Osteoporosis in Youth, Aging and Illness

Premier Fitness

October 14, 2009

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

Case Presentation

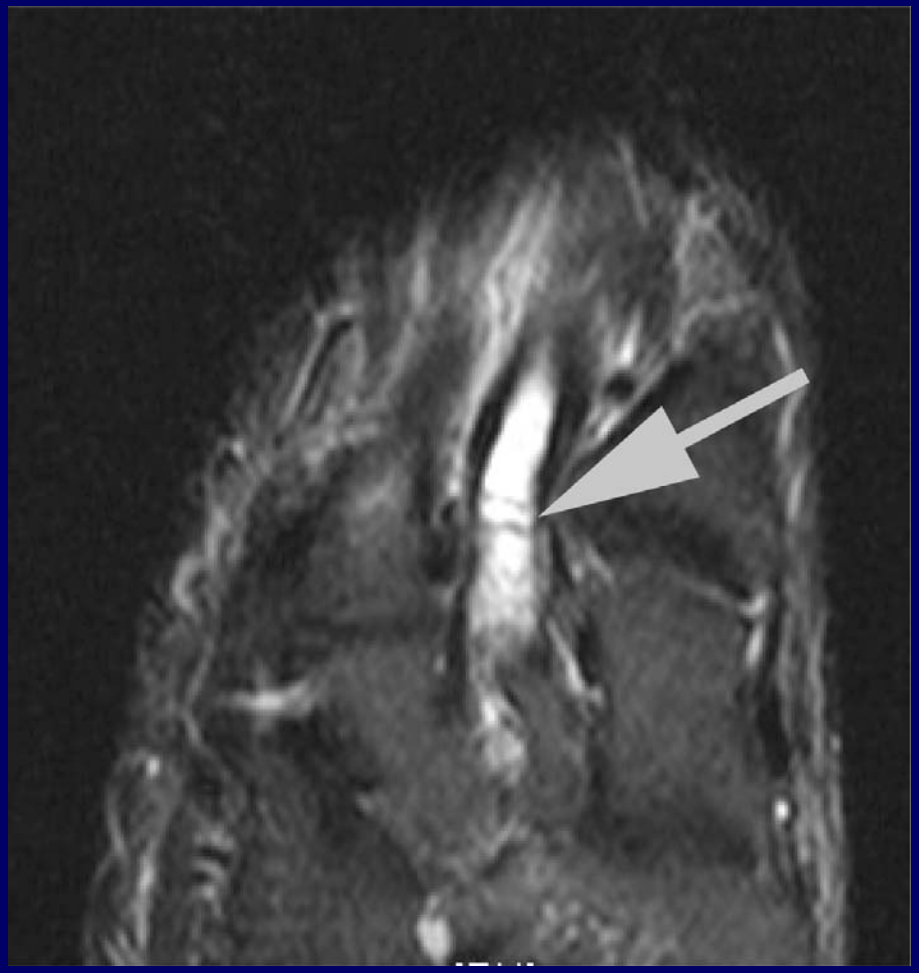
Case Presentation -- Deena Kastor

- 35 year-old world-class long distance runner
- Bronze medalist in Athens Olympics (2004)
- In peak of physical health
- For several weeks prior to 2008 Beijing 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…

The Triad of the Female Athlete

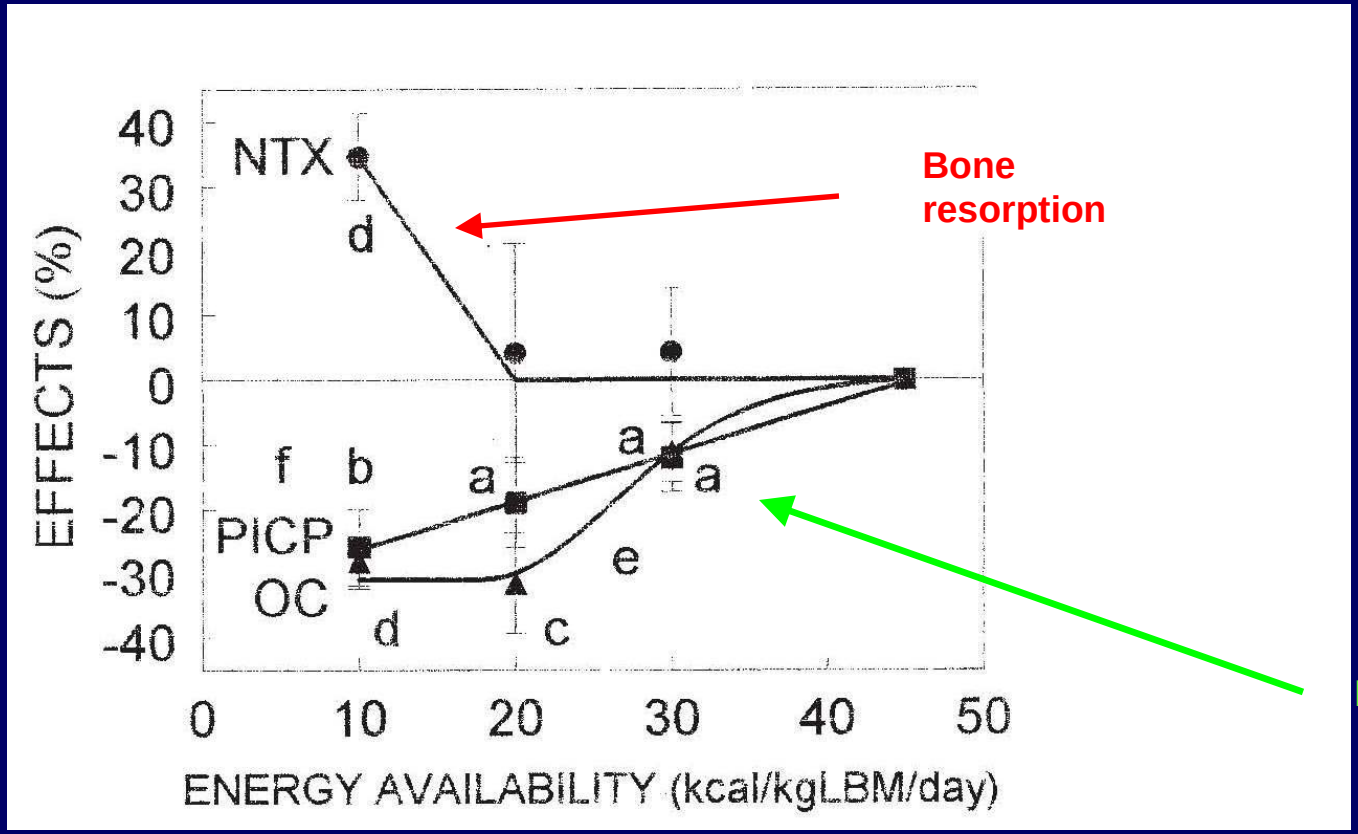
- Eating disorder
- Amenorrhea
- Osteoporosis

- 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)

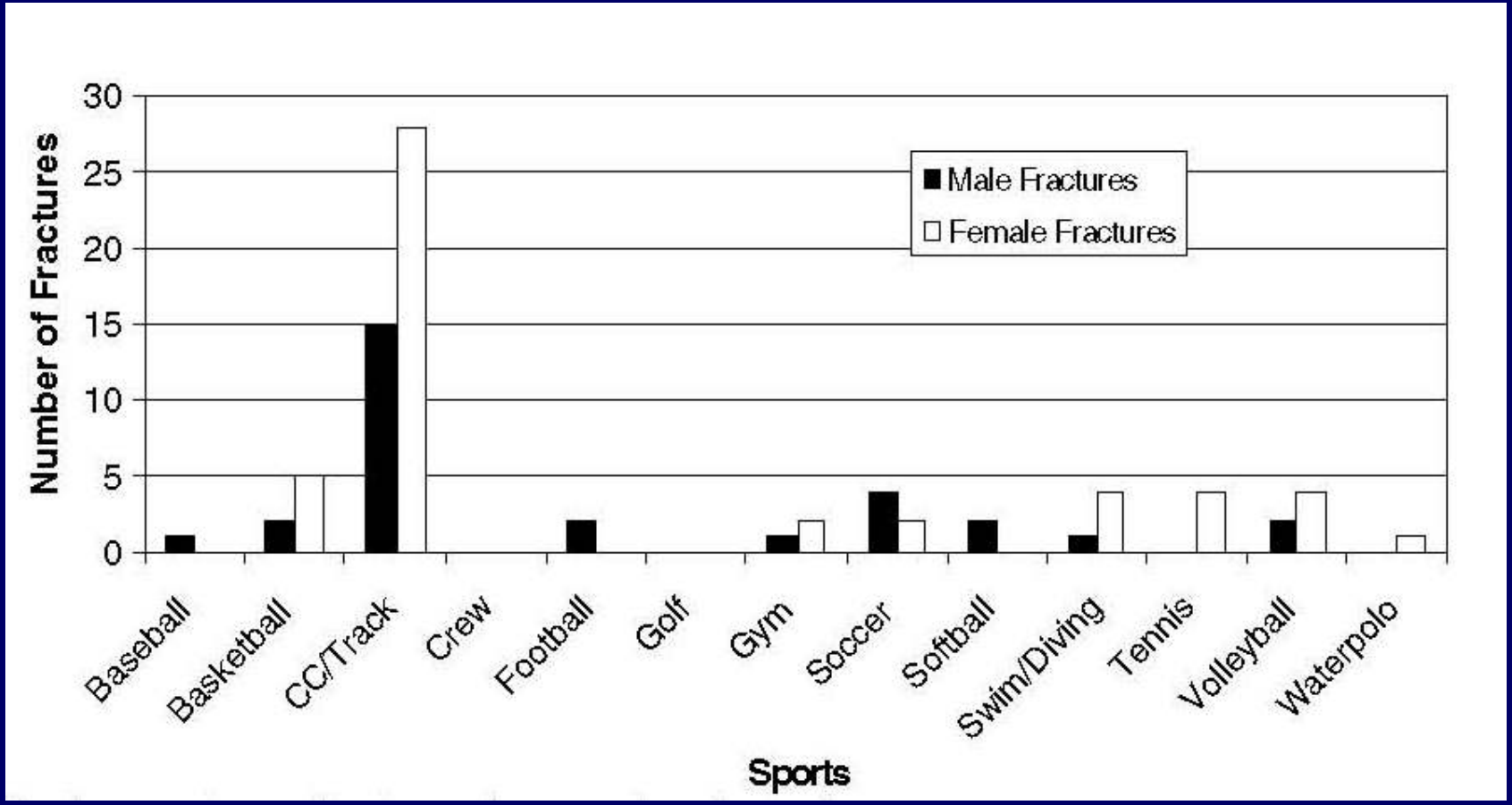
- What happens to their bones when young female athletes do not eat enough?

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



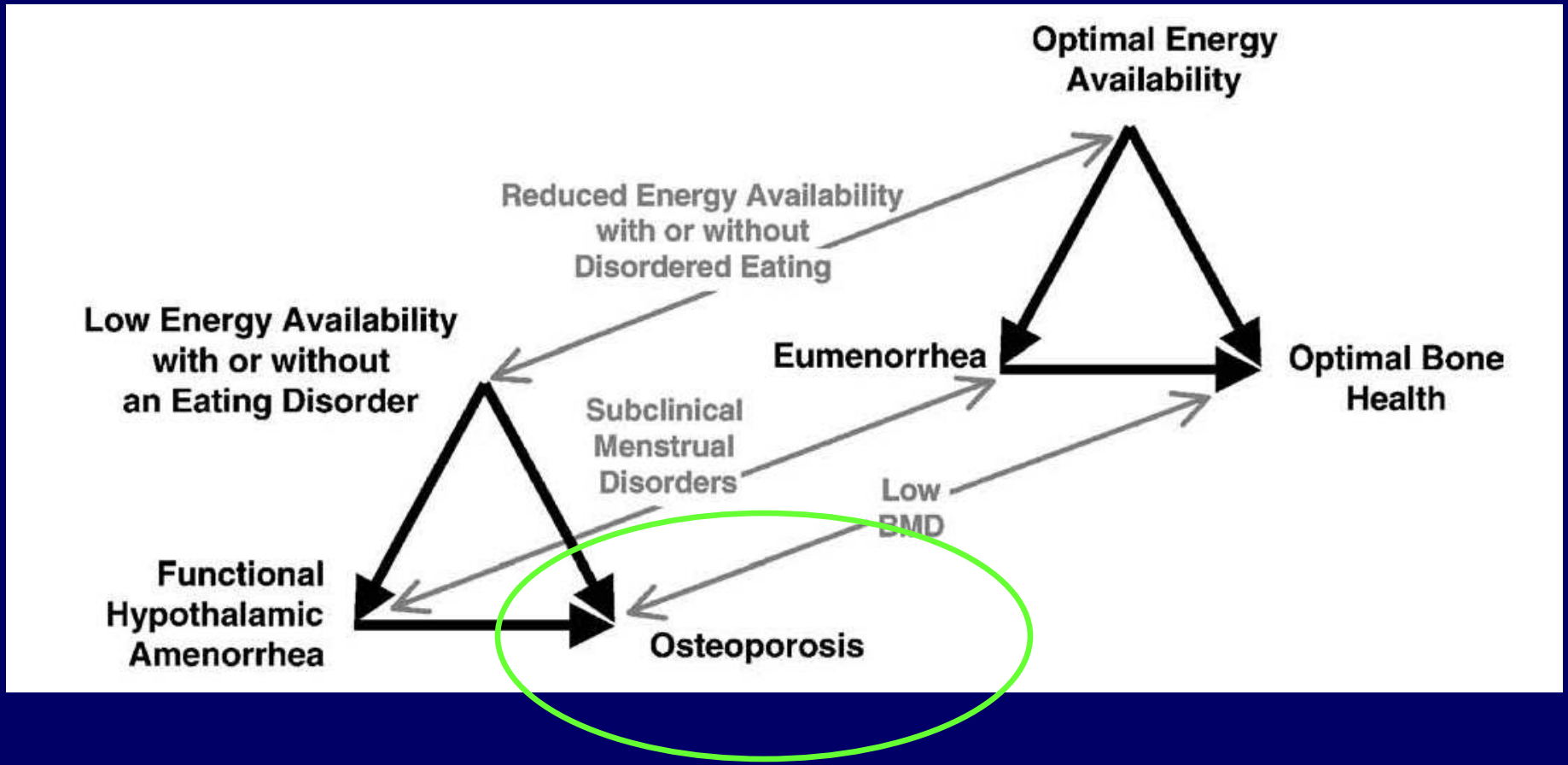
Ihle and Louks *Journal of Bone and Mineral Research* 19:1231-40, 2004

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

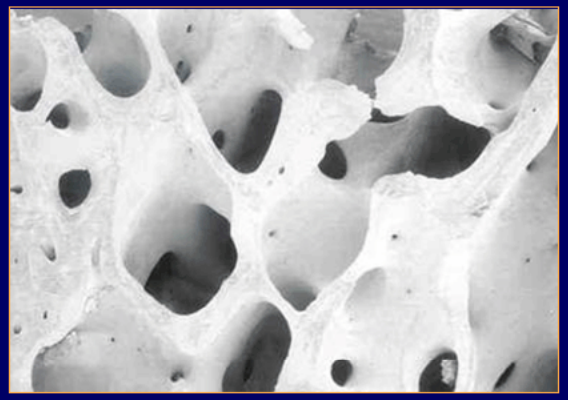
- Recognizing entity by performing DEXA scan after first stress fracture especially if amenorrhea present
- Calcium and Vitamin D supplementation; lack of body fat makes storage of D problematic
- Consideration of birth-control pills to supplement deficit in natural circulating estrogens
- Usual pharmacologic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

Osteoporosis in Young Female Athletes: Summary

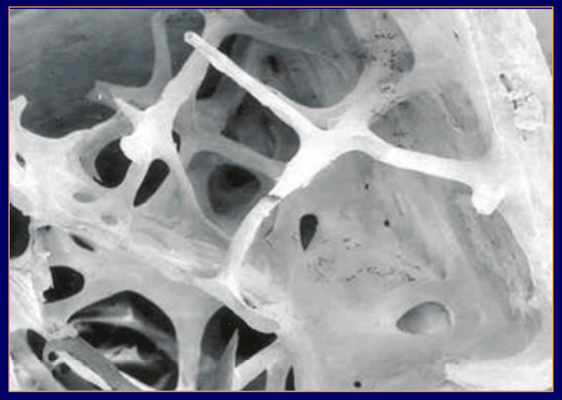
- Stress fractures in long-distance women runners very common
- Prodrome of foot pain for several days prior to actual fracture common
- Bone mineral density likely depressed because of hormonal changes associates with athletic training and altered caloric intake; and absence of body fat to store Vitamin 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, Deena promises to drink milk and eat yogurt – likely a totally inadequate band aid

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

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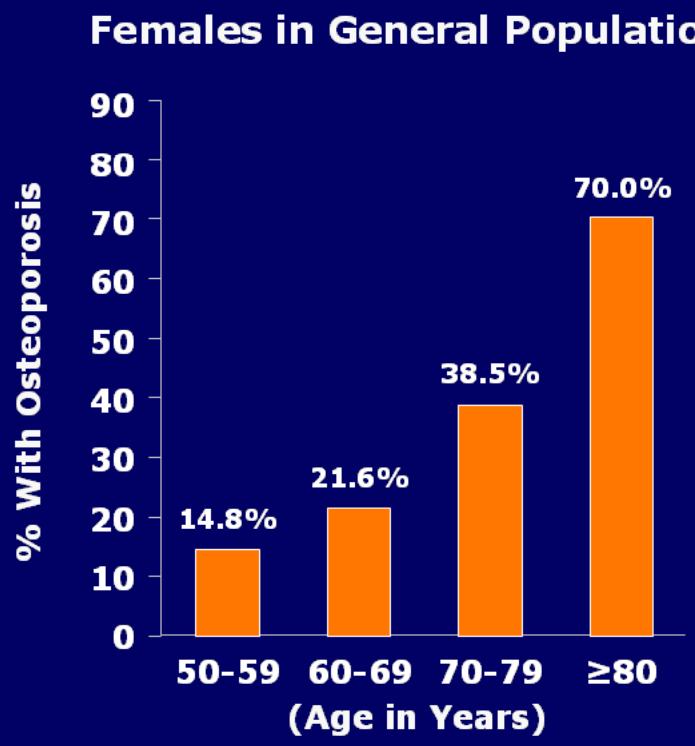
- 1.5 million fractures occur per year in US



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.

Vertebral Fractures Have Significant Consequences for Patients, Including Dorsal Kyphosis

Vertebral Fractures

- Associated with
  - Acute and chronic pain
  - Kyphosis and height loss
  - Impaired function
  - Increased morbidity and mortality
  - Increased fracture risk

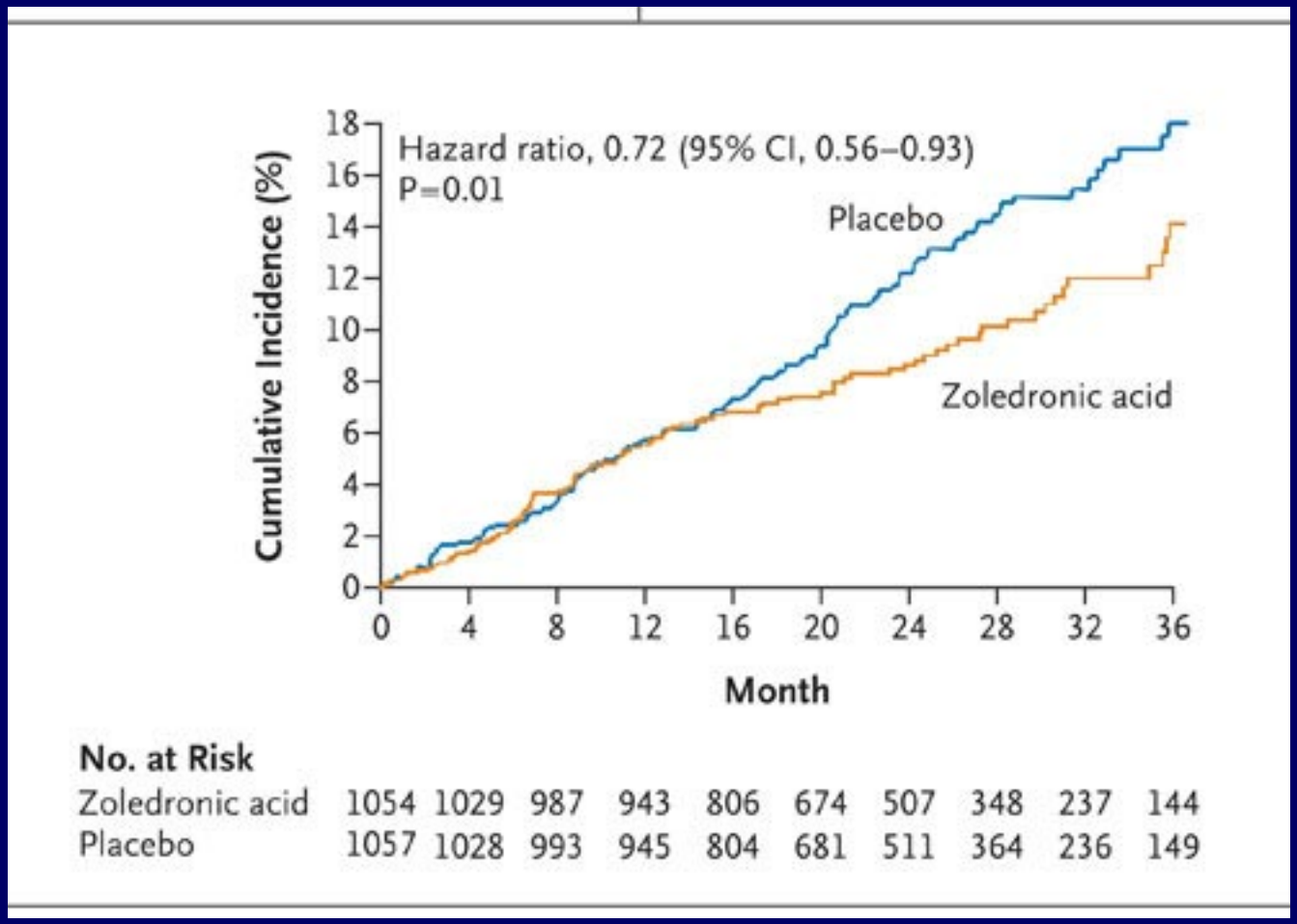
Image reprinted with permission from Whitehead MI, et al. *A Slide Atlas of Menopause*. London, UK: Parthenon Publishing Group; 1993.
Delmas PD, et al. *J Bone Miner Res*. 2005;20:557-563.

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.

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



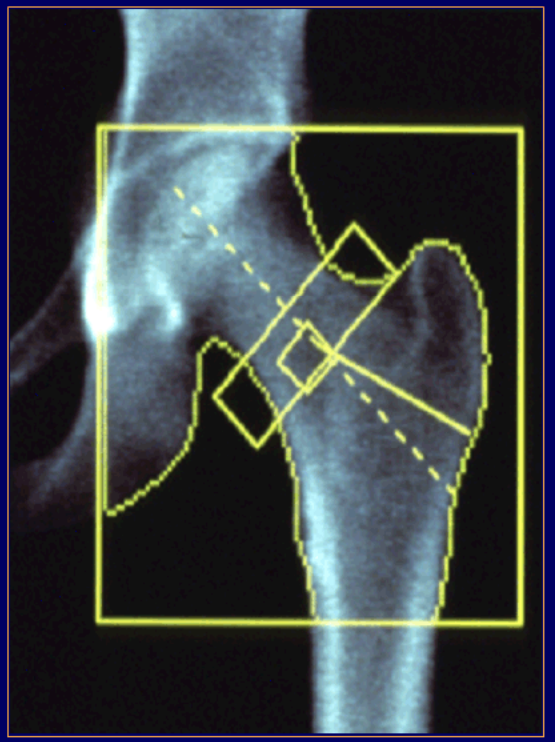
No. at Risk

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

Clinical Presentation of Osteoporosis

- Usually asymptomatic and undiagnosed
- Signs and symptoms
  - Low-trauma fractures of spine, wrist, or hip
  - Loss of height
  - Kyphosis (rounded back)
  - Acute or chronic back pain
- Diagnostic tests
  - Bone mineral density measurement
  - Spine x-ray or morphometry



Bone Health and Osteoporosis: A Report of the Surgeon General. Rockville, Md: US Department of Health and Human Services; 2004:187-217.

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

Who should be screened for osteoporosis?

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.

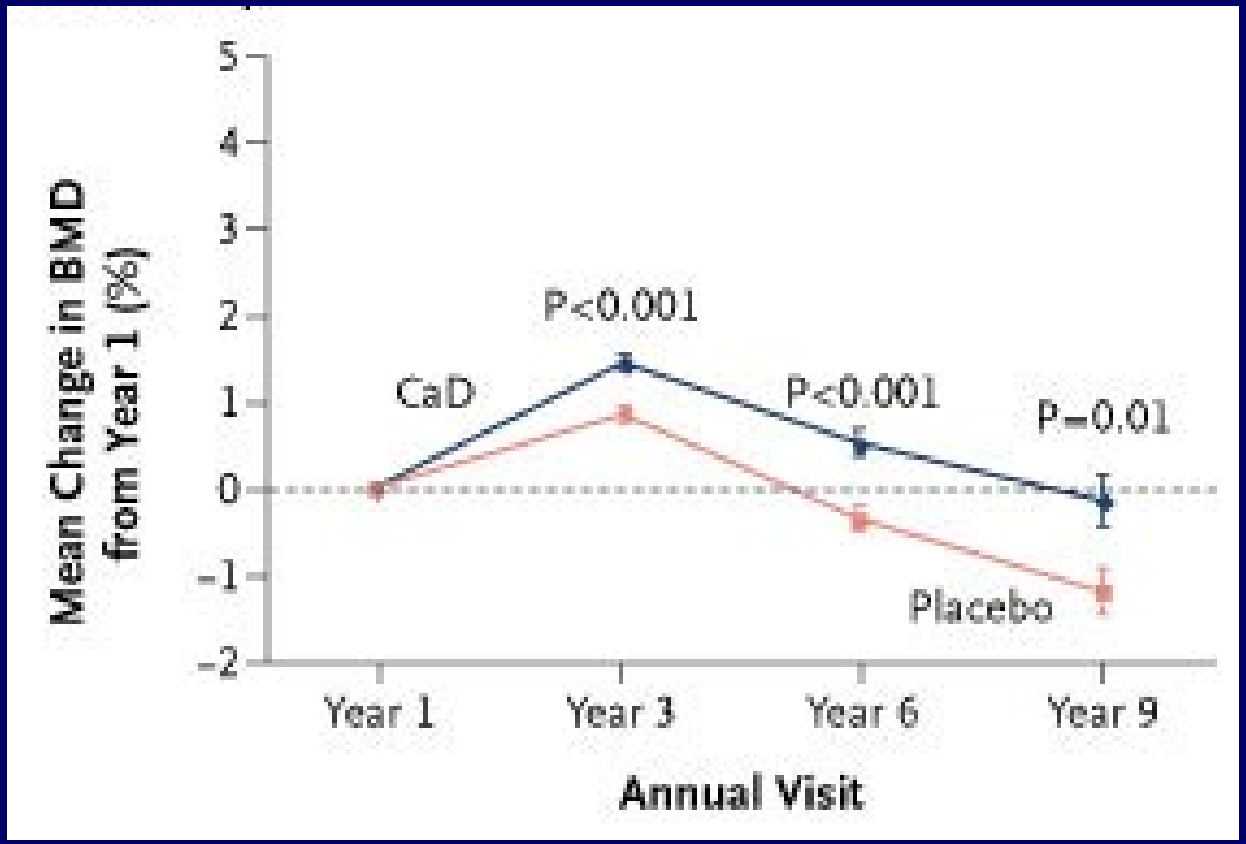
Nonpharmacologic Interventions

- 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

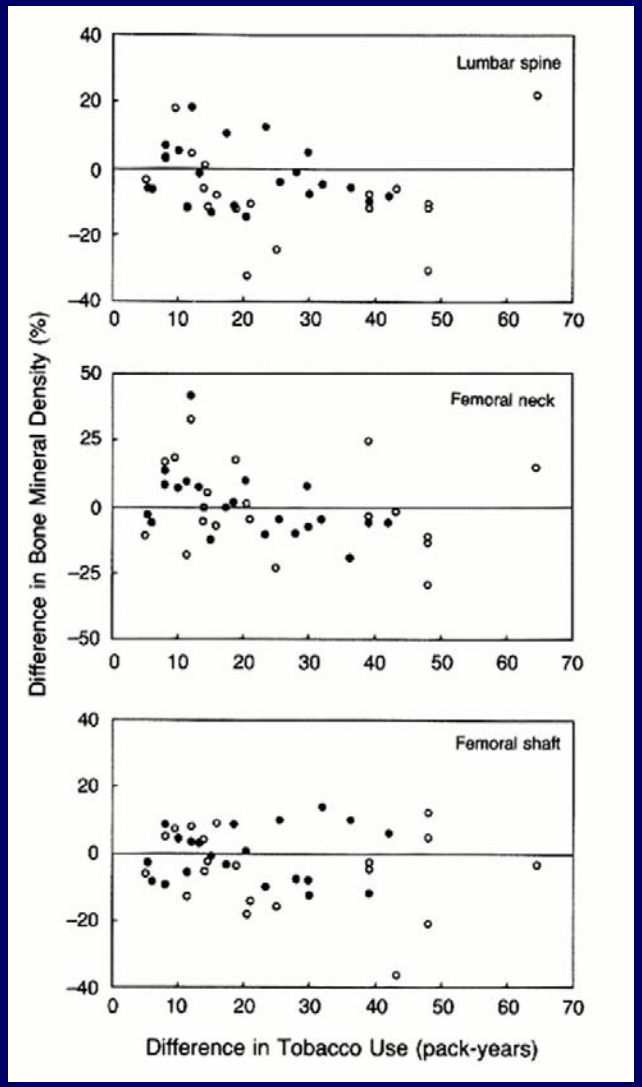
Effect of Exercise on Development of Hip Fracture – From the Nurses' Health Study (n=61,200)

	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 that of serious athletes; body fat content average as well

Feskanich et al *JAMA* 288: 2300, 2002

Impact of Smoking on Development of Osteoporosis



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 (*Miacalcin* by injection or nasal spray)
  - Selective estrogen receptor modulators (SERMs) (*Evista*)
- **Anabolic agents**
  - Parathyroid hormone *(Forteo)*
- **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.

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

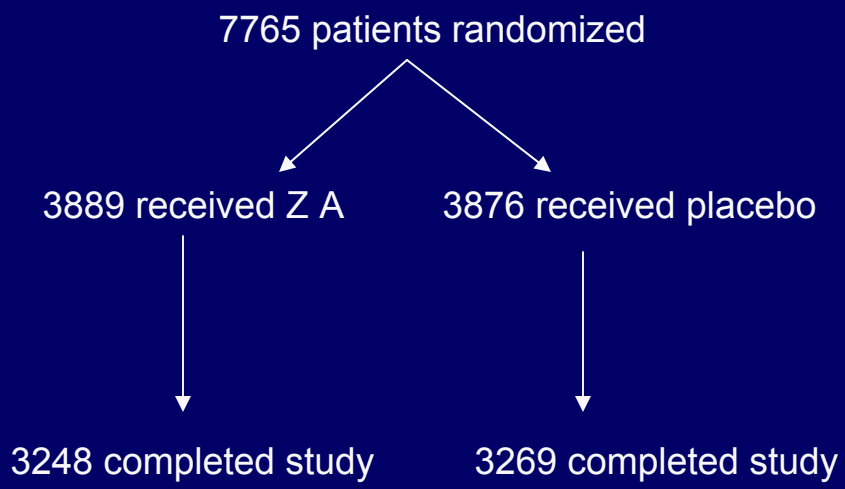
- Insufficient rates of diagnosis
- Low awareness among physicians and patients of the imperative to treat
- Global challenge of adherence to therapy in chronic diseases, compromising effectiveness
- Poor adherence is two-fold problem
  - Low persistence: patient stops taking medication
  - Poor compliance: 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

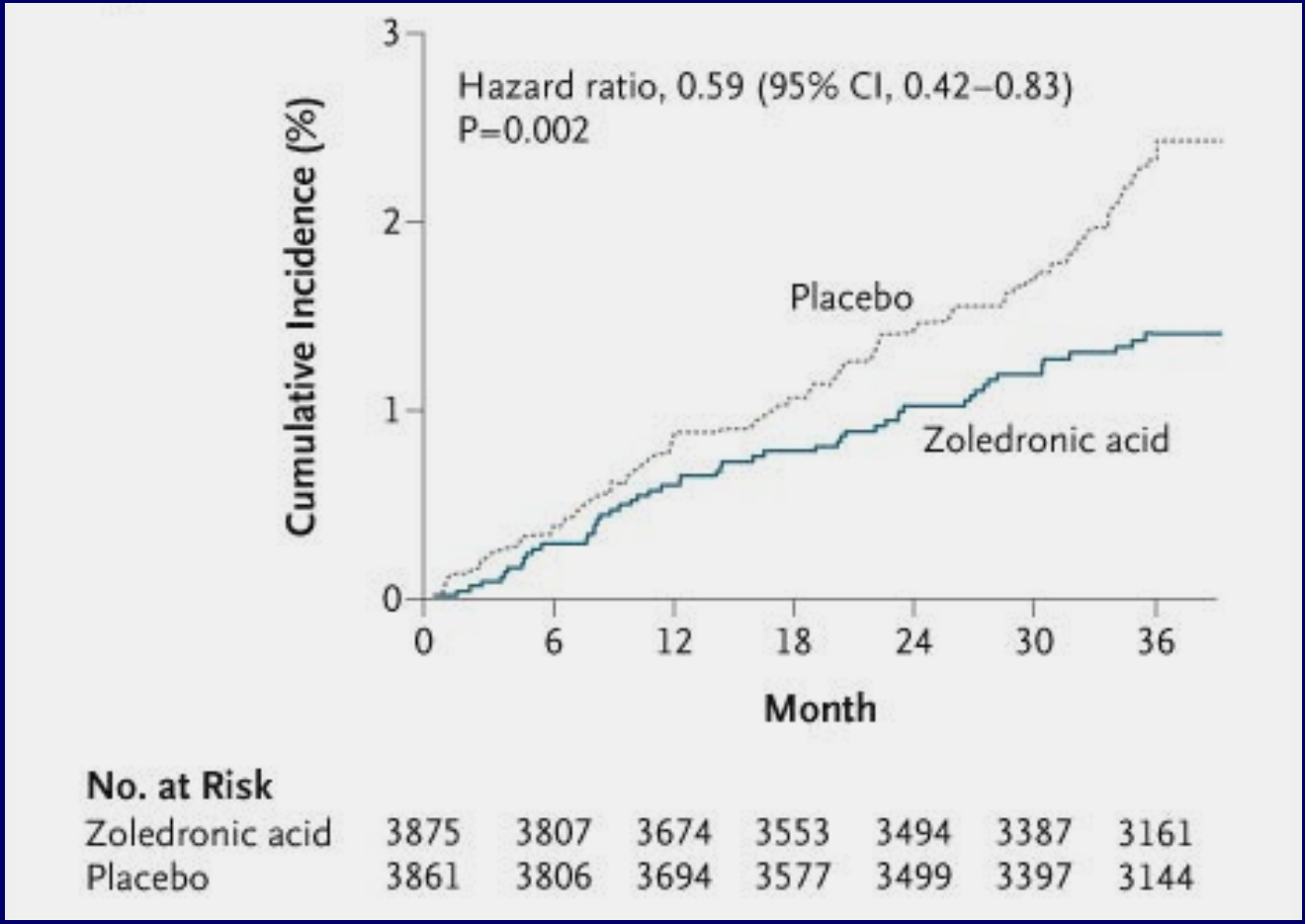
First of Two Large Studies Putting Principle of Infrequent Zolendronic Acid to the Test: Zolendronic Acid in Healthy Post-Menopausal Women



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

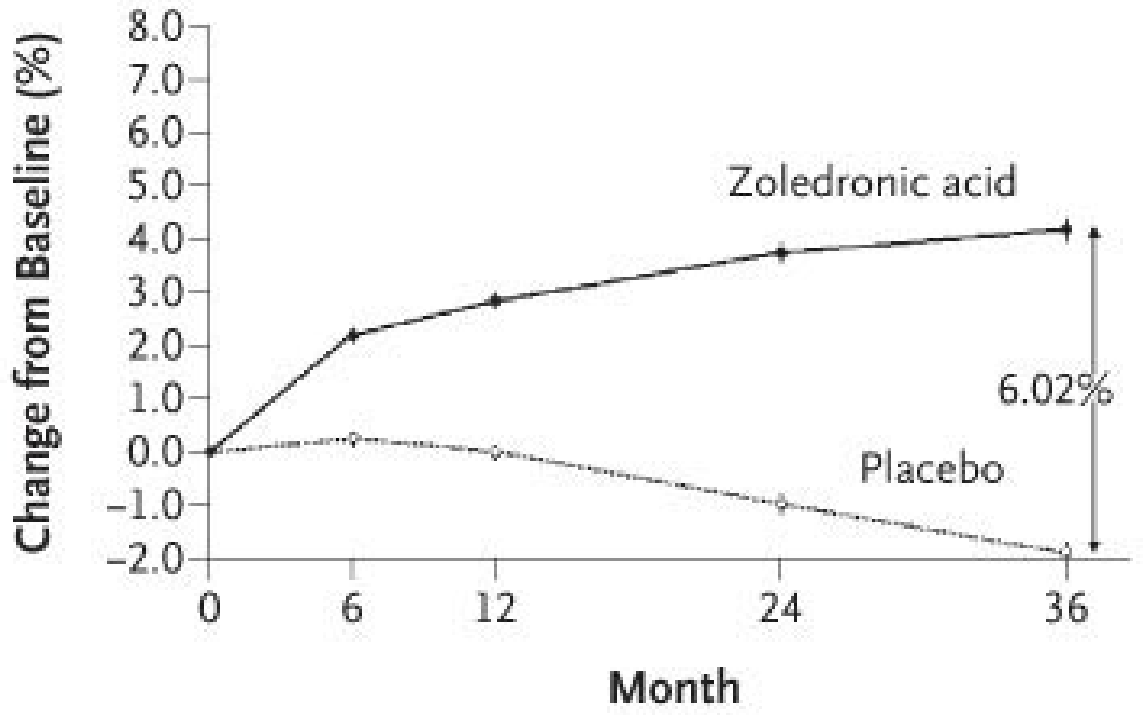


No. at Risk

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

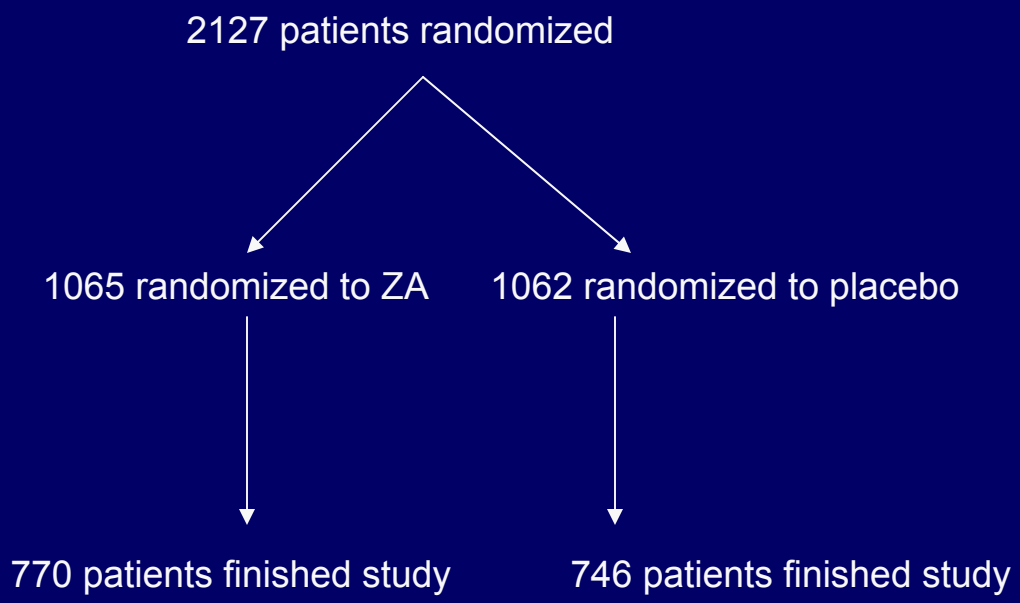
Percent Change over Time in Bone Mineral Density in Hip



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

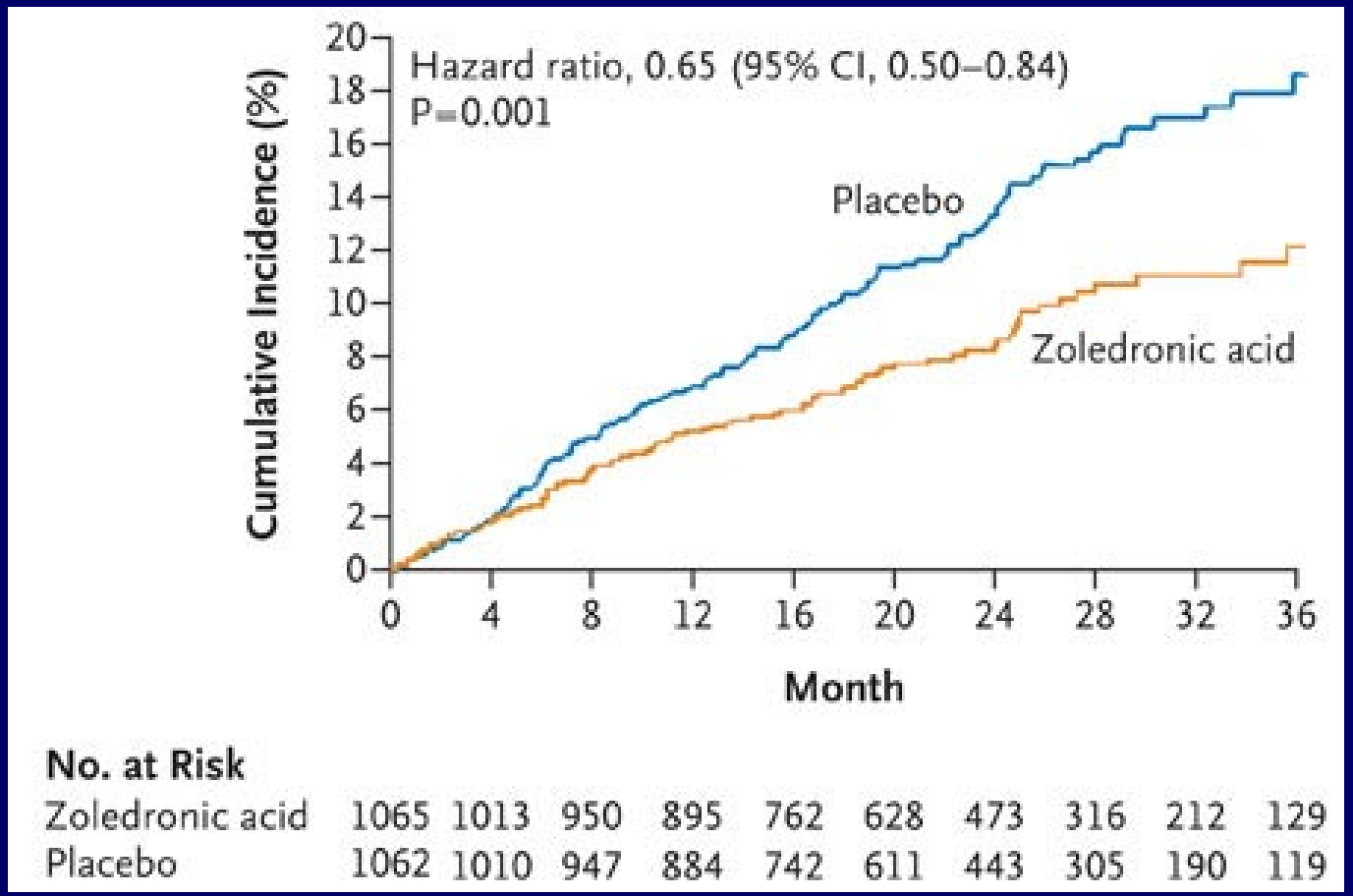
Most Recent Study Published on Outcomes Following Hip Fracture



The final groups were then analyzed…

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

Refractures Over Time: ZA versus Placebo

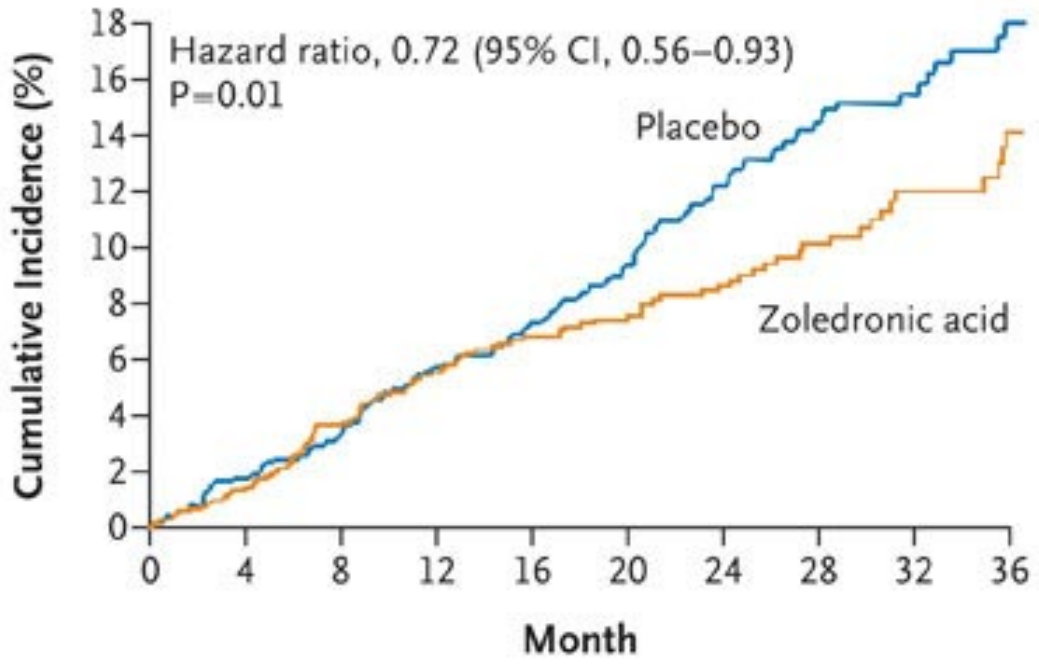


No. at Risk

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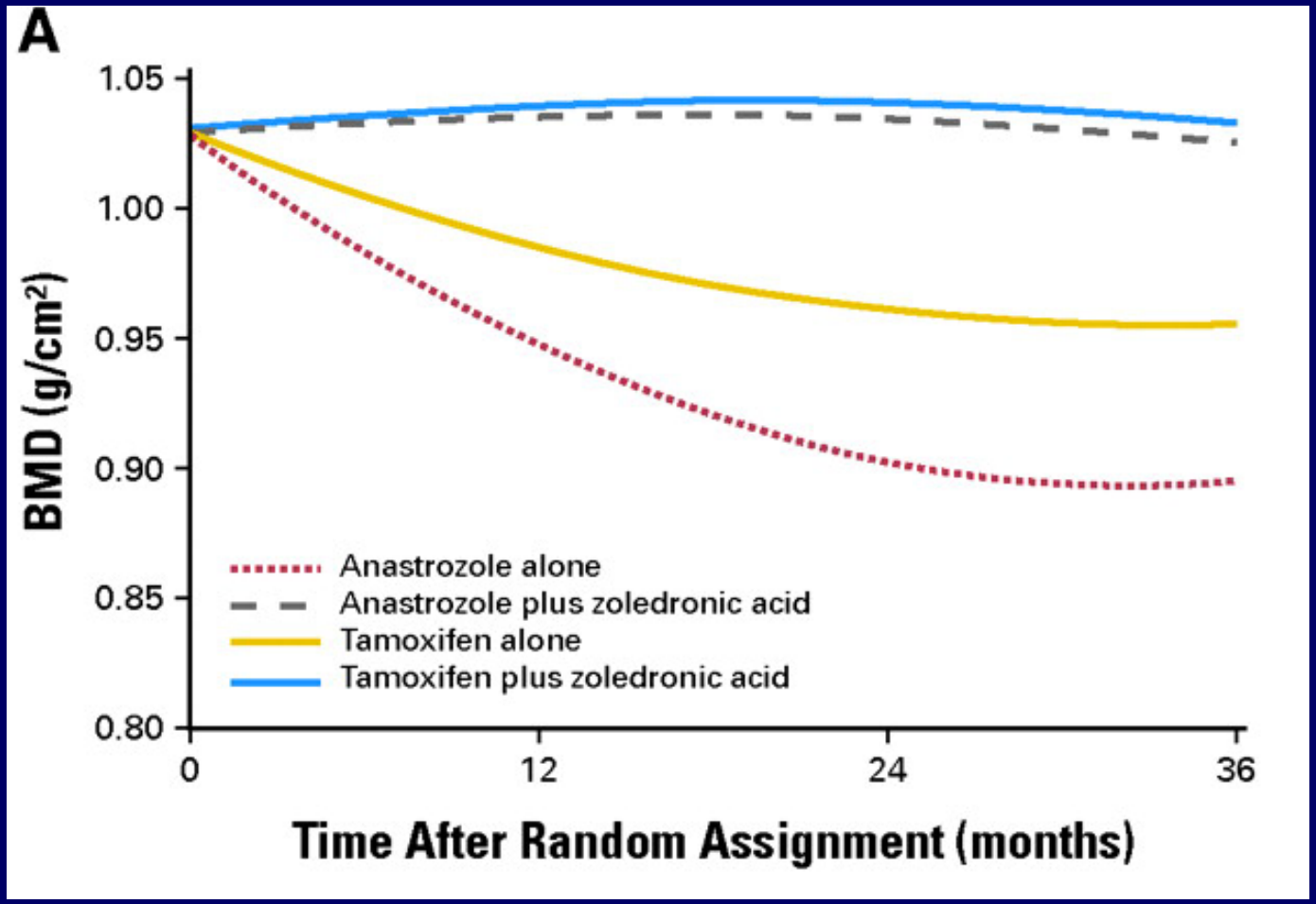
Lyles K et al. *N Engl J Med* 2007;357:1799-809

The Problem of Bone Mineral Loss in Cancer Patients

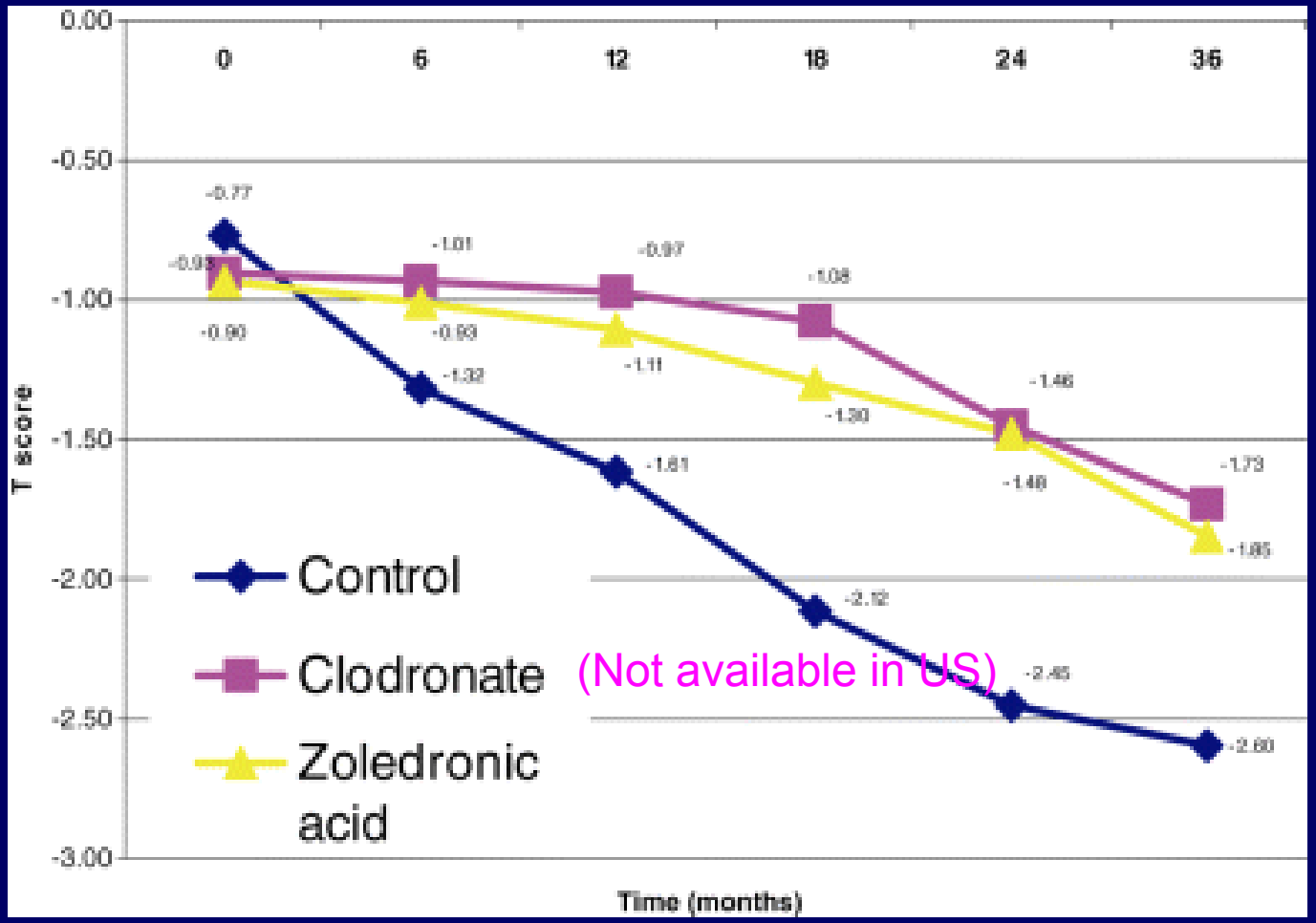
- Widespread use of hormonal manipulation in treatment of cancer greatly exacerbates problem
  - Aromatase inhibitors (Arimidex, Femara, Aromasin) in the treatment of *breast cancer*
  - Lowering testosterone levels by drugs or surgery in the treatment of *prostate cancer*
- Prophylactic treatment with bisphosphonates can prevent this loss…

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

Use of Bisphosphonates with Androgen Deprivation



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

Intravenous 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
- Requires prescreening for medical issues (dental health, adequacy of kidney function and vitamin D stores) by physician

Dental Issues??

- 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

A final cautionary note….

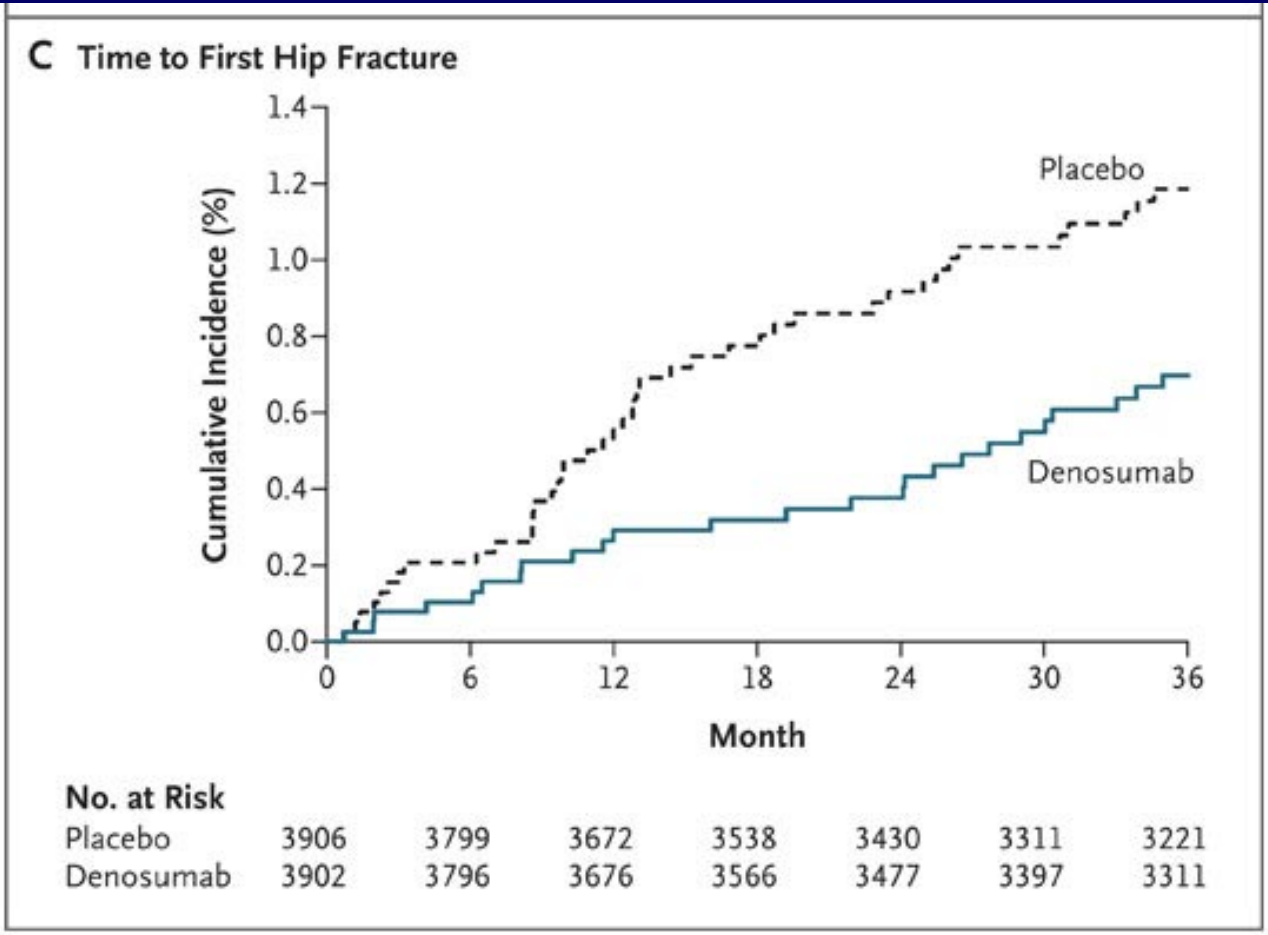
- Emerging rare isolated case reports of the development of “insufficiency” fractures in post-menopausal women on long-term (> 8 years) Alendronate (Actonel)
- Not seen with other bisphosphonates
- Risk factors murky at present
- Because of compliance issues not many women have stayed on long-term oral 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

Finally....the scoop on a brand new drug
Denosumab (Prolia)

- First in a new class of drugs to treat osteoporosis
- Whole new mechanism of action: inhibits development of osteoclasts (cells in bone responsible for loss of calcium)
- No jaw damage
- Monoclonal antibody with potential to suppress the normal immune system
  - Risk of infection
  - Risk of cancer
  - Drug too new to quantify real risk, if any
- Awaiting final FDA approval (likely)
- Be the first among your friends to have heard about this potentially blockbuster drug

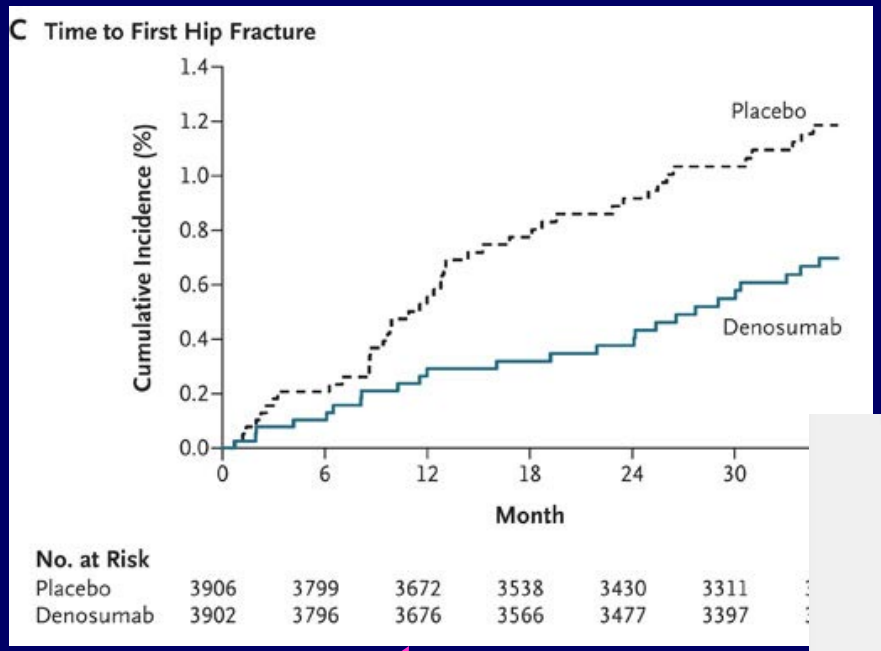
Denosumab: Incidence of New Vertebral, Nonvertebral, and Hip Fractures



Look familiar?

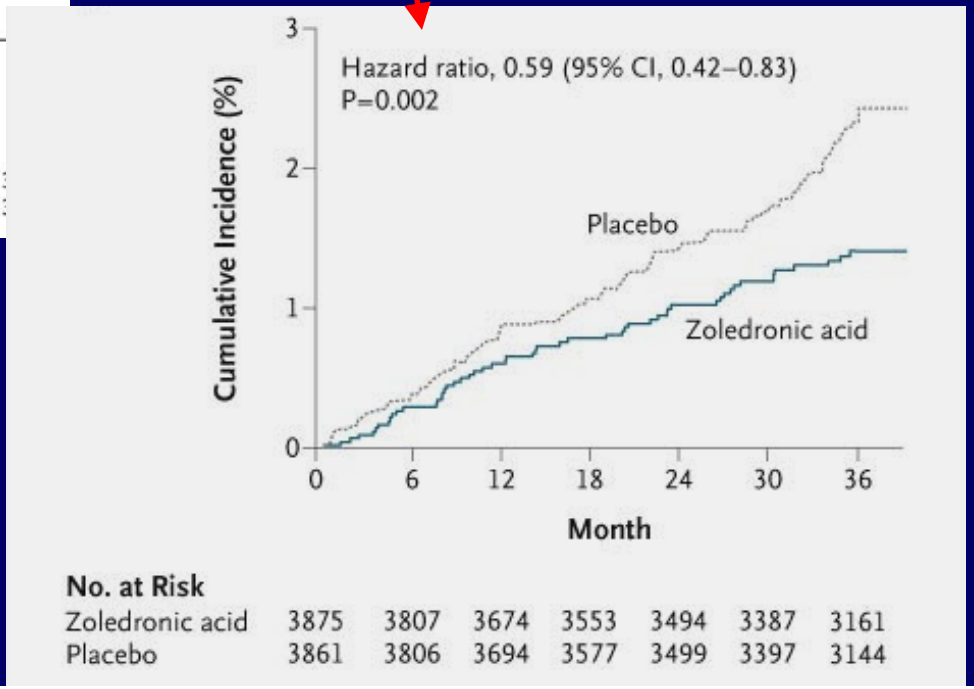
Cummings S et al. N Engl J Med 2009;361:756-765

Prolia versus Reclast: similarities and differences



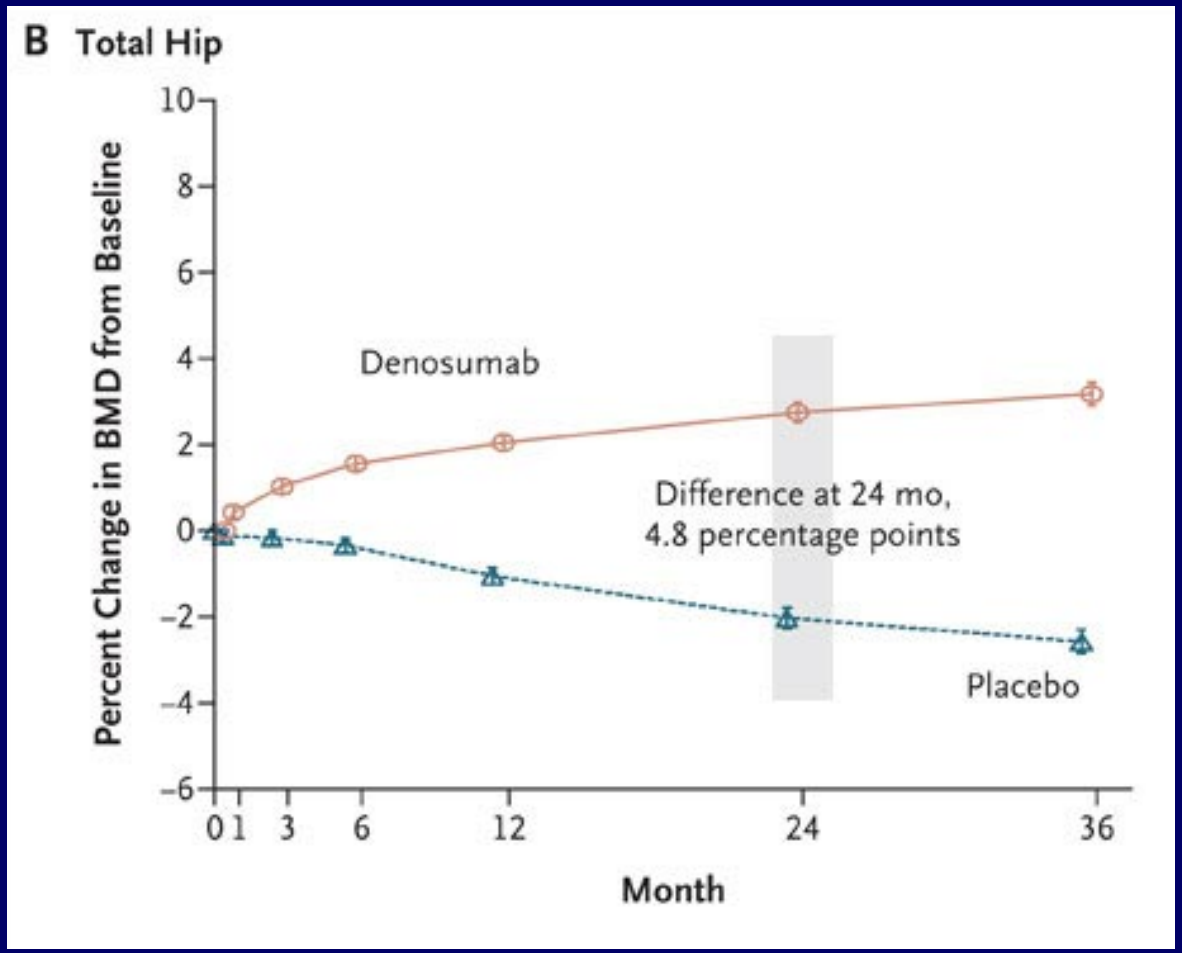
Prolia study

Reclast study



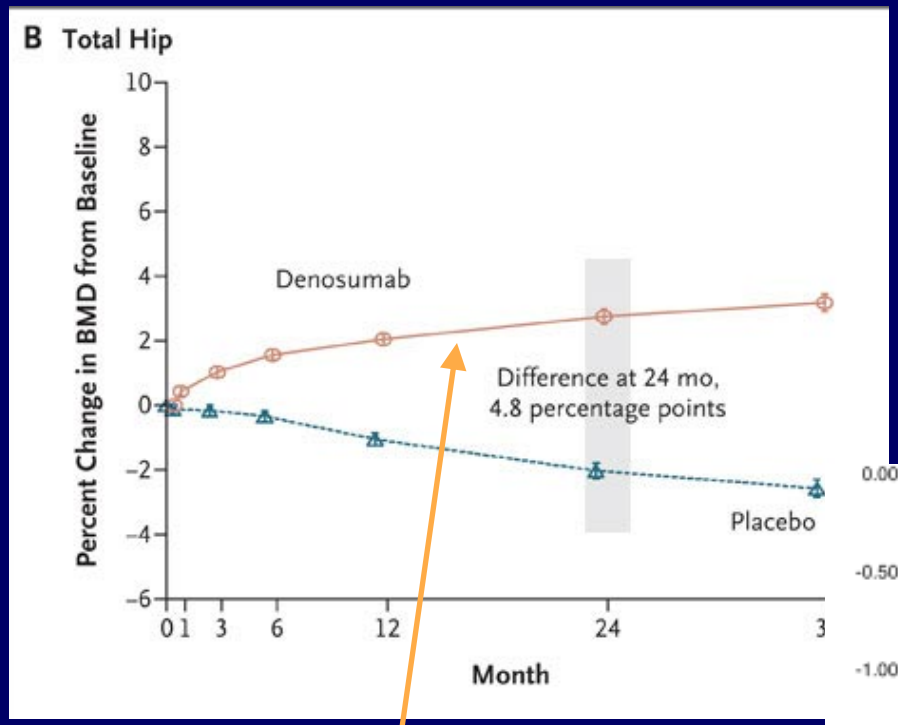
Why did more placebo patients in the Reclast trial develop hip fractures?? Demonstrates risk of interpreting data…

Effect of Denosumab on BMD among men undergoing hormone deprivation as part of treatment for prostate cancer



Smith M et al. N Engl J Med 2009;361:745-755

Effect of Denosumab compared with that of Clodronate (Bisphosphonate available only in Europe) and Reclast

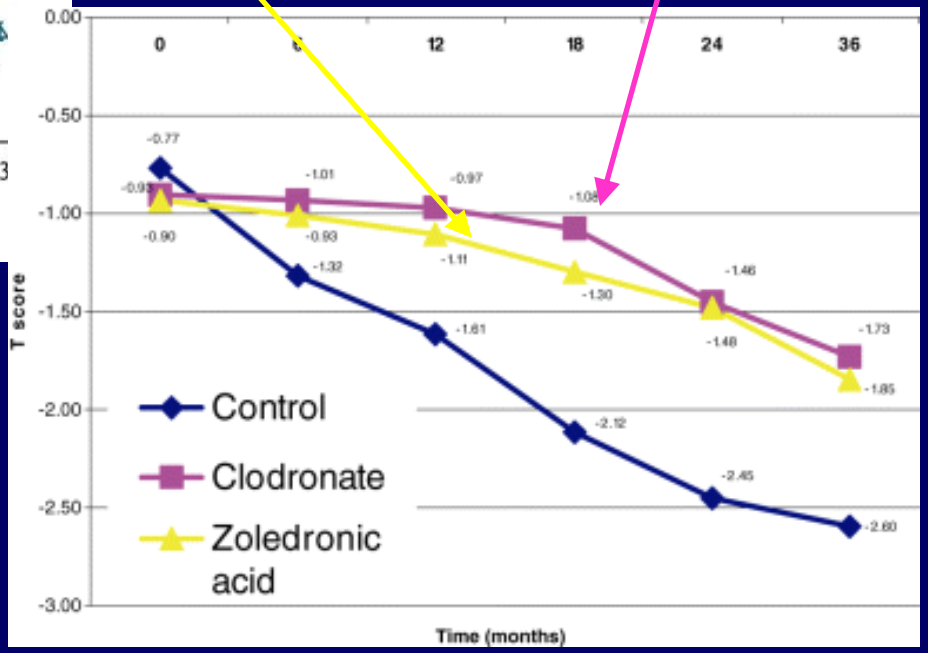


Prolia

In this study in these patients only Prolia was able to raise BMD

Reclast

Clodronate



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 need to be aware of emerging literature on the "triad" check Vitamin D levels and consider bone mineral density measurement

For more information….

- Contact us at….

- James J. Stark, MD, FACP at 397-4200…just down the driveway…

Or visit me on the web:

www.StarkOncology.com