Original article

FRAX® thresholds to identify people with high or low risk of osteoporotic fracture in Spanish female population

Rafael Azagra a,b,c,∗, Genís Roca a,d, Juan Carlos Martín-Sánchez e, Enrique Casado f, Gloria Encabo g, Marta Zwart a,h, Amada Aguyé i, Adolf Diez-Pérez a,i,k, representing the research group GROIMAP

a Departamento de Medicina, Universitat Autònoma de Barcelona, Barcelona, Spain
b Medicina de Familia, CAP Badia del Vallés, Institut Català de la Salut (ICS), USR MN-IDAPI Jordi Gol, Barcelona, Spain
c Departamento de Medicina, Universitat Internacional de Catalunya, Sant Cugat del Vallés, Barcelona, Spain
d Medicina de Familia, CAP Sant Llútzer, Corporació Sanitaria de Terrassa, Terrassa, Barcelona, Spain
e Reumatología, Hospital de Sabadell, Corporació Sanitaria Parc Taulí, Sabadell, Barcelona, Spain
f Medicina Nuclear, Hospital Universitari Vall d’Hebron, Institut Català de la Salut (ICS), Barcelona, Spain
g Medicina de Familia, CAP Girona-2, Institut Català de la Salut (ICS)-USR Girona, IDAPI Jordi Gol, Girona, Spain
h Medicina de Familia, CAP Granollers Centre, Institut Català de la Salut (ICS), Granollers, Barcelona, Spain
i Departamento de Medicina Interna, URFOA, IMIM, Parc de Salut Mar, Barcelona, Spain
j Médica de Familia, CUG, Sant Cugat del Vallés, Barcelona, Spain
k Red Temática de Investigación Cooperativa en Envejecimiento y Fragilidad (RETICEF), Instituto de Salud Carlos III-FEDER, Madrid, Spain

A R T I C L E   I N F O

Article history:
Received 18 July 2013
Accepted 7 November 2013

Keywords:
Osteoporosis
Osteoporotic fracture
FRAX®
Dual-energy X-ray absorptiometry
Cost-effectiveness

A B S T R A C T

Background and objective: To detect FRAX® threshold levels that identify groups of the population that are at high/low risk of osteoporotic fracture in the Spanish female population using a cost-effective assessment.

Patients and methods: This is a cohort study. Eight hundred and sixteen women 40–90 years old selected from the FRIDEX cohort with densitometry and risk factors for fracture at baseline who received no treatment for osteoporosis during the 10 year follow-up period and were stratified into 3 groups/levels of fracture risk (low <10%, 10–20% intermediate and high >20%) according to the real fracture incidence.

Results: The thresholds of FRAX® baseline for major osteoporotic fracture were: low risk ≤5; intermediate ≥5 to <7.5 and high ≥7.5. The incidence of fracture with these values was: low risk (3.6%; 95% CI 2.2–5.9), intermediate risk (13.7%; 95% CI 7.1–24.2) and high risk (21.4%; 95% CI 12.9–33.2). The most cost-effective option was to refer to dual energy X-ray absorptiometry (DXA-scan) for FRAX® ≥5 (Intermediate and high risk) to reclassify by FRAX® with DXA-scan at high/low risk. These thresholds select 17.5% of women for DXA-scan and 10% for treatment. With these thresholds of FRAX®, compared with the strategy of opportunistic case finding isolated risk factors, would improve the predictive parameters and reduce 82.5% the DXA-scan, 35.4% osteoporosis prescriptions and 28.7% cost to detect the same number of women who suffer fractures.

Conclusions: The use of FRAX® thresholds identified as high/low risk of osteoporotic fracture in this calibration (FRIDEX model) improve predictive parameters in Spanish women and in a more cost-effective than the traditional model based on the T-score ≤−2.5 of DXA scan.

© 2013 Elsevier España, S.L.U. All rights reserved.

Umbrales de FRAX® para identificar personas con alto o bajo riesgo de fractura osteoporótica en población femenina española

R E S U M E N

Fundamento y objetivo: Detectar los umbrales de la herramienta FRAX® que determinen los grupos de riesgo alto/bajo de fractura osteoporótica en la población femenina española y su valoración coste-efectiva.

Palabras clave:
Osteoporosis
Fractura osteoporótica


E-mail address: rafael.azagra@uab.cat (R. Azagra).

2387-0206/© 2013 Elsevier España, S.L.U. All rights reserved.
FRAX®
Absorciometría dual de rayos X
Coste-efectividad

Pacientes y métodos: Estudio de cohortes. Ochocientas dieciséis mujeres de 40-90 años de la cohorte FRIDEX con densitometría basal, factores de riesgo de fractura y sin tratamiento para la osteoporosis en los 10 años de seguimiento. Se estratificaron en 3 grupos/niveles de riesgo de fractura principal (bajo < 10%, intermedio 10-20% y alto > 20%) según la incidencia real de fractura, y se buscaron los puntos de corte equivalentes de FRAX® basal.

Resultados: Los umbrales de FRAX® basal para fractura principal fueron: riesgo bajo < 5; intermedio ≥ 5 y < 7,5 y alto ≥ 7,5. La incidencia real de fractura con estos valores fue: riesgo bajo (3,6%; IC 95% 2,2-5,9); intermedio (13,7%; IC 95% 7,1-24,2), y alto (21,4%; IC 95% 12,9-33,2). La opción más coste-efectiva fue realizar una dual energy X-ray absorptiometry (DXA, <absorciometría dual de rayos X>) para FRAX® ≥ 5 (riesgo intermedio y alto) para reclasificar los casos mediante FRAX® con DXA en riesgo alto/bajo. Así se seleccionarían 17,5% de las mujeres para DXA y 10% para tratamiento. Con estos umbrales calibrados de FRAX®, comparados con la estrategia tradicional basada en la DXA, se mejoran los parámetros predictivos y se reducen las DXA (82,5%), los tratamientos (35,4%) y el coste global (28,7%) para detectar al mismo número de mujeres que tuvieron fracturas.

Conclusiones: La utilización de los umbrales de FRAX® identificados como alto/bajo riesgo de fractura osteoporótica en la presente calibración (modelo FRIDEX®) mejorarían los parámetros predictivos en mujeres españolas y de una forma más coste-efectiva que el modelo tradicional basado en el T-score ≤ -2,5 de la DXA.

© 2013 Elsevier España, S.L.U. Todos los derechos reservados.
Fig. 1. Flowchart for the selection of the cohort of Spanish women who did not receive treatment during the 10 years of follow-up anti-OP; treatment with osteoporotic medications not supplemented with calcium/vitamin D; OPFx: osteoporotic fracture; Major Fx: major fracture (major osteoporotic in FRAX®).

during the 10 years of the study, not including calcium and/or vitamin D supplements.

Using an initial and final structured questionnaire, the following baseline clinical variables were obtained: age, body mass index (BMI); dichotomous variables (yes/no): previous fracture, hip fracture in the parents, active smoking, glucocorticoids, excessive alcohol intake, rheumatoid arthritis and presence of secondary osteoporosis, as per the FRAX® criteria.

**Determination of bone mass**

Bone mass was determined by central DXA in a single densitometer model (GE Lunar Prodigy Advance™) with software version 11.4 and daily calibrations. According to the recommendations of the International Society for Clinical Densitometry (http://www.iscd.org/official-positions/), the analysed regions were the entire L1–L4 lumbar spine and the total proximal femur and femoral neck values. The results were categorised as osteoporosis, osteopenia or normal, as per the WHO criteria from 1994.

The analyses included only the incident fractures that were able to be confirmed by patient medical files or hospital records. For the FRAX® assessment analyses, only fractures considered major osteoporotic fractures according to the FRAX® tool (hip, clinical vertebrae, proximal humerus and distal forearm) were included.

The risk estimation for major fracture with FRAX® of the participants was performed through the official web page for the Spanish population using data from the baseline interview. To calculate FRAX® with BMD, the femoral neck T-score value from the baseline DXA was used. The calculations were made separately and in parallel by 2 researchers and subsequently reviewed by another 2.

**Diagnostic reliability tests**

The discriminative capacity of the FRAX® tool for 10-year major fracture risk (with and without BMD) was determined through the area under the curve (AUC) receiver operating characteristic (ROC) analysis. The predictive capacity of the FRAX® tool was analysed through the ratio of observed fractures (ObsFx) during the 10-year follow-up of the FRIDEX cohort and the expected fractures (ExpFx) by the FRAX® tool with the formula: [ObsFx/sum of the individual probability for fracture assigned by FRAX® to women in the cohort/100].

**Detection of the best FRAX® threshold values for calibration**

The process to determine the best cut-off points was developed in various phases. In the first phase, the accumulated incidence of fragility fractures was analysed in the cohort with 816 women who did not receive pharmacological treatment during the 10-year period. The cases of major osteoporotic fractures were observed, and the descriptive analysis of the different risk factors included in the FRAX® tool was done, with the additional factor of falls in the previous year and the differences between women with fractures and those without fractures. Subsequently, the discriminative capacity of FRAX® was analysed through the AUC-ROC. To end this phase, the predictive capacity of FRAX® was evaluated with the ratio of the number of women with fractures (ObsFx) in the cohort and the number of women who could have fractures (ExpFx), estimated by FRAX®.

In the second phase, these 816 women were stratified into 3 risk groups (low, moderate and high), following the criterion used in the Canadian cohort CaMos, which considers absolute 10-year fracture risk lower than 10% as low risk, values over 20% as high risk and values between 10 and 20% as moderate risk. In the third phase, the values equivalent to the 2 cut-points among the 3 groups were observed. That is to say, the threshold below which there were women with less than 10% of 10-year fragility fractures, and the threshold that determined the group of women with a fracture in more than 20% of cases. The intermediate risk group was defined between both groups. Finally, with the FRAX® detected cut-off points, the fracture frequencies for each risk group were calculated, with a 95% confidence interval (CI 95%).

**Cost-effectiveness calculation**

For the cost-effectiveness and diagnostic precision analyses, the European Guidelines for the Treatment of Osteoporosis were followed. These guidelines recommend prescribing a healthy
lifestyle when there is low risk, ordering DXA to reevaluate low or high risk with FRAX®. BMD when there is moderate risk and, finally, pharmacological treatment in cases of high risk. However, in this study, the alternative of ordering a DXA in high fracture risk cases and reevaluating the risk was also included, as the results from the DXA of all the cases were available. Thus, in the case of low fracture risk, the cost of the actual fractures experienced in the group during follow-up was input. In the case of moderate risk groups, DXA was ordered. Cases with osteoporosis in the DXA and/or that exceeded the FRAX® threshold with high-risk BMD were considered high-risk cases. For this group, we input DXA cost, cost of the pharmacological treatments and cost of the actual fractures experienced, while subtracting those that would be potentially prevented with pharmacological treatments (a mean 50% reduction of the cases with fractures in the following 10 years was assumed). In the case of high fracture risk groups, 2 options were analysed: the administration of treatment to all the cases without a DXA and the use of DXA and reevaluation, as in the moderate risk cases. In the first option, the cost of the pharmacological treatments and the cost of the actual fractures experienced were input, while subtracting those that would be potentially prevented by pharmacological treatments (50%); in the second option, the cost of the DXA was added.

The amounts for the direct and indirect costs were taken from costs published in Spain27 (per unit): DXA 59€, hip fracture €15,536, vertebral fracture €8876, forearm fracture €2064 and humerus fracture €3034. For humerus fractures, data were extrapolated from another official publication (DOG 6079, available at: http://www.municat.gencat.cat/upload/normativa/accord_gov_14-2012.pdf). To calculate the mean cost of one year of treatment, data were taken from the same ISCIII-MS27 publication on the most commonly used drugs for the treatment of osteoporosis in Spain in 2010, without considering calcium and/or vitamin D supplements. Based on the medication consumption profile for osteoporosis in Spain, the mean cost is €427/year in 2010. For both models, the cost of 10 years of treatment was input (€4272). The cost-effective and diagnostic precision analyses for standard practice in our area were also carried out (traditional model). The traditional model is based on the request of a DXA for suspected low BMD or risk factors (in this cohort, DXA was performed for all cases) and the indication for pharmacological treatment for cases with a T-score ≤ −2.5 standard deviation,20 following the WHO criteria. In the costs calculation, for these cases we input the cost of the DXA, the cost of pharmacological treatments that would be indicated in case of osteoporosis shown by DXA and the cost of the actual fractures occurred, minus the ones that would be potentially prevented by the treatment (50%). For the diagnostic precision analysis, we also calculated the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the 2 models.

Results

Table 1 shows the profile of the cohort of 816 women, with a mean age of 56.8 ± 8.2 years old, and 15.6% had osteoporosis at any of the 3 points defined in the DXA. During the 10-year follow-up, 76 women (9.3%) experienced an osteoporotic fracture and 49 (6%) a major fracture (15 hip, 4 vertebrae, 13 proximal humerus and 17 forearm fractures). In 8 cases (16%), the women experienced more than one fracture, but these were not contemplated by the different analyses.

Among the risk factors (Table 2), age, previous fractures, falls in the previous year and a diagnosis of osteoporosis in the baseline DXA were significant. The discriminative capacity of FRAX® analysed by the ROC curve for the association between risk measurement and fractures showed that the AUC was 0.736 (95% CI 0.657–0.815) for FRAX® without BMD and 0.733 (95% CI 0.652–0.814) for FRAX® with BMD of the femoral neck. The AUC of the DXA with osteoporosis values was 0.697 (95% CI 0.614–0.780).

The predictive capacity analysed through the ratio of ObsFx and ExpFx by the FRAX® tool for major fracture (ObsFx/ExpFx) was 1.72 (95% CI 1.27–2.27) for FRAX® without BMD and 1.61 (95% CI 1.19–2.12) for FRAX® with the BMD of the femoral neck.

The values that defined the risk groups were the following: <5% for low risk, >7.5% for high risk and the values between them defined moderate risk (Table 3 and Fig. 2).

The predictive precision results of the cohort with FRAX® cut-off points to identify the risk groups showed: sensitivity 40.8%, specificity 92.3%, PPV 25.3% and NPV 96%. The values of the traditional model were: 40.8, 86.15.7 and 95.8%, respectively.

Table 4 shows the cost-effective analysis of the proposed FRAX® calibration for identifying risk thresholds compared to the traditional method. With FRAX® cut-off points, 143 DXA would be required and 82 pharmacological treatments would be indicated for 20 women with fractures. In turn, the treatment of 29 women would be discontinued. With the traditional model, 816 DXA would be required and 127 pharmacological treatments would be indicated for 20 women with fractures. In turn, the treatment of 29 women would be discontinued. The economic cost of using FRAX® with the cut-off points would be €601,852, including DXA, pharmacological treatments and the cost of unpreventedor fractures. When the traditional model was applied, the cost would be €843,081. Using the cut-off points, the moderate and risk cases (143/816;
Table 2
Risk factors in the groups of women with fracture and without fracture in the FRIDEX cohort without treatment during the 10 years.

<table>
<thead>
<tr>
<th></th>
<th>Women with fracture (n = 49)</th>
<th>Women without fracture (n = 767)</th>
<th>p</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean (SD)</td>
<td>62.6 (9.7)</td>
<td>56.5 (8.0)</td>
<td>&lt;0.001</td>
<td>3.3–9.0</td>
</tr>
<tr>
<td>BMI in kg/cm², mean (SD)</td>
<td>27.9 (4.5)</td>
<td>28.4 (4.8)</td>
<td>0.437</td>
<td>ns</td>
</tr>
<tr>
<td>BMI &lt;20 kg/cm², %</td>
<td>2.04</td>
<td>2.9</td>
<td>0.682</td>
<td>ns</td>
</tr>
<tr>
<td>Previous fracture, %</td>
<td>49.0</td>
<td>18.5</td>
<td>&lt;0.001</td>
<td>15.7–45.4</td>
</tr>
<tr>
<td>Hip fracture in parents, %</td>
<td>18.4</td>
<td>13.7</td>
<td>0.360</td>
<td>ns</td>
</tr>
<tr>
<td>Active smoker, %</td>
<td>12.2</td>
<td>12.5</td>
<td>0.956</td>
<td>ns</td>
</tr>
<tr>
<td>Alcohol ≥3 μg/day, %</td>
<td>2.01</td>
<td>0.7</td>
<td>0.311</td>
<td>ns</td>
</tr>
<tr>
<td>Glucocorticoids, %</td>
<td>2.0</td>
<td>4.8</td>
<td>0.722</td>
<td>ns</td>
</tr>
<tr>
<td>Rheumatoid arthritis, %</td>
<td>4.1</td>
<td>1.2</td>
<td>0.137</td>
<td>ns</td>
</tr>
<tr>
<td>Falls in the previous year, %</td>
<td>38.8</td>
<td>23.5</td>
<td>0.016</td>
<td>1.4–30.6</td>
</tr>
<tr>
<td>BMD with osteoporosis, %</td>
<td>60.0</td>
<td>14.7</td>
<td>&lt;0.001</td>
<td>30.1–59.2</td>
</tr>
<tr>
<td>Normal BMD, %</td>
<td>6.7</td>
<td>32.8</td>
<td>&lt;0.001</td>
<td>14.7–32.3</td>
</tr>
</tbody>
</table>

BMD: bone mineral density; FRIDEX: Fracture Risk factors and bone DEnsitometry type central dual X-ray; CI 95%: confidence interval 95%; BMI: body mass index; ns: not significant; u: units.

Table 3
Risk groups, FRAX® threshold values that define them, situation during reevaluation with FRAX® with bone mineral density, and final result in low/high risk after reevaluation.

<table>
<thead>
<tr>
<th>Fracture risk groups as per the CAROC System® criteria</th>
<th>Best cut-off points of baseline FRAX® identified in the FRIDEX cohort</th>
<th>Real results of Fx in the FRIDEX cohort after 10-year follow-up Mean (SD)</th>
<th>Situation when performing the DXA and calculating FRAX® with BMD in case of moderate or high risk</th>
<th>Cases without major Fx</th>
<th>Cases with major Fx</th>
<th>Low/high final risk after reevaluation</th>
<th>Final result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (&lt;10%): 673 cases</td>
<td>&lt;5</td>
<td>3.6% (2.2–5.9)</td>
<td>Low risk FRAX® without BMD ≤5</td>
<td>649 (96.4%)</td>
<td>24 (3.6%)</td>
<td>Low</td>
<td>673</td>
</tr>
<tr>
<td>Moderate (≥10 and &lt;20%): 73 cases</td>
<td>≥5 and &lt;7.5</td>
<td>13.7% (7.1–24.2)</td>
<td>No OP in DXA and FRAX® with BMD &lt;7.5</td>
<td>42 (91.3%)</td>
<td>4 (8.7%)</td>
<td>Low</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OP in DXA and FRAX® with BMD &lt;7.5</td>
<td>12 (85.7%)</td>
<td>2 (14.3%)</td>
<td>High</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OP in DXA and FRAX® with BMD &lt;7.5</td>
<td>3 (100.0%)</td>
<td>0 (0.0%)</td>
<td>High</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OP in DXA and FRAX® with BMD &lt;7.5</td>
<td>6 (60.0%)</td>
<td>4 (40.0%)</td>
<td>High</td>
<td>10</td>
</tr>
<tr>
<td>High (≥20%): 70 cases</td>
<td>≥7.5</td>
<td>21.4% (12.9–33.2)</td>
<td>No OP in DXA and FRAX® with BMD ≥7.5</td>
<td>14 (93.3%)</td>
<td>1 (6.7%)</td>
<td>Low</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No OP in DXA and FRAX® with BMD ≥7.5</td>
<td>13 (72.2%)</td>
<td>5 (27.8%)</td>
<td>High</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OP in DXA and FRAX® with BMD ≥7.5</td>
<td>28 (75.7%)</td>
<td>9 (24.3%)</td>
<td>High</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>All cases</td>
<td>767 (94.0%)</td>
<td>49 (6.0%)</td>
<td></td>
<td>816</td>
</tr>
</tbody>
</table>

Source: Leslie et al.®

Table 4
Cost-effectiveness parameters of the threshold values for the Spanish population and the traditional model.

<table>
<thead>
<tr>
<th></th>
<th>Model based on FRAX®</th>
<th>Traditional model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FRIDEX calibration</td>
<td>Clinical judgement and DXA</td>
</tr>
<tr>
<td></td>
<td>€</td>
<td>€</td>
</tr>
<tr>
<td>Pharmacological treatments</td>
<td>82</td>
<td>350,337</td>
</tr>
<tr>
<td>DXA in intermediate + high risk</td>
<td>143</td>
<td>8523</td>
</tr>
<tr>
<td>Cases with real Fx that ARE treated/cost in €</td>
<td>20a</td>
<td>100,082</td>
</tr>
<tr>
<td>Cases with real Fx that are NOT treated/cost in €</td>
<td>29a</td>
<td>142,910</td>
</tr>
<tr>
<td>Value in €</td>
<td>601,852</td>
<td></td>
</tr>
<tr>
<td>Difference in € in favour of FRIDEX calibration</td>
<td>–241,950</td>
<td></td>
</tr>
<tr>
<td>Savings percentage in favour of FRIDEX calibration</td>
<td>28.7%</td>
<td></td>
</tr>
</tbody>
</table>


a Fractures treated with calibrated FRAX® model: hip 11; vertebra 1; humerus 4; forearm 4.
b Fractures NOT treated with calibrated FRAX® model: hip 4; vertebra 3; humerus 9; forearm 13.
c Fractures treated with DXA model: hip 9; vertebra 2; humerus 5; forearm 4.
d Fractures NOT treated with DXA model: hip 6; vertebra 2; humerus 8; forearm 13.
Thus, some and moderate-risk cases with DXA, 82/816 (10%) of the cohort population were selected for treatment, representing 82/143 (57.3%) of the women who were required to have the DXA performed due to FRAX® detected threshold values.

Discussion

In this study, we have seen that not all the risk factors included in FRAX® have been significant. Age, previous fracture and presence of osteoporosis at baseline DXA were seen to be significant. Excessive alcohol consumption, glucocorticoids, rheumatoid arthritis, low BMI and hip fracture in the parents showed no significant differences. The first 3 are considered weak risk factors in FRAX®, and low BMI is considered a strong risk factor14: its non-significance could be justified by its scarce representation in the cohort. History of fractures in any of the parents was not significant, in spite of the fact that it is well represented in the cohort and that it constitutes a strong risk factor in FRAX®. Having suffered more than one fall in the previous year is also shown to be significant. Falls, however, are not included in the FRAX®, but they are included in other risk scales.28

FRAX® demonstrated better discriminative capacity than the traditional DXA-based model, although both models exhibit moderate capacity. This improvement has been previously observed in the Spanish population18,19 and in other populations.10,28 The low predictive capacity of FRAX® measured globally by the ObsFx/ExpFx ratio is consistent with previous studies17–19. Meanwhile, in other cohorts, such as the Canadian, FRAX® risk prediction approaches the rate of observed fractures (ratio of 1.12 and 1.09 for major fracture without and with DXA, respectively).10 This could be due to representation problems in the Spanish cohorts introduced in the FRAX® tool.19

To determine the threshold values, FRAX® baseline values were adjusted with the 10-year fracture results, stratified as proposed by the CAROC System.10,26 Thus, the equivalent results are between the real fracture results obtained in the FRIDEX cohort and the FRAX® baseline values in these women. With these threshold values, 82.5% of the women were at low risk, 8.9% at moderate risk and 8.6% at high risk. This means that, with these thresholds, 17.5% of the women in the cohort were identified at moderate to high risk, although it must be considered that these women were referred for BMD determination because they presented some signs of risk.

The economic assessment was based on European guidelines9,13 that recommend following a healthy lifestyle in low-risk cases, DXA to reevaluate risk with FRAX® in moderate-risk cases, and treatment in high-risk cases.9,13 In this study, it has been observed that the performance of DXA also in the cases at high risk of fracture is the most cost-effective option. Thus, 15 of the 70 cases identified as high risk with the FRAX® tool did not have osteoporosis in the DXA and were left outside the range of high risk of fracture. The first cost-effective proposal calibrated by FRAX® was carried out by the NOGG with a population from the United Kingdom13 for primary prevention.13 Other countries have followed the same example and made proposals regarding thresholds.14,15

The diagnostic precision analysis showed a sensitivity of 40.8% in both methods, but the use of FRAX® calibration thresholds improved specificity by more than 6 points and PPV by almost 10 points compared to the traditional diagnosis model based on the T-score ≤−2.5 of the DXA. The low sensitivity of the DXA13 was already known, and FRAX® calibrated thresholds do not improve sensitivity; however, the remaining predictive parameters do. It should be noted that neither of the two systems is recommended for population screening, but they should instead be used for the opportunistic identification of cases with potential risk factors.13

In the cost-benefit analysis, direct and indirect costs of fractures have been included, as well as the costs corresponding to the DXA and the pharmacological treatments that both models would assign according to the fractures and real treatment profile costs in Spain27 (Table 4). In the treatment cases, a 50% fracture reduction risk was assumed, as medical literature shows different percentages of relative risk reduction and also variable percentages for the different types of fractures, ranging from 19 to 44% for alendronate.14 In summary, the use of FRAX® calibrated thresholds would allow us to avoid more than 82% of DXA and more than 35% of treatments to treat the same number of women with fractures, but at an almost 30% cheaper global cost when compared to standard practice or the traditional model based on DXA. Although in the traditional model all DXA have been counted and this model may seem disadvantaged in the comparison, the real cost of DXA only accounts for 3.2% of the difference between the models. If the DXAs were not included, the difference would change from 28.7 to 25.5% in favour of the use of FRAX® calibrated thresholds. The treatments were estimated for 10 years, and if the estimation were for 5 years, the difference would be reduced by 5%. It has been proven that the most cost-effective option is also DXA in the cases of high fracture risk, basically because there are cases with high-risk FRAX® values, but with BMD without osteoporosis. Although numerous societies recommend the administration of pharmacological treatment in cases of fractures in postmenopausal women without the need for DXA13–15 some experts specify that this option should be specifically used in cases of hip or vertebral fracture.10,26

Among the limitations of the study, it is worth mentioning that the FRIDEX cohort includes women who were referred by their physician for DXA, which could affect the results as it is a potentially higher risk population. However, this analysis excluded women who had initiated anti-osteoerotic treatment during follow-up, so mean age and fracture cases of the cohort were reduced. However,
this particularity would not affect the comparative analyses of diagnostic precision and cost-effectiveness between the models.

Another potential limitation may be the non-inclusion in the analysis of the women who died during follow-up, and for whom the study could not be completed. The mortality rate of the 10-year study was 5.8%. There were few cases of previous fractures but, given the low percentage and the difficulty to confirm the fractures with clinical records, they were excluded from the study. This aspect might affect the predictive capacity analysis, but not the comparative cost-effective study.

Although it is the most commonly used system, retrospective case registration of incident fractures is considered less reliable than prospective studies due to the memory effect and possible patient confusion. To minimize this effect, all the fracture cases were verified in the clinical records. Thus, 16% of the women initially detected with fractures were excluded from the study, mostly due to lack of records. Only 2 cases of humerus fracture were excluded due to a difference in interpretation between the questionnaire and the records, along with one hip fracture due to a traffic accident. Without this exclusion, the ObtFS/ExpFx ratio would be still higher. Unlike most of the epidemiological studies on osteoporotic fractures that centre on hip fractures and perform extrapolations for the remainder, however, clinical judgement shall always prevail in the decision making process, as the results of this study offer excellent specificity but deficient sensitivity. It is likely that an improvement in risk estimation by FRAX\textsuperscript{®} (for example, including falls) could increase its PPV.

In conclusion, osteoporotic fractures have a multifactorial pathogenesis, so it is difficult to predict them using only one risk factor, although strongly associated, as happens with osteoporosis values in DXA. Clinical judgement should prevail, and to adjust the risk of fragility fracture, it is more efficient to consider the greater number of fracture risk factors possible among those that demonstrated evidence. The FRIDEX model to calibrate the Spanish FRAX\textsuperscript{®} improves the predictive parameters of fracture risk and is more cost-effective than standard clinical practice based on DXA. However, new studies are necessary for the external validation of these FRAX\textsuperscript{®} thresholds or cut-off points in other cohorts and in the general population.

**Funding**

This project was financed by grants of the Instituto de Salud Carlos III, Ministry of Science [PI09/90507], and the Instituto Universitario de Investigación en Atención Primaria IDIAP Jordi Gol, Institut Català de la Salut, Barcelona, Spain.

**Conflict of interest**

The authors have no conflicts of interest to declare.

**References**

27. Ministerio de Ciencia e Innovación. Análisis coste-utility de los tratamientos farmacológicos para la prevención de fracturas en mujeres con
