

Increased Fracture Risk in Women Treated with Aromatase Inhibitors versus Tamoxifen: Beneficial Effect of Bisphosphonates

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Supplemental data have been included with the submission

Abstract

Aromatase inhibitors have been associated with accelerated bone loss and an increased risk of osteoporotic fractures. Currently, bisphosphonates are recommended to reduce fracture risk in these patients. The aim of this study is to evaluate the fracture risk in breast cancer patients receiving aromatase inhibitors, compared to tamoxifen users, and to assess the effectiveness of oral bisphosphonates in reducing fracture risk. We performed an observational cohort study up to 10 years of follow-up. Data were extracted from primary care records in a population database. Women diagnosed with breast cancer between 2006 and 2015 and treated with tamoxifen or aromatase inhibitors (n=36,472) were stratified according to low (without osteoporosis diagnosis nor bisphosphonates exposure) or high (with osteoporosis and/or treated with bisphosphonates) fracture risk. Cox models were used to calculate hazard ratios (HR [95%CI]) of fracture from the propensity score matched patients. Sensitivity analyses account for competing risk of death were performed (SHR [95%CI]). In postmenopausal women, fracture risk in aromatase inhibitor users showed a HR: 1.40 [1.05 to 1.87] and SHR: 1.48 [1.11 to 1.98], compared to tamoxifen. Observing aromatase inhibitors patients at high-risk of fracture, bisphosphonate treated patients had a HR: 0.73 [0.51 to 1.04] and SHR: 0.69 [0.48 to 0.98] compared to non-treated.

In conclusion, fracture risk in postmenopausal women during aromatase inhibitor treatment, in real-life conditions, was >40% compared to tamoxifen, corroborating previous randomized controlled trials results. In high-risk patients, bisphosphonate users had lower significant fracture incidence during aromatase

inhibitor therapy than non-bisphosphonate-users. Monitoring fracture risk and related risk factors in aromatase inhibitor patients is advisable.

Keywords: General population studies, Fracture risk assessment, Fracture prevention, Aromatase Inhibitors, Estrogens and SERMs

Introduction

First-line therapies for women with diagnosis of hormone receptor-positive breast cancer are aromatase inhibitors (AI) and tamoxifen (TAM). Their effectiveness in reducing the risk of recurrence and mortality in breast cancer patients is well known.^(1, 2) However, these two adjuvant treatments have also been associated with side effects that may negatively affect the patient's quality of life, treatment adherence, and the associated mortality.⁽³⁾

In AI treatment, one of the most common side effects is accelerated bone loss, which is associated with an increased risk of osteoporotic fractures.⁽⁴⁾ A Danish cohort study reported a higher risk of fracture occurrence related to AIs, compared to endocrine-untreated patients, while TAM had a protective effect on bone mass in postmenopausal women with breast cancer.⁽⁵⁾ In a 2018 report on a population-based, retrospective cohort study, Neuner et al. further corroborate this finding. They describe an increased risk for non-vertebral fractures in patients treated with AI, compared to TAM.⁽⁶⁾

The current recommendation to reduce the fracture risk in these patients is to improve bone mineral density (BMD) using antiresorptive treatment, mainly bisphosphonates (BP) or, in cases of low adherence or BP intolerance, denosumab.⁽⁷⁻⁹⁾ Several phase III trials and population-based cohort studies have shown the efficacy of BP in preventing the bone loss induced by AI.⁽⁹⁻¹¹⁾

A meta-analysis of 26 randomized clinical trials (RCTs), including both intravenous and oral BP administration, reported a small reduction of fracture risk in BP-treated patients with breast cancer.(12) However, these trials analyzed the BP effect in oncological outcomes, not for fractures. Thus, a wide range of fracture incidence was reported in these studies, perhaps due to underreporting, limiting the results interpretation. Furthermore, there is a lack of data from real clinical practice about the influence of oral BPs on fracture risk in AI-treated patients.

The aim of this study was to evaluate the fracture risk in patients with breast cancer receiving AI, compared to TAM-treated patients in a large population database of real-world practice in primary care centers. Additionally, effectiveness of oral BP in reducing fracture risk was assessed in this population.

Materials and Methods

Data source/s

More than 7 million patient records are anonymously collected from more than 370 primary care teams of Catalonia in the System for the Development of Research in Primary Care (SIDIAP) database, covering >80% of the total Catalan population (<http://www.sidiap.org>). Available information includes socio-demographic data, lifestyle risk factors (alcohol use, obesity, smoking, etc.), comorbidities, and prescriptions dispensed. Data are collected by health professionals, using ICD-10 codes and structured forms designed for the gathering of clinical variables (smoking, body mass index, etc.). Data on death,

provided by the universal health insurance database of Catalonia (in Catalan, Registre Central de Persones Assegurades), and migration out of the catchment area are also registered in the SIDIAP database.

Study design and participants

This observational cohort study included women with a first diagnosis of breast cancer and treated with TAM or AIs who were registered in the SIDIAP database from January 2006 to December 2015. This study was approved by the Idiap Jordi Gol Research Ethics Committee and by the SIDIAP Database Scientific Committee.

Pharmacy dispensing records (pharmacy invoicing) include the anatomical therapeutic chemical (ATC) classification of the therapeutic regimen: L02BA01 for TAM, L02BG for AIs (L02BG03 for anastrozole, L02BG04 for letrozole and, L02BG06 for exemestane), M05BA for BP (etidronic acid, M05BA01; clodronic acid, M05BA02; alendronic acid, M05BA04; tiludronic acid, M05BA05; ibandronic acid, M05BA06; and risedronic acid, M05BA07), and M05BB03 for a combination of alendronic acid and cholecalciferol.

Patient diagnoses were registered by primary care professionals using ICD-10 codes. In case of osteoporosis, it was complemented by available T-score values (patients with values equal or lower than -2.5 SD were classified as osteoporotic).

Exclusion criteria were previous history of cancer (except non-melanoma skin cancers), Cushing's syndrome, Rickets, Osteomalacia or Paget's disease, switching therapy (TAM followed by AI or vice versa), and use of bone-active drugs other than BP during adjuvant treatment (i.e. strontium ranelate,

M05BX03; raloxifene, G03XC01; and bazedoxifene, G03XC02). Participants with less than 6-month follow-up were also excluded.

Classification of low and high risk of fracture

Selected records were dichotomized according to AI or TAM exposure, then stratified into 4 groups according to risk of fracture: a) Low-risk AI-treated patients (AI-lowRF); patients without evidence of osteoporosis diagnosis and without BP exposure. b) High-risk AI-treated patients (AI-highRF); patients with a diagnosis of osteoporosis (according to WHO criteria) and/or BP users. c) Low-risk TAM-treated patients (TAM-lowRF); patients without evidence of osteoporosis diagnosis and without BP exposure. d) High-risk TAM patients (TAM-highRF); patients with a diagnosis of osteoporosis and/or BP users.

Follow-up

Participants were followed up from therapy initiation (first TAM, TAM-plus-BP, AI, or AI-plus-BP prescription dispensed) until the earliest of three endpoints: 1) adjuvant hormone treatment or BP treatment cessation (defined by a refill gap of six months or more with no dispensation of the index therapy) plus one month wash-out (for carry-over effects), 2) study outcome/s date, as recorded in electronic medical records, or 3) death, migration out of catchment area, or current end-date of SIDIAP data availability (31/12/2015).

Variables

Outcomes

The study evaluated two outcomes: first fracture diagnosis of participants during AI vs. TAM treatment, and first fracture diagnosis according to BP exposure

within high risk groups. Fracture locations included hip or proximal femur, vertebra, proximal humerus, and wrist or forearm. Fracture diagnosis was registered using the ICD-10 code based on clinical criteria.

Confounders

Using established clinical knowledge, a pre-specified list of variables was extracted from SIDIAP and used as confounders. These confounding factors fell into three clusters:

Sociodemographics: age (at treatment initiation), body mass index (BMI), and socioeconomic status (assessed by MEDEA, a validated deprivation index).⁽¹³⁾

Lifestyle factors: smoking (current/former >1year/never-smoker/ex-smoker) and weekly alcohol consumption, categorized by the Catalan Health Care System as none/low (mean of zero grams), moderate (not exceeding 170 grams); high/alcoholic (170 grams of alcohol or more per week).

Past medical history: Charlson co-morbidity index (measured at treatment initiation date); any previous history of fracture, rheumatoid arthritis, hyperthyroidism, liver cirrhosis, or chronic kidney disease; diagnosis of osteoporosis previous to adjuvant therapy outset; concomitant use of sedative-hypnotic drugs at cohort entry; and previous use of systemic glucocorticoids.

Sociodemographic and lifestyle factors were included at the closest date to treatment initiation until the previous 12 months.

Statistical Analysis

Differences in baseline characteristics between TAM and AI participants were described using mean (standard deviation) and median (inter-quartile range) for

quantitative variables with normal and non-normal distribution, respectively; n(%) per treatment group were used for categorical variables.

Incidence rates of fractures during TAM or AI treatment were assessed using the ERIC Notebook person-time methodology.⁽¹⁴⁾

To account for missing confounder data (BMI, smoking, alcohol drinking), multiple imputation by chained equations was carried out, obtaining 10 imputed datasets that were analyzed separately and results combined using Rubin rules. Imputed variables were evaluated by comparing them with their original values to validate its prediction. Drug-use cohorts were matched using propensity score matching (PSM) to minimize confounding by indication when comparing treatment groups. Propensity scores (PS) represent the probability of receiving a given treatment, conditioned by baseline characteristics. PS was estimated using logistic regression models, where treatment exposure group was the outcome and the previously listed confounders were the adjustment variables. Matching was conducted using a 5:1 ratio ("the biggest group:the lowest group"), and nearest-neighbor method to select for the most similar PS. Standardized mean difference < 0.1 in PS in each matched group was verified.

Survival analysis was performed, including Kaplan–Meier to estimate cumulative probability plots and Cox proportional hazards model to estimate hazard ratios (HR) according to the exposure treatment. Proportional hazard assumption was verified in each model. Additionally, Fine and Gray models (sensitivity analyses accounting for a competing risk of death) were fitted to estimate sub-distribution hazard ratios (SHR) of the outcomes. HR and SHR are reported with 95% confidence intervals (95%CI).

Menopause status in TAM users was unknown. To minimize the imbalance of premenopausal and postmenopausal effect between AI and TAM groups, a subset of participants older than 55 years was selected to compare fracture risk of TAM vs. AI users.

All statistical analysis was performed with R for Windows version 3.3.3 using Hmisc, compareGroups, survival, survminer, ggplot2, mice, MatchIt and dplyr packages.

Results

A total of 36,472 women treated with AI and/or TAM in the period 2006-2015 were screened and 22,591 (61.94%) were eligible for this study (7,539 TAM and 15,052 AI) (Figure 1). Median follow-up (months [Q1; Q3]) in each group was 27.0 [15.00; 48.0] in TAM and 29.0 [15.00; 50.0] in AI groups. Baseline characteristics of participants are shown in Table 1. AI users were older, had higher BMI, and were more likely to have chronic kidney disease, osteoporosis, and a previous fracture history. Additionally, AI users had greater exposure to BP, systemic corticosteroids, and sedative-hypnotic drugs, but were less likely to be current smokers than TAM users.

Fracture incidence

During the study, 658 (2.91%) patients had a fracture during the adjuvant treatment. Incidence rates (per 1,000 person-years) of fractures in all participants are reported in Table 2. The highest incidence rate was found in AI users, mainly in those classified at high risk of fracture. Cumulative incidence function plot of fracture events is illustrated in Figure 2.

In the subset of participants older than 55 years, age, BMI, any previous fracture, and glucocorticoids intake did not differ between AI and TAM users. In this subset, 581 (3.86%) fractures were reported out of a total of 15,038 patients. Incidence rates are described in Table 3. As is expected, patients identified as having high risk of fracture, whether treated with TAM or AI, had the highest fracture rates.

Fracture risk analysis

TAM vs. AI users:

Fracture risk of AI users compared to TAM users was evaluated in patients older than 55 years. From 10 imputed datasets, PSM selected a mean \pm (SD) of 2,236.4 (3.37) TAM and 10,394.6 (275.39) AI users (Table 4). Cox analysis showed an increased fracture risk of 40% (HR: 1.40 [95%CI: 1.05 to 1.87]) in AI users compared to TAM users. After competing risk adjustment, fracture risk in AI increased to 48% (SHR:1.48 [95%CI:1.11 to 1.98]).

Considering only patients at low risk of fracture, PSM selected a mean \pm (SD) of 1,737.7 (1.25) patients in TAM-lowRF and 7,895.9 (85.02) patients in AI-lowRF groups. Characteristics of selected participants are reported at Supplemental Table 1. Similar results of survival analysis were obtained: AI-lowRF users had an increased fracture risk of 40% compared with TAM-lowRF users (HR: 1.40 [95%CI: 0.99 to 1.96]); this risk increased to 48% after competing risk adjustment (SHR: 1.48 [95%CI: 1.05 to 2.08]).

After matching patients at high risk of fracture treated with AI or TAM (see supplemental Table 2), no significant differences were observed in fracture risk

between both groups (HR: 1.36 [95CI%: 0.75 to 2.46]; SHR: 1.44 [CI95%: 0.80 to 2.59]). However, we cannot rule out a lack of statistical power due to the reduced sample size in the TAM-highRF group (n= 478).

BP effect analysis:

Within AI-highRF patients (see characteristics in table 5), the incidence rate was lower in BP-treated patients than in patients without BP exposure: 18.57 [95CI%: 14.85 to 22.29] vs 26.21 [95CI%: 19.00 to 33.43], respectively. Cox analysis showed a fracture reduction trend in BP users compared to non-users that was confirmed after competing risk analysis (HR: 0.73 [95CI%: 0.51 to 1.04]; SHR: 0.69 [95CI%: 0.48 to 0.98]).

After stratifying according to different oral BPs, risendronic acid and alendronic acid plus cholecalciferol raised as the most effective BPs (supplemental table 3, 4 and supplemental figure 1).

In TAM-highRF patients (see characteristics in table 6), incidence rates were 10.20 [95CI%: 0.20 to 20.20] in patients without BP exposure, and 11.87 [95CI%: 1.07 to 22.67] in patients with BP exposure. No significant differences were detected in Cox analysis (TAM-highRF patients with BP: HR 1.36 [95CI%: 0.30 to 6.20], SHR 1.13 [95CI%: 0.25 to 5.08], compared with non-BP)

Discussion

In this massive real-world cohort study of women diagnosed with hormone receptor-positive early breast cancer, the fracture risk was assessed according to adjuvant therapy. It is well known that a number of risk factors (age,

menopausal status, BMD, history of fractures, etc.) are involved in the individual's propensity to fragility fracture. Classification of patients according to fracture risk levels at baseline (osteoporotic diagnosis and/or on anti-osteoporotic treatment) allowed a more accurate analysis. To minimize the potential bias of menopause effect, women older than 55 years were selected to assess the differences in fracture risk between AI and TAM users. In this subset of postmenopausal women, AI users showed about 40% increased fracture risk, compared to TAM users. Similar results were obtained in the subset of patients at low risk of fracture. In the subgroup of AI-highRF patients, lower fracture incidence was detected in BP-treated patients who had a fracture risk reduction of 30% compared to non-BP users. On the other hand, no significant differences were detected within TAM-highRF patients. To the best of our knowledge, this is the first study assessing BPs effect on breast cancer patients at high risk of fracture, observing BP-users vs non-BP users in a real-world, non-controlled population.

The difference in risk detected between AI and TAM therapies was in line with previous studies. A recent meta-analysis by Tseng et al. reported a 35% higher fracture risk associated with AI therapy compared to TAM ($p < 0.01$)⁽¹⁵⁾ and two cohort studies found an increased risk of fractures associated with AI therapy in postmenopausal participants.^(5, 16)

The protective effect of BP on fracture risk by increasing BMD, even in women treated with AI, is well known.⁽⁹⁻¹¹⁾ However, these studies are based on strictly controlled cohorts and RCTs, not on data from real-life primary care. In our cohort study, BP use reduced fracture risk by 30% in patients at high risk of

fracture. Our results are in line with reported risk reductions of 30% to 40% in a general population treated with oral BP.⁽¹⁷⁾

Although similar fracture risk was observed in the TAM-highRF patients despite BP treatment, we cannot rule out a lack of statistical power due to the reduced sample size in the TAM-highRF group.

Overall, AI patients experienced more fractures than TAM users, especially AI users at high risk. In these AI patients, strict monitoring is recommended to identify patients at high risk of fracture during AI therapy for rapid BPs prescribing.

One limitation of the study was that data of severity and grade of breast cancer were not accessible. However, TAM and AI monotherapies are recommended and mainly used for hormone receptor-positive early breast cancer.⁽¹⁸⁾ Likewise, available data could not distinguish between osteoporotic fracture and high-energy impact fracture. However, a random distribution of impact fracture across patient groups would be expected. On the other hand, SIDIAP does not contain BMD data and the direct effect of BP on this parameter could not be assessed. In this line, osteoporosis diagnosis was registered using ICD-10 codes by the grand practitioner, which is based on BMD assessment, plus available T-scores in SIDIAP data. However, we cannot discard a misclassification of osteoporotic patients due to the lack of an accurate diagnosis. As 29.5–46.5% of vertebral fractures are not identified,⁽¹⁹⁾ the risk of all fractures associated with AI use in our cohort could be underestimated.

The strength of this study is that results are based on a large population database that comprises anonymized electronic medical records of more than 7 million patients in primary care (>80% of the population of Catalonia). The

Catalan healthcare system is universal in coverage; general practitioners act as gatekeepers to the system and are responsible for long-term prescriptions. A recent study by Gray et al. validates the use of PSM in a real-world cohort to estimate a treatment effect.⁽²⁰⁾ Additionally, the SIDIAP database has been successfully used to assess fracture risk after oral BP treatment, a study that validated this database for real-world epidemiology studies.⁽²¹⁾ To improve the validity of the study results, patients with a follow-up shorter than six months were excluded, diminishing the probability of including events unrelated to the purpose of the study.

In summary, in real-life conditions fracture risk was increased by more than 40% during AI treatment, compared to TAM therapy, in women older than 55 years; this corroborated previous RCT results. In patients at high risk, BP users had lower significant fracture incidence during AI adjuvant therapy than non-users of BP. Monitoring fracture risk and related risk factors in AI patients is advisable in order to improve the quality of life of these patients. Furthermore, it is convenient to provide antiresorptive treatment according to clinical guidelines recommendations.

Disclosures

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Authors' roles: Study design: MPM, NGG, ADP, DPA, and XN. Data collection: SS, IT, and XN. Data analysis: MPM, DPA, and NGG. Interpretation of data: All authors. Drafting of the manuscript: MPM and NGG. Critical revision of the manuscript for important intellectual content: ADP, SS, IT, DPA, XN. Approving final version of manuscript: All authors. MPM takes responsibility for the integrity of the data analysis.

References

1. Cuzick J, Sestak I, Baum M, Buzdar A, Howell A, Dowsett M, et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. *Lancet Oncol.* 2010;11(12):1135-41.
2. Regan MM, Neven P, Giobbie-Hurder A, Goldhirsch A, Ejlertsen B, Mauriac L, et al. Assessment of letrozole and tamoxifen alone and in sequence for postmenopausal women with steroid hormone receptor-positive breast cancer: the BIG 1-98 randomised clinical trial at 8.1 years median follow-up. *Lancet Oncol.* 2011;12(12):1101-8.

3. Ryden L, Heibert Arnlin M, Vitols S, Hoistad M, Ahlgren J. Aromatase inhibitors alone or sequentially combined with tamoxifen in postmenopausal early breast cancer compared with tamoxifen or placebo - Meta-analyses on efficacy and adverse events based on randomized clinical trials. *Breast*. 2016;26:106-14.
4. Goldvaser H, Barnes TA, Seruga B, Cescon DW, Ocana A, Ribnikar D, et al. Toxicity of Extended Adjuvant Therapy With Aromatase Inhibitors in Early Breast Cancer: A Systematic Review and Meta-analysis. *J Natl Cancer Inst*. 2018;110(1).
5. Kristensen B, Ejlersen B, Jensen MB, Mouridsen HT. The occurrence of fractures after adjuvant treatment of breast cancer: a DBCG register study. *Acta Oncol*. 2018;57(1):141-5.
6. Neuner JM, Shi Y, Kong AL, Kamaraju S, Smith EC, Smallwood AJ, et al. Fractures in a nationwide population-based cohort of users of breast cancer hormonal therapy. *J Cancer Surviv*. 2018;12(2):268-75.
7. Hadji P, Aapro MS, Body JJ, Gnant M, Brandi ML, Reginster JY, et al. Management of Aromatase Inhibitor-Associated Bone Loss (AIBL) in postmenopausal women with hormone sensitive breast cancer: Joint position statement of the IOF, CABS, ECTS, IEG, ESCEO IMS, and SIOG. *Journal of bone oncology*. 2017;7:1-12.
8. Hadji P, Coleman RE, Wilson C, Powles TJ, Clezardin P, Aapro M, et al. Adjuvant bisphosphonates in early breast cancer: consensus guidance for clinical practice from a European Panel. *Annals of oncology : official journal of the European Society for Medical Oncology*. 2016;27(3):379-90.
9. Tremollieres FA, Ceausu I, Depypere H, Lambrinoudaki I, Mueck A, Perez-Lopez FR, et al. Osteoporosis management in patients with breast cancer: EMAS position statement. *Maturitas*. 2017;95:65-71.
10. María R-S, Marta P-M, Sonia S, Natalia G-G, Tamara M, Ignasi T, et al. TBS and BMD at the end of AI-therapy: A prospective study of the B-ABLE cohort. *Bone*. 2016;92:1-8.
11. Pineda-Moncusi M, Servitja S, Casamayor G, Cos ML, Rial A, Rodriguez-Morera J, et al. Bone health evaluation one year after aromatase inhibitors completion. *Bone*. 2018;117:54-9.
12. EBCTCG EBCTCG. Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. *Lancet*. 2015;386(10001):1353-61.
13. Caro-Mendivelso J E-RJ, Hermosilla E, Méndez-Boo L, García-Gil M, Prieto-Alhambra D, Medina M. Associations between socioeconomic index and mortality in rural and urban small geographic areas of Catalonia, Spain: Ecological study. *J Epidemiol Res*. 2016;2(1):80-6.
14. Lorraine K. Alexander BL, Kristen Ricchetti-Masterson, Karin B. Yeatts. Calculating Person-time. *ERIC Notebook*. 2015;Second Edition (4):1 - 3.
15. Tseng OL, Spinelli JJ, Gotay CC, Ho WY, McBride ML, Dawes MG. Aromatase inhibitors are associated with a higher fracture risk than tamoxifen: a systematic review and meta-analysis. *Ther Adv Musculoskelet Dis*. 2018;10(4):71-90.
16. Schmidt N, Jacob L, Coleman R, Kostev K, Hadji P. The impact of treatment compliance on fracture risk in women with breast cancer treated with aromatase inhibitors in the United Kingdom. *Breast cancer research and treatment*. 2016;155(1):151-7.
17. Rizzoli R. Postmenopausal osteoporosis: Assessment and management. *Best Pract Res Clin Endocrinol Metab*. 2018;32(5):739-57.
18. Burstein HJ, Lacchetti C, Anderson H, Buchholz TA, Davidson NE, Gelmon KA, et al. Adjuvant Endocrine Therapy for Women With Hormone Receptor-Positive Breast Cancer: ASCO Clinical Practice Guideline Focused Update. *J Clin Oncol*. 2019;37(5):423-38.
19. Delmas PD, van de Langerijt L, Watts NB, Eastell R, Genant H, Grauer A, et al. Underdiagnosis of vertebral fractures is a worldwide problem: the IMPACT study. *J Bone Miner Res*. 2005;20(4):557-63.
20. Gray E, Marti J, Brewster DH, Wyatt JC, Piaget-Rossel R, Hall PS. Real-world evidence was feasible for estimating effectiveness of chemotherapy in breast cancer; a cohort study. *J Clin Epidemiol*. 2019.

21. Khalid S, Calderon-Larranaga S, Hawley S, Ali MS, Judge A, Arden N, et al. Comparative anti-fracture effectiveness of different oral anti-osteoporosis therapies based on "real-world" data: a meta-analysis of propensity-matched cohort findings from the UK Clinical Practice Research Database and the Catalan SIDIAP Database. *Clinical epidemiology*. 2018;10:1417-31.

Figures

Figure 1. Flow chart of SIDIAP cohort study. Patients at low risk are those without osteoporosis diagnosis and without BPs. Patients at high risk are those with diagnosis of osteoporosis and/or candidates to BP treatment. Abbreviations: AI, aromatase inhibitor; BP, bisphosphonates; highRF, high risk of fracture; lowRF, low risk of fracture; TAM, tamoxifen.

Figure 2. Cumulative hazard plot of fracture events in study groups according to risk of fracture. Graphs show Kaplan-Meier curves representing the outcome of the study in terms of cumulative hazards. Abbreviations: AI, aromatase inhibitor; highRF, high risk of fracture; lowRF, low risk of fracture; TAM, tamoxifen.

Supplemental figure 1 Cumulative hazard plot of fracture events within AI-highRF patients according to risk its BP use. Graphs show Kaplan-Meier curves representing the outcome of the study in terms of cumulative hazards. Abbreviations: BP, bisphosphonate; VitD₃, cholecalciferol supplements.

Tables

Table 1. Baseline characteristics of patients

Variable	AI N=15,052	TAM N=7,539
Mean age (years) ± (SD)	67.30 ± 11.20	52.3 ± 13.60
Mean BMI (kg/m²) ± (SD)	29.80 ± 5.32	28.2 ± 5.57
Missing (n(%))	11,031 (73.29%)	6,153 (81.62%)
Charlson co-morbidity index (n(%)):		
0	1,896 (12.60%)	824 (10.90%)
1	594 (3.95%)	139 (1.84%)
2	8,159 (54.20%)	5,467 (72.50%)
3	2,896 (19.20%)	825 (10.90%)
4 or >4	1,507 (10.00%)	284 (3.77%)
Smoke (n(%)):		
Never smokers	8,387 (55.70%)	2,853 (37.80%)
Current smokers	1,072 (7.12%)	1,249 (16.60%)
Ex-smokers	808 (5.37%)	653 (8.66%)
Missing	4,785 (31.80%)	2,784 (36.90%)
Risk of alcoholism (n(%)):		
None/low	2006 (13.33%)	693 (9.19%)
Moderate	331 (2.20%)	184 (2.44%)
High/Alcoholic	14 (0.09%)	5 (0.07%)
Missing	12,701 (84.38%)	6,657 (88.30%)
Bisphosphonates use (n(%))	3,450 (22.90%)	480 (6.37%)
Previous fracture (n(%))	603 (4.01%)	152 (2.02%)
Previous use of systemic glucocorticoids (n(%))	215 (1.43%)	62 (0.82%)
Rheumatoid arthritis (n(%))	117 (0.78%)	43 (0.57%)
Chronic kidney disease (n(%))	513 (3.41%)	75 (0.99%)
Osteoporosis (n(%))	1,859 (12.40%)	371 (4.92%)
Hypnotics/sedative (n(%))	8,843 (58.70%)	3,621 (48.00%)
Abbreviations: AI, aromatase inhibitor; BMI, body mass index; TAM, tamoxifen.		

Table 2. Fracture incidence in all participants

Exposure group	FX	Incidence rate [95%CI] (cases/1,000py)
TAM-lowRF	76/6,876 (1.11%)	4.10 [3.26 to 5.11]
TAM-highRF	15/663 (2.26%)	13.24 [7.69 to 21.34]
AI-lowRF	401/10,899 (3.67%)	12.32 [11.15 to 13.57]
AI-highRF	166/4,153 (4.00%)	20.06 [17.18 to 23.30]
Abbreviations: AI, aromatase inhibitors; CI, confidence interval; FX, fracture; py, person-years; lowRF, patients at low risk of fracture; highRF, patients at high risk of fracture; TAM, tamoxifen.		

Table 3. Fracture incidence in women older than 55 years

Exposure group	FX	Incidence rate [95%CI] (cases/1,000py)
TAM-lowRF	38/1,741 (2.18%)	9.02 [6.48 to 12.26]
TAM-highRF	15/502 (2.99%)	16.57 [9.63 to 26.72]
AI-lowRF	368/9,076 (4.05%)	13.55 [12.22 to 14.99]
AI-highRF	160/3,719 (4.30%)	21.35 [18.23 to 24.85]
Abbreviations: AI, aromatase inhibitors; CI, confidence interval; FX, fracture; py, person-years; lowRF, patients at low risk of fracture; highRF, patients at high risk of fracture; TAM, tamoxifen.		

Table 4. Baseline characteristics of >55-year-old matched patients from AI and TAM users

Variable	TAM N=2,236.4	AI N=10,394.6
Mean age (years) \pm (SD)	69.80 \pm 10.10	70.00 \pm 9.27
Mean BMI (kg/m ²) \pm (SD)	27.20 \pm 6.65	27.00 \pm 6.68
Charlson co-morbidity index (n(%)):		
0	287.9 (12.9%)	1,354.3 (13.0%)
1	96.6 (4.32%)	452.9 (4.36%)
2	1,238.4 (55.4%)	5,623.4 (54.1%)
3	410.1 (18.3%)	1975.3 (19.0%)
4 or >4	203.4 (9.09%)	988.7 (9.51%)
Smoke (n(%)):		
Never Smokers	1,931.3 (86.4%)	8,967.7 (86.3%)
Current Smokers	156.2 (6.98%)	739.3 (7.11%)
Ex-smokers	148.9 (6.66%)	687.6 (6.61%)
Alcoholism, n (%):		
None/Low	1,557.3 (69.6%)	7,281.4 (70.0%)
Moderate	675.5 (30.2%)	3,097.3 (29.8%)
High/Alcoholic	3.6 (0.16%)	15.9 (0.15%)
Bisphosphonates use (n(%))	335.5 (15.0%)	2,475.5 (23.8%)
Previous fracture (n(%))	94.7 (4.23%)	435.6 (4.19%)
Previous use of systemic glucocorticoids (n(%))	29.8 (1.33%)	139.8 (1.34%)
Rheumatoid arthritis (n(%))	20.7 (0.93%)	86.2 (0.83%)
Chronic kidney disease (n(%))	58.9 (2.63%)	296.9 (2.86%)
Osteoporosis (n(%))	317.2 (14.2%)	1,421.3 (13.7%)
Hypnotics/sedative (n(%))	1,248.8 (55.8%)	5,954.1 (57.3%)
All values are the mean of the ten imputed datasets.		
Abbreviations: AI-lowRF, aromatase inhibitors at low risk of fracture; BMI, body mass index; TAM-lowRF, tamoxifen patients at low risk of fracture.		

Table 5. Baseline characteristics of matched patients within AI-highRF group: BP-treated vs non-BP-treated patients

Variable	AI-highRF	
	No BP-treated N=764.9	BP-treated N=2,741.1
Mean Age (years) ± (SD)	72.1± 9.82	69.4± 9.34
Mean BMI (kg/m2) ± (SD)	24.3± 3.74	24.4± 3.89
Charlson co-morbidity index (n):		
0	79.9 (10.4%)	335.7 (12.2%)
1	35.9 (4.69%)	112.7 (4.11%)
2	392 (51.2%)	1,554.2 (56.7%)
3	161.7 (21.1%)	513.1 (18.7%)
4 or >4	225.4 (8.22%)	225.4 (8.22%)
Smoke (n(%)):		
Never Smokers	656.2 (85.8%)	2,305.2 (84.1%)
Current Smokers	61.8 (8.08%)	263.1 (9.60%)
Ex-smokers	46.9 (6.13%)	172.8 (6.30%)
Previous fracture (n(%))	58.5 (7.65%)	164.4 (6.00%)
Previous use of systemic corticosteroids (n(%))	14.6 (1.91%)	37.7 (1.38%)
Rheumatoid arthritis (n(%))	9 (1.18%)	27.2 (0.99%)
Chronic kidney failure (n(%))	32.1 (4.20%)	65.5 (2.39%)
Hypnotics/sedative (n(%))	480.8 (62.9%)	1,726.1 (63.0%)
Abbreviations: AI-highRF, aromatase inhibitors patients at high risk of fracture; BMI, body mass index; BP, bisphosphonates.		

Table 6. Baseline characteristics of matched patients within TAM-highRF groups: BP-treated vs non-BP-treated patients

Variable	TAM-highRF	
	No BP-treated N=158.7	BP-treated N=254.4
Mean Age (years) \pm (SD)	67.2 \pm 11.5	66.6 \pm 12.1
Mean BMI (kg/m²) \pm (SD)	24.2 \pm 3.95	23.9 \pm 3.93
Charlson co-morbidity index (n):		
0	18.7 (11.8%)	32.3 (12.7%)
1	7 (4.41%)	11.6 (4.56%)
2	96.7 (60.9%)	153.3 (60.3%)
3	27.8 (17.5%)	45.7 (18.0%)
4 or >4	8.5 (5.36%)	11.5 (4.52%)
Smoke (n(%)):		
Never Smokers	138 (87.0%)	219.2 (86.2%)
Current Smokers	12 (7.56%)	19.7 (7.74%)
Ex-smokers	8.7 (5.48%)	15.5 (6.09%)
Previous fracture (n(%))	14.4 (9.07%)	20.3 (7.98%)
Previous use of systemic corticosteroids (n(%))	1.3 (0.82%)	3.5 (1.38%)
Rheumatoid arthritis (n(%))	1.4 (0.88%)	2.4 (0.94%)
Chronic kidney failure (n(%))	1.6 (1.01%)	1.8 (0.71%)
Hypnotics/sedative (n(%))	87 (54.8%)	144.5 (56.8%)
Abbreviations: BMI, body mass index; BP, bisphosphonates; TAM-highRF, tamoxifen patients at high risk of fracture.		