# Long-Term Effect of Aromatase Inhibitors on Fracture Risk Compared to Tamoxifen: a "Real World" Cohort Study of Continued Treatment Up to Ten Years of Follow-Up

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## Introduction

Recommended adjuvant treatments for estrogen receptor positive breast cancer include aromatase inhibitors (AI) and tamoxifen (TAM). AI therapy has been associated with increased bone loss and excess fracture risk in pivotal RCTs. Bisphosphonates (BP) are recommended in clinical guidelines to minimize bone loss. We conducted an observational cohort study to assess fracture risk during long-term AI therapy compared with tamoxifen, and to study the association with BP use.

## Methods

Data on 27,695 breast cancer women on either AI or TAM were obtained from primary care records in Catalonia (SIDIAP database) between 2006 and 2015. Patients were included from the first day of TAM or AI treatment until the earliest of: AI/TAM or BP (if applicable) cessation, death or migration, end of data availability, or fracture event. BP use was introduced as a time-varying exposure, with patients considered non-users at first, but contributing to the BP user cohort from BP therapy initiation. Survival analyses were performed by a)Kaplan–Meier to estimate cumulative probability plots, and b)Cox proportional hazards models accounting for competing risk of death (Fine and Gray models) adjusted for propensity scores to calculate event-specific hazard ratios (SHR [95%CI]) according to exposure and using TAM as reference group.

## Results

A total of 9,233 TAM, 564 TAM+BP, 17,028 AI, and 3,914 AI+BP records were included, with fracture incidence rates [95%CI] of 5.45/1,000 person-years [4.49 to 6.56], 24.95 [15.02 to 39.14], 15.08 [13.88 to 16.36], and 25.71 [22.02 to 29.85] respectively (Fig. 1). TAM-treated patients had the lowest fracture risk: propensity-adjusted SHR 2.15 [1.26 to 3.68] in TAM+BP, 1.77 [1.43 to 2.21] in AI, and 2.42 [1.86 to 3.15] in AI+BP (Table 1). Significant higher risk was observed in AI+BP (SHR 1.33 [1.10 to 1.61]) compared to AI users (Table 2).

**Table 1. Fracture risk of each treatment group compared with TAM, using the competing risk analysis**

| Outcome | Unadjusted SHR [95%CI] | Adjusted SHR [95%CI] |
|---|---|---|
| TAM | ref. | ref. |
| TAM+BP | 3.52 [2.08 to 5.95] | 2.15 [1.26 to 3.68] |
| AI | 2.61 [2.12 to 3.21] | 1.77 [1.43 to 2.21] |
| AI+BP | 4.22 [3.30 to 5.39] | 2.42 [1.86 to 3.15] |

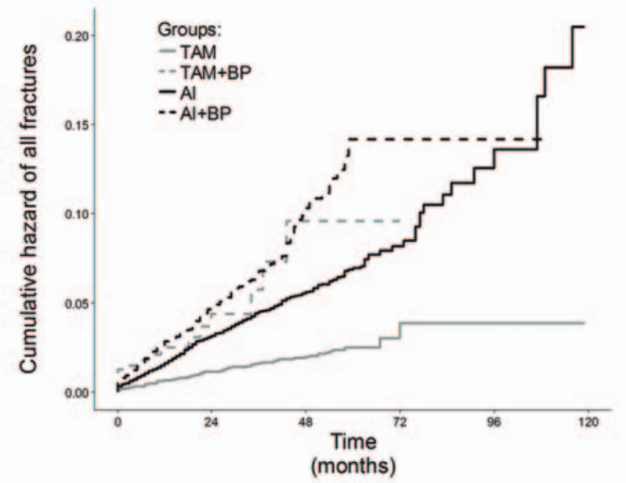
Abbreviations: AI, aromatase inhibitors; BP, bisphosphonates; CI, confidence interval; SHR, subdistribution hazard ratio; ref, reference group; TAM, tamoxifen. In 95%CI, AI values are compared with TAM.

**Table 2. Fracture risk of AI+BP treatment compared with AI treatment, using the competing risk analysis**

| Outcome | Unadjusted SHR [95%CI] | Adjusted SHR [95%CI] |
|---|---|---|
| AI | ref. | ref. |
| AI+BP | 1.61 [1.35 to 1.92] | 1.33 [1.10 to 1.61] |

Abbreviations: AI, aromatase inhibitors; BP, bisphosphonates; CI, confidence interval; SHR, subdistribution hazard ratio; ref, reference group. In 95%CI, AI+BP values are compared with AI.

**Fig 1. Cumulative hazard plot of fracture risk in each treatment group**




**Number of patients at risk (n):**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Exposure group: | TAM | 9,233 | 4,211 | 1,906 | 120 | 16 | 4 |
| | TAM+BP | 564 | 144 | 32 | 1 | 0 | 0 |
| | AI | 17,028 | 8,075 | 3,831 | 342 | 98 | 18 |
| | AI+BP | 3,914 | 1,409 | 436 | 13 | 1 | 0 |
| | Time (months) | 0 | 24 | 48 | 72 | 96 | 119 |

**Cumulative number of events (n):**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Exposure group: | TAM | 10 | 74 | 98 | 107 | 107 | 107 |
| | TAM+BP | 7 | 14 | 17 | 17 | 17 | 17 |
| | AI | 53 | 373 | 512 | 558 | 568 | 572 |
| | AI+BP | 23 | 117 | 158 | 166 | 166 | 166 |
| | Time (months) | 0 | 24 | 48 | 72 | 96 | 119 |

## Conclusions

AI therapy is associated with substantial increase in fracture risk compared to TAM, where the BP users manifested the worst outcomes. Monitoring fracture risk factors in AI patients is recommended. More data are needed on the protective efficacy of BP therapy in AI-induced bone fragility.

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