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ORIGINAL ARTICLE

What was your fracture risk evaluated by FRAX® the day before your osteoporotic fracture?

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Abstract Osteoporotic fracture (OF) is one of the major causes of morbidity and mortality in industrialized countries. Switzerland is among the countries with the greatest risk. Our aim was (1) to calculate the FRAX® in a selected Swiss population the day before the occurrence of an OF and (2) to compare the results with the proposed Swiss FRAX® thresholds. The Swiss Association Against Osteoporosis proposed guidelines for the treatment of osteoporosis based on age-dependent thresholds. To identify a population at a very high risk of osteoporotic fracture, we included all consecutive patients in the active OF pathway cohort from the Lausanne University Hospital, Switzerland. FRAX® was calculated with the available data the day before the actual OF. People with a FRAX® body mass index (BMI) or a FRAX® (bone mineral density) BMD lower than the Swiss thresholds were not considered at high risk. Two-hundred thirty-seven patients were included with a mean age of 77.2 years, and 80 % were female. Major types of fracture included hip (58 %) and proximal humerus (25 %) fractures. Mean FRAX® BMI values were 28.0, 10.0, 13.0, 26.0, and 37.0 % for age groups 50–59, 60–69, 70–79, and 80–89 years old, respectively. Fifty percent of the population was not considered at high risk by the FRAX® BMI. FRAX® BMD was available for 95 patients, and 45 % had a *T* score<−2.5 standard deviation. Only 30 % of patients with a normal or osteopenic BMD were classified at high risk by FRAX® BMD. The current proposed Swiss thresholds were not able to classify at high risk in 50 to 70 % of the studied population the day before a major OF.

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Introduction

Osteoporotic fracture (OF) is one of the major causes of morbidity and mortality in industrialized countries, with Switzerland among the countries with the greatest risk [1]. Recent studies have shown that 30 to 54 % of osteoporotic fractures occur in individuals whose bone mineral density (BMD) *T* score is higher than the cutoff of −2.5 standard deviation (SD), with some falling within the range defined for osteopenia (*T*=−2.5 to −1.0 SD), or "normal" range (*T*>−1.0 SD) [2–4].

To identify major clinical risk factors for OF, data from 20 studies, incorporating more than 275,000 patients, were analyzed [5]. The validation analysis included results from the Swiss SEMOF cohort [4, 6]. Factors such as prior fragility fracture after the age of 50 years old, age, sex, body mass index (BMI), use of glucocorticoids, secondary osteoporosis, rheumatoid arthritis, parental history of hip fracture, current smoking, and alcohol intake were considered. These factors were identified as clinical predictors of osteoporotic fracture independently from BMD [5]. Taking into account local epidemiological data for specific fracture outcome and mortality, a Swiss-specific FRAX® model was proposed [6]. The FRAX® can be calculated either incorporating (FRAX® BMD) or not incorporating the BMD (FRAX® BMI).

The challenge is now to find the ideal FRAX® thresholds, country by country, from a health economic perspective to determine the best intervention threshold. Ideally, an appropriate threshold should be established using population-based prospective studies, but such studies tend to be long and quite expensive. Before having these results, some countries have decided to establish new guidelines for the

identification of individuals at high fracture risk based on previously existing guidelines and some local epidemiological data.

With these considerations, the Swiss Association Against Osteoporosis (SVGO) proposed new guidelines for the treatment of osteoporosis based on age-dependent thresholds according to the new Swiss FRAX® model (www.SVGO.ch).

The aim of our study was to calculate FRAX® in a very high-risk population with a recent suspected OF and to compare the results with the proposed Swiss thresholds.

Materials and methods

Patients and measurements

To define a population at high risk of osteoporotic fracture, we selected patients in the active OF pathway cohort from the Lausanne University Hospital, Switzerland. For this study, patients were selected with the following inclusion criteria:

1. They should have been hospitalized at the Lausanne University Hospital for a suspected OF (hip, spine, pelvis, forearm, proximal humerus) between November 2008 and April 2009.
2. They should have been included in the database of the active management protocol for OF [2, 7, 8].
3. They should have given their agreement to participate in this study.

During this active management, a specific questionnaire, including all data for the FRAX® score calculation, was completed. We met 608 consecutive patients during the study period. Only patients with all data available for the FRAX® calculation score were included in the analysis. One-hundred eighty-seven patients had missing data (weight and height principally). All patients included in this study had a diagnosis of osteoporotic fracture, suspected by a clinician expert in osteoporosis management, while 85 were not suspected to have typical OF.

To calculate the FRAX® the day before the actual fracture, we did not consider the actual fracture as a previous fracture. Patients with a traumatic fracture, younger than 50 years old and older than 90 years old, or currently or previously on specific treatment for osteoporosis (e.g., bisphosphonate or teriparatide) were excluded, as proposed in the FRAX® model (24 patients were >90 or <40 and 75 years old and have already received a specific treatment). Finally, out of the 608 consecutive patients considered, 237 met the inclusion criteria, of whom 95 had undergone BMD measurement.

Swiss thresholds and FRAX® calculations

The threshold limits proposed by the SVGO depend upon the patient's age (Table 1). The thresholds were calculated by the FRAX® Swiss calculator using a fictitious population that had suffered one previous fracture (translating existing guidelines) with a standard BMI.

To test the Swiss thresholds, we calculated the FRAX® BMI. The Swiss-specific calculation was generated using the WHO FRAX® website. Patients with a result lower than their "range of age thresholds" were considered not detected at high risk by FRAX® the day before a suspected OF. If patients underwent a rapid dual-energy X-ray absorptiometry (DXA) (not more than 3 months after the actual fracture), we included the femoral neck *T* score and calculated the FRAX® BMD. Patients with a *T* score>−2.5 (lumbar spine and/or femoral neck and/or total hip) and/or a FRAX® BMD lower than their range of age thresholds were considered not detected at high risk neither by FRAX® BMD nor by BMD the day before a suspected OF.

Statistical analysis

Studied parameters were tested for normality, and descriptive statistics as mean ±SD were provided. Results comparing Swiss thresholds and FRAX® BMI are presented in absolute number and percentage of patients. The different models were tested using the SVGO thresholds.

Results

The mean age of the population (n=237) was 77.2±9.4 years, and 80 % were female. The mean weight and height were 66.4±18.8 kg and 162.3±14.0 cm, respectively. The major fracture site was the hip (58.1 %) followed by the proximal humerus (25.0 %), the forearm (22.7 %), the spine (11.0 %), and the pelvis (8.2 %). Only one FRAX® clinical risk factor was present in 41.7 % of the population and one or more FRAX® clinical risks factors in 70.8 % of the population. Clinical risk factors for osteoporosis were more prevalent in

Table 1 Lower threshold limits before initiating specific treatment for osteoporotic fractures in Switzerland

Age (in years)	Threshold (all major osteoporotic fractures) (%)
50	>10
60	>15
70	>30
80	>40

Based upon calculating the 10-year absolute probability of fracture using the FRAX® calculator for Switzerland

Table 2 FRAX® clinical risk factors

Age/risk factors	Previous fracture (%)	Parental hip fracture (%)	Corticotherapy (%)	RA (%)	Alcohol (%)	Tobacco (%)
50–59 (n=17)	66.0	22 .0	5.5	0.0	50.0	55.0
60–69 (n=37)	45.0	9.0	13.0	3.0	42.0	42.0
70–79 (n=63)	55.0	4 .0	14.0	2.8	13.0	24.0
80–89 (n=120)	52.0	12.0	5.6	0 .0	4.8	7.2

RA rheumatoid arthritis

the youngest group (50–59 years old) than in the oldest group (Table 2).

The mean FRAX® BMI (the 10-year probability of a major OF percentage) was 28.0 %. The mean FRAX® BMI was 10.0, 13.0, 26.0, and 37.0 % for those aging 50–59, 60–69, 70–79, and 80–89 years old, respectively (Fig. 1). According to the Swiss thresholds, 47.0, 57.0, 56.0, and 54.5 % of patients (for ages 50–59, 60–69, 70–79, and 80–89 years old, respectively) were not considered at high risk by the FRAX® BMI the day before a major OF. Results by fracture site are shown in Table 3. A DXA was realized in 95 patients, of whom 45 % had an osteoporosis with a T score<−2.5 SD (lumbar spine and/or femoral neck and/or total hip).

Patients with a normal or osteopenic BMD had a FRAX® BMD lower than the Swiss age thresholds in 50, 71, 85, and 84 % for the groups aging 50–59, 60–69, 70–79, and 80–89 years old, respectively. In other words, the FRAX® BMD identified less than 30 % of patients with a normal or osteopenic BMD the day before an OF to be at high risk of fracture.

Discussion

The development of new scientifically supported treatments against osteoporosis, and society's increasing preoccupation with the economic costs of osteoporotic fractures, has brought about the need for not only effective, but also efficient management of osteoporosis [3, 9–13]. The new FRAX® model for the prediction of osteoporotic fractures is the cheapest and is probably an efficient means to identify populations at low, medium, or high risk for an OF. FRAX® has been developed to predict the 10-year fracture risk probability and to improve the positive predictive value of BMD [5]. It is a powerful tool that can be developed and adapted for any specific country to calculate its "local" risk [3]. In a second step, thresholds and FRAX® prediction have to be calibrated and established, thanks to prospective studies. Sometimes, the FRAX® calibration has changed the initial FRAX® after adjustment by specific prospective studies. In Canada, the Manitoba cohort and the Canadian Multicentre Osteoporosis study (CaMOs) cohort allowed to calibrate the FRAX® Canadian prediction. In the CaMOs, FRAX® based on clinical factor risks (CRFs) and BMD was found to be a more accurate predictor of fracture risk than BMD alone or FRAX® estimated on CRFs alone [14]. In France, two independent cohorts, Os des Femmes de Lyon (OFELY) [15] and a subset of the Osteoporosis and Ultrasound Study (OPUS) [16], compared the observed incidence of fracture with the predicted probability of fracture from FRAX®. In the OFELY study, among women ≥65 years old with low BMD values, the 10-year predicted probability of major osteoporotic fracture with BMD was 48 % lower than the observed incidence of fracture. In the

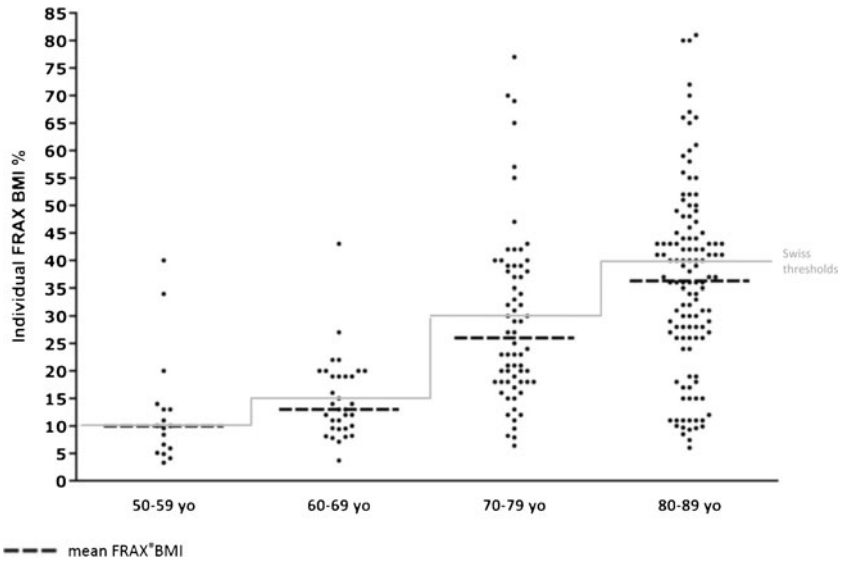

Fig. 1 Results of FRAX® BMI for the overall population by age group. *yo* Years old

Table 3 Results by fracture site

	All fractures			Hip			Vertebral			Pelvic			Forearm			Humeral		
Age	Swiss thresholds (%)	*N*	FRAX® m (%)	Percentage < *T*	*N*	FRAX® m (%)	Percentage < *T*	*N*	FRAX® m (%)	Percentage < *T*	*N*	FRAX® m (%)	Percentage < *T*	*N*	FRAX® m (%)	Percentage < *T*	*N*	FRAX® m (%)	Percentage < *T*
50–59	>10	17	10.0	*47*	8	14.4	*37*	2	4.5	*100*	0			3	6.0	*66*	4	15.0	*75*
60–69	>15	37	13.0	*57*	14	13.8	*56*	5	23.0	*40*	1	11.0	*100*	8	7.0	*62*	9	19.4	*33*
70–79	>30	63	26.0	*56*	38	31.4	*50*	7	23.0	*85*	5	36.4	*40*	3	13.0	*66*	10	33.2	*50*
80–89	>40	120	37.0	*54*	75	35.6	*60*	16	40.0	*37*	9	28.9	*55*	8	25.6	*38*	12	41.5	*33*
		237			135			30			15			22			35		

N number of patients, *FRAX® m* FRAX® BMI mean, *Percentage < T* percentage of patients with a FRAX® score below the Swiss threshold

OPUS cohort (with a following of 6 years), FRAX® with or without BMD could not predict hip OFs. Nevertheless, we have to interpret these external validations of FRAX® with caution as mentioned by Kanis et al. [17]. In Switzerland, there is no post-FRAX® model prospective data available yet. The thresholds proposed by SVGO were calculated by age group to account for major OFs. Our objective was to calculate FRAX® (and not to do an external validation) and to compare results with these thresholds within a population that had actually suffered recent suspected OFs. Half of the population we studied had a FRAX® BMI value below the Swiss thresholds. Regarding the site of the osteoporotic fracture (Table 3), we cannot draw conclusions as the number of patients per group is too small.

Interestingly, in the subpopulation with a DXA measurement, BMD alone identified 45 % of the population to be at high fracture risk. FRAX® BMD has identified at high risk less than 30 % of patients with a normal or osteopenic BMD the day before a suspected OF. Finally, in our population, FRAX® BMD does not seem to improve the detection of patients at high risk comparatively with BMD. Some can argue that in our country, BMD is limited within the condition of reimbursement. However, in all age groups, 45 to 66 % of patients could have had a reimbursement only based on one clinical risk factor: a previous low traumatic fracture (Table 2). This is the only one homogenous CRF regarding age group in our population. Moreover, in our younger population, we found more CRFs than others and lower *T* scores. These observations could probably explain the high FRAX® BMI found in this subgroup. Among the limitations of FRAX®, some can argue that using neck BMD as the sole BMD site to calculate the probability of fracture may not be appropriate in all situations [18]. We tested if our patients could have had a different result if the FRAX® BMD was performed with the result of the spine BMD (for those with a lower spine BMD than femoral neck BMD). We followed the hypothesis that the fracture risk for a given patient could lead to a different FRAX® outcome when a difference of at least 1 SD exists between both BMDs of the neck and spine [19]. None of our patients fulfilled this criterion.

Our study has several limitations. First, number of patients in each age strata is small. Although our sample size is relatively small, it is homogeneous and representative of our inpatient population (median age, sex, and high prevalence of hip fracture). Second, the FRAX® tool was done to predict a 10-year probability risk of fracture and not an immediate risk of fracture. However, a fracture occurring the day after an evaluation is included in the 10-year probability. Third, we did not have a control population (non-fractured patients) to calculate the sensitivity, specificity, and positive/negative predictive values of the thresholds, but our objective was not to propose new thresholds, only to test it in a very high-risk population. Fourth, fall is not

evaluated in FRAX®, and it is possible that our population was at high risk of fall. Finally, to be able to compare our result with SVGO thresholds, we only considered the result of FRAX® for major OF, not for hip fracture, in >50 % of our population suffering from a hip fracture.

In summary, the current proposed Swiss thresholds were not able to classify to be at high risk in 50 to 70 % of the studied population the day before a major OF.

Disclosures None.

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