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Probability of fractures predicted by FRAX® and observed incidence in the Spanish ECOSAP Study cohort

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ABSTRACT

Purpose: To assess the ability of the Spanish version of the WHO fracture risk assessment tool (FRAX®) to predict the observed incident fractures in the ECOSAP Study cohort.
Methods: 5201 women, aged 65 or older, were enrolled in a three-year, prospective study by a non-randomized sampling of consecutive cases in 58 primary care centers in Spain. Participants completed an osteoporosis and fracture risk questionnaire and attended follow-up visits every 6 months. All radiologically or surgically confirmed low-trauma, non-spinal fractures were collected. The individual 10-year absolute risks of hip and major osteoporotic fractures were calculated with the FRAX® algorithms for Spain without the inclusion of the bone mineral density (BMD) measurements. Calibration was evaluated by comparing the three-year estimated (E) fractures predicted with FRAX® with the number of observed (O) fractures, and their discriminative ability for the probability of new fractures with the area under the receiving operating characteristic (ROC) curves.
Results: Fifty (0.96%) women sustained an incident hip fracture, and 201 (3.81%) women presented with major osteoporotic fractures (hip, forearm or humerus). The E/O ratios for hip and major osteoporotic fractures were 1.10 and 0.66 respectively. Clinical vertebral fractures were not collected; therefore, the E/O ratio for major fractures should be expected to be lower. The difference between E and O cases reached statistical significance (χ^2, $p<0.001$). Areas under the ROC curves were 0.640 and 0.615 for hip and major osteoporotic fractures respectively.
Conclusions: The Spanish FRAX® underestimates the risk for major osteoporotic fractures. The estimated risk for hip fractures was similar to the observed fractures; however the algorithm had only modest discriminative ability. These results should be interpreted in the context of the relatively low number of observed fractures, especially at the hip.

Introduction

The ability to accurately gauge absolute fracture risk is crucial for implementing preventive measures, making clinical decisions in the individual patient as well as for identifying cost-effective thresholds for pharmacological intervention. This approach has previously been introduced in highly prevalent diseases such as cardiovascular diseases, stroke, and breast cancer [1–3]. The WHO Collaborating Center for Metabolic Bone Diseases at Sheffield has recently developed algorithms to compute age-specific fracture probabilities in men and women from clinical risk factors (CRFs) and bone mineral density (BMD) measurements at the femoral neck. The algorithms (FRAX®) are based on a series of analyses using the primary data from large population-based cohorts that have identified several CRFs for fracture. The performance characteristics of CRFs have been validated in independent, population-based prospectively studied cohorts with over a million person-years of observation [4]. The FRAX® tools calculate the 10-year probability of a major osteoporotic fracture (clinical spine, hip, forearm or proximal humerus) and hip fracture adjusted to the fracture and death hazards of several countries, including Spain [4]. However, there were no Spanish population-based cohorts included in the meta-analysis for the development of the FRAX® algorithm. Moreover, it has been assumed that the Spanish algorithm for the 10-year major osteoporotic fracture prediction is robust enough to be rolled out for clinical use and development of treatment guidelines. This may not be necessarily correct, since the rate of major osteoporotic fractures in

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the Spanish version of FRAX® was derived by extrapolation from the ratio of hip fractures/major osteoporotic fractures in Sweden (Malmö) [5], and not from country-specific studies that were not available at the time the Spanish algorithm was developed. Therefore, it is important to look for additional independent cohorts in which the country-specific predictions from FRAX® can be objectively tested.

The ECOSAP (Ecografía Osea en Atención Primaria) Study, the largest epidemiological, prospective fracture study performed in Spain to date, was a 3-year, prospective study to test the ability of calcaneal quantitative ultrasound (QUS) and several clinical risk factors, including those used in the FRAX® tool, of osteoporosis and fractures to predict the non-vertebral fracture risk in 5201 postmenopausal women in Spain [6].

To evaluate the ability of the Spanish algorithm of FRAX®, we compared calculated FRAX® predicted probabilities of hip and major osteoporotic fractures to the actual fracture incidence observed in the ECOSAP Study cohort.

Patients and methods

The details of the study cohort and assessment methods have been previously published [6]. The study comprised a total of 5201 Caucasian women aged 65 or older, recruited in 58 primary care centers of the National Health Service (NHS) throughout Spain between March 2000 and June 2001, regardless of the reason for consultation. An average of 90 women was included in each study site (range: 26 to161). A non-randomized sampling of consecutive cases attending the study sites was carried out, though only women giving informed consent were included in the study, which had been approved by the appropriate institutional review committees. Only 1.7% of the approximately 5300 women who were invited to be enrolled in the study declined their participation. Given the characteristics of the medical care provided by the Spanish NHS to women aged 65 years or older, the ECOSAP Study cohort is considered representative of the general population of Spanish women of that age group [6]. At the baseline visit, all women completed an osteoporosis and fracture risk factor questionnaire that included a review of conditions and medications constituting risk factors for osteoporosis and falls [7]. Women returned to the study center approximately every six months, and were followed for the occurrence of incident non-vertebral low-trauma fractures for three years. Only low-energy trauma fractures, defined as secondary to minor trauma or a fall from the standing position to floor level, were analyzed. Pathological fractures were excluded, as were those caused by severe trauma (traffic accidents, impact of moving objects, falling from greater than standing height) and fractures of the skull, face, metacarpals and phalanges. All fractures were confirmed by the site investigator, who reviewed the original X-ray film or the radiological or surgical reports.

At each scheduled visit, if patients failed to attend, information about their clinical situation was obtained by telephone interviews. In case of death, cause was verified by the investigating physician by means of the medical records. Of the women who were included initially, 4453 (87.3%) completed the planned 3-year visits, representing a total follow-up of 14,999 women-years.

Exclusion criteria

Since the study was originally designed to establish absolute fracture risk, the following conditions constituted study exclusion criteria: Paget's disease of the bone, multiple myeloma, bone metastases, renal failure (serum creatinine >265 μmol/dl), hypercalcemia (serum calcium >11 mg/dl), immobilization for >3 months in the preceding year, anatomical anomalies of the right foot interfering with calcaneal ultrasound measurement, therapeutic doses of fluoride (>20 mg/day) for more than 3 months in the past two years or for more than two years at any time in life, a life expectancy (as estimated by the physician) of less than 3 years, or participation in any other investigational study involving drugs.

Outcome variables and statistical analysis

Descriptive baseline demographic and subject characteristics are presented by mean and standard deviation or percentages. For each patient, the probabilities of sustaining a fracture within the next 10 years were calculated according to the baseline clinical risk factors with the use of the FRAX® tool calibrated for Spain (www.shef.ac.uk/FRAX/index.htm). The calculations were based on the age of the patient, gender, body mass index (BMI), previous fracture, family history, current smoking, glucocorticoid use, rheumatoid arthritis, other secondary osteoporosis and alcohol use. There were no BMD measurements made at the femoral neck in this cohort and the 10-year probabilities were, therefore, calculated without BMD. When the age of the patient was above 90 years (n=11), the probability was calculated for the age of 90. The probabilities computed were the 10-year probability of hip fracture and the 10-year probability of a major osteoporotic fracture (clinical spine, forearm, hip or humerus). In 81 cases (1.5%), absolute fracture risk could not be calculated because at least one variable of the FRAX® tool was missing. These patients were excluded from the evaluation of the FRAX® tool performance analysis. No clinical vertebral fracture data were collected in the ECOSAP Study; therefore, the major osteoporotic fracture sites that were considered for the analysis were forearm, hip and humerus only. For those cases with two or more incident fractures (n=52, 1.0%), only the first fracture was considered for the analysis [5].

The 10-year fracture probabilities calculated with the FRAX® tool were annualized to extrapolate the 3-year fracture probabilities, assuming a linear fracture risk over time.

This approach allowed the calibration of the model based on the ratio of the *"estimated"* (E) versus the *"observed"* (O) probabilities of fracture during the 3-year follow-up of the ECOSAP cohort. The differences between the E and the O cases follow a χ^2 distribution. The D'Agostino-Na version of the Hosmer and Lemeshow goodness-of-fit test was used to calculate a Chi square value [8]. The discrimination of the model, i.e. the ability of the FRAX algorithms to discriminate those women who will develop a fracture and those who will not, was measured as the areas under the receiver operating characteristic (ROC) curves (AUC). For the calculation of the AUCs we used the index of rank correlation, Somers' D, which equals $2\times(c-1/2)$ where c is the concordance (discrimination) probability [9]. Statistical analyses were performed with R 2.11.0 (R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria) (www.R-project.org).

Results

Table 1 shows the baseline characteristics of the risk factors of the FRAX® tool in the ECOSAP Study cohort. A more comprehensive description of the baseline characteristics of the cohort is available in

Table 1
Baseline characteristics of the ECOSAP Study cohort.

	n	Mean (SD) or %	Range
Age at baseline (years)	5146	72.3 (5.3)	65–100
Body mass index (kg/m^2)	5128	29.2 (4.7)	15–51
Any fracture since age 35	5146	20.2%	
1st degree family history of fracture[a]	5140	16.8%	
Current smoking	5144	2.2%	
Current glucocorticoids use	5146	2.1%	
Alcohol use (≥3 units per day)	5146	1.6%	
Rheumatoid Arthritis	5146	0.8%	

SD: Standard Deviation.
[a] Biological parents and/or sister/brothers.