# Osteoporosis

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# Identifying Patients with Low Bone Strength

Bone strength primarily reflects the integration of **bone quality** and **bone mineral density**.[1]

**Low Bone Strength** = **Poor Bone Quality** and **Low BMD**

## Bone Characteristics

1. Rate of bone remodeling
2. Trabecular connectivity
3. Degree of mineralization
4. Damage accumulation

## Clinical Indicators

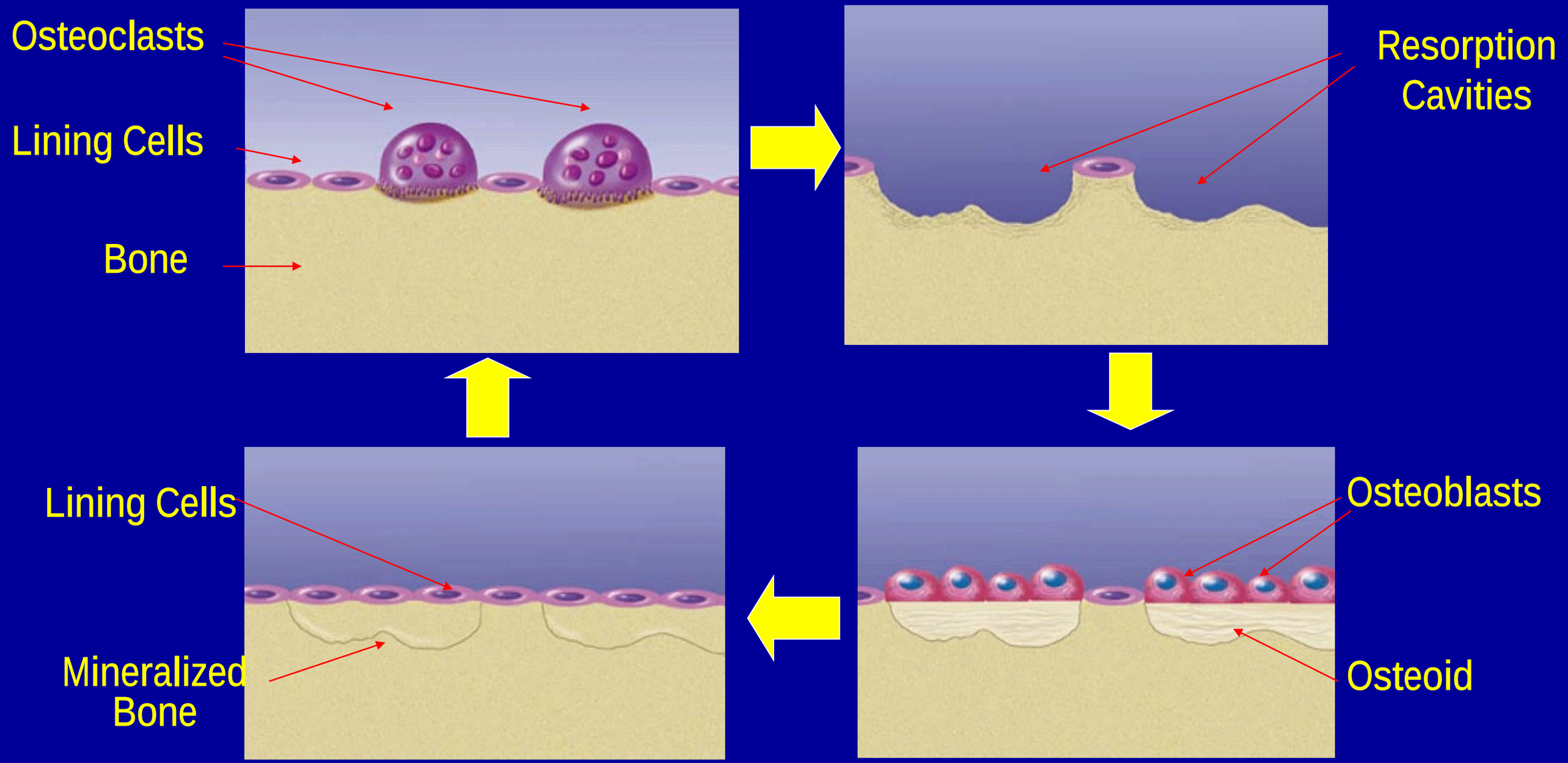
1. Increasing age
2. Minimal trauma fractures

**Easy to obtain through a DXA test**

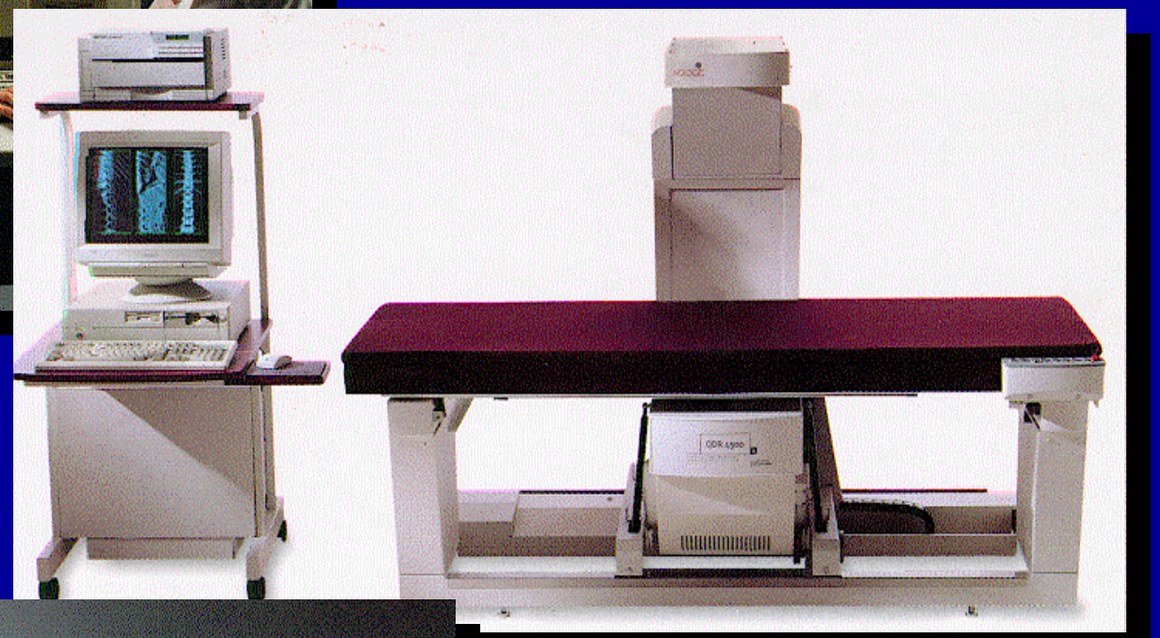
DXA = dual-energy x-ray absorptiometry.

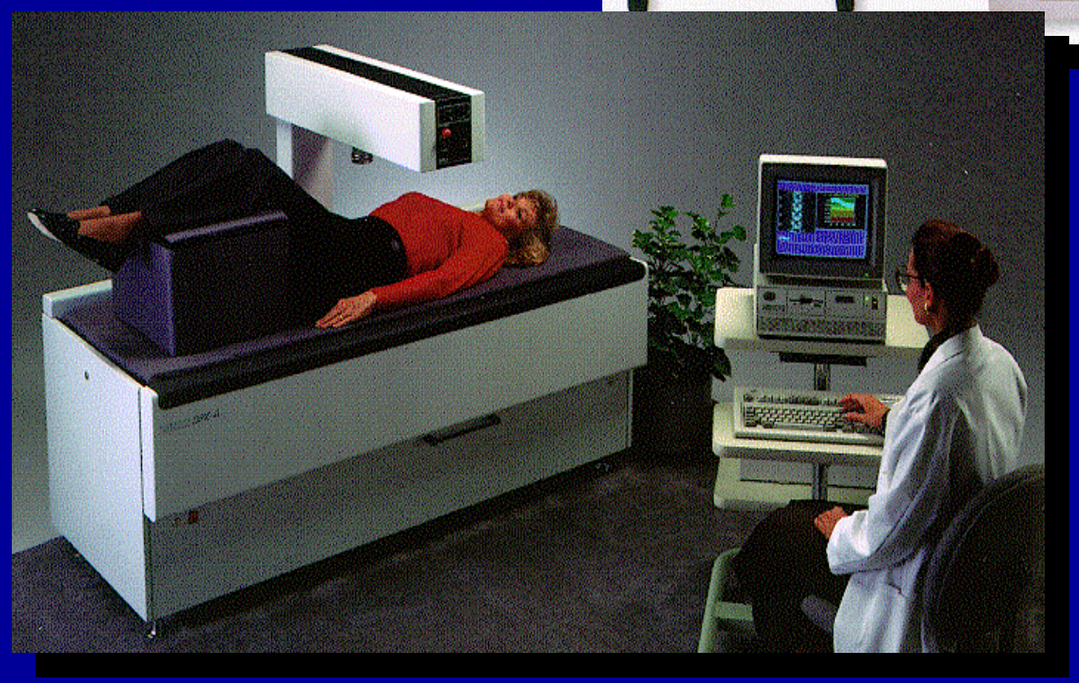
1. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. *JAMA*. 2001;285:785-795.

# Bone Remodeling Process



# Dual Energy X-ray Absorptiometry

# WHO Classification of Postmenopausal Osteoporosis, T-scores can only be used for postmenopausal women and men over 50

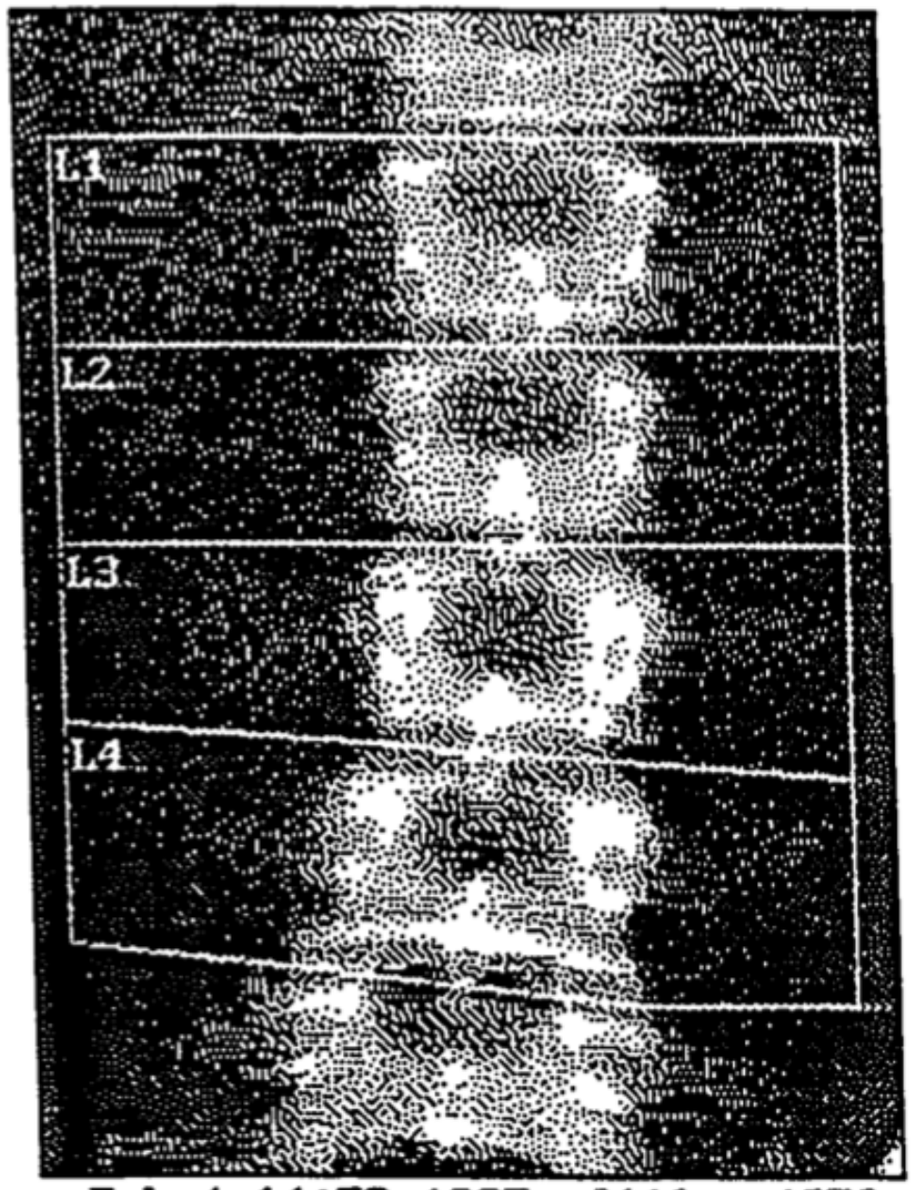
| | T- Score (SD) |
|---|---|
| Normal | Equal to -1.0 or higher |
| Low Bone Mass (Osteopenia) | Between -1.0 and -2.5 |
| Osteoporosis | Equal to -2.5 or lower |
| Severe Osteoporosis | Equal to -2.5 or lower with fracture |

World Health Organization. Technical Report Series 843 WHO, Geneva.1994.

# Derivation of WHO Classification

- Only postmenopausal Caucasian women
  - Not men, premenopausal women, children
  - No other racial or ethnic groups
- Only PA spine, hip and forearm DXA
  - Not lateral spine, heel, finger, etc
- Only for central DXA and forearm
  - Not peripheral DXA (other than forearm)
  - Not for QCT, QUS, RA, etc

k = 1.138  d0 = 44.2(1.000H)  6.402




·Feb 4 14:53 1997  [116 x 127]
(S/N 45316)

Lumbar Spine V8.16a:3

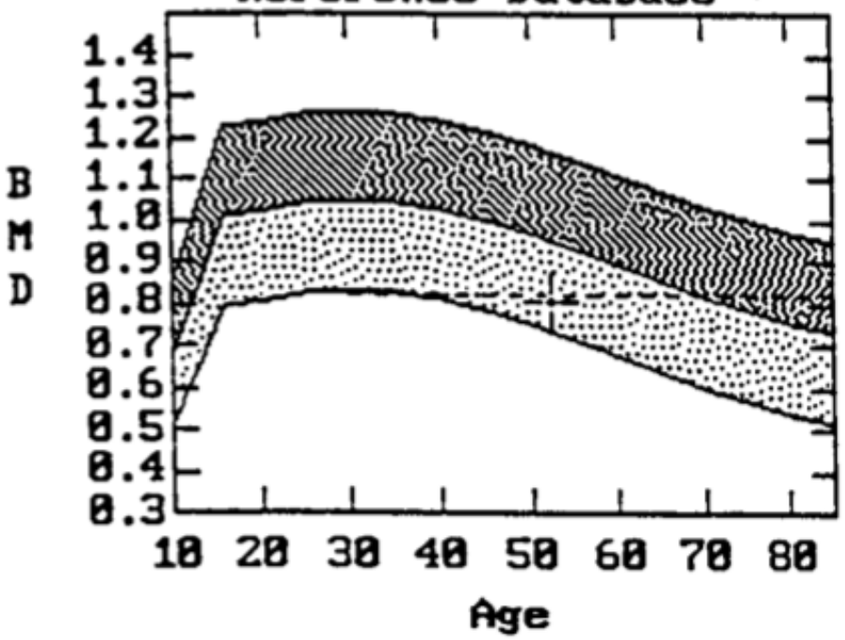
D0204970I  Tue Feb 4 14:41 1997
Name:
Comment:  SPINE & LT HIP
I.D.:  0248840  Sex:  F
S.S.#:  - -  Ethnic:  W
ZIP Code:  Height:5' 0"
Operator:  VJL  Weight:  115
BirthDate:  Age:
Physician:
Image not for diagnostic use

TOTAL BMD CV FOR L1 - L4  1.0%

C.F.  1.028  1.020  1.000

| Region | Est.Area ($cm^2$) | Est.BMC (grams) | BMD ($gms/cm^2$) |
|---|---|---|---|
| L1 | 10.70 | 7.40 | 0.692 |
| L2 | 10.94 | 8.28 | 0.757 |
| L3 | 12.54 | 10.67 | 0.851 |
| L4 | 15.37 | 13.20 | 0.859 |
| TOTAL | 49.55 | 39.55 | 0.798 |

a Lumbar Spine
Reference Database •



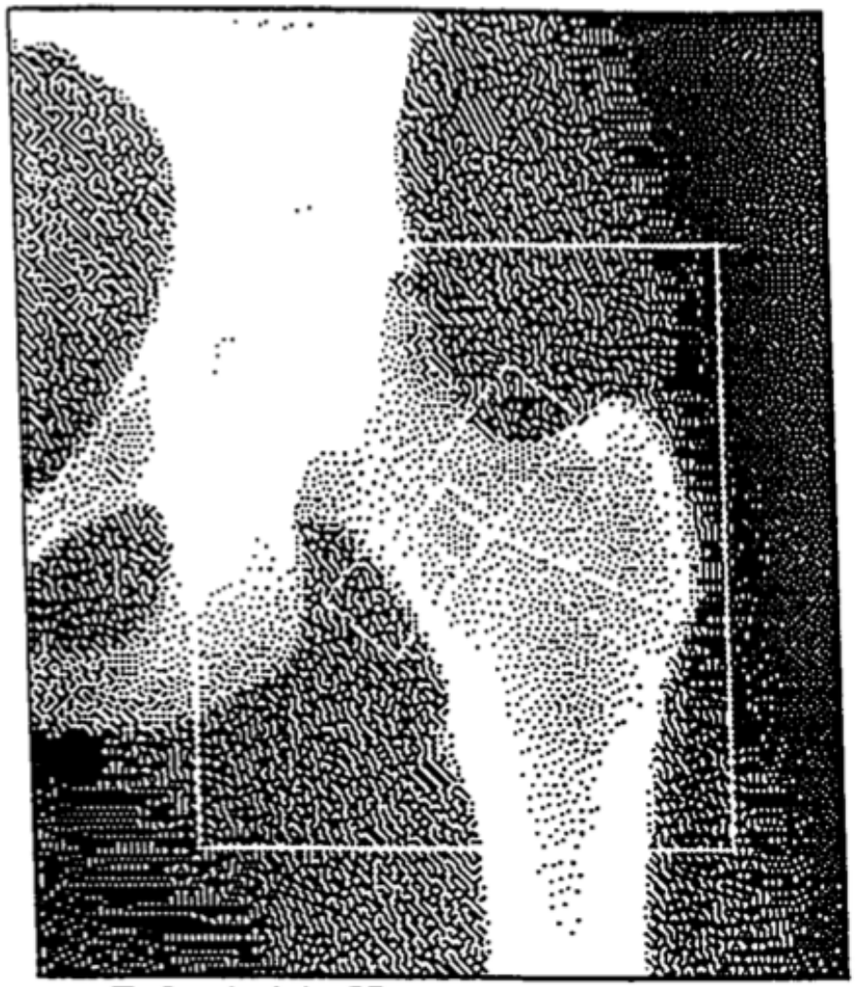

BMD(L1-L4) = 0.798 g/cm$^2$

D02049701 Tue Feb 4 14:41 1997
Name:
Comment: SPINE & LT HIP
I.D.: 0248840 Sex: F
S.S.#: - - Ethnic: W
ZIP Code: Height:5' 0"
Operator: VJL Weight: 115
BirthDate: Age:
Physician:

| Region | BMD | T(30.0) | | Z | |
|---|---|---|---|---|---|
| L1 | 0.692 | -2.12 | 75% | -1.33 | 83% |
| L2 | 0.757 | -2.47 | 74% | -1.58 | 81% |
| L3 | 0.851 | -2.12 | 79% | -1.18 | 87% |
| L4 | 0.859 | -2.34 | 77% | -1.38 | 85% |
| L1-L4 | 0.798 | -2.26 | 76% | -1.35 | 84% |

• Age and sex matched
T = peak bone mass
Z = age matched

k = 1.140  d0 =  47.5(1.000H)  5.713



·Feb 4 14:52 1997  [85 x 95]
(S/N 45316)
Left Hip V8.16a:3

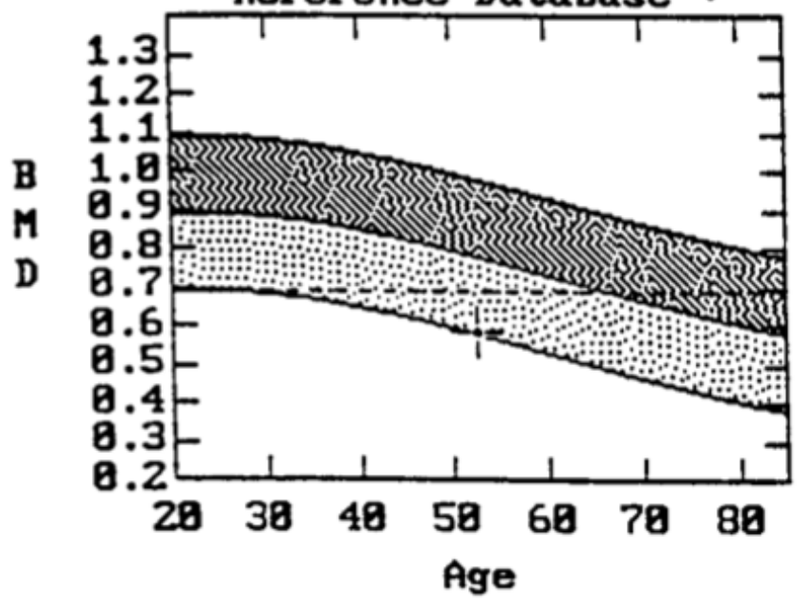
D0204970J  Tue Feb 4 14:44 1997
Name:
Comment:  SPINE & LT HIP
I.D.:  0248840  Sex:  F
S.S.#:  -  -  Ethnic:  W
ZIP Code:  Height:5' 0"
Operator:  VJL  Weight:  115
BirthDate:  Age:
Physician:
Image not for diagnostic use

TOTAL BMD CV 1.0%

| | C.F. 1.028 | 1.020 | 1.000 |
|---|---|---|---|
| Region | Est.Area ($cm^2$) | Est.BMC (grams) | BMD (gms/$cm^2$) |
| Neck | 4.60 | 2.68 | 0.583 |
| Troch | 7.37 | 4.99 | 0.676 |
| Inter | 14.09 | 12.81 | 0.909 |
| TOTAL | 26.06 | 20.48 | 0.786 |
| Ward's | 1.15 | 0.60 | 0.521 |

Midline ( 88,102)-(148, 54)
Neck  -49 x  15 at [ 24, 10]
Troch  11 x  36 at [  0,  0]
Ward's  -11 x  11 at [  4,  6]

a Left Hip
Reference Database •



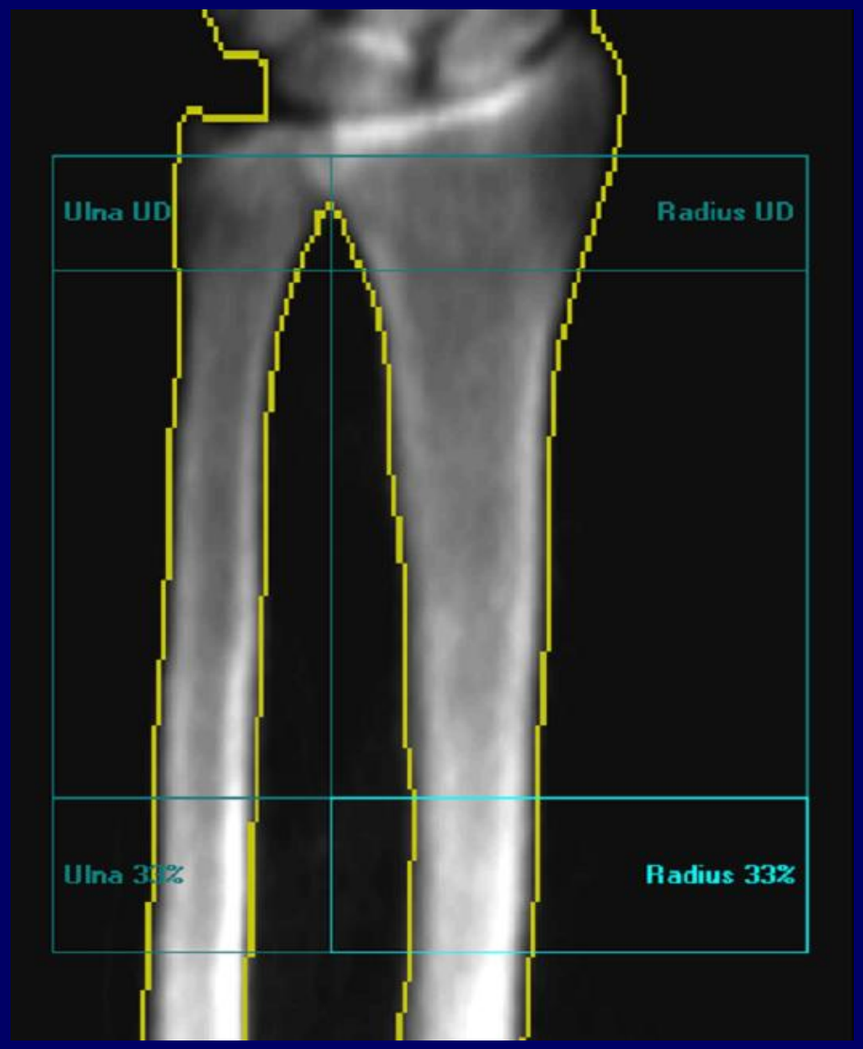

D0204970J Tue Feb 4 14:44 1997
Name:
Comment: SPINE & LT HIP
I.D.: 0248840 Sex: F
S.S.#: - - Ethnic: W
ZIP Code: Height:5' 0"
Operator: VJL Weight: 115
BirthDate: Age:
Physician:

BMD(Neck[L]) = 0.583 g/cm$^2$

| Region | BMD | T | | Z | |
|---|---|---|---|---|---|
| Neck | 0.583 | -3.12 (22.0) | 65% | -1.97 | 75% |
| Troch | 0.676 | -0.51 (30.0) | 94% | +0.13 | 102% |
| Inter | 0.909 | -1.70 (29.0) | 79% | -1.09 | 86% |
| TOTAL | 0.786 | -1.58 (28.0) | 81% | -0.91 | 88% |
| Ward's | 0.521 | -2.58 (20.0) | 65% | -0.65 | 88% |

• Age and sex matched
T = peak bone mass
Z = age matched

# Forearm: Optimal Positioning

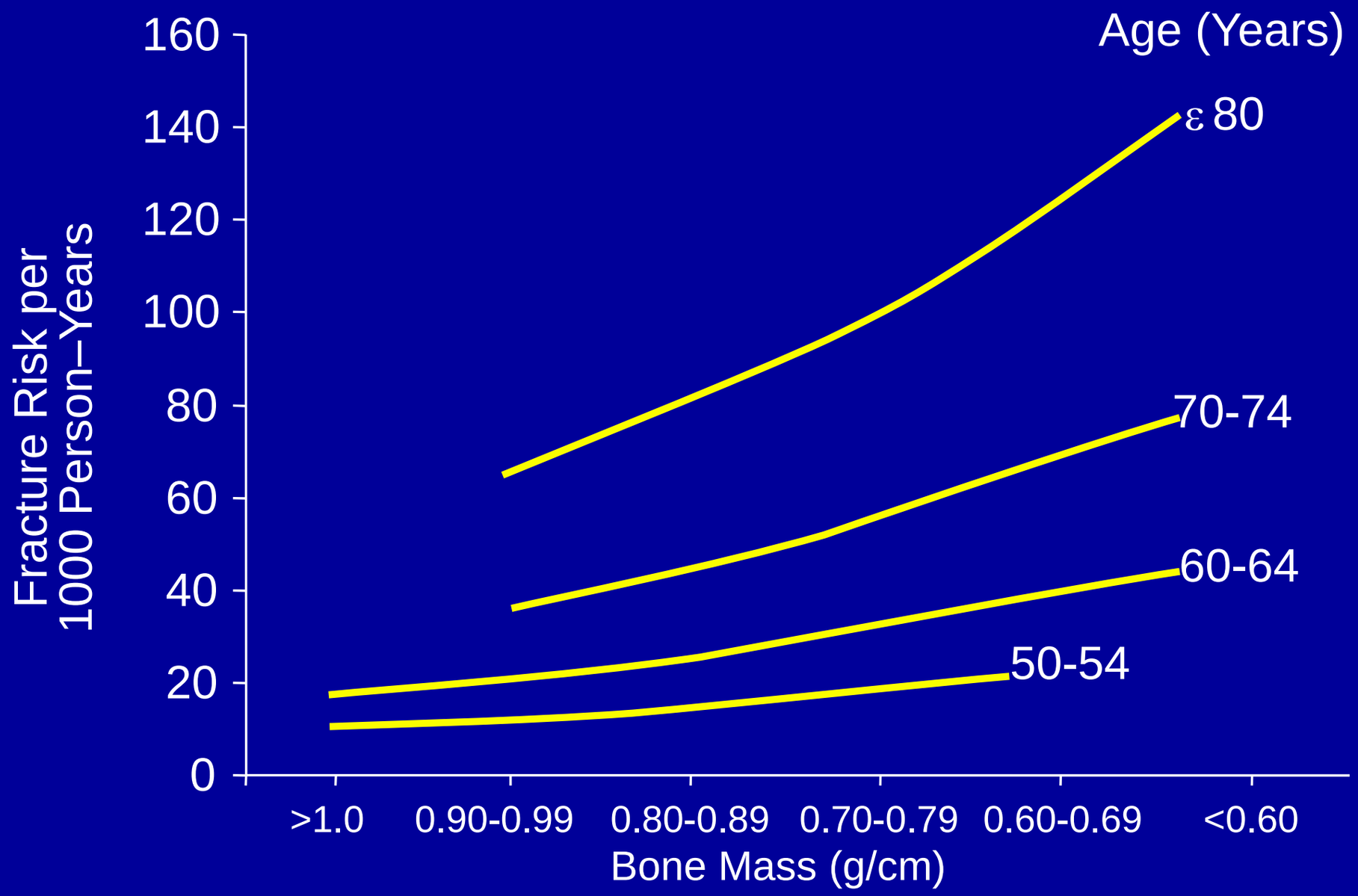



- Forearm is centered
- Radius and ulna straight
  - Aligned with long axis of table
- Distal cortex of radius and ulna visible
- No avoidable artifacts

# BMD Is a Strong Predictor of Fracture


Data available on request from Merck & Co., Inc. Please specify 20350477(3)-FOS.

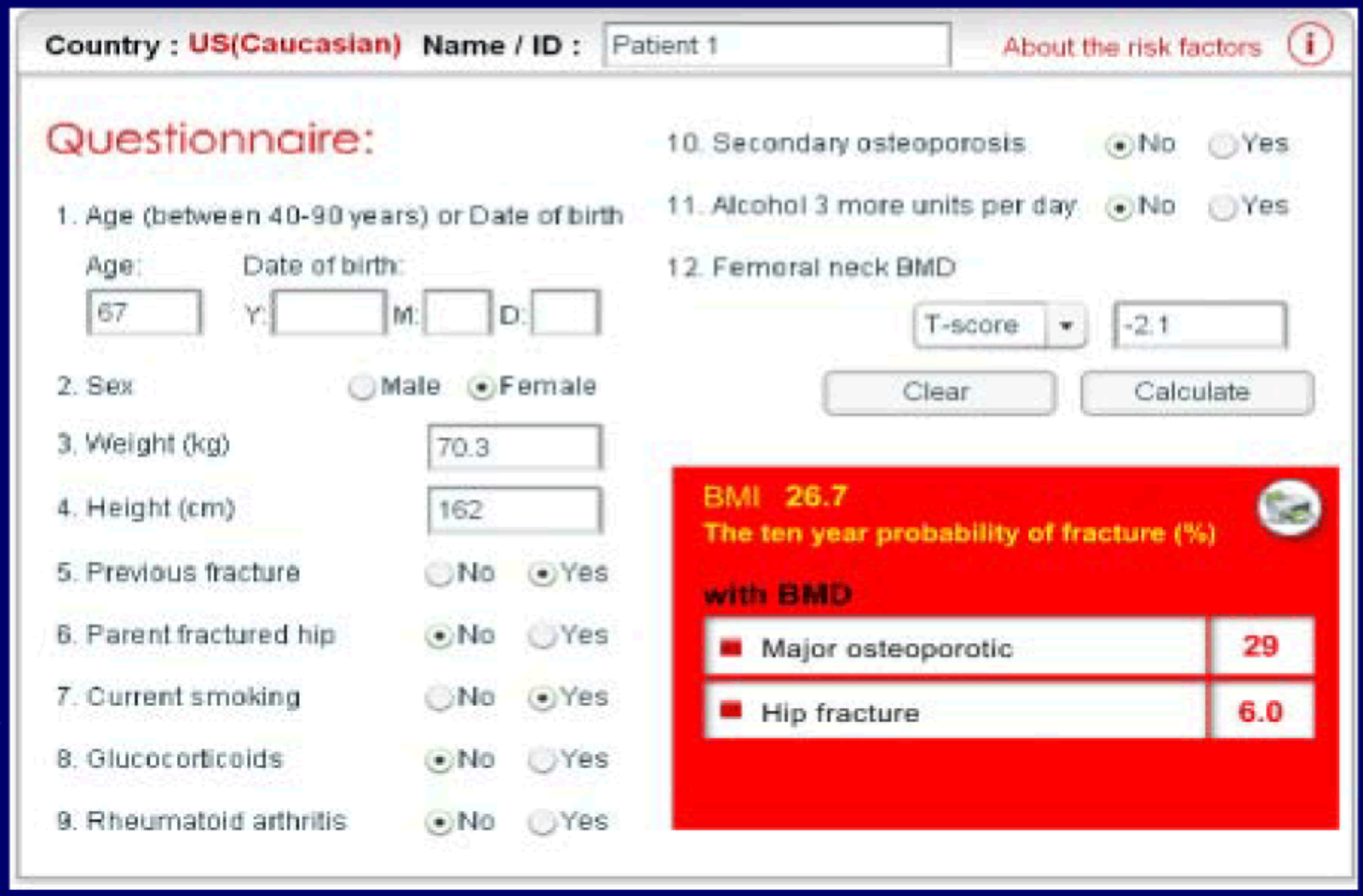
# Age and Bone Mass as Predictors of Osteoporotic Fracture




Adapted from Hui SL, et al. *J Clin Invest*. 1988;81:1804-1809.

# FRAX®: Gauging 10-Year Fracture Probability

- FRAX is a WHO algorithm to determine 10-year fracture risk
- Takes into account BMD and specific risk factors
- Determines patient's absolute fracture risk as opposed to relative risk
- Identifies the high-risk patients who could benefit from treatment
- FRAX web site at: http://www.shef.ac.uk/FRAX/





1. FRAX® WHO Fracture Risk Assessment Tool. Available at: http://www.shef.ac.uk/FRAX/. Accessed February 2008.
2. Dawson-Hughes B et al. *Osteoporos Int*. DOI: 10.1007/s00198-008-0559-5.

# NOF Guidelines

- www.shef.ac.uk/FRAX/
- Treatment is recommended for:
  - Pts with hip or vertebral fractures
  - Pts with osteoporosis T-score – 2.5
  - Postmenopausal men or women with low bone mass -1 to -2.5 at the FN, total hip or total spine and a ten year hip fracture probability of >3% or a ten year all major osteoporosis related fracture of 20% based on the US adapted WHO absolute risk model

# Precision

- Expresses reproducibility or consistency of repeat measurements
- Precision error helps determine how much of a change in BMD is required to know that the difference is real

C

# Impact of Vertebral Fractures

- Pain
- Possible permanent disfigurement
- Loss of height
- Loss of self-esteem
- Increased risk of hip fracture
- Increased morbidity

# 250,000 Hip Fractures Each Year

- Up to 24% excess mortality within 1 year[1]
- Nearly 65,000 American women die from complications of hip fracture each year.[2]
- 50% of hip fracture survivors are permanently incapacitated[3]
- 20% of hip fracture survivors require long-term nursing home care[4]

# Distal Forearm Fractures

- Third most common osteoporotic fracture
- Most are caused by fall on outstretched hand
- Diagnosis
  - Most are diagnosed clinically
  - Often confirmed with radiography

# Does Calcium Increase Vascular Risk?

## Calcium Supplements and Heart Events

- Calcium subcommittee of the Professional Practice Committee of ASBMR, “Commentary on Calcium Supplements and Cardiovascular Events”, JCD, vol 15, no 2, 130 – 134, 2012
- Data reviewed from randomized Controlled trials and 3 meta-analyses
  - Maintenance of target levels for the supplement and placebo group are difficult – compliance in the supplement group must be 80%
  - Clear, definable and fully adjudicated endpoints must be used
  - The most appropriate and stringent  methods of data evaluation must be applied

# Does Calcium Increase Vascular Risk?

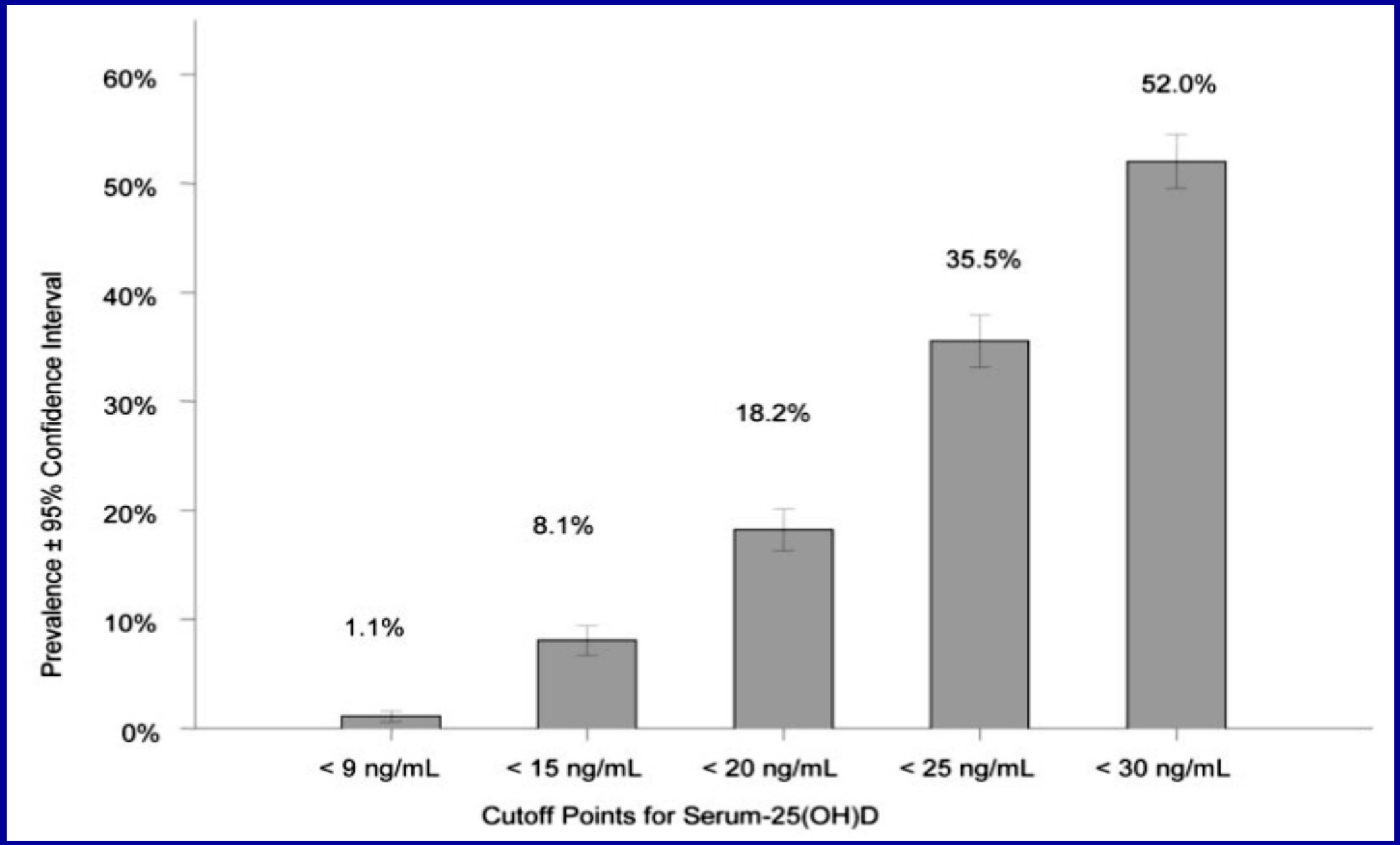
## Calcium Supplements and Heart Events

- Tang meta-analysis was noted for benefit of calcium intake, NNT was 63 patients for 3 – 5 years to prevent one fracture, in elderly individuals with low calcium intake, NNT was 30
- Bolland :
  - 12 RCT of calcium supplementation vs placebo
  - Large clinical trials of subjects receiving or not receiving calcium
  - Adverse cardiovascular events were not the primary outcome
    - Cardiovascular outcomes were obtained from self reports, hospital admissions and death certificated
    - Data was only available for 63% of the patients
    - Data did not reach statistical significance for stroke or the composite of MI, stroke or sudden death

# Calcium and Vitamin D Intake and Mortality

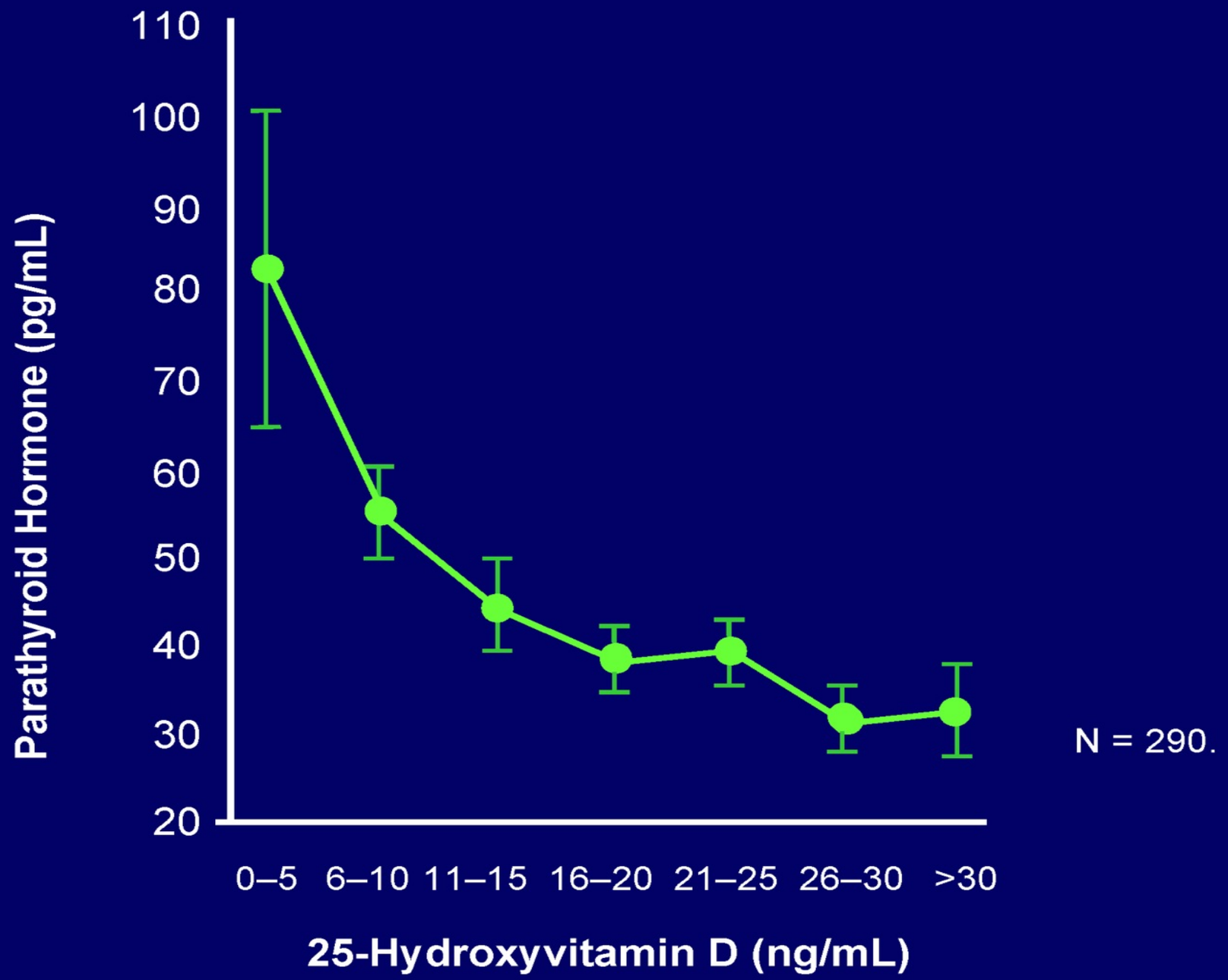
- Canadian Multocentre Osteoporosis Study (JCEM, May 24, 2012, doi:10.1210/jc.2013-1516
- Population based longitudinal cohort 115-2007
- 9033 participants
- Among women (over age 25), calcium supplement users had a lower risk of mortality than non users HR .78 (95%CI .66-.92)
- No dose response effect noted among users, there was attenuation of the association, showing statistically significant lower mortality only for supplement users with a daily dose of <1000mg

# Prevalence of Vitamin D Deficiency in Postmenopausal Women Receiving Osteoporosis Therapy




JCEM 2005;90:3215-3224

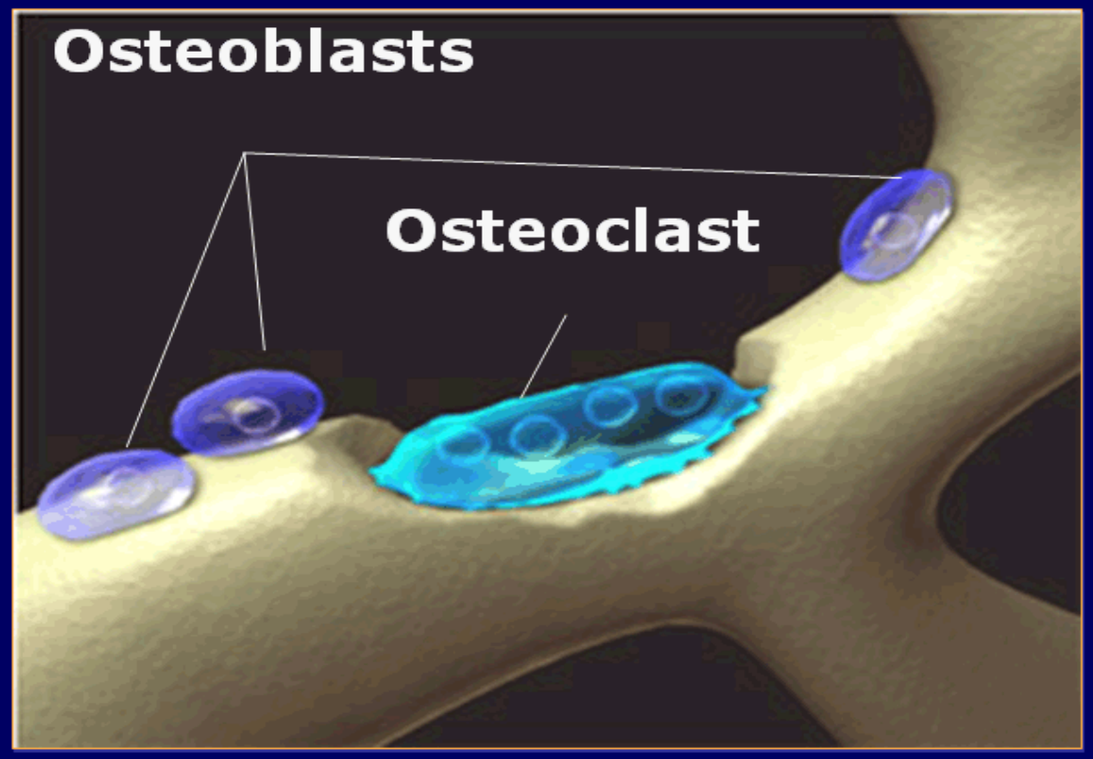
# Relationship Between Serum 25-(OH)D and PTH in Medical Inpatients




Thomas MK et al. *N Engl J Med.* 1998;338:777–783.

# Commonly Used Biochemical Markers of Bone Turnover

- **Formation**
  - Bone-specific alkaline phosphatase (BSAP)
  - Osteocalcin (OC)
  - Propeptide of type I collagen (P1NP)
- **Resorption**
  - N-telopeptide of type I collagen (NTX)
  - C-telopeptide of type I collagen (CTX)




**Active Bone Resorption Site**

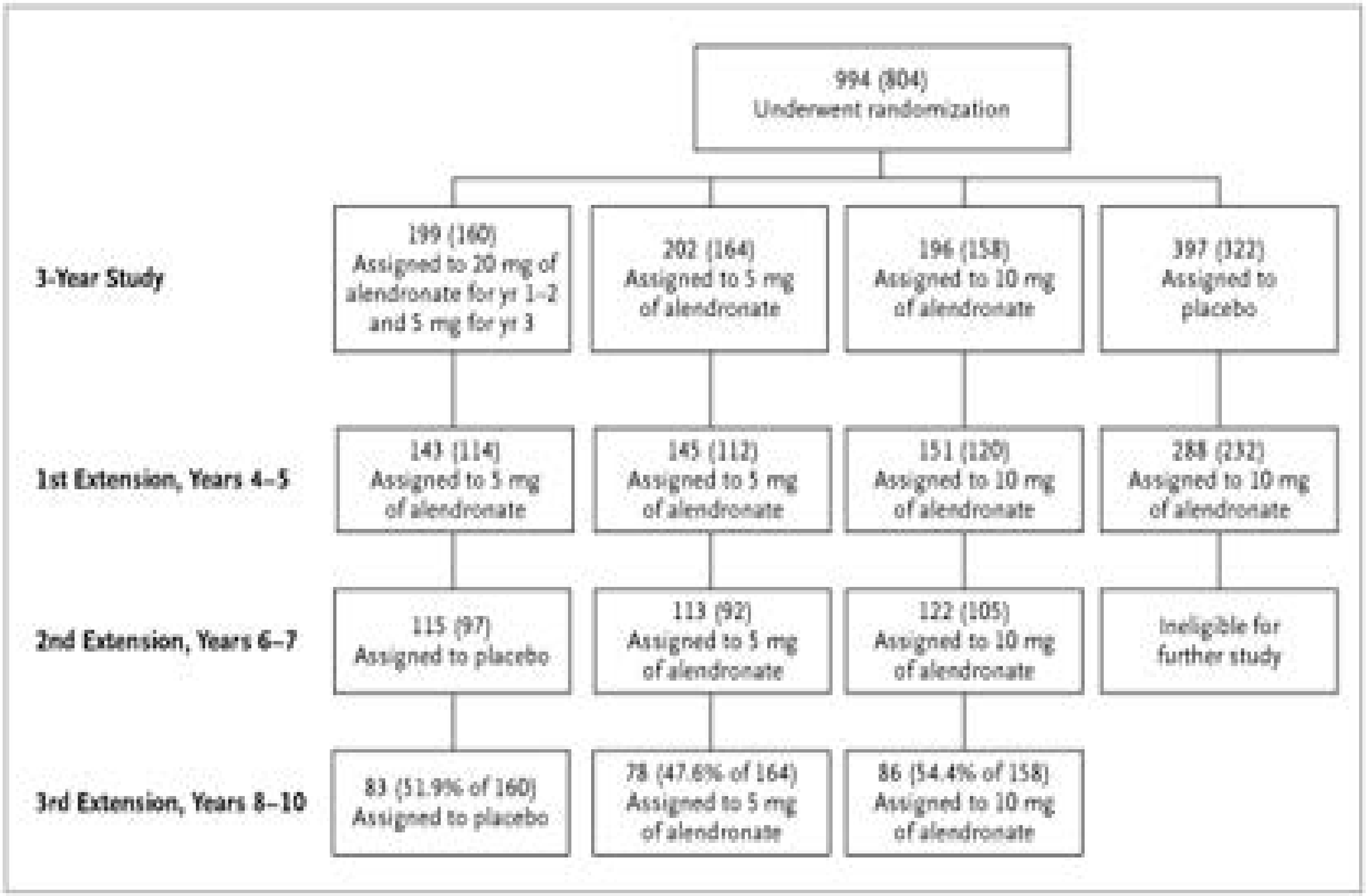
Bone Health and Osteoporosis: A Report of the Surgeon General. Rockville, Md: US Department of Health and Human Services; 2004:187-217.

# Vertebral Fracture Reduction Trials

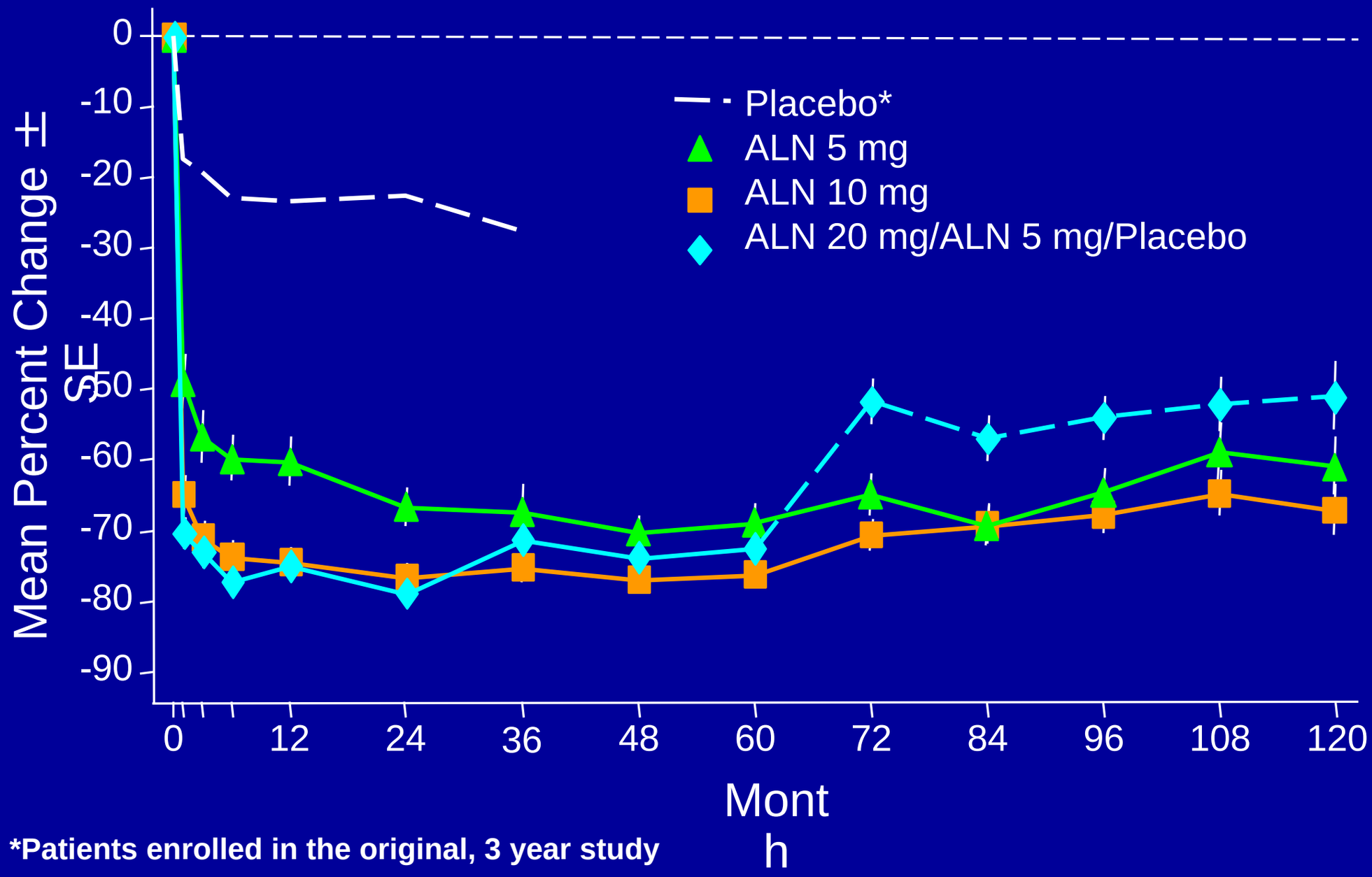
| | FIT VFA<br>Alendronate |
|---|---|
| **Number of patients** | 2027 |
| **Baseline LS-BMD** | –2.3 |
| **Mean age** | 71 (post menopausal) |
| **Drug** | 5 or 10 mg daily |
| **Calcium intake** | 1000 mg daily |
| **Design** | randomized, double-blind placebo controlled |
| **% with prevalent VFx** | 100% |
| **Mean prevalent VFXs** | 1 VFX |
| **Study duration** | 3 yrs. |
| **Primary endpoint** | VFx |
| **Secondary endpoint** | NonVFx |

[#] Black DM, et al. *Lancet*. 1996;348:1535–1541.

# NEJM 3/04 Ten year data

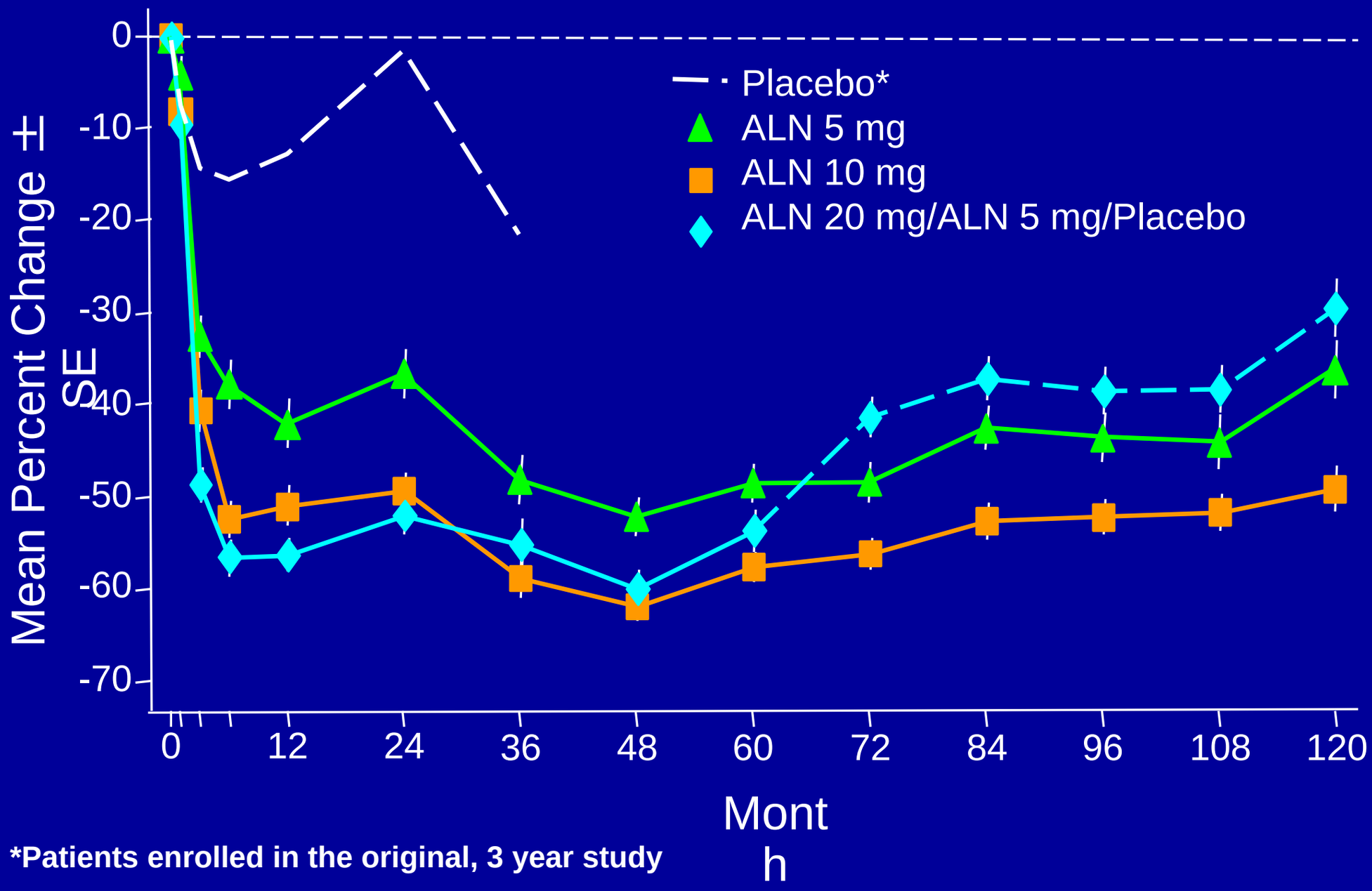


# Alendronate 10 Year Efficacy Data Urinary NTx



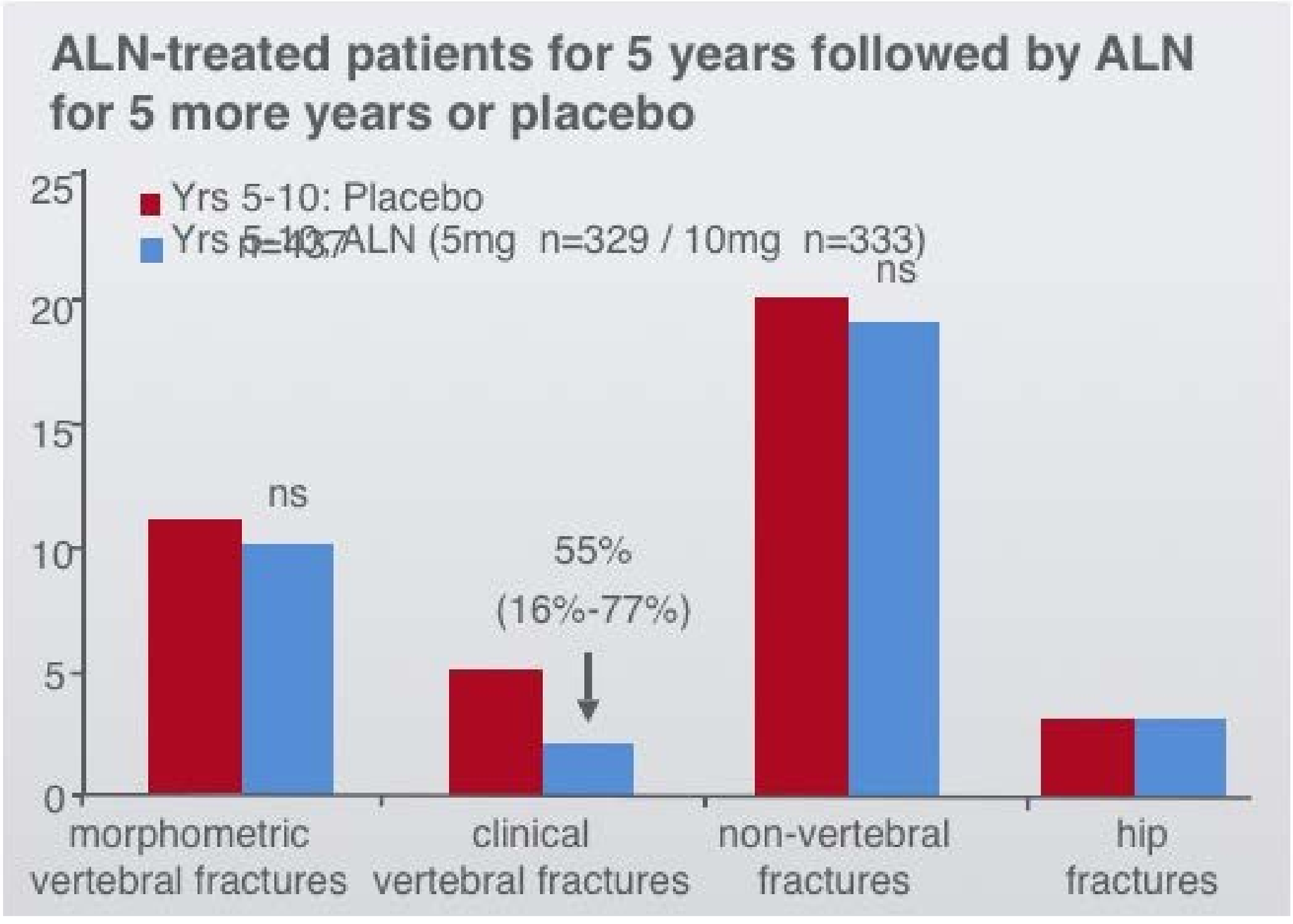

*Patients enrolled in the original, 3 year study

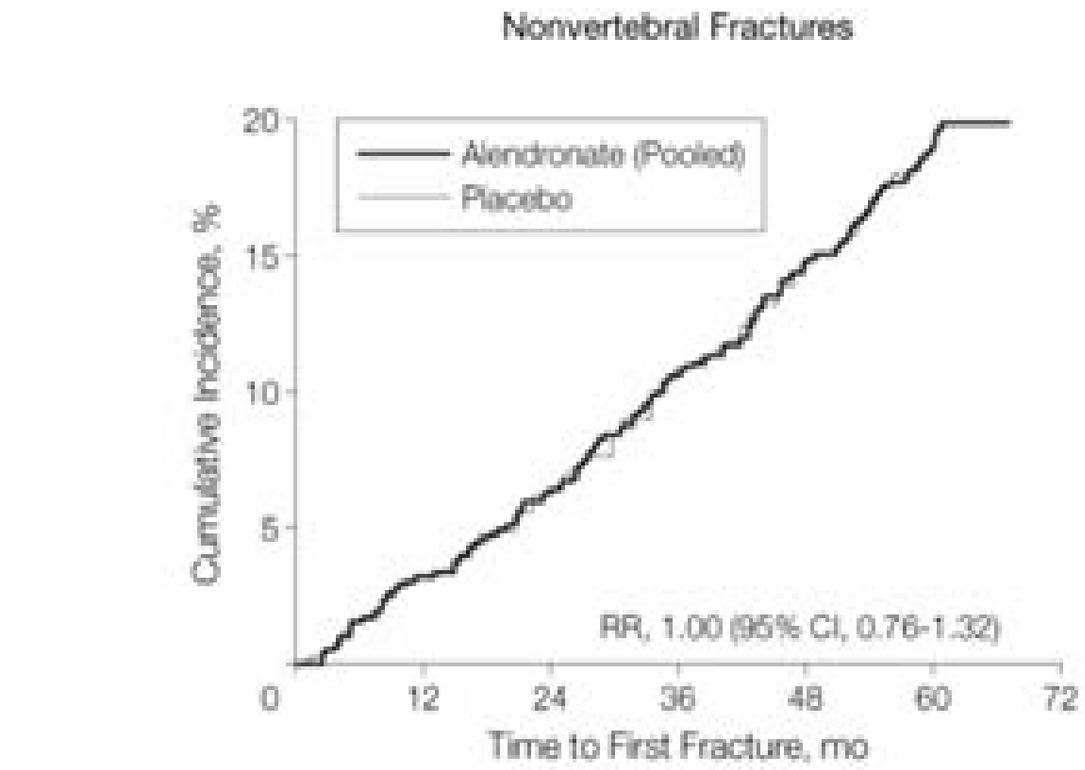
# Alendronate 10 Year Efficacy Data
# Bone Specific Alkaline Phosphatase




*Patients enrolled in the original, 3 year study

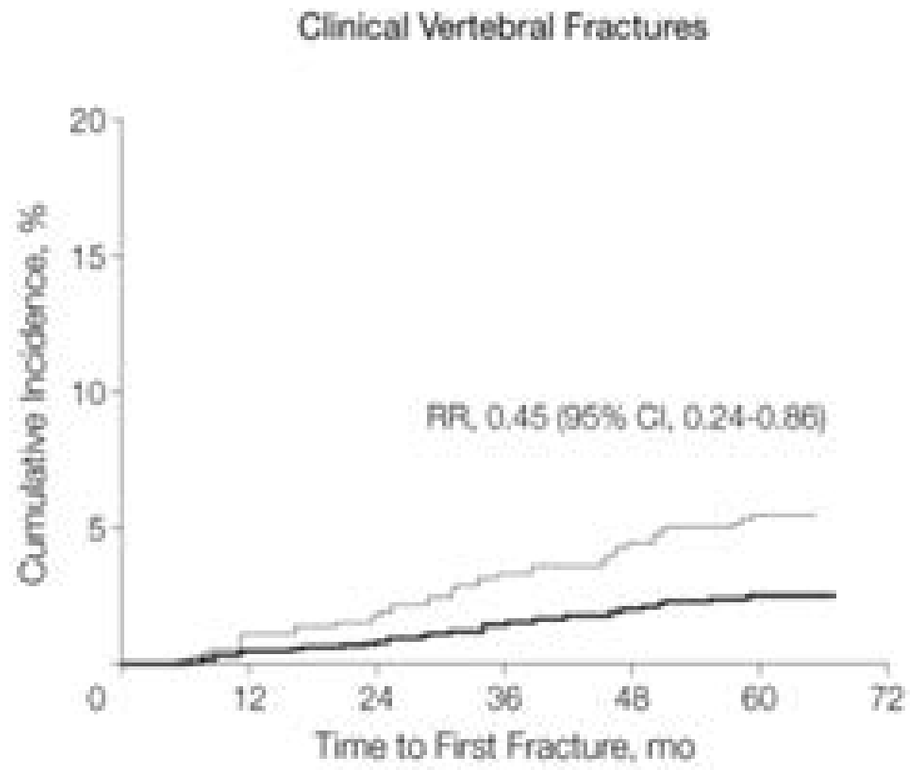
# FLEX Trial: Fracture Assessment






No. at Risk

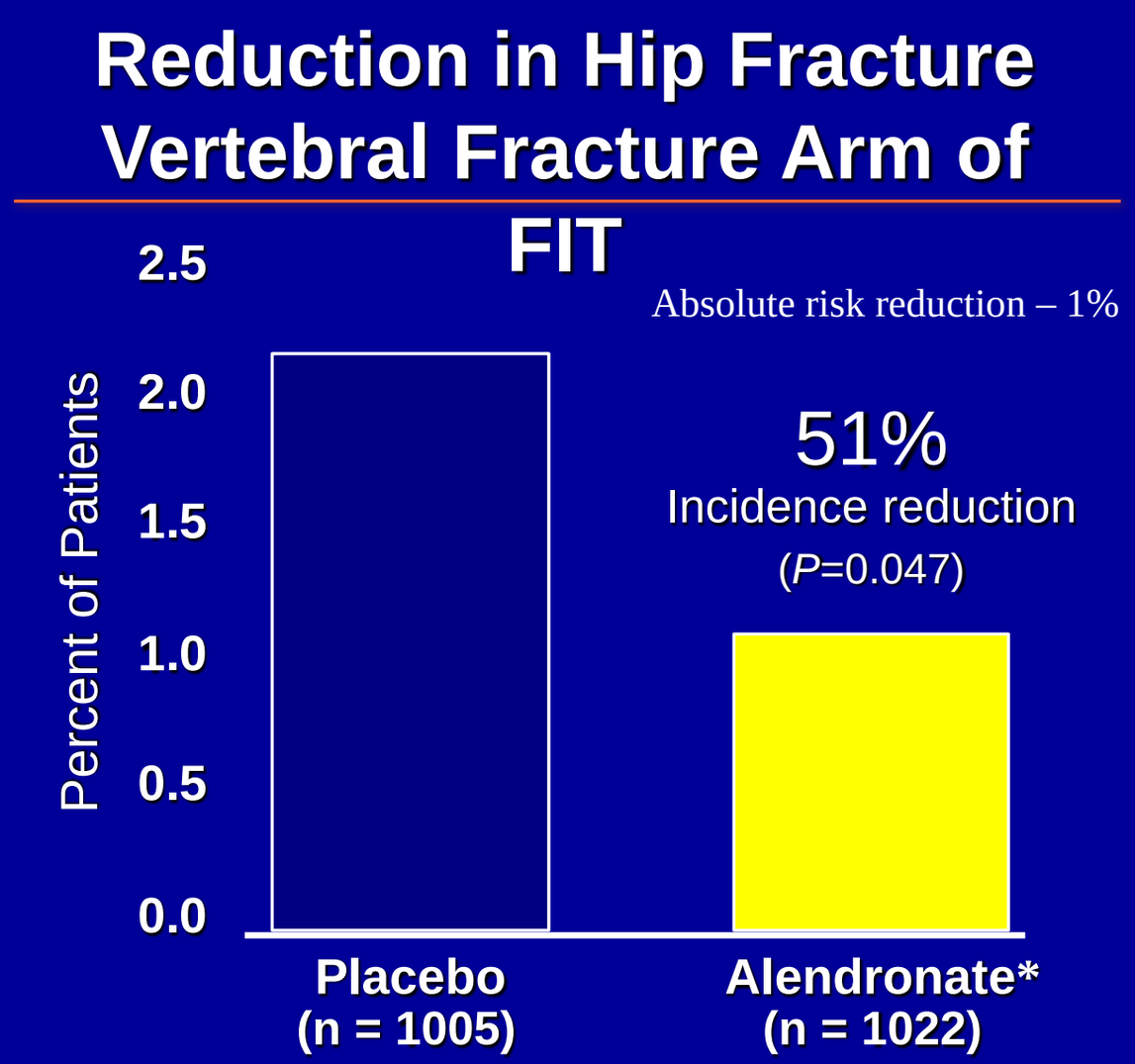
| | | | | | | |
|---|---|---|---|---|---|---|
| Placebo | 437 | 421 | 410 | 396 | 373 | 355 |
| Alendronate | 662 | 642 | 619 | 585 | 565 | 537 |




No. at Risk

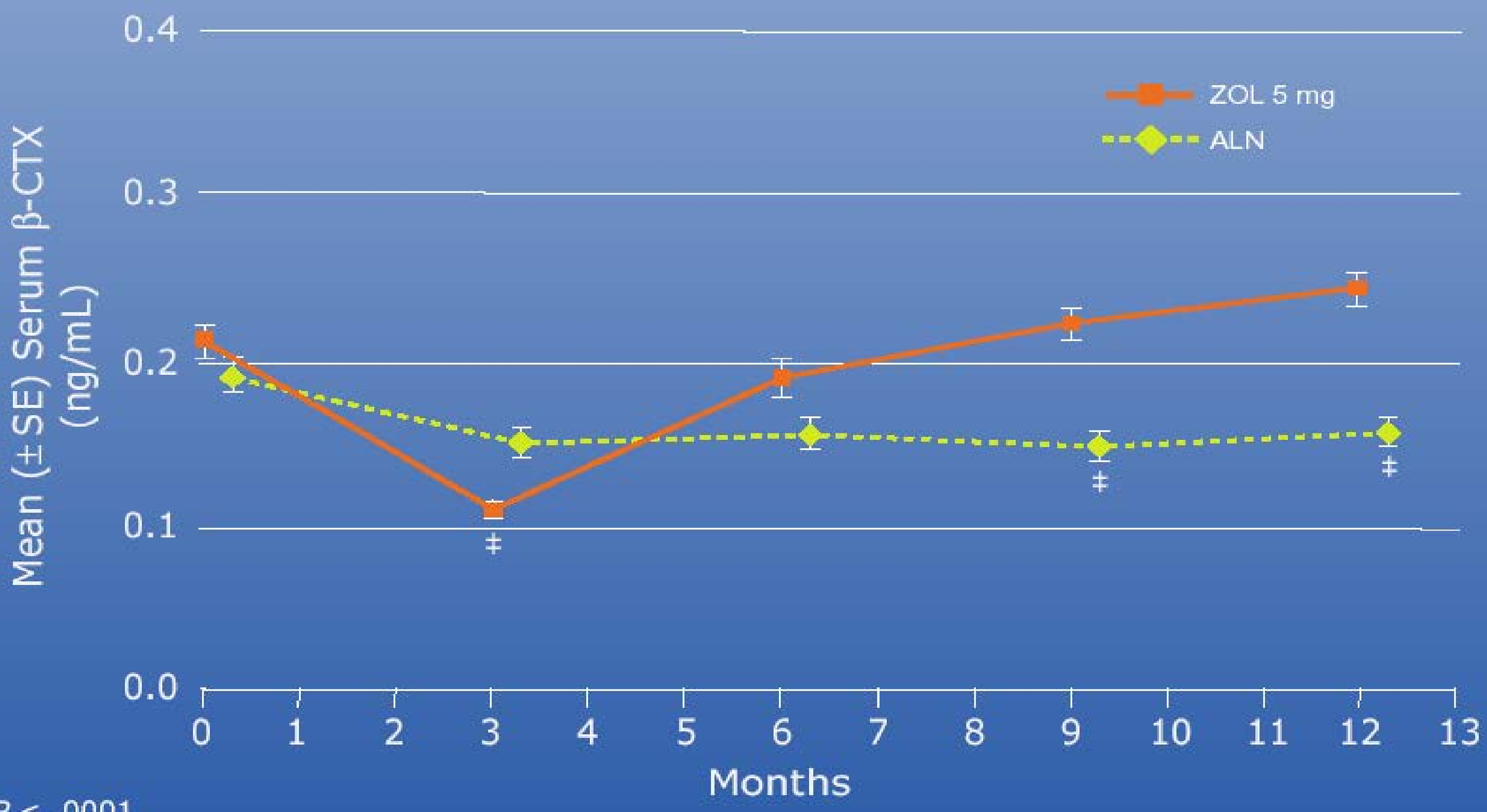
| | | | | | | |
|---|---|---|---|---|---|---|
| Placebo | 437 | 428 | 429 | 421 | 417 | 414 |
| Alendronate | 662 | 659 | 657 | 654 | 650 | 646 |

# Efficacy of Alendronate
# FIT Vertebral Fracture Data




*Patients received either placebo or alendronate 5 mg once daily for the first two years and either placebo or alendronate 10 mg once daily for the 3rd year with maintenance of double-blind. Black, D.M. et al. Randomized trial of alendronate on the risk of fracture in women with existing vertebral fractures. *Lancet.* 1996; 348: 1535–1541.

# ZOL 2313 – ZOL 5mg x1 vs ALN 70mg weekly - βCTX levels

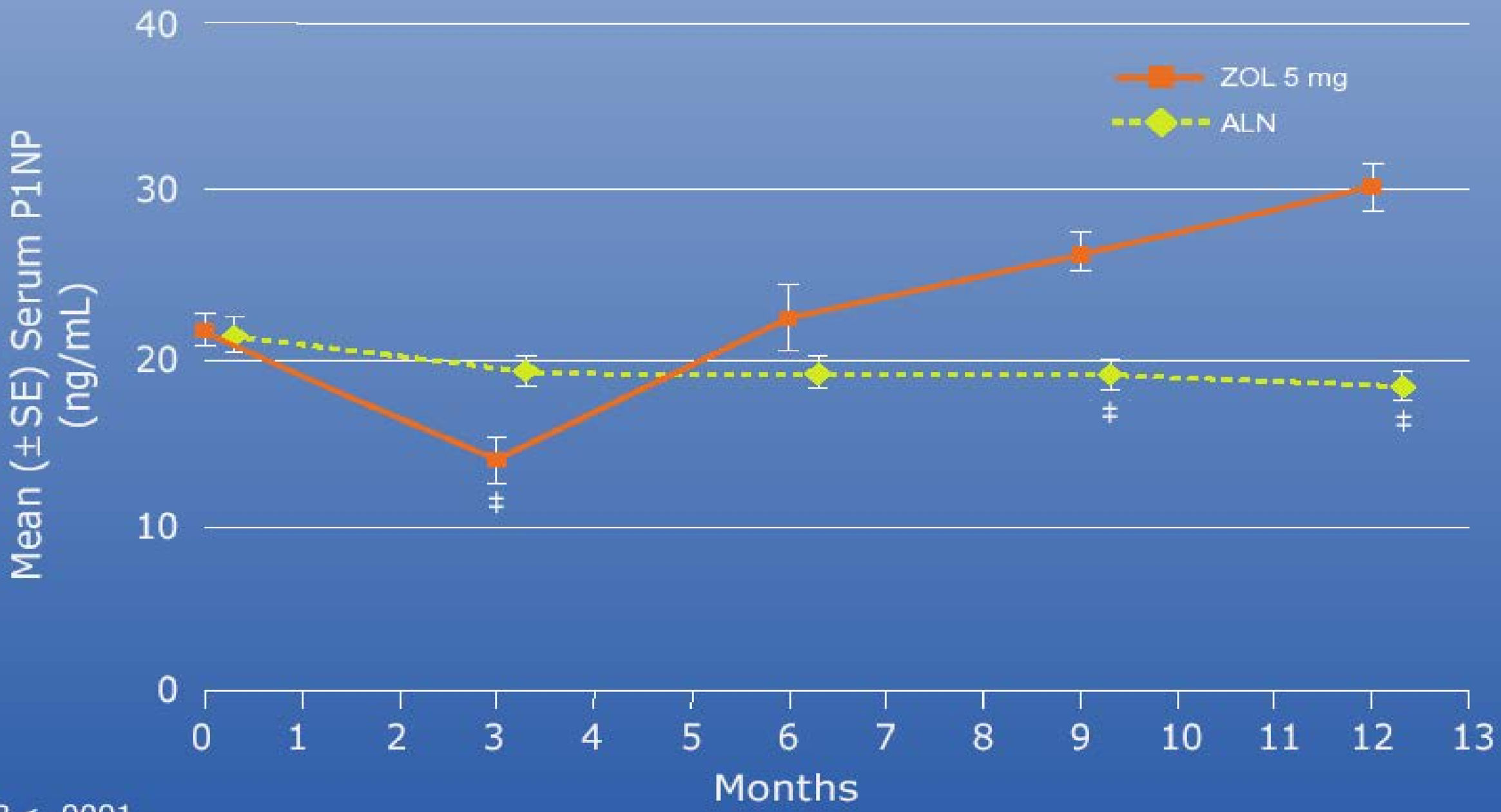



‡*P* < .0001

Bone (2007); 41: 122-128

Bone (2007); 41: 122-128

# ZOL 2313 – ZOL 5mg x1 vs ALN 70mg weekly - P1NP

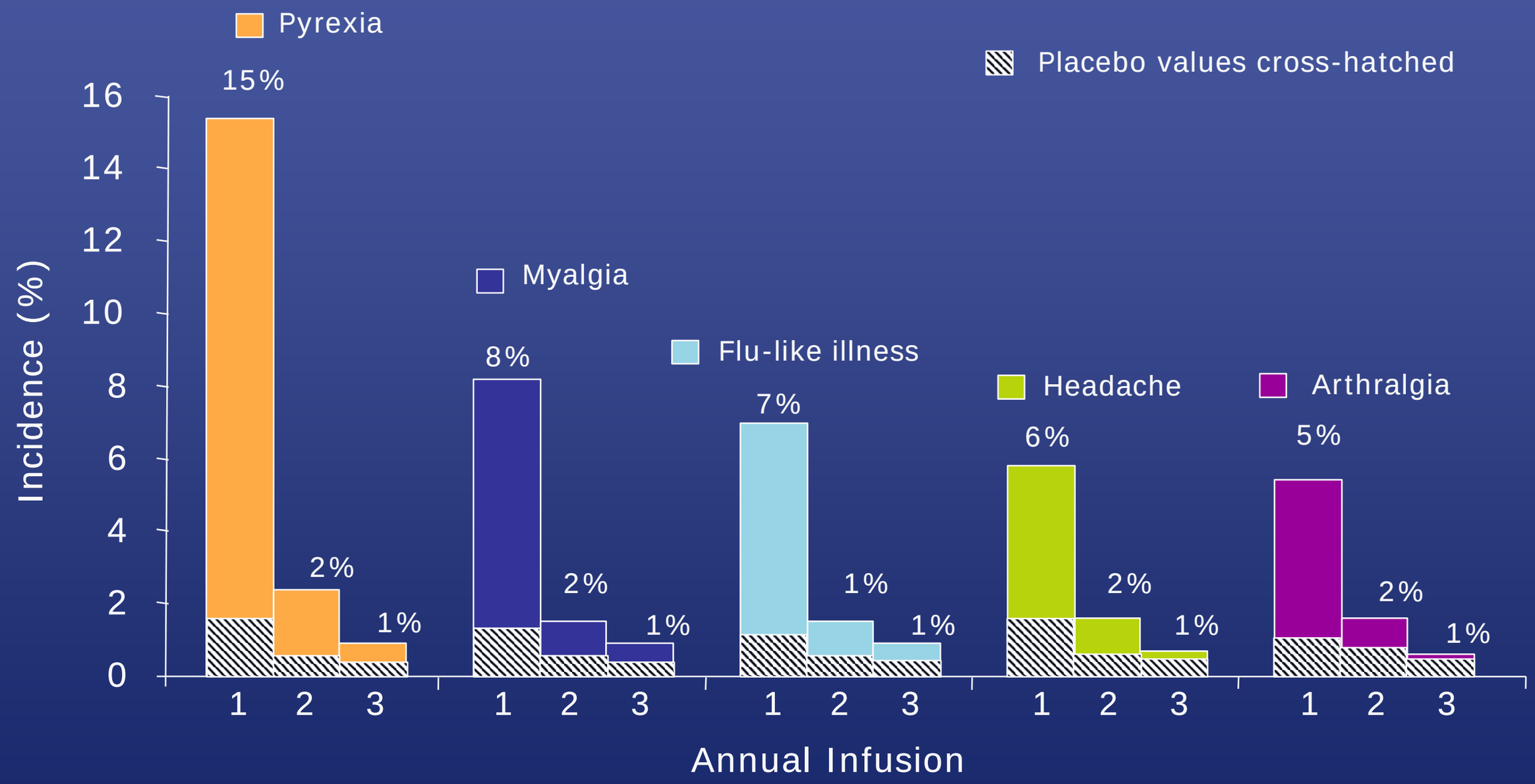



‡*P* < .0001

Bone (2007); 41: 122-128

Bone (2007); 41: 122-128

# Common (≥5% in ZOL) Post-Dose Symptoms Occurring Within 3 Days After Infusion



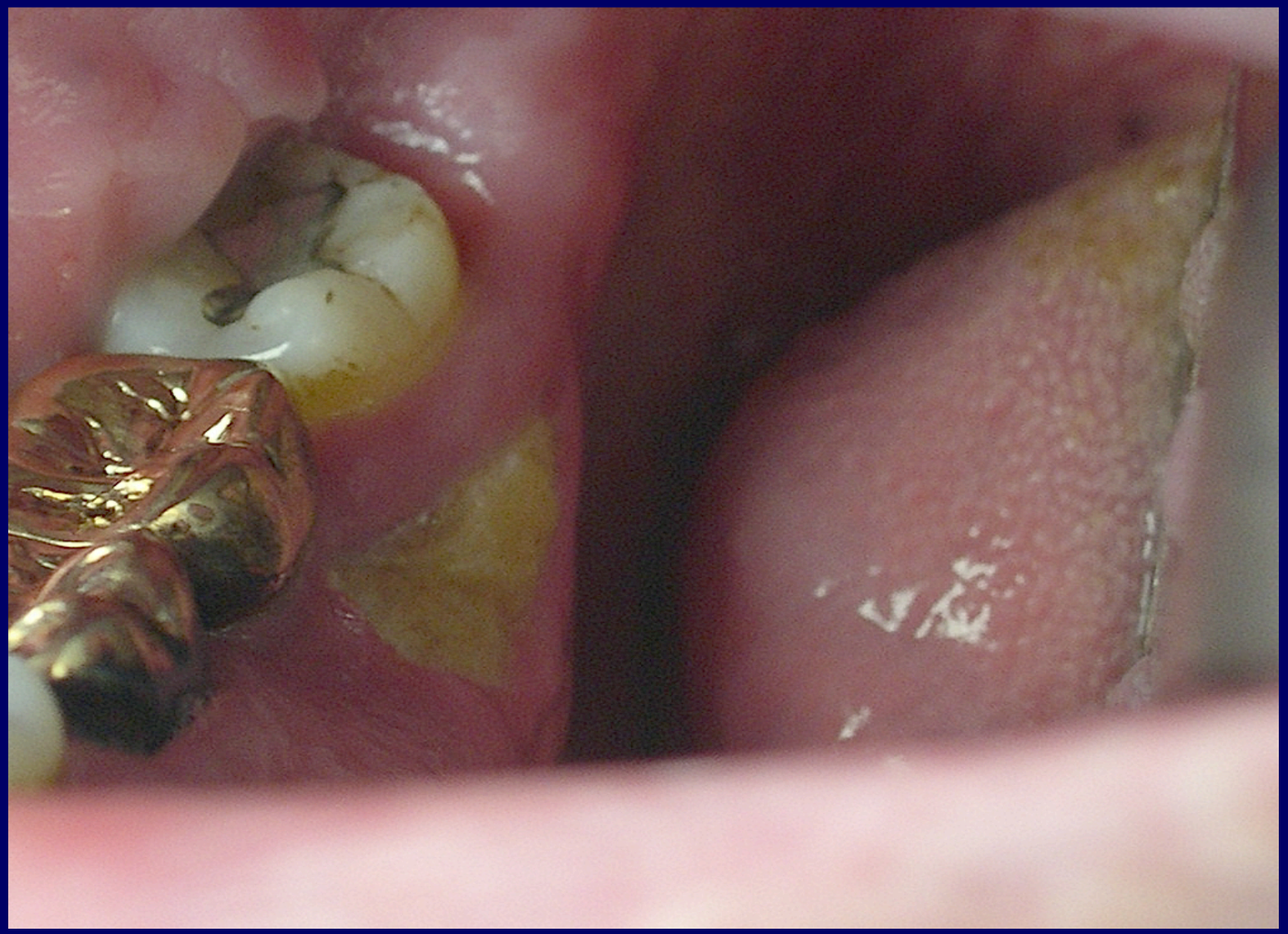

Black DM, et al. Presented at: ASBMR 28th Annual Meeting; September 15-19, 2006; Philadelphia, Pa. Abstract 1054

# Osteonecrosis of the Jaw

- Although there is no universally accepted definition of ONJ, several authors have observed that ONJ is an oral cavity lesion characterized by 1 or more spots of bare maxillary or mandibular bone, in the absence of local malignancy or radiation therapy to the head or neck.[1–6]
- Known risk factors for ONJ include:
  - Diagnosis of cancer
  - Concomitant therapies (eg, chemotherapy, radiotherapy, and corticosteroids)
  - Poor oral hygiene
  - Smoking
  - Comorbid disorders (eg, pre-existing dental disease, anemia, coagulopathy, and infection)
- The mechanism by which ONJ occurs is currently uncertain.[1]


**1.** Migliorati CA et al. *J Am Dent Assoc.* 2005;136:1658–1668.
**2.** Ruggiero SL et al. *J Oral Maxillofac Surg.* 2004;62:527–534.
**3.** Marx RE et al. *J Oral Maxillofac Surg.* 2005;63:1567–1575.
**4.** Bamias A et al. *J Clin Oncol.* 2005;23:8580–8587.
**5.** Lenz JH et al. *J Craniomaxillofac Surg.* 2005;33:395–403.
**6.** Farrugia MC et al. *Laryngoscope.* 2006;116:115–120.

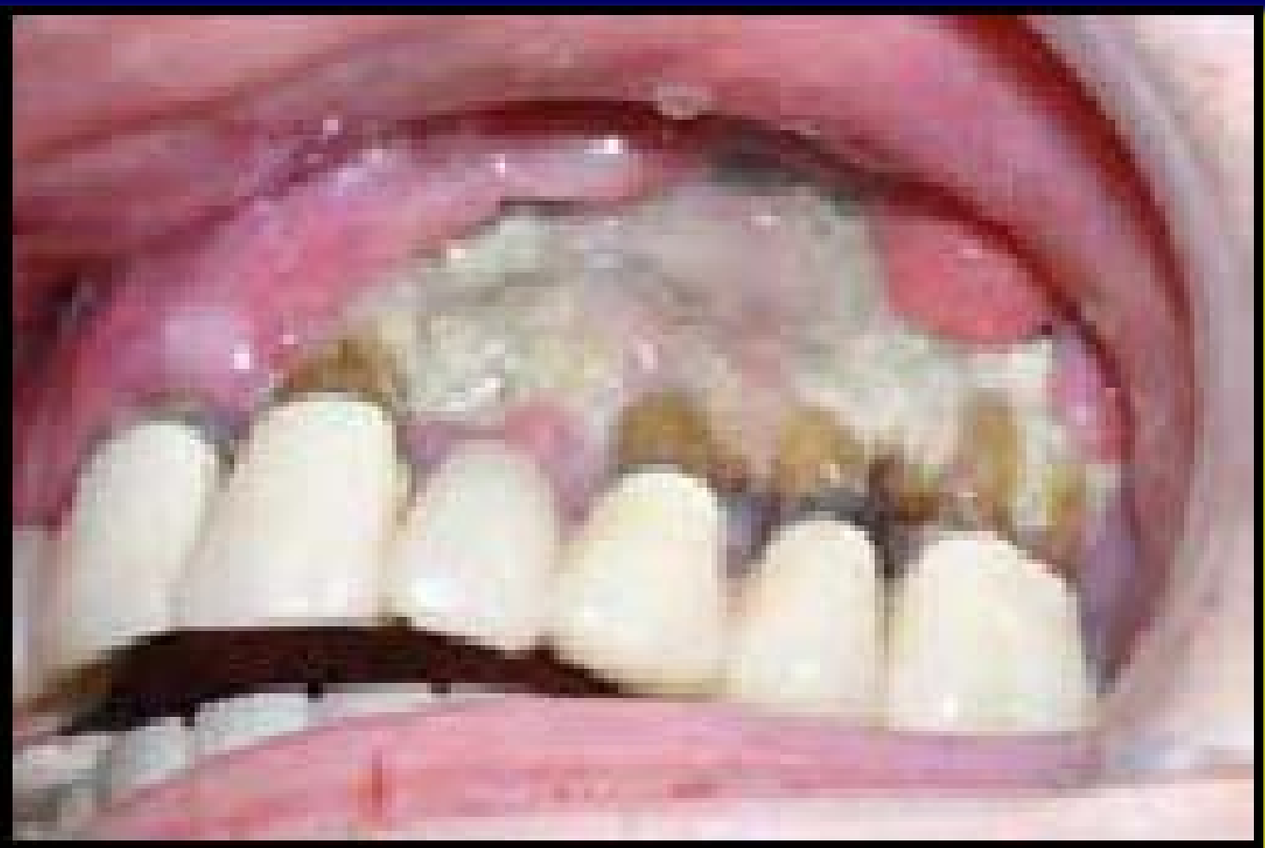
# Exposed Bone in ONJ: Internal Oblique Ridge



Photograph courtesy of Leon Assael, DMD.

# Stage 3

- Exposed bone
- Pathologic fracture
- Soft tissue inflammation or infection not responsive to antibiotics
- Large amount of bone involved
- Extraoral fistula
- osteolysis



# AAOMS Position Paper

- **Definition of Medication Related Osteonecrosis of the Jaw:**
  - **Current or previous treatment with anti-resorptive or antiangiogenic medications**

  - **Exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for more than eight weeks and**

  - **No history of radiation therapy to the jaws or obvious metastatic disease to the jaws**

# AAOS Position Paper

- **Commonly misdiagnosed condition include:**

- **Alveolar osteitis**
- **Sinusitis**
- **Ginigivitis**
- **Caries**
- **Periapical pathology**
- **Fibro-osseous lesion**
- **Sarcoma**
- **Scleorosing osteomyelitis**
- **TMJ disorders**

# AAOS Position Paper

**Recommendations for patients taking bisphosphonates for osteoporosis:**

- **1. The efficacy of utilizing a systemic marker of bone turnover to assess the risk of developing jaw necrosis in patients at risk has not been validated. Therefore, the use of markers of bone turnover is not recommended.**

- **2. For individuals who have taken an oral BSP for less than four years and have no clinical risk factors no alteration or delay in the planned surgery is necessary. This includes any and all procedures common to oral and maxillofacial surgeons, periodontists and other dental providers.**

# AAOS Position Paper

- **3. For those patients who have taken an oral BSP for less than four years and have also taken corticosteroids or antiangiogenic medications concomitantly, the prescribing provider should be contacted to consider discontinuation for two months prior to the procedure.**
- **4. For those who have taken or BSP for more than four years with or without concomitant therapy, the prescribing provider should be contacted to consider discontinuation for the antiresorptive medication for two months prior to the procedure.**

# ONJ in the Reclast trials

- HORIZON PFT – Reclast Arm: 3,862 women, placebo: 3,852, three years of treatment, one ONJ in each arm.

- HORIZON #2 – post hip fracture trial: Reclast: 1,065, placebo 1,062 – no ONJ reported

- HORIZON #3 – Glucocorticoid induced osteoporosis: two year study: Reclast: 416, alendronate 417, no ONJ reported

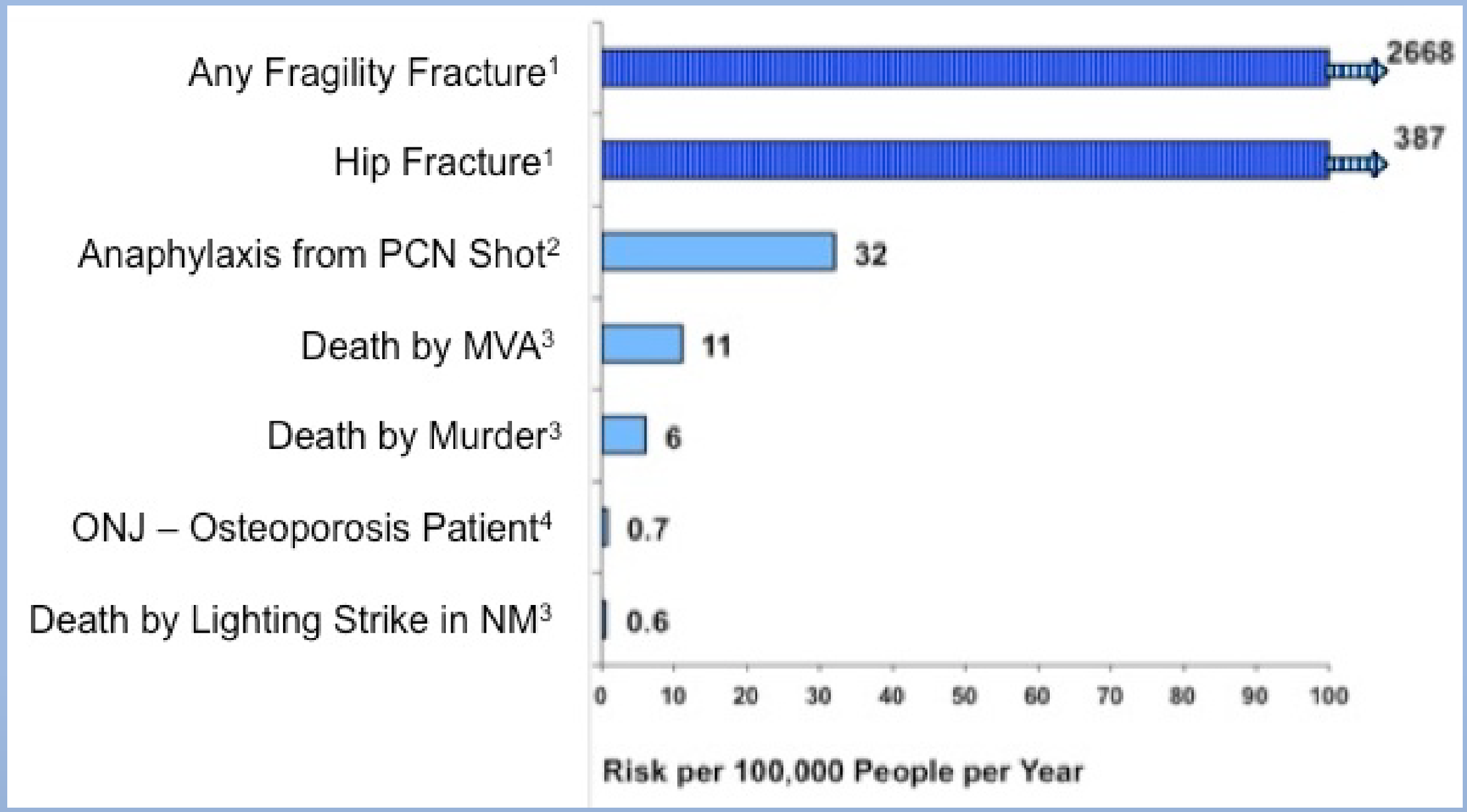
- HORIZON #4 Male Osteoporosis: Reclast: 154, placebo: 148, no ONJ reported

- HORIZON #5 Osteopenia, every two year infusion: Reclast: 198, placebo: 202, no ONJ reported

# ONJ with denosumab

- FREEDOM trial – three year pivotal fracture trial – no cases seen in either arm.
- FREEDOM extension 10 years- no placebo arm, patients were given questionnaires to fill out every six months.  ONJ cases were reported from 3,536 patients. 7/8 had oral procedures, the one who did not had dentures. 4.2/10,000 patient years.

# Balancing Risks vs. Benefits




Slide courtesy of E Michael Lewiecki

[1]Kanis JA et al. Osteoporos Int. 2001;12:417-427

[2]Pharmacoepidemiol Drug Saf, 2003; 12:195-202

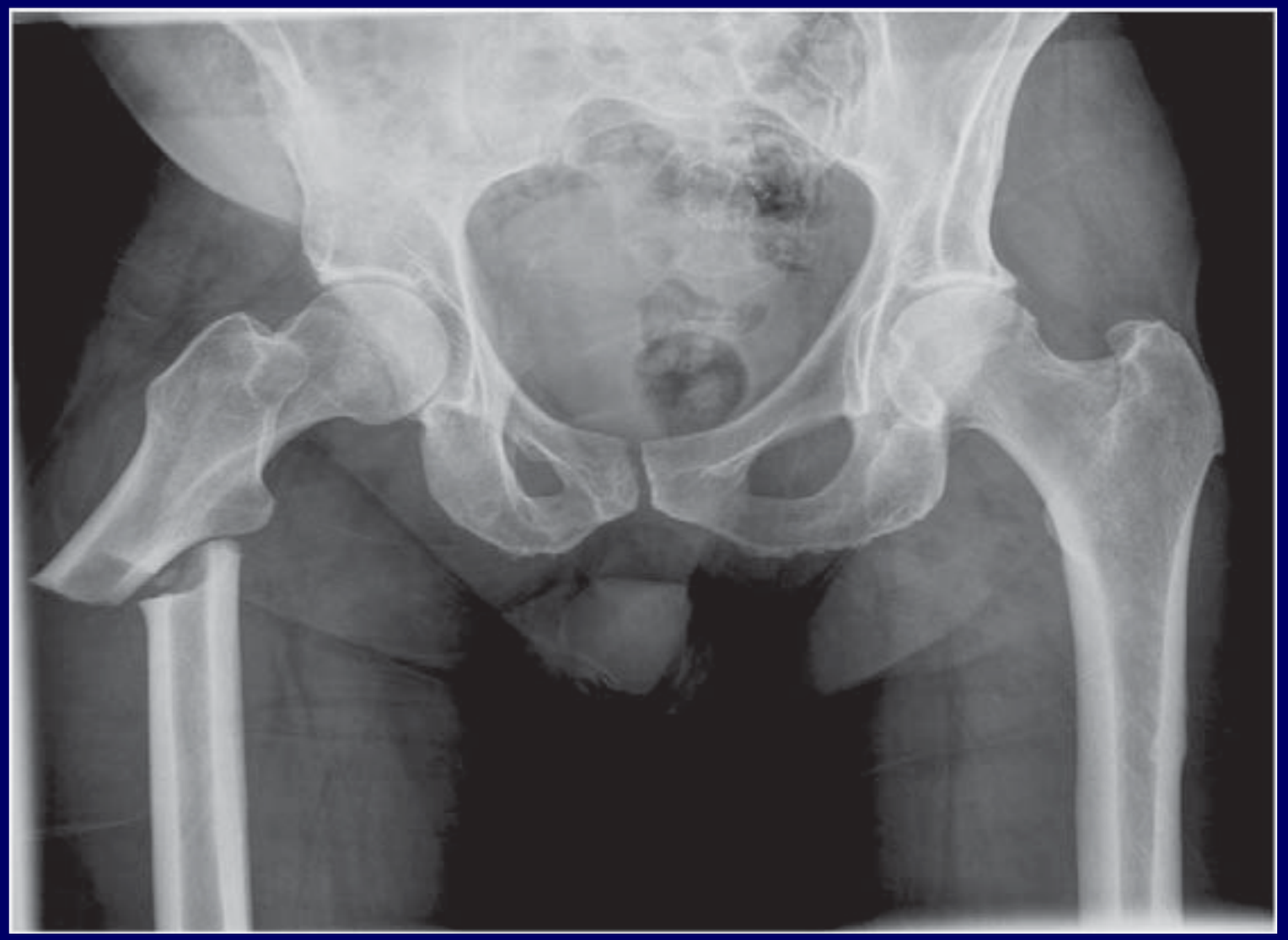
[3]National Center for Health Statistics

[4]JADA, 2006; 137:1144-1150

# Femur Fractures

- Case reports of atypical femur fractures have been published since 2005
- An increasing number of case reports occurred 2008 – 2010
- The low trauma fractures are described as horizontal with cortical thickening, bilateral fractures have been reported.
- Often, a “prodrome” of leg pain with a cortical stress reaction is seen on prefracture radiographs

# Femoral Fracture - spontaneous



# Bisphosphonates and Fractures of the Subtrochanteric or Diaphyseal Femur

- NEJM March 24,2010
- Analysis of Fracture Intervention Trial, Fit Extension (FLEX), and HORIZON (Reclast) Trial
- 14,195 women in these trial
- 12 fractures were classified as subtrochanteric or diaphyseal (rate 2.3 per 10,000 patient-years)
- Relative hazard rate was 1.03 (CI .06 – 16.46)

# Bone Turnover in Bone Biopsies of Patients with Low Energy Cortical Fractures

- All available radiographs of hip fractures were reviewed
- Exclusions: pathological fractures, periprosthetic fractures, and high trauma fractures.
- In all three trials, there were 283 hip or femur fractures.
- After the above exclusions there were 134 fractures.
- There were 12 subtrochanteric fractures.
- In the FIT trial, there were two fractures that met criteria – rate .8 per 10,000 fracture-years
- In FLEX, there were 4 fractures that met criteria: rate 6.3 per 10,000 patient years
- HORIZON: 5 women had six fractures that met criteria – rate: 2.8 per 10,000 patient years.

## Atypical Femur Fractures Increased After 5 Years of Bisphosphonate Use

Adjusted OR and 95% CI

- Atypical hip fractures
  - Cases (n = 716) versus Controls (n = 3580)
    - Zero to 5 years of treatment — NS
    - Long term (5 years or more) — 2.74 (1.25-6.02)
- Typical hip fractures
  - Cases (n = 9723) versus Controls (n = 48564)
    - Intermediate (3-5 years) — 0.86 (0.73-1.00)
    - Long term (5 years or more) — 0.76 (0.63-0.93)

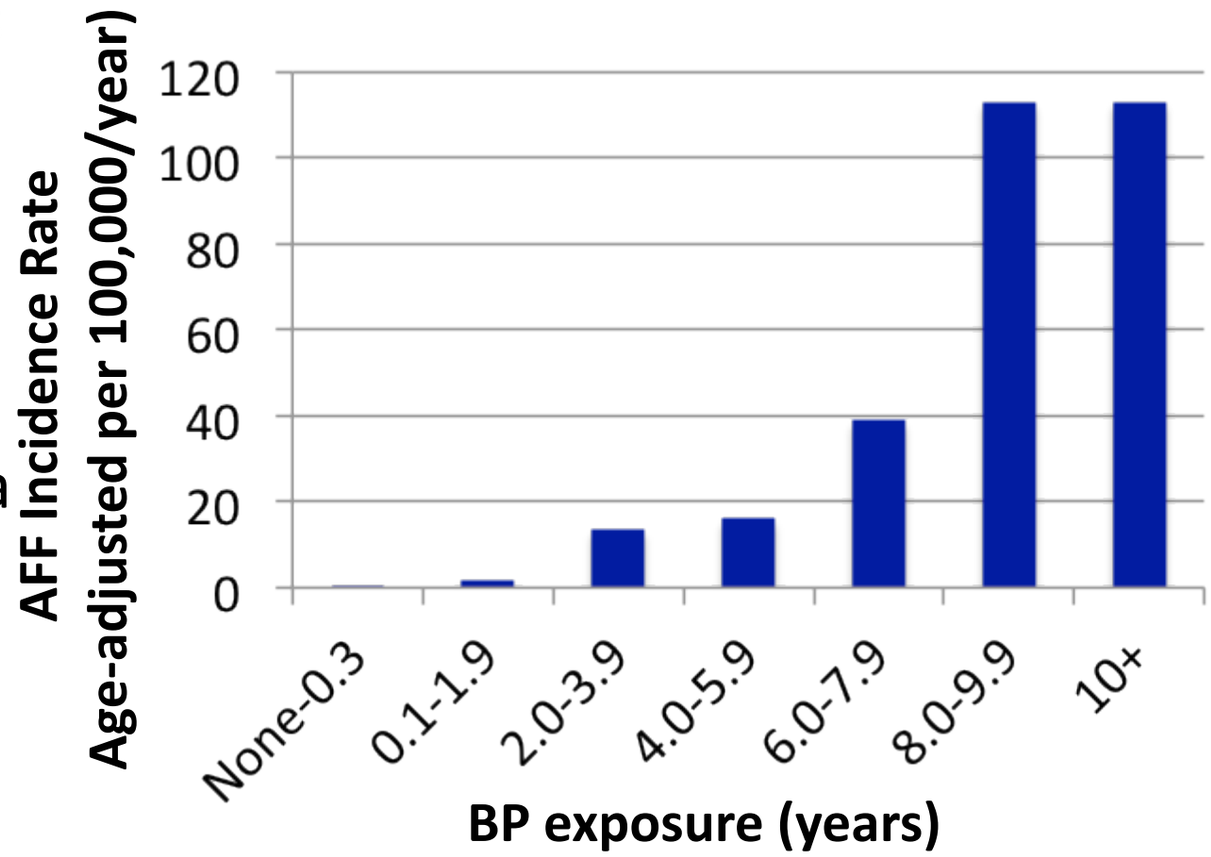
Park-Wyllie LY et al *JAMA* 2011;305:783-789

If you treat 1000 women with bisphosphonates for 5 years prevent 35-50 non-vertebral fractures, 50-115 vertebral fractures. You might cause 5 atypical femur fractures

ASBMR Task Force, J Bone Miner Res, 2010

# Atypical Femoral Fracture Incidence Increases With Duration of Bisphosphonate Exposure

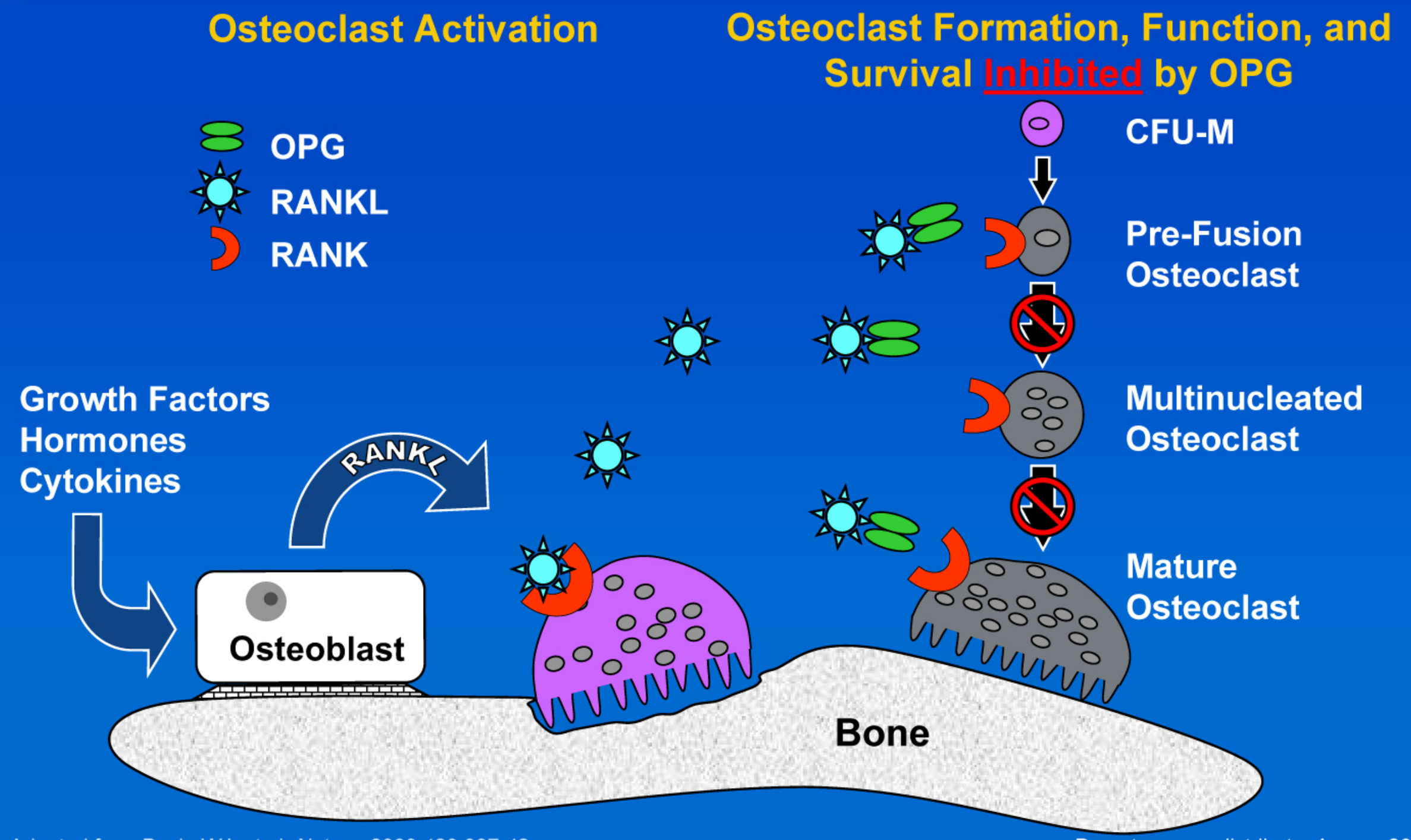
- 1.8 million Kaiser Permanente enrollees ≥ 45 years of age
- Potential AFF identified by ICD-9 diagnosis and CPT procedure codes
  - All radiographs reviewed
- 142 femur fractures met ASBMR criteria for AFF
  - 128 (90%) had previous BP exposure
  - 14 (10%) no prior BP exposure
  - Age adjusted incidence rose with increasing duration of BP exposure




**~ 1 per 1000 pt-yrs after 10 years**

Adapted from Dell RM, J Bone Miner Res, 2012;27:2544-50

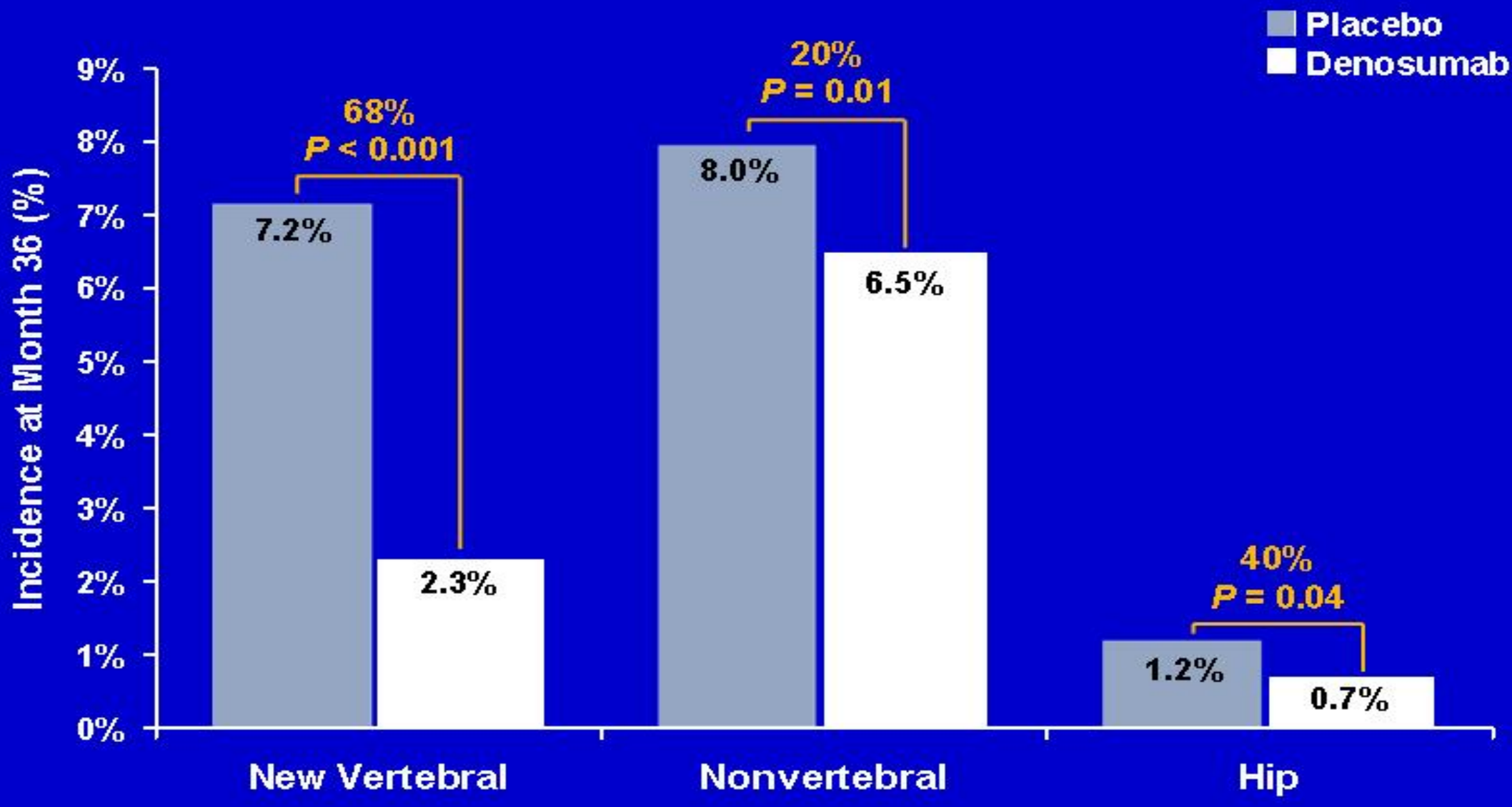
# To Defend Against Bone Loss, the Body Produces a Protein Called Osteoprotegerin (OPG)




Adapted from Boyle WJ, et al. *Nature.* 2003;423:337-42.

# The Effect of Denosumab on Fracture Risks at 36 Months

*Phase 3: The FREEDOM Trial*

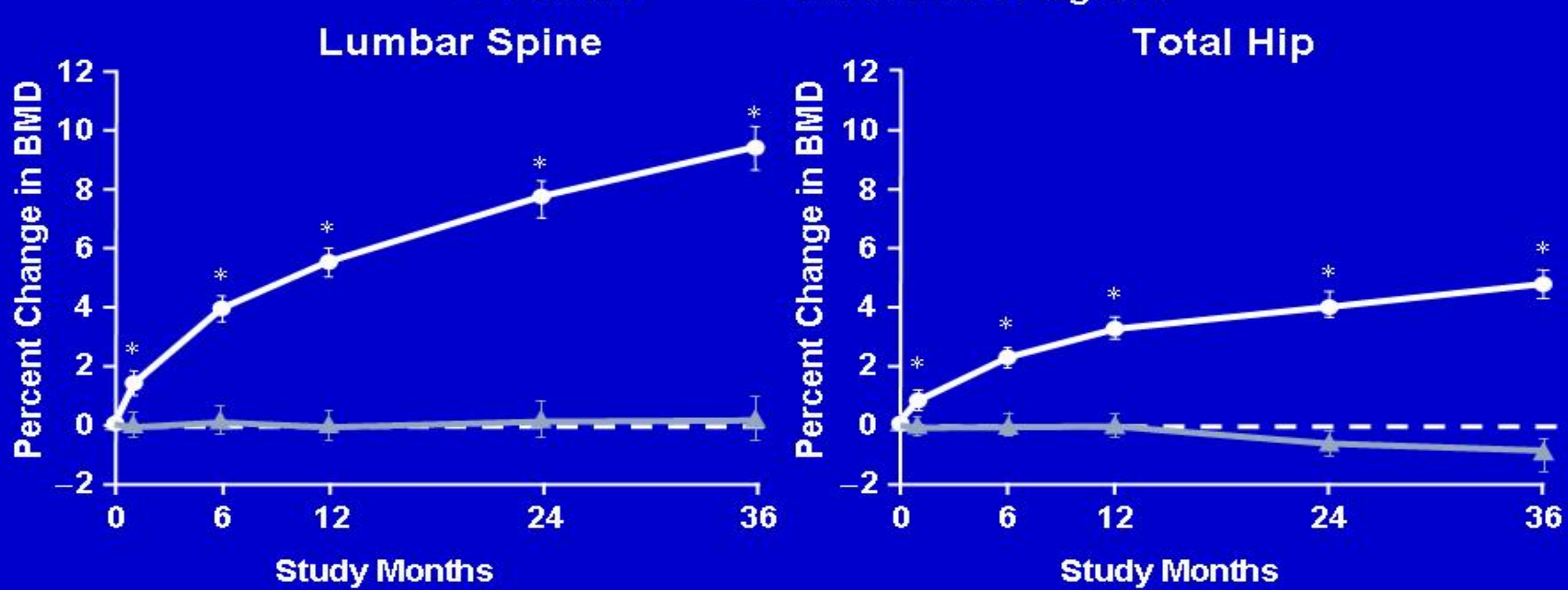



Cummings SR, et al. [Published online ahead of print August 11, 2009]. *N Engl J Med.* doi: 10.1056/NEJMoa0809493.

# The Percent Change in Bone Mineral Density Over 36 Months With Denosumab

*Phase 3: The FREEDOM Trial*

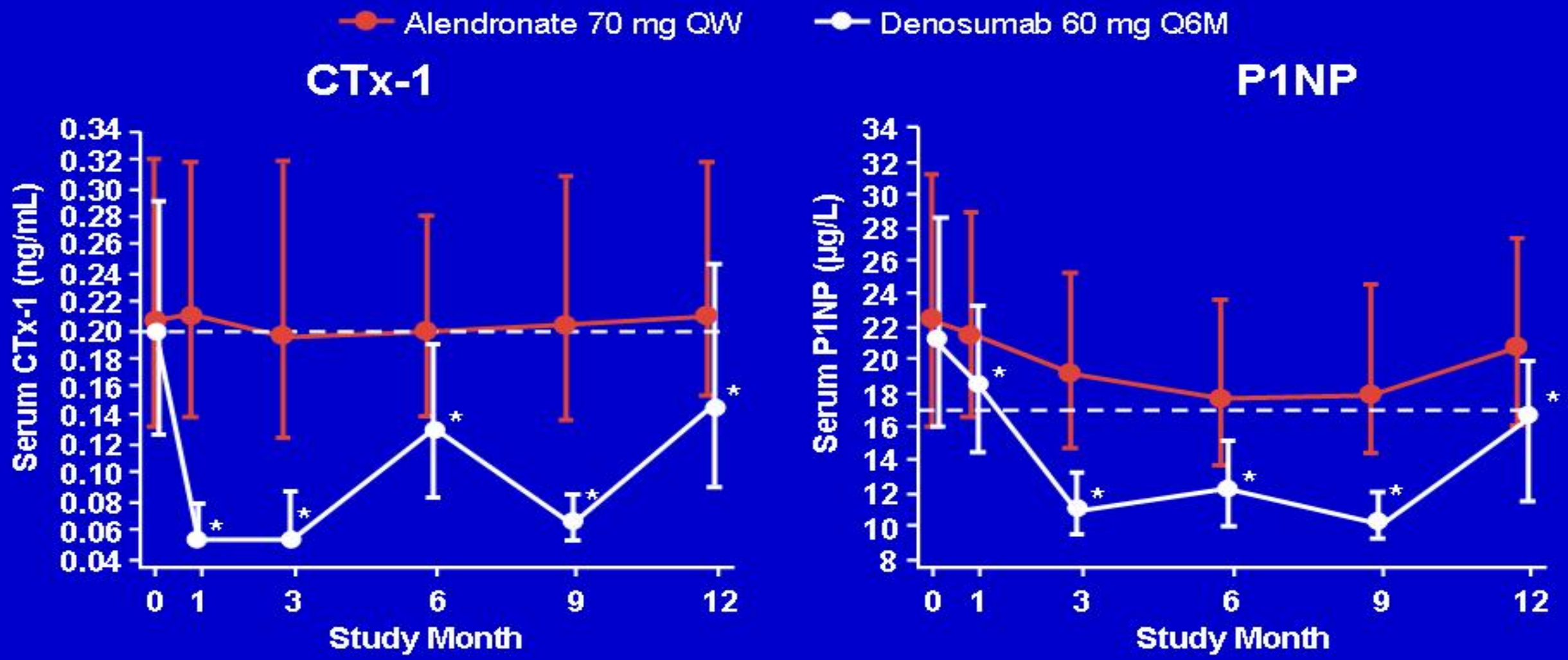
**Bone Mineral Density Substudy**
**n = 441**




Intent-to-treat, last observation carried forward analysis
*$P < 0.001$ for denosumab vs placebo
Cummings SR, et al. [Published online ahead of print August 11, 2009]. *N Engl J Med.* doi: 10.1056/NEJMoa0809493. Copyright © 2009 *Massachusetts Medical Society. All rights reserved.*

# Effects of Treatment on Biochemical Markers of Bone Turnover Over 12 Months

*Phase 3: The STAND Trial*



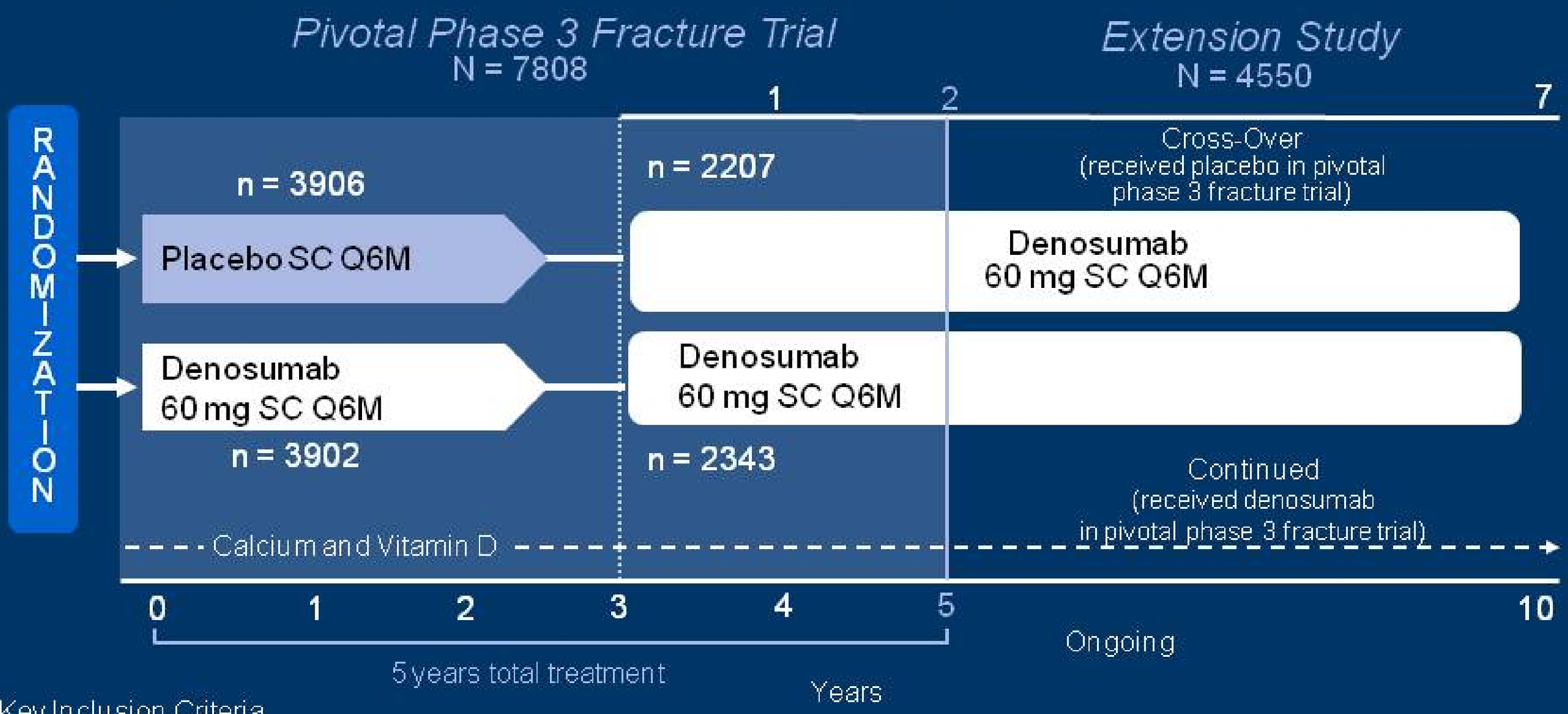

Dotted line is lower limit of premenopausal reference range.
Values are medians; error bars represent the interquartile range.
Analysis carried out in the observed data set; missing values were not imputed.
*$P < 0.0001$.

Adapted from: Kendler DL, et al. [Published online ahead of print July 13, 2009]. *J Bone Miner Res.* doi:10.1359/JBMR.090716.

# Study Design

## *The Pivotal Phase 3 Study – Extension*

- **7-year, international, multicenter, open-label, single-arm extension study**
- **Primary endpoint: safety and tolerability of up to 10 years of Prolia® administration**



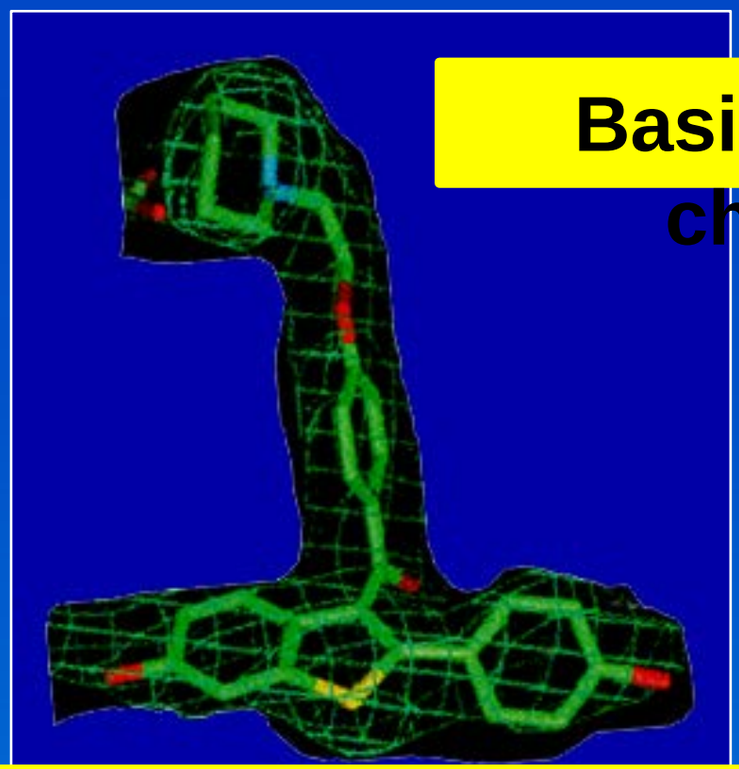

Key Inclusion Criteria

- Must have completed the pivotal phase 3 fracture trial (received denosumab or placebo)
- Not receiving any other osteoporosis medications

Adapted from Chapurlat R, et al. Presented at: American College of Rheumatology Annual Scientific Meeting; November 7-11, 2010; Atlanta, GA.

# raloxifene HCl as a SERM

## 3-Dimensional Model of Raloxifene



**Basic side chain** → **Estrogen antagonist**
- Uterus
- Breast

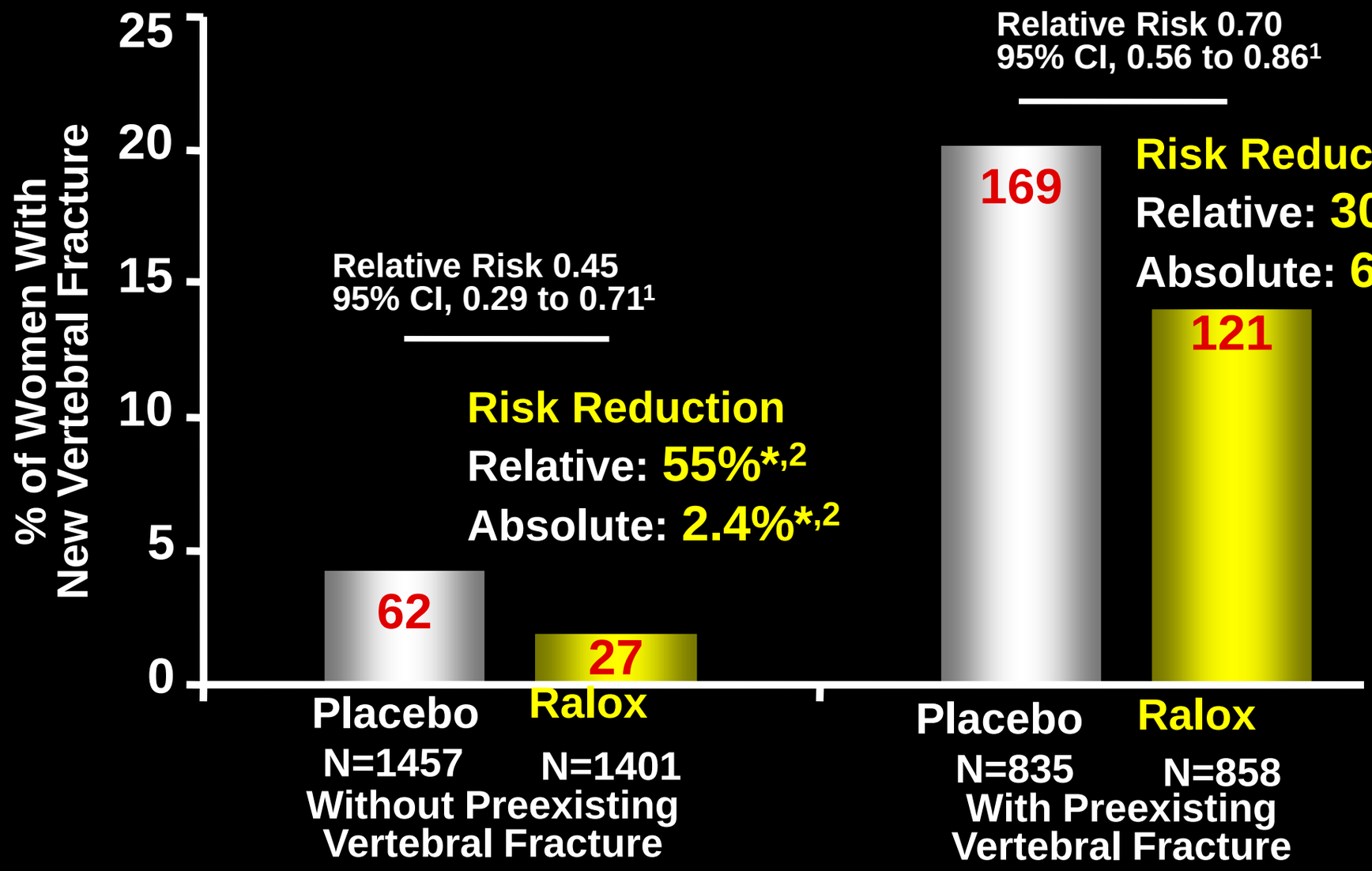
**Benzothiophene moiety** → **Estrogen agonist**
- Bone
- Serum lipids

Raloxifene is not an estrogen, progestin, or hormone

.

# Effect of raloxifene HCL in Postmenopausal Women With or Without Preexisting Vertebral Fractures

## MORE Trial - 3 Years




The MORE trial was a prospective, randomized, double-blind, placebo-controlled, clinical trial of 7705 postmenopausal women (mean age 67) with osteoporosis (-2.6 at the spine; -3.2 at the femoral neck[2]). All were given calcium (500 mg/day) and vitamin D (400-600 IU/day).[3]


1. *Rheum Dis Clin N Am*. 2001:27:163-185.
2. Data on file, Lilly Research Laboratories (199910005).
3. *JAMA*.1999;282:637-645.


*$p<.001$

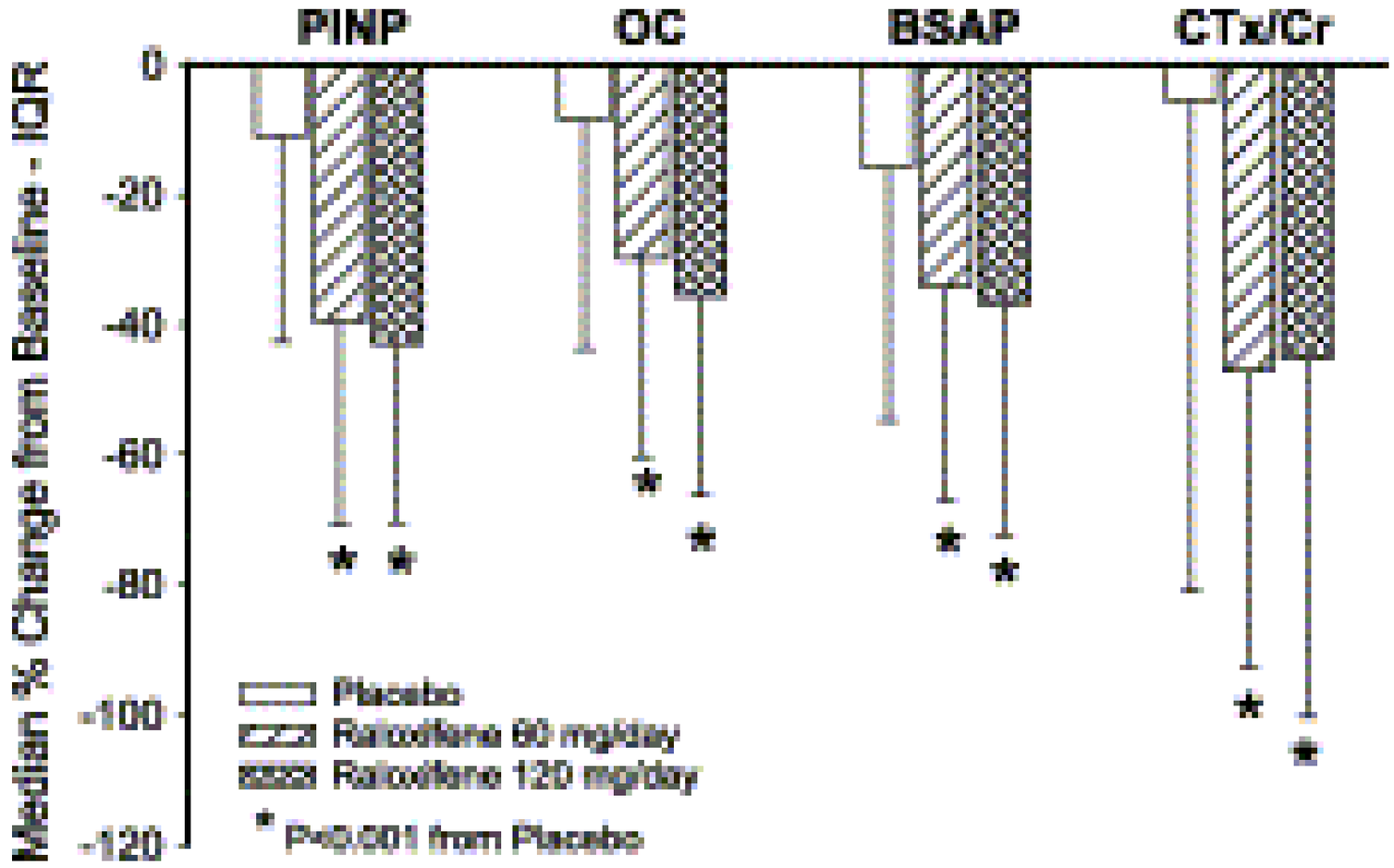



Fig. 1The median percentage change from baseline to 1 year in the biochemical markers of bone metabolism, type I procollagen N-terminal propeptide (PINP), serum osteocalcin (OC), bone-specific alkaline phosphatase (BSAP), and urinary type I collagen C-telopept...

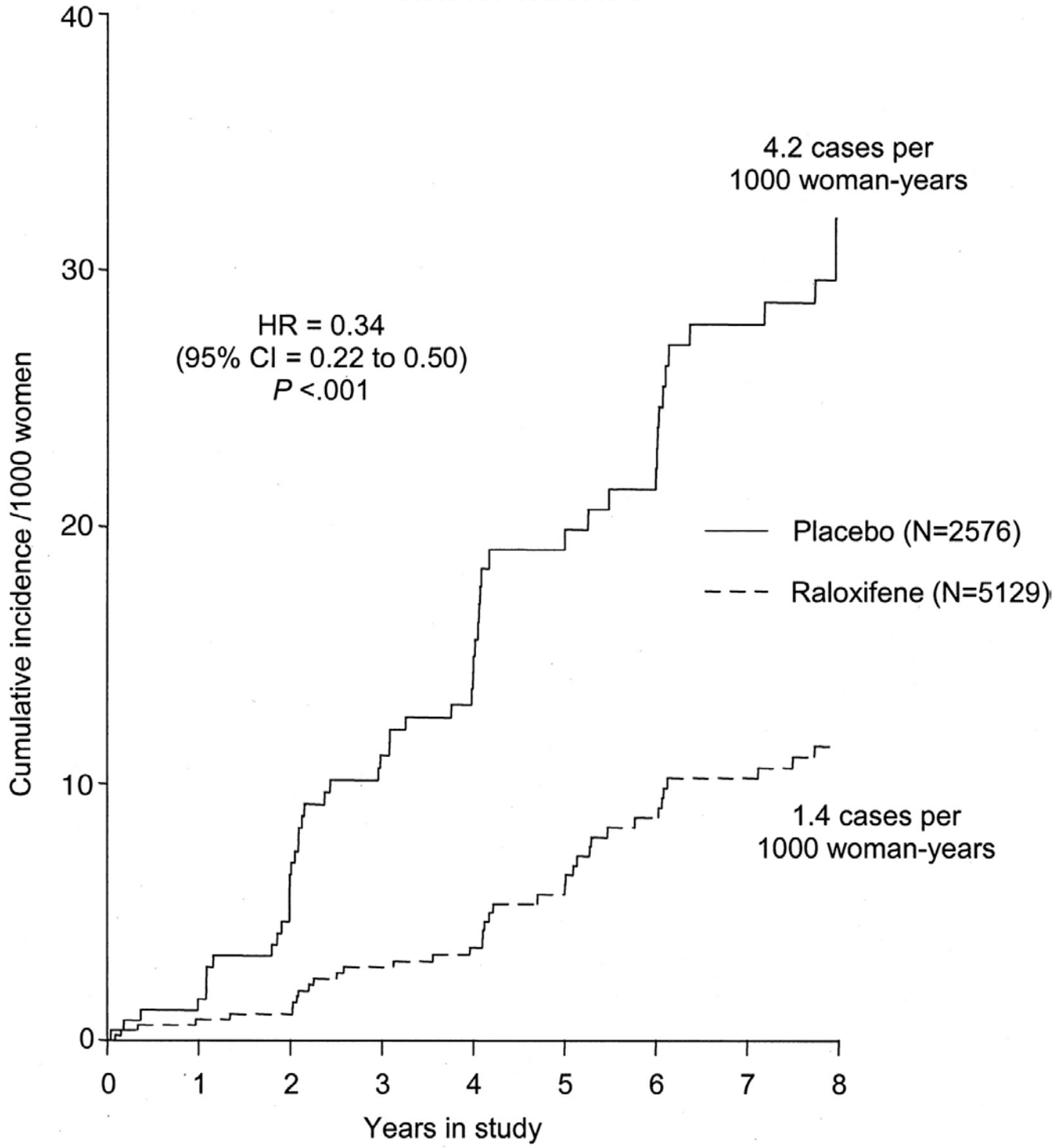
J.-Y ReginsterJ.-Y Reginster, S SarkarJ.-Y ReginsterJ.-Y Reginster, S Sarkar, B ZegelsJ.-Y ReginsterJ.-Y Reg...

**Reduction in PINP, a marker of bone metabolism, with raloxifene treatment and its relationship with vertebral fracture risk**

Bone, Volume 34, Issue 2, 2004, 344 - 351

http://dx.doi.org/10.1016/j.bone.2003.10.004

# Cumulative incidence of adjudicated invasive breast cancers per 1000 women over the 8 years from randomization in the MORE trial to the end of the CORE trial for the 7705 MORE participants




**Silvana Martino et al. JNCI J Natl Cancer Inst 2004;96:1751-1761**



JNCI

# Mode of delivery determines skeletal response to PTH

## PTH

### once-daily

- ↓ osteoblast apoptosis
- bone lining cells
- ↑ cbfa1 (pre-OB)

Stimulate osteoblast differentiation

- ↑ osteoblast number/function
- ↑ bone formation
- ↑ bone mass/strength

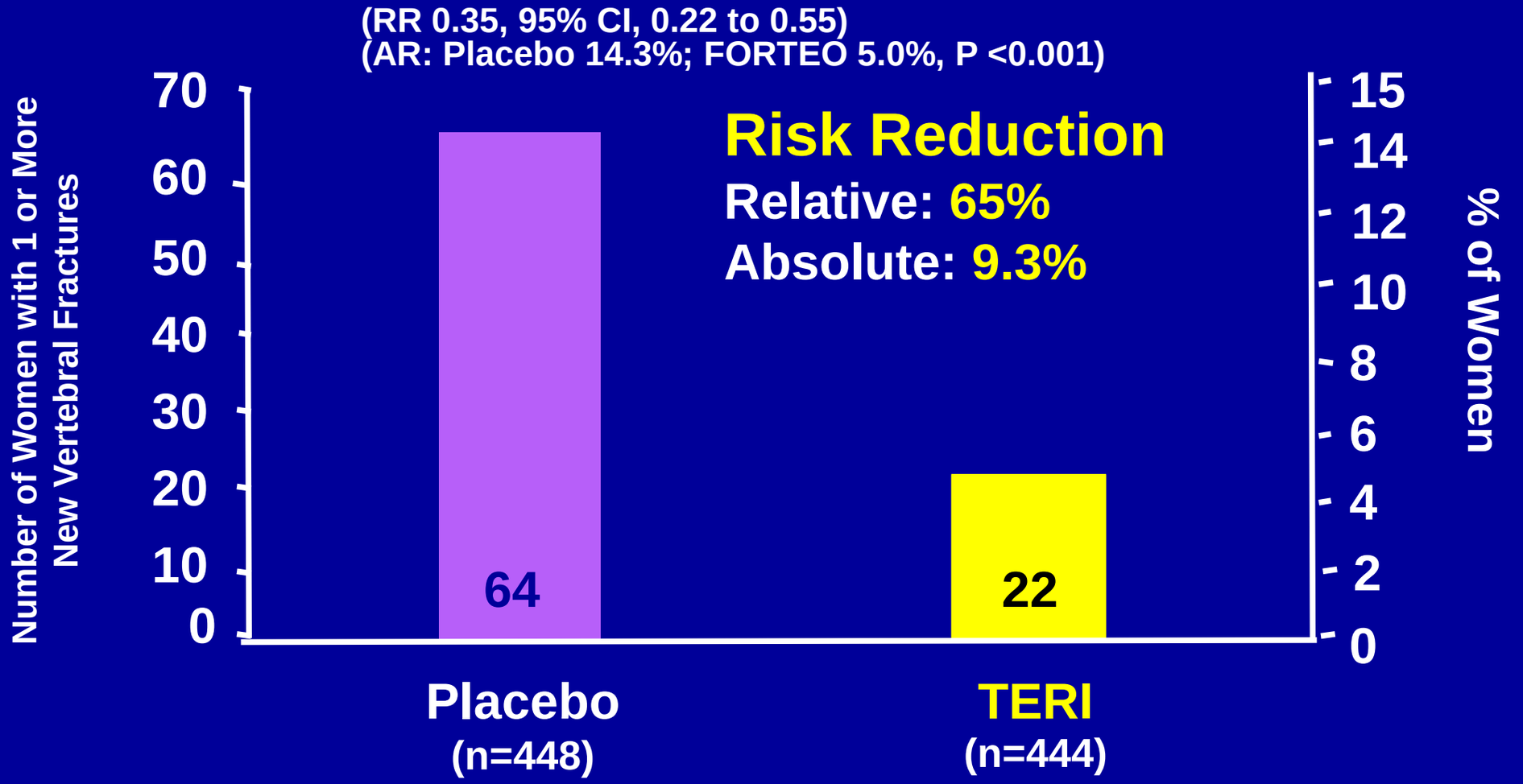
### continuous

- ↑ RANKL
- ↓ OPG

Stimulates osteoclast differentiation

- ↑ osteoclast
- ↑ bone resorption
- ↑ serum $Ca^{++}$

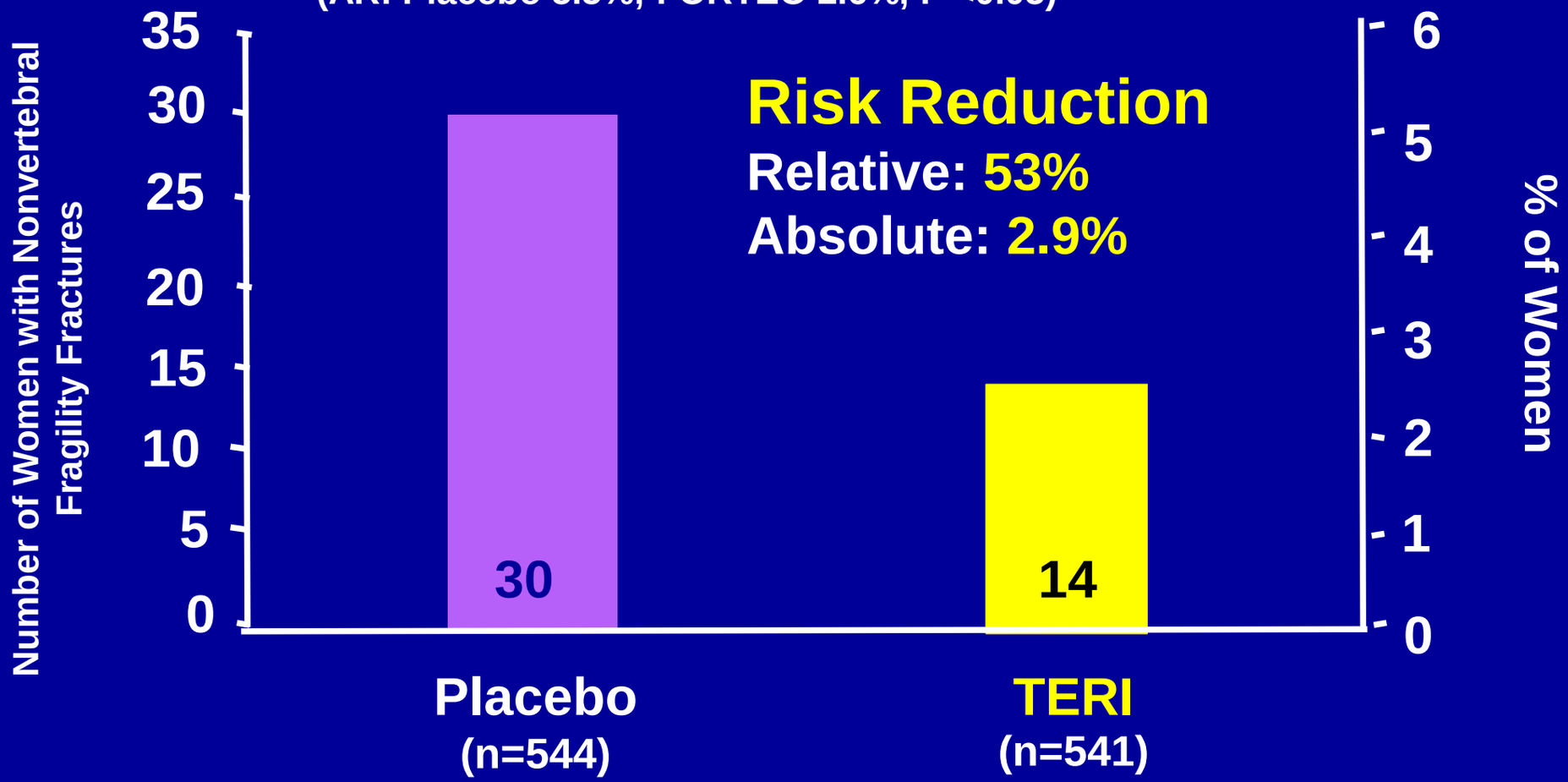
# Teriparatide (rDNA origin) injection Reduces the Risk of ε 1 New Vertebral Fractures




Neer RM, et al. *N Engl J Med*. 2001;344:1434-1441

# Teriparatide (rDNA origin) injection Reduces the Risk of Nonvertebral Fragility Fractures[1]

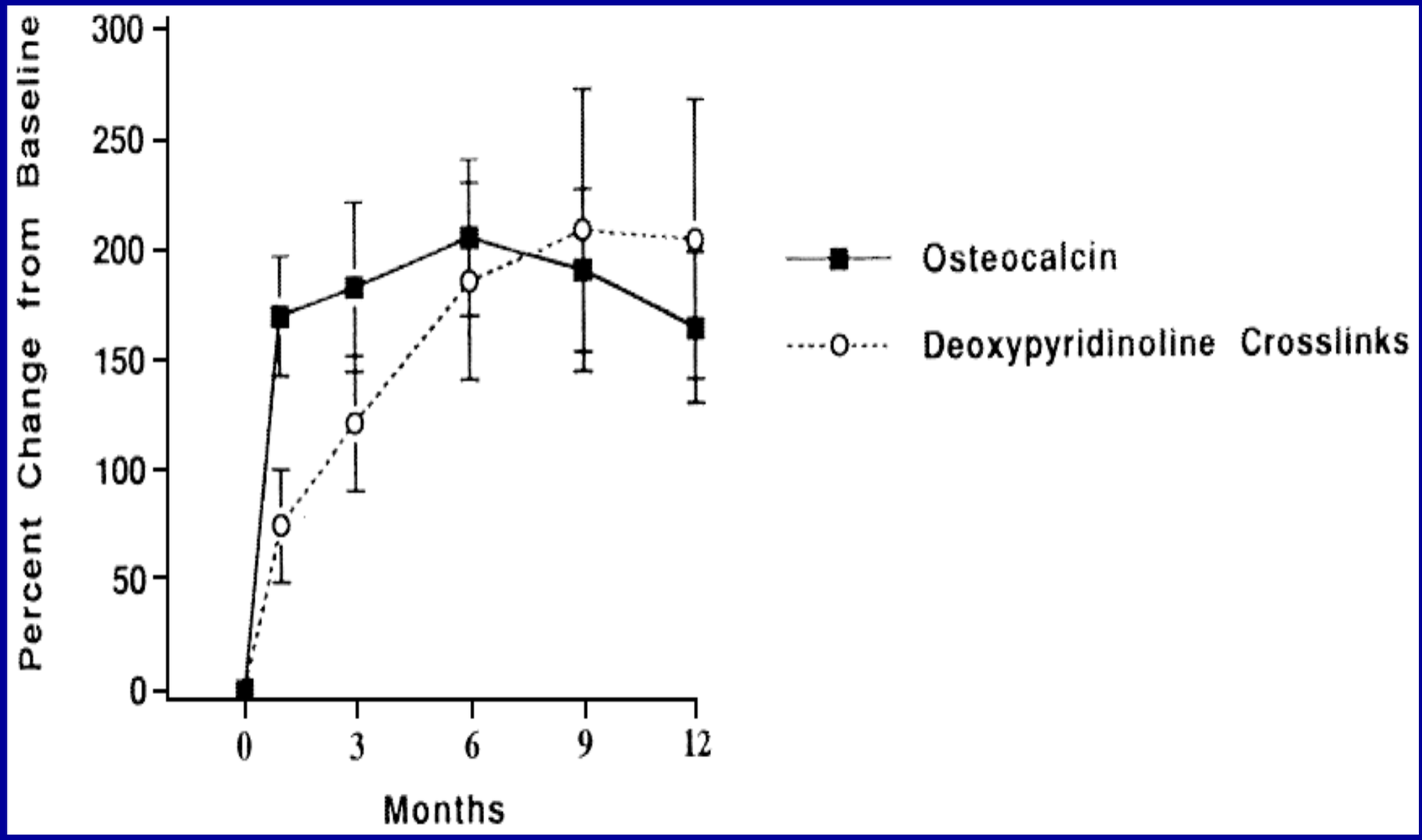
(RR 0.47, 95% CI, 0.25 to 0.88)
(AR: Placebo 5.5%; FORTEO 2.6%, P <0.05)




[1] defined as occurring with minimal trauma

Neer RM, et al. *N Engl J Med*. 2001;344:1434-1441

# Biochemical Markers

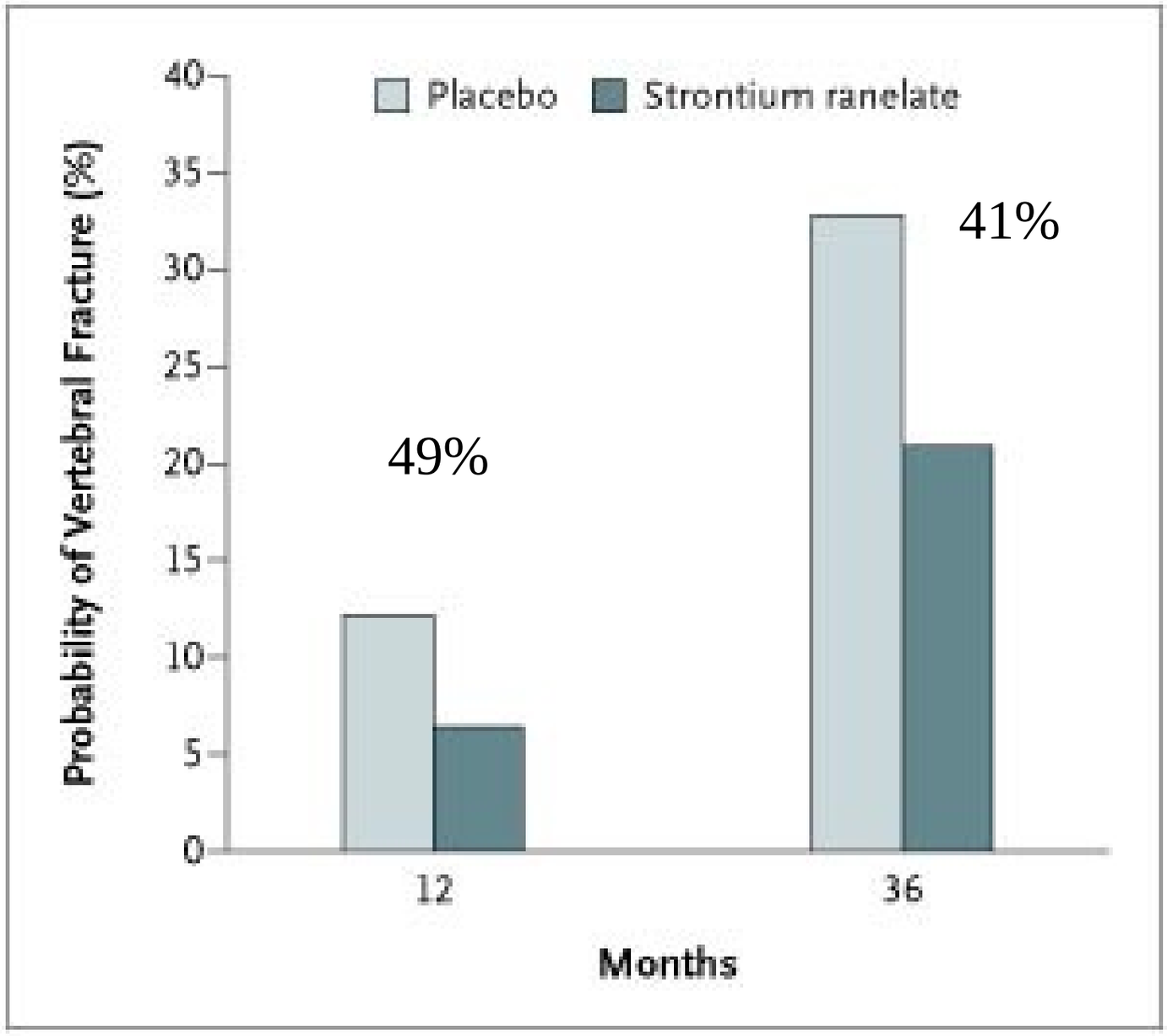



JCI Vol 102 (8) Oct 1998 PTH in Steroid induced Osteoporosis

# Warning

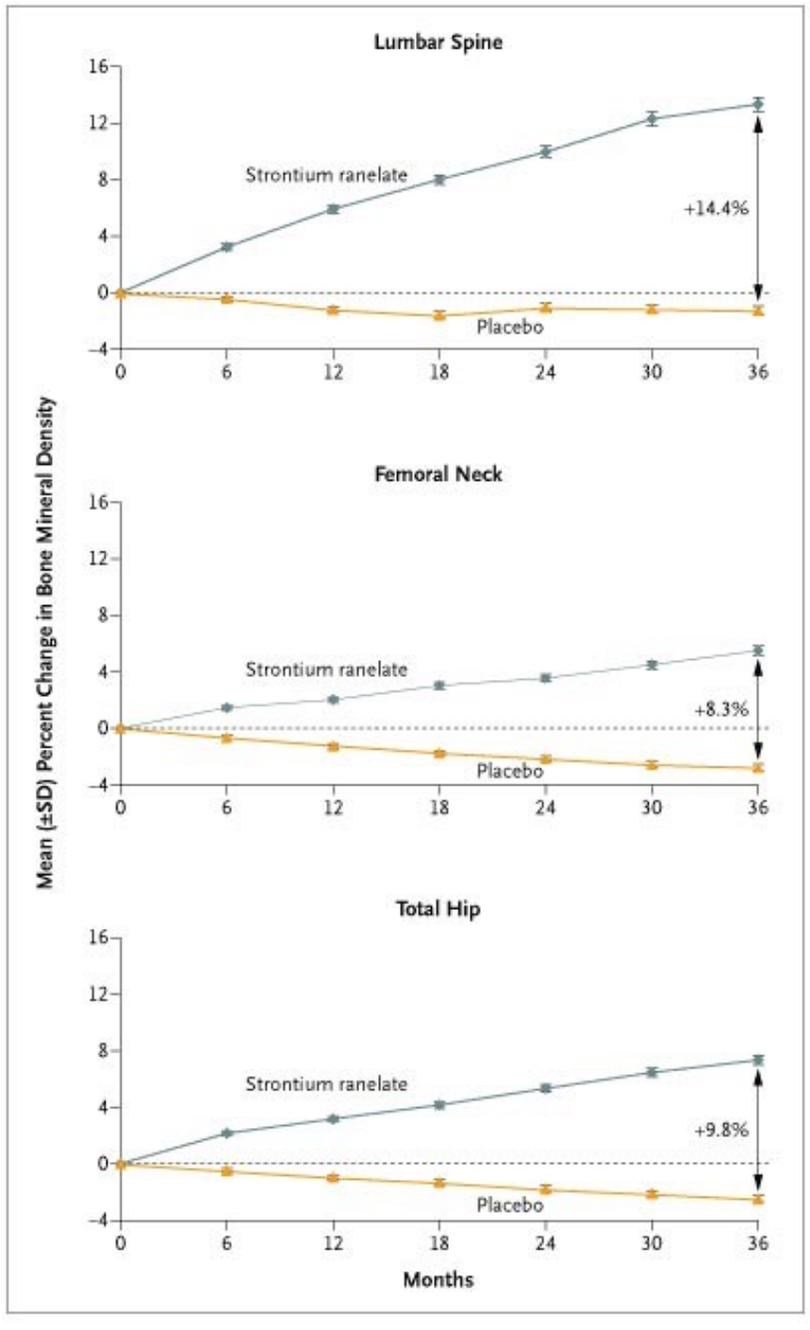
**In male and female rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor), that was dependent on dose and treatment duration. The effect was observed at systemic exposures to teriparatide ranging from 3 to 60 times the exposure in humans given a 20-mcg dose. Because of the uncertain relevance of the rat osteosarcoma finding to humans, teriparatide should be prescribed only to patients for whom the potential benefits are considered to outweigh the potential risk. Teriparatide should not be prescribed for patients who are at increased baseline risk for osteosarcoma (including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, open epiphyses, or prior radiation therapy involving the skeleton) (*see* WARNINGS *and* PRECAUTIONS, Carcinogenesis).**

# Proportion of Patients in the Intention-to-Treat Population Who Had One or More New Vertebral Fractures, Assessed According to the Semiquantitative Method




Meunier, P. et al. N Engl J Med 2004;350:459-468

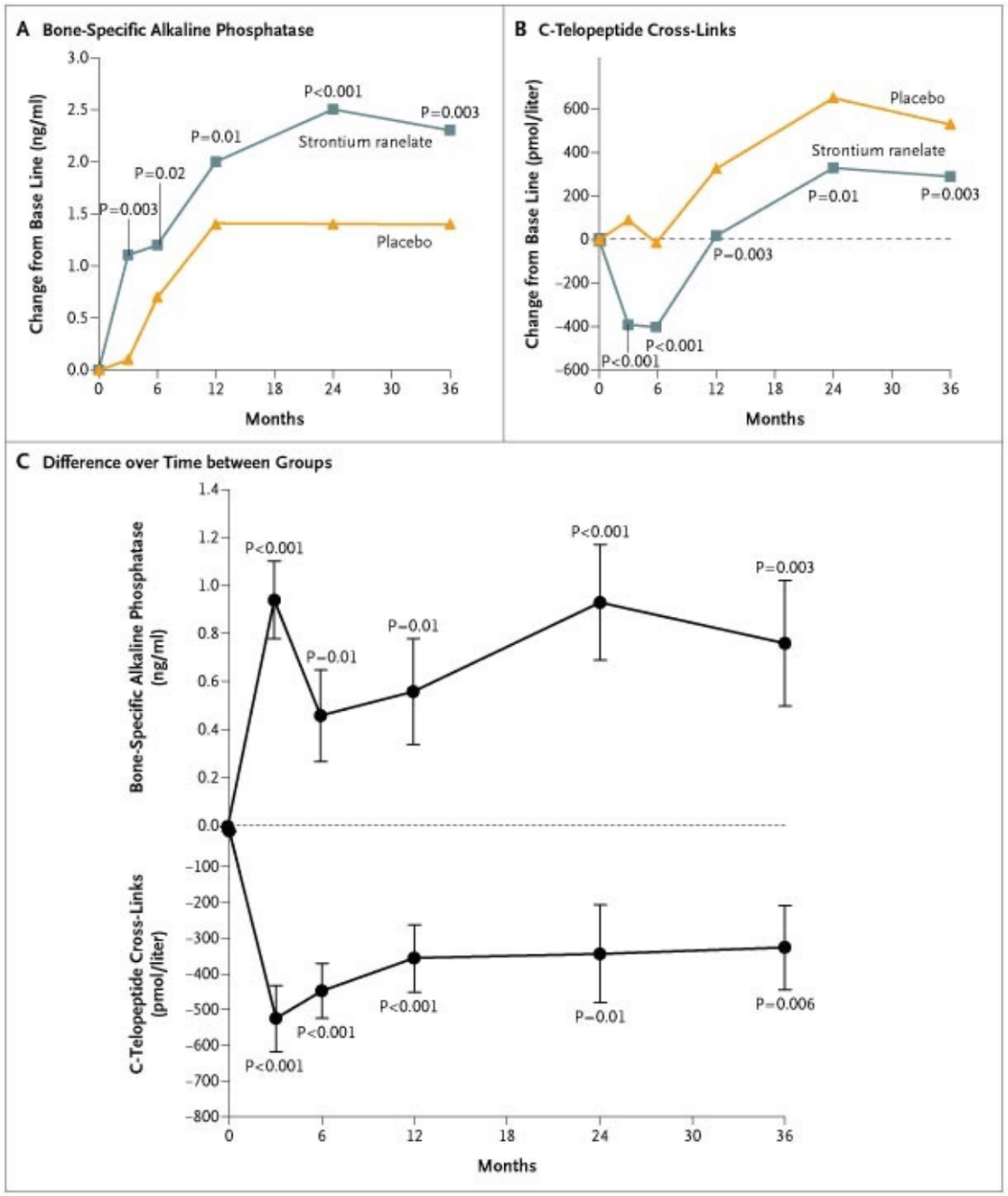
# Effects of Strontium Ranelate on Bone Mineral Density in All Patients Receiving 2 g a Day of Oral Strontium Ranelate




Meunier, P. et al. N Engl J Med 2004;350:459-468

The NEW ENGLAND JOURNAL of MEDICINE

# Strontium Ranelate-Induced Changes in Serum Biochemical Markers of Bone Metabolism




Meunier, P. et al. N Engl J Med 2004;350:459-468

The NEW ENGLAND JOURNAL of MEDICINE

# Summary

- Osteoporosis is a disease with significant consequences
- Fractures can be prevented with multiple FDA approved agents that are proven to be very safe
- Bone densitometry is the best predictor of fractures in women without previous fractures
- Calcium and Vitamin D is part of every treatment regimen
- The goal of treatment is fracture reduction – this should be the primary marker of treatment efficacy.
- Understanding bone turnover can help us direct our treatment choices