

Osteoporosis: Emerging Techniques in Detection and Management

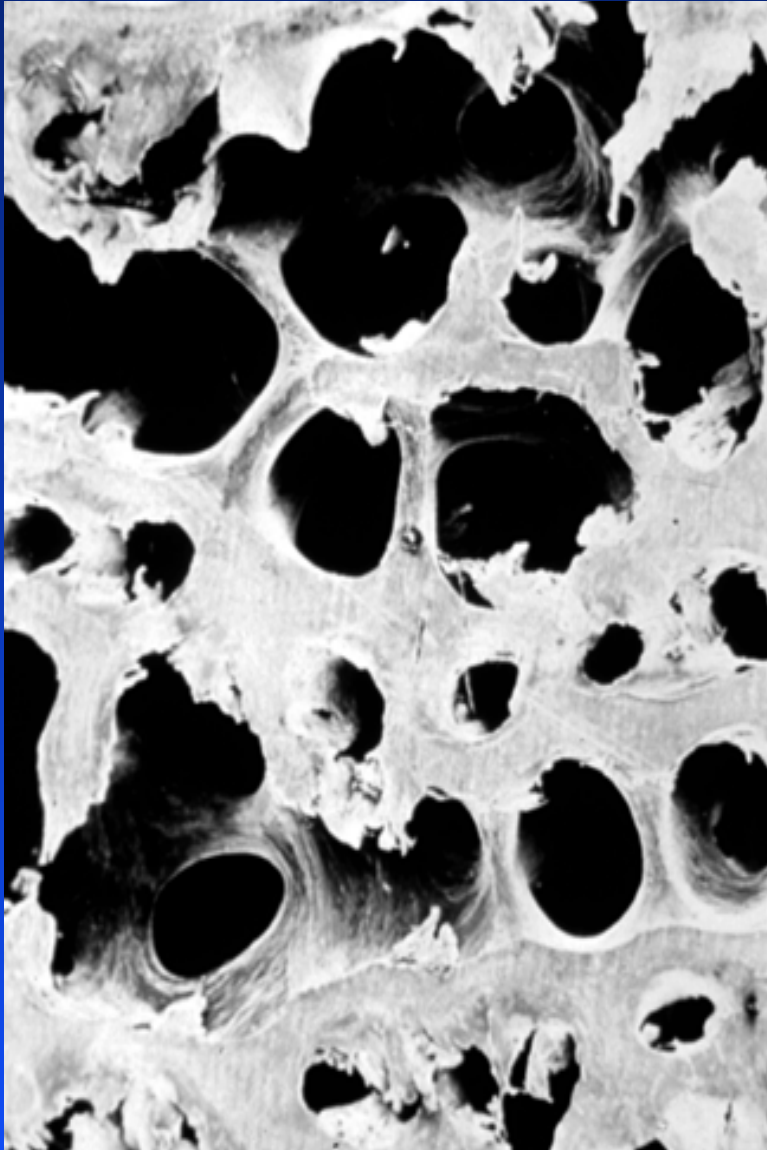
Definition of Osteoporosis

“A systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fractures.”

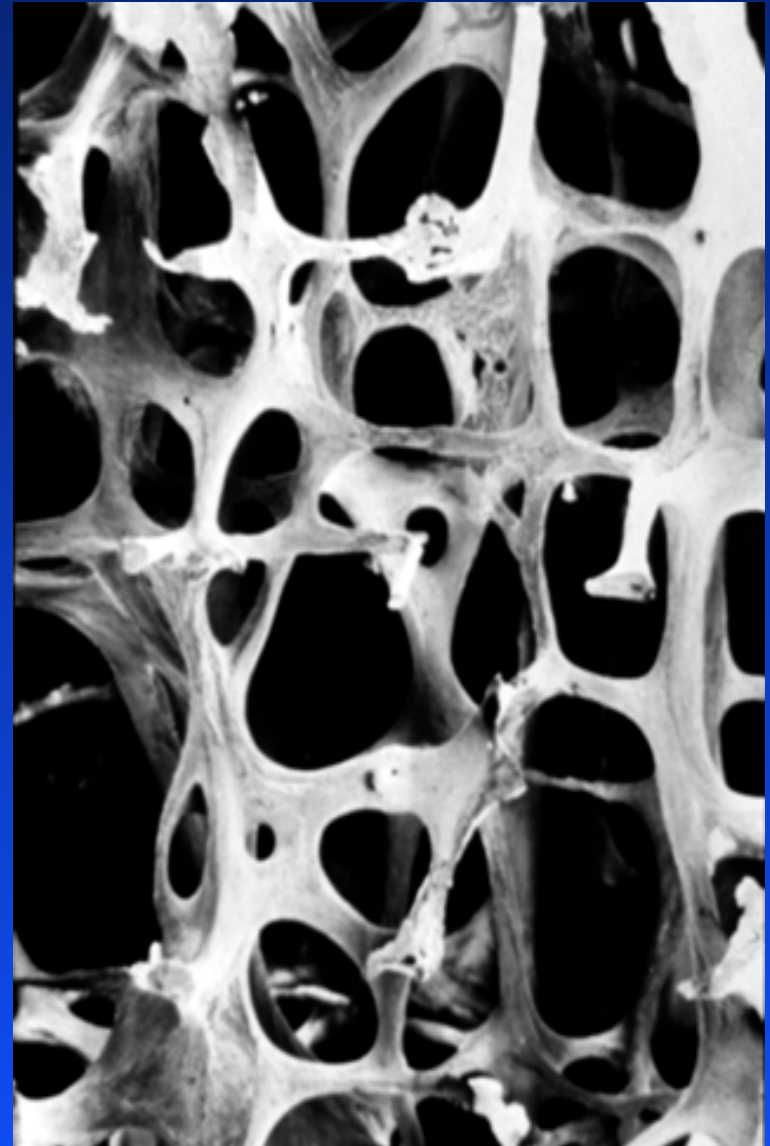
Osteoporosis

- A silent disease
- Often asymptomatic until fractures occur
- Early diagnosis and treatment are essential

Normal Trabecular Bone



Osteoporotic Bone

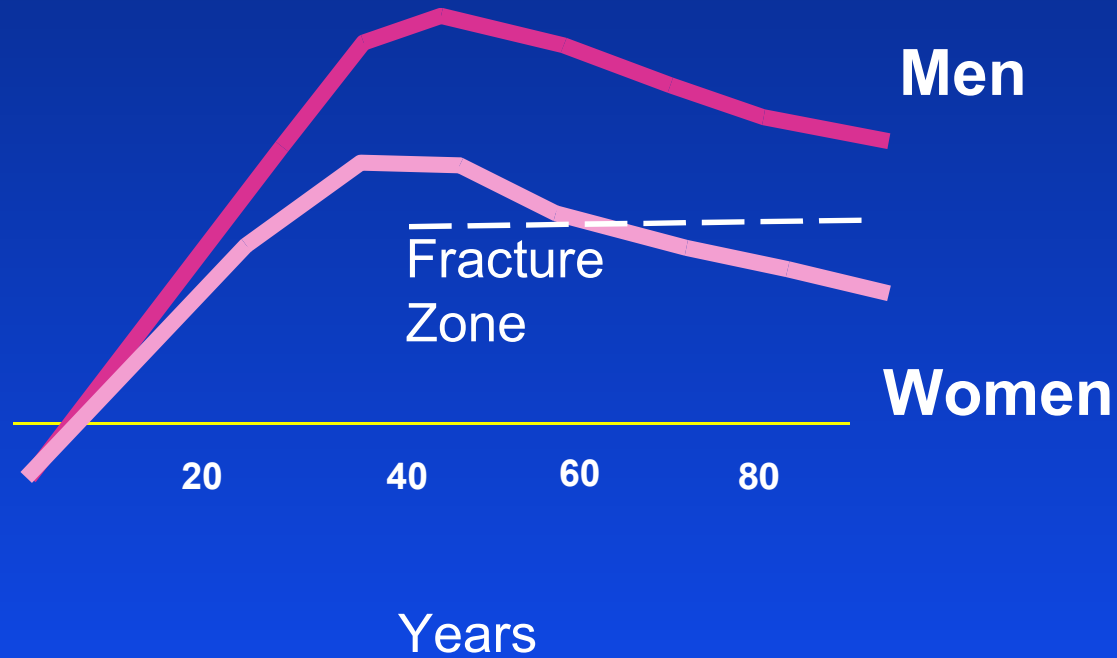


Diagnostic Categories for Bone Mass Measurement

Status

Normal	Within 1 SD of young adult mean
Osteopenia	1 SD to 2.5 SD below young adult mean
Osteoporosis	More than 2.5 SD below young adult mean
Severe osteoporosis	More than 2.5 SD below young adult mean, with fragility fractures

Change in Bone Mass with Age



Comparative Yearly Incidence

	Estimate
Osteoporosis-related fractures	1,500,000
Breast cancer	184,000
Ovarian cancer	26,000
Cervical and endometrial cancer	15,000
Prostate cancer	317,000

Osteoporosis Is Pervasive

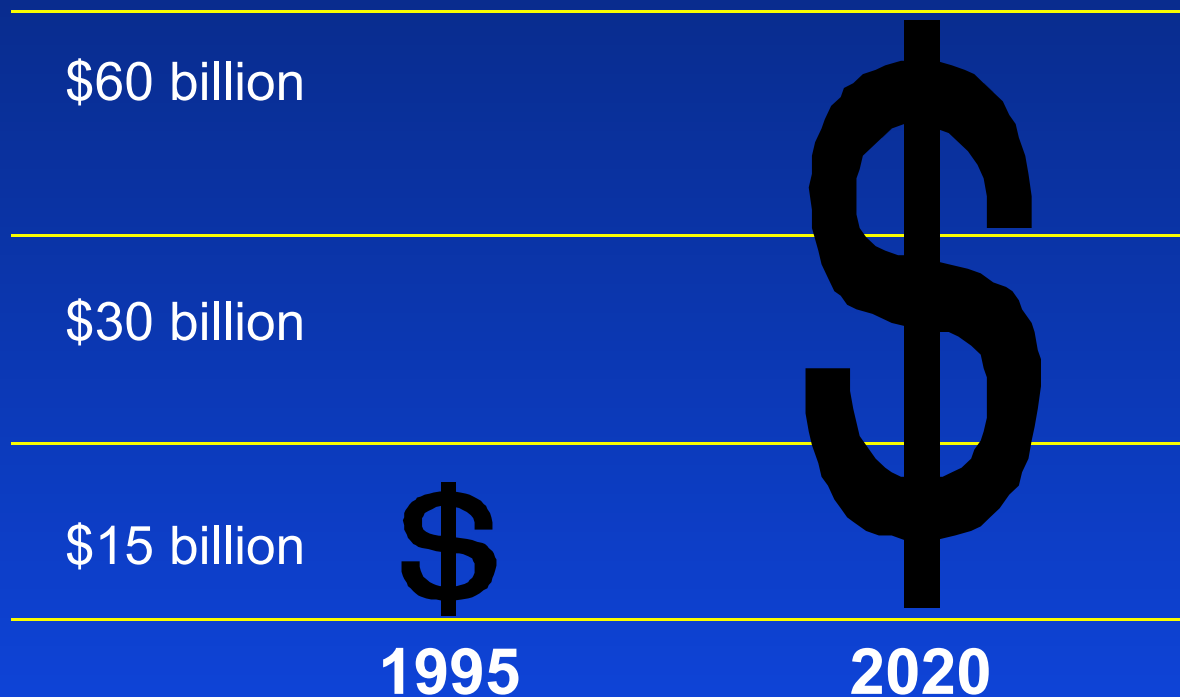
- Afflicts 25 million Americans
- 15% of women and 5% of men will experience a hip fracture in their lifetime
- Total cost of osteoporosis is estimated at about \$14 billion each year

Consequences of Osteoporosis

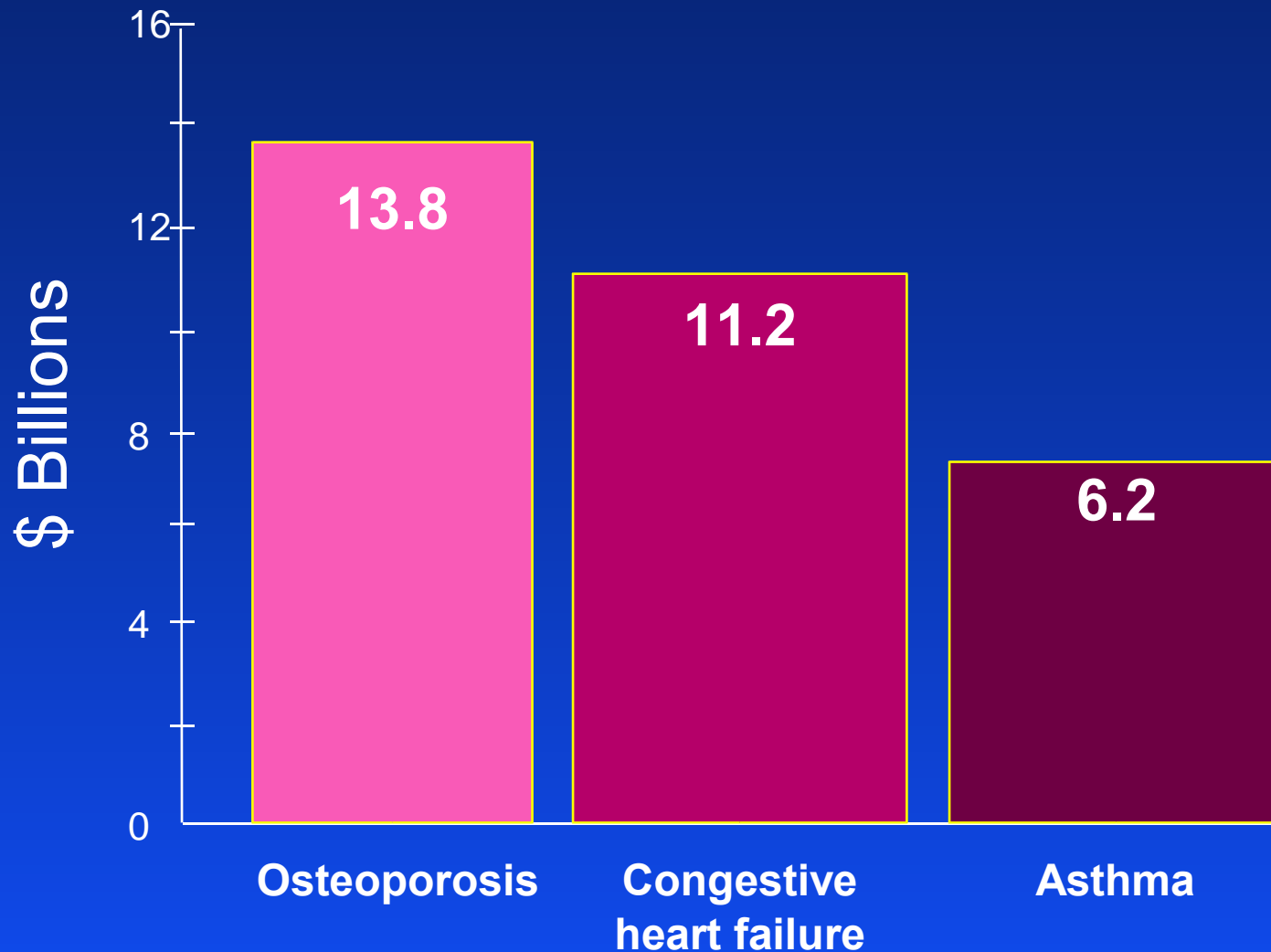
Over 90% of hip fractures are osteoporosis associated

Die of complications	12-20%
Long-term care	15-20%
Impaired lifestyle	~ 50%
Require hospitalization	> 95%

Medical, Nursing Home and Social Costs of Osteoporotic Fractures



Annual Costs of Various Chronic Diseases

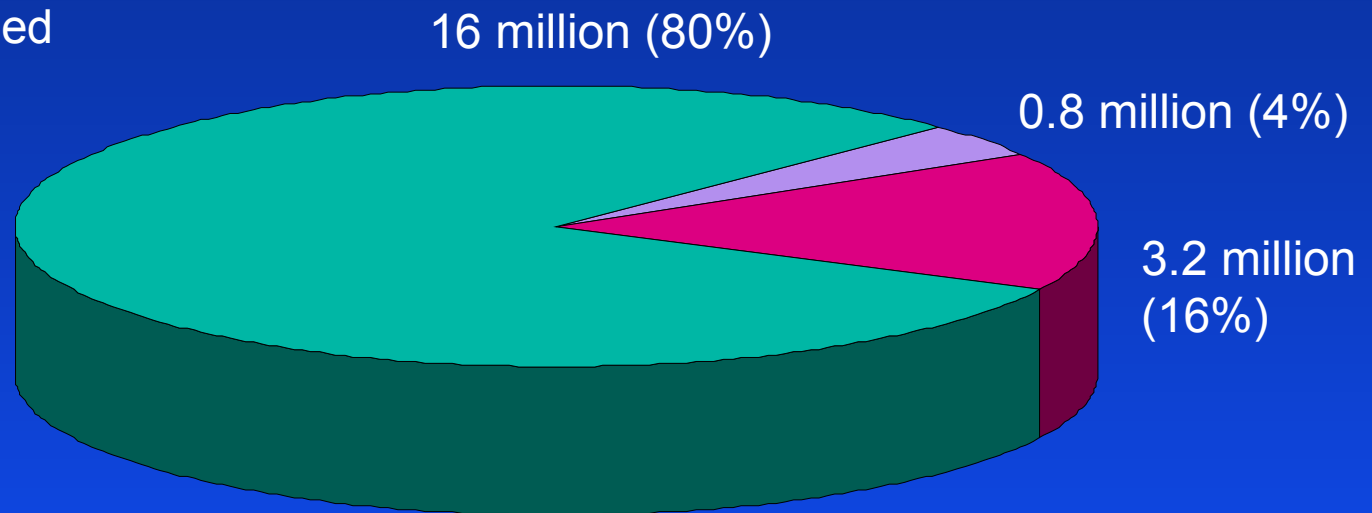


Ray NF et al. *J Bone Miner Res* 1997;12:24-35; DHHS pub. no. PHS 92-1774;

Irwin et al. *Battelle Med Tech Assess Pol Res Cen* 1992; Weiss et al. *N Engl J Med* 1992;326:862

Recognition of Osteoporosis: Very Few Diagnosed and Treated

- Diagnosed/Treated
- Diagnosed/No Rx
- Undiagnosed



Established Risk Factors for Osteoporosis

Genetic

- Female
- White or Asian races
- Thin or low peak bone mass
- Family history of fractures

Medical

- Menopause
- Menstrual dysfunction or early menopause
- Glucocorticoid, thyroid, GnRH use

Lifestyle

- Smoking
- Excessive alcohol use
- Lack of exercise

Nutritional

- Low calcium
- Vitamin D deficiency

Independent Risk Factors for Hip Fracture

Factor	Relative Risk
Anticonvulsants	2.8
Inability to rise from chair	2.1
Maternal history	2.0
Previous hyperthyroidism	1.8
Resting pulse > 80	1.8
Self-rated poor health	1.7
On feet > 4 hours/day	1.7
Benzodiazepines	1.6
Age	1.5
Poor depth perception	1.5

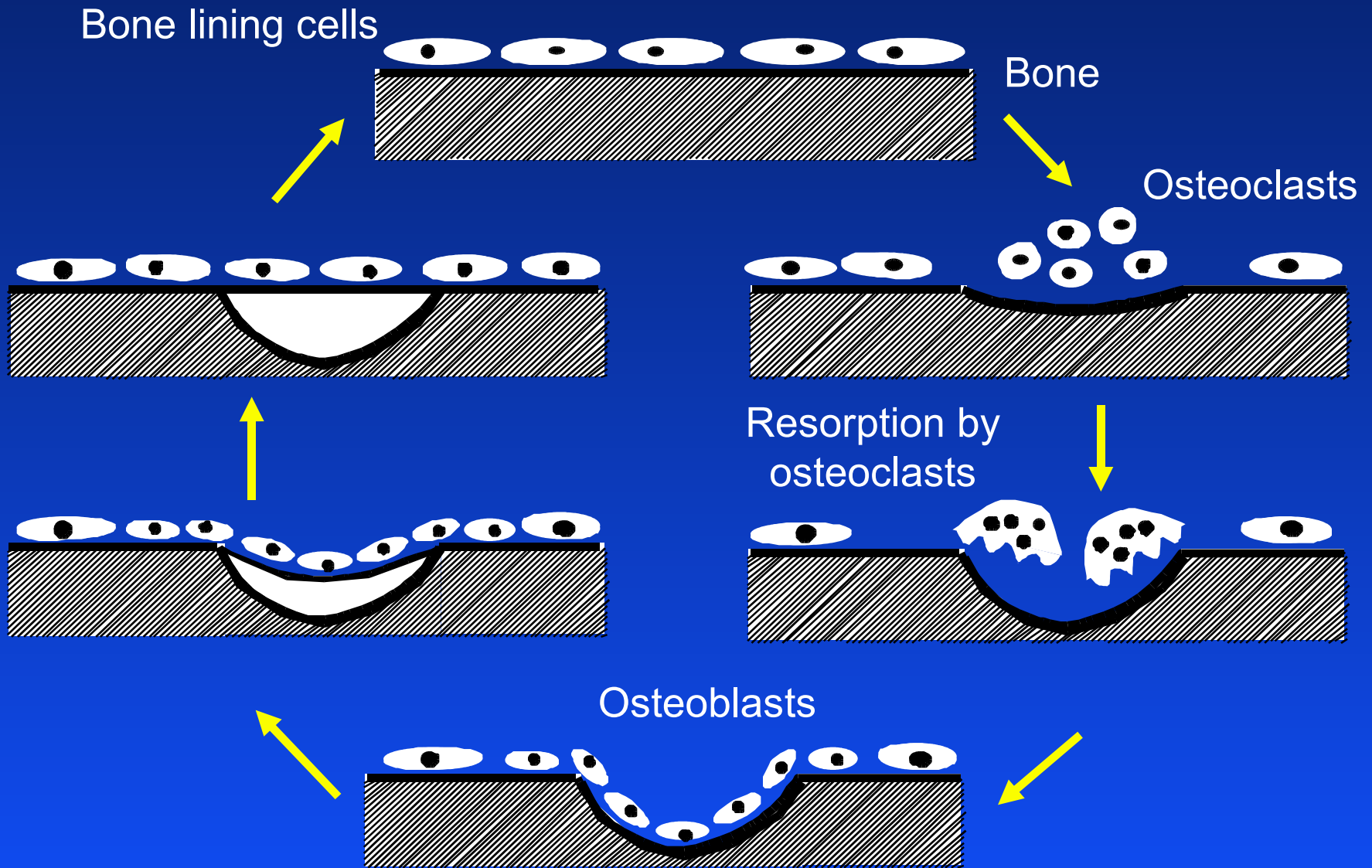
Drugs That May Contribute to Bone Loss

- Corticosteroid therapy
- Excessive thyroid medication
- GnRH analogs
- Aluminum-containing antacids
- Anticonvulsants (Dilantin and phenobarbital)
- Immunosuppressive agents
- Heparin
- Cholestyramine

Bone: A Dynamic Tissue

- Bone is a living tissue
 - ~ 10% of the entire skeleton is replaced each year
- Bone consists of mineralized organic matrix
 - 90% of the organic matrix is type I collagen
 - Calcification gives bone its “hardness”

Bone Remodeling Cycle

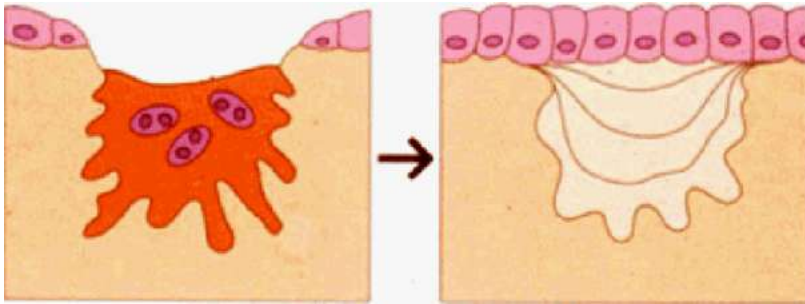


Bone Turnover

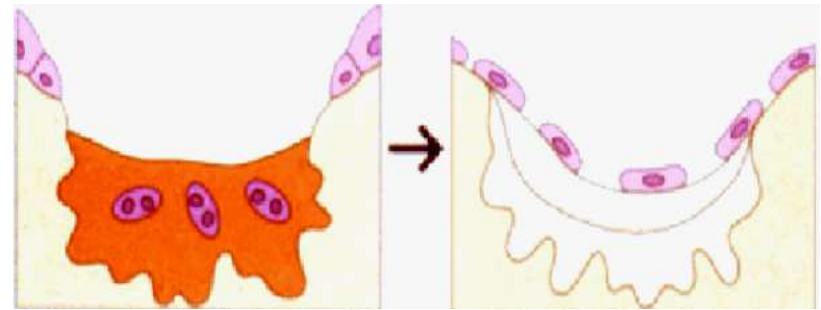
- Bone is renewed by continuous remodeling or turnover
- Bone is resorbed by osteoclasts
- Resorption releases calcium and collagen metabolites
- Bone is formed by osteoblasts
- Resorption and formation are normally in balance (coupled)
- Uncoupling of bone turnover leads to bone loss

Bone Balance

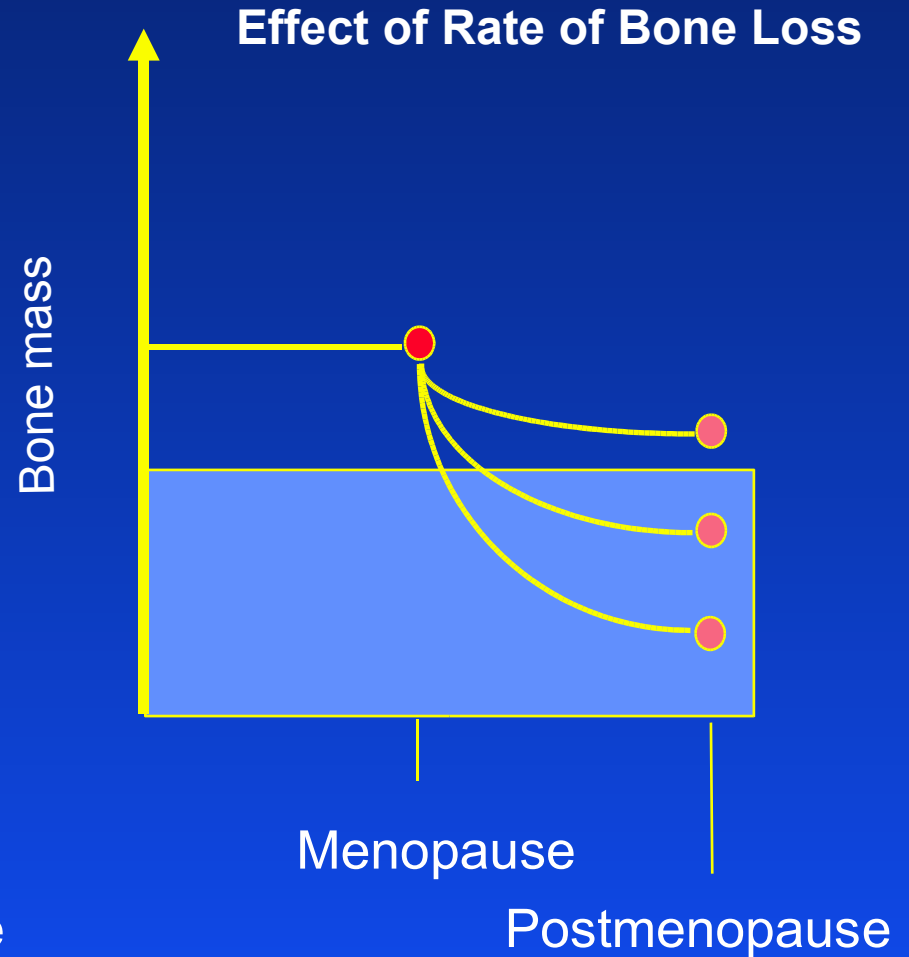
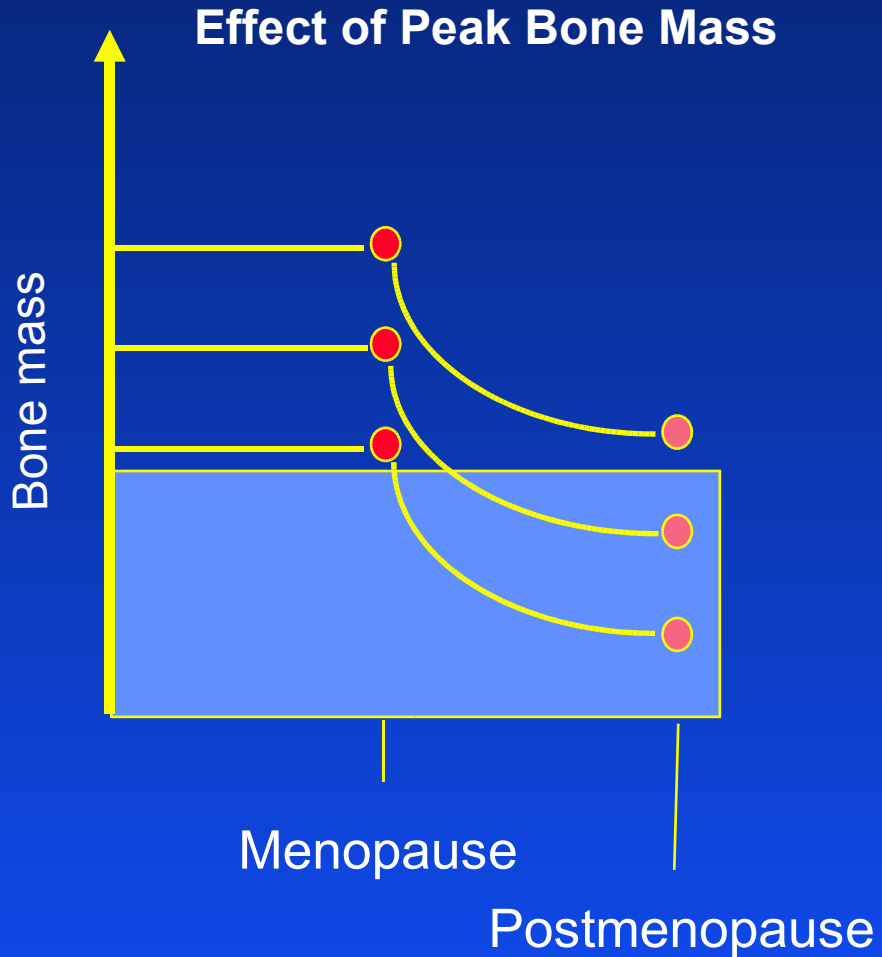
**Resorption and
Formation
Are Equal**



**Resorption Exceeds
Formation**



Peak Bone Mass vs. Rate of Bone Loss



Biochemical Markers of Bone Formation

- Alkaline phosphatase
 - Bone-specific alkaline phosphatase
- Osteocalcin
- Propeptide of type I collagen

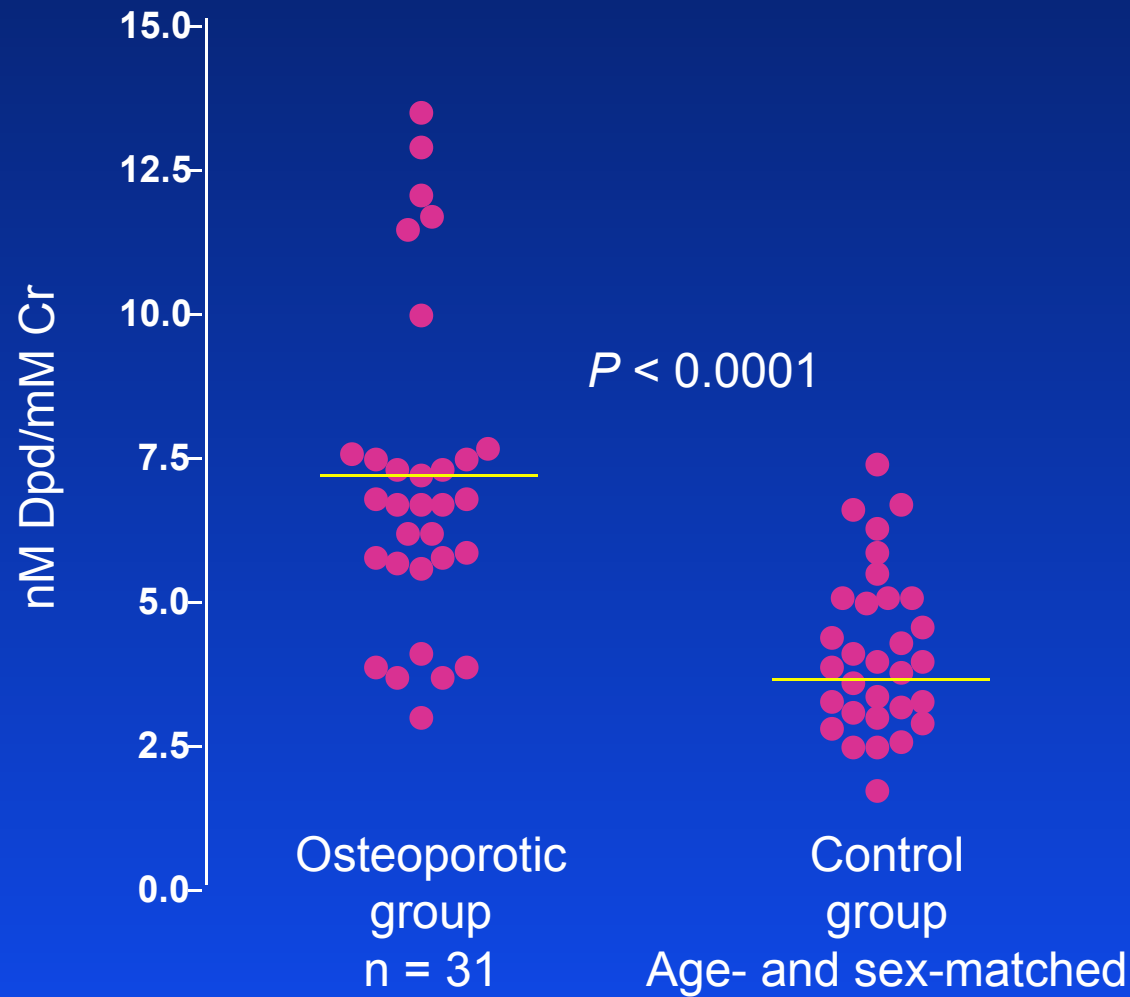
Biochemical Markers of Bone Resorption

- Pyridinium crosslinks and associated peptides
 - Pyridinoline
 - Deoxypyridinoline
 - Telopeptides
- Hydroxyproline

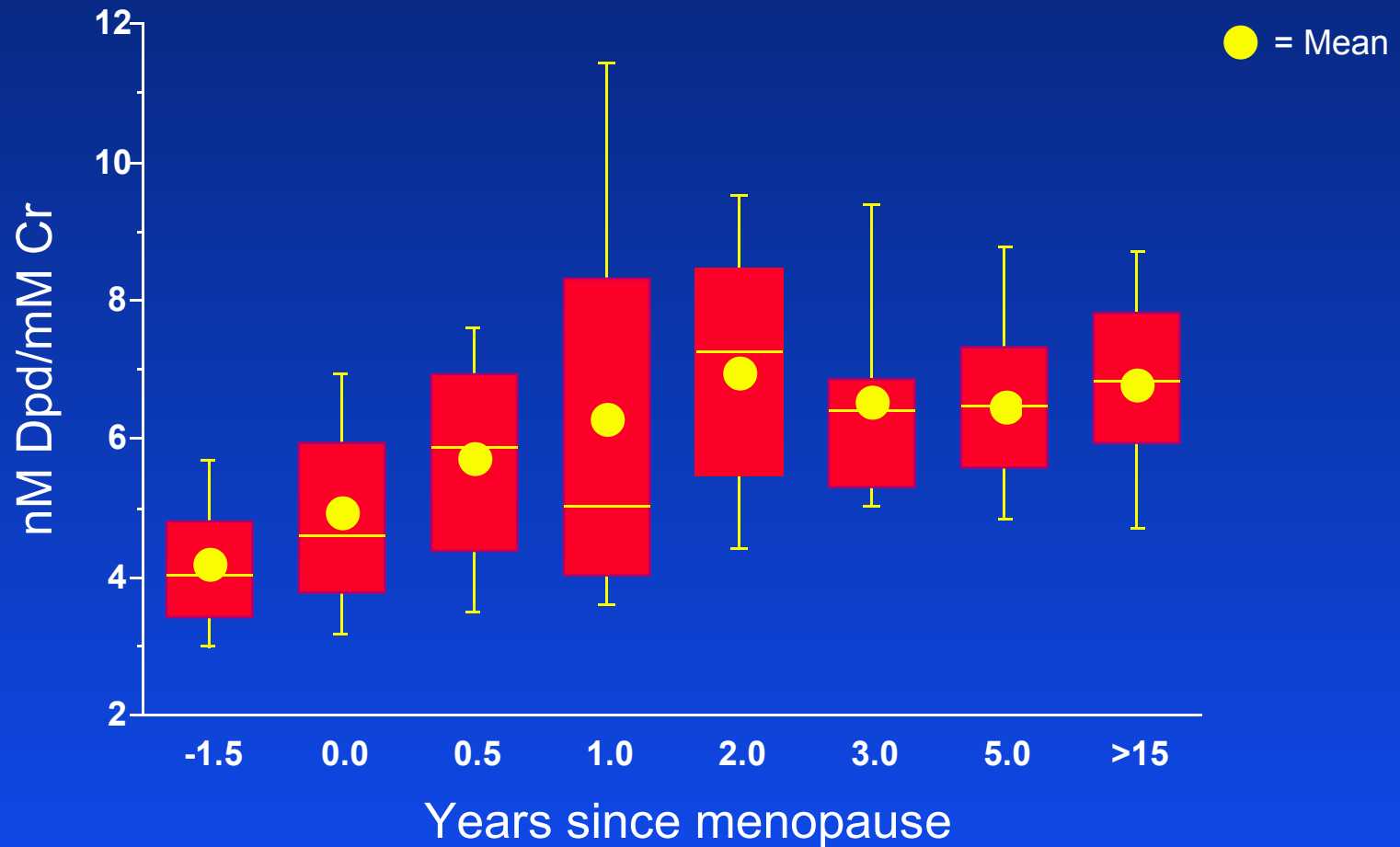
Deoxypyridinoline: A Marker of Bone Resorption

- Found almost exclusively in bone collagen
- Product of collagen maturation; cannot be reused for new collagen synthesis
- Correlated with bone resorption histomorphometry and radioisotopic techniques
- Associated with bone loss measured by changes in bone mineral density

Bone Resorption in Osteoporosis



Bone Resorption Relates to Menopause



Biochemical Markers

Densitometry

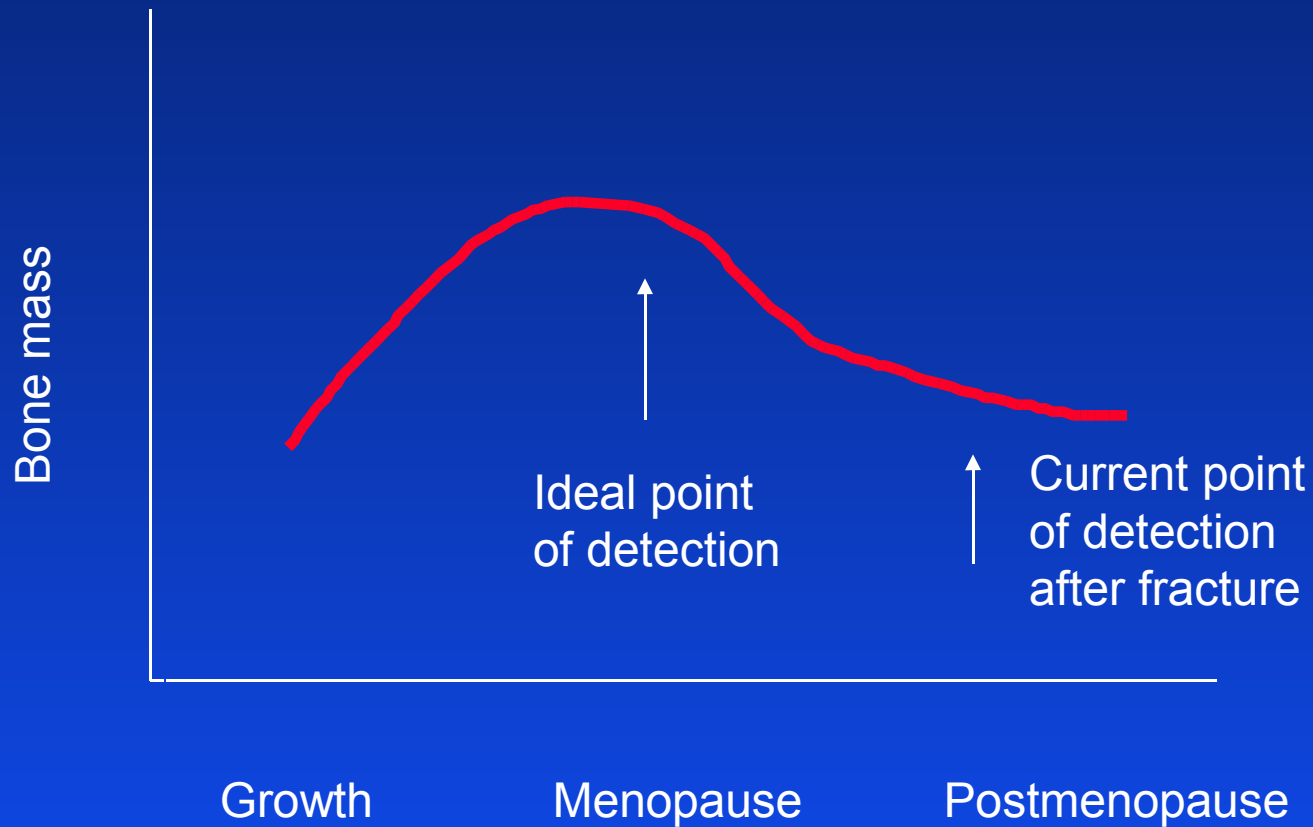
Measure of bone turnover

- Assessment of risk
- Dynamic measure of bone turnover
- Identifies patients for treatment “potential”
- Short-term therapeutic monitoring

Measure of bone mass

- Assessment of risk
- Static measure of bone mass
- Identifies patients for osteoporosis treatment
- Long-term therapeutic monitoring

Time of Detection May Determine Outcome



Prediction of Bone Loss by Markers of Bone Metabolism: 12-Year Study in Postmenopausal Women

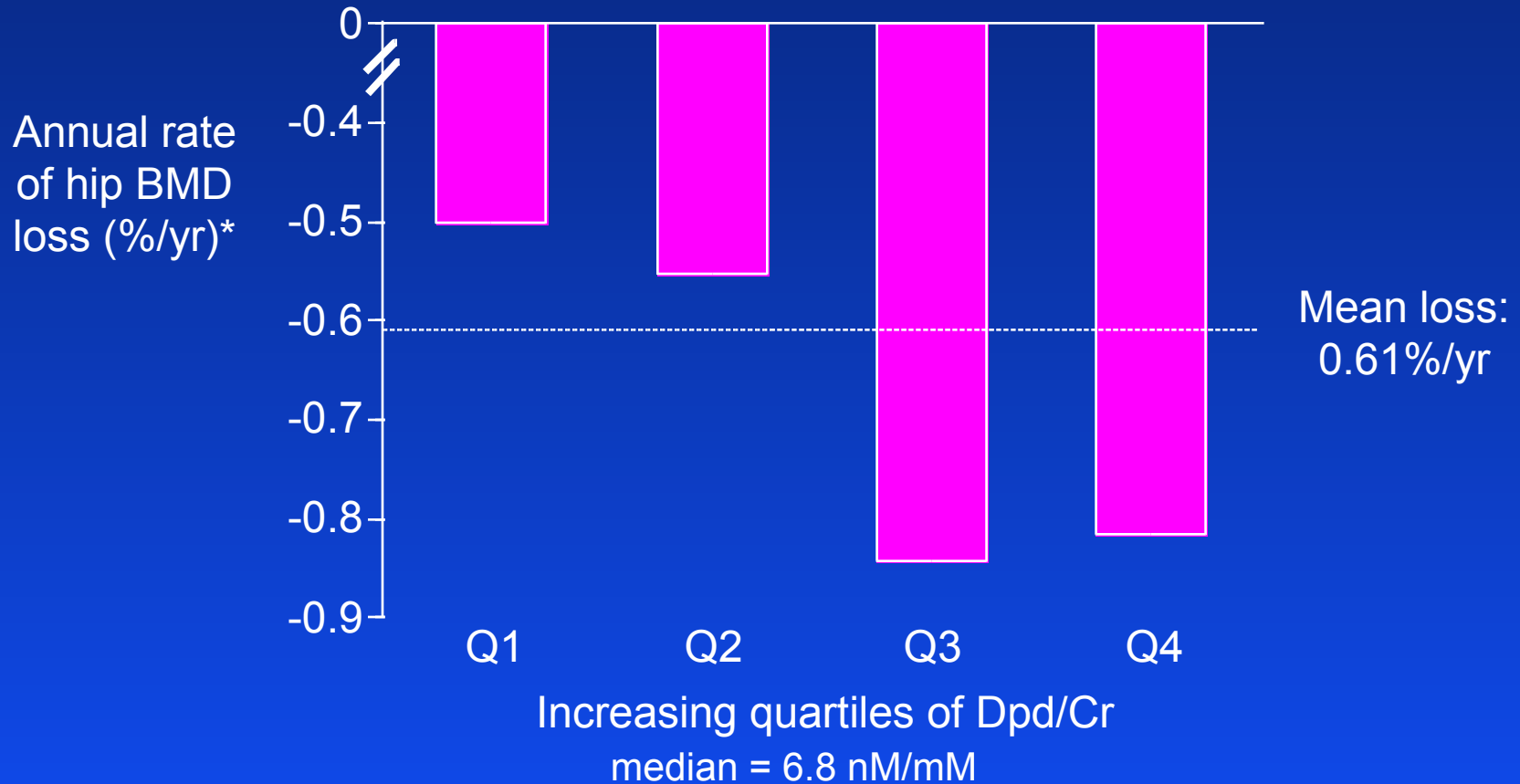
	Initial Rate of Loss (%/year)	n	Loss Predicted by Bone Markers (%)	Actual Loss s BMC (%)
Slow losers	< 1.5	55	-16.5	-17.0
Intermediate losers	1.5 - 3	34	-20.6	-19.3
Fast losers	> 3.0	32	-25.6	-26.4

Adapted from Hansen et al. *BMJ* 1991; 303:961-4

Dpd is Associated with Rapid Bone Loss

Study of Osteoporotic Fractures

3.8 Years Average Follow-up



* Age-adjusted

Adapted from Cummings et al. *J Bone Miner Res* 1996;11:S128

Prospective Studies of Fracture Risk

EPIDOS Study

- 7,598 women, ≥ 75 years of age from 5 centers in France
- 109 hip fractures
- 22-month follow-up, 3 controls per case

Baseline Levels of Markers: Bone Turnover

EPIDOS Study

	Premenopausal		Elderly Women		P *
	Controls (n = 134)	Controls (n = 292)	Hip fracture (n = 109)		
Bone Resorption					
Free Dpd (nmol/mmol Cr)	4.4	5.8†	6.4†	0.005	
C-telopeptide (µg/mmol Cr)	189	266†	305†	0.02	
N-telopeptide (nmol/mmol Cr)	25.7	50.8†	56.2†	ns	
Bone Formation					
Osteocalcin (ng/ml)	18.3	27.8†	27.7†	ns	
Bone Alkaline Phosphatase (ng/ml)	8.7	16.0†	15.4†	ns	

* Hip fracture vs age-matched controls

† P < 0.001 vs premenopausal controls
Adapted from Camero et al. J Bone Miner Res 1996;11:1531-8

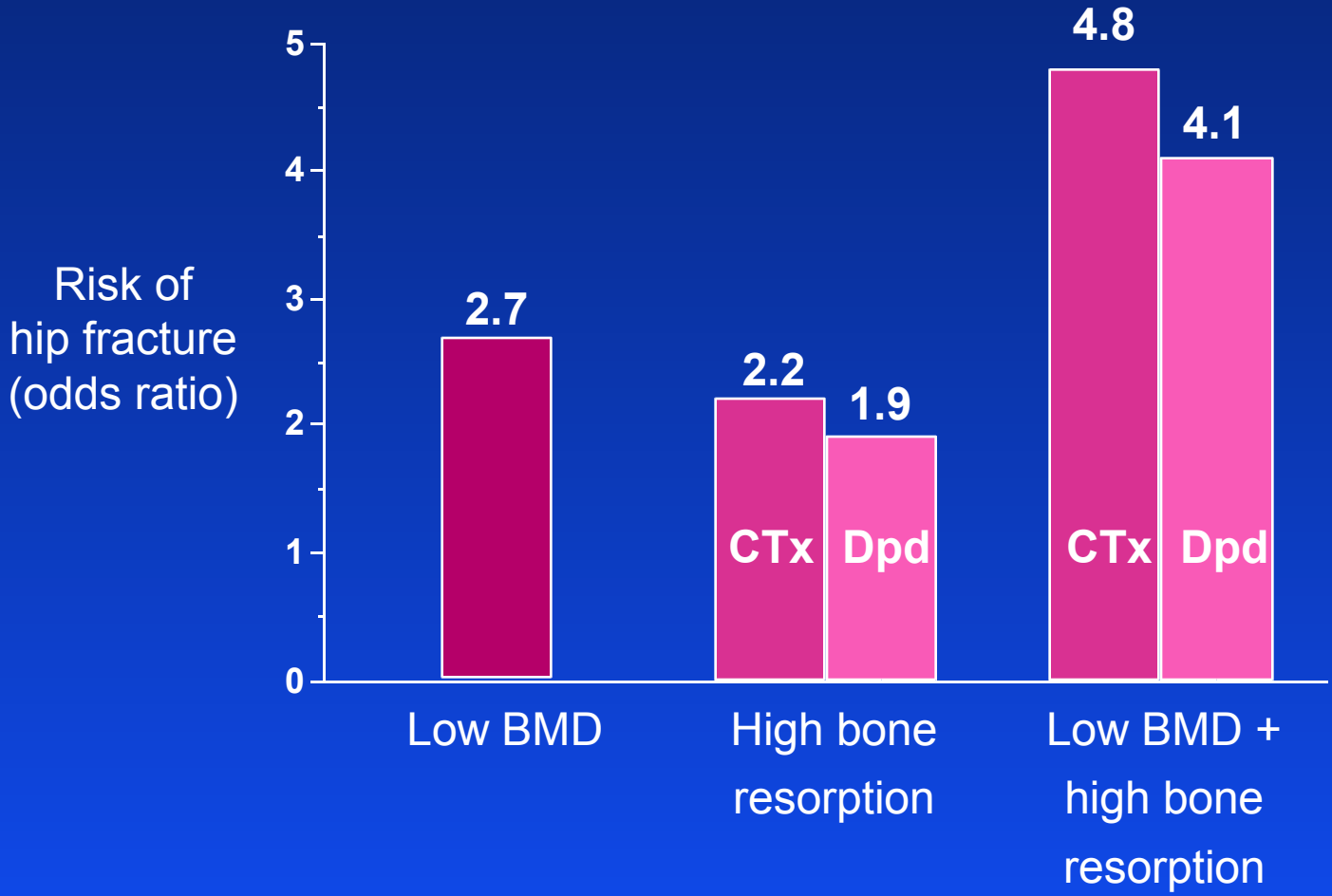
Bone Markers, BMD, and Hip Fracture Risk: EPIDOS Study

Odds Ratios (OR)
for 1 SD $P = 0.05$

<i>Femoral neck BMD*</i>	1.7*
Deoxypyridinoline (Dpd)	1.4
C-telopeptide (CTX)	1.3
N-telopeptide (NTx)	1.1
Osteocalcin	1.0
Bone alkaline phosphatase	0.9

* 1 SD decrease in femoral neck BMD

Bone Markers, BMD, and Hip Fracture Risk: EPIDOS Study



Adapted from Garnero et al. *J Bone Miner Res* 1996;11:1531-8

Prospective Studies of Fracture Risk

Rotterdam Study

- 7,983 women and men, ≥ 55 years of age in Rotterdam, Netherlands
- 36 hip fractures (women), 169 total fractures (women)
- 2.4-year follow-up, 3 controls per case (hip)

Bone Markers and Nonvertebral Fracture Risk Rotterdam Study

	Odds Ratios
Dpd*	1.7
Osteocalcin†	0.9
Bone alkaline phosphatase†	0.9

* Above median

† Below median

Bone Markers and Hip Fracture Risk: Rotterdam Study

	Adjusted for	Odds Ratio	
Dpd Above median	Age	3.9*	<i>* Significant association</i>
	BMD	3.8*	
	Disability	3.5*	
Osteocalcin Below median	Age	3.1*	
	BMD	3.2*	
	Disability	2.5	
BAP Below median	Age	1.0	
	BMD	1.2	
	Disability	1.0	

Recommendations for Prevention of Osteoporosis

- Hormone replacement therapy
- Weight-bearing exercise
- Adequate intake of calcium & vitamin D
- Discourage smoking and excessive alcohol intake
- Other antiresorptive therapy
 - alendronate, raloxifene currently approved

Therapies for Prevention and Treatment of Osteoporosis

Antiresorptive Agents

- Calcium
- Estrogens
- Selective estrogen receptor modulators
- Bisphosphonates
- Calcitonin
- Calcitriol, other vitamin D metabolites

Formation-Stimulating Agents*

- Sodium fluoride
- Parathyroid hormone
- Growth factors

* Currently under investigation; none FDA-approved

Osteoporosis Medication Issues

- Few actually treated
 - Only 12-20% of patients diagnosed with osteoporosis are on medication
- Low compliance
 - 20-40% discontinue HRT within 12 months
 - Only 8-10% of HRT users continue treatment for 2 years or longer

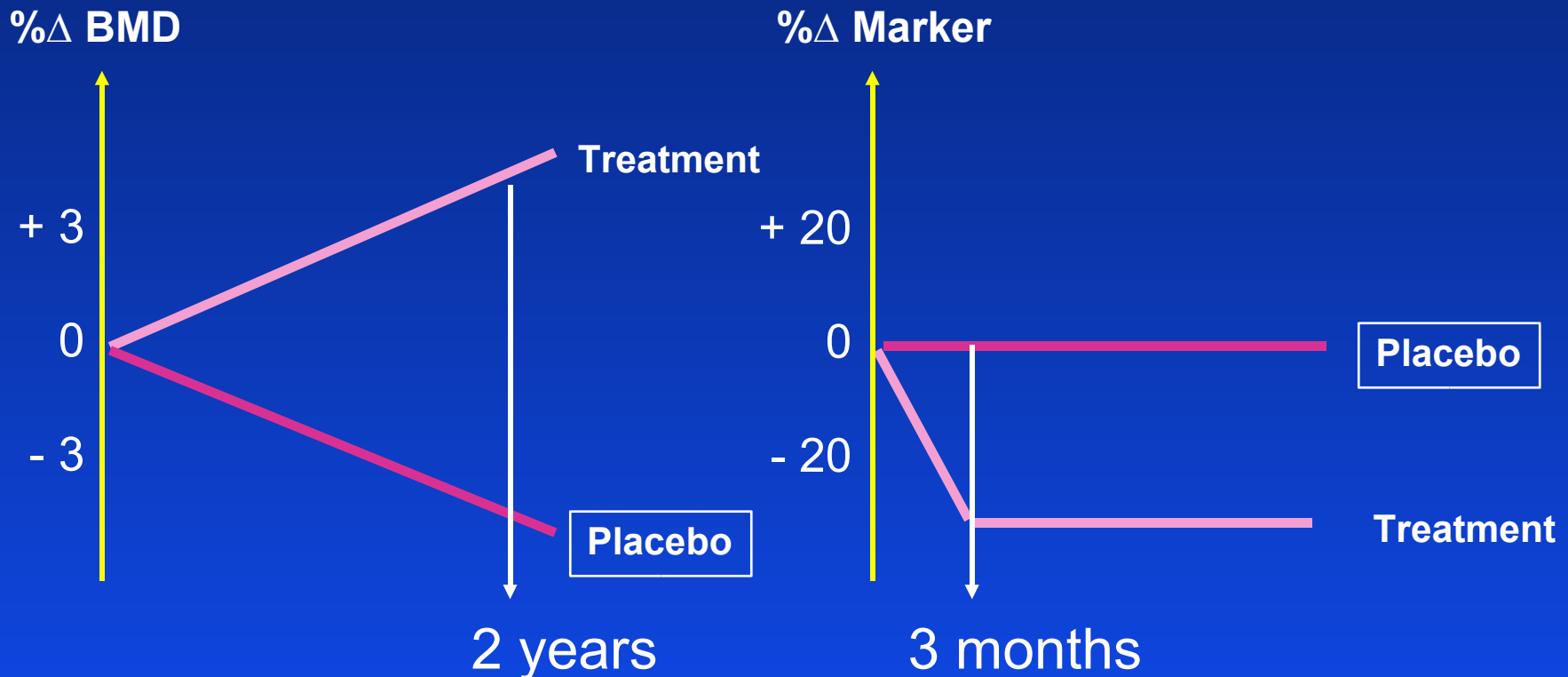
Osteoporosis Medication: Tolerance and Regimen Issues

- HRT
 - Bleeding problems
 - Perceived cancer risk
- Bisphosphonates
 - GI side effects
 - Rigid administration schedule
- Calcitonin
 - Decreased tolerance with long-term use

Clinical Utility of Biochemical Bone Turnover Markers

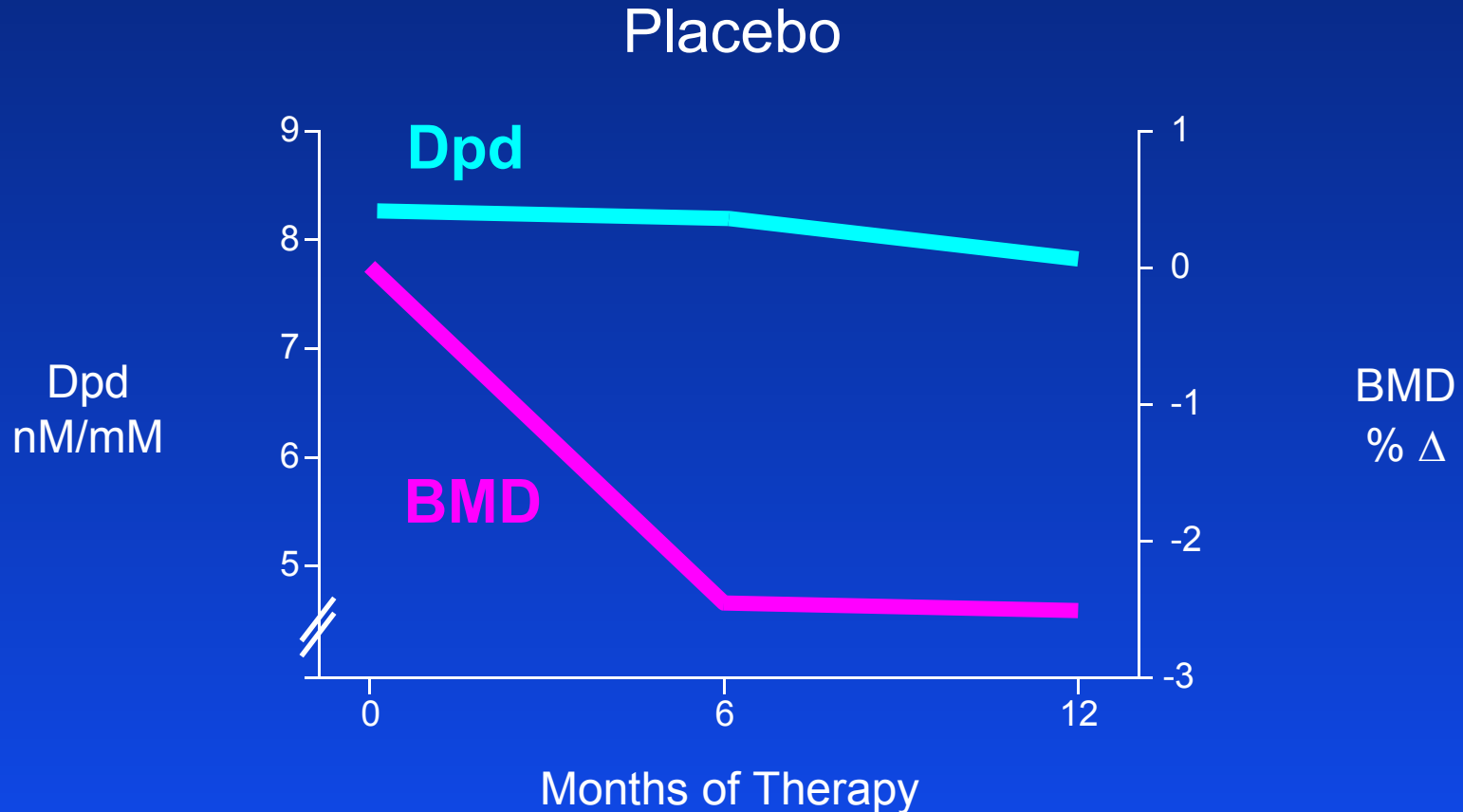
- Complementary to BMD measurements
- Identify and monitor patients at risk for significant bone loss
- Encourage patients to start and continue therapy
- Monitor progress of and compliance with antiresorptive therapy

BMD and Marker Changes During Antiresorptive Therapy

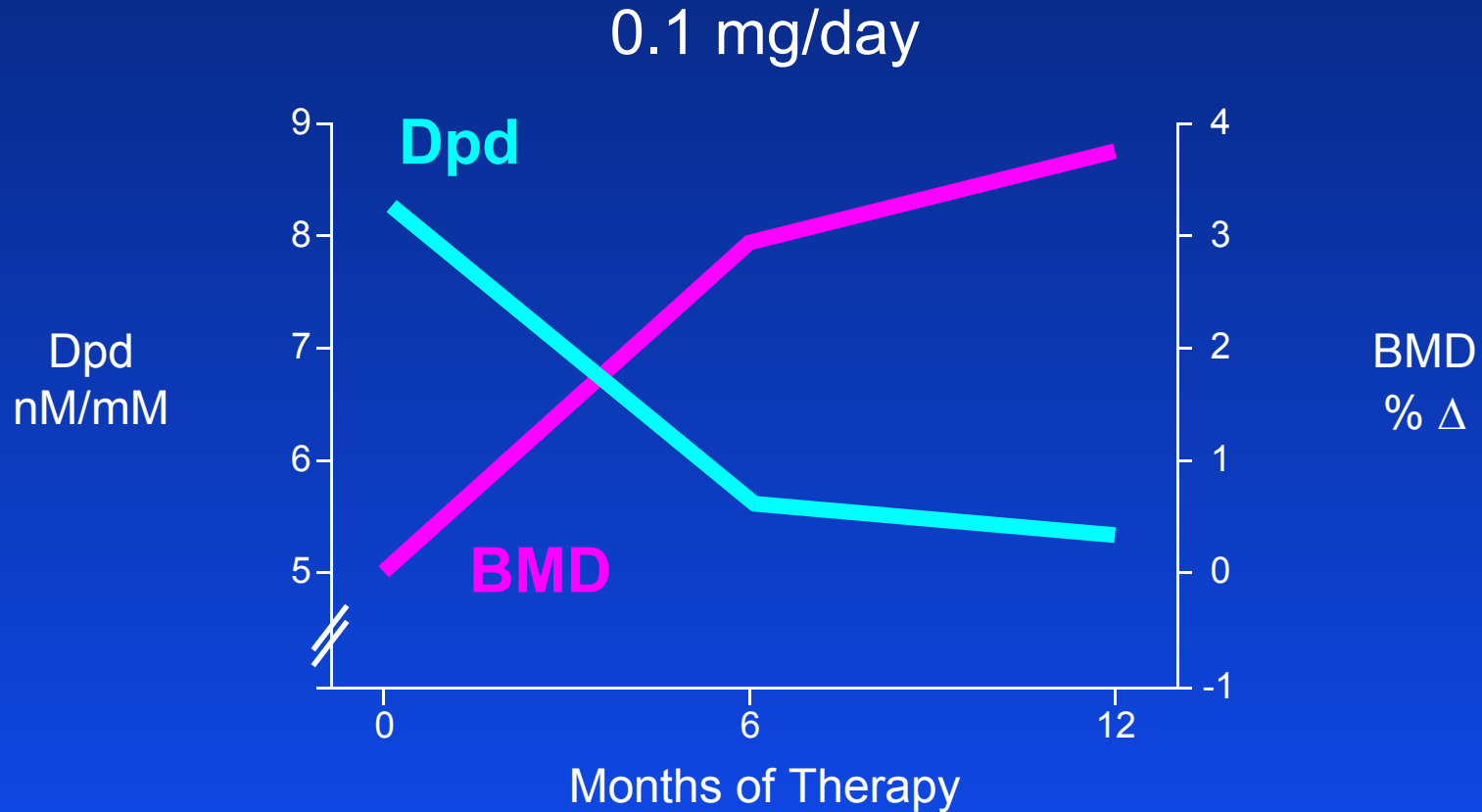


Adapted from: Delmas PD. In: *Osteoporosis: Etiology, Diagnosis, and Management*. Philadelphia: Lippincott-Raven Publishers;1995:329

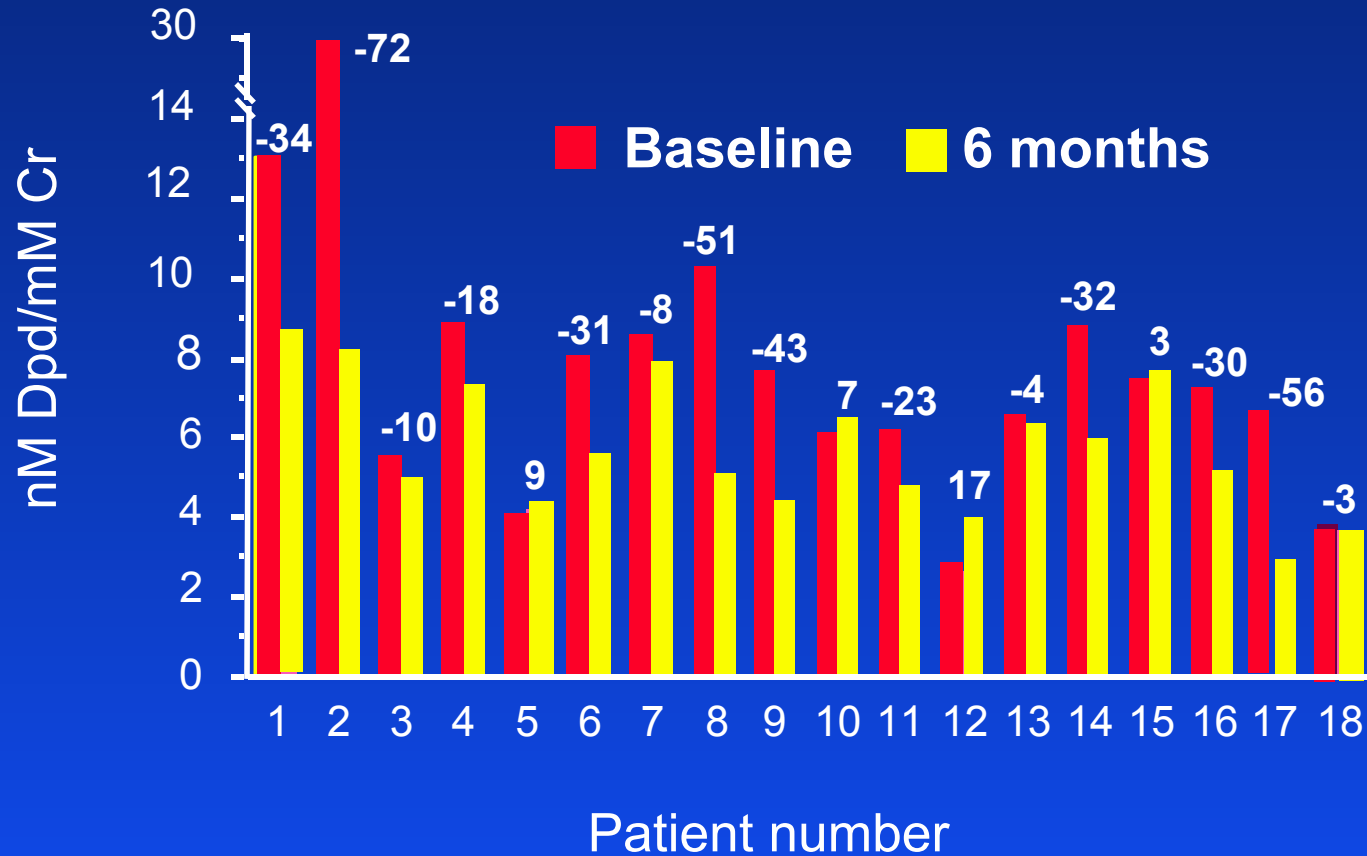
Increased Dpd Reflects Bone Loss Following Menopause



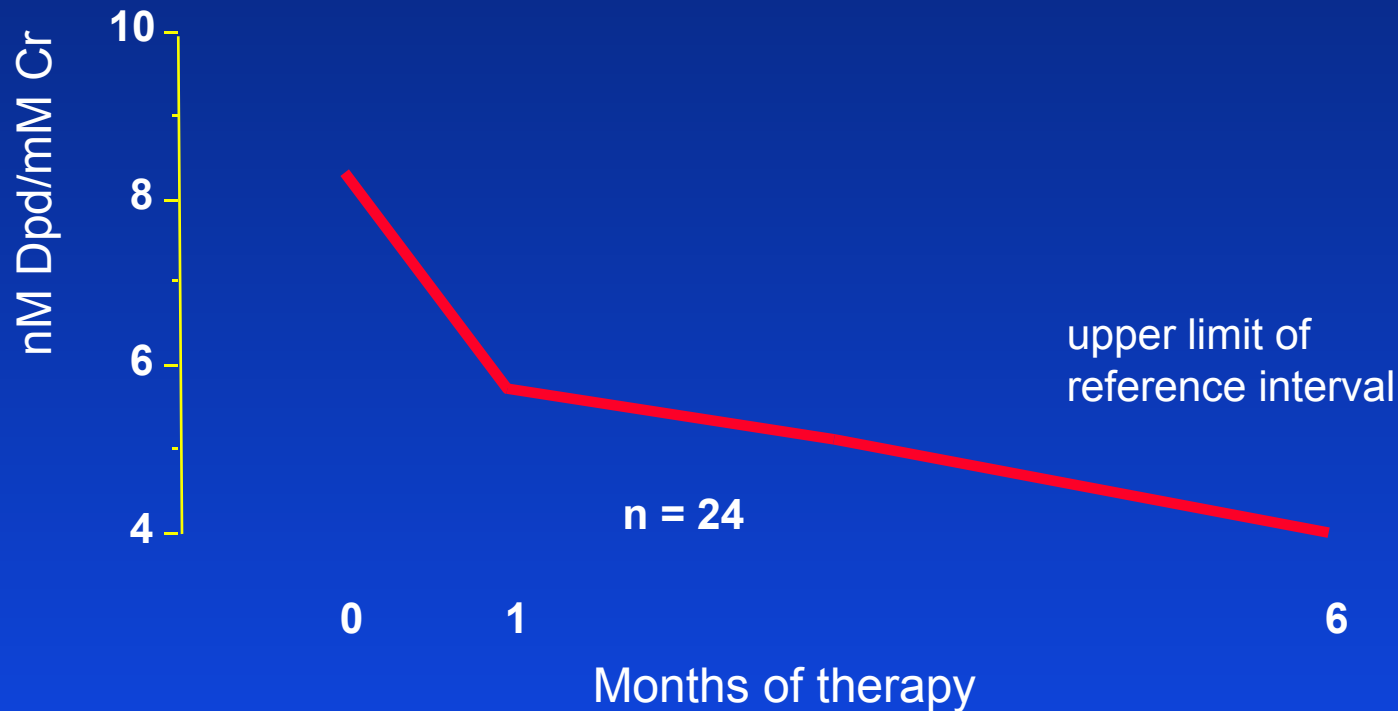
Dpd Monitors Estrogen-Induced Changes in Vertebral Bone Mass



Individual Dpd Response During Transdermal Estrogen Replacement Therapy (0.1 mg)



Dpd During Alendronate Therapy in Postmenopausal Women with Low Bone Mass (10 mg/day open-label study)

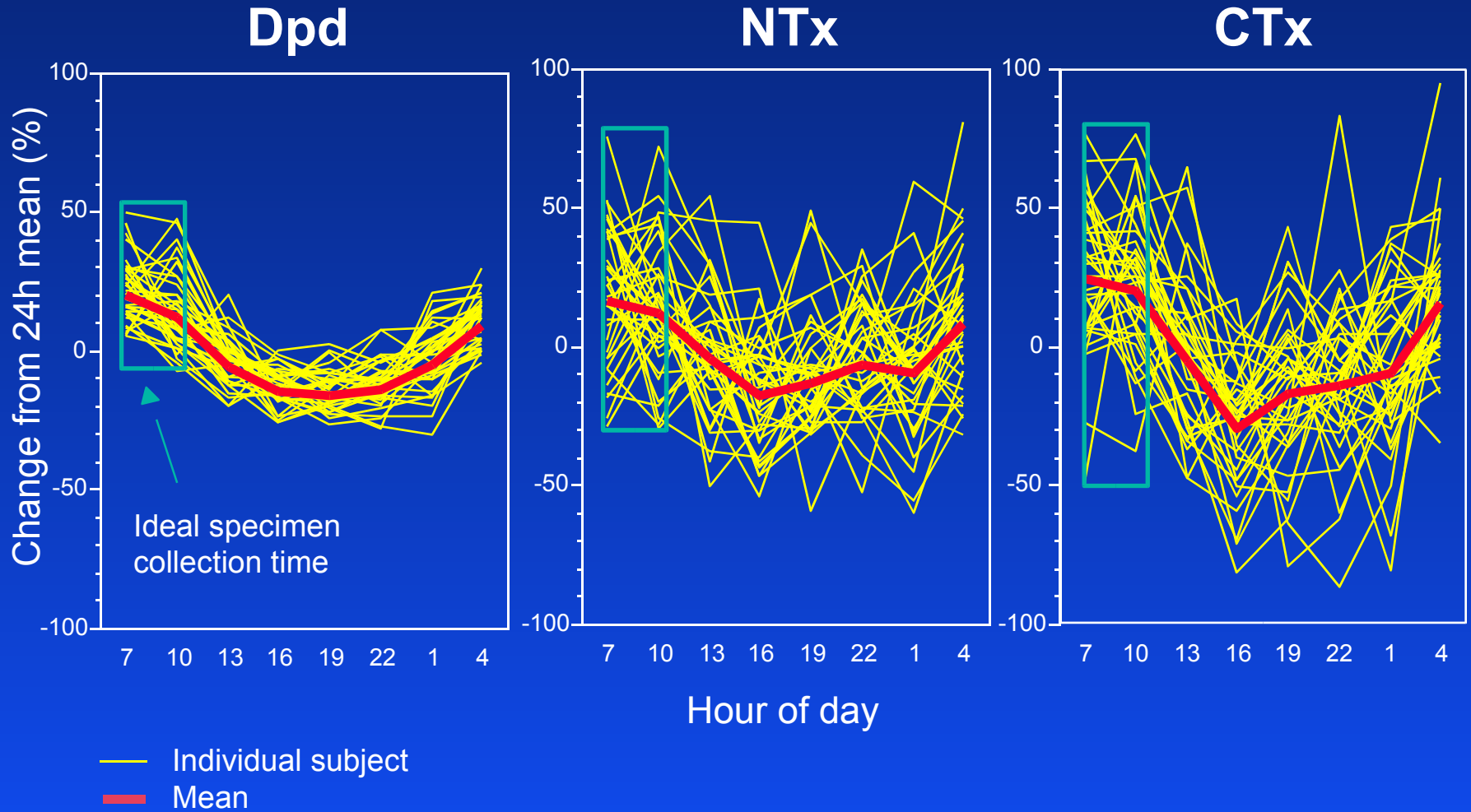


Population Variation

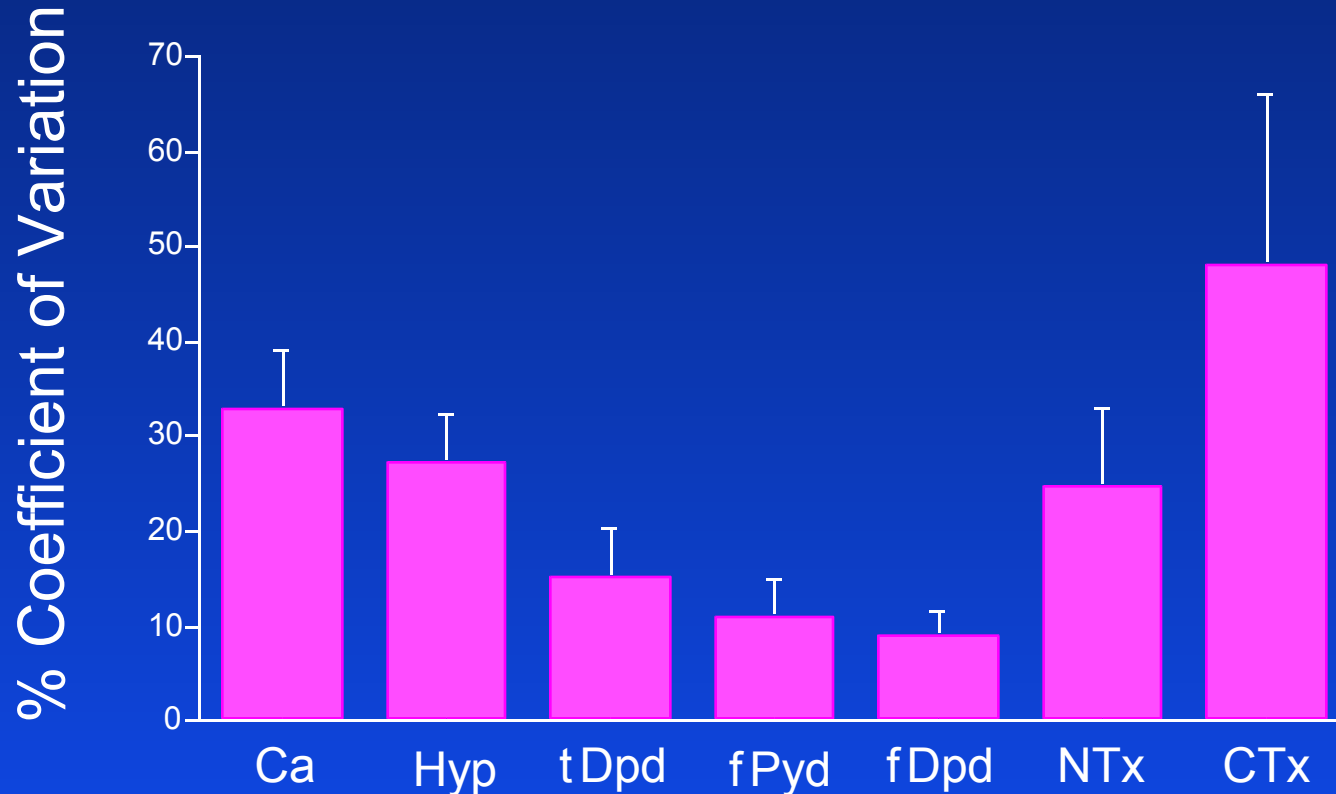
	Dpd	NTx	CTx
Mean	4.93	37.3	229
SD	1.40	21.4	128
Coefficient of Variation (CV)	28%	57%	56%

216 healthy, premenopausal women

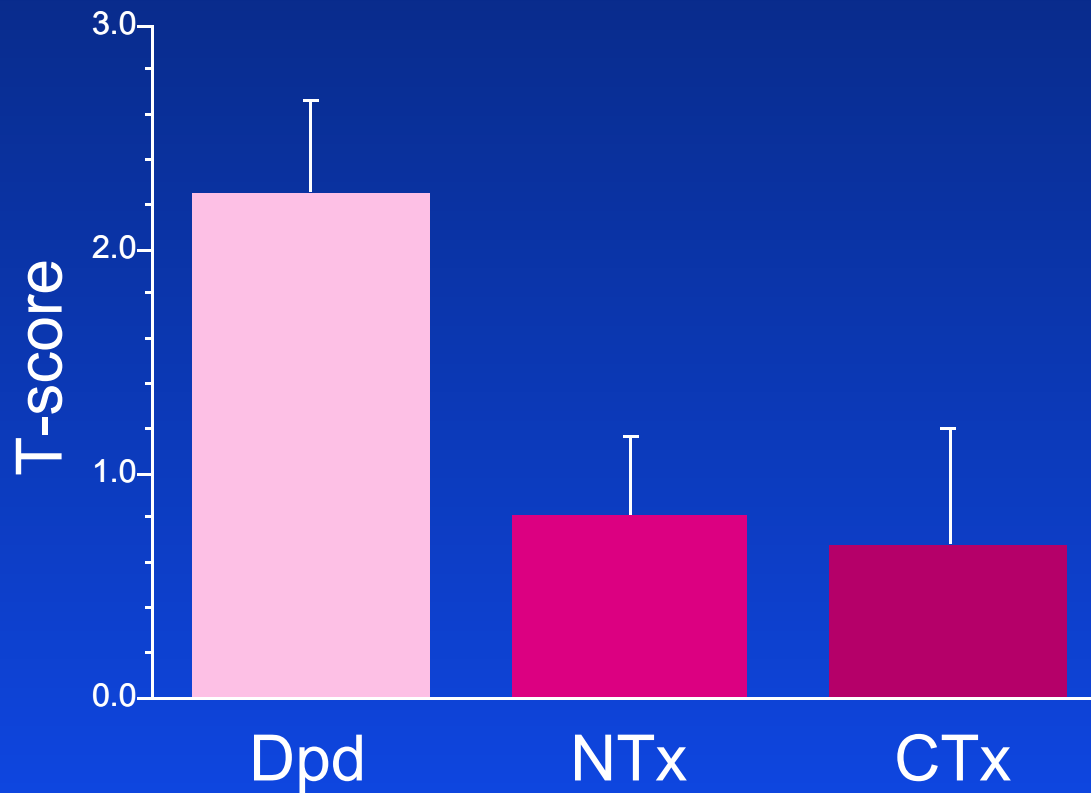
Diurnal Variation



Day-to-Day Variation of Urinary Bone Resorption Markers



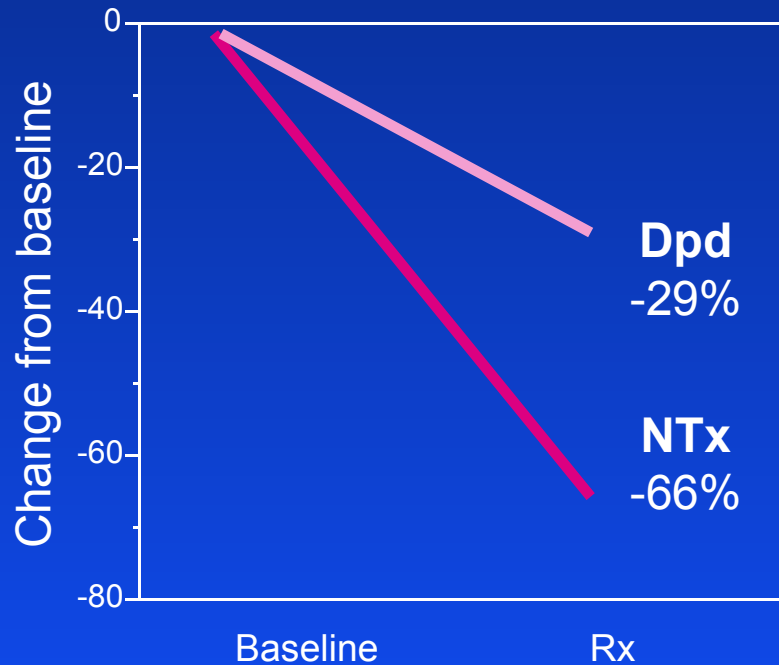
Women with Low Bone Mass: Baseline (Untreated)



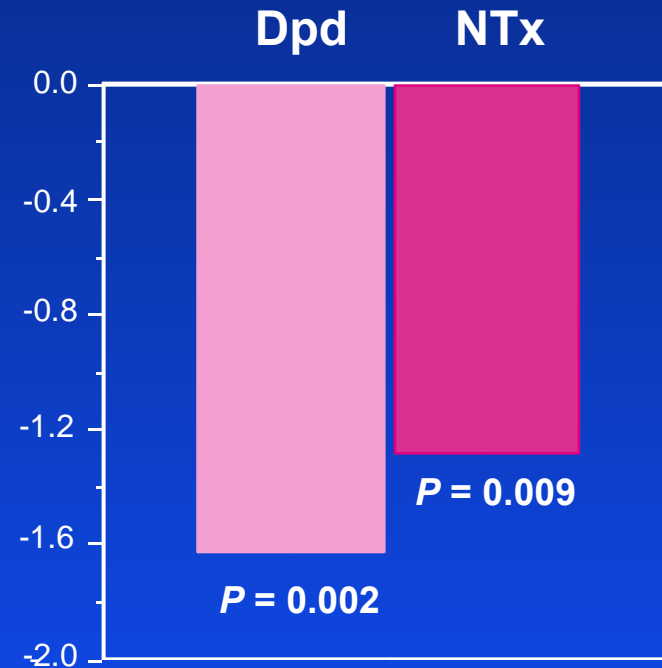
Mean \pm sem

Influence of Variability on Interpretation of Response to Alendronate

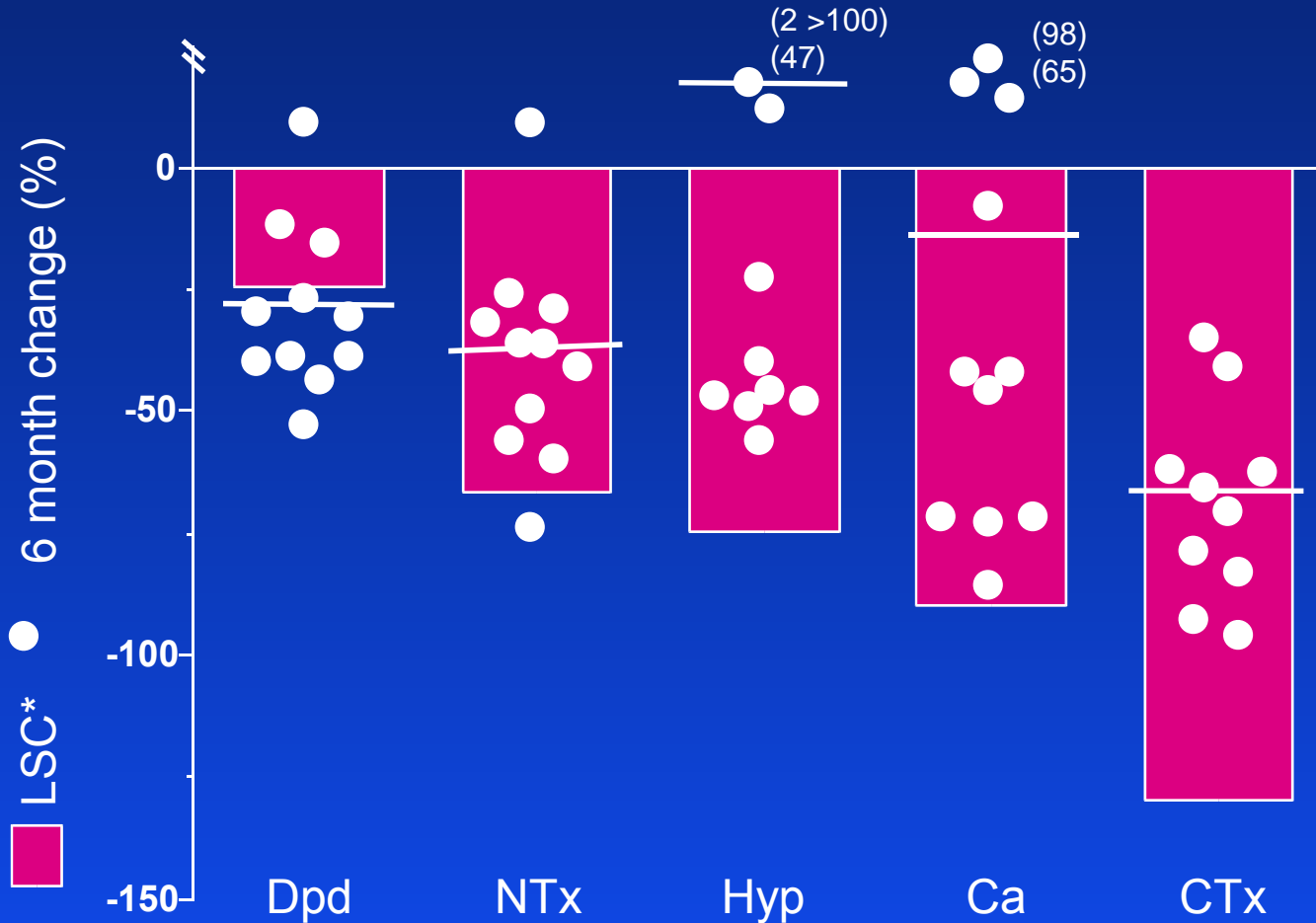
Percent Change



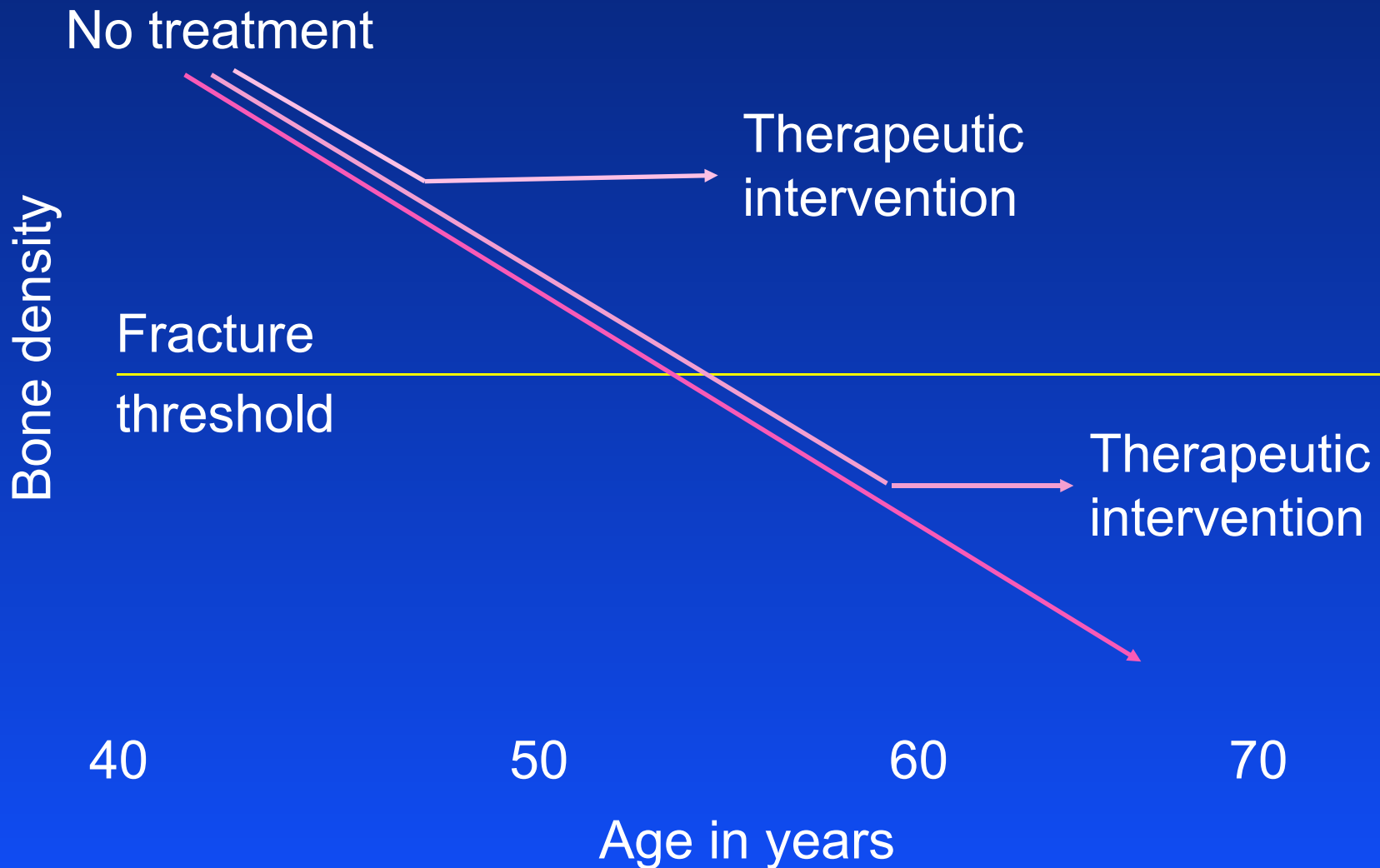
T-score Change



Effect of Assay Analytical and Day-to-Day Variability on Interpretation of Response to HRT



Timing of Initiation of Antiresorptive Therapy Is Important



Case Study

57-year-old postmenopausal woman

- Normal bone mass
- Mother died at age 74 of complications following hip surgery
- Increased bone resorption (elevated Dpd)

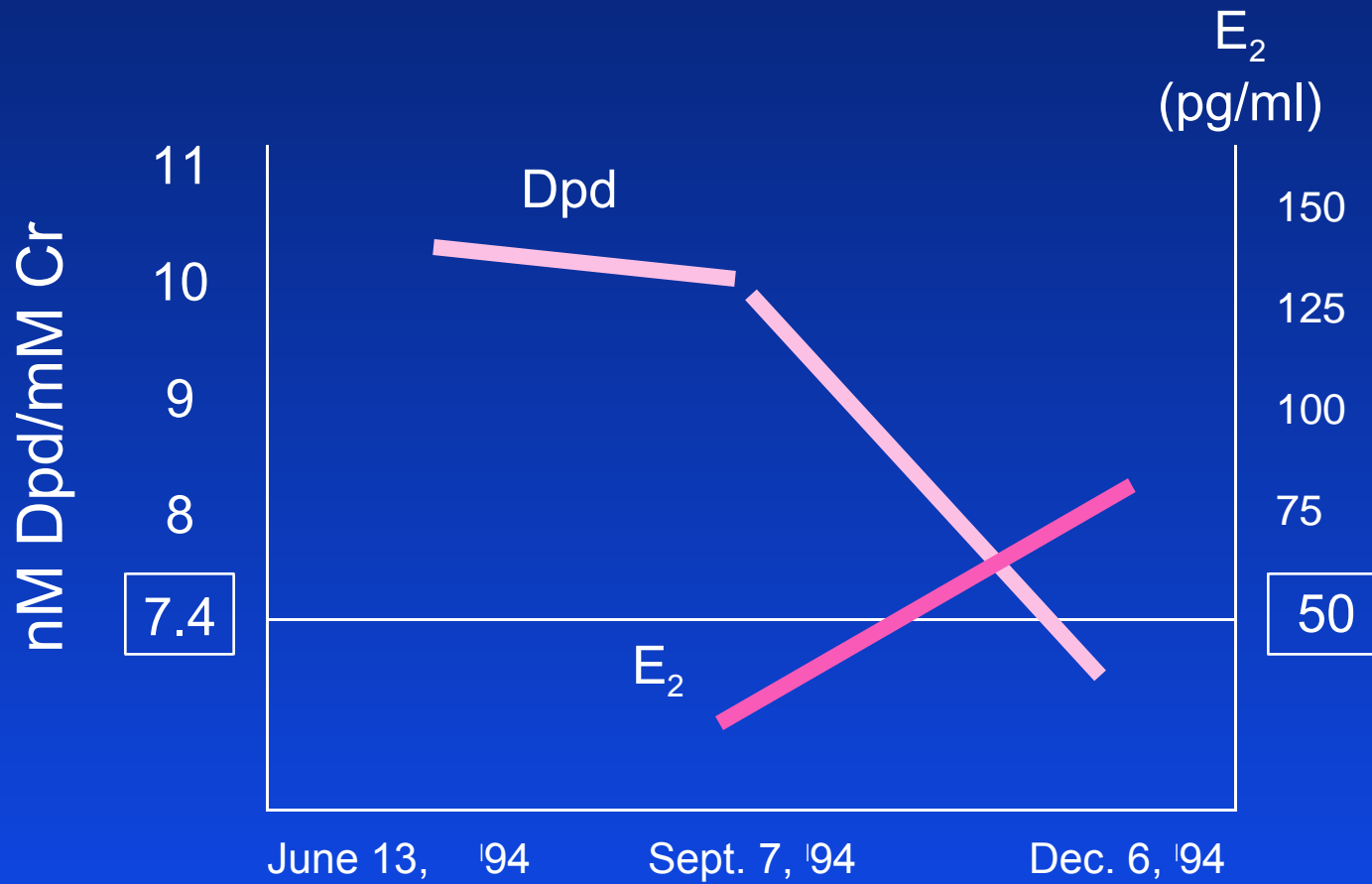
3 months after HRT prescribed

- Serum estradiol low
- Dpd still elevated
- Noncompliance suspected

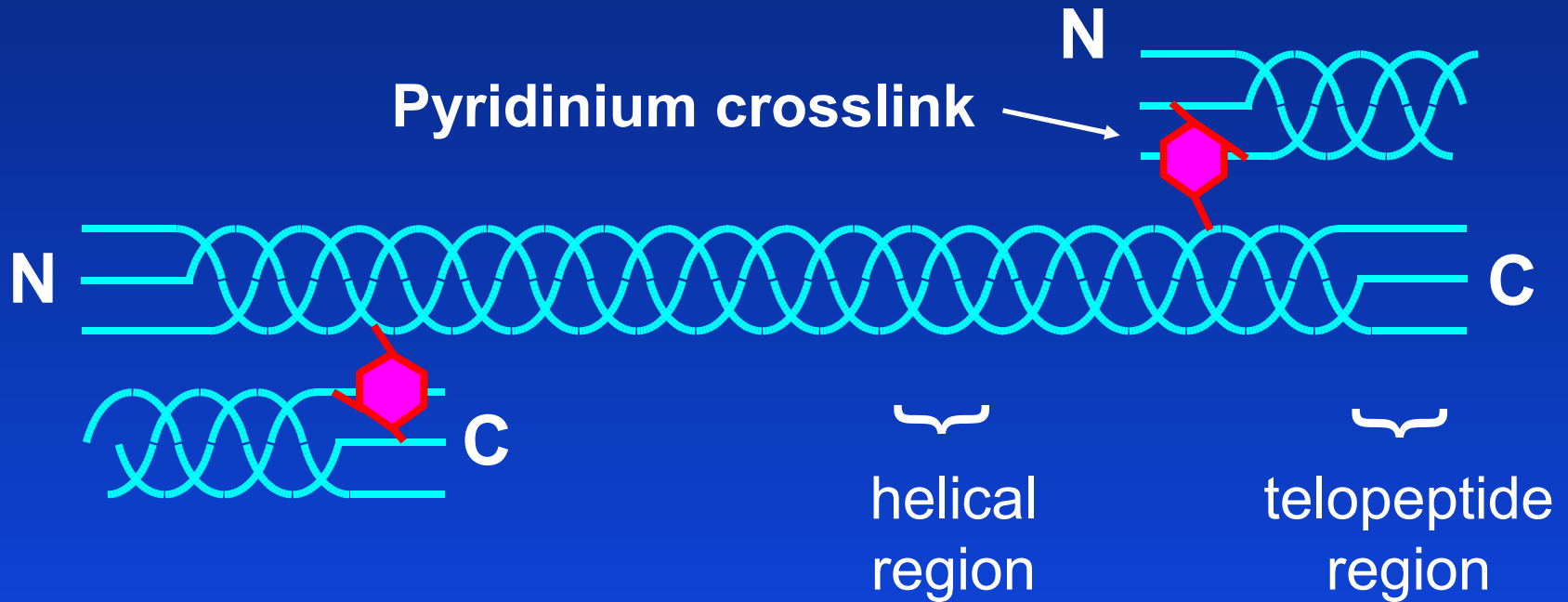
3 months later, after transdermal HRT and counseling

- Dpd normalized
- Serum estradiol returned to premenopausal level

Case Study



Pyridinium Crosslinking in Bone Collagen



Molecular Structure of the Pyridinium Crosslinks of Collagen



Pyridinoline

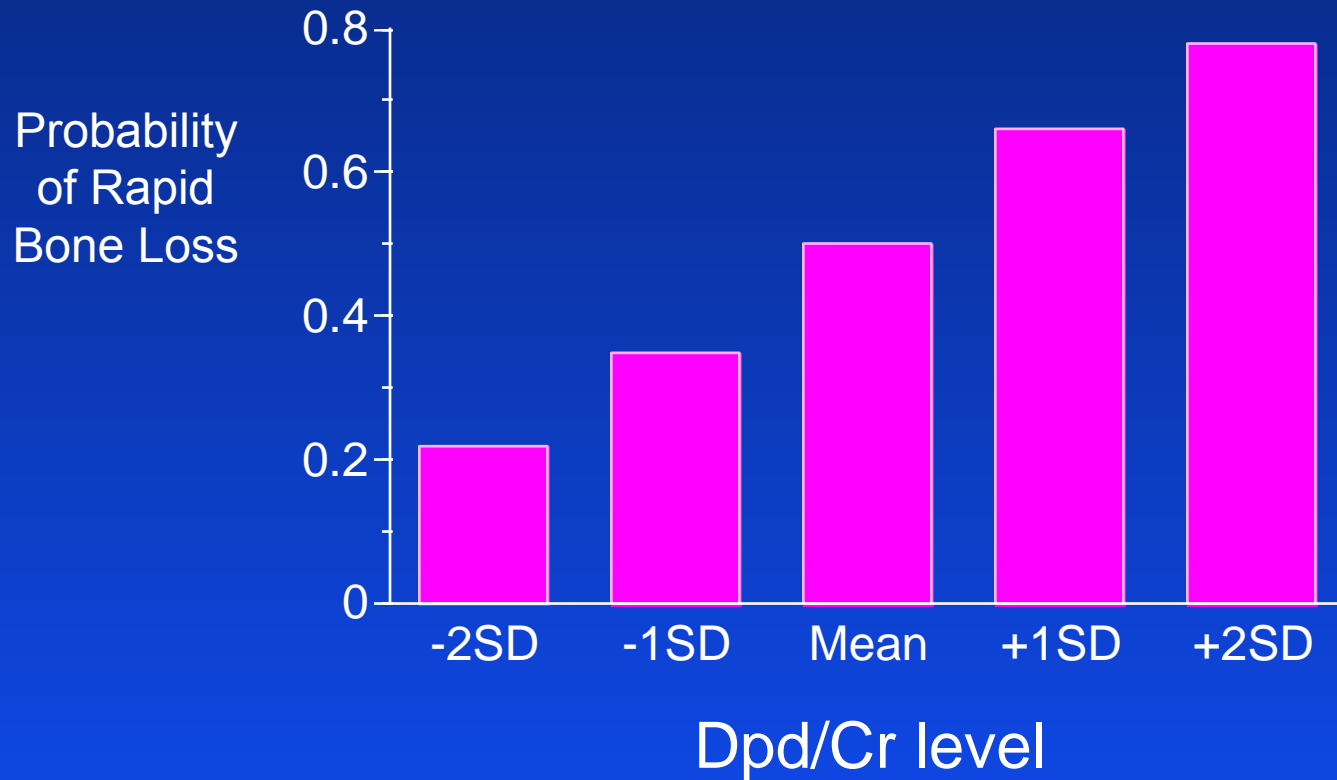


Deoxypyridinoline

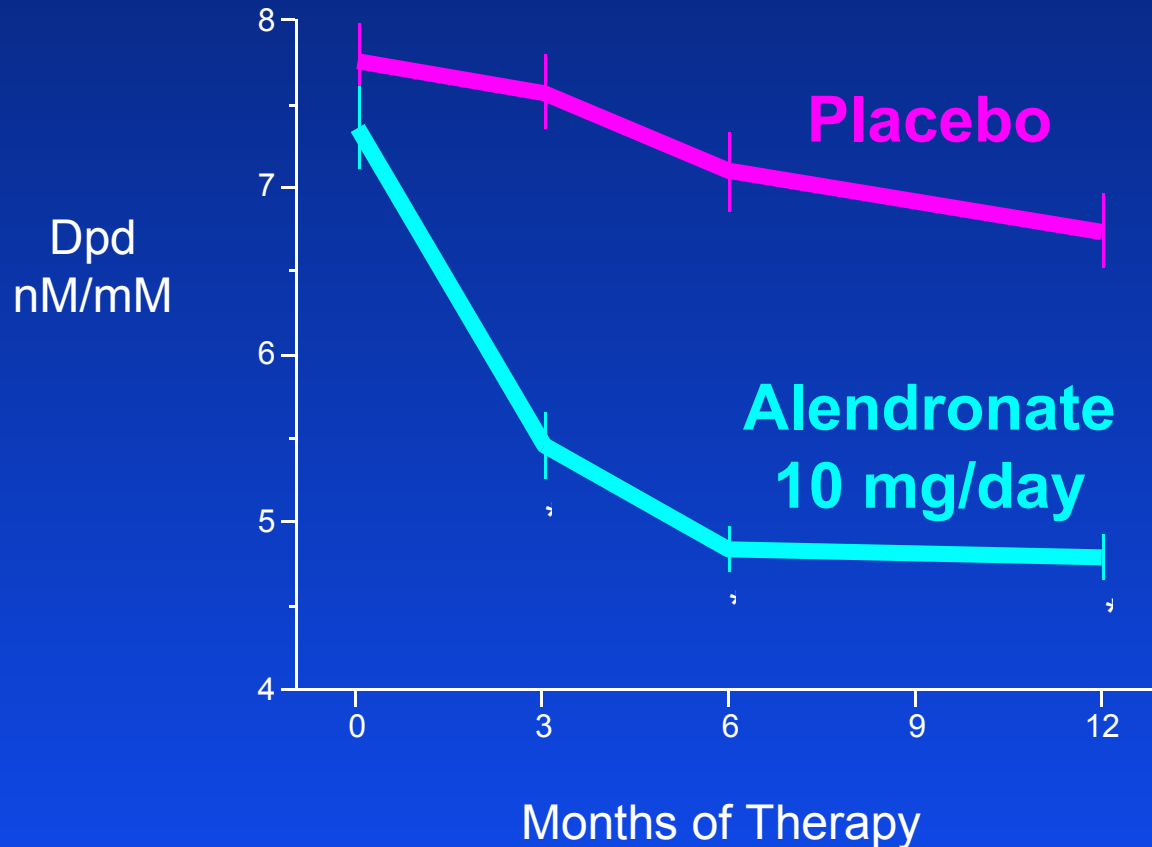
Dpd is Associated with Rapid Bone Loss

Hawaii Osteoporosis Study

13.4 Years Average Follow-up



Dpd Reflects Antiresorptive Effect of Alendronate in Osteoporotic Women

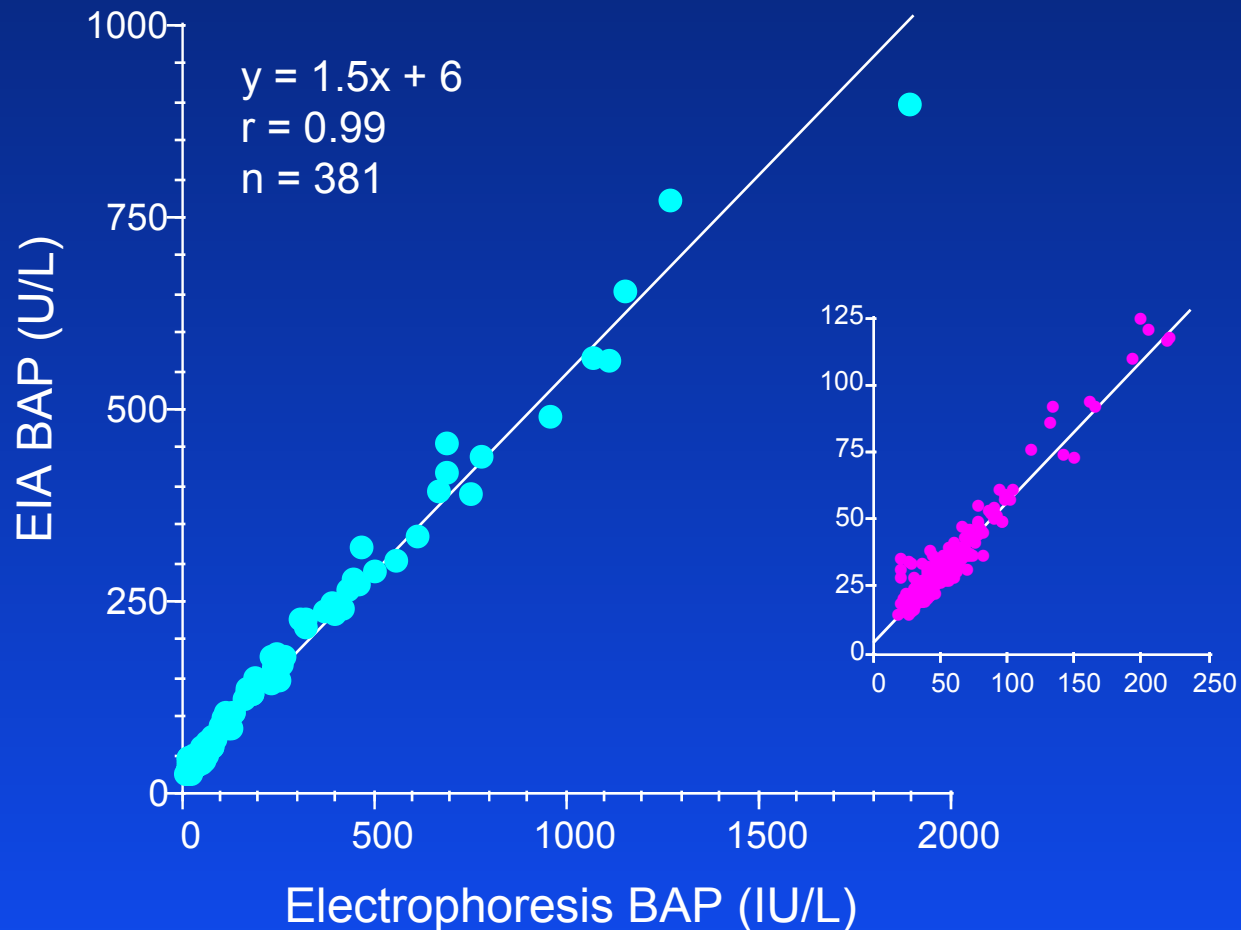


* $p < 0.00001$ compared to placebo; N=360; all subjects received calcium supplements (500 mg/day)
Data on file, Metra Biosystems; Source: Merck Research Laboratories

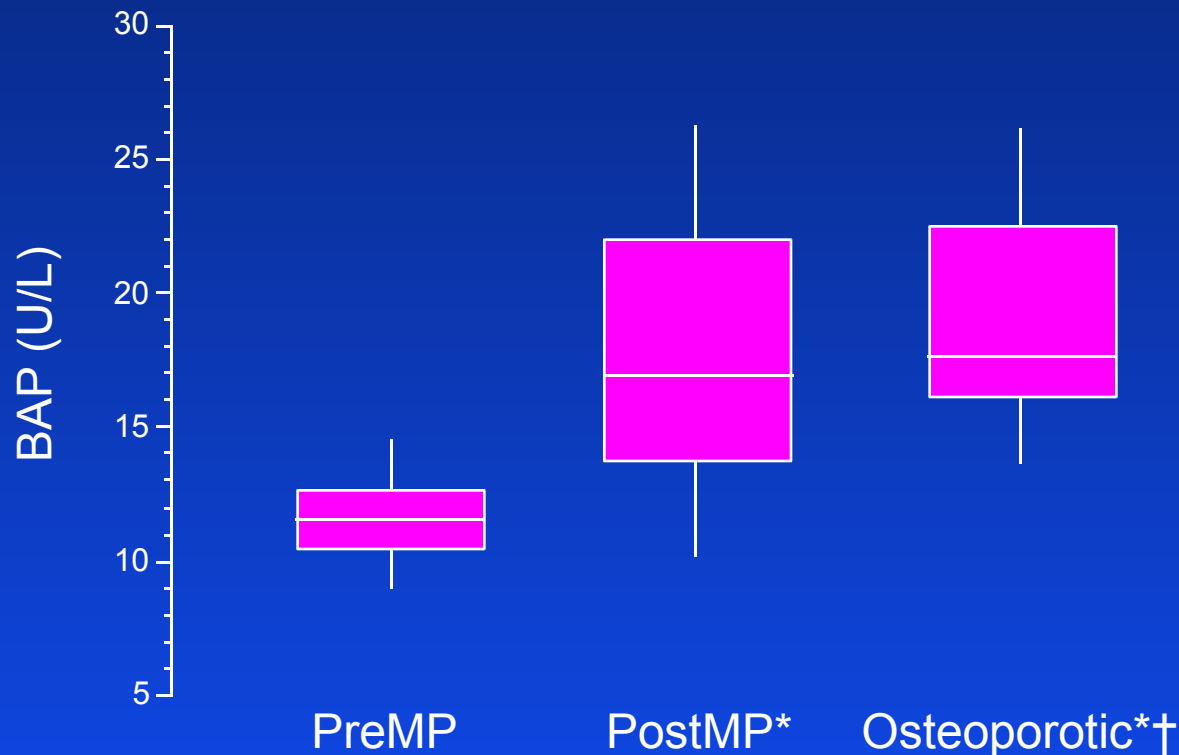
A Sensitive and Specific EIA for Bone Alkaline Phosphatase (BAP)

- Identifies rapid bone losers
- Monitors efficacy of HRT, bisphosphonates
- Unaffected by renal insufficiency
- Very low cross-reactivity with liver alk. phos.
- Highly correlated with electrophoresis and IRMA

EIA BAP is Highly Correlated with BAP Determined by Electrophoresis



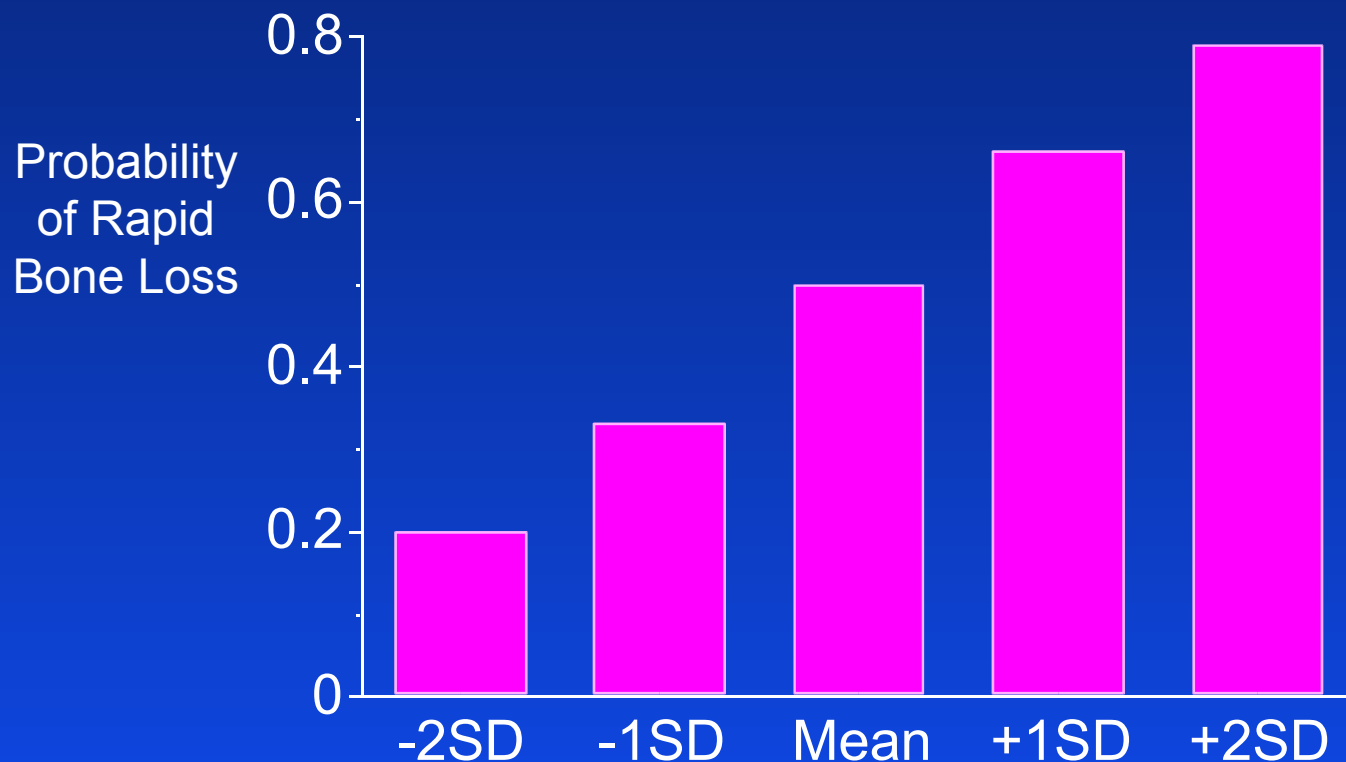
BAP Is a Sensitive Indicator of Increased Bone Turnover in Healthy and Osteoporotic Postmenopausal Women



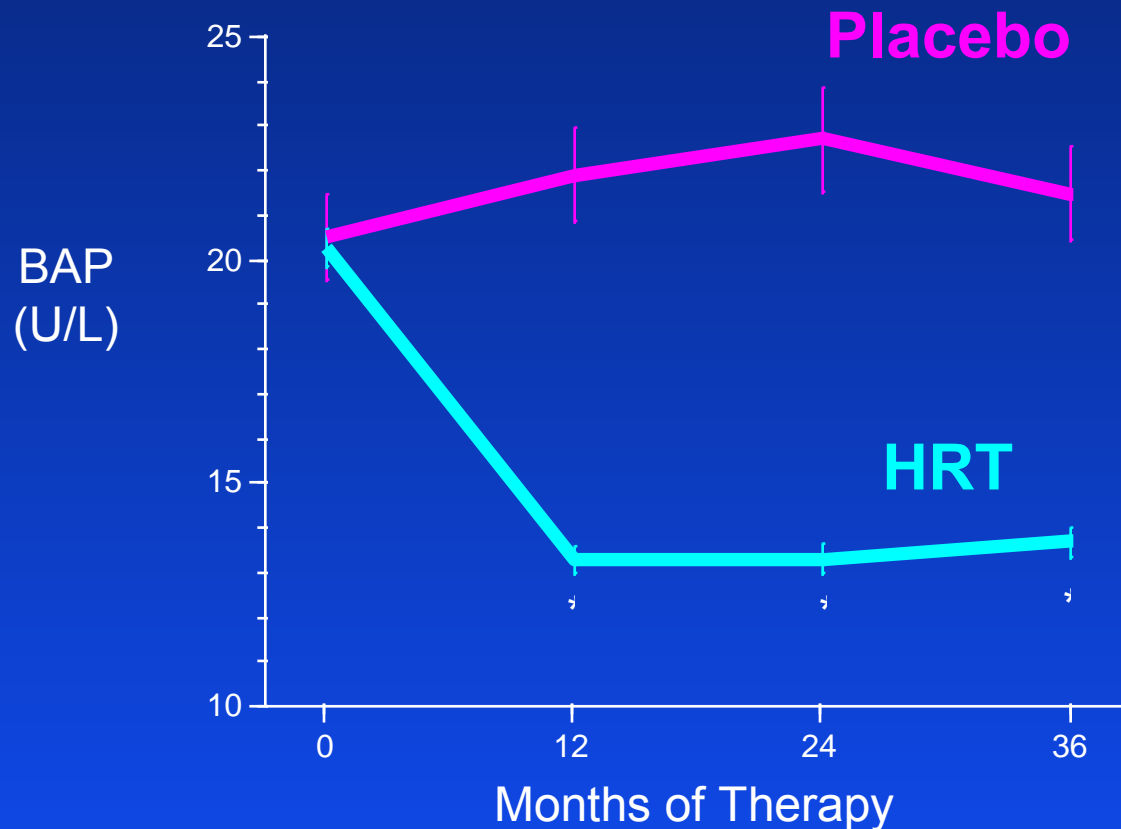
* $p < 0.01$ compared to PreMP; † $p < 0.05$ compared to PostMP
Pedrazzoni et al. *Calcif Tissue Int* 1996;59:334-8

BAP is Associated with Rapid Bone Loss

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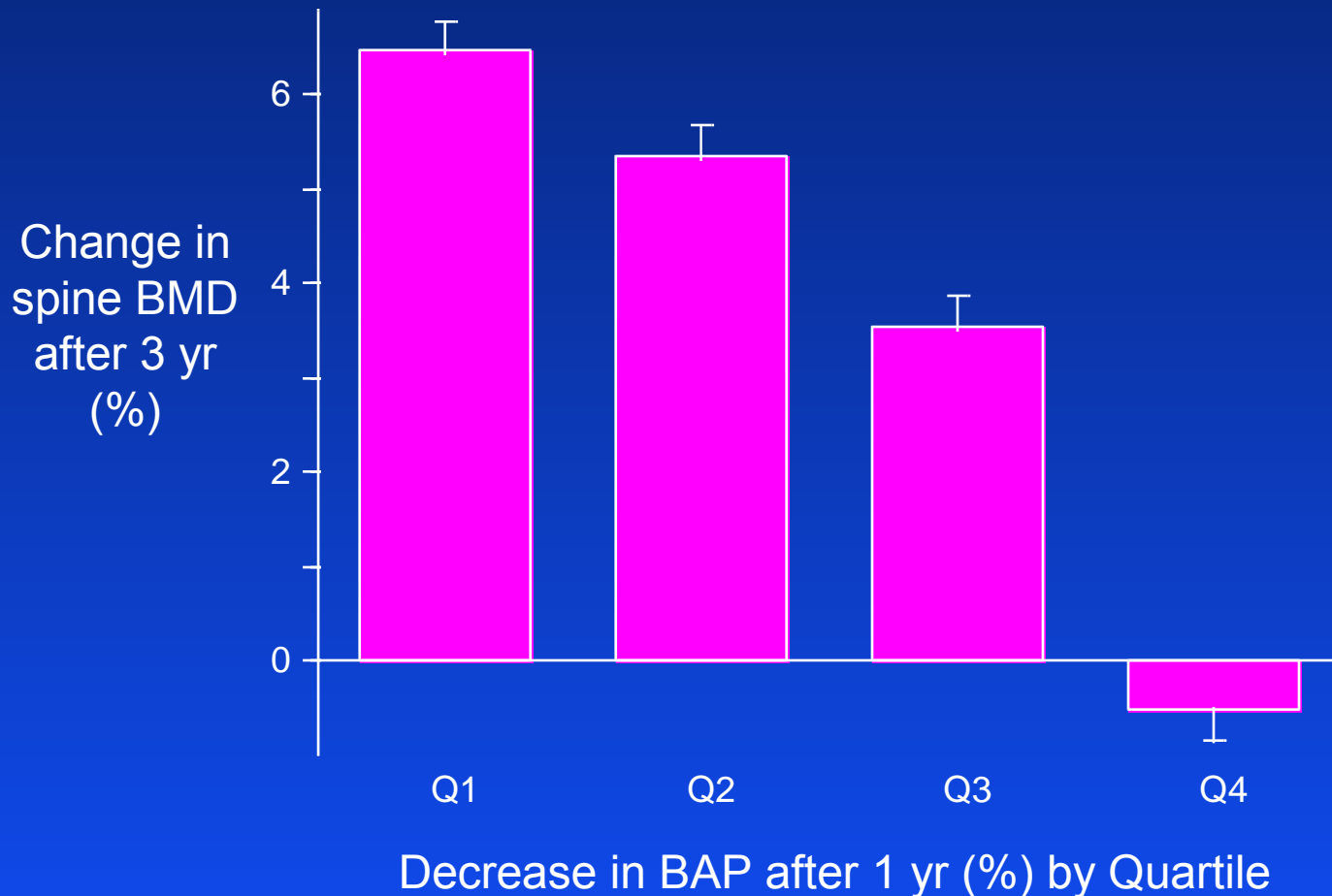
BAP Reflects Antiresorptive Effect of HRT in Postmenopausal Women



* $p < 0.00001$ compared to placebo; placebo $n = 61$, HRT $n = 269$

Data on file, Metra Biosystems; Source: Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial

Change in BAP Predicts BMD Change in HRT- & Placebo-treated Women



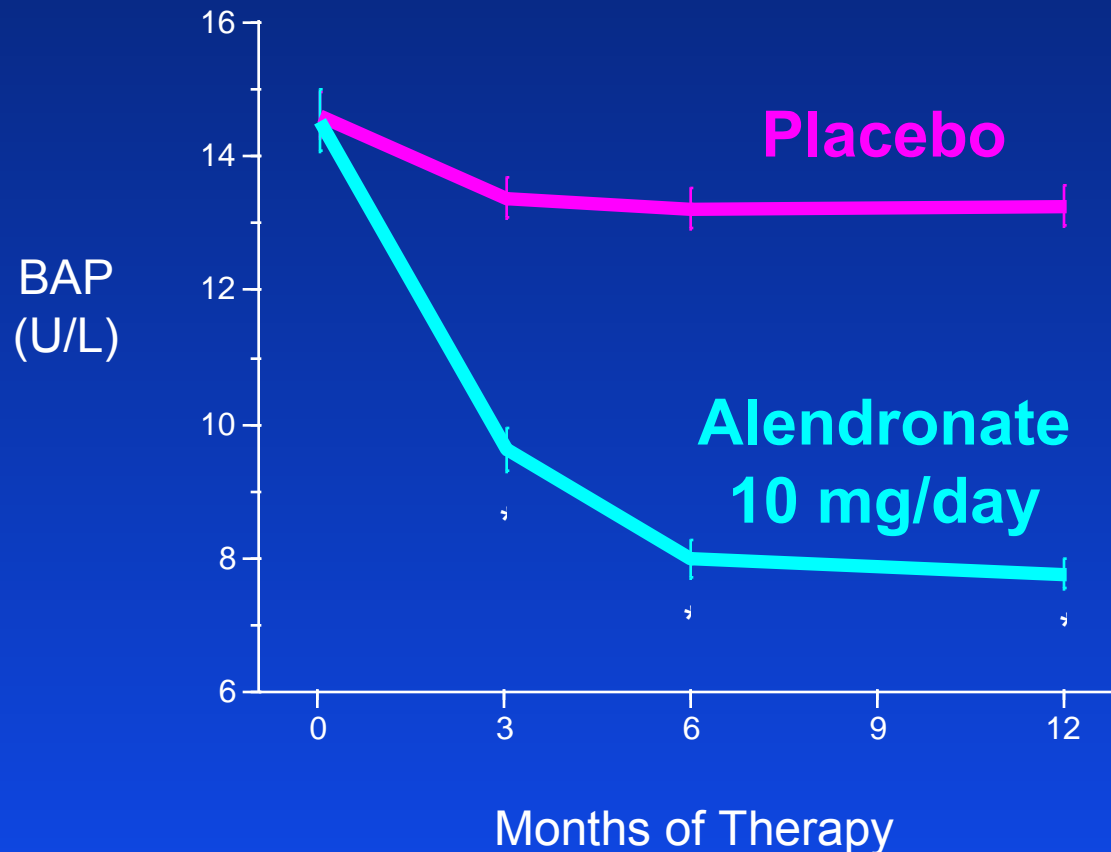
BAP Rapidly Identifies More Responders to HRT than BMD

Time (mo)	% Identified as Responders	
	12	36
%Δ BAP		
< 0	96	
< -1 x CV*	92	
< -2 x CV	85	
%Δ LS BMD		
> 0	91	93
> 1 x CV *†	80	86
> 2 x CV	69	78

* median intraindividual CV of placebo-treated women; † LS BMD CV corrected for slope of 3-yr change
n=264 postmenopausal women receiving hormone replacement therapy (HRT)

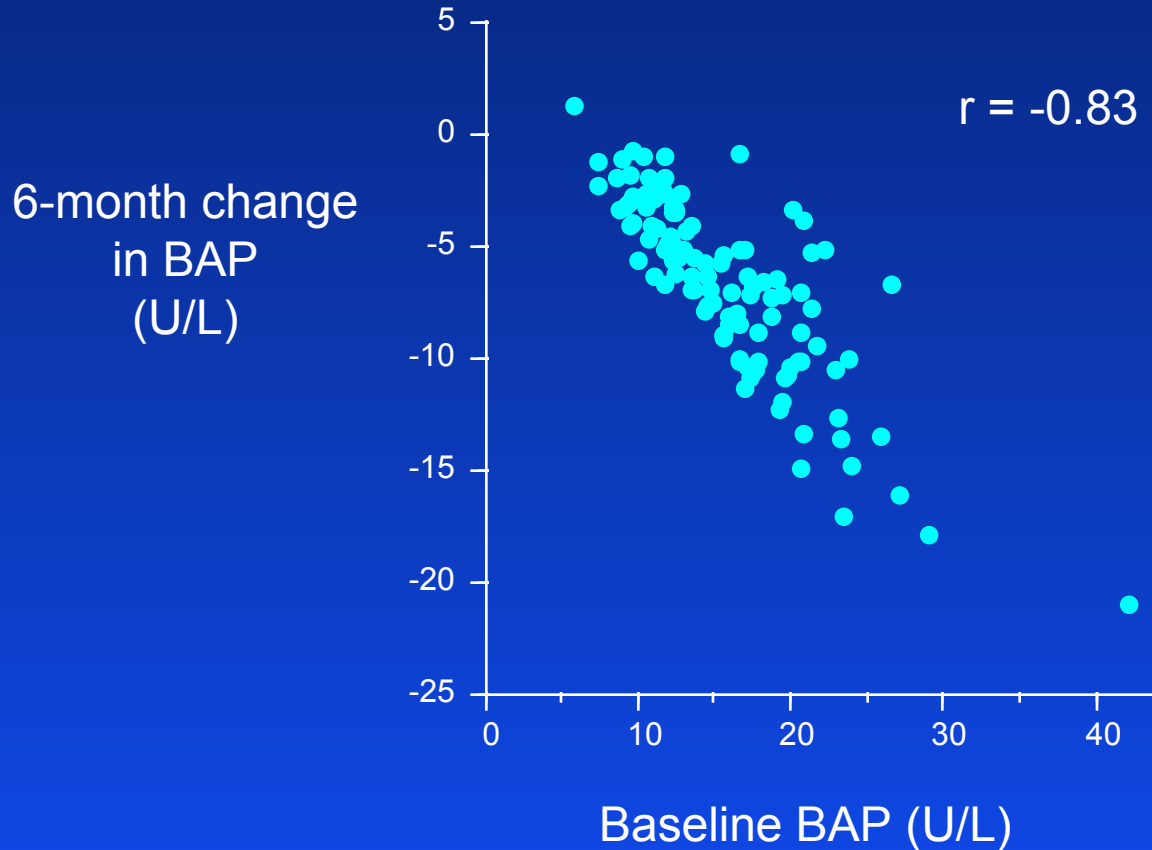
Data on file, Metra Biosystems; Source: Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial

BAP Reflects Antiresorptive Effect of Alendronate in Osteoporotic Women



Mean \pm SEM; * $p < 0.00001$ compared to placebo; placebo n = 180, alendronate n = 134; all subjects received calcium supplements (500 mg/day)
Data on file, Metra Biosystems; Source: Merck Research Laboratories

Baseline Bone Turnover Predicts Turnover Response to Alendronate



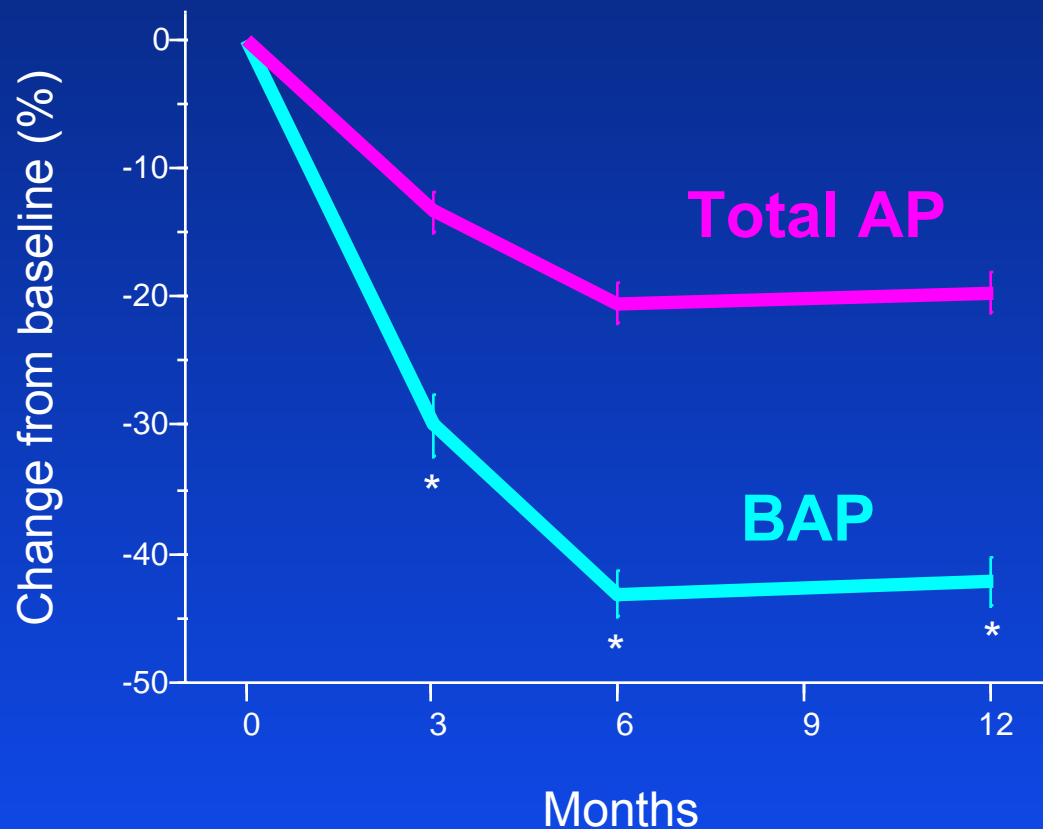
N=126 osteoporotic women received alendronate 10 mg/day and calcium supplements (500 mg/day)
Data on file, Metra Biosystems; Source: Merck Research Laboratories

Response to Alendronate Is More Rapidly Identified by BAP than by BMD

Time (mo)	Percent Identified as Responders					
	3	6	12	18	24	36
%Δ BAP						
< 0	95	99	98			
< -1 x CV*	94	96	96			
< -2 x CV	75	90	86			
%Δ LS BMD						
> 0	72	87	91	92	95	96
> 1 x CV*	56	72	83	83	90	91
> 2 x CV	33	49	65	73	77	80

* median intraindividual CV of placebo-treated women; 10% for BAP, 1.9% for LS BMD
n=134 osteoporotic women receiving alendronate (ALN) 10 mg/day and calcium 500 mg/day
Data on file, Metra Biosystems; Source: Merck Research Laboratories

BAP Is More Sensitive Than Total AP to Alendronate in Osteoporosis



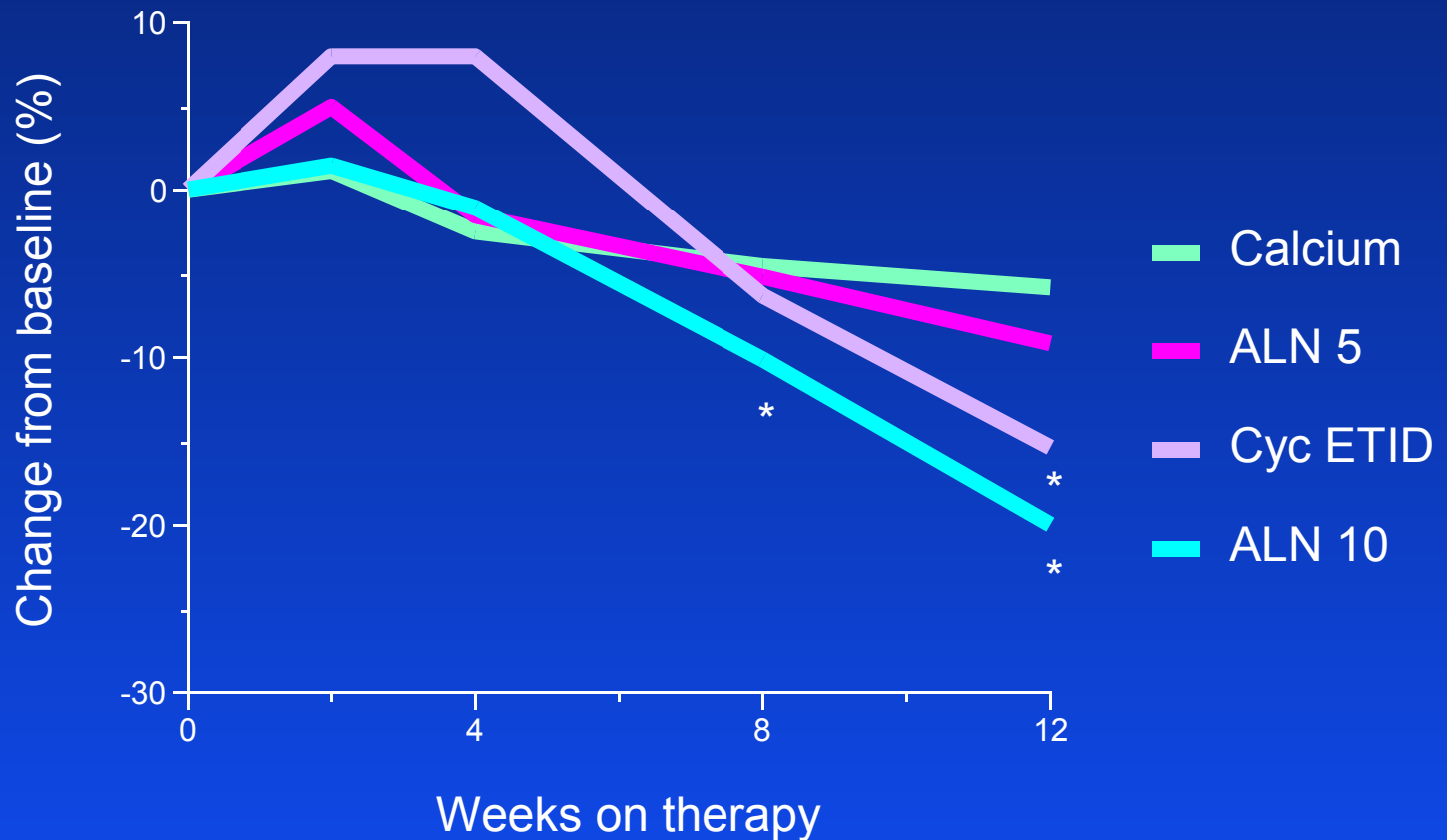
Mean \pm SEM; * $p < 0.00001$ for change in BAP compared to change in total AP, N=121
Data on file, Metra Biosystems; Source: Merck Research Laboratories

BAP Is More Sensitive than Total AP for Identifying Responders to Alendronate

Time (mo)	% Identified as Responders	
	3	6
%Δ BAP		
< 0	95	99
< -1 x CV*	94	95
< -2 x CV	75	89
%Δ Total AP		
< 0	83	86
< -1 x CV*	72	81
< -2 x CV	55	71

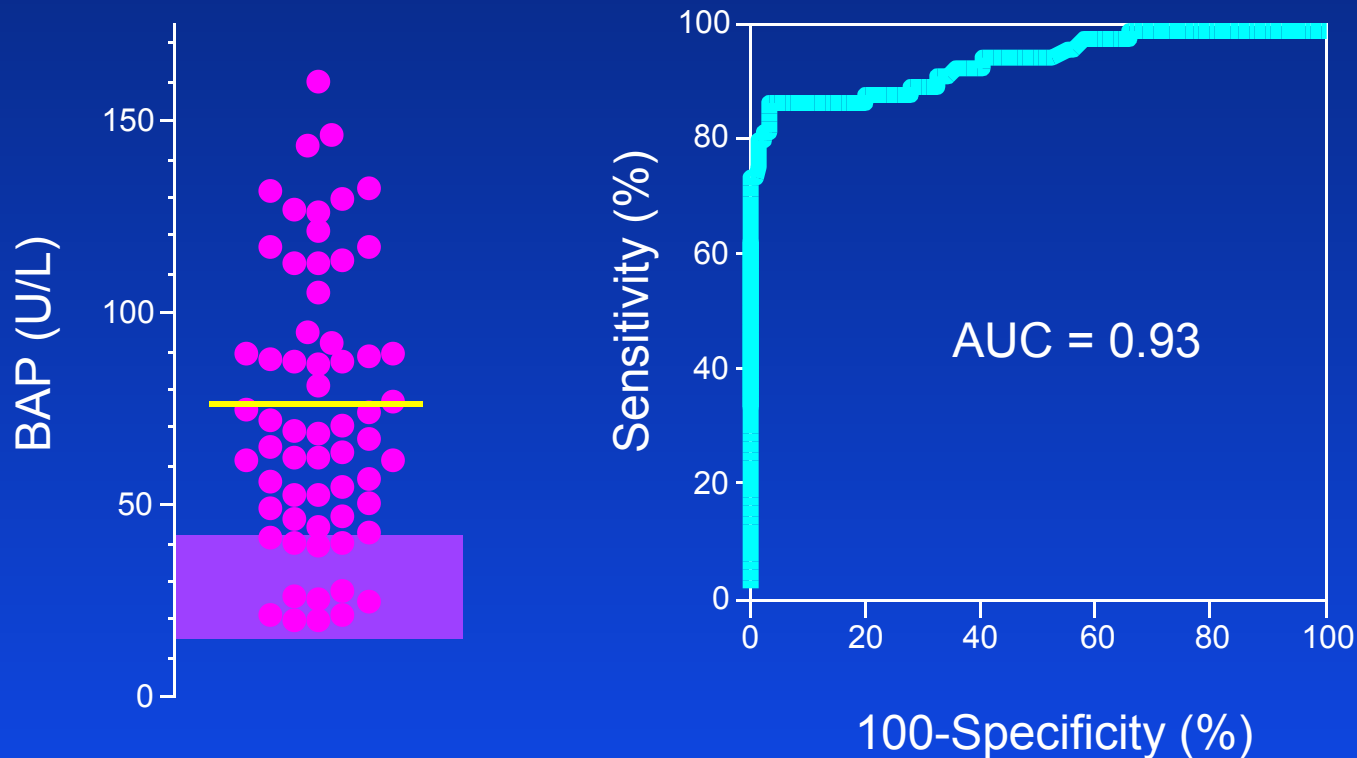
* median intraindividual CV of placebo-treated women; 10% for BAP, 7% for total AP
 n=120 osteoporotic women receiving alendronate (ALN) 10 mg/day and calcium 500 mg/day
 Data on file, Metra Biosystems; Source: Merck Research Laboratories

BAP Responds to Antiresorptive Therapy as Early as 8 Weeks

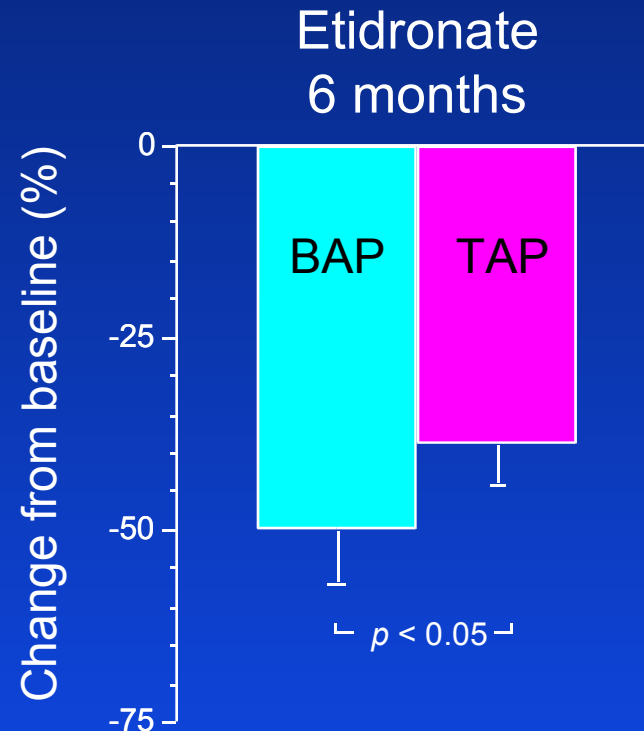
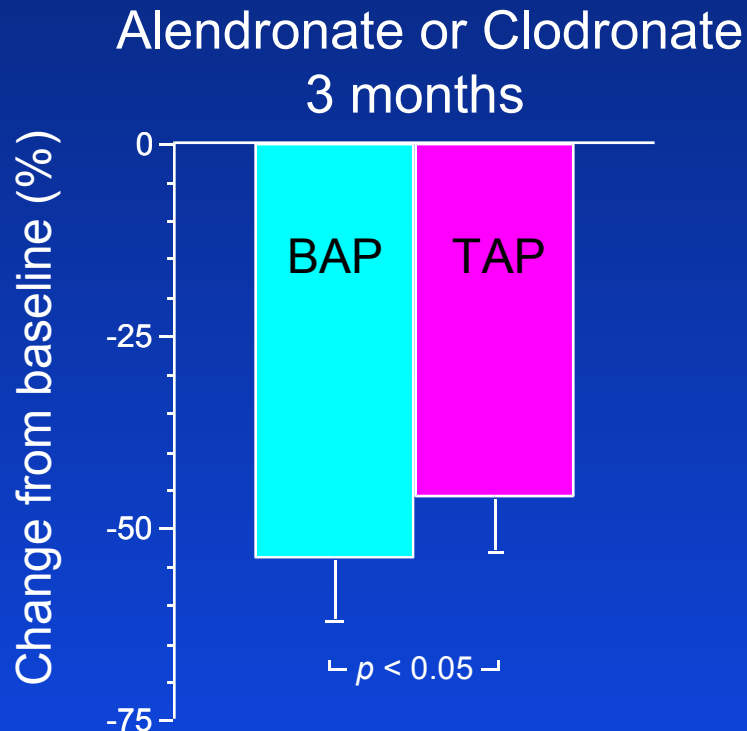


* $p < 0.05$ compared to baseline

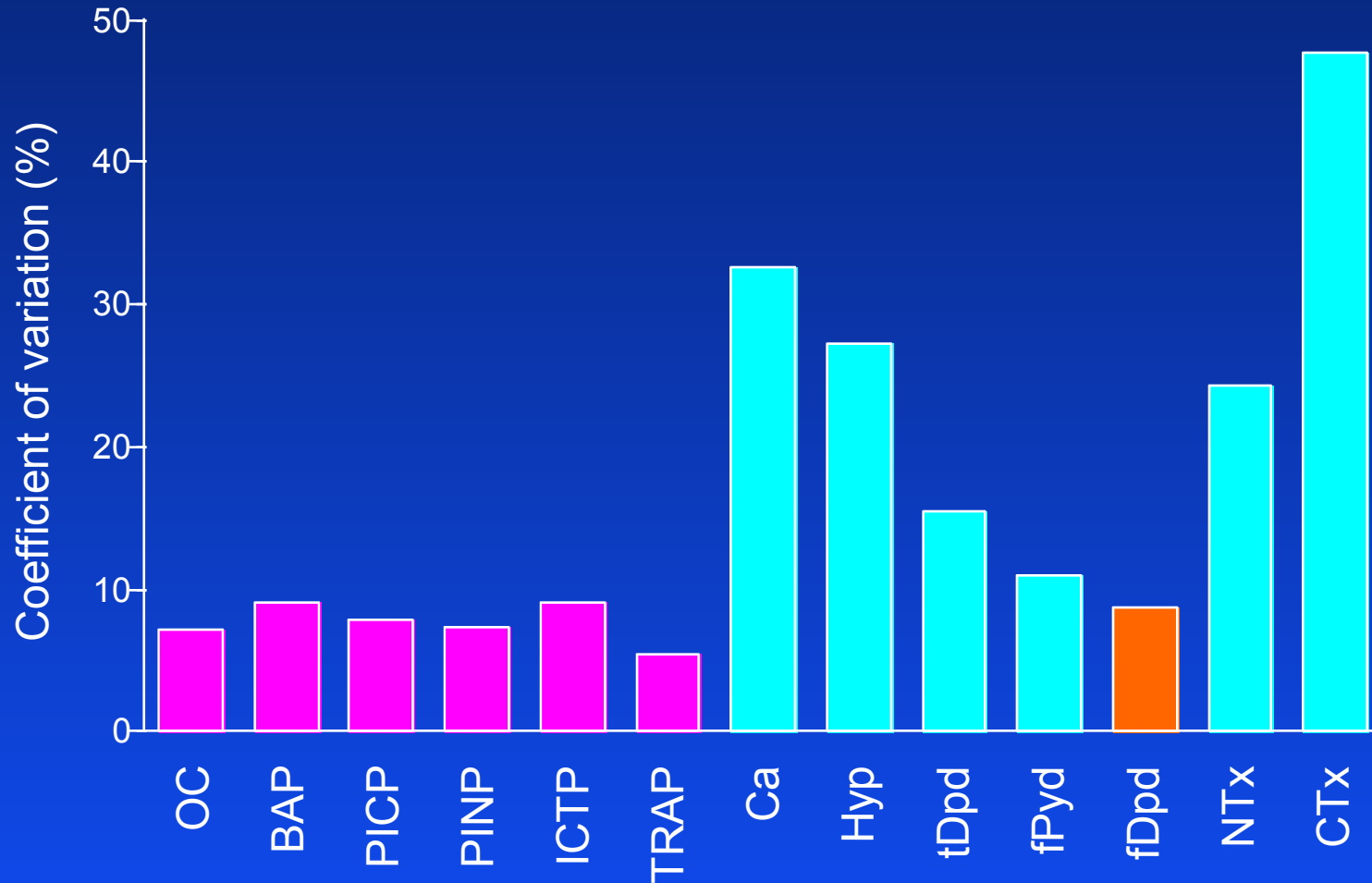
BAP Exhibits Diagnostic Accuracy Even in Mild Paget's Disease (Total AP <2X Upper Limit of Normal)



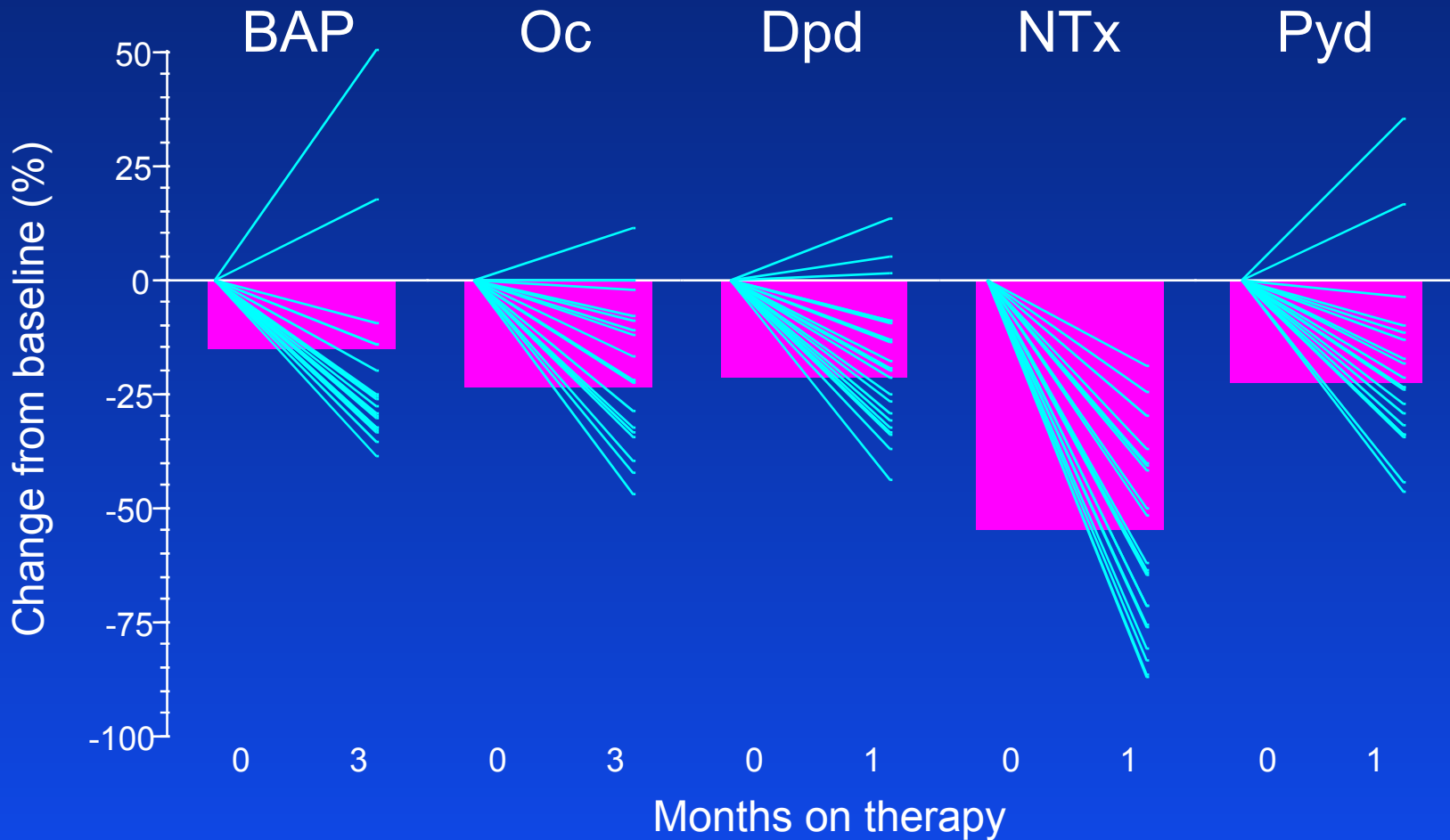
BAP Is More Sensitive than TAP to Bisphosphonates in Paget's Disease



Serum Markers Exhibit Lower Long-term Variability than Most Urine Markers



Individual Response to Pamidronate Therapy Relative to Minimum Significant Change



BAP Therapeutic Response Is Much Greater than Long-term Variability

	Long-term Variability*	Treatment Response†
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Postmenopausal

Women

9%

36% HRT

Osteoporotic

Women

10%

43% Alendronate

* Median CV in placebo-treated women followed 4X in 3 yr (HRT study) or 4X in 1 yr (alendronate study)

† Median decrease following 12 months of therapy

Data on file, Metra Biosystems

Measuring BAP Improves Patient Management

- Identify patients at risk for significant bone loss
- Monitor antiresorptive therapy
- Improve patient compliance by demonstrating benefits of therapy
- Follow the clinical course of bone disease

Interpretation of BAP Assay Results

Cut-off level – 30 U/L for women – determined in healthy, premenopausal population not losing bone

Identification

Values above 30 indicate risk for bone loss

Monitoring

Values below 30 or a change of $\geq 20\%$ after 3-6 months indicate therapeutic efficacy