

Bone Markers in Osteoporosis: Prediction of Fractures & Treatment Monitoring

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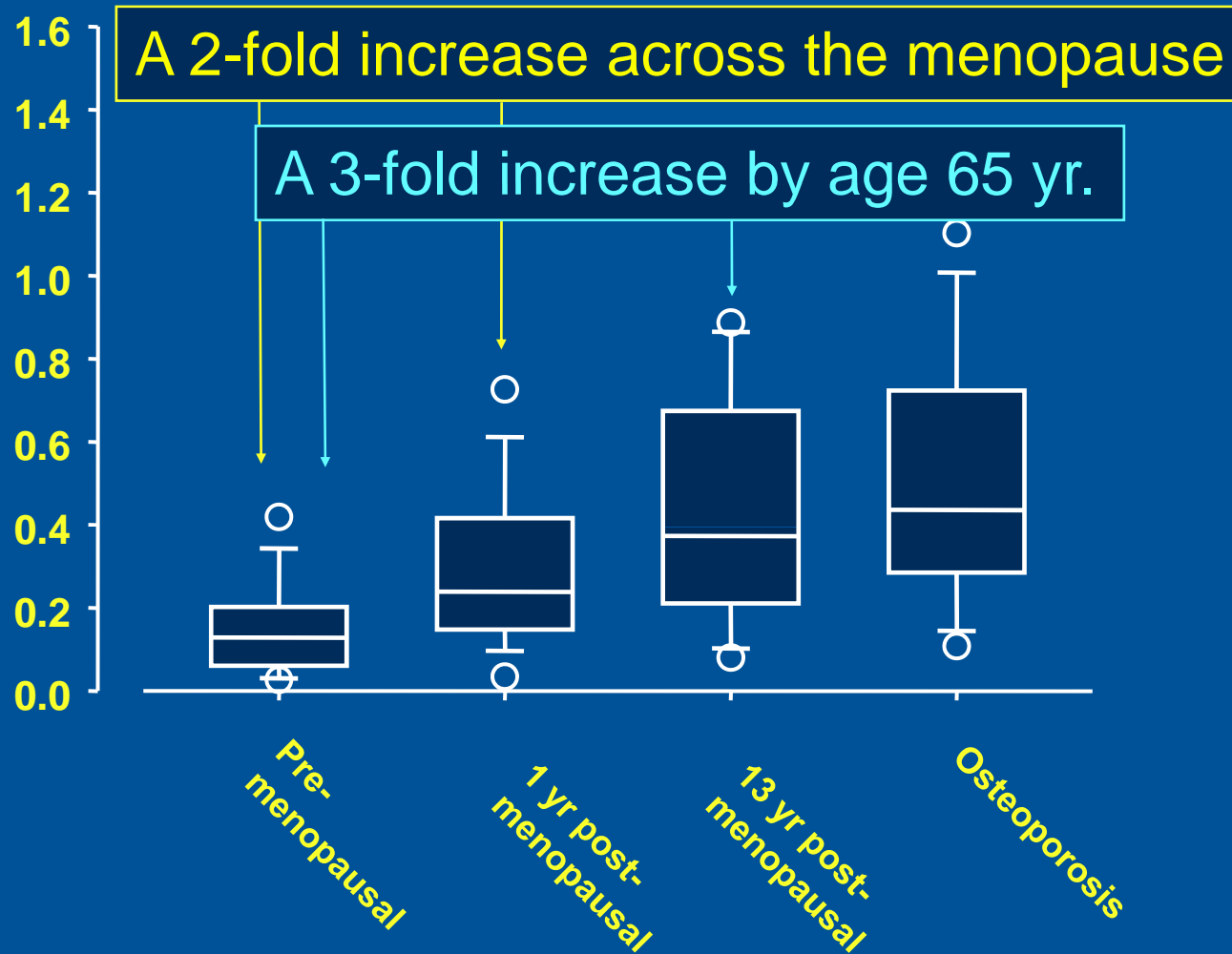
Usefulness of Markers in the Individual Patient

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)

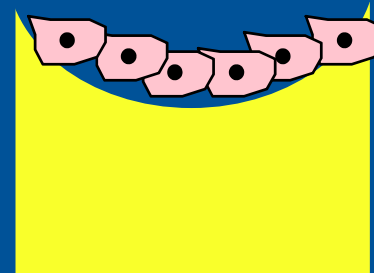
– Enzyme

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

• Related factors

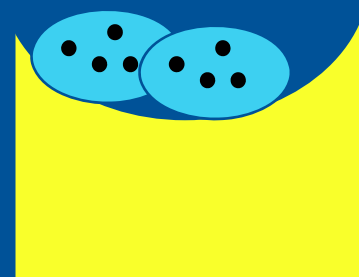
- OPG, RANK-L

Formation

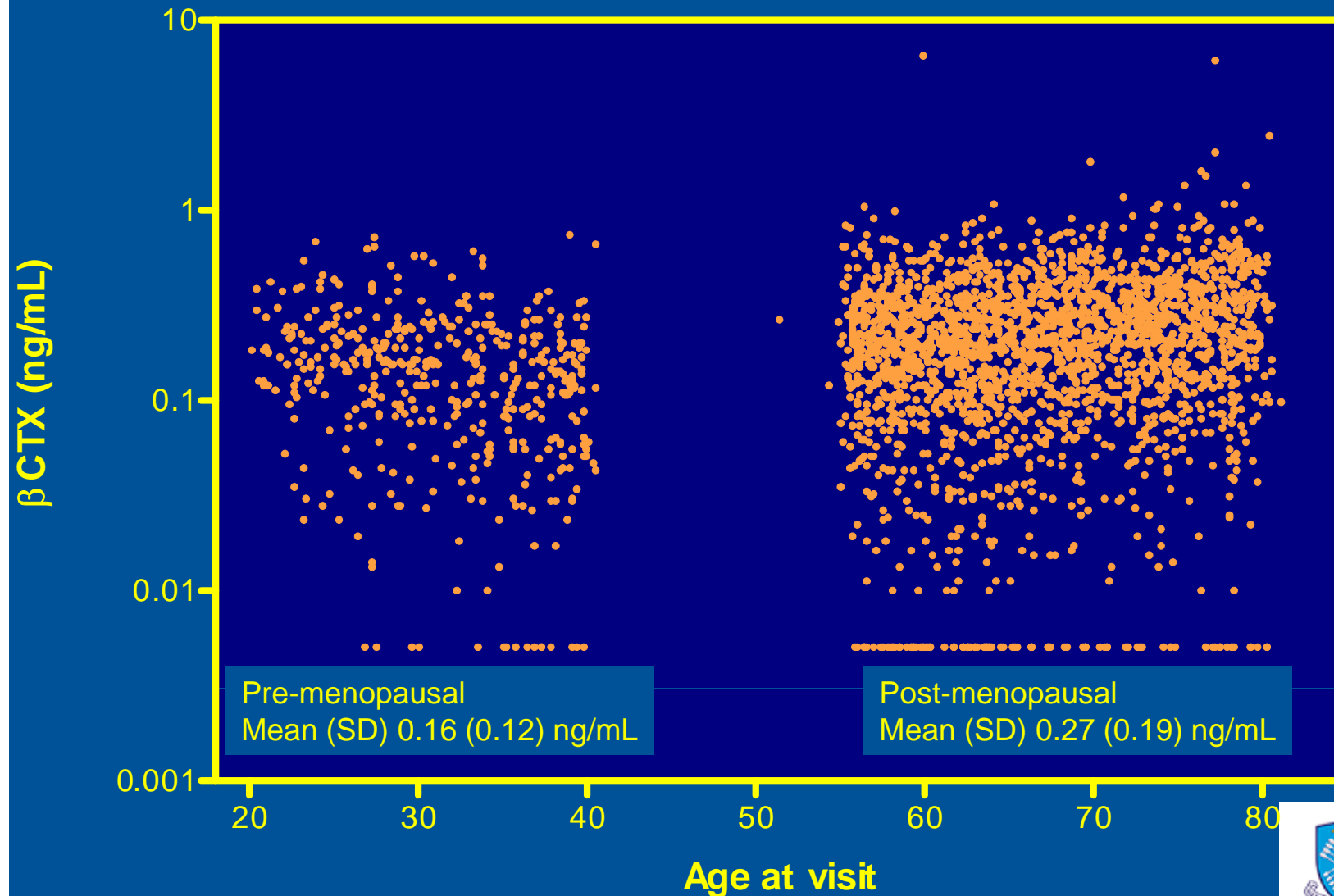


Commercially available assays
Serum: OC, PICP, PINP,
bone ALP, NTX, CTX, TRACP 5b
Urinary: CTX, NTX, free DPD

Resorption



Levels of Serum β 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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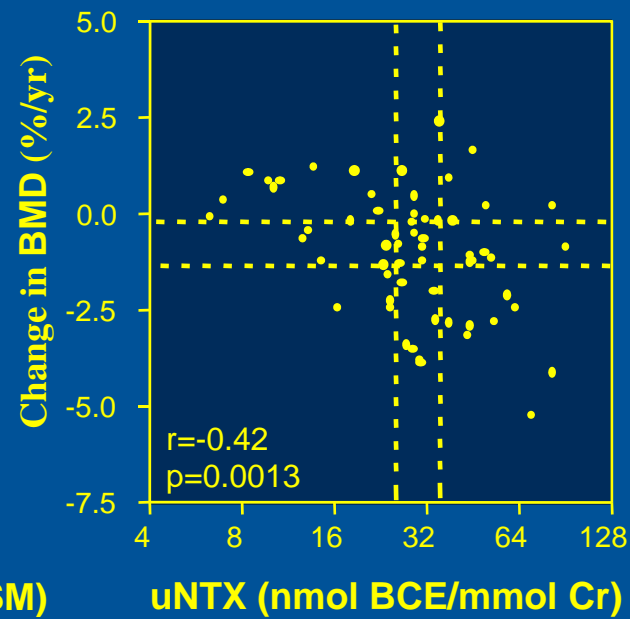
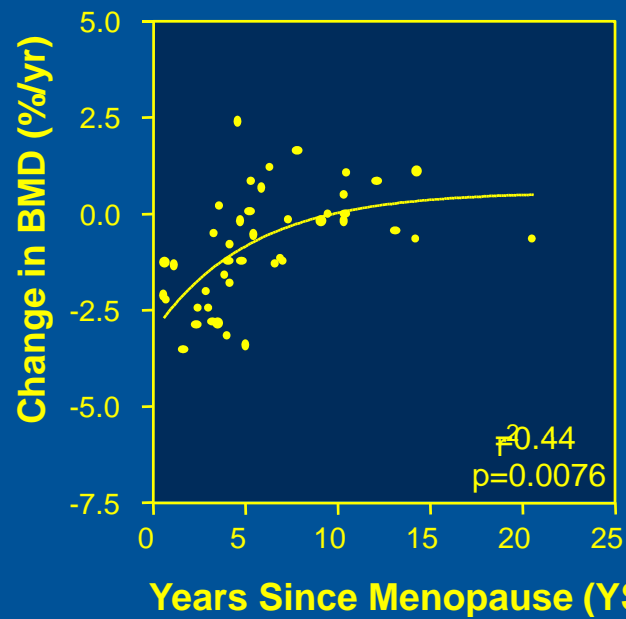
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Bone Turnover Markers in Relation to Bone Loss and Fracture Risk

- **A high bone remodelling rate is associated with**
 - More rapid bone loss in postmenopausal women¹
 - Increased risk of fractures²
- **The association with fracture is variable²**
 - 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



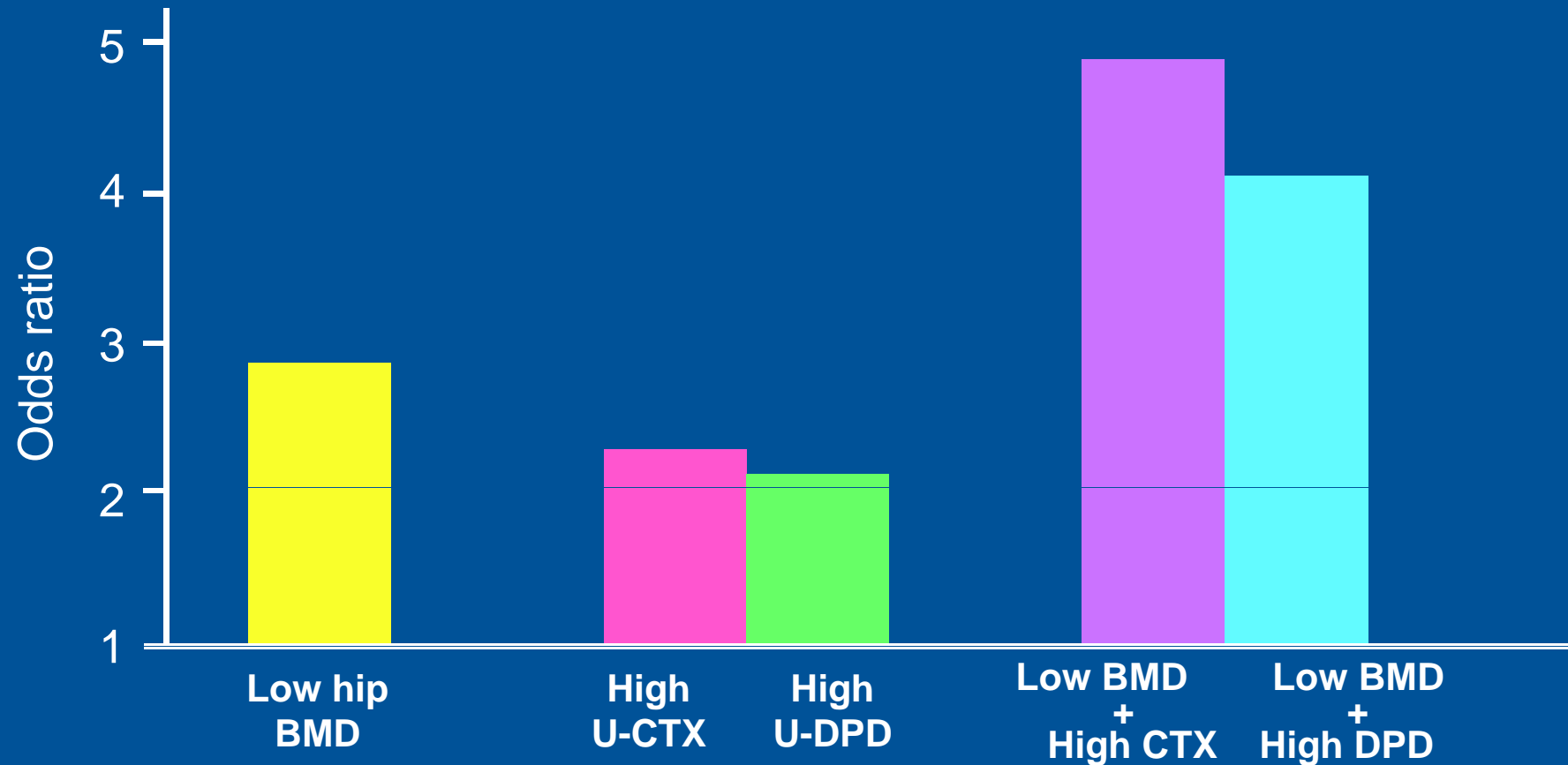
Rogers A, et al. *J Bone Miner Res.* 2000;15:1398-1404.



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

EPIDOS = Epidemiologie de l'Osteoporose



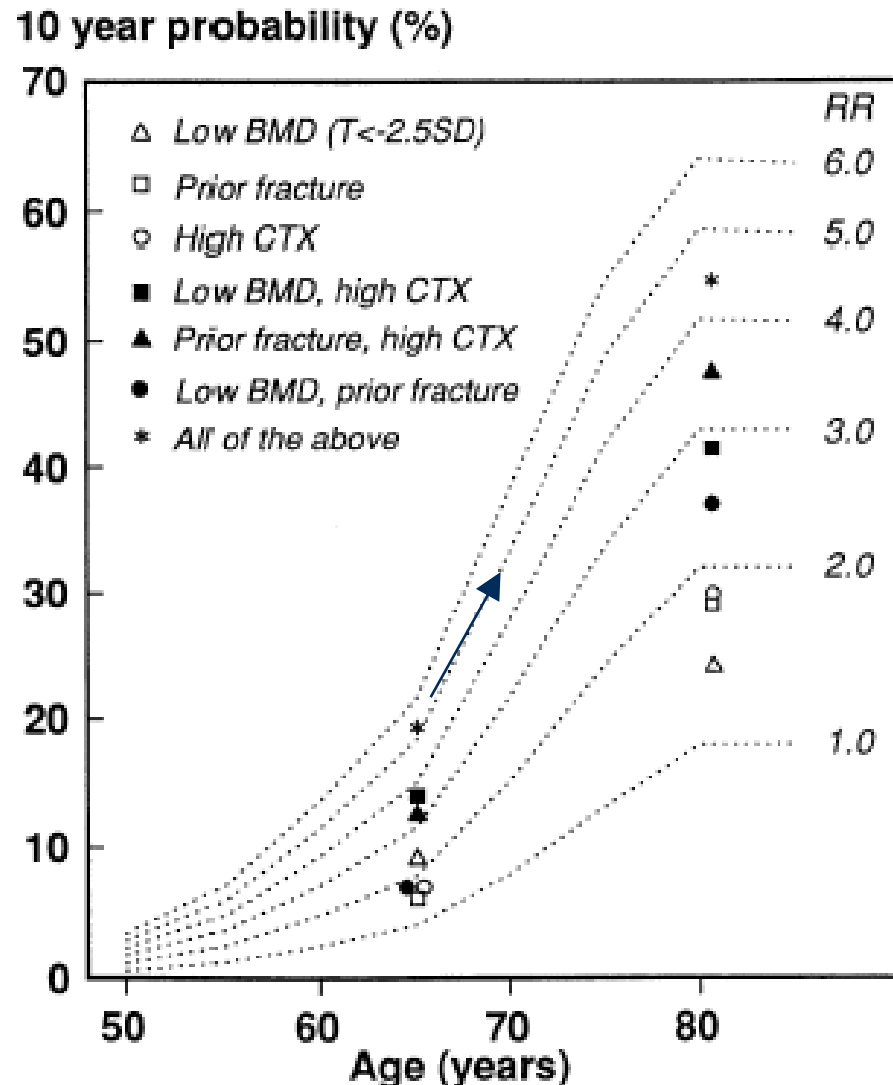
BMD = bone mineral density; U = urinary.

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



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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



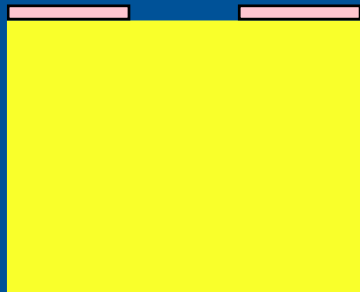
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Postmenopausal Osteoporosis

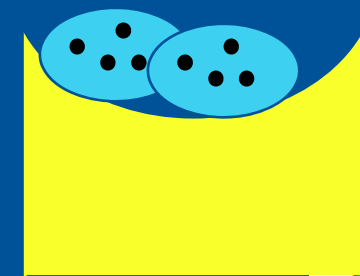
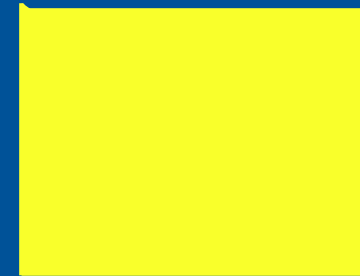
Effects of Treatments

Quiescence



✦ **Activation**

Remodelling Balance



Resorption

Anti-catabolic Drugs

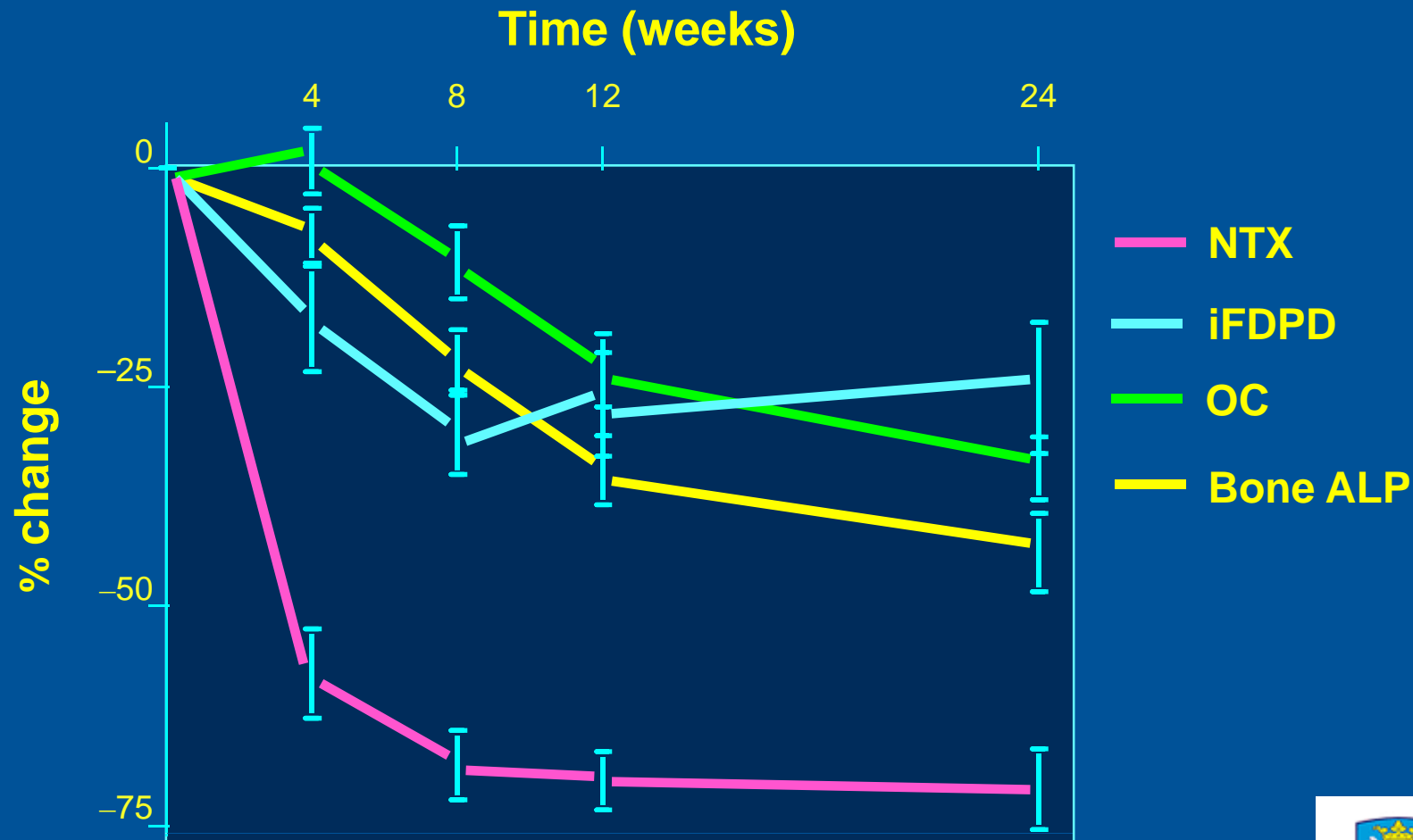
- Decrease activation frequency
- Restore remodelling balance



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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.



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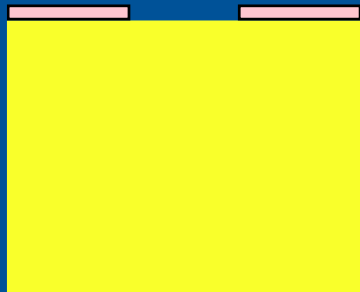
Treatment Effects on Telopeptide Markers CTX and NTX

- **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

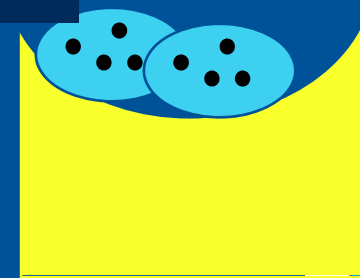
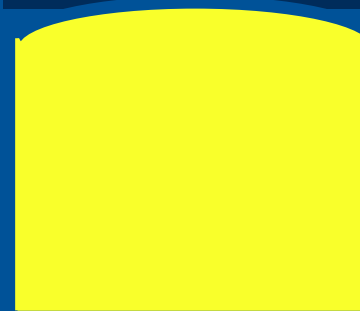


Anabolic Drugs

- Increase activation frequency
- Induce positive remodelling balance



Positive Remodelling Imbalance



↑↑ ↑ Activation

Resorption

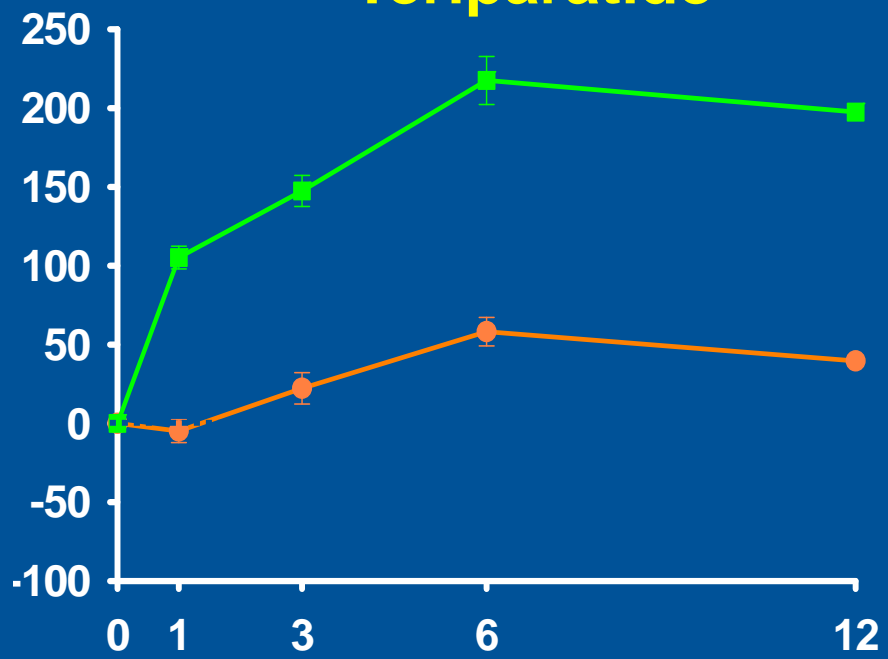


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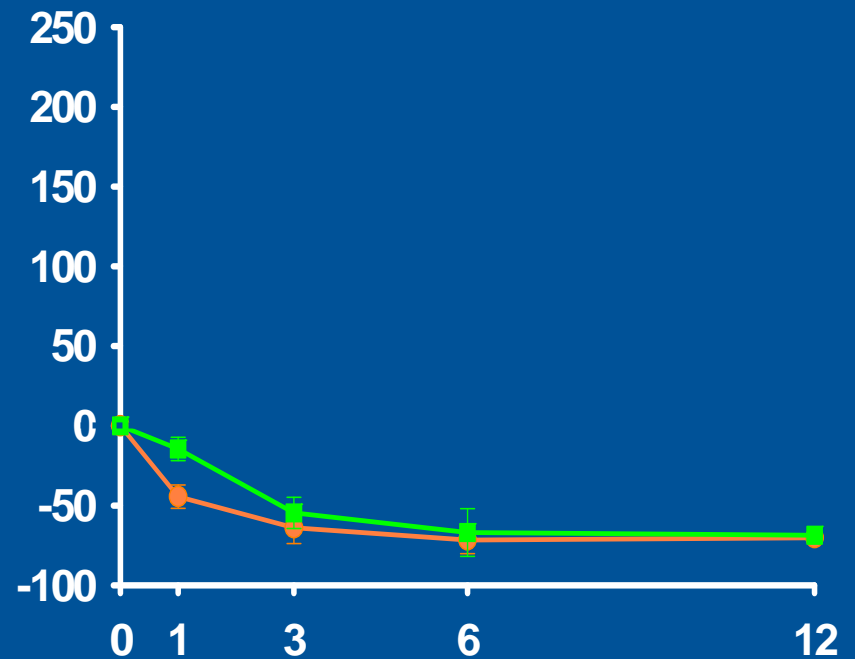
Randomized, Controlled Trial of Alendronate or Teriparatide in Postmenopausal Osteoporosis

% Change from baseline (Mean \pm SE)

Teriparatide



Alendronate

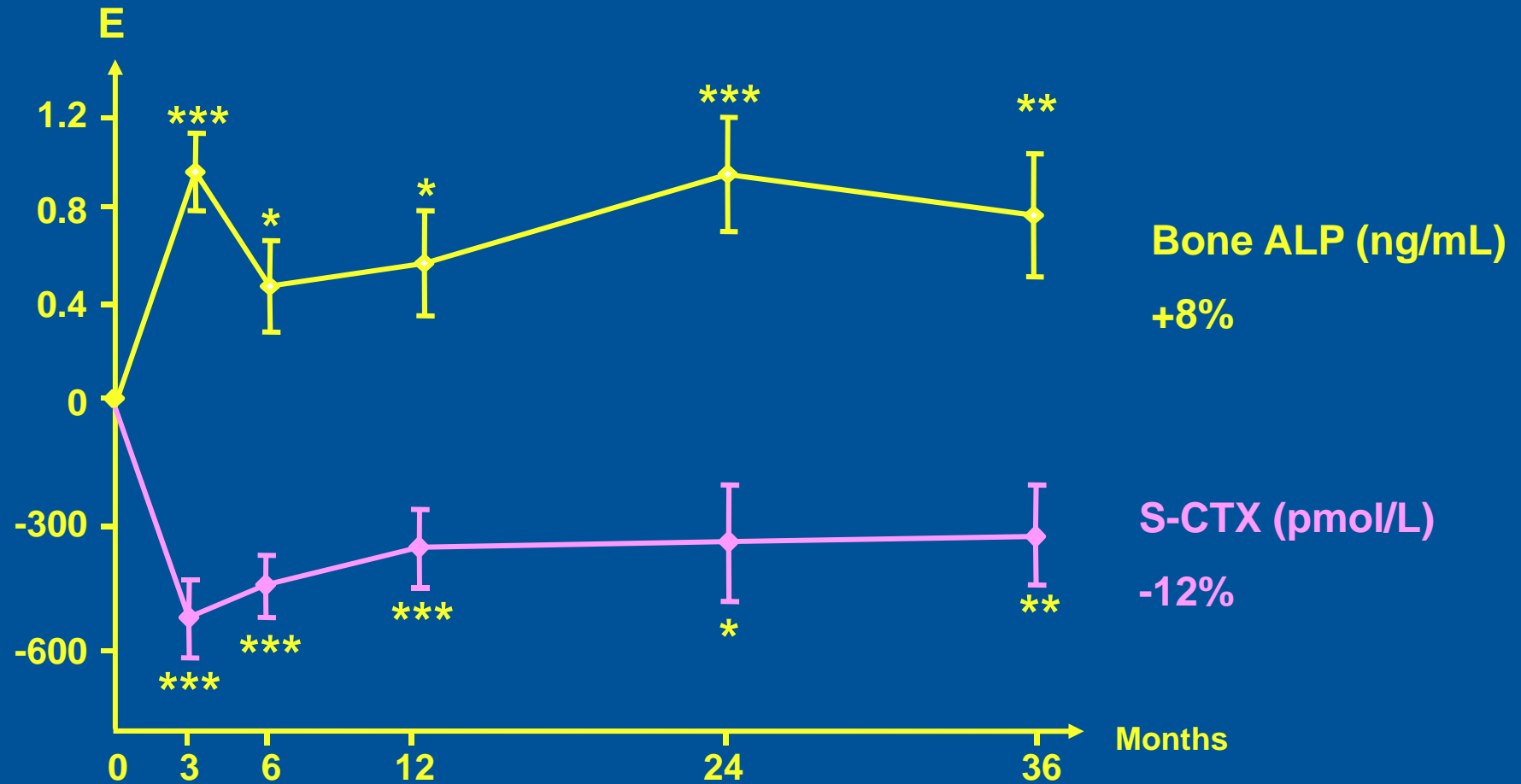


■ PINP (Formation)
● NTX (Resorption)

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



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

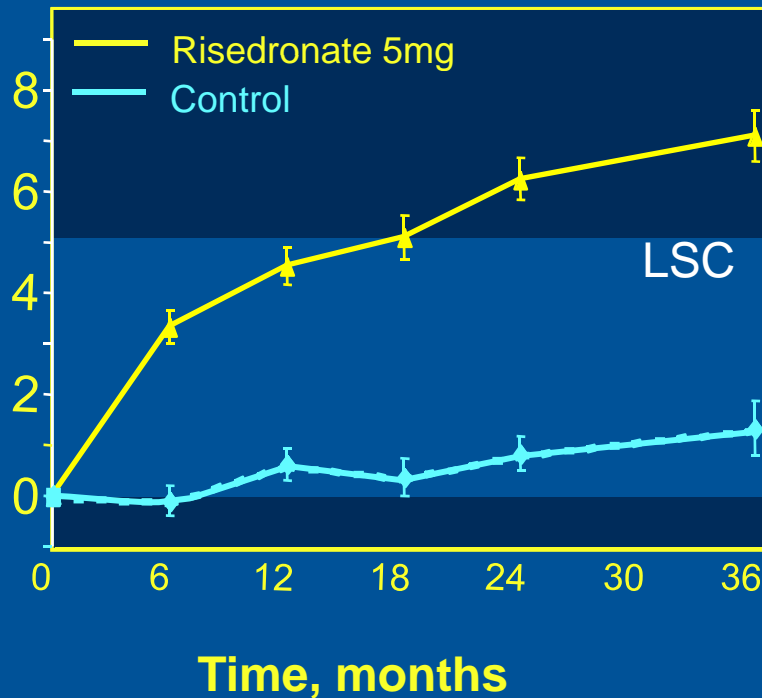


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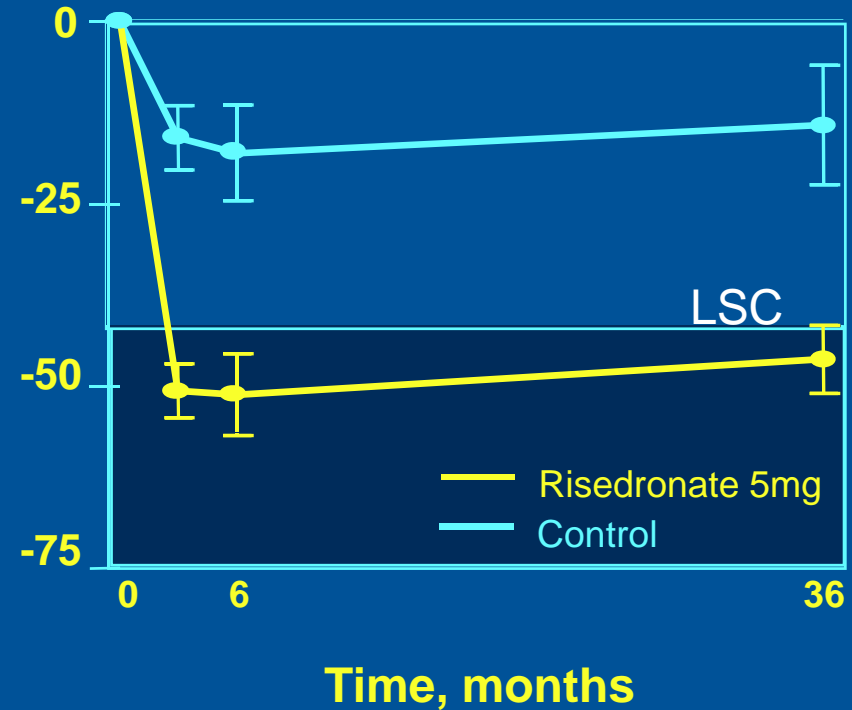
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The average response to risedronate 5 mg exceeds LSC earlier for BTM (3 months) than BMD (18 months)

Spine BMD, % Δ from baseline



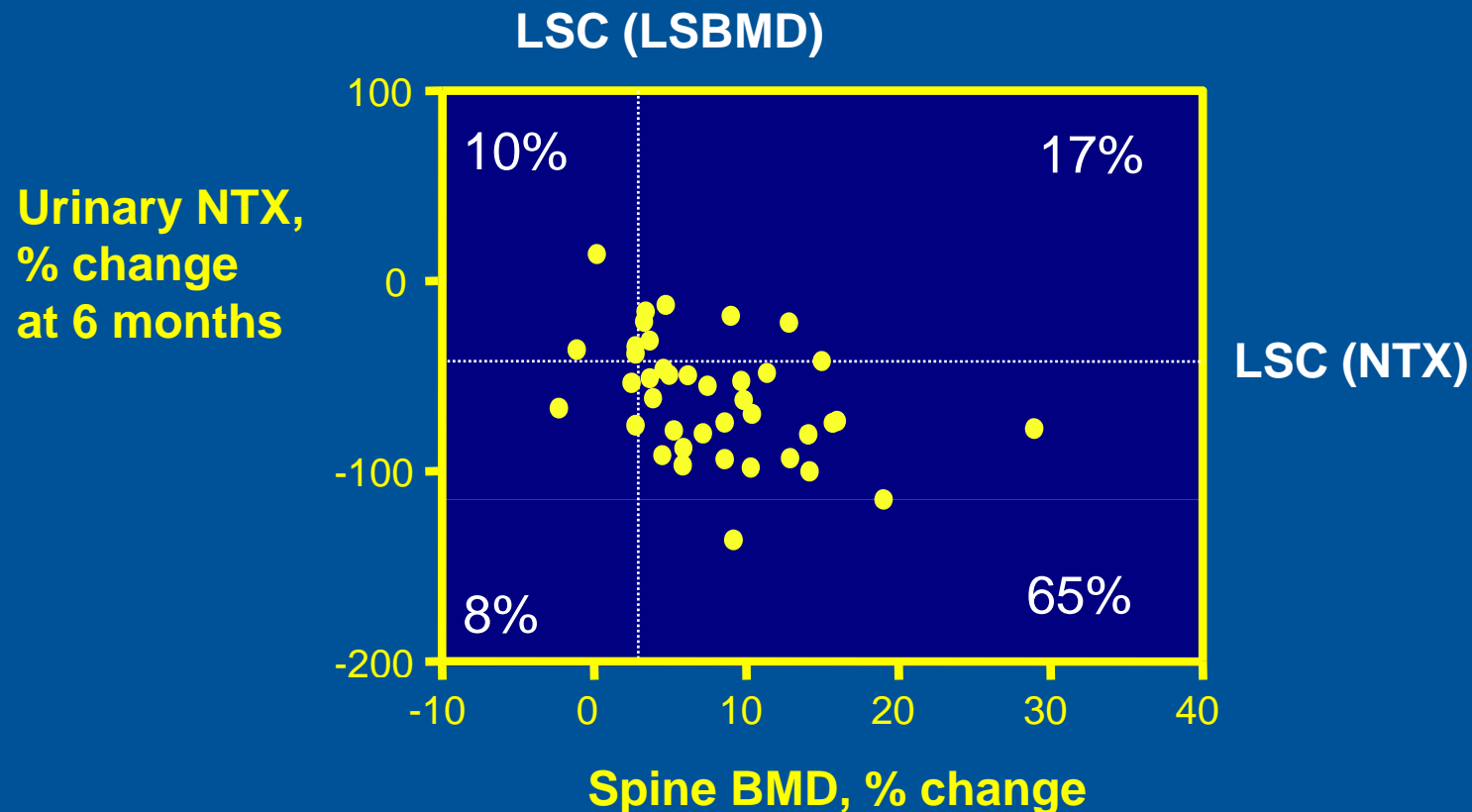
NTX, % Δ from baseline



LSC, least significant change



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

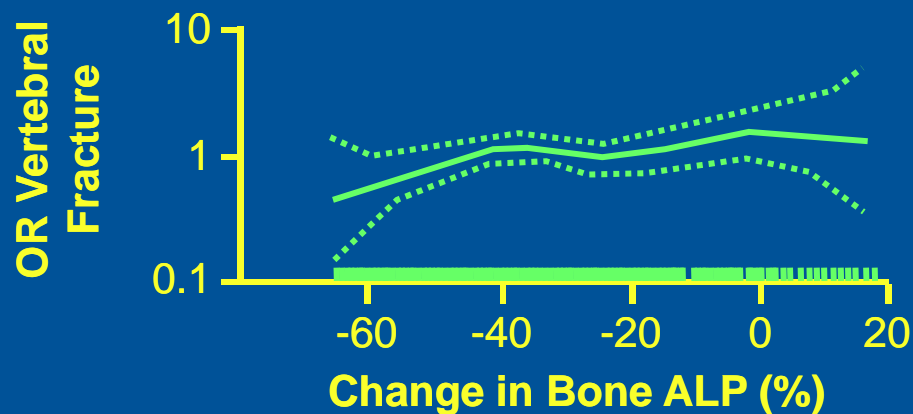
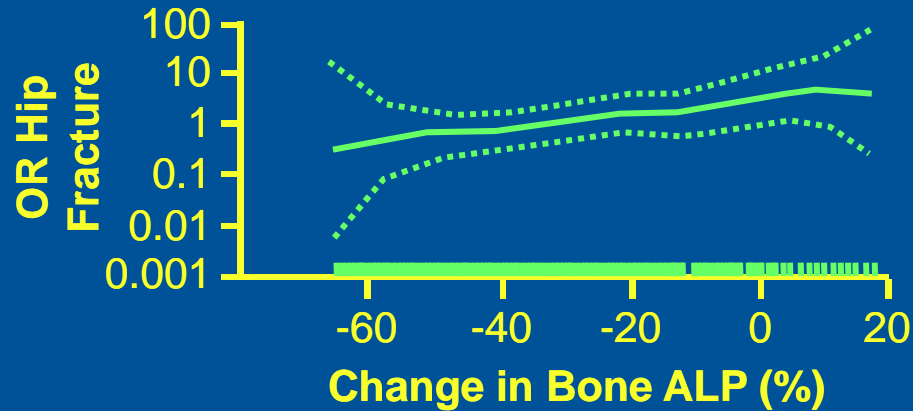


LSC, least significant change
BMD, bone mineral density



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

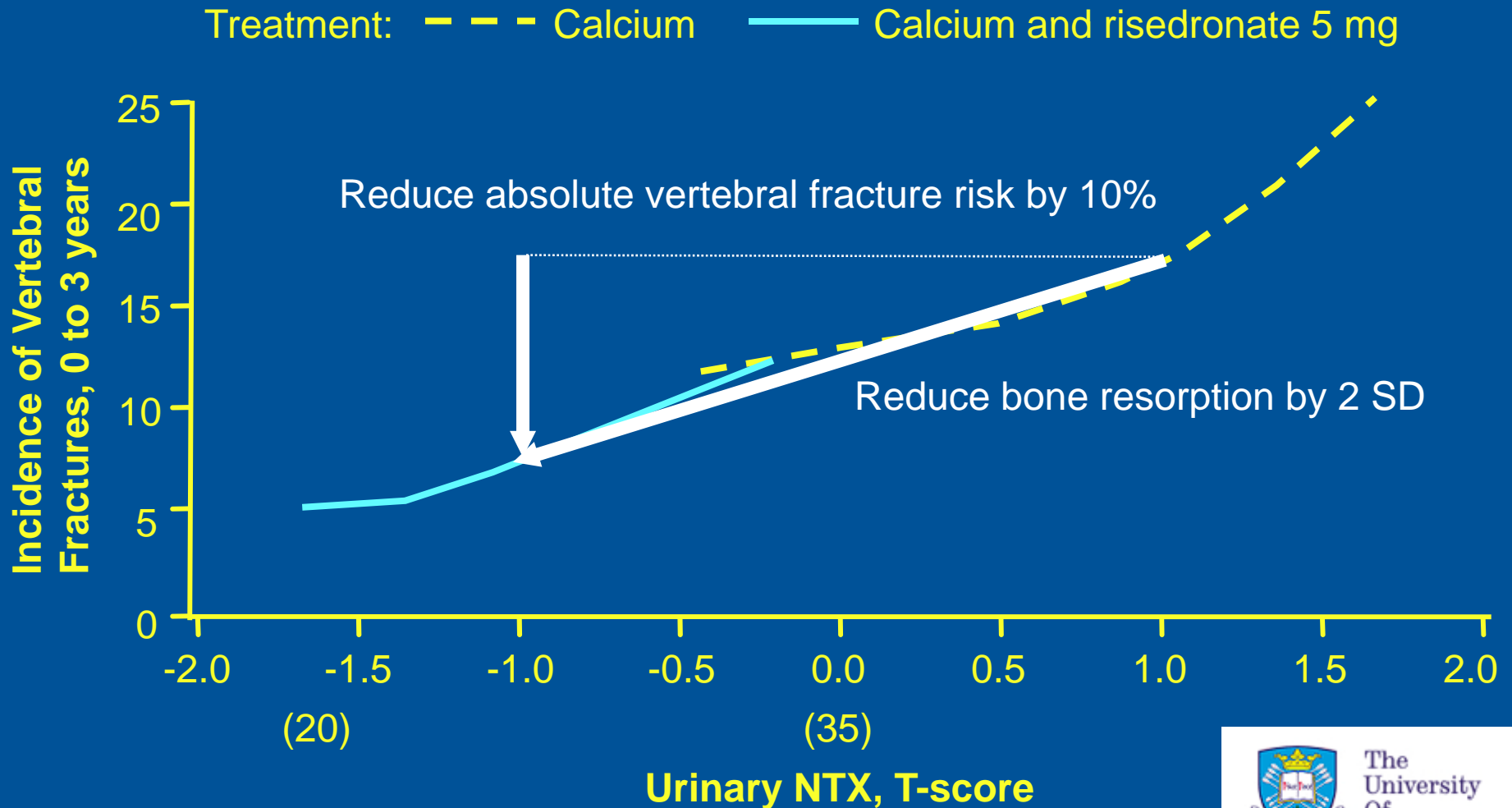
- 3105 in alendronate arm
- One-year change in bone ALP (insufficient samples for PINP or CTX)
- 3.6 years of follow-up for fracture

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.

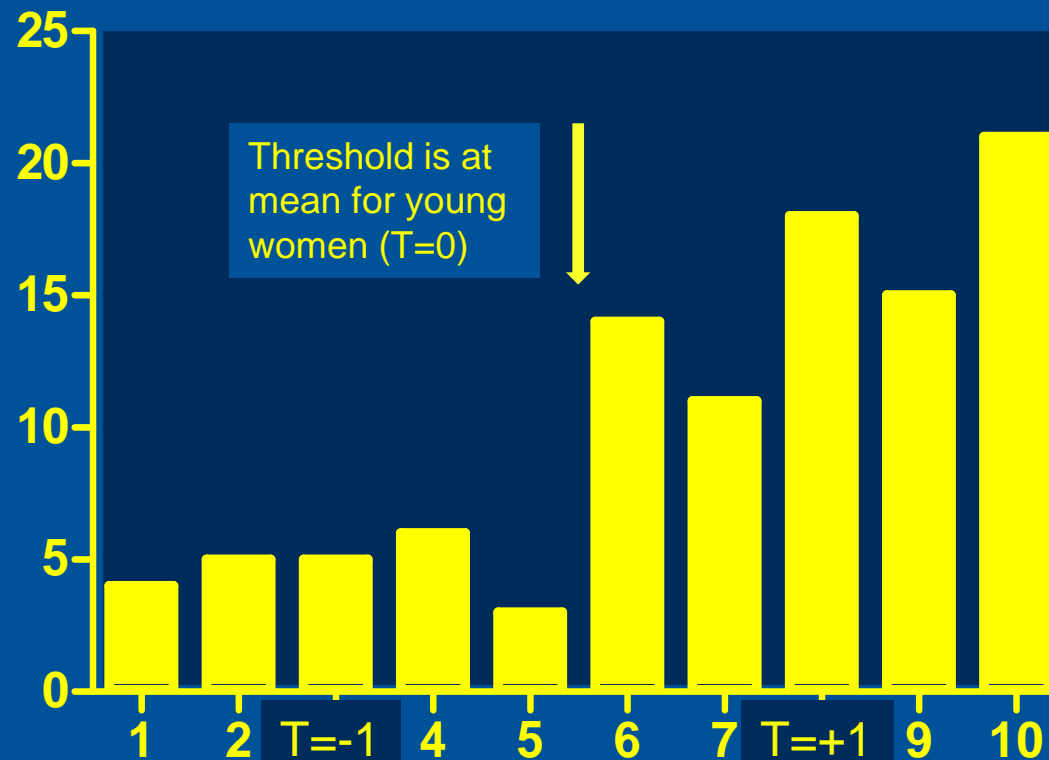


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Vertebral Fractures over 3 years and Bone Resorption Combined Treated and Placebo Groups

Decile Analysis, about 66/decile

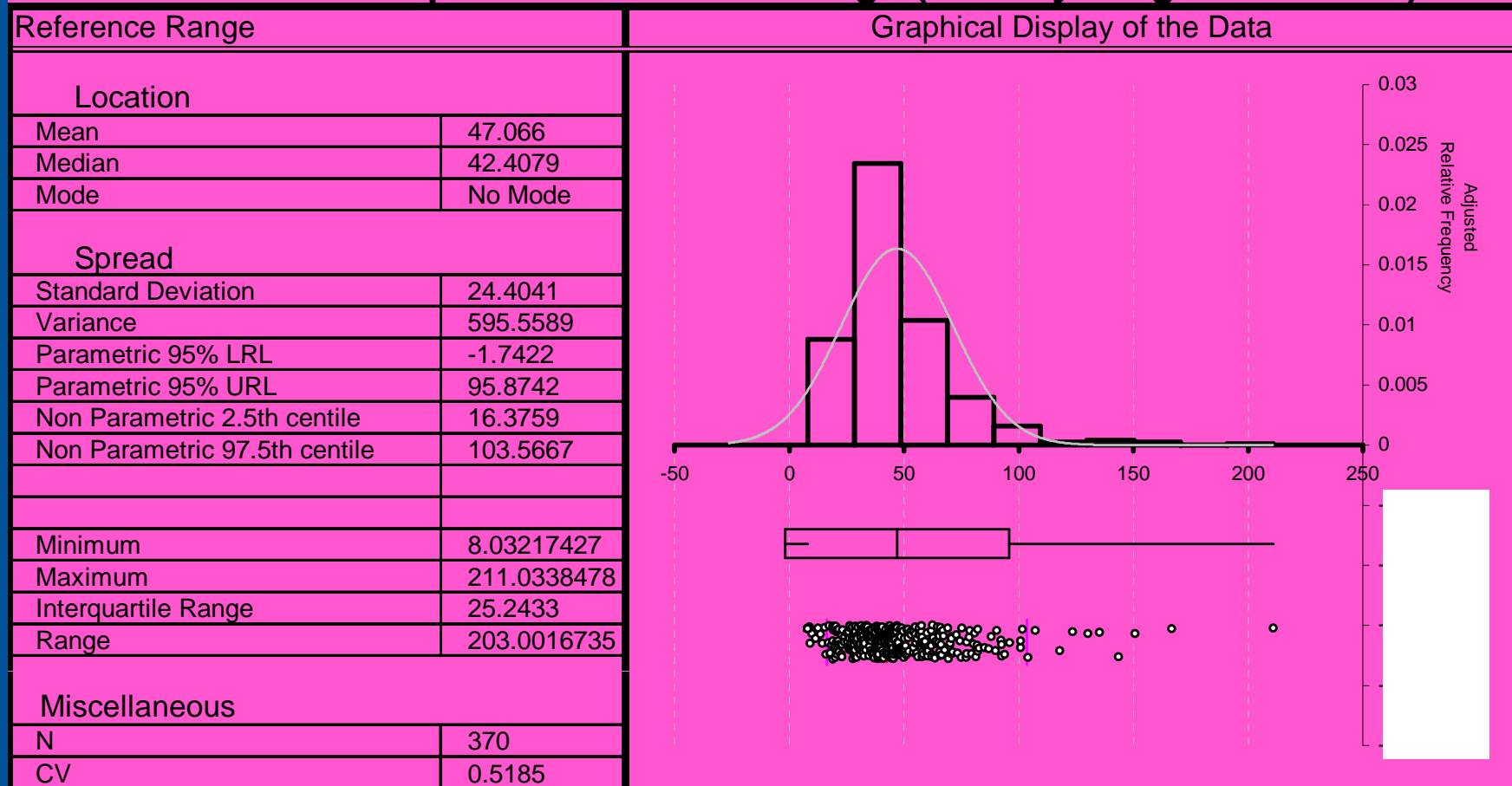
No. women with
vertebral fractures



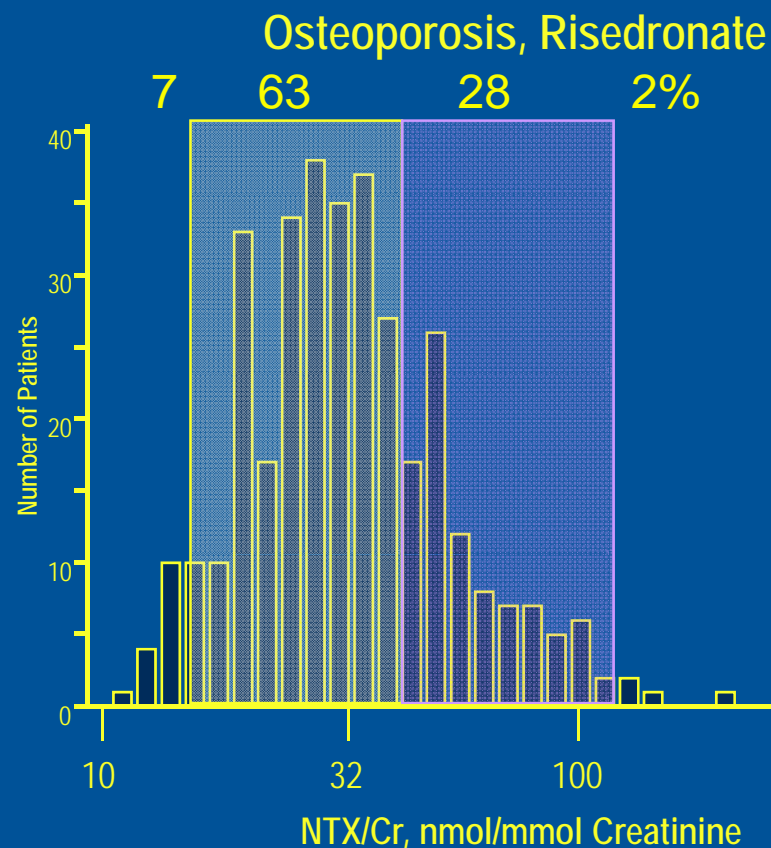
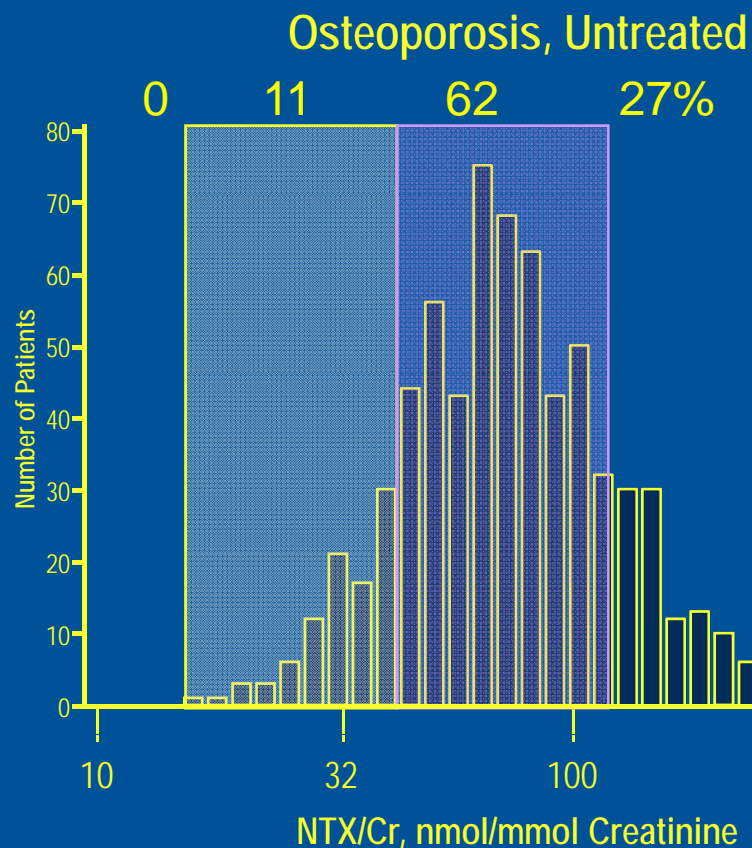
Urinary CTX (T-score) at 3 to 6 months, decile

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



Does monitoring affect adherence?



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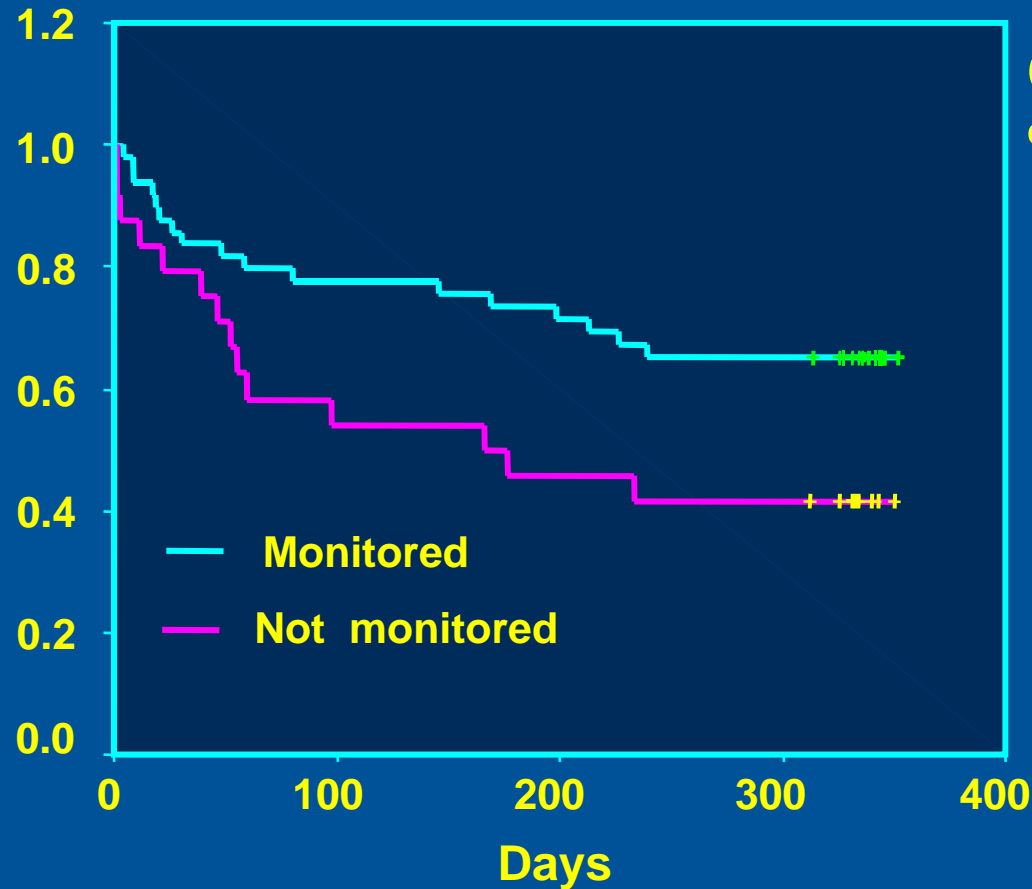
Does Monitoring affect Adherence?

- **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

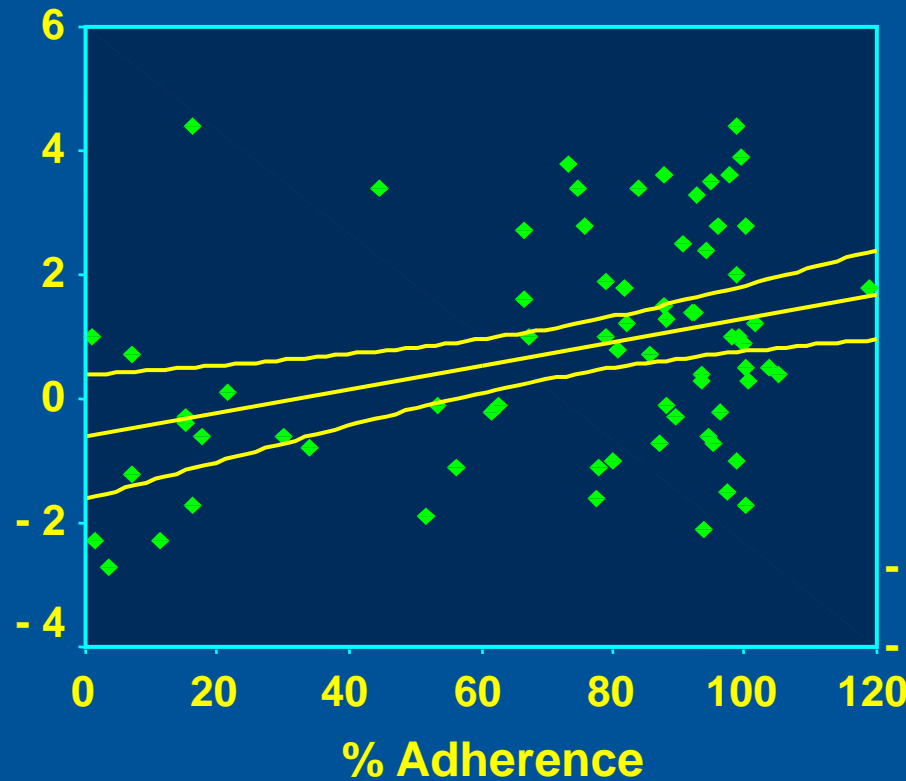


Cumulative adherence >75 %

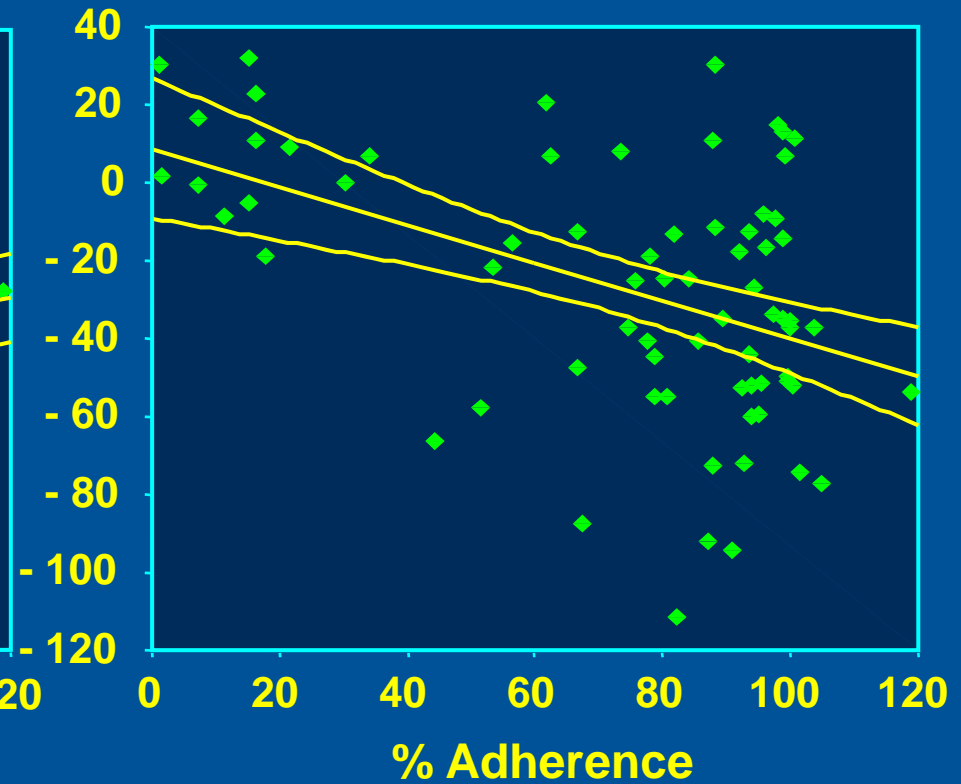
- Proportion of adherent subjects increased by 57% in those monitored
- P = 0.04

Greater adherence is associated with greater biological response

% Change Hip BMD

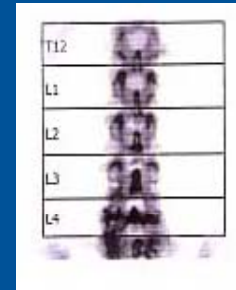


% Change uNTX



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)

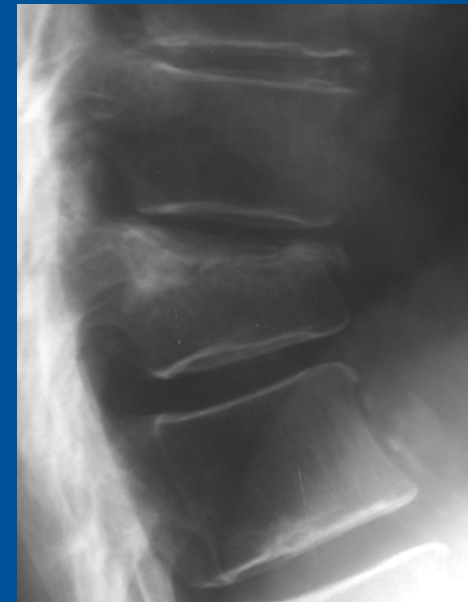


-3.2

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?

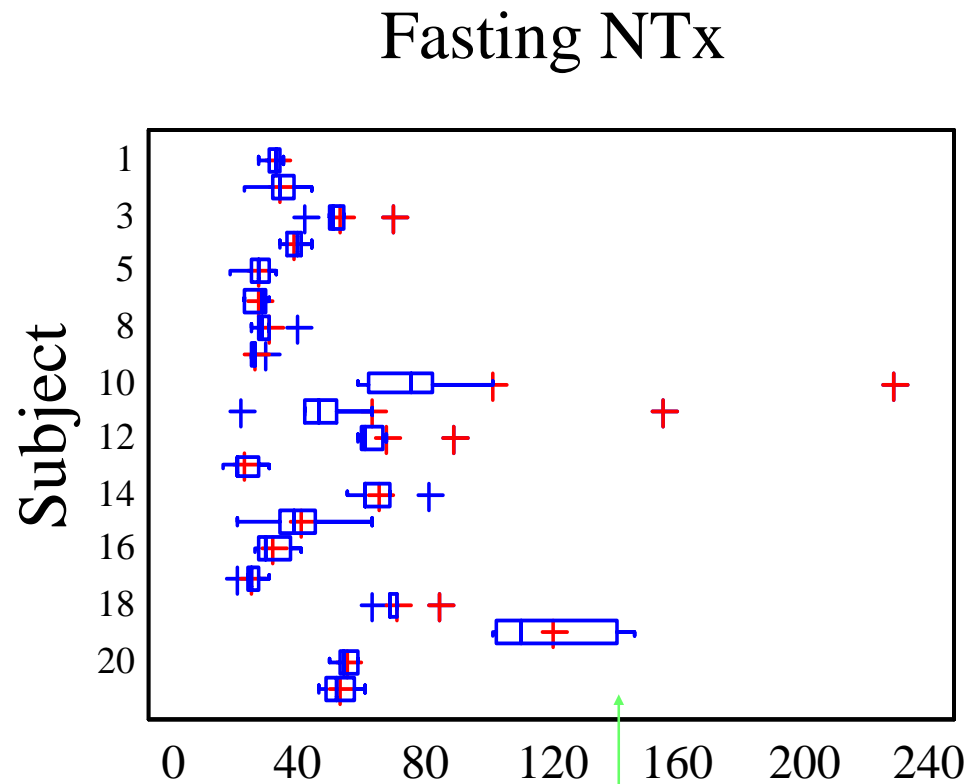


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Bone resorption markers do vary from day to day, but it is very likely that she is in a high turnover state

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

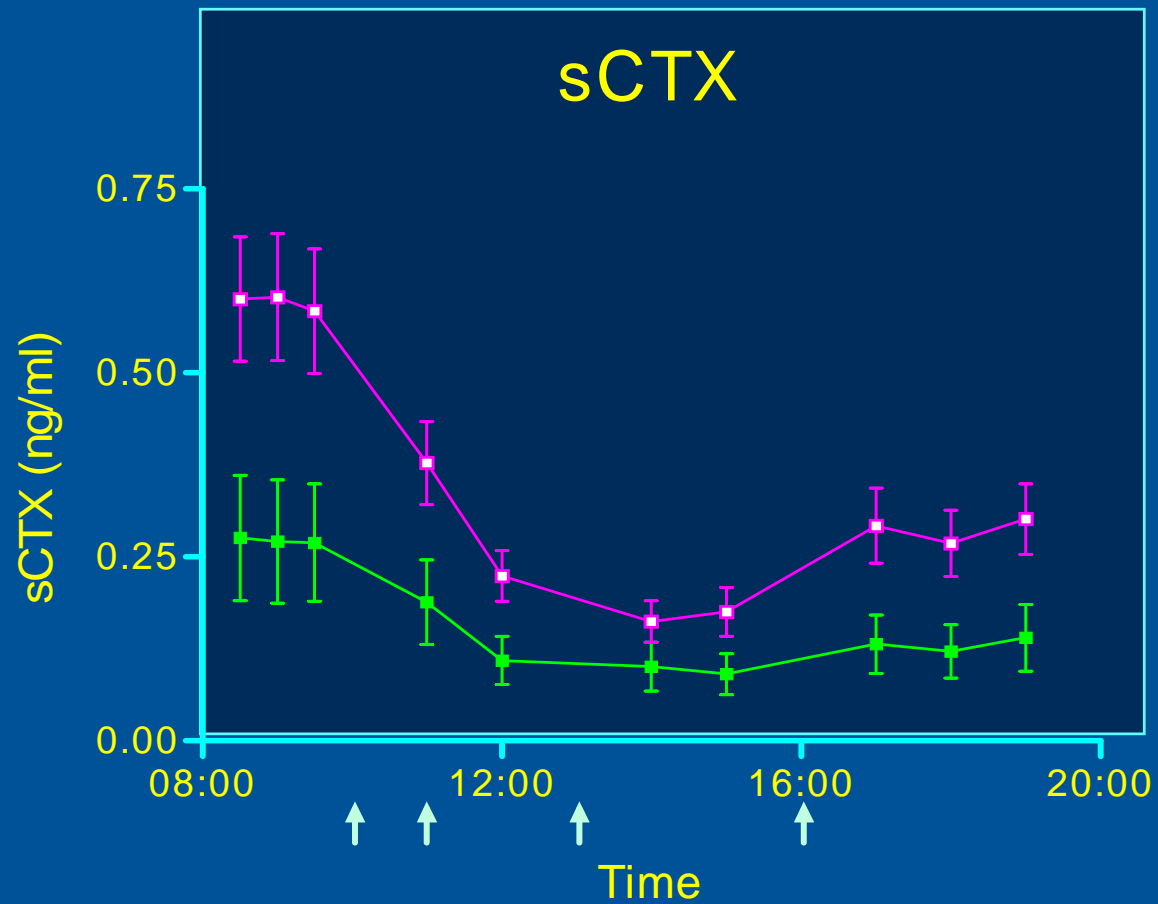


If we know why bone turnover markers vary, we can allow for it

- **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

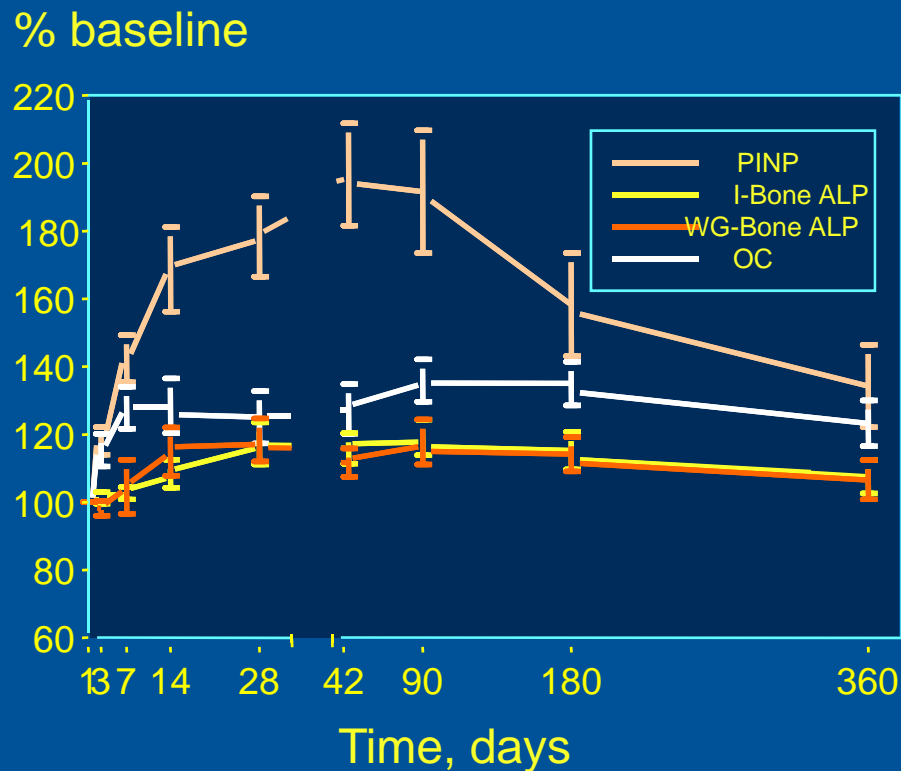


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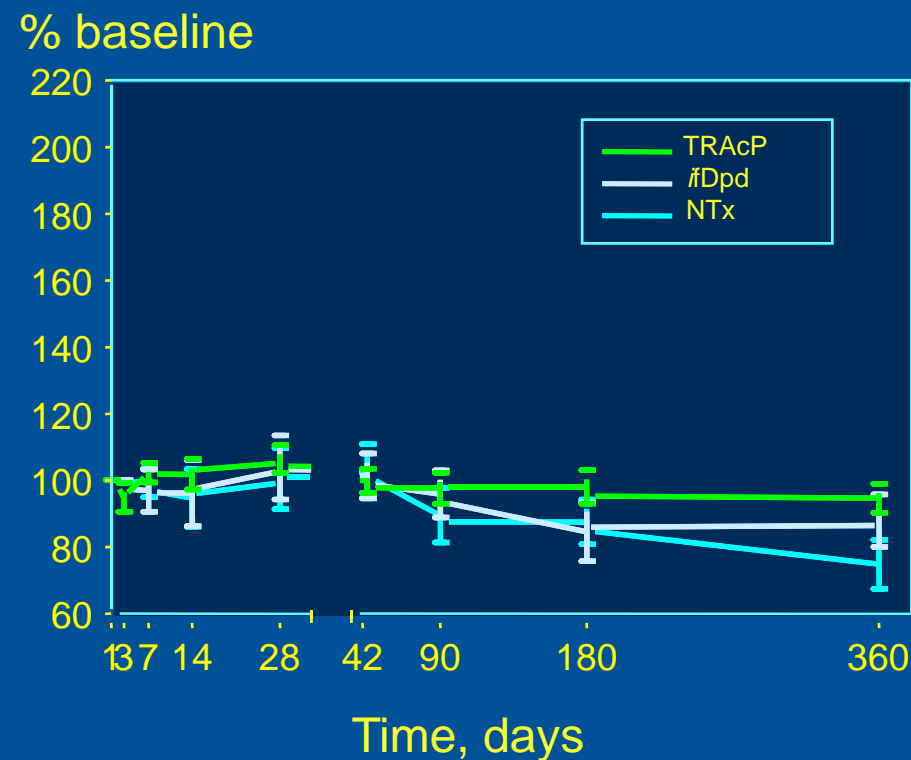
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Biochemical Markers following Ankle Fracture

Formation



Resorption



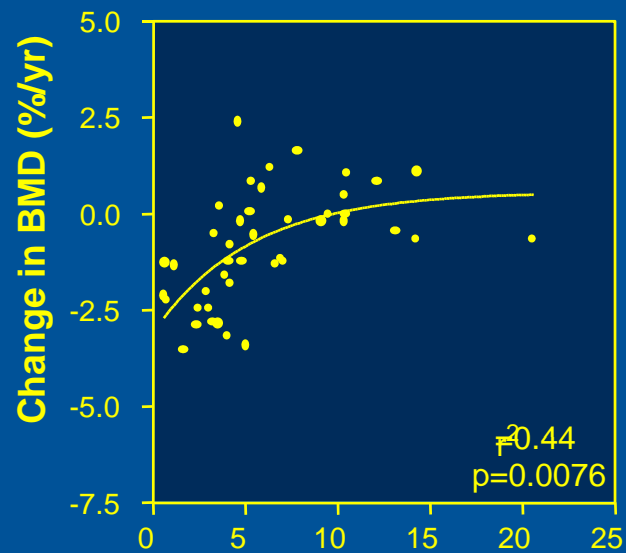
Is the patients more likely than average to have rapid bone loss or an increased risk of fracture?



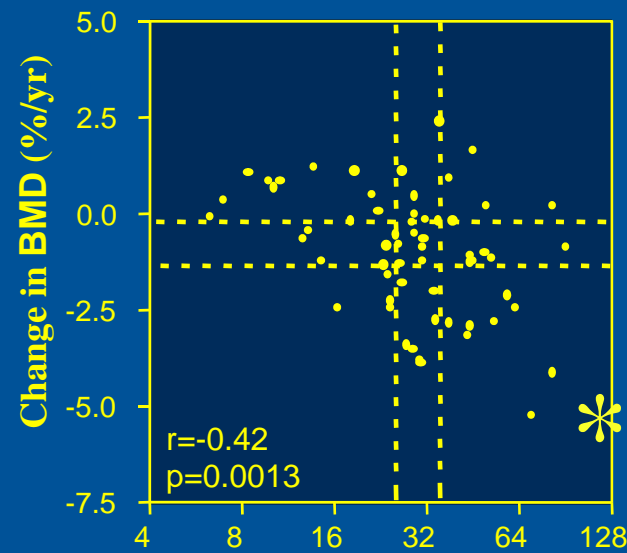
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She is likely to be a 'fast bone loser' Would she really lose 5% per year?



Years Since Menopause (YSM)



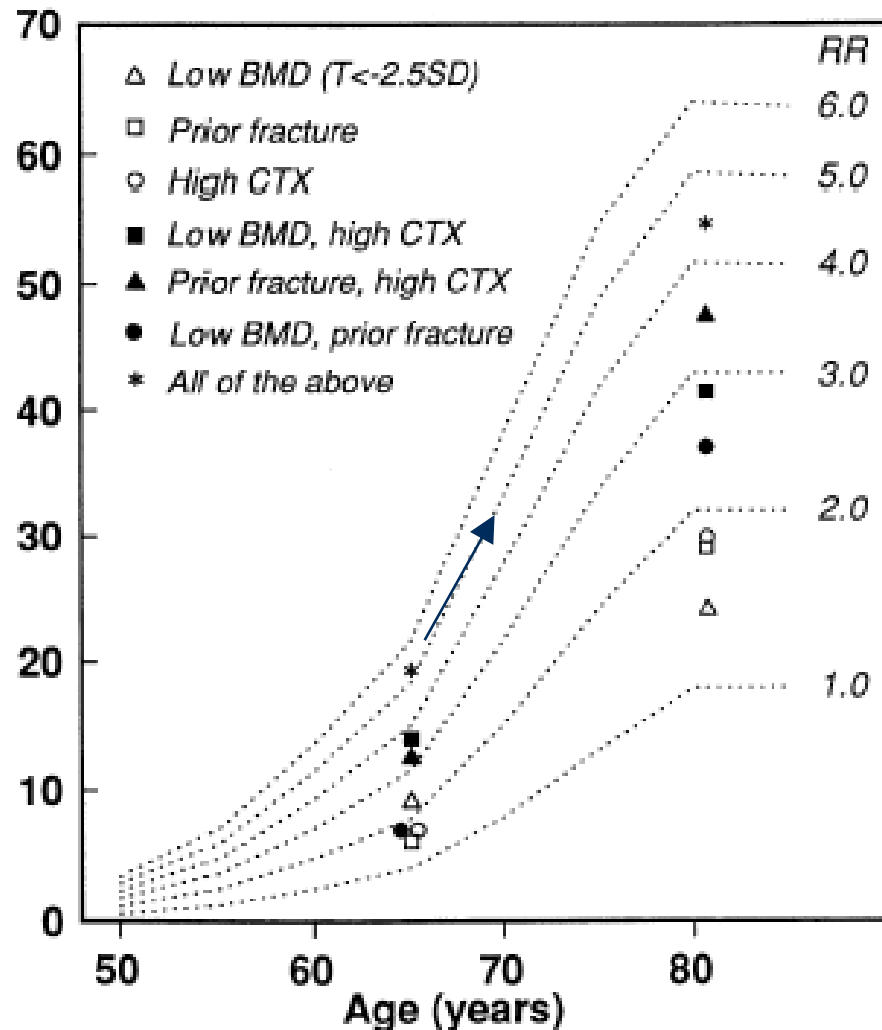
uNTX (nmol BCE/mmol Cr)

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 turnover¹ or only with high turnover²
 - Teriparatide most effective if bone turnover is high!³
- **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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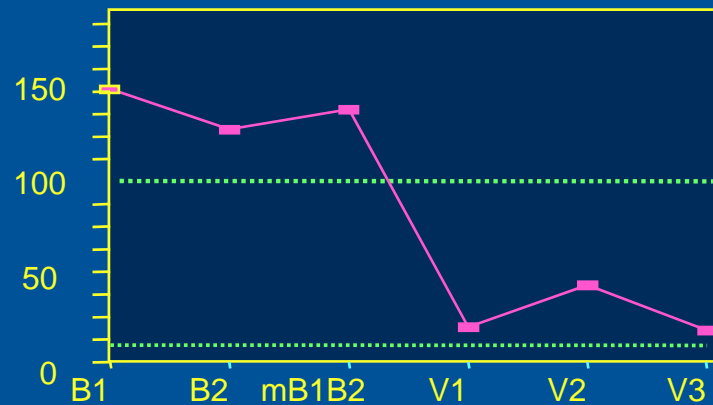
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After starting antiresorptive therapy, should we make follow-up measurements of bone turnover?

- **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

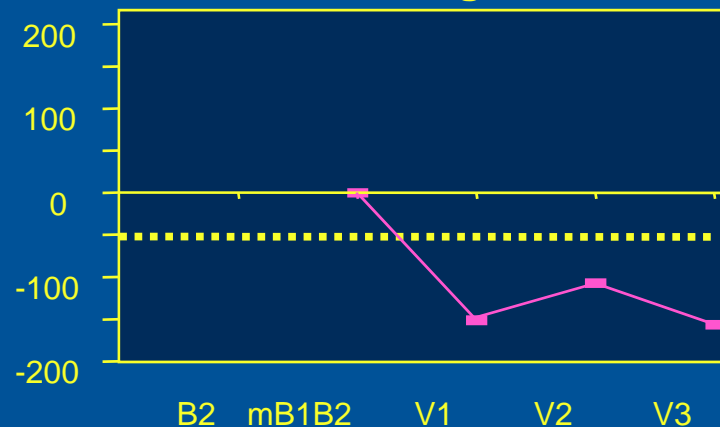
NTX/Cr, nmol BCE/mmol



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