of beer (285 ml), a single measure of spirits (30 ml), a medium-sized glass of wine (120 ml) or one measure of an aperitif (60 ml). Intake of alcohol appears to have a dose-dependent effect, i.e. the higher the exposure, the greater the risk. This is not taken into account and the computations in FRAX assume average exposure in those above or below the limit. Clinical judgement should be used for low or high exposures, and some guidance is given in Table 5, which is drawn from the meta-analysis used for the population of the FRAX models [42]. Risk ratios were similar in men and women, though the prevalence of high intakes of alcohol is higher in men than in women.

Table 5 Hazard ratio and 95% CI according to intake of alcohol in men and women combined with and without BMD [42] (with kind permission from Springer Science+Business Media B.V.)

Category (units/day)	Without BMD		With BMD	
	RR	95% CI	RR	95% CI
Osteoporotic fracture				
3 or more	1.38	1.16–1.65	1.36	1.13–1.63
4 or more	1.55	1.26–1.92	1.53	1.23–1.91
5 or more	1.70	1.30–2.22	1.64	1.24–2.17
Hip fracture				
3 or more	1.68	1.19–2.36	1.70	1.20–2.42
4 or more	1.92	1.28–2.88	2.05	1.35–3.11
5 or more	2.26	1.35–3.79	2.39	1.39–4.09

95% CI 95% confidence intervals

A similar conclusion was reached in another independent meta-analysis published by Berg and colleagues [43]. A more recent meta-analysis was undertaken for the FRAX initiative [44], which showed no significant effect of alcohol exposure below an intake of 6 U/day. Unfortunately, the analysis was not based on individual data and was dominated by a large study of 2.3 million women in whom general practitioner records were used of unknown but dubious validity [6].

Parental history of fracture

FRAX enquires for a history of hip fracture in the patient's mother or father which is entered as a yes/no response. It might be expected that a family history of fracture at other sites would be a risk factor and there is some evidence to support this view [33, 45–47]. The effect, however, is small and in the FRAX cohorts, for example, a family history of any osteoporotic fracture amongst first degree relatives was associated with a small but significant increase in fracture risk in women (relative risk (RR)=1.21; 95% CI=1.09–1.35). The association was stronger when hip fracture was the outcome measured (RR=1.40; 95% CI=1.09–1.80).

It has been suggested that a family history in any first degree relative would be a better variable to use in FRAX than a parental history. This would increase the prevalence of the risk factor. A sibling history of any osteoporotic fracture was associated with a small increase in fracture risk in women (RR=1.13; 95% CI=0.94–1.36) but in neither case was the association significant [47]. FRAX elected to use a parental history of hip fracture because of the strong and consistent association and to exclude a sibling history, since the probability of a sibling varies markedly worldwide.

On this basis, it is difficult to give firm advice on the further interpretation of FRAX probability estimates outside the limits of the FRAX questionnaire that is supported by an evidence base. In the future, it will be important to assess the independent contribution of genetic risk markers to fracture probability in large epidemiologic cohorts.

Current tobacco smoking

Tobacco smoking is entered into FRAX as yes or no depending on whether the patient currently smokes tobacco. The fracture risks are derived from meta-analyses of the WHO cohorts [48] and are consistent with other large surveys [49, 50]. There is some evidence for dose–response effects on fracture risk [51]. First, the risk is higher in men than in women, possibly related to the higher exposure in men [48]. Second, the risk of hip fracture rises progressively with age [48, 49], possibly related to the duration of exposure. Third, the risk is lower in ex-smokers compared with current smokers [48, 51]. These observations are consistent with a dose–response relationship but do not provide information that helps in the interpretation of FRAX probabilities. In addition, smoking increases the mortality risk which may offset in part or in whole the increase in fracture risk.

Rheumatoid arthritis

Although input for rheumatoid arthritis in the FRAX algorithm is a dichotomous variable, intuitively, one would expect that more severe or active disease would be associated with more severe osteoporosis. Associations have been reported between functional disability and clinical fracture risk in patients with rheumatoid arthritis [52], but evidence is limited that more severe or active disease is associated with a greater risk for fracture. There is also little evidence that interventions for rheumatoid arthritis (other than glucocorticoids) adversely affect fracture risk. Indeed, anti-TNF therapies may have beneficial effects on bone mineral density [53] though the impact on fracture risk is unknown.

The risk associated with rheumatoid arthritis may be underestimated by FRAX due to reporting bias. The prevalence of rheumatoid arthritis in the FRAX cohorts is approximately 4% [35], whereas the true prevalence in the general population may be closer to 1–2%. Thus, the apparent risk may be diluted somewhat by patients reporting osteoarthritis as rheumatoid arthritis. Osteoarthritis is, if anything, protective. The underestimate may be partly offset by improved therapy of rheumatoid arthritis, though this remains to be quantified. Nonetheless, reliance should not be placed on a patient's report of 'arthritis' unless there is clinical or laboratory evidence to support the diagnosis.

Risk factors not considered in FRAX

Many clinicians have a wish list of risk factors not considered in FRAX. These include enlargement of the number of secondary causes of osteoporosis, the inclusion of falls risk, markers of bone turnover and bone mineral measurements at other sites (e.g. lumbar spine) and with technologies other than DXA (e.g. quantitative ultrasonography, QUS).

Other causes of secondary osteoporosis

Many clinicians have suggested secondary causes of osteoporosis that should be considered in FRAX. For example, it has been noted that there are more than 80 causes of secondary osteoporosis given in the US Surgeon General's report on osteoporosis [54] of which a minority are described in FRAX [55]. Of the many secondary causes of osteoporosis, those in Table 6 have been consistently documented to be associated with a significant increase in fracture risk. With the exception of chronic obstructive pulmonary disease [56, 57], these remain as listed in the Technical Report on FRAX [3]. Of these, their effect on fracture risk can usually be explained by the effect of the disease on decreasing bone density. Rheumatoid arthritis is the only secondary cause of osteoporosis that is considered independent of BMD in the FRAX algorithm [35]. Whereas this may hold true for some other secondary causes of osteoporosis, the evidence base is weak.

Falls

A criticism of the FRAX model by some users has been the lack of consideration of falls or falls risk in predicting fractures. A remit of the FRAX Clinical Task Force was to review the evidence and consider if falls should be incorporated into the FRAX model or alternatively provide guidance to clinicians on how a history of falls should be used in conjunction with FRAX in clinical decision making.

The Task Force strongly recommended that falls should be incorporated into FRAX [58]. Whereas this view is a sound academic conclusion from the literature on falls risk, the incorporation into FRAX is problematic for several reasons. First, existing data are not of adequate quality to incorporate quantitative adjustment to FRAX at the present time. Information on falls was available in a minority of cohorts used to derive or validate FRAX. In addition, the construct of questions on falls was very heterogeneous, and perhaps for this reason, meta-analysis showed no significant increase in fracture risk (E McCloskey, JA Kanis, H Johansson, unpublished data provided to the Task Force, 2010).

Second, falls risk is inherently taken into account in the algorithm, though not as an input variable. Thus, the fracture probability given for any combination of risk

Table 6 Secondary causes of osteoporosis associated with an increase in fracture risk (adapted from [3]; with permission from the WHO Collaborating Centre for Metabolic Bone Diseases, University of Sheffield Medical School)

Secondary cause	Example
Glucocorticoids	Any dose, by mouth for three months or more
	High doses of inhaled glucocorticoids
	Cushing's disease
Rheumatoid arthritis	
Chronic liver disease	Alcoholism
Untreated hypogonadism in men and women	Bilateral oophorectomy or orchidectomy
	Anorexia nervosa
	Chemotherapy for breast cancer
	Tamoxifen in premenopausal women
	Aromatase inhibitors
	GnRH inhibitors for prostate cancer
	Hypopituitarism
Prolonged immobility	Spinal cord injury
	Parkinson's disease
	Stroke
	Muscular dystrophy
	Ankylosing spondylitis
Organ transplantation	
Type I diabetes	
Thyroid disorders	Untreated hyperthyroidism
	Over-treated hypothyroidism
Gastrointestinal disease	Crohn's disease
	Ulcerative colitis
Chronic obstructive pulmonary disease	

factors assumes that the falls risk is that observed (but not documented) in the cohorts used to construct FRAX. In this regard, it is of interest that a small study in a hospital setting showed that FRAX identified fallers who fracture with a higher predictive value than the STRATIFY (St. Thomas risk assessment tool in falling elderly) [59] instrument designed to predict falls [60]. In order to incorporate the falls risk, the fracture risk must first be quantified in the FRAX cohorts for individuals who do not fall frequently. These data do not exist in sufficient cohorts. Third, the interrelationship of falls risk with the other FRAX variables has been inadequately explored on an international basis. Fourth, the relationship between the risk variable and mortality needs to be accounted for, but there are no data available.

These technical problems aside, FRAX is intended to identify a risk that is amenable to a therapeutic intervention. In a single study, a post hoc analysis of a community-based intervention study with clodronate in elderly women [61] showed that fracture reduction was similar in women with or without recent multiple falls or in those with impaired ability in rising from a chair [62]. This finding suggests that falls or falls risk may identify a risk amenable to intervention. In contrast, in the phase III trial of risedronate, where hip fracture was the primary end point, hip fracture risk was not significantly decreased in patients over the age of 80 years, the majority of whom were purportedly selected on the basis of falls risk [63]. Thus, more data are required before falls can be safely incorporated into assessment algorithms.

Unfortunately, falls risk is not routinely incorporated into phase III studies of osteoporosis treatment. In contrast, the risk factors used in the current version of FRAX have all undergone a thorough investigation in the majority of phase III studies to determine that they identify a risk amenable to therapeutic intervention—'reversible risk' or more accurately—reversibility of risk [11, 12].

It has been argued that falls can be prevented and that this provides a further reason for the inclusion of falls risk in FRAX [58]. However, the relevant question is whether intervention for falls decreases the risk of fracture. Whereas some studies report that falls may be prevented by multidimensional interventions, the evidence that these reduce the risk of fracture is plausible but not proven in meta-analysis [64–66], with the possible exception of exercise interventions. There is also evidence that vitamin D may decrease the risk of fracture by preventing falls [67], but this is uncertain [64]. The case for incorporating falls into risk algorithms would be strengthened by knowledge that the treatment of falls risk can reduce fracture risk. In the

absence of this information, risk assessment algorithms that incorporate falls fail in their primary intent [6, 7].

Thus, it is not possible to provide good clinical advice to clinicians on how a history of falls should be used in conjunction with FRAX in their clinical decision making, despite recommendations to the contrary [58]. The only sound advice is that individuals who fall more frequently than average are likely to have a higher fracture probability than that provided by FRAX. The obverse is also true in that individuals who fall less frequently than average are likely to have a lower fracture probability than that provided by FRAX.

Biochemical markers of bone turnover

Bone turnover markers (BTMs) reflect the metabolic activity of bone. They are traditionally categorised as markers of bone formation or bone resorption. Oestrogen deficiency, associated with menopause, results in a generalised increase in bone remodelling and an imbalance between bone formation and resorption that is maintained for several decades after the menopause and is associated with accelerated bone loss and fracture risk [68]. Thus, it is logical to consider that high bone turnover might predict fracture and a large number of studies support this view [69–72]. The evidence is less convincing in men. Some, but not all, studies have shown that in women with a low BMD, the presence of increased BTMs has an effect on fracture risk that is independent of BMD. This has led to calls for the incorporation of these markers into FRAX.

There are a number of limitations to the incorporation of markers into risk prediction models. They include their biological variability and, in some cases, the multiple methodologies used for the same analyte (e.g. the assays for osteocalcin). It is not surprising, therefore, that associations between markers and fracture outcomes have been heterogeneous [68]. Moreover, there are few studies that have examined the interactions between the BTMs and other FRAX variables and none that takes an international perspective.

For these reasons, it is not yet possible to provide information that helps in the interpretation of FRAX probabilities. In the future, it is expected that the adoption of reference analytes and analytical standards will allow studies to be pooled more easily and determine their role in fracture risk assessment [68].

Assessment of BMD at the lumbar spine and elsewhere

Lumbar spine BMD is frequently measured by DXA and indeed is incorporated into several clinical guidelines including those of ISCD [13, 23, 73, 74]. It is the site favoured for monitoring treatment, and there is thus much interest in the incorporation into FRAX of measurements at the lumbar spine. The same is true for peripheral measurements (and QUS) where there are no facilities for central DXA.

The femoral neck is the only skeletal region of interest currently validated for use with FRAX [3]. The T-score derived from measurement of BMD at the femoral neck by DXA is also the WHO international reference standard for the diagnosis of osteoporosis [2, 75]. It has the advantage that for any given age and BMD, the fracture risk is approximately the same in men and women [76]. Because of this, the T-score used in FRAX is derived from a single reference standard (the NHANES III database for female Caucasians aged 20–29 years) [77].

The principal reason for the use of femoral neck BMD in FRAX was the wide availability of measurements at this site. For example, in the meta-analysis of the source cohorts used to construct FRAX, femoral neck BMD was available in about 40,000 individuals whereas information was available in approximately half this number for BMD at the lumbar spine [76] and half again for BMD at peripheral sites. Moreover, femoral neck BMD is associated with a higher gradient of risk (increase in fracture risk/unit decrease in BMD) for hip fracture than BMD measurements at the lumbar spine [78]. The same probably holds true for the prediction of major fractures when appropriate adjustment is made to the units of BMD [79]. Notwithstanding, measurements of BMD at sites other than the femoral neck provide significant information on fracture risk [76, 78, 79].

In the absence of specific models that incorporate BMD at the lumbar spine, the question arises whether lumbar spine BMD or the T-score might be used in FRAX where information is lacking on femoral neck BMD. The short answer is no. A major impediment is that the age-related decrease in T-score differs at different skeletal sites [80] and that the gradient of risk (the increase in fracture risk/unit decrease in BMD) for specific fracture outcomes is known to differ by site [78]. Additional difficulties include the age-related degenerative changes at the lumbar spine, the uncertain interactions of spine measurements with the other FRAX variables and the lack of an international reference standard for lumbar spine BMD [81].

Although the measurement of two skeletal sites does not improve the general performance characteristics (sensitivity/specificity) of the BMD test in a given population [82–84], there are situations where there is a large discordance in the T-score at different skeletal sites in individuals for whom the use of this information will enhance the accuracy for the characterisation of risk, particularly if they lie close to an intervention threshold. An example is provided from the Canadian guidelines that recommend treatment in men and women with 10-year probabilities for a major fracture that exceed 20% [23]. A 70-year-old woman with a maternal

history of hip fracture, a BMI of 22 kg/m^2 and a T-score of −2.2 SD at the femoral neck has a fracture probability of 19% when calculated with FRAX (Canadian model, version 3.1). With a T-score of −3.5 SD at the lumbar spine, it is expected that her true risk would be higher and likely lie above the treatment threshold of 20%. The impact of spine/femoral neck T-score discordance has recently been explored in a large BMD-referral population from Manitoba, Canada. Fracture outcomes were available over a 10-year time frame. There was an approximately 10% change in fracture risk for each unit of T-score discordance [85].

On this basis, the authors propose that the clinician may 'Increase/decrease FRAX estimate for a major fracture by one-tenth for each rounded T-score difference between the lumbar spine and femoral neck'. An example is provided in the case above in which the T-score for femoral neck BMD was −2.2 SD with a FRAX-calculated fracture probability of 19%. In this case, the T-score discordance was 1.3 SD (3.5–2.2). If the figure is rounded off (to 1.0 SD), the estimated probability with the inclusion of lumbar BMD is upward revised by 10% (19+1.9) to 21%.

The rule is intended to provide some guidance for physicians, particularly those that report on the output of DXA to primary care. Approximately 16% of individuals will have a T-score at the lumbar spine that is lower by 1 SD or more than that at the femoral neck. Conversely, approximately 16% of individuals will have a T-score at the lumbar spine that is higher by 1 SD than that at the femoral neck. There are, however, several caveats to consider. Firstly, this approach requires external validation in independent cohorts and with other DXA technologies. Secondly, its application should be not only to revise probabilities upwards. The obverse may also apply and probabilities revised downwards in patients with higher T-scores at the lumbar spine than at the femoral neck. Thirdly, the adjustment is only relevant for those close to an intervention threshold.

The incorporation of quantitative ultrasonography

QUS is an attractive method for assessing fracture risk because it is portable, inexpensive, without ionizing radiation and available in areas of the world where DXA is not readily accessible or affordable. Validated techniques for QUS at the heel have been shown to predict hip fracture and other fractures as well as central DXA [81, 86]. As in the case of lumbar spine BMD, and for the same reasons, ultrasound measurements should not be entered in FRAX models in place of femoral neck BMD.

One study has shown that the consideration of clinical risk factors can enhance fracture risk prediction with QUS [87]. Age, BMI, history of fracture, results of the chair test, a history of a fall over the last 12 months, current cigarette smoking and diabetes mellitus were independent covariates. The value of this approach requires further development before clinical application but illustrates a proof of principle that the addition of clinical risk factors may improve the performance characteristics of QUS alone.

Other limitations of FRAX

The Task Force examined several other limitations of FRAX (see Table 1), some of which are reviewed below.

Concurrent treatment

FRAX is intended to identify patients for treatment. Thus, FRAX is unnecessary in patients for whom treatment is clearly indicated, e.g. an elderly patient with multiple fragility fractures [81]. In those receiving treatment for osteoporosis, FRAX is likely to overestimate fracture probability since treatment effects are not accommodated in the model. The empirical data suggest that FRAX remains a good predictive tool in women currently or previously on treatments for osteoporosis [88], possibly related to the contribution of treatment-induced changes in BMD.

Within country variation in fracture rates

In addition to large variations in fracture rates around the world, fracture rates may vary within countries. In addition to ethnic-specific differences [3, 89, 90], up to two-fold differences in hip fracture incidence have been reported using common methodology with the higher rates in urban communities in Argentina [91], Turkey [92], Sweden [93], Norway [94–96] Switzerland [97], Croatia [98] and in the USA [99, 100]. Where possible, FRAX models are built using national rather than regional data, the former generally being of higher quality and based on large population-based sample sizes. It is not feasible to build regional models and probably not desirable, but clinicians should be aware of this variation.

An additional feature of multi-ethnic populations is that fracture risk and mortality may vary widely across ethnic groups. Where sufficient information is available, ethnic-specific FRAX models have been built (for the USA and for Singapore). In most other societies, there are insufficient data on fracture rates and mortality in ethnic minorities, though differences in fracture risk may be less than that suggested from the ethnicity of origin. For example, blacks in the US have lower fracture probabilities than Caucasians, but the probability of fracture in US blacks is much higher than in African blacks [90] in part due to the higher fracture rates and lower mortality risks in those from the USA. A

similar 'acclimatisation' is seen in the Japanese population of Hawaii [101].

In view of the variations in hip fracture risks between urban and rural communities, it is relevant to question whether ethnic-specific models are of real utility where the differences in fracture rates are modest. In addition, fracture rates may vary within ethnic groups. A case in point is the US Hispanic population which is very diverse in origin and ethnic background with both 'black' and 'white' Hispanics. As a result, the risk of fracture may differ substantially for Hispanics in different areas of the country [102]. Regions such as New York with more black Hispanics from Puerto Rico have lower hip fracture risk than Florida which has many Cuban Americans. Hispanics in the Southwest have hip fracture risks that are in between. At the end of the day, it may be more profitable to recognise these differences to temper interpretation of FRAX results rather than to strive for a spurious sense of accuracy.

Secular trends

In addition to the large geographic variation reported in the incidence of hip fracture throughout the world, the age- and sex-specific incidence of fracture is changing. This has been well characterised for hip fracture, but also noted at other sites of fracture [103, 104]. Estimates of incidence trends have varied widely and variously reported an increase, plateau and decrease, in age-adjusted incidence rates for hip fracture among both men and women. Studies in western populations, whether in North America, Europe or Oceania, have generally reported increases in hip fracture incidence through the second half of the last century, but those studies continuing to follow trends over the last two decades have found that rates stabilise, with age-adjusted decreases being observed in certain centres. In contrast, the mortality hazard has continued to decrease in most regions of the world.

These shifts in fracture and death hazards have implications for FRAX. In the USA, the FRAX model was revised in 2009 to take account of changing death and hip fracture rates and improvements in the descriptive epidemiology of other outcome fractures. Recent data from the USA suggest that, while hip fracture rates are declining among Caucasians, there has been an increase in the age- and sex-specific hip fracture risk in Hispanic Americans from California [105], possibly related to social admixture. If confirmed, then the Hispanic model may need revision or the Caucasian model used instead [90]. In Turkey, a country with low fracture probabilities, the FRAX model is based on hip fracture rates acquired more than 20 years ago. Studies in progress, stimulated by the availability of FRAX for Turkey, will address whether hip fracture incidence has changed in the interim. Thus, FRAX models may need to be updated from time to time to take account of changing epidemiology.

Probability of clinical spine, humeral and forearm fracture fractures

A minority of countries that have a FRAX model also have robust information on the risk of the other major fractures (clinical spine, forearm and humerus). Where available, these are incorporated in the models (e.g. UK, USA, Switzerland, Sweden, Japan, Mexico). In the absence of information, FRAX models are based on the assumption that the age- and sex- specific pattern of these fractures is similar to that observed in Sweden.

Despite a large number of studies that have examined the incidence of fractures by age and sex, there are problems in defining the pattern of fractures in different countries [106]. For example, there are differences in the population studied. Some studies have been from random samples of the general population, from self-selected populations, from accident departments, radiology departments, fracture clinics or inpatient records. Clinical vertebral fractures are variously defined, even within a single study [107]. These different sampling frames give rise to large differences in the pattern of fractures reported. Moreover, several surveys do not study or report all fracture types relevant to the outcomes of FRAX, have small samples, an age range not relevant to osteoporosis or do not include men. A further problem is that the incidence and therefore the apparent pattern of fracture may change with time-discordant samples, so that historical data may not be relevant. The most complete information comes from Sweden, UK, Canada, Australia and the USA.

The available information suggests that the pattern of fractures is similar in the Western world and Australia, despite differences in incidence [106]. In the USA, Sweden and the UK the incidence of forearm, proximal humeral and hip fracture varies. For example, in women aged 80–84 years, the rates of these fractures are 3,206, 5,157 and 2,558/100.000 in the USA, Sweden and UK, respectively [108–110], but the pattern of these fractures with age is remarkably similar (Fig. 2). The relationship between the incidences of hip, clinical vertebral and forearm fracture is also similar between Sweden and Australia [111]. Within the USA, the pattern appears to be similar amongst blacks and whites. For example, amongst white women aged 65–79 years, the ratio of frequency of hip, distal forearm and proximal humerus is 43%, 38% and 19%, respectively. For black women, the ratio is 45%, 36% and 18% [112].

This commonality of pattern is supported by register studies, which indicate that in those regions where hip fracture rates are high, so too is the risk of forearm fracture

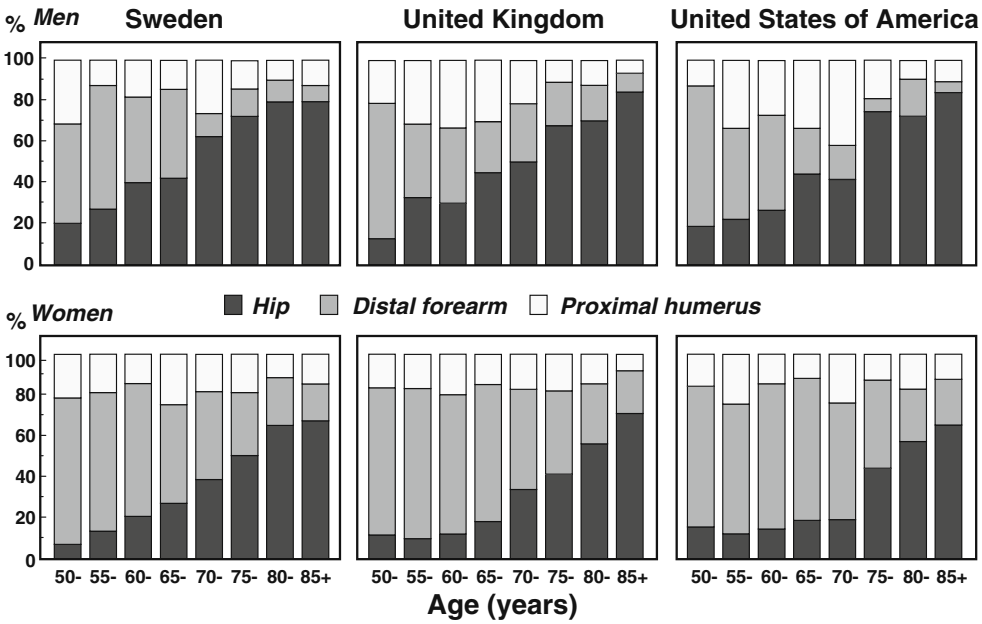

Fig. 2 Pattern of common osteoporotic fractures expressed as a proportion (%) of the total in the US, Sweden and the UK [106] (with kind permission from Springer Science+Business Media B.V.)

and vertebral fractures (requiring hospital admission) (Fig. 3) [113, 114].

Since the pattern of osteoporotic fractures appears to be broadly similar in the Western world, this suggests that the imputed rates clinical (but not morphometric) vertebral, forearm and humeral fractures used in FRAX are unlikely to be grossly over- or underestimated. The pattern of fractures elsewhere is, however, less secure [90].

Surrogate models

Fracture probability varies markedly in different regions of the world [10] (Fig. 4). Thus, the FRAX models need to be calibrated to those countries where the epidemiology of fracture and death is known. At present, FRAX models are available for 31 countries. Other models are being developed, where sufficient data are available.

Thus, in the absence of a FRAX model for a particular country, a surrogate country should be chosen, preferably based on the likelihood that it is representative of the index country. Where limited data of uncertain quality are available, it may be appropriate to choose a surrogate that best approximates the fracture risk of the index country. Mortality data are available for nearly all countries, so that the Task Force recommend that the FRAX model should incorporate the death hazard of the index country [90]. A case in point at present is Poland which has adopted the UK as its surrogate country. The entire UK FRAX model was used whereas it may have been more appropriate to

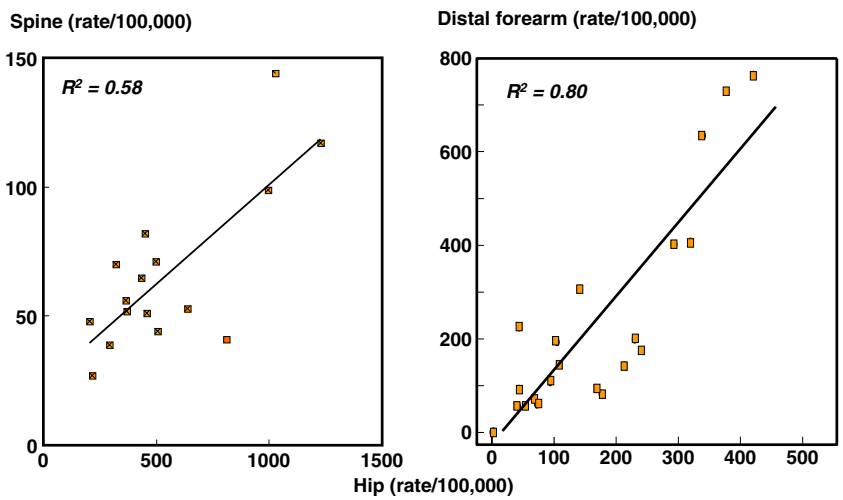

Fig. 3 Discharge rates for vertebral fractures and hip fractures in Europe (*left*) and discharge rates for forearm fractures and hip fractures in Western countries (*right*). Data from [113] and [114]

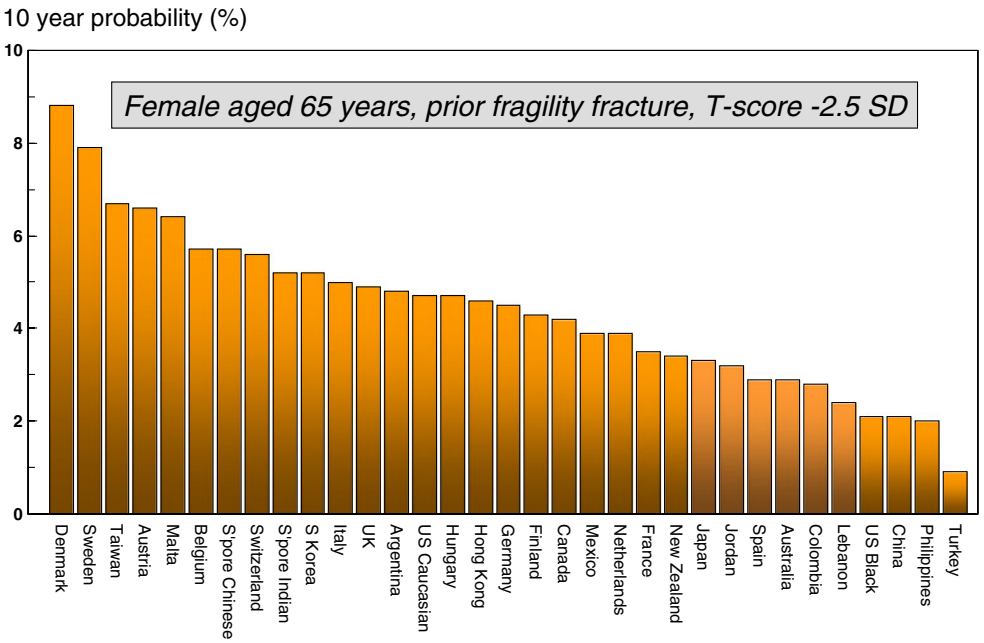

Fig. 4 Ten-year probability of hip fracture in women aged 65 years with a prior fracture and a T-score of −2.5 SD at the femoral neck in the different countries with FRAX models (FRAX version 3.2)

accommodate the death hazard for Poland if the recommendation was followed. New data on fracture rates in Poland will, however, obviate the need for adjustment.

In the absence of any country-specific data, it has been suggested that a regional model might be constructed, but the heterogeneity of fracture risks in different regions of the world makes this approach less secure (see Fig. 4). On the other hand, accuracy errors have little impact on the rank order with which the FRAX tool categorises risk in a given population [115], but they do change the absolute number generated and thus have implications where treatment guidelines are based on cost-effectiveness or the economic burden of disease.

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

Conclusions

FRAX represents a significant advance in the assessment of both women and men at risk for osteoporosis-related fracture and allows the tailoring of pharmacological interventions to high-risk subjects. While FRAX does not define intervention thresholds, which depend on country-specific considerations, it provides a platform to assess fracture probability which is needed to make rational treatment decisions by clinicians and public health agencies. The tool is, however, far from perfect, but better than BMD alone. The widespread use and interest in FRAX and its adoption into management guidelines has fuelled interest as to how models can be improved, extended to other countries and, in particular, how the limitations of FRAX should temper clinical judgement.

The wish list of clinicians for the modulation of FRAX is large, and in many instances, these wishes cannot presently be fulfilled, but an explanation and understanding of the reasons may be helpful in translating the information provided by FRAX into clinical practice.

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