Bone Turnover Markers

Educational Course

IOF International Osteoporosis Foundation

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www.iofbonehealth.org

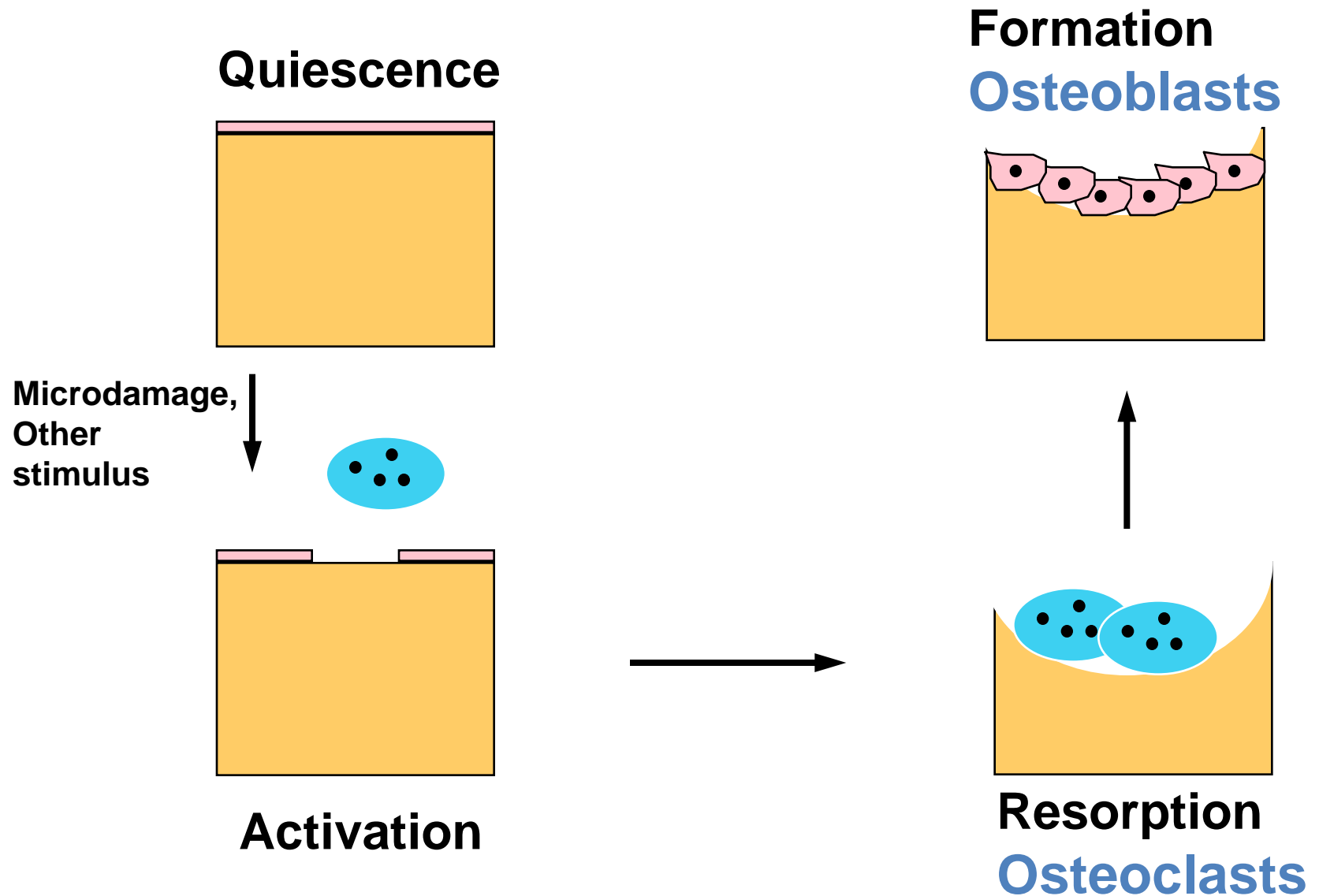International Osteoporosis Foundation

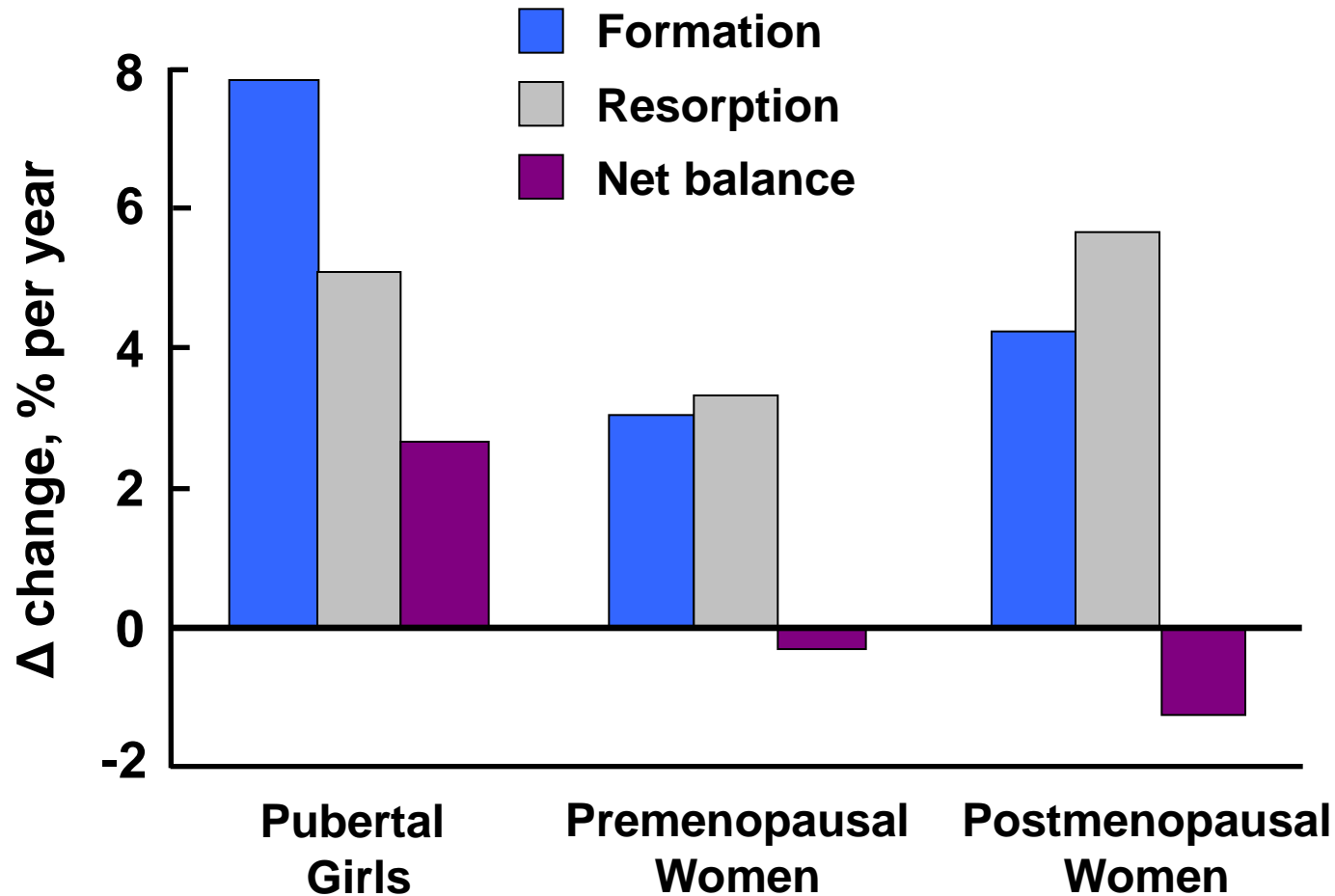# Clinical Needs In Osteoporosis

- Identification of individuals who would best benefit from intervention

- For those on treatment, the optimal manner in which response to treatment should be monitored

What is the role of bone turnover markers?

International Osteoporosis Foundation

Bone Remodelling Cycle

Quiescence

Formation
Osteoblasts

Microdamage,
Other
stimulus

Activation

Resorption

Osteoclasts

Age Dependency Patterns In Women

Classification of BTMs

Resorption

DPD*	Deoxypyridinoline
PYD*	Pyridinoline
NTX*	Amino-terminal crosslinking telopeptide of type I collagen
CTX*	Carboxy-terminal crosslinking telopeptide of type I collagen
TRACP &	Tartrate-resistant acid phosphatase

Formation

OC #	Osteocalcin
ALP&	Alkaline phosphatase (Total)
BALP &	Bone-specific alkaline phosphatase
P1CP#	Procollagen type I C propeptide
P1NP#	Procollagen type I N propeptide

*collagen degradation product; # matrix protein; & enzyme

Attractiveness of BTMs

- Samples of blood and urine easily collected

- Relative specificity for bone resorption or bone formation

- Variety of assays available

- Complementary information to BMD

- Changes in bone turnover markers occur earlier than changes in BMD

Limitations of BTMs

- Reflect total skeletal turnover

- Not always specific to bone metabolism

- Substantial biological variability (controllable and uncontrollable)

- Multiple assays for same analyte

- Do not assess osteocyte activity

Uncontrollable Sources of Pre-analytical Variability

Very important

Important

Less important
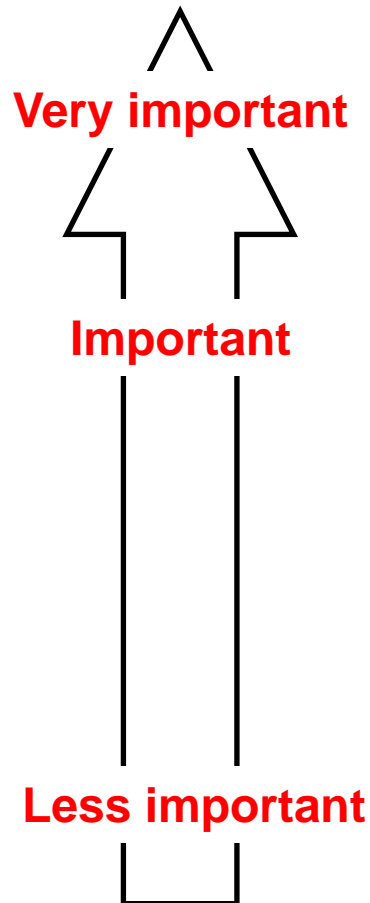
- Age
- Menopausal status
- Gender
- Fractures
- Pregnancy and lactation
- Drugs
- Disease
- Bed rest/immobility
- Geography
- Ethnicity
- Oral contraception

Vasikaran et al (2011) Osteoporos Int 22:391-420
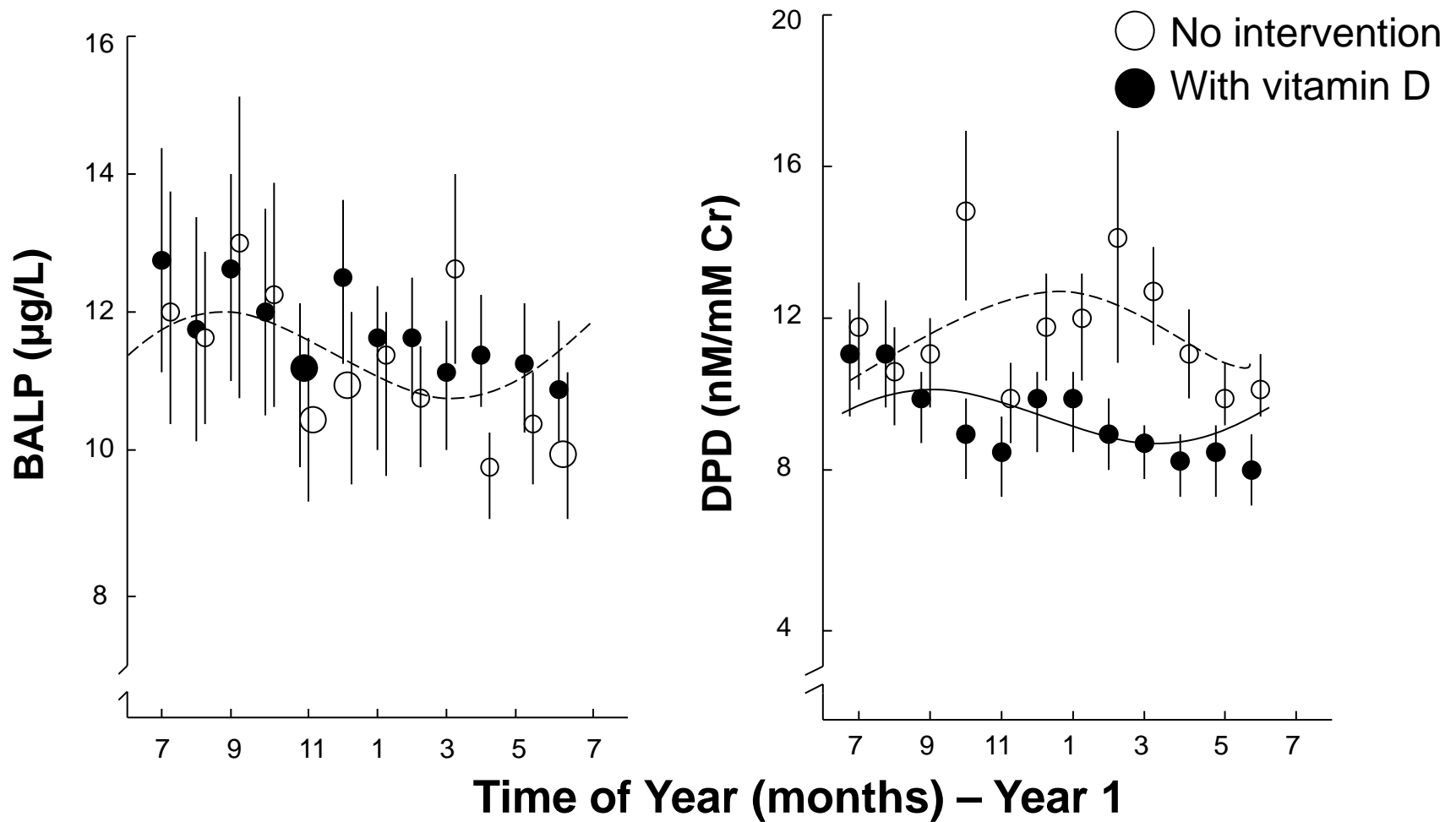
Controllable Sources of Pre-analytical Variability

Very important

Important

Less important
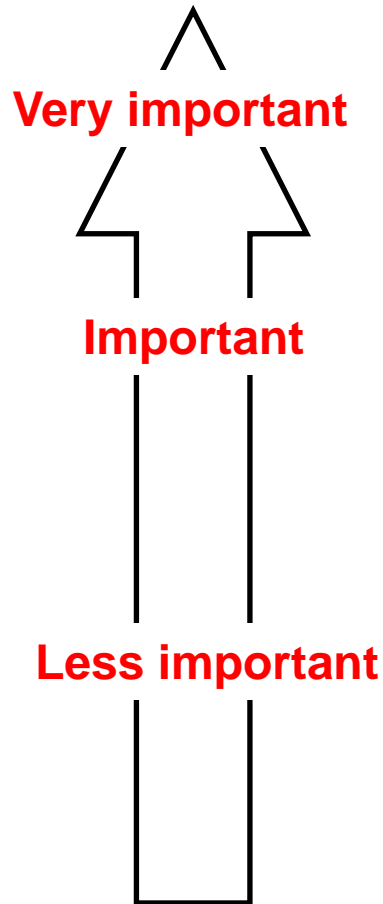
- Circadian

- Fasting status
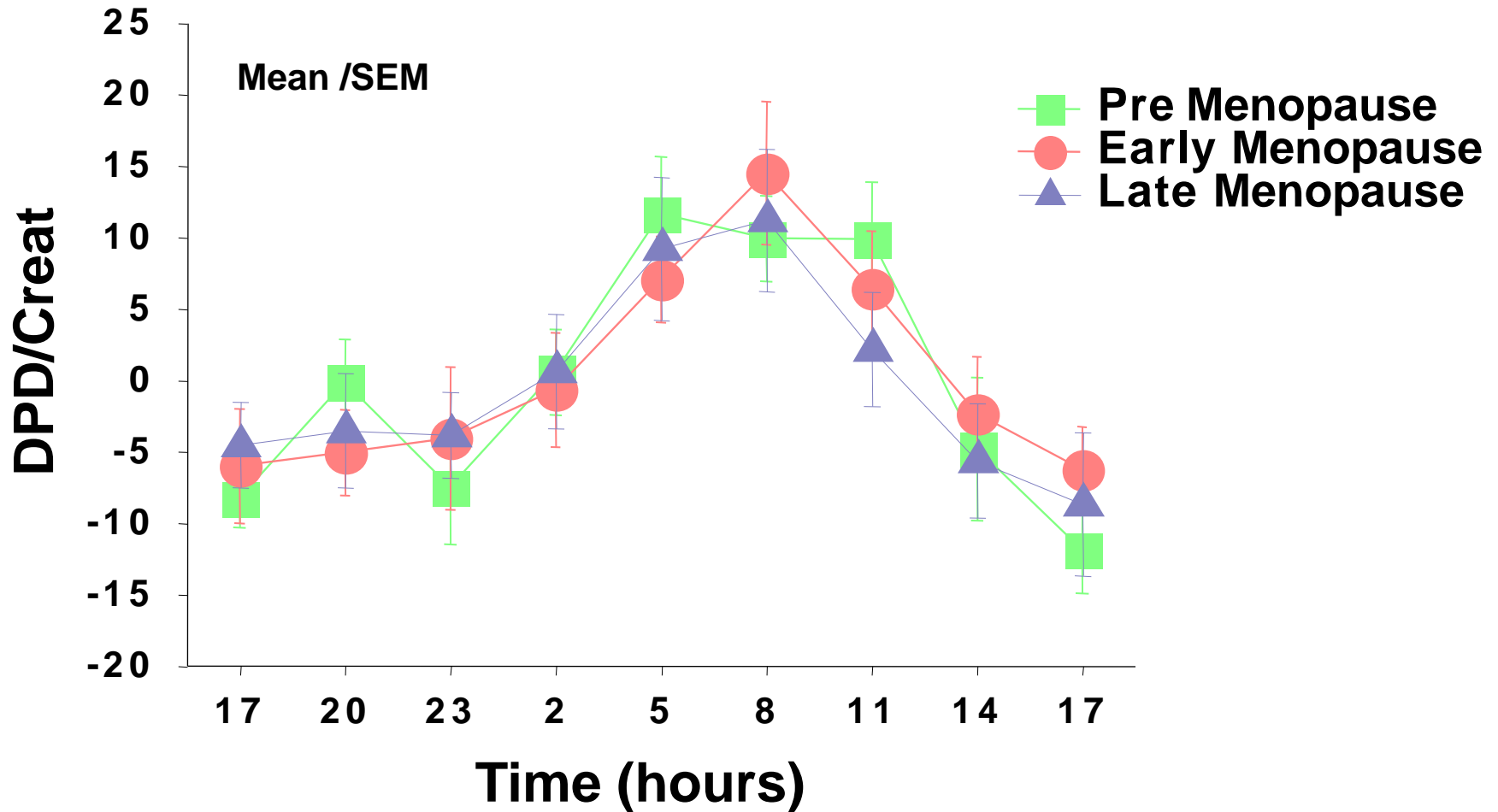- Exercise

- Menstrual

- Seasonal

- Diet

Vasikaran et al (2011) Osteoporos Int 22:391-420

Seasonal Variability
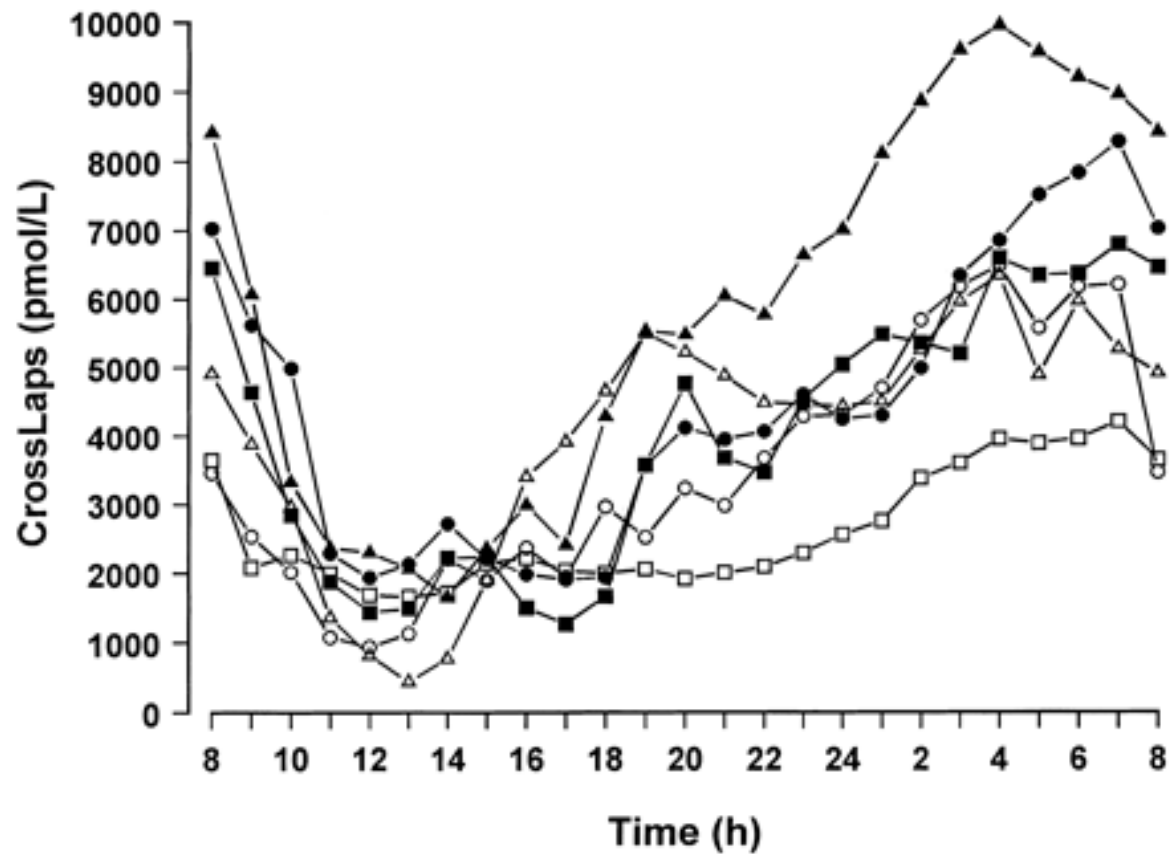

Meier et al (2004) JBMR 19: 1221-1230

Diurnal Variation in Urine Dpd

Schlemmer et al (1994) JBMR 9:1883-1888
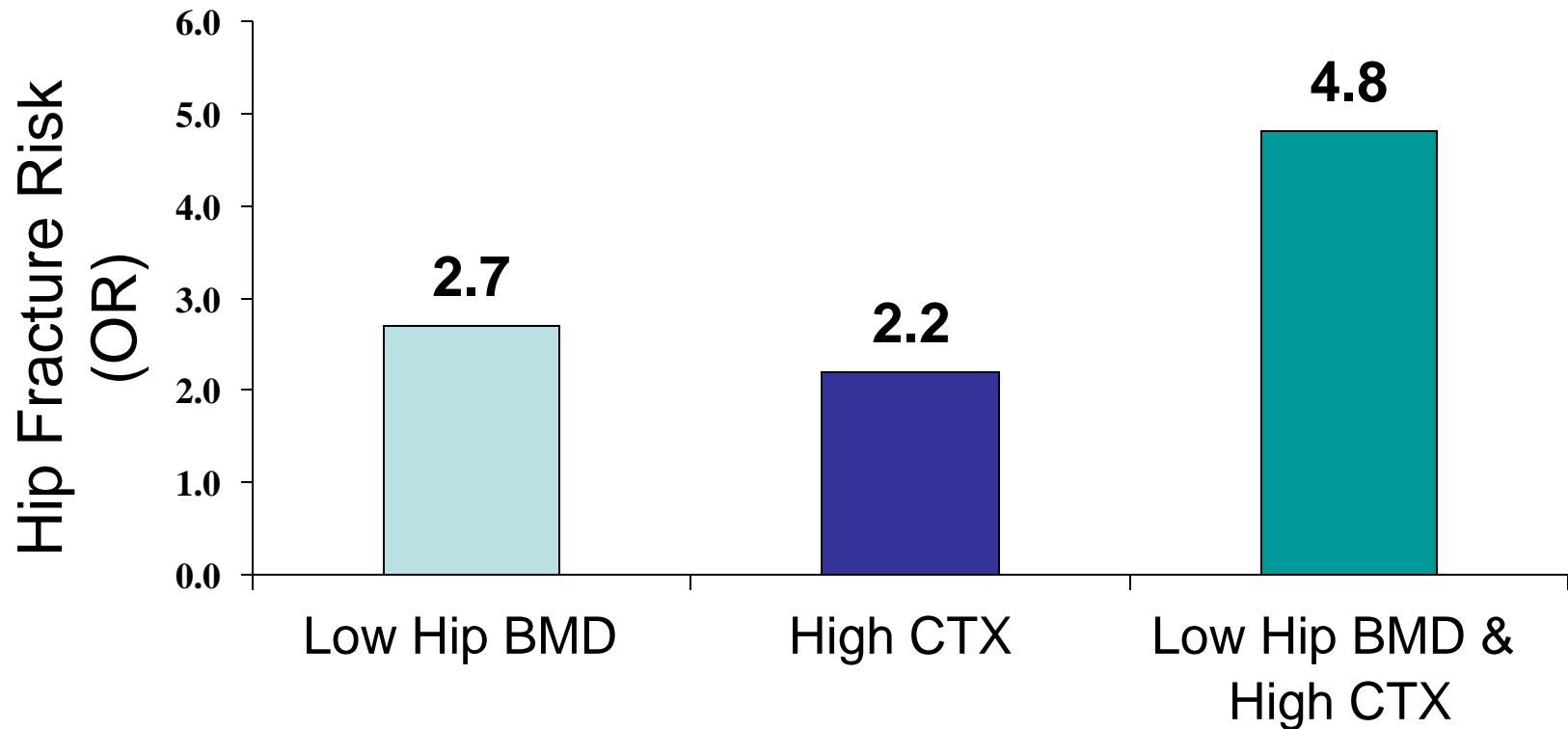
Diurnal Variation in Serum CTX

Individual profile of 6 healthy male volunteers

Wichers et al (1999) Clin Chem 45:1858-60

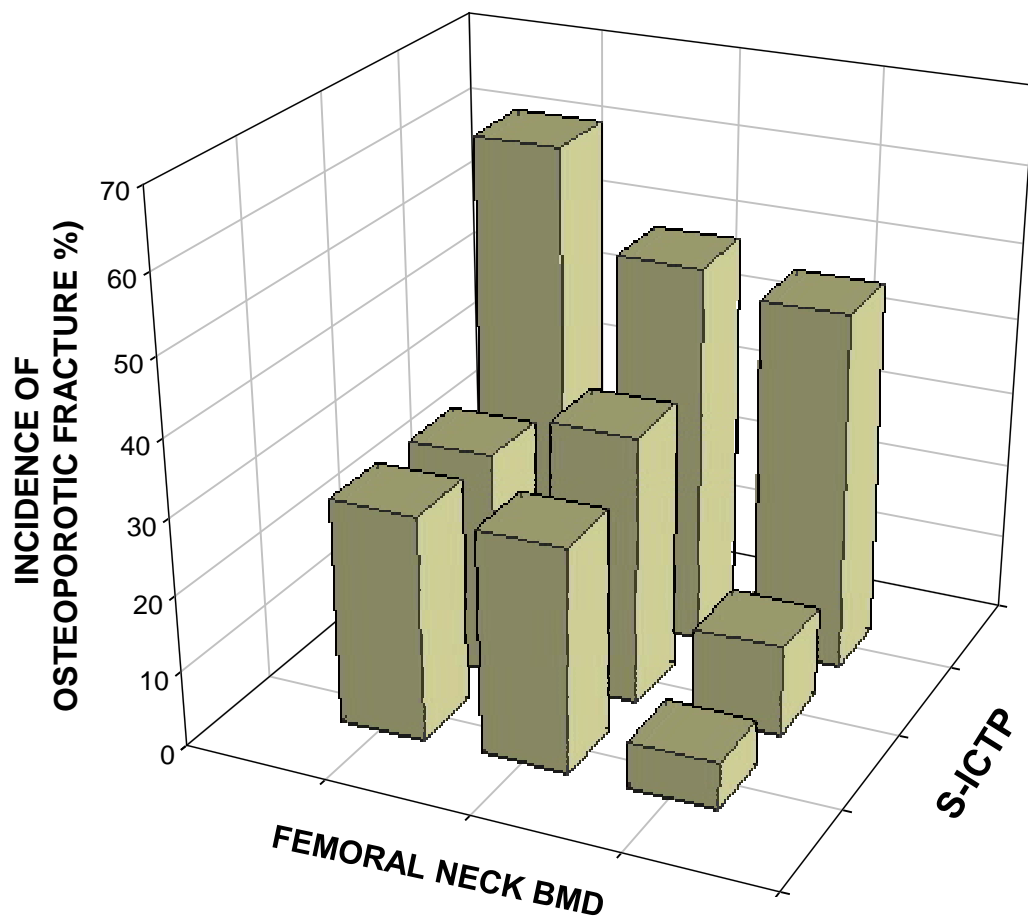# BTMs Predict Fracture Independently of BMD

EPIDOS prospective cohort study of 7598 healthy women; age 75+ yrs

Garnero et al (1996) JBMR 11:1531-1538

The Additive Effects of BTMs and BMD on Fracture Risk

Case-cohort control study of 151 older men from the Dubbo Study followed prospectively over 6.3 years.
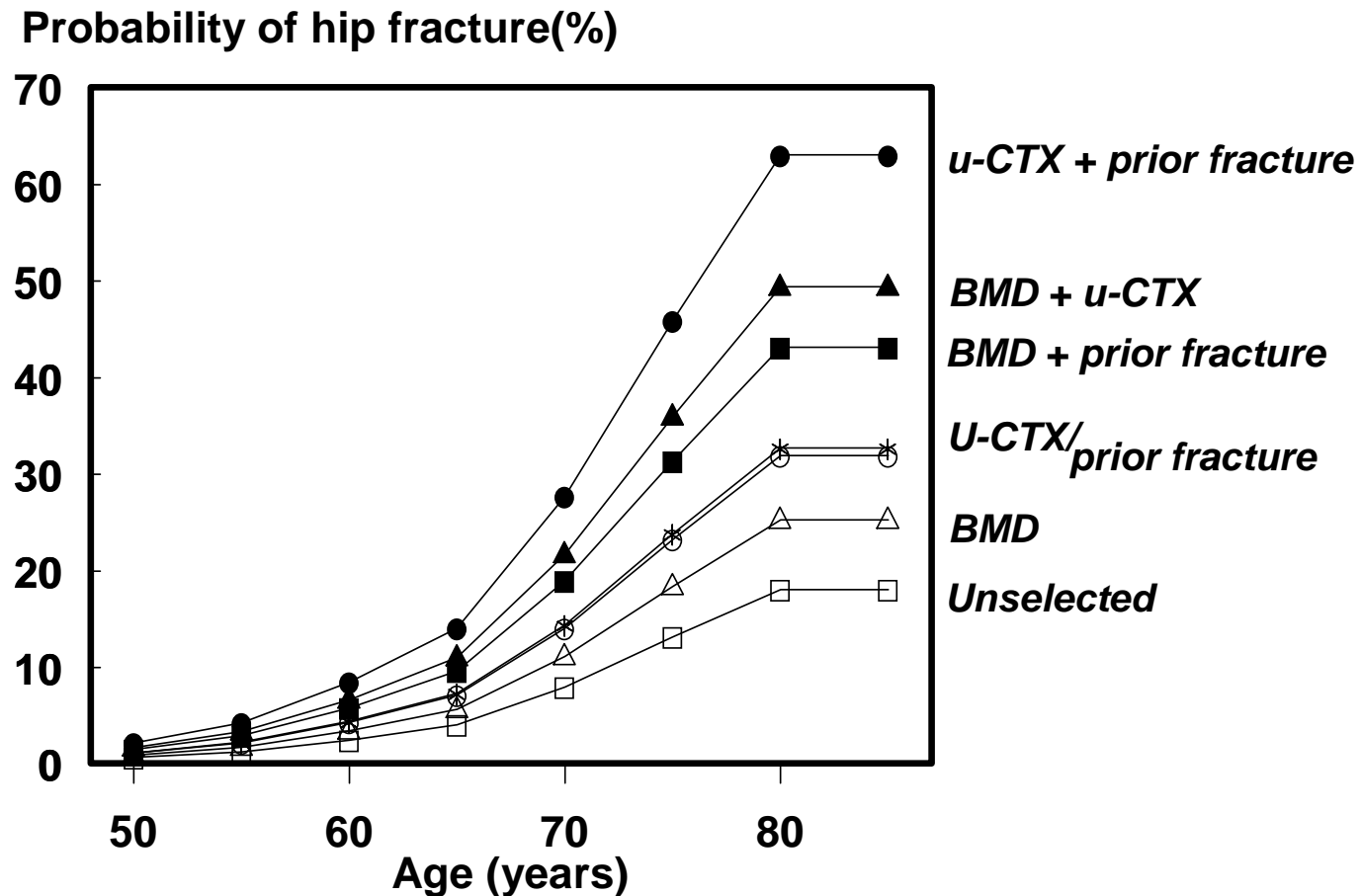

Patients with raised bone resorption markers have an increased risk of future fractures

This is independent of the current BMD

Patients with low BMD and high resorption markers have a 4-5-fold higher risk of future fractures

Meier et al (2005) JBMR 20:579-586

BTMs Predict Fracture Independently of Prior Fracture

Johnell O et al (2002) Osteoporos Int 13: 523-526

Markers of Bone Formation and Prediction of Fracture

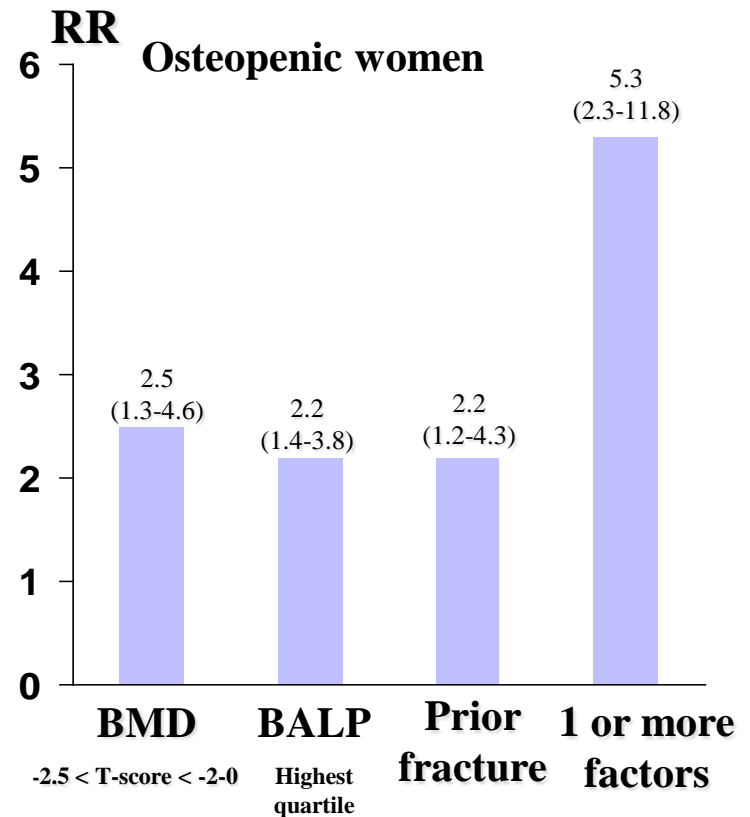**Bone formation markers have yielded contradictory results in the assessment of fracture risk**

No association

Elderly

- Any fracture (bALP, OC)[1]

- Hip fracture (bALP, OC)[2]

- Hip & non-vertebral fracture (OC)[3]

Postmenopausal women

- Any fracture (bALP, OC)[4]

1. Ivaska, JBMR 2010; 2. Garnero, JBMR 1996;

3. Dobnig, JCEM 2007; 4. Metlton III, JBMR

RR — Osteopenic women

| | 2.5 (1.3-4.6) | 2.2 (1.4-3.8) | 2.2 (1.2-4.3) | 5.3 (2.3-11.8) |

Chart bars:
- BMD (-2.5 < T-score < -2.0): 2.5 (1.3-4.6)
- BALP (Highest quartile): 2.2 (1.4-3.8)
- Prior fracture: 2.2 (1.2-4.3)
- 1 or more factors: 5.3 (2.3-11.8)

Sornay-Rendu, 2005 JBMR

International Osteoporosis Foundation

Limitations

- Altogether 17 different BTMs available (various methods)

- In a given study, there have been up to 10 different BTMs measured. The large number of predictions published raises the possibility of false positive results.

- Heterogeneity in the fracture outcomes reported. Up to four different fracture classifications, such as spine, hip, non-spine and all fractures

- Multiple statistical approaches ,e.g.,
    - bone turnover considered as odds ratio per standard deviation increase in BTM;
    - a BTM lying within the top three quartiles (compared to the lowest quartile); or
    - value more than 2 standard deviations above the premenopausal reference interval

Limitations (2)

- For any given analyte, there is some inconsistency in the predictive value of specific markers. For example, s-OC is variously a strong, moderate, borderline or non-significant predictor of fracture risk.

- The association with bone formation markers and fracture risk was usually, though not invariably, not statistically significant

- The association of bone resorption markers and fracture risk was somewhat more consistent

- The time of day is critical to the concentration of some BTMs

- There is a negative correlation between BMD and BTMs, which becomes stronger with advancing age. The prediction of BTMs for fracture was independent of BMD in some studies, but not in all

Predictive Capacity of BTMs Attenuates with Time
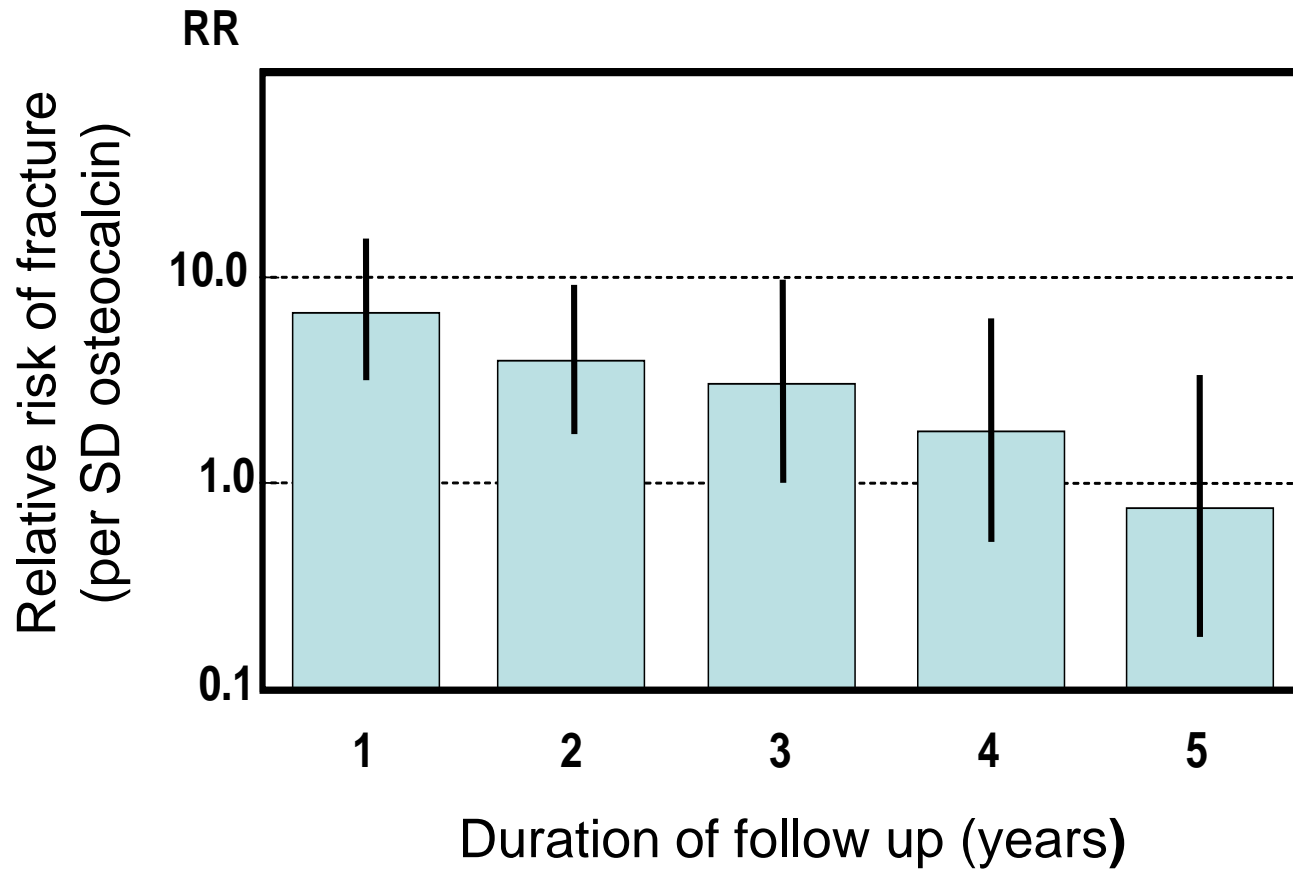
Luukinen et al (2000) JBMR 15:2473-2478

BTMs in Fracture Risk Algorithms

- BTMs are currently not included in the FRAX algorithms because

  1. of the scarcity of population based prospective studies with any single analyte

  2. the applicability of the research database in an international setting is also insecure

      - e.g. > 1/3 studies are from France

      - none from Asia

- Garvan model uses age, BMD, previous fractures and falls

sCTX and Fracture Prediction in Postmenopausal Women

Prospective Studies	Age (years)	Study f-u (years)	Fx type	Marker	Outcome risk (95%CI)
EPIDOS	>74	1.8	hip	u-CTX	OR 2.2 (1.3, 3.6)
	>74	3.3	hip	s-CTX u-CTX	HR 1.9 (1.0, 3.8) HR 1.7 (1.2, 2.3)
OFELY	50-89	5.0	all	u-CTX s-CTX	RR 2.3 (1.3, 4.1) RR 1.9 (1.0, 3.6)
HOS	43-80	2.7	all	u-CTX	OR 1.5 (1.2, 2.0) **OR 1.4 (1.1-1.8)**
Malmö	75	3-6.5	spine all	s-CTX S-CTX	OR 1.9 (1.0, 3.6) **OR 1.5 (0.8–3.0)**
MrOs (men)	>65	5	hip non-spine	s-CTX s-CTX	**HR 1.2 (0.6-2.4)** **HR 1.3 (0.98-1.7)**

*Vasikaran et al (2011) Osteoporos Int 22:391-420*

Bold – adjusted for BMD

sP1NP and Fracture Prediction in Postmenopausal Women

Prospective Studies	Age (years)	Study f-u (years)	Fx type	Expression of risk	Relative risk (95%CI)
OFELY	50-89	5.0	all	Highest vs. lowest quartile	1.3 (0.7, 2.4)
				Concentrations >2SD of prem. women	1.6 (0.8, 3.4)
DOES	>70	6.3	all	1Highest quartile of the distribution compared to lowest	1.4 (0.8-1.6)
				Univariate analysis, RR for 1SD change (+15 g/L)	1.1 (0.9-1.4)
MrOS (men)	>65	5	hip	Highest quartile versus three lower quartiles	2.1 (1.2-3.7)
			non-spine		1.6 (1.2- 2.0)

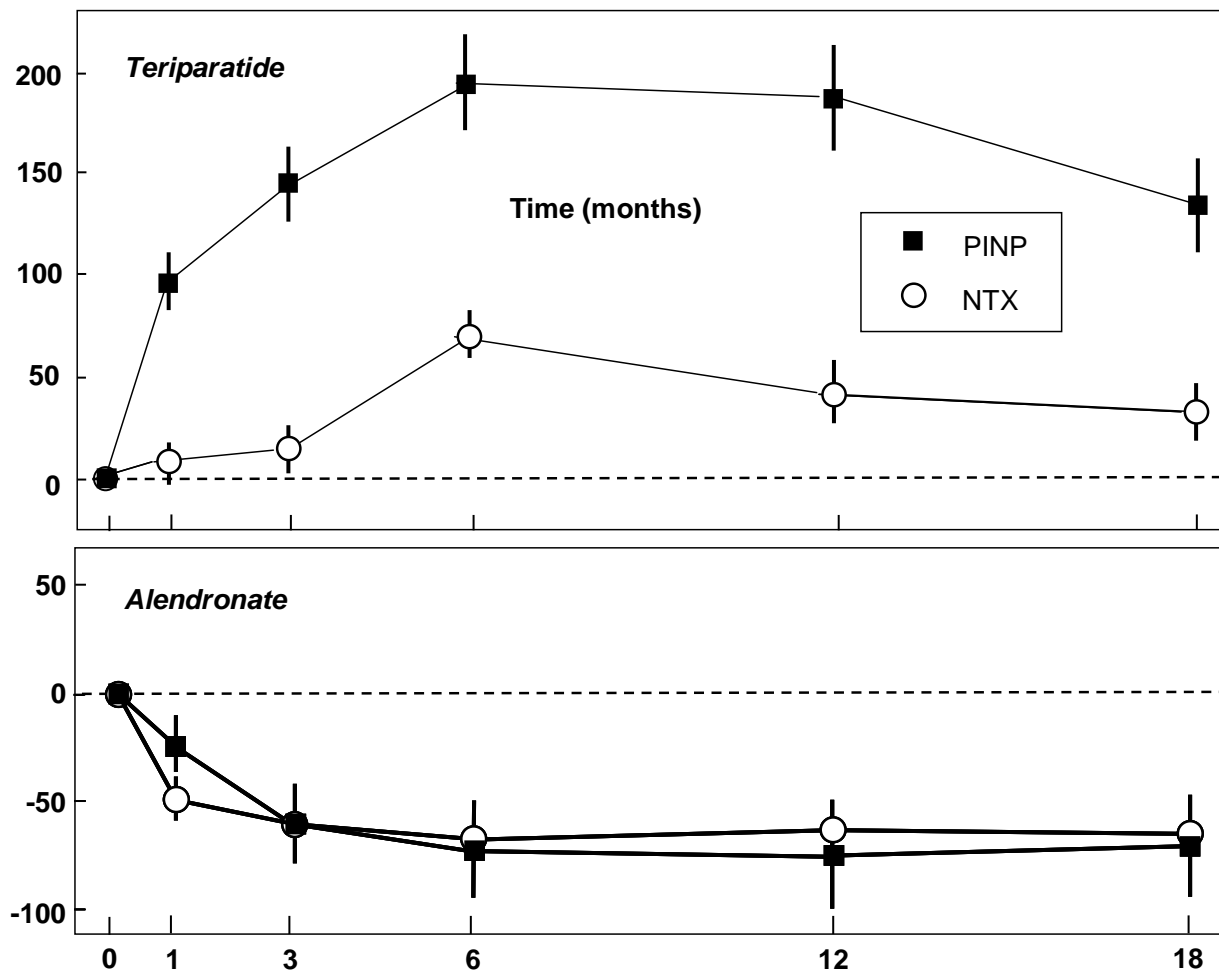*Vasikaran et al (2011) Osteoporos Int 22:391-420*

Relationship Between Bone Turnover and Bone Loss
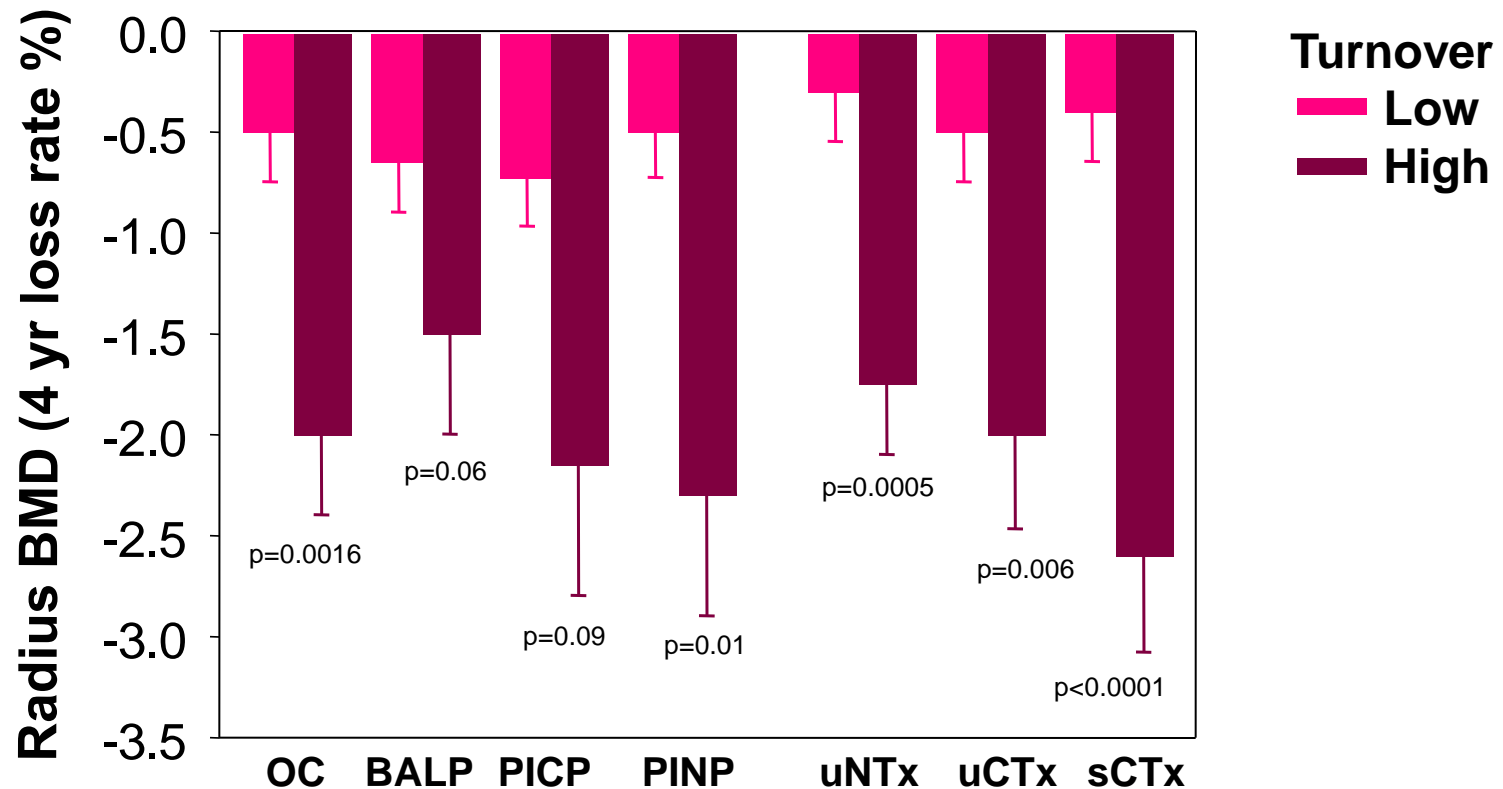
Garnero et al (1999) JBMR 14: 1614-1621

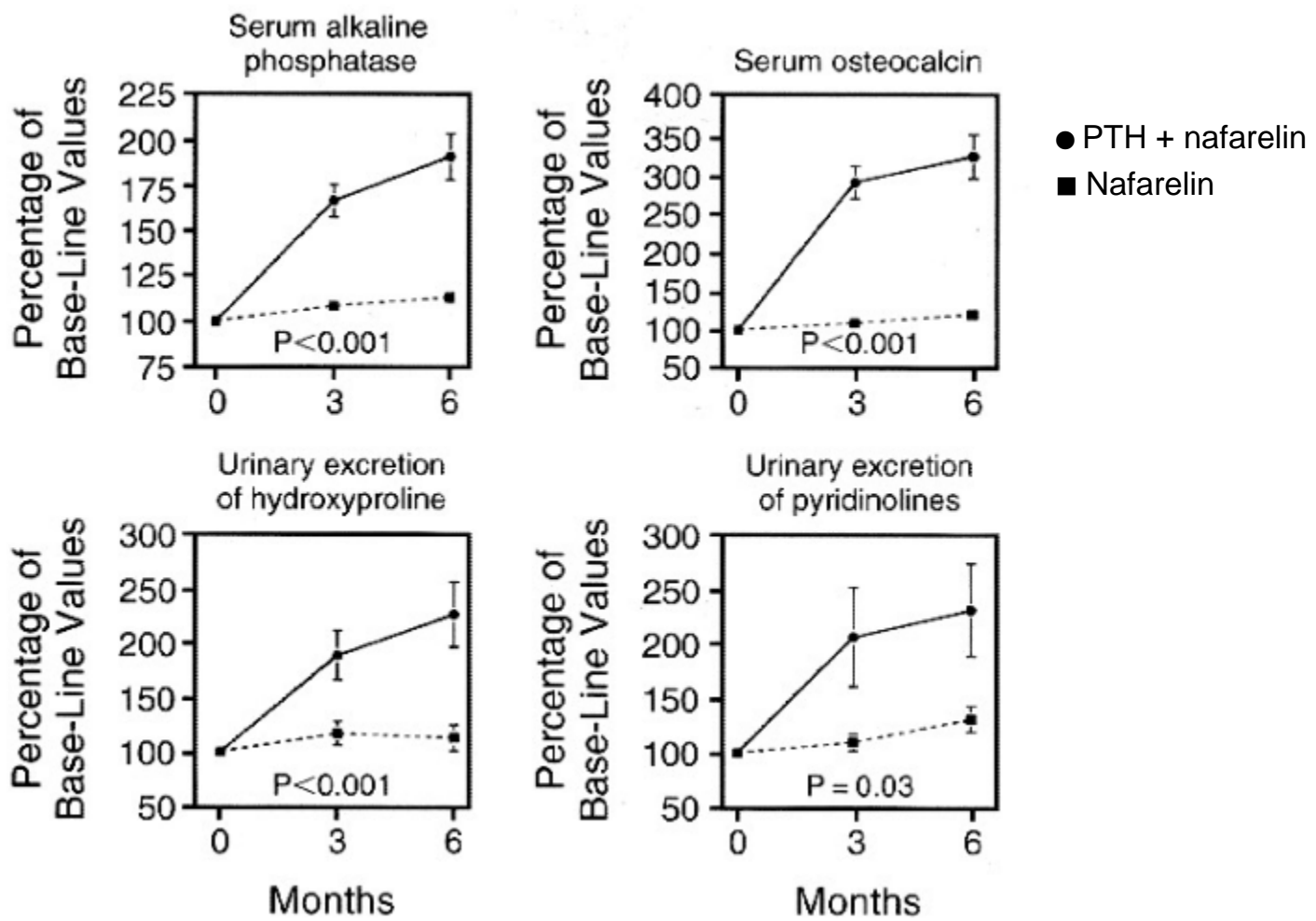# Typical BTM Changes After Anti-Resorptive vs Anabolic Therapy

Arlot et al (2005) JBMR 20: 1244-53

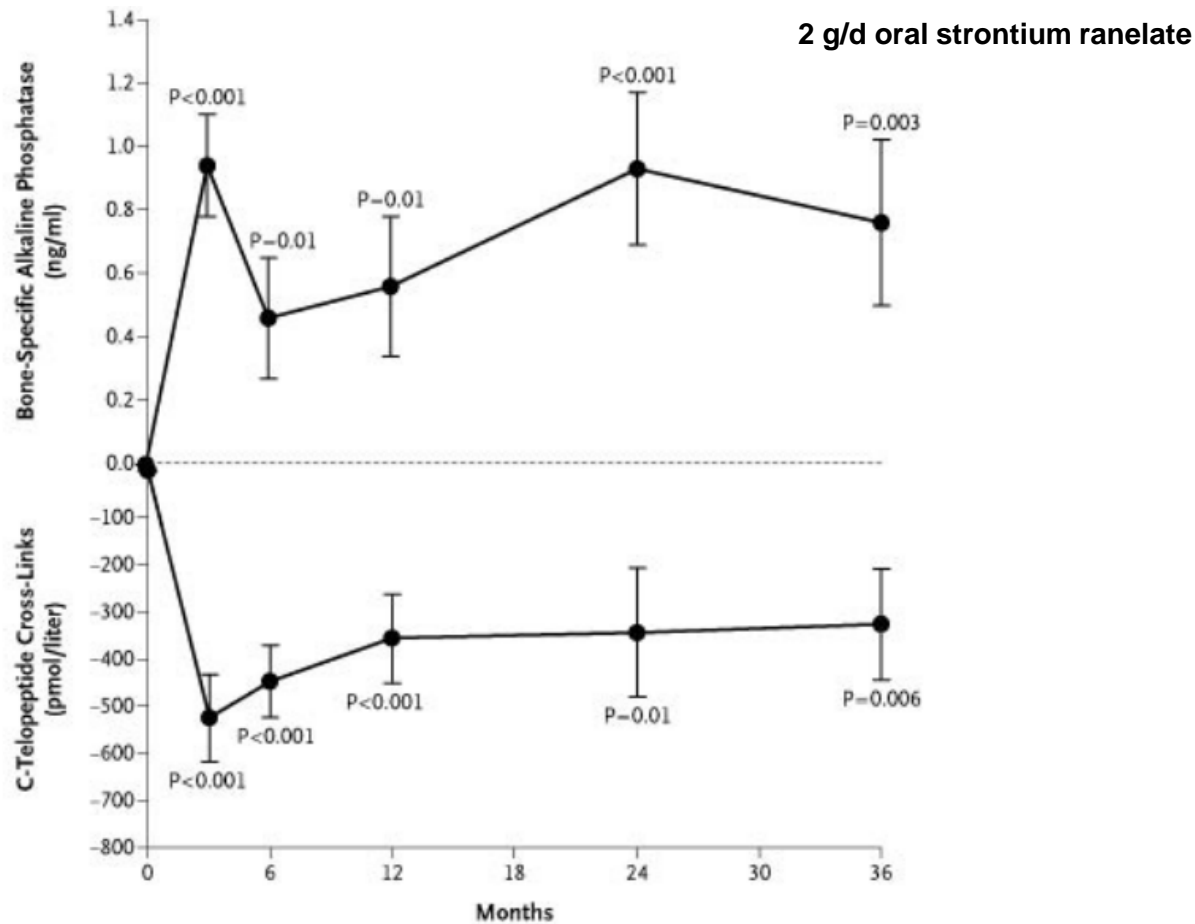# Response of BTMs To Anabolic Therapy (hPTH1-34)

Finkelstein et al (1994) NEJM 331:1618-1623
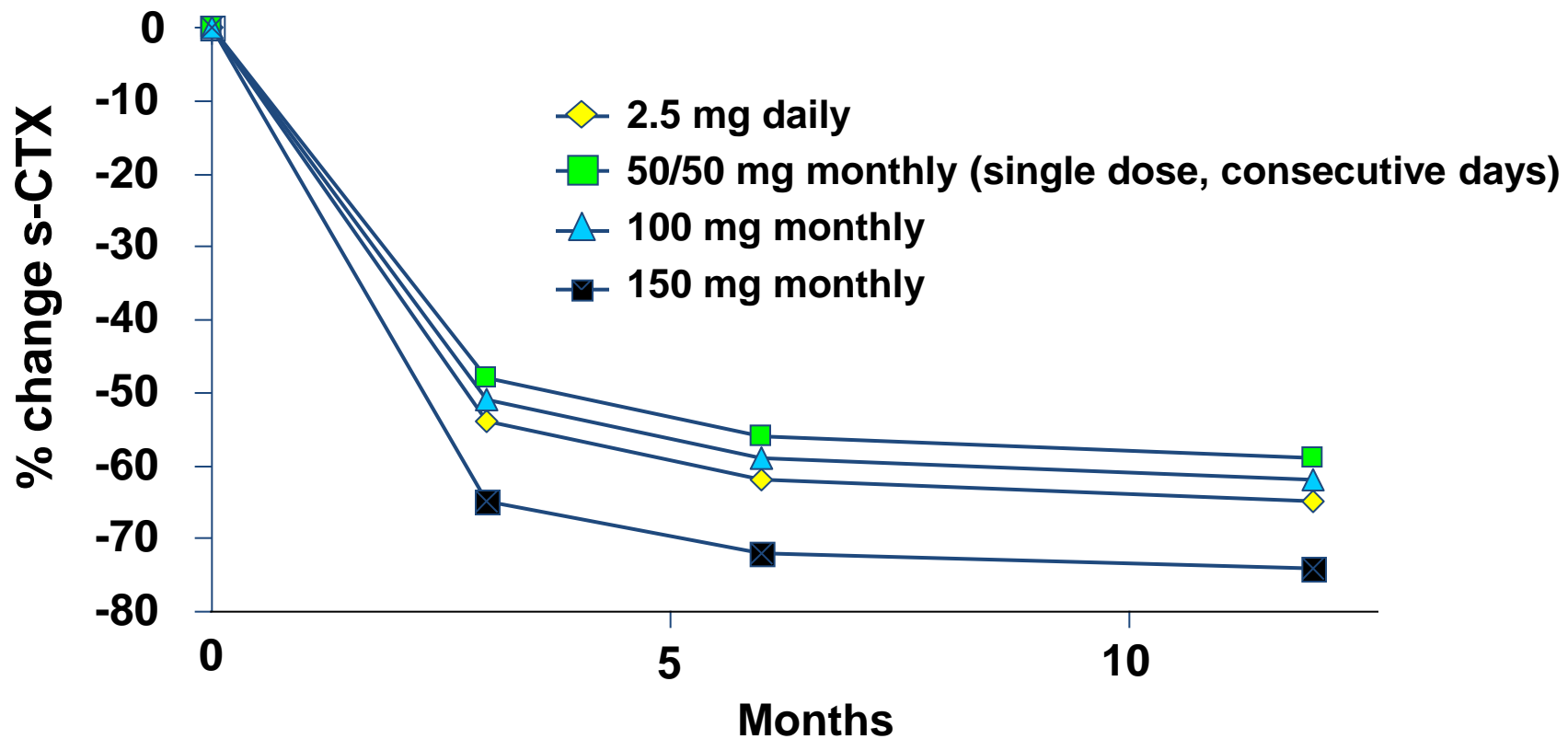
Response of BTMs to Strontium Ranelate

2 g/d oral strontium ranelate

Meunier et al (2004) N Engl J Med 350:459-68

Dose Response of Serum CTX With Ibandronate

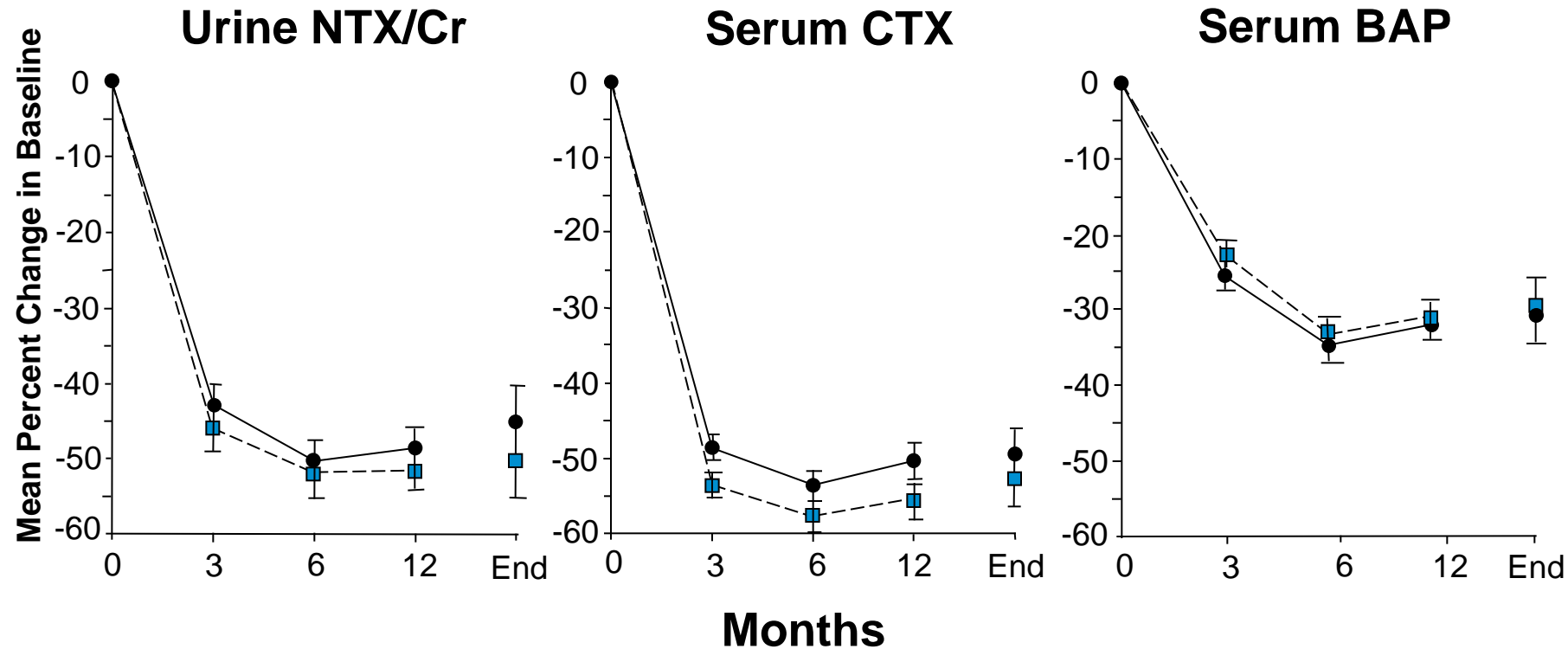**MOBILE study: 1609 women with postmenopausal osteoporosis**

Miller et al (2005) JBMR 20:1315-1322

Frequency of Administration of an Anti-Resorptive Therapy

DAILY VS. MONTHLY RISEDRONATE

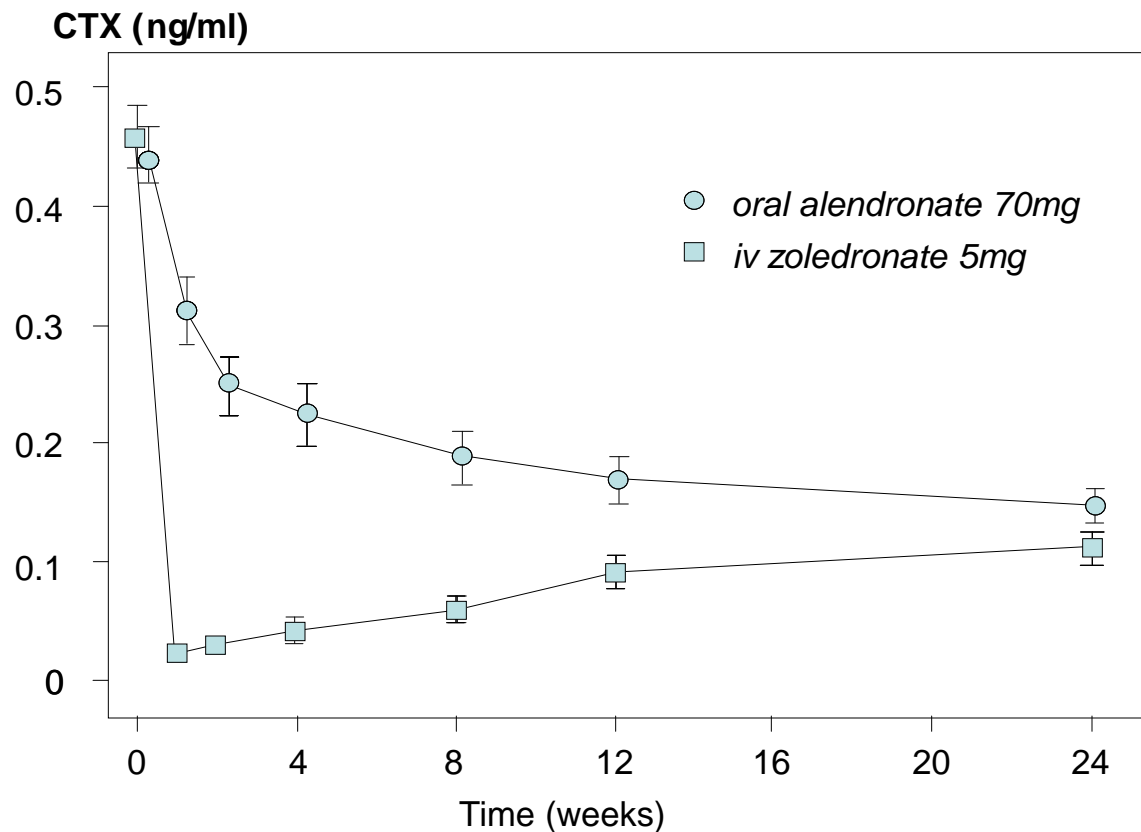*Delmas et al (2008) Bone 42:36-42*

Route of Administration Determines BTM Response

Changes in s-CTX following treatment with oral alendronate given weekly and zoledronic acid given as a single annual IV dose.


Saag K et al (2007) Bone 40: 1238-43

Wide Variability of Changes in BTM After Therapy

| Treatment	Author	Dose	PINP	OC	BALP	s-CTX	u-NTX
Strontium ranelate	Meunier	2 g/d			+8	-12	
	Bruyère	2 g/d					-11
Raloxifene	Naylor	60 mg/d	-34				-25
	Chesnut	60 mg/d		-21		-21	
	Meunier	60 mg/d		-20		-28	
	Ettinger	60 mg/d		-18			
Risedronate	Harris	5 mg/d			-23		
	Rosen	35 mg/w	-48 *		-28 *	-55 *	-40 *
Alendronate	Naylor	10 mg/d		-28	-31		-49
	Hannon	10 mg/d				-71	
	Rosen	70 mg/w	-64 *		-41 *	-74 *	-53 *
	Emkey	70 mg/w	-68 *			-81 *	
	Arlot	70 mg/w	-70 *				-70 *
Zoledronate	Black	5 mg/y i.v.	-59		-30	-58	
Denosumab	Cummings	60 mg/6/12 sc	-50			-72	
	Bone	60 mg/6/12 sc	-60			75	
	Lewiecki	60 mg/6/12 sc			-60	-70	-60
Teriparatide	Glover	20 µg/d	+111 *[a]	+76 *[a]	+18 *[a]	+5 *[a]	+8 *[a]
	Arlot	20 µg/d	+135 *				+32 *

Effects of Discontinuing Alendronate on sCTX and BSAP

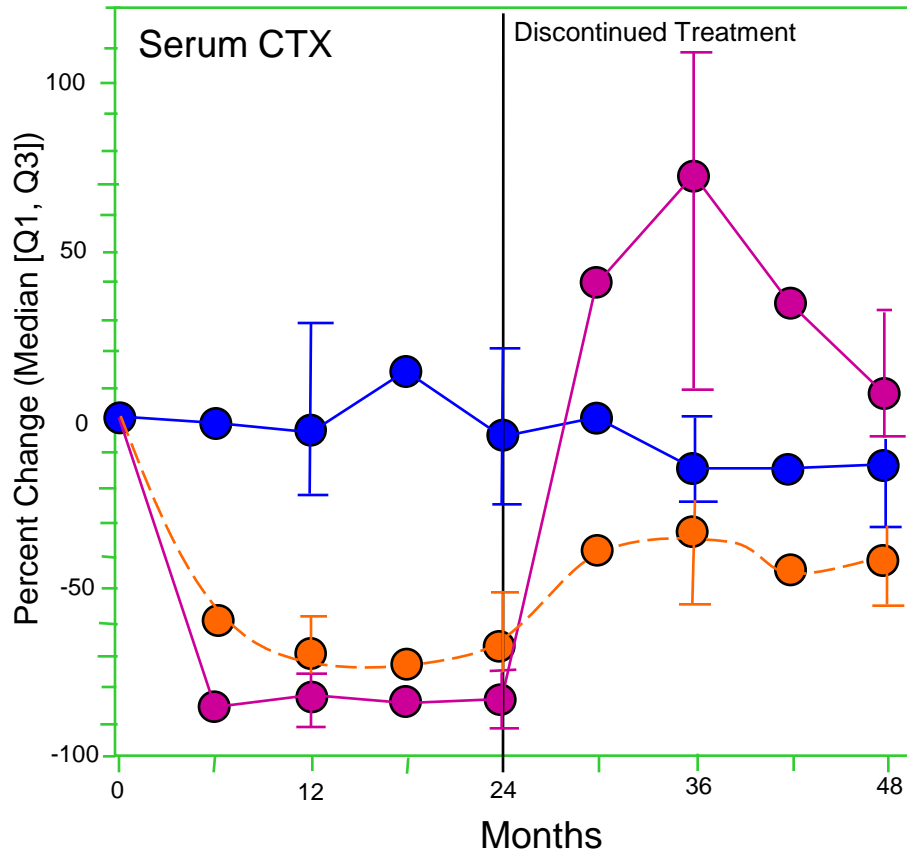FLEX trial: the effects of continuing alendronate (ALN) for 5 years compared with cessation of treatment for the next 5 years

sCTX (ng/mL)   BALP (ng/mL)
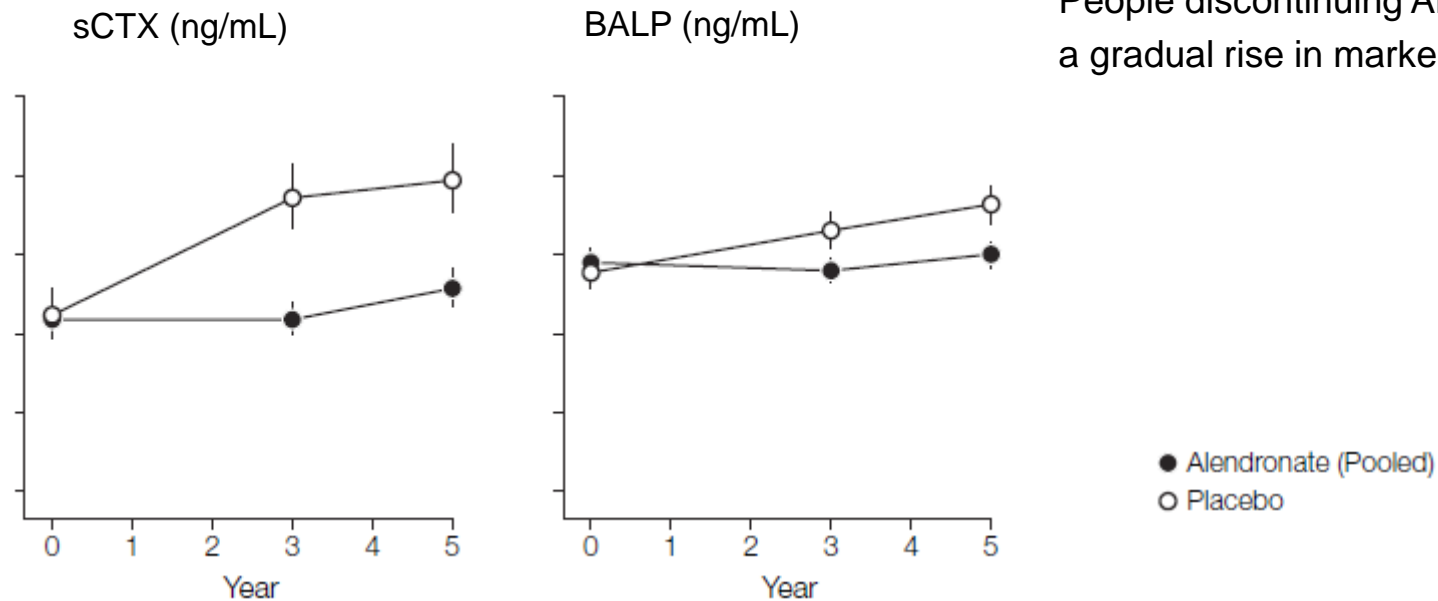
People discontinuing Aln experinece a gradual rise in markers over 5 years

● Alendronate (Pooled)
○ Placebo

Black et al (2006) JAMA 296:2927-2938

Effects of Discontinuing Denosumab on Serum CTX and BSAP
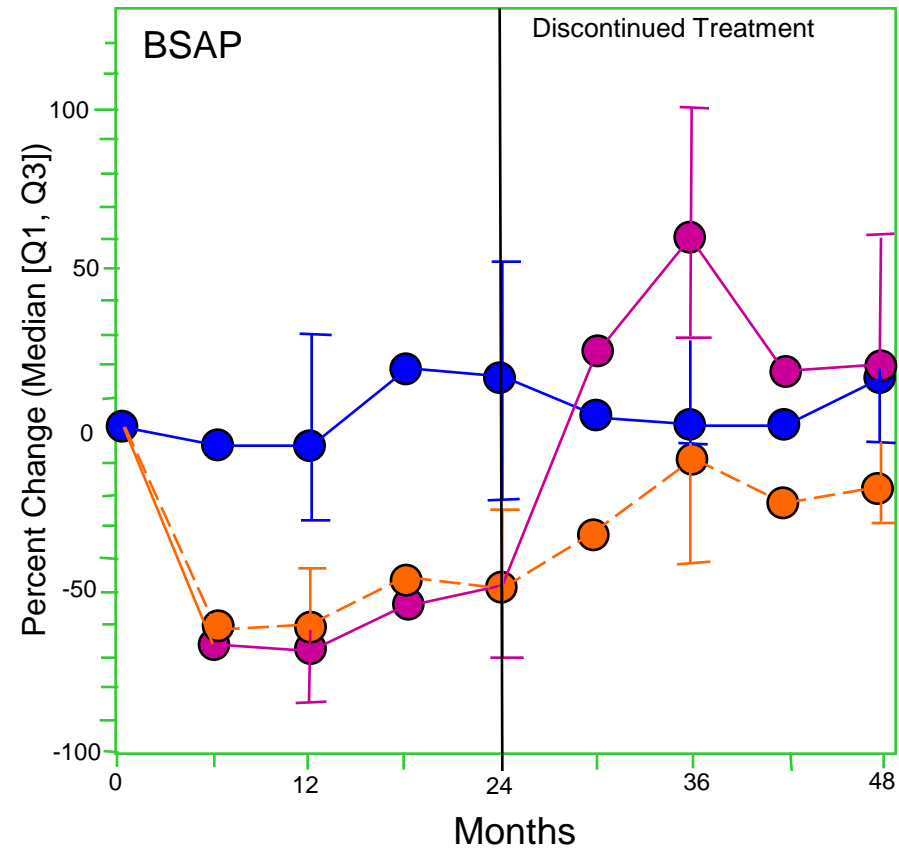
Miller et al (2008) Bone 43:222-229

Effect of Denosumab Re-treatment on Serum CTX and BSAP
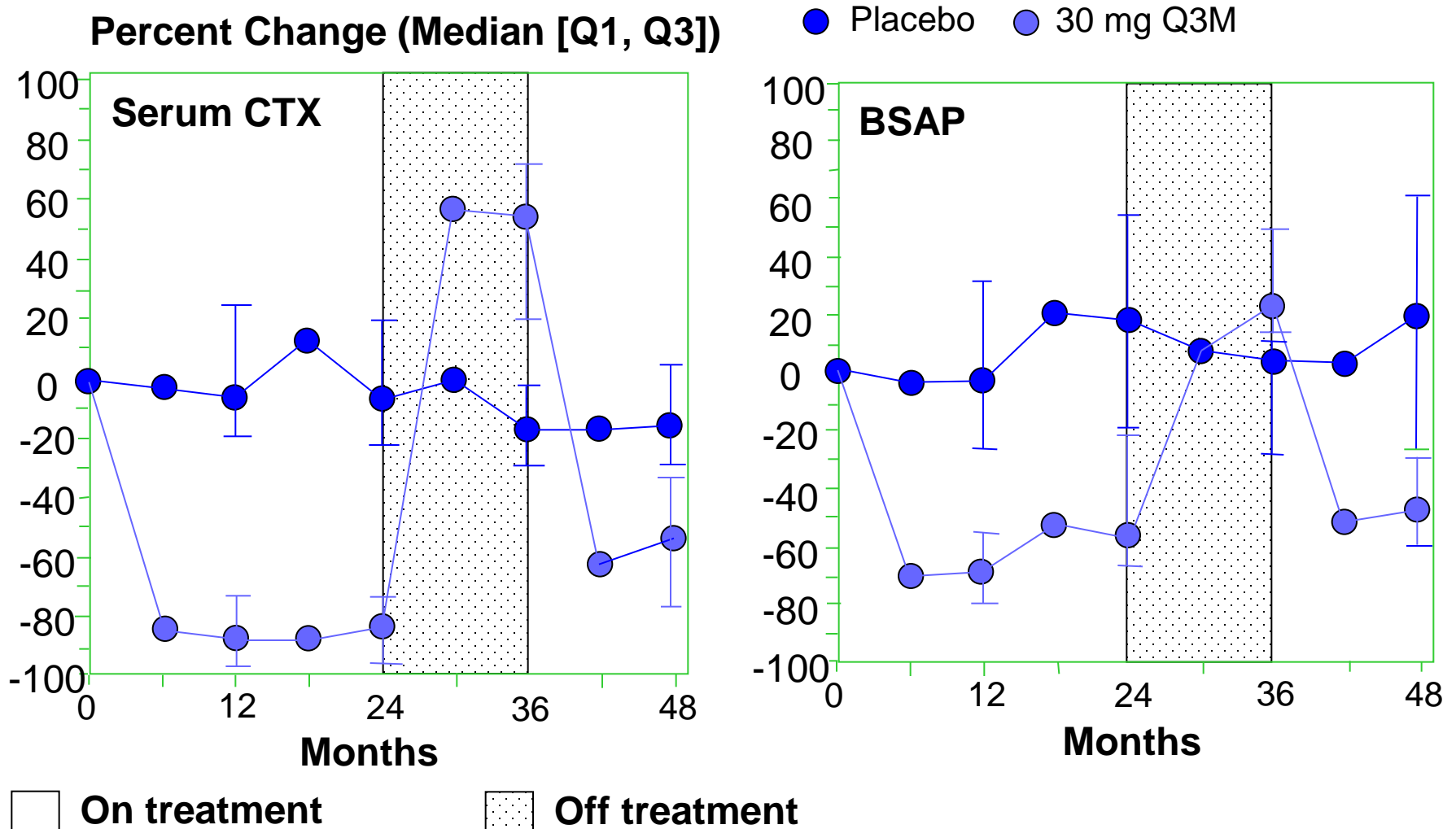
Baseline sCTX and P1NP Predict Change in BMD with Alendronate or Denosumab Therapy

1 yr treatment with alendronate and denosumab

Alendronate 70 mg QW   *Denosumab 60 mg Q6M*

sCTX

P1NP

Percent Change From Baseline in BMD Least Squares Mean (95% CI)

Baseline sCTx1 (ng/mL): < 0.477, 0.477 to < 0.631, 0.631 to < 0.836, ≥ 0.836

Baseline P1NP (μg/mL): < 39.08, 39.08 to < 49.06, 49.06 to < 62.15, ≥ 62.15

*$P \le 0.014$
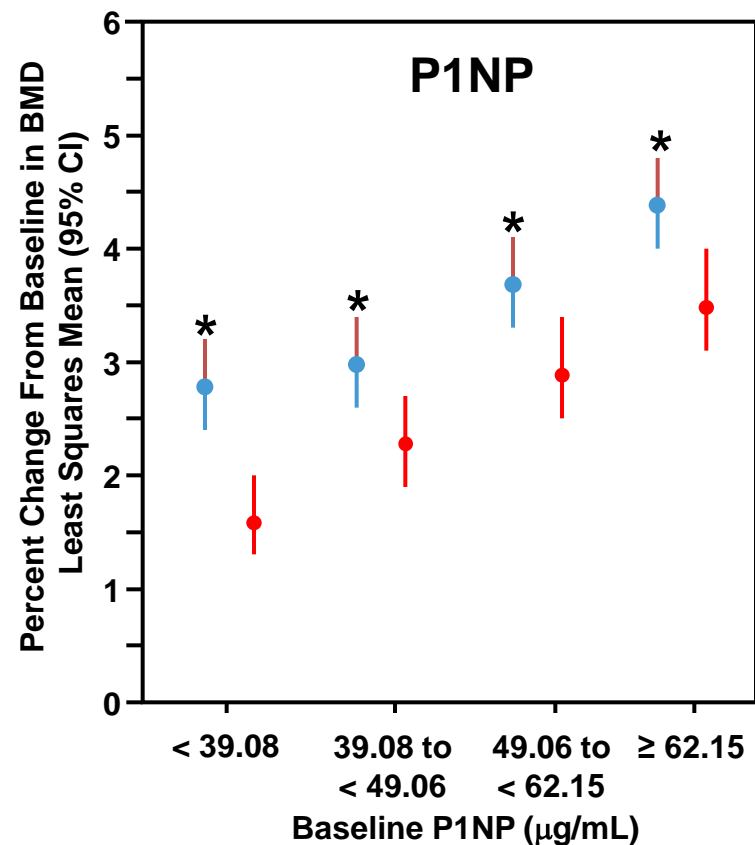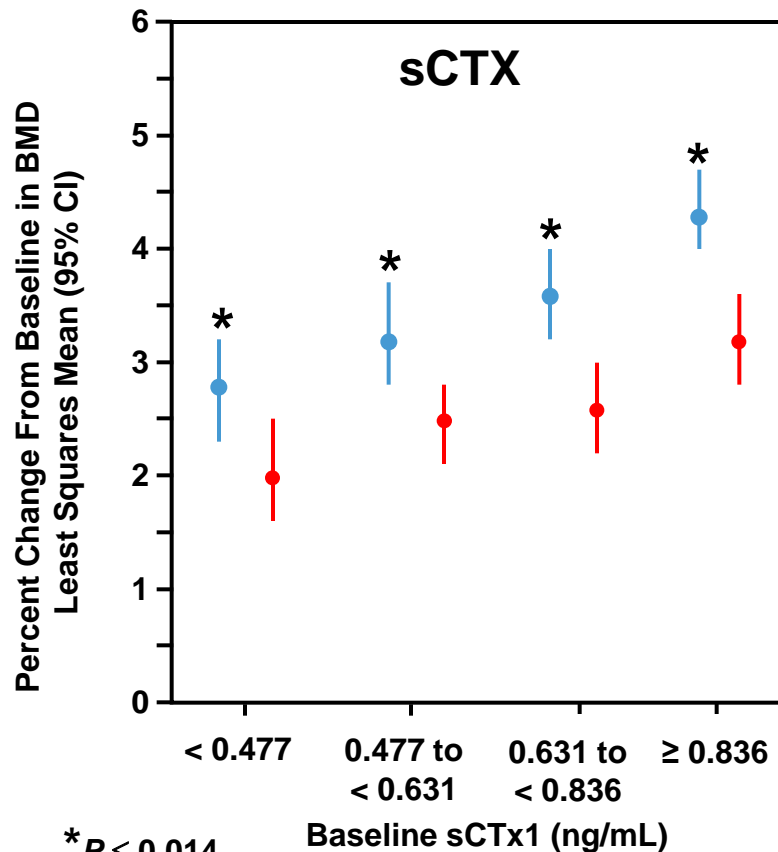
Brown et al (2008) JBMR 24:153-161

Changes in BTMs After Treatment Correlate With Fracture Risk Reduction
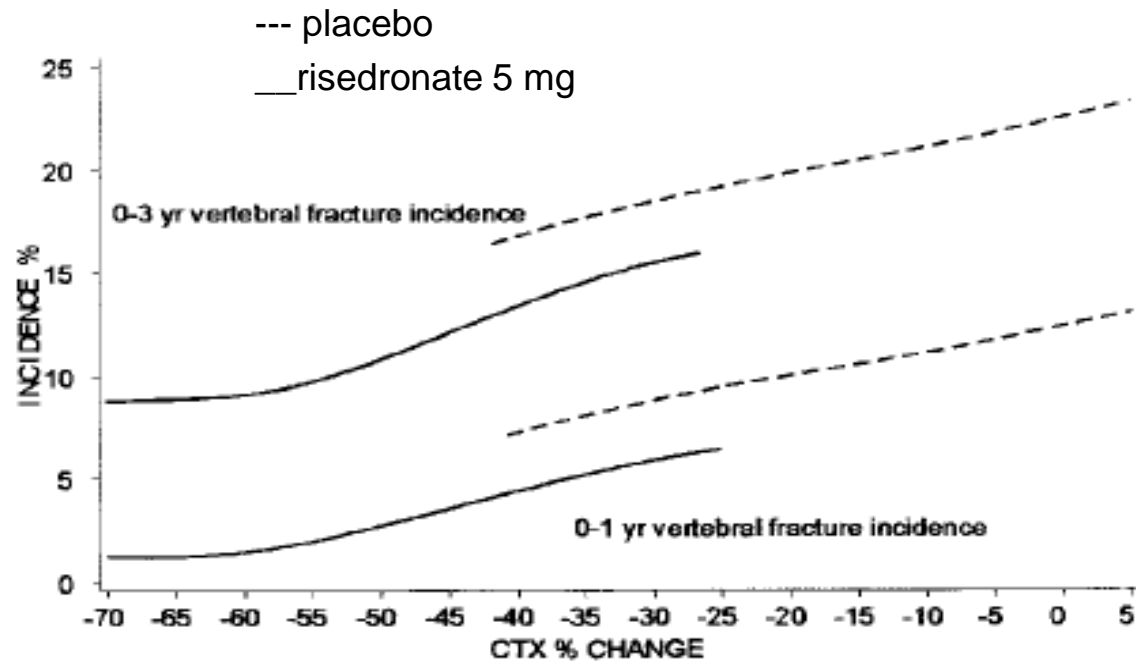
Eastell et al (2003) JBMR 18:1051-1056

Percent of Treatment Effect Explained by Bone Turnover Markers

- In the VERT study, the change in u-CTX and u-NTX at 3 to 6 months explained between 54 to 77% of the fracture risk reduction with risedronate, depending on the marker, the method of analysis and the fracture type (*Harris et al, 1999, Reginster et al, 2000, Watts et al, 2003)*

- In the MORE study, the change in PINP and OC explained 28% and 34%, respectively, of the vertebral fracture risk reduction with raloxifene *(Ettinger et al, 1999, Delmas et al, 2002)*

BTM vs BMD Monitoring

- The decrease in marker values, particularly the indices of bone resorption occurs within days or weeks of starting treatment with anti-resorptive agents.

- In contrast, the change in BMD occurs over months or years so that BTMs may give earlier information on the response to treatment than BMD.

- Moreover, the decrement in marker values is large in the case of bisphosphonates (e.g. by 50% or more), whereas the increment in BMD is modest (e.g. 5%).

Evidence for the Utility of Bone Turnover Markers In Monitoring Osteoporosis Treatment

- Changes in BTMs with treatment are associated with changes in BMD, both for anti-resorptive therapy and for anabolic therapy

- However, the changes in BMD with therapy are not closely related to the fracture risk reduction, particularly with anti-resorptive therapy

- For example, the change in spine BMD over three years explained
  - only 11% of the reduction in spine fracture risk with alendronate
  - 18% for risedronate and
  - close to zero for raloxifene

BMD vs BTMs for Monitoring

	BMD	BTMs
Expected change ("signal")	~6-8%	~20-300%
LSC ("noise")	~3%	~14-133%
Signal:Noise Ratio	~2	~2 or better
Time for significant change	1-3 years	~days to 3 months
Standardised methodology	+++	+
Clinical practice guidelines	+++	+

Adapted from Miller et al. (1999) J Clin Densitom. 2:323-342.

BTMs Vary With Age In Premenopausal Women
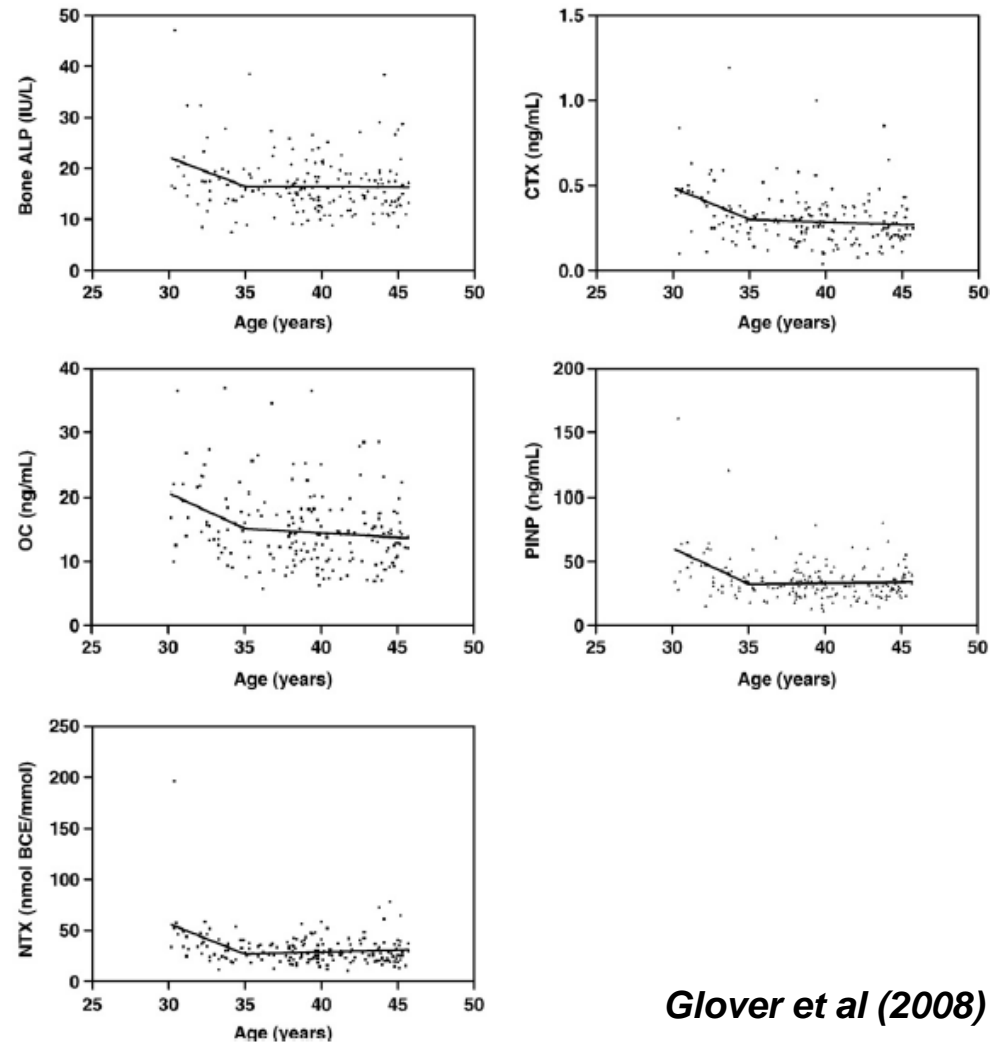
Glover et al (2008) Bone 42: 623-630

Reference Intervals For sCTX
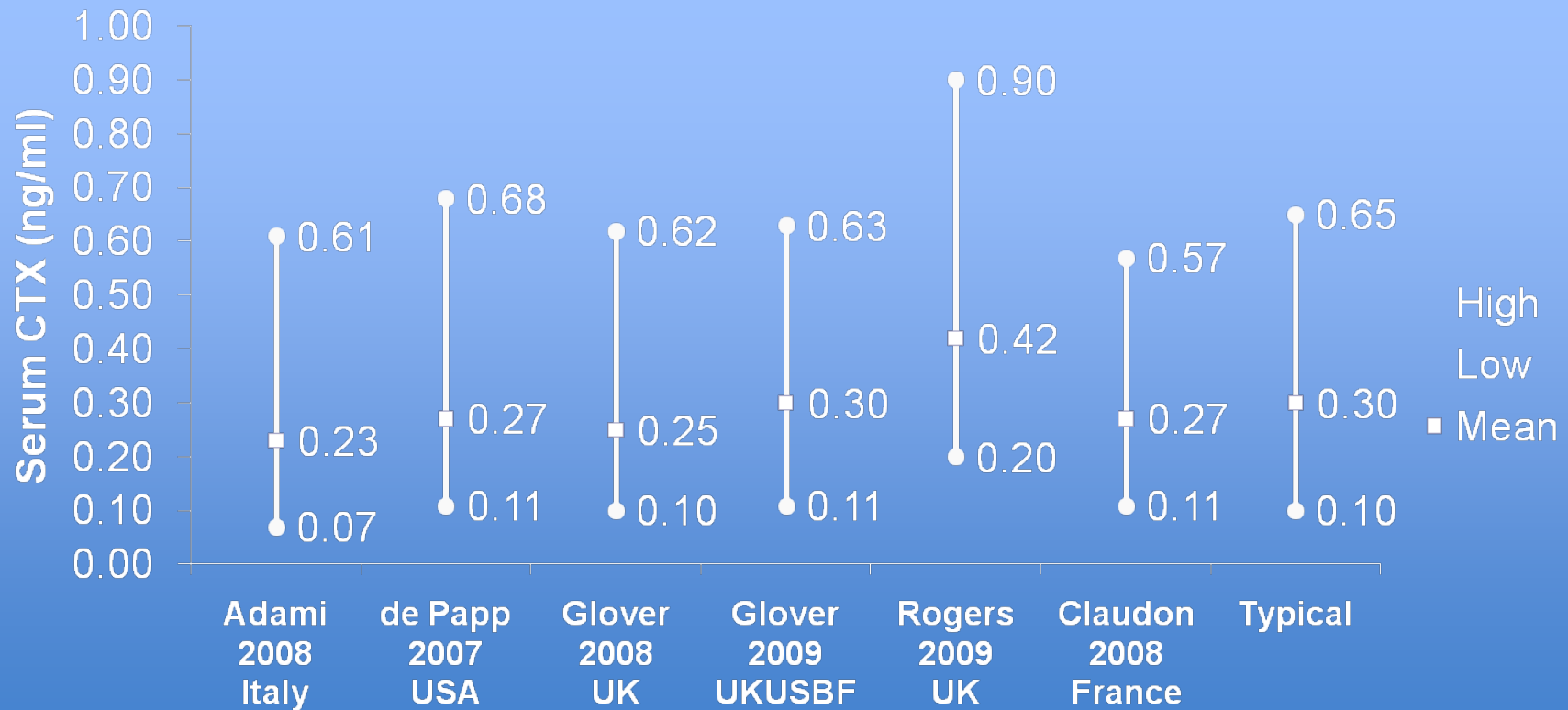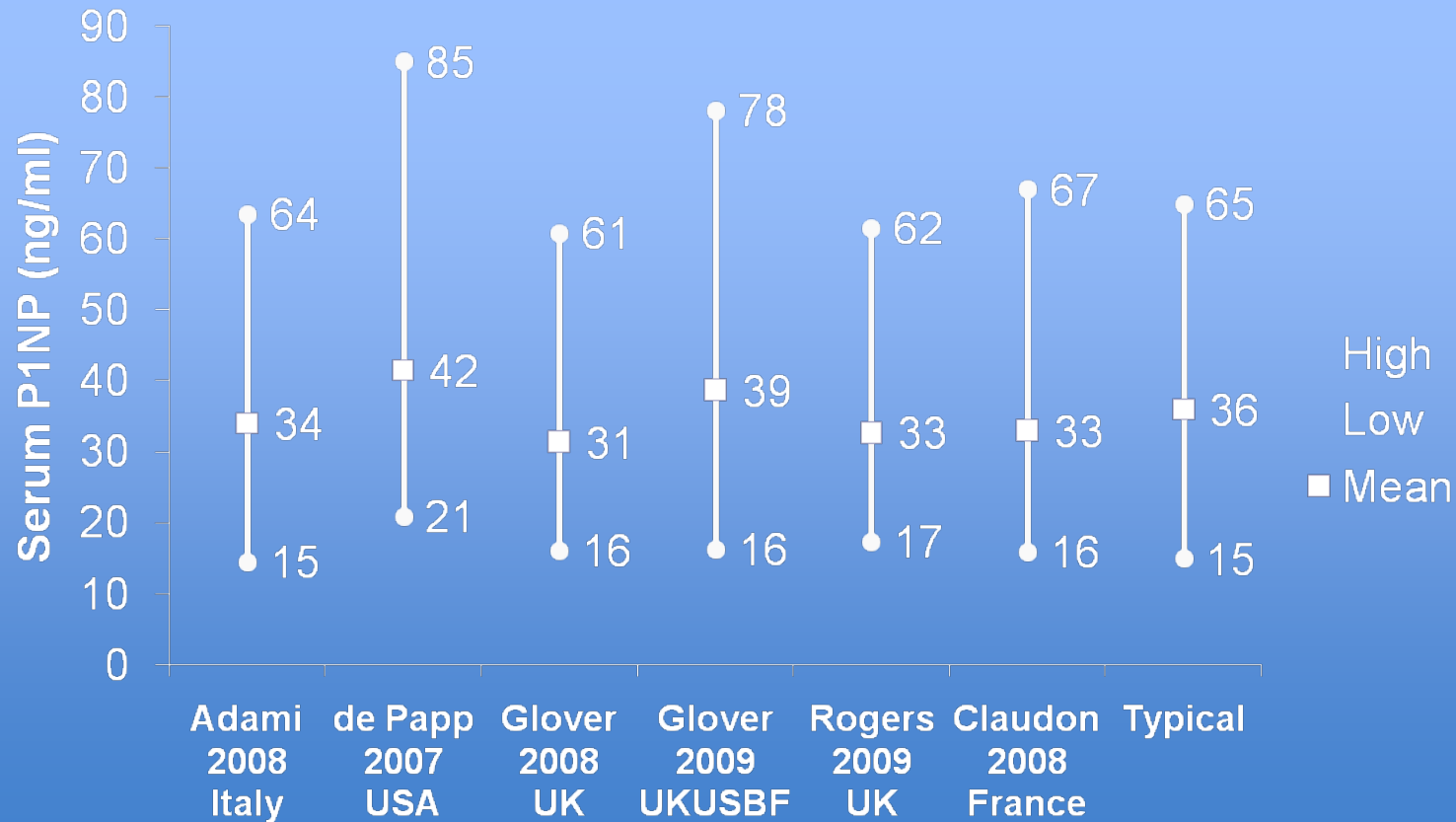

Adapted from slide provided by Eastell R.

Reference Intervals For sP1NP

Adapted from slide provided by Eastell R

« Drug Holidays »

- Concern: long-term suppression of remodelling could result in fragility

- From clinical studies, some biphosphonates (alendronate, zoledronic acid) have a prolonged effect after stopping and others (risedronate) a more rapid offset.

- Potential biophysical explanation: affinity of alendronate and zoledronic acid to hydroxyapatite is greater than risedronate and ibandronate *(Nancollas, Bone, 2006).*

- A pratical approach:
  - If after 5 years FN T-score <-2.5, then continue therapy
  - If FN T-score is >-2.5, take a drug holiday

Algorithm For Drug Holidays

TABLE 5. Suggested duration of bisphosphonate treatment and drug holidays

Patient's fracture risk	Suggested duration of treatment	Suggested duration of drug holiday[a]
Low	Treatment rarely indicated	NA
Mildly increased	Treat for approximately 5 yr	Stay off bisphosphonate until BMD decreases significantly or fracture occurs
Moderately increased	Treat for 5–10 yr	Stay off bisphosphonate for 2–3 yr (or less if BMD decreases or fracture occurs)
High	Treat for 10 yr	Stay off bisphosphonate for 1–2 yr (or less if BMD decreases or fracture occurs); alternate medication (*e.g.* raloxifene, teriparatide) may be given during the holiday from bisphosphonates

Duration is based largely on personal opinion.

[a] Longer holidays might be appropriate for patients treated with bisphosphonates that bind most strongly to bone (*i.e.* zoledronic acid, alendronate), whereas shorter holidays might be considered for patients treated with compounds that bind less strongly (*i.e.* risedronate, ibandronate).

Watts et al (2010) JCEM 95:1555-1565

International Osteoporosis Foundation

BTMs Could Identify Secondary Osteoporosis

- No systematic study of this study available
- It is possible that BTMs could be used for this purpose
  - ↑BTMs
    - Osteomalacia
    - Paget's disease
    - Various endocrine disorders
      - Primary hyperparathyroidism
    - Malignant bone diseases
      - Multiple myeloma
  - ↓BTMs
    - Glucocorticoid-induced osteoporosis

BTMs Could Predict the Response to Therapy

- ↑bone resorption in untreated patient →good response to anti-resorptive therapy

- ↓bone formation →favourable response to anabolic therapy

- Do baseline BMTs predict better the reduction in fracture risk?
  - Variable results in the FIT trial
  - Baseline BTMs predict BMD

BTMs Could Improve Adherence to Treatment

- Studies have examined the effect of monitoring treatment on adherence

- Randomised open study of women treated with biphosphonates

  - Providing BTM results is not a way to enhance compliance and persistence with alendronate therapy *(Silverman, Osteoporosis International, 2012)*

  - IMPACT study was a controlled trial of risedronate

    - No difference in persistence was seen between the 2 groups at one year

IOF-IFCC Recommendations

- An increase in BTM concentration predicts fracture risk independently of BMD and prior fracture

- More data needed before routine clinical use can be recommended
  - Which marker?
  - What threshold?
  - How to combine with other risk assessment approaches e.g., FRAX?

- BTMs widely adopted in monitoring treatment. Application limited by:
  - Inadequate appreciation of sources of variability
  - Limited data on comparison of treatments using the same BTM
  - Inadequate quality control.

IOF-IFCC Recommendations

A need for international reference standards

- Reference standard marker for bone resorption
  serum CTX

- Reference standard marker for bone formation
  serum P1NP

"Assays based on these standards should be used consistently in future clinical trials and observational studies in order to generate data which will eventually guide clinicians to the appropriate use of BTMs in routine clinical practice."

sCTX: Reference Standard for Bone Resorption

- well characterised

- most CTX is derived from osteoclastic bone resorption

- has been evaluated both for fracture prediction and monitoring osteoporosis therapies

- assays widely available

- biological and analytical variabilities have been well documented as are requirements of sample handling and stability

- measurable in serum / plasma

sP1NP: Reference Standard For Bone Formation

- less well characterised than CTX
- most PINP is produced during bone formation; reflects synthesis of bone collagen
- found as trimeric (intact) molecule and as monomer
- has been evaluated both for fracture prediction and monitoring osteoporosis therapies
- assays widely available
- biological and analytical variabilities have been well documented as are requirements of sample handling and stability
- measurable in serum or plasma

THANK YOU