Bisphosphonates in Health and Disease

James J. Stark, MD, FACP

Medical Director, Cancer Program and Palliative Care

Maryview Medical Center

Professor of Medicine, EVMS

Case Presentation

- 52 y.o. woman presented in April 2003 with Stage II breast cancer (3.8 cm tumor, 2/11 positive axillary lymph nodes); underwent modified radical mastectomy
- ER+ PR-
- Her-2/neu 3+
- Prior simple hysterectomy with ovaries left in; hot flashes for last five years; no HRT
- Treated with Adriamycin/Cytoxan chemotherapy followed by Taxol

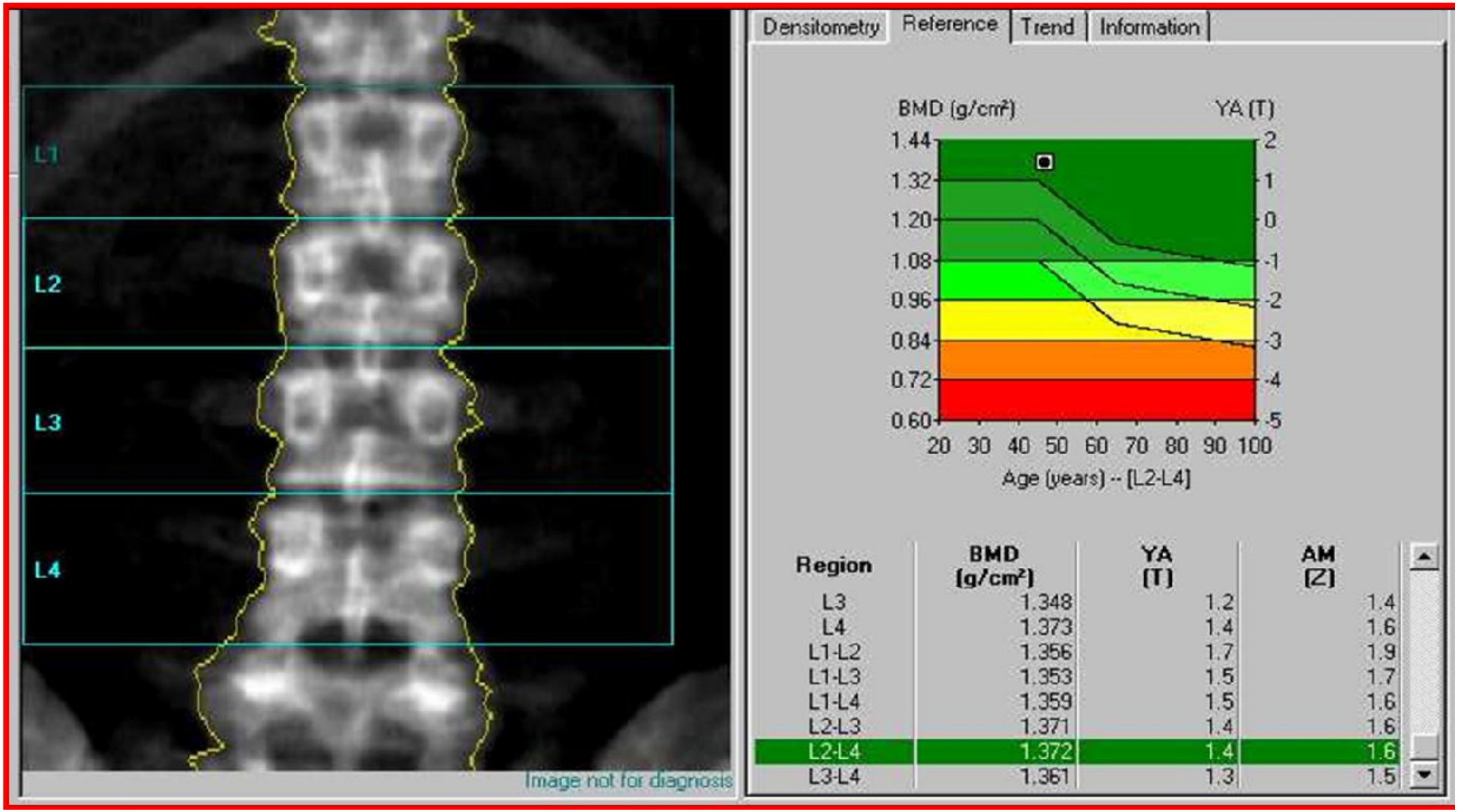
Case, continued

- Started on Tamoxifen at the end of chemotherapy (August, 2003)
- Bone density done June, 2006:
  - T-score of lumbar spine-0.8
  - T-score of femoral heads -1.1
- Based on emerging data switched to Letrozole (Femara®) in early 2007
- Anticipating worsening of bone mineral density started on oral Ibandronate (Boniva®) as well

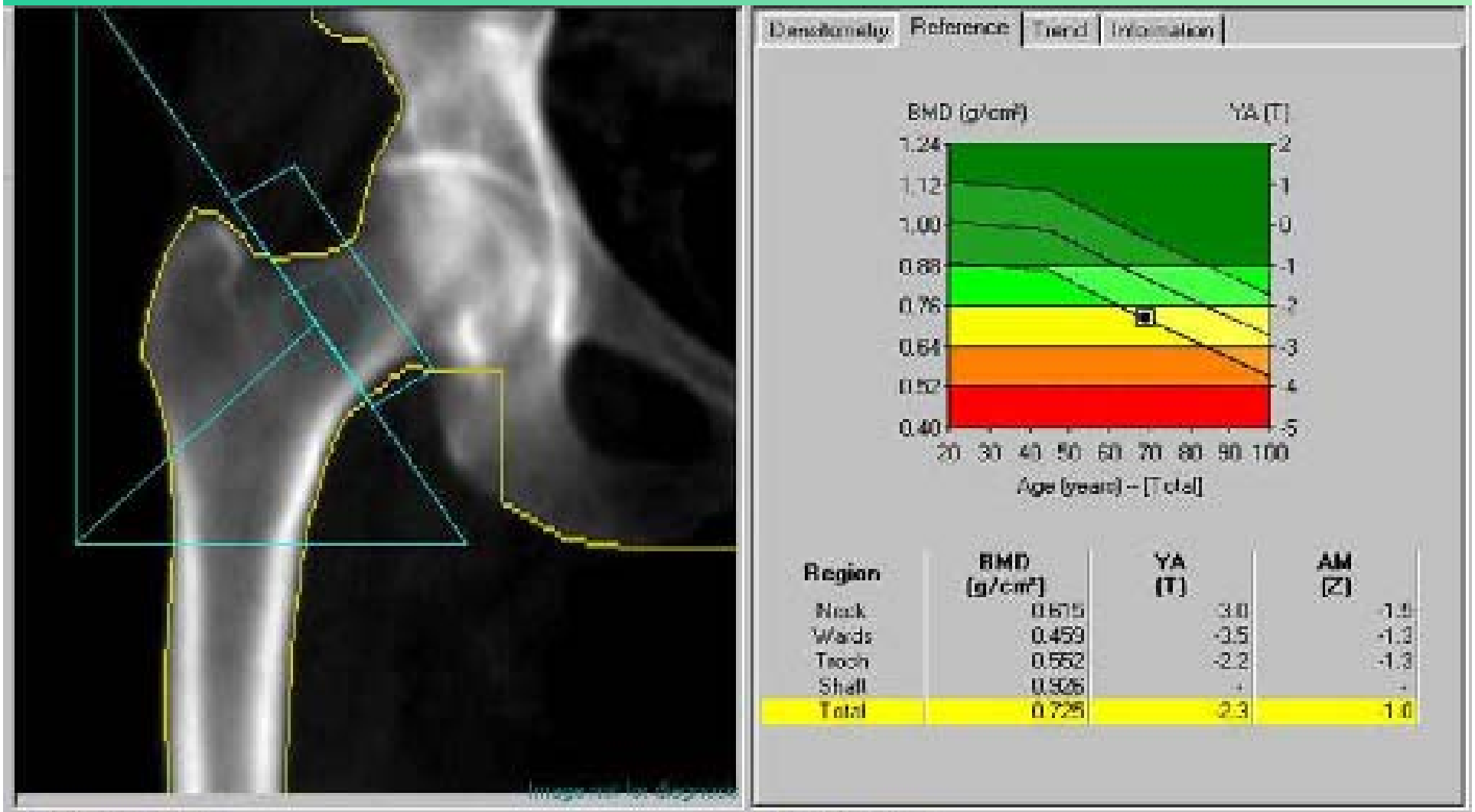
Case, continued

- Switched to Alendronate (Fosamax®) because of cost issues (insurance company panel of “approved” drugs)
- Total bisphosphonate exposure 9 months to date
- Repeat bone density done in September, 2007:
  - T-score of lumbar spine -1.1 (prior: -0.8)
  - T-score of femoral heads -1.3 (prior: -1.1)
- Plan to switch her to Zoledronic Acid (Reclast®) at next visit (lives 200 miles away, visits every six months)
- Continues free of cancer recurrence

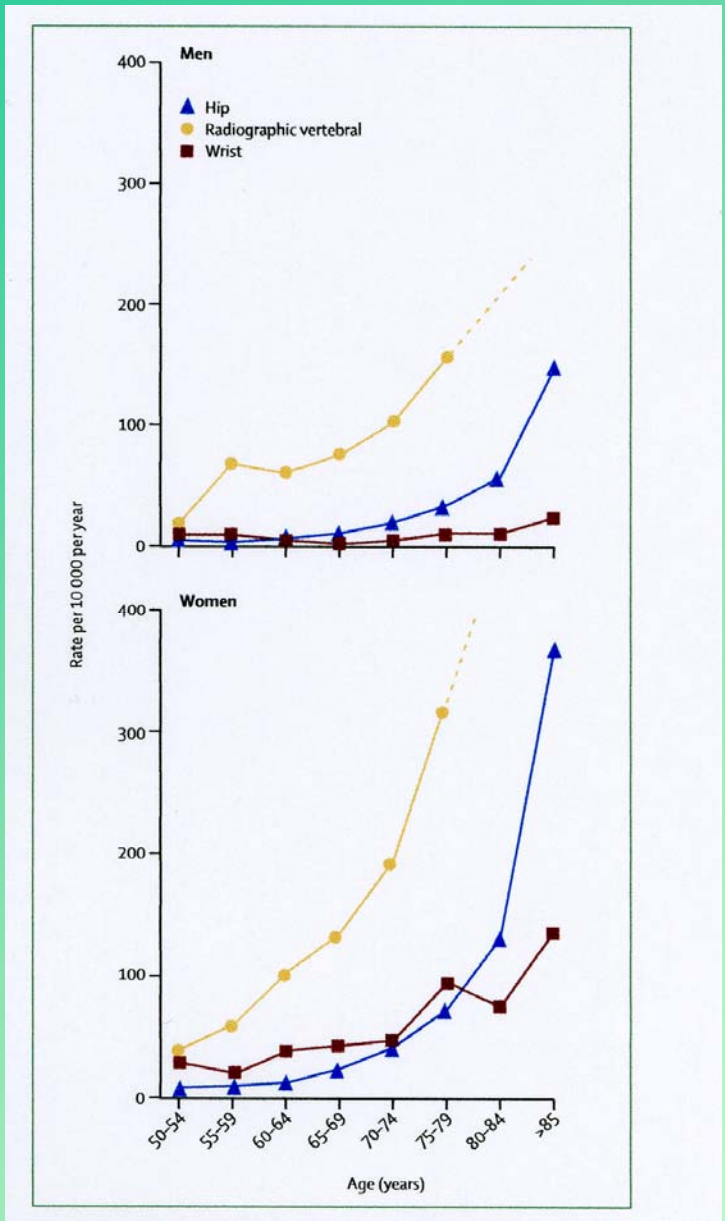
Typical Dexa Scan of Lumbar Spine



Dexa Image of Femoral Head



Impact of Osteoporosis



Osteoporotic fractures cost US health-care system $20B/year

Hip fracture leads to 36% mortality in first two years after event

Risk of second fracture 2.5 X that of population without hip fracture

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Osteoporosis

Sambrook et al *Lancet* 367:2010, 2006

What level of bone mineral loss should trigger intervention?

- National Osteoporosis Foundation
- World Health Organization

- Differ in recommendations
- Summary
  - T < -2 if no special risk factors
  - T<-1.5 if risk factors

Risk Factors*

- Being Caucasian or Asian postmenopausal woman
- Personal history of fracture as adult
- Family history of low-trauma fractures
- Small, thin frame
- Smoking
- Advancing Age, frailty, uncorrectable visual impairment

***Adapted from NOF guidelines**

Risk factors, continued*

- Low physical activity
- Lifelong low calcium intake
- Excessive alcohol consumption
- Co-morbid conditions:
  - Rheumatoid arthritis/Lupus
  - Inflammatory Bowel Disease/Celiac Disease
  - Liver Disease
  - Insulin-dependent Diabetes Mellitus
- Long-term steroid use

- ***Most people with bone mineral loss have at least one of these factors***

***from NOF**

Non-Pharmacologic Approaches to the Treatment of Osteoporosis

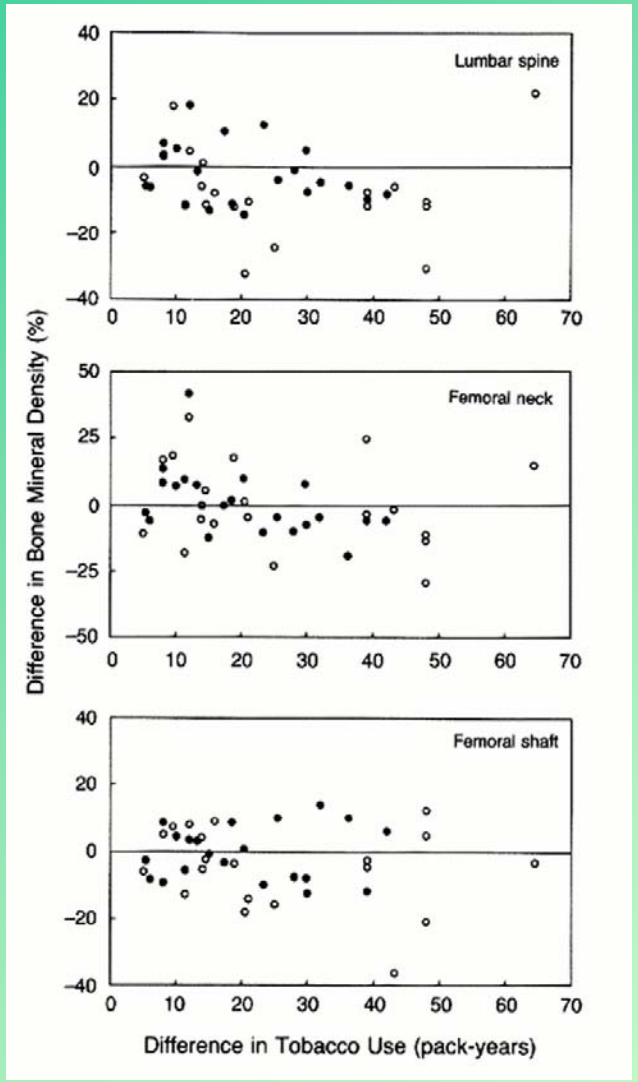
- Exercise
- Smoking Cessation
- Calcium and Vitamin D intake

Effect of Exercise on Development of Hip Fracture – From the Nurses' Health Study (n=61,200)

	Activity, MET-h/wk†				
	<3	3-8.9	9-14.9	15-23.9	≥24
Age, y	60	61	61	61	61
Type of activity, h/wk					
Walking	0.2	0.6	1.0	1.6	2.7
Standing	30	33	35	37	39
Sitting‡	38	37	37	36	36
Body mass index	25.6	25.1	24.7	24.3	23.6
Current use, %					
Hormone replacement therapy	29	36	40	40	40
Cigarettes	23	17	14	13	13
Thiazide diuretic	17	15	14	13	12
Calcium supplement	37	43	36	48	50
Multivitamin	38	43	36	47	48
Daily intake					
Calcium, mg	868	917	953	978	1007
Vitamin D, µg	7.5	7.9	8.3	8.5	8.8
Retinol, µg	1255	1302	1359	1397	1453
Vitamin K, µg	165	175	186	194	210
Protein, g	73	74	75	75	76
Alcohol, g	6.1	5.8	6.1	6.5	7.0
Caffeine, mg	336	320	310	308	299
Total energy, kcal	1663	1688	1699	1709	1729
Hip fracture incidence/100 000 women per year					
Age-standardized	118	82.4	70.2	52.7	46.6
Adjusted§	230	184	155	124	100

Feskanich et al *JAMA* 288: 2300, 2002

Within-Pair Differences in Bone Density at the Lumbar Spine, Femoral Neck, and Femoral Shaft as a Function of Within-Pair Differences in Pack-Years of Tobacco Use in 41 Pairs of Female Twins



Complicated study: dots below the line show effect of smoking…the more smoking the greater the effect

Hopper J and Seeman E. *N Engl J Med* 1994;330:387-392

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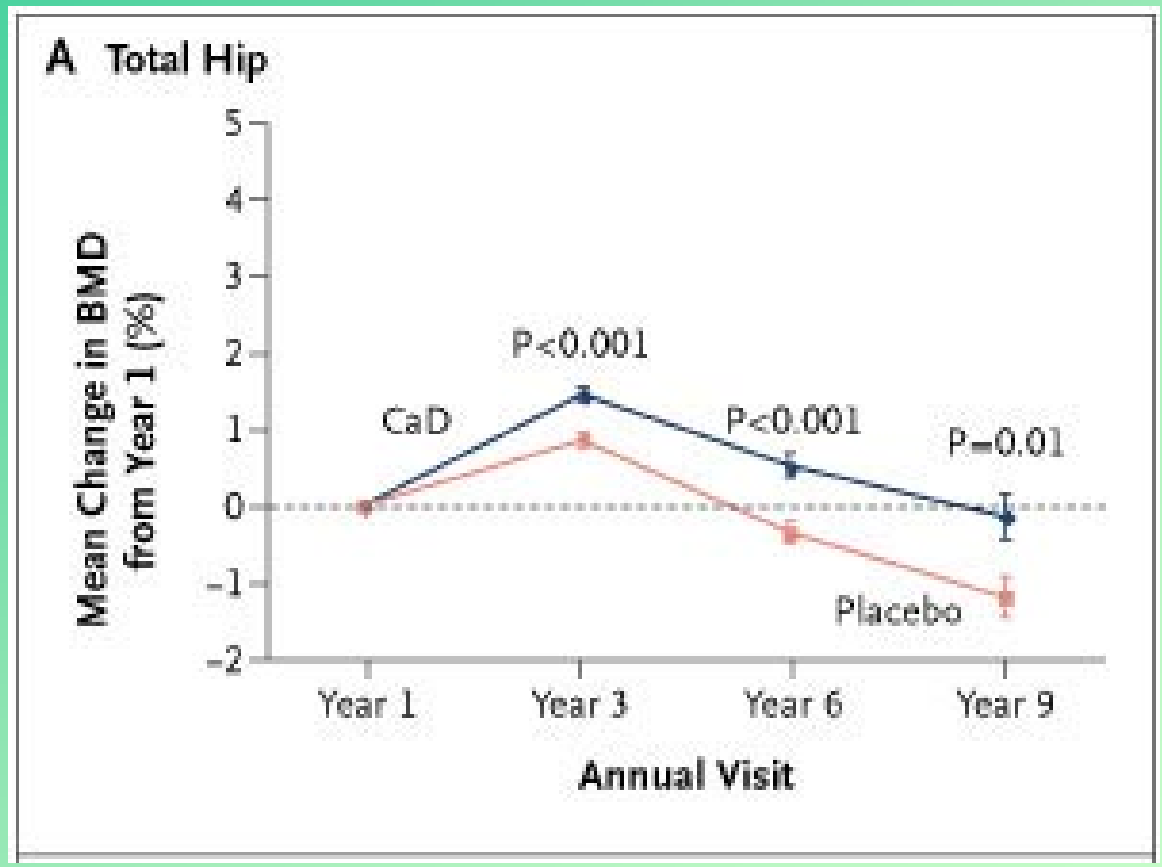
Hip Bone Mineral Density (BMD): Calcium + Vitamin D Supplementation vs. Placebo



Jackson R et al. *N Engl J Med* 2006;354:669-683

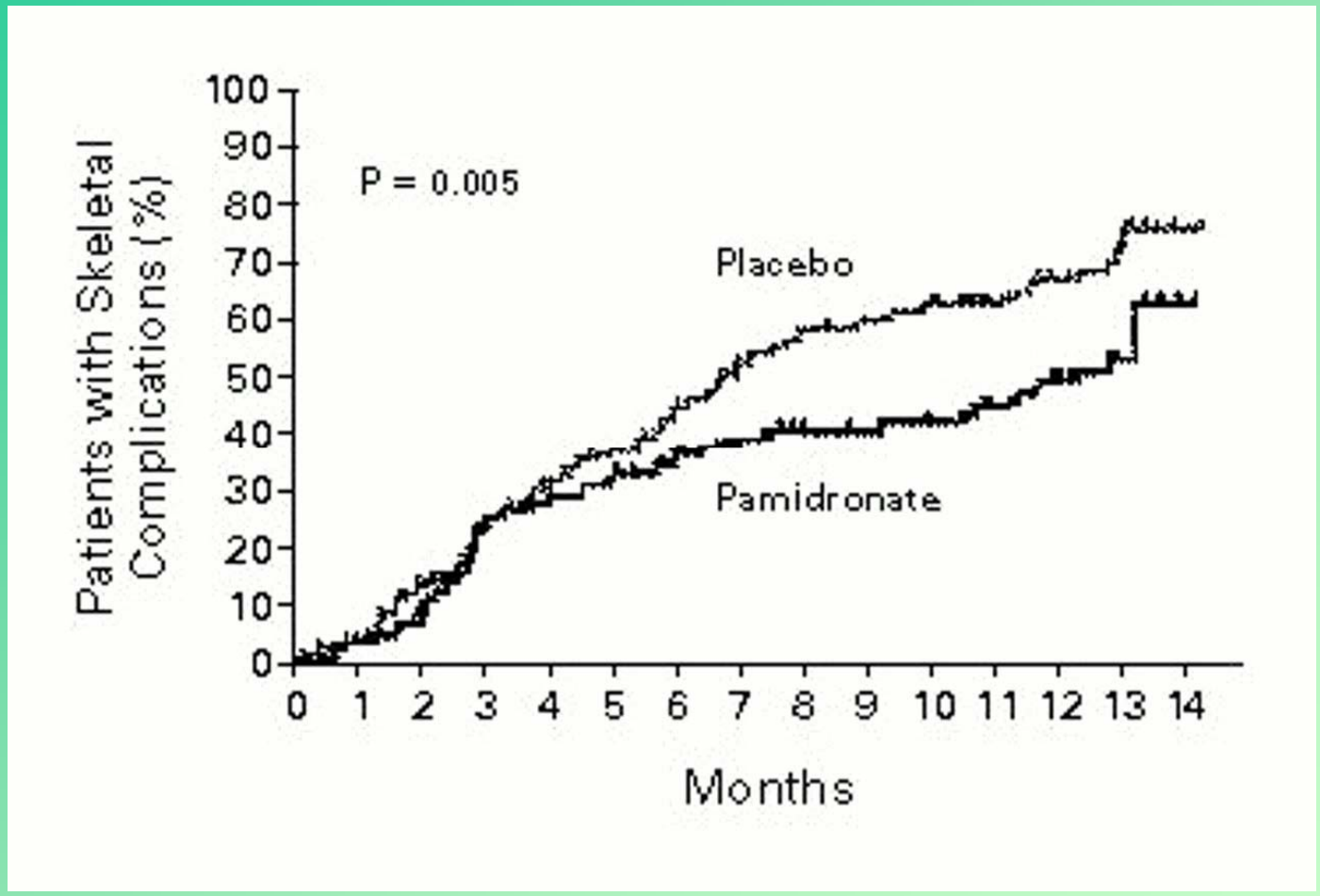
Beyond Exercise, Smoking Cessation and Dietary Supplements: How do we approach patients with and without cancer who have, or are at risk for, bone mineral loss?

First, let's talk about cancer….

The Problem of Bone Mineral Loss in Cancer Patients

- Widespread use of hormonal manipulation in treatment of cancer greatly exacerbates problem
  - Aromatase inhibitors in the treatment of breast cancer
  - Weak LHRH agonists or orchiectomy in the treatment of prostate cancer
- Use of bisphosphonates to prevent fracture in patients with lytic metastases was an important clue to their usefulness

Kaplan-Meier Estimates of the Time to the First Skeletal Complication in Patients with Breast Cancer and Multiple Myeloma



Hortobagyi G et al. *N Engl J Med* 1996;335:1785-1792

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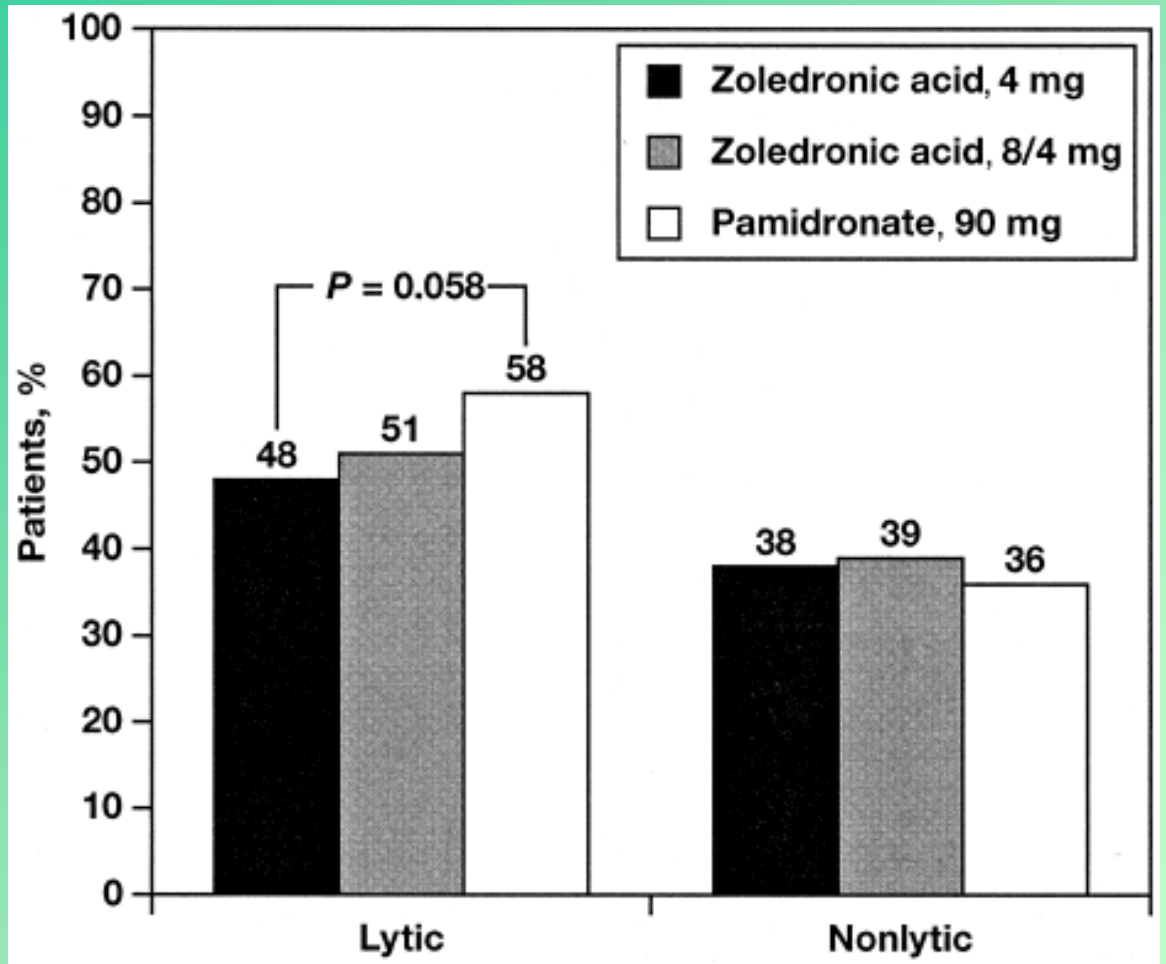
Further Improvement in Outcome with Zoledronic Acid (Zometa®)



Percentage of patients with at least one adverse event over 13 months

Rosen et al *Cancer* 2004, 100:26-43

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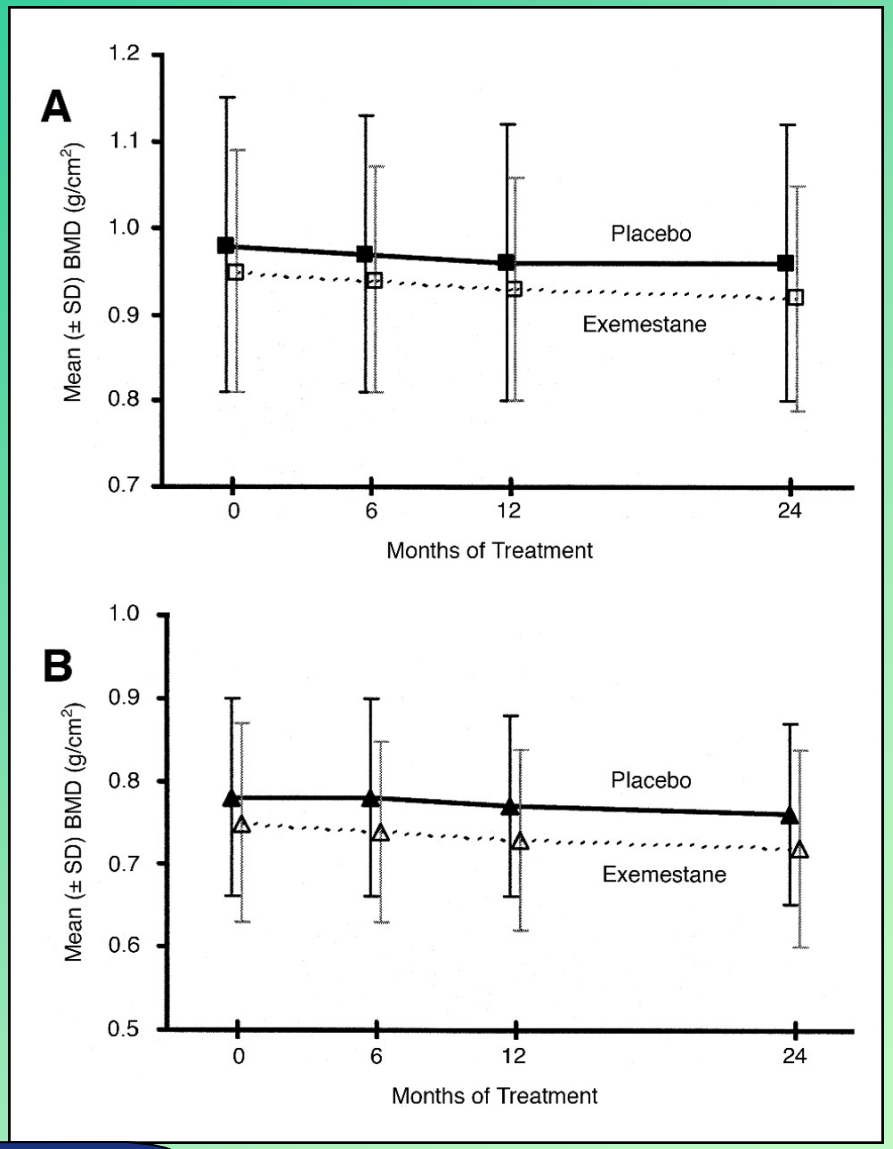
Bisphophonates as part of rational approach to the use of Aromatase Inhibitors: biggest issue is in the adjuvant setting, where large numbers of women are involved and expectation for longevity is great.

How can we prevent osteoporosis, which will then lead to fractures?

Effect of 2-year treatment with placebo or exemestane on bone mineral density (BMD) of the lumbar spine (A) and femoral neck (B)



The Problem with Aromatase Inhibitors

Lonning, P. E. et al. *J Clin Oncol*; 23:5126-5137 2005

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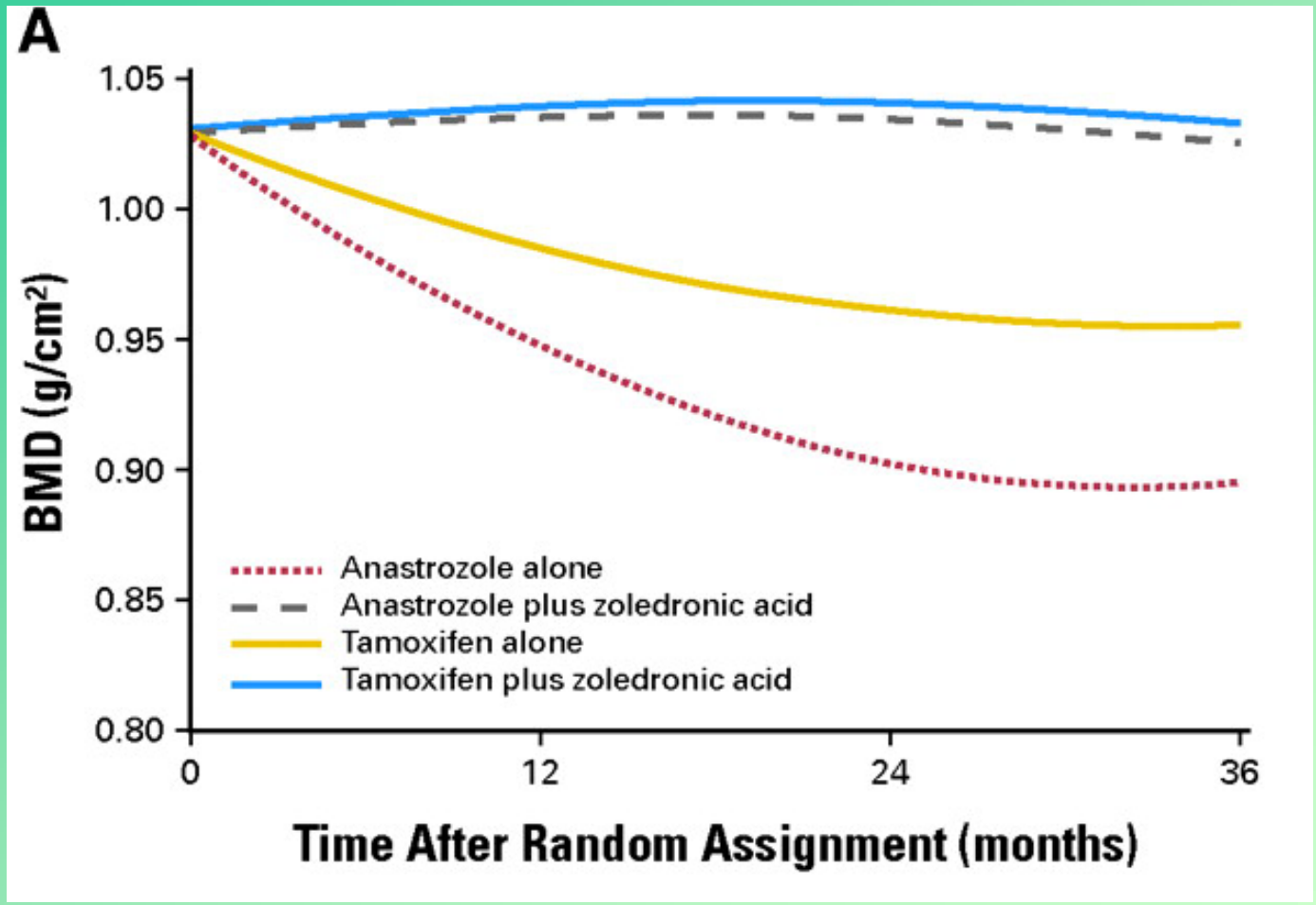
Aromatase Inhibitors and Bisphosphonates

- Widely used together in women with any evidence of bone mineral loss
- Can BP's halt or reverse loss of bone mineral density associated with AI's?

Changes from baseline bone mineral density (BMD) over time in the lumbar spine over time in patients treated for 36 months with anastrozole or tamoxifen {+/-} zoledronic acid

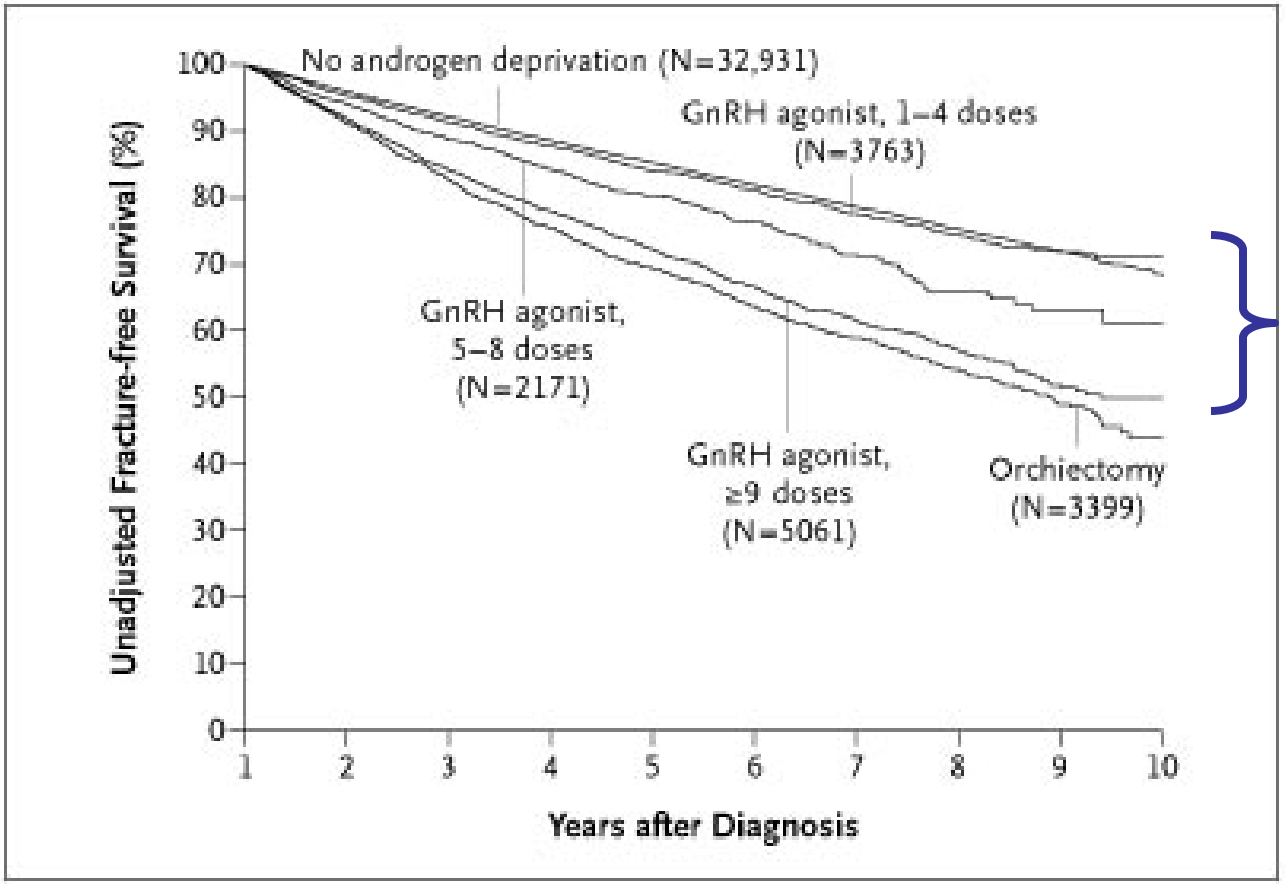


Gnant, M. F.X. et al. *J Clin Oncol*; 25:820-828 2007

Osteoporosis in the Treatment of Prostate Cancer

- Hormone deprivation with castration or drugs designed to lower testosterone levels results in bone mineral loss
- Fracture rate increases in this setting…

Unadjusted Fracture-free Survival among Patients with Prostate Cancer, According to Androgen-Deprivation Therapy



Dose-dependent impact of Lupron therapy

Shahinian V et al. *N Engl J Med* 2005;352:154-164

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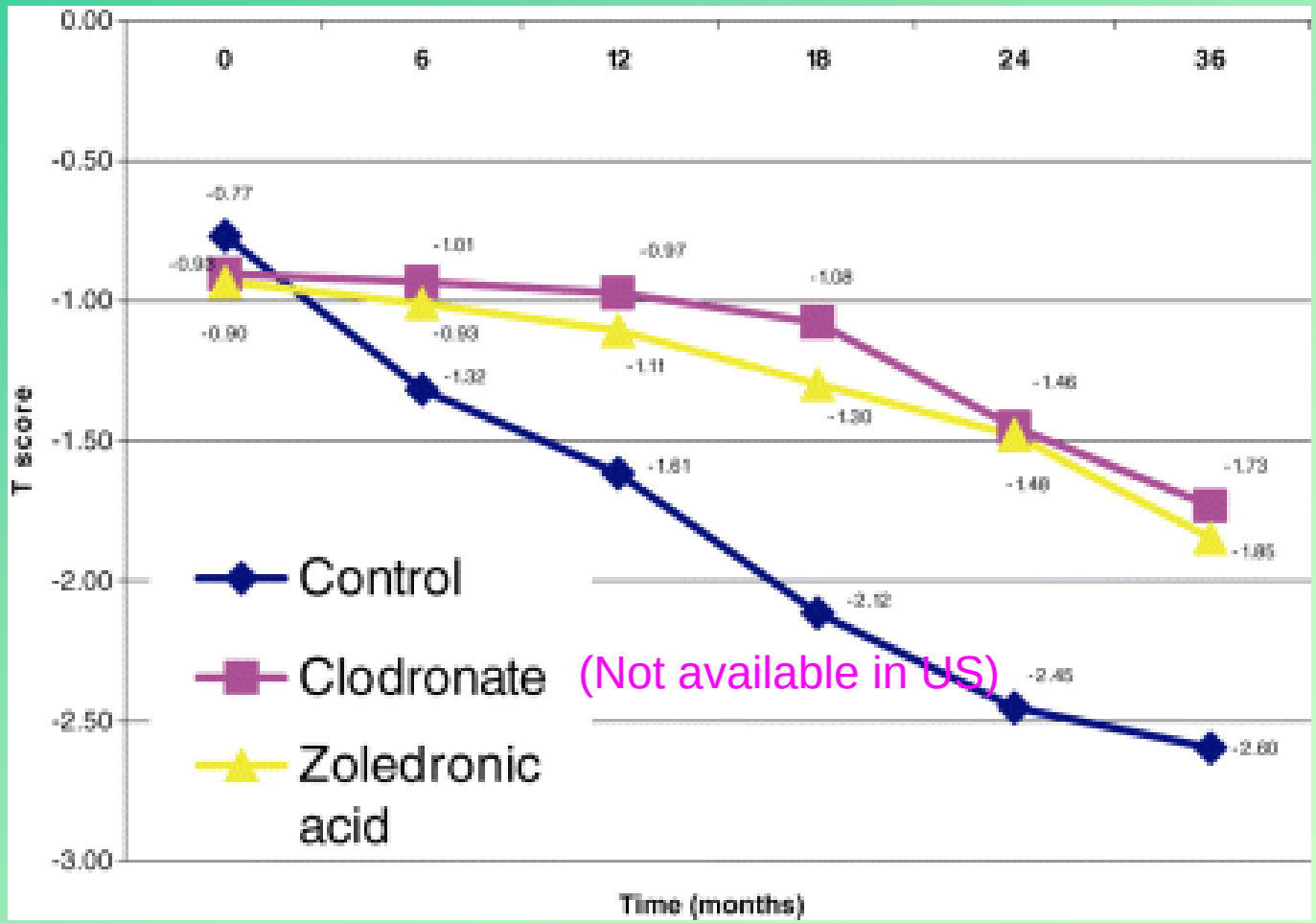
Use of Bisphosphonates with Androgen Deprivation



Rodrigues, *Int. J. Urol.* 14(4): 317-20, 2007

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Pharmacologic Approach to Osteoporosis in Women Without Cancer

- Large number of drugs to choose from
- Range of possible drugs of proven benefit:
  - (HRT)
  - Antiestrogens (Tamoxifen and Raloxifine)
  - Calcitonin
  - Parathormone
  - Bisphosphonates
- What is rational sequence of drugs?
  - Which ones work best? What is the correct order for their use?

How do Anti-Estrogens fit in to the rational treatment of osteoporosis?

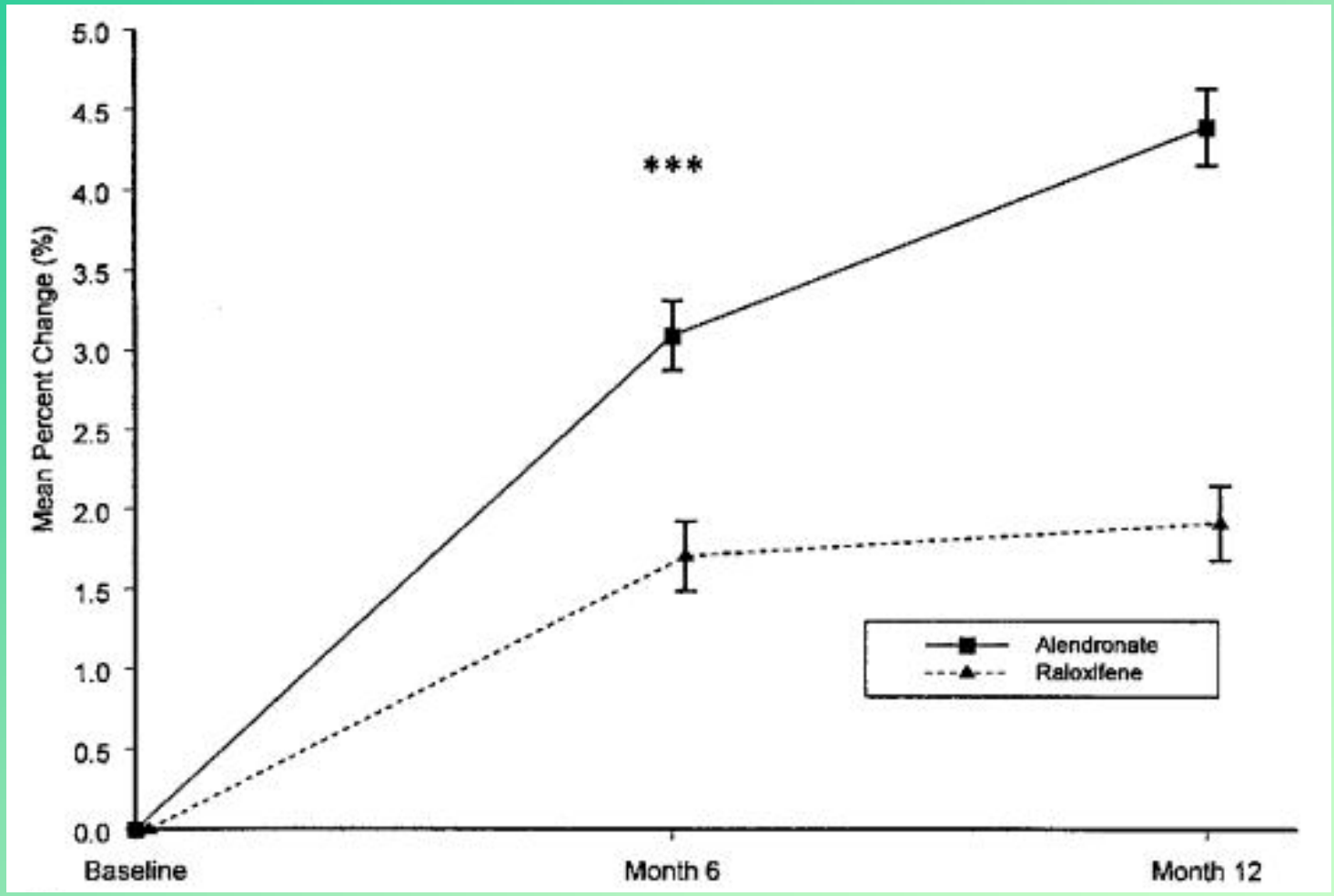
- Raloxifine (Evista®) useful in preventing fractures
- Avoids problem of uterine cancer seen with Tamoxifen
- How does it compare in efficacy with bisphosphonates?
- Head-to-head comparison done…

Alendronate vs. Raloxifine

- Alendronate (Fosamax®) 70 mg weekly
- Raloxifine (Evista®) 60 mg daily
- Fracture rate and bone loss examined…

Luckey et al, *Menopause* 2004, 11:405-15

Change in BMD over one year in lumbar spine



***p<0.001

Combination of the two may work better than either drug alone; being studied

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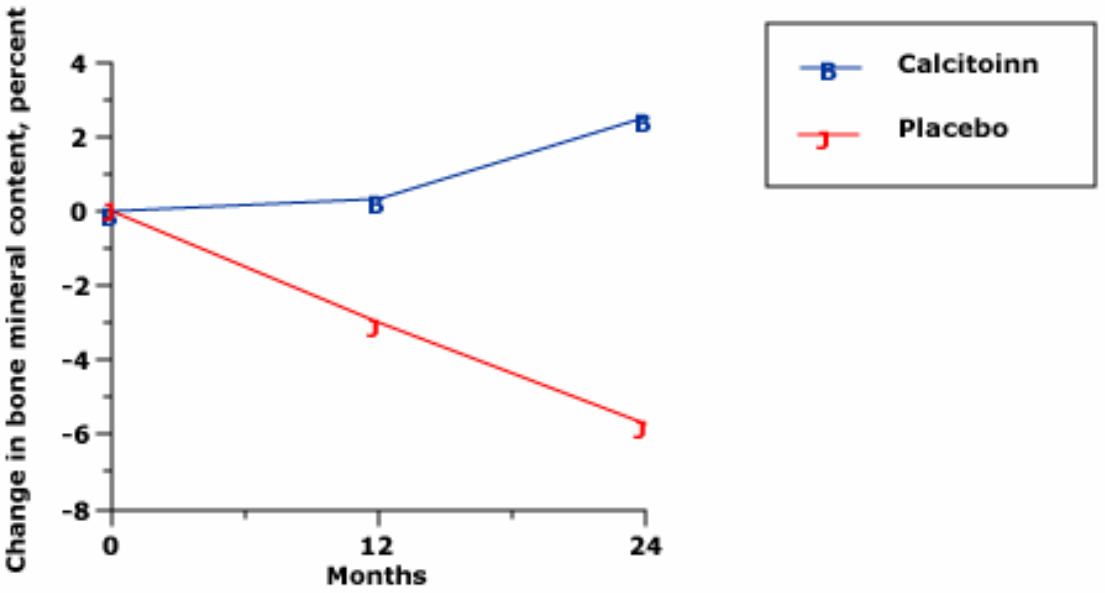
What About Calcitonin?

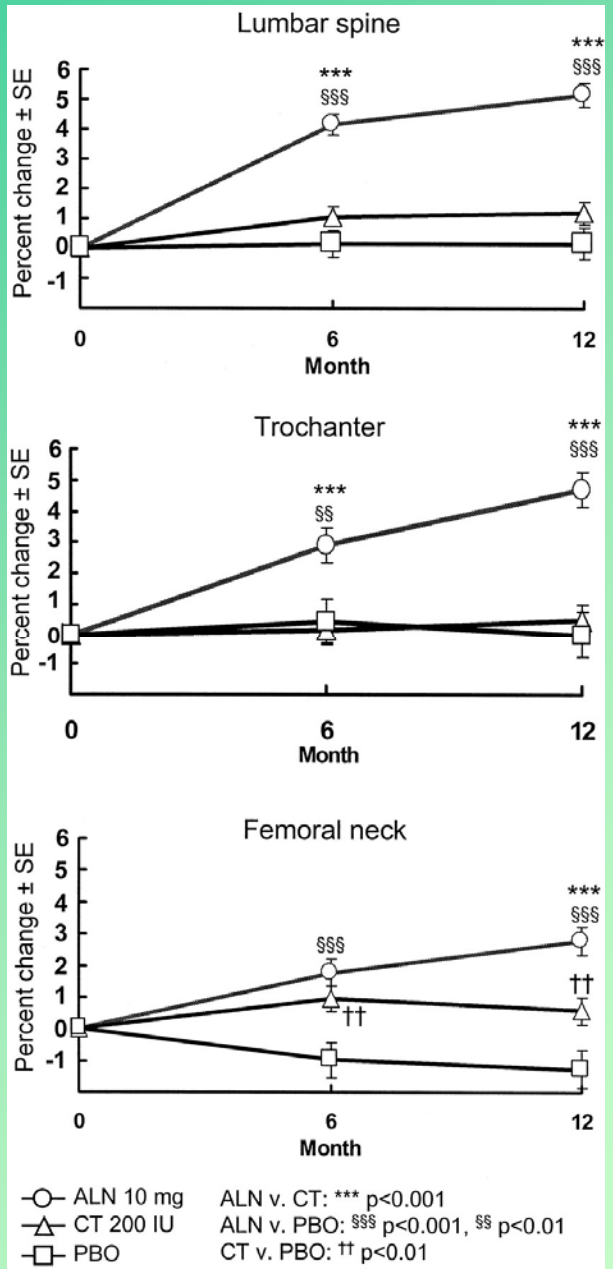
- In most studies has modest benefit in the treatment of osteoporosis
- Improvement site dependent (better in lumbar spine than hips – reason unknown)
- Most effective agent in relieving pain of vertebral fracture
- Anti-calcitonin antibodies limit its effectiveness
- More effective agents available

Efficacy of Salmon Calcitonin in Lumbar Spine BMD



Mean change in lumbar bone mineral content in 39 postmenopausal women treated for two years with intranasal salmon calcitonin or placebo. Bone mineral content was stable with calcitonin but fell in the placebo group ($p < 0.001$ at two years). *Data from Overgaard, K, Riis, BJ, Christiansen, C, et al, BMJ 1989; 299:477.*

What About the Efficacy of Calcitonin?
Comparison of Alendronate (Fosamax®) vs. Intra-Nasal Calcitonin vs. Placebo



Downs, R. W. et al.
J Clin Endocrinol Metab
2000;85:1783-1788

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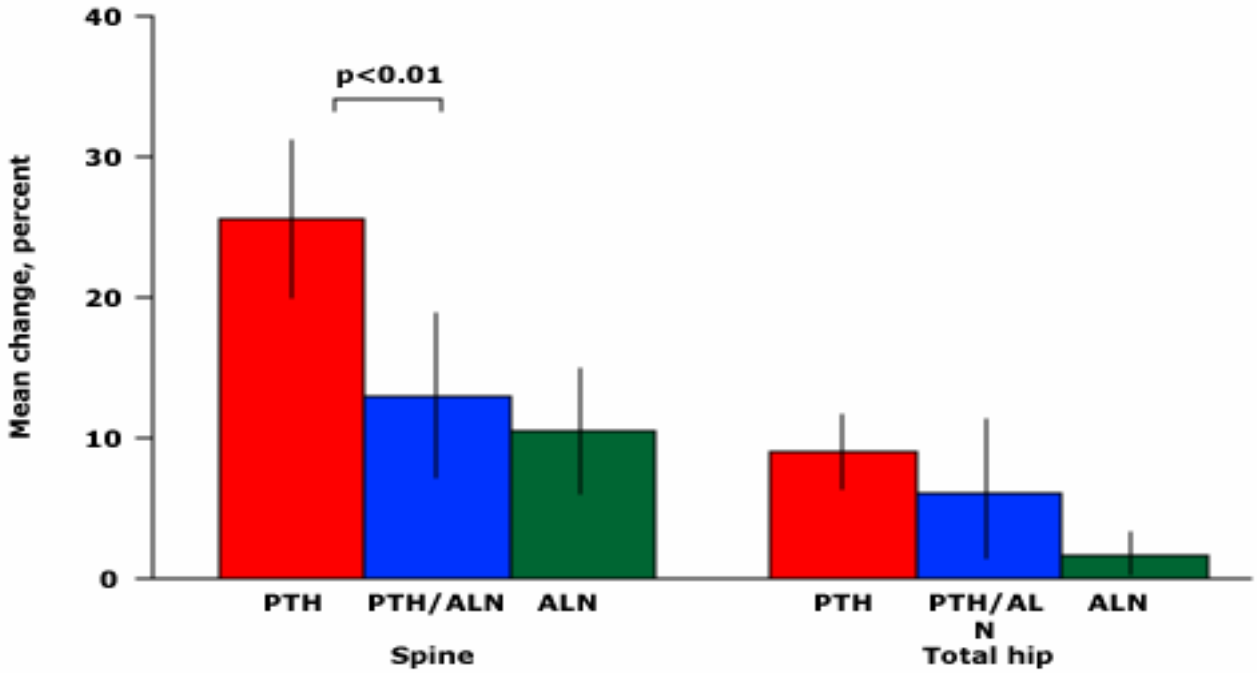
What about the use of PTH??

- Counterintuitive but very potent agent for accruing new bone/mineral substance
- May work in the recovery phase after injection
- Question of carcinogenicity limits its use to two years, greatly ameliorating long-term value
- Study using PTH (Forteo®) with or without Alendronate…

Trabecular volumetric BMD with different therapies



Changes in trabecular volumetric BMD in the lumbar spine and total hip by Quantitative CT (g/cm3) after 12 months of treatment with PTH 1-84 (100 mcg in red), PTH and alendronate (10 mg/day in blue) or alendronate (10 mg/day alone in green). *Data from: Black, DM, Greenspan, SL, Ensrud, KE, Palermo, L, et al. The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. N Engl J Med 2003; 349:1207.*

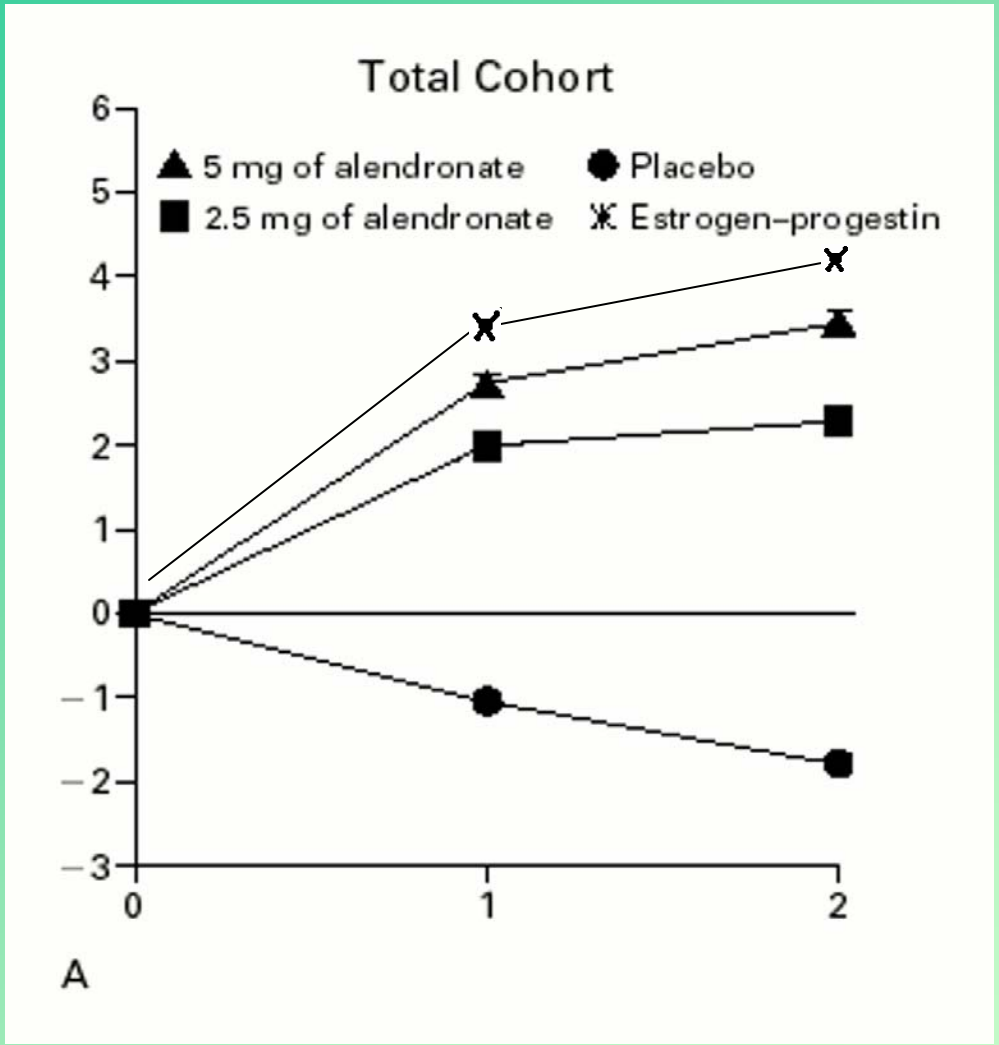
PTH, continued

- Benefits of PTH quickly lost upon discontinuation of drug; rapid post-therapy decrease in BMD
- Greatly limits its value in women with long life expectancy
- Alendronate following PTH likely helps prevent this phenomenon even though the two together are not synergistic

Bisphosphonates in Women Without Cancer

- Overwhelming evidence for their role in treating post-menopausal osteoporosis
- Drugs in use:
  - Alendronate (Fosamax®) weekly
  - Risedronate (Actonel®) weekly
  - Ibandronate (Boniva®) monthly
  - Intravenous Ibandronate quarterly (reserved for intolerance to oral agents)
  - Intravenous Zolendronic Acid (Reclast®) just approved in absence of cancer; *no BP oral intolerance required*

Impact of daily Alendronate (Fosamax®) on lumbar spine BMD over 2 years



Hosking D et al. *N Engl J Med* 1998;338:485492

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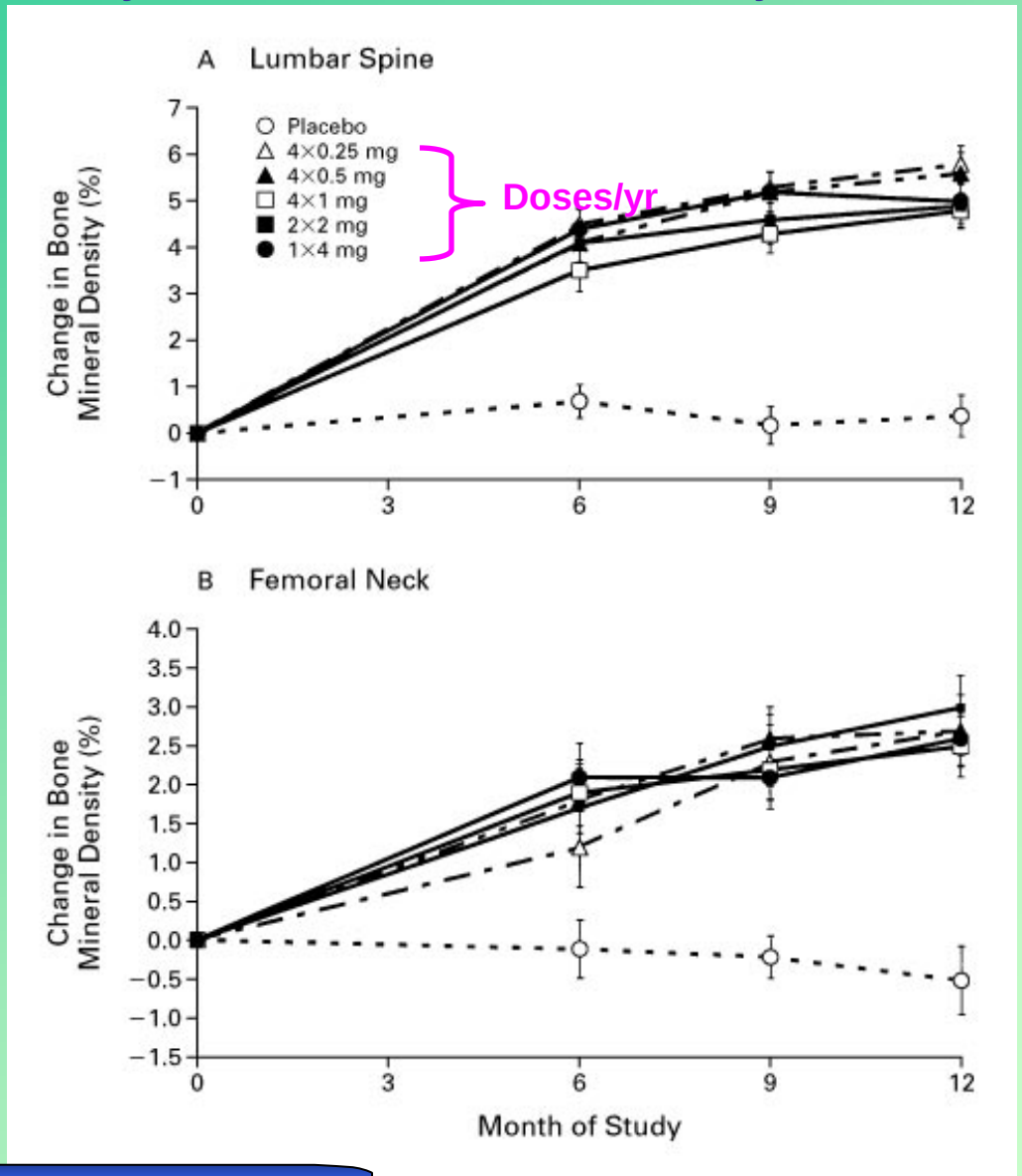
Effects of Various Regimens of Zoledronic Acid and Placebo on Bone Mineral Density in the Lumbar Spine (Panel A) and the Femoral Neck (Panel B) in Postmenopausal Women with Low Bone Mineral Density: The first Zolendronic Acid study in non-cancer women



Reid I et al. *N Engl J Med* 2002;346:653-661

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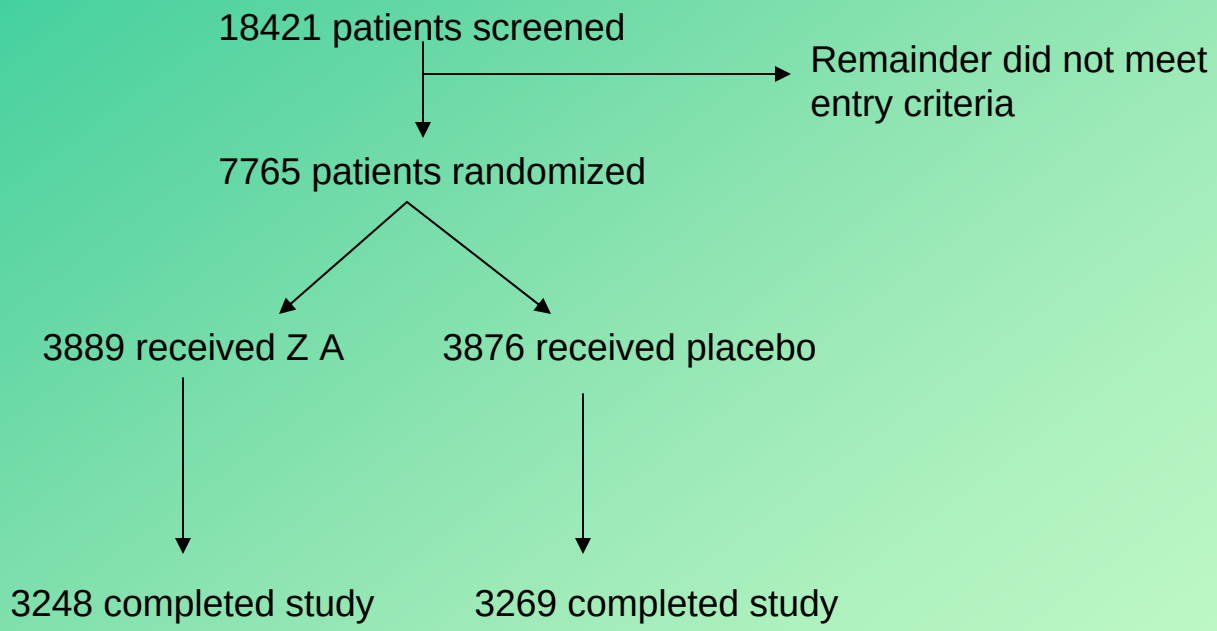
First of Two Large Studies Putting Principle of Infrequent Zolendronic Acid to the Test: Zolendronic Acid in Healthy Post-Menopausal Women



The final groups were then analyzed…

Black D et al.
N Engl J Med
2007;356:1809-1822

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Recent Zoledronic Acid Study: Relative Risk of Fracture Incidence in the Two Study Groups

Table 2. Relative Risk of Fracture Incidence in the Two Study Groups.*

Type of Fracture	Placebo	Zoledronic Acid	Relative Risk or Hazard Ratio (95% CI)†	P Value
	no. of patients (%)			
Primary end points				
Morphometric vertebral fracture (stratum 1)	310 (10.9)	92 (3.3)	0.30 (0.24–0.38)	<0.001
Hip fracture	88 (2.5)	52 (1.4)	0.59 (0.42–0.83)	0.002
Secondary end points				
Nonvertebral fracture	388 (10.7)	292 (8.0)	0.75 (0.64–0.87)	<0.001
Any clinical fracture	456 (12.8)	308 (8.4)	0.67 (0.58–0.77)	<0.001
Clinical vertebral fracture	84 (2.6)	19 (0.5)	0.23 (0.14–0.37)	<0.001
Multiple (≥2) morphometric vertebral fractures (stratum 1)	66 (2.3)	7 (0.2)	0.11 (0.05–0.23)	<0.001

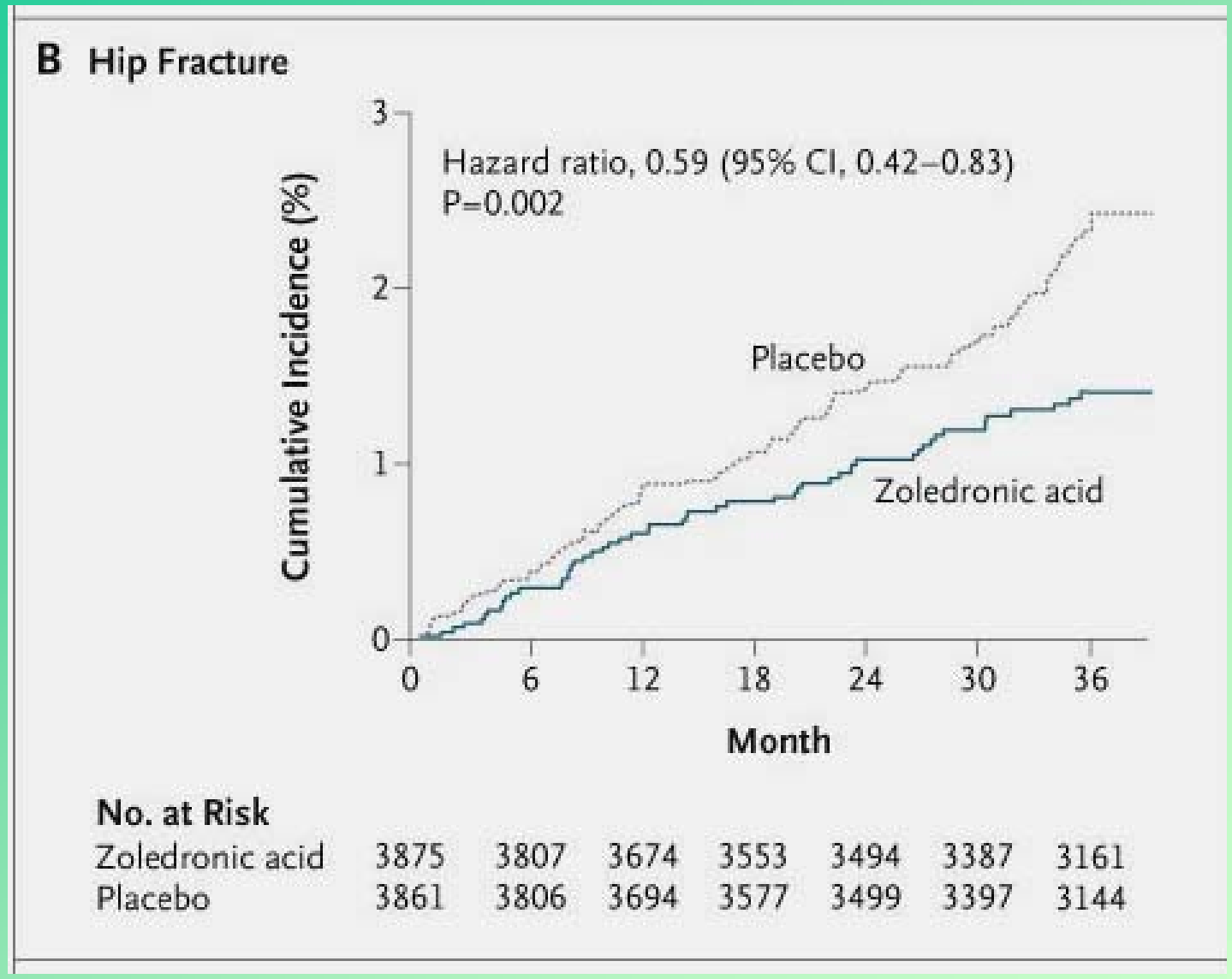
* The percentage of morphometric fractures is the proportion of patients with a baseline radiograph, at least one follow-up radiograph, and a fracture (2853 patients in the placebo group and 2822 patients in the zoledronic-acid group). The percentage of clinical fractures is based on Kaplan–Meier estimates of the 3-year cumulative incidence (3875 patients with clinical fractures in the placebo group and 3861 in the zoledronic-acid group).

† For morphometric vertebral fractures, the relative risk is presented; for all other end points, the adjusted hazard ratio is presented. The significance level for morphometric vertebral fractures is based on an adjusted logistic-regression analysis.

Black D et al. *N Engl J Med* 2007;356:1809-1822

Study group received 15-minute infusion of Zoledronic Acid at time 0, months 12 and 24; all patients followed for 36 months

Incidence of Hip Fractures during the 3-Year Study Period



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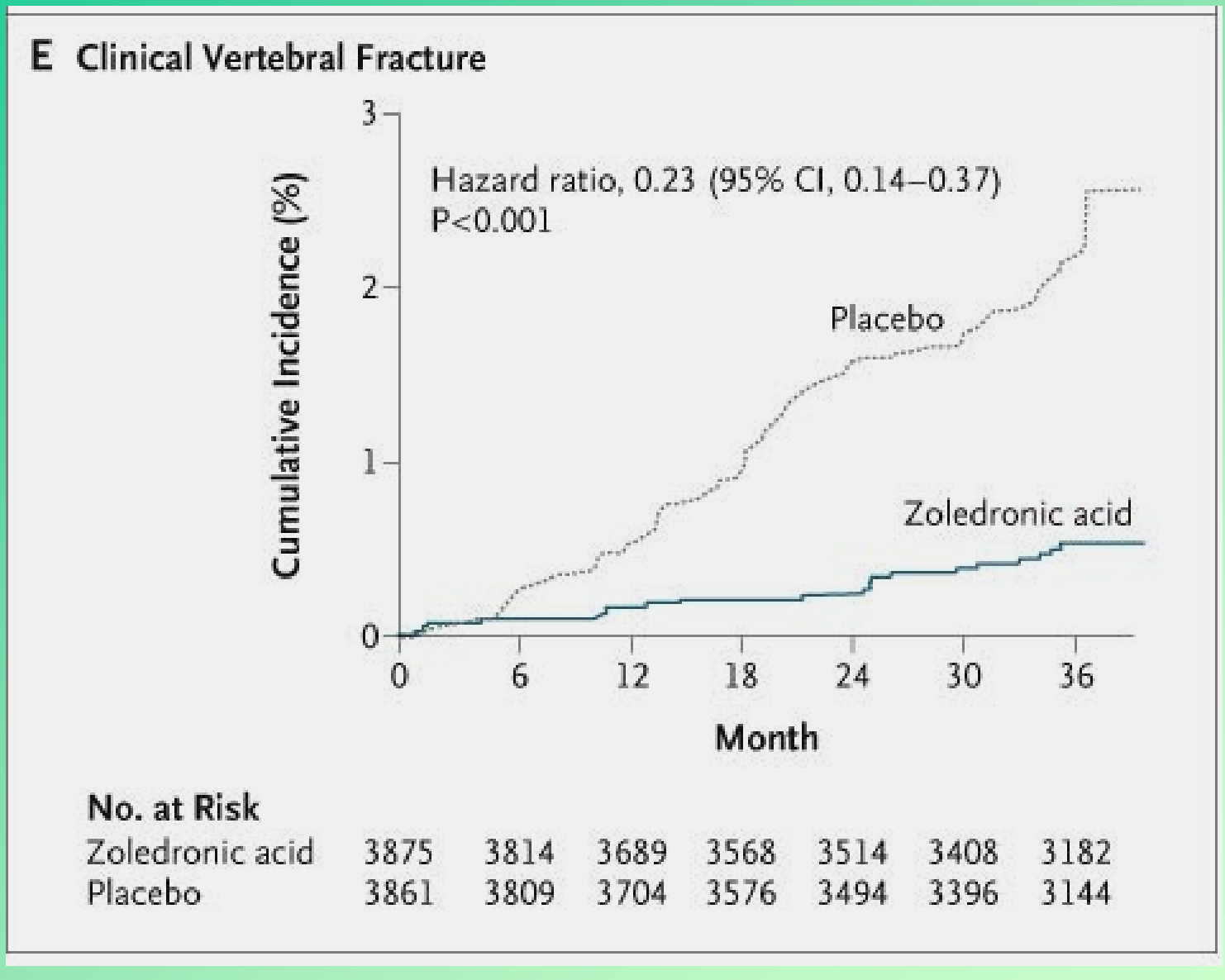
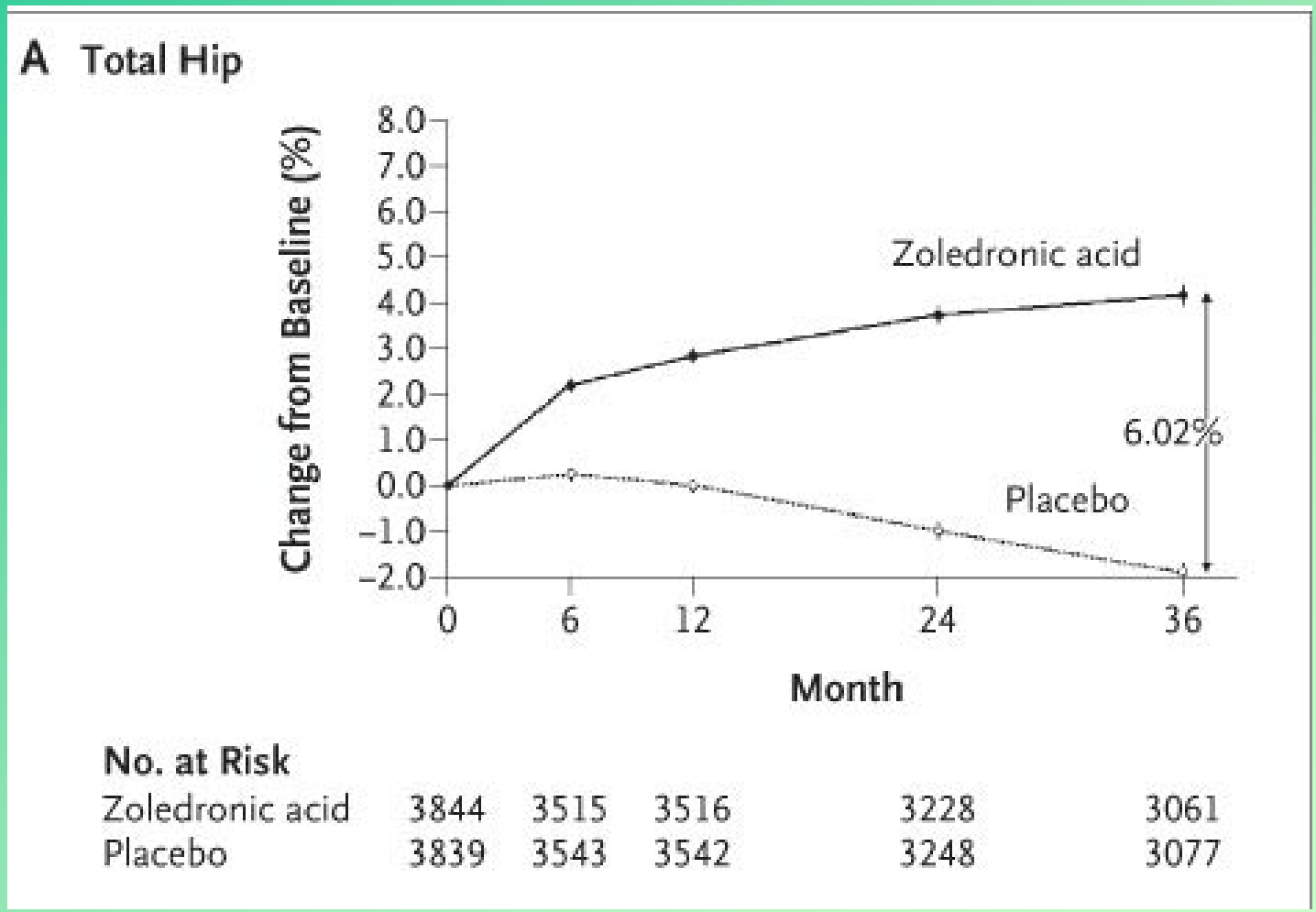
Black D et al. *N Engl J Med* 2007;356:1809-1822

Incidence of Vertebral Fractures during the 3-Year Study Period



Black D et al. *N Engl J Med* 2007;356:1809-1822

Percent Change over Time in Bone Mineral Density



Black D et al. *N Engl J Med* 2007;356:1809-1822

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Adverse Events

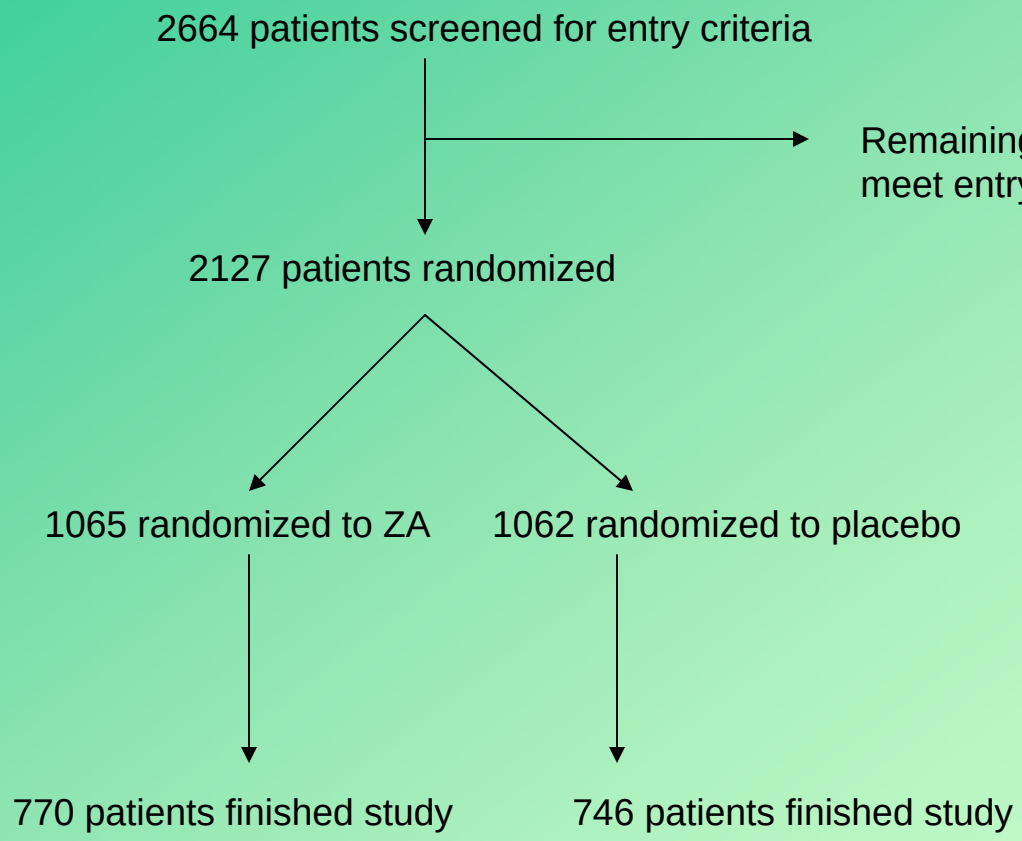
Table 3. Adverse Events.*

Event	Placebo (N=3852)	Zoledronic Acid (N=3862)	P Value
	no. of patients (%)		
General			
Any adverse event	3616 (93.9)	3688 (95.5)	0.002
Any serious adverse event	1158 (30.1)	1126 (29.2)	0.40
Death	112 (2.9)	130 (3.4)	0.27
Discontinuation of follow-up owing to adverse event	70 (1.8)	80 (2.1)	0.41
Renal events			
Increase in serum creatinine >0.5 mg/dl†	10 (0.4)	31 (1.2)	0.001
Urinary protein >2+†	5 (0.2)	13 (0.5)	0.06
Calculated creatinine clearance <30 ml/min	152 (3.9)	160 (4.1)	0.69
Five most common post-dose symptoms (≤3 days after infusion)‡			
Pyrexia	79 (2.1)	621 (16.1)	<0.001
Myalgia	66 (1.7)	365 (9.5)	<0.001
Influenza-like symptoms	61 (1.6)	301 (7.8)	<0.001
Headache	90 (2.3)	273 (7.1)	<0.001
Arthralgia	76 (2.0)	245 (6.3)	<0.001
Any of the five most common post-dose symptoms			
After first infusion	237 (6.2)	1221 (31.6)	<0.001
After second infusion	79 (2.1)	253 (6.6)	<0.001
After third infusion	42 (1.1)	108 (2.8)	<0.001
Cardiovascular events			
Atrial fibrillation			
Any event	73 (1.9)	94 (2.4)	0.12
Serious adverse event	20 (0.5)	50 (1.3)	<0.001
Stroke§			
Serious adverse event	88 (2.3)	87 (2.3)	0.94
Death from stroke	11 (0.3)	20 (0.5)	0.15
Myocardial infarction	45 (1.2)	38 (1.0)	0.44
Death from cardiovascular causes	33 (0.9)	39 (1.0)	0.55

No cases of osteonecrosis of the mandible

Black D et al. *N Engl J Med* 2007;356:1809-1822

Most Recent Study Published on Outcomes Following Hip Fracture



The final groups were then analyzed…

Lyles K et al.
N Engl J Med
2007;357:1799-809

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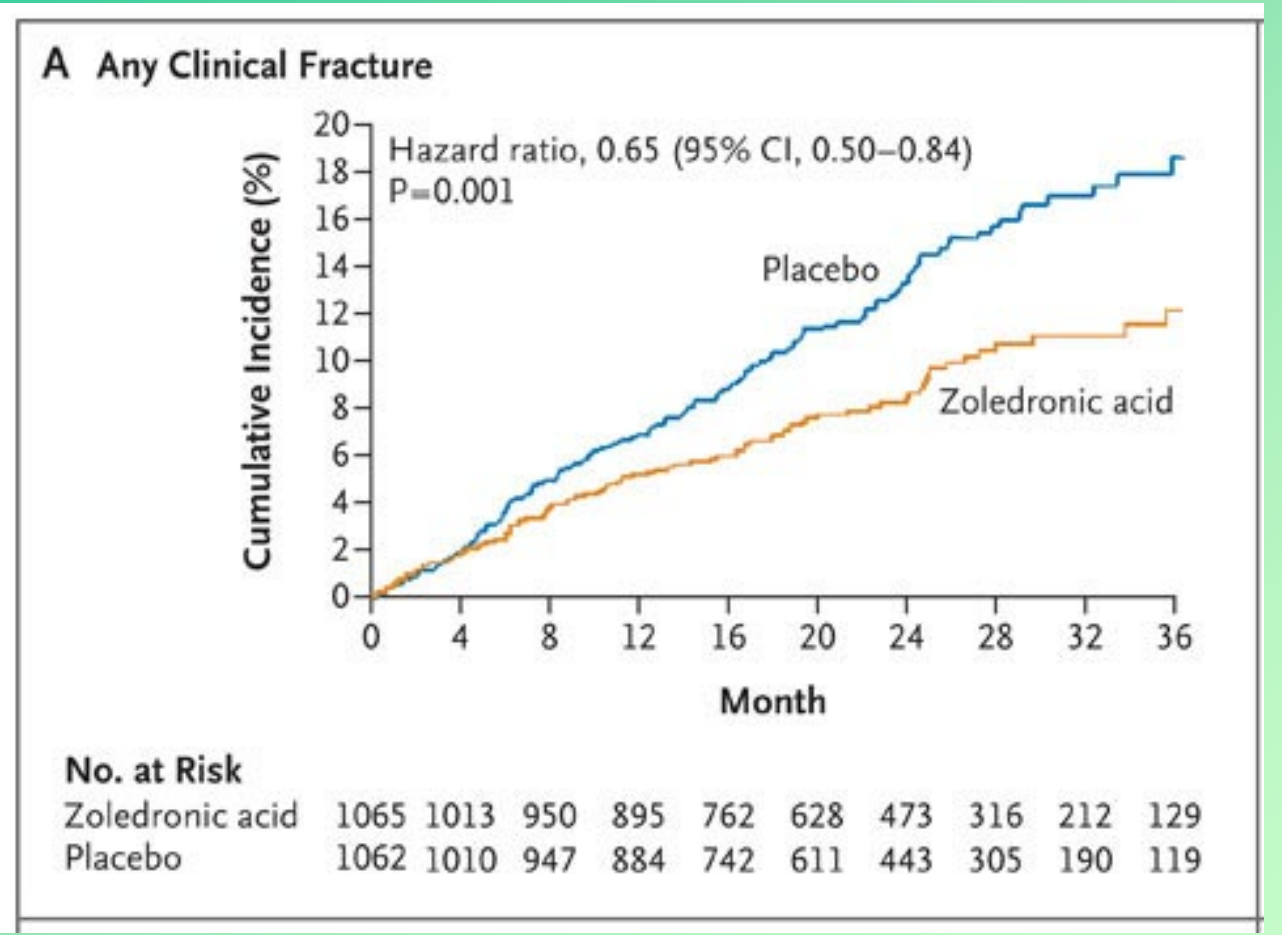
Time to Primary or Secondary End Points



Lyles K et al. *N Engl J Med* 2007;357:1799-809

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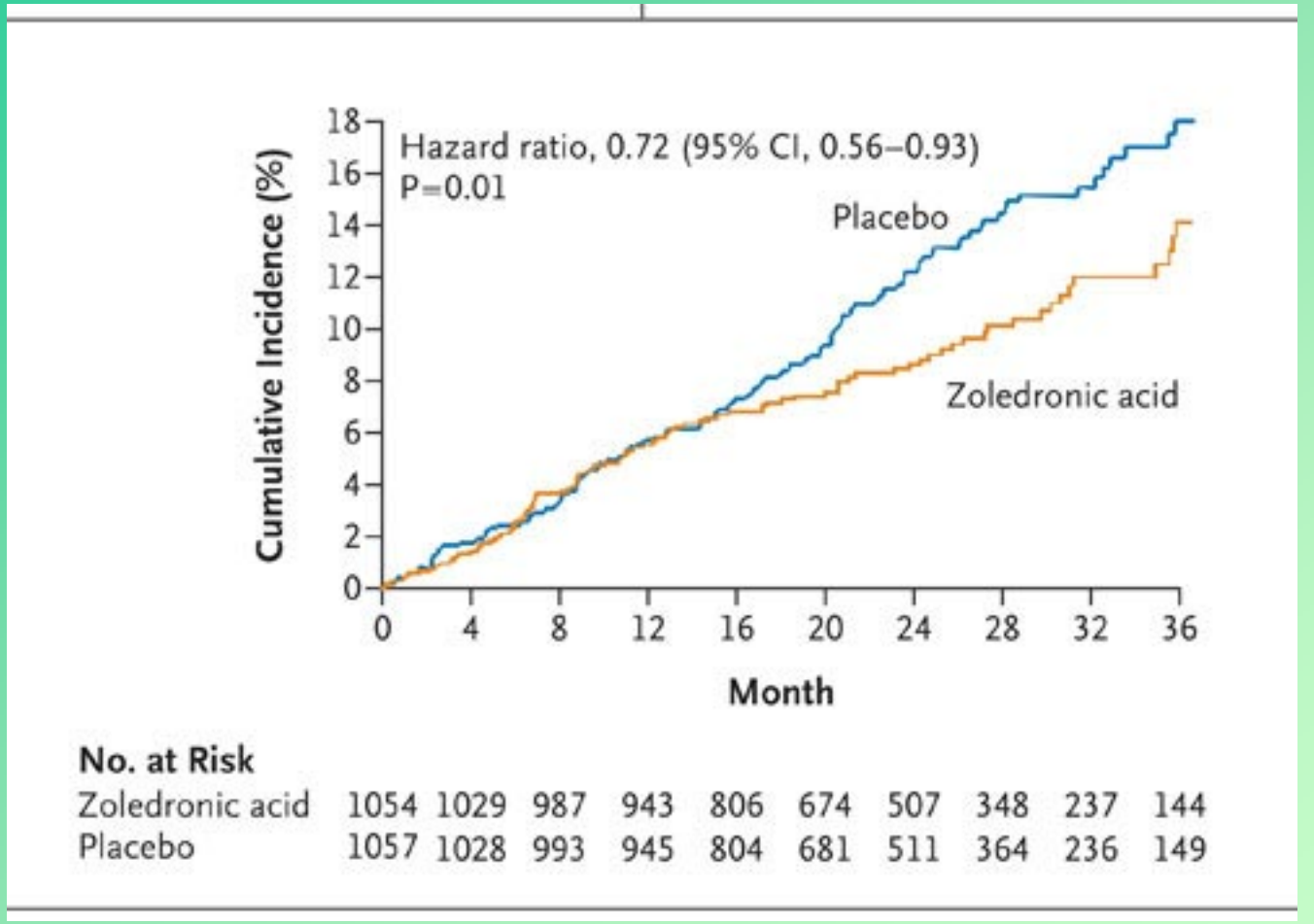
Time to Primary or Secondary End Points: Overall deaths



No. at Risk

Zoledronic acid	1054	1029	987	943	806	674	507	348	237	144
Placebo	1057	1028	993	945	804	681	511	364	236	149

Lyles K et al. *N Engl J Med* 2007;357:1799-809

Rates of Fracture and Death in the Study Groups

Table 2. Rates of Fracture and Death in the Study Groups.*

Variable	Placebo	Zoledronic Acid	Hazard Ratio (95% CI)	P Value
Fracture — no. (cumulative %)				
Any	139 (13.9)	92 (8.6)	0.65 (0.50–0.84)	0.001
Nonvertebral	107 (10.7)	79 (7.6)	0.73 (0.55–0.98)	0.03
Hip	33 (3.5)	23 (2.0)	0.70 (0.41–1.19)	0.18
Vertebral	39 (3.8)	21 (1.7)	0.54 (0.32–0.92)	0.02
Death — no. (%)	141 (13.3)	101 (9.6)	0.72 (0.56–0.93)	0.01

* Rates of clinical fracture were calculated by Kaplan–Meier methods at 24 months and therefore are not simple percentages. There were 1062 patients in the placebo group, and 1065 in the zoledronic acid group. Because of variable follow-up, the number and percentage of patients who died are provided on the basis of 1057 patients in the placebo group and 1054 patients in the zoledronic acid group in the safety population.

Lyles K et al. *N Engl J Med* 2007;357:1799-809

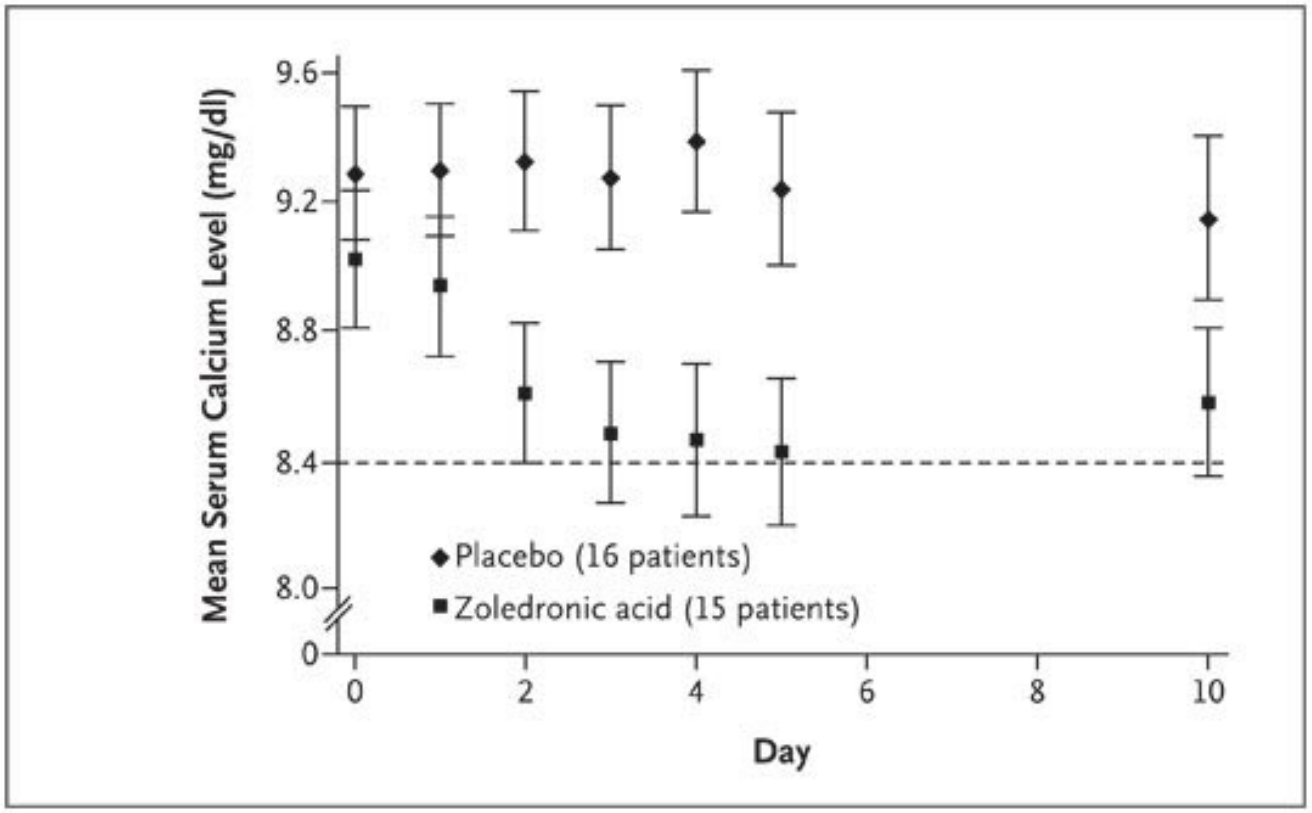
Editorial Comments in NEJM*

- …it is noteworthy that no other controlled clinical trial has previously shown efficacy of any osteoporosis medication for reducing the recurrence of fracture in patients who already had broken a hip …
- The results of the study by Lyles et al. appear both powerful and compelling. The reduction in fracture incidence and death was striking and clearly establishes the need for pharmacologic intervention in patients who fracture a hip.

*Calis et al *NEJM* 357:1861-2, 2007

Potential complication from use of iv BP's in women with osteoporosis….

Serial Changes in Mean Serum Calcium Levels in Patients Treated with Zoledronic Acid or Placebo



de Nijs R et al.
N Engl J Med
2007;357:711-715

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The Problem of Calcium and Vitamin D in Bisphosphonate Therapy

- Subclinical Vitamin D deficiency in post-menopausal women is very common – especially in the northern US and Canada
- Vitamin D supplementation in this age group is underutilized
- Measurement of Vitamin D levels (as 25-OH D3) is usually not done but probably should be
- Additional surrogate marker is PTH level
- If Vitamin D deficiency present, administration of BP's can lead to severe hypocalcemia and tetany

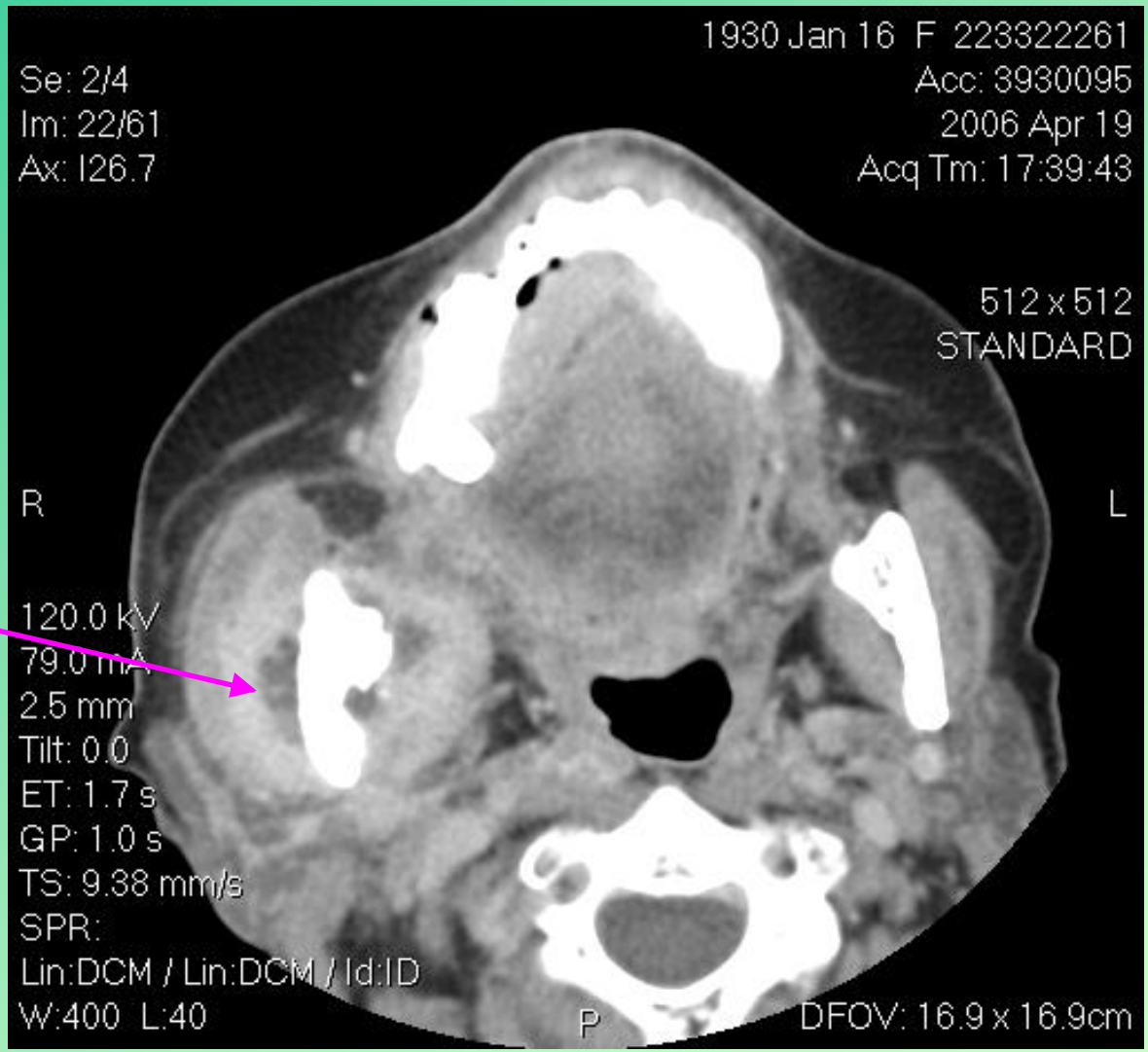
What to do about supplementation with Calcium and Vitamin D

- Prior to staring bisphosphonate load patient with Vitamin D
  - 50,000 U/week for a month typical schedule
- Continue with Vitamin D 1000 U/day after BP started (more than in typical combination pill)
- Measure 25-OH D and PTH levels before starting and periodically thereafter

What about Osteonecrosis of the Jaw?

- Great deal of fuss made about this complication in the press
- Subject of some litigation
- How frequent is it?
- Who will get it?
- How is it treated?

CT of facial bones – soft tissue window



Soft tissue swelling

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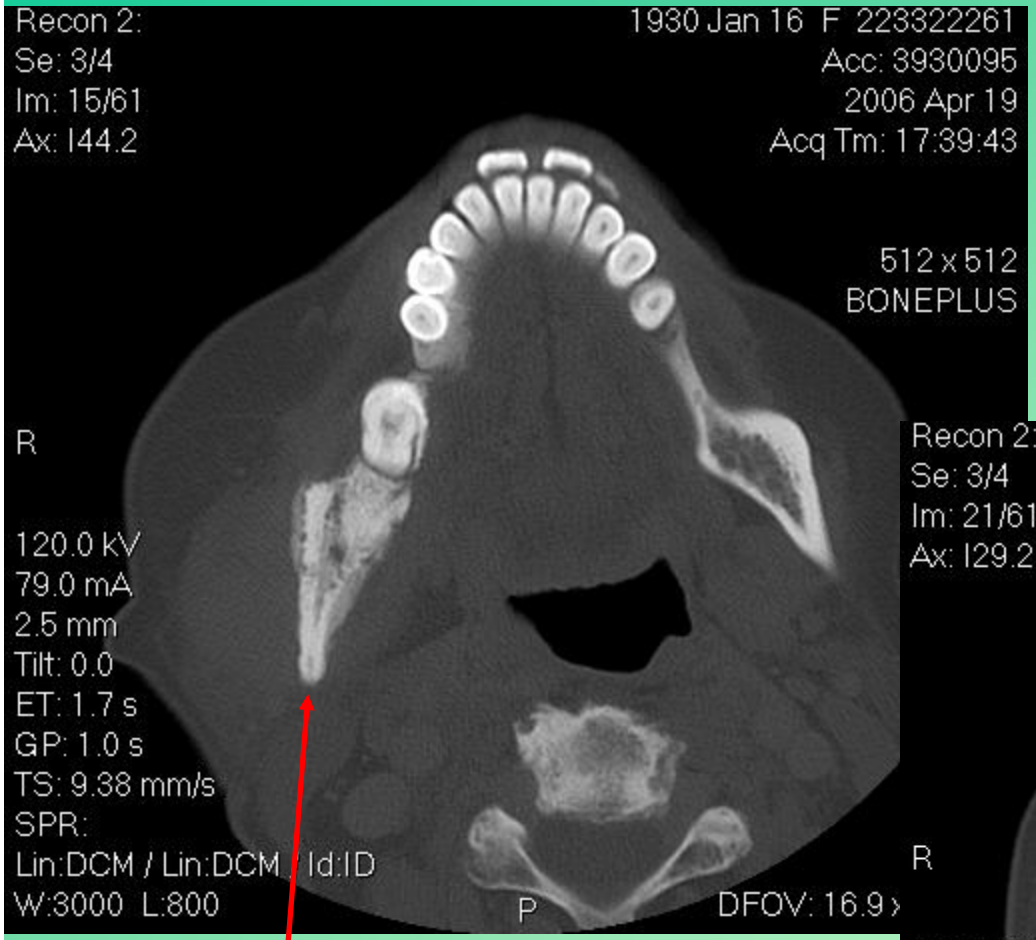
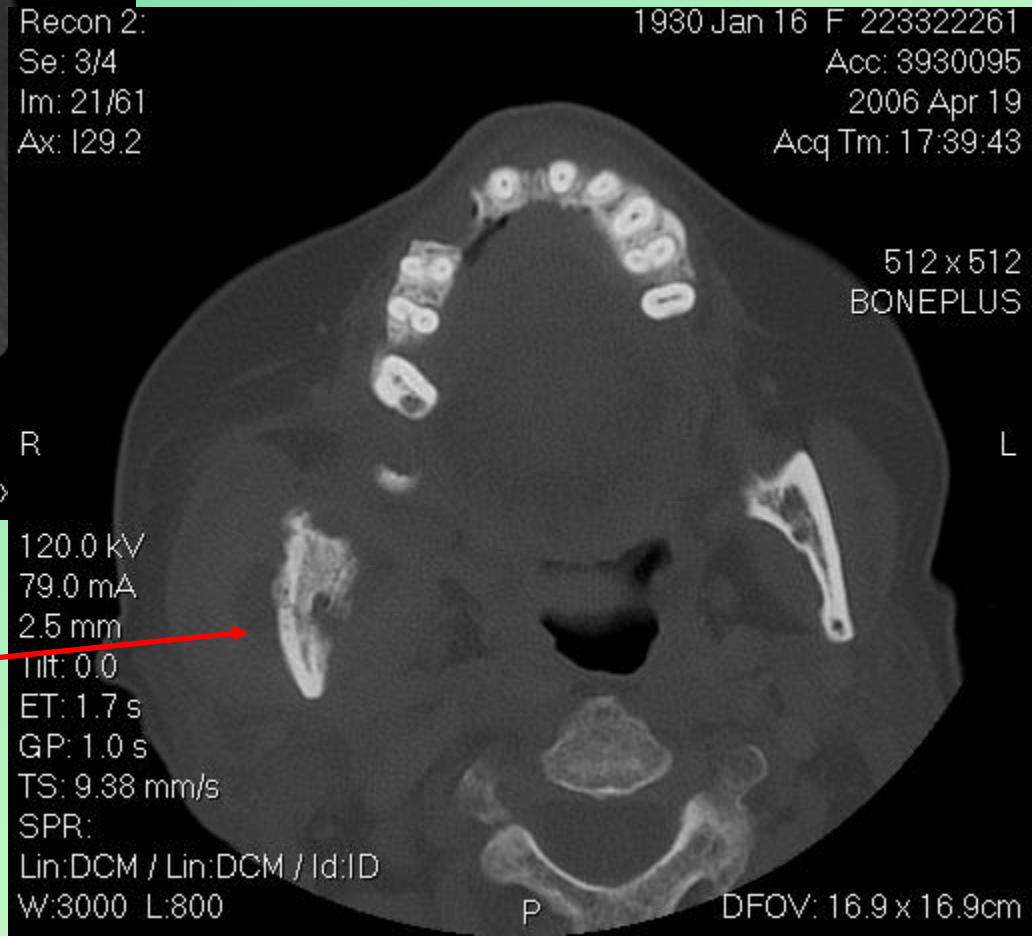
Bone windows at two different levels

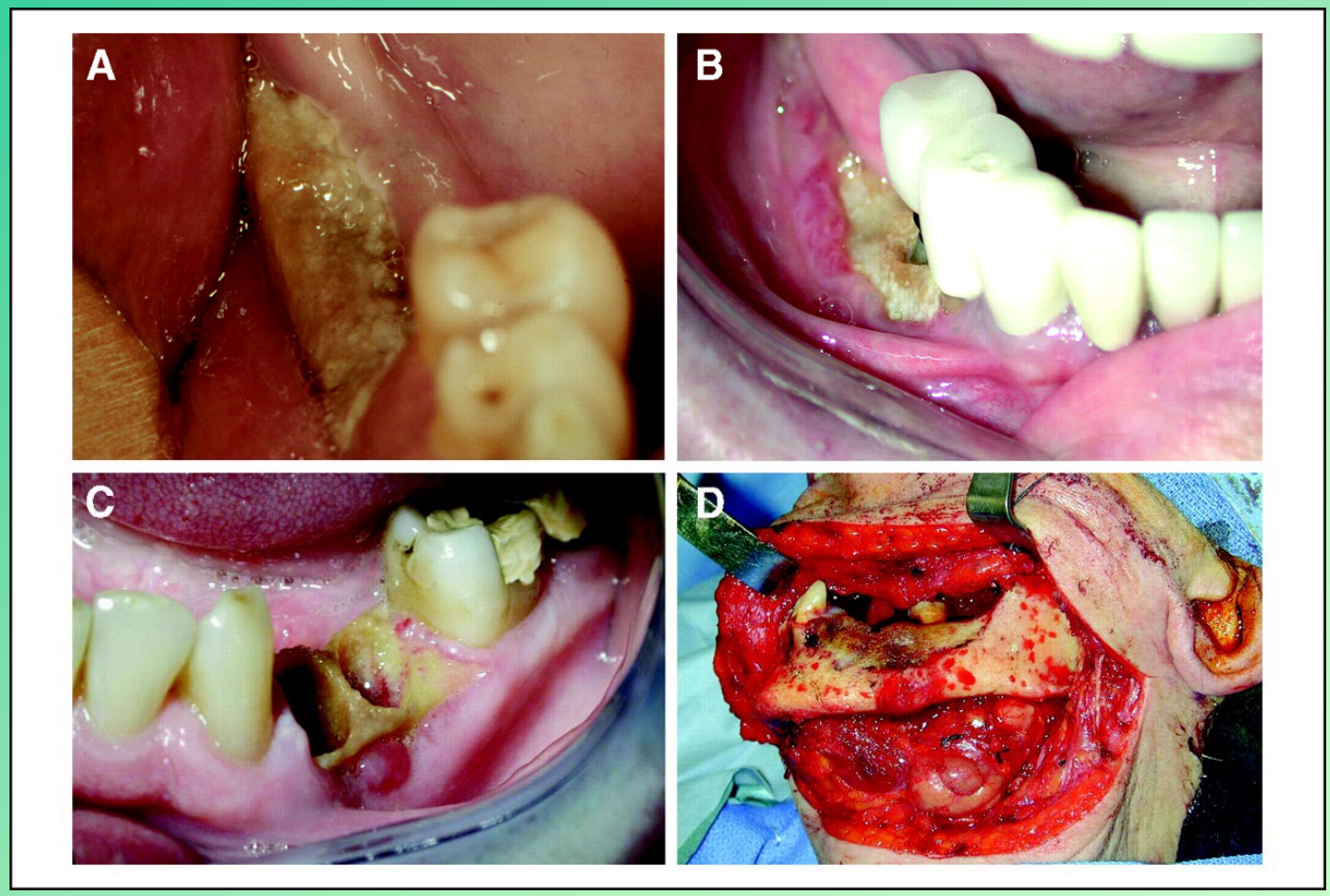




Abnormal bone

Osteonecrosis of the Jaw

Clinical presentation of osteonecrosis of the jaw



Badros, A. et al. *J Clin Oncol*; 24:945-952 2006

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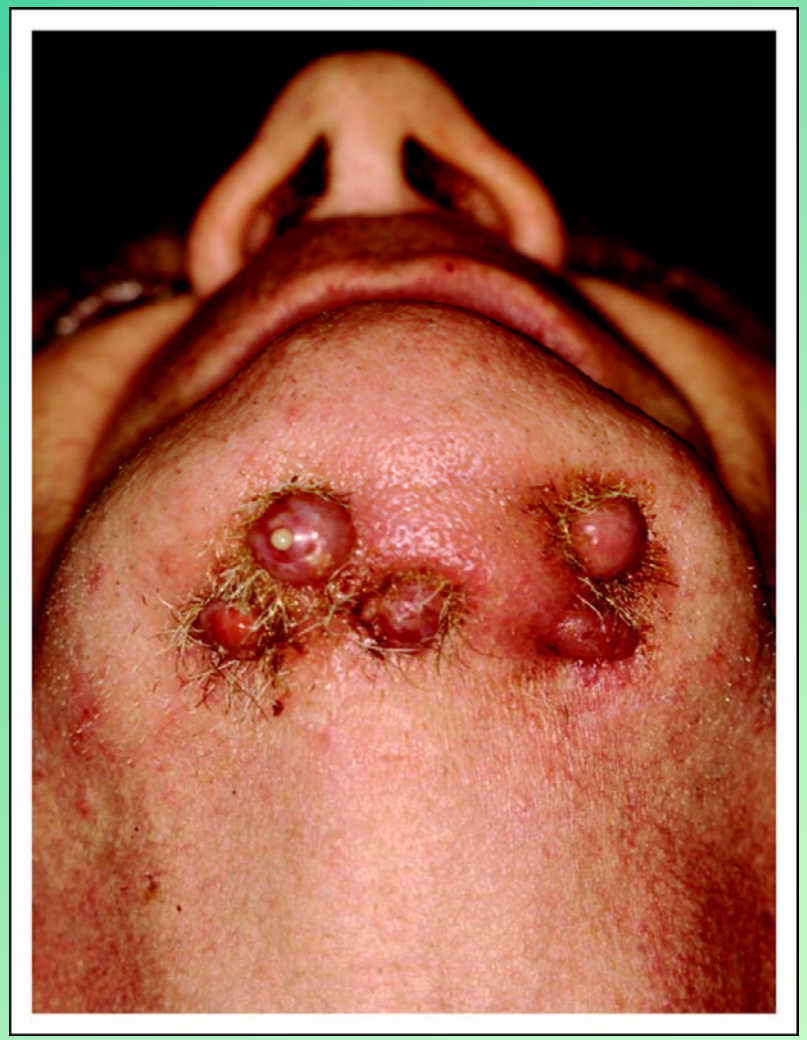
Fistulous tracts from Osteonecrosis of Mandible



Mignogna, M. D. et al. *J Clin Oncol*; 24:1475-1477 2006

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ONJ: Risk Factors*

- Prior head-and-neck radiotherapy
- Chemotherapy
- Corticosteroids
- Periodontal disease or infection
- Recent dental surgery
- Trauma from ill-fitting dentures
- Smoking
- Alcoholism
- Duration of bisphosphonate therapy
- Incidence among high-risk patients quoted as between 0.4 and 8.2%
- Likelihood in patients with no risk factors currently thought to be *extremely low*

***Ruggiero et al *J Oncol Practice* Jan 2006 pp. 7-14**

ONJ: Clinical Presentation

- Long (?) silent period
- Often discovered by accident during dental examination wherein exposed bone is discovered
- Symptoms include:
  - Primarily pain
  - Soft-tissue swelling
  - Loosening of previously stable teeth
  - Fistulous tract formation

ONJ: Diagnosis

- X-ray to rule out osteomyelitis or metastasis
- Cultures to rule out Actinomycosis
- What is left is a clinical/radiological diagnosis

ONJ: Treatment

- No “best available” therapy defines at the present
- Large surgical debridement has not yielded good outcomes
- Antibiotics topically or systemically have been tried with uneven results
- Removable appliance or protective stent can be used to protect exposed bone from further trauma or infection
- If patient already has dentures be sure they fit well, are taken out at night and are thoroughly and regularly cleaned
- ??Hyperbaric oxygen: being studied; preliminary results uneven

Summary of Various Pharmacologic Approaches to Osteoporosis

- Bisphosphonates have best track record for decreasing fracture rate and preserving BMD; most robust studies
  - Zolendronic Acid (Reclast®) has best data, is best tolerated
- PTH short term is potent but at the moment cannot be used for > 2 years, greatly limiting its value
- Calcitonin is a weak agent compared with BP's
- Raloxifine works to preserve BMD but is also less active than BP's
- Calcium and Vitamin D supplementation should be given with BP therapy; VitD and PTH levels should be measured periodically
- Combinations of drug classes being tested for superiority over one drug at a time; results not in

Future of Therapy

- Zoledronic Acid (known as Reclast® for the treatment of osteoporosis in non-cancer patients) has just been FDA approved
- Should turn out to be the most efficacious with best toxic therapeutic ratio of existing agents
- Available at few locations at present (including StarkOncology)

For a copy of this talk…

- Visit us on the web (www.StarkOncology.com) or at the office…