

# **Battling Metabolic Bone Disease**

*26<sup>th</sup> Annual Oley Foundation  
Consumer-Clinician Conference*

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# **DISCLOSURE**

**Relevant Financial Relationship(s)**

**None**

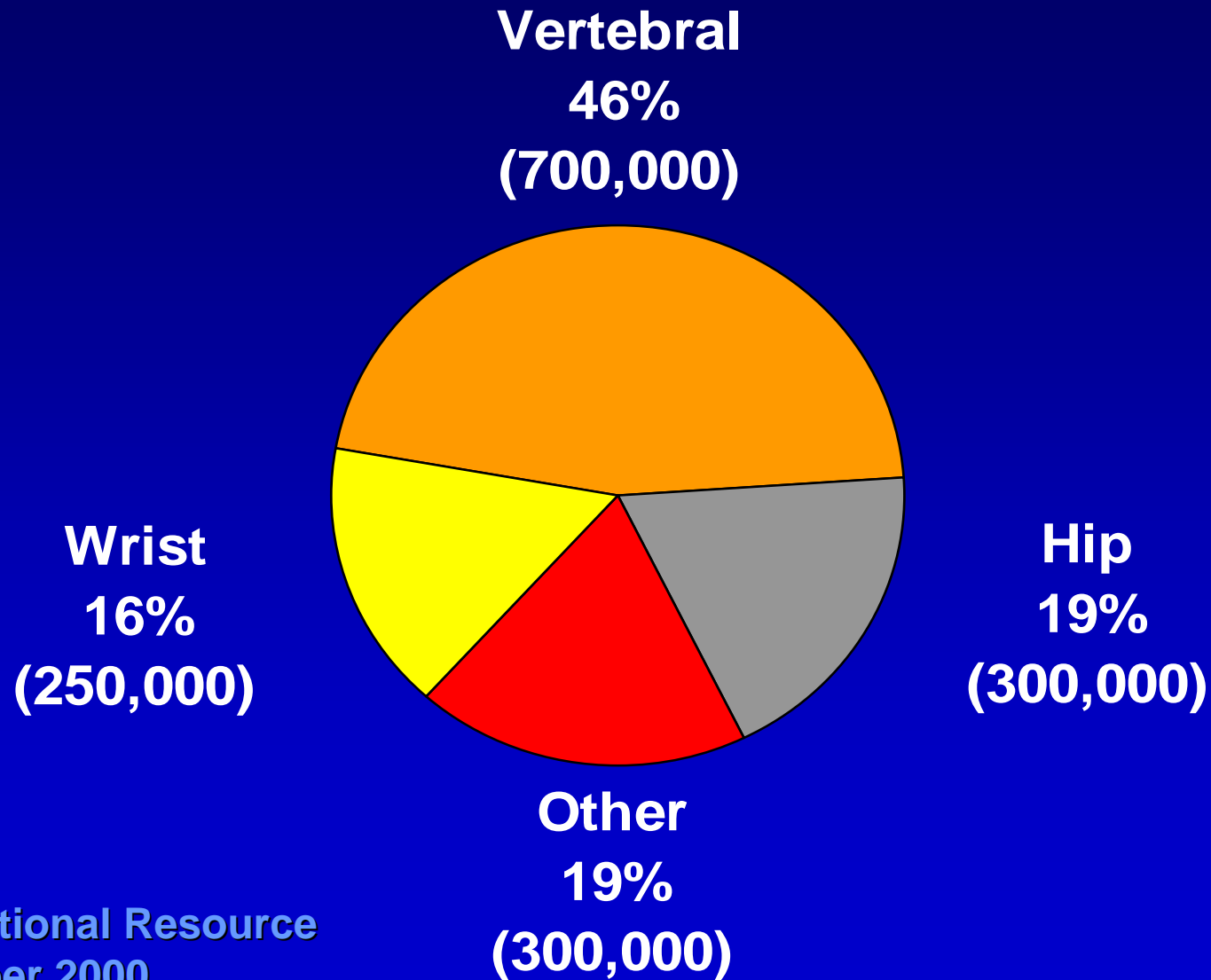
**Off Label Usage**

**None**

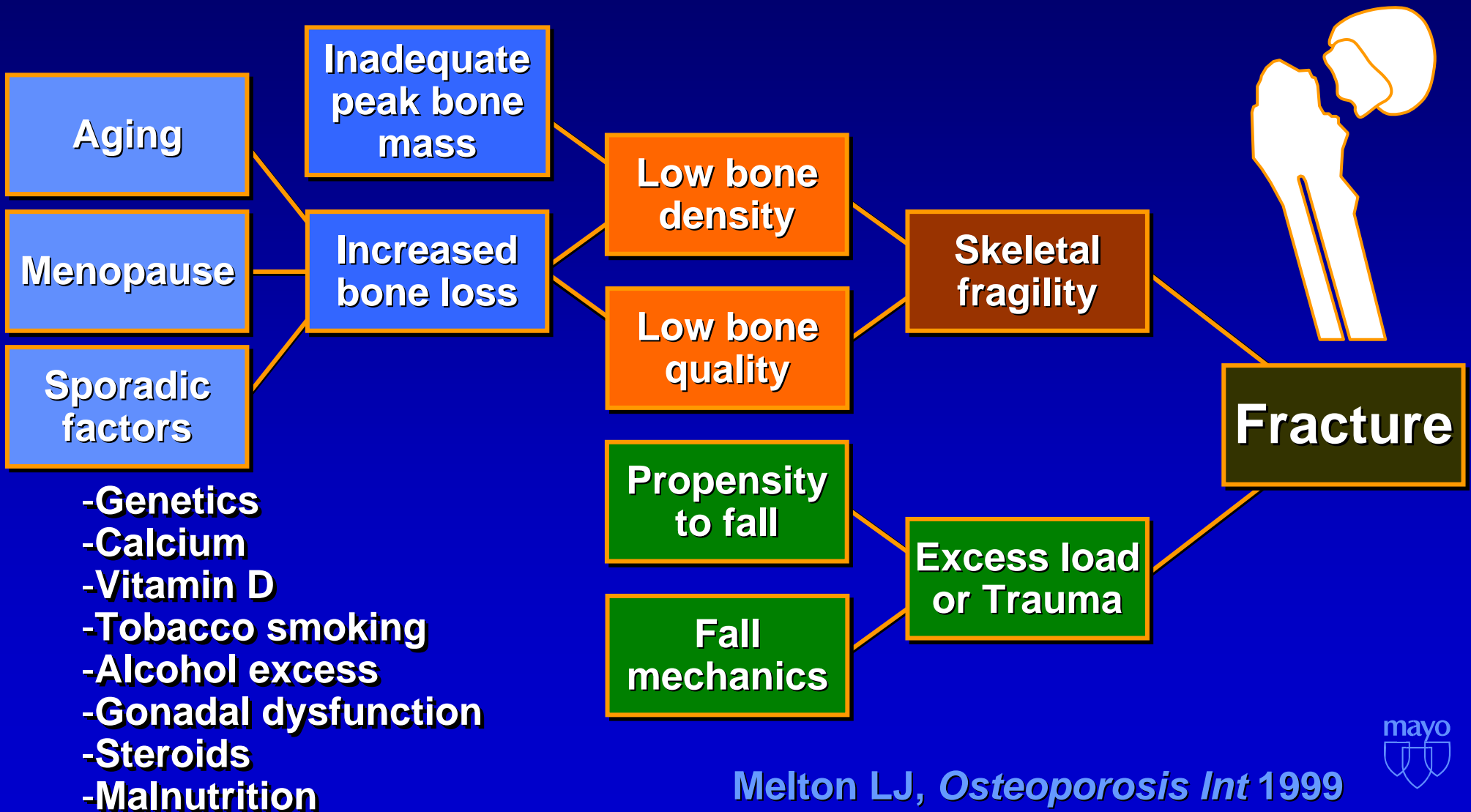
# OBJECTIVES

- **Discuss factors as to future fracture risk**
  - Age, previous fracture(s), bone mineral density (BMD)
  - FRAX<sup>®</sup> WHO fracture risk assessment tool
  - Biochemical markers (BCM) of bone turnover
- **Review FDA approved drug treatments**
  - Calcium and vitamin D
  - Anti-resorptive therapy
  - Anabolic therapy
- **Monitoring therapy**

# More Than 1.5 Million Fractures Yearly



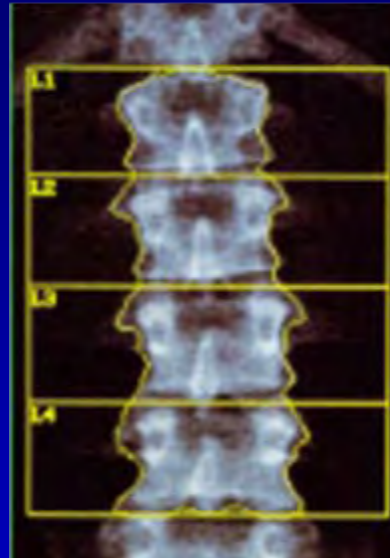
# Pathogenesis of Fractures



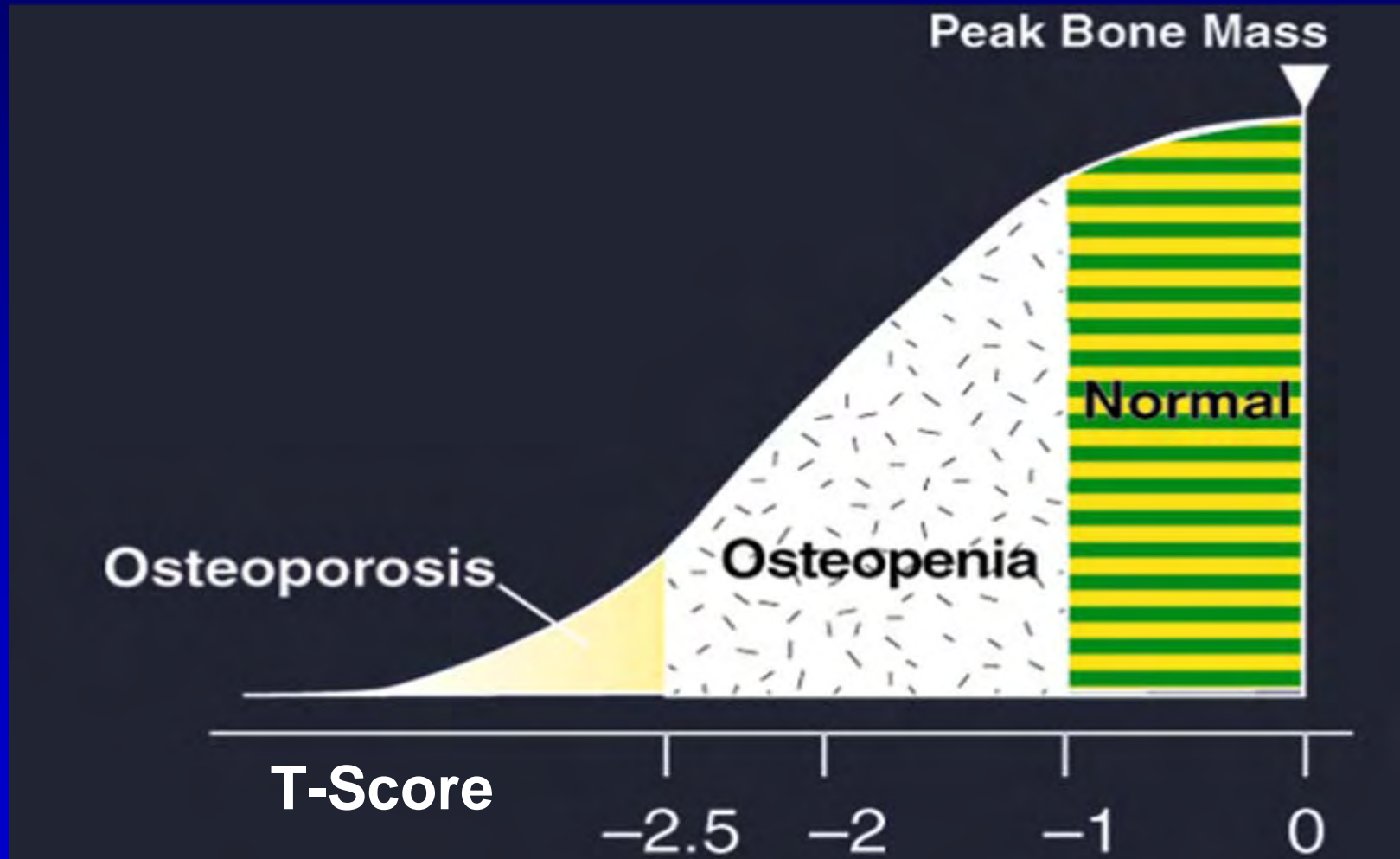
# Assessing Fracture Risk

# Central (Hip-Spine) Dual-Energy-Xray-Absorptiometry (DXA) Measurement

- OP clinical 'surrogate' in absence of fracture
- DXA bone density considered the clinical standard
- Measures multiple skeletal sites  
Spine, hip, forearm, and total body

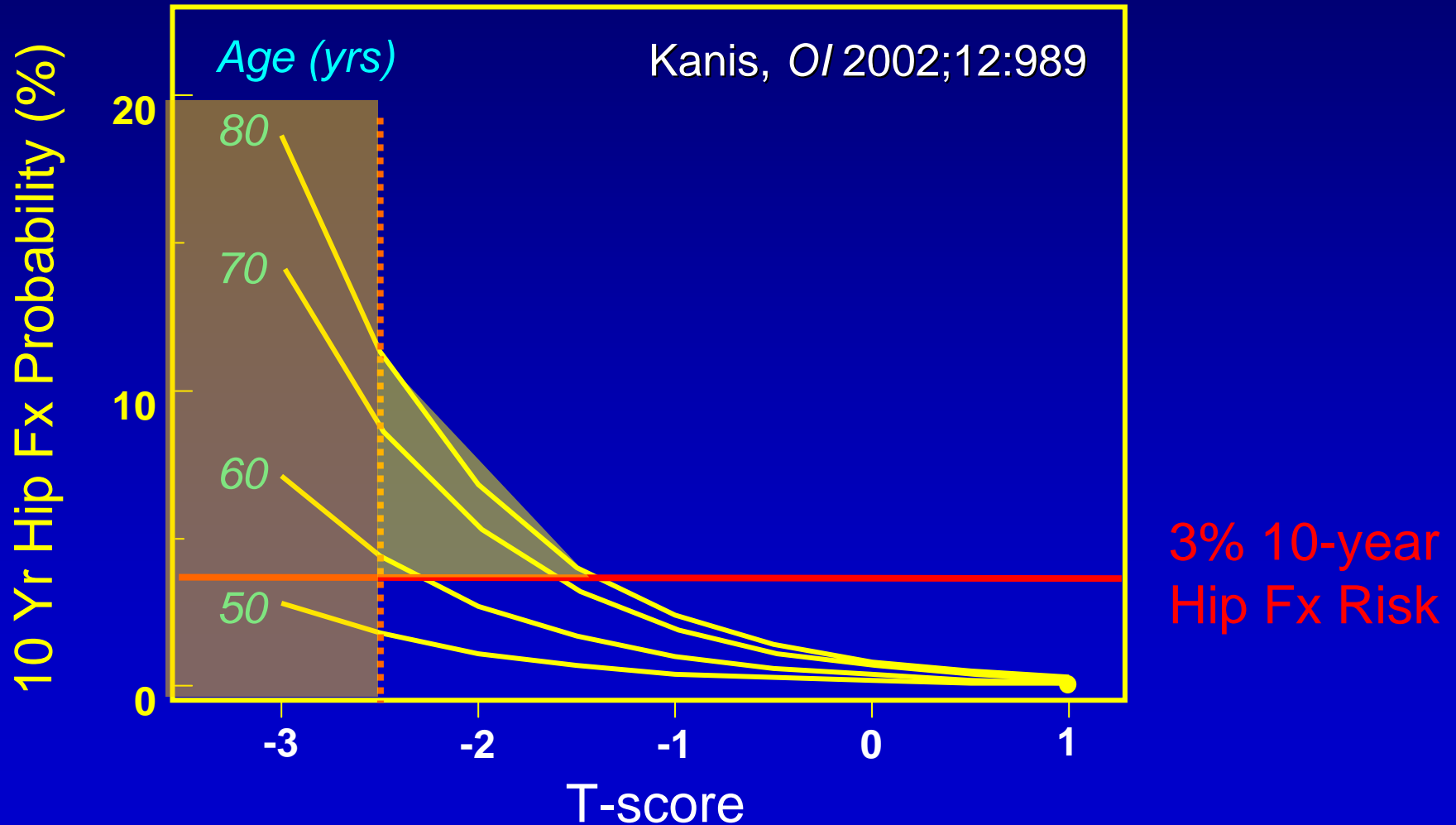


# World Health Organization (WHO) Diagnostic DXA Criteria for Osteoporosis

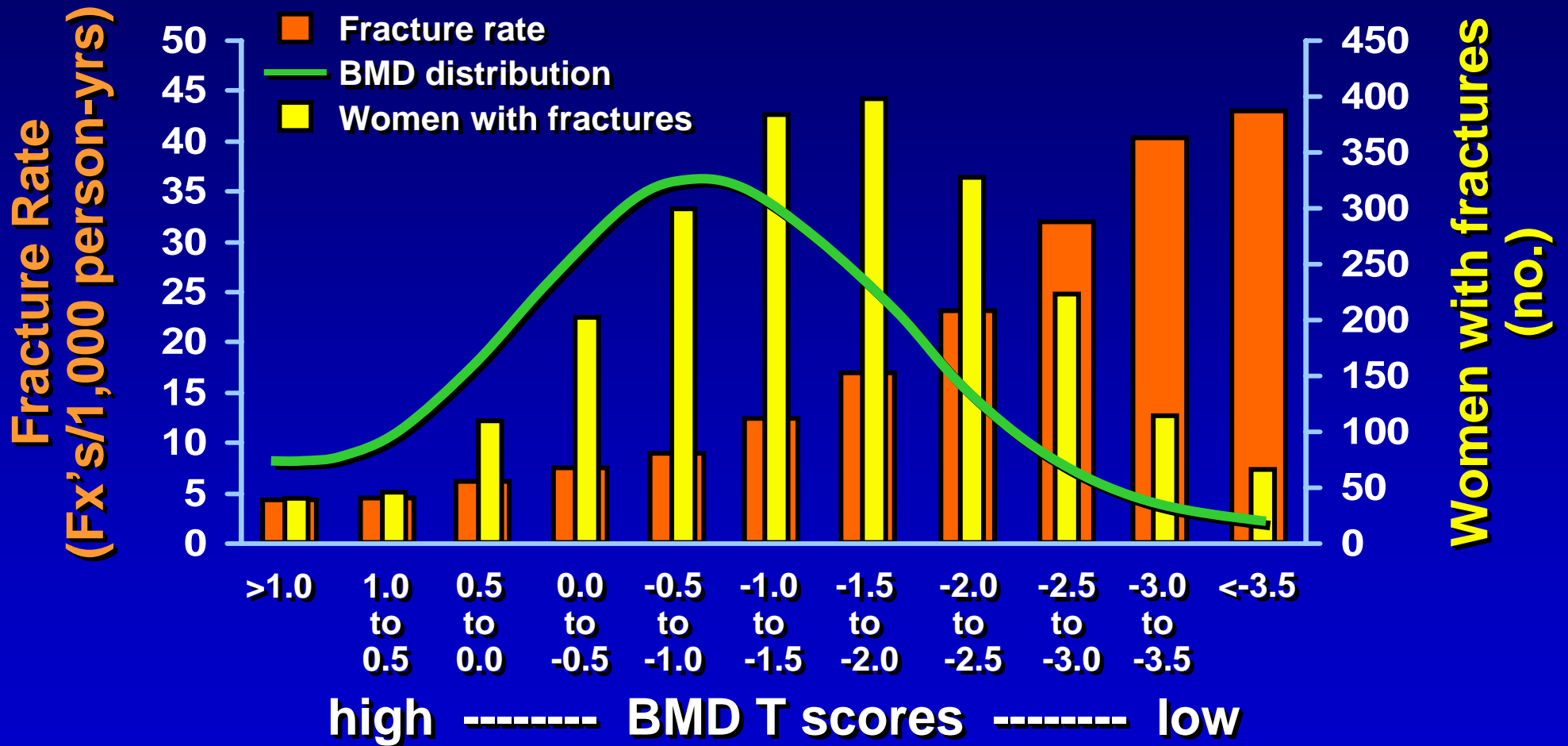


The WHO criteria were established for use in postmenopausal women

# Age and BMD are Independent Risk Factors for Hip Fracture

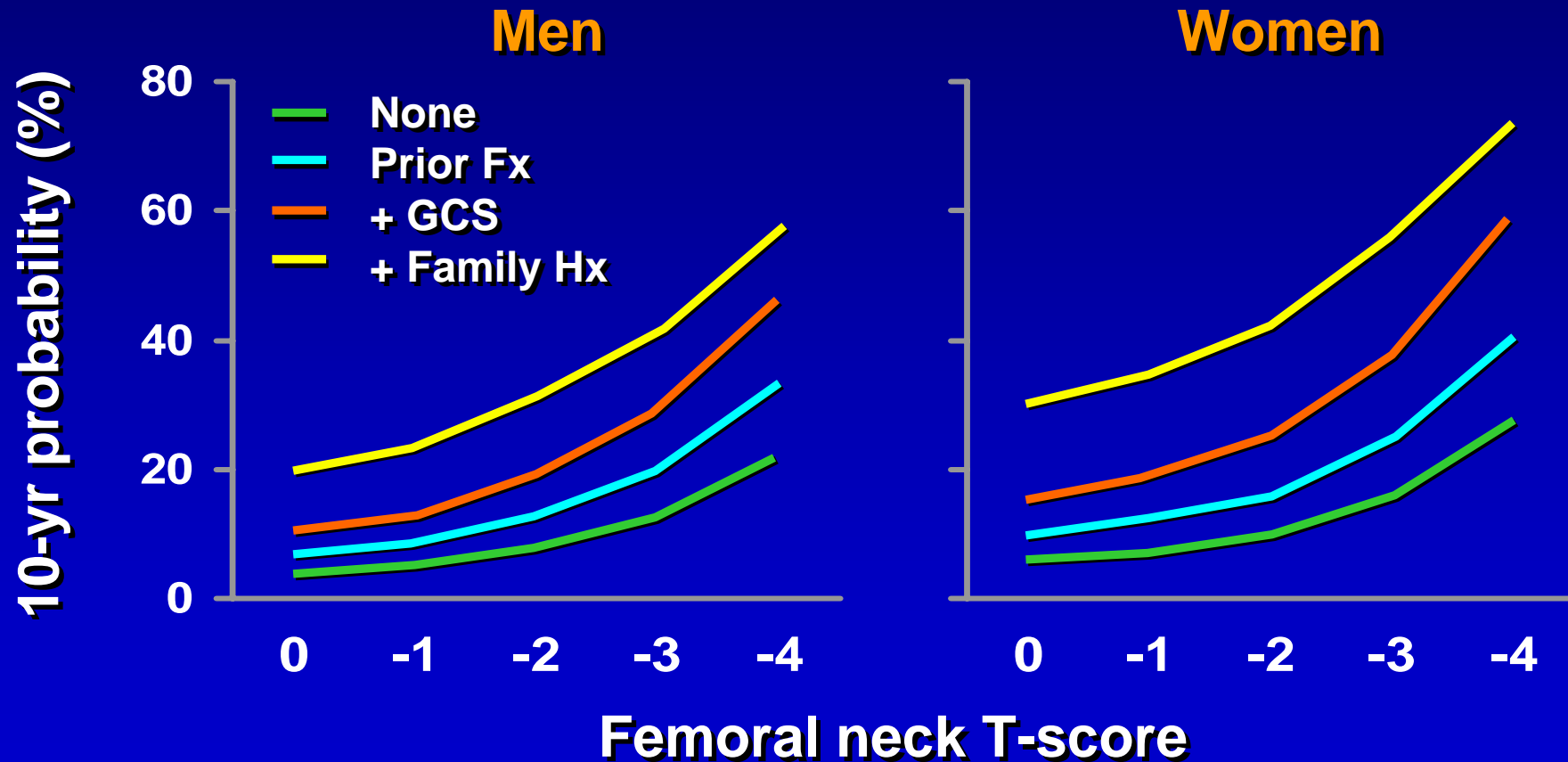


# Osteoporotic Fracture Rates, Numbers and BMD Distribution



# 10-Yr Probability of Major OP Fx

Men and women aged 65 yrs and BMI 25 kg/m<sup>2</sup>; Fx risk according to T score and number of clinical risk factors



## Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture



Country : **US (Caucasian)** Name / ID :

[About the risk factors](#)



### Questionnaire:

1. Age (between 40-90 years) or Date of birth

Age:   
Date of birth: Y:  M:  D:

2. Sex  Male  Female

3. Weight (kg)

4. Height (cm)

5. Previous fracture  No  Yes

6. Parent fractured hip  No  Yes

7. Current smoking  No  Yes

8. Glucocorticoids  No  Yes

9. Rheumatoid arthritis  No  Yes

10. Secondary osteoporosis  No  Yes

11. Alcohol 3 or more units per day  No  Yes

12. Femoral neck BMD (g/cm<sup>2</sup>)

Select DXA

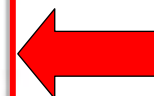
Select DXA

GE-Lunar

Hologic

Norland

T-Score



### Weight Conversion:

pound:

### Height Conversion:

inch:

Country : **US (Caucasian)** Name / ID :

About the risk factors



## Questionnaire:

1. Age (between 40-90 years) or Date of birth

Age:

69

Date of birth:

Y:

M:

D:

2. Sex

Male

Female

3. Weight (kg)

55.9

4. Height (cm)

162.9

5. Previous fracture

No

Yes

6. Parent fractured hip

No

Yes

7. Current smoking

No

Yes

8. Glucocorticoids

No

Yes

9. Rheumatoid arthritis

No

Yes

10. Secondary osteoporosis

No

Yes

11. Alcohol 3 or more units per day

No

Yes

12. Femoral neck BMD (g/cm<sup>2</sup>)

GE-Lunar



0.781

**T-score: -1.8**

Clear

Calculate



# Limitations of WHO FRAX\*

- Fracture risk may be over-estimated
  - Without the inclusion of DXA BMD
- Fracture risk may be under-estimated
  - If >1 prevalent vertebral Fx present
  - If bone turnover increased
  - With high-dose steroid use
  - For vertebral fracture (VFX) risk, as FRAX uses only hip DXA BMD to assess 10-yr hip fracture and all skeletal fracture
- Only for postmenopausal women, and men >50 yrs
  - WHO BMD criteria should not be applied in children, premenopausal women, men <50 yr

\*World Health Organization Fracture Risk Assessment tool

# Calcium and Vitamin D

# National Academy of Sciences

## Institute of Medicine (IOM) 2011 Guidelines

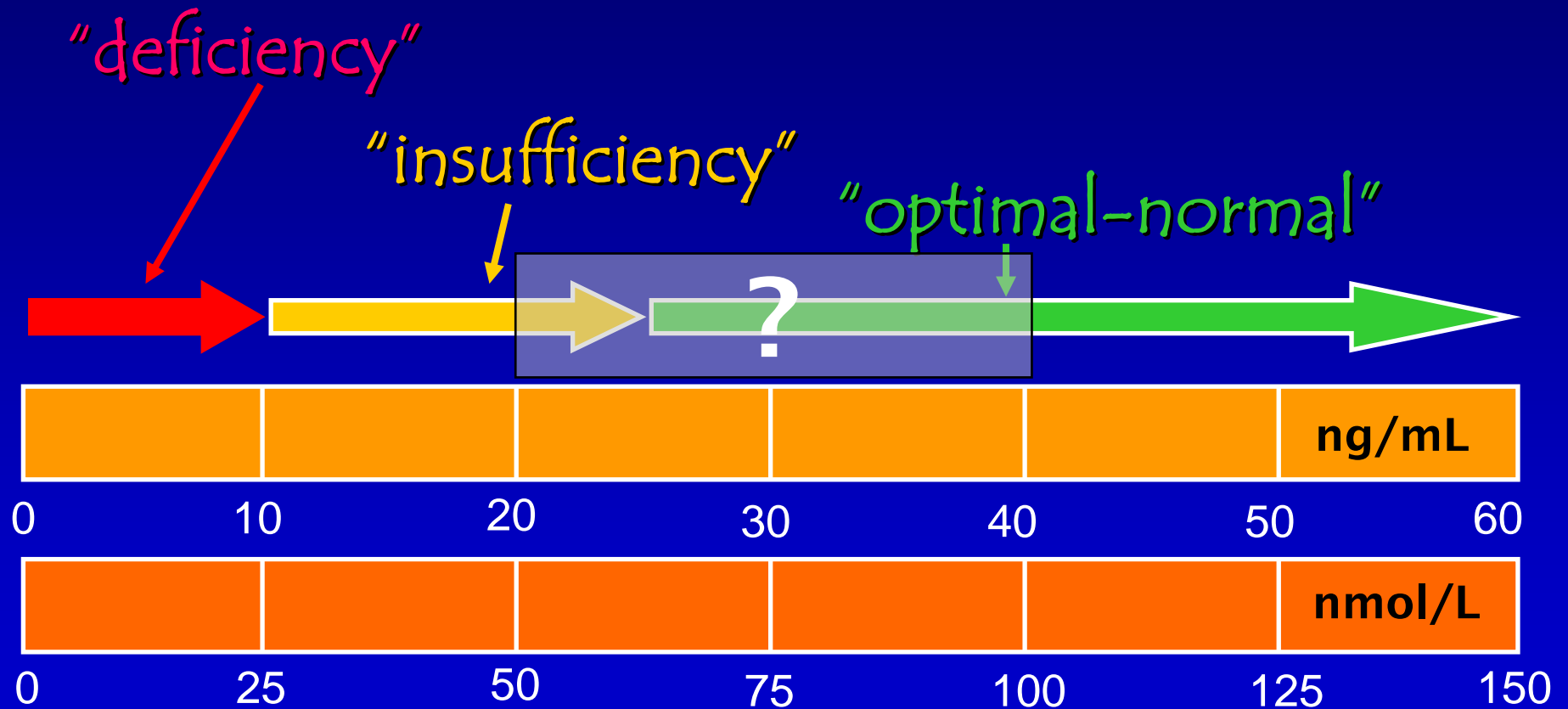
Life Stage Group (age and gender)	Calcium		Vitamin D	
	RDA (mg/d) <sup>a</sup>	Upper Limit (UL) (mg/d)	RDA (IU/d)*	Upper Limit (UL) (IU/d)
0-6 mo (M+F)	200 <sup>b</sup>	1000 <sup>b</sup>	400 <sup>b</sup>	1000 <sup>b</sup>
6-12 mo (M+F)	260 <sup>b</sup>	1500 <sup>b</sup>	400 <sup>b</sup>	1500 <sup>b</sup>
1-3yr (M+F)	700	2500	600	2500
4-8yr (M+F)	1000	2500	600	3000
9-13yr (M+F)	1300	3000	600	4000
14-18yr (M+F) <sup>c</sup>	1300	3000	600	4000
19-30yr (M+F) <sup>c</sup>	1000	2500	600	4000
31-50 yr (M+F)	1000	2500	600	4000
51-70 yr (M)	1000	2000	600	4000
51-70yr (F)	1200	2000	600	4000
71+yr (M+F)	1200	2000	800	4000

<sup>a</sup> RDA = intake that covers needs of 97.5% of the healthy normal population.

<sup>b</sup> Reflects Adequate Intake (AI) reference value rather than RDA. RDAs have not been established for infants due to insufficient data.

<sup>c</sup> Calcium and vitamin D RDAs are the same for pregnant or lactating females in these age groups.

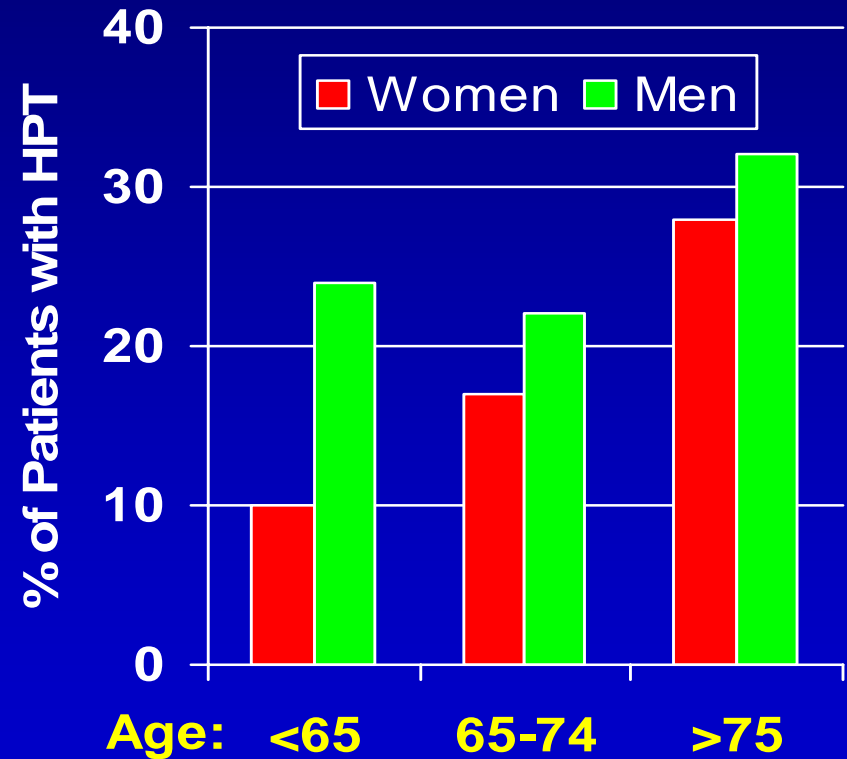
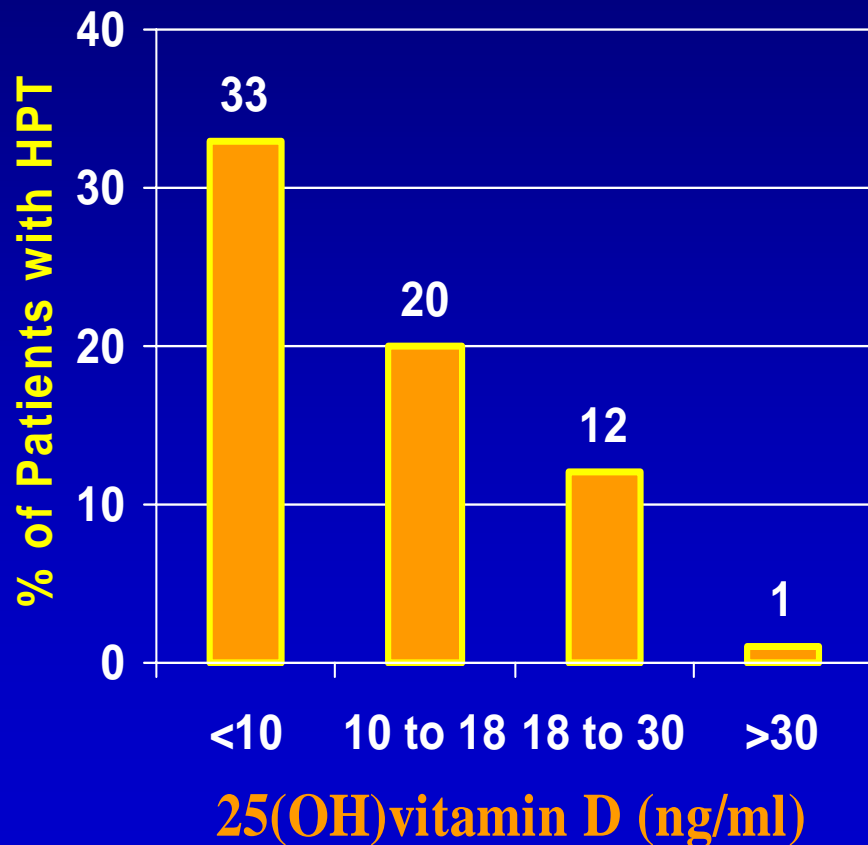
# Is There an Optimal Vit-D Level? Who is at risk?



\*modified after RP Heaney (10 ng/mL = 25 nmol/L)

# Bone Loss, Vitamin D and 2°HPT

Ambulatory EVOS\* Subjects (Spain, latitude 43°N, n=268, mean age 68 years). **Prevalence 2° HPT: F 24.1%, M 18.5%**



\*European Vertebral Osteoporosis Study, Kidney International. 2003;63(S85):S44

# When To Consider Vit-D Deficiency

## Clinical Setting

Decreased sun exposure

Poor vitamin D intake

Malabsorption

Gastric bypass, Celiac sprue, short bowel

Chronic illness

Pain, weakness, falls

CKD, seizure Rx

Underweight-malnourished

Bone loss or fracture

## Laboratory

↓ 24-hr urine calcium

↑ Total or bone alk phos

↑ Parathyroid hormone

↑ Creatinine (GFR < 60)

## Radiographs

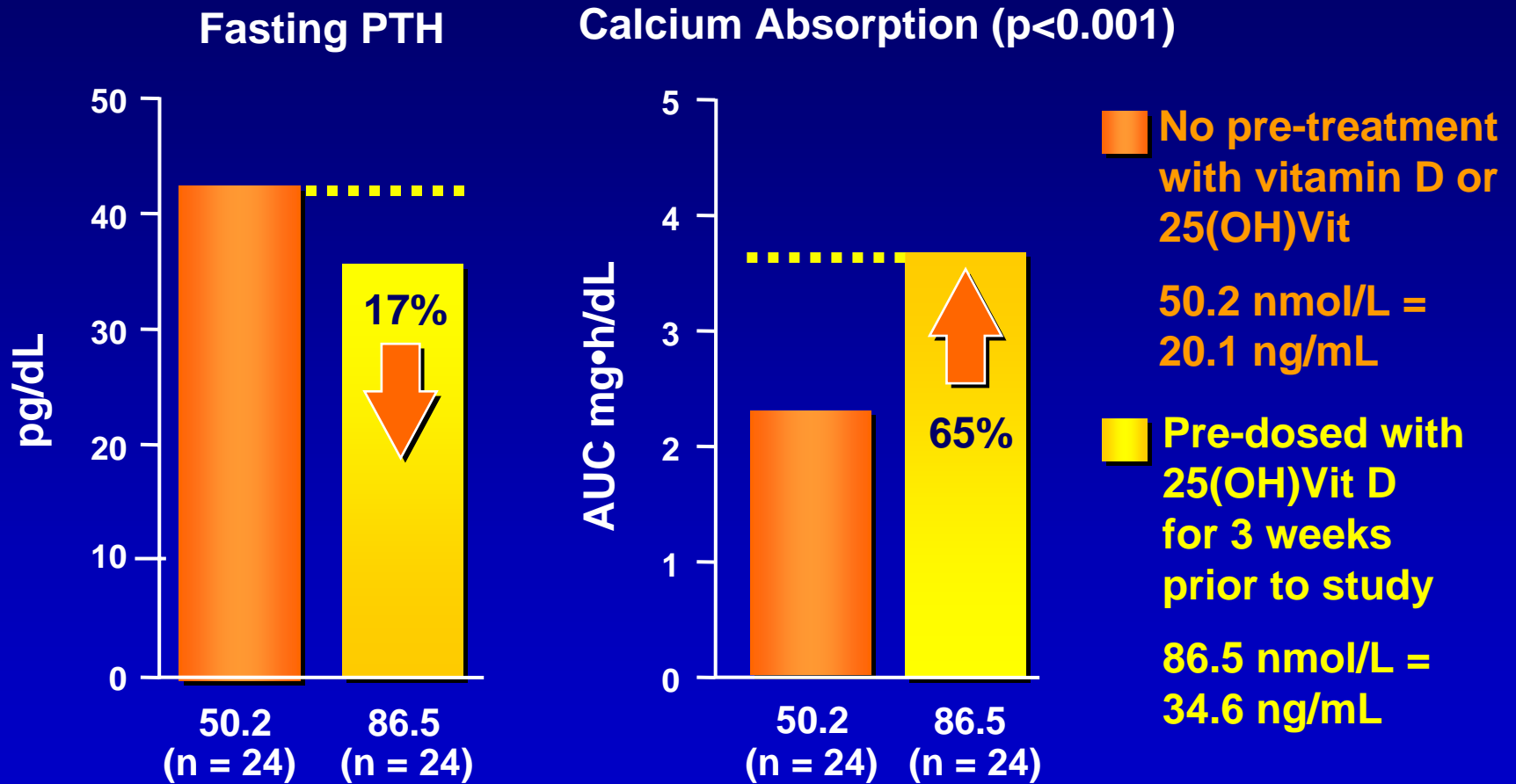
Radiographic bone loss

Low bone mineral density

Skeletal fracture

Skeletal pseudofracture

# Vit D, Calcium Absorption, and PTH

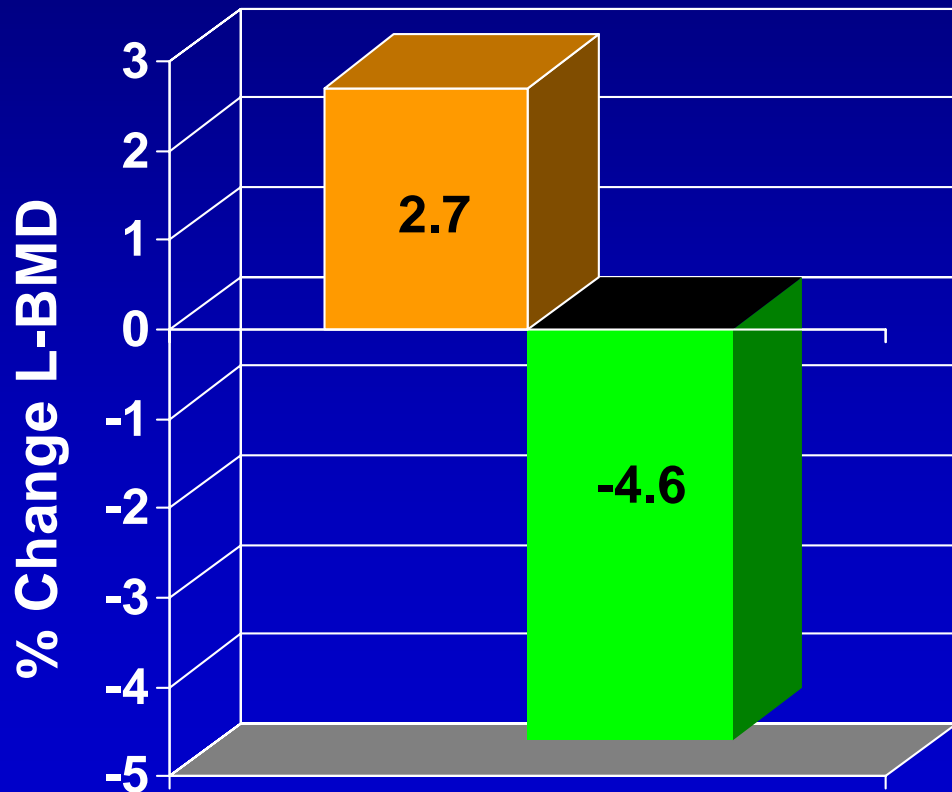


Mean serum 25(OH)D level, nmol/L

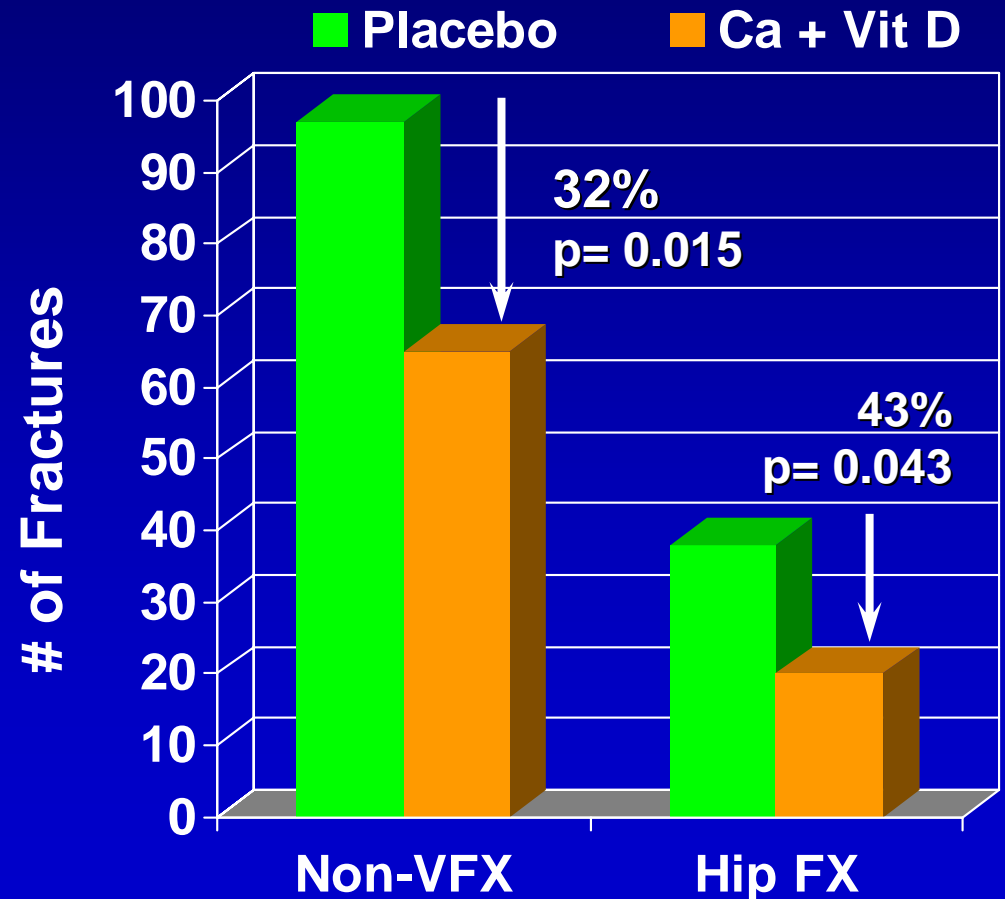
# Vit D Deficiency and Osteoporosis

## Treatment Effect On BMD and Fx at 18 Mo

Ave. age 84 years, n = 3270



Chapuy, NEJM 1992; 327:1637



Calcium 1200 mg + Vitamin D 800 IU

# HPN

## ● Calcium

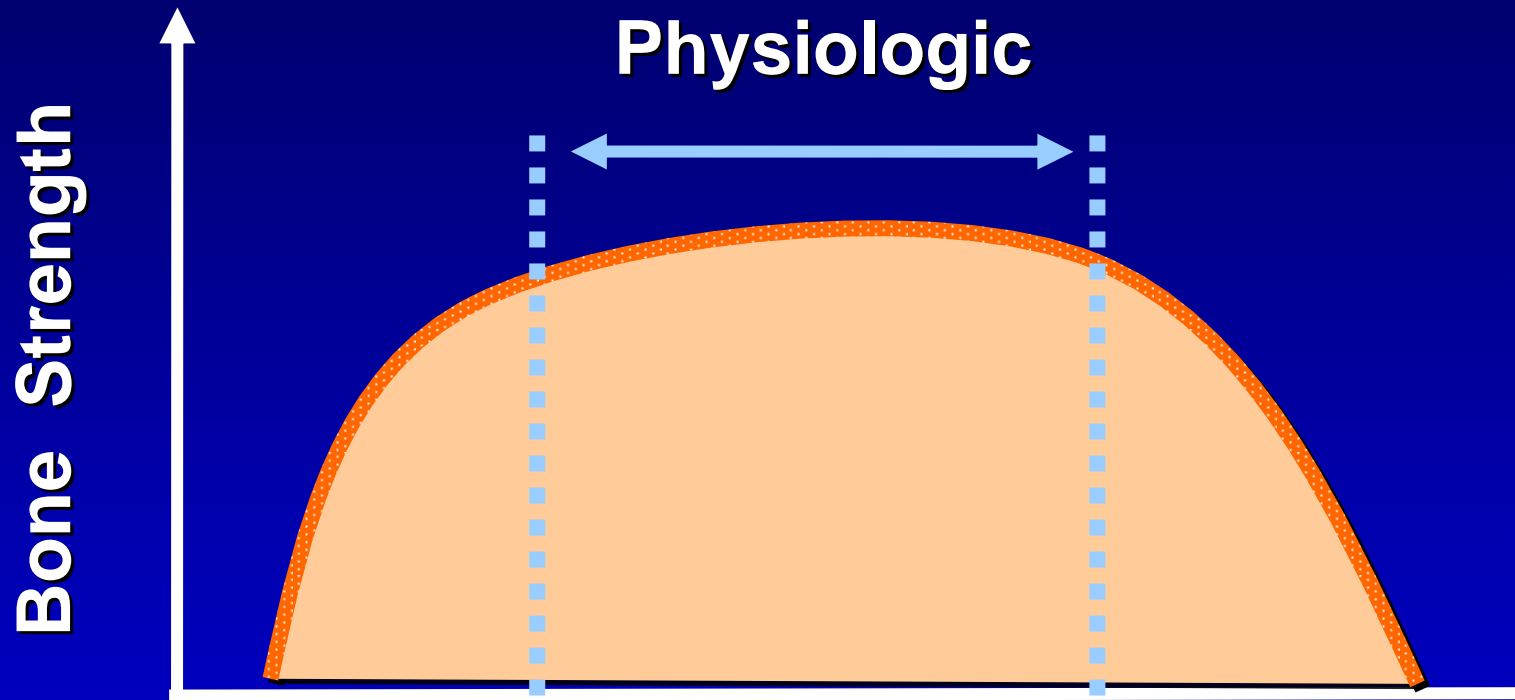
- 1 gram IV calcium gluconate; provides 4.7 mEq calcium, or 9% (90 mg) elemental calcium
  - ✓ Oral calcium may be poorly absorbed
  - ✓ Normal urine calcium excretion  $\leq$  275-300 mg/day; may be increased by sodium/salt intake

## ● Vitamin D

- MVI (multivitamin injectable); provides 200 I.U. (international units) vitamin D3 (cholecalciferol)
  - ✓ Oral intake may need to be in large doses
  - ✓ IM source limited; uVB sunlight exposure if needed
- Blood measurement desirable

# **Anti-resorptive Therapy**

# Bone “Remodeling” Activity



## Remodeling Too Low

- Poor growth
- Poorly-mineralized

**Ex. Osteo-malacia**

## Normal Bone

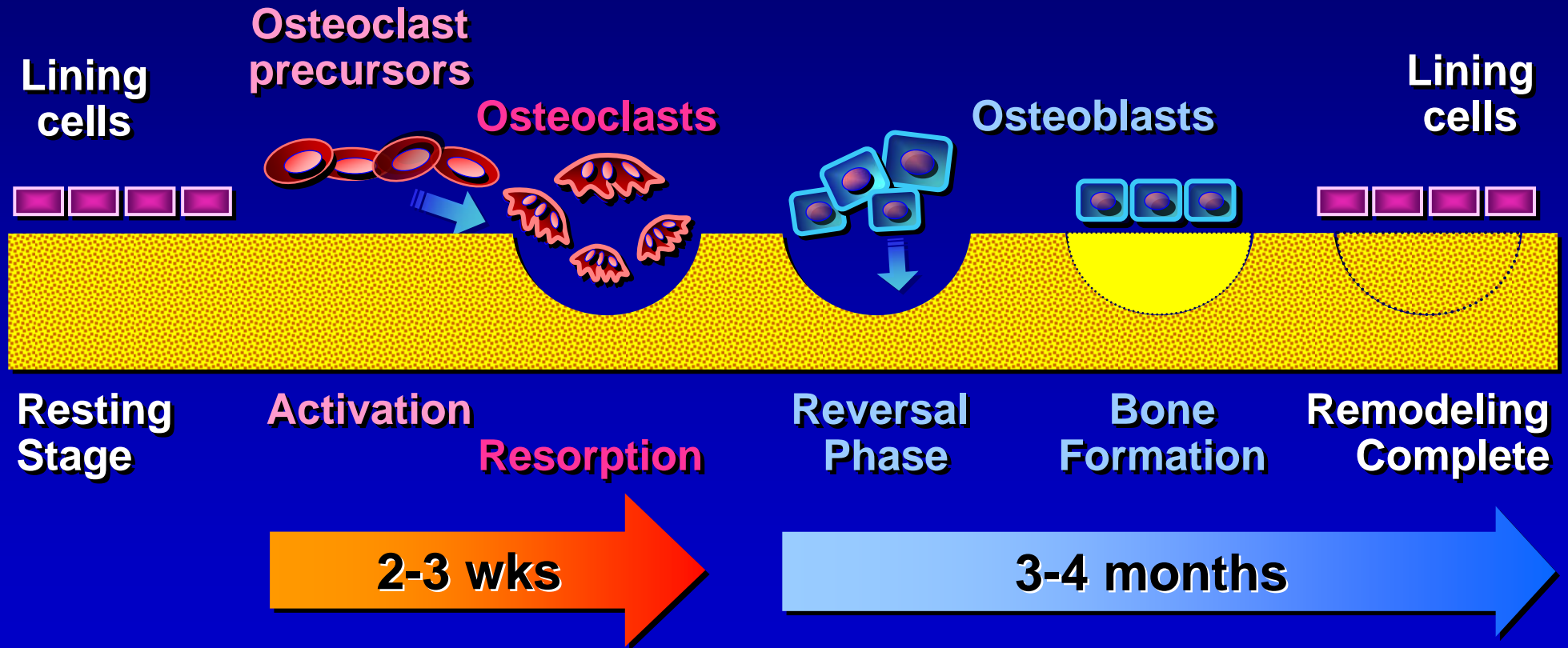
## Remodeling Too High

- ↓ Bone mass/structure
- Stress risers

**Ex. Osteo-porosis**

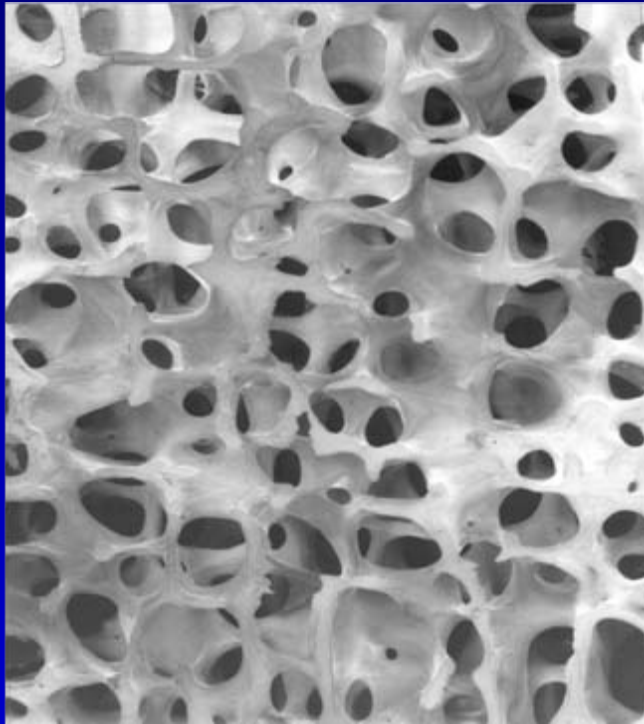
# Normal Bone “Remodeling” Activity

## A Coupled Homeostatic Process



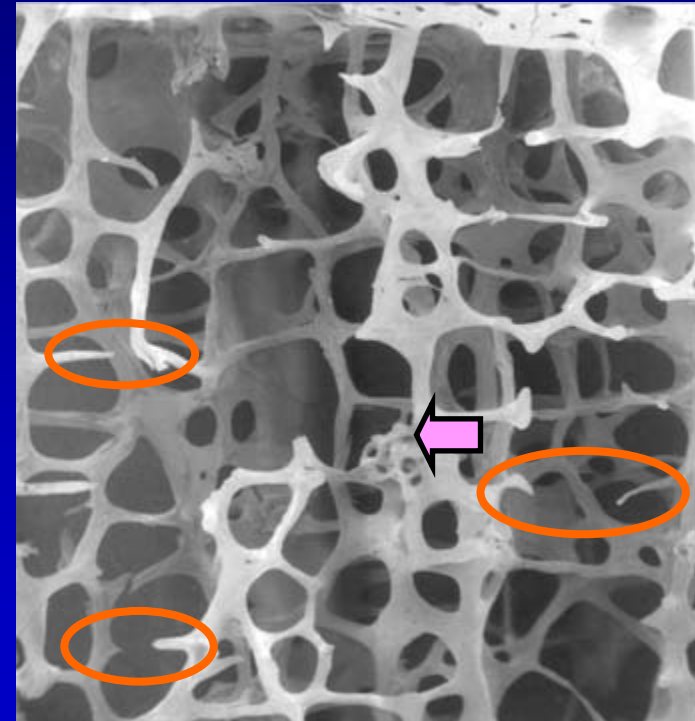
# Postmenopausal Osteoporosis Trabecular Micro-architectural Change

Normal



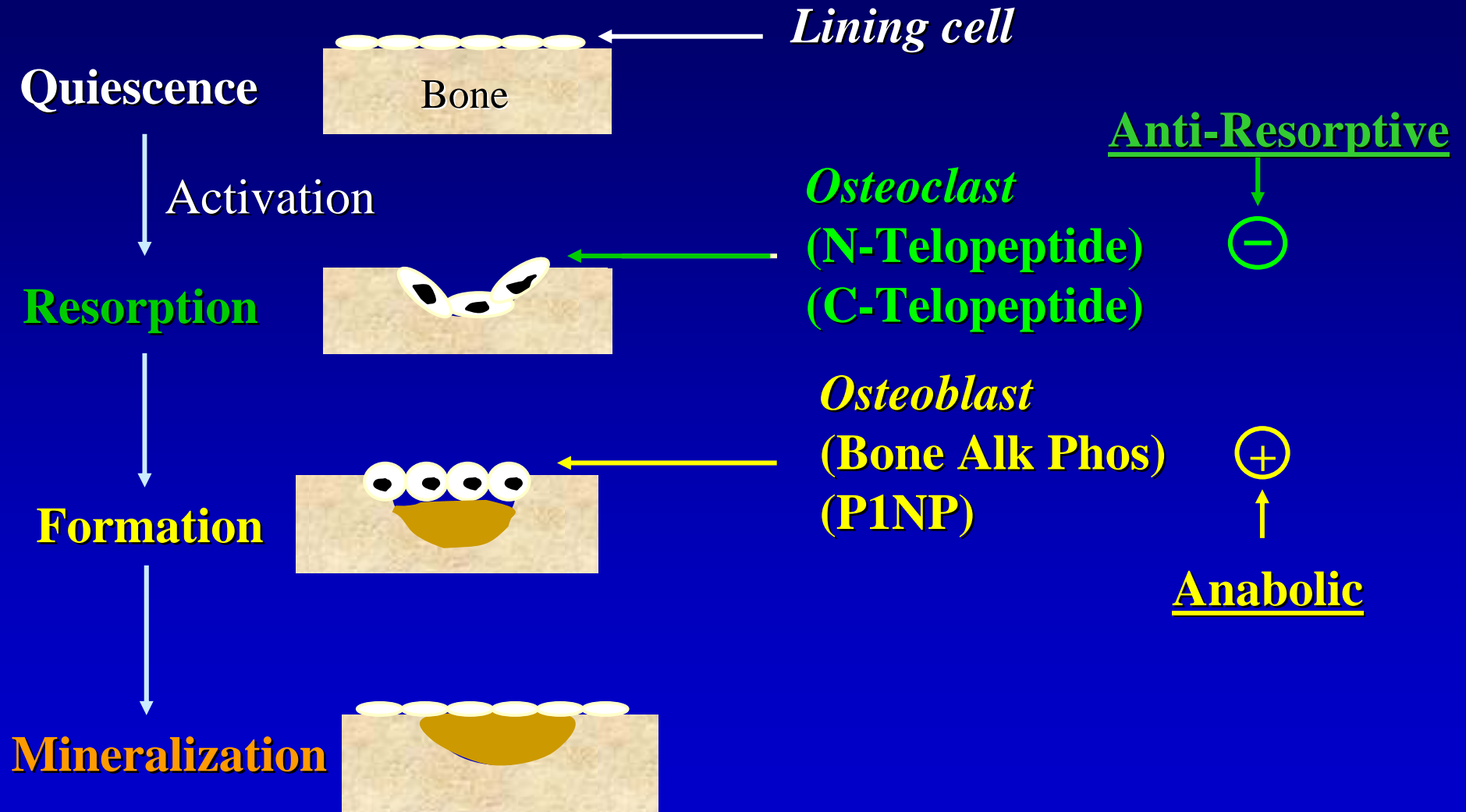
Dempster, 2000

Osteoporosis



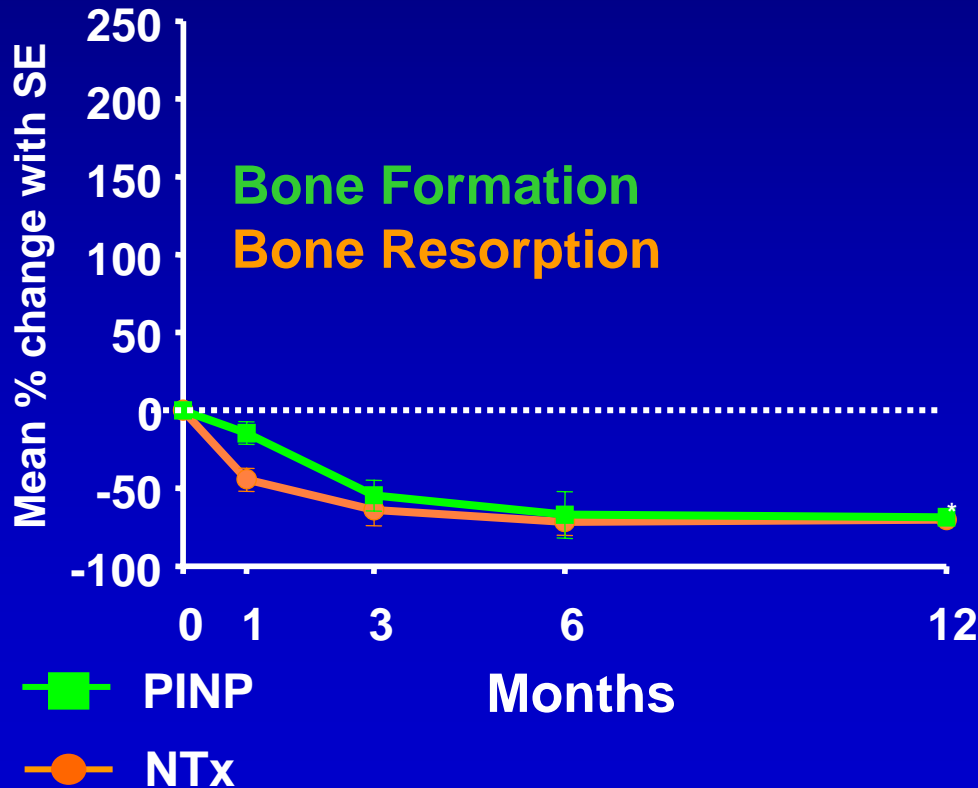
Horizontal Perforations  
Micro-callous

# Bone Remodeling Unit

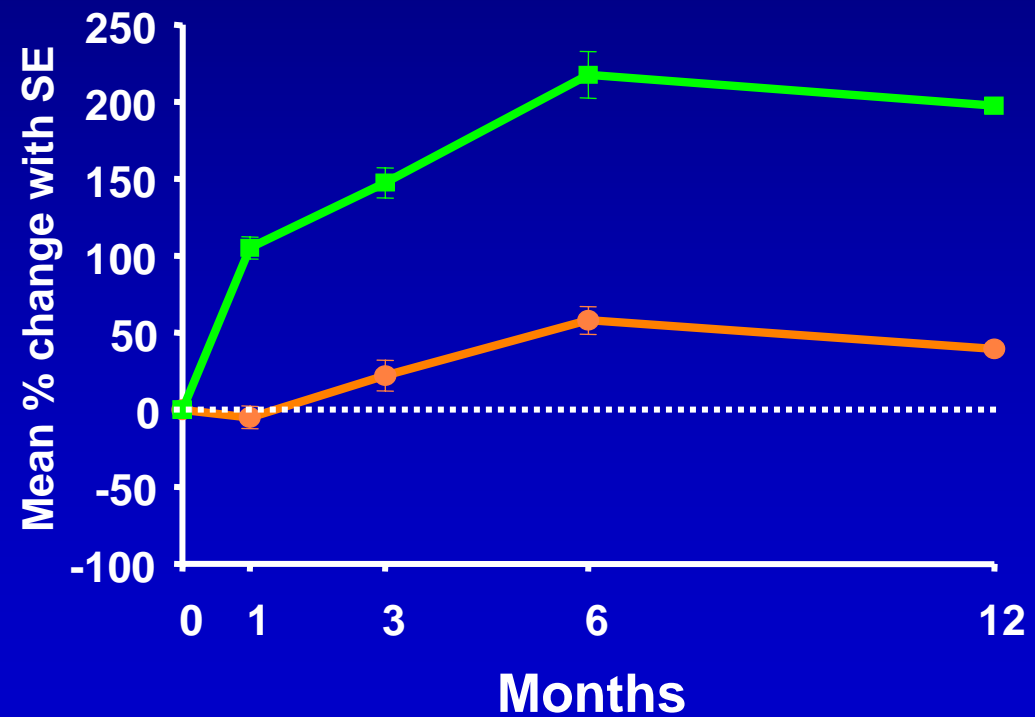


# Biochemical Bone Turnover Marker Response to Therapy

## Anti-resorptive Rx (Alendronate-Fosamax)



## Anabolic Rx (Teriparatide-Forteo)



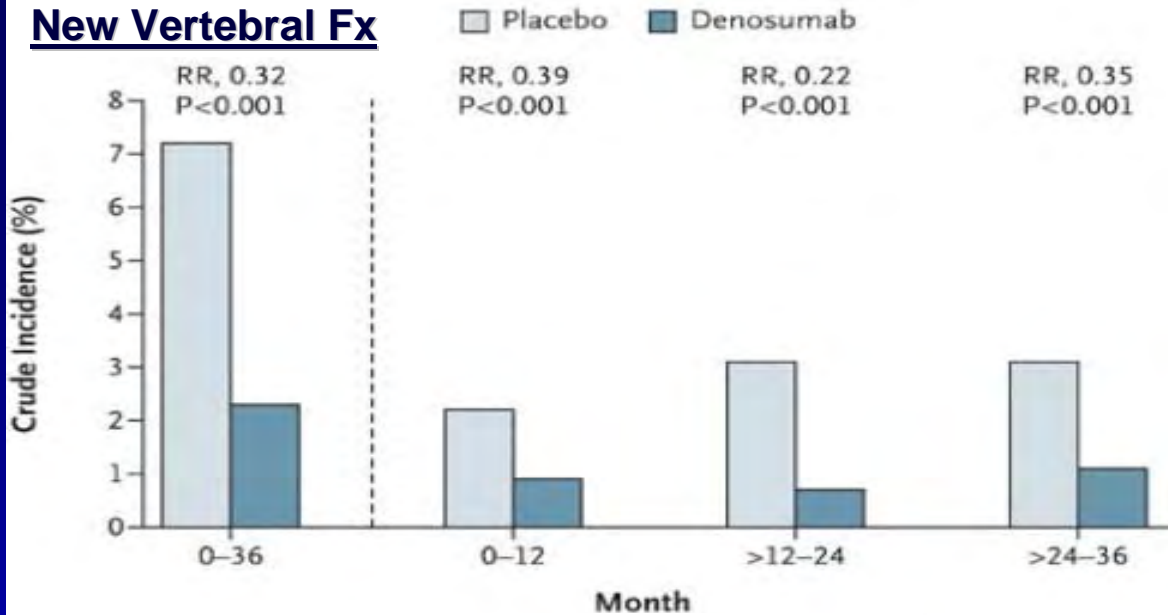
# Denosumab (Prolia)

- A fully human monoclonal antibody to the receptor activator of nuclear factor-kappa B ligand (RANK-L)
  - Blocks RANK-L binding to RANK, inhibiting osteoclast recruitment and activity
- Denosumab 60 mg q6mo (Cummings et al. *NEJM* 2009;361:756)
  - 7868 women with PMO (T scores <-2.5)
  - Significant ↓ (p<0.001) in bone markers (CTX, P1NP); n=160

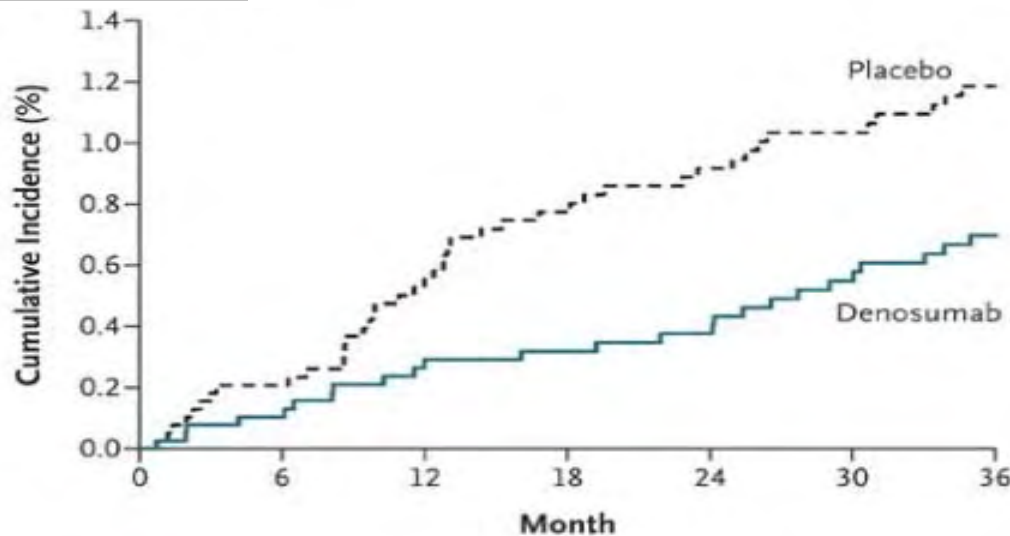
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- Denosumab 60 mg q6mo (Cummings et al. *NEJM* 2009;361:756)
  - 7868 women with PMO (T scores <-2.5)
    - ✓ 441 subset of patients with BMD
  - Significant 9.2% ↑ in L-spine BMD vs PBO at 36 mo
  - Significant 6.0% ↑ in total hip BMD vs PBO at 36 mo

## New Vertebral Fx



## Time to 1<sup>st</sup> Hip Fx



### No. at Risk

Placebo	3906	3799	3672	3538	3430	3311	3221
Denosumab	3902	3796	3676	3566	3477	3397	3311

# Denosumab

A monoclonal antibody to RANKL

*NEJM* 2009;361:756

7868 women with PMO,  
mean age 72 yrs

60 mg SQ q6mo X3 yrs

Calcium 1000 mg/d

Vit-D 400-800 IU/d

**Vertebral fractures**

AR 2.3% vs 7.2%

RR 68% ↓

**Hip fractures**

AR 0.7% vs 1.2%

RR 40% ↓

# FDA Approved Anti-resorptive Rx

RCT's of 3-5 Years Duration (\*parenteral form available)

<u>Drug</u>	<u>Study</u>	<u>Pt.No.</u>	<u>VFx RR↓</u>	<u>Hip Fx RR↓</u>
<sup>1</sup> Calcitonin*	PROOF	1255	36%	ns
<sup>2</sup> Evista	MORE	7704	30-55%	ns
<sup>3</sup> HRT/ERT*	WHI	16608	34%	34%-39%
<sup>4</sup> Alendronate	FIT-1	2027	47%	51%
<sup>5</sup> Risedronate	VERT	2458	41-49%	(na)
<sup>6</sup> Risedronate	HIP-OP	5445	(na)	40%
<sup>7</sup> Ibandronate*	BONE	2946	52%	ns
<sup>8</sup> Zoledronate*	HORIZON	7765	70%	41%
<sup>9</sup> Denosumab*	FREEDOM	7868	68%	40%

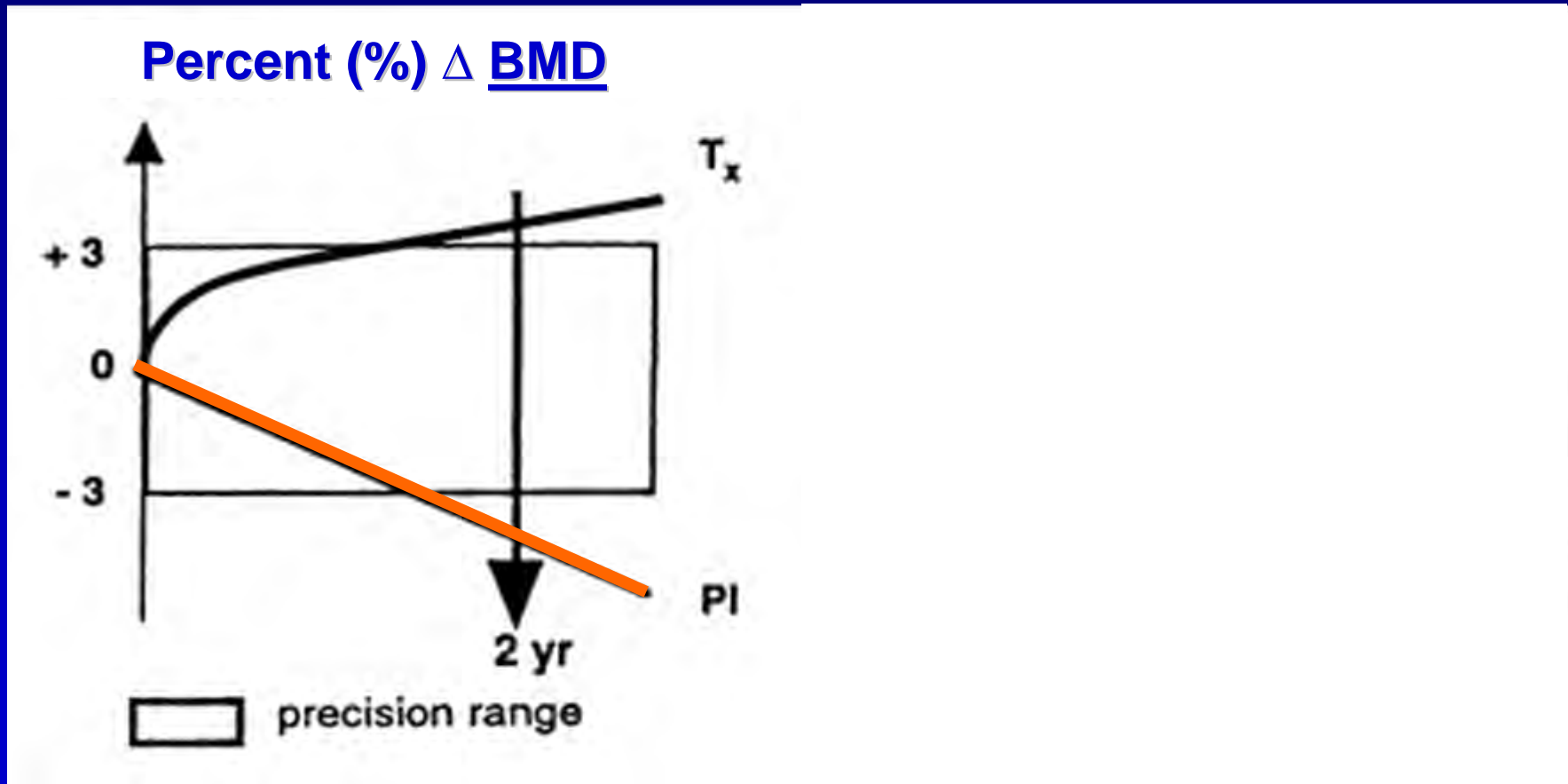
<sup>1</sup>Am J Med 2000;109 <sup>2</sup>JAMA 1999;282 <sup>3</sup>JAMA 2002;288 <sup>4</sup>Lancet 1996;348:1535 <sup>5</sup>JAMA 1999;282

<sup>5</sup>Osteopor Int 2000;11 <sup>6</sup>NEJM 2001;344 <sup>7</sup>JBMR 2004;19 <sup>8</sup>NEJM 2007;356 <sup>9</sup>NEJM 2009;361:756

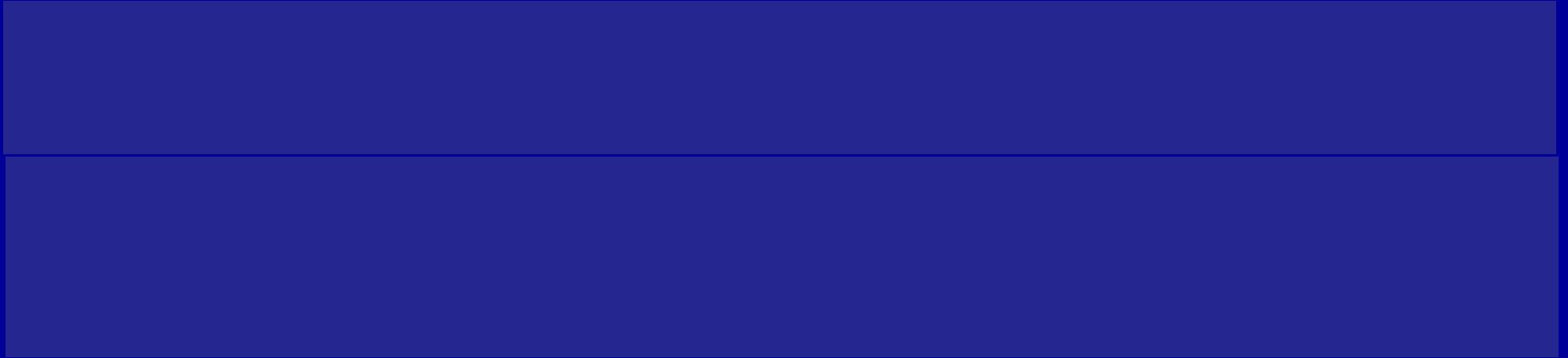
# Monitoring Therapy

# Monitoring Anti-resorptive Therapy

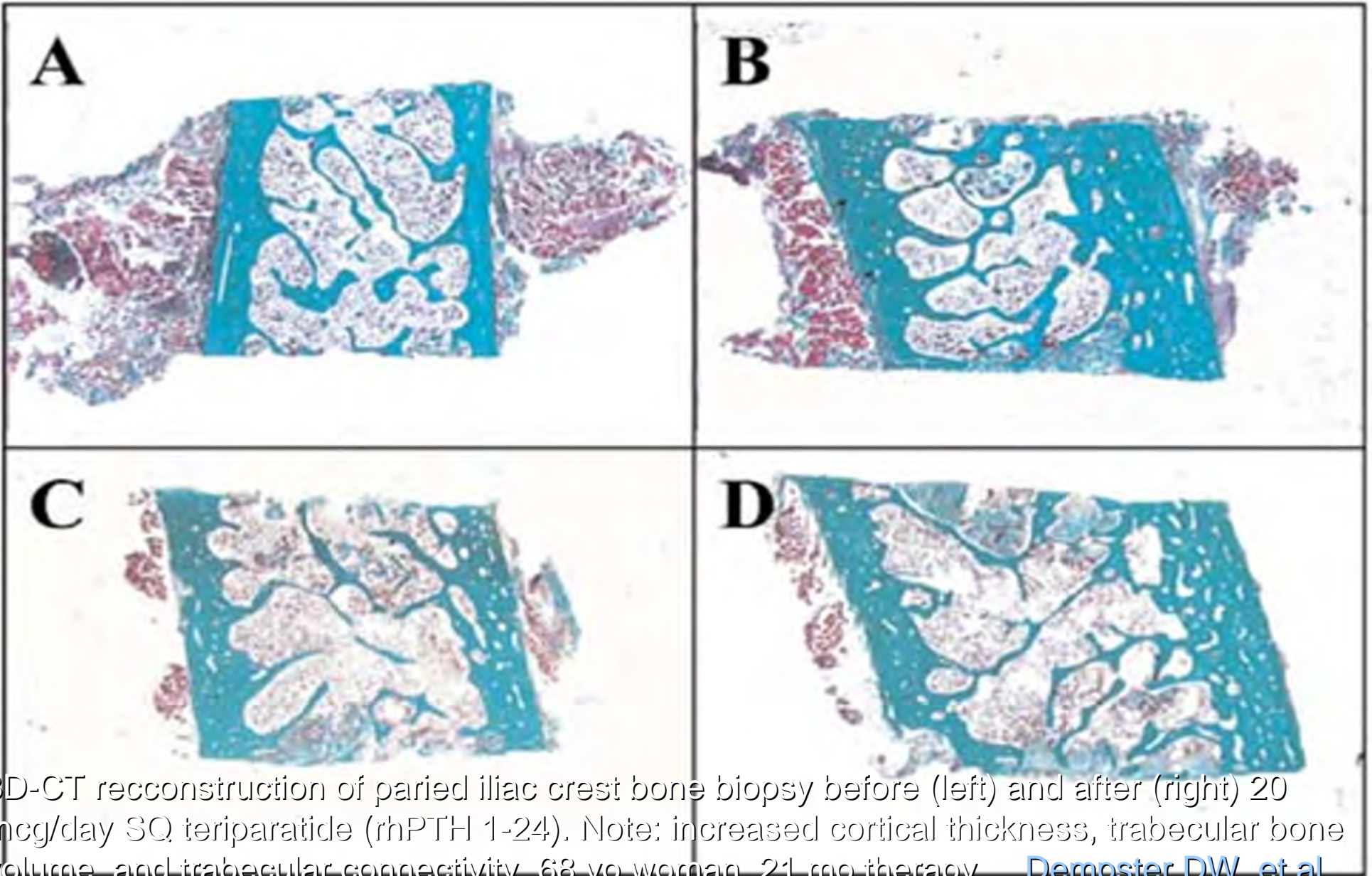
**Left:** Given a 1-1.5% precision error of BMD, a 2-yr Rx is likely to be needed to observe a significant change. **Right:** With 10-15% precision error of BCM-BTO, the effect of Rx will likely be seen at 3 mo, especially for resorption markers.



# Anti-resorptive Effects on BMD and Bone Turnover During & After 2-Yr Rx



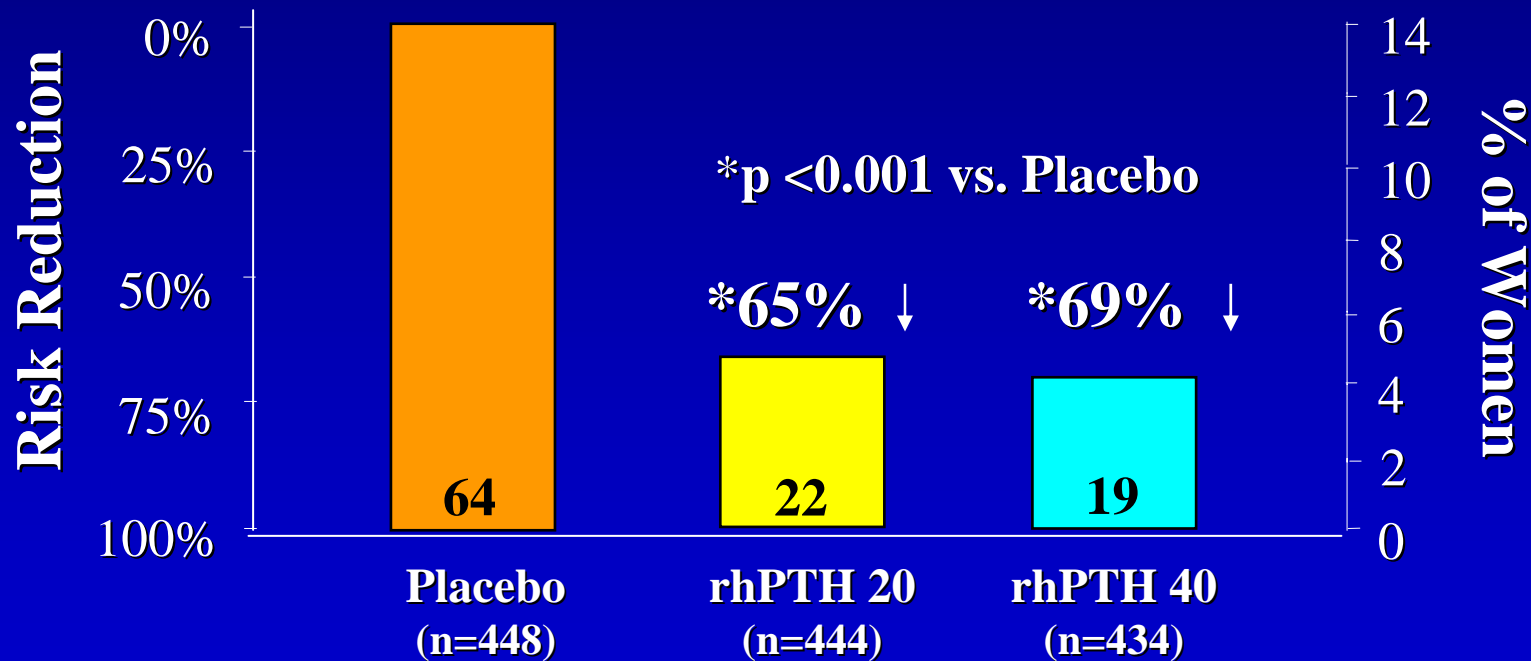
# **Anabolic Therapy**



3D-CT reconstruction of parietal iliac crest bone biopsy before (left) and after (right) 20 mcg/day SQ teriparatide (rhPTH 1-24). Note: increased cortical thickness, trabecular bone volume, and trabecular connectivity. 68-yr woman, 21 mo therapy. Demoster DW, et al. Pre (A-C) and post (B-D) rhPTH. Jiang Y, et al. J Bone Miner Res, 2003;18:1932

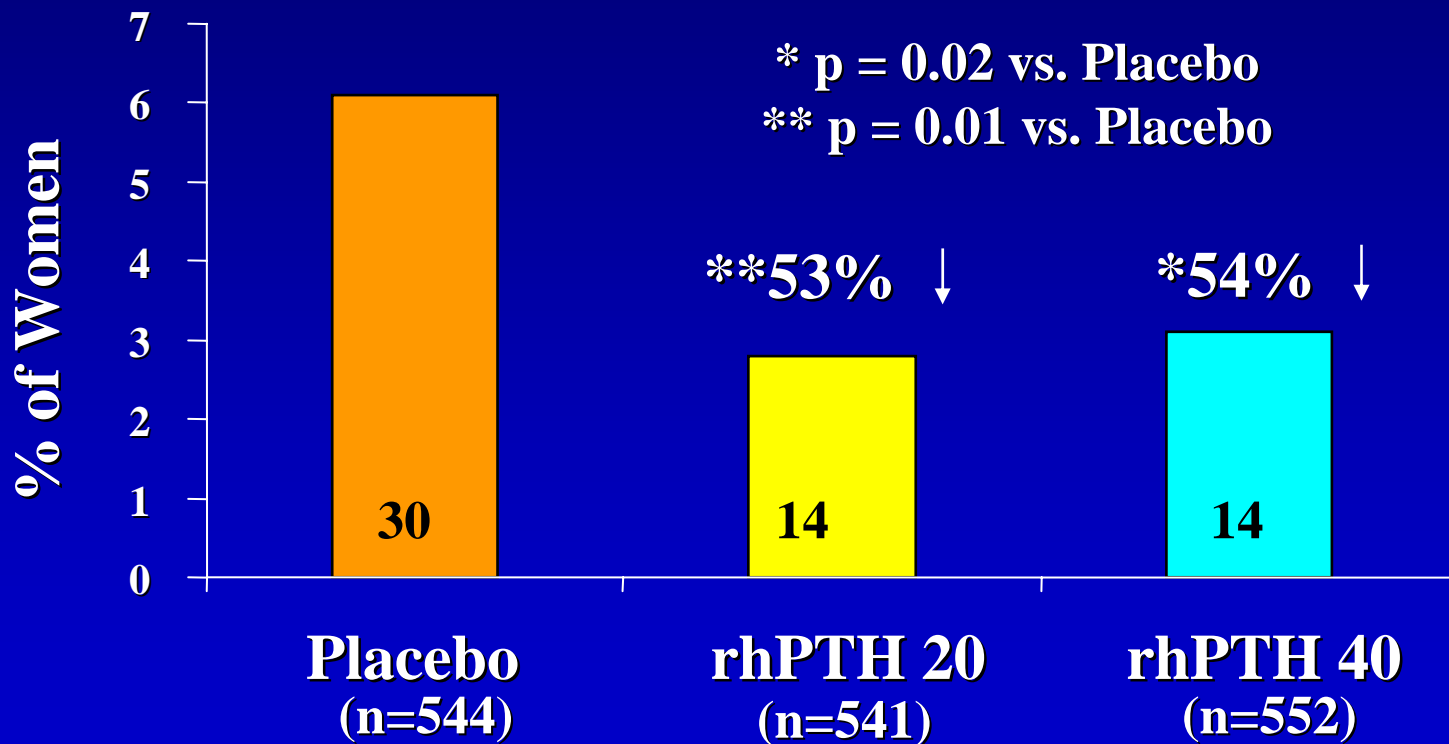
# Teriparatide (Forteo®) Effect on Vertebral Fracture Risk

No. of women who had  $\geq 1$  vertebral fracture

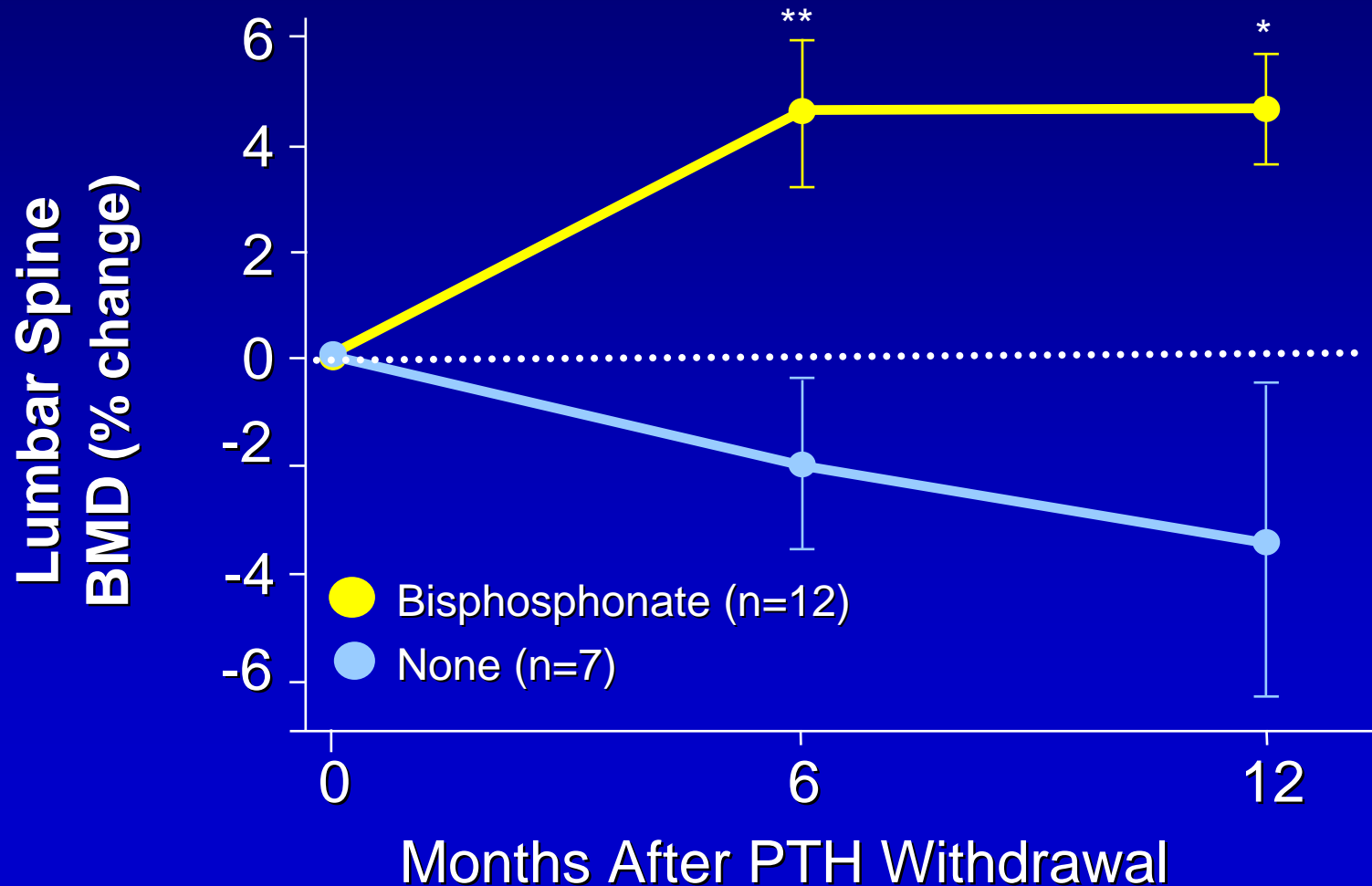


# Teriparatide (Forteo<sup>®</sup>) Effect on Non-vertebral Fracture Risk

No. of women who had  $\geq 1$  non-vertebral fragility fracture

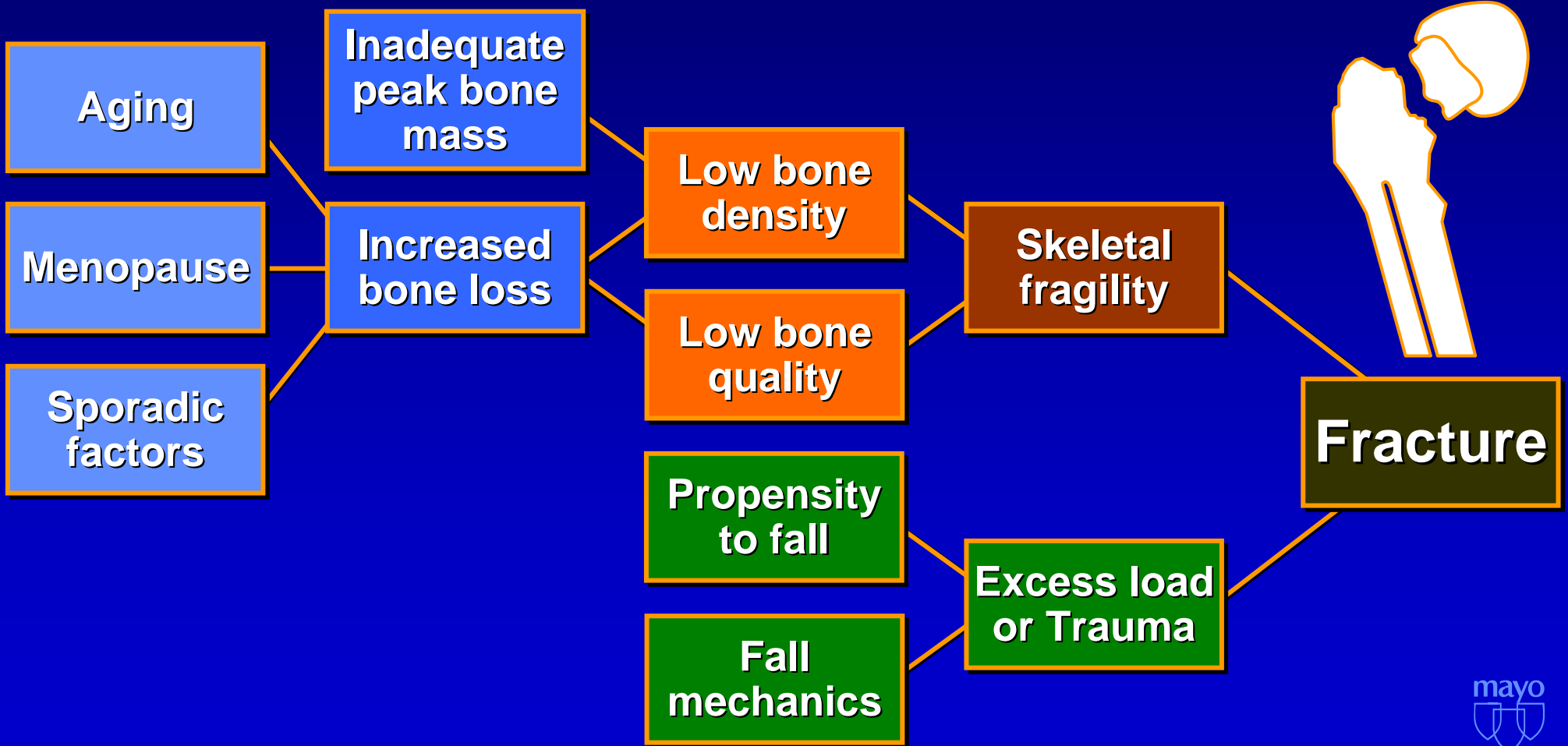


# Bisphosphonate Preserves BMD Gain after PTH



# SUMMARY

## Etiology of fractures is multi-faceted



# SUMMARY

## HPN Treatment:

- Calcium
- Vitamin D
- Anti-resorptive therapy
  - No oral bisphosphonates
  - IV bisphosphonates
  - SQ denosumab (Prolia)
- Anabolic therapy
  - SQ teriparatide (Forteo)
  - Hormone therapy: topical estrogen/testosterone

## Assessing therapy:

- FRAX<sup>®</sup>
  - WHO 10-yr hip fracture risk
- Skeletal x-rays
  - Thoracic and lumbar spine
- Bone mineral density
- Labs/blood tests
  - Bone alkaline phosphatase
  - C-telopeptide
  - 24-hour urine calcium
  - 25-hydroxyvitamin D

**Thank you!**

**hurley.daniel@mayo.edu**

# REFERENCES

- “Clinician’s Guide to Prevention and Treatment of Osteoporosis”

[www.nof.org](http://www.nof.org) web site for the National Osteoporosis Foundation (NOF) and clinical guidelines

[www.shef.ac.uk/FRAX](http://www.shef.ac.uk/FRAX) web site for the World Health Organization (WHO) Fracture Risk Assessment tool (FRAX)