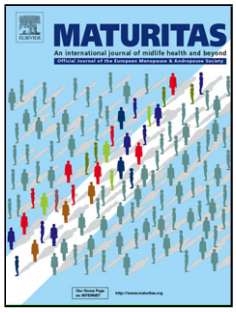

Title: Fracture experience among participants from the FROCAT study: what thresholding is appropriate using the FRAX tool?

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Fracture experience among participants from the FROCAT study: what thresholding is appropriate using the FRAX tool?

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Highlights

- Previously, a Spanish FRAX risk thresholds of risk had been proposed from FRIDEX cohort.
- We display the suggested algorithm in the FROCAT, a population based cohort.
- The main fracture risk categories (low, intermediate, high) show concordance.
- The frequencies of fragility fractures over 10-year period are similar in FRIDEX and FROCAT cohorts.

Abstract

Objective

To perform an external validation of FRAX algorithm thresholds for reporting level of risk of fracture in Spanish women (low <5%; intermediate ≥5% and <7.5%; high ≥7.5%) taken from a prospective cohort "FRIDEX".

Methods

A retrospective study of 1090 women aged ≥40 and ≤90 years old obtained from the general population (FROCAT cohort). FRAX was calculated with data registered in 2002. All fractures were validated in 2012. Sensitivity analysis was performed.

Results

When analyzing the cohort (884) excluding current or past anti osteoporotic medication (AOM), using our nominated thresholds, among the 621 (70.2%) women at low risk of fracture, 5.2% [CI95%: 3.4-7.6] sustained a fragility fracture; among the 99 at intermediate risk, 12.1% [6.4-20.2]; and among the 164 defined as high risk, 15.9% [10.6-24.2]. Sensitivity analysis against model risk stratification FRIDEX of FRAX Spain shows no significant difference. By including 206 women with AOM, the sensitivity analysis shows no difference in the group of intermediate and high risk and minimal differences in the low risk group.

Conclusions

Our findings support and validate the use of FRIDEX thresholds of FRAX when discussing the risk of fracture and the initiation of therapy with patients.

Key words

Osteoporotic fractures; FRAX thresholds.

Introduction

Osteoporosis is an asymptomatic bone disease that can lead to an increased risk of fragility fractures, commonly occurring after minor falls. It is the most common musculoskeletal disease in humans and has a growing impact on the public health systems of developed countries due to their aging populations[1-6].

Traditionally, Bone Mineral Density (BMD), measured by a Dual-energy X-ray Absorptiometry (DXA) scan, has been the main predictor of fragility fracture[7-8]. Despite the significant influence of BMD on the overall risk of fracture, several studies have shown that taken in isolation, it fails to deliver a cost-effective population screening test[7-9]. The current practice in most developed countries is to identify patients at high risk of fragility fractures taking into account the presence of other risk factors besides densitometric osteoporosis[9-14].

The European Society for Clinical and Economic Evaluation of Osteoporosis and Osteoarthritis (ESCEO)[15], proposes a combined assessment of BMD and clinical risk factors for fracture to decide both diagnostic and therapeutic interventions, and the best known and most widely used is the FRAX® Tool (Fracture Risk Assessment®), which is freely available online[16]. This tool calculates the absolute risk of osteoporotic fracture over a 10-year period, considering clinical risk factors independent of bone mass in the male and female population between 40 and 90 years old, who have not received anti osteoporotic medication (AOM)[17]. FRAX is a computer-based algorithm, developed to evaluate the 10-year probability (absolute risk) of a major osteoporotic fracture (clinical spine, forearm, hip or shoulder) and the 10-year probability of hip fracture alone [http://www.shef.ac.uk/FRAX/]. This tool integrates 10 of the clinical risk factors that have shown a strong association with the incidence of fracture in previous studies according to WHO experts. It is able to recalculate the risk itself with inclusion of BMD at the femoral neck (FN) (g/cm^2 or T-score). Therefore the FRAX algorithm gives the overall absolute risk for the four main fractures as well as proximal femur alone if needed[15-19].

The FRAX models have been developed from studying population-based cohorts from Europe, North America, Asia and Australia[20,21]. As its developers specify, FRAX is calibrated to countries where population fracture risks and mortality rates are known. This is because the probability of fracture is calculated taking into account both the risk of fracture and the mortality rate[20,21]. There is a consensus in approaching fracture probability based on the combined

assessment of clinical risk factors, along with BMD and age, to improve sensitivity fracture prediction without specificity being adversely affected[22]. FRAX authors also specify that due to the epidemiological and economical variability across countries for medical interventions for preventing fractures, cost-effective intervention thresholds have to be country-specific as, for example, it has been made in the United Kingdom[23].

In Spain, to evaluate the fracture risk, the data used for the FRAX country specific algorithm came from different studies, most of which were retrospective hospital studies from the 1990s although a later study showed similar results[24]. There is hence an urgent need for updating fracture incidence and mortality data to provide a better approach to fracture predictions[20,21]. In addition to what has been said, recent Spanish female population cohort studies have assessed the predictive ability of the FRAX tool locally, and analyzed the FRAX discriminative and predictive ability to predict major osteoporotic fractures[5,25-28]. The ability of the FRAX tool to discriminate between Spanish women with high or low fracture risk shows acceptable values that are similar to studies in other populations[26-28]. A more recent refinement led to the construction of a calibrated model to determine three levels of FRAX risk (low, intermediate, high) based on the analysis of the main fracture outcomes of women from the FRIDEX cohort over a 10-year period of follow up[25,26] that better identified women at high risk of fracture (figure 1).

The aim of this study was to apply the same thresholds proposed by the FRIDEX study in another general population of women recruited to the FROCAT cohort.

Methods

The FROCAT cohort represents a Spanish cohort of men and women aged ≥ 40 and ≤ 90 years old assigned to family physicians participating in the study that were working in the Public Health Services and practices managed by the Catalan Health Institute. This institution is the main public provider of health services in Catalonia-Spain and covers around 83% of the 7.5 million population and has computerized medical records of their patients since 2001. Each family physician has in charge a group of patients who are visited on a practice.

Fieldwork for this study was conducted during 2012. An invitation to primary care physicians in Catalonia was sent out inviting them to take part in the project, recruiting their own pa-

tients. The sample of patients was taken from those who were assigned to the family physicians in 2001 and who had been previously selected by simple randomization by stratified age and sex groups according to the Catalan population census and province. Patients' and relatives verbal informed consent was obtained and recorded in the patients' medical records.

The sample for this study consists of 1,434 Caucasian women from ethnicity, ≥ 40 and ≤ 90 years of age in 2001. Medical history was recorded according to ICD-10 coding. Patients were excluded if they developed cancer during the 10 years of study period (14) or lived outside of the study area (29), were unable to be contacted (191) or refused participation (42). Patients who died (68) during the study were also excluded. After exclusions the participants were 1,090 women (figure 2).

During a follow up 10-years period the incident fracture was recorded, and validated against hospital and electronic records. Only fracture information that coincided both in medical records and patients' reports was used as reliable data. The fragility fracture risk was calculated using the FRAX® Spanish version with data registered from 2001 without BMD in all participants and with BMD in 234 (21.5%) cases that had DXA scan results following the general practice.

The FRAX osteoporotic fracture risk thresholds that have been used in this study of the general population come from the analysis of first osteoporotic fractures during a 10-year period in a prospective cohort of Spanish women (FRIDEX cohort). The FRIDEX study set up 3 levels of risk of osteoporotic fracture with FRAX without DXA: low risk at baseline FRAX <5%, intermediate risk at baseline FRAX between ≥ 5 and <7.5% and high risk at baseline FRAX ≥ 7.5% (figure 1). FRIDEX model requires a FRAX reassessment when the FRAX risk is intermediate, including a T-score of FN and also, the results in terms of densitometric osteoporosis must be taken into consideration. When the risk is high, pharmacological treatment with anti osteoporotic medication must be considered and promoting a healthy lifestyle when the risk of osteoporotic fracture is low.

Statistical methods

The characteristics of the population were described according to descriptive univariate analysis. The results were reported as mean and standard deviation for quantitative data, as

frequency and percentage for qualitative data. In statistical comparisons for cases with or without prior fracture we used the Chi-square test to evaluate qualitative variables and the Student's t-test or the Mann–Whitney *U* test to evaluate quantitative variables. In case of significant differences ($p < 0.05$) a confidence interval of 95% was calculated. All the statistical tests were undertaken with a confidence interval of 95 % and with the use of the 17th version of the SPSS statistical package (*Statistical Package for the Social Sciences* 2008. SPSS Inc).

To know the differences in clinical risk factors (CRFs) between fractured/ non fractured individuals we performed a Chi-square test. Sample size calculations based on our previous paper had indicated that we required a minimum of 750 participants.

Results

The study population was comprised of 1,090 women. Table 1 shows the baseline characteristics of the participants with the most important measurements and risk factors analyzed. A total of 154 women (14.1%) reported previous fragility fractures and 119 (10.9%) reported parental hip fracture. There were 331 (30.4%) women that suffered falls during the previous year of the end of study (2011-2012) and 206 (18.9%) women were categorized as current or past users of anti osteoporotic medication. There were also 234 cases with DXA and 85 of them (36.3%) with osteoporosis (table 1 and 2).

We analyzed the distribution of CRFs included in FRAX, plus falls during the previous year to the end of study (2011-2012) comparing women who had suffered fractures during the study period, and those who did not, as displayed in table 2. The CRFs showing significant differences between fractured/nonfractured individuals were: age, previous fractures, those having suffered falls in the previous year; in current smokers and also in normal results of DXA a lower percentage of fractures was found.

The cumulative incidence of suffering a major osteoporotic fracture over the 10-year period is shown in table 3. Significant differences in osteoporotic fractures were found, above all, in hip and spinal fractures between the groups of over and fewer than 65 years of age.

The selected women from FROCAT cohort (884), using FRAX to calculate the major osteoporotic fracture probability cutoffs suggested in the FRIDEX stratification model calculated

without BMD (<5%; ≥5% and <7.5% and ≥7.5%)[5], were categorised as low, intermediate and high risk, respectively (table 4). The analysis carried out shows 8.1% of fractures during the 10-year period and the low risk group (70.2%) sustained 5.2% of osteoporotic fractures and the high risk group (18.6%) of the cohort sustained 15.9% of fractures by the end of the 10-year period. Sensitivity analysis against model risk stratification FRIDEX of FRAX Spain shows no significant difference.

When the 206 cases with AOM are included in the data (table 5) the fracture figure comes to 11.7%. The low risk group (67.8%) of the cohort was found to have sustained 6.8% of osteoporotic fractures, the intermediate risk group (11.9%) sustained 18.5% and the high risk group (20.3%) of the cohort, were found to have sustained 24% of fractures at the end of the 10-year period. By including 206 women with AOM, the sensitivity analysis shows no difference in the group of intermediate and high risk and minimal differences in the low risk group.

Discussion

The study results show that at a population level, the adjusted thresholds suggested based on the FRAX algorithm for low, intermediate or high risk of fracture in a Spanish female population perform well for prediction of incident fracture in a general population based cohort study.

Family history of hip fracture has been shown as an independent contributory factor to fracture risk in meta analyses and other studies[1,5,19], but no significance has been shown in this study, even though a relatively high percentage (11%) was recorded. This observation has been made in prior Spanish female population studies[5,26-28], and may reflect our slightly younger population, since parental fracture will become more common as an individual (and their parent) ages. Previous fracture shows statistical significance as shown in some studies[22,26].In previous meta-analysis, smoking has been found to be a risk factor when it comes to fractures. Surprisingly, however, smokers among the female cohort taken from the general Spanish population shows discordant data. This may be due to the mean age of the cohort, although no significant differences have been found in other Spanish cohort studies[26].

Number of falls in the last year are not incorporated as a variable in the FRAX tool[16,17] and this population based study shows significant differences in the risk of a fall among women

with and without fractures. This factor has been shown to be a BMD independent risk factor in the available Spanish female data[5,26] and might add to growing evidence that proposes that fall history might be included as a predictor in other osteoporotic fracture scales[29].

The overall hip fracture incidence data standardized per 100,000 people per year is in accord with other Spanish cohorts[5]. Clinical symptomatic spine fracture incidence data standardized per 100,000 people per year was, in this overall cohort, higher than observed in the FRIDEX cohort, but about 5 times lower than observed in another Spanish cohort, where radiographic criteria were used for detection and clinical vertebral fractures accounted for only 17% of the ultimately found by X-rays[30]. Humeral fractures have been included in a few studies in Spain and have traditionally been considered of little relevance until the widespread use of the FRAX algorithm; in this FROCAT cohort proximal humeral fractures were of similar frequency to other studies[19,26-28].

Our study has both strengths and limitations. Regarding limitations, in this cohort there are low representation of women with arthritis, glucocorticoids takers, risk drinkers or smokers. Given that FROCAT is a cohort of the general population and the decision to establish the BMD was taken according to general practice, only 234 cases had DXA scans to reassess the FRAX with FN in cases of intermediate risk as recommended by FRIDEX model and sensitivity analysis was performed using FRAX without DXA. Regarding exclusions, 18.2% of subjects for whom we were unable to obtain medical data were excluded: no consent, migrations, unable to contact and 5.7% for deaths or cancer (figure 2). Other type of exclusions were women who had started on AOM over the 10 years follow up period, because FRAX is validated only for use in the treatment of naïve individuals. When we analyze the cohort including the group of 206 cases with AOM we observe that the breakdown in the three groups -fracture risk is similar to the analysis of the 884 women cohort. However, osteoporotic fractures increase 44.4% (from 8.1% to 11.7%) due to the fact that the groups of intermediate and high risk fracture are increased substantially going from 12.1% to 18.5% and 15.9% to 24%, respectively, increasing the risk of fracture 2.5. This is consistent with women receiving more AOM at increased risk of fracture due to the existence of risk factors not included in FRAX tool, such as frequent falls, aromatase inhibitor prescriptions, androgen-deprivation therapies, comorbidities, sarcopenia, a sedentary lifestyle and other conditions. We also asked retrospectively about fractures, but these were validated against electronic records registered during the period since 2001. The FRAX tool itself, has certain limitations,such as being un-

able to discriminate between heavy and moderate smokers or between high and low glucocorticoid dosage and that only the femoral neck T-score can be applied. In this study the sensitivity analysis against model risk stratification FRIDEX of FRAX Spain shows no significant difference. Although FRAX is not recommended for people who have been under AOM at some time, by including 206 women with AOM, the sensitivity analysis shows no difference in the group of intermediate and high risk and minimal differences in the low risk group about the FRIDEX cohort thresholds. These results support what has been suggested by two recent publications with minimal differences in terms of FRAX results[18,19]. Use of AOM in Spain, as elsewhere, is still infrequent, as evidenced by the large number of women at significant risk of fracture who received no treatment over follow up.

In conclusion, FRAX tool is a commonly used fracture risk prediction tool with demonstrated utility in daily practice. Our findings strongly validate the use of FRIDEX thresholds of FRAX among Spanish women: low risk at baseline FRAX <5%, intermediate risk at baseline FRAX between ≥ 5 and <7.5% and high risk at baseline FRAX ≥ 7.5% (figure 1), when discussing the risk of fracture and the initiation of medical treatment with patients. Previous studies in three cohorts of Spanish women have also shown that fracture is common, and might incline a clinician toward using more stringent thresholds of low, intermediate and high risk. Further prospective epidemiological studies of fracture incidence, and cost-effectiveness analyses to inform use of AOM, are now required in Spain.

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Conflict of Interest Statement

The authors declare no conflict of interest.

Ethical approval

This study was approved by the Clinical Research Ethics Committee of the Institut d'Investigació en Atenció Primària IDIAP Jordi Gol. Barcelona. Spain.

Informed consent was obtained from all patients.

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RA takes responsibility for the integrity of the data analysis.

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Conflicts of interest: None.

Artwork

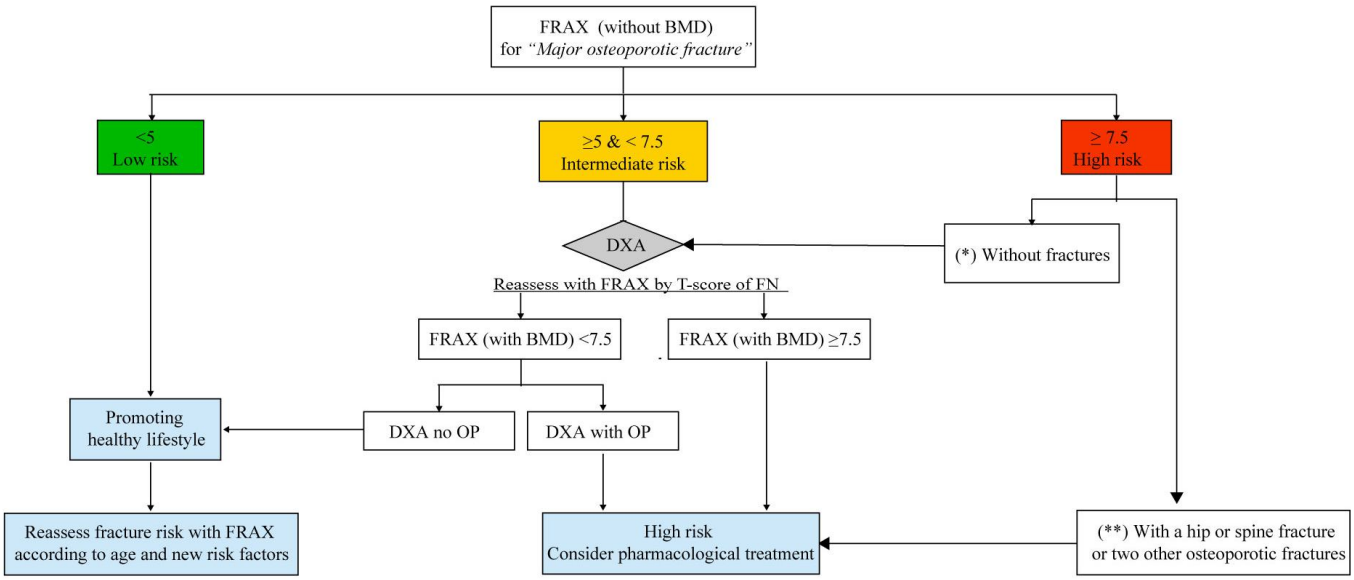
Figure 1:

Color print is required.

Caption: Flow chart to determine osteoporotic fracture risk in the Spanish female population based on FRAX Spain with FRIDEX thresholds. Modified with permission from Azagra et al. Med Clin (Barc). 2015;144(1):1-8. http://dx.doi.org/10.1016/j.medcli.2013.11.014

Footnotes:

- FRAX®: Absolute risk of risk fracture: http://www.shef.ac.uk/FRAX/tool.jsp?lang=sp; *"Major osteoporotic fracture"* including: hip, clinical spine, humerus and wrist.
- BMD: Bone Mineral Density.
- DXA: Dual absorptiometry of x-ray.
- FM: Femoral neck.
- OP: Densitometric osteoporosis with T-score ≤ -2.5 SD (WHO 1994), at least in one of theses 3 regions of DXA: L1-L4, total hip or FN (ISCD 2007 official position).
- (*): Cost-effective option without fractures or one non-hip or clinical spine fractures[5].

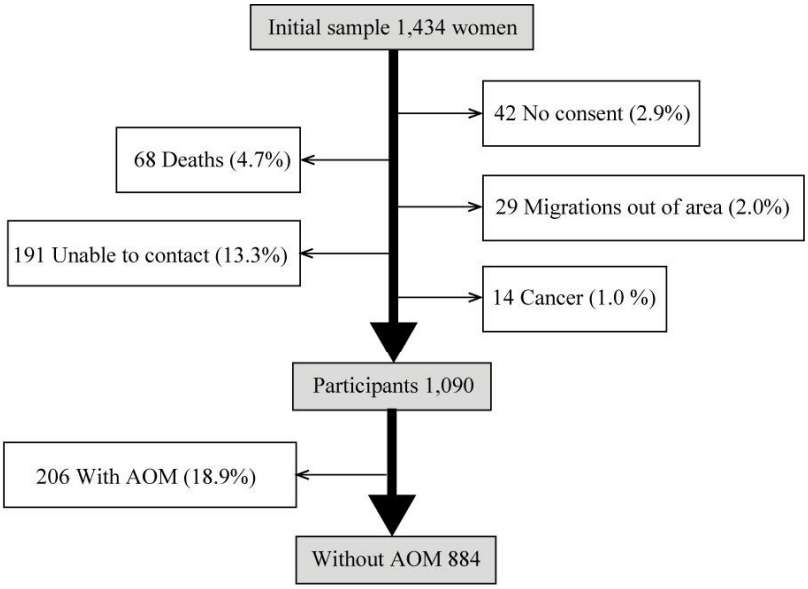


- (**): Following other international considerations[10].

Figure 2:

Color print is required.

Caption: Flow chart FROCAT Study



Footnote:

- AOM: Anti osteoporotic medication.

Tables with Captions

Table 1:

Color print is required.

Caption: Cohort profile with the prevalence of fracture risk factors: FROCAT cohort.

Variables	n	% / SD
Women	1090	100%
Age (years)	59.1	± 12.4
≥ 65 years (n ± %)	375	34.4%
≥ 50 to 64 years (n ± %)	715	65.6%
Weight (kg)	68	± 13
Height (cm)	155.9	± 6.9
BMI (kg/m2)	28	± 5.3
Smoking	172	15.8%
Alcohol ≥ 3 units per day	17	1.6%
Previous fractures	154	14.1%
Parental hip fracture	119	10.9%
Glucocorticoids	45	4.1%
Rheumatoid Arthritis	21	1.9%
≥ 2 Falls in previous year	331	30.4%
Osteoporosis (FN, TF or L1-L4)	85	36.3%
Calcium or Vitamin D supplements	263	24.1%
AOM with or without supplements	206	18.9%

Footnotes:

- SD: Standard deviation.
- BMI: Body mass index.
- FN: Femoral neck.
- TF: Total proximal femur.
- L1-L4: Lumbar spine.
- AOM: Anti osteoporotic medication.

Table 2:

Color print is required.

Caption: Comparative analysis between women with or without fractures. FROCAT cohort.

	With fractures	**Without fractures**	**p-value**	**95% CI**
	n= 127	n= 963		
Age (SD)	66.9 (11.3)	58.1 (12.1)	<0.001	6.64-11.09
BMI Kg/cm2 (SD)	27.9 (5.1)	28.0 (5.4)	0.782	
BMI <20 Kg/cm2	5 (4.0%)	30 (3.3%)	0.591	
Previous fractures	41 (32.3%)	113 (11.7%)	<0.001	12.2-29.0
Parental hip fracture	14 (11.0%)	105 (10.9%)	0.973	
Smoking	11 (8.7%)	161 (16.7%)	0.02	2.56-13.4
Alcohol ≥ 3 units per day	3 (2.4%)	14 (1.5%)	0.436	
Glucocorticoids (%)	6 (4.7%)	39 (4.1%)	0.721	
Rheumatoid Arthritis	2 (1.6%)	19 (2.0%)	0.758	
≥ 2 Falls in previous year	62 (48.8%)	269 (27.9%)	<0.001	11.8-30.0
Results DXA [available in 234/1090 (21.5%)]	n= 40	n= 194		
Osteoporosis 85/234 (36.3%)	16 (40.0%)	69 (35.6%)	0.332	
Osteopenia 101/234 (43.2%)	21 (52.5%)	80 (41.2%)	0.016	2.1-20.5
Normal 48/234 (20.5%)	3 (7.50%)	45 (23.2%)	<0.001	10.4-21.0

Footnotes:

- CI: Confidence interval.
- SD: Standar deviation.
- BMI: Body mass index.
- DXA: Dual absorptiometry of x-ray.

Table 3:

Color print is required.

Caption: Analysis of accumulate incidence over 10 years and fractures standardised by 100,000 women/year among women of FROCAT cohort.

	< 65 years		≥ 65 years		**Total**		**p-value**
	n: 715		n: 375		n: 1090		< 65 vs ≥ 65 years
	n (%)	**100,000/year**	**n (%)**	**100,000/year**	**n (%)**	**100,000/year**	
All Fx*	95 (13.3%)	1348	93 (24.8%)	2480	188 (17.2%)	1706	<0.001
Osteoporotic Fx**	50 (7.0%)	699	77 (20.5%)	2053	127 (11.7%)	1165	<0.001
Hip Fx	3 (0.4%)	42	21 (5.6%)	560	24 (2.2%)	220	<0.001
Spine Fx	4 (0.6%)	56	24 (6.4%)	640	28 (2.6%)	257	<0.001
Humeral Fx	10 (1.4%)	140	11 (2.9%)	293	21 (1.9%)	193	0.079
Wrist Fx	33 (4.6%)	468	21 (5.6%)	560	54 (5.0%)	495	0.475

Footnotes:

- Fx: Fractures.
- (*): All fractures excluding fingers and head.
- (**): Including hip, spine, humeral and wrist fractures.

Table 4:

Color print is required.

Caption: Relationship between risk levels according FRIDEX model of FRAX® Spain for major osteoporotic fracture applied to the results of the FROCAT cohort, excluded 206 women treated during the period.

	% of cohort	Total women	Women with osteoporotic fracture	% of women with fractures in each level of risk	95% CI
Low risk [FRAX < 5]	70.2	621	34	5.2%	3.4-7.6
Intermediate risk [FRAX ≥ 5 and < 7.5]	11.2	99	12	12.1%	6.4-20.2
High risk [FRAX ≥ 7.5]	18.6	164	26	15.9%	10.6-24.2
Total		884	72	8.1%	6.4-10.2

Footnotes:

- CI: Confidence interval.

Table 5:

Color print is required.

Caption: Relationship between risk levels according FRIDEX model of FRAX® Spain for major osteoporotic fracture applied to the results of the FROCAT cohort including women with anti osteoporotic medication.

	% of cohort	Total women	Women with osteoporotic fracture	% of women with fractures in each level of risk	95% CI
Low risk [FRAX < 5]	67.8	739	50	6.8%	5.0-8.8
Intermediate risk [FRAX ≥ 5 and < 7.5]	11.9	130	24	18.5%	12.2-26.2
High risk [FRAX ≥ 7.5]	20.3	221	53	24.0%	18.5-30.2
Total		1090	127	11.7%	9.8-13.7

Footnotes:

- CI: Confidence interval.