Clinical Question 6

- What is the risk of fracture in patients on aromatase inhibitor therapy?

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Learning Objectives

Upon completion of this module, participants will be better able to:

- Explain the impact of co-morbidities on the risk profile of patients with osteoporosis
- Describe why aromatase inhibitor therapy is associated with bone loss and increased fracture risk
- Mitigate the impact of medication-related factors which may increase the risk of bone loss and fragility fractures

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Clinical Question 6

What is the risk of fracture in patients on aromatase inhibitor therapy?

With the expanding use and longer therapy duration of aromatase inhibitor in patients with breast cancer, attention to bone health is important. The declines in BMD on aromatase inhibitor contribute to a high long-term risk of fracture. Guidelines would suggest initiating osteoporosis therapy at T-scores of -1.5 or -2.

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Clinical Vignette

Margaret
68 years old

- Breast Cancer
- FRAX MOF: 15%
- Femoral Neck T-score: -1.8
- HF: 1.8%
- Initiated on letrozole with a plan to continue for 10 years

Does Margaret require bone protective therapy?

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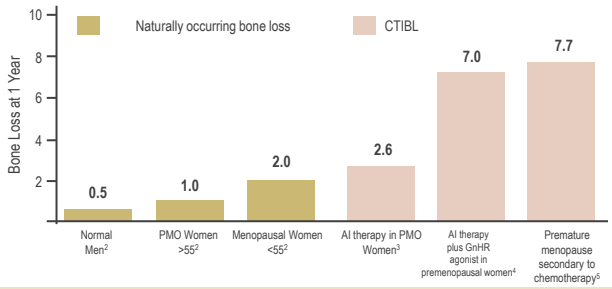
Cancer Treatment Induced Bone Loss (CTIBL)

- **2.6% loss in lumbar spine BMD in postmenopausal women receiving AI therapy[1]**
  - → With concomitant increase in fracture incidence
- **For postmenopausal patients, aromatase inhibitors (AIs) have emerged as the standard of care because of their superior efficacy compared with tamoxifen[1]**
  - → However, the reported rate of fractures[6] was lower with tamoxifen (5.8% vs 8.6%, p<0.001)

Normal and Cancer Treatment Related Bone Loss Rates



1. Hadji P. *Breast Care (Basel)* 2010;5(5):290-296; 2. Kanis JA. *Osteoporosis* 1997;22-55; 3. Eastell R. *J Bone Mineral Res* 2003;18(6):1051-6;
4. Gnant M. (2002). San Antonio Breast Cancer Symposium. 5. Shapiro CL. *J Clin Oncol* 2001;19(14):3306-3311; 6. Coates AS, et al. J Clin Oncol 2007;25:486-492.

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Recommendations for Patients with Moderate Risk

Moderate risk
(10-year fracture risk 10%-20%)

Lateral thoracolumbar radiography (T4-L4) or vertebral fracture assessment may aid in decision-making by identifying vertebral fractures

Factors warranting consideration of pharmacologic therapy:

- Additional vertebral fracture(s) (by vertebral fracture assessment or lateral spine radiograph)
- Previous wrist fracture in individuals aged > 65 or those with T-score ≤ -2.5
- Lumbar spine T-score much lower than femoral neck T-score
- Rapid bone loss
- Men undergoing androgen-deprivation therapy for prostate cancer
- Women undergoing aromatase inhibitor therapy for breast cancer
- Long-term or repeated use of systemic glucocorticoids (oral or parenteral) not meeting conventional criteria for recent prolonged use
- Recurrent falls (≥ 2 in the past 12 mo)
- Other disorders strongly associated with osteoporosis, rapid bone loss or fractures

Repeat BMD in 1-3 yr and reassess risk

Good evidence of benefit from pharmacotherapy

Adapted from Papaioannou A, et al. CMAJ 2010; 182(17):1864-73.

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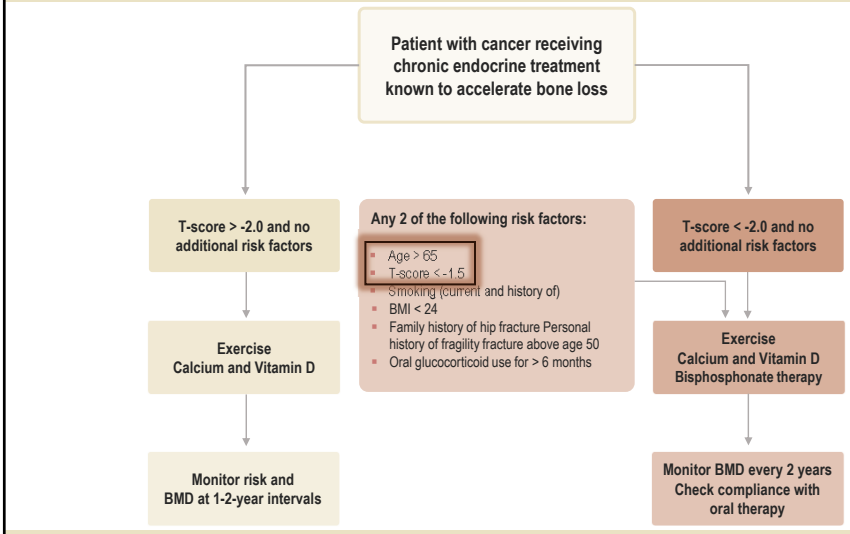
Management of Aromatase Inhibitor-Associated Bone Loss (AIBL) in postmenopausal women with hormone sensitive breast cancer:
Joint position statement of the IOF, CABS, ECTS, IEG, ESCEO, IMS, and SIOG



Hadji P et al. J Bone Oncology 2017; 7: 1-12.

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Cochrane Database Review:
CTIBL-Breast Cancer Patients

- 44 RCTs involving 37,302 women
- In early breast cancer, BPs reduce the risk of bone metastases and provide an overall survival benefit compared to placebo or no BPs

Oral Bisphosphonates 9 studies (n=2891)	Denosumab 3 studies (n=2345)
▪ Delayed median time to skeletal related event ▪ Median ratio 1.43 (95% CI 1.29 to 1.58; P < 0.00001) ▪ Reduced bone pain compared to placebo/no BP	▪ Reduced the risk of developing skeletal related event compared with BPs by 22% (RR 0.78, 0.72 to 0.85; P < 0.001)

Skeletal related event = pathologic fracture, spinal cord compression, necessity for radiation to bone (for pain or impending fracture) or surgery to bone.
O'Carrigan B, et al. *Cochrane Database Syst Rev* 2017 Oct 30;10:CD003474.

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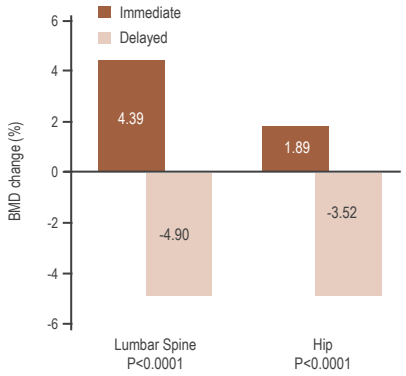
RCT: CTIBL-Breast Cancer Patients: Effect of Zoledronic Acid on Total Hip and Lumbar Spine BMD

- At month 61, the adjusted mean difference in LS 8.9% (95% CI: 7,4-10.5) and total hip 6.7% (95% CI: 5.5-8.0) BMDs between the upfront and delayed groups



602 PMO with early, hormone receptor-positive BC receiving adjuvant letrozole were randomized to receive upfront or delayed-start zoledronic acid (4 mg intravenously every 6 months) for 5 years.
Adapted from Brufsky AM, et al. *Cancer* 2012;118(5):1192-201.

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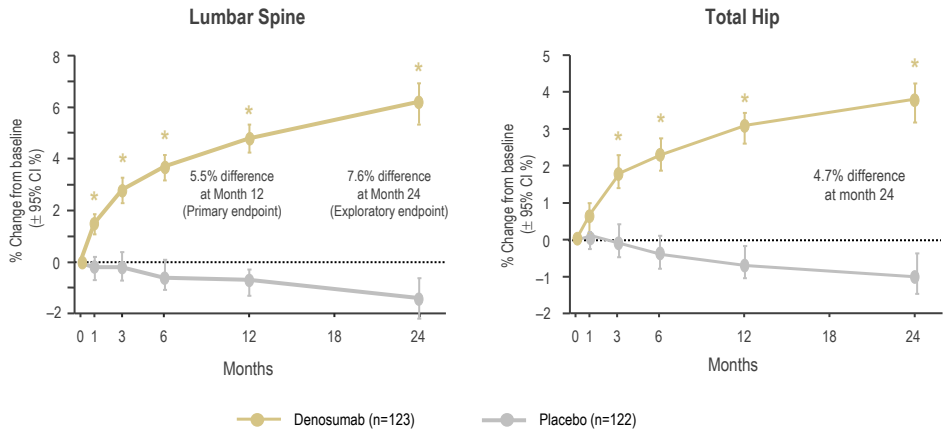
Phase 3: CTIBL-Breast Cancer Patients: Effect of Denosumab on Total Hip and Lumbar Spine BMD



*p < 0.0001 vs placebo. CI = confidence interval.
Adapted from Ellis GK, et al. *J Clin Oncol* 2008;26:4875-4882.

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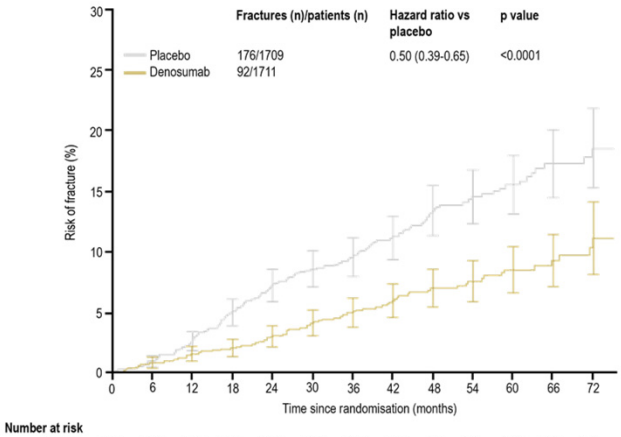
Effect of Denosumab 60 mg q 6 mo on the Occurrence of Clinical Fracture in Postmenopausal, Aromatase Inhibitor-Treated Patients with Early-Stage Hormone Receptor-Positive Breast Cancer (ABCSG-18)



Percentage risk of fracture based on Kaplan-Meier time-to-event analysis within each treatment group at 6-month intervals. The hazard ratio and p value were calculated from a Cox model including treatment groups as the independent variable and stratified by the randomisation stratification factors. Error bars are 95% CIs.

Gnant M, Lancet 2015 Aug 1;386(9992):433-43.

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20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years

- After 5 years of adjuvant endocrine therapy, breast-cancer recurrences continued to occur steadily throughout the study period from 5 to 20 years.
- In conclusion, **even after 5 years of adjuvant endocrine therapy**, women with ER-positive, **early stage breast cancer still had a persistent risk of recurrence and death** from breast cancer for at least 20 years after the original diagnosis.
- Recognition of the magnitude of the long-term risks of ER-positive disease can help women and their health care professionals decide **whether to extend therapy beyond 5 years and whether to persist if adverse events occur**

Pan H et al. N Engl J Med 2017;377:1836-1846

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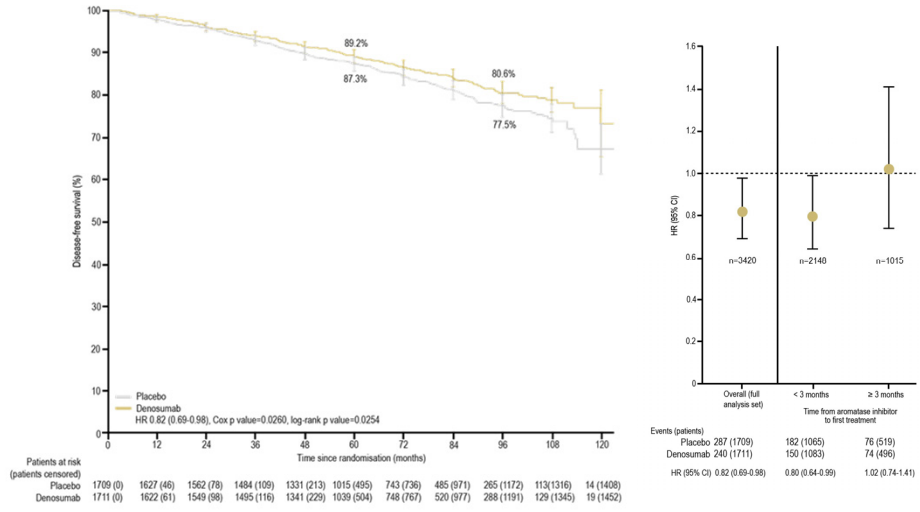
Adjuvant Denosumab in Postmenopausal Patients with Hormone Receptor-Positive Breast Cancer (ABCSG-18): Disease-Free Survival Results from a Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial



Gnant M et al. The Lancet Oncology 2019;20(3): 339-351.

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Discussion: Clinical Takeaways

1. For postmenopausal patients, aromatase inhibitors (AIs) have emerged as the standard of care for hormone receptor-positive breast cancer because of their superior efficacy compared with tamoxifen.
2. AIs are associated with a rapid bone loss and a long-term risk of fracture
3. Good evidence of benefit from pharmacotherapy when FN T score < -1.5
4. Oral bisphosphonates and denosumab reduce the risk of bone metastases
5. IV Zoledronic (4 mg) acid given early and every 6 months prevents bone loss
6. Denosumab 60 mg s.c. q 6 months prevents bone loss, reduces fracture risk and decreases disease-free survival if initiated early (< 3 months)

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