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**Original Article**

# FRAX Update

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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, models are now available for 63 countries, covering 79% 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. However, the application of FRAX in guidelines has been heterogeneous with the adoption of several different approaches to setting intervention thresholds. The relationship between FRAX and efficacy of intervention has been explored and is expected to influence treatment guidelines in the future. A more unified approach to setting intervention thresholds with FRAX is a research priority.

**Key Words:** Clinical risk factors; fracture probability; FRAX; intervention thresholds; risk assessment.

## 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)*. In 2008, the World Health Organization 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) *(3)*. The FRAX tool integrates 8 clinical risk factors (CRFs; prior fragility fracture, parental hip fracture, smoking, systemic glucocorticoid use, excess alcohol intake, body mass index, rheumatoid arthritis, and other causes of secondary osteoporosis), which, in addition to age and sex, contribute to a 10-year fracture risk estimate independently of bone mineral density (BMD) *(2,4)*. 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 from other causes *(5,6)*.

The aim of this brief review is to update developments in FRAX since its release in 2008.

## New Models and Uptake of FRAX

Fracture probability differs markedly within and across regions of the world *(7,8)* so that FRAX models are calibrated to the epidemiology of fracture and death in

Conflicts 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, Oden, Harvey, and Dr Johansson are members of the FRAX team. Professors Kanis, Harvey, and McCloskey are members of the advisory body the National Osteoporosis Guideline Group.

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individual nations. At the launch of FRAX, models were available for 8 countries. Models are now available for 63 countries, comprising 79% of the world population *(9)*. FRAX is available in 32 languages and the website (http://www.shef.ac.uk/FRAX) receives approximately 3 million visits annually. This underestimates the uptake of FRAX because the website is not the sole portal for the calculation of fracture probabilities. For example, FRAX is available in BMD equipment, on smartphones, and, in some countries, through hand-held calculators.

With regard to website visits, calculations arose from 173 countries in 2012–2013. 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 Southeast 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 *(9)*. When uptake is expressed per million of the population, highest usage is seen for Slovenia, Switzerland, the United States, 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 relative risk per standard deviation (SD) unit increase in risk score—termed the gradient of risk. The gradient of risk with the use of FRAX is shown in Table 1 for the use of the CRFs alone, femoral neck BMD alone, and the combination *(10)*. Overall, the predictive value compares very favorably with other risk engines such as the Gail score for breast cancer *(11)*.

Whereas both BMD and the CRFs 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 recognize that the impact of the CRFs and BMD are not purely multiplicative as there is some interdependence (r = –0.25). 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. For example, in a population sample of approximately 2000 older women (aged 75 years or more), those characterized at higher fracture probability (by a precursor of FRAX but not FRAX) without the inclusion of BMD had progressively lower mean femoral neck BMD values (Fig. 1). In women above an arbitrary risk threshold (e.g., 30% 10-year fracture probability), mean femoral neck BMD was approximately 1 SD lower than in women below the threshold *(12)*.

Similar findings were reported in a large referral population from Manitoba, Canada *(13)*. In this study, the minimum T-score (of measurements at the femoral neck, total hip, trochanter, or lumbar spine) decreased progressively with increasing FRAX probability measured without BMD. Thus, in patients categorized at low risk using FRAX without BMD (<10% probability of a major fracture), the mean minimum T-score was –1.5 SD. In those at intermediate risk (10%–19% probability), the T-score was –2.2 SD, and in those at high risk (≥20% probability) was –2.8 SD. These findings consistently indicate that the categorization of patients at high risk on the basis of FRAX without BMD selects patients with low BMD, and the higher the probability, the lower the BMD. This has obvious significance for case finding in the absence of access to BMD.

**Table 1**
Gradients of Risk (RR per SD Change in Risk Score With 95% Confidence Intervals) With the Use of BMD at the Femoral Neck, Clinical Risk Factors, or the Combination *(10)* (With Kind Permission From Springer Science+Business Media B.V.)

| | Gradient of risk | | |
|---|---|---|---|
| Age (yr) | BMD only | Clinical risk factors alone | Clinical risk factors + BMD |
| *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) |
| *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) |