ORIGINAL ARTICLE

Comparison of selected methods for fracture risk assessment in postmenopausal women

Analysis of the Łódź population in the EPOLOS study

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KEY WORDS

fracture risk, FRAX™, intervention threshold

ABSTRACT

INTRODUCTION The major challenge when administering osteoporosis treatment is to identify patients with the highest fracture risk. FRAX™ is a new algorithm that integrates clinical risk factors of fracture and the results of densitometry.

OBJECTIVES The aim of the study was to evaluate the use of FRAX™ in identifying patients that should receive osteoporosis treatment and compare it with other methods of fracture risk assessment.

PATIENTS AND METHODS The study involved a random sample of 94 postmenopausal women, aged 55 to 79 years, who had not been previously treated for osteoporosis (a part of the EPOLOS [European Polish Osteoporosis Study] population recruited from the region of Łódź, Poland). Clinical risk factors were evaluated and densitometry of the femoral neck was performed. Patients were eligible for treatment on the basis of previous osteoporotic fractures, densitometry results, semiquantitative tabular method (SQM) (according to the Osteoporosis Society of Canada Recommendations for Bone Mineral Density Reporting), and a 10-year fracture risk (calculated with the British FRAX™ tool, using different thresholds).

RESULTS Using the FRAX™ method, between 5.2% to 52% of the examined women would be eligible for treatment, depending on the threshold applied. If the treatment decision was based on a history of vertebral fractures, 4.2% of women would be eligible for treatment, and if other fractures were considered – 20.2%. If the decision was based on densitometry results, 8.5% of women would be eligible for treatment. We observed a high fracture risk in 7%, moderate risk in 19%, and low risk in 74% of women examined by the SQM.

CONCLUSIONS Proper use of FRAX™ in Poland requires determination of the intervention threshold. Use of FRAX™ changes the demographic profile of women eligible for therapy, increasing their number in older age groups.

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INTRODUCTION Osteoporosis was defined in 1994 by the World Health Organization (WHO) as bone mineral density (BMD) 2.5 standard deviation (SD) or more below the average value for young adults.[1] Since then, many publications have shown that BMD measurement alone is insufficient to identify individuals that have the highest fracture risk and would benefit from treatment.[2,3] Numerous clinical risk factors that provide information on fracture risk independent of BMD have been identified.[4] The most important include age and sex. For several years, attempts have been made to design a method combining the assessment of risk factors and BMD. In 2007, Polish experts recommended the use of a semiquantative tabular method (SQM),[5] but the implementation of this method was limited. Recently, computer-based algorithms (FRAX™) have been published.[6] The FRAX™ tool calculates the 10-year probability of a major osteoporotic fracture (clinical spine, hip, forearm, or proximal humerus) and hip fracture.[6] It integrates the data on BMD and

clinical risk factors including age, sex, low body mass index (BMI), parental history of hip fracture, prior history of fragility fracture, long-term use of oral glucocorticoids, rheumatoid arthritis, other secondary causes of osteoporosis, current smoking, and an average alcohol intake of ≥3 units daily. The FRAX™ model was developed through identification of strong clinical risk factors, quantification of their interactions, along with BMD of the femoral neck, in the analysis of 9 large, prospective, population-based study cohorts from around the world. The criteria for inclusion of a clinical risk factor in FRAX™ included international validation, independence from BMD in predicting fractures, availability of information in clinical practice, and the potential for modification with drug therapy.[7] The combined cohort comprised over 60,000 subjects, who were followed for a quarter of a million person-years. A total of 5563 fractures, including 978 hip fractures, were observed during the follow-up.[6] The use of these interrelationships allowed to estimate the probability of fractures for various combinations of risk factors in the Poisson regression model with death taken into account as a competing risk. At present, FRAX™ has several limitations. It has not been tested in people aged <40 years and in treated patients. Its calculation does not include other important risk factors, such as falling, the rate of bone loss, and the effect of steroid dose.[7]

The aim of this study was to compare various methods of fracture risk assessment in postmenopausal women from the region of Łódź, Poland.

PATIENTS AND METHODS EPOLOS (European Polish Osteoporosis Study) was a multicenter, population-based study in osteoporosis and its determinants in Poland. Invitations to the study were sent to people aged 20 to 80 years, randomly selected from the registry of Polish national identification numbers. The exclusion criteria were as follow: personal history of osteoporosis, pregnancy, cancer, fracture in the previous year, and excessive weight (>100 kg). This part of the study involved 94 postmenopausal women, from the Łódź region, aged 55 to 79 years, mean age 65.9 ±6 years (mean ± SD), not treated for osteoporosis before. The study was approved by the Ethics Committee of The Children's Memorial Health Institute, Warsaw, Poland.

Women were divided into 5 age groups: 55–59 years (n = 19), 60–64 years (n = 23), 65–69 years (n = 25), 70–74 years (n = 16), and 75–79 years (n = 11). All participants were examined by a physician. Body height (cm) and weight (kg) were measured and body BMI was calculated as body weight (kg) divided by height (m^2). Subsequently, based on the patient's history, the physician filled out an epidemiological questionnaire in order to determine clinical risk factors including a self-reported history of fragility fracture, parental history of hip fracture, long-term use of oral glucocorticoids, rheumatoid arthritis, other secondary causes of osteoporosis (type 1 diabetes, osteogenesis imperfecta, long-lasting untreated hyperthyroidism, hypogonadism, early menopause, age <45 years, malnutrition or malabsorption, chronic liver disease), current smoking, and an average alcohol intake of ≥3 units daily. BMD of the femoral neck was measured by dual energy X-ray absorptiometry (DXA; Expert, GE, United States). Clinical characteristics of the examined population are presented in TABLE 1. Of all patients, 11.7% were smokers, no patient consumed more than 3 intakes of alcohol daily, 2% described their health condition as very good, 28% as good, 30% as satisfying, 30% as not very good, and 10% as bad. The incidence of secondary osteoporosis was 4.2% (hyperthyroidism, rheumatoid arthritis, type 1 diabetes, renal failure).

Ten-year probability of hip fracture (FRAX™ hip [FH]) and of major osteoporotic fracture (FRAX™ major [FM]: clinical spine, hip, humerus, and forearm) were estimated using the English version of FRAX™ BMD tool.[6] Patients were considered eligible for therapy according to the following intervention thresholds: FM >20%,[5,8] FM >14%,[9] FM >7%,[10] and FH >3%.[8] The results were compared to treatment eligibility evaluated on the basis of the prevalence of osteoporotic fractures (vertebral and hip fractures), or the results of densitometry,[1] or using SQM,[5] which includes the effect of age, sex and densitometric data. The results were shown as mean ± SD.

TABLE 1 Characteristics of the study group; fractures and their selected risk factors

Age (years)	BMD (g/cm^2)	BMI (kg/m^2)	Personal fracures	Parental fractures	Smoking	Secondary osteoporosis	Use of steroids
55–59	0.968 ±0.14	27.8 ±4.8	1	1	4	0	0
60–64	0.916 ±0.14	26.9 ±4.1	3	1	5	0	0
65–69	0.907 ±0.14	27.8 ±4.3	6	0	1	1	1
70–74	0.909 ±0.17	27.5 ±4.9	6	0	1	0	1
75–79	0.836 ±0.12	26.5 ±3.9	3	0	0	1	0
total			19	2	11	2	2
			20.2%	2.12%	11.7%	2.12%	2.12%

Data presented as mean ± standard deviation

Abbreviations: BMD – bone mineral density, BMI – body mass index

TABLE 2 Number of patients eligible for treatment using different methods and thresholds

	55–59 years	60–64 years	65–69 years	70–74 years	75–79 years	Total
FM >20%	0	0	2	1	2	5/94 5.3%
FM >14%	0	2	4	1	5	12/94 12.77%
FM >7%	3	8	15	11	12	49/94 52%
FH >3%	1	2	6	2	5	16/94 17.02%
T-sc <–2.5	1	1	4	1	1	8/94 8.5%
SQM	0	1	4	1	4	11/94 11.7%

Abbreviations: FH – FRAX™ hip: 10-year risk of a hip fracture, FM – FRAX™ major: 10-year risk of all fractures, SQM – semiquantative tabular method, T-sc – T-score: number of standard deviations above or below the average for young adults at peak bone density

TABLE 3 Results of the 10-year fracture risk in particular age groups

Age (years)	FM (%)	FH (%)	T-sc
55–59	5.5 ±2.3	0.64 ±1.2	–0.45 ±(–0.25)
60–64	7.4 ±2.4	0.92 ±1.1	–0.88 ±0.77
65–69	9.5 ±7.22	1.74 ±2.7	–0.91 ±1.33
70–74	11.4 ±9.6	2.7 ±5.8	–0.925 ±1.24
75–79	11.9 ±4.7	3 ±2.6	–1.68 ±0.89

Data presented as mean ± standard deviation

Abbreviations: see TABLE 2

RESULTS We observed that the number and type of patients eligible for therapy was different depending on the threshold values used. TABLE 2 shows the differences between the applied methods and intervention thresholds. If the therapeutic decision was based on the presence of previous vertebral fractures, 4.2% of patients would be treated. If other fragility fractures were considered (forearm and rib fractures), 20.2% of patients would be treated. In 4.2% of patients, secondary osteoporosis was possible (rheumatoid arthritis, type 1 diabetes, renal failure). The most frequent risk factors in postmenopausal women in our study included a history of fragility fracture (20.2%) and smoking (11.7%) (TABLE 1).

Risk of FM increased from 5.5% in women aged 55 to 60 years to 11.9% in women aged 75 to 79 years (FIGURE 1) in contrast to a decreasing T-score (TABLE 3). Using the FRAX™ tool, from 5.2% to 52% of the examined women were identified as eligible for treatment, depending on the applied threshold (FIGURE 2). Regardless of the threshold, mainly elderly women were identified as eligible for treatment. With the threshold level of 20%, FM excluded 4.2% of women, who were eligible for treatment according to densitometry. With the threshold level of 7%, 4.2% of women with normal densitometry were identified by FM as eligible for therapy. When therapeutic decision was based only on densitometry, 8.5% women were qualified for treatment. A high risk of fractures was observed in 11.7% of the examined women when assessed by SQM (FIGURE 2).

None of the women aged 55 to 64 years met treatment criteria according to FRAX™ (FM >20%), despite densitometric signs of osteoporosis. When the intervention threshold was lowered to 7%, 52% of women were eligible for therapy, including the eldest women with normal BMD. We observed a high risk of fractures in 7%, moderate in 19%, and low in 74% of the examined women when assessed by the SQM (FIGURE 2).

DISCUSSION The aim of the study was to assess fracture risk factors and analyze eligibility criteria for osteoporosis treatment. We also studied how the intervention threshold influences the type and number of patients that should be treated. The study is preliminary because it analyzed only 1 group of postmenopausal women recruited from 1 research center (a part of the EPOLOS study recruited from the region of Łódź, Poland).

Regardless of the threshold, the use of FRAX™ changed the demographic profile of women who were likely to receive treatment from a younger to an older age group when compared with other methods. The significance of age in the FRAX™ method is a result of the observation that fracture

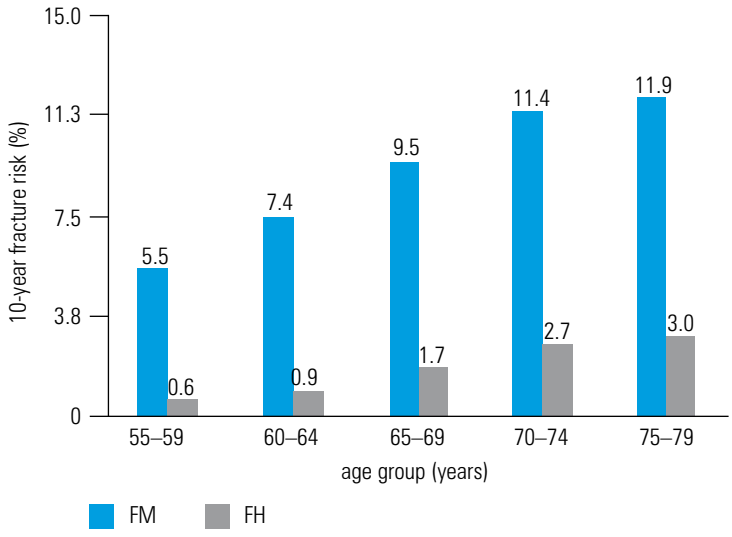

FIGURE 1 10-year fracture risk calculated with the FRAX™ algorithm in particular age groups
Abbreviations: see TABLE 2

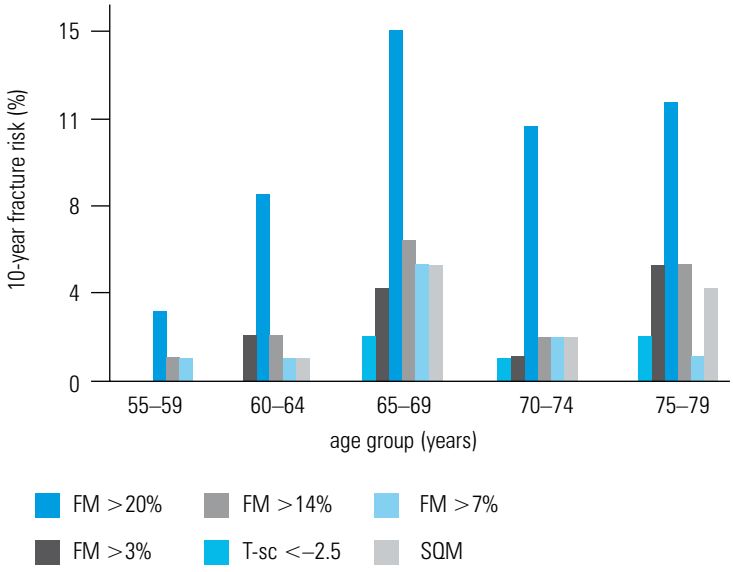

FIGURE 2 Number of patients meeting criteria for therapy using the following methods and thresholds: FH >3%; FM >20%, >14%, >7%; SQM; T-sc
Abbreviations: see TABLES 2 and 3

risk, which increases with age, is sevenfold higher than that demonstrated by the analysis of BMD.[11] On one hand, we observed a small group of younger women who were candidates for treatment on the basis of densitometry but were not qualified by FRAX™, and on the other hand, there was a small group of women, who were candidates for treatment despite normal BMD. Similar discrepancies have been reported by other authors.[12-14] Therefore, it was suggested that densitometry should not be performed in older women.[15] Use of FRAX™ for making treatment decisions only in patients with osteopenia is a likely solution to these discrepancies. It allows clinicians to differentiate high-risk patients with osteopenia from those at a lower risk, and thus treat those patients who are most likely to benefit from treatment.[7] According to new recommendations of the National Osteoporosis Foundation (NOF), patients with a densitometric or clinical diagnosis of osteoporosis and a history of hip or spine fracture should be treated regardless of FRAX™.[7,8] An analysis of the United States population, conducted according to these guidelines, identified potential candidates for therapy in 37% of postmenopausal women.[16] After application of the NOF guidelines in the Framingham Osteoporosis Study, 50% of postmenopausal women and 17% of men over the age of 50 were found to meet the criteria for treatment. Authors conclude that the NOF guidelines may need to be re-evaluated with respect to budget impact.[14]

Another issue to be considered when using FRAX™ is the choice of intervention threshold. A number of women who are eligible for preventive treatment differs depending on the applied method and intervention thresholds; in our study it varied from 5.2% to 52%. The difference shows how important it is to establish a proper threshold value. According to the WHO Commission on Macroeconomics and Health, interventions with a cost-effectiveness ratio lower than 3 times the gross domestic product per capita for each averted disability-adjusted life-year could be considered a good value for money in developing countries.[17] Furthermore, the will to pay for healthcare and the proportion of population at risk of osteoporotic fracture should also be taken into account in the analysis of national cost-effectiveness. Since then, intervention thresholds have been estimated for the United Kingdom, United States, and Sweden,[10,18,19] but not for Poland. Polish authors have suggested the threshold levels of 20%[5] and 14%.[9]

Other studies on the prevalence of clinical risk factors used in FRAX™, conducted in Poland, did not affect the whole population, but subpopulation of individuals referred to outpatient clinics.[12,13,15,20] This may affect the incidence of osteoporosis and its risk factors. Previous fracture was the most frequent clinical risk factor observed in our study, but the incidence of fractures in our study was lower compared with other Polish studies (20% vs. 30%).[12,20] A similar observation was made on secondary osteoporosis (4% vs. 8%[12] or 13%[20]) and smoking (11.7% vs. 13.8%,[20] 17%,[13] or 15%[12]).

We examined a random sample of patients that had not been treated for osteoporosis before. The analysis of such population may help assess the number of candidates for treatment in the whole country. This information has considerable epidemiologic and economic implications, significant for balancing costs and benefits of fracture prevention. The data presented in this study are preliminary and selective. Men and premenopausal women have not been studied before in this setting. Still, even such selective data prove that it is necessary to specify the criteria

of selection for treatment and determine intervention thresholds.

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ARTYKUŁ ORYGINALNY

Porównanie wybranych metod oceny ryzyka złamań u kobiet po menopauzie

Analiza populacji łódzkiej badania EPOLOS

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SŁOWA KLUCZOWE

FRAX™, próg interwencyjny, ryzyko złamań

STRESZCZENIE

WPROWADZENIE Podstawowym problemem podczas kwalifikacji do leczenia osteoporozy jest identyfikacja pacjentów z największym ryzykiem złamań. FRAX™ jest nowym algorytmem, integrującym kliniczne czynniki ryzyka złamań i wynik badania densytometrycznego.

CELE Celem badania była ocena zastosowania metody FRAX™ w kwalifikacji do leczenia osteoporozy w porównaniu z innymi metodami oceny ryzyka złamań.

PACJENCI I METODY Do badania włączono 94 pacjentki po menopauzie w wieku 55–79 lat, wybrane losowo, dotąd nieleczone z powodu osteoporozy (grupa łódzka programu EPOLOS [European Polish Osteoporosis Study]). Oceniono czynniki ryzyka złamań, wykonano badanie densytometryczne szyjki kości udowej. Następnie kwalifikowano pacjentów do terapii na podstawie obecności przebytych złamań, wyników densytometrii oraz metody półilościowej tabelarycznej (*semiqantative tabular method* – SQM) (wg Osteoporosis Society of Canada Recommendations for Bone Mineral Density Reporting), 10-letniego ryzyka złamań (obliczane metodą FRAX™ przy użyciu różnych progów interwencyjnych).

WYNIKI Przy użyciu metody FRAX™, w zależności od przyjętego progu interwencyjnego, do terapii kwalifikowało się 5,2–52% badanych kobiet. Jeśli decyzja terapeutyczna zostałaby oparta na obecności przebytych złamań trzonów kręgowych, do terapii zostałoby zakwalifikowanych 4,2% pacjentów, po włączeniu pozostałych złamań – 20,2%. Jeśli decyzja zostałaby oparta wyłącznie na wyniku badania densytometrycznego, do leczenia zostałoby zakwalifikowanych 8,5% kobiet. Duże ryzyko złamań metodą SQM występowało u 7% badanych kobiet, średnie u 19% i małe – u 74%.

WNIOSKI Właściwe wykorzystanie metody FRAX™ w Polsce wymaga określenia progu interwencyjnego. Zastosowanie metody FRAX™ zmienia demograficzny profil pacjentów kwalifikowanych do terapii, zwiększając liczbę osób zakwalifikowanych w starszych grupach wiekowych.

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