

# **Bone Markers in Osteoporosis: Prediction of Fractures & Treatment Monitoring**

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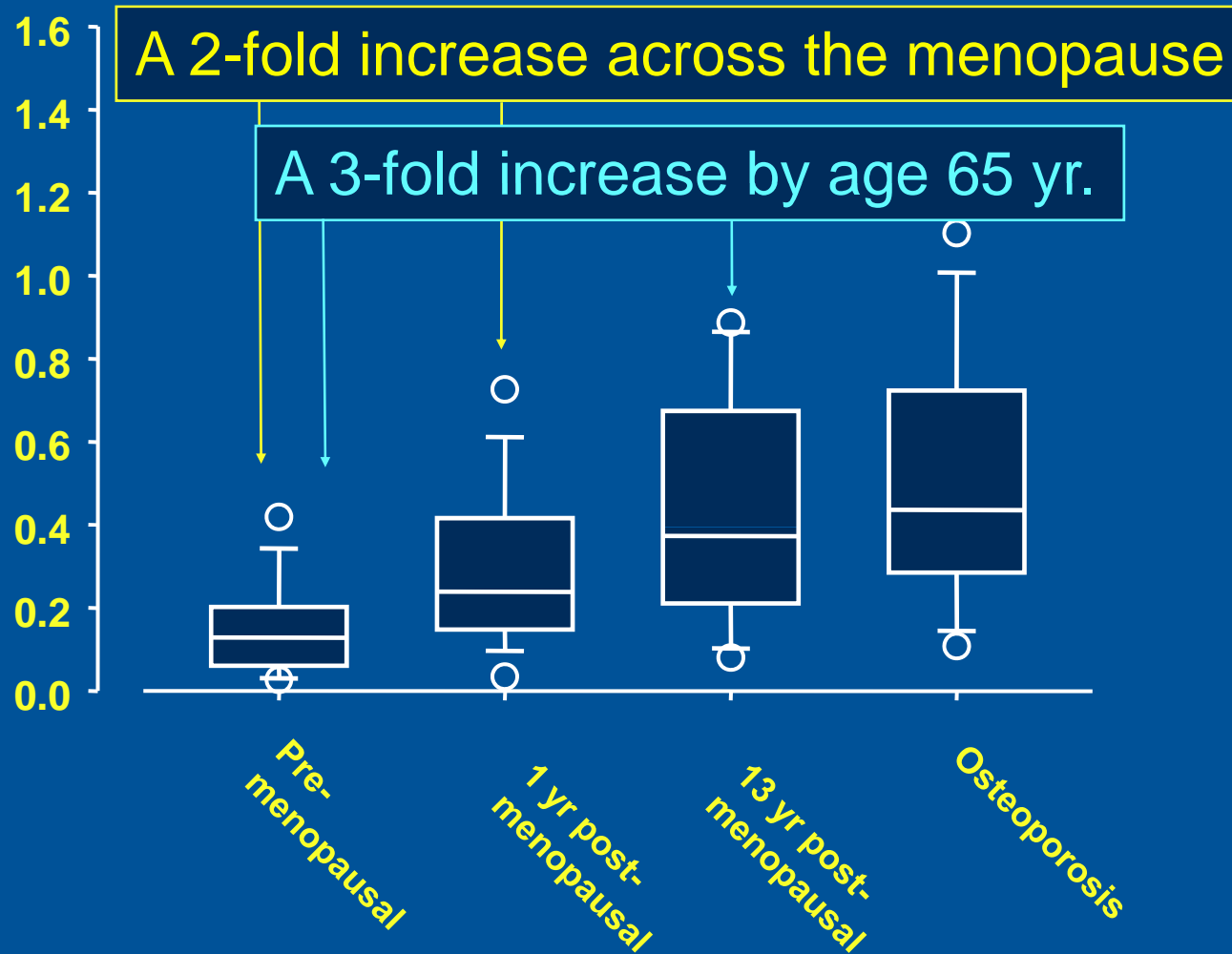
# Usefulness of Markers in the Individual Patient

## Outline

- **Bone turnover**
  - Changes at the menopause and with osteoporosis
- **High bone turnover markers**
  - Association with bone loss and fracture
- **Effects of treatment on bone turnover**
- **Treatment monitoring**
- **Example**

# The Effects of Age and Estrogen Status on Bone Remodeling

Activation frequency (#/yr)



\*Recker R, et al. *J Bone Miner Res* 2004;19:1628-33



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# BTMs Reflect Resorption and Formation

## – Matrix proteins

- osteocalcin (OC)
- procollagen type I propeptides
  - C-terminal (PICP)
  - N-terminal (PINP)

## – Enzyme

- bone isoform of alkaline phosphatase (bone ALP)

## – Collagen degradation products

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

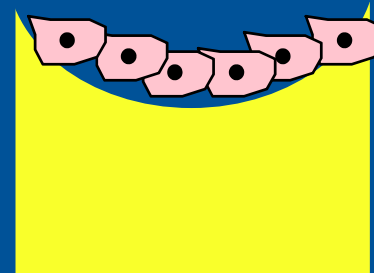
## – Enzyme

- tartrate-resistant acid phosphatase (TRACP), type 5b
- Cathepsin K

## • Related factors

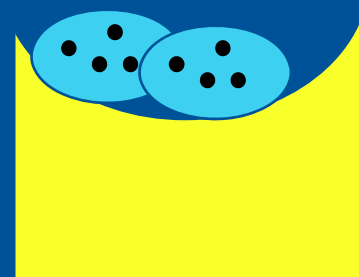
- OPG, RANK-L

## Formation



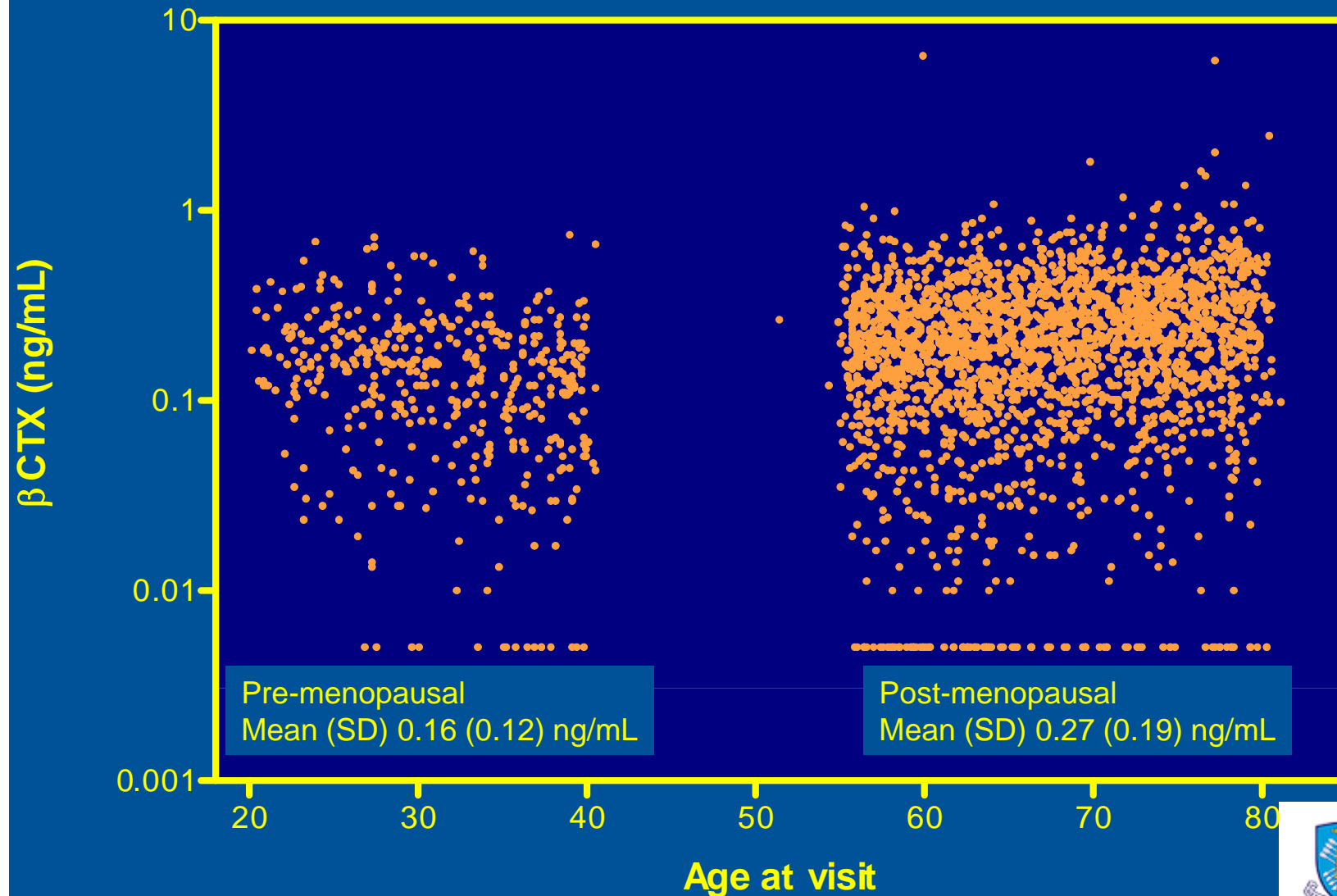
Commercially available assays  
Serum: OC, PICP, PINP,  
bone ALP, NTX, CTX, TRACP 5b  
Urinary: CTX, NTX, free DPD

## Resorption



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## Levels of Serum $\beta$ CTX in Women Community-based study, OPUS (n=2780)



Data from Blumsohn A et al, *J Bone Miner Res* 2003;18:1274-81

# High Bone Turnover Markers



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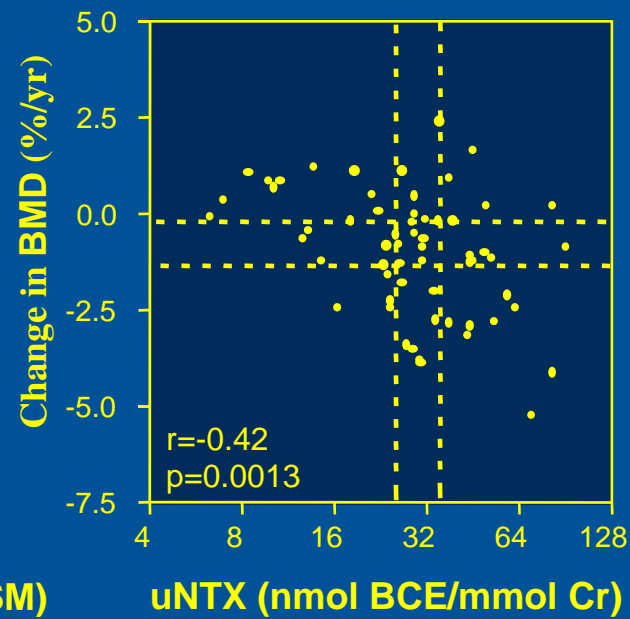
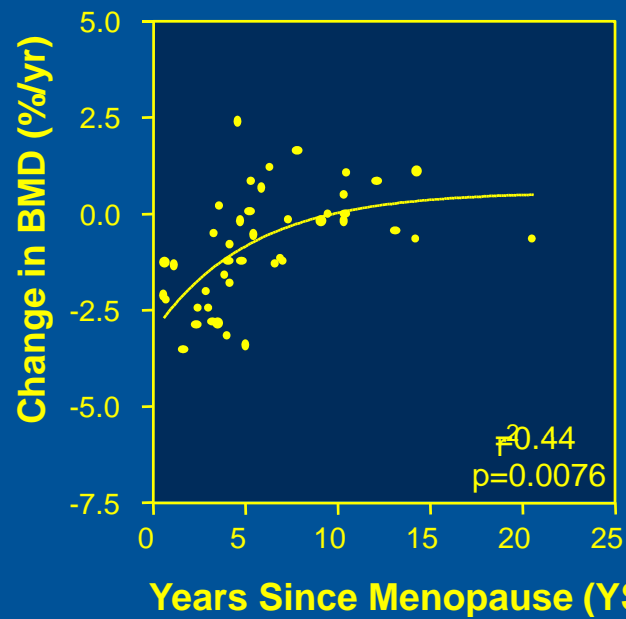
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## Bone Turnover Markers in Relation to Bone Loss and Fracture Risk

- **A high bone remodelling rate is associated with**
  - More rapid bone loss in postmenopausal women<sup>1</sup>
  - Increased risk of fractures<sup>2</sup>
- **The association with fracture is variable<sup>2</sup>**
  - Hazard ratios of between 1 and 2
  - More consistently observed for bone resorption than bone formation markers

1. Stepan JJ. Osteoporos Int. 2000; 11 Suppl.6:S45-54;  
2. Garnero P. Osteoporos Int. 2000; 11 Suppl.6:S55-65.

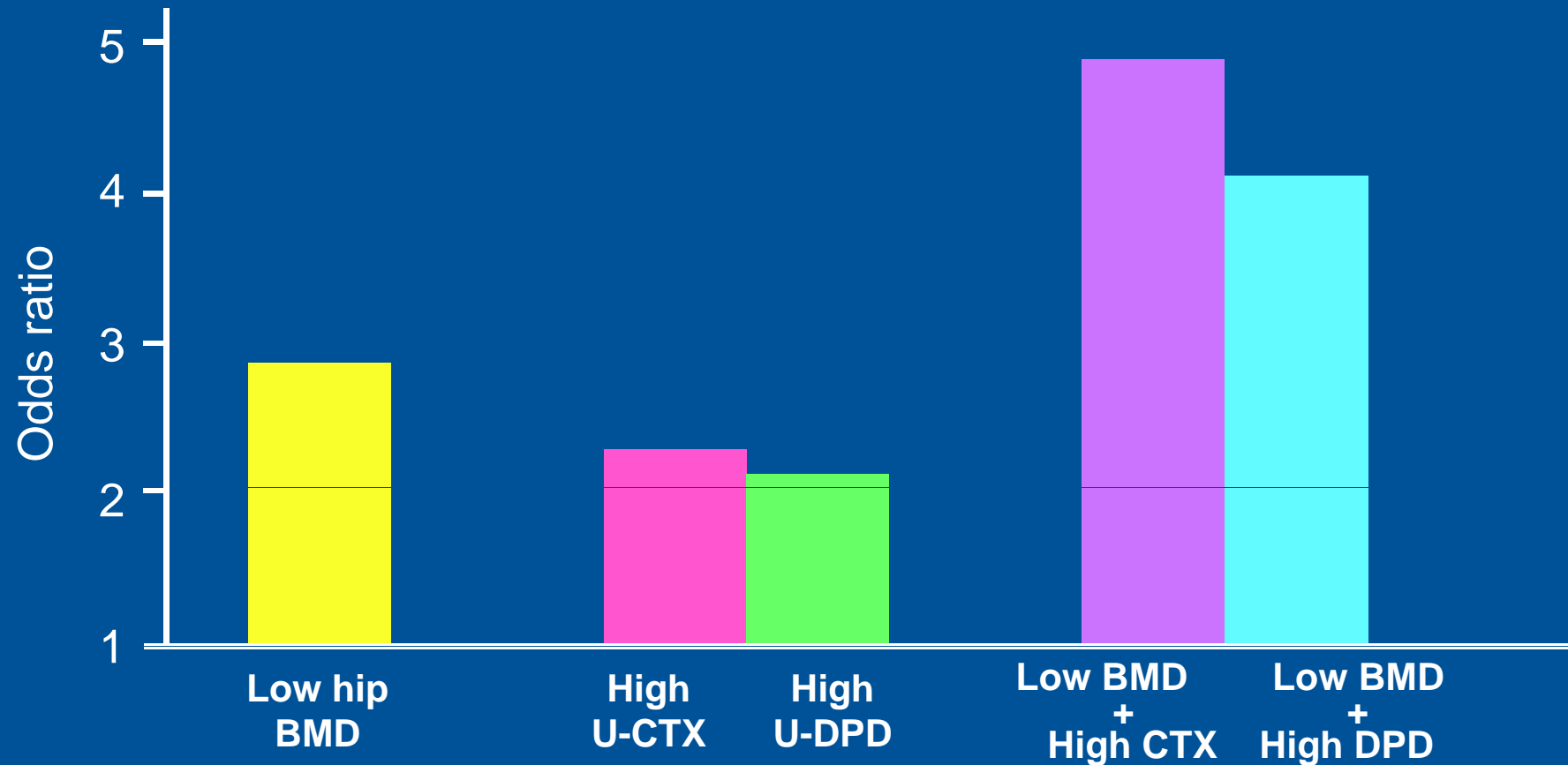
# Bone Turnover and Bone Loss from the Spine



Rogers A, et al. *J Bone Miner Res.* 2000;15:1398-1404.

# High Bone Resorption Markers May Predict Hip Fracture Risk in Elderly Women – the EPIDOS Study

EPIDOS = Epidemiologie de l'Osteoporose



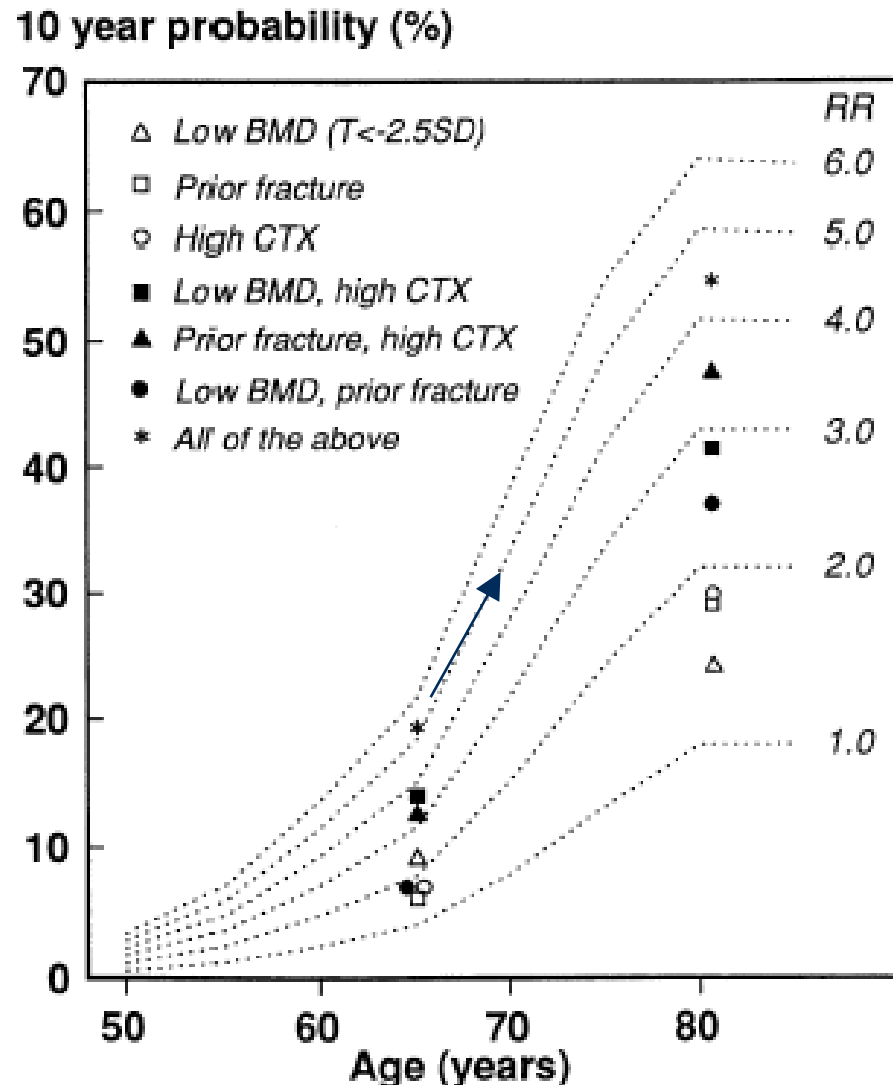
BMD = bone mineral density; U = urinary.

Garnero P, et al. *J Bone Miner Res.* 1996;11:1531-38.



[www.shef.ac.uk/bmg](http://www.shef.ac.uk/bmg)

# 10-year Risk of Hip Fracture



- This approach has now been implemented as the WHO FRAX™ score

– Doesn't include bone markers

Johnell O, et al. *Osteoporosis Int.* 2002;13:523-6.

# Treatment Effects



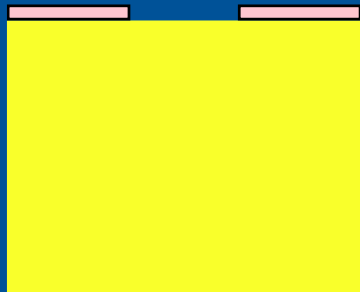
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# Postmenopausal Osteoporosis

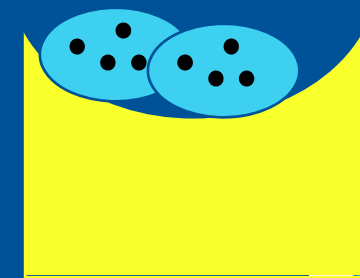
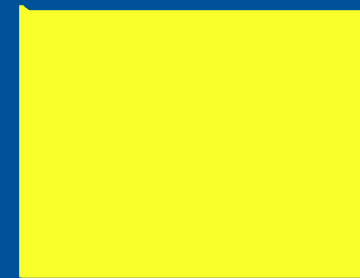
## Effects of Treatments

Quiescence



✦ Activation

Remodelling Balance



Resorption

*Anti-catabolic* Drugs

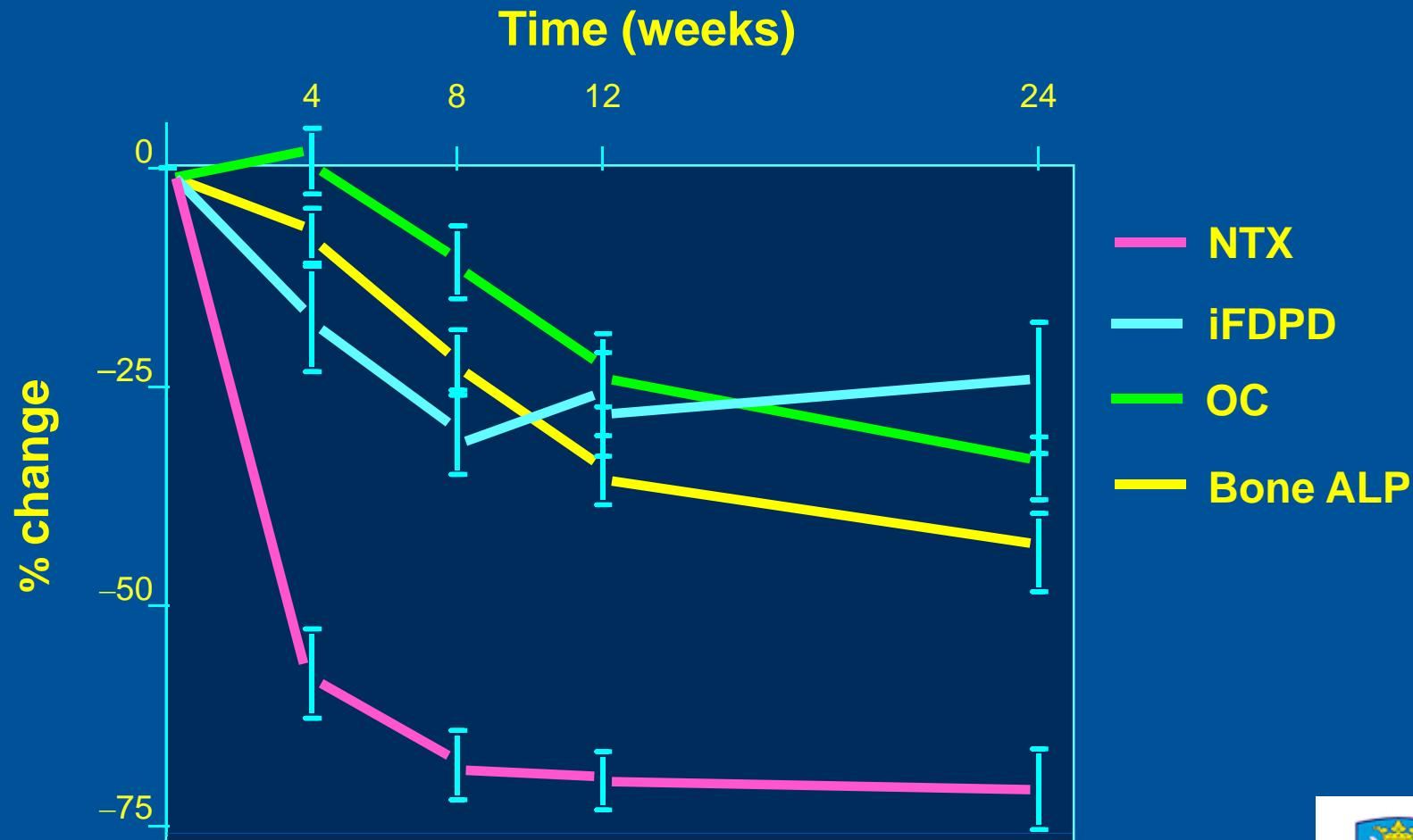
- Decrease activation frequency
- Restore remodelling balance



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# Changes in Bone Resorption Marker NTX With Alendronate Therapy in Osteoporosis – Mean Decrease 75%



ALP = alkaline phosphatase; iFDPD = free deoxypyridinoline;  
OC = osteocalcin; NTX = N-terminal telopeptide.

Machado A, et al. *J Bone Miner Res.* 1999;14:602-8.



[www.shef.ac.uk/bmg](http://www.shef.ac.uk/bmg)

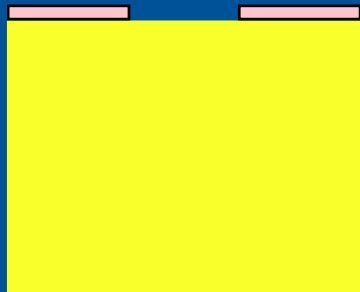
# Treatment Effects on Telopeptide Markers CTX and NTX

- **Different responses to treatments**
  - Strontium, calcium, 10 to 20%
  - Raloxifene, 30 to 40%
  - HRT and risedronate, 50 to 60%
  - Zoledronic acid, ibandronate, alendronate, 70 to 80%
- **All reduce vertebral fractures**
  - Mechanism may involve effects other than a decrease in bone resorption
- **The telopeptide response helpful for any particular treatment**

# Postmenopausal Osteoporosis

## Effects of Treatments

Quiescence

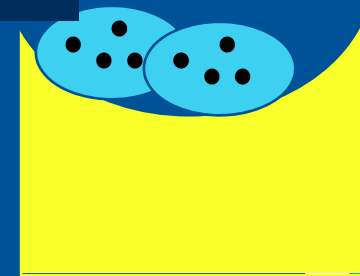
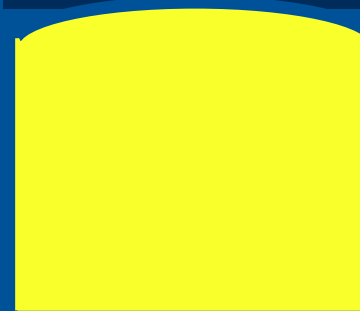


*Anabolic Drugs*

- Increase activation frequency
- Induce positive remodelling balance



Positive Remodelling Imbalance



↑↑ ↑ Activation

Resorption

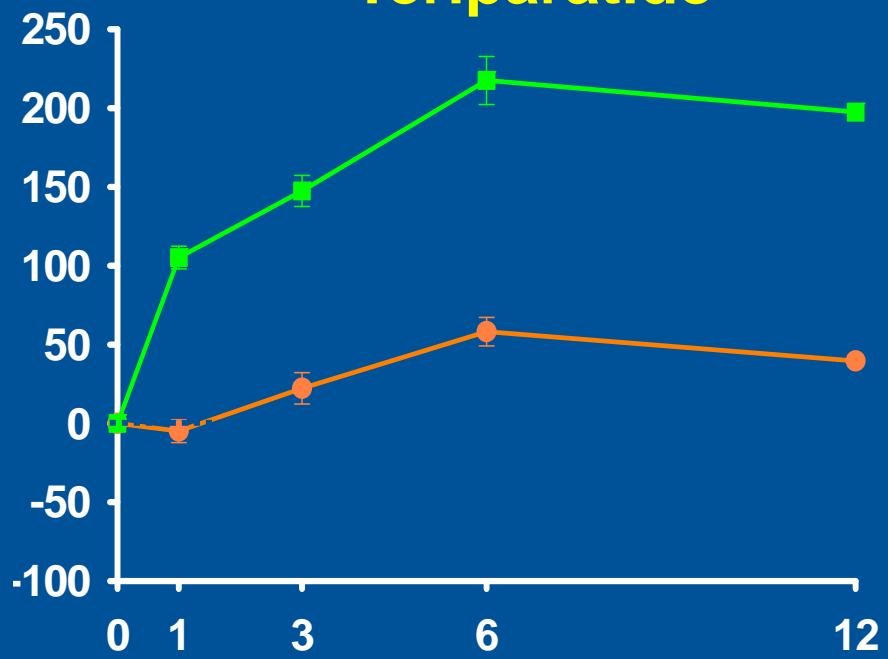


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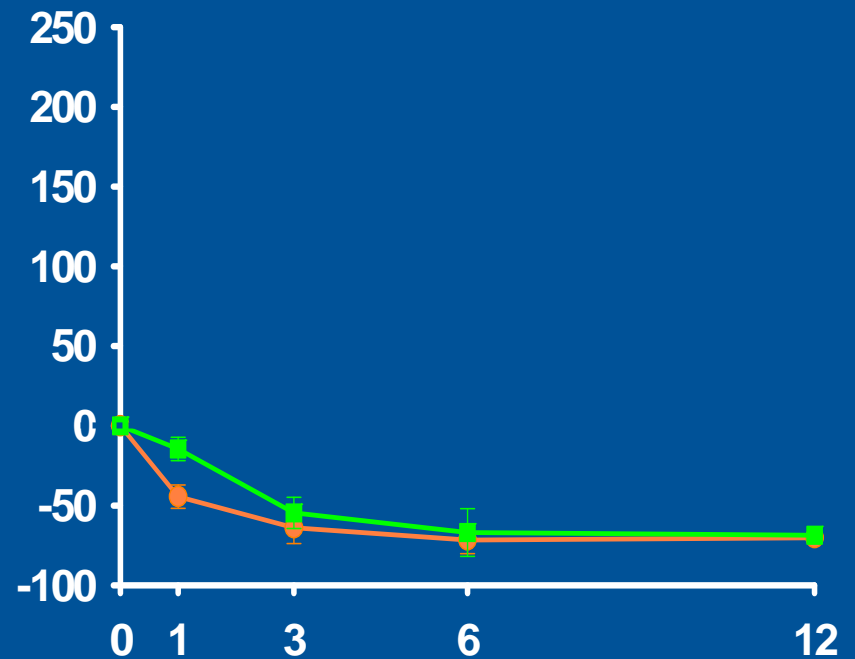
# Randomized, Controlled Trial of Alendronate or Teriparatide in Postmenopausal Osteoporosis

% Change from baseline (Mean  $\pm$  SE)

## Teriparatide



## Alendronate



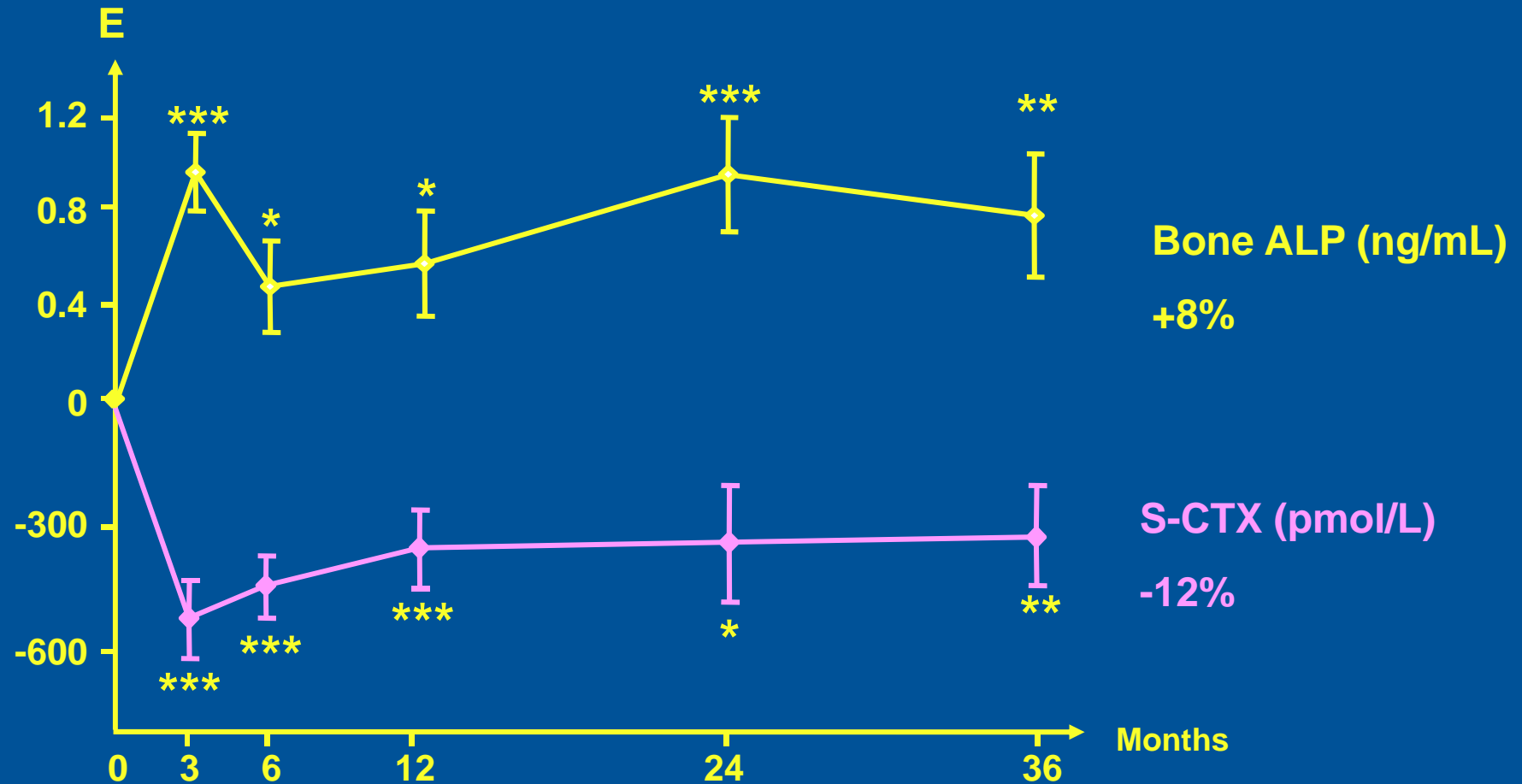
- PINP (Formation)
- NTX (Resorption)

$P < 0.001$   
between-group difference  
teriparatide vs. alendronate



Arlot M, et al. J Bone Miner Res. 2005;20:1244-53.

# Strontium increases bone formation markers and decreases bone resorption markers, but the effects are small (<10%)



E= Estimate of difference between strontium group and placebo group, covariance analysis, baseline adjusted \*\*\*  $p < 0.001$ ; \*\*  $p < 0.01$ ; \*  $p < 0.05$



# Treatment Monitoring

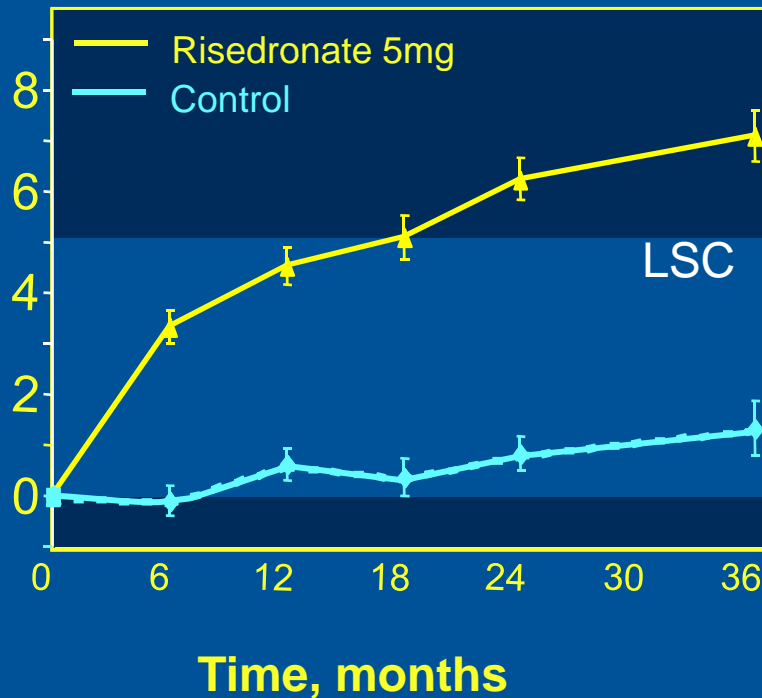


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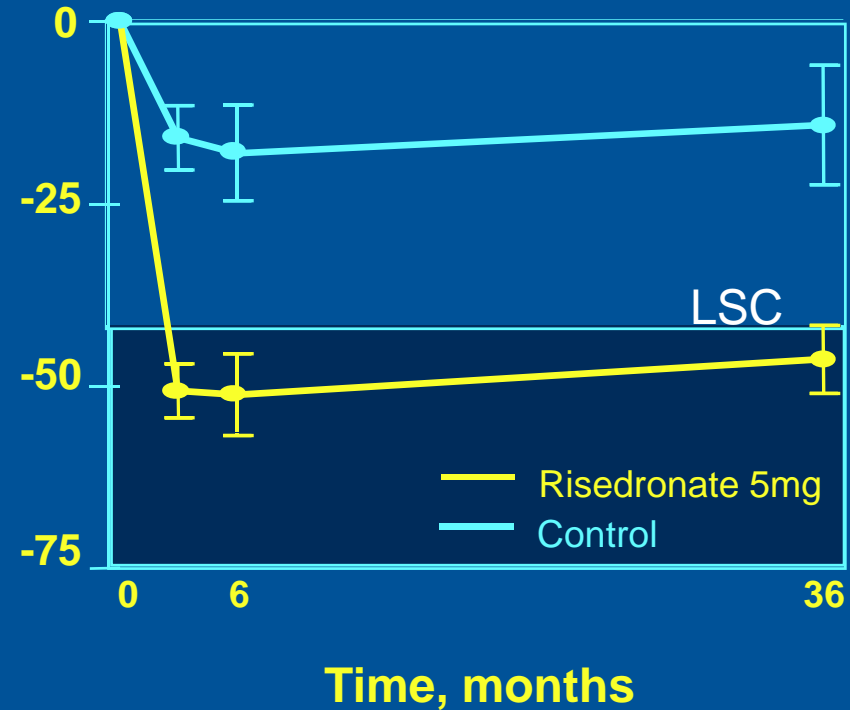
[www.shef.ac.uk/bmq](http://www.shef.ac.uk/bmq)

# The average response to risedronate 5 mg exceeds LSC earlier for BTM (3 months) than BMD (18 months)

### Spine BMD, % $\Delta$ from baseline



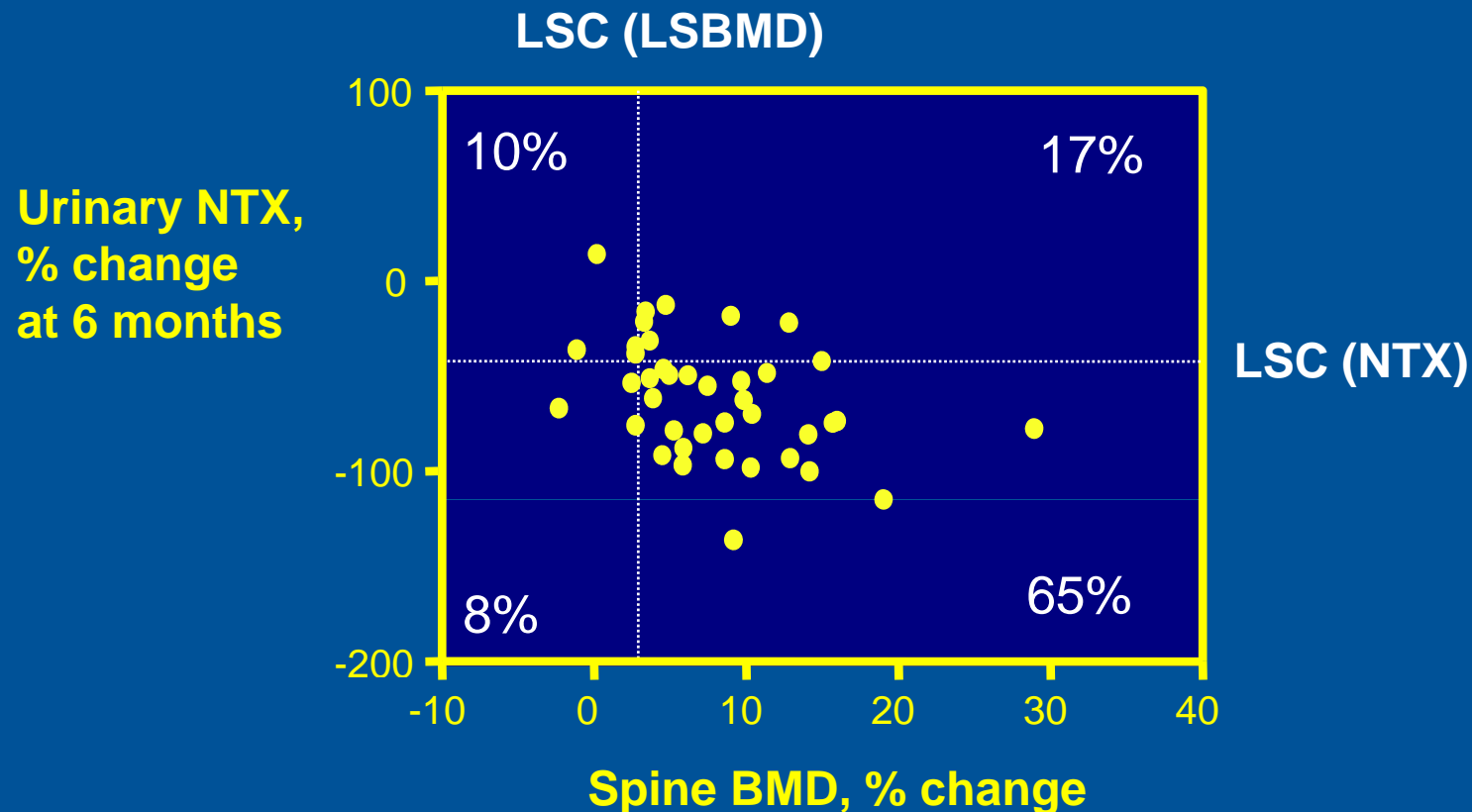
### NTX, % $\Delta$ from baseline



LSC, least significant change



# Using BMD and Bone Turnover Markers in Clinical Practice: Anti-Catabolic Therapies

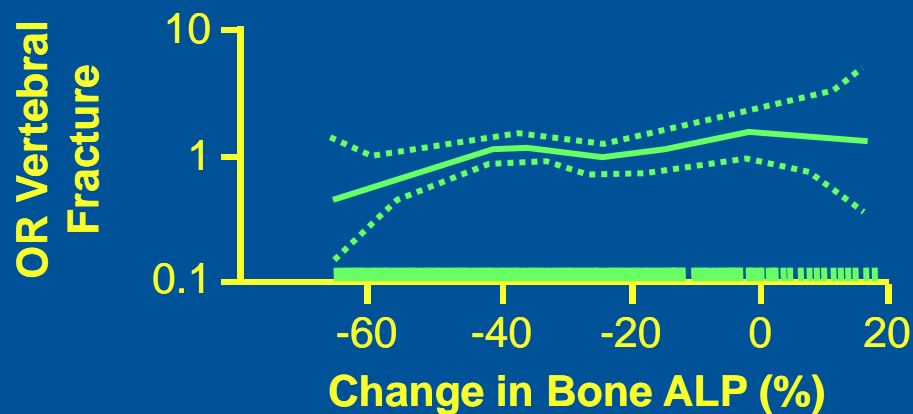
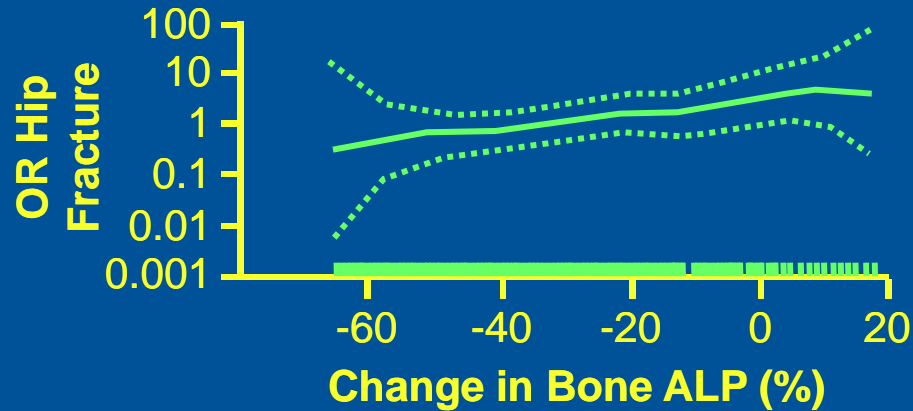


LSC, least significant change  
BMD, bone mineral density



## Fracture Incidence Over 3.6 Years of Alendronate, vs 12-Month Bone ALP: % Change From Baseline

- One year change in bone ALP in alendronate-treated women



OR=Odds ratio.

Bauer DC et al. *J Bone Mineral Res.* 2004;19:1250-1258.

- FIT study

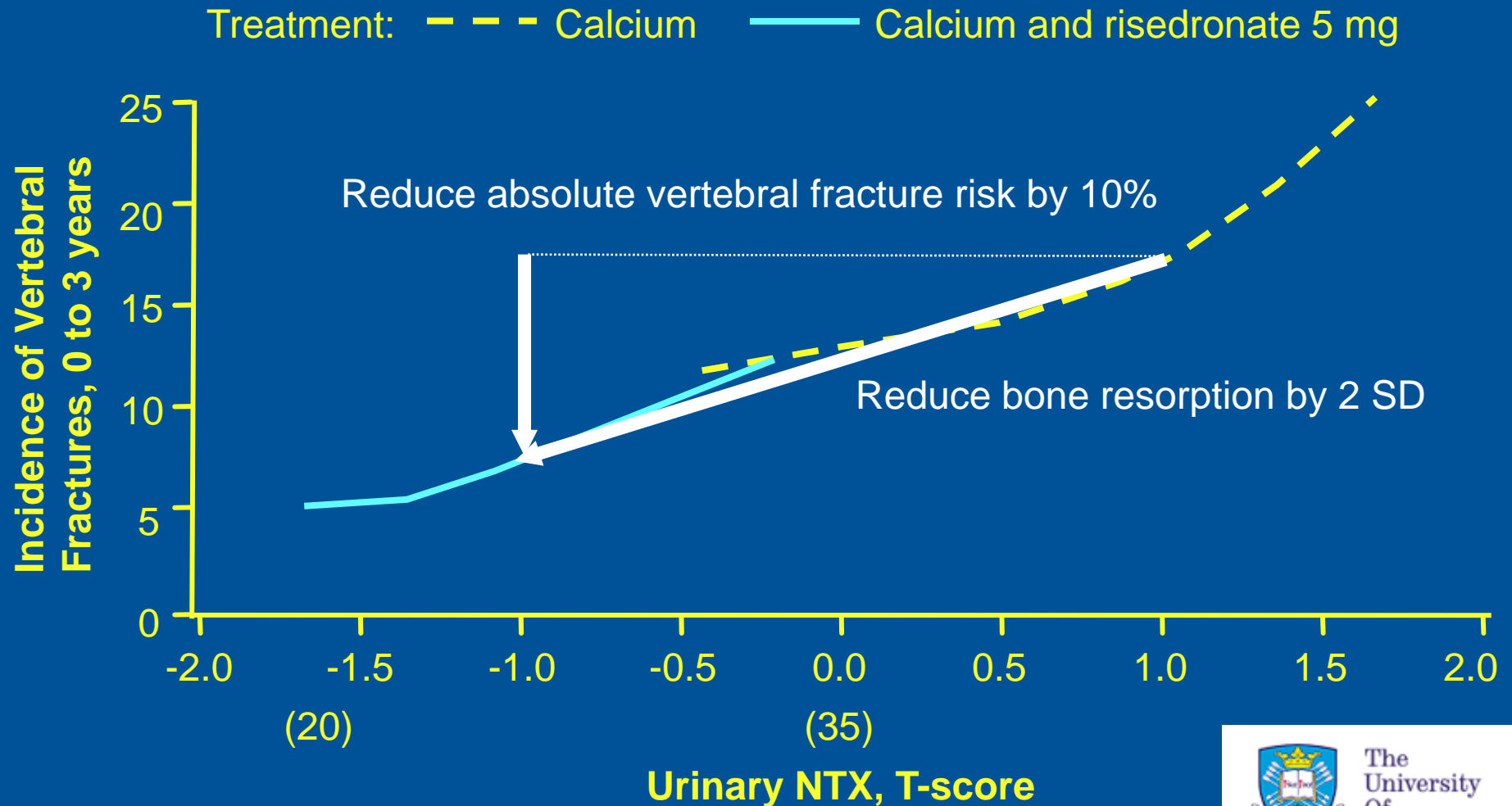
- 3105 in alendronate arm
- One-year change in bone ALP (insufficient samples for PINP or CTX)
- 3.6 years of follow-up for fracture

# Surrogates for Fracture Risk Reduction

Proportion of 3 year fragility fracture treatment effect explained by surrogates

Surrogate	Proportion explained	95% CI
Femoral neck BMD	14%	7, 21%
Urinary NTX	52%	29, 75%
NTX and FNBMD	67%	39, 100%

# We Would Like to Suppress Bone Turnover to Levels Found in Healthy Young Women (Who Have an Average T-Score of 0)



Eastell R, et al. *J Bone Miner Res.* 2003;18:1051-1056.

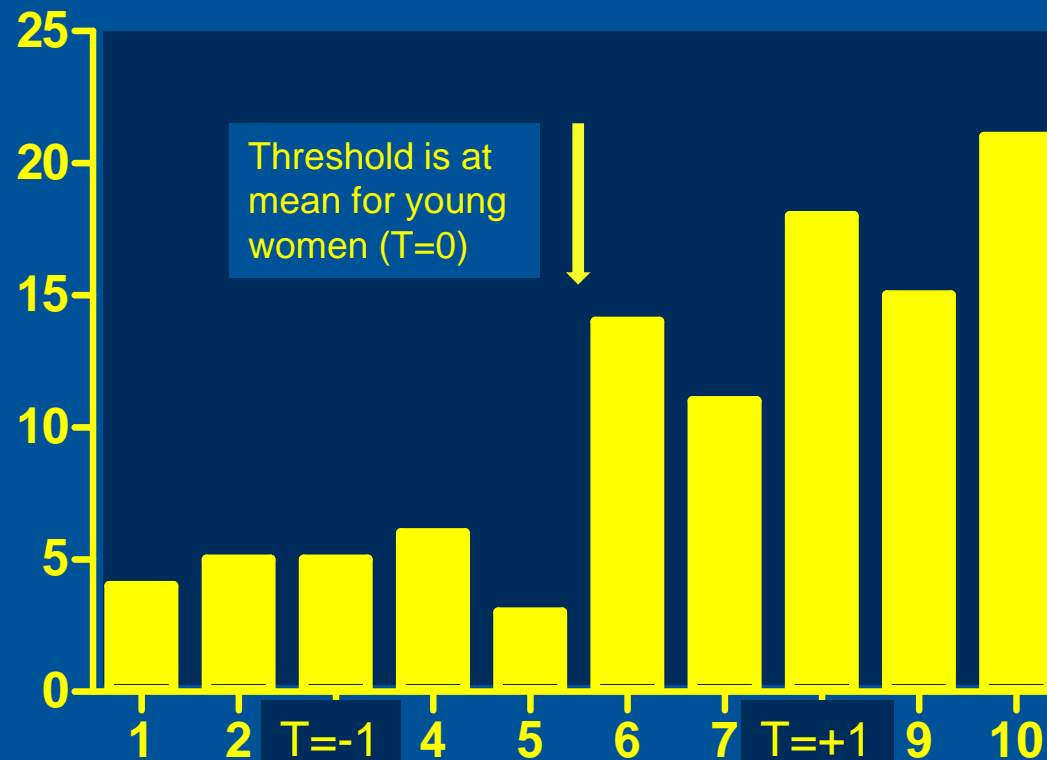


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# Vertebral Fractures over 3 years and Bone Resorption Combined Treated and Placebo Groups

## Decile Analysis, about 66/decile

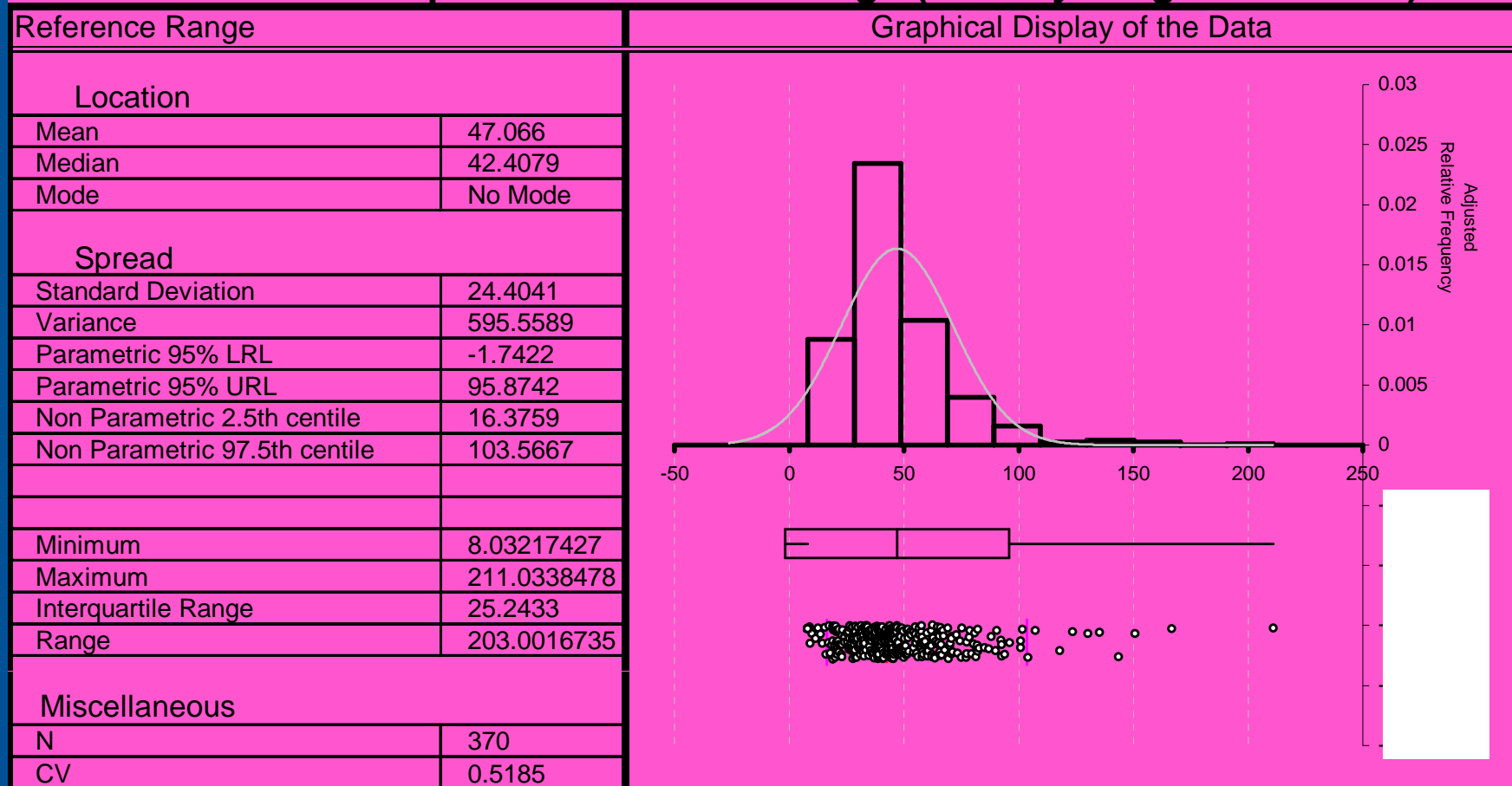
No. women with  
vertebral fractures



Urinary CTX (T-score) at 3 to 6 months, decile

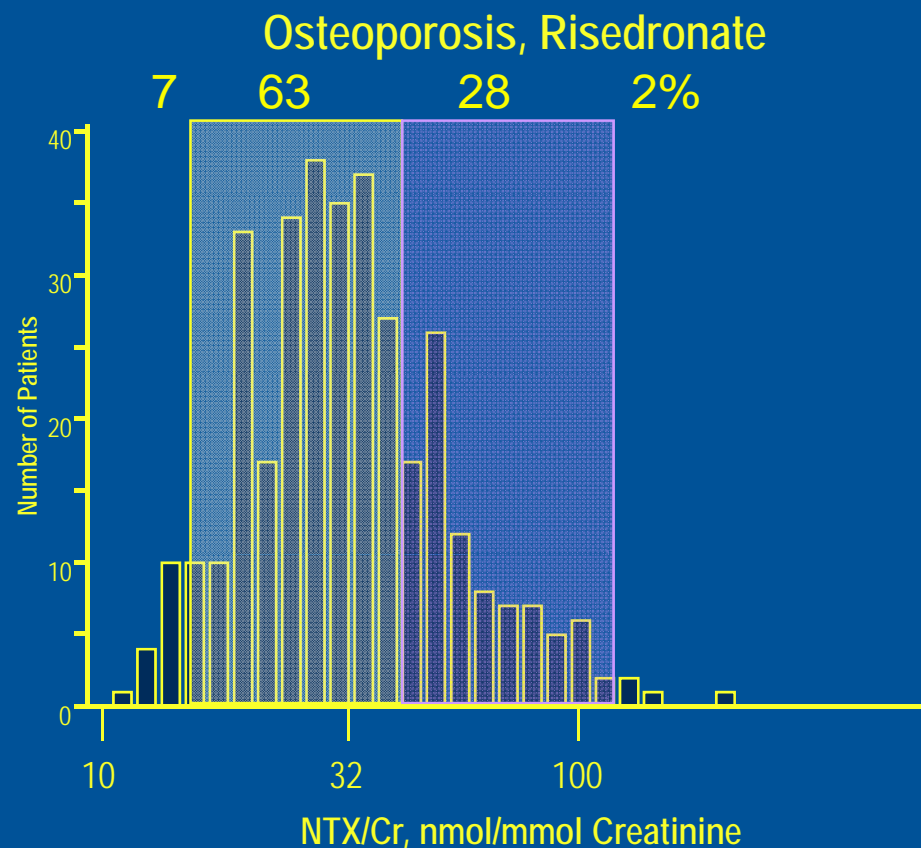
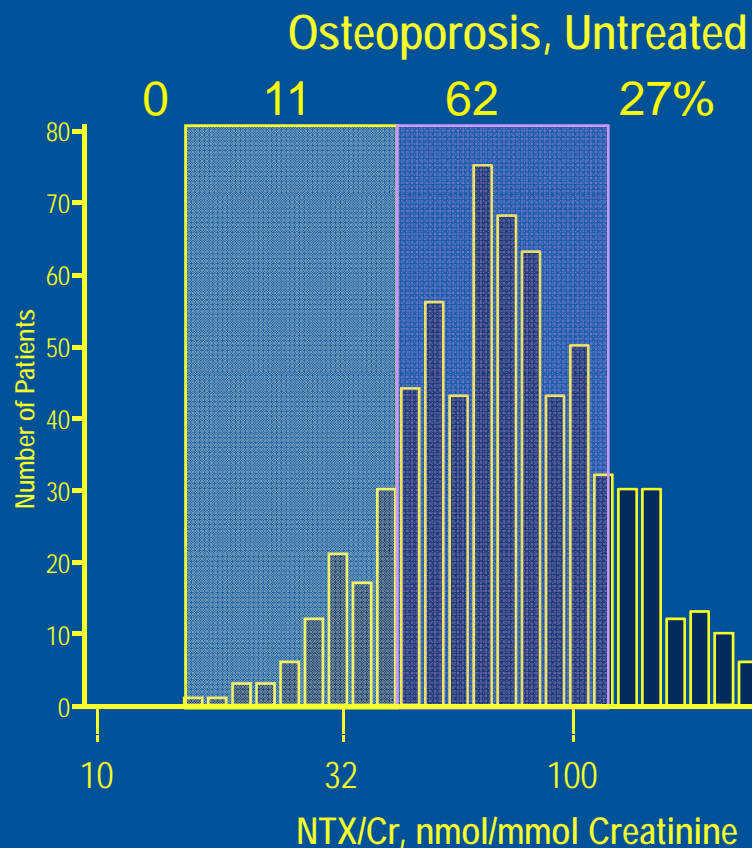
# Develop Reference Range for Women Based on at least 150 Healthy Young Women

## NTx/Cr Premenopausal Reference Range (Healthy drug-free subset)



# Effect of Risedronate Therapy on Bone Resorption

Lower half of reference interval
  Upper half of reference interval



# Does monitoring affect adherence?



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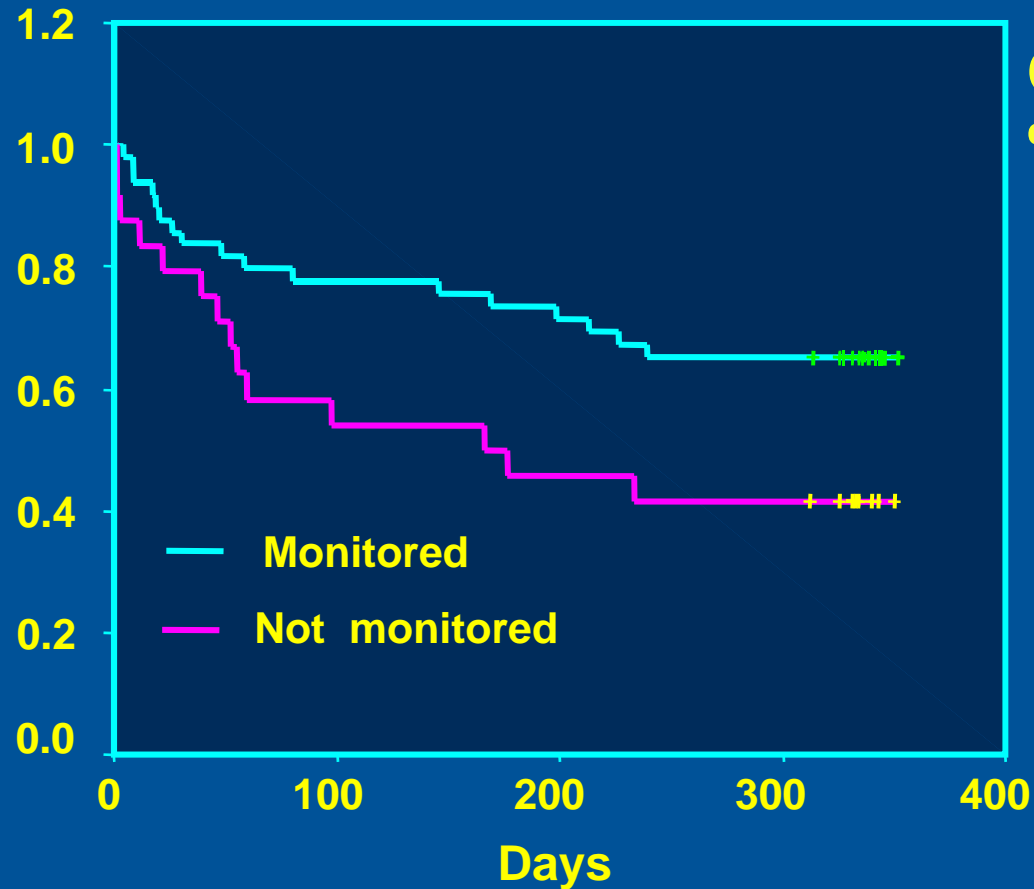
## Does Monitoring affect Adherence?

- **75 women with osteopenia**
- **Treated with Raloxifene and randomised**
  - Repeat prescriptions (no medical contact)
  - Visit nurse every 3 months
  - Visit nurse and monitor BTM every 3 months
- **Measured compliance using MEMS caps**



# Monitoring improves adherence to treatment with Raloxifene

Proportion of patients who remained adherent



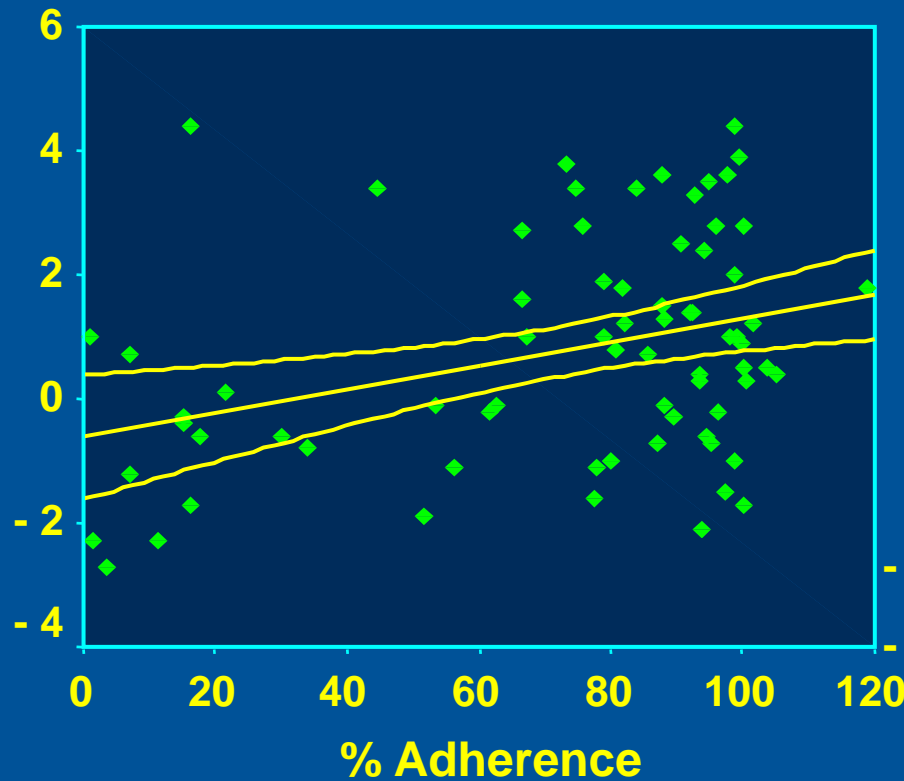
Cumulative adherence >75%

%

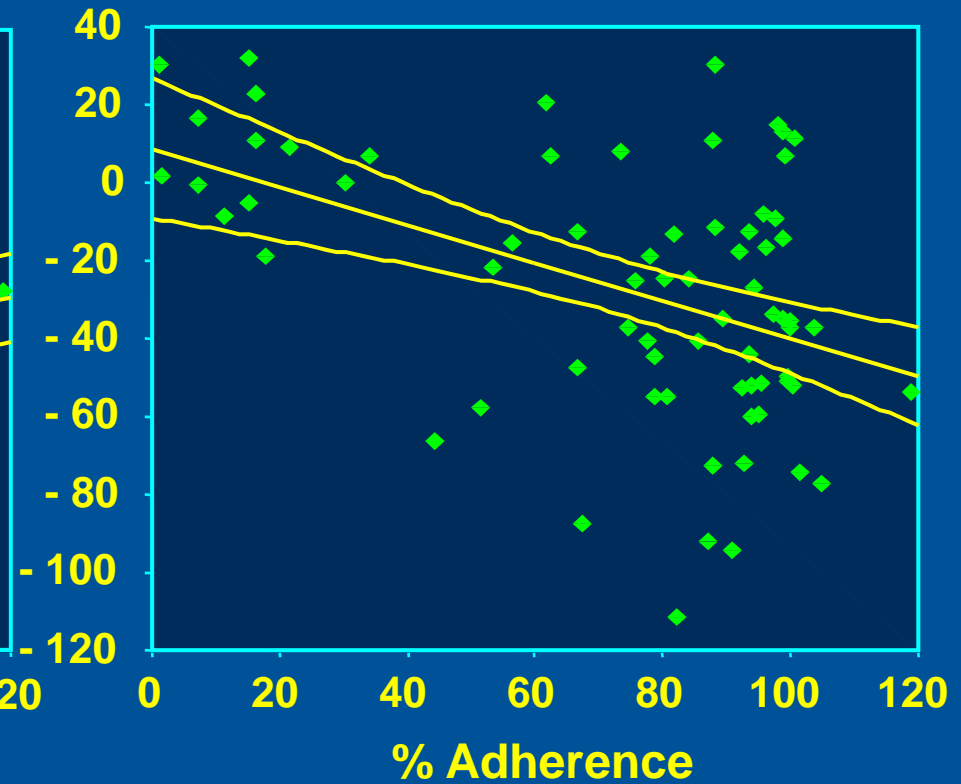
- Proportion of adherent subjects increased by 57% in those monitored
- $P = 0.04$

# Greater adherence is associated with greater biological response

% Change Hip BMD

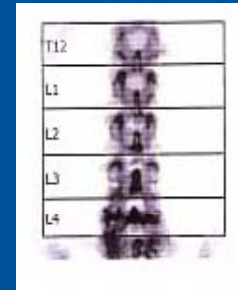


% Change uNTX



# Case Presentation

- **Woman (71) develops acute onset back pain**
- **There are no clear risk factors for osteoporosis from the questionnaire or the biochemical workup**
- **Bone turnover marker**
  - NTX T-score +4 (150 nmol BCE/mmol Cr)
  - Bone alkaline phosphatase T-score +3 (90 ug/L)

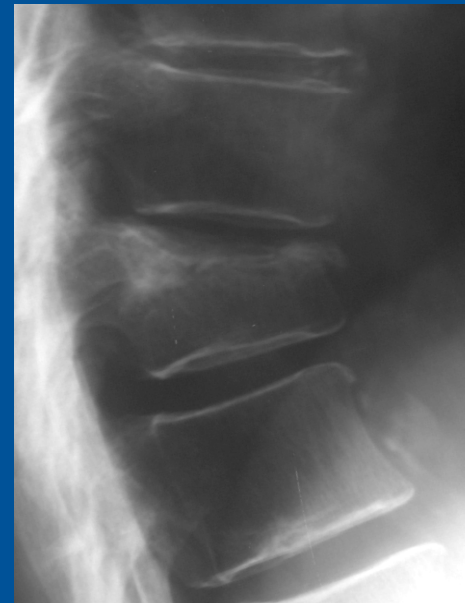


-3.2

T-score



-2.8



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## What does a high bone turnover marker mean in osteoporosis?

- **Could it just be a spurious result?**
- **How can we use the information?**
  - Is the patients more likely than average to have rapid bone loss or an increased risk of fracture?
  - Does this high result mean she might have secondary osteoporosis?
  - What do we expect to happen to the result when we treat her? What is the goal of our treatment?

**Could it just be a spurious result?**

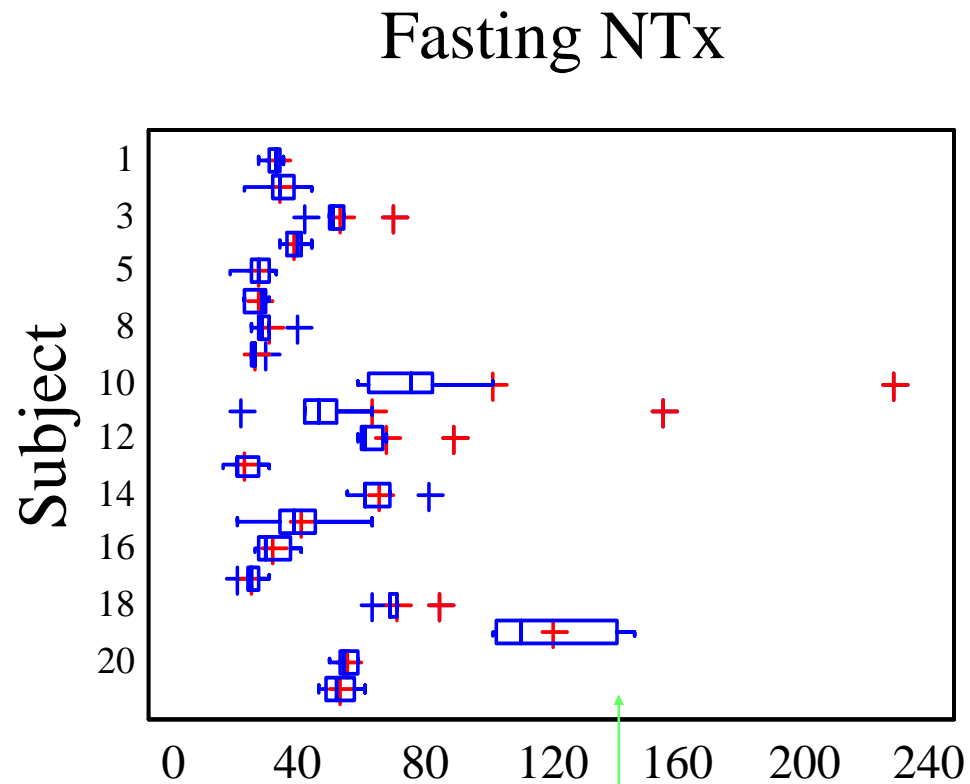


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# Bone resorption markers do vary from day to day, but it is very likely that she is in a high turnover state

Data from Clowes JA, et al. *J Bone*. 2002;30:886-90.

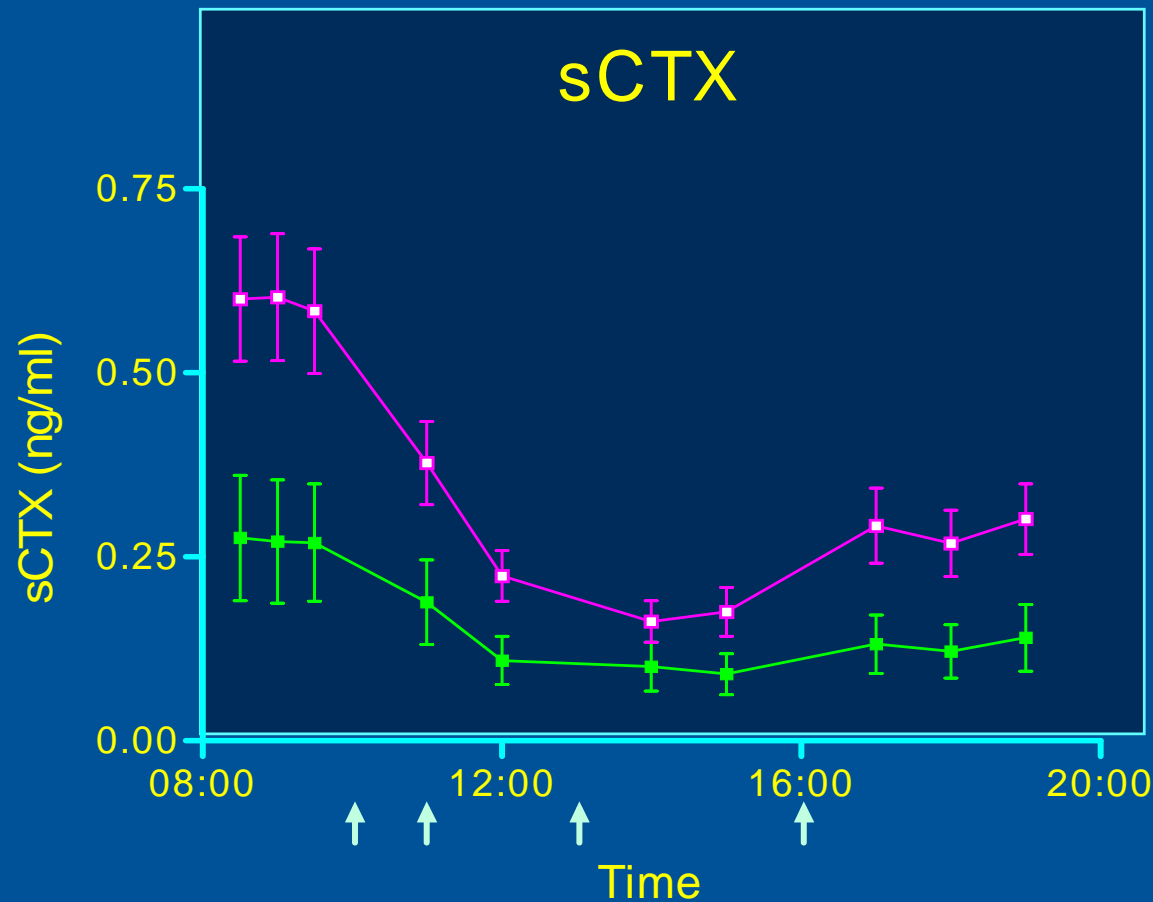


# If we know why bone turnover markers vary, we can allow for it

- **Controllable source**
  - Circadian
  - Day to day
  - Diet
  - Exercise
- **Uncontrollable source**
  - Growth
  - Age and gender
  - Fractures
  - Diseases and drugs
- **Consequence**
  - Morning, fasting samples
  - Take average of more than one measurement
- **Consequence**
  - Establish age and gender-specific reference range

# Circadian Rhythm of Serum CTX

Eagleton A, PhD thesis, 2003.

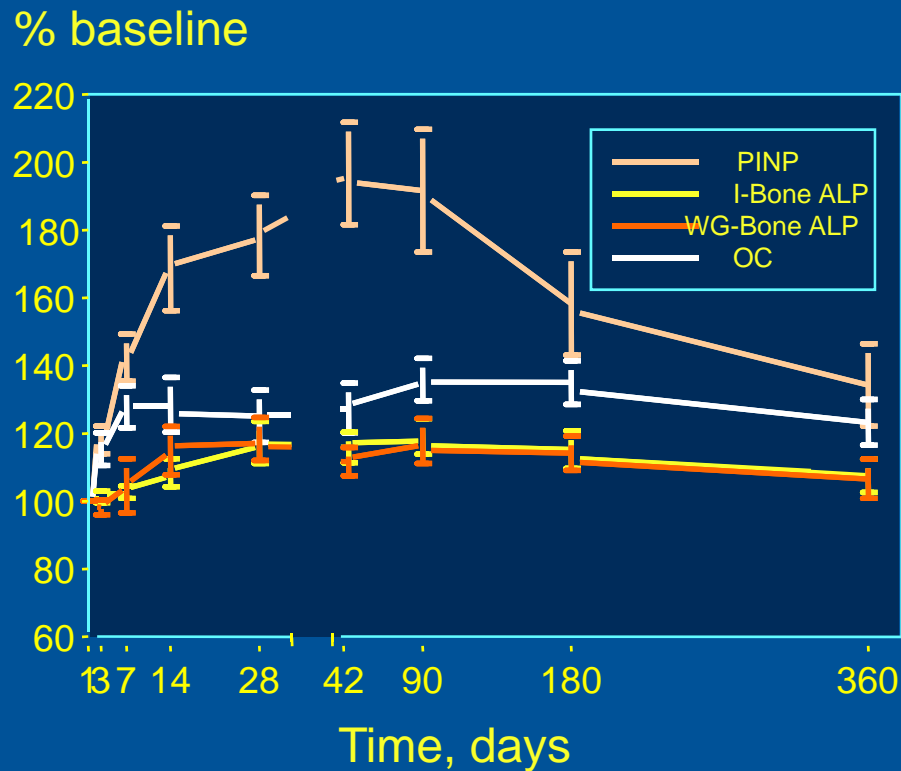


- Arrows indicate meal times
- Untreated osteoporosis, n = 15
- Osteoporosis treated with risedronate for 3 months, n = 15

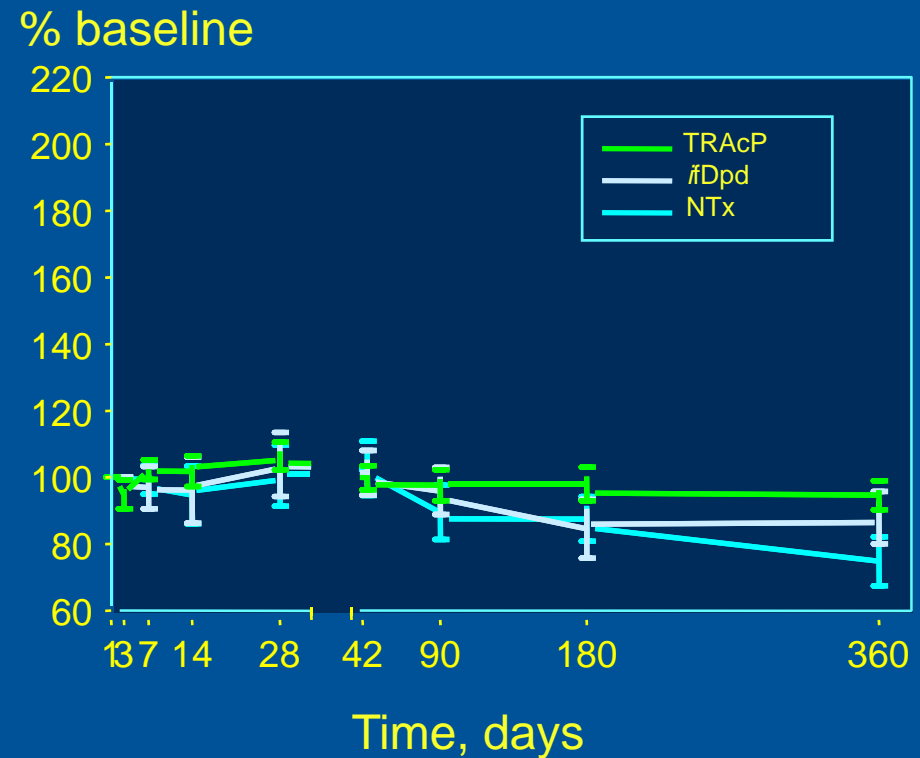


# Biochemical Markers following Ankle Fracture

## Formation



## Resorption



**Is the patients more likely than average to have rapid bone loss or an increased risk of fracture?**

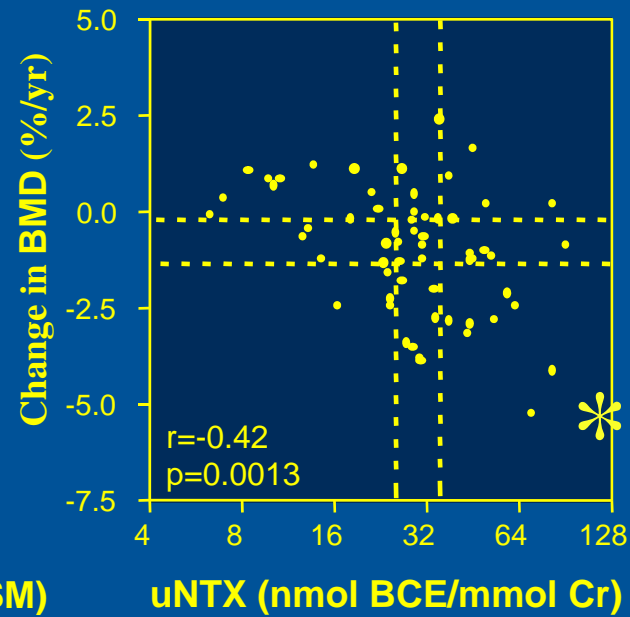
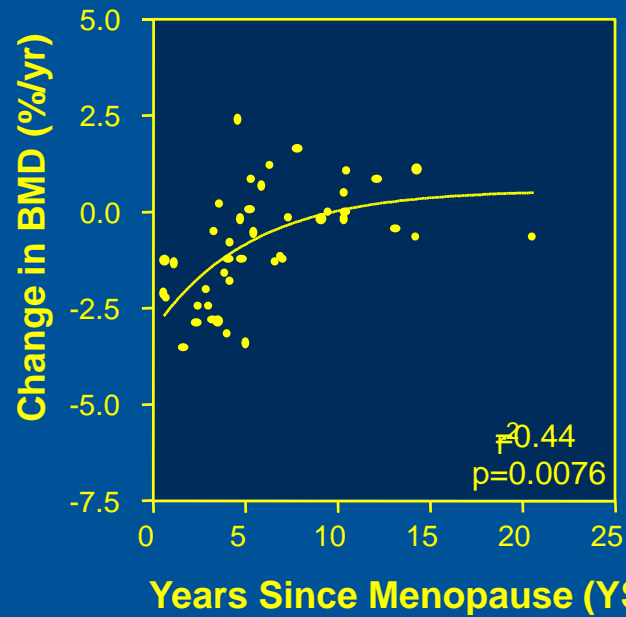


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# She is likely to be a 'fast bone loser'

## Would she really lose 5% per year?

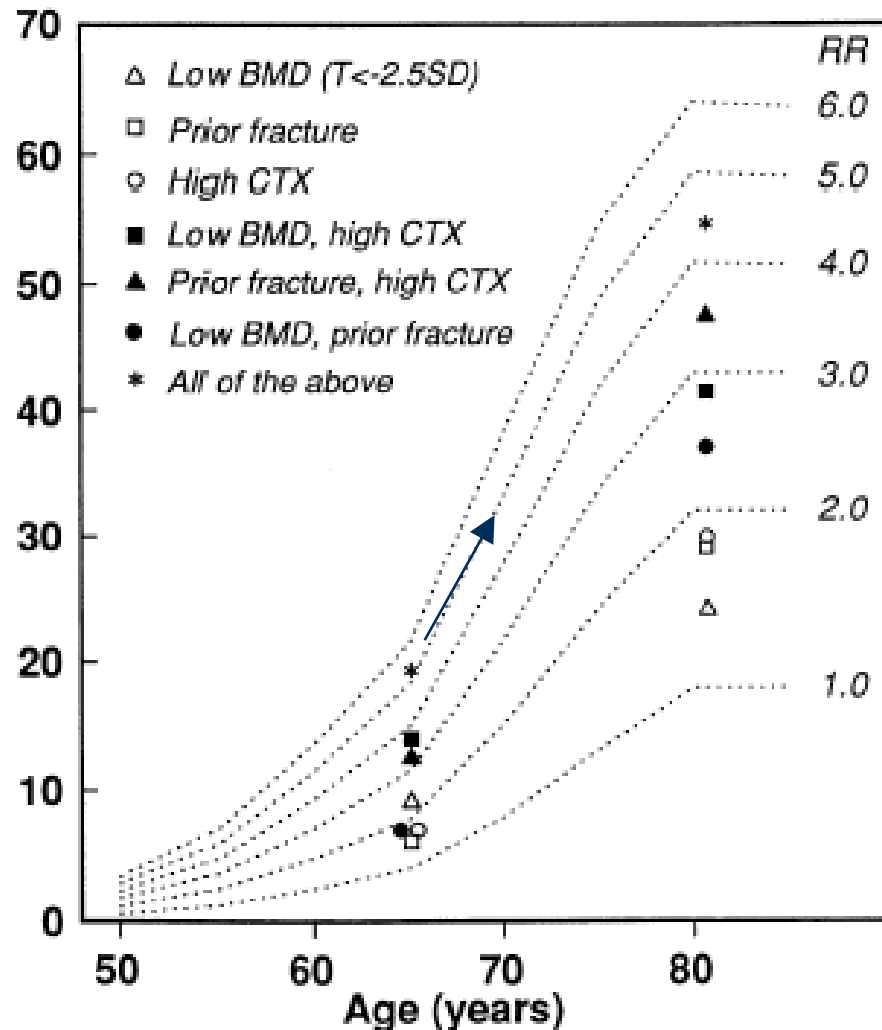


Rogers A, et al. *J Bone Miner Res.* 2000;15:1398-1404.



# 10-year Risk of Hip Fracture

10 year probability (%)



With low BMD, prior fracture and high bone turnover marker she has a 30% 10-year risk of fracturing, better do something soon!

Johnell O, et al. *Osteoporosis Int.* 2002;13:523-6.

## Use in Decision-Making

- Does this help us diagnose osteoporosis?
- Does this help us select the best treatment?
- Does the result make us suspect secondary osteoporosis?

**The high turnover doesn't allow us to diagnose osteoporosis, or choose the best treatment; it might point us to secondary osteoporosis**

- **Bone turnover markers are increased in about 25% of women with primary osteoporosis**
- **Bone turnover markers have not yet proven useful in the selection of treatment**
  - Bisphosphonates are effective at all levels of bone turnover<sup>1</sup> or only with high turnover<sup>2</sup>
  - Teriparatide most effective if bone turnover is high!<sup>3</sup>
- **A high level of bone turnover may indicate the presence of secondary osteoporosis**

1. Seibel MJ, et al. J Bone Miner Res. 2004;19:323-329
2. Bauer DC, et al. J Bone Miner Res. 2006;21:292-299
3. Ettinger B, et al. J Bone Miner Res. 2004;19:745-751



# What are the causes of high bone turnover? Watch out particularly for endocrine or other bone diseases

## HIGH

- **Metabolic bone diseases**
  - Paget's disease
  - Secondary hyperparathyroidism
    - osteomalacia
    - renal osteodystrophy
    - malabsorption syndrome
- **Endocrine diseases**
  - Primary hyperparathyroidism
  - Thyrotoxicosis
  - Hypogonadism
- **Malignancy, e.g. myeloma**
- **Recent fracture**

## LOW

- **Cushing's syndrome**
  - low osteocalcin
- **Osteogenesis imperfecta**
  - low PICP
- **Hypophosphatasia**
  - low alkaline phosphatase



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**What do we expect to happen to the result when we treat her? What is the goal of our treatment?**



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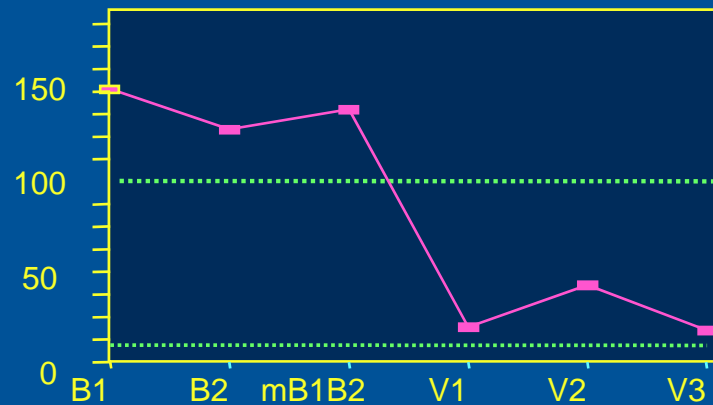
[www.shef.ac.uk/bmq](http://www.shef.ac.uk/bmq)

## After starting antiresorptive therapy, should we make follow-up measurements of bone turnover?

- **Identify poor response that can be caused by**
  - Poor compliance
  - Secondary osteoporosis
  - Ineffective therapies
- **Take action to improve response**
  - Advise on correct dosing instructions
  - Investigate for secondary osteoporosis
  - Consider larger dose or different treatment
- **Encourage compliance**
  - No immediate symptomatic benefit to patient

# Our patient was treated with alendronate 70 mg once a week, and met both of our targets

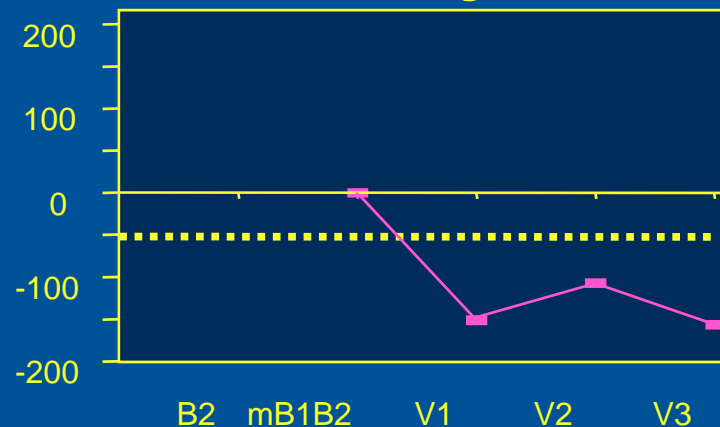
NTX/Cr, nmol BCE/mmol



## Goals

Decrease to levels in the lower half of the reference range for young women, <35 nmol/mmol Cr

NTX, % change



Decrease by more than the least significant change, 50%

BMD increase of 5.3% at lumbar spine at 1 year



# Usefulness of Markers in the Individual Patient

## Summary

- **Bone turnover**
  - Increases at the menopause and increases further in osteoporosis
- **High bone turnover markers**
  - Associated with higher risk of bone loss and fractures
- **Treatments for osteoporosis**
  - Result in changes in bone turnover markers
- **Treatment monitoring**
  - Goal is to decrease bone turnover markers beyond least significant change and into pre-menopausal range