Progetto CANOA

Carcinoma mammario: quali novità per il 2021?

La gestione della paziente con EBC: situazioni particolari

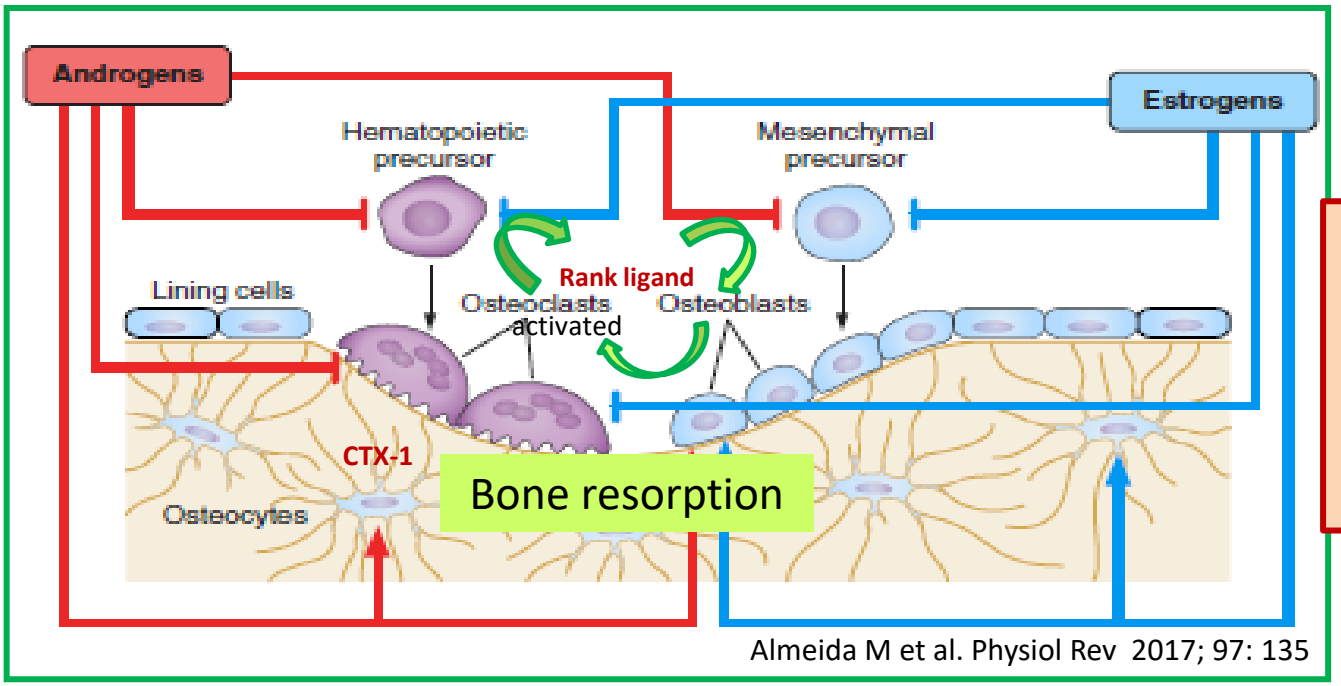
LA SALUTE DELL'OSSO DURANTE ORMONOTERAPIA ADIUVANTE PER EBC: DALLE EVIDENZE SCIENTIFICHE ALLA GESTIONE DELLA PAZIENTE

Dr.ssa Monica Turazza

UOC Oncologia medica

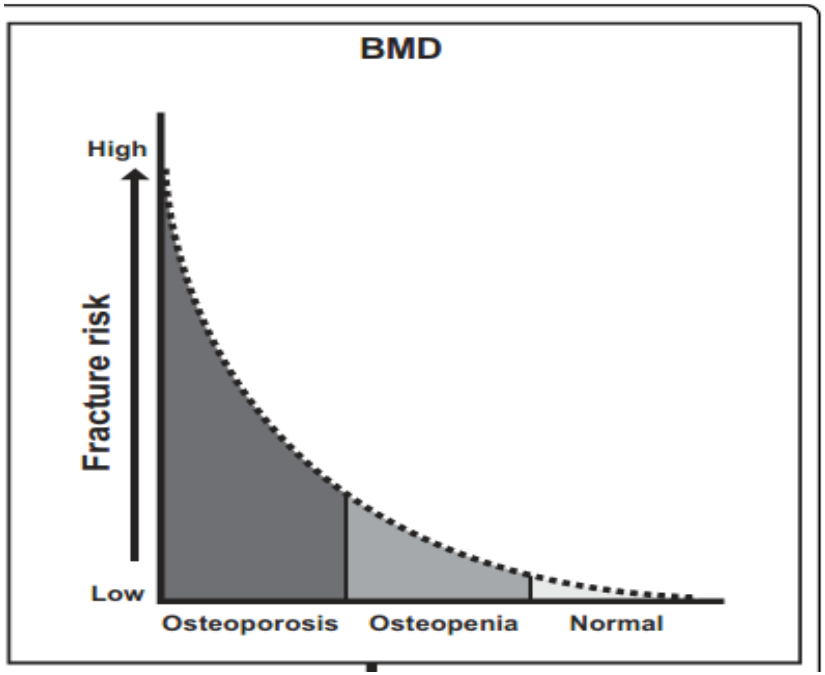
IRCSS Sacro Cuore-Don Calabria, Negrar di Valpolicella (VR)

Con il patrocinio di



Almeida M et al. Physiol Rev 2017; 97: 135

In women peak bone mass occured around age 30 years



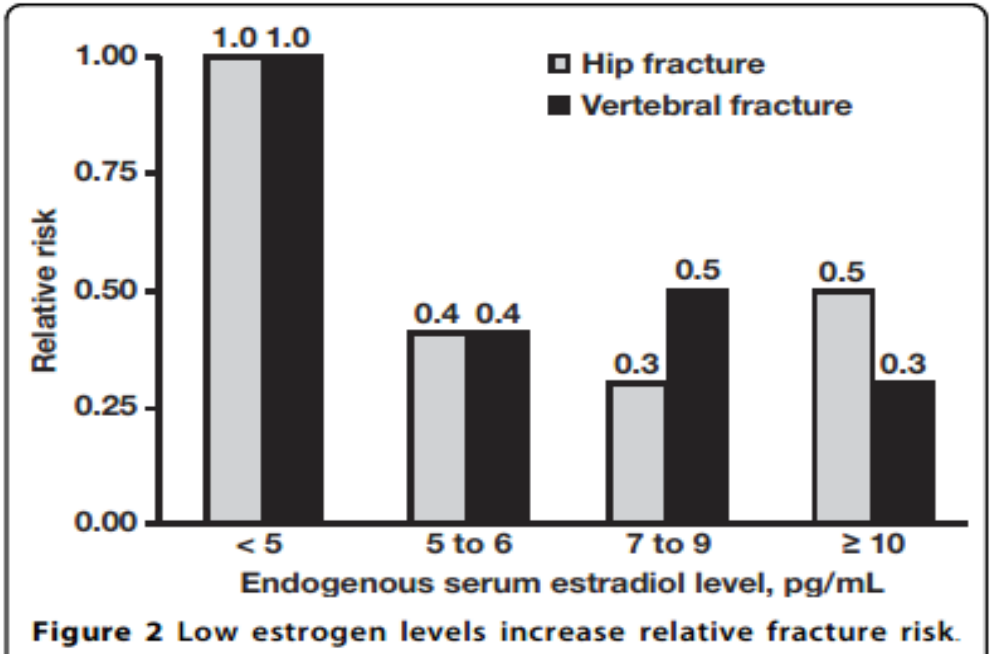


Figure 2 Low estrogen levels increase relative fracture risk.

Cuming Sr et al. N Engl J Med, 1998; 339: 733

TABLE 1. World Health Organization Diagnostic Thresholds for Low Bone Mass Using DXA Results for Men and Women[44,52,53]

	Interpretation of DXA Measurement	T Score
Normal	BMD more than 1 SD below the young adult female reference mean	≥ 1
Osteopenia	BMD more than 1 SD but less than 2.5 SD below the young adult mean	< 1 and > 2.5
Osteoporosis	BMD 2.5 SD or more below the young adult female mean	≤ 2.5
Severe Osteoporosis	BMD 2.5 SD or more below the young female adult mean in the presence of one or more fragility fractures	≤ 2.5 and clinical fragility fracture

Indagine radiologica: tecnica dual-energy x-ray absorptiometry (DXA) che misura la densità minerale (BMD) in g/cmq.
T-score: unità di misura ossia deviazione standard dal picco medio di massa corporea inteso come densità minerale media di adulti sani
Z-score: unità di misura ossia di deviazione standard da una popolazione di riferimento analoga per sesso, età, etnia

Indagini di laboratorio con dosaggio di: vitamina D, PTH (paratormone sierico) CTX (marker sierico sensibile e specifico del turnover osseo). Indicato nel monitorare la risposta alle terapia riassorbitiva in tempi rapidi senza aspettare i 16-24 mesi per la densitometria.

FRAX e DeFRA: **algoritmi complessi** che calcolano il rischio delle principali fratture da fragilità (vertebre, femore, omero, polso) integrando la misurazione della BMD con i fattori di rischio anamnestici

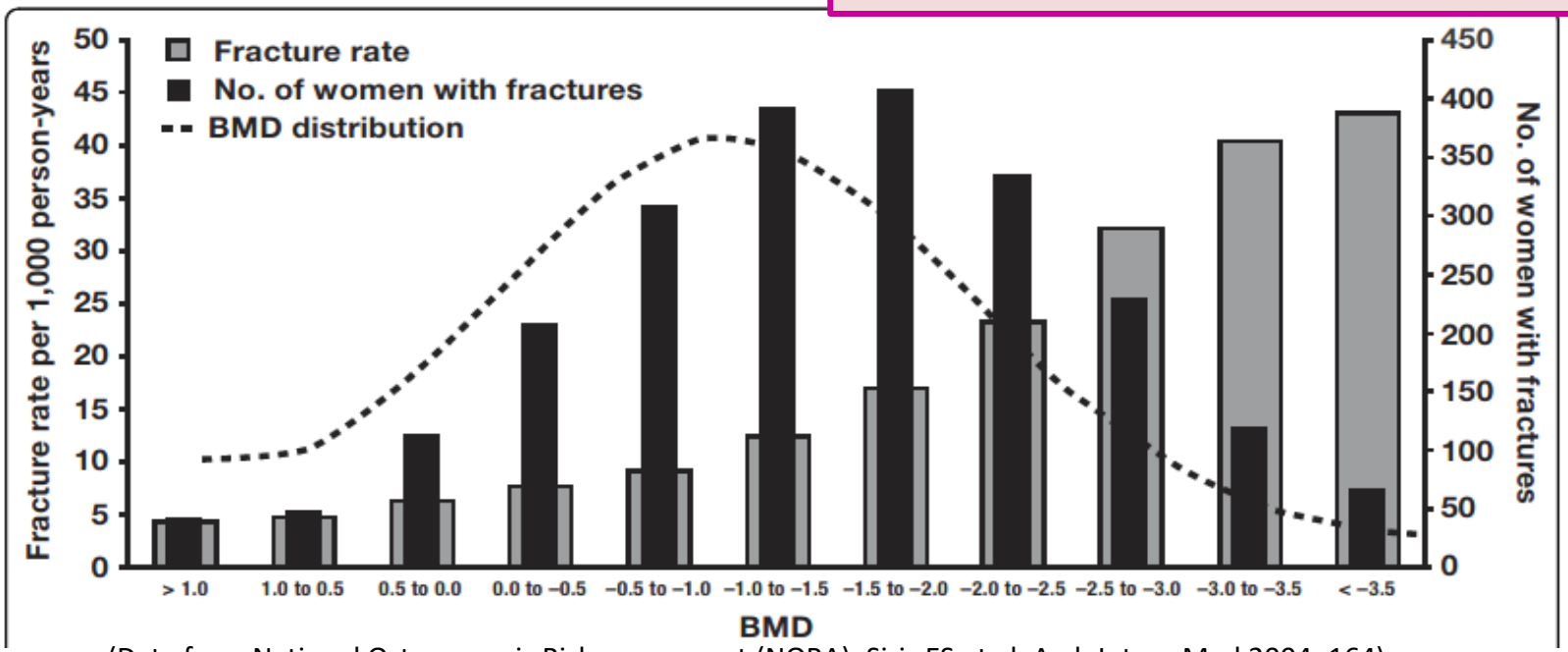
Rossini M et al. Reumatismo, 2016; 68(1): 1.

Table 2 Risk factors for development of fractures or bone mineral density loss[a]

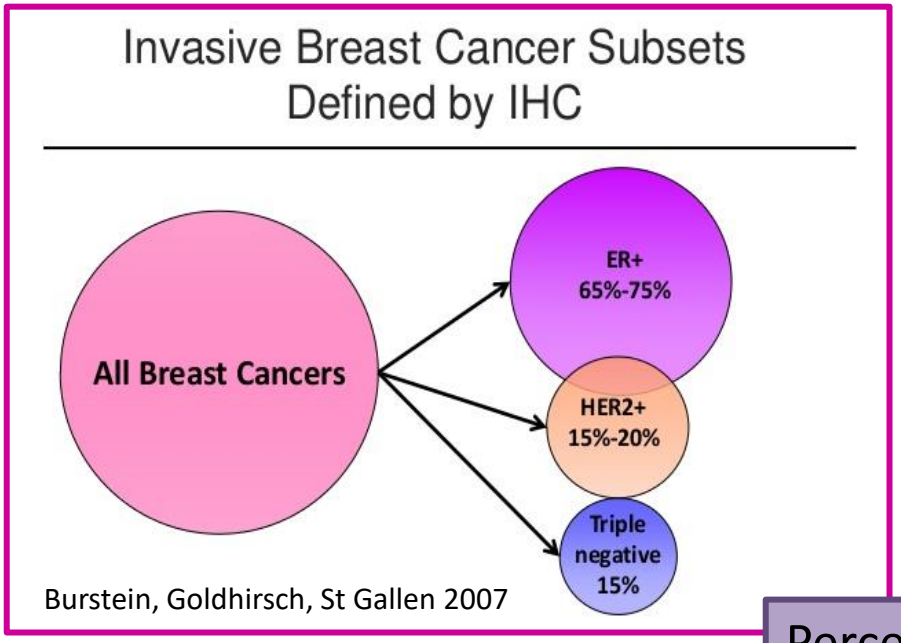
Oncologist 2006; 11:1121

Modifiable risk factors	Other risk factors
Excessive alcohol consumption	Age
Tobacco use	Low bone mass
Existing low body mass index (< 20 kg/m^2) and excessive weight loss	Race (Asian, white)
Falls	Fracture history (personal, familial)[b]
Sedentary lifestyle[b]	Diabetes
Low calcium or vitamin D intake	Rheumatoid arthritis
Use of medications affecting absorption of calcium or absorption or production of vitamin D[b]	Emphysema, chronic bronchitis
Use of corticosteroids[b]	Renal insufficiency
Use of medications decreasing the production of estrogen or testosterone[b]	
Low estrogen or testosterone levels	

A proportion of women experienced fracture without "osteporosis" (defined as T-score<-2.5) due other factors not defined with BMD (bone size, bone geometry, microarchitecture change) but supported by FRAX or DeFRA algoritms



(Data from National Osteoporosis Risk assessment (NORA). Siris ES et al. Arch Intern Med 2004; 164)



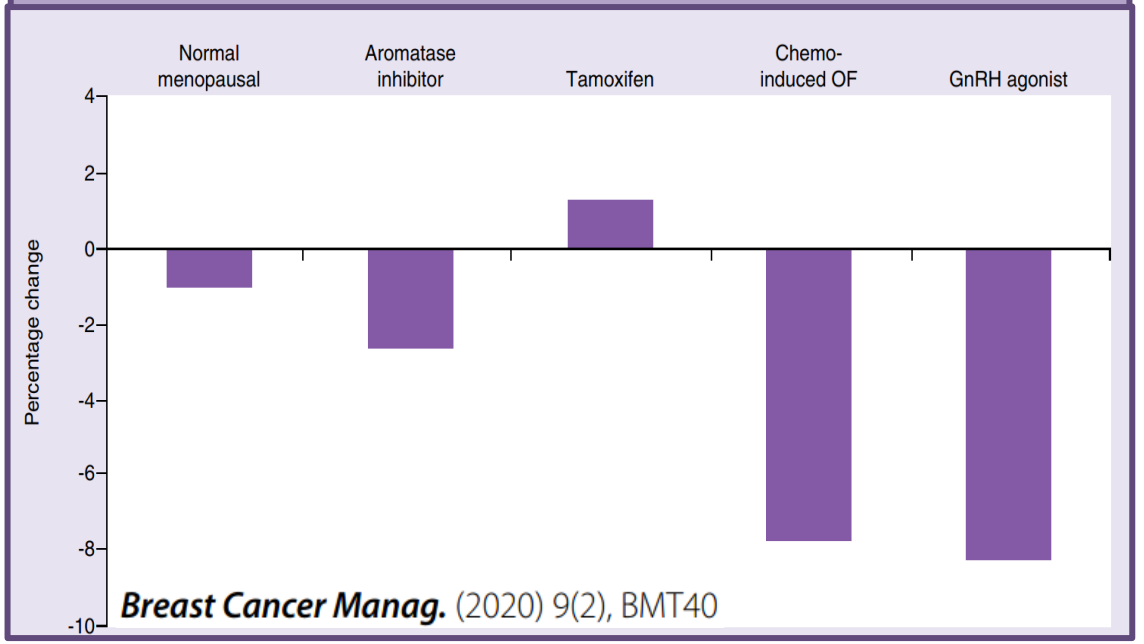
Mammella	dati AIRTUM (edizione 2020)
Incidenza (nuove diagnosi attese nelle donne nel 2020)	circa 55.000 nuovi casi
Mortalità (stimati nel 2020)	12.300 decessi
Sopravvivenza netta a 5 anni dalla diagnosi	87%
Sopravvivenza di ulteriori 5 anni condizionata ad aver superato il 1° anno dalla diagnosi	89%
Prevalenza in Italia (viventi dopo diagnosi di tumore mammario)	834.000 donne viventi

Prognosis of early breast cancer improves

⇩

Long-term safety of adjuvant treatment increases

Percentage change in bone mineral density loss in spine at 12 months with breast cancer therapies



ORIGINAL INVESTIGATION

Arch Intern Med. 2005;165:552-558

Fracture Risk Among Breast Cancer Survivors

Results From the Women's Health Initiative Observational Study

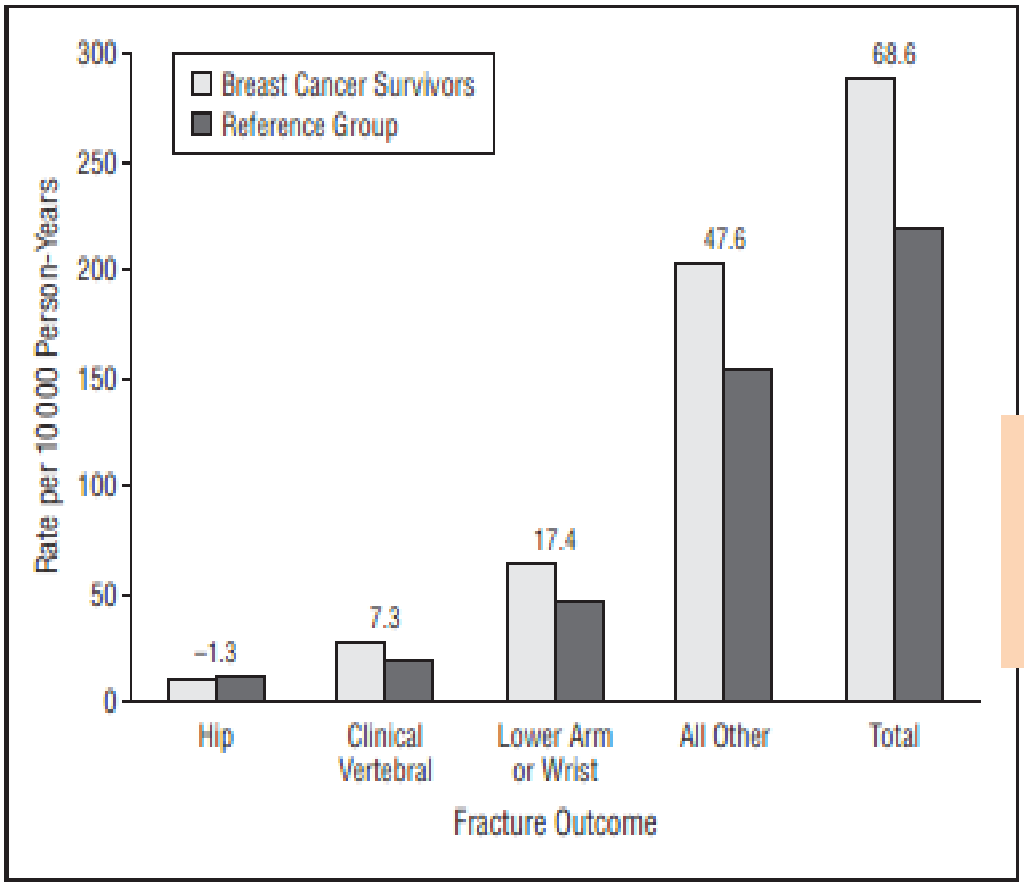


Figure 2. Hazard ratios (95% confidence intervals) of fractures among breast cancer survivors compared with the reference group. The dashed lines indicate the crude estimate, and the solid lines indicate estimates from models adjusted for age, weight, ethnicity, and geographic region of enrollment.

Prospective cohort study
5.1 years follow up
5298 BC patients
80848 women as reference group

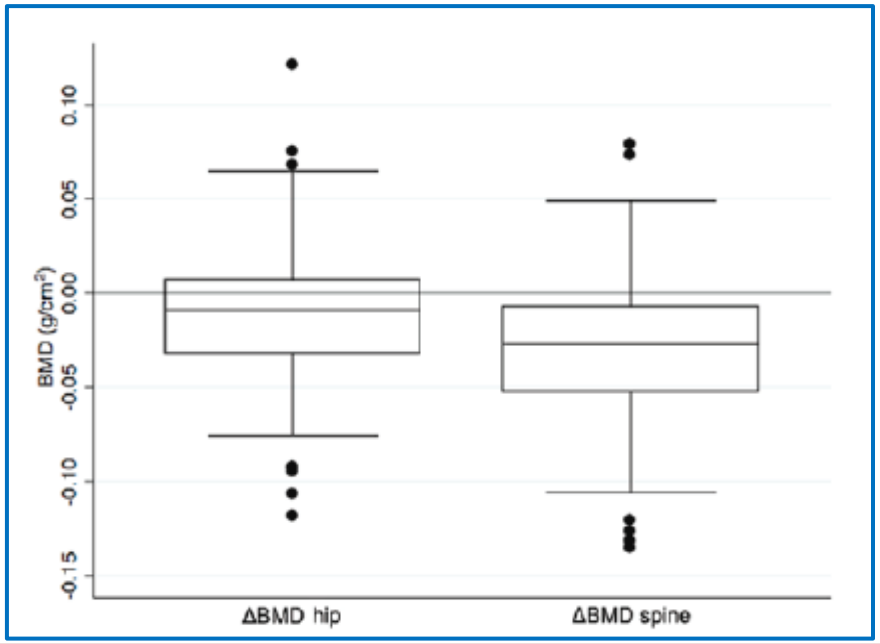
Breast cancer survivors had a significantly increased risk for all the fractures except for hip

MONITORING AND TREATMENT RECOMANDATIONS TO REDUCE FRACTURE RISK IN WOMEN WITH EARLY BREAST CANCER

MOLECULAR AND CLINICAL ONCOLOGY 8: 767-772, 2018

Bone loss during neoadjuvant/adjuvant chemotherapy for early stage breast cancer: A retrospective cohort study

CHRISTIAN TANG AXELSEN[1], ANDERS BONDE JENSEN[1,2], ERIK HUGGER JAKOBSEN[3] and TROELS BECHMANN[3,4]



Overall changes in BMD. Patients receiving neoadjuvant/adjuvant chemotherapy had a significant loss in mean BMD. The mean change in BMD was -0.0124 g/cm^2 (95% CI -0.018; -0.007 P<0.001) in the hip and -0.029 g/cm^2 (95% CI: -0.036; -0.023 P<0.001) in the lumbar spine corresponding to a reduction in BMD of 1.3 and 2.9% for the hip and lumbar spine.

Acute toxicity of anticancer therapies routinely monitored and treated

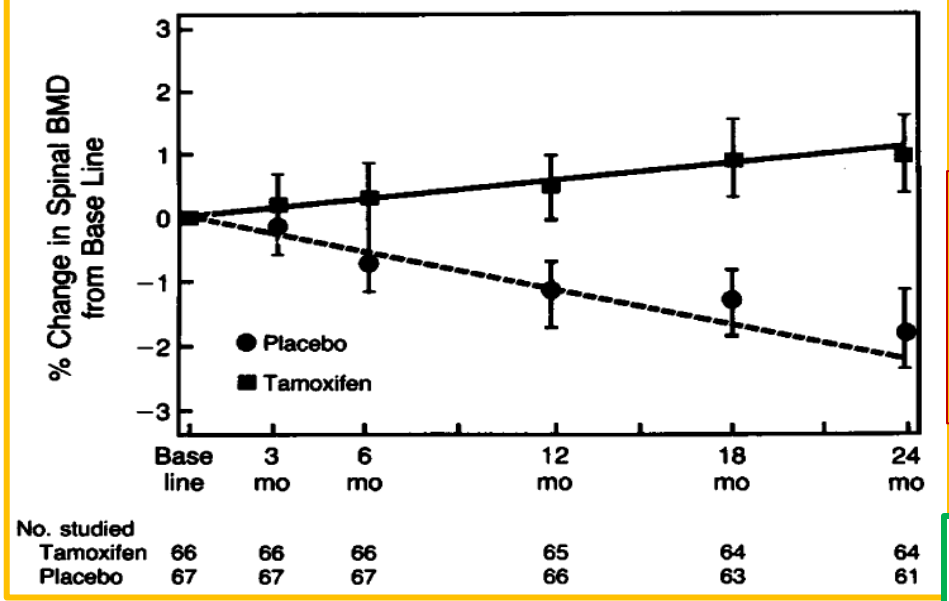
Late side effect → **Bone** due to chemo-regimens:

- ovarian failure
- loss of vitamin D and calcium for vomiting
- use of glucortisteroids as antiemetic
- immobility fatigue-related

Nina H et al. Acta Oncolo, 2008; 47: 747

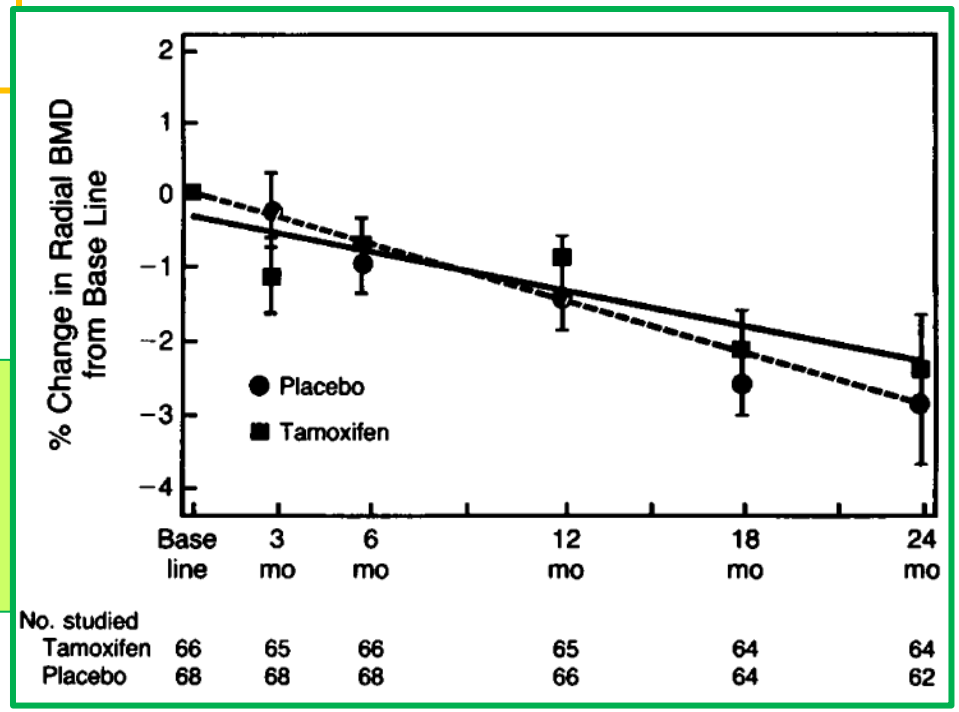
Effects on BMD in post-menopausal breast cancer patients treated for two years with either Tamoxifen 20 mg daily or placebo (randomized, double-blind trial)

N Engl J Med 1992;326:852-6



Change in mean (+/- SE) lumbar spine BMD in women with early breast cancer given Tamoxifen or Placebo for 2 years

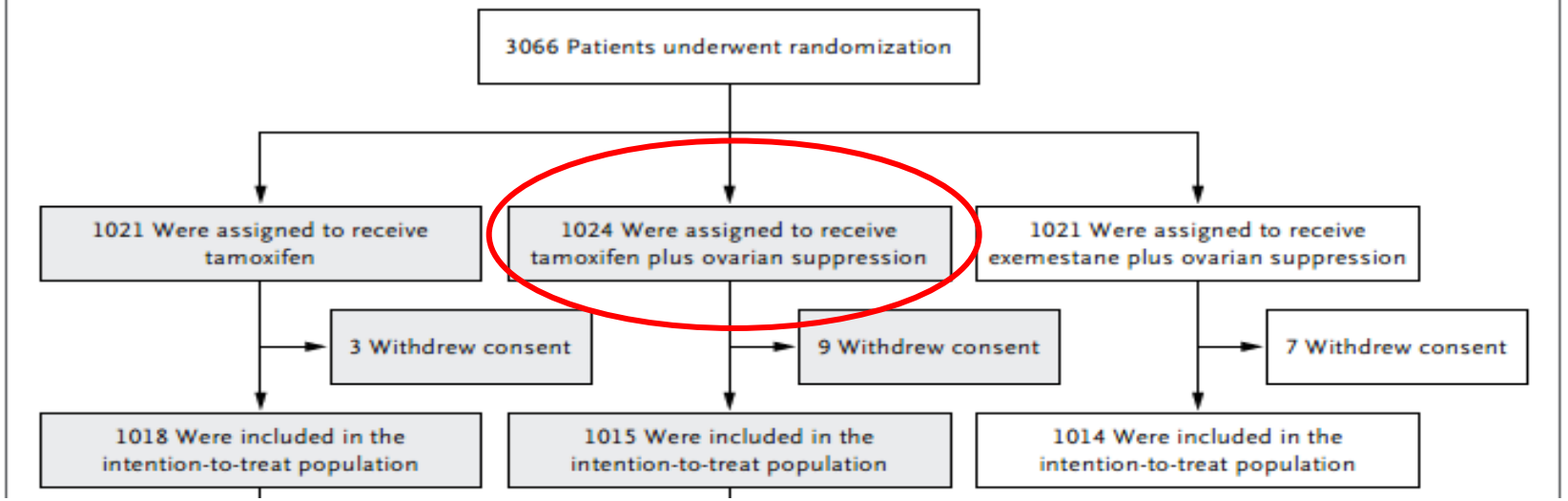
Change in mean (+/- SE) Radial BMD in women with early breast cancer given Tamoxifen or Placebo for 2 years



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Ovarian Suppression in Premenopausal Breast Cancer



BACKGROUND

Suppression of ovarian estrogen production reduces the recurrence of hormone-receptor–positive early breast cancer in premenopausal women, but its value when added to tamoxifen is uncertain.

Table 2. **Key Targeted Adverse Events Reported during Follow-up, According to Treatment Assignment.***

Adverse Event	Tamoxifen (N=1006)				Tamoxifen plus Ovarian Suppression (N=1005)			
	Any Event		Grade 3 or 4 Event		Any Event		Grade 3 or 4 Event	
	no. of patients with event	*% (95% CI)*	*no. of patients with event*	*% (95% CI)*	*no. of patients with event*	*% (95% CI)*	*no. of patients with event*	*% (95% CI)*
Hot flushes	803	79.8 (77.2–82.3)	76	7.6 (6.0–9.4)	939	93.4 (91.7–94.9)	133	13.2 (11.2–15.5)
Depression	469	46.6 (43.5–49.8)	38	3.8 (2.7–5.1)	522	51.9 (48.8–55.1)	44	4.4 (3.2–5.8)
Sweating	486	48.3 (45.2–51.4)	—	—	621	61.8 (58.7–64.8)	—	—
Insomnia	466	46.3 (43.2–49.5)	29	2.9 (1.9–4.1)	575	57.2 (54.1–60.3)	46	4.6 (3.4–6.1)
Hypertension	173	17.2 (14.9–19.7)	54	5.4 (4.1–6.9)	233	23.2 (20.6–25.9)	75	7.5 (5.9–9.3)
Musculoskeletal symptoms	694	69.0 (66.0–71.8)	63	6.3 (4.8–7.9)	755	75.1 (72.3–77.8)	55	5.5 (4.1–7.1)
Osteoporosis	124	12.3 (10.4–14.5)	1	0.1 (0.0–0.6)	201	20.0 (17.6–22.6)	3	0.3 (0.1–0.9)
Vaginal dryness	421	41.8 (38.8–45.0)	—	—	500	49.8 (46.6–52.9)	—	—
Decreased libido	427	42.4 (39.4–45.6)	—	—	477	47.5 (44.3–50.6)	—	—
Glucose intolerance†	18	1.8 (1.1–2.8)	3	0.3 (0.1–0.9)	35	3.5 (2.4–4.8)	14	1.4 (0.8–2.3)
Any targeted adverse event‡	959	95.3 (93.8–96.5)	238	23.7 (21.1–26.4)	989	98.4 (97.4–99.1)	315	31.3 (28.5–34.3)

* Data are for the 2011 patients in the safety population who received a protocol-assigned treatment (except for 3 patients who withdrew consent within 1 month after randomization and had no adverse-event data submitted). Targeted adverse events (22 events; see Table S6 in the Supplementary Appendix) and other adverse events of grade 3 or higher were categorized according to the *Common Terminology Criteria for Adverse Events*, version 3.0.[11] A dash indicates that grade 3 or 4 was not a possible grade for the specified adverse event. There was one targeted adverse event of grade 5 (cardiac ischemia or infarction in a patient randomly assigned to tamoxifen).

† Glucose intolerance (diabetes) was added as a targeted adverse event in 2011 and therefore may be underreported.

‡ The category of any targeted adverse event includes the 22 targeted adverse events summarized in Table S6 in the Supplementary Appendix.

EUROPEAN JOURNAL OF CANCER 43 (2007) 2523–2531

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Effects of third generation aromatase inhibitors on bone health and other safety parameters: Results of an open, randomised, multi-centre study of letrozole, exemestane and anastrozole in healthy postmenopausal women

Eugene V. McCloskey[a,], Rosemary A. Hannon[a], Geza Lakner[b], William D. Fraser[c], Glen Clack[d], Anna Miyamoto[e], Richard D. Finkelman[e], Richard Eastell[a]*

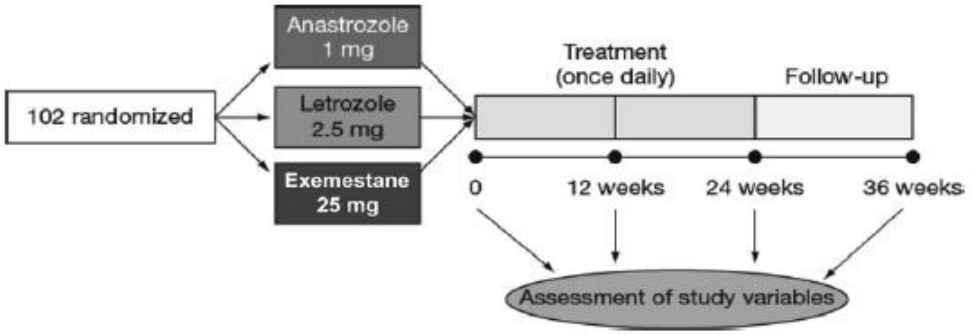


Fig. 1 – Overview of the design of the LEAP study.

Biochemical bone markers analyzed:

Bone ALP

Serum-collagen type I amino-terminal propeptide (PINP)

Resorption marker serum beta C-terminal crosslinkingtelopeptide of type I colagen (beta-CTX)

Serum intact parathyroid hormone (PTH)

Index calcium flux to and from bone

DXA

Eur J Cancer, 2007; 43:2523

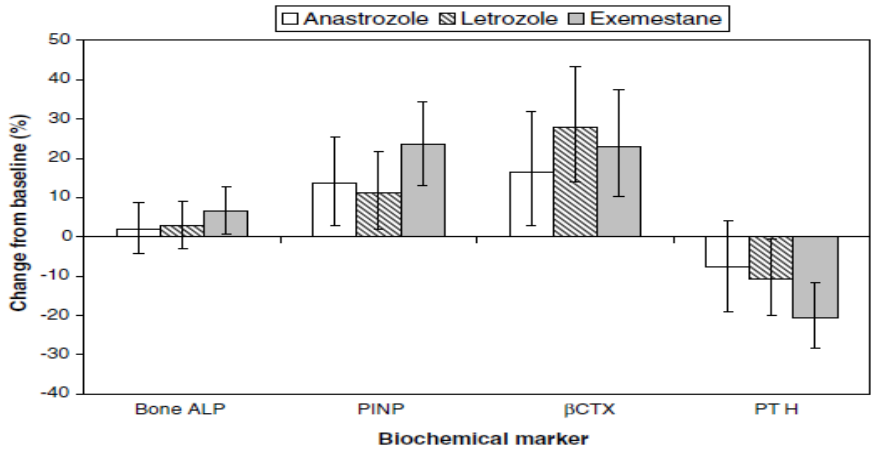
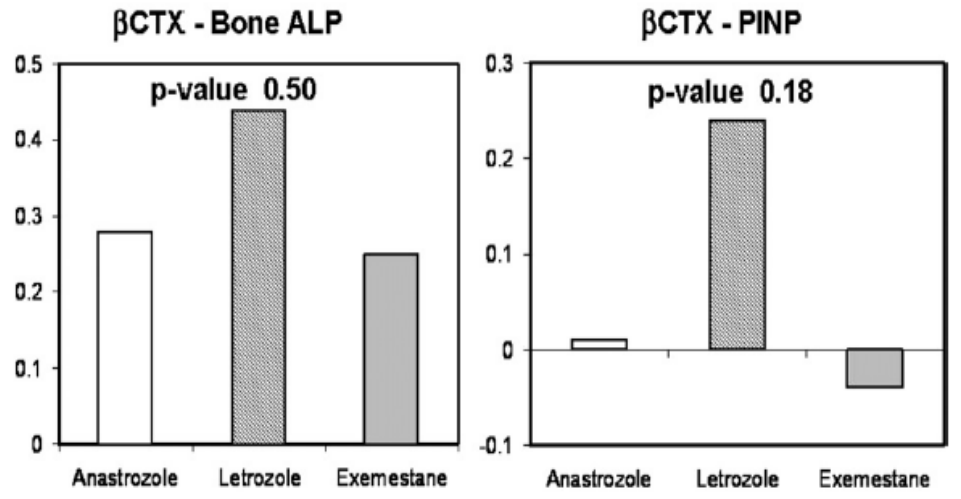
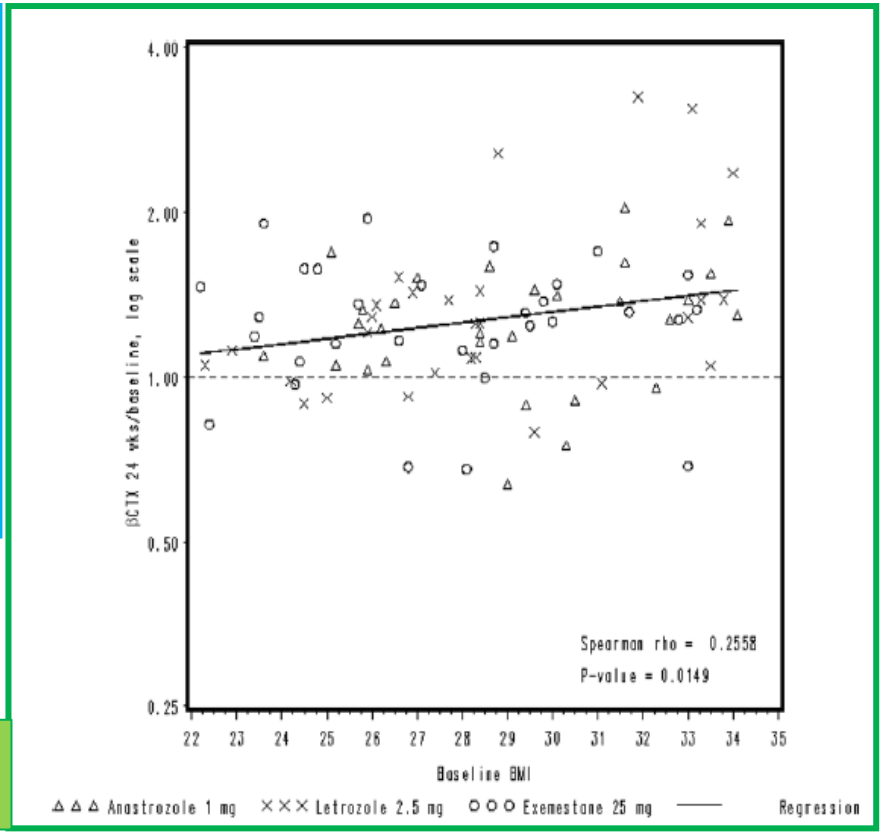


Fig. 2 – Changes in biochemical markers of bone turnover and PTH between baseline and 24 weeks (end of treatment) in the primary analysis population. No overall statistical differences were observed between the three groups (see Table 3).



Preponderance of resorption over formation
Non statistical differences observed between three groups



Both BMI and circulating oestradiol correlated with beta-CTX and PINP

Annals of Oncology 23: 1474–1481, 2012
doi:10.1093/annonc/mdr448
Published online 13 October 2011

Bone mineral density in breast cancer patients treated with adjuvant letrozole, tamoxifen, or sequences of letrozole and tamoxifen in the BIG 1-98 study (SAKK 21/07)

K. Zaman[1]*, B. Thürlimann[2], J. Huober[2], A. Schönenberger[3], O. Pagani[4], J. Lüthi[5], M. Simcock[6], A. Giobbie-Hurder[7], G. Berthod[1], C. Genton[6], P. Brauchli[6] & S. Aebi[8] on behalf of the Swiss Group for Clinical Cancer Research (SAKK)

Background: The risk of osteoporosis and fracture influences the selection of adjuvant endocrine therapy. We analyzed bone mineral density (BMD) in Swiss patients of the Breast International Group (BIG) 1-98 trial [treatment arms: A, tamoxifen (T) for 5 years; B, letrozole (L) for 5 years; C, 2 years of T followed by 3 years of L; D, 2 years of L followed by 3 years of T].

Type of measurement	Number of patients per treatment arm				Total number of patients
	A	B	C	D	
Lumbar BMD	66	63	55	62	246
Lumbar *T* score	66	63	59	63	251
Total hip BMD	65	59	56	56	236
Total hip *T* score	61	55	51	53	220

BMD, bone mineral density.

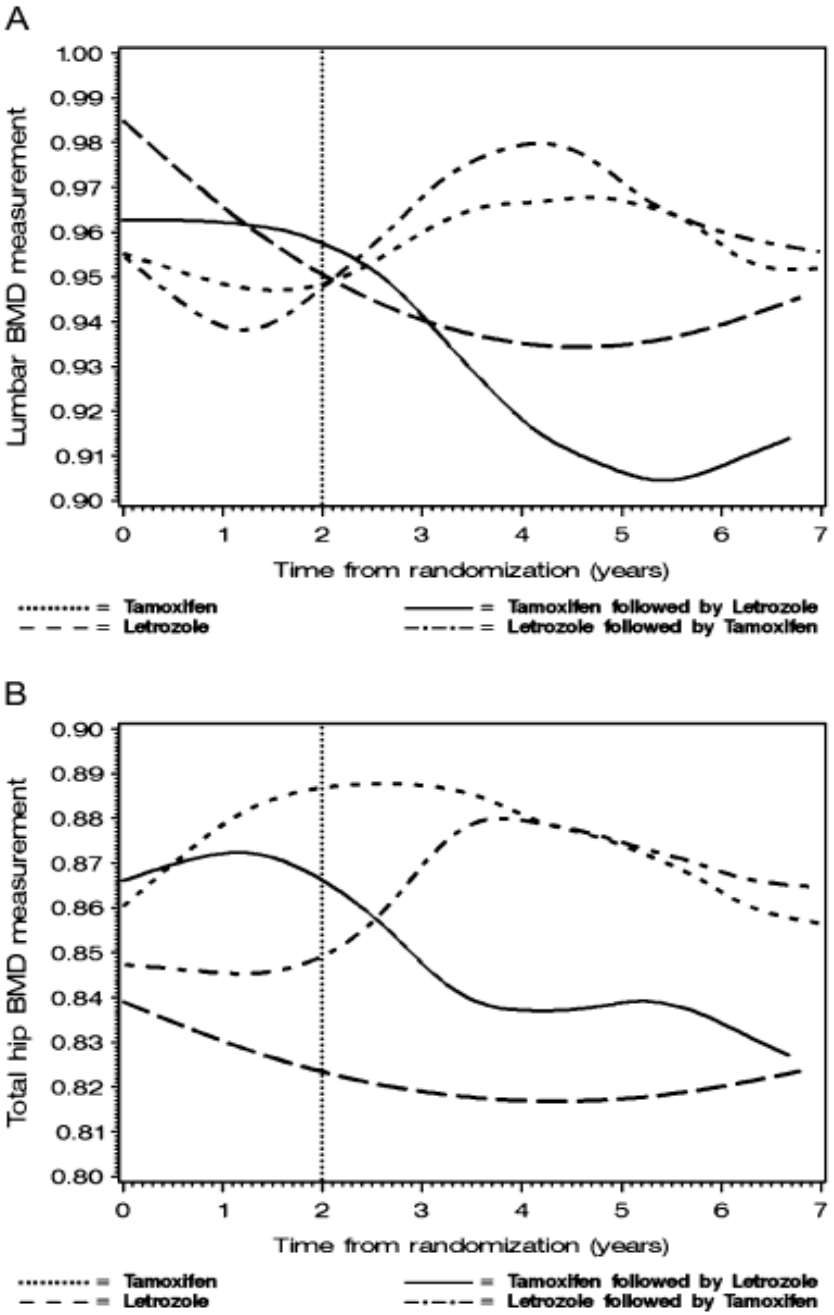


Figure 2. Bone mineral density evolution over time: (A) lumbar; (B) total hip.

The three letrozole-containing arms: higher BMD loss than tamoxifen-only arm

Sequential administration tamoxifen followed by letrozole: no long-term protective effect on BMD despite shother exposure to AI (due to rapid fall in estrogen levels →accelerated loss of BMD)

Letrozolo up-front induce a loss in BMD but switching to tamoxifen after 2 years increased BMD

Annals of Oncology 23: 1474–1481, 2012

original article

Annals of Oncology 22: 857–862, 2011
doi:10.1093/annonc/mdq541
Published online 7 October 2010

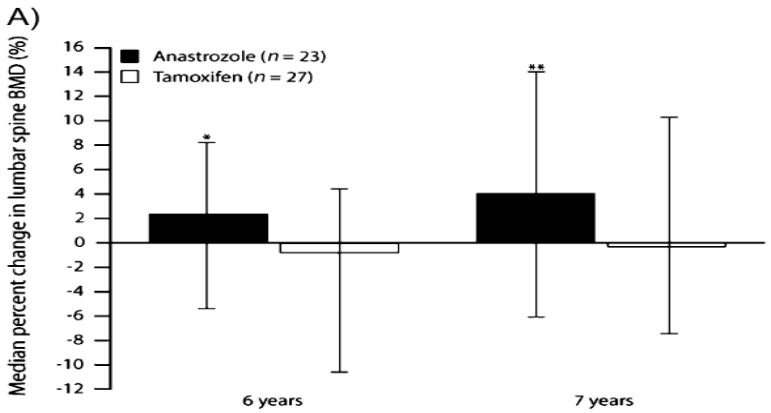
Long-term effects of anastrozole on bone mineral density: 7-year results from the ATAC trial

R. Eastell[1], J. Adams[2], G. Clack[3], A. Howell[4], J. Cuzick[5], J. Mackey[6], M. W. Beckmann[7] & R. E. Coleman[8*]

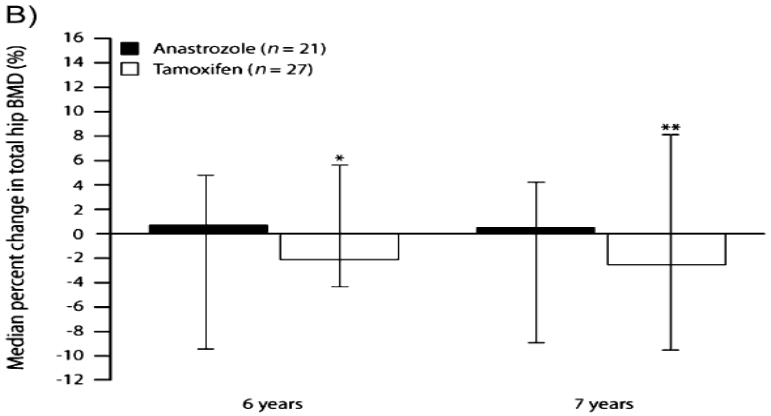
Background: This 'Arimidex', Tamoxifen, Alone or in Combination (ATAC) trial sub-study examined the effects of anastrozole and tamoxifen on bone mineral density (BMD) following 5 years of treatment.

Patients and methods: Lumbar spine and total hip BMD were assessed at years 6 and 7 in a total of 71 eligible patients. In total, 50 patients had evaluable data.

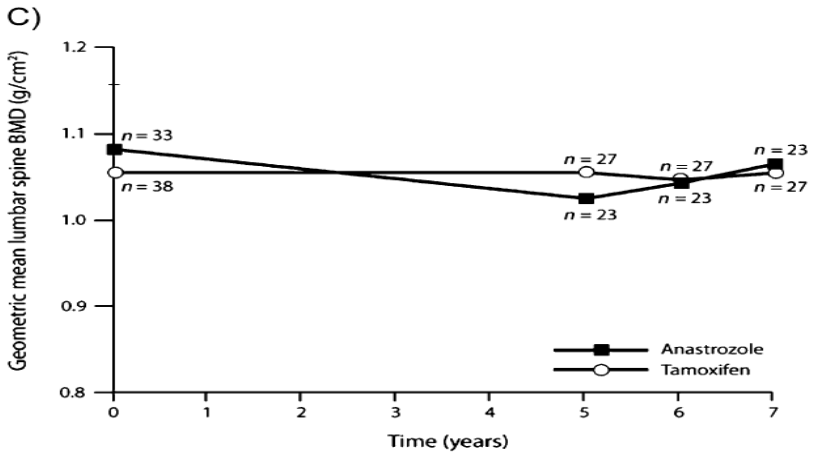
changes in BMD following completion of treatment

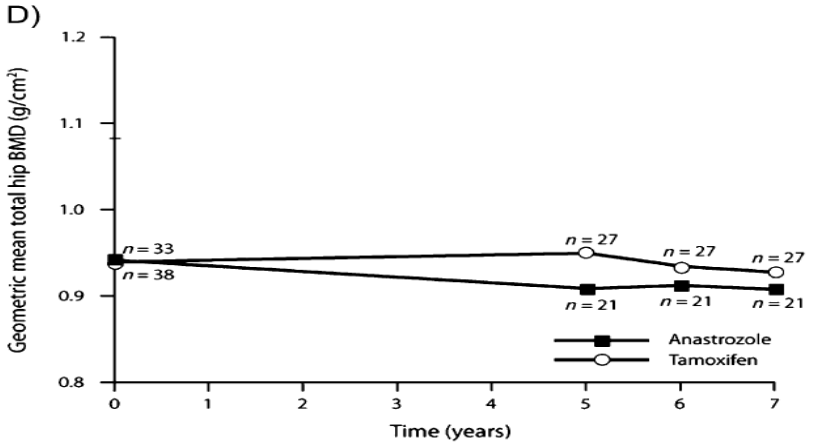


*year 6 vs year 5, $P = 0.0385$; **year 7 vs year 5, $P = 0.0004$



*Year 6 vs Year 5, $P = 0.0003$; **Year 7 vs Year 5, $P = 0.0002$
Analysis was for patients on whom there was data at each timepoint





Time 0 years plots the baseline BMD data for those patients who subsequently entered the extension protocol. Data at Years 5, 6 and 7 are based on the patients within this group with available data for each time point at years 5, 6 and 7.

Conclusions: Anastrozole treatment-related bone loss did not continue into the off-treatment follow-up period. The recovery in lumbar spine BMD and absence of further loss at the hip is consistent with the reduction in the annual rate of fracture observed after treatment cessation in the main ATAC trial.

Annals of Oncology 22: 857–862, 2011

Trial	n. of patients	Follow up (months)	Treatment	% Fractures	P value
AI vs TAM					
ATAC (1)	9366	100	ANA vs TAM	11 vs 7.7	<0.001
BIG 1-98 (2)	4922	60	LET vs TAM	9.3 vs 6.5	0.002
AI after 2-3 years of TAM					
TEAM (3)	9779	61	EXE vs TAM	5.0 vs 3.0	0.0001
ABCSGB/ARNO (4)	3224	28	ANA vs TAM	2.0 vs 1.0	0.015
AI after 5 years of TAM					
MA-17 (5)	5187	63	LET vs Placebo	5.2 vs 3.1	0.02

(1) HowellA et al. Lancet, 2005; 365(9453):60. (2) Rabaglio M et al. Annn Oncolol, 2009; 20(9): 1489. (3) Van de Velde CJ et al. Lancet, 2011; 377(9762): 321. (4) Jakesz Ret al. Lancet, 2005; 366(9484): 455. (5) Goss PE et al. J Natl Cancer Inst, 2005; 97(17): 1262

	Exemestane plus ovarian suppression (N=2318)				Tamoxifen plus ovarian suppression (N=2325)			
Adverse event	**n. patients**	**% (95%CI)**	**Grade 3-4**	**% (95%CI)**	**n. patients**	**% (95%CI)**	**Grade 3-4**	**% (95%CI)**
osteporosis	894	38.6 (36.6-40.6)	10	0.4 (0.2-0.8)	586	25.2 (23.5-27.0)	6	0.3 (0.1-0.6)
fractures	158	6.8 (5.8-7.9)	29	1.3 (0.8-1.8)	120	5.2 (4.3-6.1)	18	0.8 (0.5-1.2)

Pagani O et al. N Engl J med, 2014; 371(2)

LIFESTYLE CHOICES AND PREVENTION

EXERCISE

Aerobic excercise for 15-60 minutes 3 times a week with straining training (low-medium impact) Coonenberg JJ et al. Osteoporos Int 1999; 9:1

ALCOHOL

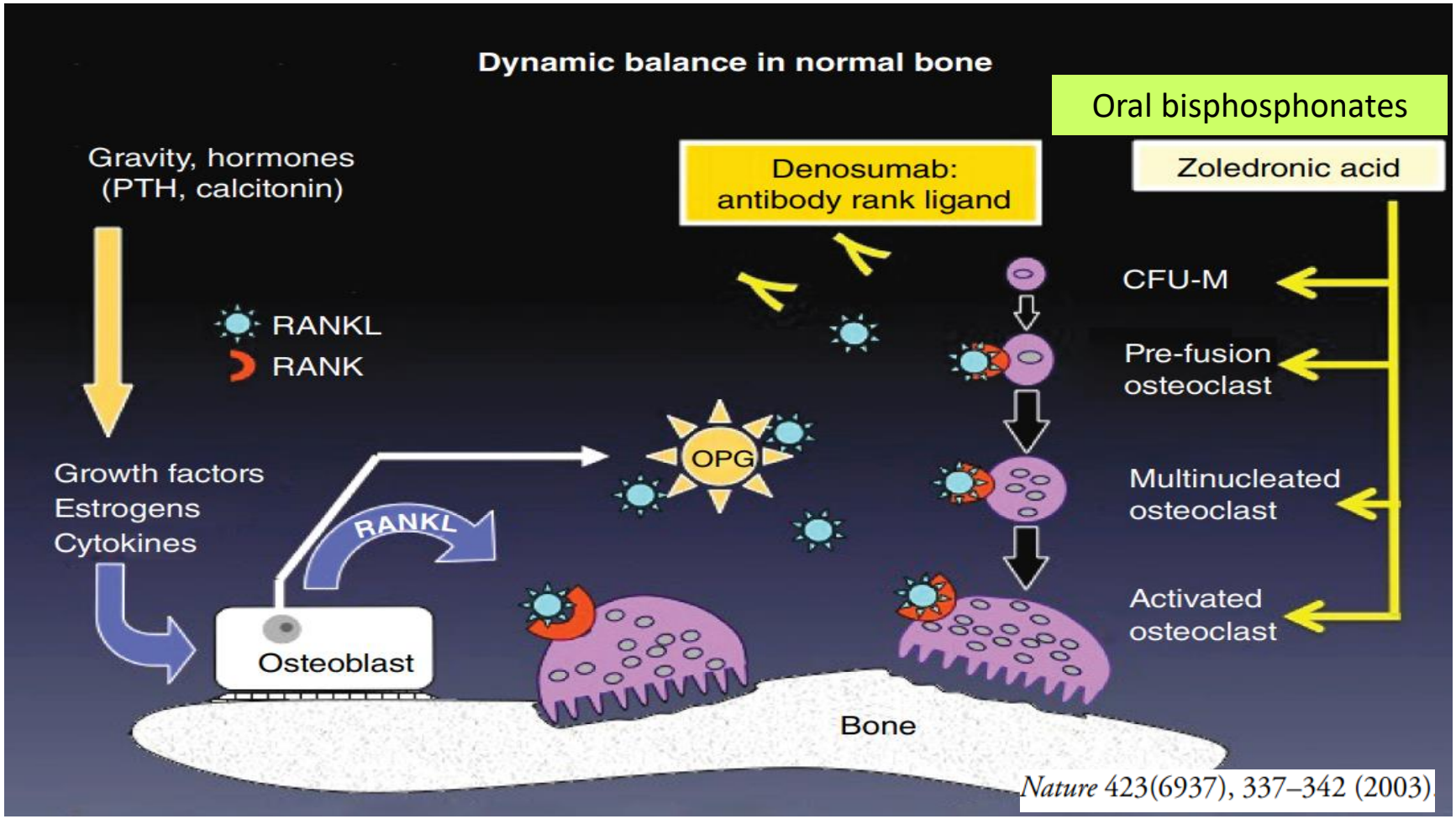
Direct toxic effects on osteoblasts. Light consumption may have a beneficial effect on BMD, heavy intake and binge drinking is associated with drecreased BMD in men. Maurel DB et al. Osteoporos Int 2012; 23:1.

SMOKING

It is known to have adverse effects on bone with increased risk of fractures.
Kenis JA et al. Osteporos Int 2005; 16:155.

FOOD

It is the best source of calcium supplements and vitamin D.
If insufficient, supplements may be used.
Milk and derivates, vegetables (cabbages, spinach), fruits, fish, eggs, almonds.



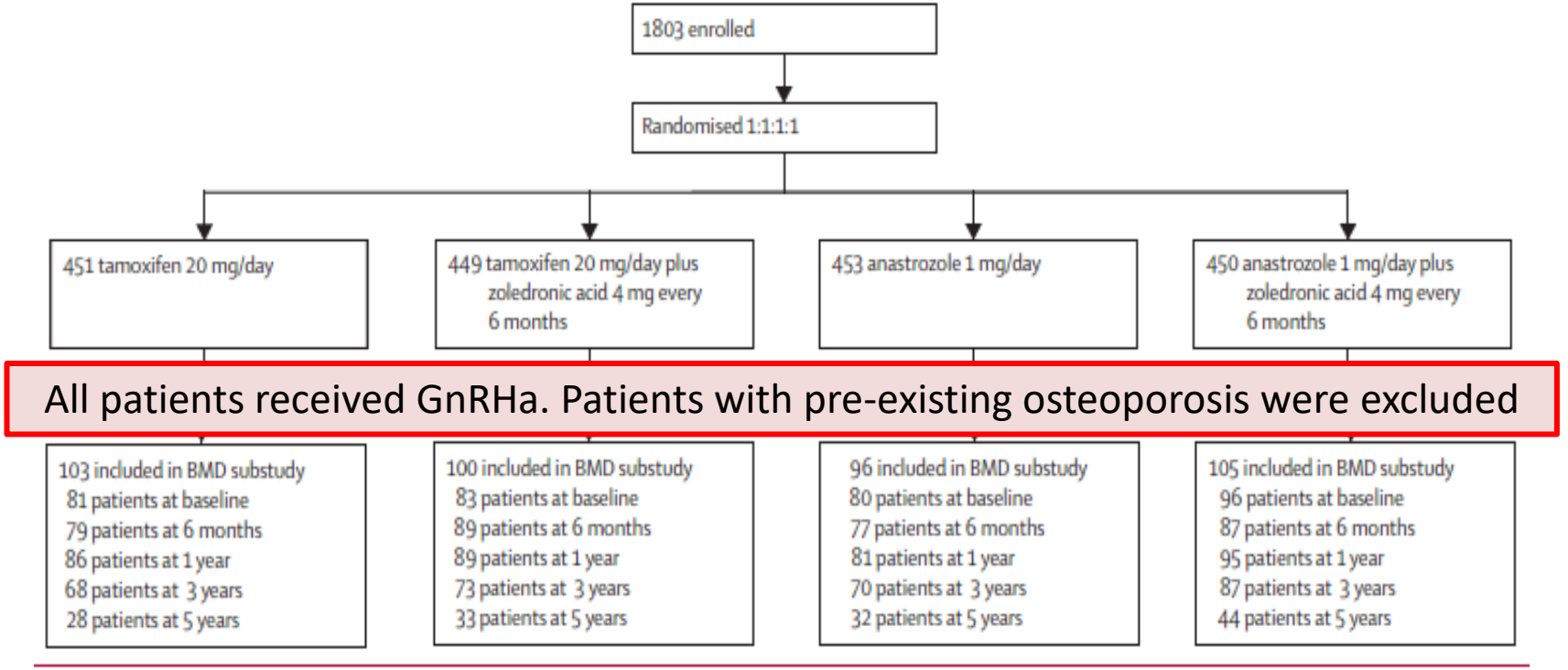
RANKL binds RANKL receptors on osteoclast precursor Differentiation in mature osteoclasts
Immunesystem with T cells secrete TNF-alpha that activate osteclasts

Bone resorption

Osteoblast secrets osteoprotegerin
Reduces osteoclast activity

Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 5-year follow-up of the ABCSG-12 bone-mineral density substudy

*Michael Gnant, Brigitte Mlineritsch, Gero Luschin-Ebengreuth, Franz Kainberger, Helmut Kässmann, Jutta Claudia Piswanger-Sölkner, Michael Seifert, Ferdinand Ploner, Christian Menzel, Peter Dubsky, Florian Fitzal, Vesna Bjelic-Radisic, Günther Steger, Richard Greil, Christian Marth, Ernst Kubista, Hellmut Samonigg, Peter Wohlmuth, Martina Mittlböck, Raimund Jakesz, on behalf of the Austrian Breast and Colorectal Cancer Study Group (ABCSG), Vienna, Austria**



Lancet Oncol 2008; 9: 840–49

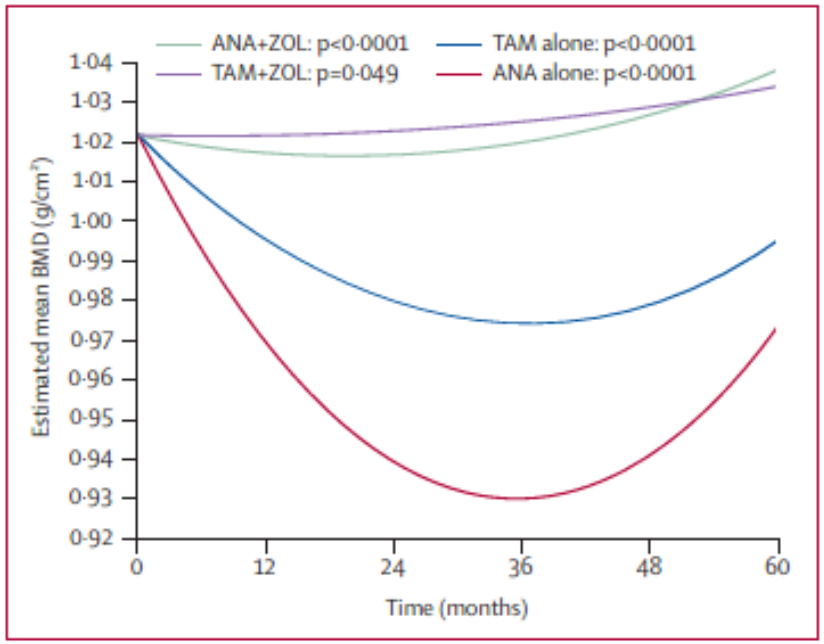


Figure 2: **Changes from baseline to 60 months in bone-mineral density (BMD) of lumbar spine**

Patients were randomly assigned to anastrozole (ANA) or tamoxifen (TAM) with or without zoledronic acid (ZOL; 4 mg every 6 months) for 36 months and then no treatment from 36 to 60 months. Estimated least-square means from the model with quadratic time effects. p values correspond to BMD change from baseline to 60 months (estimated within the model).

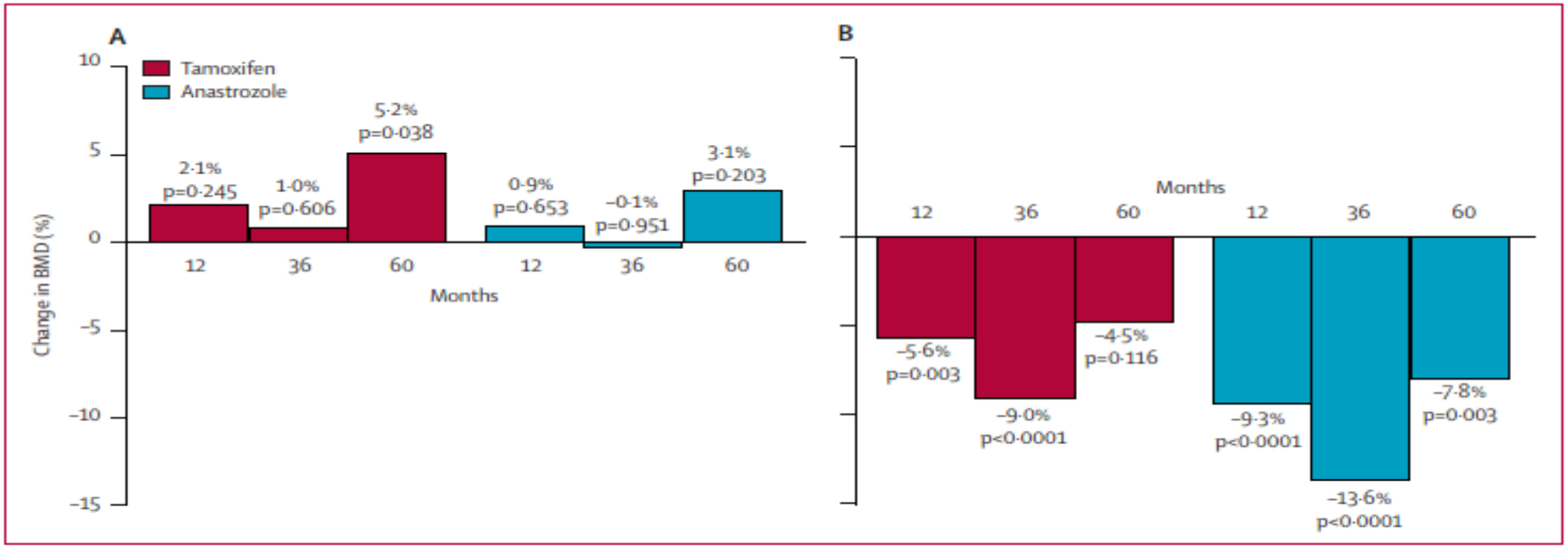


Figure 3: **Percentage change in lumbar spine bone-mineral density (BMD) from baseline to 12, 36, and 60 months**

Patients were randomly assigned to anastrozole or tamoxifen with (A) or without (B) zoledronic acid (4 mg every 6 months) for 36 months and then no treatment from 36 to 60 months. p values were calculated using two-sample *t* tests for mean differences from baseline.

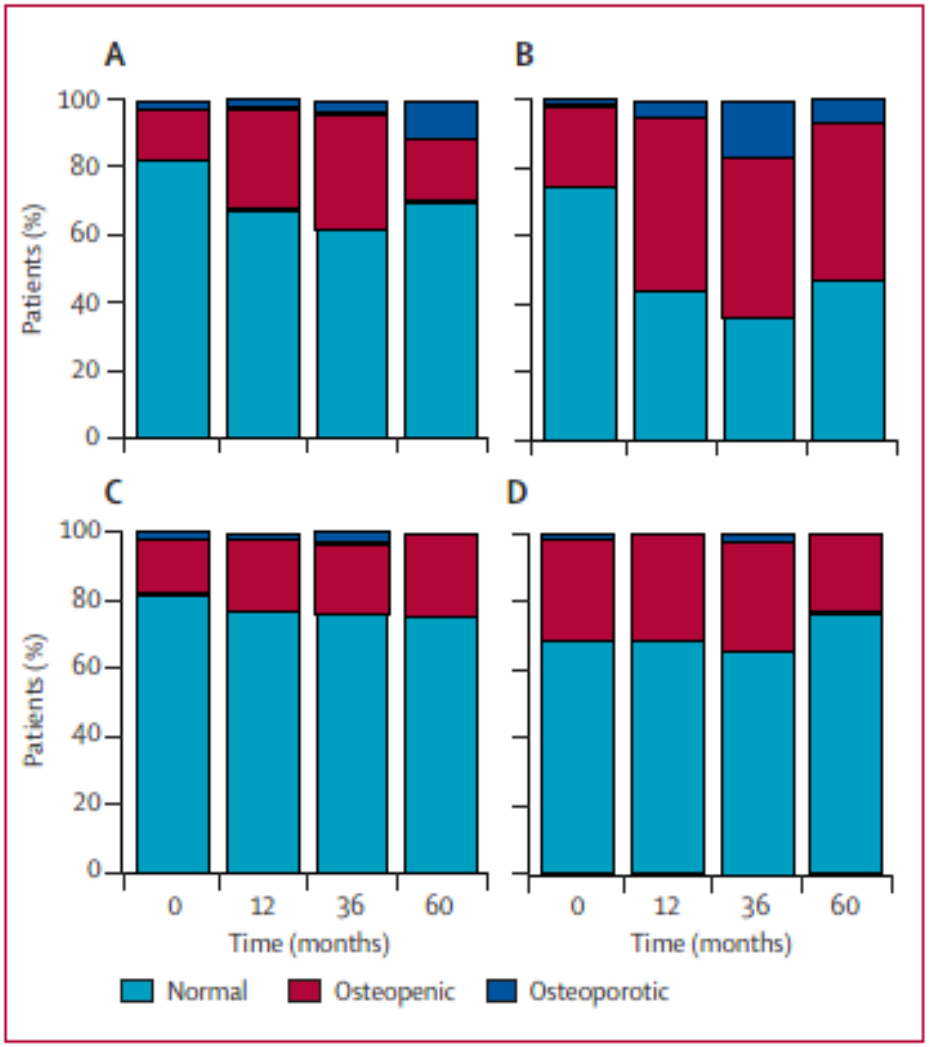


Figure 4: Percentages of patients with normal, osteopenic, or osteoporotic bone-mineral density T scores at the lumbar spine

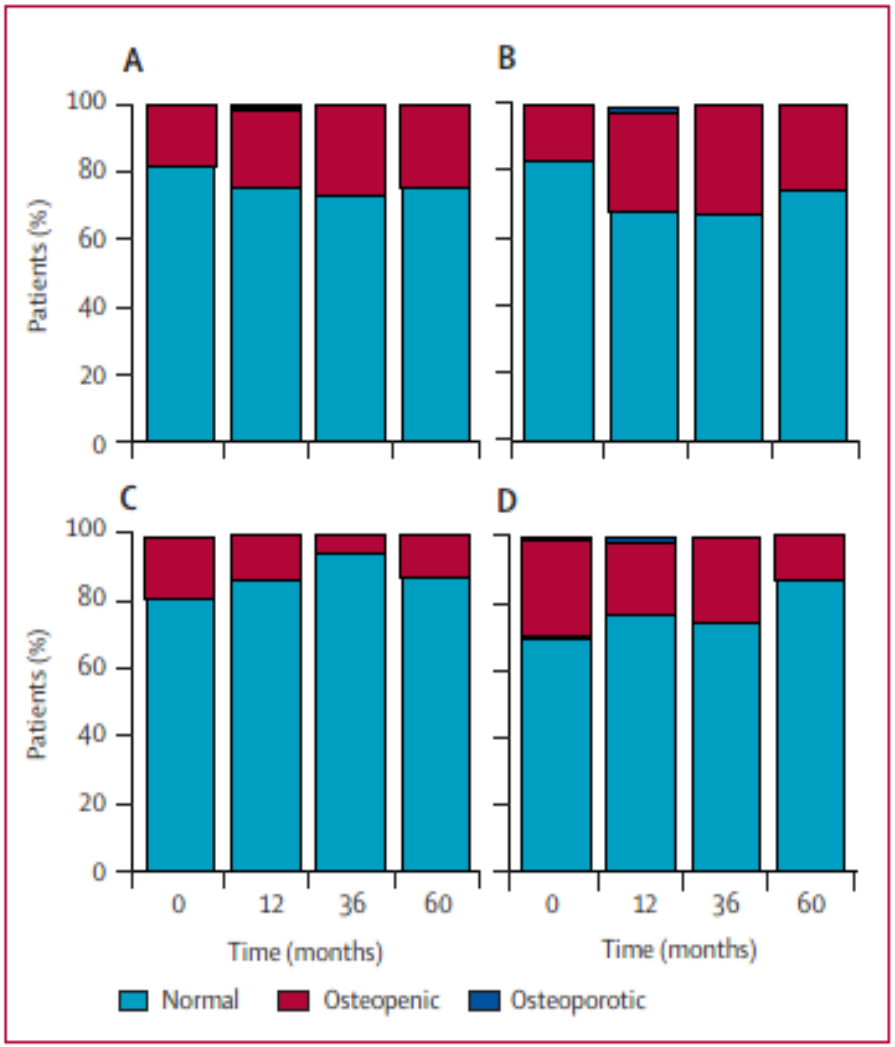


Figure 5: Percentages of patients with normal, osteopenic, or osteoporotic bone-mineral density T-scores at the trochanter

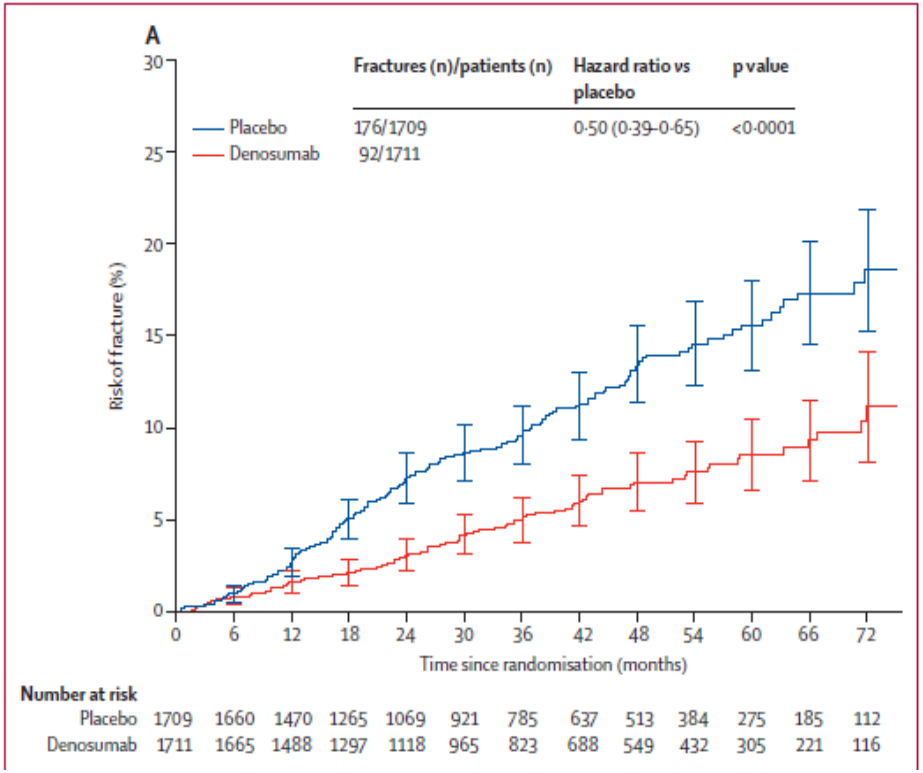
A. TAM alone
B. ANA alone
C. TAM+zolendronic acid
D. ANA+Zolendronic acid

Lancet Oncol 2008; 9: 840–49

Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial

Lancet 2015; 386: 433–43

Prospective, double-blind, placebo-controlled, phase 3
From december 2006 to July 2012
3425 postmenopausal EBC HR+, receiving aromatase inhibitors
Random 1:1: denosumab 60 mg or placebo every 6 months



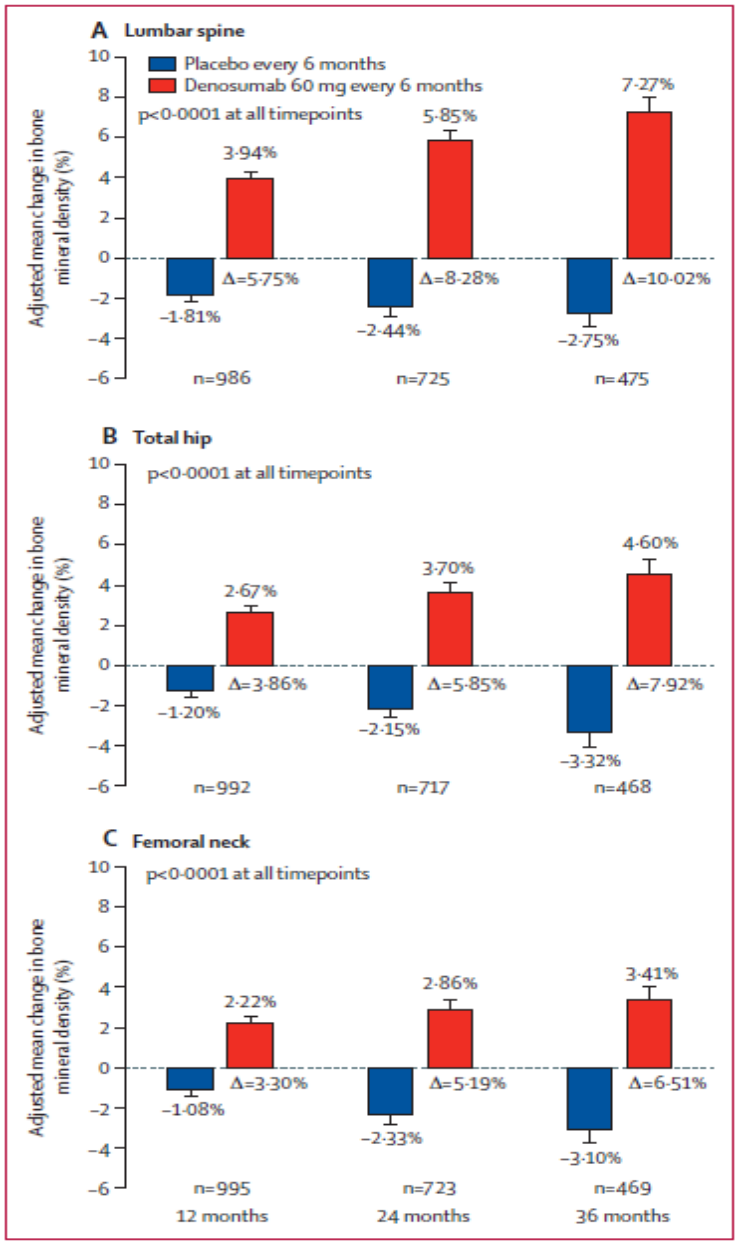


Figure 3: Bone mineral density changes

Trial	Treatments	n. of patients	Results	P-value
Chemo-induced ovarian failure				
Hershman Dl et al J Clin Oncol, 2008; 26(29): 4739	ZA 4 mg q 3 months vs placebo for 1 year	101	L/S BMD 0% ZA vs -3.0% placebo	<0.001
Shapiro Cl et al Eur J Cancer, 2011; 47(5): 683	ZA 4 mg q 3 months vs control for 1 year	441	L/S BMD 1.2% ZA vs -6.7% control	<0.001
GnRH-agonist				
Gnant M et al Lancet Oncol, 2008; 9(9):840	ZA 4 mg q 6 months vs control for 3 years	404	L/S BMD 4.0% ZA vs baseline L/S BMD -6.7% vs baseline	0.02 0.001
AI				
Coleman R et al Ann Oncol, 2013; 24(2):398	ZA 4 mg q 6 months for 5 years vs delayed ZA	1065	L/S BMD 5.7% vs delayed	<0.001
Gnant M et al Lancet 2015; 386(9992): 433	Denosumab q 6months vs placebo for 5 years	3425	Fractures in denosumab group 92 vs 176 in placebo	<0.0001

Bone 49 (2011) 82–88

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Review

Bisphosphonates for postmenopausal osteoporosis☆

Richard Eastell [a,*], Jennifer S. Walsh [a], Nelson B. Watts [b], Ethel Siris [c]

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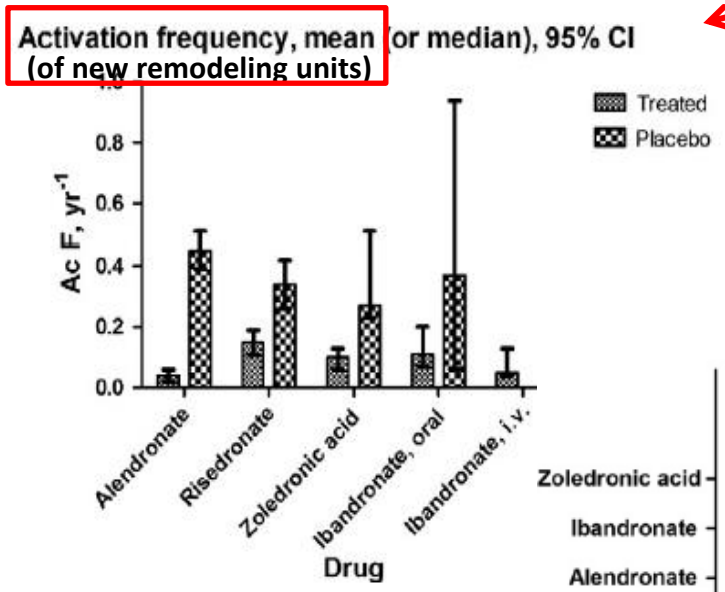
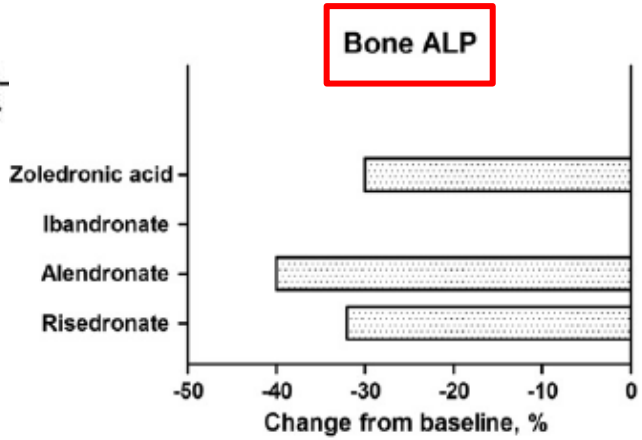
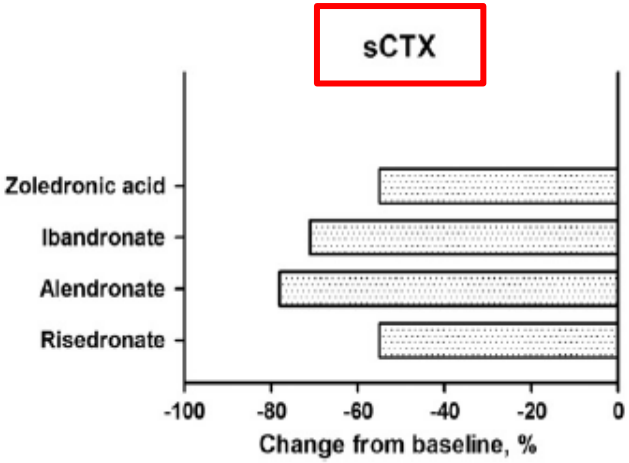
[b] University of Cincinnati Bone Health and Osteoporosis Center, Cincinnati, OH, USA
[c] Toni Stabile Osteoporosis Center, Department of Medicine, Columbia University Medical Center, New York, NY, USA

Effects on







(Oral therapy: alendronate e risendronate)

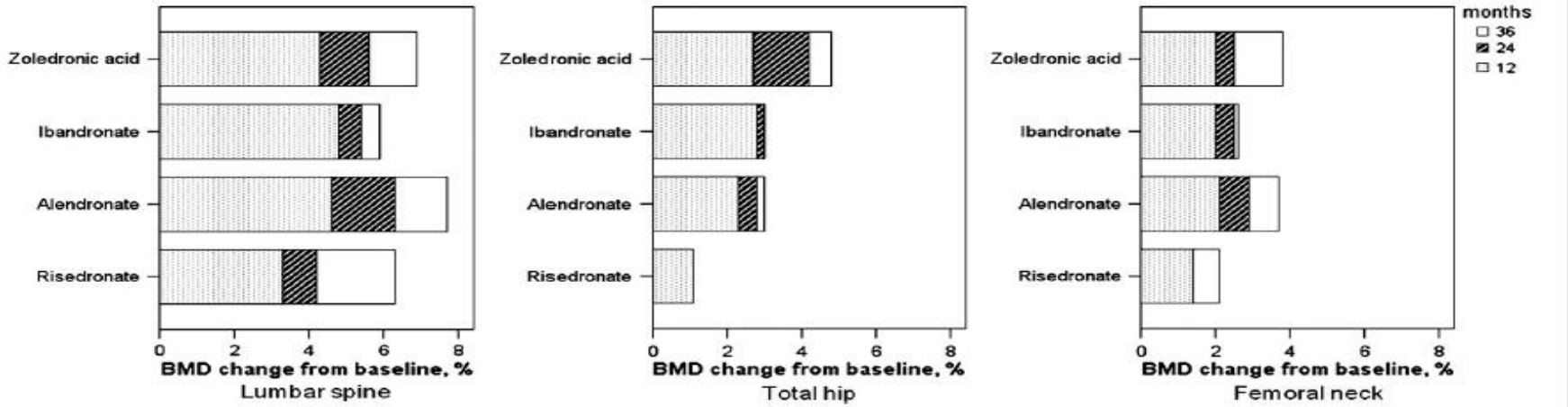
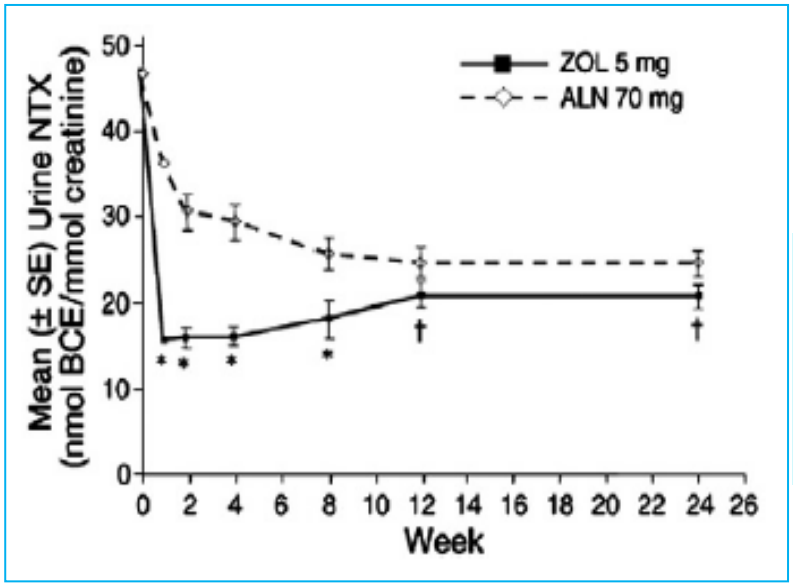


Fig. 4. Percent difference in BMD response to treatment at licensed dose compared to baseline. The BMD sites studied are lumbar spine, total hip, and femoral neck. Figures based on publications on zoledronic acid [69], ibandronate [11,63–65], alendronate [11,12,66–68], and risedronate [12,57]. Note that most of these data did not arise from head-to-head studies and so patient characteristics (such as baseline bone turnover) differed between studies.

Greater BMD response at the spine than at the hip for all agents due to differences in bone turnover marker response



Early decrease (2-4 weeks) in bone resorption markers: zolendronic acid has more rapid effects than alendronate

The New England
Journal of Medicine

Volume 333 NOVEMBER 30, 1995 Number 22

EFFECT OF ORAL ALENDRONATE ON BONE MINERAL DENSITY AND THE INCIDENCE OF FRACTURES IN POSTMENOPAUSAL OSTEOPOROSIS

994 postmenopusal women with osteoporosis and all with supplement of calcium
Placebo or alendronate (5 or 10mg/daily for 36 months -20 mg for 24 months and 5 mg for 12 months)

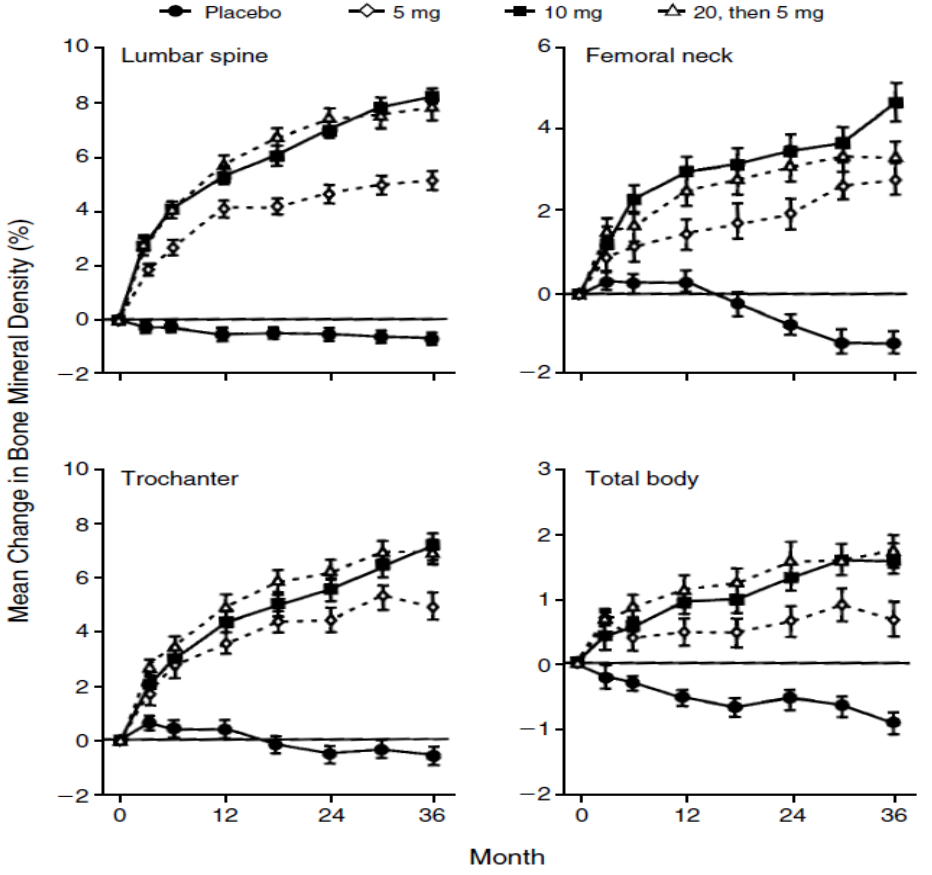


Figure 1. Mean (±SE) Changes in Bone Mineral Density from Base-Line Values in Women with Postmenopausal Osteoporosis Receiving Alendronate or Placebo for Three Years.

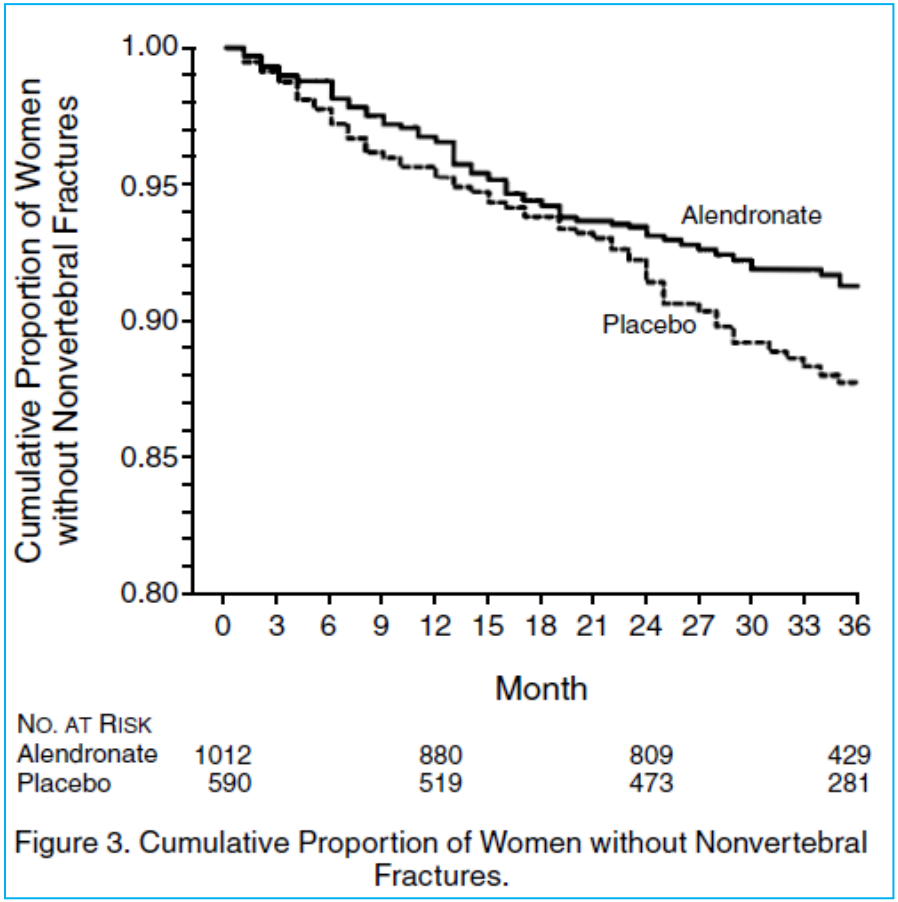


Figure 3. Cumulative Proportion of Women without Nonvertebral Fractures.

TABLE 3. FDA-Approved Pharmacologic Therapies for the Prevention and/or Treatment of Osteoporosis*

Drug Class	Drug Name	Indications for Women	Indications for Men	Concerns/Warnings
Bisphosphonates	Alendronate	Treat or prevent postmenopausal osteoporosis	Increase bone mass in osteoporosis	Uncommon risks include hypocalcemia, osteonecrosis of the jaw, and atypical fractures. Intravenous formulations may cause acute phase reactions and renal dysfunction
	Ibandronate	Treat or prevent postmenopausal osteoporosis		
	Risedronate	Treat or prevent postmenopausal osteoporosis	Increase bone mass in osteoporosis	
	Zoledronic acid (5 mg)	Treat or prevent postmenopausal osteoporosis	Increase bone mass in osteoporosis	
Monoclonal Antibody	Denosumab (60 mg)	Treatment of postmenopausal osteoporosis with high risk for fracture. Treatment to increase bone mass in women at high risk for fracture who are receiving adjuvant AI for breast cancer	Treatment to increase bone mass in osteoporosis at high risk for fracture. Treatment to increase bone mass in men at high risk for fracture receiving ADT for non-metastatic prostate cancer	Uncommon risks include hypocalcemia, osteonecrosis of the jaw, and atypical fractures

2015 ASCO EDUCATIONAL BOOK e567

Other controndications to the use of oral bisphosphonate:

Severe gastrointestinal effects:
-Dyspepsia, nausea, vomiting, abdominal pain
-Severe esophageal irritation in 1.3-1.5% of patients
(gastoesophageal reflux is a relative controindication)

Inability of patients to drink at least 8 oz of water and maintains an upright posture for at least 30 minutes

Hypocalcemia and hypersensitivity to bisphosphonates use

Mayo Clin Proc. 2000;75:821-829

Factor	ZA (iv.)	Denosumab (sc.)
Dose	4 mg	60 mg
Mechanism	Osteoclast inhibitor	RANKL monoclonal antibody
Metabolism	Not metabolized	Not metabolized
Half-life	188 days (The majority goes to bone)	28 days
Clearance	Renal (44% of the dose excreted in urine within 24 h after administration)	The reticuloendothelial system most likely clears denosumab with minimal renal filtration and excretion
Common side effects	Fever and chills; muscle, bone or joint pain; nausea; fatigue and headache	Joint, muscle pains and hypocalcemia
Rare side effects	Renal insufficiency and osteonecrosis	Osteonecrosis
Cost ($)[†] (61)	252.00	1906.00

Breast Cancer Manag. (2020) 9(2), BMT40

HOW LONG TO TREAT – WHAT HAPPENS WHEN BISPHOSPHONATE THERAPY IS STOPPED?

Women at high risk of vertebral fractures or those with very low BMD: best continue after 5 years

Women without high risk of vertebral fractures or very low BMD: “drug holiday” after 5 years.

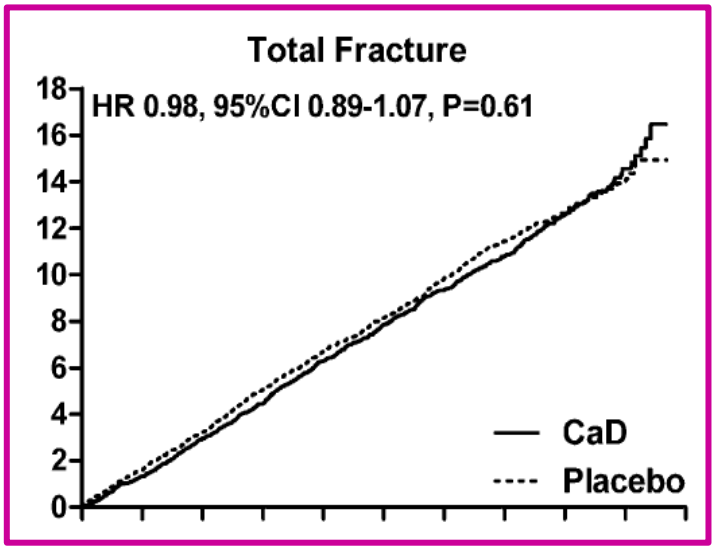
Residual effect of some biphosphonates such as alendronate and zolendronic acid after stopping for up to 5 years: BMD results were supported by a continued reduction in bone turnover marker due to a greater affinity for hydroxyapatite than risendronate and ibandronate

(Data from FLEX study . BlacK DM et al. JAMA, 2006; 296)

Calcium and vitamin D supplements and health outcomes: a reanalysis of the Women's Health Initiative (WHI) limited-access data set[1–4]

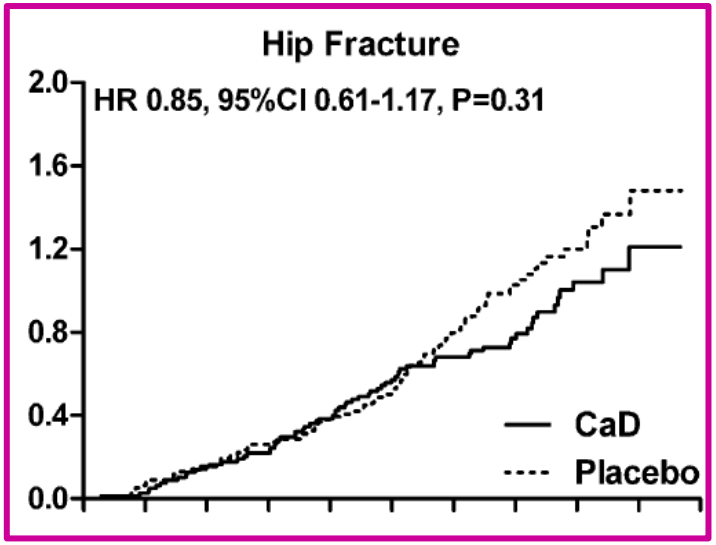
Mark J Bolland, Andrew Grey, Greg D Gamble, and Ian R Reid

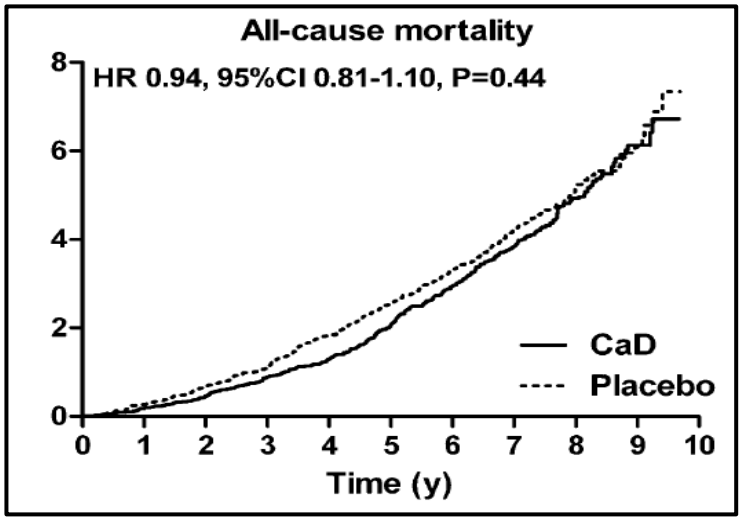
Am J Clin Nutr 2011;94:1144–9.



Background: Frequent use of personal, nonprotocol calcium supplements obscured an adverse effect of coadministered calcium and vitamin D (CaD) on cardiovascular risk in the Women's Health Initiative (WHI).

7-year randomized, placebo-controlled trial of supplement of calcium and vitamin D in 36282 postmenopausal women





Calcium supplements

It showed a reduction of bone turnover by 20%
and a fracture reduction by 10%.
Side effects include GI discomfort, renal calculi, increased occurence of vascular disease by 13-22% (debate on going)

Reid IR et al. Am J Med 2006; 119:777. Tang BMP et al. Lancet 2007; 370:657 Bolland MJ et al. BMJ 2008; 336:262

Vitamin D

The optimal level of vitamin D remains a matter of further research, and the data on its ability to reduces fractures is limited.

Ross AC et al. J Clin Endocrinol Metab 2011; 96:53.

NCCN Guidelines Version 3.2020 (BINV-16)

«Women on an aromarase inhibitor or who experience ovarian failure secondary to treatment shoul have monitoring of bone health with a bone mieral density determination at baseline and periodically thereafter. The use of a bisphosphonate (oral/IV) ore denosumab is acceptable to maintain or to improve bone mineral density and reduce rik of fractures in postmenopausal (natural or induced) patients receiving adjuvant endocrine therapy».

Estimating the benefits of therapy for early-stage breast cancer: the St. Gallen International Consensus Guidelines for the primary therapy of early breast cancer 2019

Adjuvant bisphosphonates	Bisphosphonates should be standard adjuvant therapy for postmenopausal patients with breast cancers

LINEE GUIDA AIOM 2019

Si raccomanda di considerare l'uso di bisfosfonati o denosumab all'inizio della terapia endocrina adiuvante con antiaromatasi per pazienti postmenopausali o per pazienti premenopausali al momento dell'amenorrea indotta da chemioterapici o da GnRH.

PREVENZIONE PRIMARIA DELLE FRATTURE OSTEOPOROTICHE IN DONNE IN MENOPAUSA DA TERAPIE ADIUVANTI PER CARCINOMA MAMMARIO

Anamnesi :
fumo, alcool, familiarità per osteopatia, patologie osteoarticolari pre-esistenti, farmaci

MOC-DEX basale e ogni 24 mesi a seguire

Dosaggio vitD, PTH, CTX

Ortopantomografia e valutazione odontoiatrica

Secondo la **nota AIFA 79** (determina n. 589 della GU n. 115 del 20/05/2015) sono prescrivibili a carico del SSN come **farmaci di 1° scelta**:
-Alendronato (+/-vitD) 70mg/OS, 1 volta/settimana
-Risendronato 35mg/OS, 1 volta/settimana
-Zolendronato 5mg/IV (non prescrivibile dall'oncologo)
-Denosumab 60 mg/SC/ ogni 6 mesi (piano terapeutico, rinnovabile ogni 12 mesi)