Evaluation of the validity of treatment decisions based on surrogate country models before introduction of the Polish FRAX and recommendations in comparison to current practice

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Abstract

Introduction: Patients diagnosed before the Polish FRAX was introduced may require re-evaluation and treatment changes if the diagnosis was established according to a surrogate country FRAX score. The aim of the study was to evaluate the validity of treatment decisions based on the surrogate country model before introduction of the Polish FRAX and to provide recommendations based on the current practice.

Material and methods: We evaluated a group of 142 postmenopausal women (70.7 ±8.9 years) who underwent bone mineral density measurements. We used 22 country-specific FRAX models and compared these to the Polish model.

Results: The mean risk values for hip and major osteoporotic fractures within 10 years were 4.575 (from 0.82 to 8.46) and 12.47% (from 2.18 to 21.65), respectively. In the case of a major fracture, 94.4% of women would receive lifestyle advice, and 5.6% would receive treatment according to the Polish FRAX using the guidelines of the National Osteoporosis Foundation (NOF). Polish treatment thresholds would implement pharmacotherapy in 32.4% of the study group. In the case of hip fractures, 45% of women according to the NOF would require pharmacotherapy but only 9.8% of women would qualify according to Polish guidelines. Nearly all surrogate FRAX calculator scores proved significantly different form Polish ($p > 0.05$).

Conclusions: More patients might have received antiresorptive medication before the Polish FRAX. This study recommends re-evaluation of patients who received medical therapy before the Polish FRAX was introduced and a review of the recommendations, considering the side effects of antiresorptive medication.

Key words: FRAX, recommendations, pharmacotherapy, osteoporosis.

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Introduction

Decision making in osteoporosis became significantly enhanced after the introduction of FRAX. Administration of antiresorptive medication or bone-forming therapy improves the quality of life and lowers the incidence of osteoporotic fractures. Fracture is the most severe complication of osteoporosis. Identification of patients at risk of fracture is of the greatest priority to clinicians who struggle to prevent the dire consequence of the disease, by effective interventions. Risk assessment implies setting a threshold which encompasses those patients who would benefit from pharmacological treatment [1, 2].

The most important step in evaluating bone strength is determining bone mineral density (BMD). However, densitometric measurements are not accurate enough, since most patients who suffer from a fracture do not meet the criteria for osteoporosis [3]. The fracture risk is multifactorial. Thus, only BMD is insufficient as the sole evaluation factor.

FRAX is the Web-based World Health Organization's (WHO) tool, introduced in 2008, to calculate the 10-year risk of "major fracture" and "hip fracture" [4]. The calculation uses an algorithm and incorporates information on the epidemiology of osteoporotic fractures, the combination of clinical risk factors, and BMD. All of these risk factors contribute independently to fracture risk [4]. The widespread application of the algorithm stimulated the creation of multiple country-specific models, based on the local epidemiology of hip fractures and deaths.

Most countries have published their reference data for the FRAX calculator. Countries without references could use a surrogate country model with potentially similar epidemiology. The Polish version of FRAX became available on 1 June, 2011. It has already served to assess the risk of fracture of 82,569 patients (as of 3 January, 2015). Until 2011, Polish patients were evaluated with various FRAX models including US Caucasian, British, German, French and Austrian [5–7].

The aim of this study was to determine the applicability and reliability of potential surrogate country models compared to the Polish calculator and to evaluate the potential inaccuracies in decision making for osteoporosis treatment.

Material and methods

Between January 2008 and November 2009, data were acquired from the Department of Orthopaedics and Traumatology of the Locomotor System, Baby Jesus Clinical Hospital in Warsaw. We identified a group of 142 postmenopausal women (70.7 ±8.9 years). All women underwent BMD measurements of the lumbar spine and hip. Hip-derived T-scores were used for statistical analysis.

We used FRAX country-specific models suggested as surrogates before the Polish epidemiological data in our study. The United Kingdom model was the most widely used model and was the one officially recommended model [6]. A suggested surrogate country for Central and Eastern Europe countries was Austria [7]. Polish authors also compared the US Caucasian model and German model, according to hip fracture probability [8]. We used other country-specific FRAX models as well.

We divided patients into two subgroups depending on whether they had sustained at least one fracture previously. Major and hip fracture risks in 10 years' time were assessed by FRAX for each patient. In addition, the FRAX tool questionnaire was used to interview patients about their pain perception at the time of examination using the visual analogue scale (VAS). The Oswestry Disability Index (ODI) was used to evaluate the disability for low back pain. We examined the relationship between Polish FRAX scores and patient's age, T-score, weight, height, body mass index (BMI), VAS score, and ODI score. Data from each patient were used to calculate the FRAX score in a country-specific manner for 22 populations in 18 countries. We compared computed scores between countries and separately for major and hip fractures. The differences in qualifications for the osteoporosis treatment, related to country-specific intervention thresholds, were noted. Additionally, the FRAX scores of other countries were compared with the Polish reference data, which became available in June 2011.

Statistical analysis

We evaluated correlation coefficients and their statistical significance for selected variables. We used SAS 9.3 (SAS Institute Inc., Cary, NC, USA) to conduct all statistical analysis. All the results of statistical tests were considered statistically significant at $p < 0.05$.

Results

The average weight was 63.53 ±9.83 kg, the average height was 159.33 ±7.27 cm, and the mean BMI was 25.79 ±3.62 kg/m^2. A group of 43 (30.3%) women presented with a T-score for femoral neck BMD below –2.5. Mean T-score for femoral neck BMD was –2.13 ±1.44. Table I presents the number and percentage of clinical risk factors.

The mean risk values for hip and major osteoporotic fractures within 10 years are presented in Tables II and III. We used the National Osteo-

Table I. Clinical risk factors that were taken into consideration during fracture risk assessment by FRAX stratified by fracture status

Clinical risk factors	Number and percentage of women with given risk factors		
	Whole group	Non-fractured	Fractured
Fractures	71 (50%)	71 (0%)	71 (100%)
Hip fracture in parents	11 (7.7%)	3 (4.2%)	8 (11.3%)
Steroid use	17 (12%)	12 (17%)	5 (7%)
Rheumatoid arthritis	24 (17%)	11 (15.5%)	13 (18.3%)
Secondary osteoporosis	19 (13.4%)	10 (14.1%)	9 (12.7%)
Tobacco smoking	18 (12.7%)	8 (11.3%)	10 (14.1%)
Alcohol use	0 (0%)	0 (0%)	0 (0%)

Table II. Ten-year probability of major fracture

Country	Mean FRAX (%)	SD
Poland	10.3	6.9
Argentina	11.3	8.4
Austria	18.2	11.7
Belgium	14.7	9.8
China	3.9	3.1
Finland	12.2	8.7
France	12.3	9.6
Germany	13.3	9.4
Hong Kong	13.9	10.5
Italy	14.1	9.8
Japan	16.3	10.7
Lebanon	5.8	3.9
New Zealand	11.5	8.8
Spain	9.7	7.8
Sweden	20.6	12.9
Switzerland	21.7	12.8
Turkey	2.2	3.3
United Kingdom	15.5	9.7
US Caucasian	17.5	10.5
US Black	8.3	5.8
US Hispanic	10.7	7.5
US Asian	10.8	7.7

Table III. Ten-year fracture probability for hip fracture

Country	Mean FRAX (%)	SD
Poland	4.2	4.8
Argentina	4.4	6.2
Austria	7.4	9.5
Belgium	5.7	7.6
China	1.3	2.0
Finland	4.9	6.8
France	5.1	7.4
Germany	5.4	7.3
Hong Kong	5.8	8.2
Italy	5.7	7.7
Japan	4.6	6.8
Lebanon	2.0	2.6
New Zealand	4.7	6.7
Spain	3.9	5.8
Sweden	8.5	10.8
Switzerland	6.8	9.2
Turkey	0.8	1.8
United Kingdom	5.1	6.8
US Caucasian	5.4	7.5
US Black	2.5	3.8
US Hispanic	3.3	5.0
US Asian	3.3	5.2

porosis Foundation (NOF) and Polish guidelines for treatment to stratify the study group. The subgroups contained patients with the fracture risk threshold below and equal to or above: 20% for major fracture in accordance with the NOF [9, 10]; 3% for hip fracture in accordance with the NOF [9, 10]; and 10% for both hip and major fracture in accordance with Polish guidelines [11].

Table IV presents the number of patients who would qualify for pharmacological treatment, de-

Table IV. Number of patients qualified for pharmacological treatment based on FRAX

Country	NOF	NOF HIP	PL	PL HIP
Poland	8	64	46	14
Argentina	12	55	55	15
Austria	40	86	107	24
Belgium	25	74	84	20
China	2	13	5	2
Finland	20	59	58	19
France	24	60	59	21
Germany	22	68	68	21
Hong Kong	24	69	76	22
Italy	23	69	76	21
Japan	34	55	93	18
Lebanon	2	27	15	4
New Zealand	19	58	55	18
Spain	10	48	42	14
Sweden	50	92	119	33
Switzerland	52	77	128	24
Turkey	1	5	1	1
United Kingdom	30	65	95	20
US Caucasian	35	66	110	21
US Black	7	28	31	6
US Hispanic	12	43	47	7
US Asian	12	43	48	7

NOF – National Osteoporosis Foundation recommendations for major fractures, NOF HIP – National Osteoporosis Foundation recommendations for hip fractures, PL – Polish recommendations for major fractures, PL HIP – Polish recommendations for hip fractures.

pending on the chosen intervention threshold. In the case of a major fracture, 94.4% of women would receive lifestyle advice and 5.6% would receive treatment according to the FRAX calculation for the Polish population using the NOF guidelines. Treatment thresholds proposed by Polish experts would consider recommendations for pharmacotherapy in 32.4% of patients. In the case of hip fractures, 45% of women according to the NOF would require pharmacotherapy, but only 9.8% of women qualified for treatment according to Polish guidelines.

Many more patients qualified for treatment after application of the Swiss model and NOF guidelines (90.1%). Thirty-seven percent of patients would receive the same qualification with Polish specific recommendations. The Swedish model of proximal hip fracture risk would lead to pharma-

cotherapy decision making based on the NOF intervention threshold in 64.8% of patients, but only 23.2% of these patients would qualify for therapy according to Polish recommendations and intervention thresholds.

Fisher's exact test was performed to compare country-specific FRAX scores with Polish FRAX scores. The difference between major fracture and hip fracture risk was statistically significant ($p < 0.0001$) for the NOF guidelines. All relationships between groups derived from Polish, British, Austrian, German and US Caucasian FRAX calculators were statistically significant regarding major or hip fracture risk category.

We assessed fracture risk differences using the Wilcoxon two-sample test. Hip fracture risk calculated with a Polish FRAX score was not significantly different from British ($p = 0.8972$), Caucasian American ($p = 0.7994$) and German ($p = 0.6876$) epidemiological data. This confirms, in part, the capacity of these country-specific scores to substitute the Polish scores. The Austrian model was significantly different ($p = 0.0013$).

The results of the major fracture risk for the country-specific models are presented in Table V. After dividing the study group into two subgroups based on whether the patient had sustained at least one fracture previously, comparisons were made regarding major fracture risk, hip fracture risk (both based on the Polish version of FRAX), *T*-score, age, height, weight, VAS score, and ODI score. Differences were evaluated using the Wilcoxon two-sample test. Age, *T*-score, height, weight, BMI, VAS, and ODI scores were not significantly different ($p > 0.05$). The differences for major fracture risk reached statistical significance ($p < 0.0001$), as did hip fracture risk ($p = 0.002$) as expected in the fractured group. The empirical distribution of the Polish FRAX scores and differences between the fractured and non-fractured groups are presented in Figure 1.

Pearson's correlation coefficients between FRAX scores for Poland (major fracture and hip fracture) and other countries were statistically significant with $p < 0.0001$. Upon the comparison of coefficients regarding major fracture, 19 out of the 43 country scores were above 80%. Thirty-seven countries obtained acceptable scores for hip fracture. We considered both major and hip fracture scores of 21 countries, excluding the correlation between the Polish scores. The least correlated country-specific FRAX score was Turkey for major fracture ($r = 0.39$) and hip fracture scores ($r = 0.38$). Major fracture risk score showed a weak, statistically significant correlation with age ($r = 0.22$; $p = 0.009$) only. The hip fracture score correlated with age ($r = 0.23$; $p = 0.006$) and with BMI ($r = -0.18$; $p = 0.03$).

Discussion

FRAX is a Web-based computer algorithm (http://www.shef.ac.uk/FRAX) that calculates the 10-year probability of a major osteoporotic fracture (vertebral, proximal femur, distal radius, or proximal humerus) and proximal femur fracture. The online calculator integrates BMD values (measured at the femoral neck) with the following clinical risk factors: sex, age, BMI, prior history of fracture, parental history of fracture, use of steroids, tobacco smoking and alcohol intake (≥ 3 U per day) [4].

We assessed the selection of clinical risk factors based on nine prospective international study cohorts, which consisted of 5,563 fractures, including 978 proximal femur fractures [12–15]. Validation was performed on 11 prospective cohorts, with 275,000 subjects, corresponding to 1.4 million person-years. The number of reported fractures exceeded 22,000. Interrelationships observed during the follow-up served to estimate the probability of fracture. Various combinations of risk factors were taken into account in the Poisson regression model, with death as a competing risk [4].

The literature confirms that the algorithm overcomes the limitations of BMD-based risk evaluation [15–19]. It estimates parallel fracture rates in population studies [20]. The BMD fails to provide precise risk projections since over 50% of patients who suffer from an osteoporotic fracture do not meet the densitometric criteria for osteoporosis [3].

The calculator has major limitations, which are emphasized in the literature [18, 19, 21]. It does not recognize significant risk factors such as falls, vertebral BMD measurement, the number of fractures, or rate of bone deterioration. The questionnaire supports only 'yes' or 'no' answers to steroid use, rheumatoid arthritis, and tobacco use. Since bone loss is dependent on dosage and duration of steroid use, this should be taken into account. Tobacco use encompasses multiple types of usage, and it is culture- and age-dependent. One should consider the time span during which the patient has used tobacco. FRAX has not been evaluated in a population of people who underwent pharmacological therapy (for osteoporosis or drugs affecting bone turnover) or in people less than 40 years of age. It omits the activity and duration of predisposing diseases.

The principal reason for the inclusion of femoral neck BMD in the FRAX algorithm was its availability in international cohorts, as compared to lumbar spine BMD. The femoral neck BMD measure is included in the NHANES III study. It is equal for males and females at any given age [22, 23]. It predicts major fractures better than BMD measurements at other sites, especially in women

Table V. Significance of differences between FRAX calculations based on data from selected countries and Poland (acceptable surrogate if $p > 0.05$)

| Country	Major fracture risk	Hip fracture risk
Argentina	0.5	0.2
Austria	< 0.0001	0.001
Belgium	< 0.0001	0.2
China	< 0.0001	< 0.0001
Finland	0.04	0.8
France	0.2	0.6
Germany	0.001	0.7
Hong Kong	0.001	0.6
Italy	< 0.0001	0.4
Japan	< 0.0001	0.2
Lebanon	< 0.0001	< 0.0001
New Zealand	0.7	0.3
Spain	0.02	0.01
Sweden	< 0.0001	< 0.0001
Switzerland	< 0.0001	0.03
Turkey	< 0.0001	< 0.0001
United Kingdom	< 0.0001	0.9
US Caucasian	< 0.0001	0.8
US Black	0.0003	< 0.0001
US Hispanic	0.8	0.0001
US Asian	0.9	0.0002
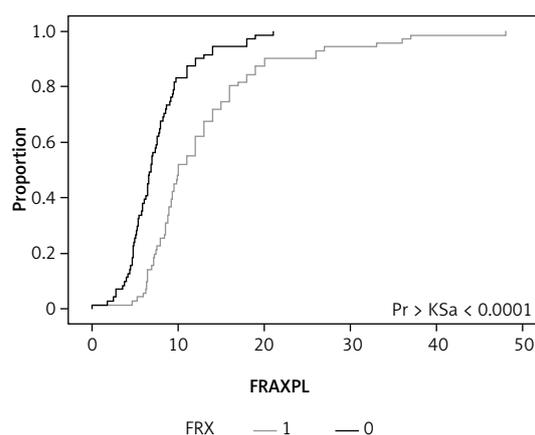
Figure 1. Empirical distribution for Polish FRAX scores and differences between fractured (1) and non-fractured (0) group

around 50 years of age [3, 24]. Leslie *et al.* [25] evaluated the discordance between femoral neck and lumbar spine BMD. They stated that there was approximately "a 10% change in fracture probability for each unit of *T*-score" difference.

The WHO's tool was created by a team from Sheffield in the UK in 2008, as an easy, quick, diagnostic screening method for fracture risk evaluation and support of individual therapeutic decisions [4]. FRAX is available in 56 country-specific versions. It is necessary to incorporate the local epidemiology of fractures and deaths to improve the FRAX tool reliability. A few countries have provided sufficient data to calculate the fracture risk for an individual patient. It was recommended to use the FRAX model for a country with similar epidemiology. The most frequently used model for Poland was the UK model [5]. Czerwinski *et al.* [6] found that the UK FRAX model overestimates fracture risk regardless of its type (major or hip fracture) for Polish patients. The results of the present study confirmed these conclusions. The largest differences occurred in major fracture risk. If we consider categorization based on the NOF criteria, the Polish FRAX will qualify 8 women for pharmacological therapy, whereas the UK model will qualify 30. Although according to the Polish guidelines the difference is smaller, it will still qualify less than half the number of women. In the case of hip fracture risk, the UK model has the capability to mimic Polish epidemiology. The differences are small if any (64 vs. 65 and 14 vs. 20 women at high risk of fracture based on the NOF and Polish guidelines, respectively). One of the reasons behind the discrepancies might relate to the fracture or death risks, as pointed out by Kanis *et al.* [8]. The average life expectancy in Poland is 3.7 years less than in the UK.

Germany was another surrogate country for Poland considered due to its geographical proximity. Mann *et al.* [26] reported hip fracture incidence of 93 per 100,000 subjects among men and 149/100,000 among women, which is similar to the Polish incidence rates of 89/100,000 for men, 165/100,000 for women [27]. There are, however, epidemiological data which show much higher figures for Germany [8]. Observations from this study resemble those made for the UK if we consider major fracture and hip fracture risk or their risk categorization. The German FRAX model could serve as a surrogate only for hip fracture risk assessment. However, it overestimates the fracture risk.

Experts posted a position paper [7] at the 2nd Summit on Osteoporosis – Central and Eastern Europe, in 2009. They suggested the Austrian FRAX model as a surrogate for other Central and Eastern European countries until sufficient epidemiological data are available [7]. Calculations of this study show that the Austrian model heavily over-categorizes women's fracture risk. The difference is in the major fracture risk assessment, independent of the criteria used.

The FRAX tool calibrated to the Polish population was developed in 2011 [6]. No country-spe-cific model for Poland was available for the three years after the introduction of FRAX (the original version). The model is built on data of hip fractures. This model is not currently implemented in Poland due to varied reports of fractures of the hip [8, 27, 28]. A large multicenter program of the Polish Ministry of Health and Committee for Scientific Research – "Early risk identification and effective prevention of osteoporosis based on bone fractures in Polish population – EPOLOS" (# 4 P05D 004 98 C/3959) – and implementation programs led to the development of the Polish version of the algorithm [11, 29].

This research compared the study group with 10 international cohorts (total 21,158 patients) regarding baseline characteristics [30–35]. Prior fracture prevalence in this study surpasses cohorts from the CaMOs (41%) [32] and Opus (43%) [34] reports. The results are in contrast to the above-mentioned study concerning family history of hip fracture. Similarly to this research, the Rochester study [31] reported 5% prevalence of family history of hip fracture. The percentage of women suffering from rheumatoid arthritis and taking steroids exceeds the percentage reported in other studies at least 2.5-fold. Unexpectedly, this report shows lower prevalence of tobacco smoking and alcohol intake in the Polish group. Age and sex may help explain this observation. The FRAX score calculated with the Polish version of the tool is comparable with six of the analyzed cohorts. However, the average *T*-score for the femoral neck was substantially lower. The direct comparison could be a challenge if the definitions concerning various risk factors in the FRAX calculator are read differently. For example, in the present study, we captured the current status of tobacco use, whereas in the Rochester Cohort "yes" in the questionnaire was selected if the patient ever smoked. In the DOES study, a family history of osteoporosis was used instead of the parental history of proximal femur fracture [33]. In the Adult Health Study from Japan, family history, rheumatoid arthritis, and alcohol intake were not captured; thus the answer "no" was selected [30].

The introduction of the FRAX tool for fracture risk assessment has brought the need for country-specific recommendations for treatment. Guidelines also reflect the epidemiology of fractures, life expectancy, availability of densitometry, organization of healthcare, cost of pharmaceuticals, and the cost of treatment (surgical and conservative) [5, 7, 9, 11, 36]. FRAX is widely recommended by the international community for fracture prevention by facilitating diagnosis [37].

Identification of patients who require pharmacological intervention remains a challenge for each country. The cost-effectiveness is highly de-

pendent on society's capabilities and varies greatly among countries. Recently, Polish thresholds [11] were set at 10% for major fracture and hip fracture regardless of age. Comparable thresholds for Japan (range: 5–20%), Belgium (range: 7.5–26%), and the UK (range: 13–30%) are stratified by age [38–40].

The NOF developed their recommendations based on work of Tosteson *et al.* [9] and Dawson-Hughes [10], which involved FRAX risk evaluation. The latest Polish guidelines [11] recommend treatment if the risk of fracture (based on FRAX) exceeds 10%, irrespectively of fracture site or history of sustained fracture. Current assessment using the Polish version of the algorithm qualified 5.6% of women for treatment, which is nearly 6-fold lower than recommendations based on major fracture risk. Thirty-five percent of subjects were overqualified for increased risk of hip fracture. These observations prove the need for case-specific tailored recommendations.

A substantial discrepancy occurs when one compares different treatment thresholds, even in the case of one version of the FRAX calculator. American guidelines (NOF guidelines) do not rely on Polish local epidemiological data of fractures or economic health policy, including reimbursement of treatment. Although they reflect data from multiple sources, including the WHO, they fail to recognize the specific environment of each country, including Poland. Their data are based largely on US incidence and cost of osteoporosis, thus indicating the level of risk at which it is cost-effective to consider treatment, which does not take specific Polish economic conditions into consideration.

Polish and NOF therapeutic intervention thresholds are based on economic analyses that take into consideration the cost-effectiveness of treatments and competition for resources in Poland and the United States, respectively. They vary, as do other European guidelines, depending on their domestic economic environment and available resources. Both considered national guidelines underline the importance of a case-by-case analysis of each patient. Recommendations should not mandate treatment. Although our choice of NOF thresholds was arbitrary, we did it to stress the need to create country-specific models and recommendations for evaluation and treatment vividly.

Over-qualification for antiresorptive treatment may lead to an increased number of patients suffering from adverse effects associated with the medication. Oral bisphosphonates are the therapy of choice for the prevention of osteoporotic fractures. Although of substantial benefits, they may expose patients to serious adverse effects including severe musculoskeletal pain, oesopha-

geal cancer, ocular inflammation, osteonecrosis of the jaw, over-suppression of bone turnover, and subtrochanteric femoral fractures. Unfortunately, we cannot evaluate the number of patients who were administered medication but would receive lifestyle advice according to current practice.

There are some limitations to this study. The study group consisted of patients who experienced low-back pain. Few patients sustained a vertebral fracture. Fracture risk factors for this study group may not necessarily reflect those of the general population. Additionally, none of the patients, upon interview, stated an increased alcohol intake, which further limits the knowledge about the influence of this risk factor. The study group's specific nature was also manifested in the advanced mean age. Stratification of the fracture risk was not appropriately done due to the low variation of patients' age.

In conclusion, the results revealed the capability of country-specific and surrogate FRAX models to predict fracture risk in the Polish population. The study confirms that more patients might have received antiresorptive medication before the Polish FRAX, and that Polish recommendations became available if the physician used the surrogate country model of FRAX. Finally, the comparison between different guidelines proved the necessity to adapt the recommendations to an individual country's needs.

Conflict of interest

The authors declare no conflict of interest.

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