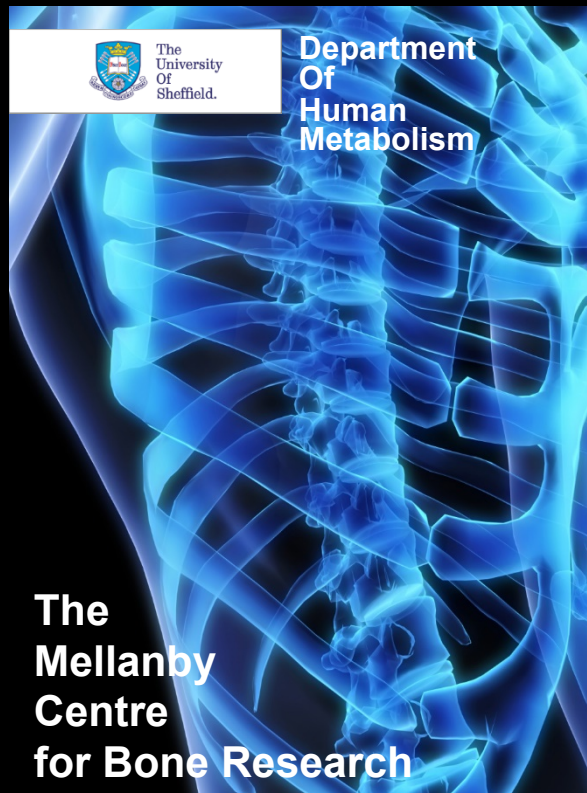




ITALIAN CHAPTER

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# Bone turnover markers in clinical practice

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# Disclosures

- **Consultant/Advisor/Speaker for:**

- ActiveSignal, AgNovos, Amgen, AstraZeneca, Consilient Healthcare, Fresenius Kabi, GSK, Hologic, Internis, Lilly, Medtronic, Merck, Novartis, Pfizer, Roche, Sanofi-Aventis, Servier, Synexus, Tethys, UCB, Warner Chilcott

- **Research support:**

- Including above plus ARUK, I3 Innovus, MRC, IOF, Unilever

- **Financial holdings:**

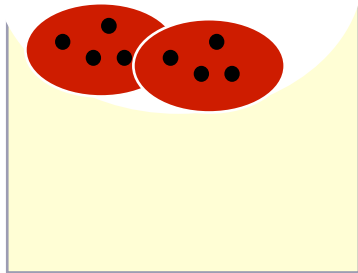
- None

# BTM in Metabolic Bone Diseases in Adults

- Generalised diseases
  - Osteoporosis
  - Primary hyperparathyroidism
  - Osteomalacia
- Focal bone disease
  - Paget's disease
  - Fibrous dysplasia
  - Metastatic cancer
- Rare bone disease
  - Hypophosphatasia

# Bone Turnover Markers

## Resorption



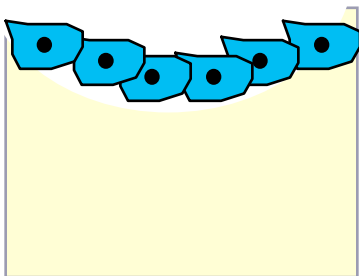
### Collagen degradation products

- Pyridinium cross-links of collagen
  - Deoxypyridinoline (DPD)
  - C- and N-telopeptides (**CTX**, CTX-MMP, **NTX**)

### Enzyme

- Tartrate-resistant acid phosphatase (TRACP)

## Formation



### Matrix protein

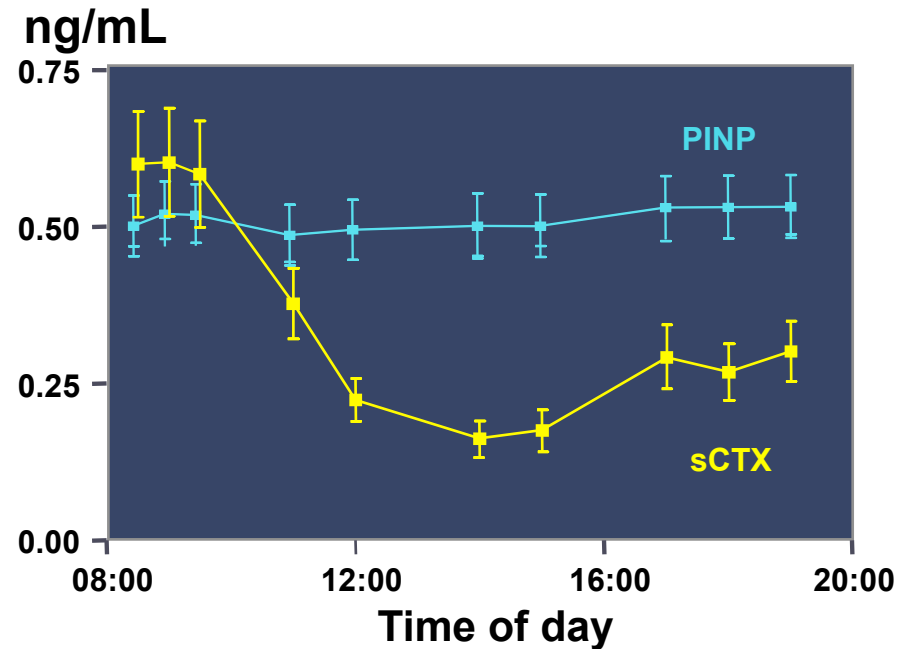
- Osteocalcin (**OC**)
- Propeptides of type I procollagen
  - C- and N-terminal (PICP, **PINP**)

### Enzyme

- Bone alkaline phosphatase (**Bone ALP**)

# Controlling variability

Use markers with least variability



- Timed sample
  - Usually morning
- Fasting

# Brenda, age 63

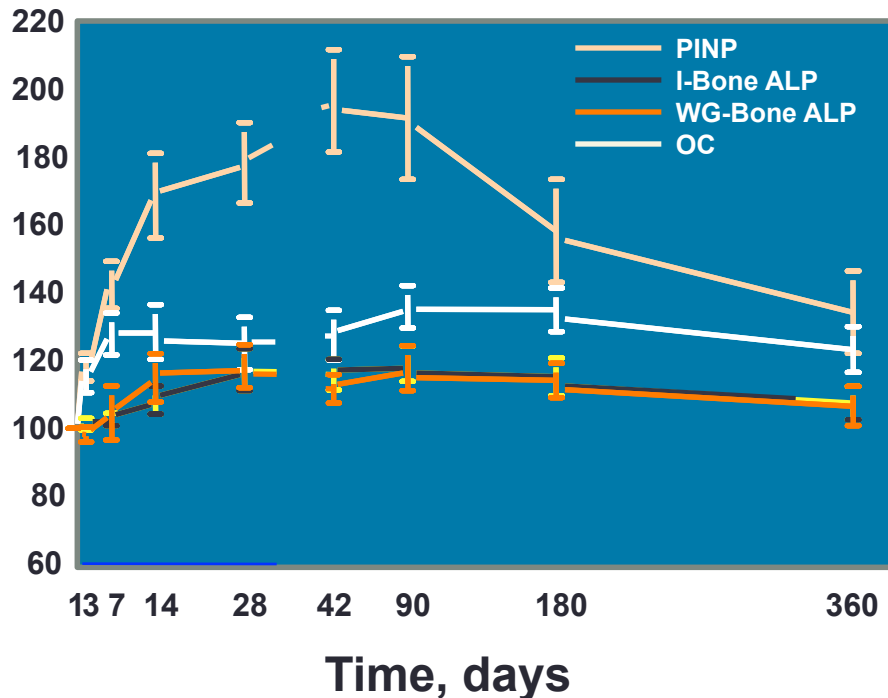
- Wrist fracture at 62
  - Menopause at 39, no HRT



# Biochemical markers after ankle fracture

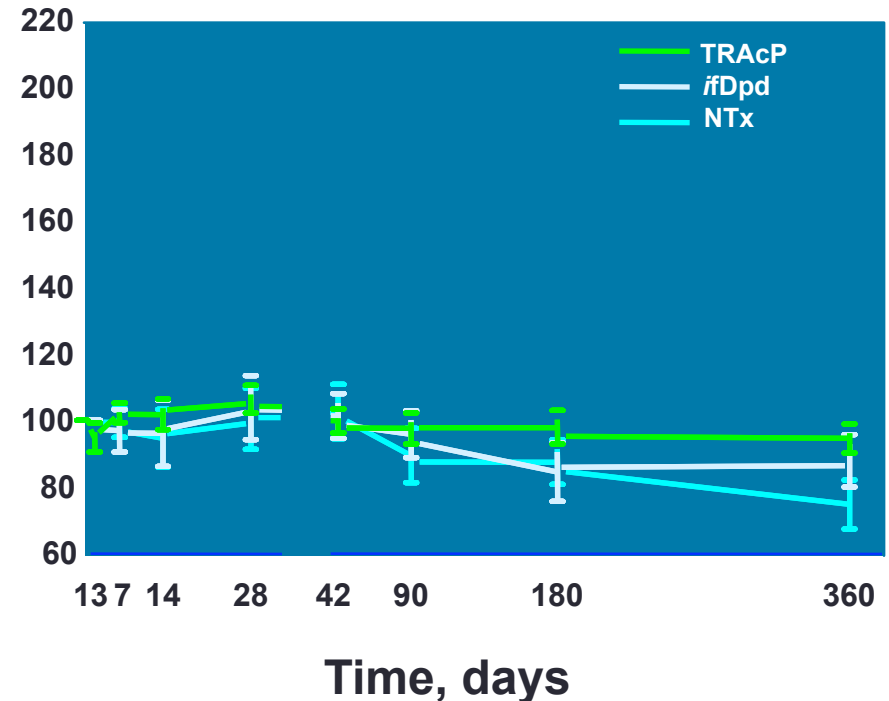
## Formation

% baseline



## Resorption

% baseline



Size of marker increase relates to size of bone fractured

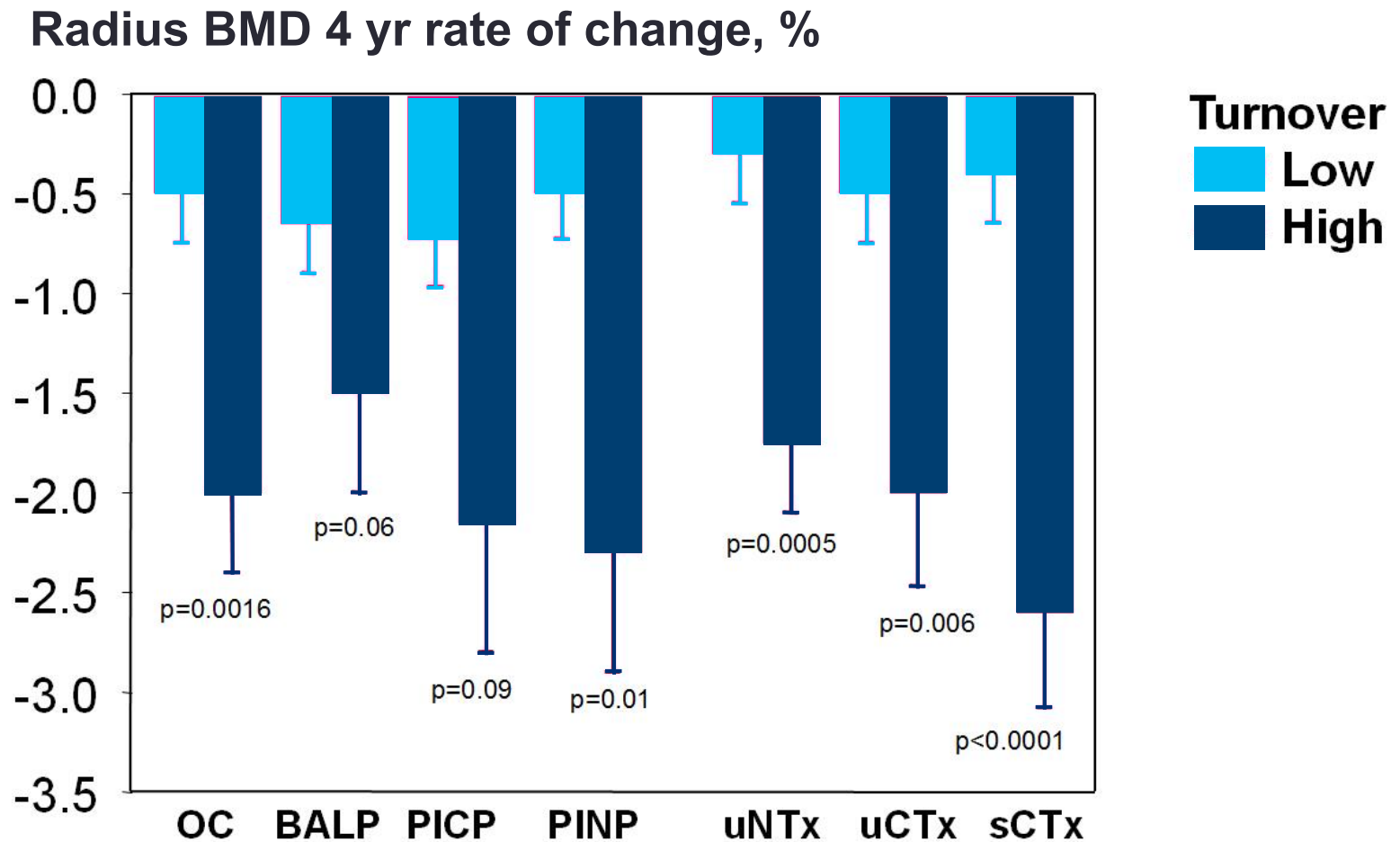
# Brenda, age 63

- Wrist fracture at 62
  - Menopause at 39, no HRT
- Is there a role for BTM to predict her:
  - Rate of bone loss?
  - Future fracture risk?

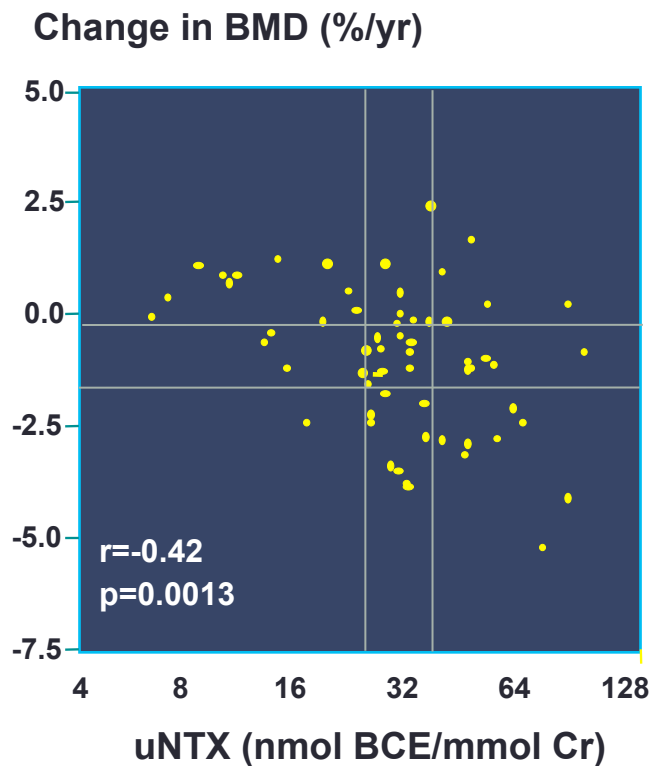
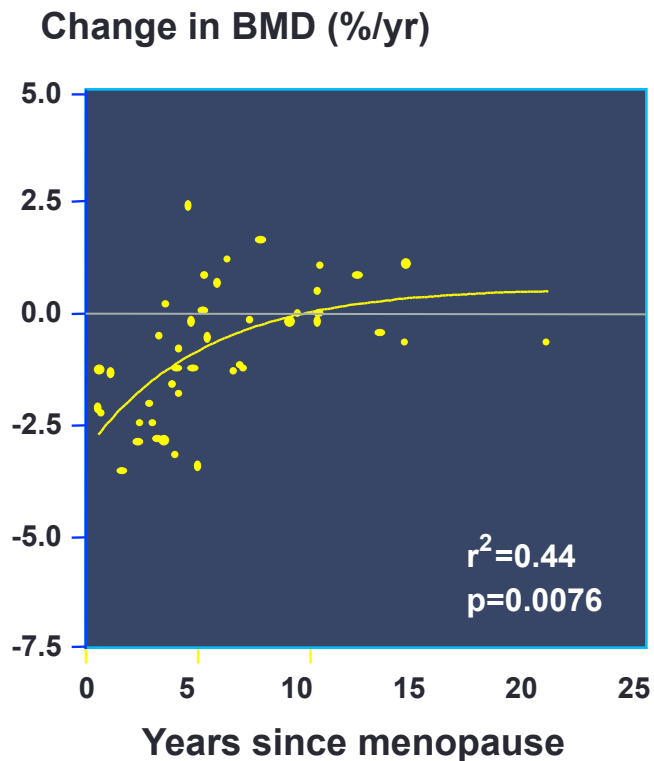




# High bone turnover predicts rapid bone loss



# High bone turnover predicts rapid bone loss in populations but not individuals

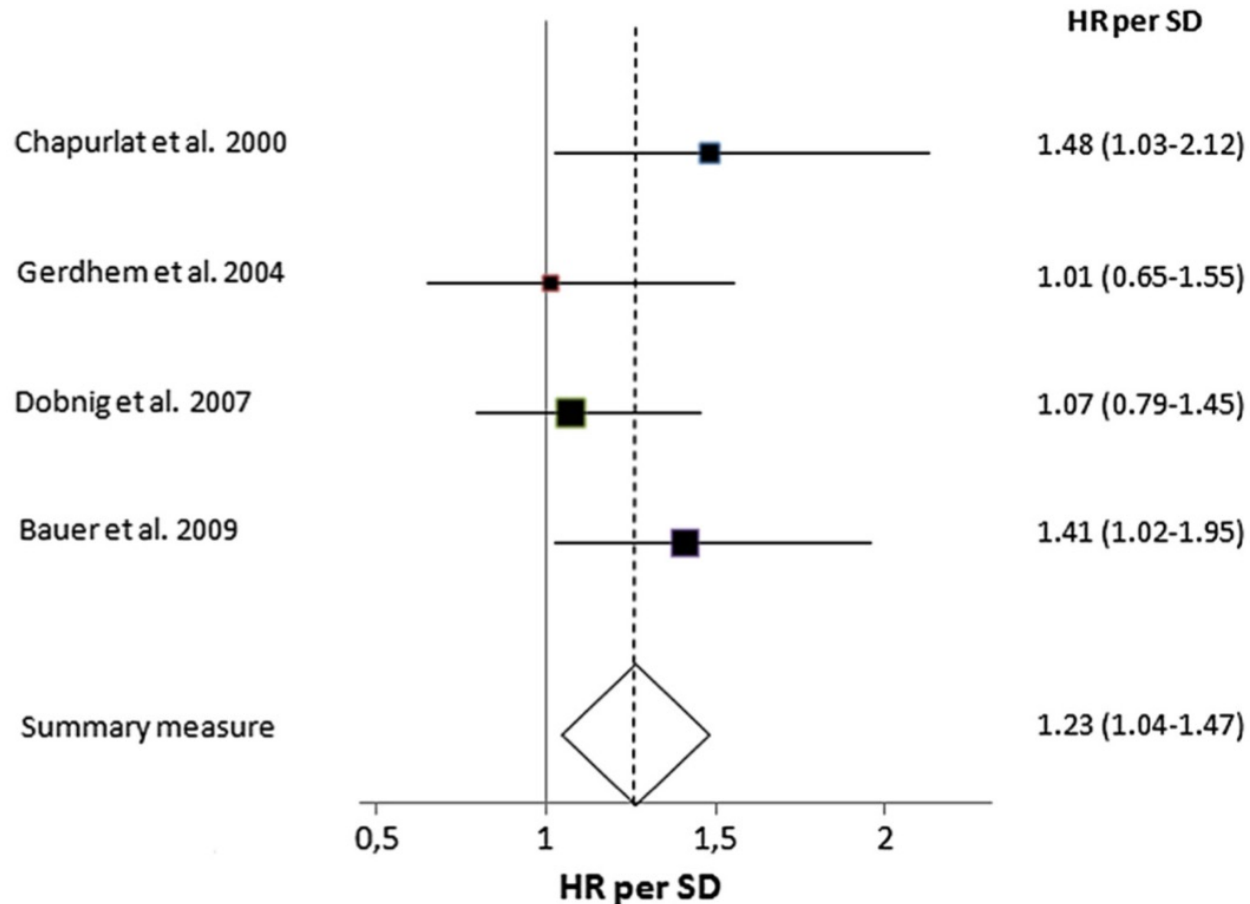


**Delta BMD**

<b>U</b>	<b>11</b>	<b>4</b>	<b>5</b>
<b>M</b>	<b>4</b>	<b>9</b>	<b>7</b>
<b>L</b>	<b>5</b>	<b>7</b>	<b>8</b>
	<b>L</b>	<b>M</b>	<b>U</b>

**U NTX**  
**Kappa = 0.125**  
**(95%CI, 0.002 to -0.152)**

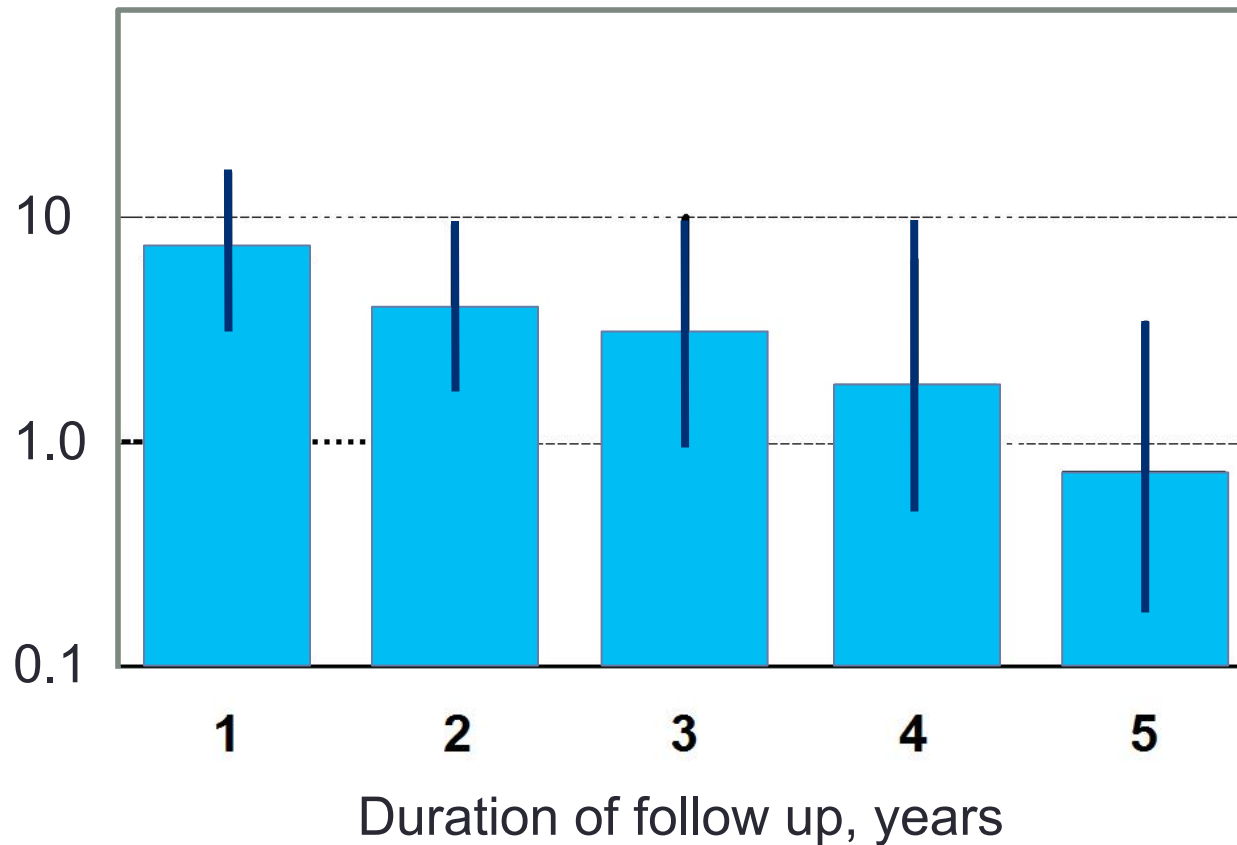
# BTM predict fracture risk independently of BMD



Forest plot showing relationship between sCTX and hip fracture risk

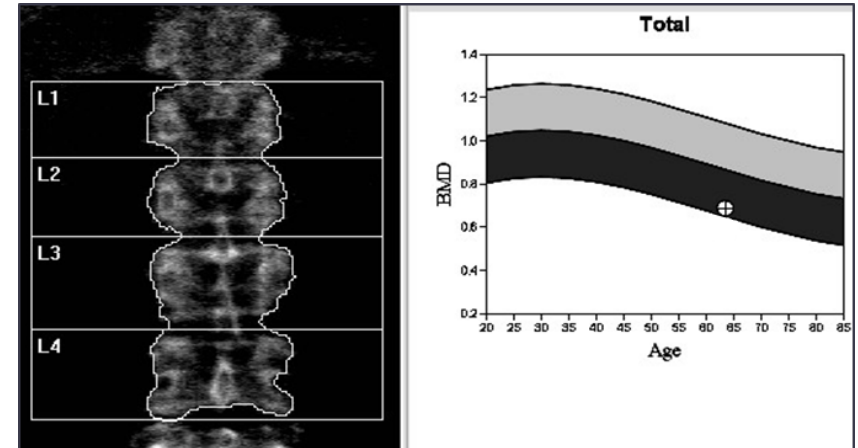
# Predictive ability of BTM attenuates over time

Relative risk of fracture per SD osteocalcin

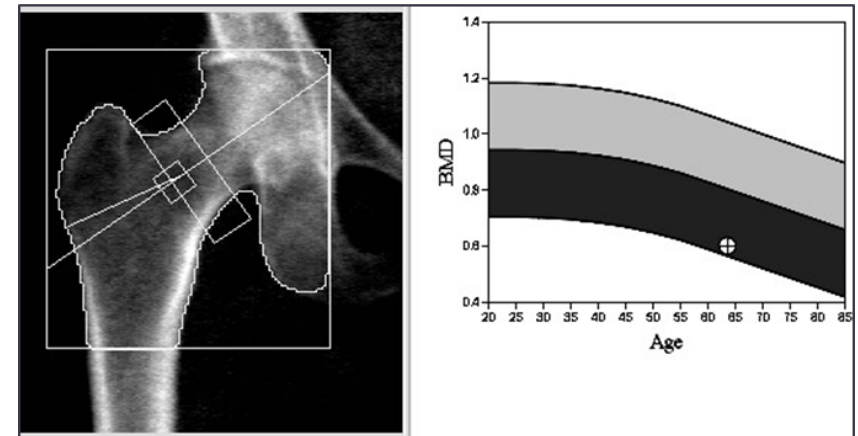


# Brenda, age 63

- DXA confirms osteoporosis
- Can BTM be used to:
  - Select appropriate treatment to reduce her risk of further fracture?



T score -3.3

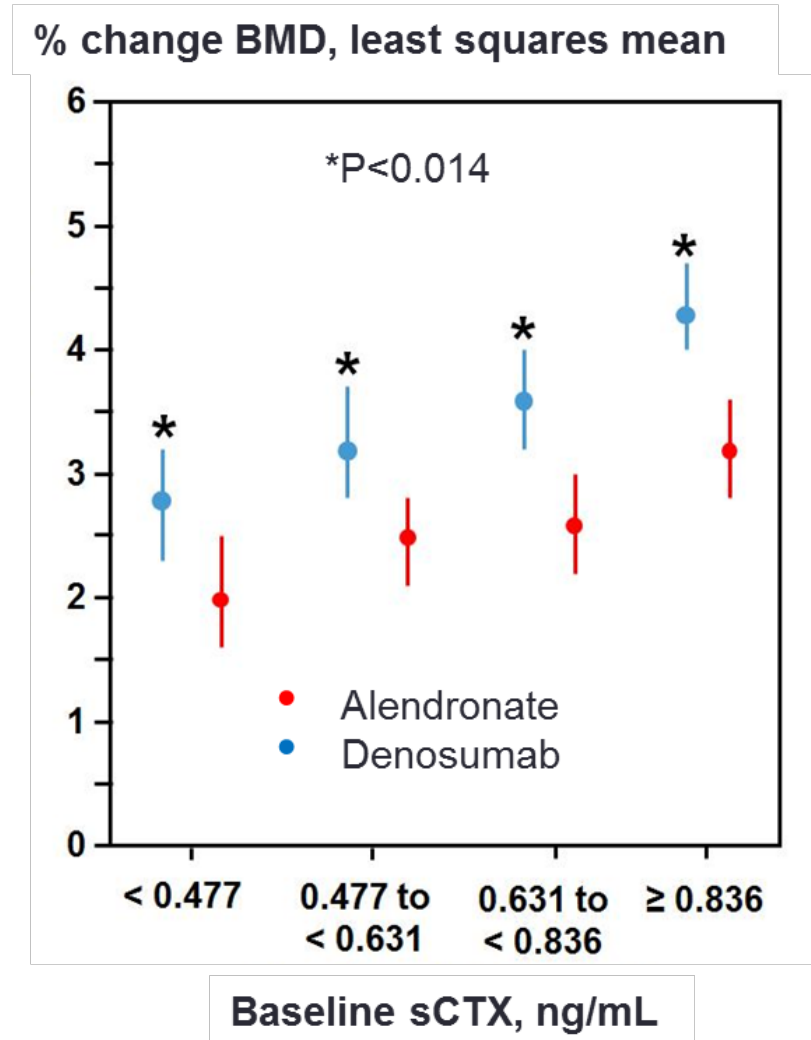


T score -2.8

# Can BTM inform choice of treatment?

- Hypothesis
  - High baseline bone turnover - treat with anti-resorptive
  - Low baseline bone turnover - treat with anabolic

# Baseline BTM predicts change in BMD



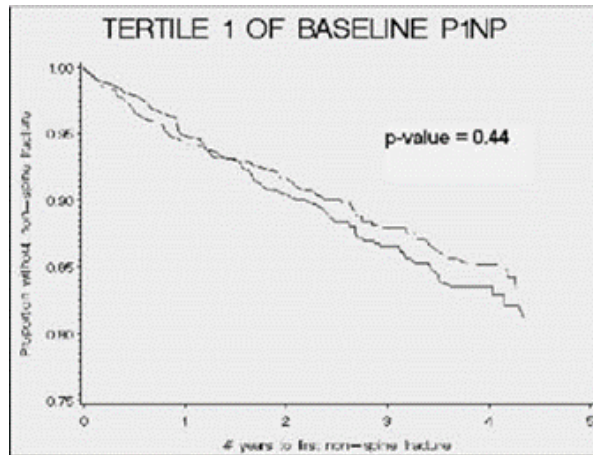
# Baseline BTM predict change in BMD

- Alendronate
  - Higher baseline BTM associated with greater spine and hip BMD increase over 3 years<sup>1</sup>
- Teriparatide
  - Higher baseline BTM associated with greater spine BMD increase over 1.5 years<sup>2</sup>

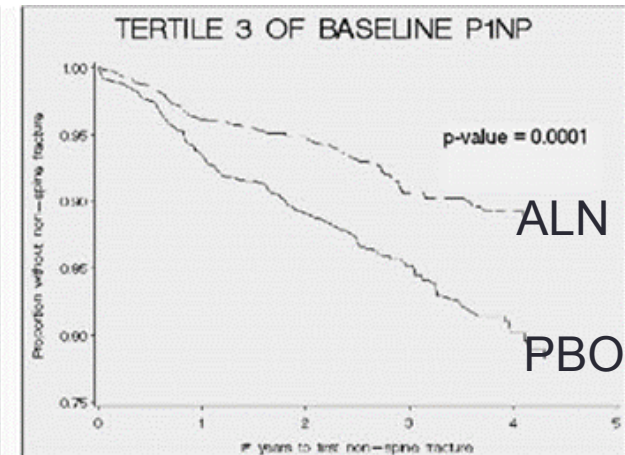
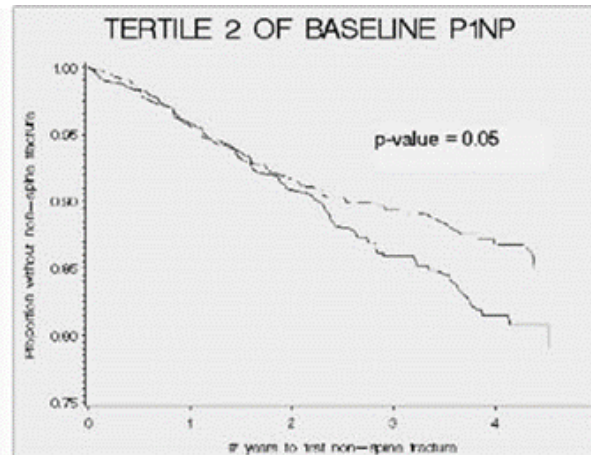


# Baseline BTM have limited predictive ability for fracture outcomes with alendronate

Low PINP < 42 ng/mL



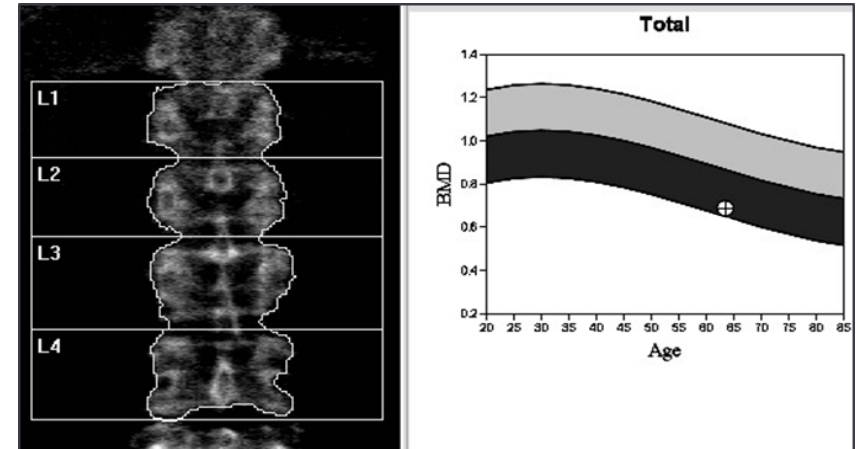
High PINP > 57 ng/mL



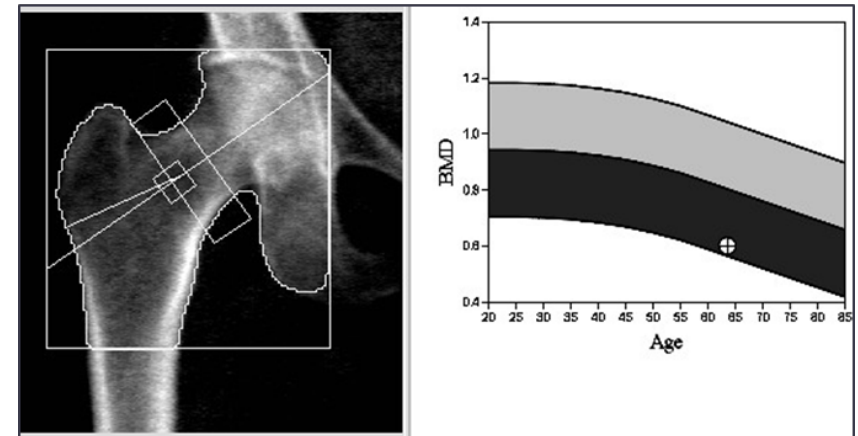
- Higher PINP predicted greater non-vertebral fracture reduction in osteoporotic women
- Higher bone ALP predicted greater vertebral fracture reduction in osteopenic women
- No significant predictive ability for CTX in this cohort

# Brenda, age 63

- Weekly oral alendronate
- Can BTM be used to:
  - Monitor her response to treatment?

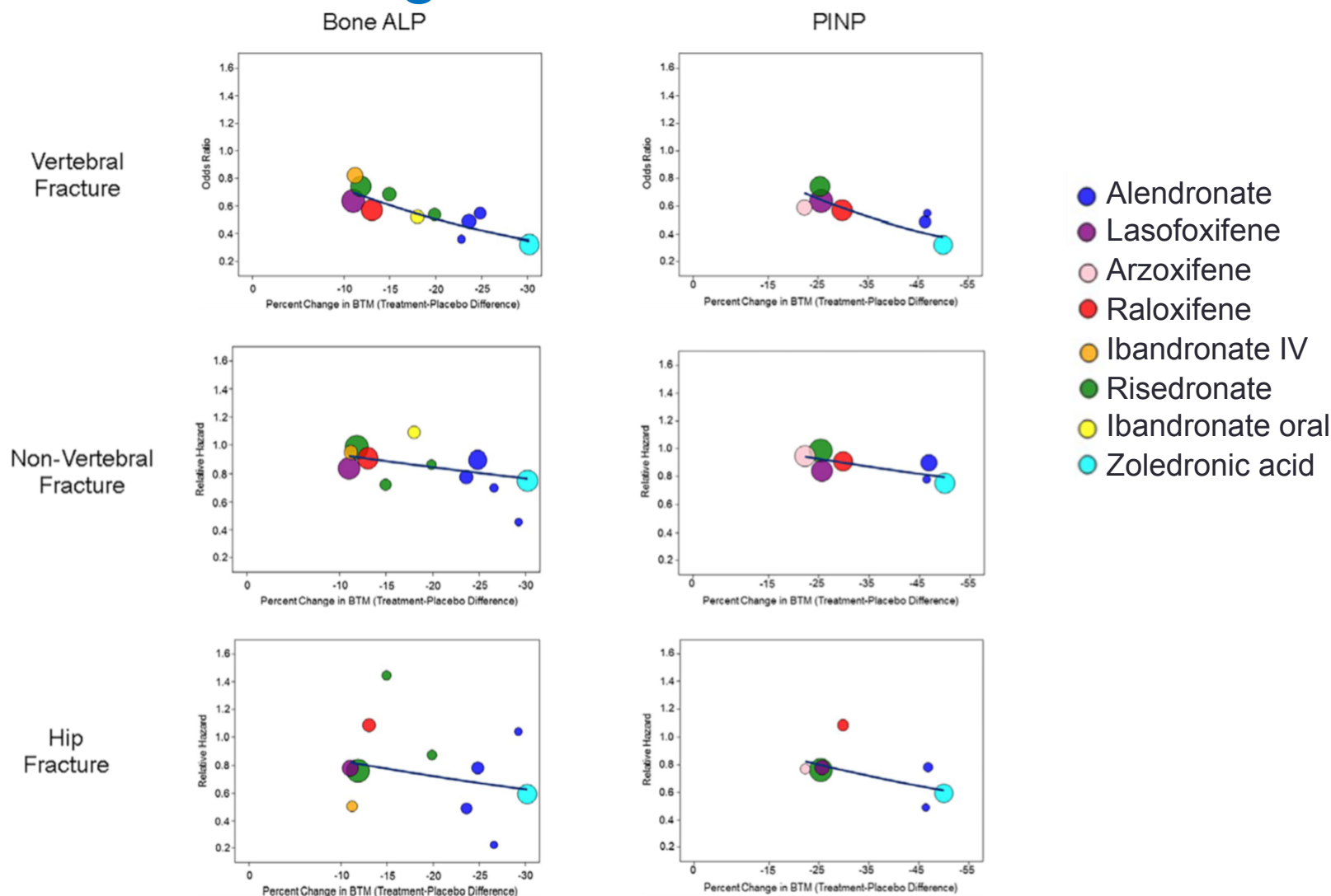


T score -3.3

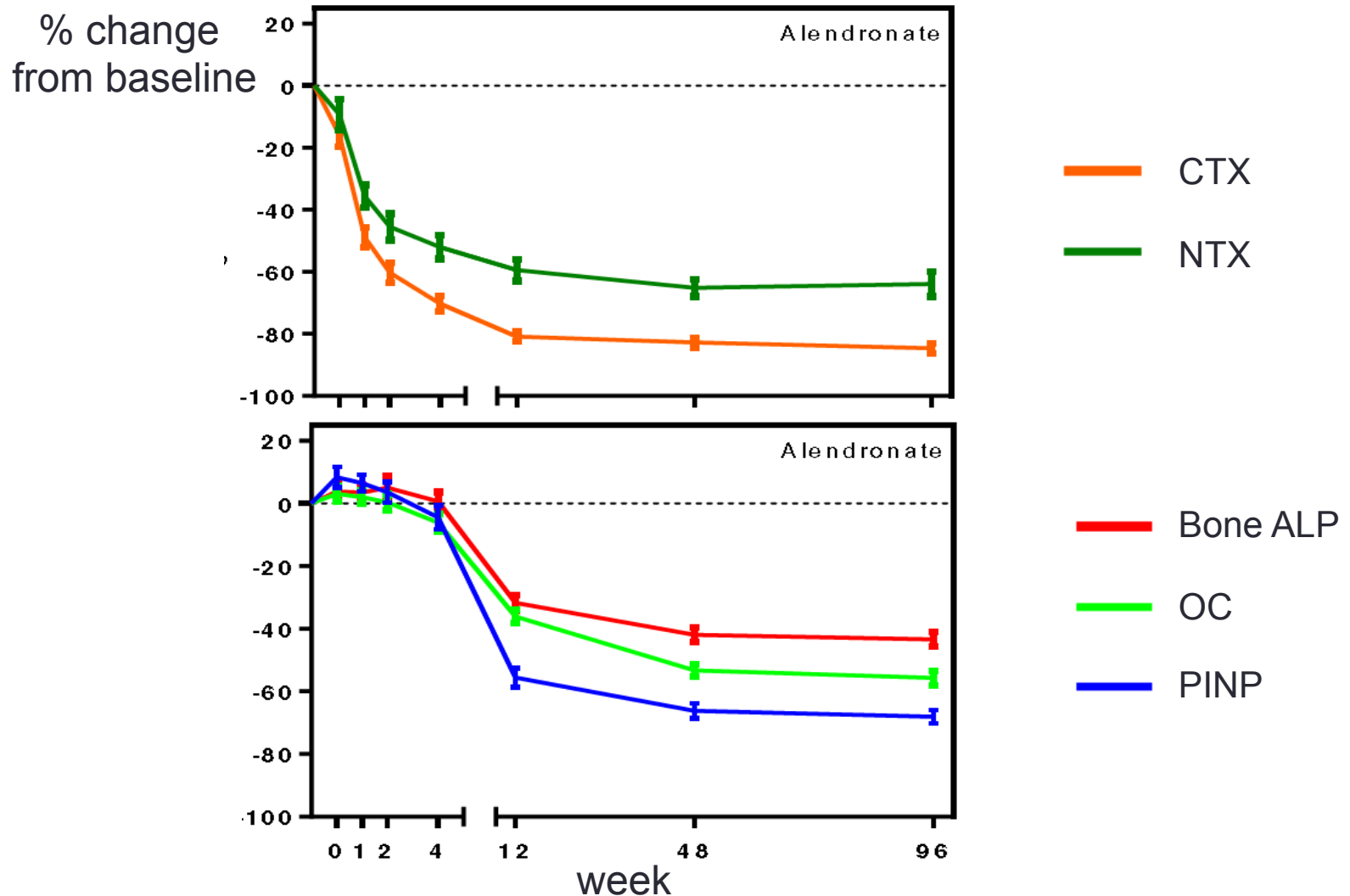


T score -2.8

# Greater suppression in bone turnover is associated with greater reduction in fracture risk

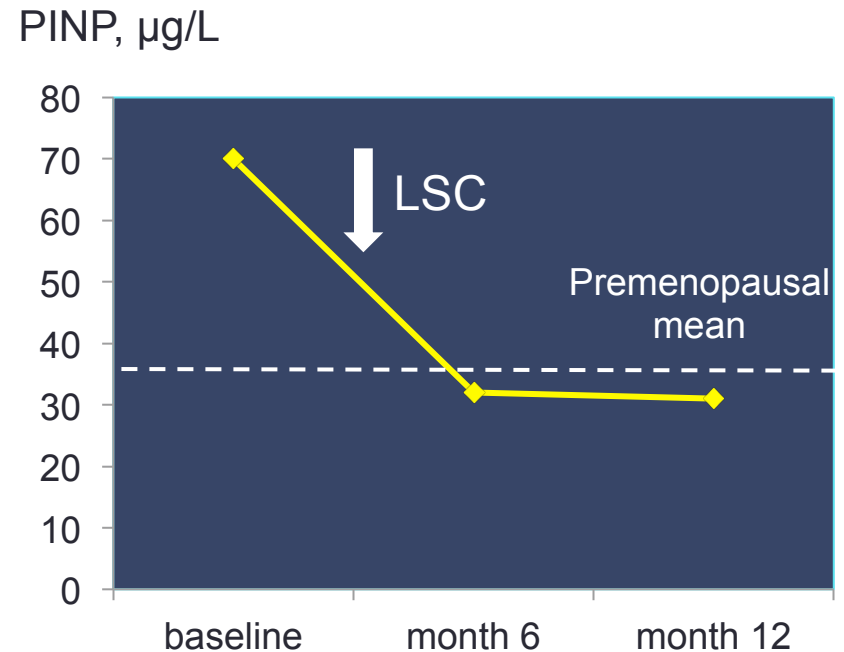


# Change in BTM with alendronate, TRIO study

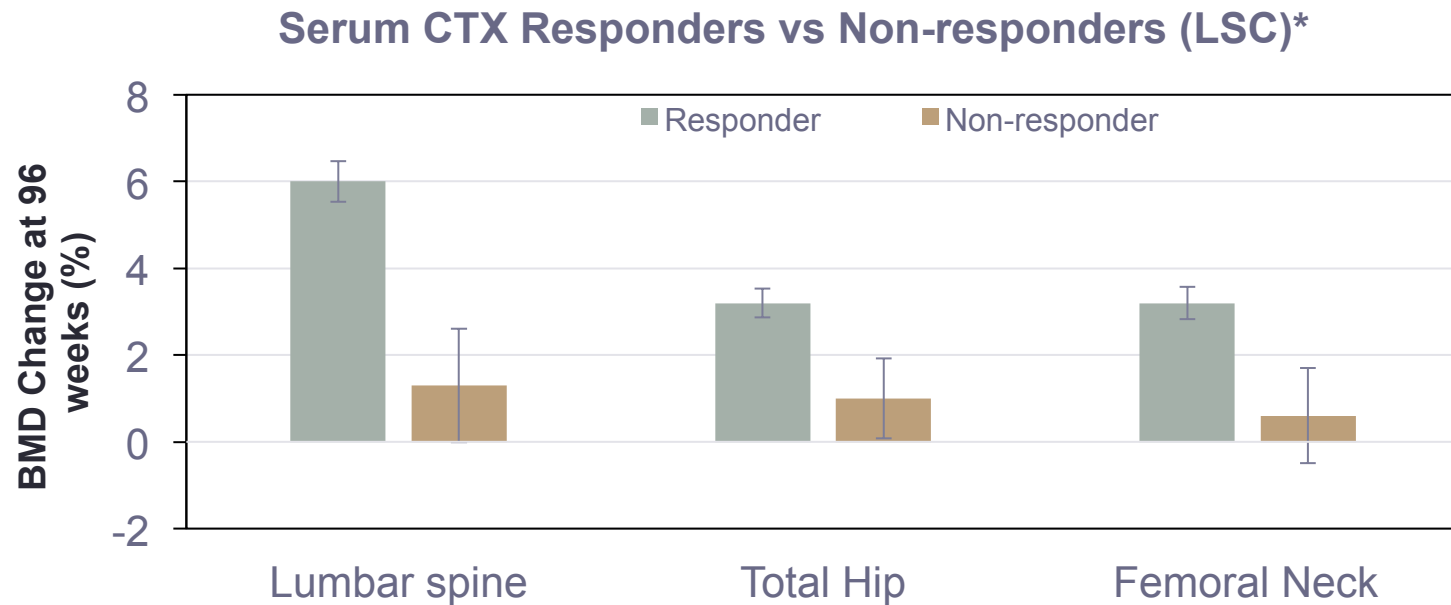


# Targets for anti-resorptive treatment

- Responder defined by change:
  - Greater than least significant change
  - To level associated with lower fracture risk
    - Clinical trial data
    - Lower half of the premenopausal reference range



# Can we identify those who fail to reach the target and do they do worse?



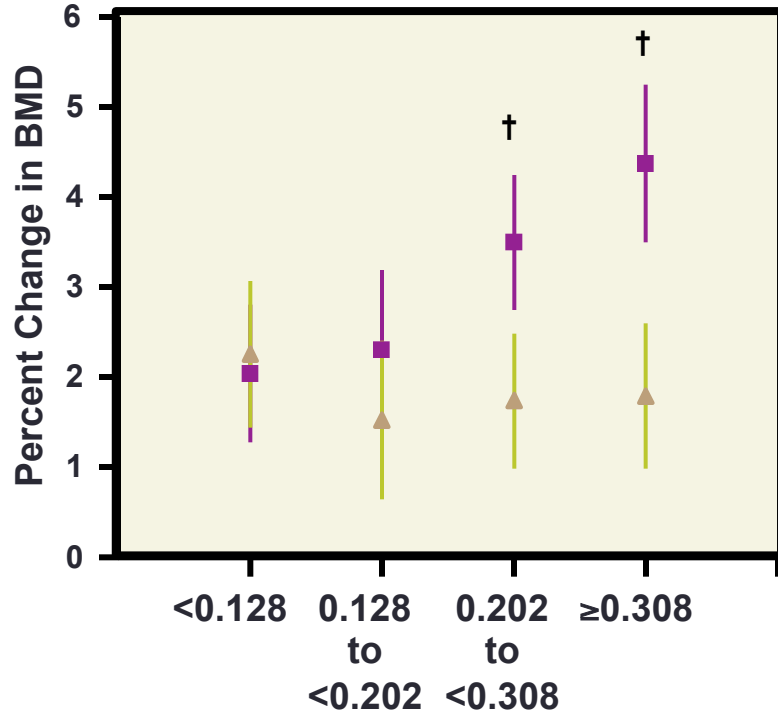
LSC – least significant change - >55% decrease at 12 weeks

CTX, type 1 C-telopeptide

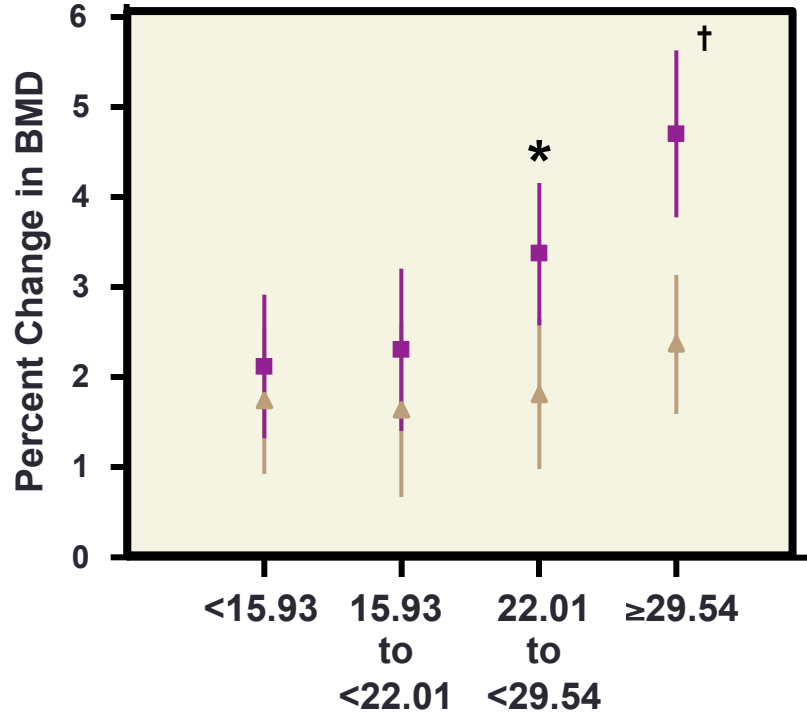
\*TRIO Study: Randomised study of alendronate, risedronate and ibandronate

# Denosumab after alendronate

■ Denosumab ▲ Alendronate



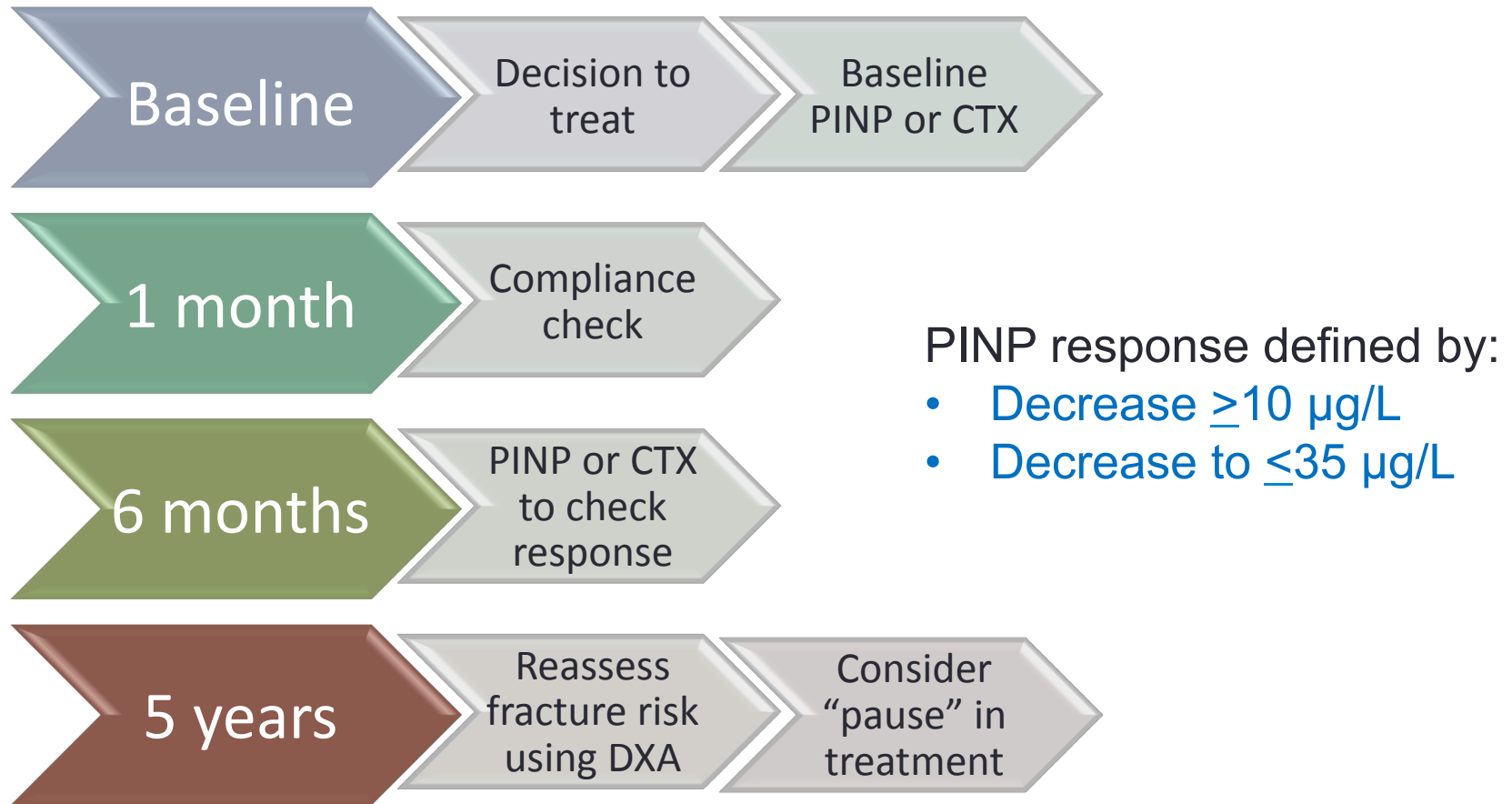
Baseline CTX (ng/mL)



Baseline P1NP (µg/L)

\* $P < 0.05$ ; † $P < 0.001$ .

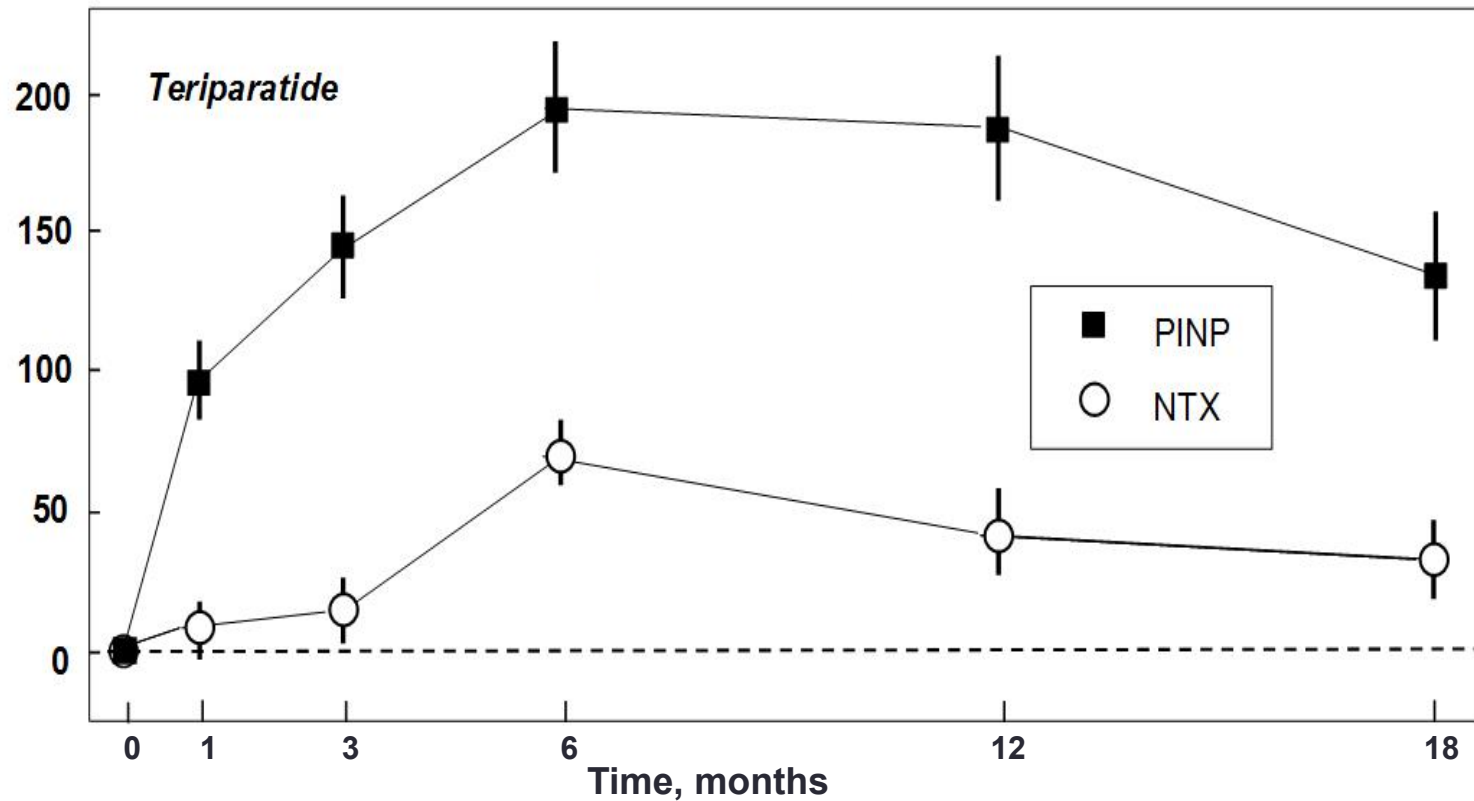
# Oral bisphosphonate monitoring algorithm



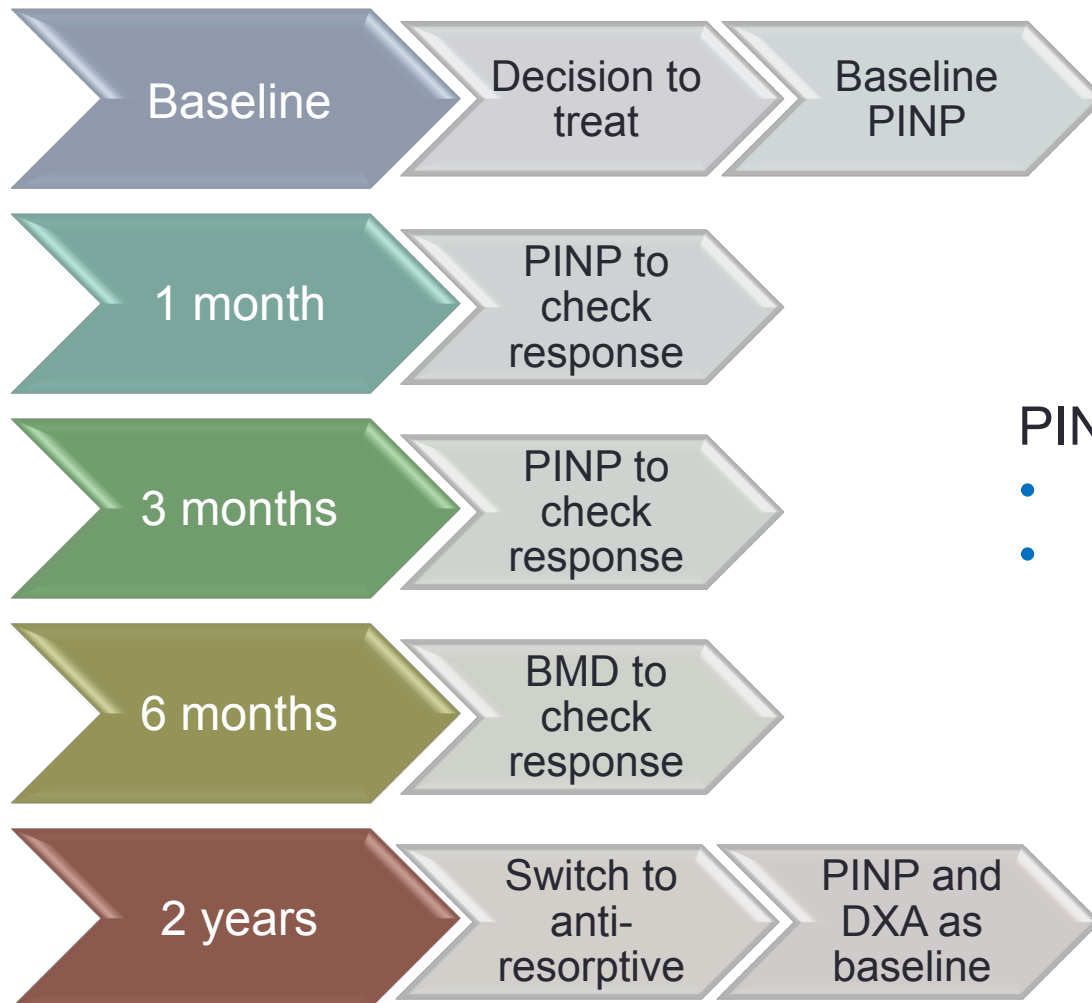


# Monitoring anabolic treatment

Change from baseline (% - mean  $\pm$  SE)



# Teriparatide monitoring algorithm

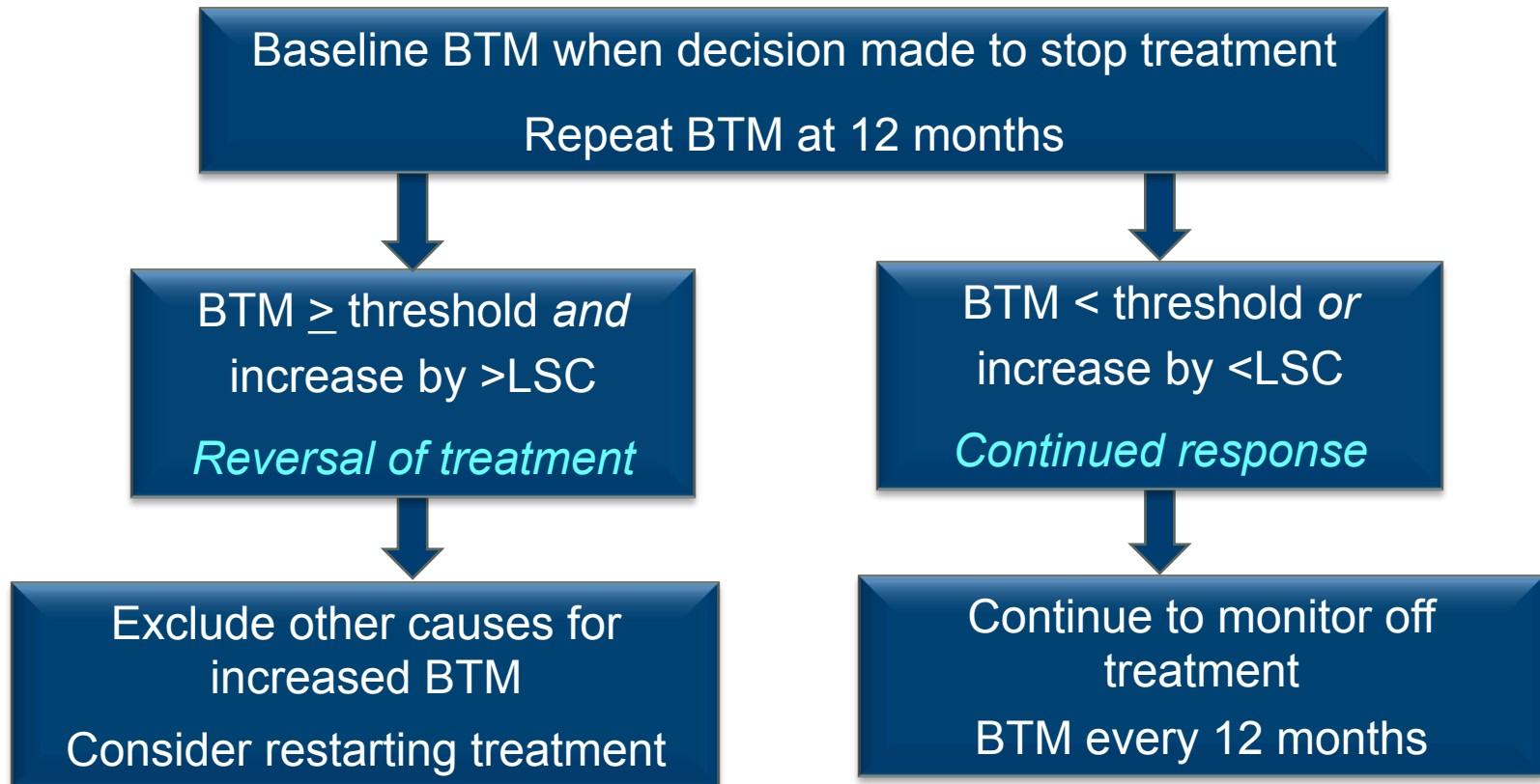


PINP response defined by:

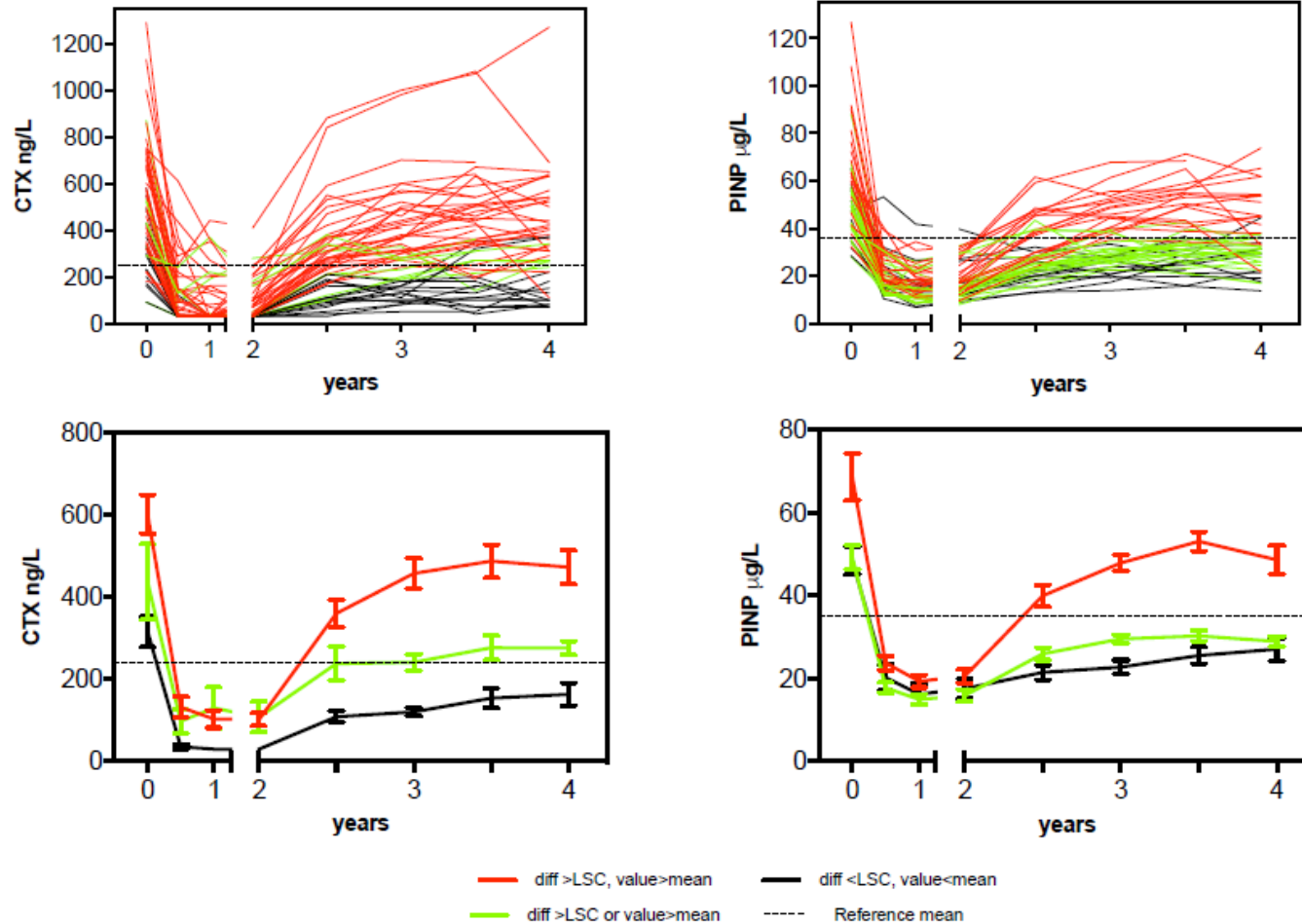
- Increase  $\geq 10$   $\mu\text{g/L}$
- Increase to  $\geq 69$   $\mu\text{g/L}$

# Monitoring offset

# BTM to monitor offset of bisphosphonate treatment



# BTM and offset – analysis from the TRIO study



# BTM and offset – analysis from the TRIO study

	Criteria	N (%)	Mean TH BMD change (95% CI) over 2 years	Mean difference (95% CI)
CTX	>mean	32 (65)	-2.34 (-3.10 to -1.58)	2.043 (0.70 to 3.39) **
	<mean	17 (35)	-0.29 (-1.54 to 0.96)	
	>LSC	32 (65)	-2.57 (-3.36 to -1.78)	2.714 (1.48 to 3.95) ***
	<LSC	17 (35)	0.145 (-0.77 to 1.05)	
PINP	>mean	21 (43)	-2.35 (-3.41 to -1.29)	1.26 (-0.10 to 2.63)
	<mean	28 (57)	-1.09 (-2.01 to -0.17)	
	>LSC	35 (71)	-2.10 (-2.91 to -1.29)	1.66 (0.19 to 3.13) *
	<LSC	14 (29)	-0.44 (-1.71 to 0.83)	

# Summary – BTM in clinical practice

- Useful for monitoring response
- Useful for guiding second-line treatment choice
- May be useful for monitoring offset
  
- No role yet in fracture prediction or first-line treatment choice
- Consider variability and validity