Battling Metabolic Bone Disease

26th Annual Oley Foundation Consumer-Clinician Conference

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DISCLOSURE

Relevant Financial Relationship(s)

None

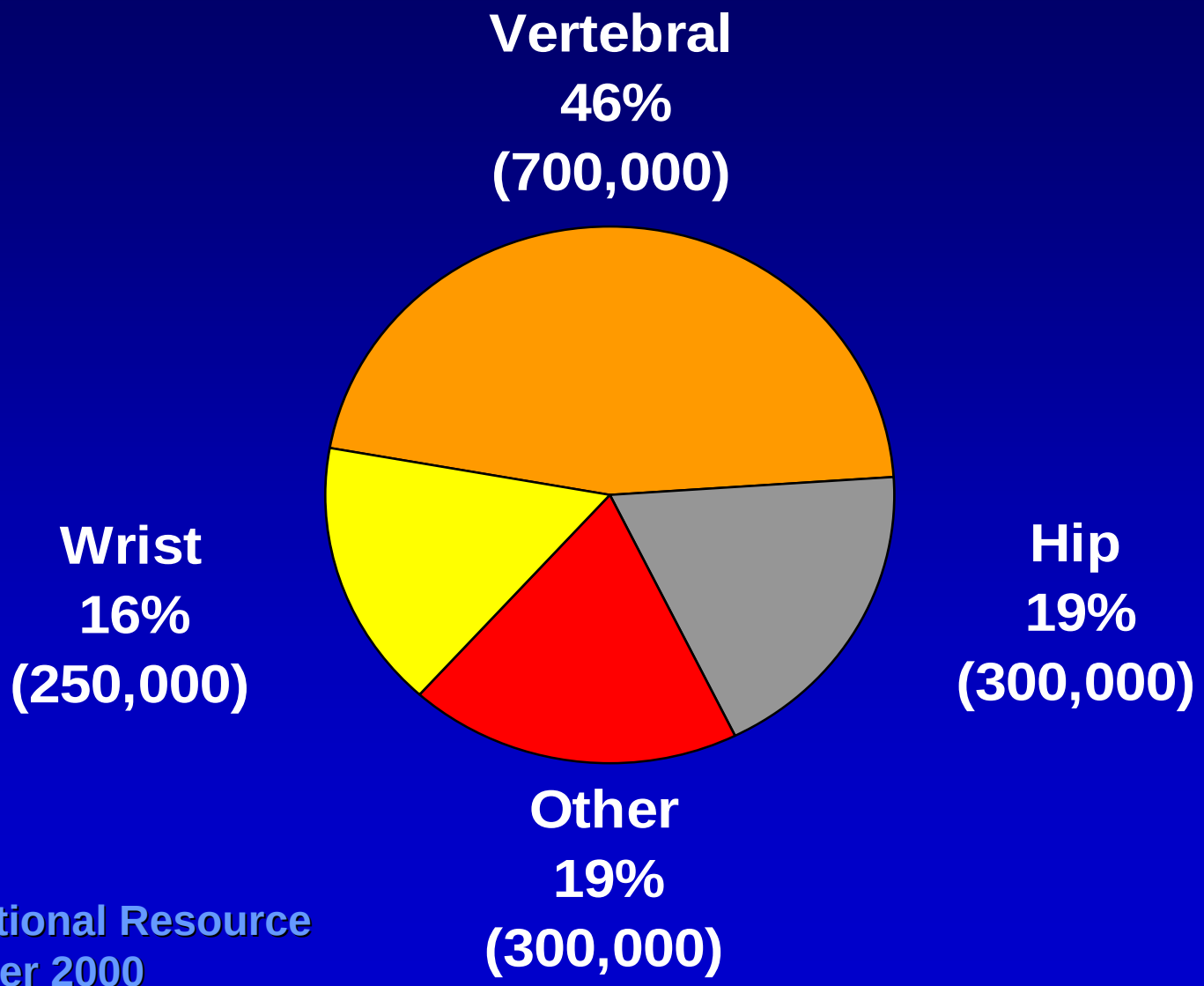
Off Label Usage

None

OBJECTIVES

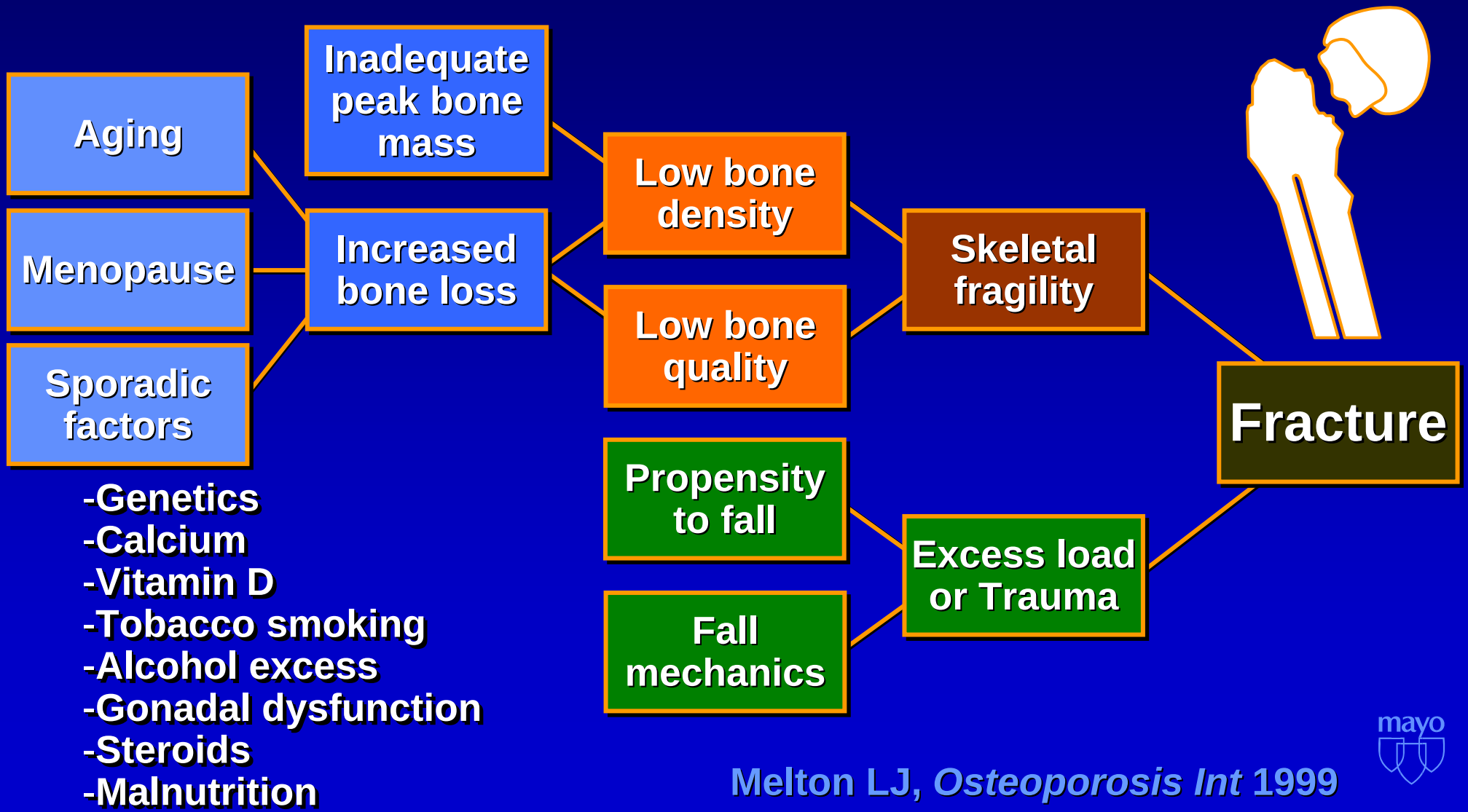
- Discuss factors as to future fracture risk
  - Age, previous fracture(s), bone mineral density (BMD)
  - FRAX® WHO fracture risk assessment tool
  - Biochemical markers (BCM) of bone turnover
- Review FDA approved drug treatments
  - Calcium and vitamin D
  - Anti-resorptive therapy
  - Anabolic therapy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

More Than 1.5 Million Fractures Yearly



NIH/ORBD National Resource Center, October 2000

Pathogenesis of Fractures



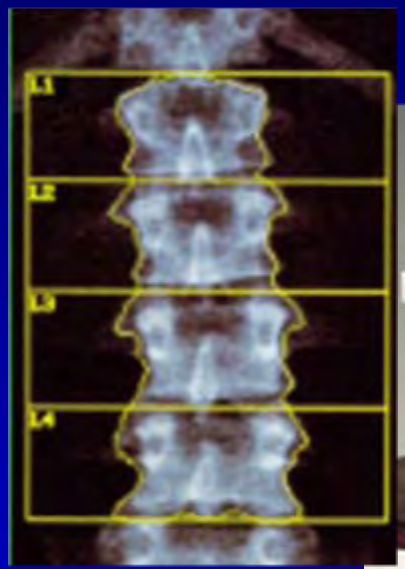
Melton LJ, *Osteoporosis Int* 1999

Assessing Fracture Risk

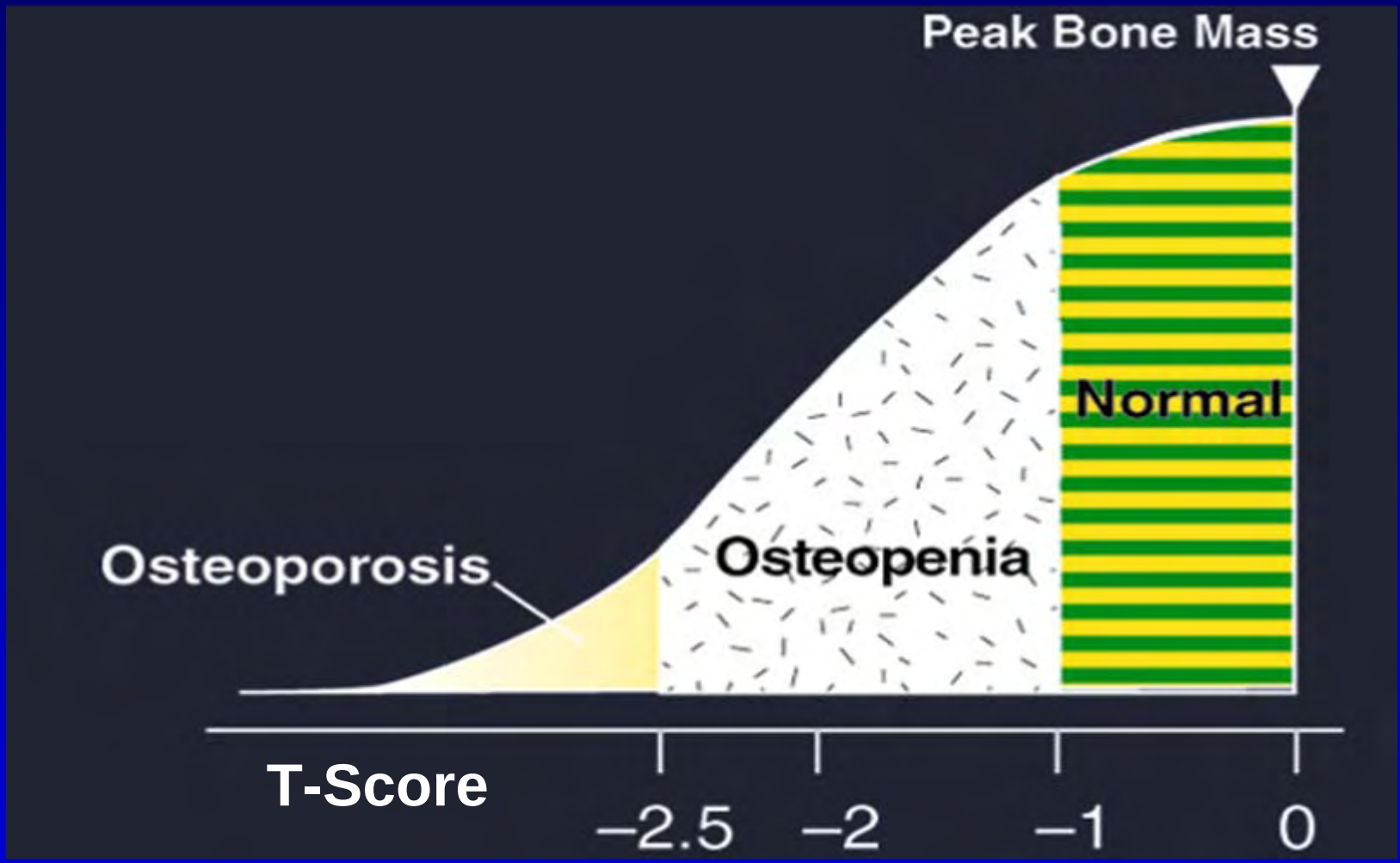
Central (Hip-Spine) Dual-Energy-Xray-Absorptiometry (DXA) Measurement

- OP clinical ‘surrogate’ in absence of fracture
- DXA bone density considered the clinical standard
- Measures multiple skeletal sites

  Spine, hip, forearm, and total body

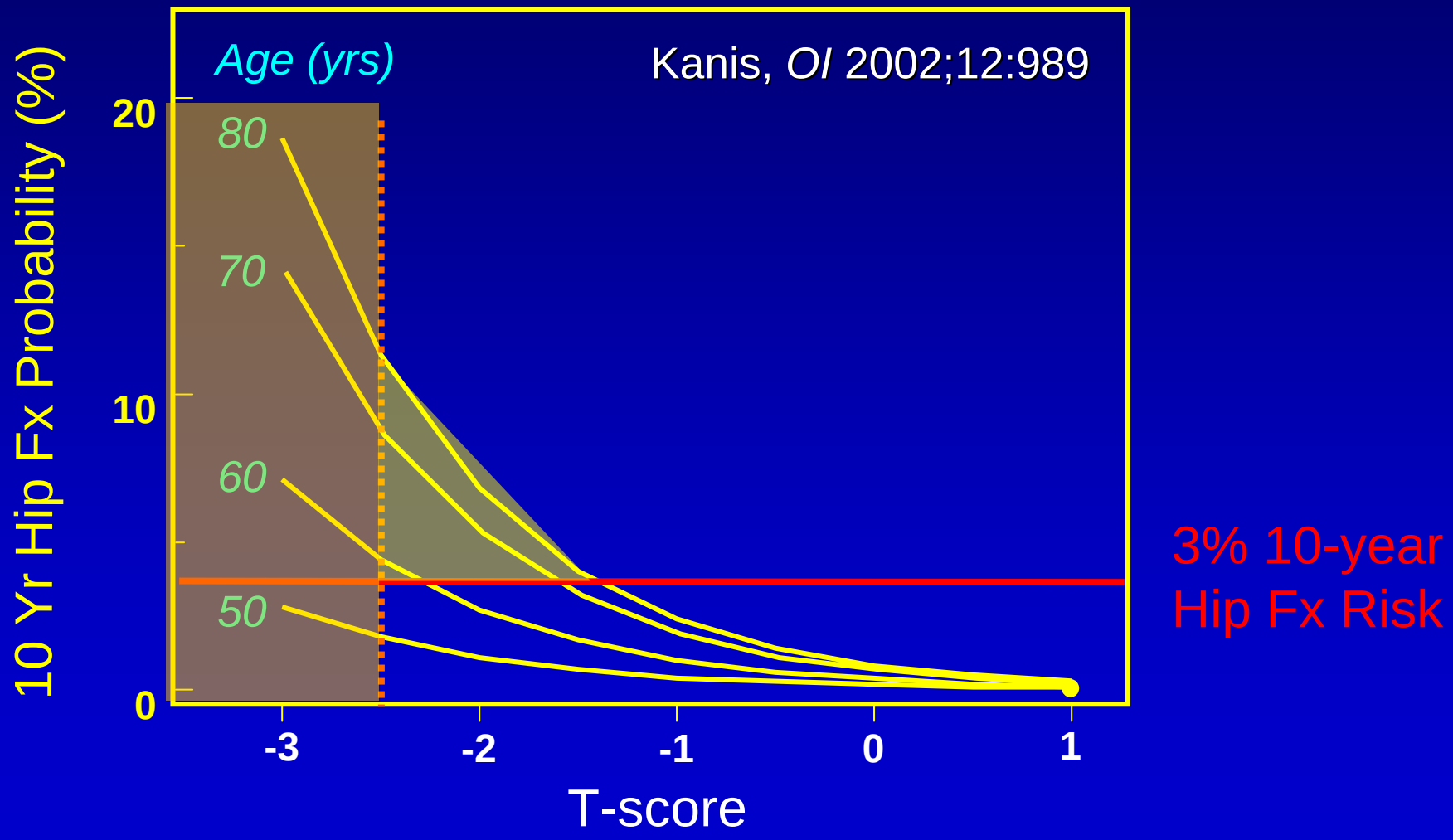


World Health Organization (WHO) Diagnostic DXA Criteria for Osteoporosis

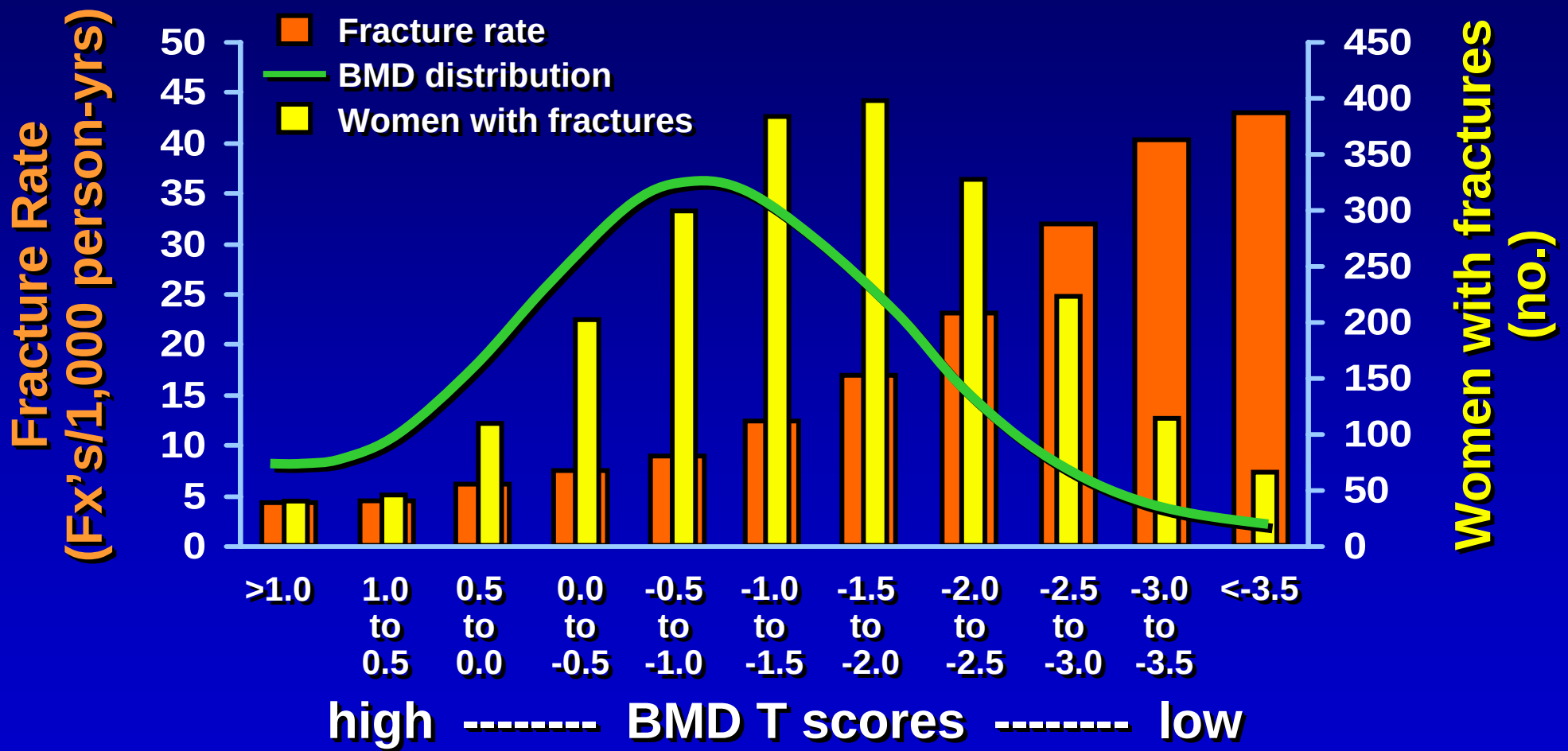


The WHO criteria were established for use in postmenopausal women

Age and BMD are Independent Risk Factors for Hip Fracture



Osteoporotic Fracture Rates, Numbers and BMD Distribution

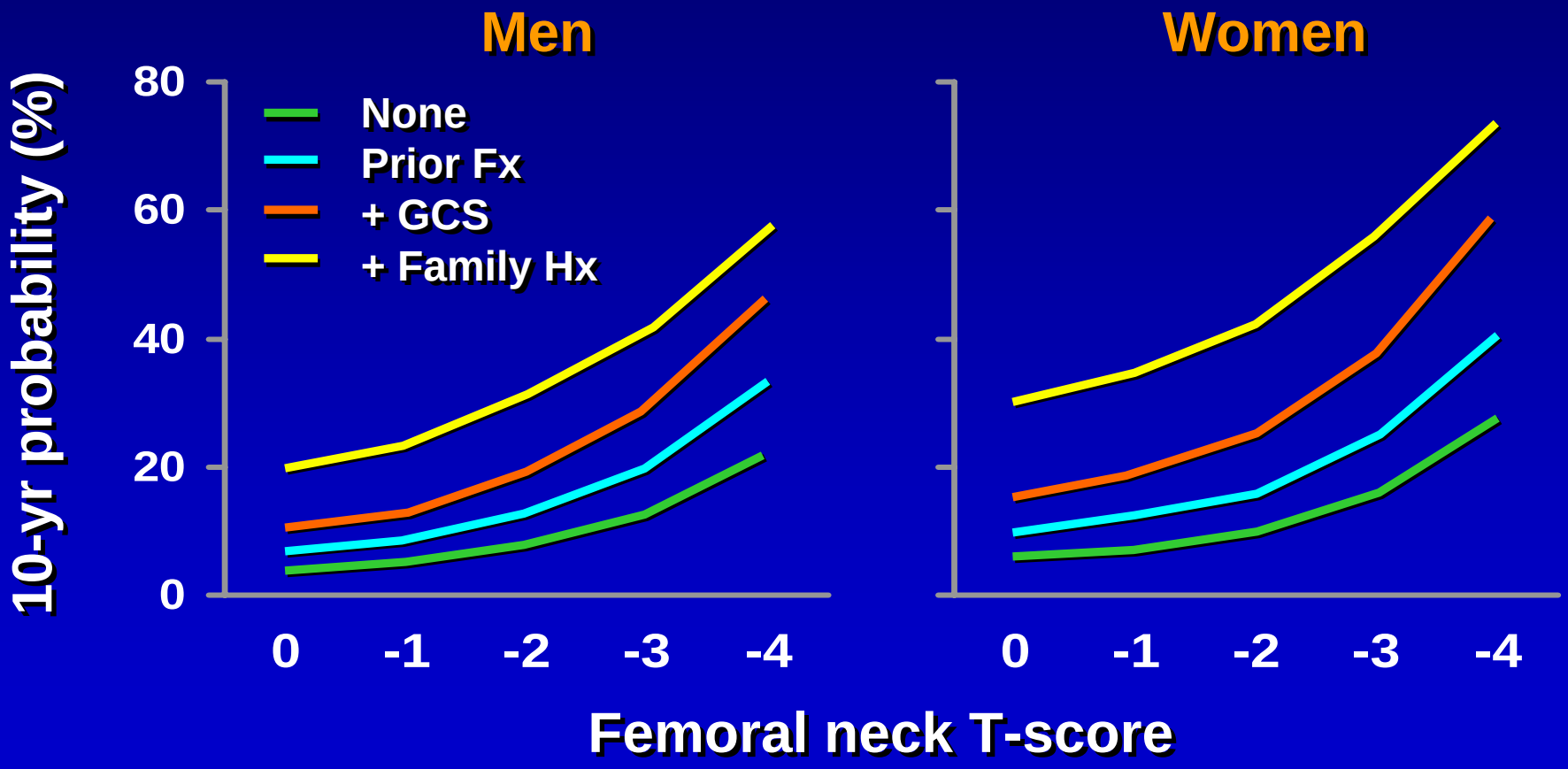


Siris: Surgeon General's Workshop on Osteoporosis and Bone Health, December 2002

MAYO CLINIC

10-Yr Probability of Major OP Fx

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



Kanis JA et al: Osteoporos Int 19:385, 2008

FRAX® WHO Fracture Risk Assessment Tool

HOME | CALCULATION TOOL | PAPER CHARTS | FAQ | REFERENCES

Calculation Tool

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

Weight Conversion:

pound: convert

Height Conversion:

inch : convert

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/cm²)

Select DXA

- Select DXA
- GE-Lunar
- Hologic
- Norland
- T-Score

Calculate

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/cm²)

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

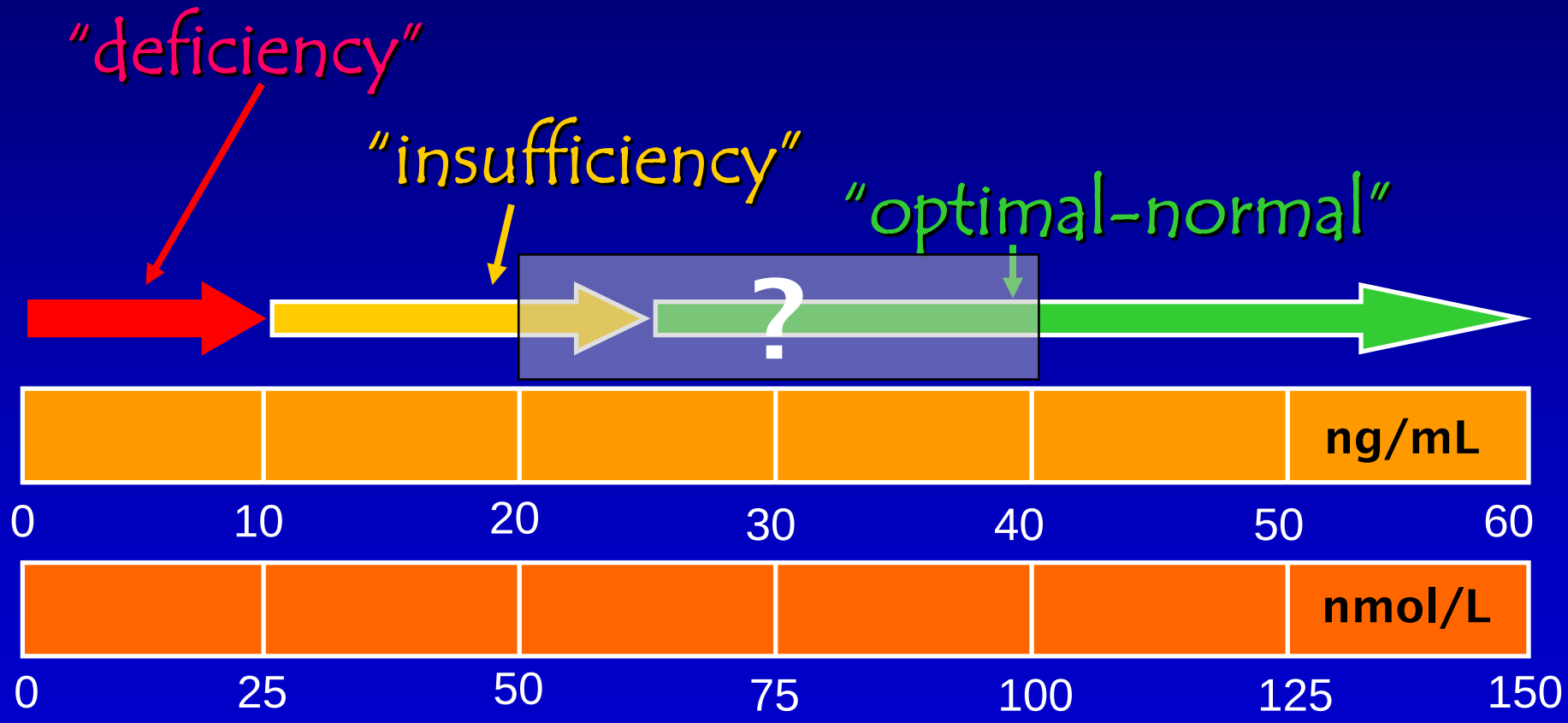
National Academy of Sciences

Institute of Medicine (IOM) 2011 Guidelines

	Calcium		Vitamin D	
Life Stage Group (age and gender)	RDA (mg/d)[a]	Upper Limit (UL) (mg/d)	RDA (IU/d)*	Upper Limit (UL) (IU/d)
0-6 mo (M+F)	200[b]	1000[b]	400[b]	1000[b]
6-12 mo (M+F)	260[b]	1500[b]	400[b]	1500[b]
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)[c]	1300	3000	600	4000
19-30yr (M+F)[c]	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

[a] RDA = intake that covers needs of 97.5% of the healthy normal population.
[b] Reflects Adequate Intake (AI) reference value rather than RDA. RDAs have not been established for infants due to insufficient data.
[c] Calcium and vitamin D RDAs are the same for pregnant or lactating females in these age groups.

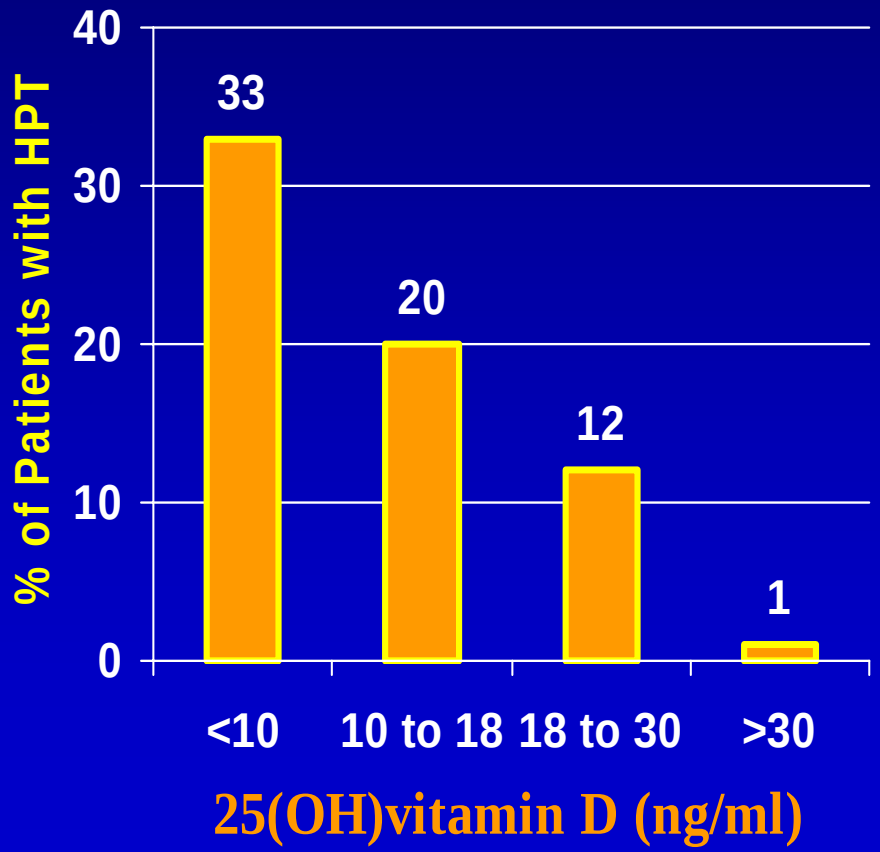
Is There an Optimal Vit-D Level?
Who is at risk?

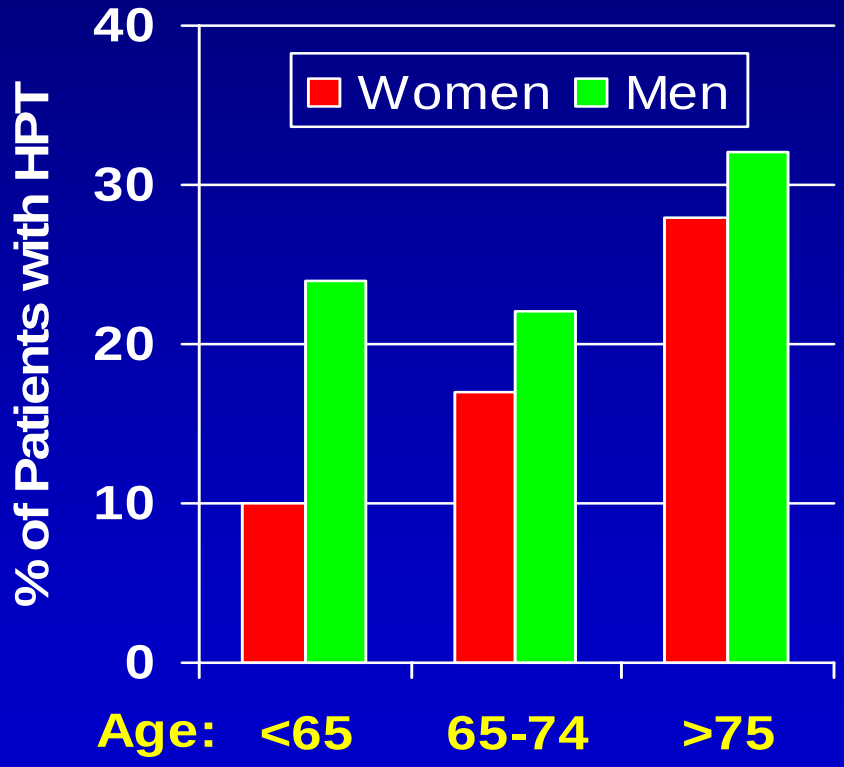


*modified after RP Heaney (10 ng/mL = 25 nmol/L)

Bone Loss, Vitamin D and 2°HPT

Ambulatory EVOS* Subjects (Spain, latitude 43°N, n=268, mean age 68 years). Prevalence 2º 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

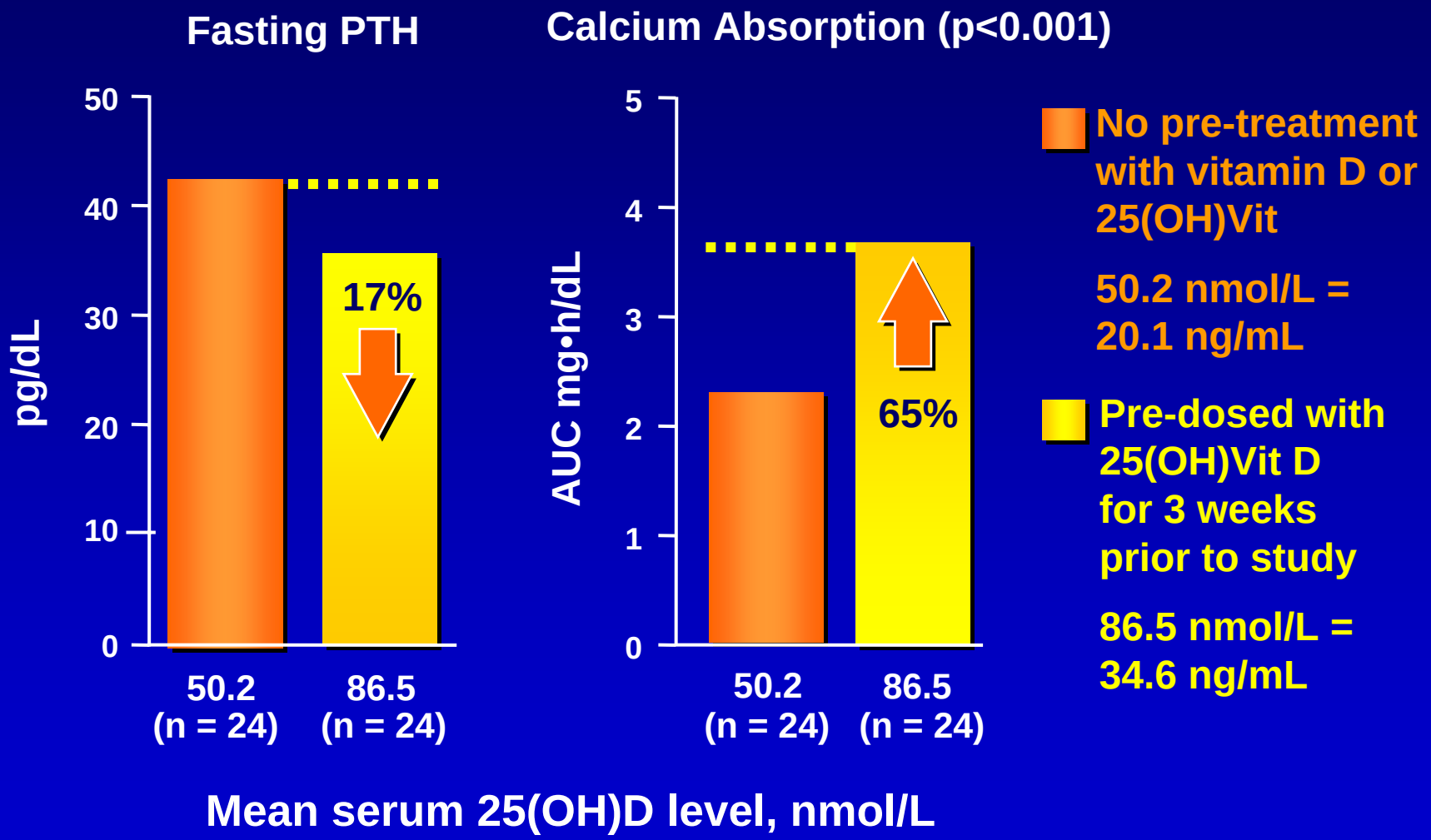
Laboratory

- ↓ 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

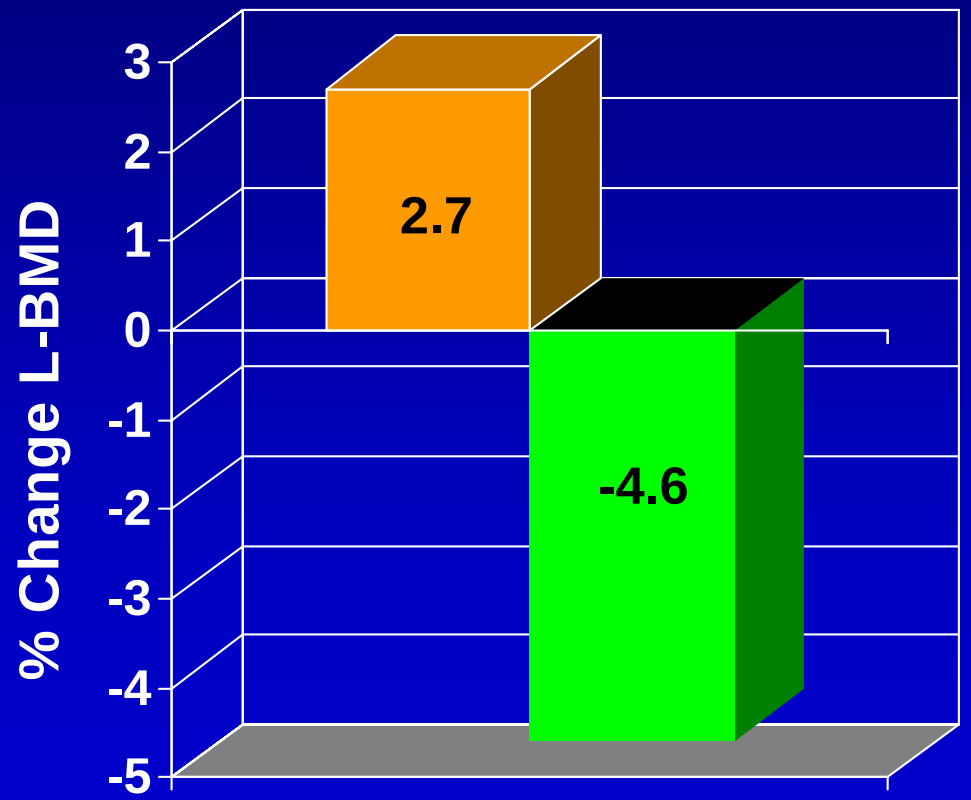


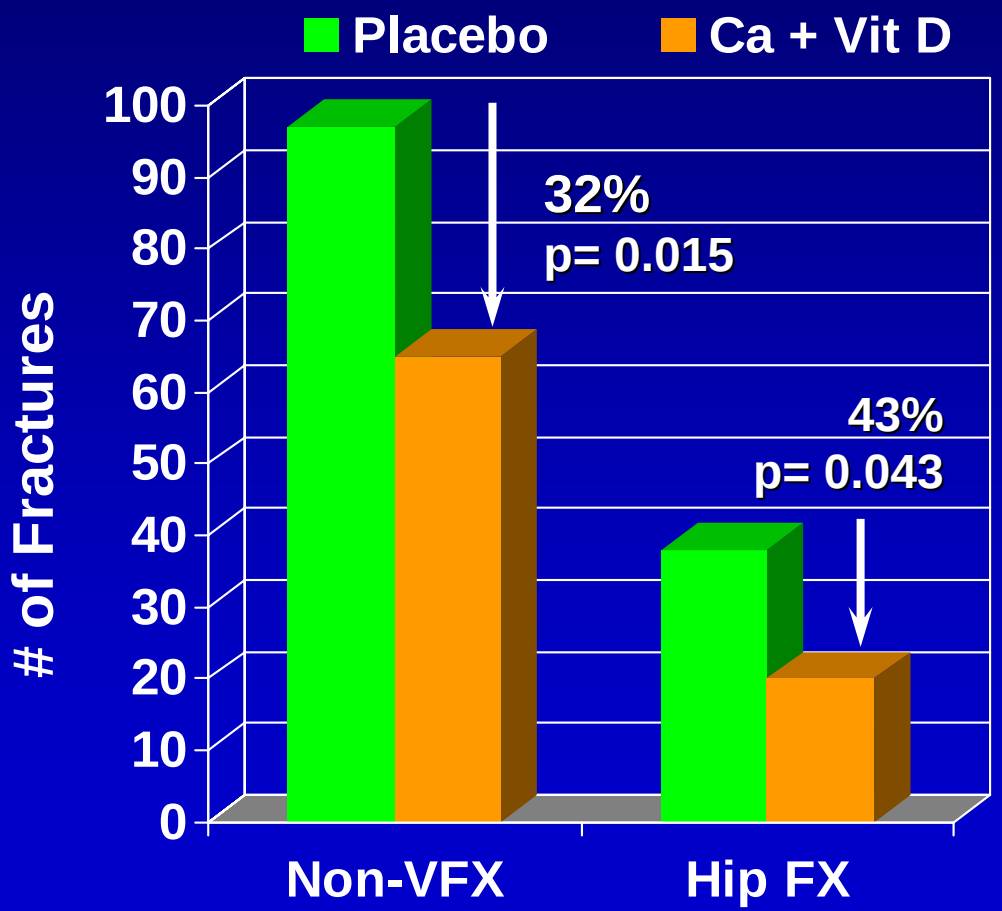
Heaney RP. *J Am Coll Nutr.* 2003;22:142

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

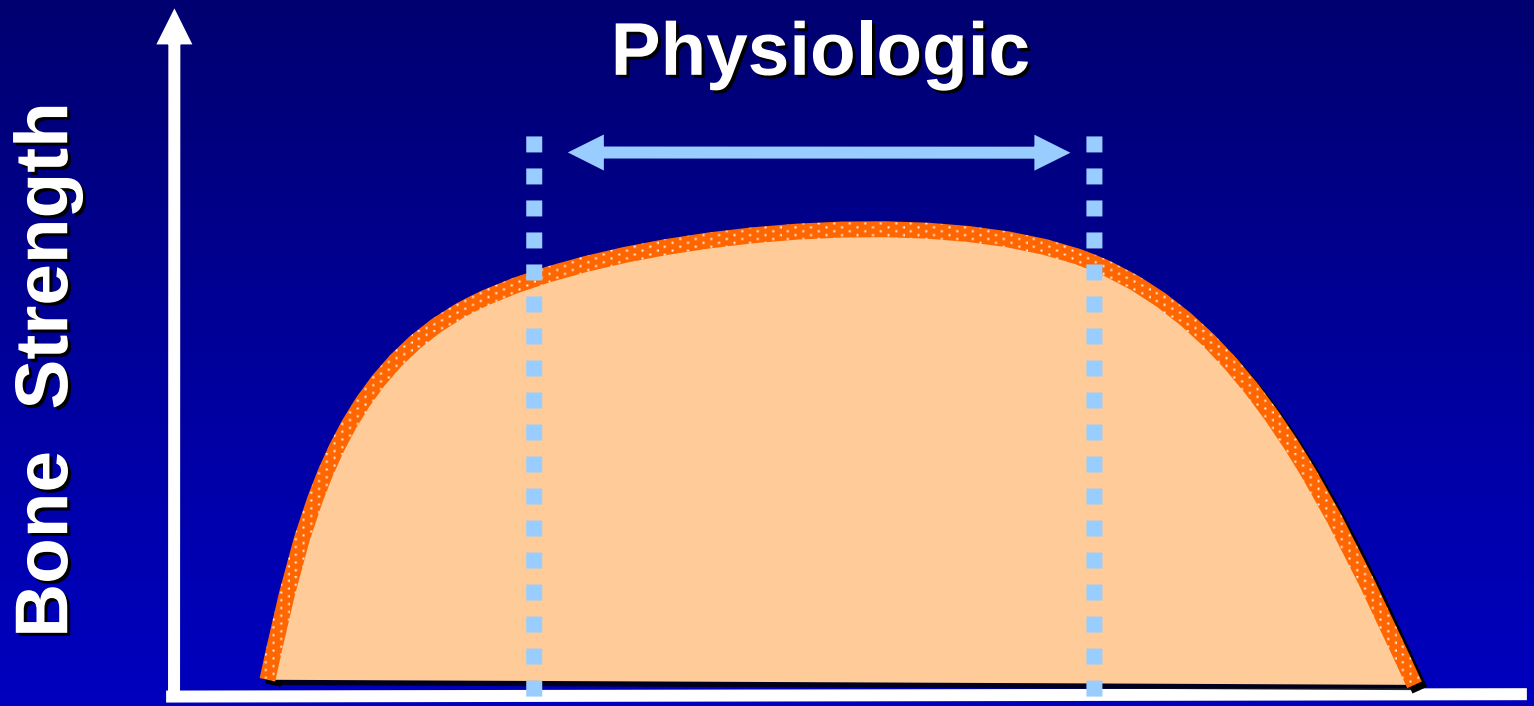
Calcium 1200 mg + Vitamin D 800 IU

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 ≤ 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

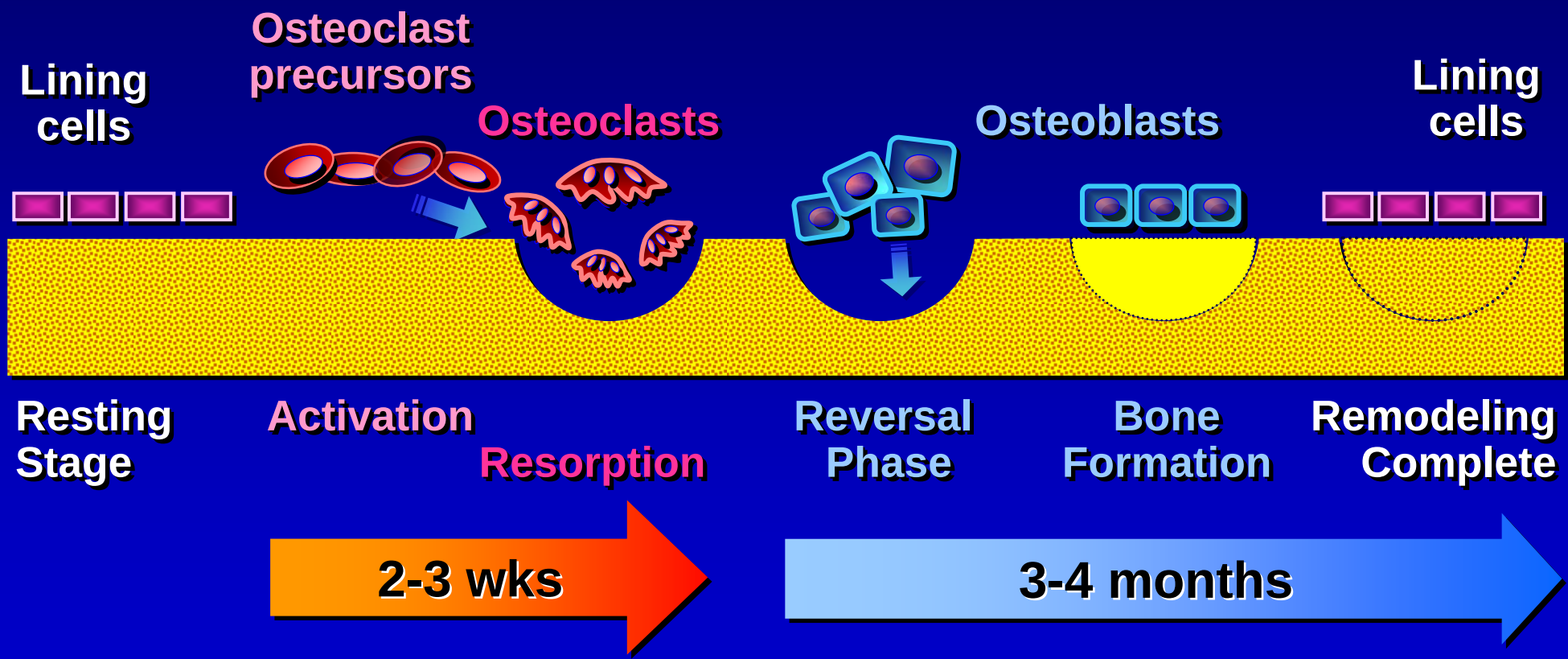
Normal Bone

Remodeling Too High
- ↓ Bone mass/structure
- Stress risers

Ex. Osteo-porosis

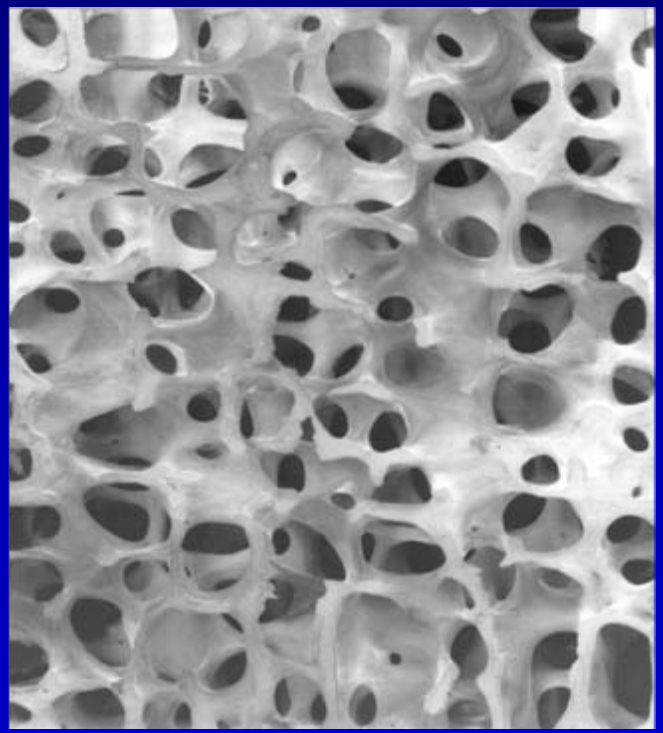
Normal Bone "Remodeling" Activity

A Coupled Homeostatic Process



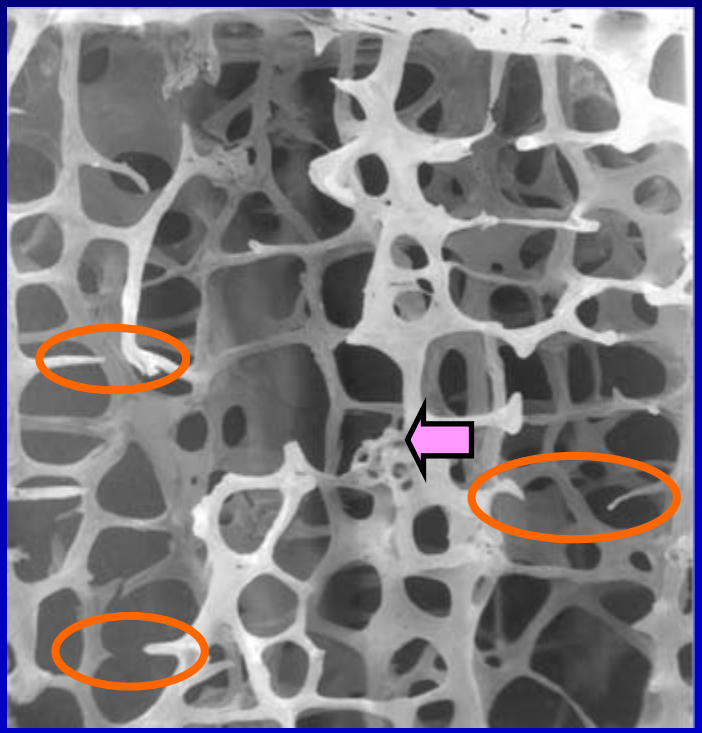
Postmenopausal Osteoporosis
Trabecular Micro-architectural Change

Normal



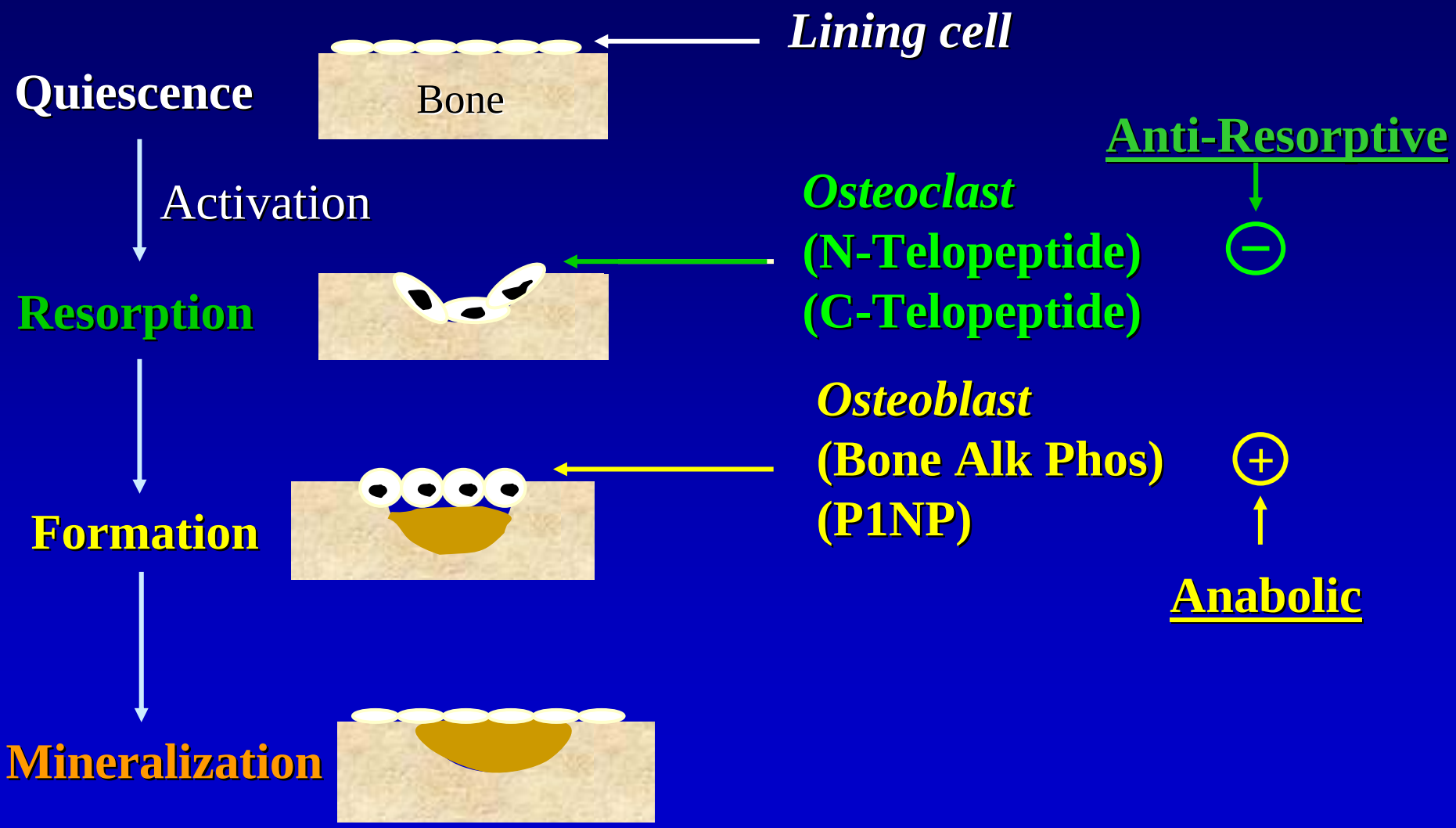
Dempster, 2000

Osteoporosis



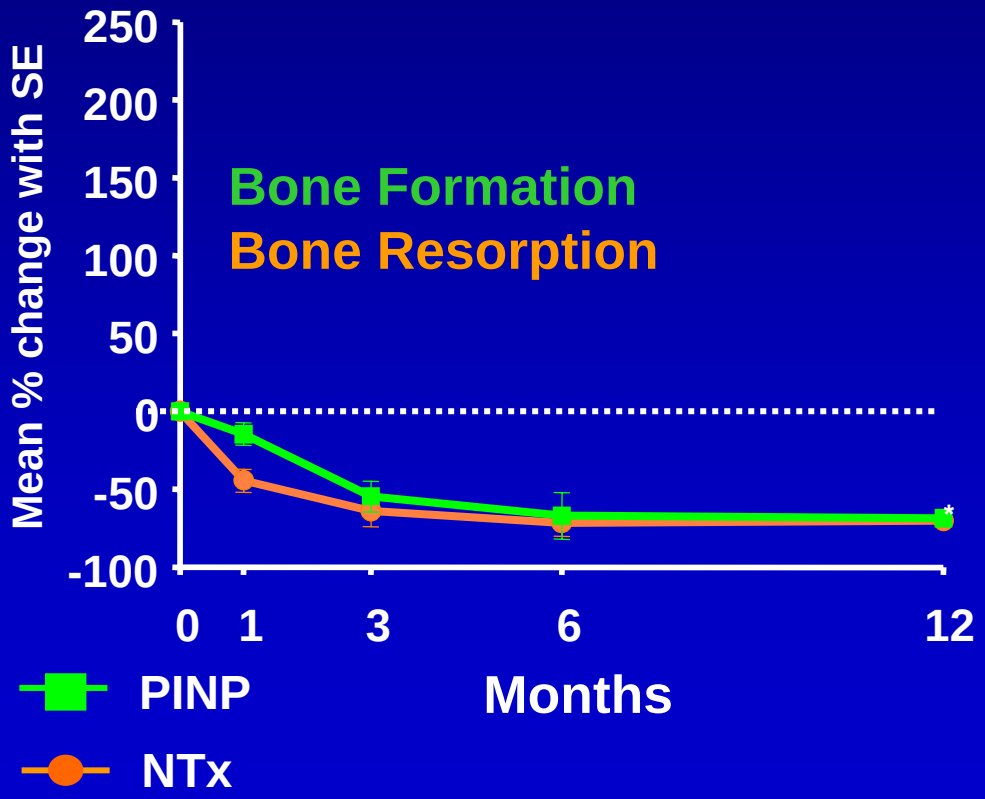
Horizontal Perforations
Micro-callous

Bone Remodeling Unit

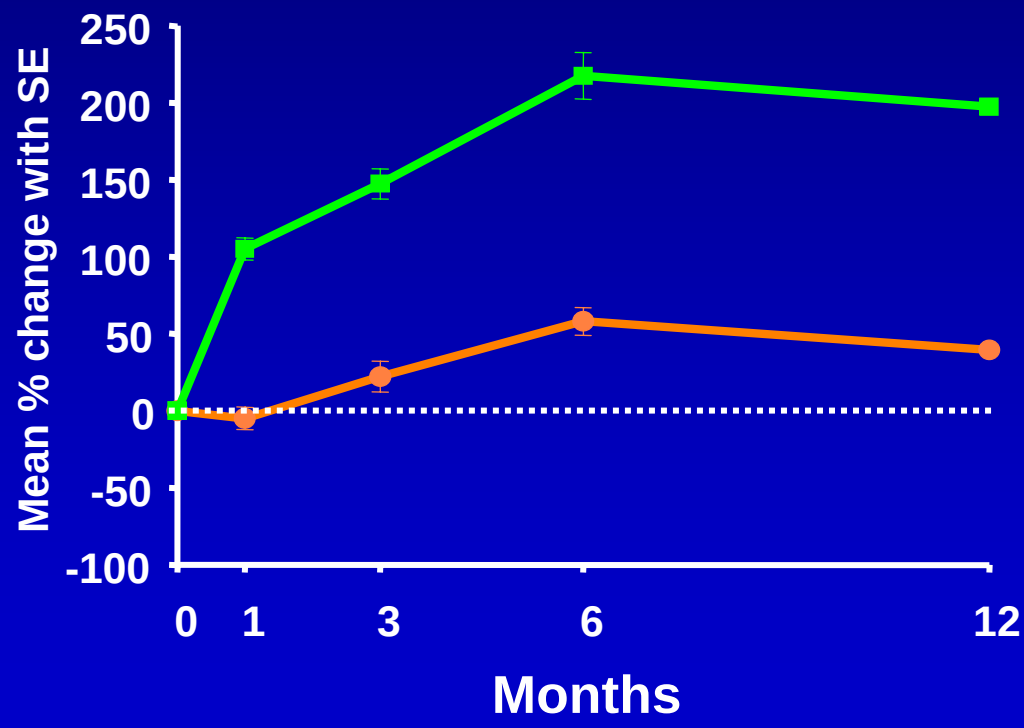


Biochemical Bone Turnover Marker Response to Therapy

Anti-resorptive Rx (Alendronate-Fosamax)



Anabolic Rx (Teriparatide-Forteo)



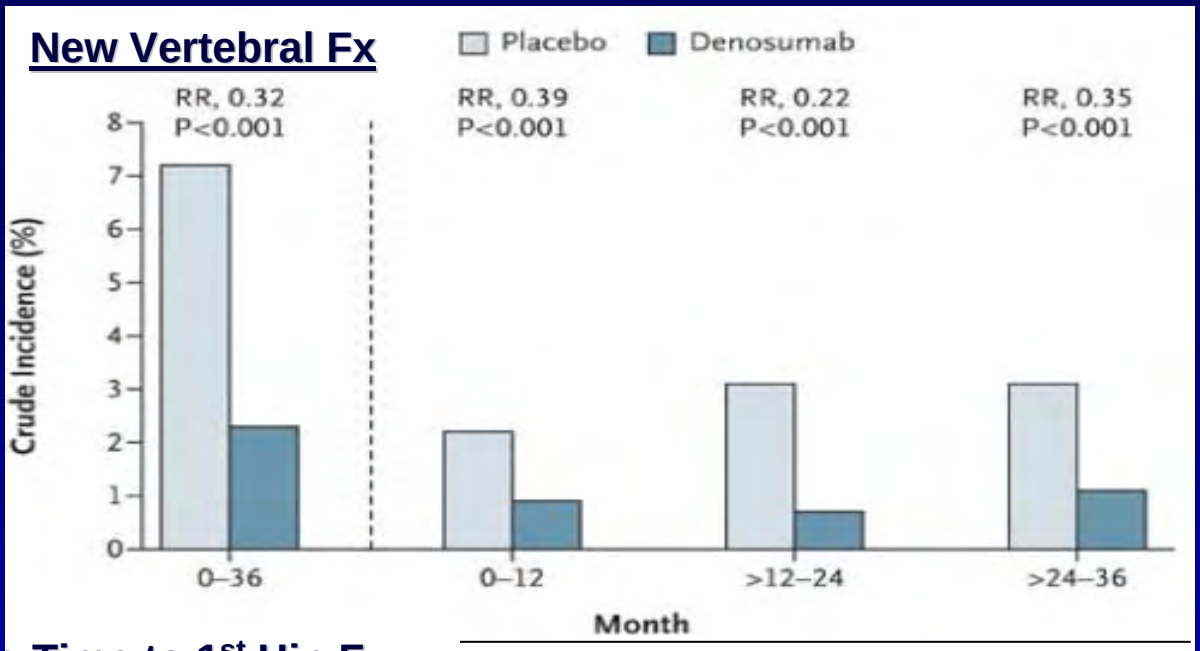
McClung, et al, ASBMR 2003

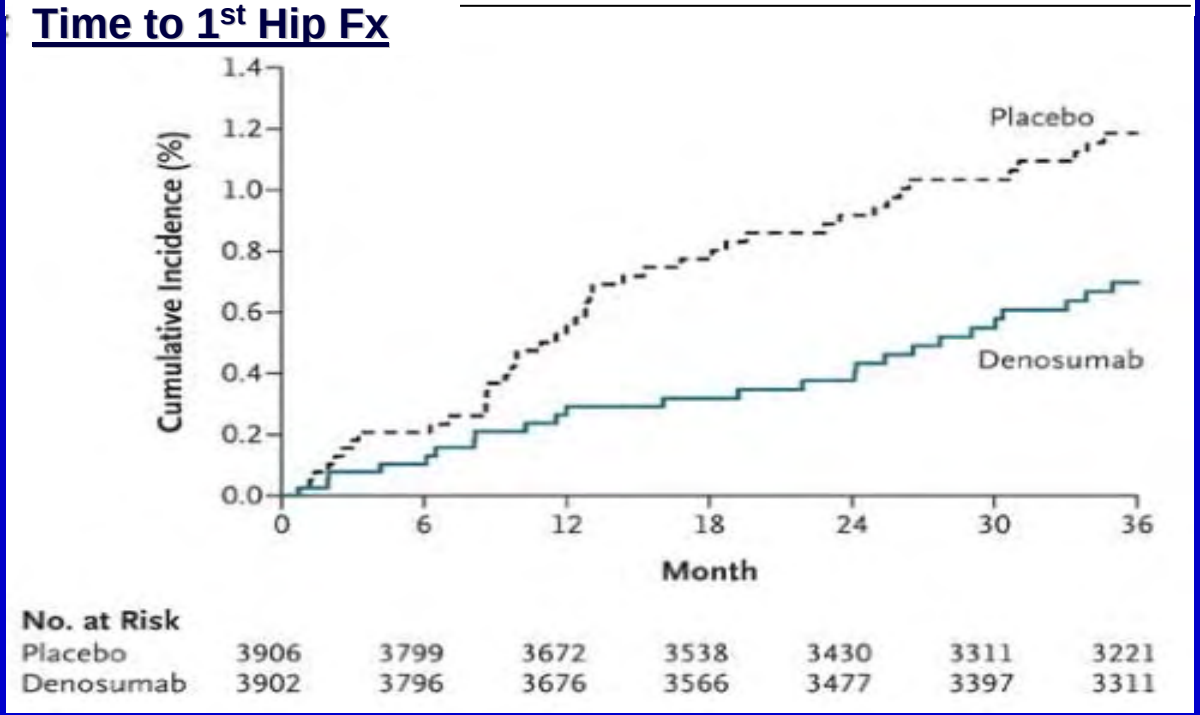
Denosumab (Prolia)

- 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

- 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





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)

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

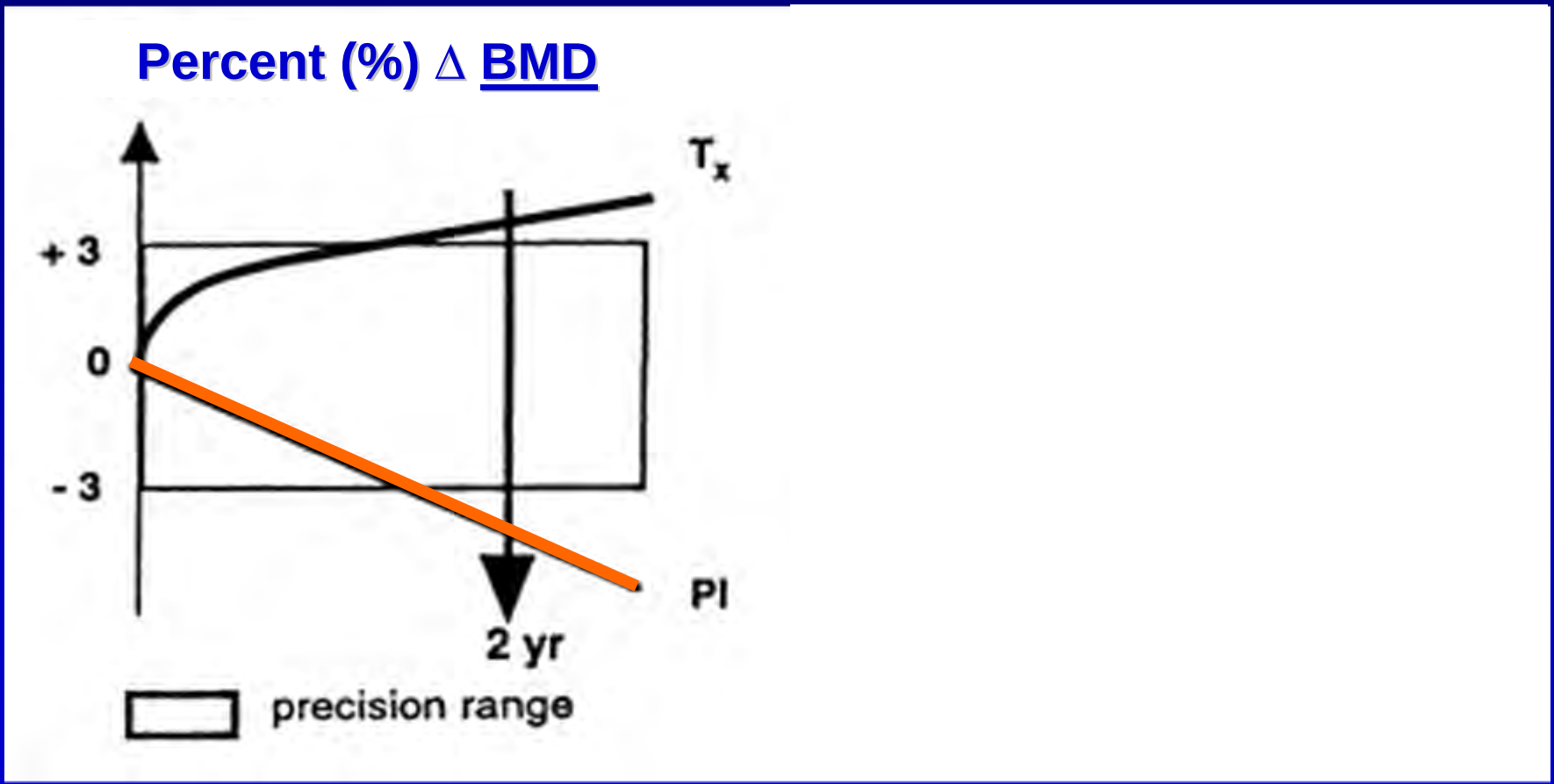
[1]*Am J Med* 2000;109 [2]*JAMA* 1999;282 [3]*JAMA* 2002;288 [4]*Lancet* 1996;348:1535 [5]*JAMA* 1999;282

[5]*Osteopor Int* 2000;11 [6]*NEJM* 2001;344 [7]*JBMR* 2004;19 [8]*NEJM* 2007;356 [9]*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.

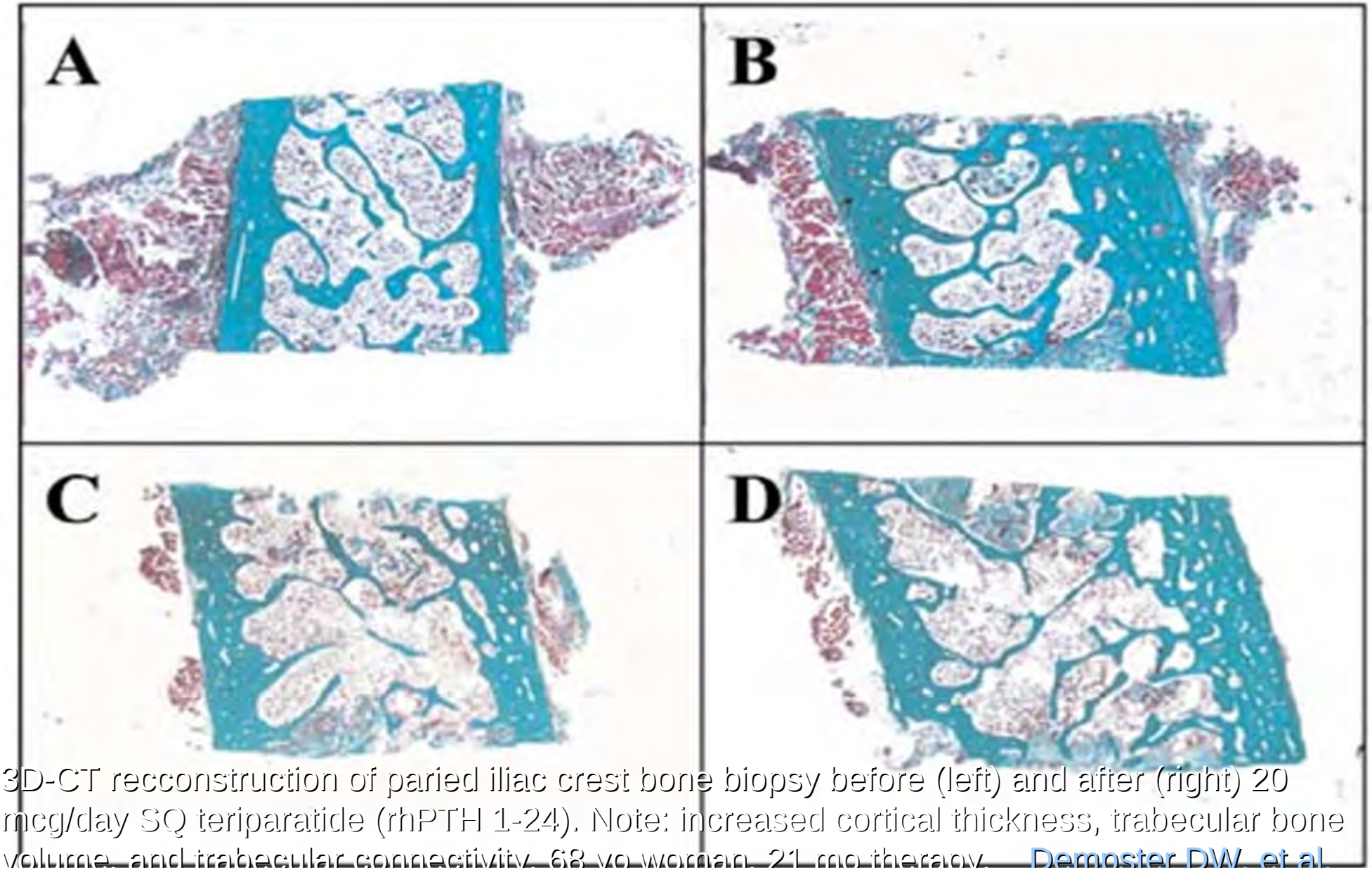


Delmas PD. *Osteoporos Int* 2000;11(18):S66-76

Tx: treatment, Pl: placebo

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

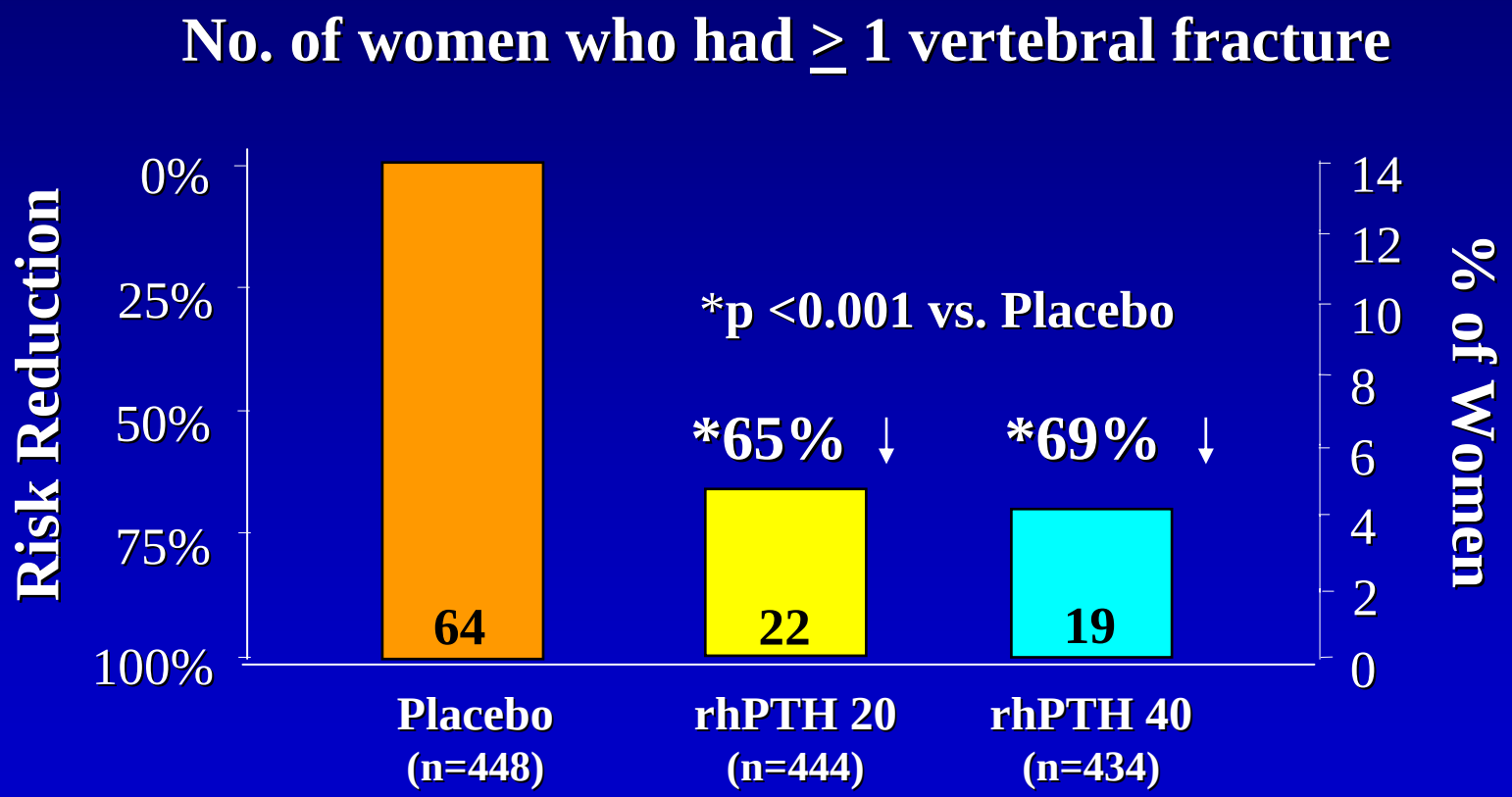
Anabolic Therapy



3D-CT recconstruction of paried 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 yo woman, 21 mo therapy. Dempster DW, et al

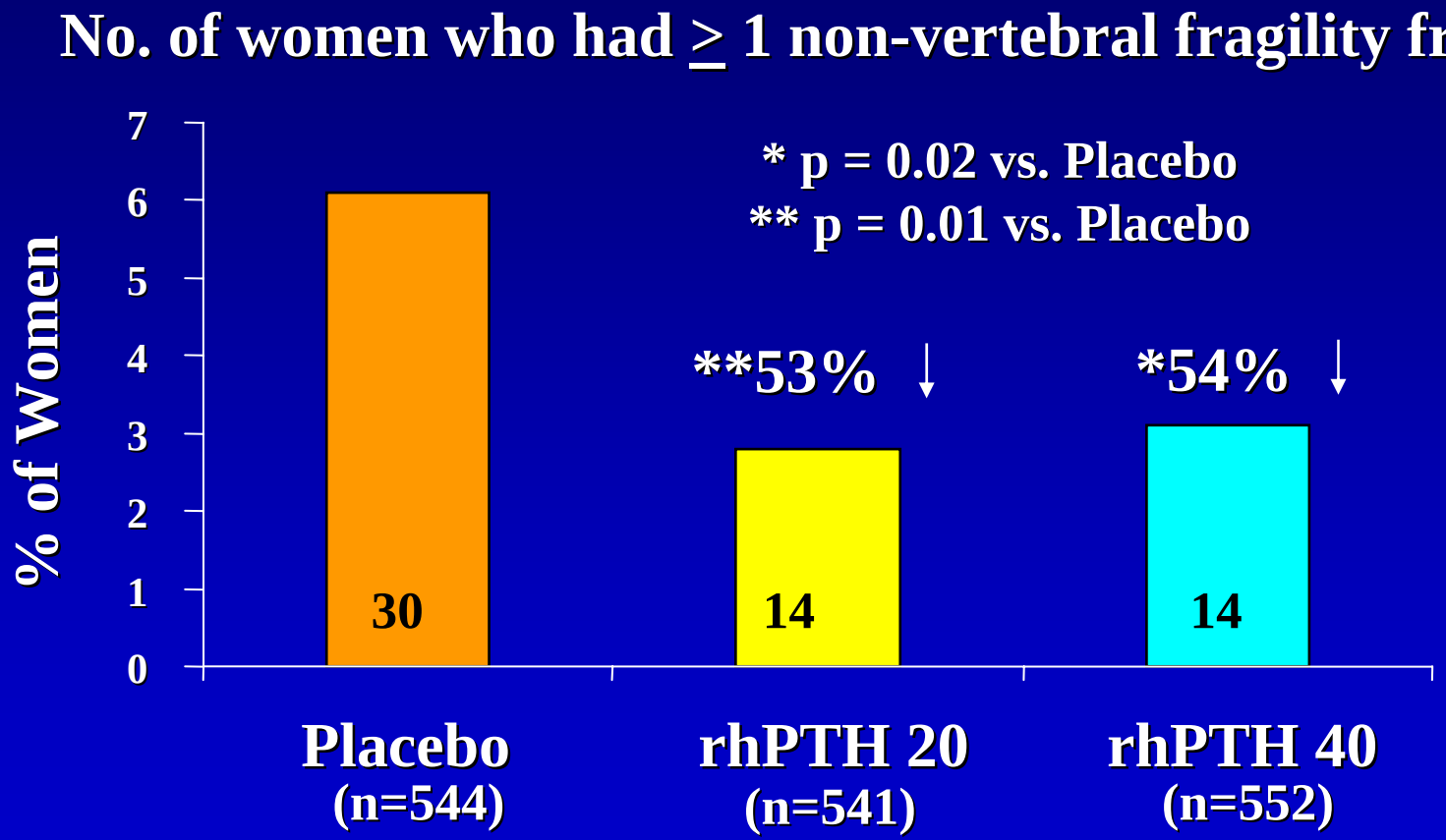
Pre (A-C) and post (B-D) rhPTH. Jiang Y, et al. J Bone Miner Res, 2003;18:1932

Teriparatide (Forteo®) Effect on Vertebral Fracture Risk



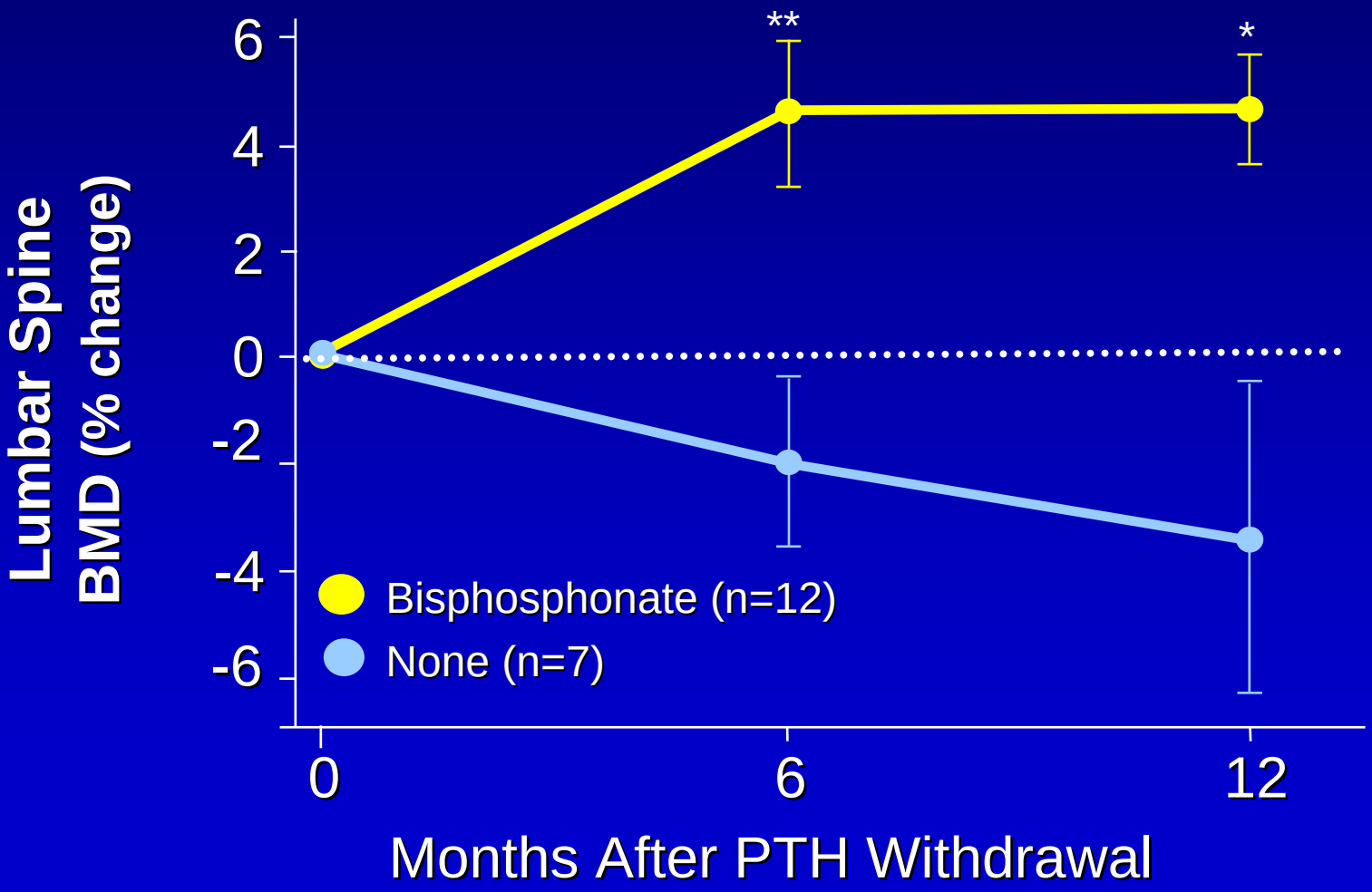
Neer, NEJM 2001; 344:1434

Teriparatide (Forteo®) Effect on Non-vertebral Fracture Risk



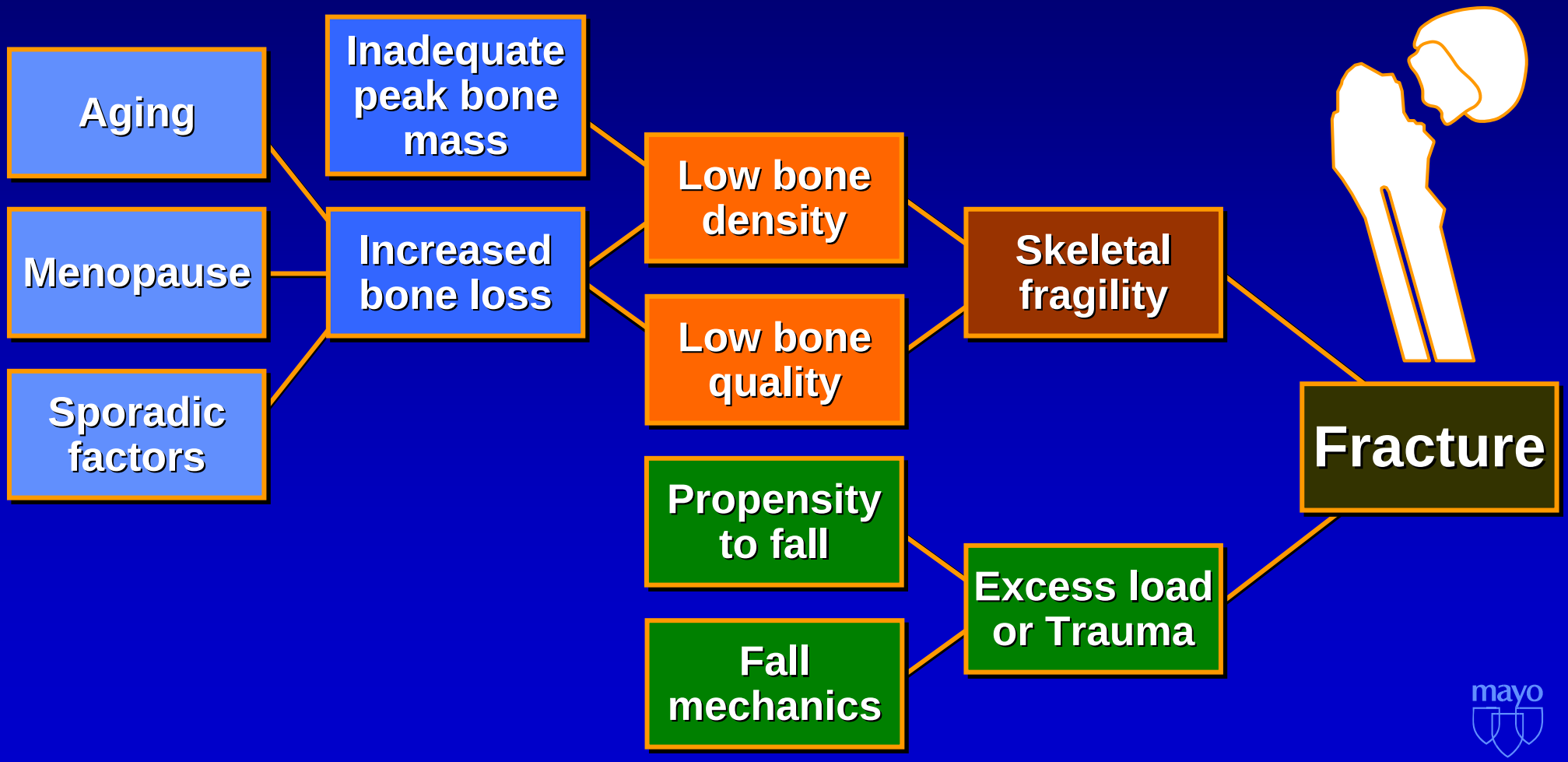
Neer, NEJM 2001; 344:1434

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®
  - 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!

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REFERENCES

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

www.nof.org web site for the National Osteoporosis Foundation (NOF) and clinical guidelines

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