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Research Article
Application of FRAX to Determine the Risk of Osteoporotic Fractures in the Ukrainian Population

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Abstract

Background and Objective: FRAX is the most widely used tool for the assessment of the risk of osteoporotic fractures. The first country-specific FRAX model for Ukraine, calibrated to the total Ukrainian population, was developed in October, 2016. This study aimed to describe the output of the Ukrainian FRAX model and to illustrate its features compared to models for neighbouring countries. **Materials and Methods:** The development of the Ukrainian model of FRAX was based on two regional epidemiological studies in Ukraine [Vinnitsa city (1997-2002), STOP-study (Uzhgorod city and Vinnitsa area, 2011-2012)], which were performed to derive the incidence of hip fractures in men and women. The construct of the FRAX model for Ukraine required the beta coefficients for risk factors in the original FRAX model and the age and sex-specific incidence rates of hip fracture and mortality for Ukraine. **Results:** As expected, 10 year probability of hip or major osteoporotic fractures was increased in patients with a clinical risk factor (CRF), female gender, higher age, lower BMI and decreased BMD T-score. Of the CRFs, a prior fracture had greatest effect in the age group 50-70 years and parental hip fracture accounted for the greatest increase in 10-year fracture probability in the age group 80-90 years. **Conclusion:** The Ukrainian FRAX tool is the first country-specific fracture prediction model available in Ukraine which is based on the original FRAX® methodology, that has been externally validated in several independent cohorts. Despite some limitations, the strengths make the Ukrainian FRAX tool a good candidate for implementation into clinical practice.

Key words: FRAX, 10-year fracture probability, hip fracture, osteoporotic fracture, osteoporosis

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Osteoporosis is an important skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue with a resulting increase in bone fragility and 'low trauma' fractures. Based on measures of bone mineral density (BMD) in Caucasians, osteoporosis is present in 15% of those 50-59 years of age and its frequency rises markedly to 70% in those over 80 years of age[1]. Osteoporosis-related fractures are major cause of morbidity and mortality and health expenditure worldwide. According to recent data, 22 million women and 5.5 million men in Europe were estimated to have osteoporosis in 2010 and 3.5 million new fragility fractures were sustained, comprising 610000 hip fractures, 520000 vertebral fractures, 560000 forearm fractures and 1800000 other osteoporotic fractures[2]. For these reasons, predicting the absolute risk of osteoporotic fractures is of the utmost importance to optimize prevention strategies[3].

Current evidence suggests that BMD is an important but far from perfect criterion to determine fracture risk. Indeed, many fractures arise in patients with osteopenia or BMD values within the normal range[4-6]. Fortunately, other clinical risk factors (CRF), such as age, prior fracture, lifestyle, co-morbidities etc., contribute independently to the risk of osteoporotic fractures. Study of their association with osteoporosis and fractures have stimulated the development of large databases to define the impact of each of the CRFs on the risk of vertebral and non-vertebral fractures. This approach subsequently led to the development of several tools for risk assessment of osteoporotic fractures[7]. Those available on line include FRAX®, the Garvan fracture risk calculator and QFracture®[8-10]. Over 100 clinical practice guidelines include FRAX in their recommendations, making it the most widely used fracture prediction tool worldwide[8].

FRAX was developed by the former World Health Organization Collaborating Centre for Metabolic Bone Diseases at Sheffield, UK and first released in 2007[11]. The algorithm calculates fracture probability from readily obtained clinical risk factors in women and men (http://www.shef.ac.uk/FRAX). 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. The framework used considers competing mortality and avoids biased over-estimates in older individuals and those with risk factors for increased death[12]. 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, long-term oral glucocorticoid use, rheumatoid arthritis, other causes of secondary osteoporosis and excessive alcohol consumption. Femoral neck BMD can be optionally input to enhance fracture risk prediction[13].

Current evidence suggests that there are regional variations in osteoporotic fracture risk[14] and to a much lesser extent, in BMD. Indeed, greater than 10-fold difference in hip fracture incidence has been reported in different countries. For this reason, FRAX models are calibrated to take into account of national variations in fracture risk (and death risk).

The required information to build a FRAX model, particularly the epidemiology of fracture incidence, is not available in all countries. In such cases, the use of a surrogate model has been proposed using the death rate of the index country and the fracture rate of a country thought to be similar to the index country in terms of fracture risk[15]. Alternatively, clinicians can use a neighbouring country model where the risks of fracture and death are assumed to be similar and, since 2009, the Ukrainian Scientific Medical Centre on Osteoporosis Problems (Kiev) has used the FRAX algorithms to estimate the osteoporotic fracture risk[16,17]. Rather than developing a surrogate model, the Austrian version of FRAX was adopted for clinical practice[18]. Recently, data have become available on hip fracture incidence in the Ukraine and a country-specific model was developed in 2017[19]. The aim of the present study was to determine the characteristics of the Ukrainian FRAX model.

MATERIALS AND METHODS

The development and validation of FRAX have been extensively described[8,11]. 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 1 million patient-years of follow-up. The construct of the FRAX model for Ukraine required the beta coefficients for risk factors in the original FRAX model and the age and sex-specific incidence rates of hip fracture and mortality for Ukraine. The relative importance of the beta coefficients for fracture was assumed to be similar in Ukraine as that determined by meta-analysis. With regard to fracture, the development of the Ukrainian model of FRAX was based on two regional epidemiological studies in Ukraine [Vinnitsa city (1997-2002), STOP-study (Uzhgorod city and Vinnitsa area, 2011-2012)], to derive the incidence of hip fractures in men and women, aged 40 years and above[19,20]. Mortality risk used data from the United Nations[21].

For the present report, estimates of fracture probability were calculated with body mass index set at 25 kg/m^2, unless otherwise indicated. The impact of FRAX CRFs and a range of

T-scores were examined on the probability of hip and major osteoporotic fractures in men and women. Values for Ukraine were compared with data from neighbouring countries where a FRAX model was available[22-25].

RESULTS

Fracture probability without BMD: The 10 year probability of major osteoporotic fractures and hip fracture in Ukrainian women and men increased progressively with age (Fig. 1). For both hip and major osteoporotic fractures, the probability of hip fracture increased with age up to the age of 85 years and decreased thereafter in women due to the competing effect of mortality on the fracture hazard. As expected, probabilities were consistently higher in women than in men.

Each of the CRFs influenced fracture probability independently (Table 1). Weak risk factors for 10 year probability of a major fracture included high alcohol intake and current smoking. For example, at the age of 80 years, alcohol use was associated with an increase in the probability for a major fracture from 2.9 to only 3.9% in men and from 6.7-8.9% in women. Smoking was also a weak risk factor for fractures. Probability of major osteoporotic fractures increased slightly in women, but probability of a major osteoporotic fractures did not change markedly in men aged from 50-70 years.

From the age of 80 years, parental history of major osteoporotic fracture was associated with the highest risk in men and women (6.6 and 14.0%, respectively at age of 80 years). Below this age, large increments in fracture probabilities in men and women were associated with a history of prior fractures (4.8 and 11.0%, respectively at 80 years). Intermediate increments in probability were associated with rheumatoid arthritis and long-term use of glucocorticoids (4.5 and 4.2% in men and 10.0% for both in women, respectively) at the age of 80 years.

Fracture probability with BMD: When BMD was entered into the FRAX model, the 10-year probability of a major osteoporotic fracture increased with decreasing T-score in men and women at any given age (Table 2). At all ages, the fracture probability was higher in women than in men for a given T-score. Whereas fracture probabilities increased with age at younger ages, with advancing age, the same T-score was associated with a lower fracture probability. For example, at a T-score of -1 SD in women, the fracture probability was lower at the age of 80 (2.5%) and 90 years (2.5%) than at the age of 70 years (3.7%). The decreasing probability at older

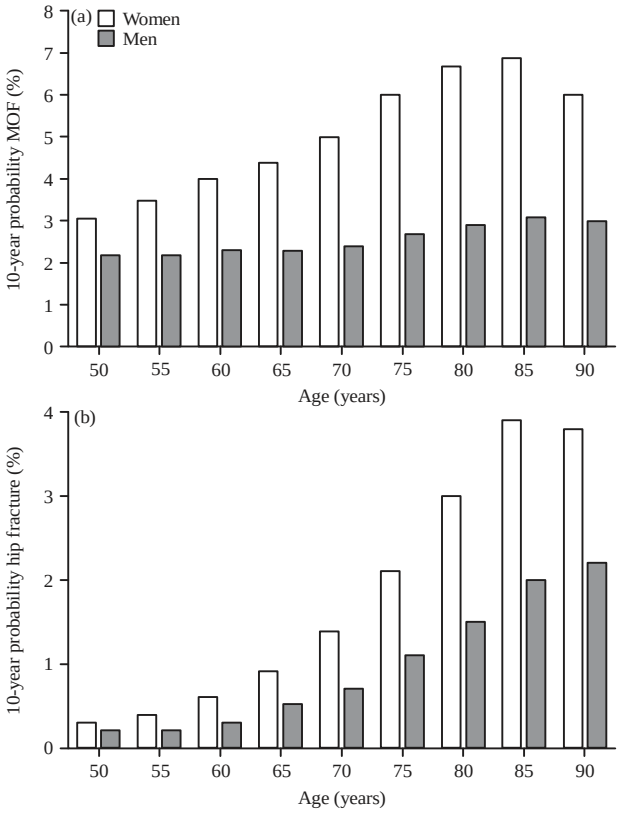

Fig. 1(a-b): Ten-year probability of a (a) Major osteoporotic fracture (MOF) and (b) Hip fracture according to age in Ukrainian women and men (No CRFs, FRAX without BMD and BMI set to 25 kg/m^2)

Table 1: Ten year probability of a major osteoporotic fracture (%) in men and women according to the presence of CRFs in the absence of BMD

	Age (years)				
CRFs	50	60	70	80	90
Men					
None	2.2	2.3	2.4	2.9	3.0
Alcohol	2.6	2.8	3.0	3.9	4.2
Smoking	2.2	2.3	2.4	3.1	3.3
Rheumatoid arthritis	2.9	3.1	3.4	4.5	4.8
Glucocorticoids	3.3	3.4	3.5	4.2	4.4
Parental history	4.3	4.4	3.9	6.6	8.1
Prior fracture	4.7	4.7	4.6	4.8	4.7
BMI at 20 kg m^{-2} [a]	2.1	2.2	2.4	3.1	3.5
Women					
None	3.1	4.0	5.0	6.7	6.0
Alcohol	3.7	4.9	6.4	8.9	8.3
Smoking	3.3	4.4	5.6	7.5	6.7
Rheumatoid arthritis	4.2	5.6	7.2	10.0	9.4
Glucocorticoids	5.1	6.6	8.2	10.0	8.9
Parental history	6.1	7.7	8.3	14.0	14.0
Prior fracture	6.7	8.3	9.6	11.0	9.7
BMI at 20 kg m^{-2} [a]	3.3	4.4	5.7	7.7	6.9

BMI is set at 25 kg/m^2 except where indicated, [a]No other CRF, CRF: Clinical risk factors

Table 2: Ten year probability of major osteoporotic fracture for women and men with a BMI of 25 kg/m^2 according to age and BMD T-score for femoral neck BMD in the absence of other CRFs

	Age (years)									
BMD T-score	Women					Men				
(SD)	50	60	70	80	90	50	60	70	80	90
0	2.9	3.1	2.9	2.6	1.7	2.2	2.0	1.7	1.5	1.1
-0.5	3.0	3.4	3.2	3.1	2.1	2.4	2.2	1.9	1.8	1.3
-1.0	3.4	3.7	3.7	3.6	2.5	2.8	2.6	2.2	2.0	1.5
-1.5	4.0	4.3	4.2	4.3	3.0	3.4	3.2	2.8	2.5	1.7
-2.0	4.8	5.3	5.2	5.2	3.6	4.3	4.0	3.5	3.1	2.0
-2.5	6.2	6.8	6.7	6.6	4.3	5.8	5.3	4.4	3.8	2.5
-3.0	8.5	9.0	8.8	8.6	5.5	8.3	7.1	5.8	4.8	3.0
-3.5	13.0	12.0	12.0	11.0	7.0	13.0	10.0	7.6	5.9	3.6
-4.0	19.0	18.0	16.0	15.0	8.9	20.0	14.0	10.0	7.5	4.3

Table 3: Ten year probability of a major osteoporotic fracture (hip, clinical spine, humerus or forearm) and a hip fracture calculated with the Ukrainian FRAX model for women (BMI set at 25 kg/m^2)

	Age (years)								
	50	55	60	65	70	75	80	85	90
Major osteoporotic fracture									
No CRFs (A)	3.1	3.5	4.0	4.4	5.0	6.0	6.7	6.9	6.0
BMD T-score-2.5 SD[a] (B)	6.2	6.6	6.8	6.7	6.7	6.9	6.6	5.6	4.3
Probability ratio (B/A)	2.0	1.9	1.7	1.5	1.3	1.2	1.0	0.8	0.7
Previous fracture (C)	6.7	7.5	8.3	8.8	9.6	11.0	11.0	11.0	9.7
Probability ratio (C/A)	2.2	2.1	2.1	2.0	1.9	1.8	1.6	1.6	1.6
Hip fracture									
No CRFs (D)	0.3	0.4	0.6	0.9	1.4	2.1	3.0	3.8	3.8
BMD T-score-2.5 SD[a] (E)	2.0	2.1	2.1	2.1	2.3	2.5	2.8	2.8	2.4
Probability ratio (D/E)	6.6	5.3	3.5	2.3	1.6	1.2	0.9	0.7	0.6
Previous fracture (F)	1.0	1.4	1.7	2.3	3.0	3.8	4.7	5.9	5.8
Probability ratio (F/D)	3.3	3.5	2.8	2.6	2.1	1.8	1.6	1.6	1.5

[a]No other CRFs

ages results from the competing effect of BMD on mortality. Similar results were seen in men, though the phenomenon of decreasing probabilities occurred 10 years earlier in men than in women.

Similar results were observed for the 10 year probability of hip fracture in men and women (data not shown) in that fracture probability increased with decreasing T-score but that the same T-score yielded different probabilities at different ages. For example, in men with a T-score of -3.5 SD, the hip fracture probability was 9.2% at the age of 50 years but was 2.5% at the age of 90 years.

Intervention thresholds: In Ukraine, the current threshold for the reimbursement of treatments is based on BMD measurements by Dual-energy X-ray Absorptiometry (DXA) with a treatment threshold set at -2.5 SD. The probabilities of a major osteoporotic fracture equivalent to a T-score of -2.5 SD are given for women in Table 3. Probabilities rose from 6.2% at the age of 50-6.9% at the age of 75 years and subsequently decreased. When these probabilities were compared to women of the same age with no CRFs and without DXA, it was evident that, at the age of 50 years, a T-score of -2.5 SD was associated with a significantly higher probability compared to women of the same age without CRFs (6.2 vs. 3.1%; probability ratio = 2.0; Table 3). With advancing age, the probability ratio fell progressively and reached unity at the age of 80 years. Above this age, a T-score of -2.5 SD was associated with a lower fracture probability compared to women of the same age with no CRFs and without DXA. The explanation is that in the oldest old, there is a decrease in the probability of fracture because of the competing effect of death risk plus the decrease in T-score with advancing age. Thus, the BMD criterion for reimbursement using a fixed T-score became progressively less appropriate with advancing age.

In the case of a prior fracture, major osteoporotic fracture probabilities rose from 6.7% at the age of 50 to 11% at the age of 75 years. When these probabilities were compared to women of the same age with no CRFs and without DXA, it was evident that, at the age of 50 years, a history of a prior fracture was associated with a significantly higher probability compared to women of the same age without CRFs (6.7 vs. 3.1%; probability ratio = 2.2; Table 3). With advancing age, the probability ratio fell modestly with age but was greater than unity at all ages. Similar observations were made in the case of

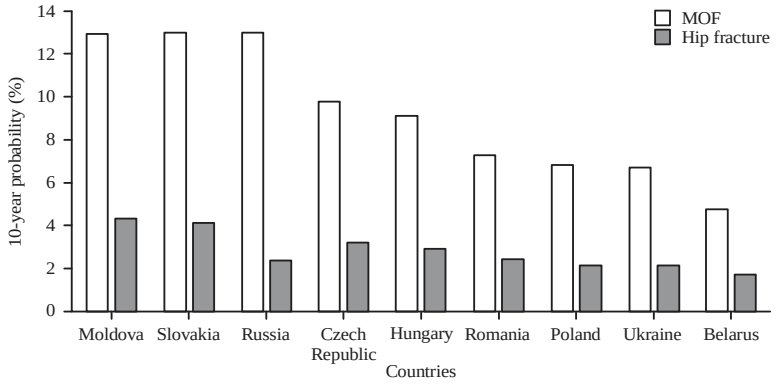

Fig. 2: Probability of the hip fracture for women and men aged 50 years with a BMI set at 25 kg/m^2 and BMD T-score for femoral neck -2.5 SD in the absence of other CRFs

hip fracture probabilities. These considerations suggest that a viable threshold for reimbursement might be the probability equivalent of a prior fracture, in the absence of BMD.

Comparison with neighbouring countries: In Fig. 2, it gives the 10-year probability of major osteoporotic fracture and hip fracture at the age of 65 years in women with BMI set at 25 kg/m^2 and BMD T-score for femoral neck of -2.5 SD in the absence of other CRFs in the Ukraine and neighbouring countries where a FRAX model was available. For major osteoporotic fracture, there was a greater than three-fold range in probabilities between countries. Of these countries, Moldova, Slovakia and Russia had the higher fracture probabilities. Intermediate values were noted for the Czech Republic, Hungary and Romania. Probabilities of major osteoporotic fracture for Ukraine were amongst the lowest and similar to those for Poland and Belarus. Comparative data for men are given in the supplementary table.

DISCUSSION

This present study describes the characteristics of a FRAX model for the assessment of 10 year probability of major osteoporotic fracture and hip fracture in the Ukrainian population according to sex, age, BMD and CRFs. In the absence of BMD, probabilities of a major fracture in the Ukrainian population increased with age in men and women up to the age of 85 years and decreased, thereafter, due to the competing effect of mortality hazard on fracture risk. The 10 year absolute probability of any major osteoporotic and hip fracture in the presence of a single risk factor increased with advancing age in both sexes, being always higher in women than in men. Each of the CRFs contributed independently to fracture probability but with a different weight. Consistent with other country-specific models, the Ukrainian model identified a parental history of hip fracture as the strongest risk factor; long-term use of glucocorticoids, rheumatoid arthritis and a prior fragility fracture were associated with moderate increments in probability.

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 did not consistently rise with increasing age in women and men (Table 2). Indeed, at the extremes of age (and T-score) probabilities decreased. The declining fracture probability at extreme old age is partly mediated by the increased and competing risk of death in the general population, an effect more marked in men than in women. Importantly, low BMD is also associated with an increased risk of death, which is captured in the FRAX algorithm[11]. This explains why the declining fracture probability with age is much more marked at low T-scores. This effect has implications for practice guidelines. In Ukraine, as in many countries, the current threshold for the reimbursement of treatments is based on BMD measurements by DXA with the treatment threshold set at a T-score of -2.5 SD. The present study confirms that the BMD criterion for reimbursement using a fixed T-score becomes less and less appropriate with advancing age. This has been recognized 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[8]. The manner in which new guidelines have accommodated probability-based assessment has been heterogeneous, with some adopting fixed probability threshold e.g. Canada[26] as a component of pre-existing guidelines e.g. Japan and the US[27,28] others have recommend an age-dependent threshold equivalent to a fracture threshold[29-31] or the risks associated with pre-existing

guidelines for reimbursement[32]. The present study indicates that age-dependent probability-based thresholds are more appropriate than T-score thresholds.

A second intervention threshold that authors examined was the risk equivalent to a woman with a prior fragility fracture, predicated by the fact that many guidelines recommend intervention in women with a prior fragility fracture[29]. In line with guidelines for the UK and Europe, an intervention threshold based on the ten-year probability of a major osteoporotic fracture for a woman was examined with a previous fracture. The intervention threshold is age-specific and ranged from 6.7% at the age of 50 years up to 11% at the age of 70 years. Thus, women who have a fracture probability that is equal to or exceeding that of a woman with a prior fracture would be eligible for treatment even in the absence of a fracture history. Such approaches, first developed by the National Osteoporosis Guideline Group (NOGG)[31], have now been widely adopted[32].

The present study has several strengths and limitations. A limitation is that the data on hip fracture rates, used to develop FRAX, are based on regional, rather than national, estimates. Thus, the FRAX model may not be representative for the whole of Ukraine. Although the epidemiological studies were able to minimize the over identification of cases (double counting), they 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. Ideally, information is required on the incidence of major fractures (hip, spine, forearm and humerus). In contrast to hip fractures, the incidence of other major fractures could not be determined because a dedicated registry with routinely recorded osteoporotic fractures does not exist in Ukraine. 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 Ukraine and the relationship between hip fracture incidence and that of the other sites in Sweden[3]. This assumes that the ratio of hip fracture incidence to the incidence of other index fractures is similar in Ukraine and Sweden. This assumption, used in the development of some FRAX models, appears to hold true for the several countries where this has been tested[15]. Despite some limitations, the strengths make the Ukrainian FRAX tool a good candidate for implementation into clinical practice. It can be recommended for widespread use in assessment of 10 year probability of major osteoporotic fractures in the Ukrainian population.

CONCLUSION

The Ukrainian FRAX tool is the first country-specific fracture prediction model available in Ukraine. It is based on the original FRAX methodology and Ukrainian epidemiological data.

SIGNIFICANCE STATEMENT

This study allowed developing the Ukrainian version of the FRAX model, calculating the national indices for men and women and comparing them with indices of neighboring countries. The Ukrainian model of FRAX can be used in assessment of 10-year probability of major osteoporotic fractures and hip fractures in the Ukrainian population. Present study results allowed to determine the place of the Ukrainian model among other European models of FRAX, to calculate the national indices for men and women and to compare them with the models of neighboring countries.

Earlier, the 10-year risk of osteoporotic fractures were determined using the Austrian model of FRAX (IOF recommend to do it when it is not possible to use country-specific models). However, it has been shown that Austrian model, like the models of other countries, can not be recommended because it does not accurately calculate this risk.

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