An Update on Bone Markers in Metabolic Bone Disease

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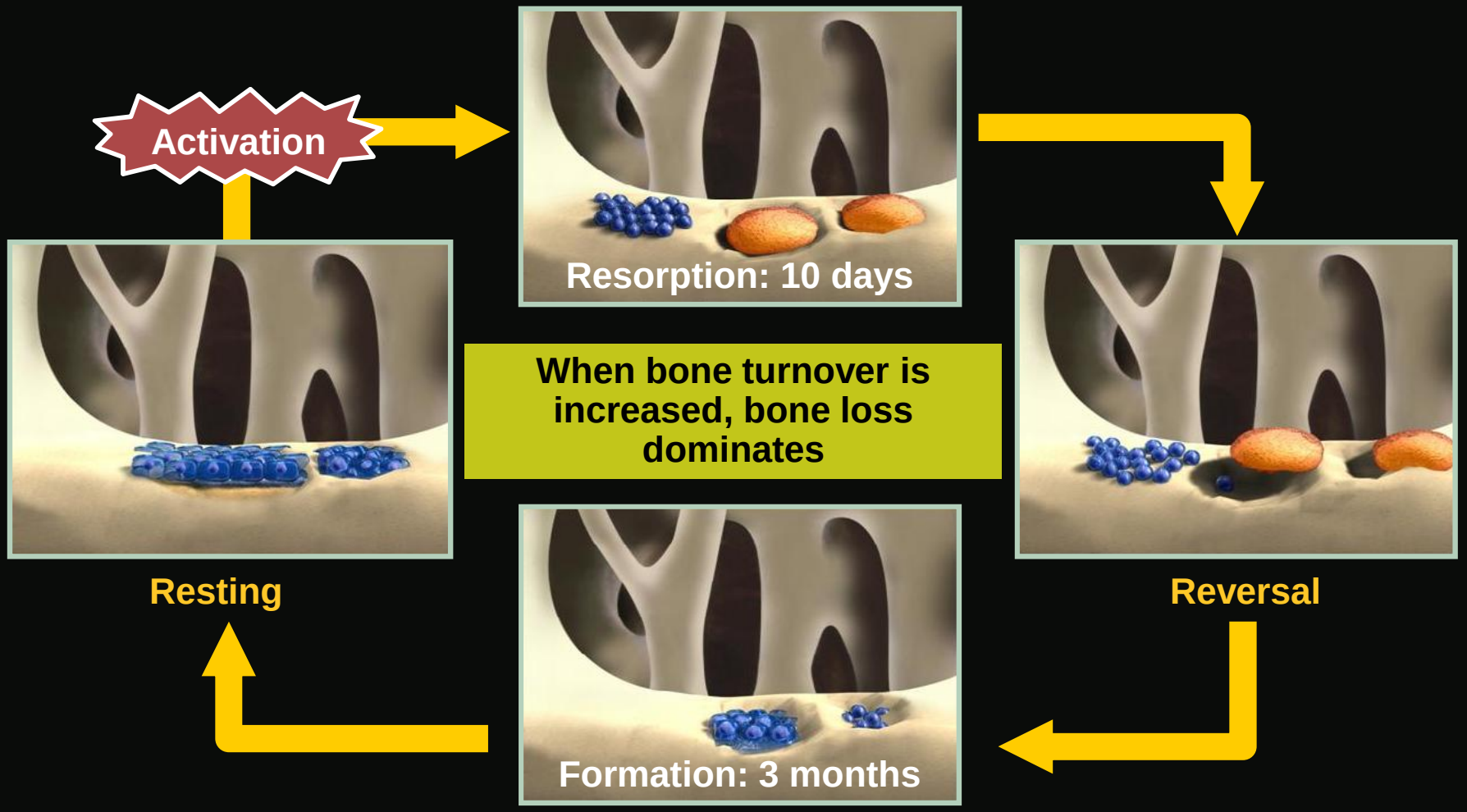
A Healthy Skeleton Requires a Balance of Bone Resorption and Bone Formation



Baron R. *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism.* 5th ed. 2003:1-8. Bringhurst FR, et al. *Harrison's Principles of Internal Medicine*. 16th ed. 2005:2238-2249.
Lindsay R, et al. *Treatment of the Postmenopausal Woman: Basic and Clinical Aspects.* 2nd ed. 1999:305-314.

Biochemical Markers of Bone Metabolism

Bone Cell Function

Bone Metabolism

Bone/Collagen Metabolism Cell Function

- **Resorption**

  Collagen Crosslinks PYD/DPD

  Telopeptides NTX/**CTX**

  Cross-linked C-terminal Telopeptide 1CTP

  Acid Phosphatase (TRAP5b)

  Hydroxyproline

  Calcium

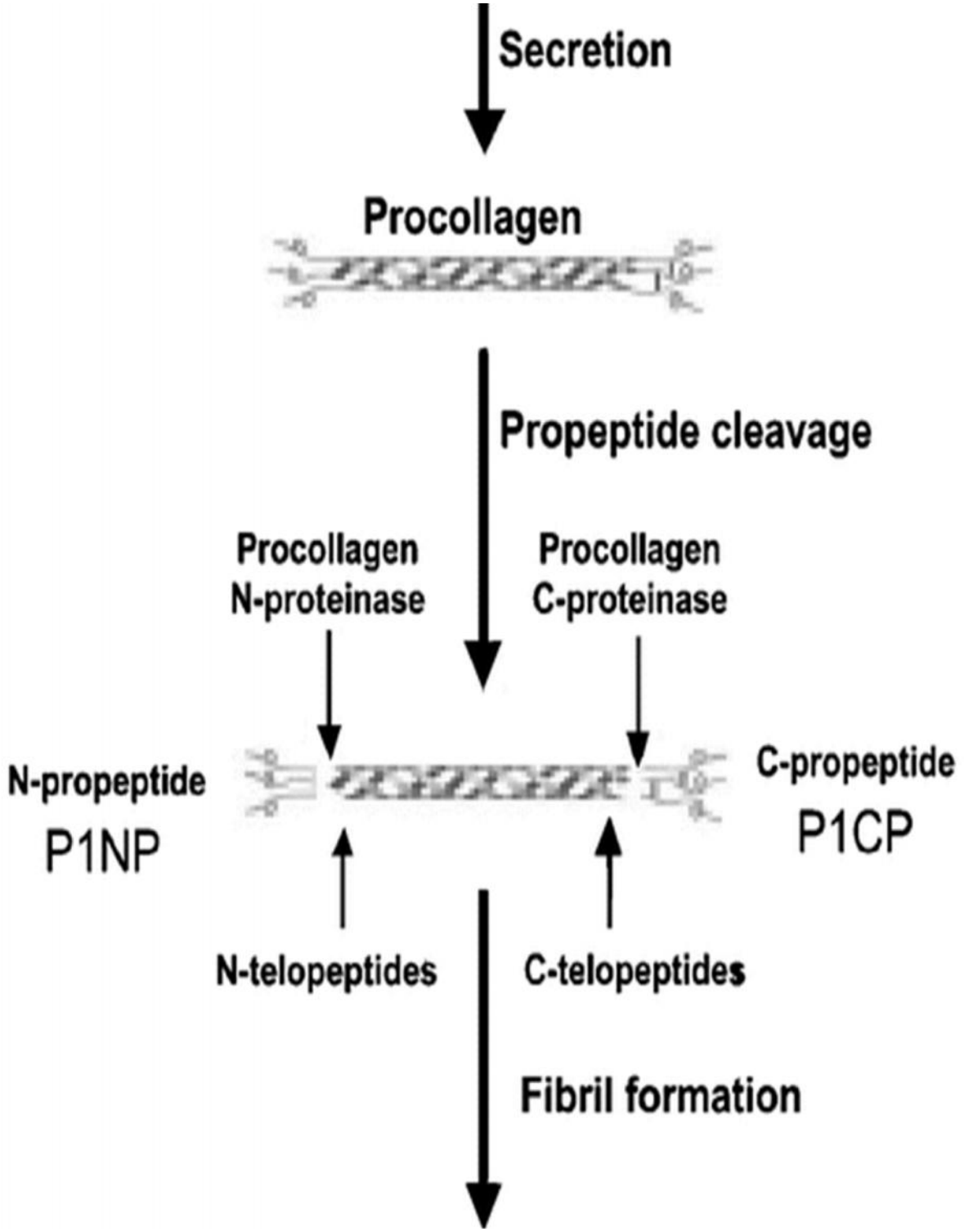
- **Formation**

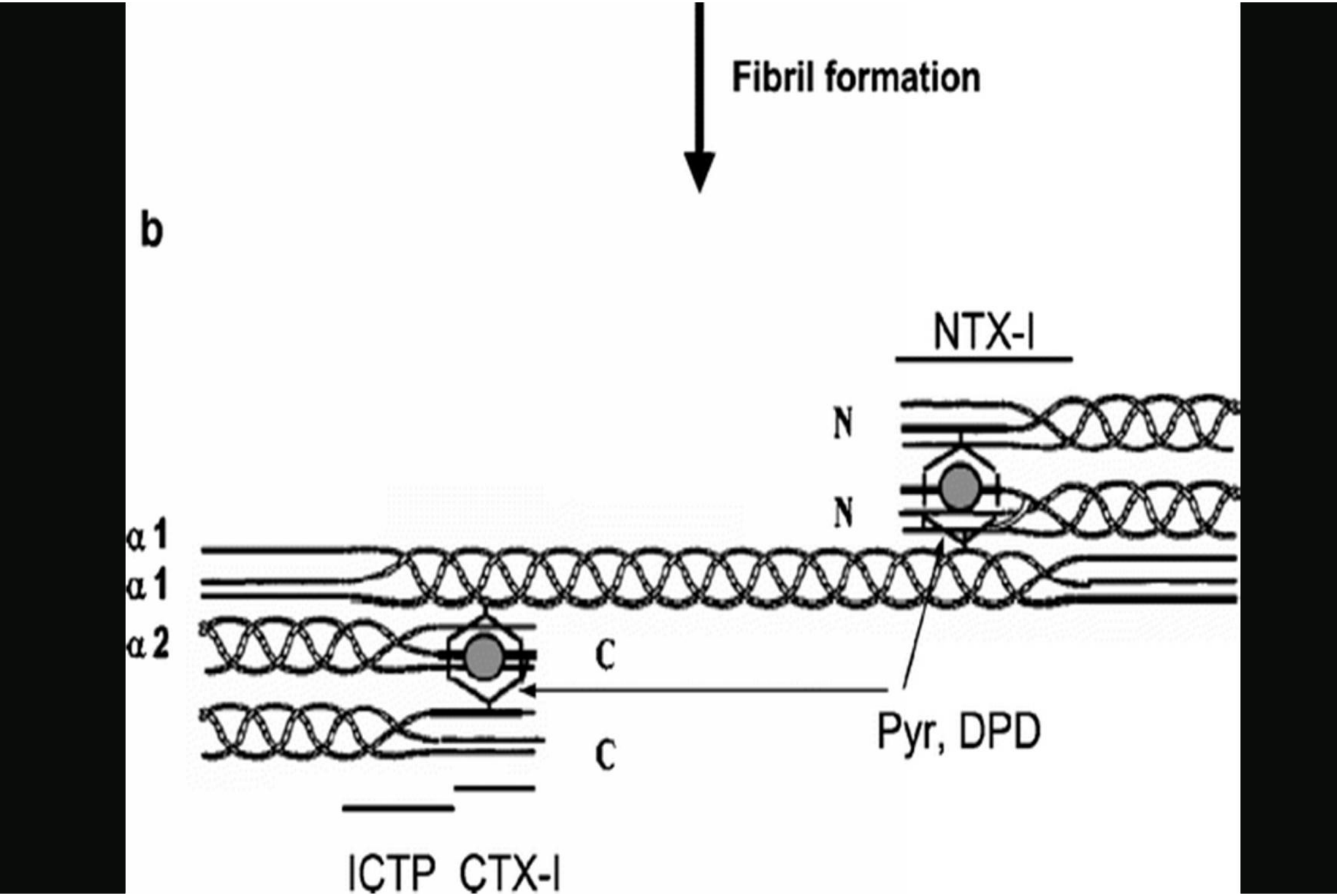
  Alkaline Phosphatase

  Osteocalcin

  Pro-collagen Peptides P1CP/**P1NP**

a

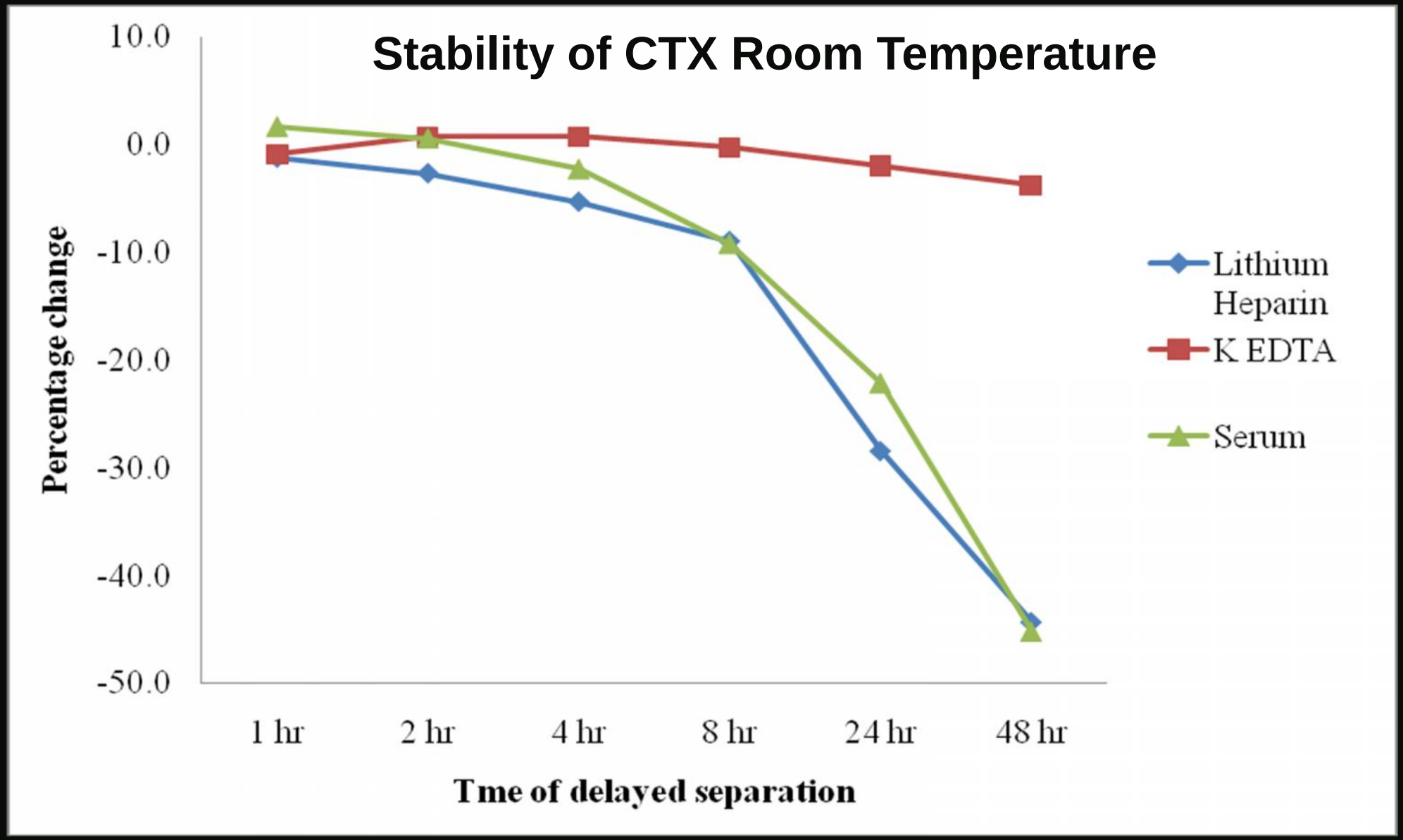

Secretion
Procollagen
Propeptide cleavage
Procollagen
N-proteinase
Procollagen
C-proteinase
N-propeptide
P1NP
C-propeptide
P1CP
N-telopeptides
C-telopeptides
Fibril formation


Fibril formation
b
NTX-I
N
N
α1
α1
α2
C
C
Pyr, DPD
ICTP CTX-I

Analytical Aspects of Bone Markers

The Importance of Sample Type and Timing

Bone Marker Automation



Stokes F et al Clin Chem 2011

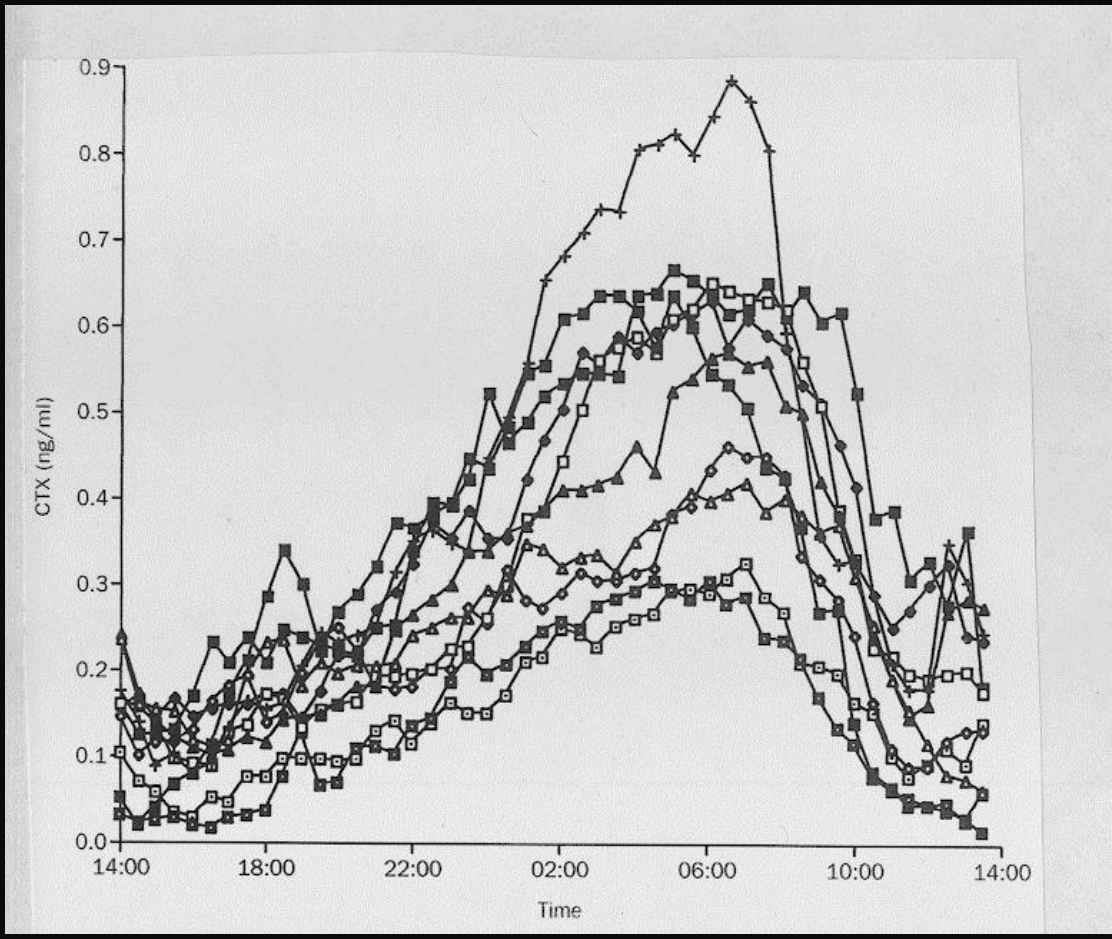
Stability of Markers Separated and Stored in the Fridge

		48 hrs	7 days	14 days	28 days
Bone ALP :Serum		102.6 ± 12.0	102.6 ± 8.1	101.3 ± 7.7	100.8 ± 7.5
βCTx: Lith-hep		89.4 ± 4.2*	70.1 ± 5.4*	46.5 ± 3.1*	38.4 ± 8.3*
	EDTA	98.5 ± 3.3	96.4 ± 4.4	91.2 ± 3.1*	89.0 ± 7.3*
	Serum	96.8 ± 4.3	88.8 ± 11.0	77.1 ± 14.4*	63.7 ± 14.7*
OC: Lith hep		95.7 ± 3.2	92.5 ± 3.8	87.7 ± 8.2*	83.5 ± 6.6*
	EDTA	102.9 ± 1.5	100.0 ± 1.9	93.4 ± 5.6	88.4 ± 4.9*
	Serum	94.4 ± 0.98	86.8 ± 2.6*	78.2 ± 7.9*	70.9 ± 11.8*
P1NP: Lith hep		99.6 ± 2.7	101.0 ± 3.3	99.8 ± 3.0	99.1 ± 2.8
	EDTA	99.4 ± 2.1	101.3 ± 2.2	100.3 ± 2.7	97.1 ± 2.4
	Serum	100.0 ± 2.8	100.3 ± 1.6	98.2 ± 1.5	99.7 ± 3.6
PTH: Lith hep		97.8 ± 3.6	96.5 ± 5.6	95.6 ± 5.6	92.2 ± 8.1
	EDTA	94.8 ± 3.9	98.3 ± 3.4	95.5 ± 4.7	91.9 ± 4.2
	Serum	96.0 ± 4.6	88.8 ± 4.1	69.6 ± 13.9*	52.6 ± 19.4*

Stokes F et al Clin Chem 2011

Circadian Rhythm of CTX in Normal Male Subjects

- Circadian rhythm
- Night time/Early morning increase in CTX
- Minimal variability daytime



Fraser et al 2001 Chp 10 in Bone Markers: Eastell, Baumann, Hoyle, Wieczorek Eds

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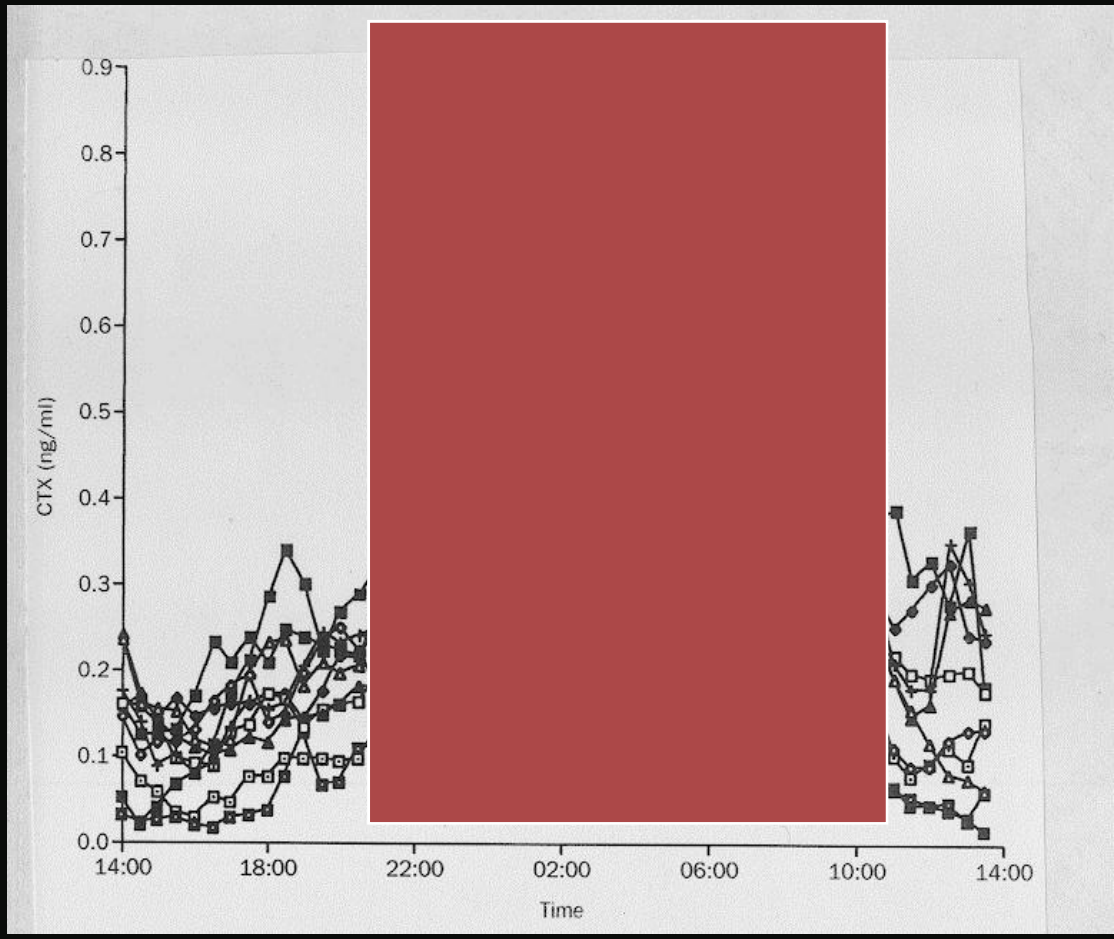
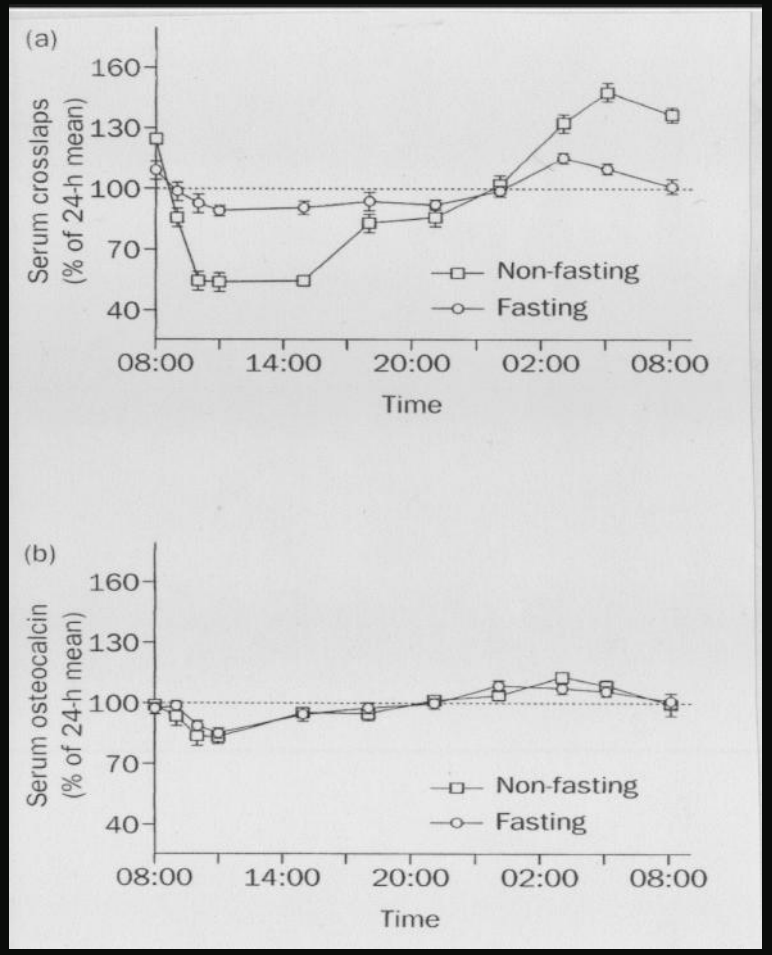


Effect of a Fast

- Fasting all day
- Normalised data
- Nocturnal (8-10h) fast identical to previous data



Christgau S Clin Chem 46: 431; 2000

Sample Type

EDTA PLASMA CTX

- Fasting AM
- Or Afternoon
- Separate then Freeze store at -20C

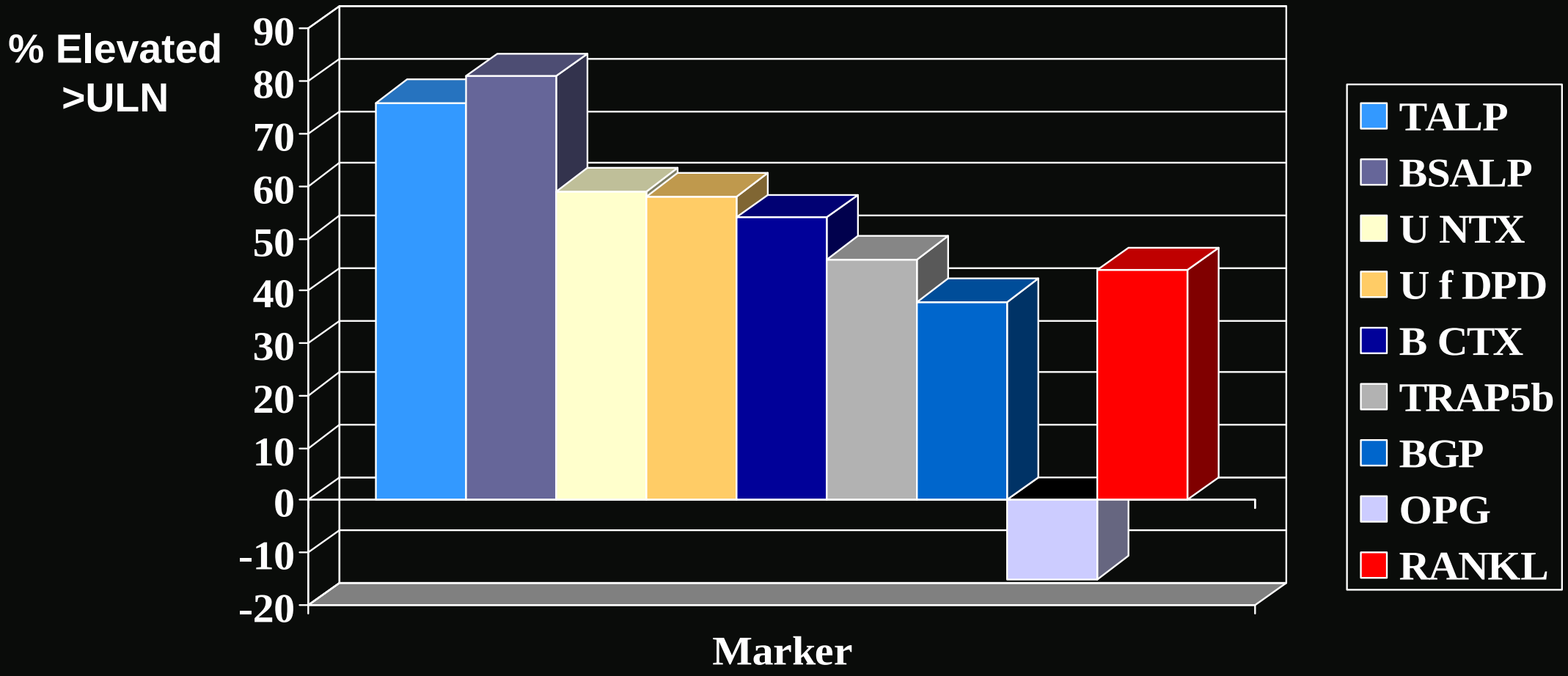
P1NP

- Any Sample Type
- Fasting AM or Afternoon
- Can transport at ambient temperature
- Store -20C

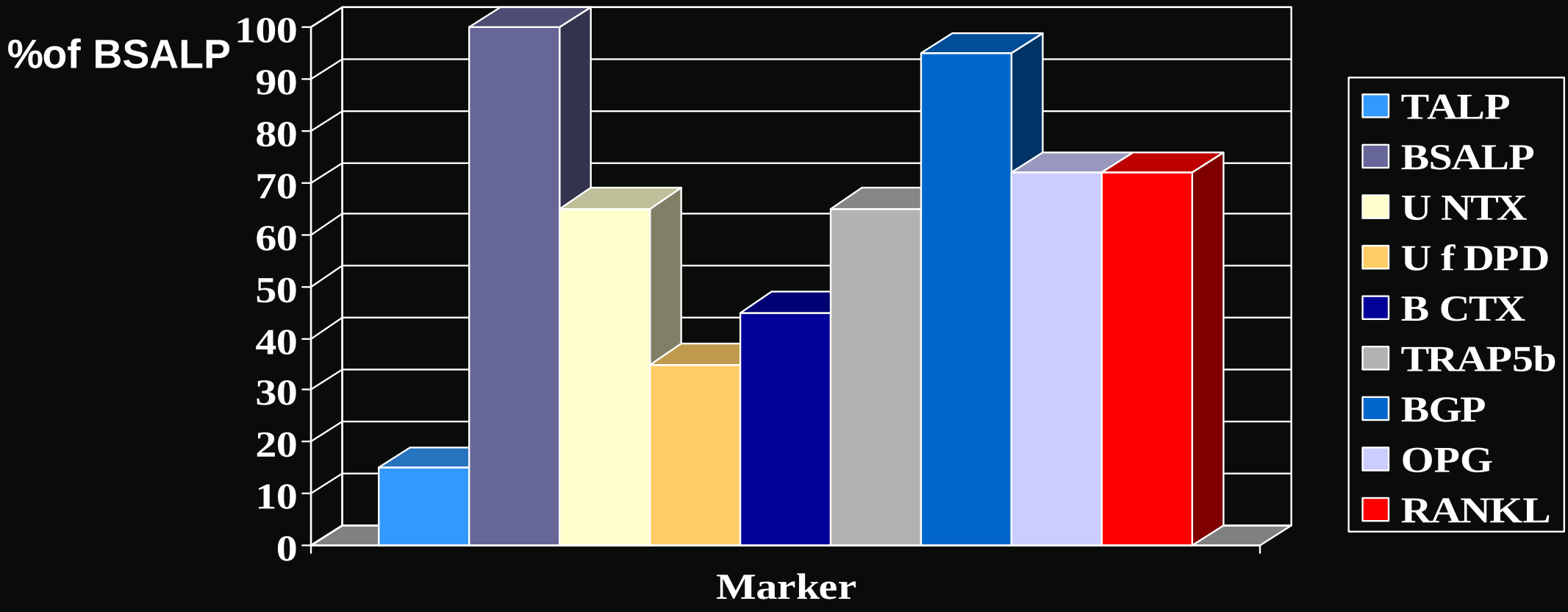
Clinical Use of Bone Markers

- Treatment of Metabolic Bone Disease
- Secondary Causes of Disease

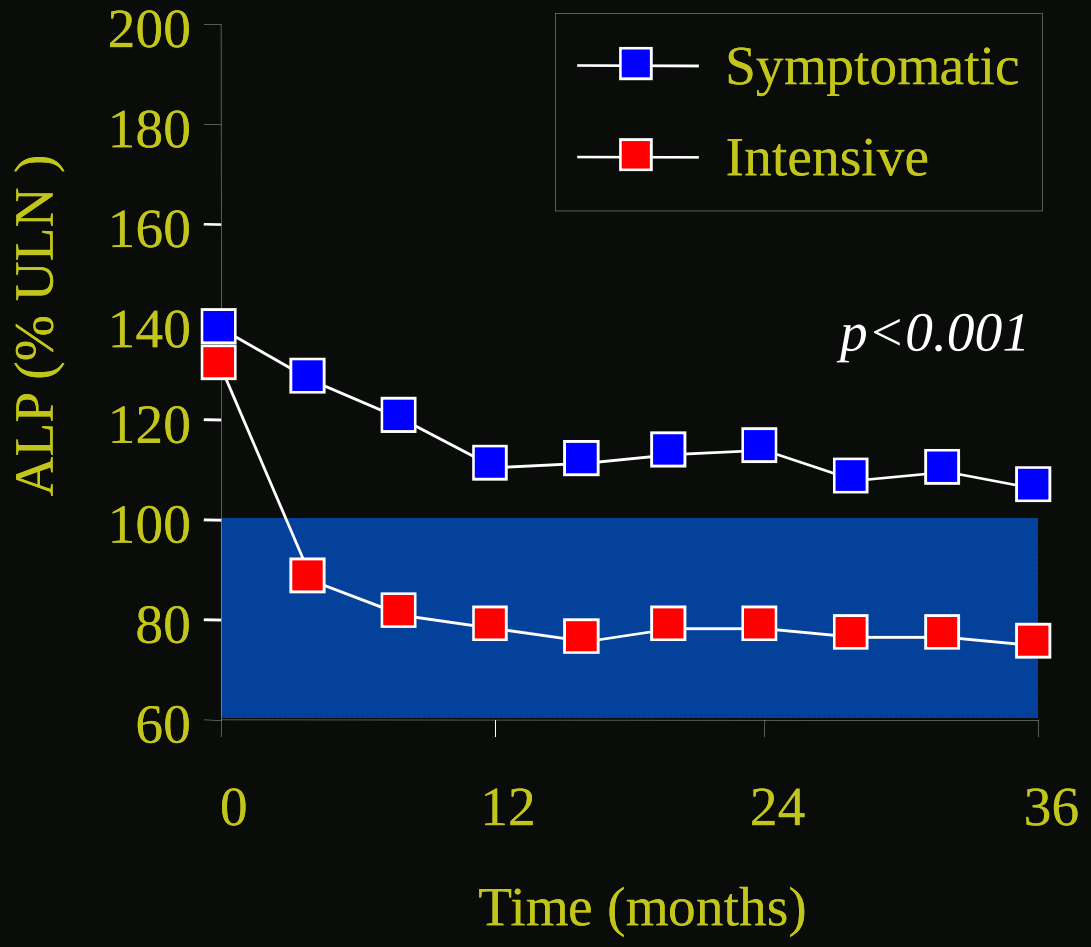
Biochemical Measurements at Presentation of Paget's Disease



Relative Costs of Markers



Effect of Intensive Bisphosphonate Therapy on Serum Alkaline Phosphatase in PDB

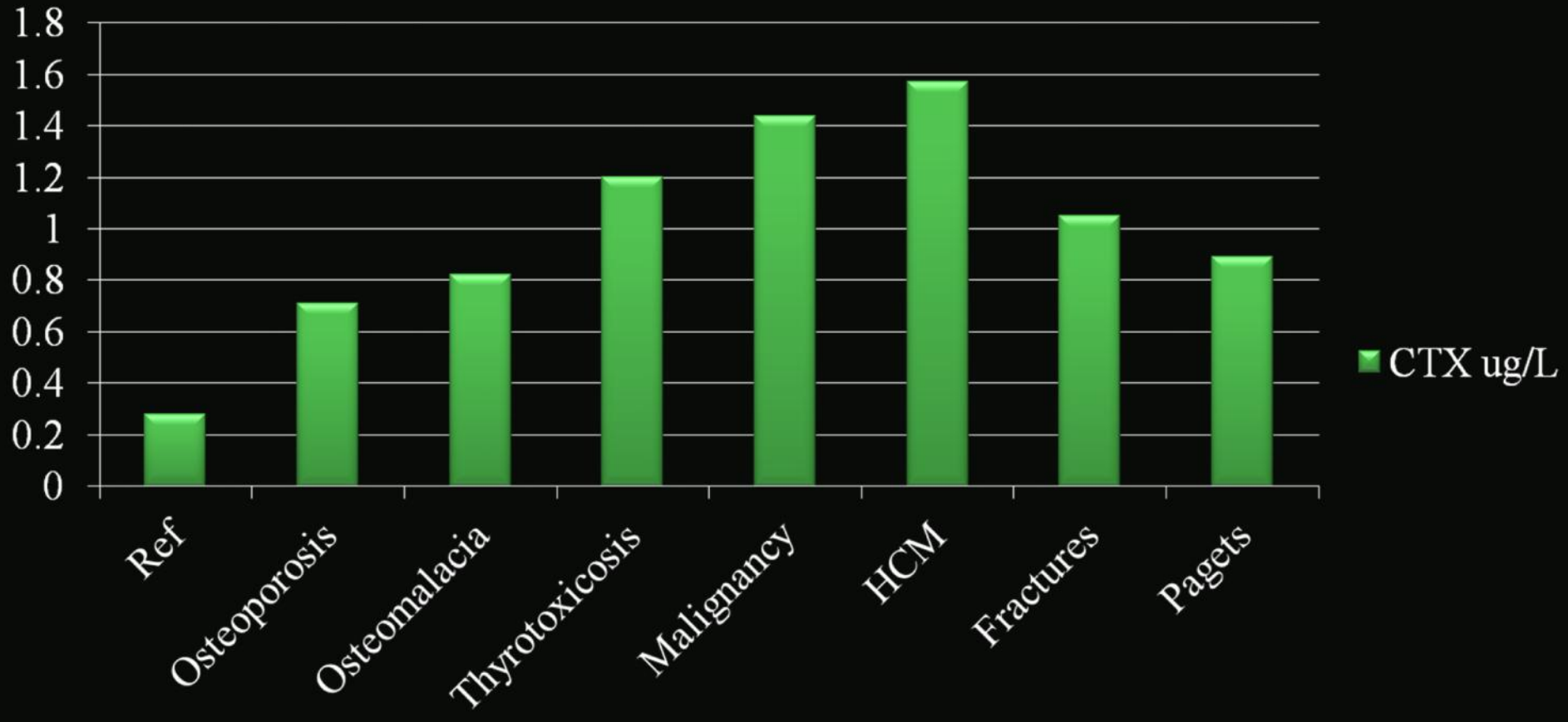


Normalisation of ALP

	Sympt	Intens
Baseline	**51.2%**	**51.5%**
2 yr	**63.2%**	**81.0%****
End	**61.2%**	**78.8%****

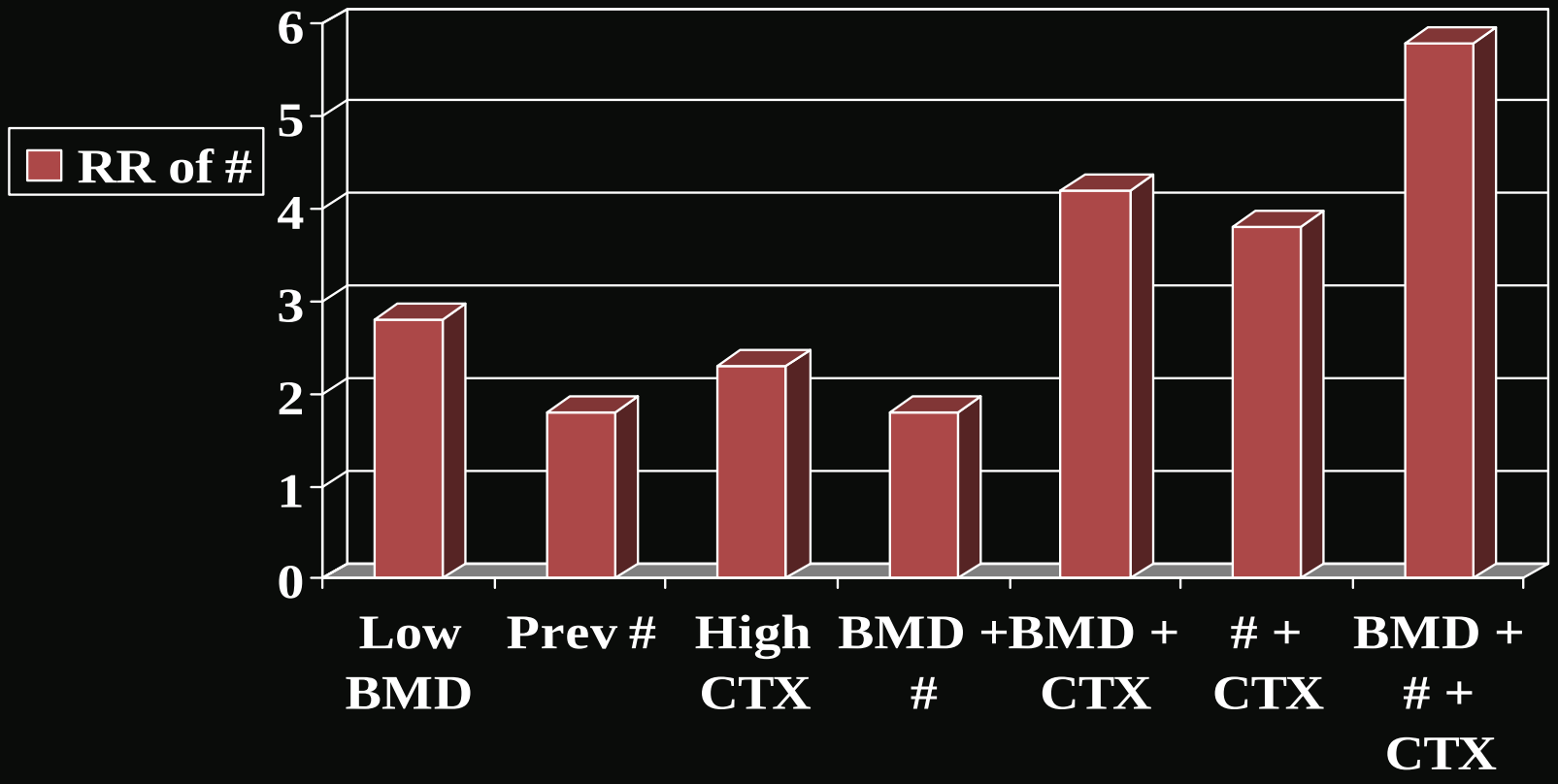
*** p<0.001*

Baseline Mean CTX at Clinic Visit



Data on File WDF

Combination of Factors to Predict Fracture



Garnero JBMR 1996

Treatments for Osteoporosis

- Hormone Replacement Therapy
- SERM
- Bisphosphonates
- Calcitonin
- Calcium and Vitamin D
- 1,25 Dihydroxyvitamin D
- Parathyroid Hormone PTH

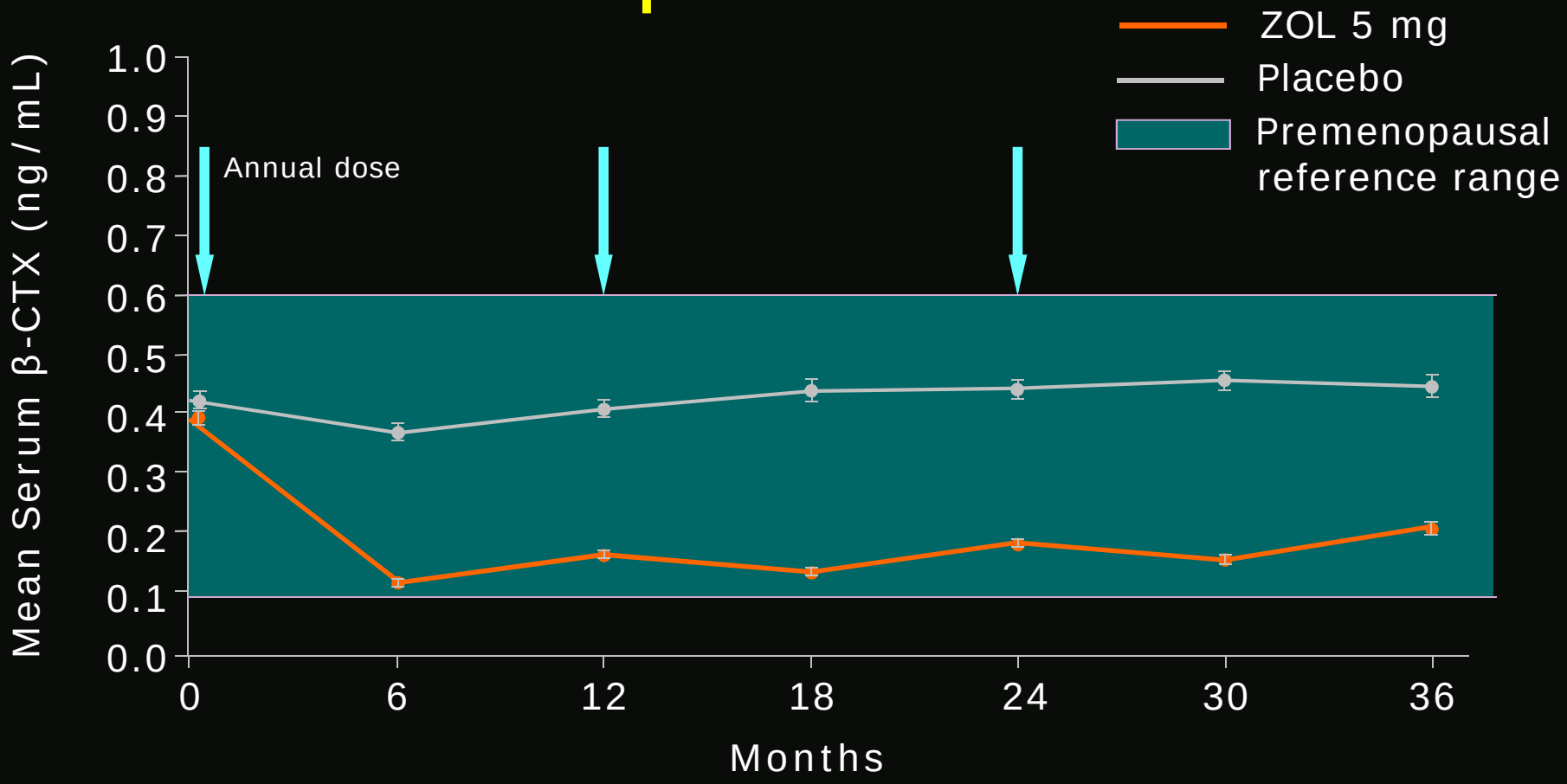
What Concentration of Marker Should We Aim For?

Is there such an entity as a non-responder to bisphosphonate treatment?

Zoledronic Acid 5mg

- Aclasta® (zoledronic acid 5 mg solution for infusion) is supplied in ready-to-infuse clear plastic bottles
- IV Infusion once per year

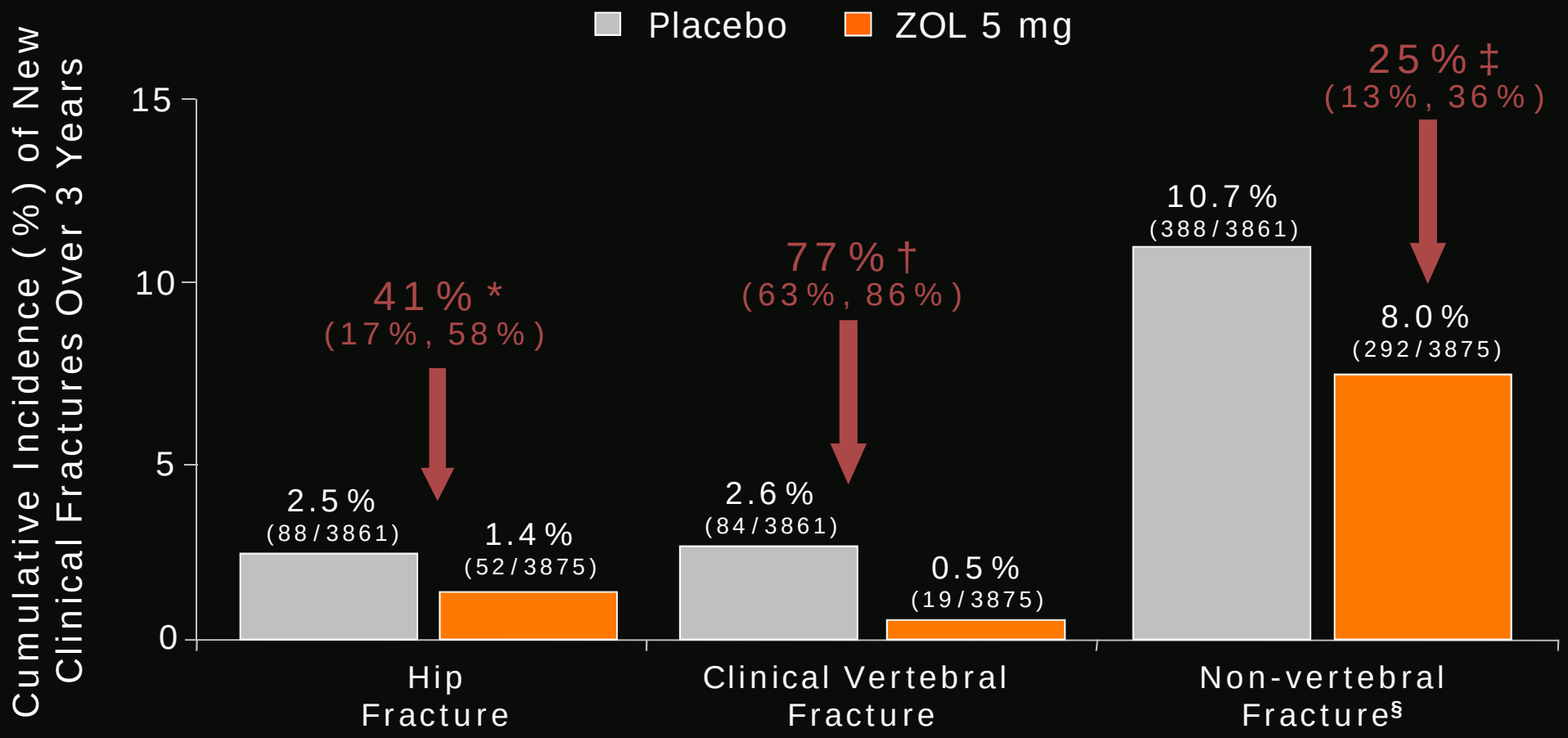
Zoledronic Acid Reduced Mean β-CTX



ZOL n =	257	237	201	136	191	190	174
PBO n =	260	248	214	156	196	197	170

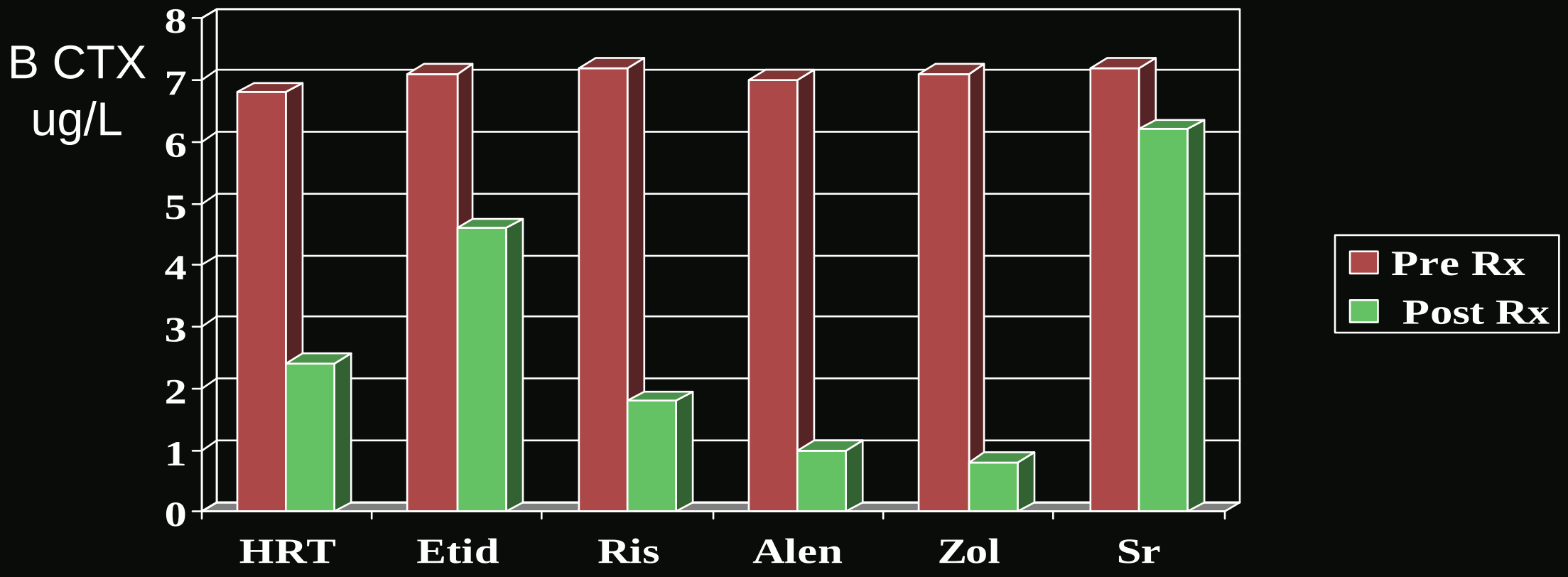
Adapted from Black DM, et al. N Engl J Med. 2007;356:1809-1822.

Zoledronic Acid Reduced Cumulative 3-Year Risk of Clinical Fractures (Hip, Clinical Vertebral, Non-vertebral)



Values above bars are 3-year cumulative event rates based on Kaplan-Meier estimates.
*P = .0024; †P < .0001; ‡P = .0002; Hazard ration; risk reduction vs placebo
§Hip fracture was not excluded from analysis of non-vertebral fracture.
Adapted from Black DM, et al. N Engl J Med. 2007;356:1809-1822.

Serum CTX Responses



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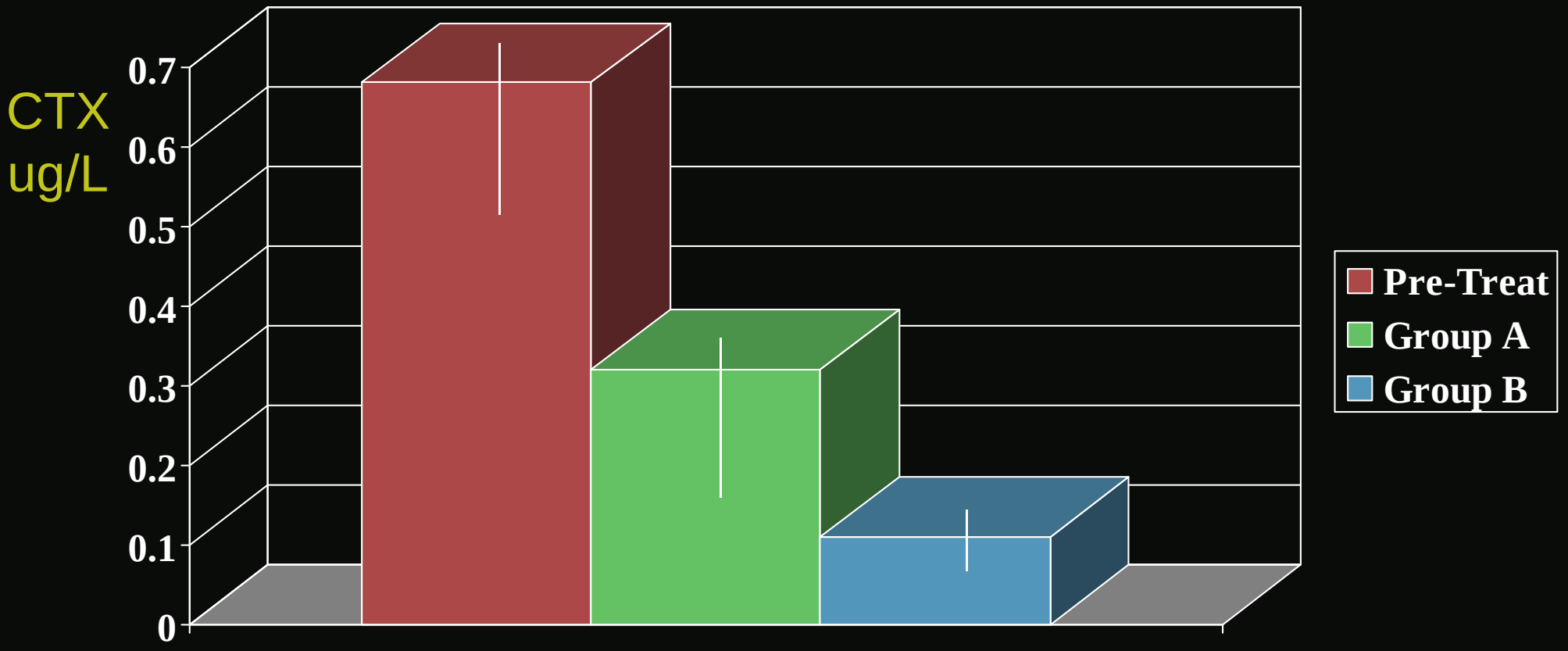
Alendronate Treatment



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Bone “Quality” and the Prediction of Fracture/Response to Therapy

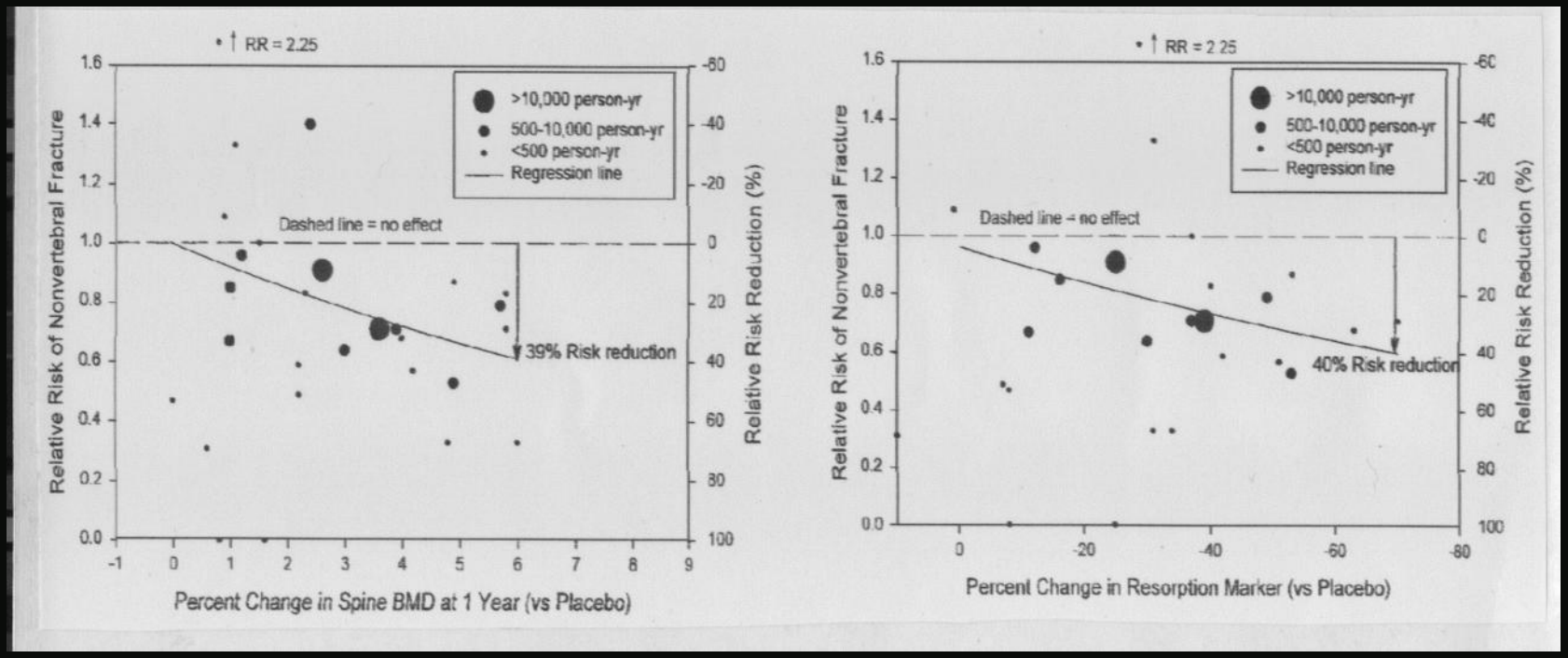
- BMD is not the only predictor of fracture

- BMD change only accounts for 4-40% of the change in fracture incidence following treatment

Bone Markers and Response to Rx

- Change in bone markers of resorption account for 25-60% of the reduction in fracture incidence following treatment with anti-resorptive therapy.

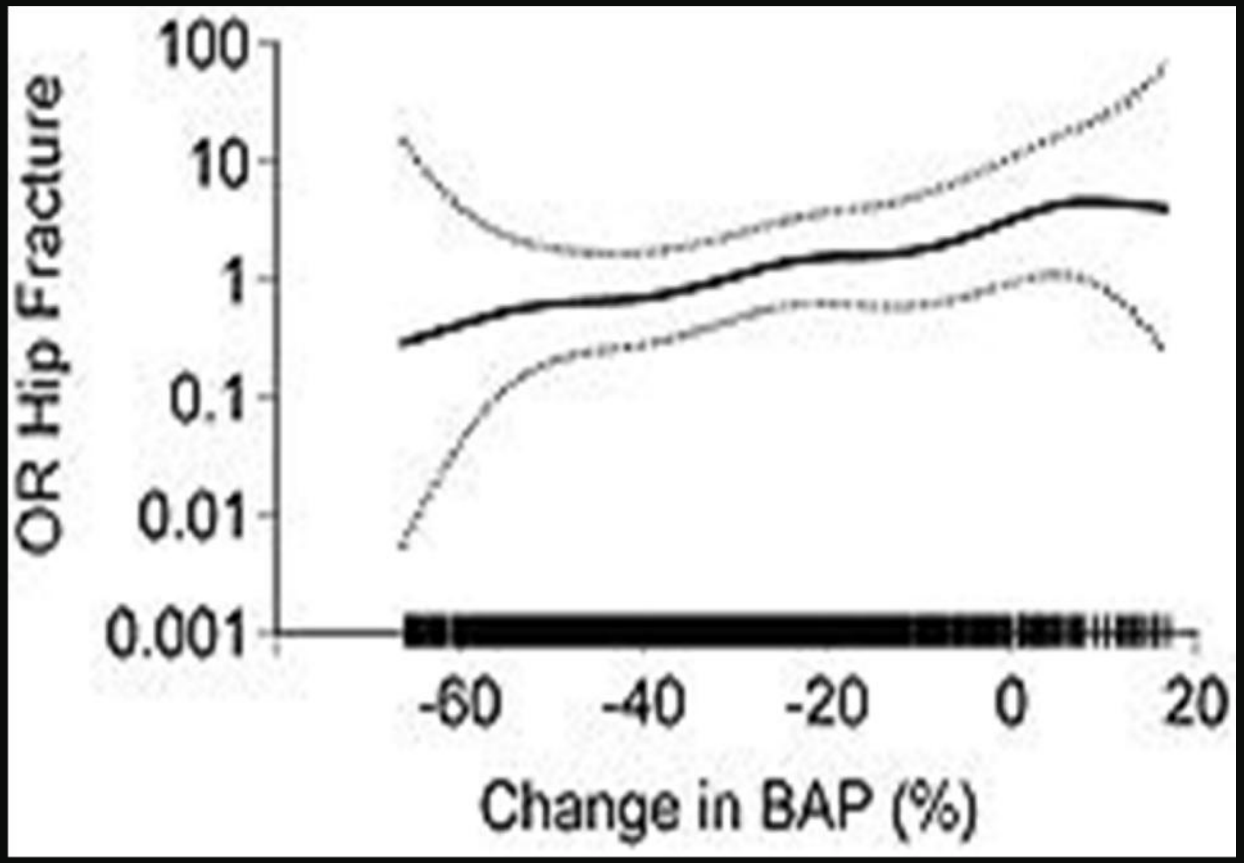
Fracture Incidence
BMD and Bone Marker Association



- 18 trials, 69,369 women years of follow-up.
- Larger increases in BMD and decreases in Bone Marker significantly associated with reductions in fracture risk

Hochberg M et al JCEM

Bone Marker and Fracture Reduction



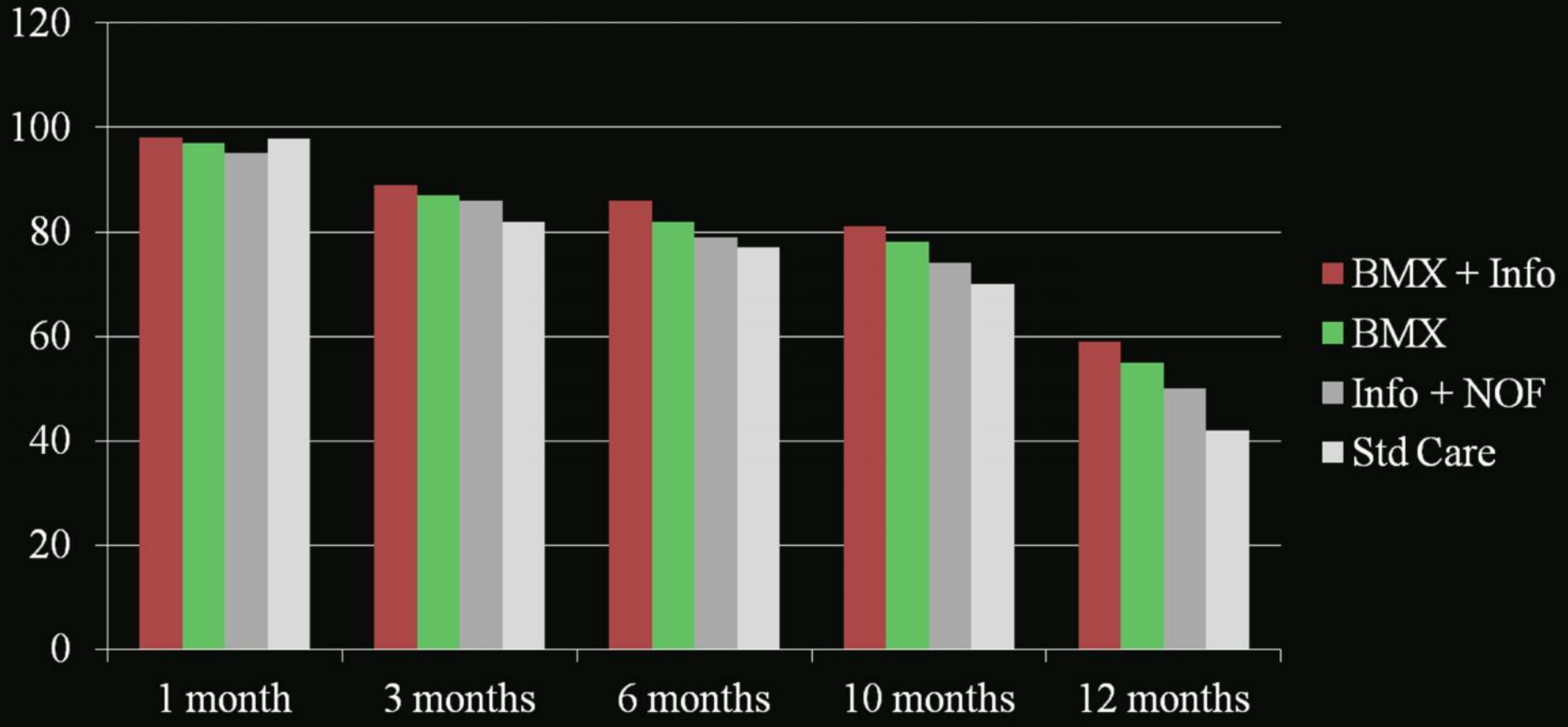
Bauer JBMR 2004; 1250-8

Suppression in Daily Practice

- Eeckman DA et al BMC 2011
  - 126 patients in 2 groups
  - Group A (New) 81% achieved better than LSC
  - Group B (Old) 95% lower half of Ref Range

  - If elevated
  - Recent #, C2H5OH, Myeloma, Non Compliance

Persistence with Oral Bisphosphonate Therapy



Silverman SL et al Osteop Int 2011

Treatment with PTH (1-34)

- PTH 20ug or 40ug given as daily subcutaneous injection v placebo

- BMD increase with PTH 2.6-13.7%
- Vertebral fracture reduction

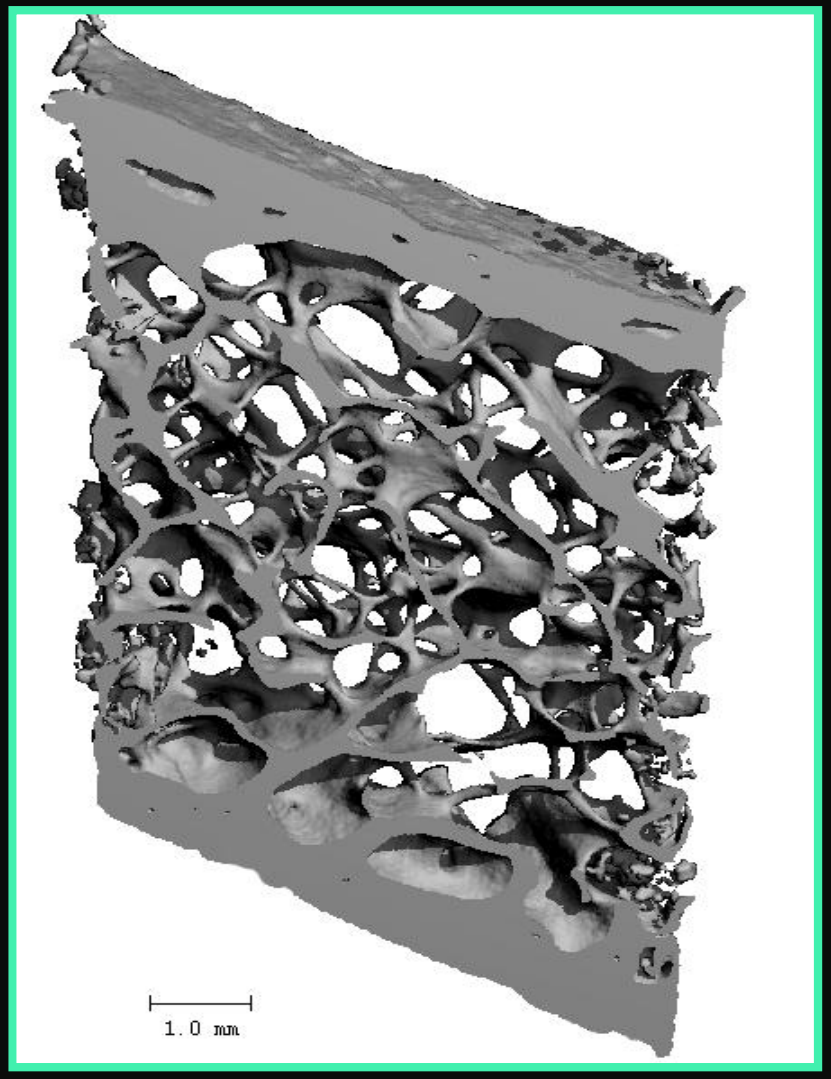
  65% for 20ug dose

  69% for 40ug dose

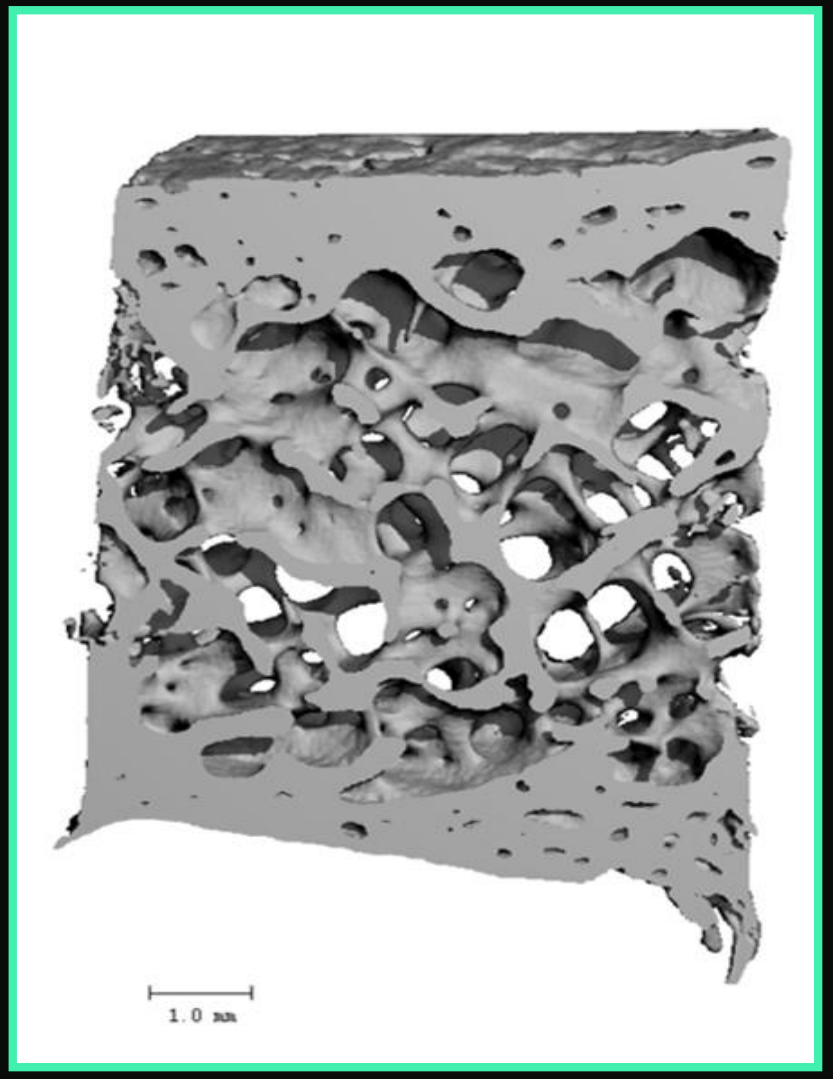
Neer et al NEJM 2001

20ug PTH (1-34) is the licensed dose for Osteoporosis

3-D µCT Images of Iliac Crest Biopsies at Month 18

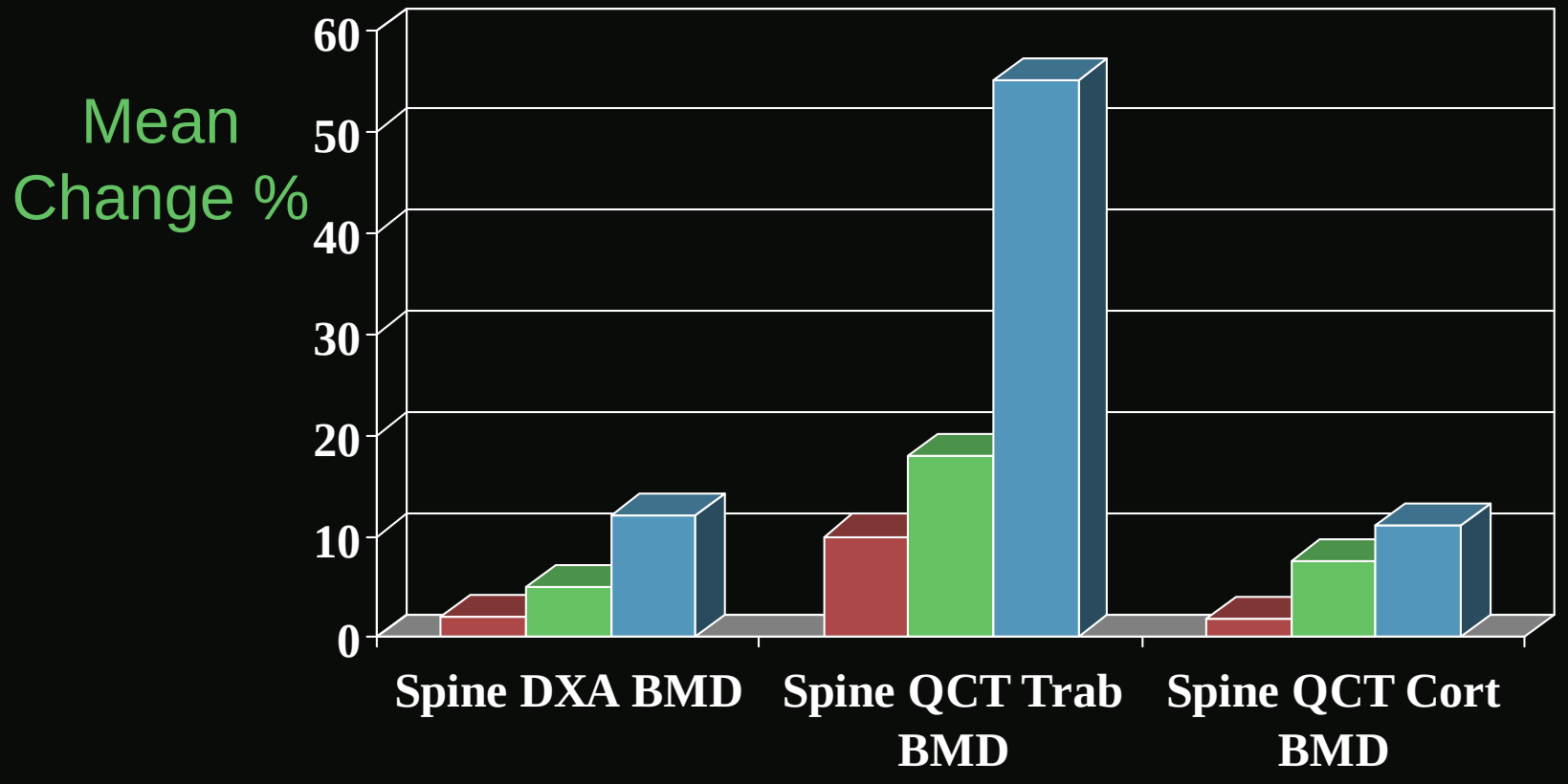


Placebo



PTH (1-84)

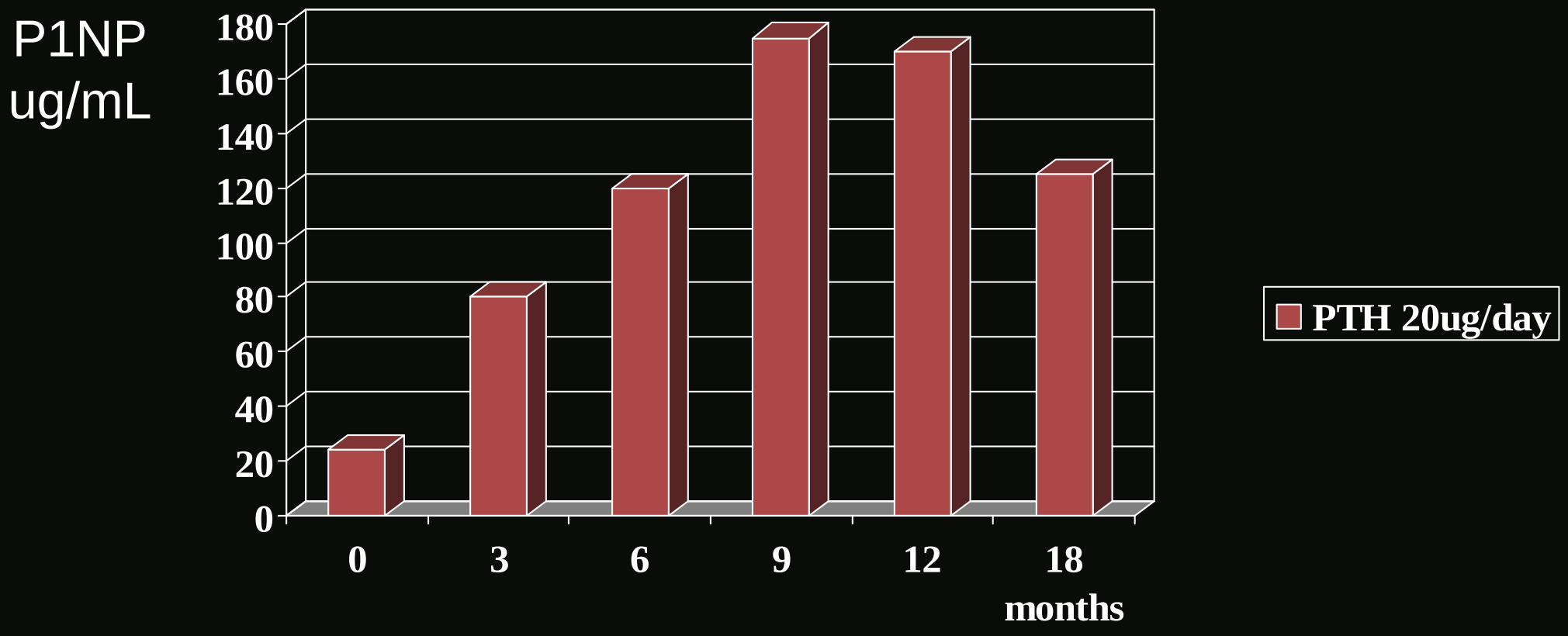
Spine DXA BMD, QCT Trabecular BMD and QCT Cortical BMD Increase with PTH (1-84) Related to P1NP Changes



P<0.001 across tertiles

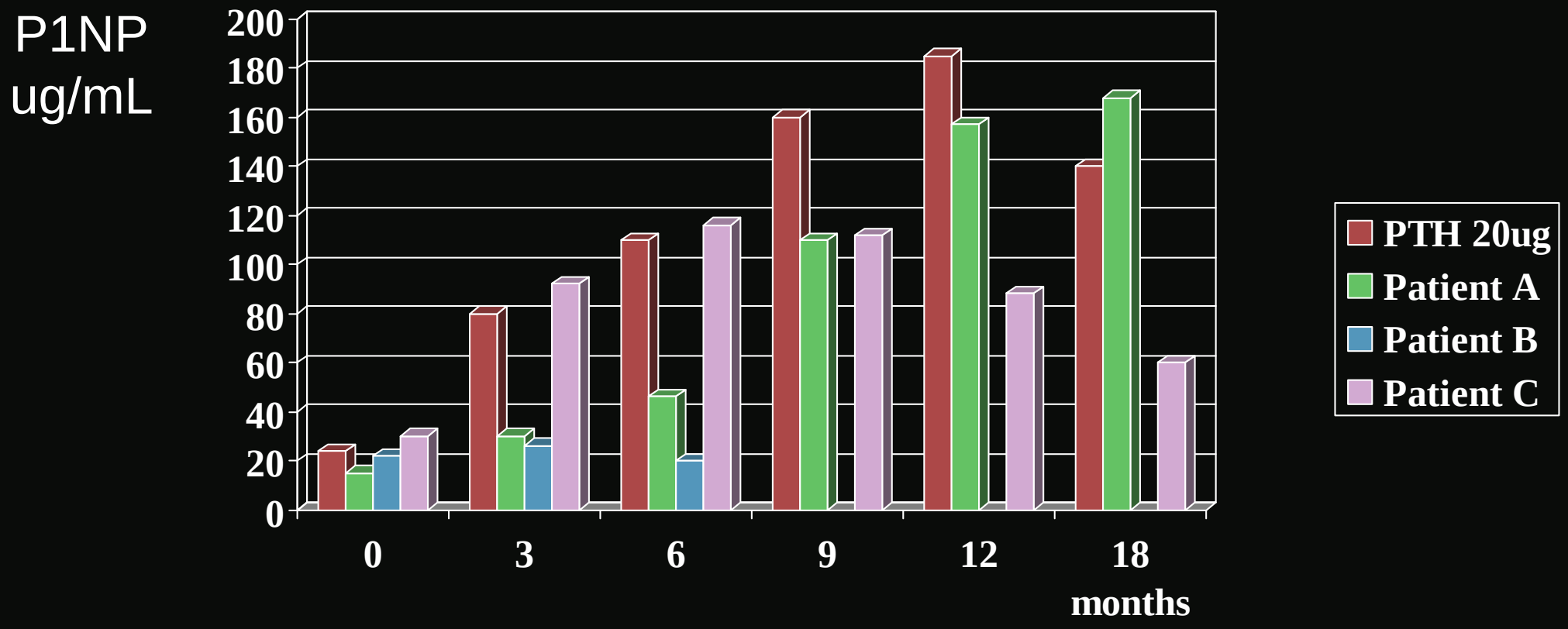
Bauer et al JCEM 2007

P1NP Response to PTH (1-34)



Data on file WDF

P1NP Response to PTH (1-34)



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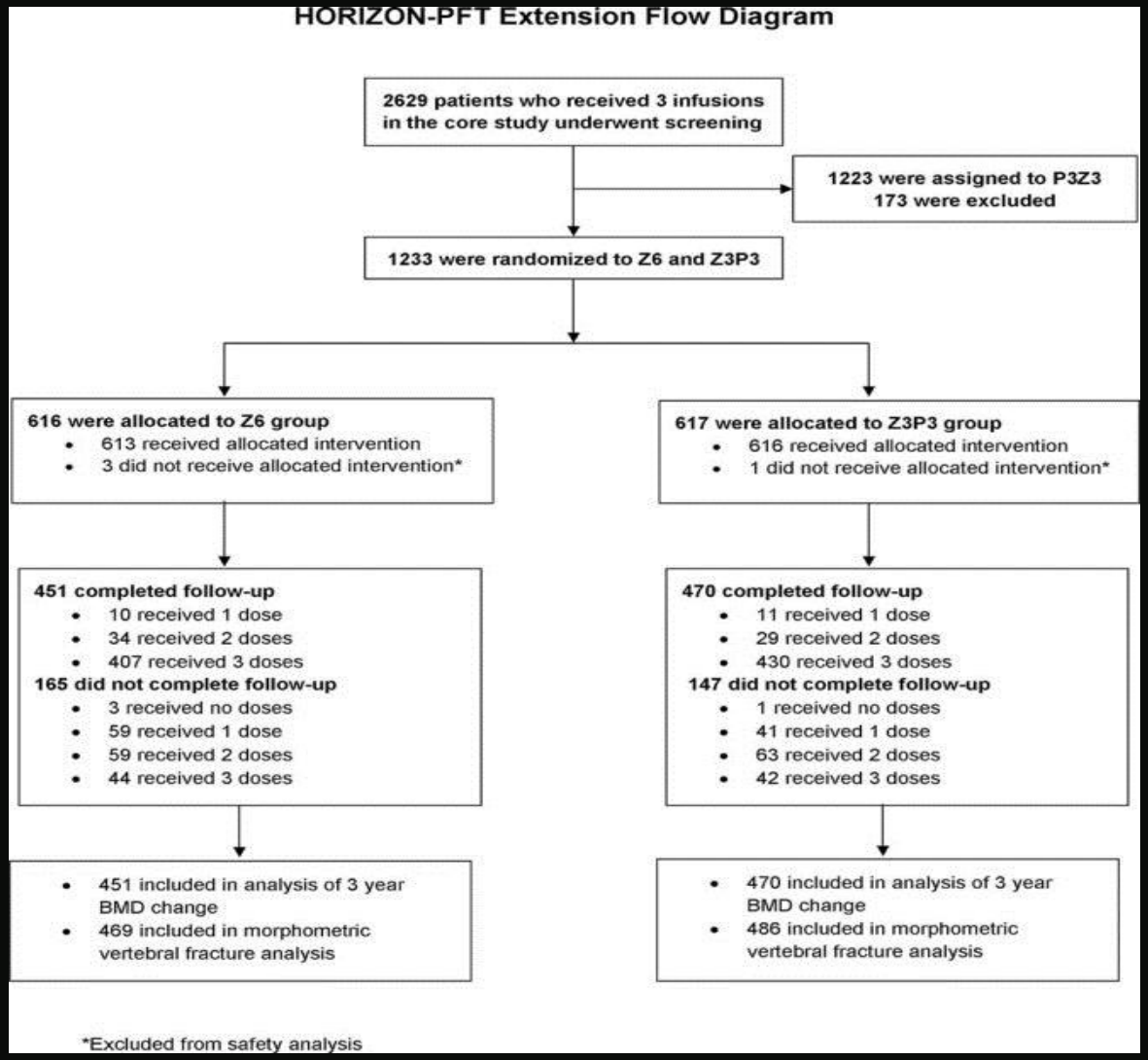
Osteoporosis Management Programme

- Diagnosis Established
- Measure Serum CTX/P1NP
- Commence Treatment
- 3-4 Months Confirm Response CTX/P1NP
- 6-12 Monthly CTX/P1NP
- 24-36 Months Repeat BMD???

Care of Metabolic Bone Disease

The Evidence Base (Drug Holiday)

Horizon Extension Study



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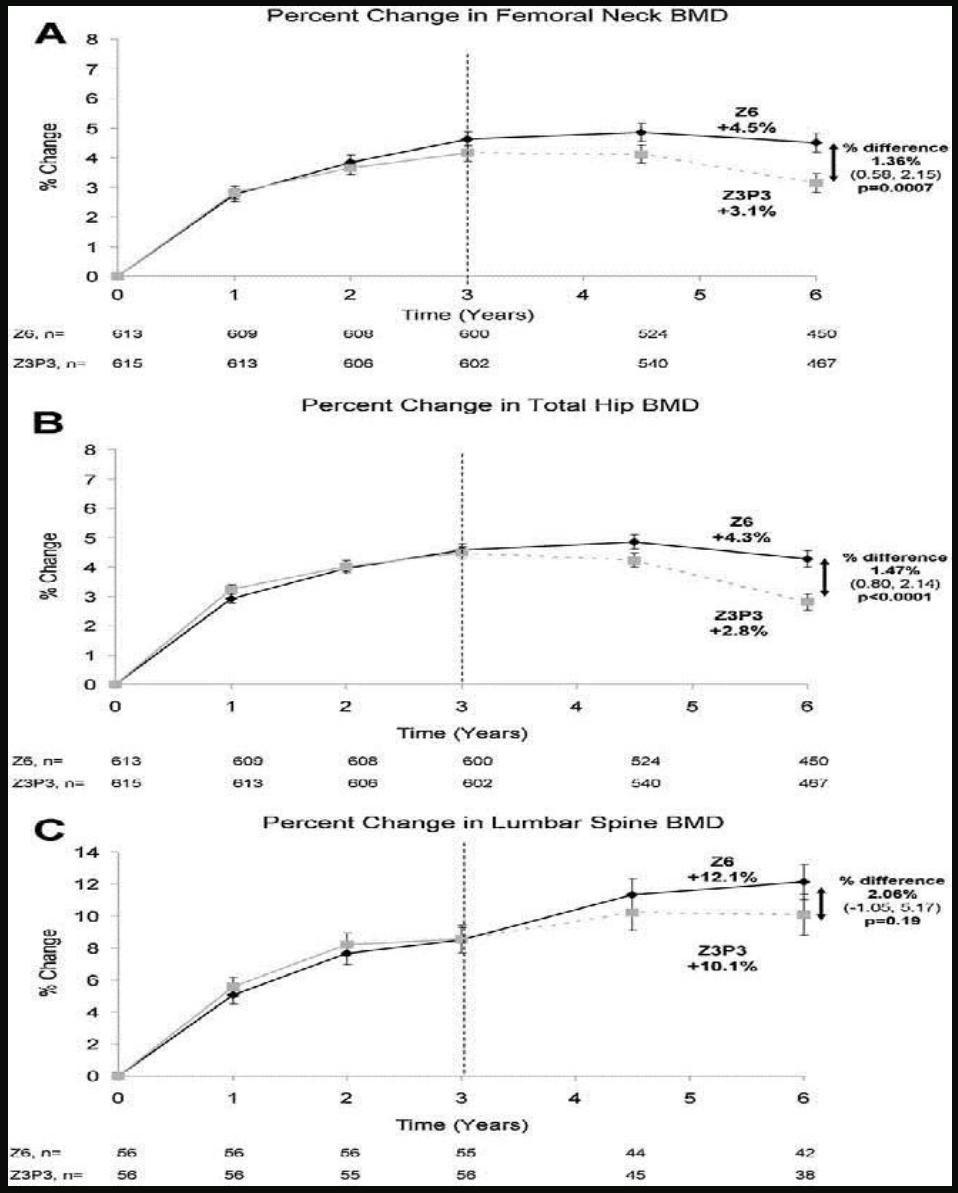

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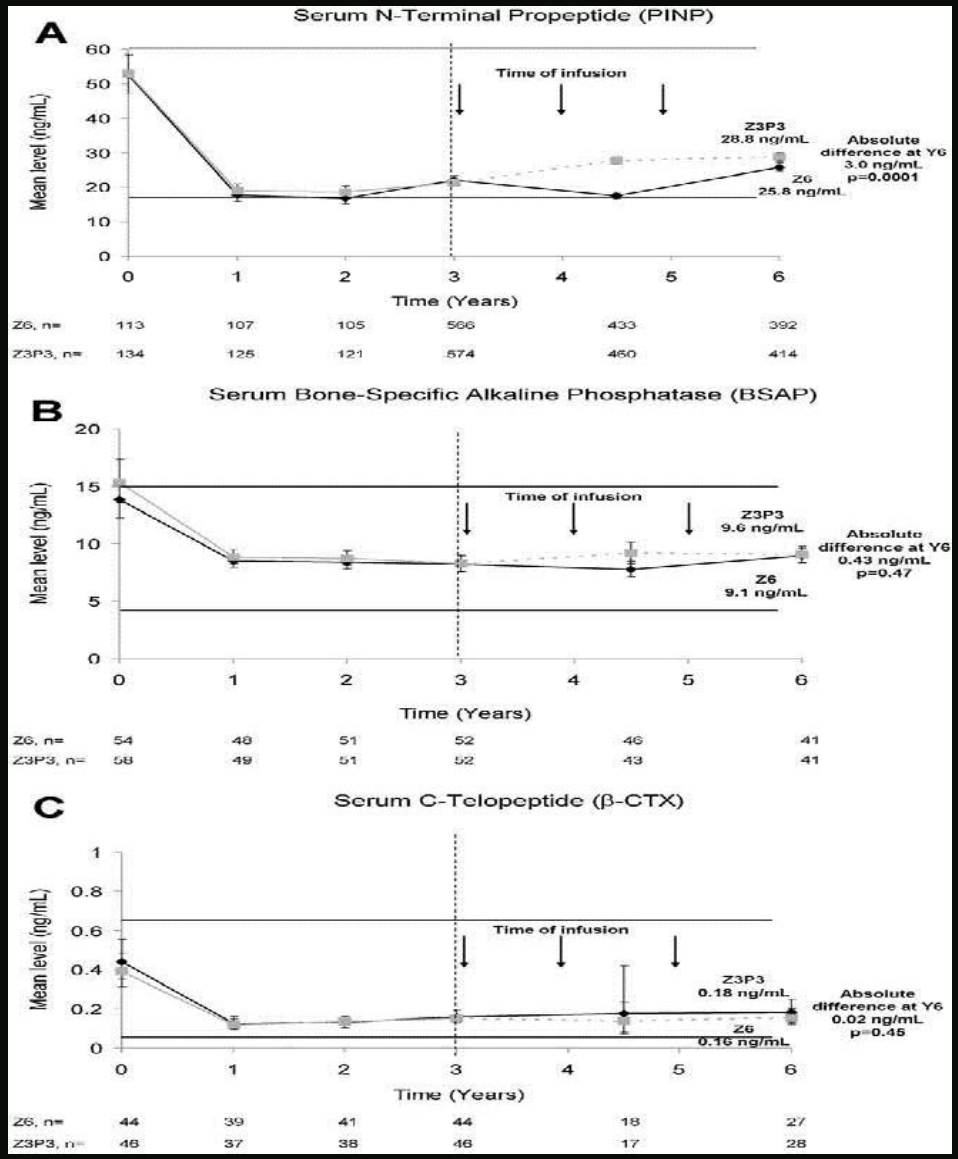

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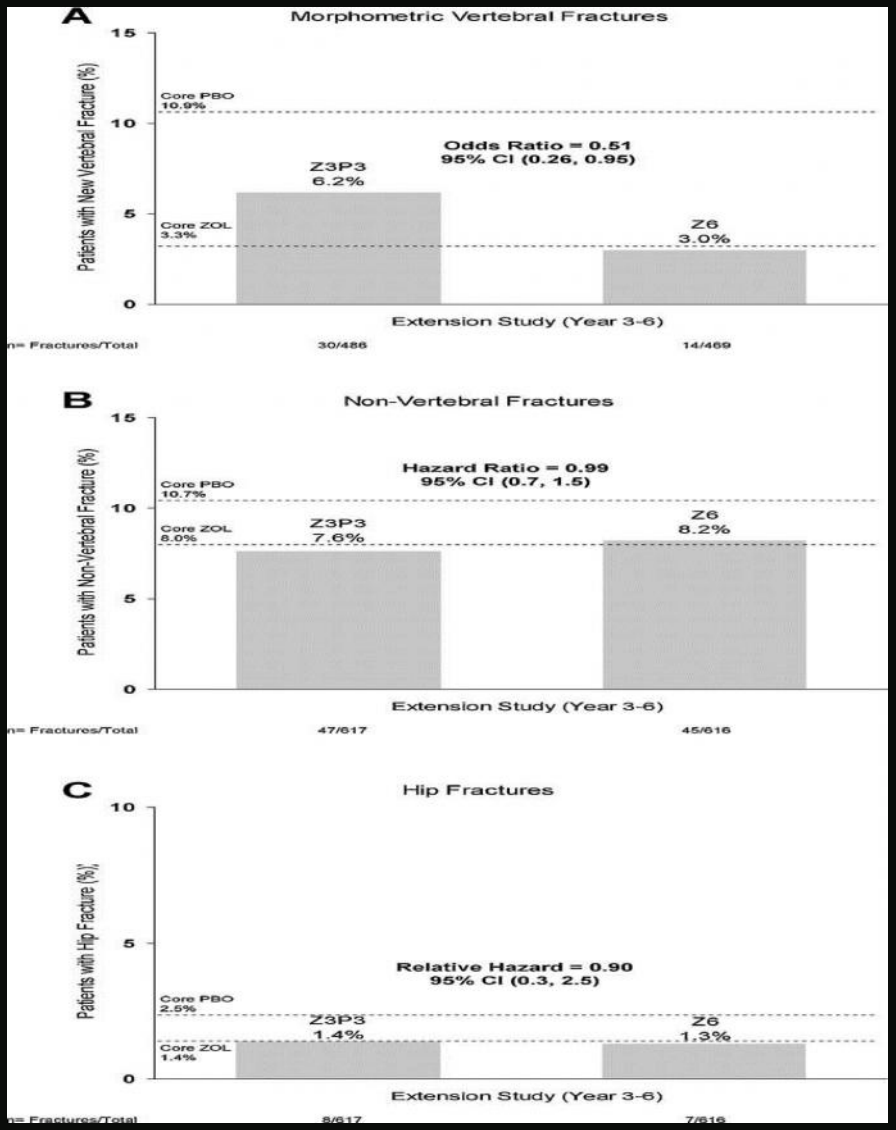

“Heterogeneity of Markers”

- 23 studies published in the literature using Biochemical Markers in an attempt to predict fracture outcome

- How many took the correct sample type and state when sample taken, how processed, how stored, when measured in relation to sampling?