

Osteoporosis: An Overview of the Disease and Its Consequences

Spirit of Women

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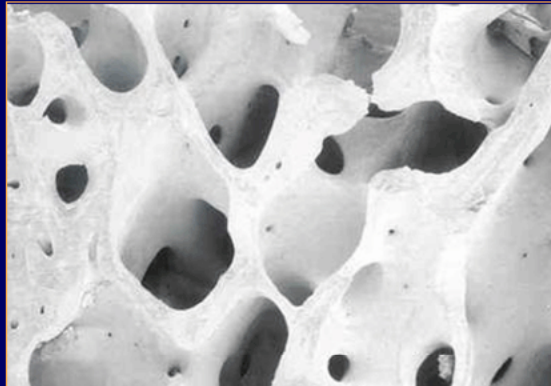
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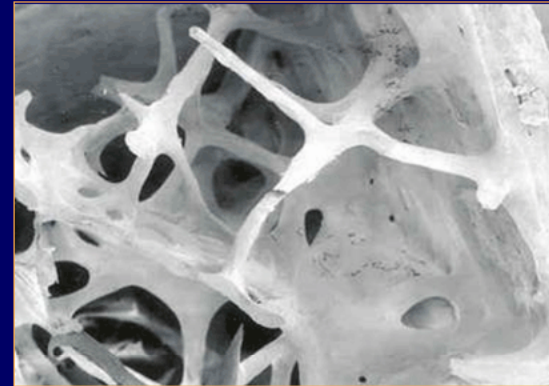
Why is an Oncologist interested in the
problem of osteoporosis? You'll find out...

Osteoporosis: Definition

Normal Bone



Osteoporotic Bone



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NIH Definition:

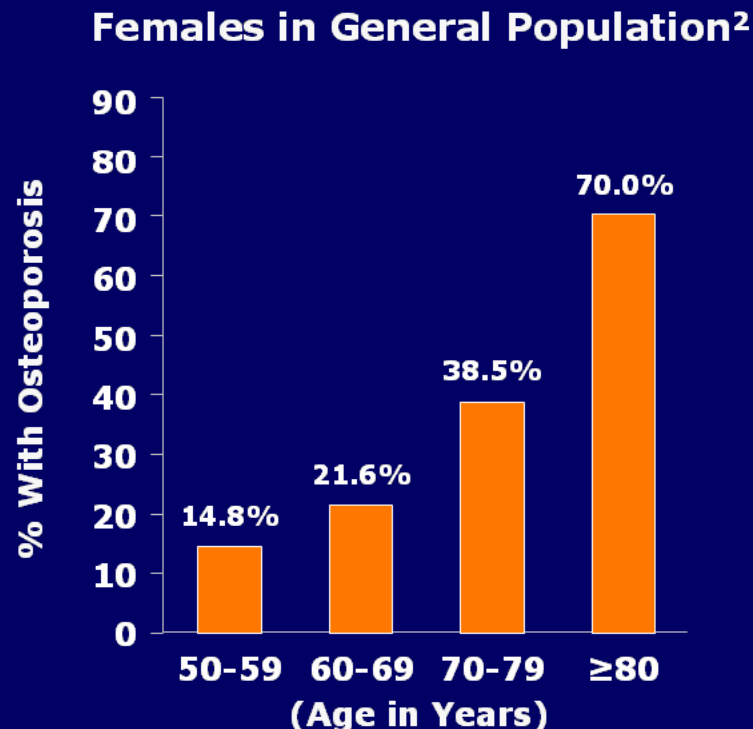
“Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture”

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

Osteoporosis is Common Among US Women

- ▶ 10 million Americans have established osteoporosis, 80% of whom are women¹
- ▶ 1.5 million fractures occur per year in US



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

Vertebral Fractures Have Significant Consequences for Patients, Including Dorsal Kyphosis



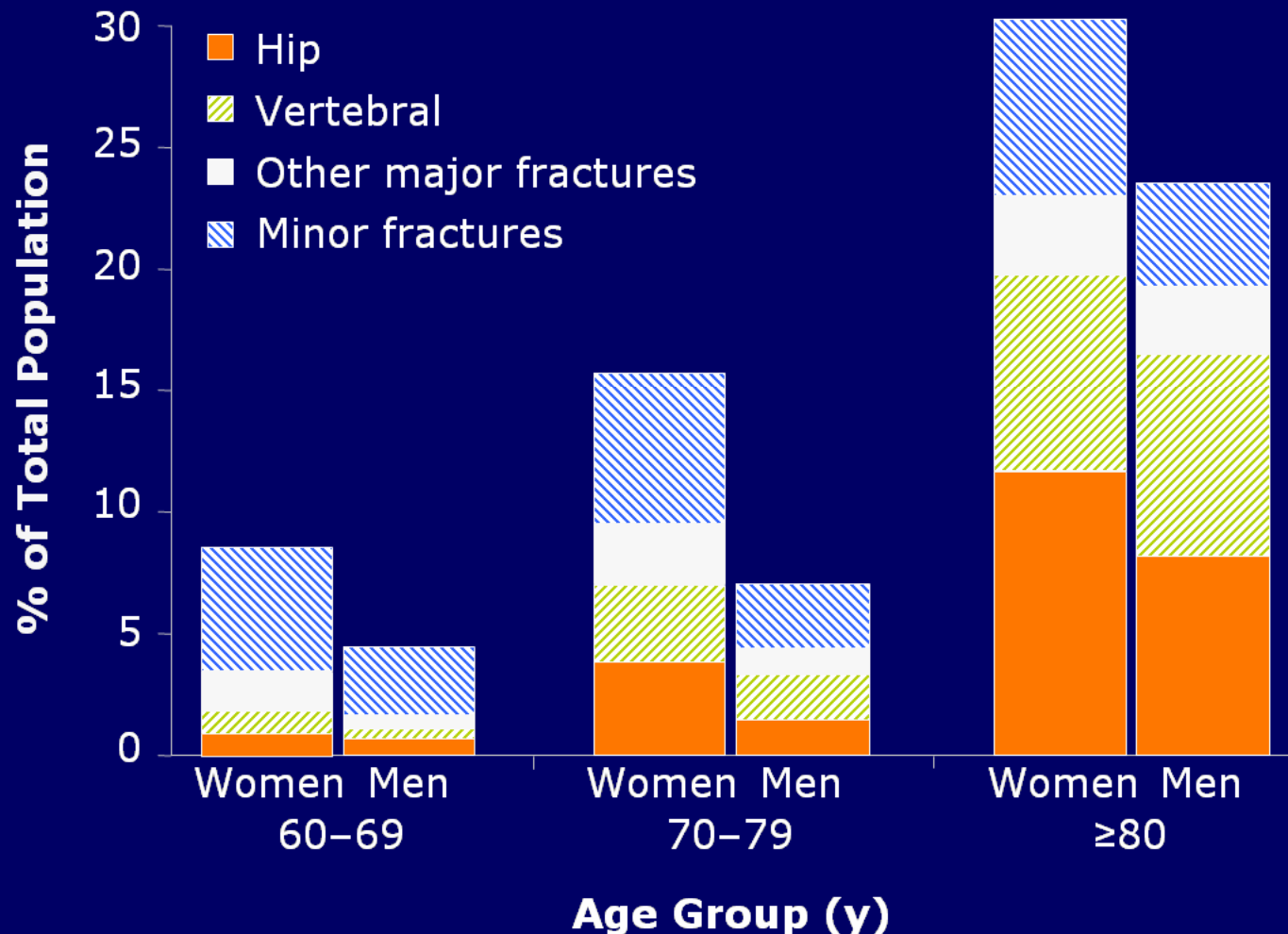
Vertebral Fractures

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

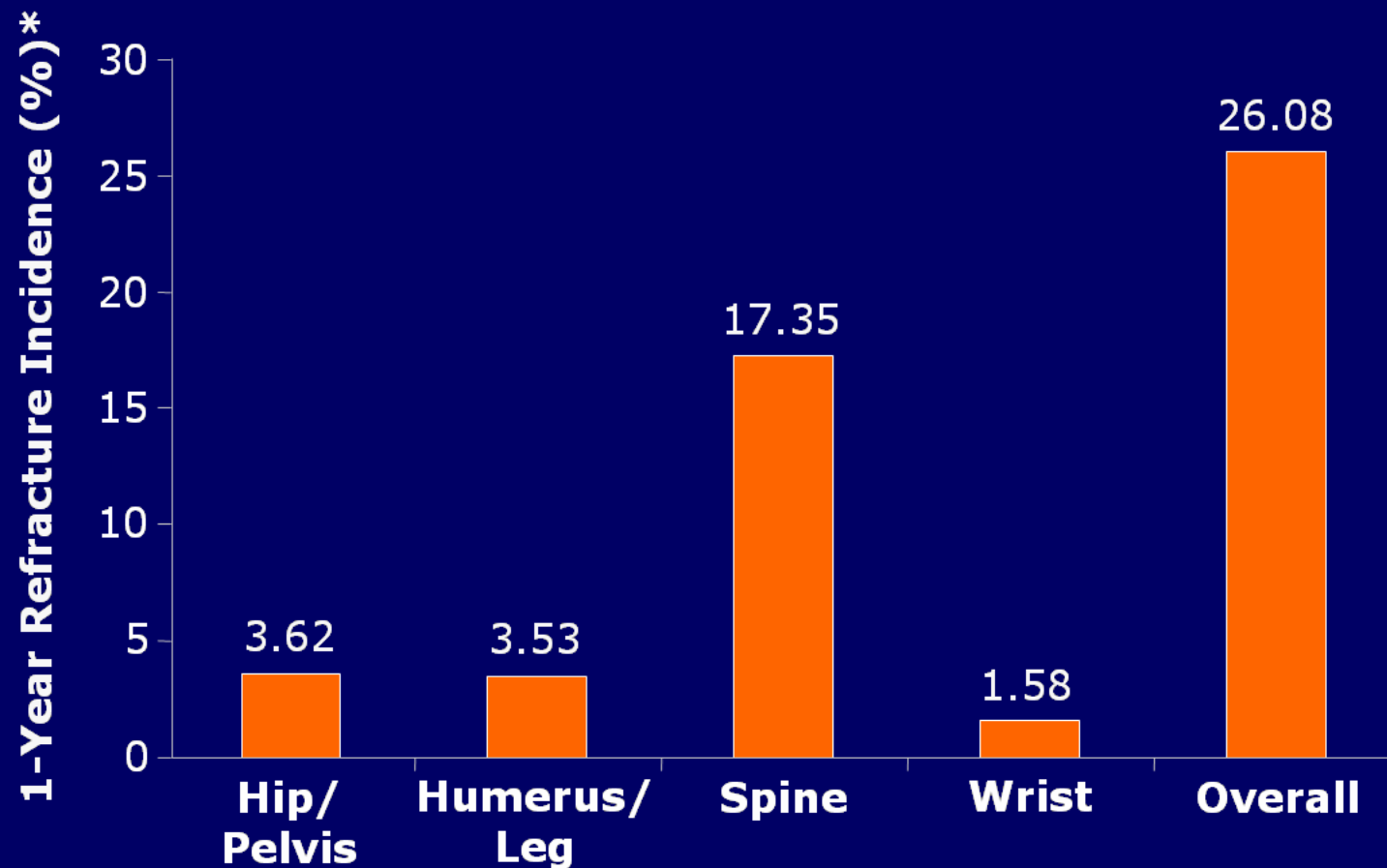
Hip and Other Non-Vertebral Fractures Have Significant Consequences

- ▶ 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

Fracture Incidence Increases With Age: 5-Year Fracture Rates in Women and Men



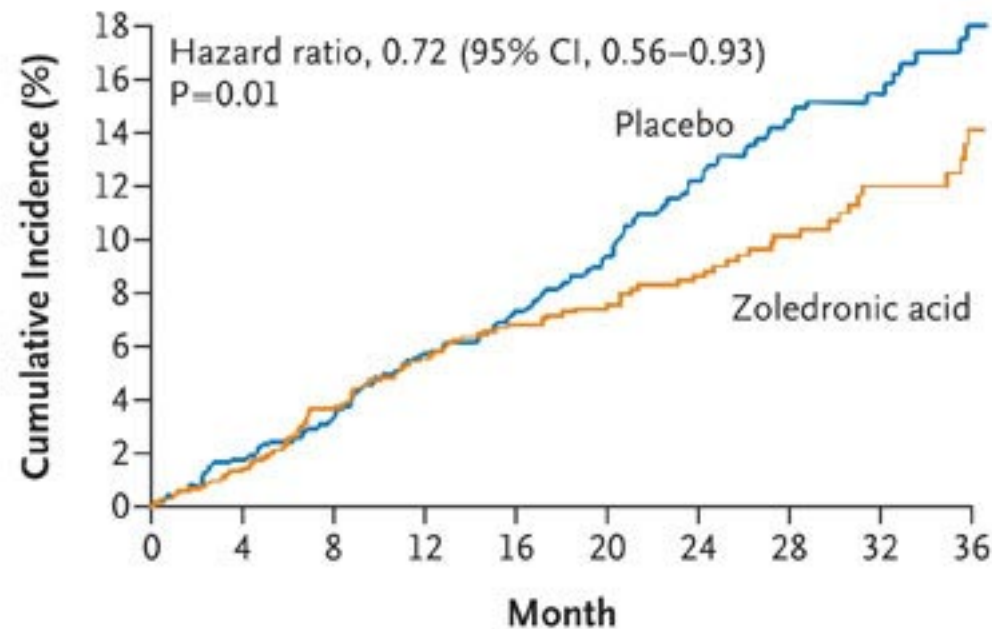
1-Year Risk of Refracture in Patients With Incident Vertebral Fracture



*Based on Kaplan-Meier analyses.

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

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

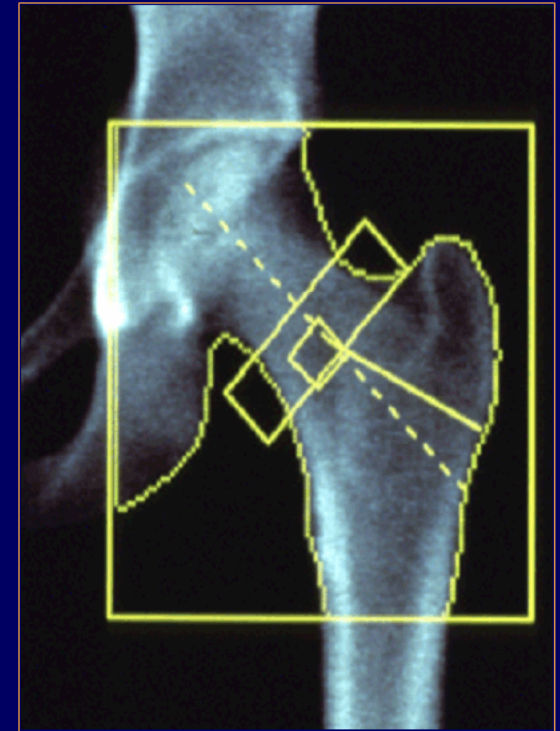


No. at Risk

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

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



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

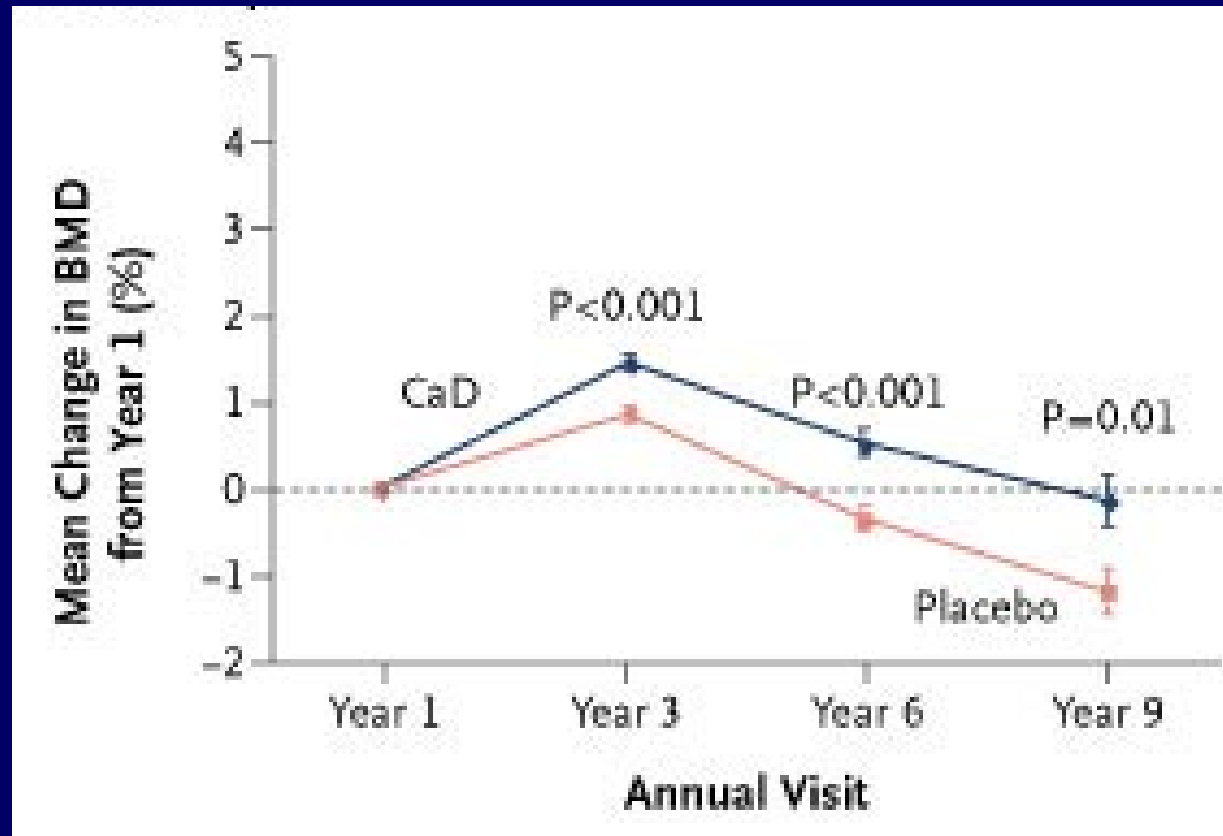
National Osteoporosis Foundation Guidelines

- ▶ 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)

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

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



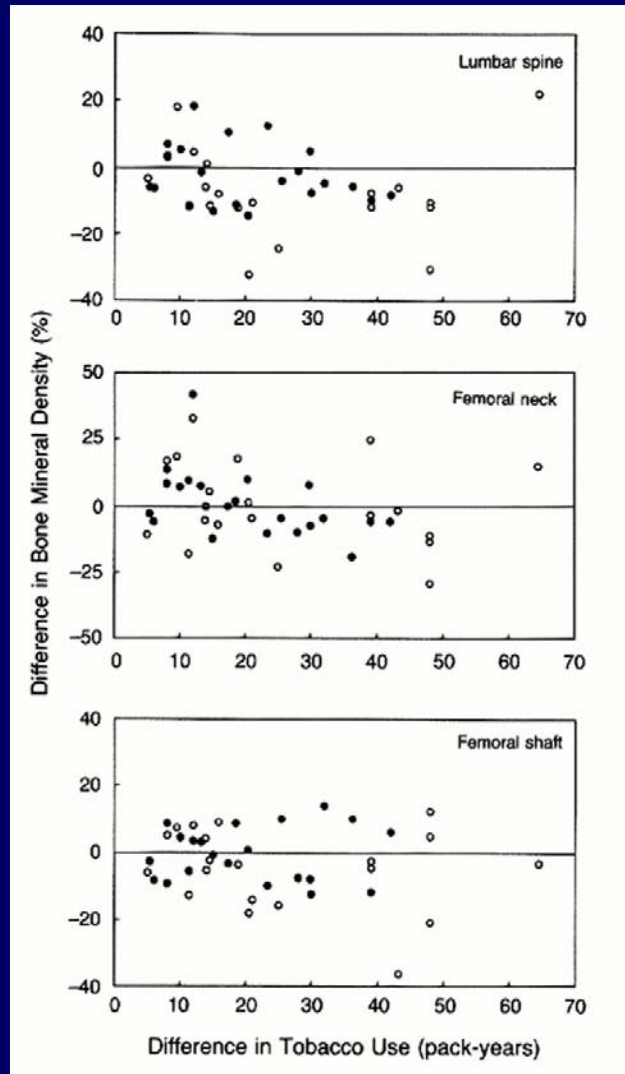
***Benefit
modest and
transient***

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

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

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)

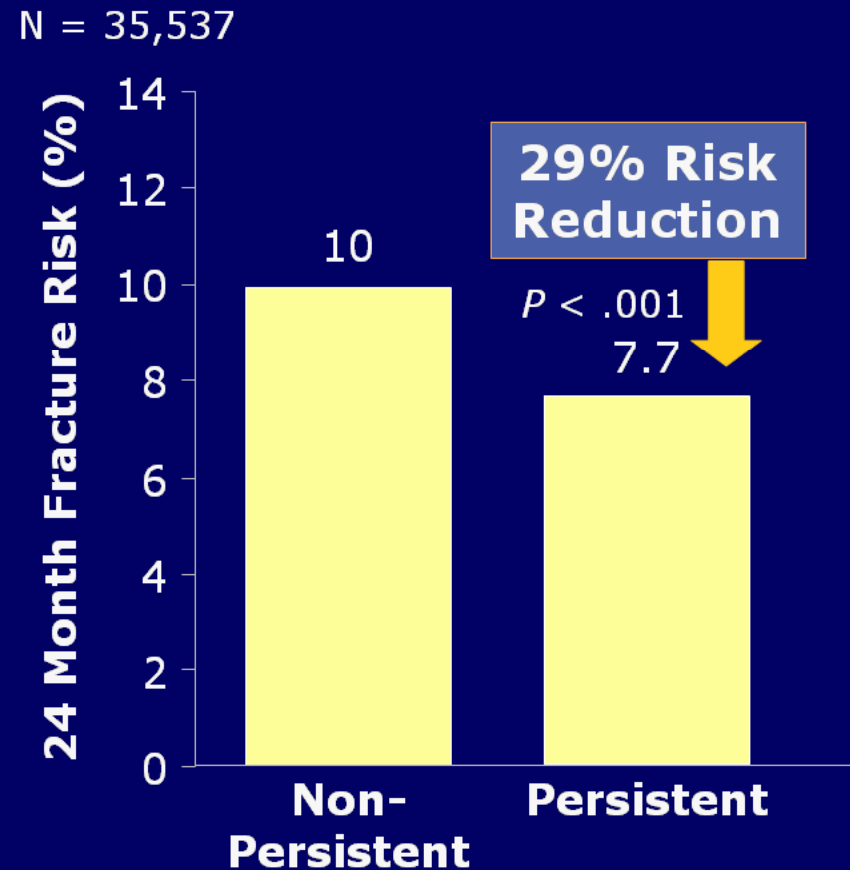
Effects of Bisphosphonates

- ▶ ↓ 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

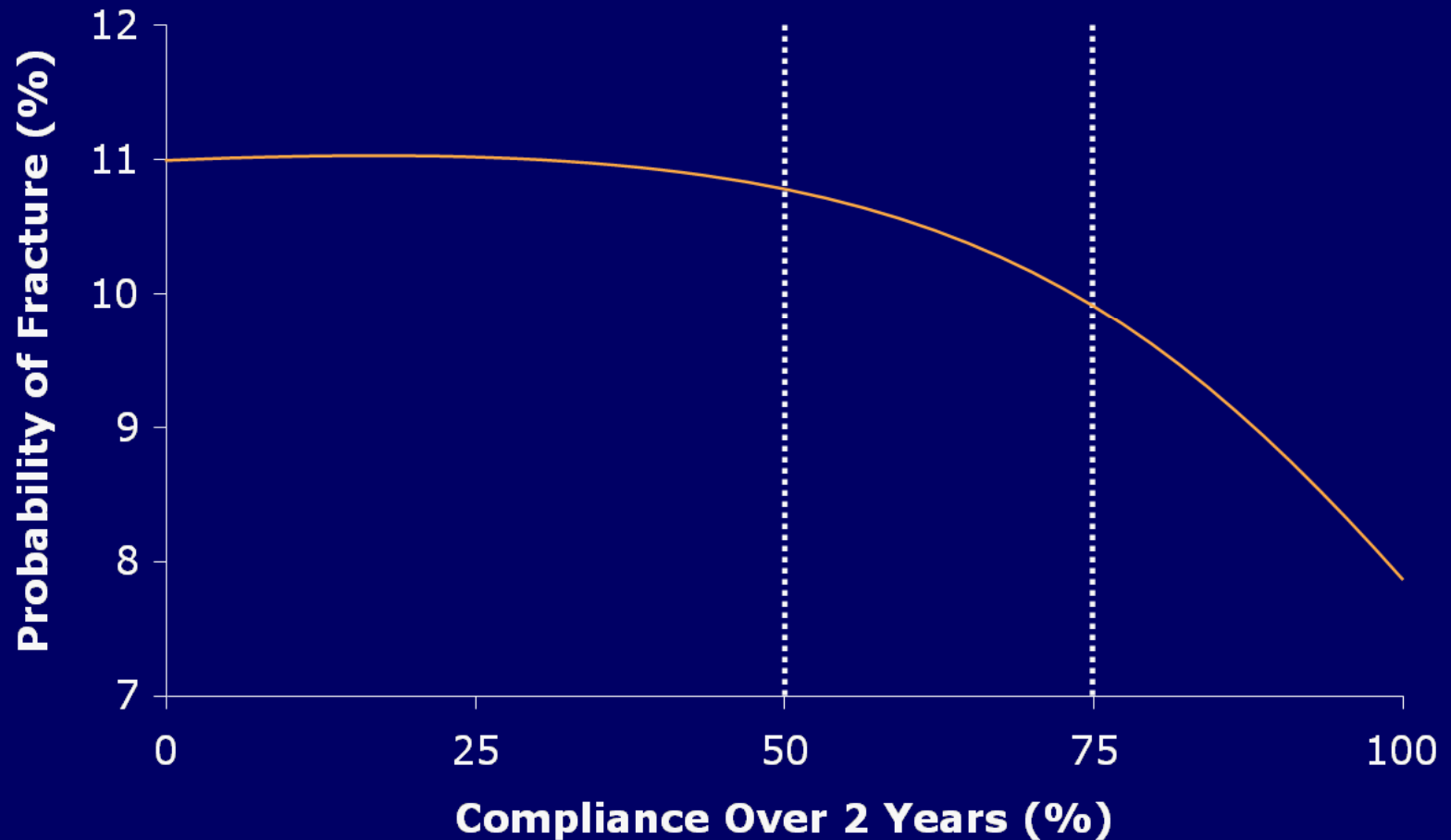
Real-World Obstacles in the Management of Osteoporosis

- ▶ 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

Poor Compliance and Persistence Lead to Compromised Fracture Risk Reduction



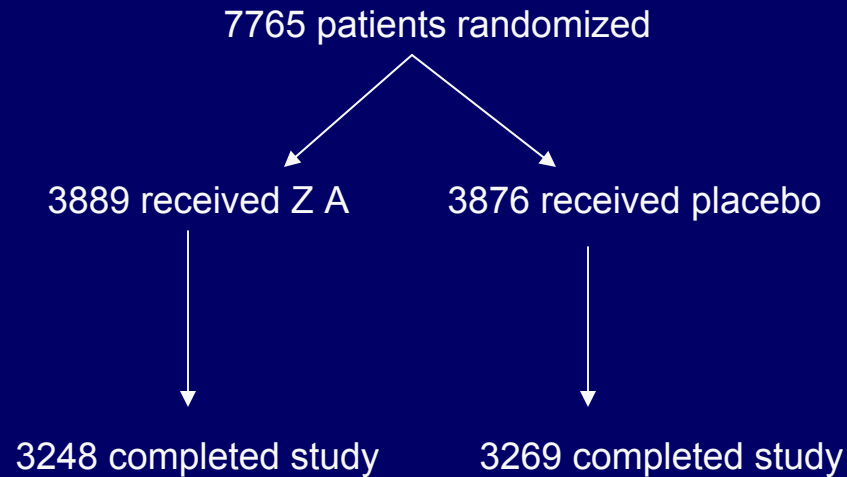
Refill Compliance and Fracture Protection Over 24 Months for Bisphosphonate-Treated Patients



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

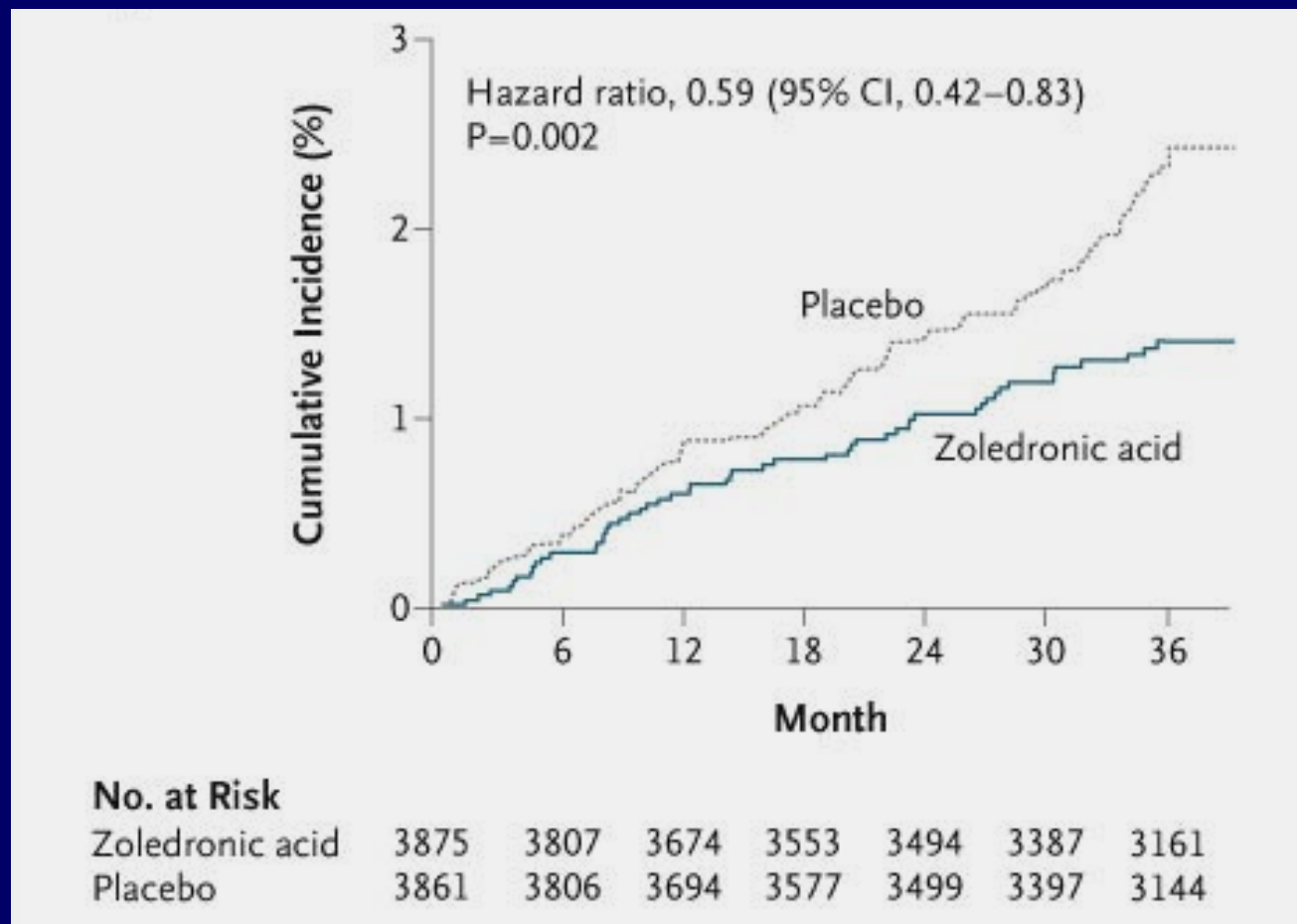
First of Two Large Studies Putting Principle of Infrequent Zolendronic Acid to the Test: Zolendronic Acid in Healthy Post-Menopausal Women



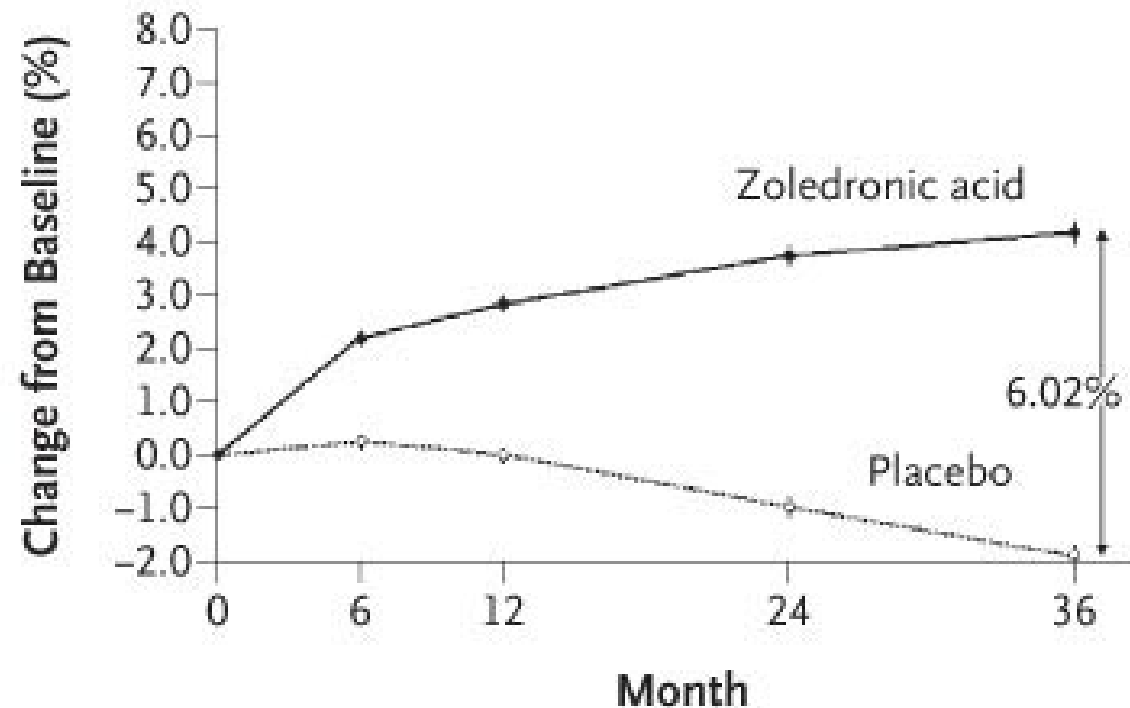
The final groups were then analyzed...

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

Incidence of Hip Fractures during the 3-Year Study Period



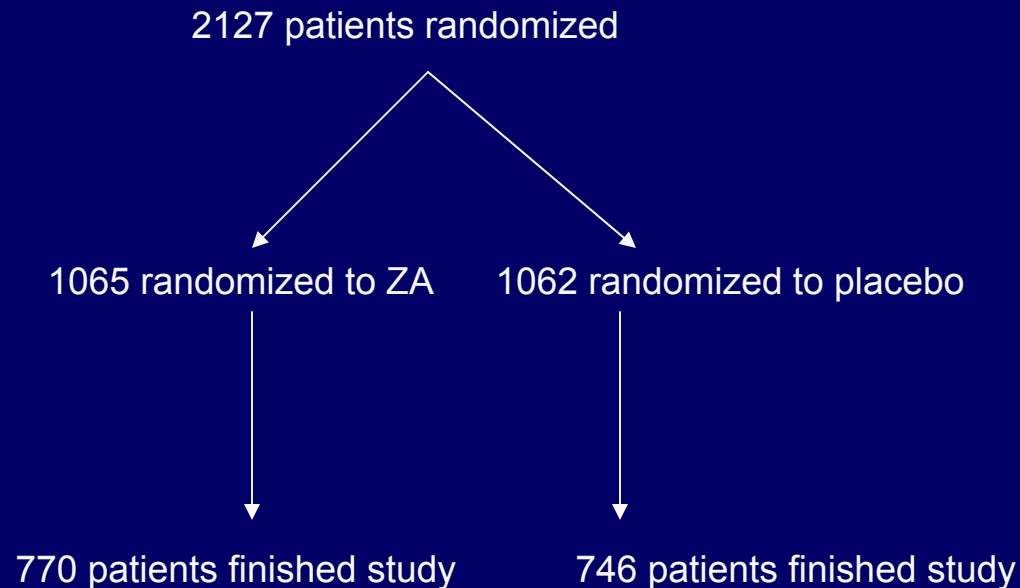
Percent Change over Time in Bone Mineral Density in Hip



No. at Risk

Zoledronic acid	3844	3515	3516	3228	3061
Placebo	3839	3543	3542	3248	3077

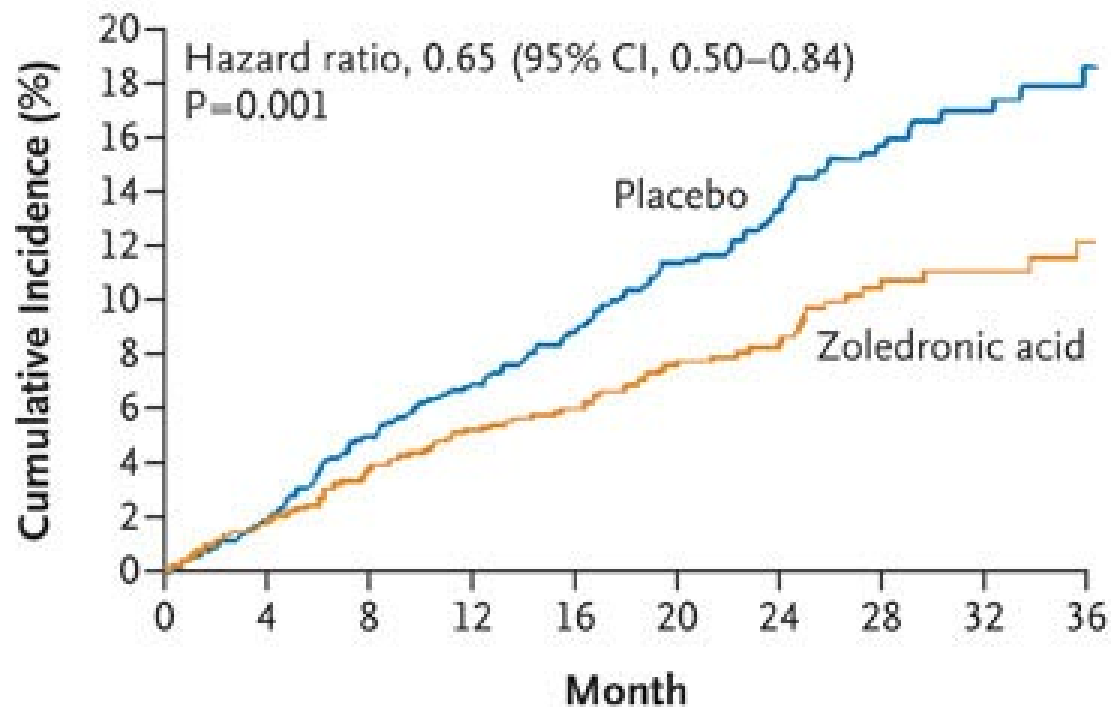
Most Recent Study Published on Outcomes Following Hip Fracture



The final groups were
then analyzed...

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

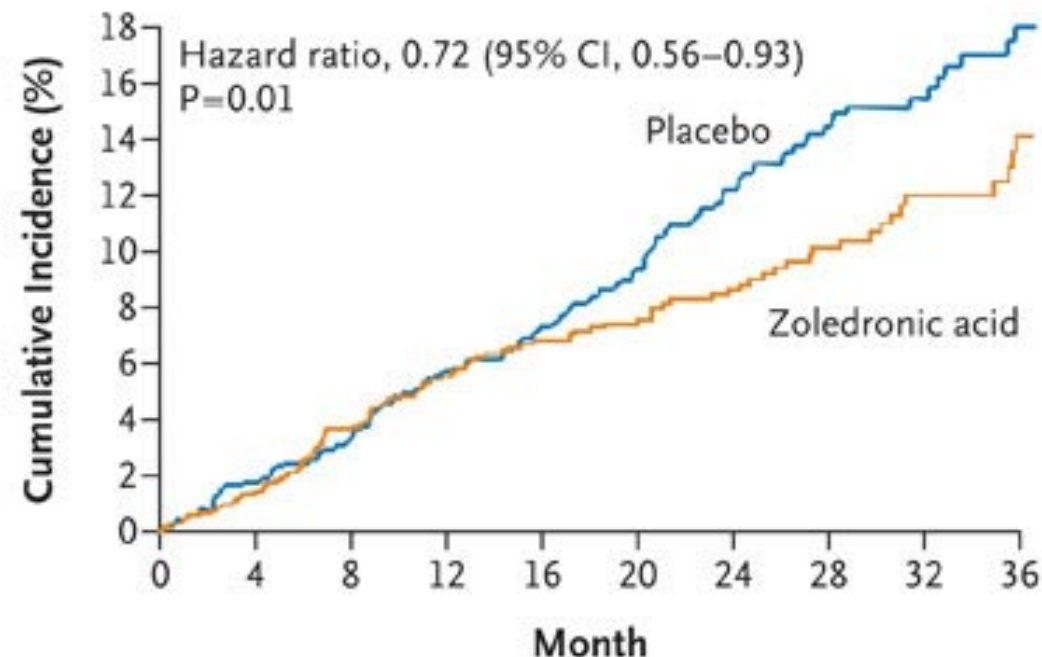
Refractures Over Time: ZA versus Placebo



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

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



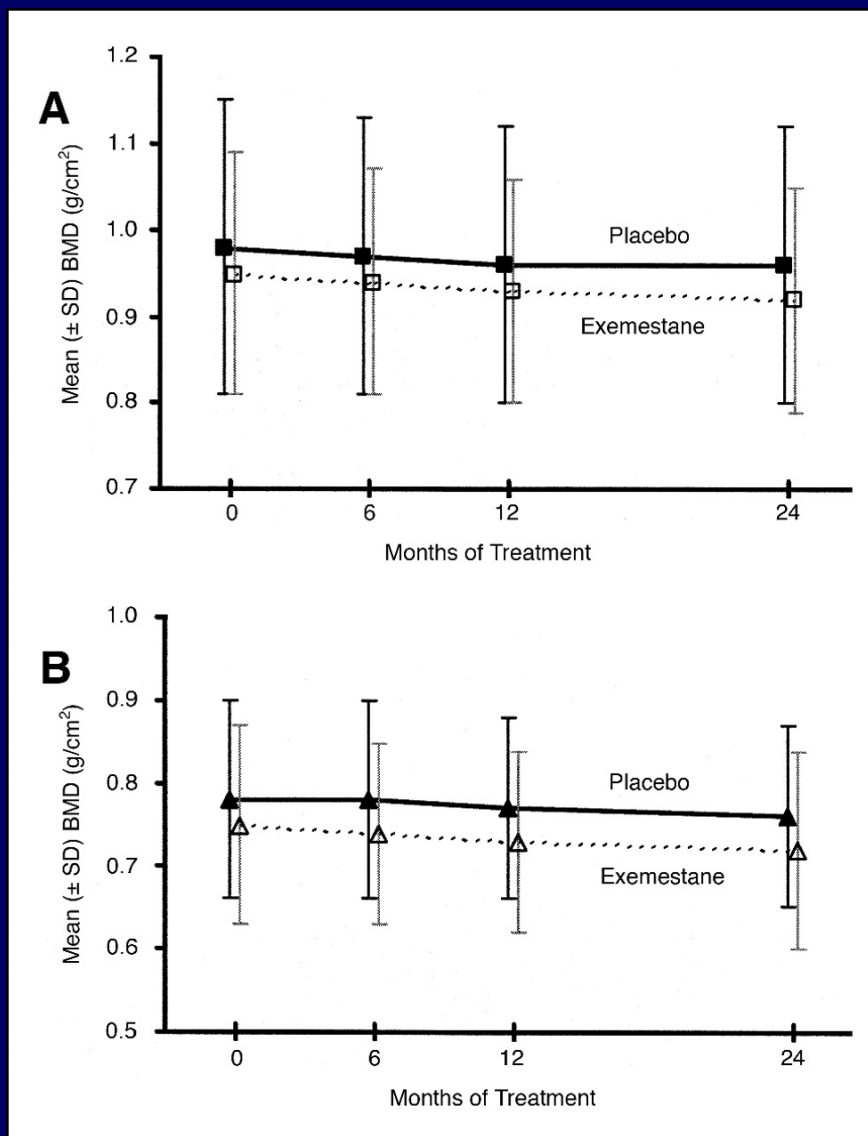
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The Problem of Bone Mineral Loss in Cancer Patients

- ▶ Widespread use of hormonal manipulation in treatment of cancer greatly exacerbates problem
 - Aromatase inhibitors in the treatment of breast cancer
 - Weak LHRH agonists (Lupron) or orchiectomy in the treatment of prostate cancer

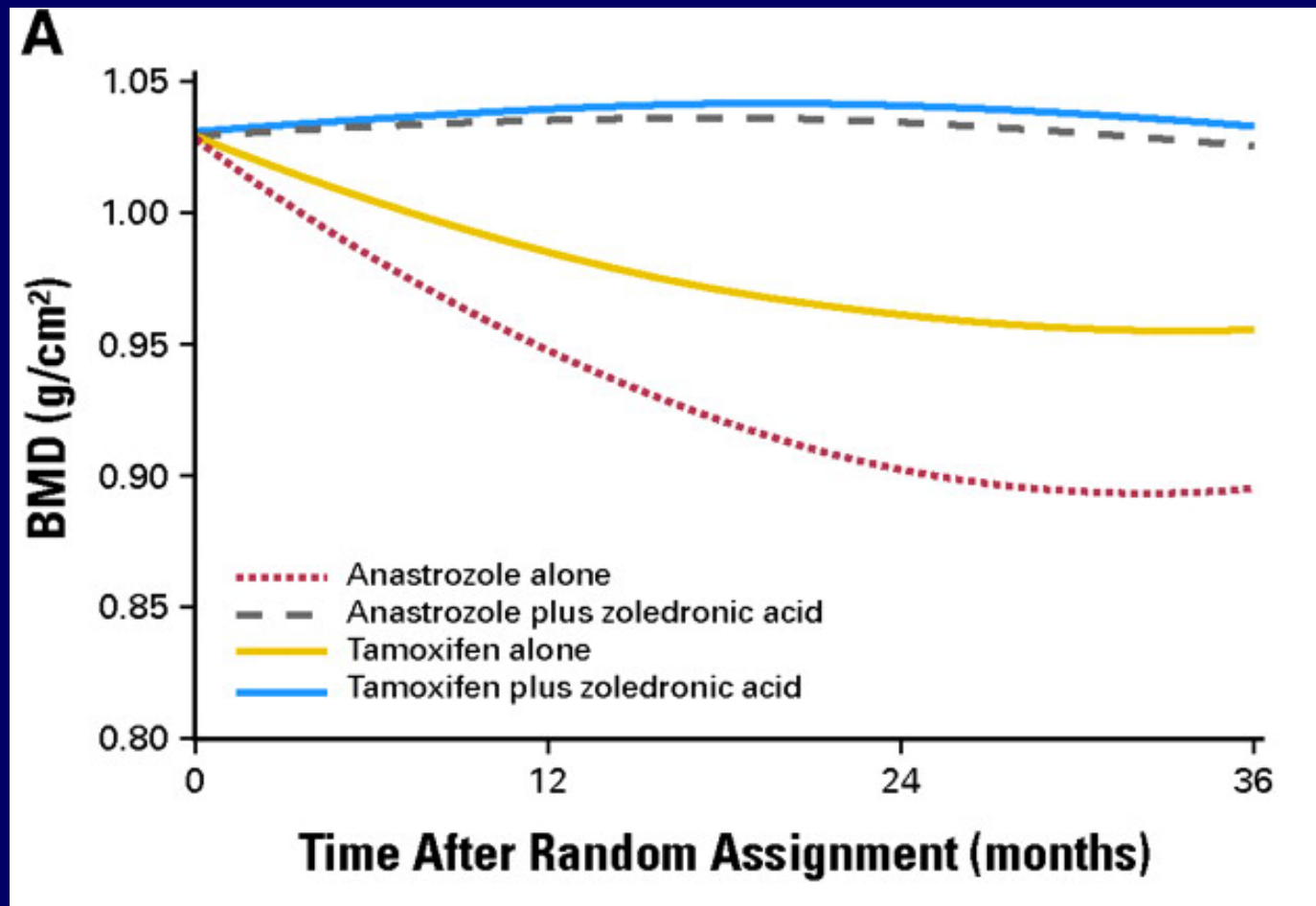
Effect of 2-year treatment with placebo or exemestane on bone mineral density (BMD) of the lumbar spine (A) and femoral neck (B)



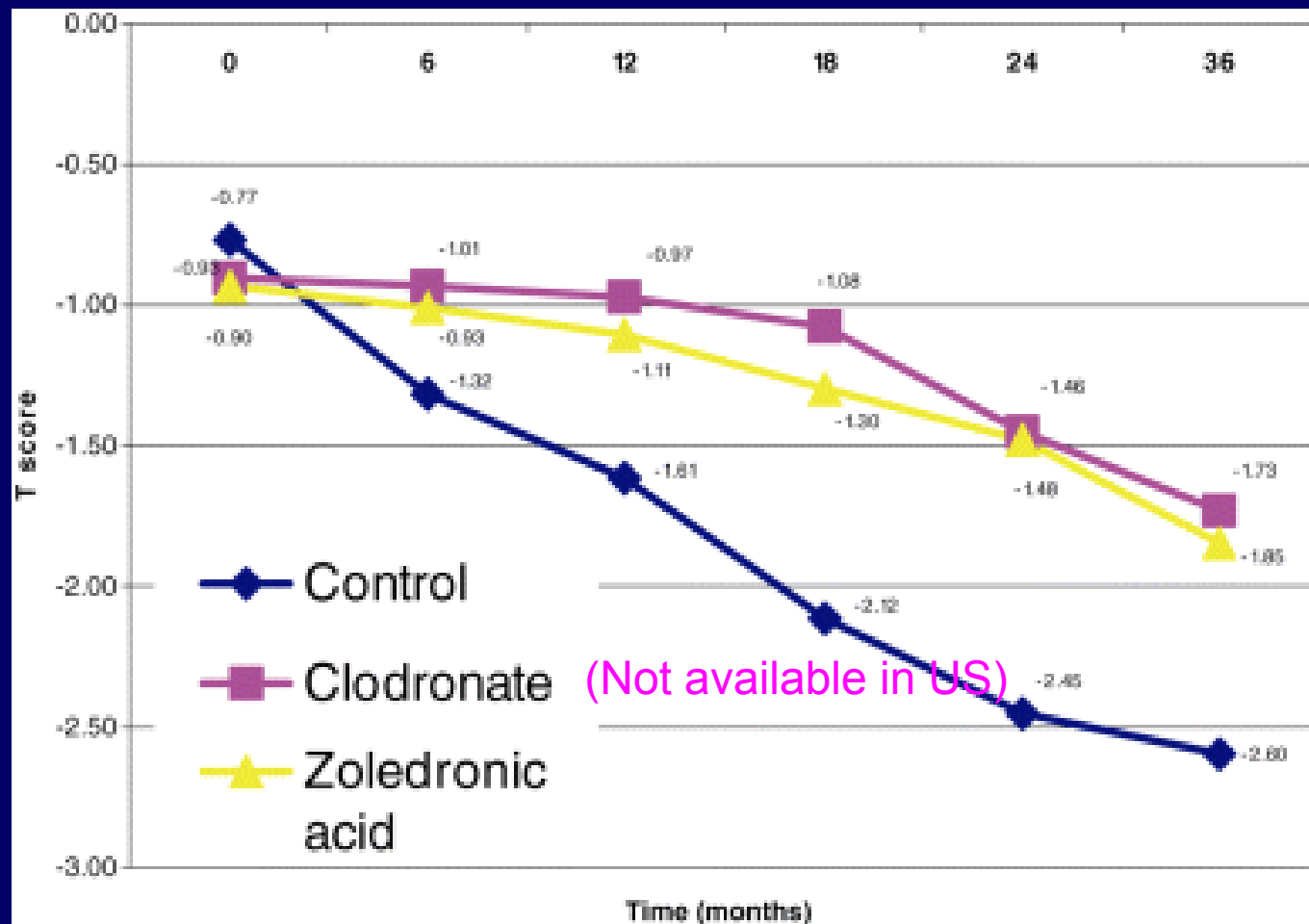
The Problem with Aromatase Inhibitors

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



Use of Bisphosphonates with Androgen Deprivation



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
-
- ▶ Available at Harbour View Women's Center by special arrangement
 - ▶ Requires prescreening for medical issues (dental health, adequacy of kidney function and vitamin D stores) by physician

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

For more information....

- ▶ Contact Laurie Jesz at 673-5861 or me...
- ▶ James J. Stark, MD, FACP at 397-4200...just across the street...



Or visit me on the web:
www.StarkOncology.com