Osteoporosis in Youth, Aging and Illness

Riverside Regional Medical Center

Medical Grand Rounds: April 29, 2009

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Why is an Oncologist interested in the problem of osteoporosis? You'll find out...

Case Presentation

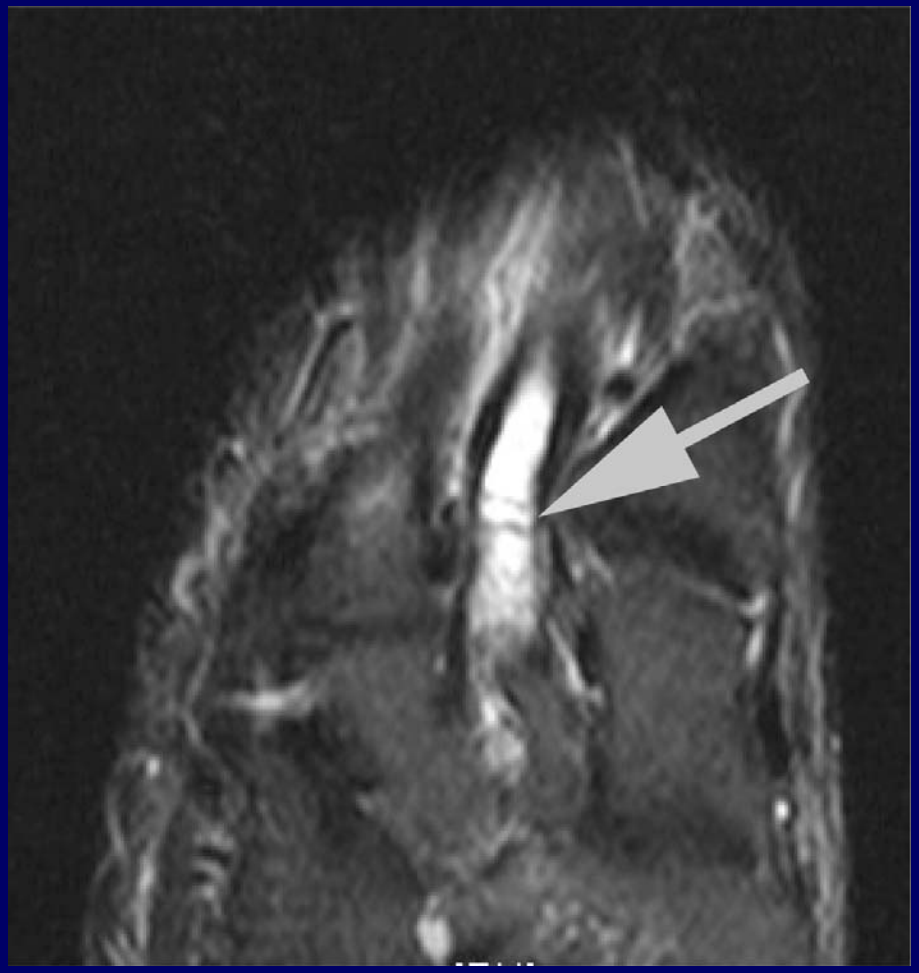
Case Presentation -- DK

- 35 year-old world-class long distance runner
- Bronze medalist in Athens Olympics (2004)
- At peak of physical fitness
- For several weeks prior to Beijing Olympics Marathon had twinges of pain in second metatarsal of right foot
- Three miles into Marathon felt a pop in her right foot, stopped in severe pain and dropped out of the race
- Findings….

X-ray of foot…

(Normal)

MRI of foot



Hair-line transverse fracture

X-ray of foot three weeks later…

Barely visible
hair-line fracture

The Triad of the Female Athlete

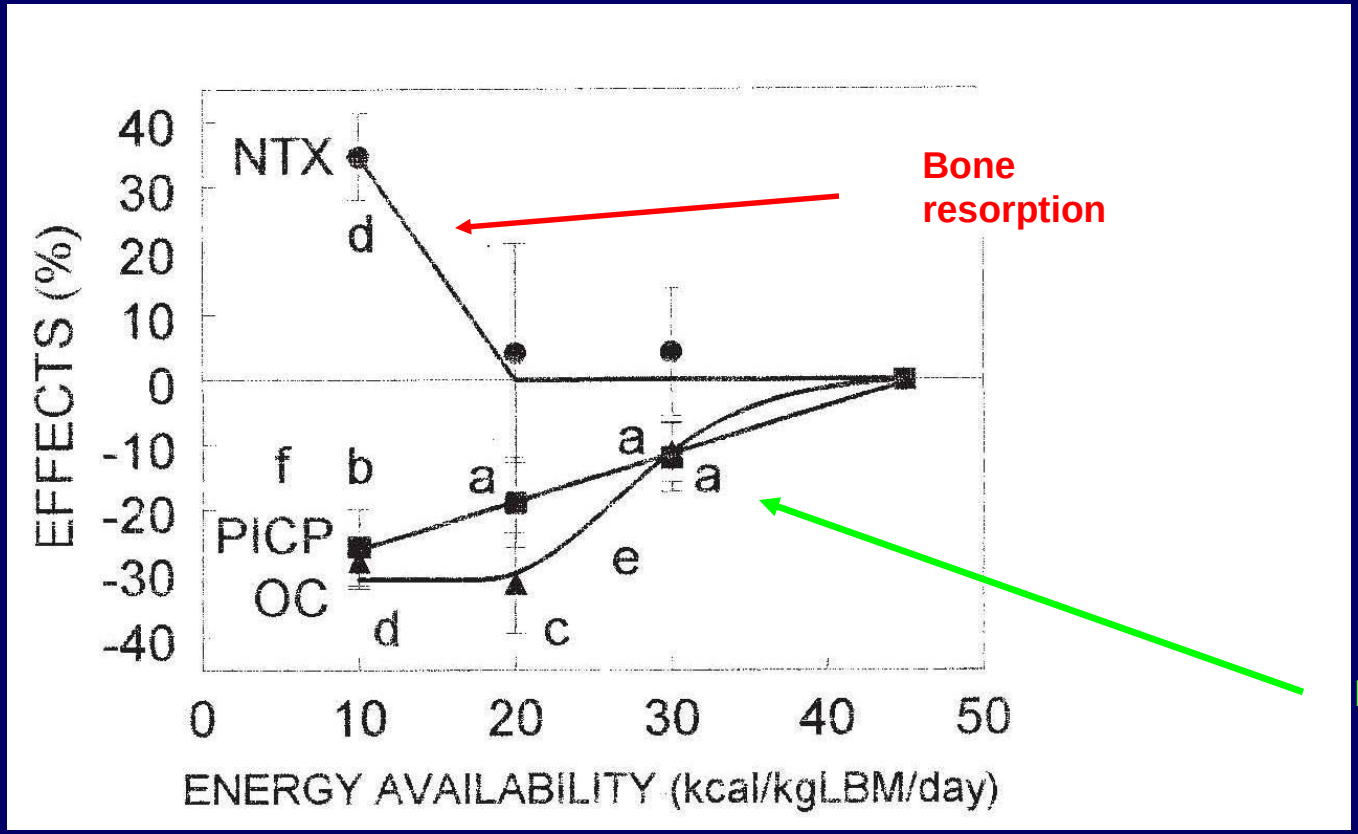
- Eating disorder
- Amenorrhea
- Osteoporosis

- The Osteoporosis is counter-intuitive because of so much weight bearing

- Amenorrhea is a function of low circulating estrogenic compounds, poor caloric intake and low body fat (storage site for estrogens)

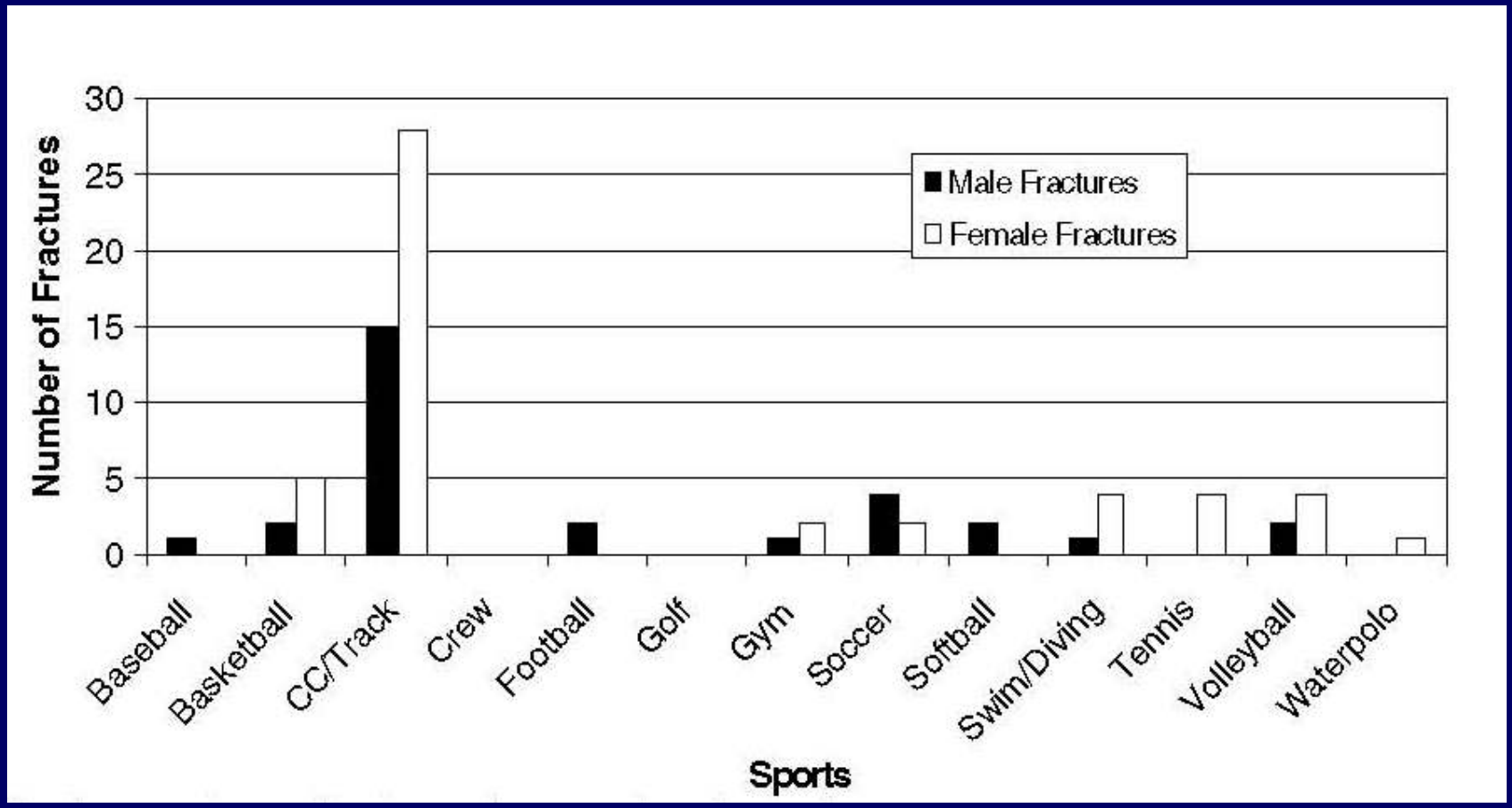
- What happens to their bones when young female athletes do not eat enough?

Effect of Controlled Caloric Intake on Markers of Bone Turnover in Female Military Recruits



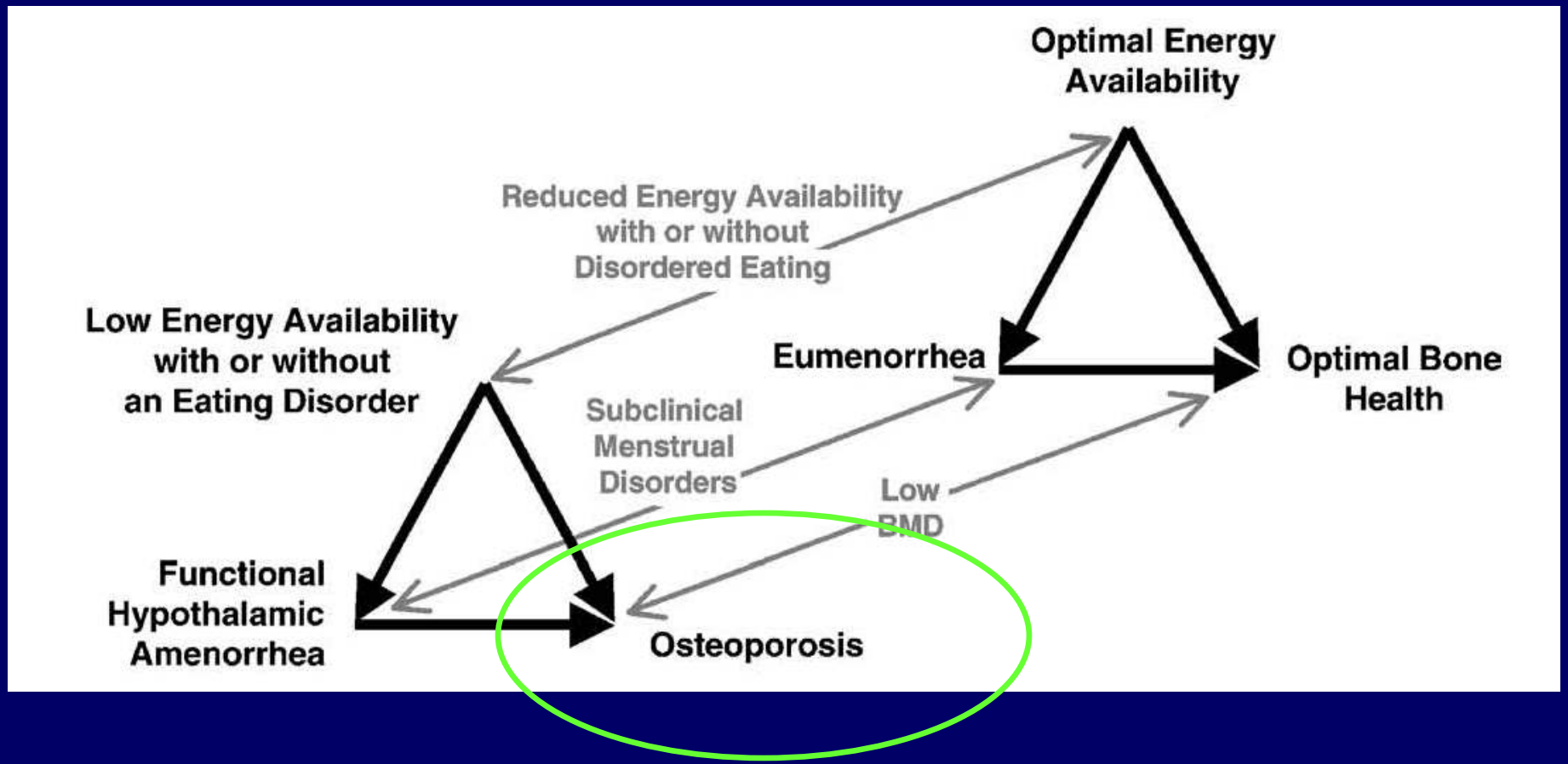
Ihle and Louks *Journal of Bone and Mineral Research* 19:1231-40, 2004

Stress Fractures 1986-2000 in NCAA Division I Athletes



Hame et al *Am J Sports Med* 32:446-52, 2004

The Female Athletic Triad – in and out of balance



Nattiv *Medicine & Science in Sports and Exercise* Special Communication, pp 1867-82, 2007

Treatment of Osteoporosis in the Young Female Athlete

- Recognizing entity by performing DEXA scan after first stress fracture especially if amenorrhea present
- Calcium and Vitamin D supplementation; lack of body fat makes storage of D problematic
- Consideration of birth-control pills to supplement deficit in natural circulating estrogens
- Usual pharmacologic interventions (bisphosphonates, teriparatide, calcitonin) have not been studied in young women; safety and efficacy not assured

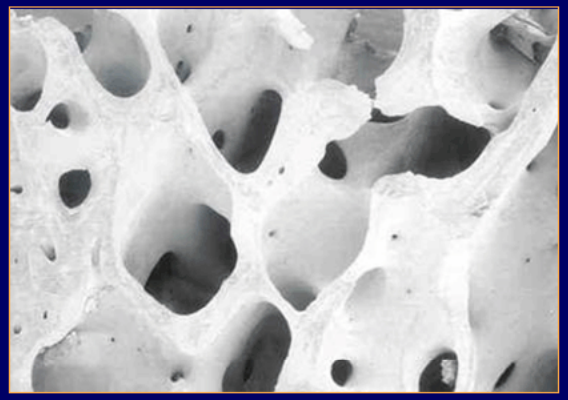
Osteoporosis in Young Female Athletes: Summary

- Stress fractures in long-distance women runners very common
- Prodrome of foot pain for several days prior to actual fracture common
- Bone mineral density likely depressed because of hormonal changes associates with athletic training and altered caloric intake; and absence of body fat to store Vitamin D
- Little scholarly work done on how to define bone disease in young women and how aggressive intervention could prevent stress fractures
- On her website, DK promises to drink milk and eat yogurt – likely a totally inadequate band aid

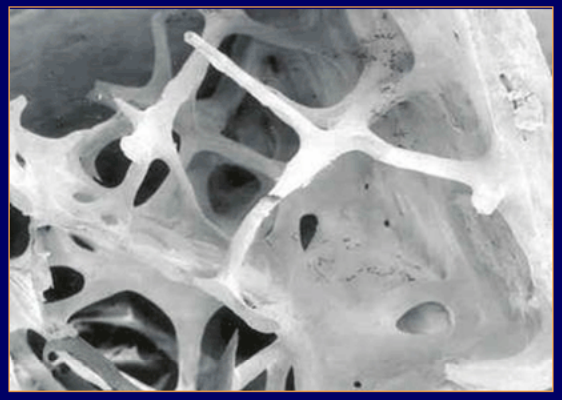
Back to Basics for a Moment…

Osteoporosis: Definition

Normal Bone



Osteoporotic Bone



NIH Definition:

"Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture"

1. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. *JAMA*. 2001;285:785-795.

Epidemiology of Osteoporosis in the US

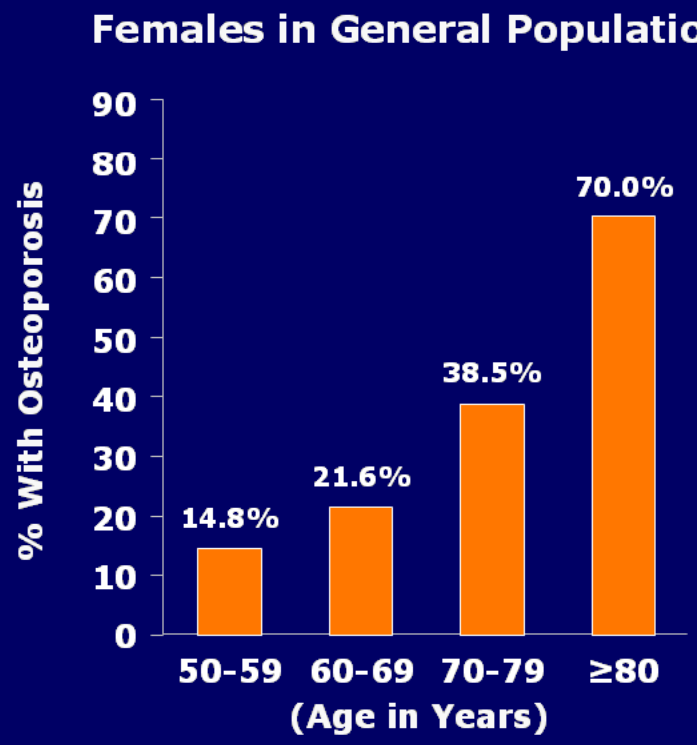
- 44 million Americans, 80% of whom are women
  - 10 million have established osteoporosis
  - 34 million have osteopenia or low bone mass
  - 1.5 million fractures occur per year in US

In spite of case presentation, the vast majority of women with osteoporosis are post-menopausal

National Osteoporosis Foundation (NOF). Available at: http://www.nof.org/osteoporosis/diseasefacts.htm. Accessed February 7, 2007.

Osteoporosis is Common Among US Women

- 10 million Americans have established osteoporosis, 80% of whom are women[1]
- 1.5 million fractures occur per year in US



1. National Osteoporosis Foundation (NOF). Available at: http://www.nof.org/osteoporosis/diseasefacts.htm. Accessed August 13, 2007. 2. Melton LJ III. *J Bone Miner Res.* 1995;10:175-177.

Risk Factors for Osteoporotic Fractures

Genetic/Nonmodifiable

- Age
- Female sex
- Asian or white ethnicity
- Previous fragility fracture
- Family history of hip fracture or osteoporosis
- Small frame

Potentially Modifiable

- Menopause-related estrogen deficiency
- Low body weight
- Calcium/vitamin D deficiency
- Inadequate physical activity
- Excessive alcohol intake
- Cigarette smoking
- Long-term glucocorticoids

National Osteoporosis Foundation (NOF). Available at: http://www.nof.org/osteoporosis/diseasefacts.htm. Accessed February 7, 2007.

Hip and Other Non-Vertebral Fractures Have Significant Consequences

- Hip fracture associated with
  - Loss of ambulatory status in 30% of patients
  - Increased morbidity and mortality
  - Increased fracture risk
  - Major reason for admission to chronic care facilities
- Non-vertebral fractures
  - Pain
  - Increased risk of future fractures

National Osteoporosis Foundation. Available at: http://www.nof.org/osteoporosis/diseasefacts.htm. Accessed August 13, 2007.

Rates of Fracture and Death in the Study Groups

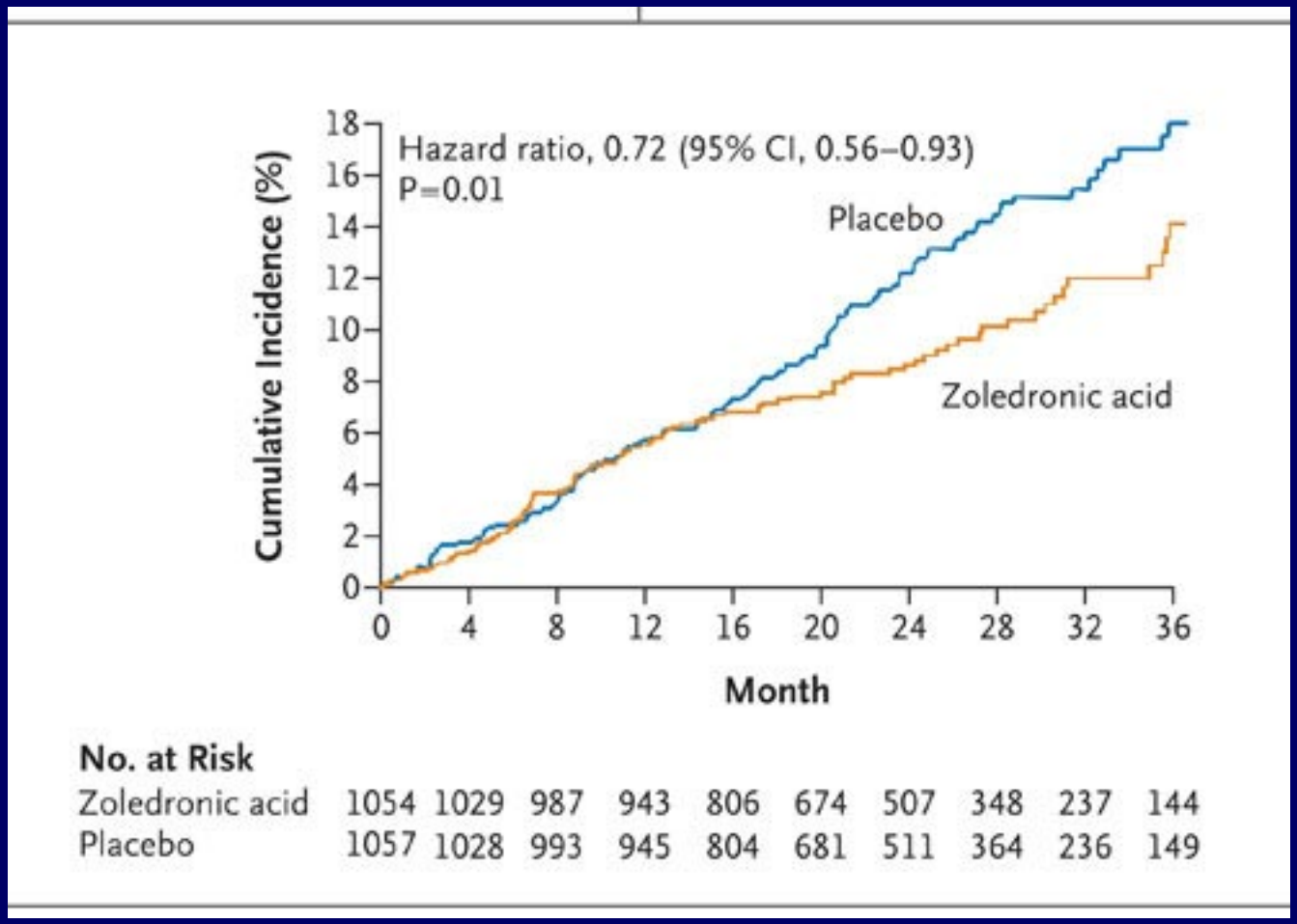
Table 2. Rates of Fracture and Death in the Study Groups.*

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

Risk of death over time with hip fracture: with and without subsequent treatment

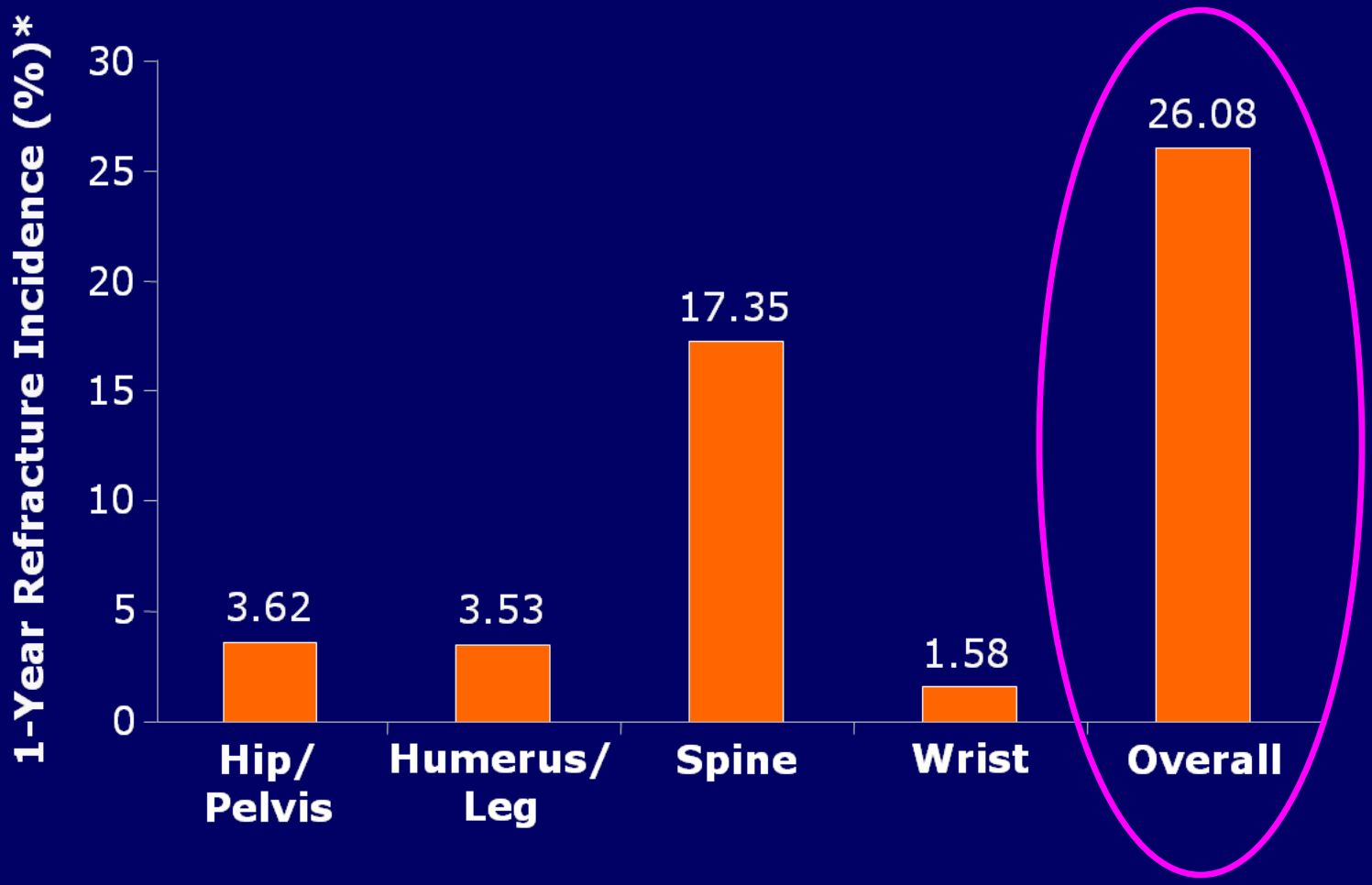


No. at Risk

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

1-Year Risk of Refracture in Patients With Incident Vertebral Fracture



*Based on Kaplan-Meier analyses.

Data from Lindsay R, et al. *Osteoporos Int.* 2005;16:78-85.

WHO Bone Density Criteria for Diagnosing Osteoporosis

Diagnosis	BMD T-Score: Number of SD Below Mean in Healthy Young Women*
Normal	−1 or above
Low bone mass [osteopenia]	Between −1 and −2.5
Osteoporosis	−2.5 or less
Severe osteoporosis	−2.5 or less with fragility fractures

- Reduction by 1 SD equals a 10% to 12% decrease in BMD
  - 1 SD change increases fracture risk by 1.5- to 2.0-fold

Adapted from WHO Technical Report Series 921. Geneva: World Health Organization; 2003.

National Osteoporosis Foundation Guidelines

- Recommend BMD testing for
  - All women 65 years of age and older
  - Younger postmenopausal women with one or more risk factors (other than being white, postmenopausal, and female)
  - Postmenopausal women who present with fractures (to confirm the diagnosis and determine disease severity)

No testing for premenopausal women recommended at present, even for serious athletes

National Osteoporosis Foundation. Available at: http://www.nof.org/osteoporosis/bonemass.htm. Accessed February 7, 2007.

Once osteoporosis is found…

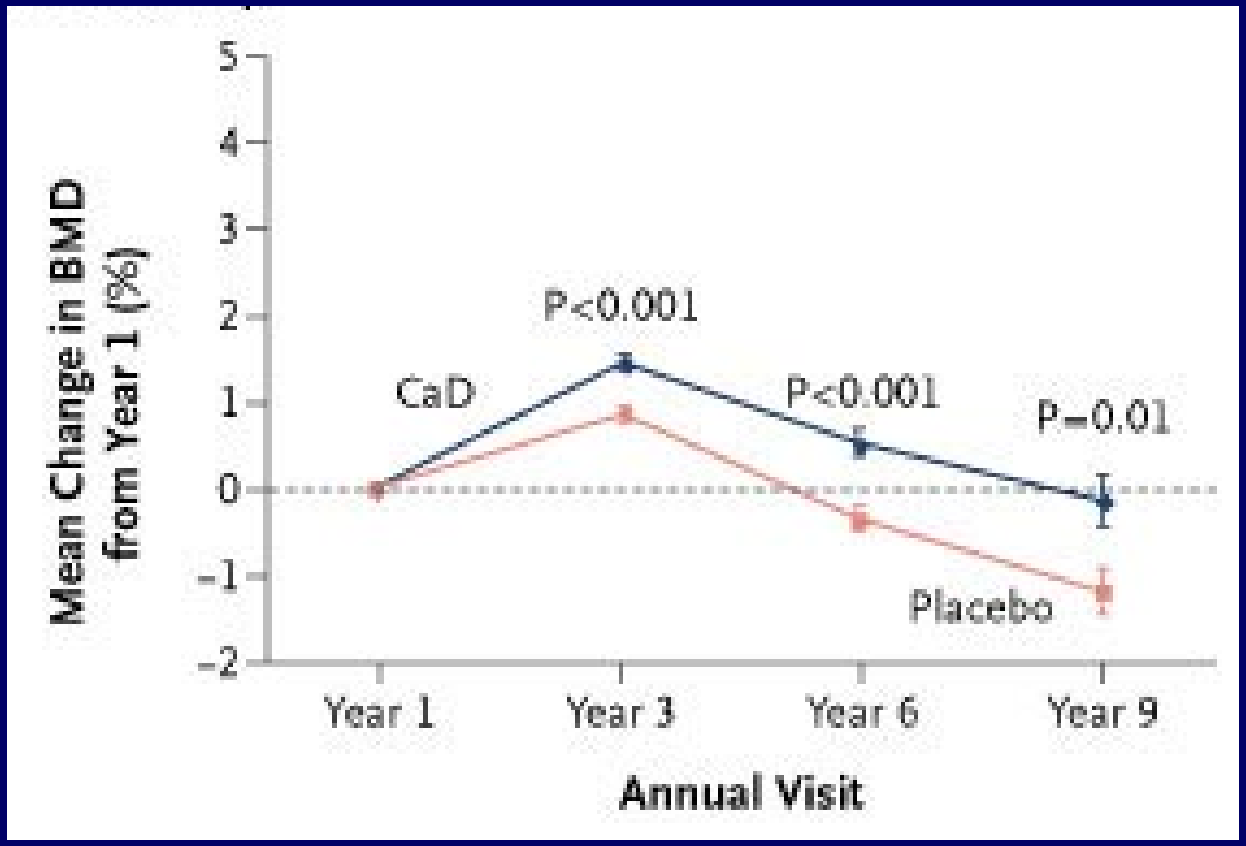
Nonpharmacologic Interventions

- Goal of nonpharmacologic interventions is to prevent future fractures through lifestyle change
  - Diet and dietary supplements
    - Calcium
    - Vitamin D
  - Exercise
  - Fall prevention
  - Smoking Cessation

Data to support these recommendations…

Bone Health and Osteoporosis: A Report of the Surgeon General. Rockville, Md: US Department of Health and Human Services; 2004:111-156.

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



Benefit modest and transient

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

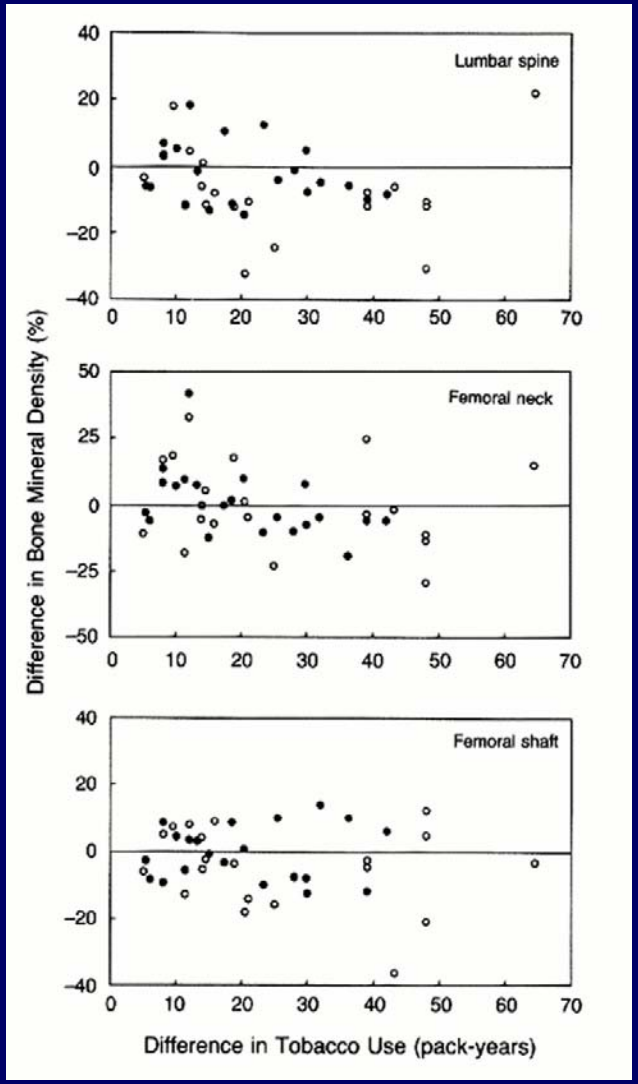
Effect of Exercise on Development of Hip Fracture – From the Nurses' Health Study (n=61,200)

	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

Exercise relatively modest compared to serious athletes; body fat content average as well

Feskanich et al *JAMA* 288: 2300, 2002

Impact of Smoking on Development of Osteoporosis:
Study of 41 pairs of female twins, only one of whom smokes



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

Decision to Treat Is Affected by Several Factors

- Current AACE position on treatment intervention
  - Women with postmenopausal osteoporosis
    - Women with low-trauma fractures and low BMD
    - Women with BMD T-scores of −2.5 and below
  - If risk factors are present, women with borderline-low BMD (T-scores of −1.5 and below)
  - Women in whom nonpharmacologic preventive measures are ineffective (bone loss continues or low trauma fractures occur)
- Individual clinician judgment is important
- Forthcoming guidelines are likely to be based on absolute fracture risk probability over 10 years rather than on BMD alone

AACE = American Academy of Clinical Endocrinologists

AACE Osteoporosis Task Force. *Endocr Pract.* 2003;9:544-564.

Classes of Pharmacologic Agents Currently Approved for the Treatment of Osteoporosis

- **Antiresorptive agents**
  - Bisphosphonates
    - Weekly oral alendronate
    - Weekly or monthly risedronate
    - Monthly oral or quarterly IV ibandronate
  - Calcitonin
  - Selective estrogen receptor modulators (SERMs)
- **Anabolic agents**
  - Parathyroid hormone
- **Estrogen therapy and hormone therapy**
  - (Indicated for prevention only)

National Osteoporosis Foundation. Medications to prevent & treat osteoporosis. Available at: http://www.nof.org/patientinfo/medications.htm. Accessed February 7, 2007.

Rational Basis for Drug Selection

- Actually very little comparative data on which class of agents works best
- Difficult to do head-to-head testing on given patient because of huge lag time to response
- Best data on bone loss and fracture prevention with bisphophonates as a class

Effects of Bisphosphonates

- ↓ Bone turnover
- ↑ BMD at lumbar spine and hip
- ↓ Risk of vertebral and hip fractures
- Sustained effects with continued treatment
- Best-studied class of agents used in osteoporosis
- Long-term safety record

1. Black DM, et al. *Lancet*. 1996;348:1535-1541. 2. Body J-J, et al. *J Clin Endocrinol Metab*. 2002;87:4528-4535.
3. Chestnut CH III et al. *J Bone Miner Res*. 2004;19:1241-1249. 4. Harris ST, et al. *JAMA*. 1999;282:1344-1352.

Real-World Obstacles in the Management of Osteoporosis

- Insufficient rates of diagnosis
- Low awareness among physicians and patients of the imperative to treat
- Global challenge of adherence to therapy in chronic diseases, compromising effectiveness
- Poor adherence is two-fold problem
  - Low persistence: patient stops taking medication
  - Poor compliance: patient does not follow dosing instructions

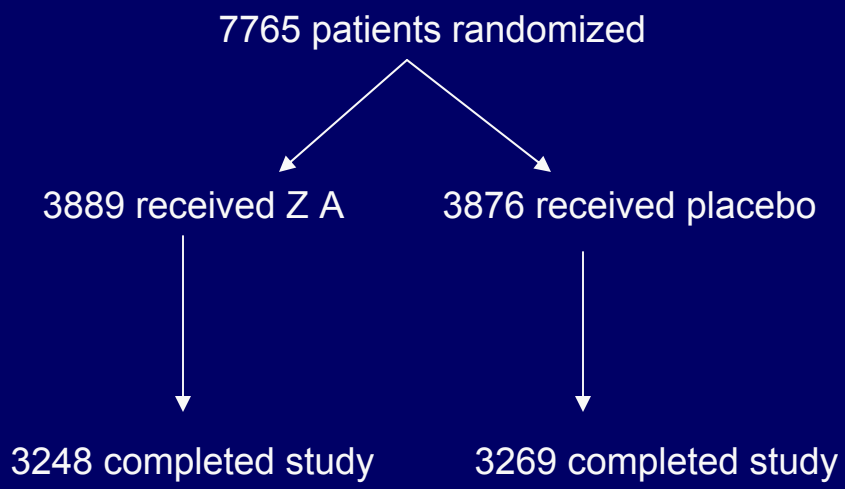
Siris, et al. *Mayo Clin Proc.* 2006;81:1013-1022

Rationale for Less-Frequent and Easier-to-Follow Dosing Regimens

- For many clinicians, bisphosphonates are the standard of care in osteoporosis because of their rapid efficacy and long-term safety
- Poor adherence to daily, weekly, and monthly regimens of oral bisphosphonates results in compromised effectiveness
- A once-yearly IV bisphosphonate therapy can deliver real-world effectiveness by assuring adherence for the entire dosing interval

…Does this approach work?

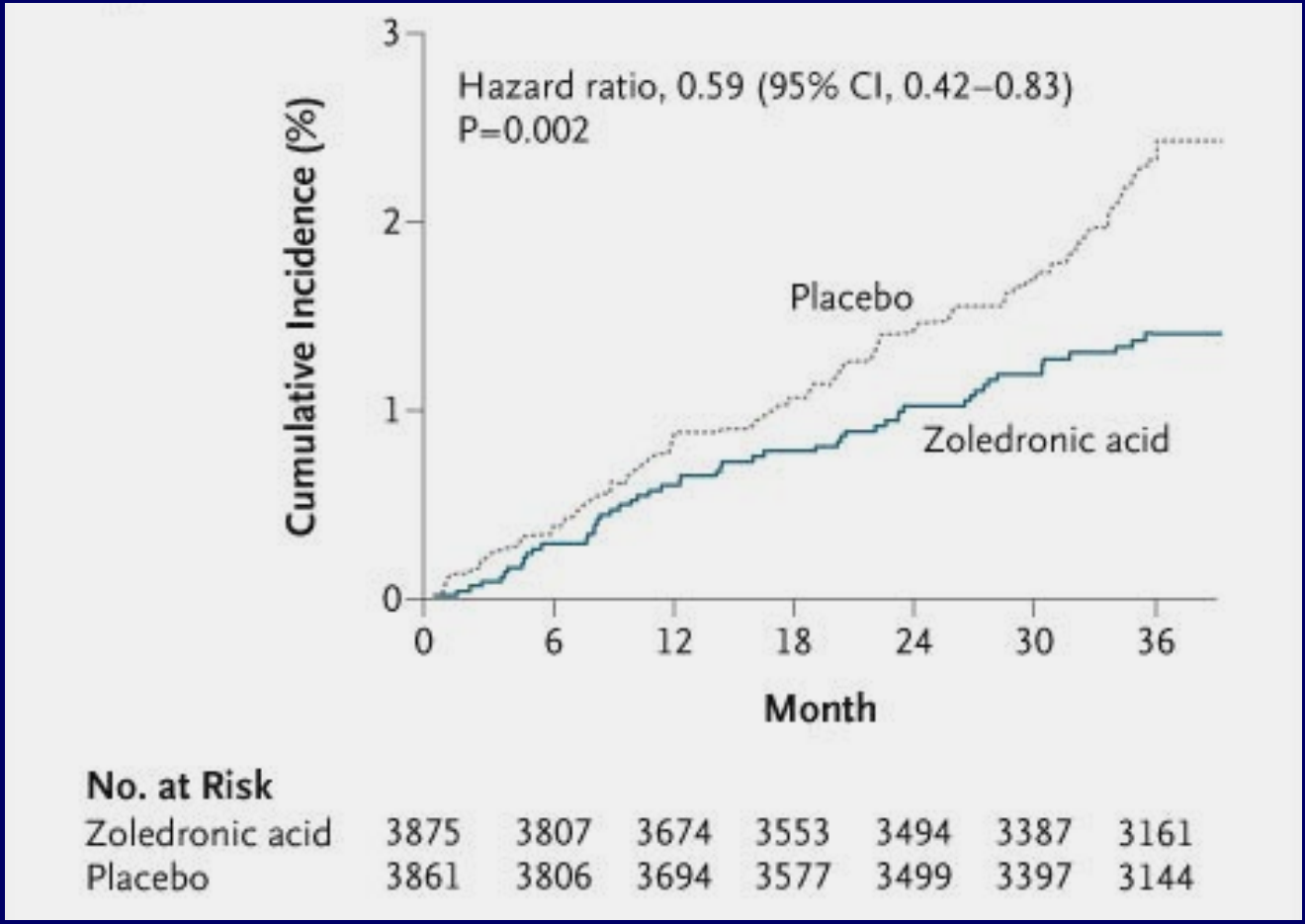
First of Two Large Studies Putting Principle of Infrequent Zolendronic Acid to the Test: Zolendronic Acid in Healthy Post-Menopausal Women



The final groups were then analyzed…

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

Incidence of Hip Fractures during the 3-Year Study Period

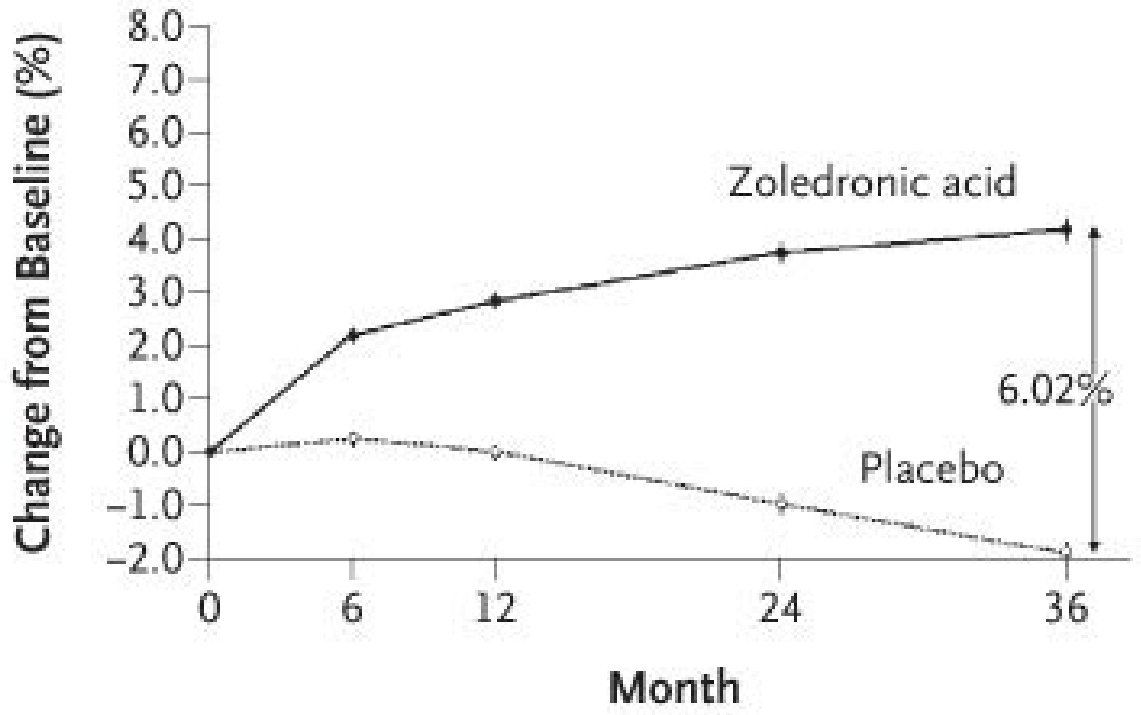


No. at Risk

Zoledronic acid	3875	3807	3674	3553	3494	3387	3161
Placebo	3861	3806	3694	3577	3499	3397	3144

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

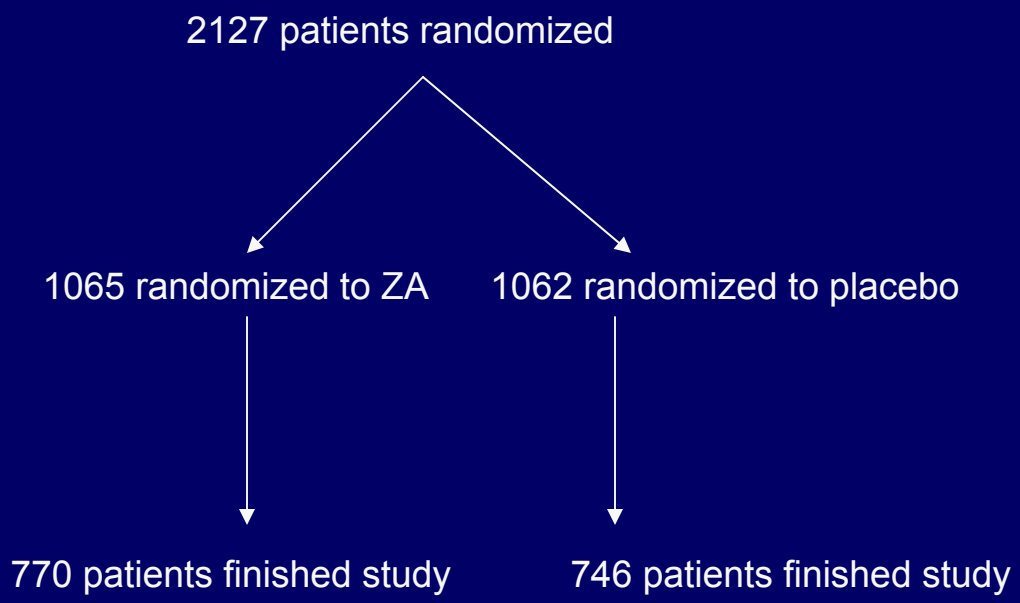
Percent Change over Time in Bone Mineral Density in Hip



No. at Risk					
Zoledronic acid	3844	3515	3516	3228	3061
Placebo	3839	3543	3542	3248	3077

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

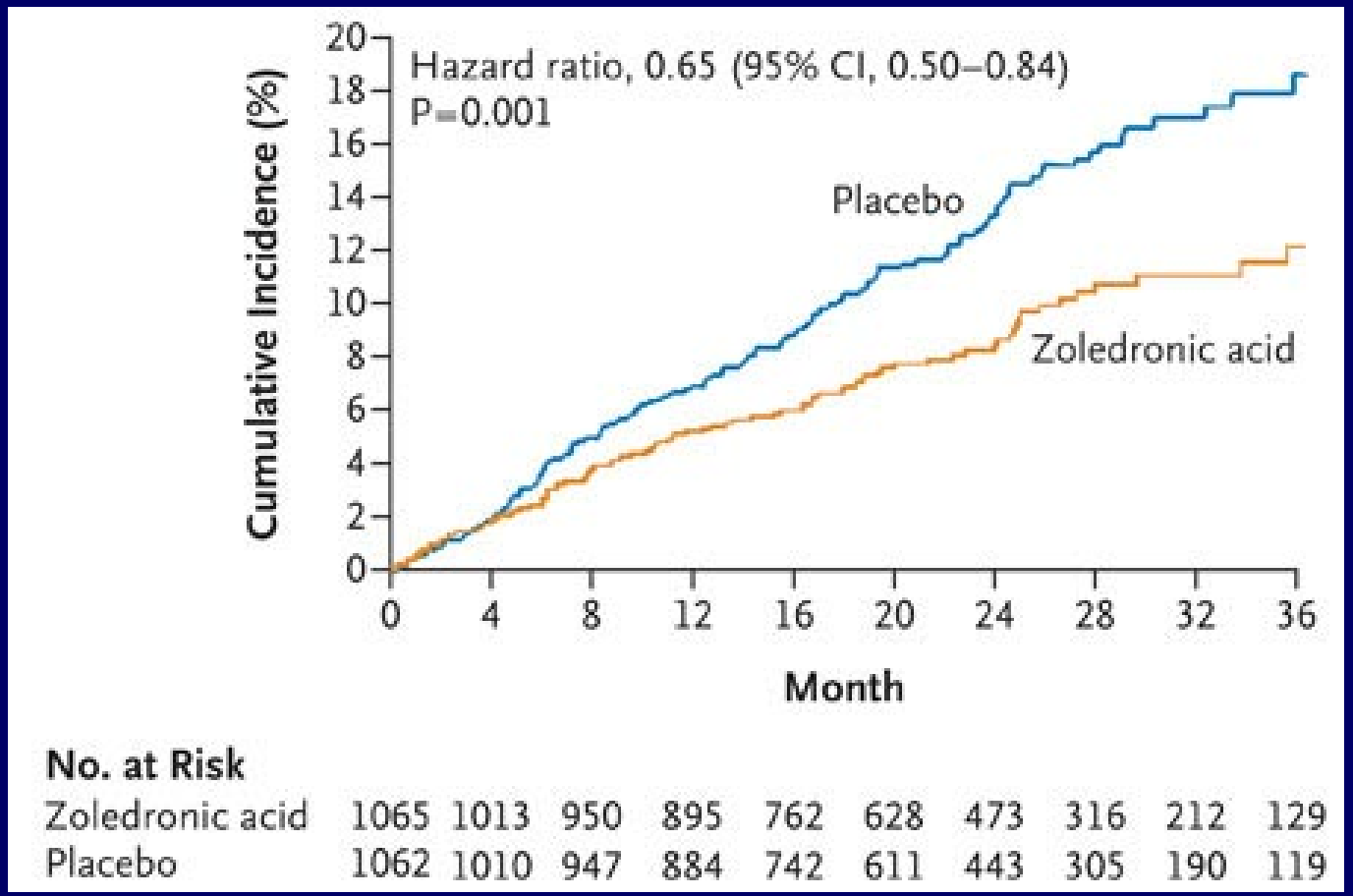
More Recent Study Published on Outcomes Following Hip Fracture



The final groups were then analyzed…

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

Refractures Over Time: ZA versus Placebo

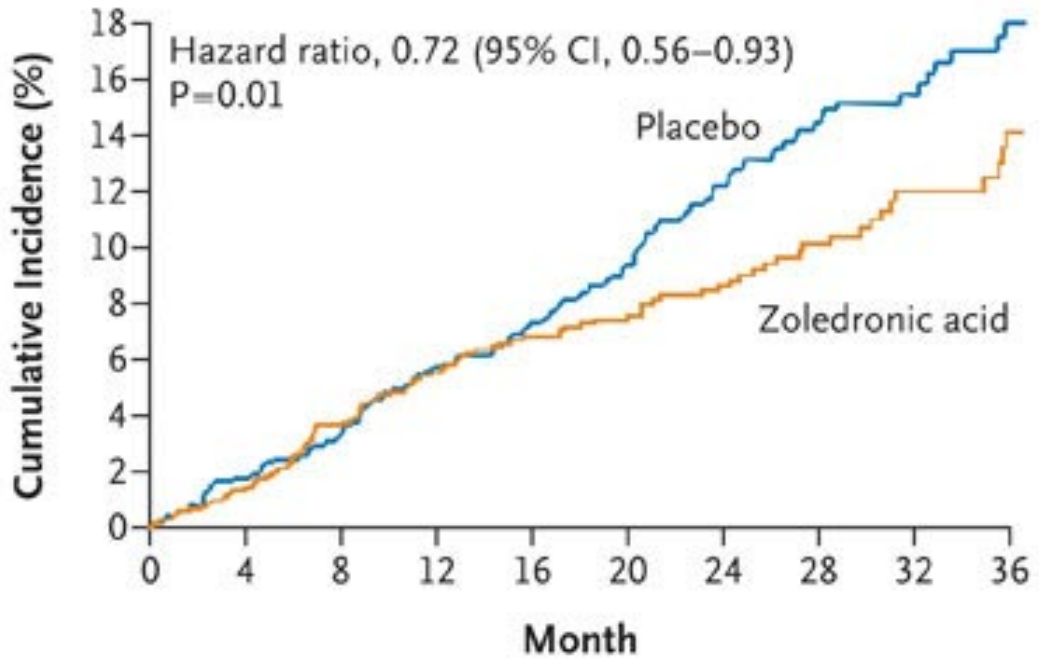


No. at Risk

Zoledronic acid	1065	1013	950	895	762	628	473	316	212	129
Placebo	1062	1010	947	884	742	611	443	305	190	119

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

Risk of death over time with hip fracture: with and without subsequent treatment



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

Intravenous Zoledronic Acid (Reclast®)for Osteoporosis

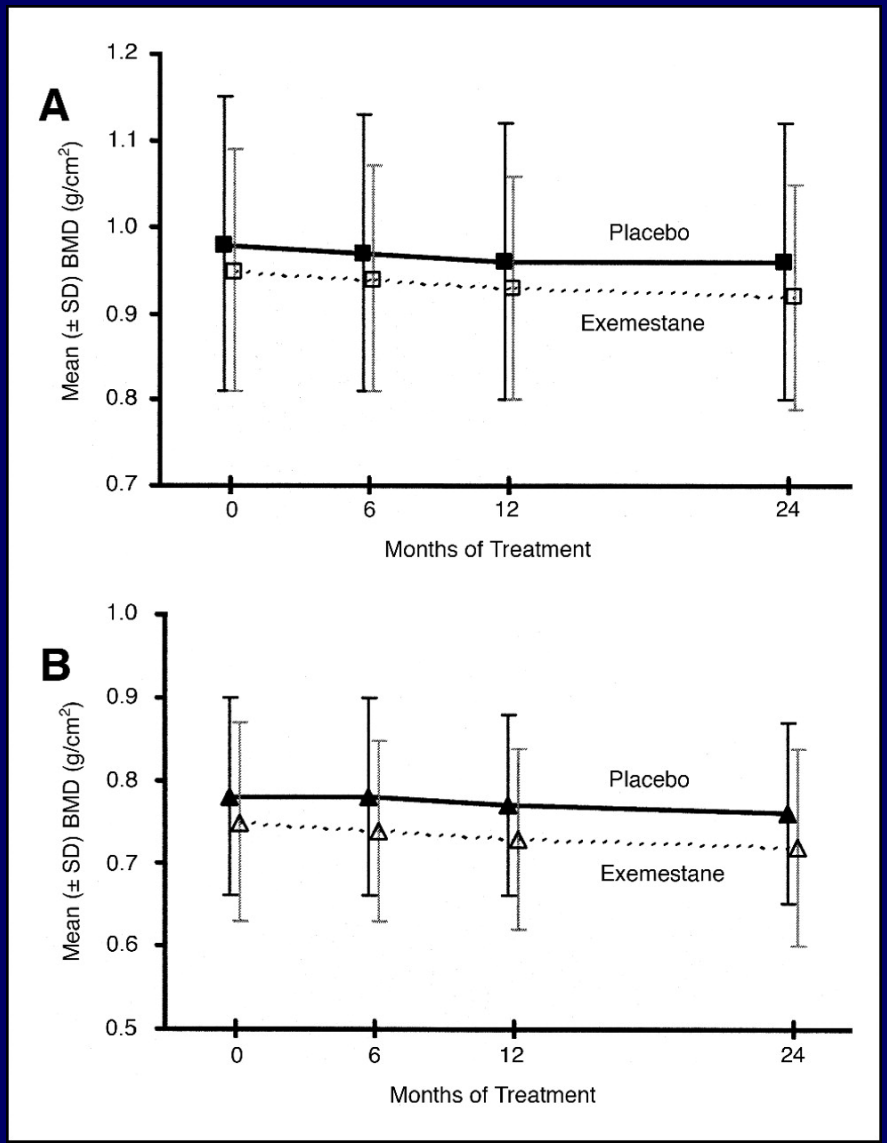
- Most aggressive approach currently available
- Avoids side effects of oral bisphosphonates
- Cost competitive
- Once-a-year dosing very convenient
- Insurance reimbursement in a state of flux but improving

- Available at my office or at Peninsula Cancer Institute
- Requires prescreening for medical issues (dental health, adequacy of kidney function and vitamin D stores) by physician

The Problem of Bone Mineral Loss in Cancer Patients

- Widespread use of hormonal manipulation in treatment of cancer greatly exacerbates problem
  - Aromatase inhibitors (Anastrozole, Letrozole, Exemestane) in the treatment of breast cancer
  - Weak LHRH agonists (Leuprolide) or orchiectomy in the treatment of prostate cancer

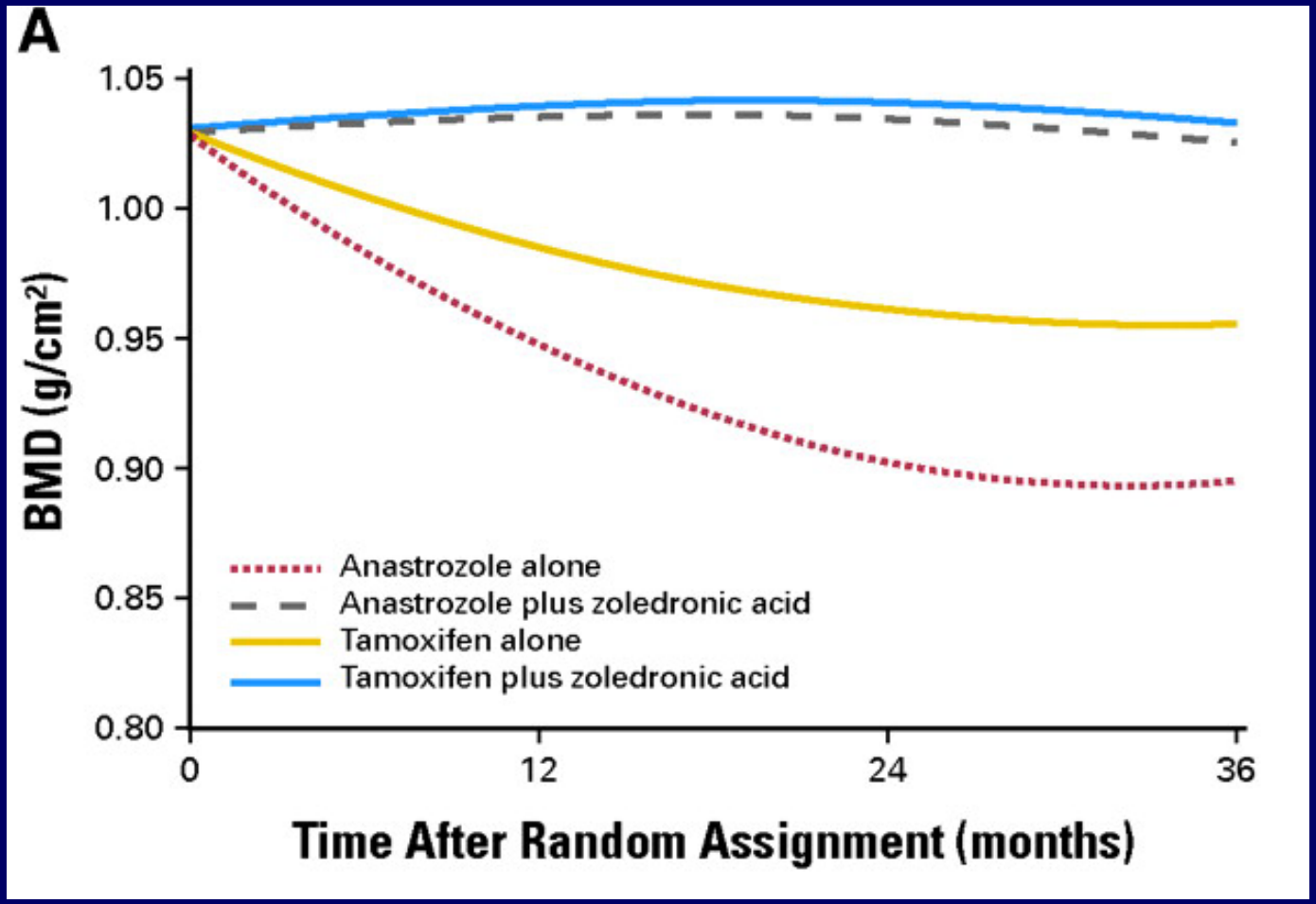
Effect of 2-year treatment with placebo or exemestane on bone mineral density (BMD) of the lumbar spine (A) and femoral neck (B)



The Problem with Aromatase Inhibitors

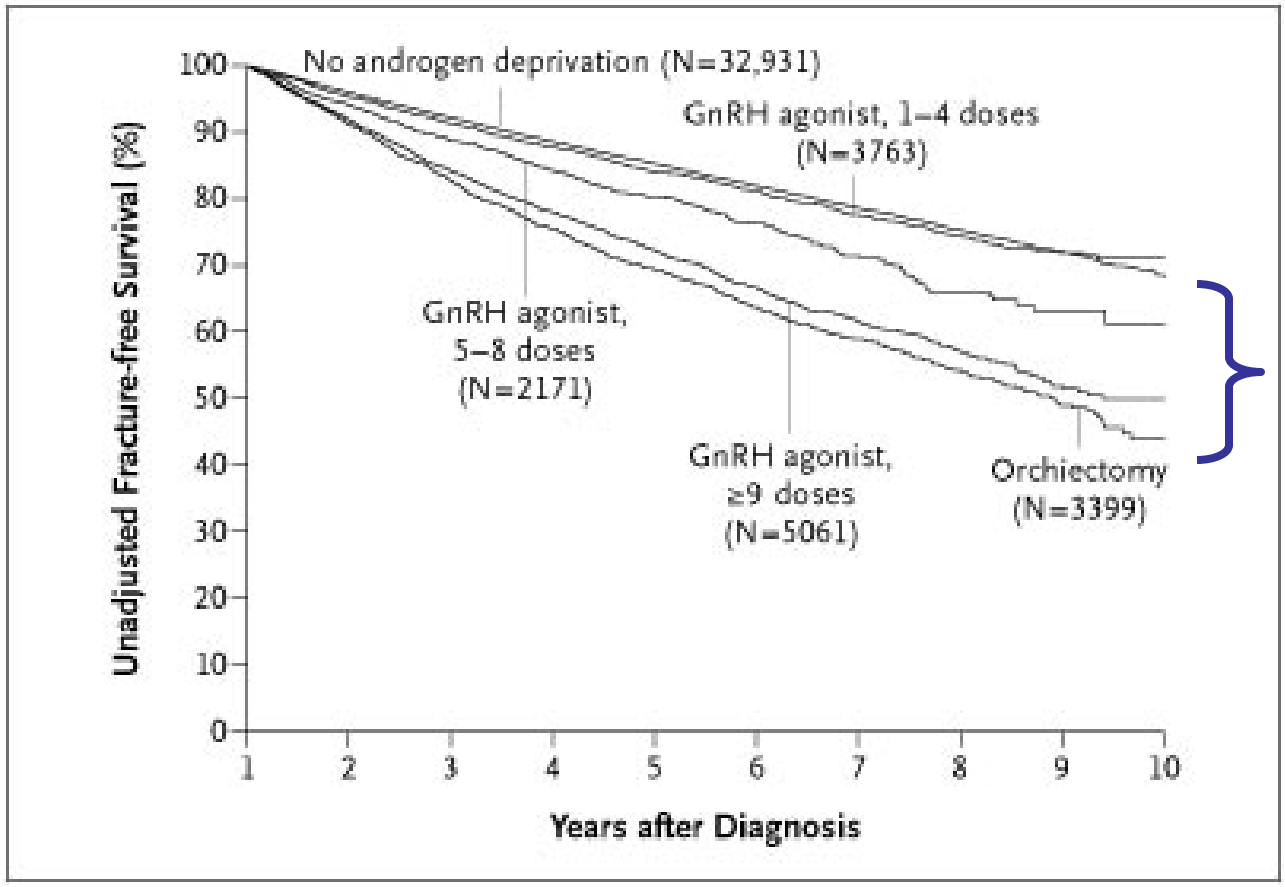
Lonning, P. E. et al. *J Clin Oncol*; 23:5126-5137 2005

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

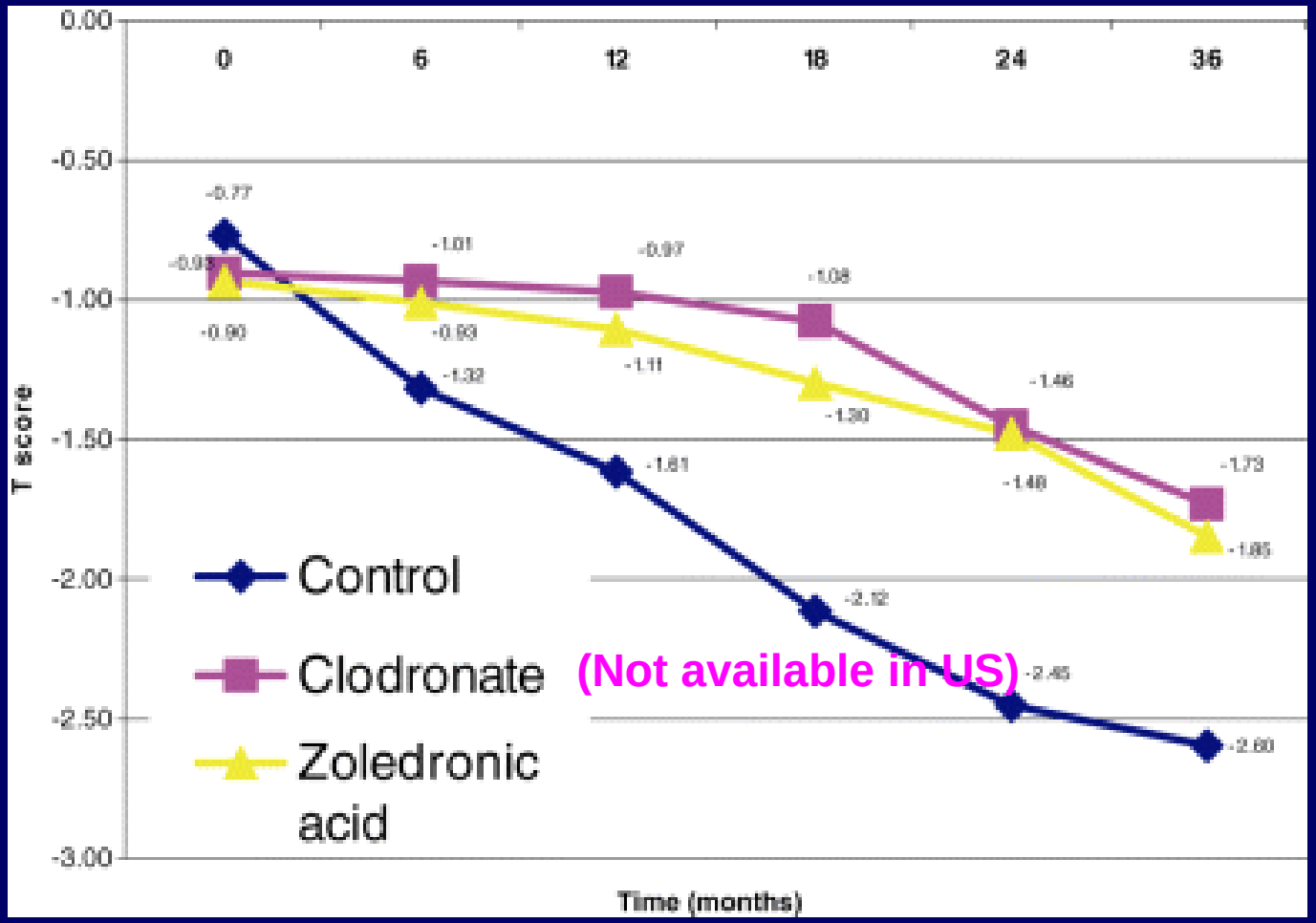
What About Androgen Deprivation in Men?



Dose-dependent impact of Leuprolide therapy vs. Orchiectomy

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

Use of Bisphosphonates with Androgen Deprivation



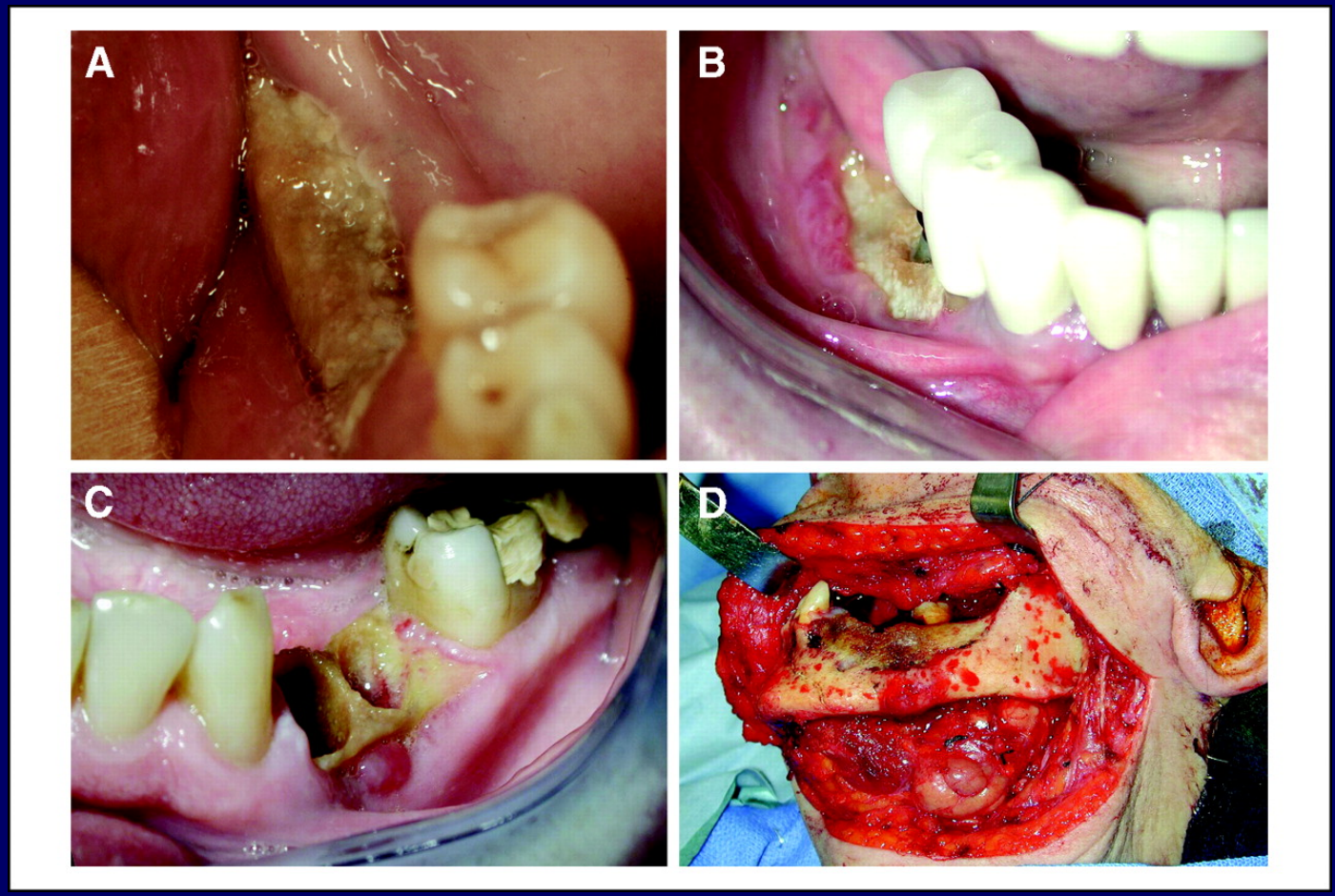
Rodrigues, *Int. J. Urol.* 14(4): 317-20, 2007

Complications of Intravenous Zoledronic Acid Therapy

- Osteonecrosis of Jaw
- Seen almost exclusively in cancer patients (rare)
- Substrate is pre-existing dental and gum disease

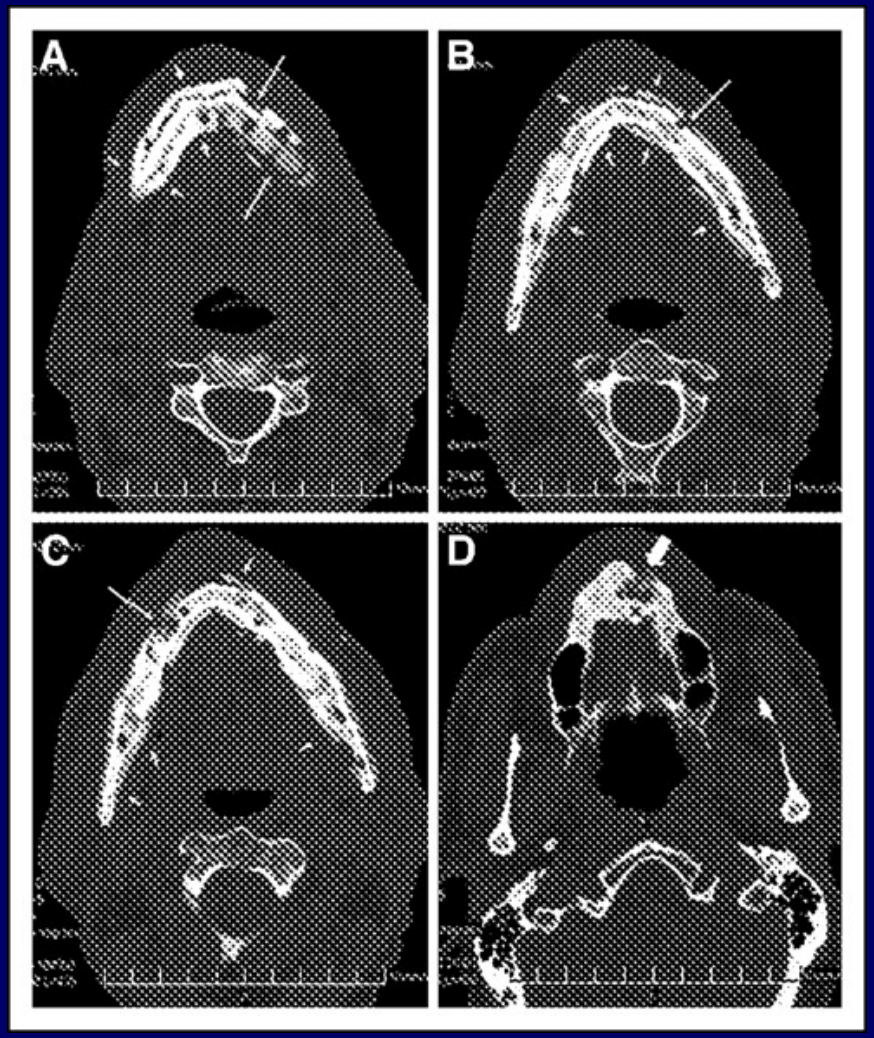
We screen for this, hold therapy until dental work is finished

Clinical presentation of osteonecrosis of the jaw



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

Axial CT scans showing a diffuse osteonecrotic/ostemyelitic process involving almost the whole mandible



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

Fistulous tracts from Osteonecrosis of Mandible

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

ONJ: Pathophysiology

- Bisphosphonates reduce bone turnover: both osteoclastic and osteoblastic activity
  - Clinically reduction of osteoblastic activity predominates
  - Reduction in osteoblastic activity may lead to “hypodynamic bone*” with resultant decreased “biomechanical competence*”)
- Seen almost exclusively with intravenous bp’s
- Incidence in patients with myeloma and breast cancer probably about 5%

*Woo et al *Annals of Int. Med.144:753*, 2006

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

*Ruggiero et al JOP 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

Complications of Intravenous Zoledronic Acid, continued

- Transient fever and malaise with initial dose – in bisphosphonate naïve patients; short-lived
- Can provoke hypocalcemia in patients with low vitamin D stores (not evident clinically unless severe)
- ??Transient Atrial Fibrillation – largely debunked, still out there for discussion
- In past patients treated with ZA had metastatic cancer and did not live long enough to develop long-term complications; situation may be changing with use of ZA in general population…

An Interesting Footnote to Long-Term ZA….

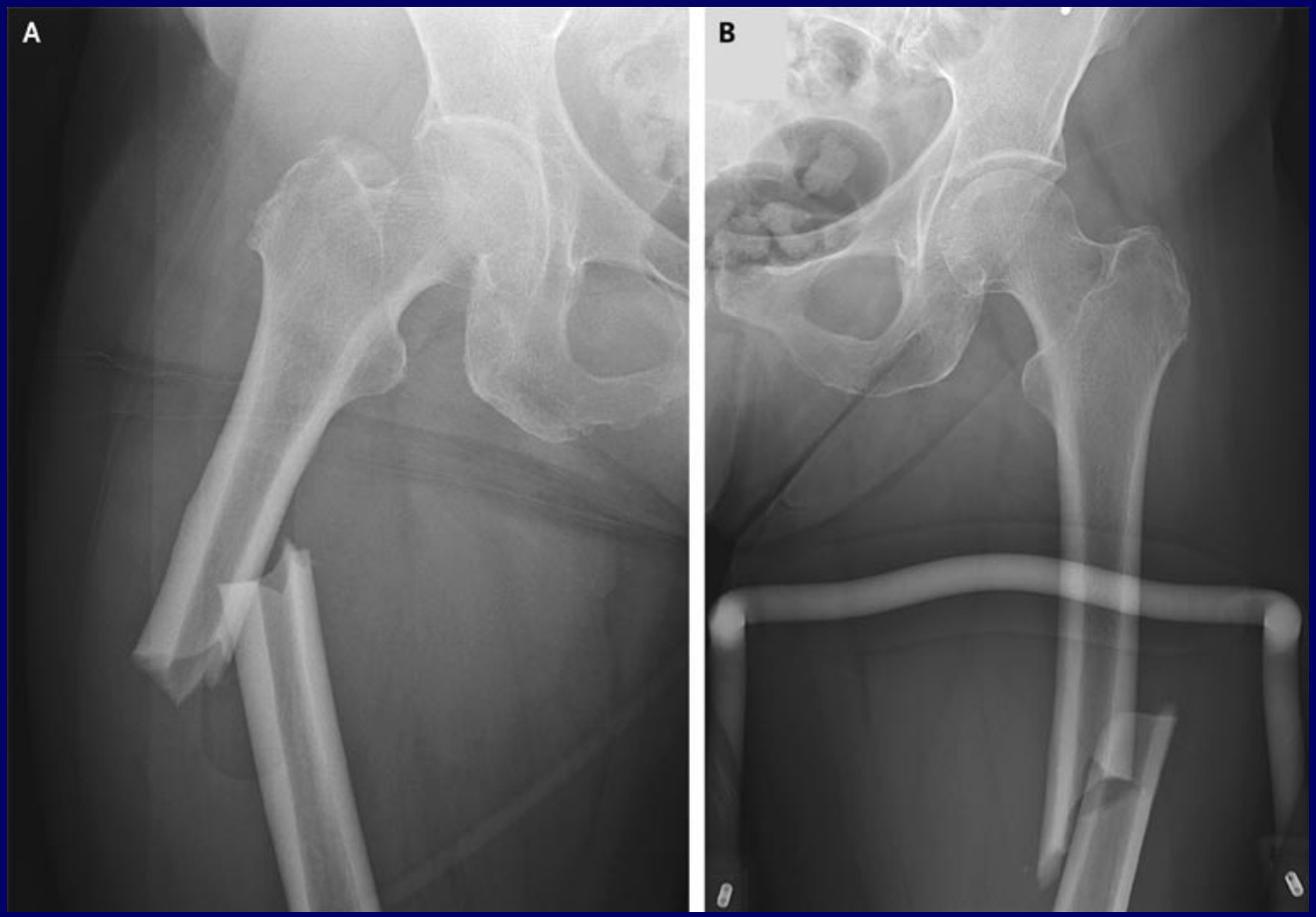
- Emerging rare isolated case reports of the development of stress fractures in post-menopausal women on long-term (> 8 years) Alendronate (Actonel)
- Not seen with other bisphosphonates
- Risk factors murky at present
- Because of compliance issues not many women have stayed on long-term oral bp's
- Reclast will make it easier to stay on long-term therapy
- No reason yet *not* to take these drugs

Kwek E et al. *N Engl J Med* 2008;359:316-318

Radiograph Showing a Subtrochanteric Stress Fracture Associated with a Typical Cortical Stress Reaction

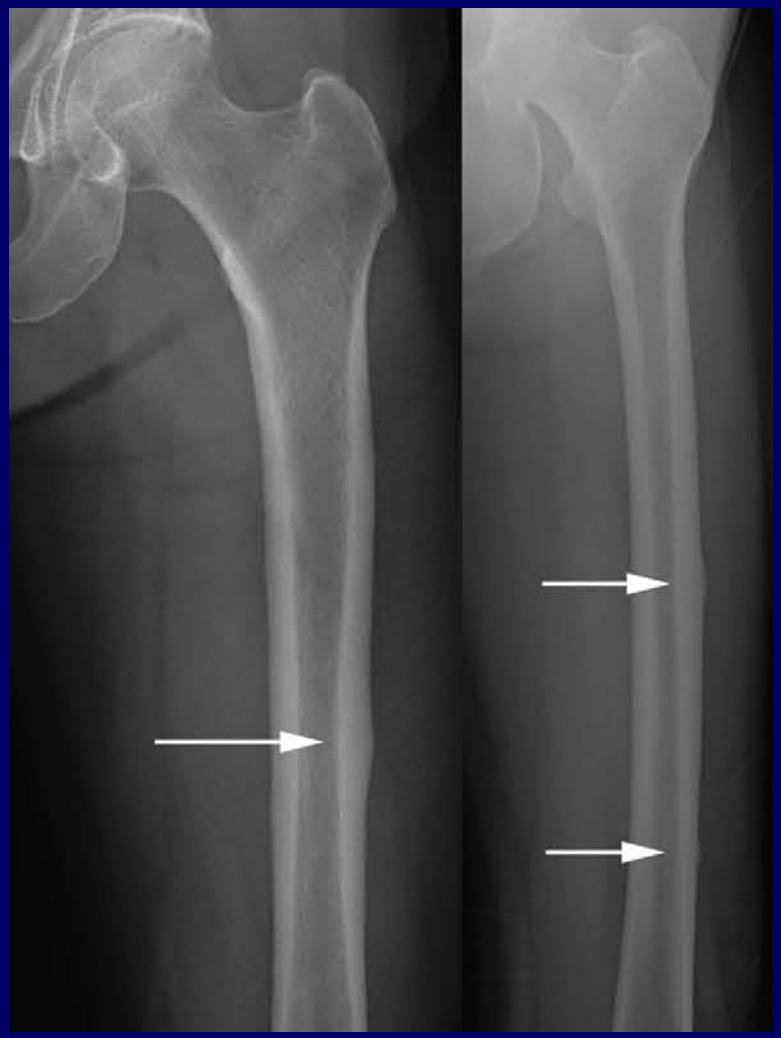
Kwek E et al. *N Engl J Med* 2008;359:316-318

Radiographs of Fractures of the Femoral Shaft Showing the "Simple with Thick Cortices" Pattern



Lenart B et al. *N Engl J Med* 2008;358:1304-1306

Contralateral Femur in These Patients



Arrows show lateral cortical stress reaction in the contralateral femur: two examples from original Alendronate report

Conclusions

- Osteoporosis is a major public health issue with significant morbidity, mortality, and health care costs
- Prevalence increasing as population ages
- Effective therapies are available, but treatment and adherence patterns are suboptimal in the real-world setting
- Better diagnosis and longer-acting therapies with few adverse events that address obstacles to adherence may improve real-world outcomes

Young thin female athletes and their caregivers need to be aware of emerging literature on the "triad," check Vitamin D levels, and consider bone mineral density measurement

For more information….

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www.StarkOncology.com