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Risk factors for incident fracture in patients with breast cancer treated with aromatase inhibitors: B-ABLE cohort

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Summary

Objetive: Aromatase inhibitors (AI) have been associated with an accelerated loss of bone mass and an increased risk of osteoporosis fractures. This study assesses the risk factors for incident fracture in breast cancer patients receiving AI.

Material and methods: Prospective-observational cohort study of women with breast cancer who begin treatment with AI (B-ABLE cohort). Patients were treated for 5 years or 2 or 3 years if they had previously received tamoxifen. Bone health was assessed from the beginning of the treatment until one year post treatment by bone densitometry, bone remodeling markers, vitamin D levels and an anteroposterior and lateral spine radiography. The fracture risk calculation was performed using the FRAX® tool before starting AI. Cox models were used to calculate the risk ratios (HR [95% CI]) of fracture.

Results: A total of 943 patients were included in the study. 5.4% suffered an incident fracture, most during AI treatment, although 21.5% occurred during the first year after the end of therapy. Most of the incident fractures were clinical vertebral (29.4%) and Colles (31.4%). 86.3% of the patients had a diagnosis of osteopenia or osteoporosis at the time of the fracture and 33% had the levels of β-CTX (β isomer of the carboxyterminal telopeptide of type I collagen) above normal.
Patients diagnosed with osteoporosis or at risk of fracture at the start of the study were treated with bone antiresorptives. No significant differences in fracture risk were found between patients with and without antiresorptive therapy: HR=1.75 [95% CI: 0.88 to 3.46]. Nor were differences found among patients who had previously treated with tamoxifen compared to those who did not (HR=1.00 [95% CI 0.39 to 2.56]). The FRAX® tool gave average values within the intermediate risk range, with 13 patients with high risk of major fracture values.

Conclusions: The main risk factor detected for incident fracture in patients treated with AI is the diagnosis of osteopenia or osteoporosis. The calculation of the FRAX® tool and the determination of β-CTX levels are useful tools to identify high-risk patients.

Key words: aromatase inhibitors, fracture, breast cancer.

Introduction

Currently, aromatase inhibitors (AI) are used as first-line adjuvant therapy for women diagnosed with breast cancer with positive hormonal receptors. Although its effectiveness in reducing the risk of recurrence and mortality is well known[1], AIs have also been associated with side effects that can negatively affect the patient's quality of life, adherence to treatment and associated mortality[2].

In AI treatment, there is a marked reduction in circulating estrogens in postmenopausal women by blocking the conversion by the enzyme aromatase from androgens to estrogens. This action leaves the woman without residual estrogens, such as estradiol and estrone, after menopause. One of the most common side effects is accelerated bone loss, which is associated with an increased risk of osteoporotic fractures[3,4]. Along these lines, there are different meta-analyzes that include randomized controlled clinical trials that have shown an association between prolonged treatment with AI and an increased risk of bone fractures, with an increase between 34% and 59%[5,6].

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Furthermore, in a cohort study that included 1,775 patients who started long-term AI therapy, the risk of osteoporotic fracture was similar to that of the general population. It should be noted that in this study, AI-treated women presented a higher baseline BMI, a higher bone mineral density and a lower prevalence of fracture prior to the start of the study than the general population[7].

The B-ABLE cohort (Barcelona–Aromatase induced Bone Loss in Early breast cancer) includes postmenopausal patients with estrogen receptor-positive breast cancer (RE+), recruited at the time of starting AI treatment. This cohort has been used to conduct a prospective observational study in which patients are monitored throughout the study with bone health data and associated factors from the start of treatment until one year after the end of treatment[3].

This study was aimed at assessing clinical fracture incidence and the characteristics of patient fractures in the B-ABLE cohort during AI regime and one-year post treatment.

Material and methods

Study group

A prospective, unselected, observational and clinical cohort study was carried out in the B-ABLE cohort that included postmenopausal patients diagnosed with positive estrogen receptor (RE+) breast cancer, treated at the Hospital del Mar in Barcelona. Participants were recruited at the beginning of AI treatment (letrozole, exemestane or anastrozole) and were treated for 5 years, according to the American Society of Clinical Oncology recommendations, starting within 6 weeks post op or 1 month after the last cycle of chemotherapy[8]. Alternatively, those patients who were pre-menopausal at the time of starting adjuvant treatment were treated with tamoxifen for 2 or 3 years, and were included in the study at the time of changing to AI due to the onset of menopause. These patients were treated with AI (3 or 2 years, respectively) until completing 5 years of adjuvant therapy. In addition, all participants received calcium and 25(OH) vitamin D3 supplements (1,000 mg and 800 IU daily, respectively), and those with vitamin D deficiency (<30 ng/ml) received an additional dose of 16,000 IU of oral calcifediol or 25,000 IU of oral cholecalciferol every 2 weeks. Patients diagnosed with osteoporosis by bone densitometry (dual energy radiological absorptiometry, DXA), fragility fractures before starting AI, and/or a bone mineral density (BMD) with a T-score <-2.0 plus a factor of increased risk for osteoporosis, they started treatment with oral bisphosphonates or denosumab in the case of digestive intolerance or previous gastroesophageal disease. The patients maintained this treatment throughout the study.

Exclusion criteria was: alcohol addiction, renal failure > grade 3b, rheumatoid arthritis, bone metabolic diseases other than osteoporosis, Paget's disease, osteomalacia, primary hyperparathyroidism, hyperthyroidism, insulin-dependent diabetes mellitus, prior or ongoing treatment with antiresorptives, oral corticosteroids or any other drug that could affect bone metabolism, except tamoxifen.

The study protocol was approved by the ethics committee of the Parc de Salut Mar (2016/6803/I) and was carried out in accordance with the Declaration of Helsinki. Written informed consent forms were obtained from all participants after reading the study information sheet and answering any questions. Patient privacy rights were respected at all times.

Data and patient measurements

Information on clinical and demographic variables was collected at the time of recruitment and during the study, including age, menarche and menopausal age, body mass index (BMI), diet and lifestyle, chemotherapy and previous radiotherapy, tamoxifen previous, antiresorptive treatments, family history, previous falls, serum levels of 25(OH) vitamin D (VitD) and paratohormone (PTH), as well as the following parameters of bone remodeling: aminoterminal propeptide of type I collagen (P1NP), the isomer beta of the carboxyterminal telopeptide of collagen type I (β-CTX), osteocalcin and bone alkaline phosphatase. Before the start and annually until after one year after the end of the AI treatment, bone mineral density (BMD) was measured at the lumbar level (CL L1–L4), femoral neck (CF) and total hip (CT), using the DXA QDR 4500 SL® densitometer (Hologic, Waltham, Massachusetts, USA). The coefficient of variation for this technique in our center is 1% in CL and 1.65% in CF. Those images that presented degenerative disc disease with osteophytes, osteoarthritis with hyperostosis of the facet joints, vertebral fractures and/or aortic calcifications and all those that could cause a false increase in BMD were excluded, according to the follow-up. description of Blake et al.[9]. Incident fractures were diagnosed by a lateral x-ray (Rx) of the dorsal and lumbar spine by a specialized doctor or by a medical report from another center. The risk of fracture at 10 years was assessed using the FRAX® tool on the platform, with access at: https://www.sheffield.ac.uk/FRAX/tool.aspx?lang=sp. The thresholds of FRAX values that were used to identify people with high or low risk of main osteoporotic fracture in the Spanish female population were: low risk, <5; intermediate, between 5 and <7.5; and high, ≥7.5[10]; and for hip fracture it was considered high risk ≥3%[11].

Statistic analysis

The risk of fracture was studied by means of a survival analysis: the Kaplan-Meier estimator was calculated, and a proportional hazard model (Cox regression) was made between users and non-users of bisphosphonates, and among patients with previous tamoxifen or without tamoxifen, adjusting for risk covariates. The proportionality of the risk over time was checked. Comparisons between groups were made using the Student's T-test or Chi-Square. The analyzes were performed with SPSS version 23 and with R 3.5.3 using the foreign, plyr, survminer, Hmisc, dplyr, ggplot packages2.

Results

A total of 943 postmenopausal patients on AI treatment were included in the study. Of these, 51 patients (5.4%) suffered an incident fracture (Figure 1). The majority of fractures occurred during treatment with AI although 21.5% occurred during the first year post therapy. 82.4% of fractured patients took letrozole, 15.7% exemestane and 1 patient took anastrozole. The majority of incident fractures detected were vertebral (29.4%) and Colles (31.4%) (Figure 1).

The characteristics of fractured patients are shown in table 1. Most fractured patients (78.5%) were in the overweight range (BMI >25-29.9 kg/m^2) (n=17) or obesity (BMI >30 kg/m^2) (n=24). All humerus fractures oc-

curred in patients with a BMI >28 kg/m^2. Only 2 patients were underweight (BMI <18.5 kg/m^2).

86.3% of the patients were diagnosed with osteopenia or osteoporosis at the time of the fracture, being a key risk factor for the fracture associated with AI. There were no significant differences in fracture risk between patients with and without antiresorptive treatment: HR=1.75 [95% CI: 0.88 to 3.46] (Figure 2). It should be noted that patients with incident fractures treated with bisphosphonates had a significantly lower BMI than patients with fracture and without bisphosphonates [mean (SD): 26.4 (6.2) vs. 30.9 (5.2), respectively; p=0.01]. No differences were found in the other parameters analyzed: age, previous chemotherapy and previous falls.

29.4% (n=15) of the patients had had falls prior to the fracture. Of these, 6 had a vertebral fracture and 8 suffered Colles fracture.

Of all the B-ABLE cohort, 293 previously took tamoxifen and 4.1% suffered a fracture. On the other hand, 650 did not receive prior tamoxifen and 6% fractured (Figure 3). There were no significant differences in the risk of fracture among patients who had previously received tamoxifen treatment compared to those who did not (HR=1.00 [95% CI 0.39 to 2.56]).

VitD levels at baseline had a mean of 17.39±8.2 ng/ml. All patients were treated with VitD at the start of AI treatment, with a mean of 48.69±42.11 ng/ml at 3 months of treatment. Thus, at the time of the incident fracture, all patients had optimal levels of VitD with a mean of 47.7±27.18 ng/ml.

Figure 1. Flowchart of breast cancer patients treated with AI (B-ABLE cohort) with incident fracture

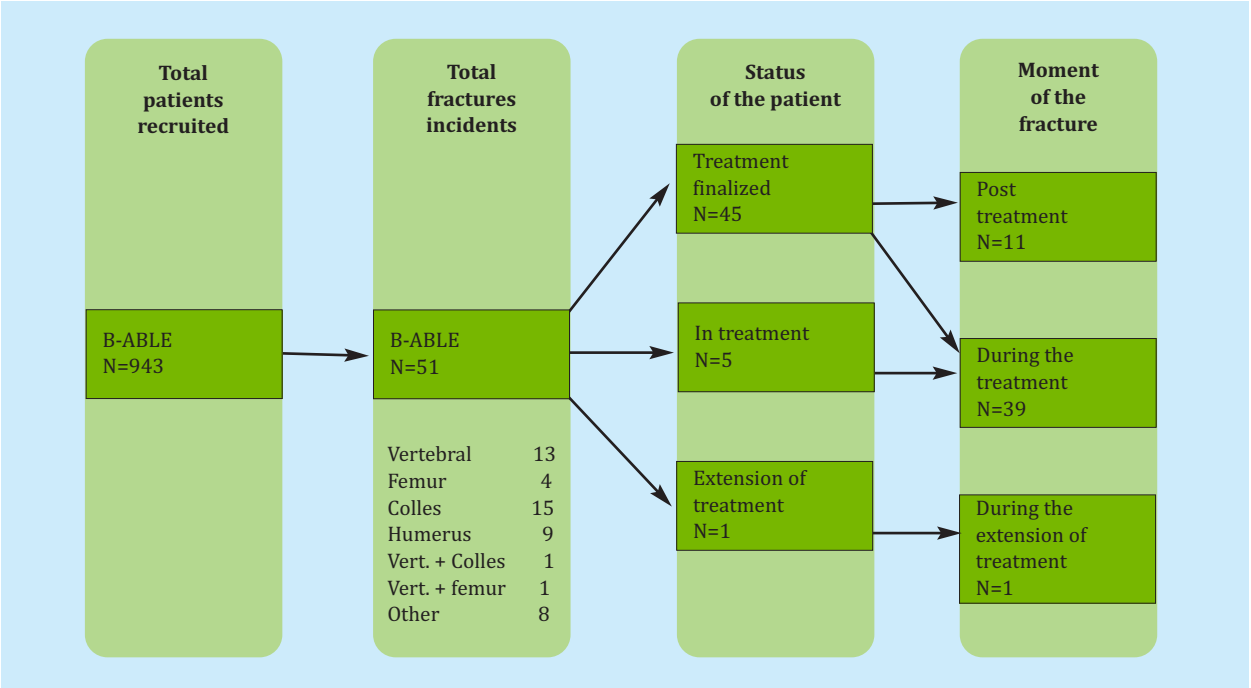
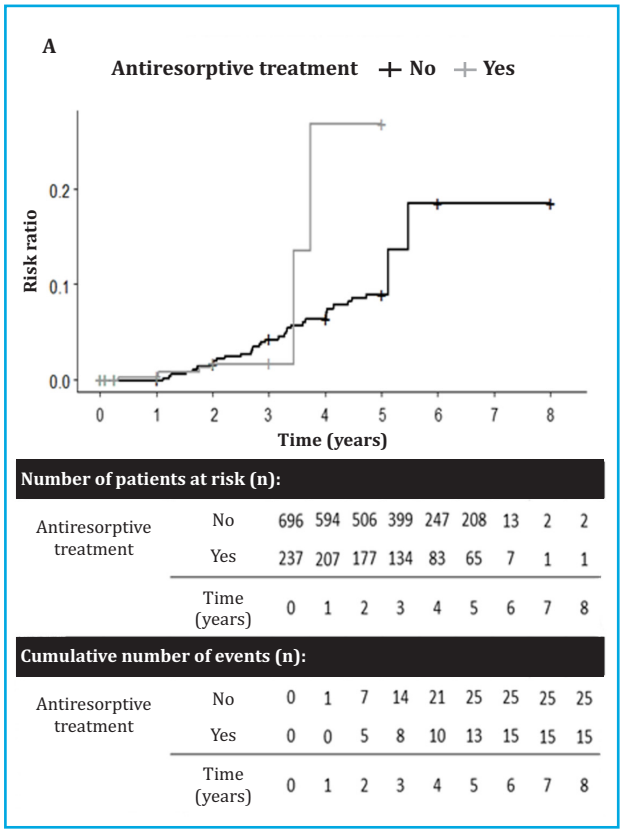


Table 1. Characteristics of the patients at the time of the incident fracture

Characteristics (N=51)	Mean ± SD	n (%)
Mean age (years)	64.45 ± 8.7	
BMI mean (kg/m^2)	29.3 ± 5.8	
Family history of fracture		16 (31.4%)
Previous falls		15 (29.4%)
Mean levels of 25(OH) vitamin D (ng / ml)	47.7 ± 27.18	
Half levels of β-CTX (ng/ml)	0.479 ± 0.25	
Osteoporosis/osteopenia		Osteopenia: 34 (66.7%) Osteoporosis: 10 (19.6%)
Prior tamoxifen		12 (23.5%)
Prior chemotherapy		34 (66.7%)
Antiresorptive treatment		BF: 17 (33.3%)
		Denosumab: 1 (2%)

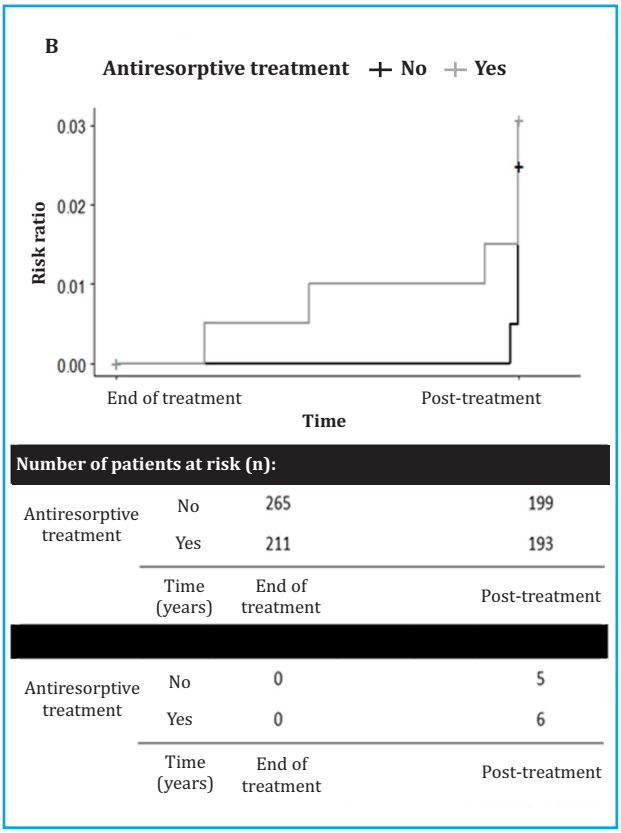
SD: standard deviation; BMI: body mass index; BF: bisphosphonates.

Figure 2. Graph of the cumulative risk of fracture events in study groups (with or without treatment with bone antiresorptives) according to the risk of fracture. The graphs show the Kaplan-Meier curves that set out the study results in terms of cumulative risks. (A) during AI treatment (B) during post treatment



Number of patients at risk (n):										
Antiresorptive treatment	No	696	594	506	399	247	208	13	2	2
	Yes	237	207	177	134	83	65	7	1	1
	Time (years)	0	1	2	3	4	5	6	7	8

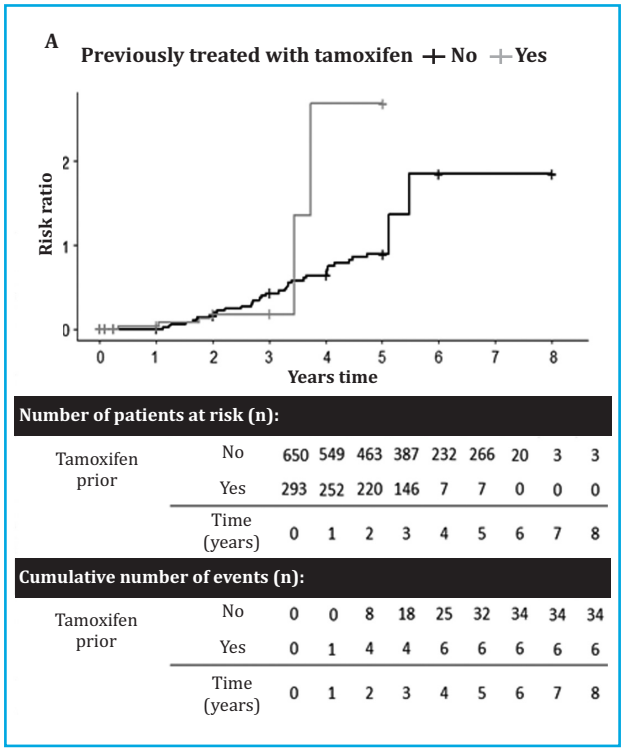
Cumulative number of events (n):										
Antiresorptive treatment	No	0	1	7	14	21	25	25	25	25
	Yes	0	0	5	8	10	13	15	15	15
	Time (years)	0	1	2	3	4	5	6	7	8



Number of patients at risk (n):			
Antiresorptive treatment	No	265	199
	Yes	211	193
	Time (years)	End of treatment	Post-treatment

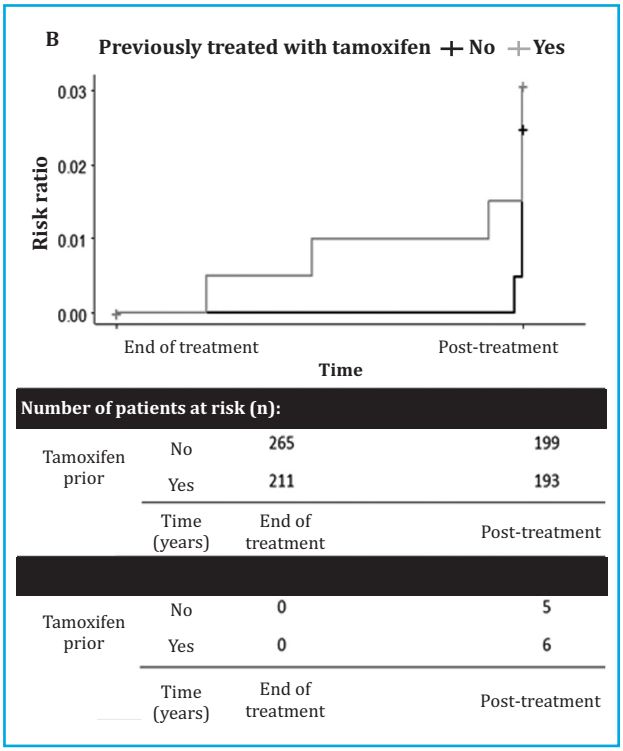
Antiresorptive treatment	No	0	5
	Yes	0	6
	Time (years)	End of treatment	Post-treatment

Figure 3. Graph of the cumulative risk of fracture events in study groups (with or without prior treatment with tamoxifen) according to the risk of fracture. The graphs show the Kaplan-Meier curves that represent the results of the study in terms of cumulative risks. (A) during treatment with aromatase inhibitors, (B) in the post-treatment



Number of patients at risk (n):										
Tamoxifen prior	No	650	549	463	387	232	266	20	3	3
	Yes	293	252	220	146	7	7	0	0	0
	Time (years)	0	1	2	3	4	5	6	7	8

Cumulative number of events (n):										
Tamoxifen prior	No	0	0	8	18	25	32	34	34	34
	Yes	0	1	4	4	6	6	6	6	6
	Time (years)	0	1	2	3	4	5	6	7	8



Number of patients at risk (n):			
Tamoxifen prior	No	265	199
	Yes	211	193
	Time (years)	End of treatment	Post-treatment

Tamoxifen prior	No	0	5
	Yes	0	6
	Time (years)	End of treatment	Post-treatment

According to the normal values of the beta isomer of the carboxyterminal telopeptide of collagen I (β-CTX) in the serum of premenopausal healthy women in the Spanish population (0.064-0.548 ng/ml)[12], 33% of fractured patients had levels of β-CTX above normal. In addition, if the total of 51 patients with fractures exclude those treated with antiresorptives, the mean of β-CTX was at levels above normal (0.585±0.228 ng/ml).

The calculation of the absolute risk of major osteoporotic and hip fractures in the next 10 years, using the FRAX® tool in patients with incident fractures, is shown in table 2. High-risk FRAX values of main fracture were detected (≥7.5) and hip fracture (≥3) in 13 and 8 patients, respectively (Figure 4). In addition, when comparing the means with the B-ABLE patients without incident fracture (Table 3), the average FRAX in the fractured patients was higher than the patients without fracture.

Discussion

AIs produce a deleterious effect on bone tissue that has already been demonstrated in the clinical trials of reference[5]. However, there is little data from prospective non-randomized clinical studies in the usual clinic. This study has focused on the evaluation of the risk factors for incident fracture in the B-ABLE cohort, which includes postmenopausal women with RE (+) breast cancer treated

Table 2. Values of the FRAX® tool for the calculation of fracture risk at 10 years in patients with fracture of the B-ABLE cohort

	Basal FRAX for major fracture	Basal FRAX for major fracture with DXA	FRAX hip	FRAX hip with DXA
Mean ± SD	5.88 ± 4.34	5.9 ± 4.25	1.89 ± 2.75	1.64 ± 2.52
Median	4.4	4.5	0.8	0.6
Minimum	1.4	1.2	0.1	0
Maximum	20	19	15	13

SD: standard deviation; DXA: bone densitometry.

Figure 4. FRAX values of each patient in the study of: A) major fracture and B) hip fracture, taking into account BMD. The horizontal lines of each figure show the threshold established for the risk of fracture at 10 years. Baseline FRAX thresholds for major fracture were: low risk, <5; intermediate, between 5 and <7.5; and high, ≥7.5. The high risk thresholds for hip fracture were ≥3

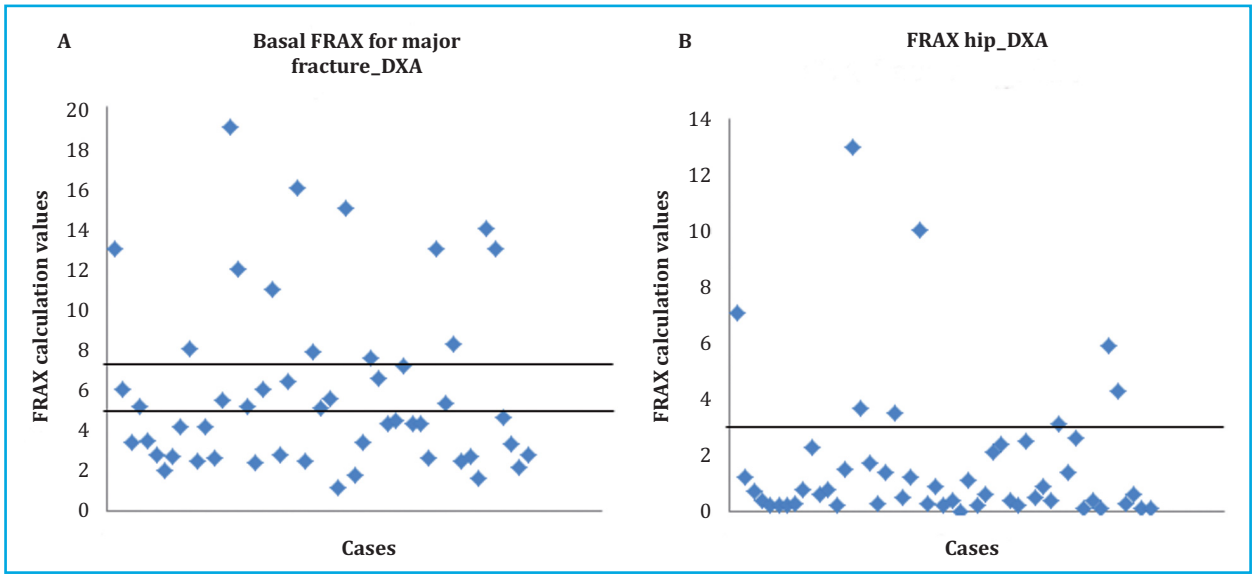


Table 3. Values of the FRAX® tool for the calculation of the fracture risk at 10 years in patients without an incident fracture of the B-ABLE cohort (N=583)

	Basal FRAX for major fracture	Basal FRAX for major fracture with DXA	FRAX hip	FRAX hip with DXA
Mean ± SD	4.92 ± 4.6	4.73 ± 4.15	1.35 ± 2.68	1.04 ± 2.26
Median	3.4	3.3	0.5	0.4
Minimum	0.9	0.9	0	0
Maximum	37	42	29	33

SD: standard deviation; DXA: bone densitometry.

with aromatase inhibitors. The main risk factor detected is the diagnosis of osteopenia or osteoporosis followed by high β-CTX values. Overweight also emerged as a risk factor for the identification of patients with humerus fracture. Likewise, the calculation of FRAX was useful to identify some patients at high risk of main and hip fractures.

All patients in the B-ABLE cohort started treatment with vitamin D supplements from the moment they were included in the study if they had values below 30 ng/ml and, therefore, in most cases vitamin levels D were placed at optimal values during the period of AI therapy. Thus, 86.3% of the patients had vitamin D values greater than 20 ng/ml at the time of the fracture, with an average of 47.7 ng/ml. This rules out sub-optimal levels of vitamin D as a risk factor for fractures in these patients. It should be noted that most of the patients (66.6%) had levels below 20 ng/ml at the time of initiating AI therapy, so we cannot know if these low levels could affect future fractures.

In addition, patients at high risk of fracture at baseline were treated with bone anti-resorptives at the outset of AI therapy, so due to antiresorptive treatment, the risk of fracture decreased. This was thus equated with the incidence of fracture in patients not receiving antiresorptive treatment. These data are in line with a recent study in the SIDIAP cohort (Information System for the Development of Research in Primary Care), in which women treated with bisphosphonates significantly reduced their risk of suffering an osteoporotic fracture[4]. However, more than 30% of the fractures were detected in patients treated with antiresorptives. Interestingly, these women treated with bisphosphonates had a lower BMI than women without antiresorptive treatment.

Although it is generally accepted that having a history of previous falls is a relevant predictor of osteoporotic fracture risk[13], more than 70% of the patients in our cohort did not report falls prior to the incident fracture. It should be noted that in patients with an incident fracture during AI treatment and who reported a history of falls, the most frequent fracture was the vertebral and/or Colles fracture.

Nor have differences in the risk of fracture been detected between patients previously treated with tamoxifen and those who only received AI. However, it was not possible to rule out a possibly insufficient sample size to detect these differences.

The risk of fracture was also assessed with the FRAX tool at baseline (prior treatment with AI), placing most of these patients at intermediate/low risk levels at the time they enter the study. A limitation of the tool is that it does not take into account treatment with aromatase inhibitors, possibly causing the risk of fracture to be underestimated in our cohort. In any case, 25% of patients with fractures had high risk values, so this index could be taken into account when detecting risk patients.

In conclusion, the diagnosis of osteopenia or osteoporosis, along with elevated levels of β-CTX could detect patients treated with AI with a high risk of suffering an incident fracture. Previous treatment with tamoxifen does not seem to affect the risk of fracture.

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Conflict of interests: Authors declare no conflict of interests.

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