Development and application of FRAX in the management of osteoporosis in Ireland

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Abstract

Summary The Irish Fracture Risk Assessment (FRAX) tool is the first fracture prediction model that has been calibrated using national hip fracture incidence data and Irish mortality rates. The Irish FRAX tool can be used to identify intervention thresholds for Ireland based on the fracture probability equivalent to that of a woman with a prior fracture.

Objectives The objective of the study is to describe the 10-year probability of osteoporotic fracture in men and women in Ireland by using the Irish version of the FRAX tool and to develop FRAX-based intervention thresholds.

Methods The FRAX model for Ireland was constructed from the age- and sex-stratified hip fracture incidence rates from 2008 to 2010. For other major osteoporotic fractures, incidence rates were imputed, using age- and sex-specific Swedish ratios for hip to osteoporotic fracture risks. Lifetime fracture probabilities and 10-year probabilities of a major osteoporotic fracture were calculated in women to determine potential intervention thresholds.

Results Based on the incidence of hip fracture and mortality, the average lifetime probability of hip fracture from the age of 50 years was 7.8 % in men and 18.2 % in women from Ireland. Probability-based intervention threshold derived from BMD T-scores were problematic. When a BMD T-score≤−2.5 standard deviations (SD) was used as an intervention threshold, the increase in risk associated with the BMD threshold decreased progressively with age such that, at the age of 80 years or more, a T-score of −2.5 SD was protective. The 10-year probability of a major osteoporotic fracture by age, equivalent to that of women with a previous fracture, rose with age, from 3.0 % at the age of 40 years to 30 % at the age of 90 years, and identified women at increased risk at all ages.

Conclusion The Irish FRAX tool is the first fracture prediction model that has been calibrated using national hip fracture incidence data and Irish mortality rates.

Introduction

Figures derived from the International Osteoporosis Foundation estimate that approximately 170,000 people over the age of 50 years have osteoporosis in Ireland [1]. It was estimated that approximately 18,000 new fragility fractures were sustained in Ireland in 2010, comprising 3,200 hip fractures, 2,700 vertebral fractures, 3,000 forearm fractures and 9,200 other fractures (i.e. fractures of the pelvis, rib, humerus, tibia, fibula, clavicle, scapula, sternum and other femoral fractures) [2]. The population above 50 years of age is expected to increase by 42 % from 1.2 million in 2010 to 1.8 million in 2025 [3]. Over the same interval, the number of fractures is estimated to rise from 18,000 in 2010 to 28,000 in 2025, corresponding to an increase of 56 %. Because of this huge burden [3, 4], assessment of an individual's risk of fracture is important so that intervention can be effectively targeted.

Bone mineral density (BMD) measured by dual X-ray absorptiometry (DXA) is the current reference standard for the diagnosis of osteoporosis. A BMD value at or below 2.5 standard deviations (SD), the average mean value of young healthy women (T-score≤−2.5 SD), was proposed by the World Health Organization (WHO) as an operational definition of osteoporosis [5]. The operational definition was established primarily for descriptive epidemiology. However, since BMD

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is one of the strongest predictors of fracture risk [6, 7], many agencies, including the Irish Osteoporosis Society, have adopted BMD-based criteria as an intervention threshold [8]. The currently accepted criterion for treatment of osteoporosis in Ireland is a BMD T-score≤−2.5 SD. A low trauma fracture is also considered to be due to osteoporosis unless proved otherwise.

The advent of Fracture Risk Assessment (FRAX®) provided a means of assessing fracture probability that is not wholly dependent on BMD. FRAX is a computer-based algorithm (http://www.shef.ac.uk/FRAX) developed by the World Health Organization Collaborating Centre for Metabolic Bone Diseases. The algorithm, intended for primary care, calculates fracture probability from easily obtained clinical risk factors in men and women [9]. The output of FRAX is the 10-year probability of a major fracture (hip, clinical spine, humerus or wrist fracture) and the 10-year probability of hip fracture. A FRAX model for Ireland calibrated to the total Irish population was released on 1 June 2012. The aim of the present study was to report age- and sex-specific hip fracture rates in Ireland that were incorporated into FRAX, explore its characteristics and develop FRAX-based intervention thresholds that might be used to identify Irish women at high fracture risk.

Methods

Fracture risk

Hospitalisation data for the treatment of hip fractures was taken from the National Hospital In-Patient Enquiry System database through the Health Atlas Ireland website [10]. By identifying the specific codes for hip fractures ICD10 code S72.0 (femoral neck), S72.1 (trochanter), S72.2 (subtrochanter) and S72.9 (unspecified fracture of the femur), hospitalisation data on all patients who were admitted to hospital for treatment of hip fractures for the years 2008, 2009 and 2010 were examined [3]. Double admissions within a 12-month period were excluded. Patients who had sustained a fracture as a direct result of severe trauma, such as a road traffic accident, were also excluded from the study. Only fractures sustained as a result of minimal trauma (defined as a fall from standing height or less, or a similar degree of injury) were included. Cases were studied from the age of 40 years since this is the lower age limit used in FRAX. Incidence rates were estimated as the number of men and women in 5-year age intervals with at least one hip fracture divided by the age- and sex-specific population of Ireland using the UN estimates for 2010 [11]. The mortality estimates for Ireland were taken from the Central Statistics Office [12]. At present, there are no complete epidemiological data on major non-hip fracture sites such as clinical spine, proximal humeral and forearm fractures.

It was assumed, therefore, that the age- and sex-specific ratio of index fracture to hip fracture in Ireland was the same as that found in Sweden. This assumption has also been used for many of the FRAX models with incomplete epidemiological information. Available information suggests that the age- and gender-stratified pattern of fracture is very similar in the Western world and Australia [13],

Fracture probability

Data on fracture and death risks were used in the construction of the Irish FRAX model. The construct and validation of FRAX have been extensively described [9, 14]. The risk factors used were based on a systematic set of meta-analyses of population-based cohorts worldwide and validated in independent cohorts with over a million patient-years of follow-up. The construct of the FRAX model for Ireland required the beta coefficients of the risk factors in the original FRAX model and the incidence rates of hip fracture and mortality rates for Ireland. The relative importance of the beta coefficients for death and fracture was assumed to be similar in Ireland, as has been shown across several European countries [15]. However, absolute age-specific fracture risk and mortality rates differ from country to country [16]. Consequently, for each age category, the hazard function was calibrated to match the mean risk (both fracture risk and mortality rate) for that specific age group in Ireland, without altering the relative importance of the beta coefficients [14].

In order to compare Irish hip fracture probabilities with those of other regions of the world, the remaining lifetime probability of hip fracture from the age of 50 years was calculated for men and women, as described by Kanis et al. [16]. In the present analysis, the values for Ireland were compared with those of other European countries.

Intervention thresholds

In Ireland, the current threshold for the recommendation to treat is based on BMD measurements with DXA with a threshold for intervention set at −2.5 SD. The 10-year probabilities of a major osteoporotic fracture were calculated by age (in 5-year increments from the age of 40 to 90 years) in women at the threshold of osteoporosis (T-score=−2.5 SD). Women were assumed to have no other clinical risk factors that might contribute to fracture probability. Since treatment is also recommended in women with a previous fragility fracture, a second intervention threshold was calculated over the same age intervals in women with a prior fracture, but no other clinical risk factors, using the Irish-specific FRAX tool, without BMD and a BMI set at 25 kg/m^2.

Results

Fracture rates

There was a high degree of consistency in the fracture rates between years January 2008 to December 2010. There is no evidence for a change in age- and sex-specific rates with time, albeit with a small time interval and the average annual incidence was used. The hip fracture rate in Ireland increased, as expected, exponentially with age up to the age of 95 years and was lower at the highest age interval (Fig. 1).

Fracture probability

The average lifetime probability of hip fracture from the age of 50 years was 7.8 % in men and 18.2 % in women. For women, Ireland ranked seventh in terms of lifetime fracture probability amongst the 21 countries of the European Union for which FRAX models were available (Fig. 2). Probabilities in men and women were higher than for the UK, in part due to a higher incidence of hip fracture in Ireland and in part to the lower mortality of the Irish population.

The effect of BMD on the 10-year probabilities of osteoporotic and hip fracture in men and women in Ireland at different ages in the absence of clinical risk factors is shown in Table 1. In both men and women, the 10-year probability of fractures increased with age and with decreasing T-score up to the age of 80 years after which the probability decreased due to the competing effect of the death with fracture risk.

As expected, each of the clinical risk factors contributed independently to fracture probability (data not shown). In the absence of BMD, the 10-year fracture probability in men was approximately half that of women at the same age. When
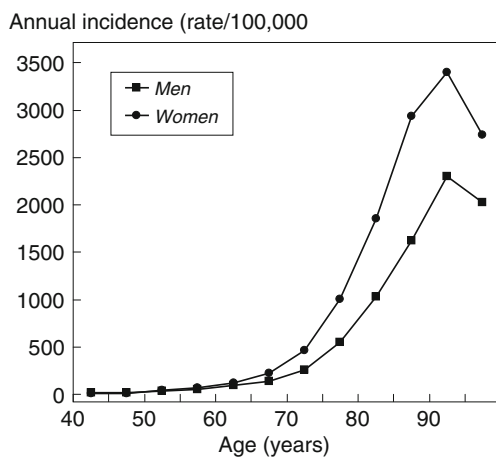

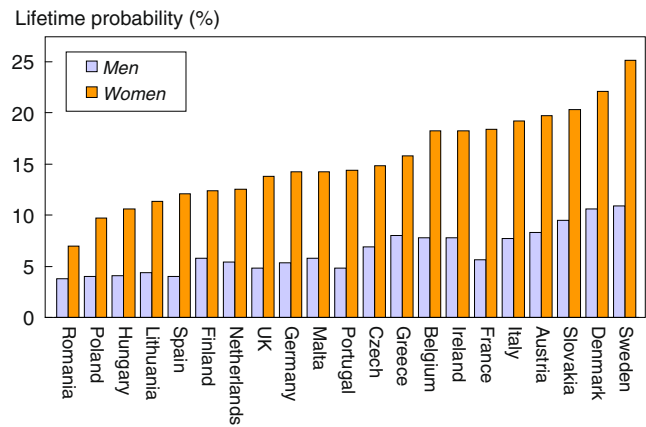Fig. 1 Annual hip fracture incidence by age and sex (2008–2010)

Fig. 2 Remaining lifetime probability of hip fracture at the age of 50 years in men and women in different countries of the EU

BMD was entered into the FRAX model, the differences between men and women were less marked.

Table 1 Ten-year fracture probability (in percentage) in men and women from Ireland and no clinical risk factors according to T-score at the femoral neck

Age (years)	T-score					
	−4	−3	−2	−1	0	1
Major osteoporotic fracture (men)						
50	23.0	9.0	4.4	2.8	2.1	1.9
60	24.0	12.0	6.6	4.2	3.2	2.7
70	23.0	14.0	8.2	5.3	4.0	3.3
80	20.0	13.0	8.7	5.8	4.3	3.3
90	12.0	8.5	6.1	4.5	3.5	2.8
Major osteoporotic fracture (women)						
50	18.0	7.7	4.2	2.9	2.4	2.2
60	24.0	12.0	7.3	5.0	4.2	3.6
70	32.0	18.0	11.0	7.9	6.2	5.0
80	38.0	23.0	14.0	10.0	7.3	5.4
90	27.0	17.0	12.0	8.7	6.3	4.6
Hip fracture (men)						
50	19.0	5.7	1.6	0.4	0.1	0.0
60	19.0	6.7	2.3	0.8	0.3	0.1
70	16.0	7.4	3.3	1.4	0.6	0.3
80	15.0	8.5	4.7	2.6	1.5	0.9
90	6.6	4.4	3.0	2.0	1.4	1.0
Hip fracture (women)						
50	14.0	3.8	1.0	0.3	0.1	0.0
60	16.0	5.2	1.6	0.5	0.2	0.1
70	20.0	8.0	3.0	1.2	0.5	0.2
80	25.0	12.0	5.8	2.8	1.3	0.6
90	13.0	7.6	4.5	2.7	1.6	0.9

BMI set at 25 kg/m^2

Intervention thresholds

In women with no clinical risk factors and an average BMD, the probability of a major fracture increased from 1.3 % at the age of 40 years to 22 % at the age of 85 years (Table 2). In women aged 50 years at the threshold of osteoporosis (a BMD T-score of −2.5 SD), fracture probability was approximately twofold higher than in women of the same age but with an average BMD. The 10-year fracture probability rose progressively with age from 3.1 % at the age of 40 years to 19 % at the age of 80 years. Thereafter, fracture probability decreased with age and, at the age of 90 years, was 15 %. Thus, at the age of 90 years, the fracture probability in women at the threshold for osteoporosis was lower than in women of the same age with no risk factors and an average BMD (15 vs. 19 %, respectively; Fig. 3). Thus, the BMD criterion for intervention using a fixed T-score became less and less appropriate with advancing age. The findings were similar using hip fracture probabilities.

The fracture probabilities equivalent to those of women with a previous fragility fracture are shown in Table 2. The probability of a major fracture rose with age, from 3.0 % at the age of 50 years to 33 % at the age of 85 years, and was relatively stable thereafter. Fracture probabilities at this threshold were consistently higher than in women with no clinical risk factors and an average BMD for age.

Discussion

In this study, we describe the development of the FRAX model for the assessment of the 10-year fracture probability in men
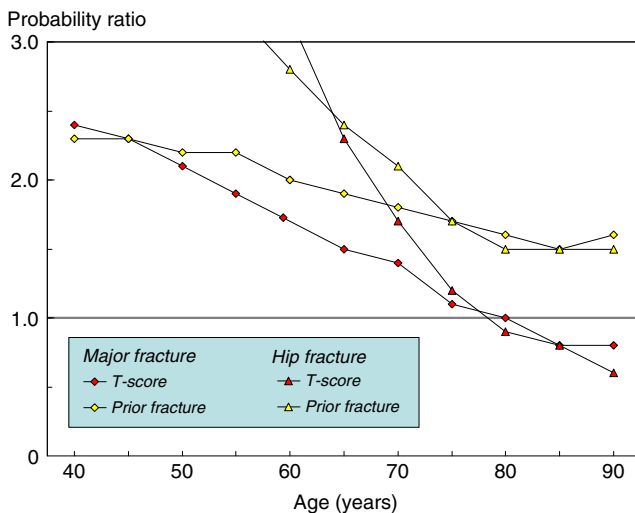

Fig. 3 The probability ratios of intervention thresholds vs. average BMD for a major fracture or a hip fracture by age in women. When thresholds were based on the T-score, the ratio fell progressively with age and was less than unity from the age of 80 years. When thresholds were based on a prior fracture, the ratio fell with age but remained greater than unity at all ages

and women in Ireland. The Irish FRAX tool was calibrated using national hip fracture data of 2008–2010. The hip fracture rate in Ireland increased exponentially with age up to the age of 95 years and declined thereafter. A similar phenomenon has been observed in the majority of countries where the relevant information at high ages has been available. A plausible explanation is a healthy survivor bias at the extreme age.

Based on lifetime fracture probability, Ireland belongs to one of the high-risk countries for osteoporosis [17]. At the age of 50 years, nearly one in 12 men and one in 5 women will sustain a hip fracture in their remaining lifetime. Demographic projections between 2010 and 2025 indicate that the number of osteoporotic fractures in men and women aged 50 years and over will increase by 53 % from 17,947 to 27,372 so that the burden of the disease will increase markedly with time [2]. Indeed, Ireland is estimated to have the highest growth rate of fractures in the EU [1].

Fracture probability depends upon the integration of death risks and fracture risks. The present study illustrates the importance of the death risk with regard to BMD. Although fracture probability increases with decreasing T-score, the relationship between probability and T-score was not linear. Thus, at any given T-score, fracture probabilities rose with age up to the age of 70 or 80 years and thereafter decreased—an effect more marked in men and at lower T-scores (see Table 1). The declining fracture probability with age is partly due to the increased risk of death in the general population—an effect more marked in men than in women. A more important component of the effect is that low BMD is associated with an increased risk of death which is captured in the FRAX algorithm [14]. This explains why the declining fracture probability with age is much more marked at low T-scores. Moreover, because the T-score declines with age, a fixed BMD threshold (e.g. a T-score of −2.5 SD) is associated with a decreasing relative risk of fracture with age. Indeed, over the age of 80 years, a T-score of −2.5 SD is higher than the average T-score at that age. In other words, the T-score threshold is a protective factor and not a risk factor. These considerations indicate that intervention thresholds based on the T-score alone do not effectively target treatment. For this reason, the use of BMD criteria alone for the targeting of treatment is problematic. This has been recognised in the development or the updating of practice guidelines which have taken more account of fracture probability and placed less reliance on the T-score for BMD [18, 19].

The manner in which new guidelines have accommodated probability-based assessment has varied with some adopting a fixed probability threshold often as a component of pre-existing guidelines and others, an age-dependent threshold equivalent to a fracture threshold or the risks associated with pre-existing guidelines for reimbursement. In line with the guidelines for Europe and Ireland in particular, we examined an intervention threshold based on the 10-year probability of a

Table 2 Ten-year probabilities of a major fracture (hip, clinical spine, humerus and forearm) and a hip fracture calculated with the Irish FRAX model for women

	Age (years)										
	40	45	50	55	60	65	70	75	80	85	90
Major fracture											
(A) No clinical risk factors	1.3	1.9	2.7	3.8	5.6	7.9	11.0	15.0	19.0	22.0	19.0
(B) BMD T-Score −2.5 SD[a]	3.1	4.3	5.6	7.3	9.5	12.0	15.0	17.0	19.0	18.0	15.0
(C) Previous fracture[a]	3.0	4.3	5.9	8.2	11.0	15.0	20.0	26.0	30.0	33.0	30.0
Ratio between probabilities											
B/A	2.4	2.3	2.1	1.9	1.7	1.5	1.4	1.1	1.0	0.8	0.8
C/A	2.3	2.3	2.2	2.2	2.0	1.9	1.8	1.7	1.6	1.5	1.6
Hip fracture											
No clinical risk factors	0.1	0.1	0.3	0.5	0.9	1.6	3.0	5.9	9.4	11.0	9.2
BMD T-Score −2.5 SD[a]	1.2	1.6	2.0	2.4	2.9	3.7	5.0	7.1	8.7	8.2	6.0
Previous fracture[a]	0.3	0.6	1.0	1.6	2.5	3.9	6.3	10.0	14.0	16.0	14.0
Ratio between probabilities											
B/A	12.0	16.0	6.7	4.8	3.2	2.3	1.7	1.2	0.9	0.7	0.7
C/A	3.0	6.0	3.3	3.2	2.8	2.4	2.1	1.7	1.5	1.5	1.5

BMI set at 25 kg/m^2

[a] No other clinical risk factors

major osteoporotic fracture for a woman with a previous fracture. The intervention threshold is age-specific and ranged from 3.0 % at the age of 40 years up to 33 % at the age of 85 years. Thus, women who have a fracture probability that is equal to or exceeds that of a woman with a prior fracture would be eligible for treatment even in the absence of a fracture history. For example, a woman aged 65 years from Ireland whose mother had a hip fracture and has a T-score of −2.0 SD has a fracture probability of 17 % which exceeds the risk in a woman of the same age with a prior fracture and no other clinical risk factors (15 %; BMI set at 25 kg/m^2). Conversely, a woman aged 80 years with a T-score of −2.5 SD and no other clinical risk factors has a fracture probability (19 %) that is well below the intervention threshold for that age (33 %). Thus, intervention thresholds based on the second approach enfranchise more women at high risk and avoid treatment in women at low risk, thereby targeting interventions more appropriately than intervention thresholds based on BMD alone. These intervention thresholds can be likened to a probability-based fracture threshold and applied using probabilities for a major fracture, probabilities for hip fracture or both (Fig. 4).

The present study has several strengths and limitations. A strength is that the data on hip fracture rates are based on national rather than regional estimates. We were able to minimise the over-identification of cases (double counting) but were not able to exclude pathological fractures or assess the accuracy of reporting or coding of fractures. There are also important limitations in the construct of the FRAX model. For

this purpose, information is required on the incidence of major fractures (hip, spine, forearm and humerus). In contrast to hip fractures, incidence of other major fractures could not be determined. As undertaken for many countries with incomplete information, the incidence of these three types of osteoporotic fractures was imputed from the hip fracture incidence in Ireland and the relationship between hip fracture incidence and that of the other sites in Sweden (Malmö) [20]. This assumes that the ratio of hip fracture incidence to the incidence of other index fractures is similar in Ireland as in Sweden. This assumption, used in the development of some FRAX models, appears to hold true for the several countries where this has been tested [13].

The FRAX tool is the first country-specific fracture prediction model available in Ireland. It is based on the original
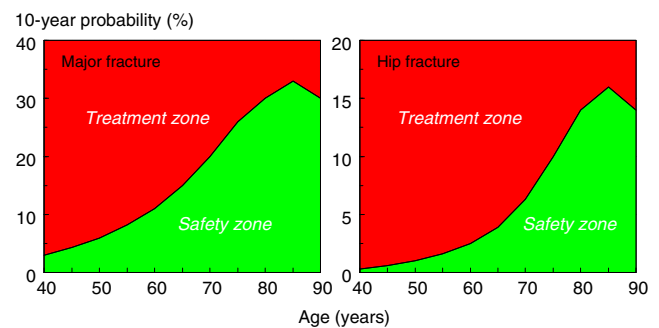

Fig. 4 Ten-year probability (in percentage) of a major osteoporotic fracture (*left panel*) and hip fracture (*right panel*) for women in Ireland with a BMI of 25 kg/m^2 according to age and the presence of prior fracture and in the absence of BMD assessment

FRAX methodology, which has been externally validated in several independent cohorts. Despite some limitations, the strengths make the Irish FRAX tool a good candidate for implementation into clinical practice. The present study also proposes thresholds for initiation of bone sparing treatment using the FRAX model for Ireland. Thresholds are similar to those suggested in other regions including the UK and Europe. A formal economic evaluation would be required to support these intervention thresholds.

Conflicts of Interest   None.

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