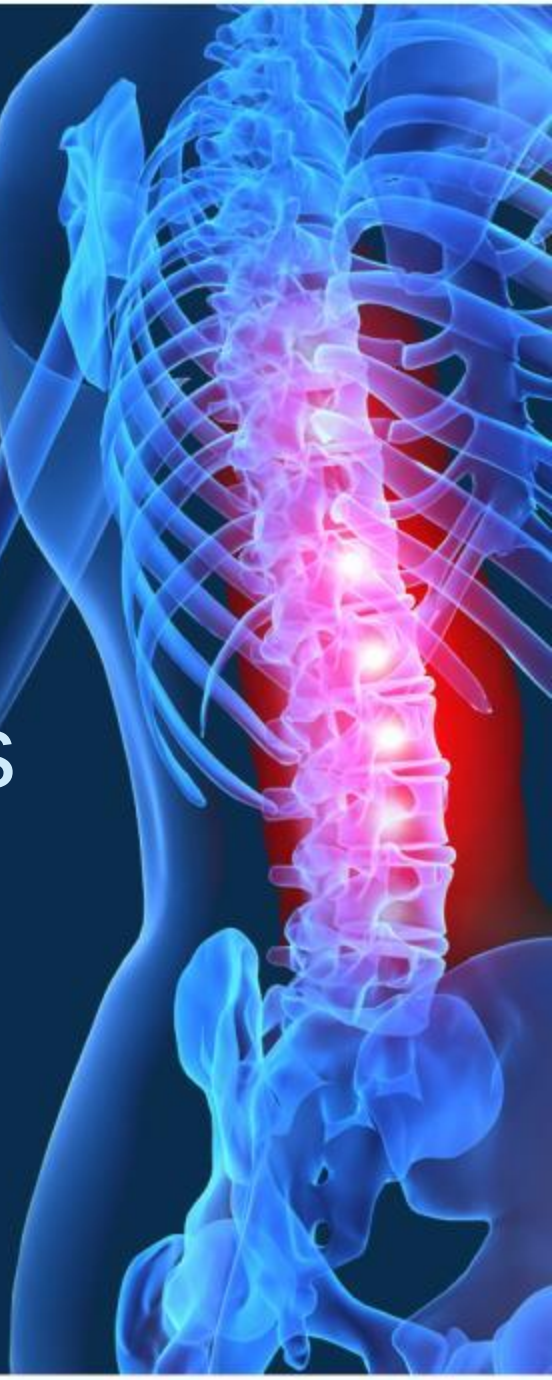
Annual Rheumatology & Therapeutics Review for Organizations & Societies

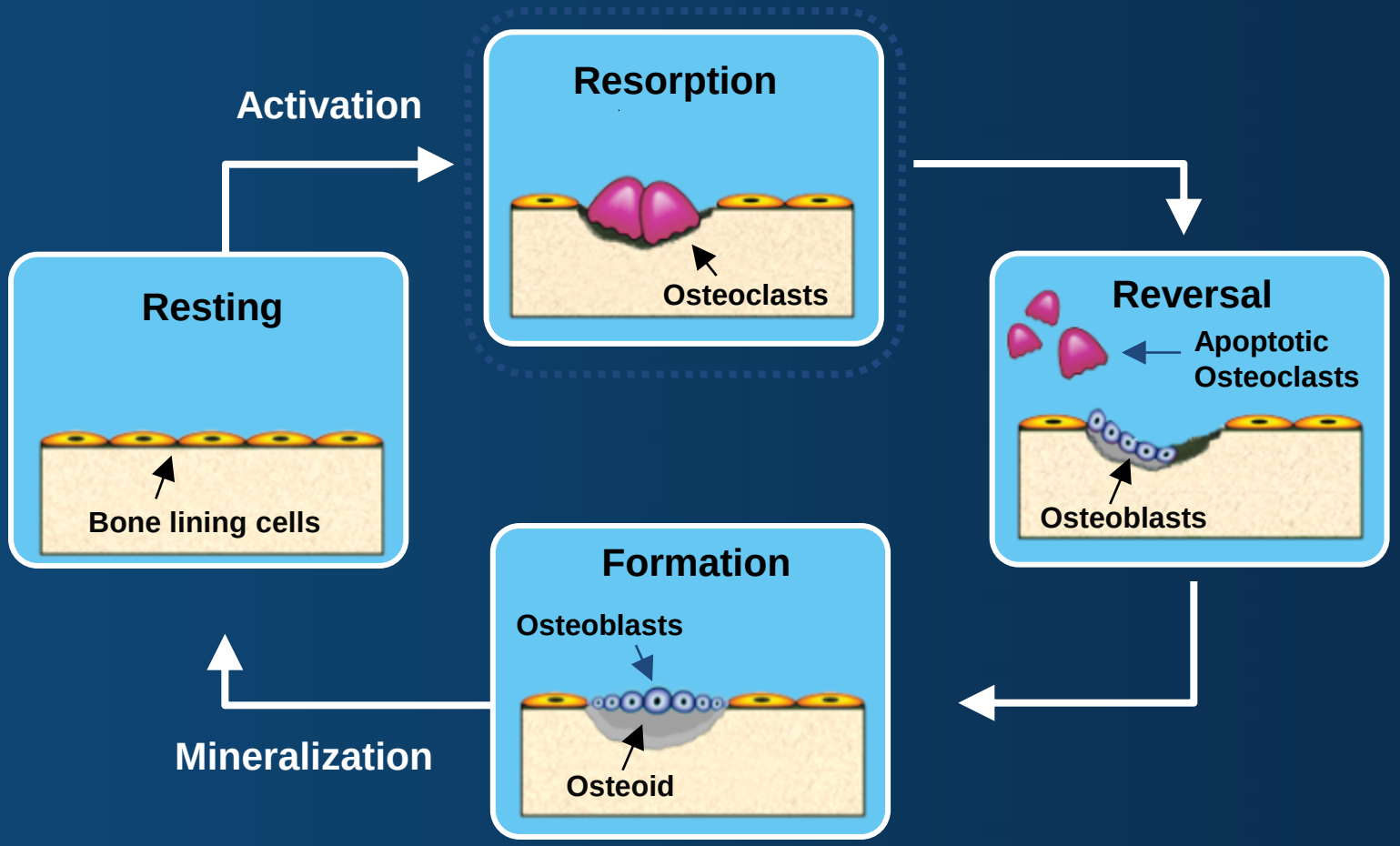


Biochemical Markers of Bone Turnover: Definitions and Recommendations for Monitoring Therapy

Learning Objectives for Biochemical Markers of Bone Turnover

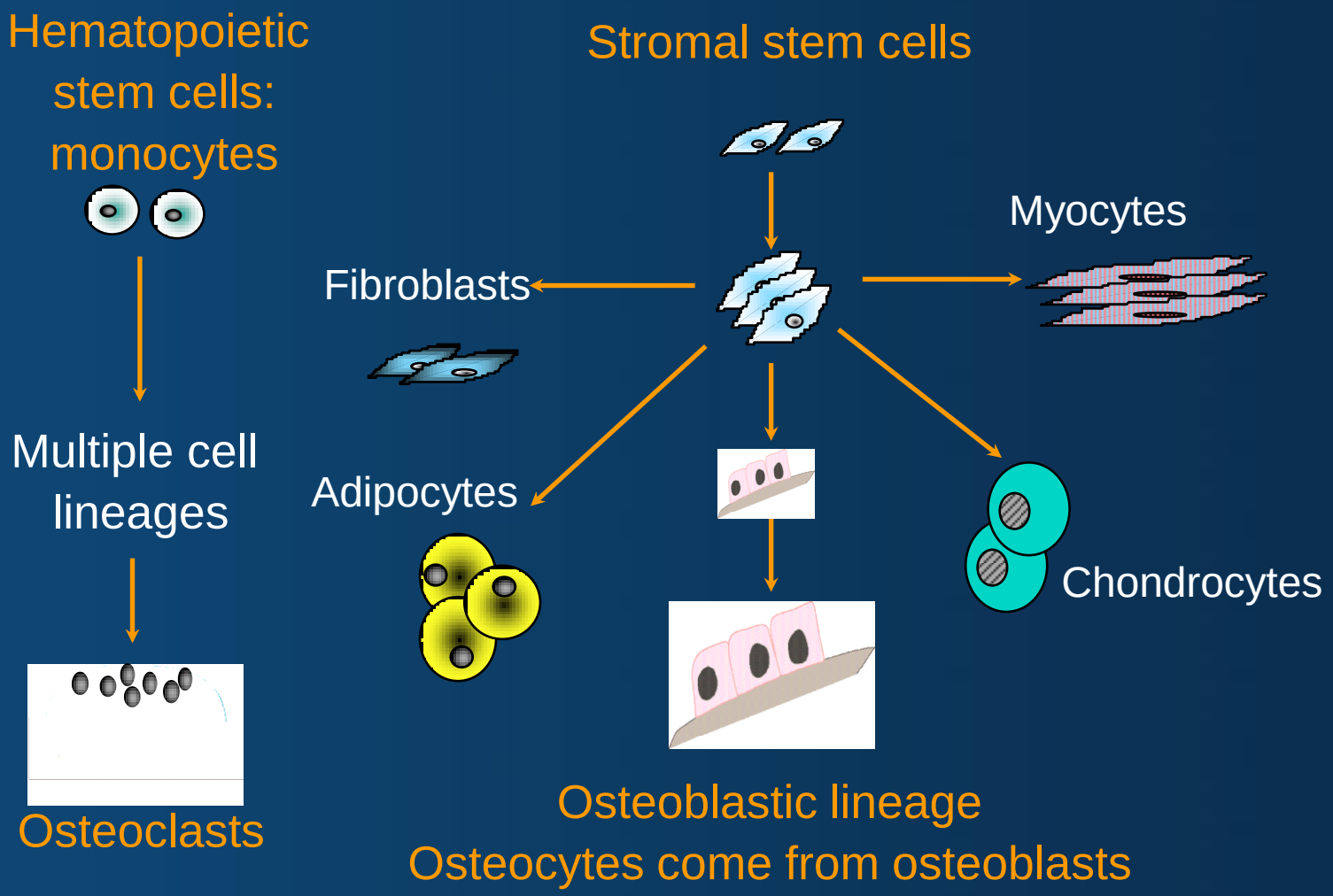
- To understand the pathophysiology of the bone remodeling process
- To understand the clinical diseases that generate different bone turnover markers
- To understand how therapy for osteoporosis can alter biochemical markers of bone turnover
- To understand how to incorporate bone turnover markers into clinical practice of osteoporosis.

The Lifecycle of Bone

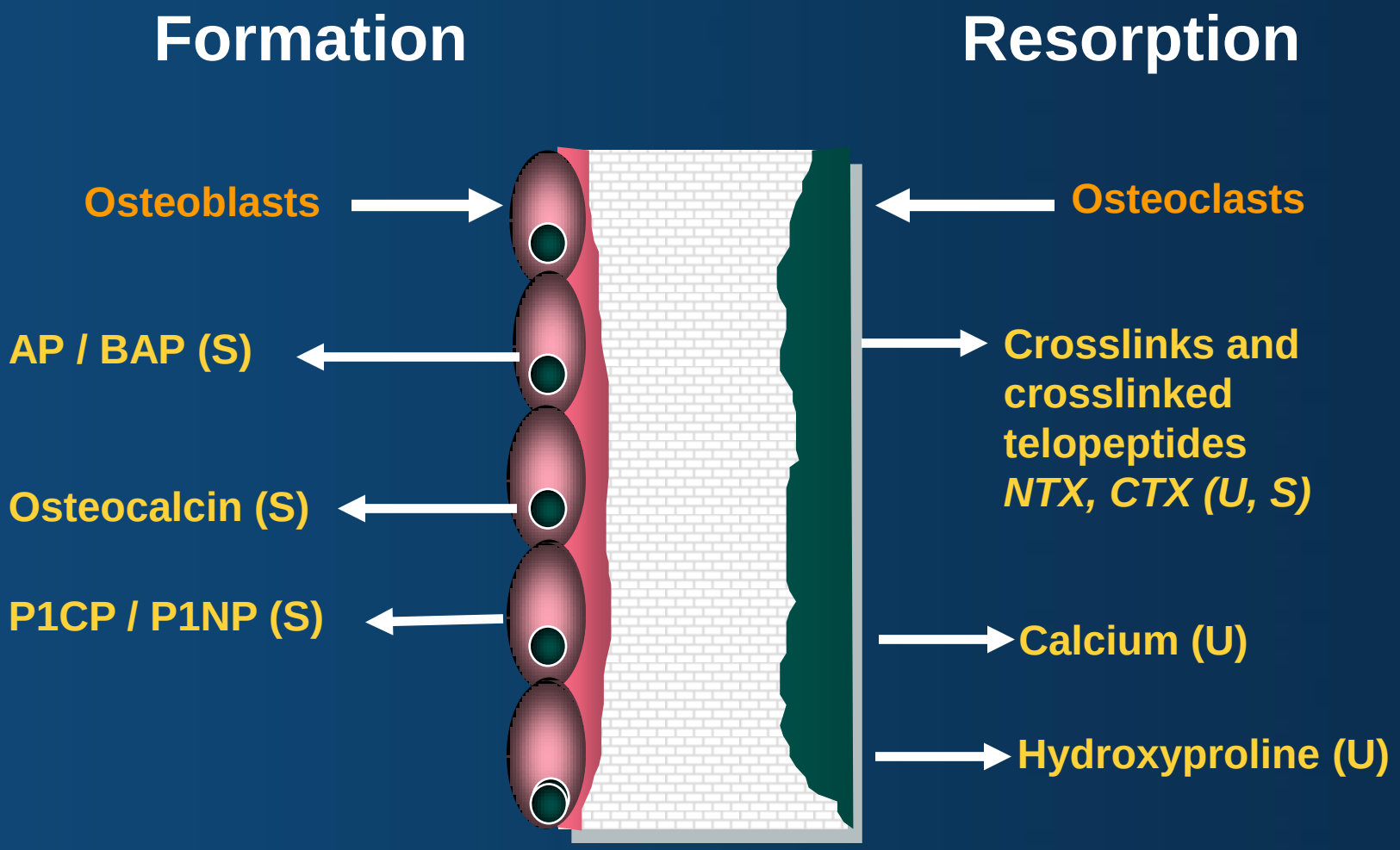


Adapted from: Baron R. *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*. 5th ed. 2003:1-8; Bringhurst FR, et al.

Bone Cell Lineages

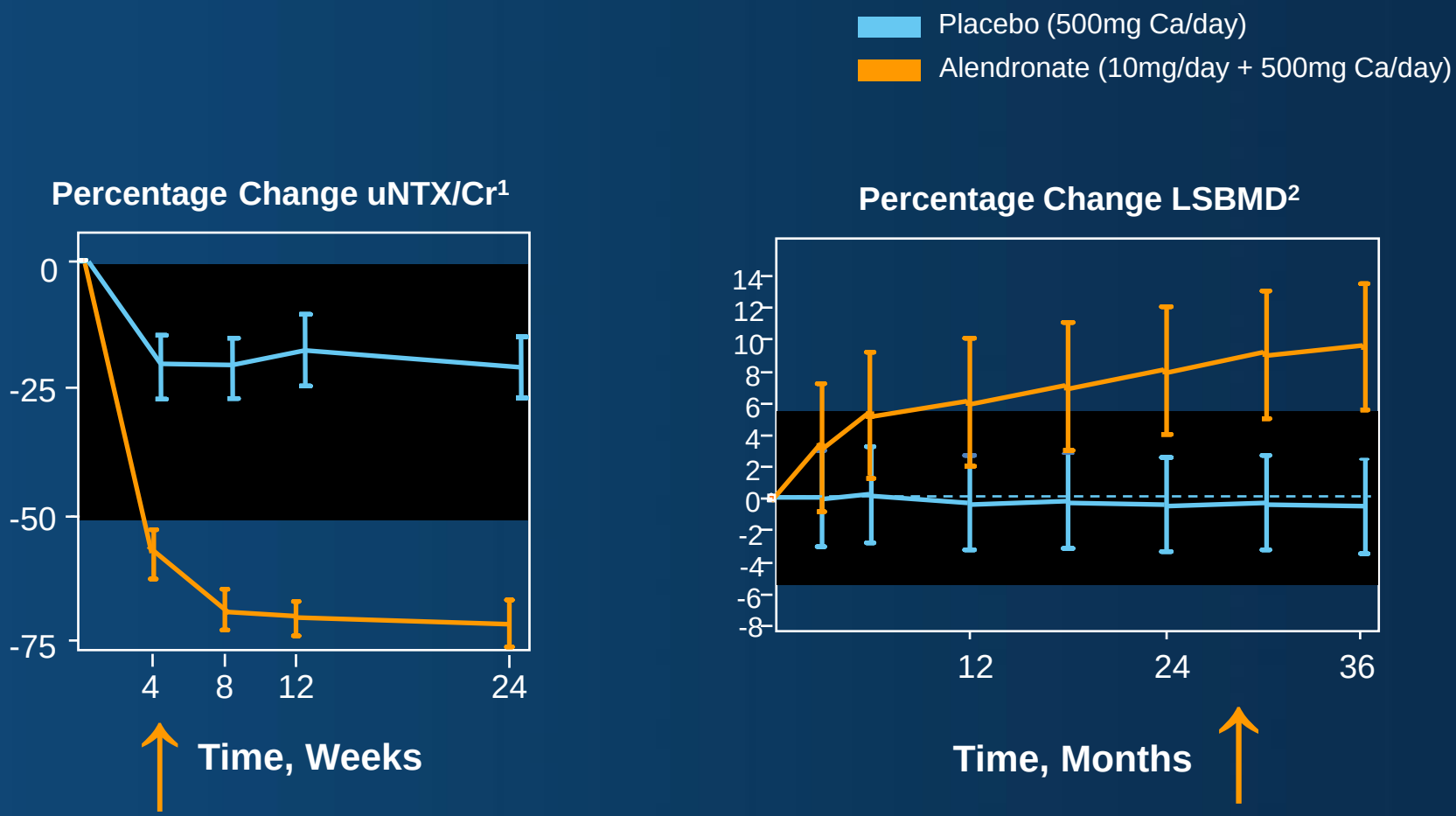


Biochemical Markers of Bone Metabolism (Monitors of Bone Loss)



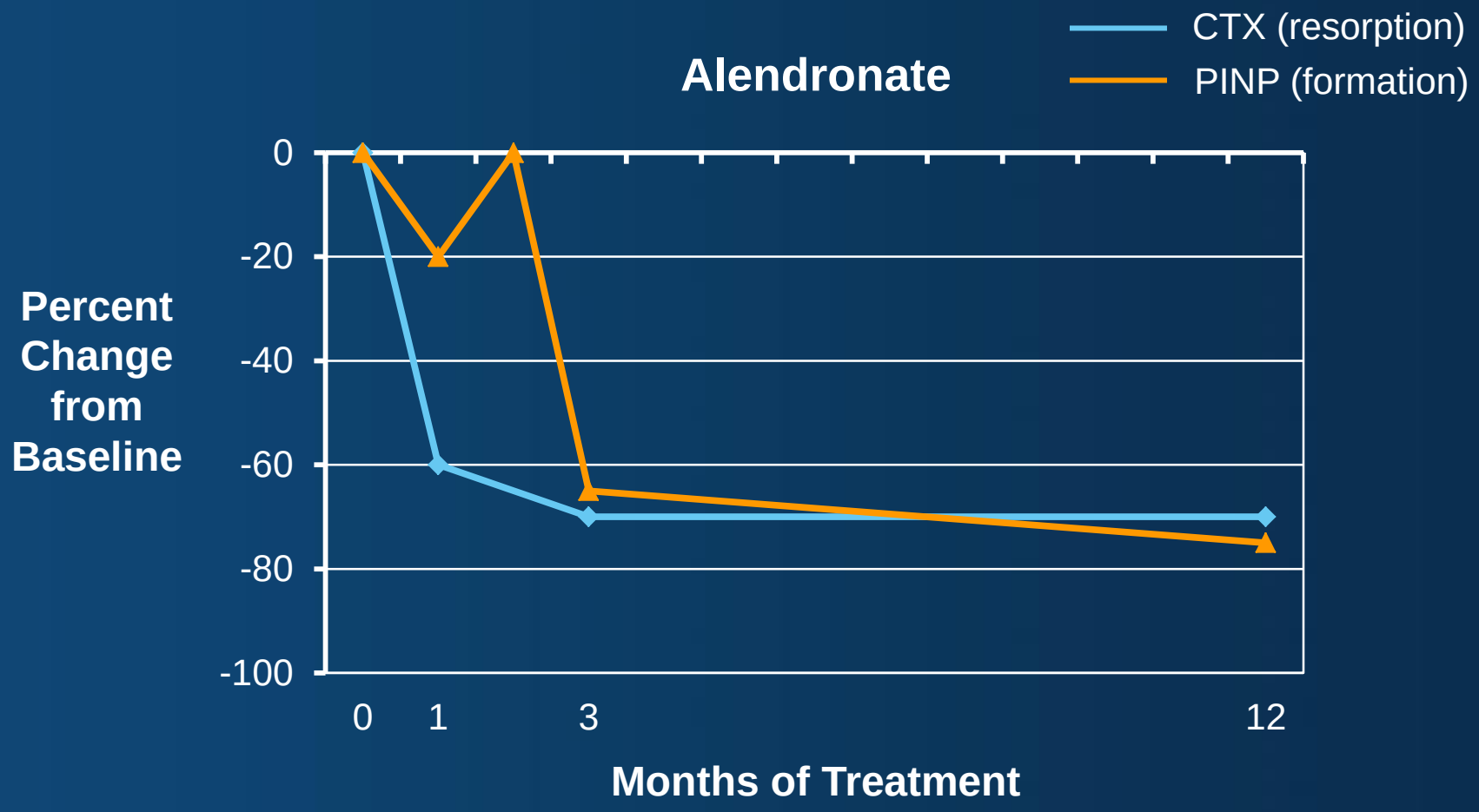
Rapid Change

BTMs Can Respond More Rapidly Than BMD



Braga de Castro Machado et al JBMR 1999;14:602-8
Liberman et al NEJM 1995:333;1437-43

Resorption Markers Change More Rapidly Than Formation Markers



Black DM et al, *N Engl J Med* 2003;349:1207-1215

Predictor of Increased Fracture Risk

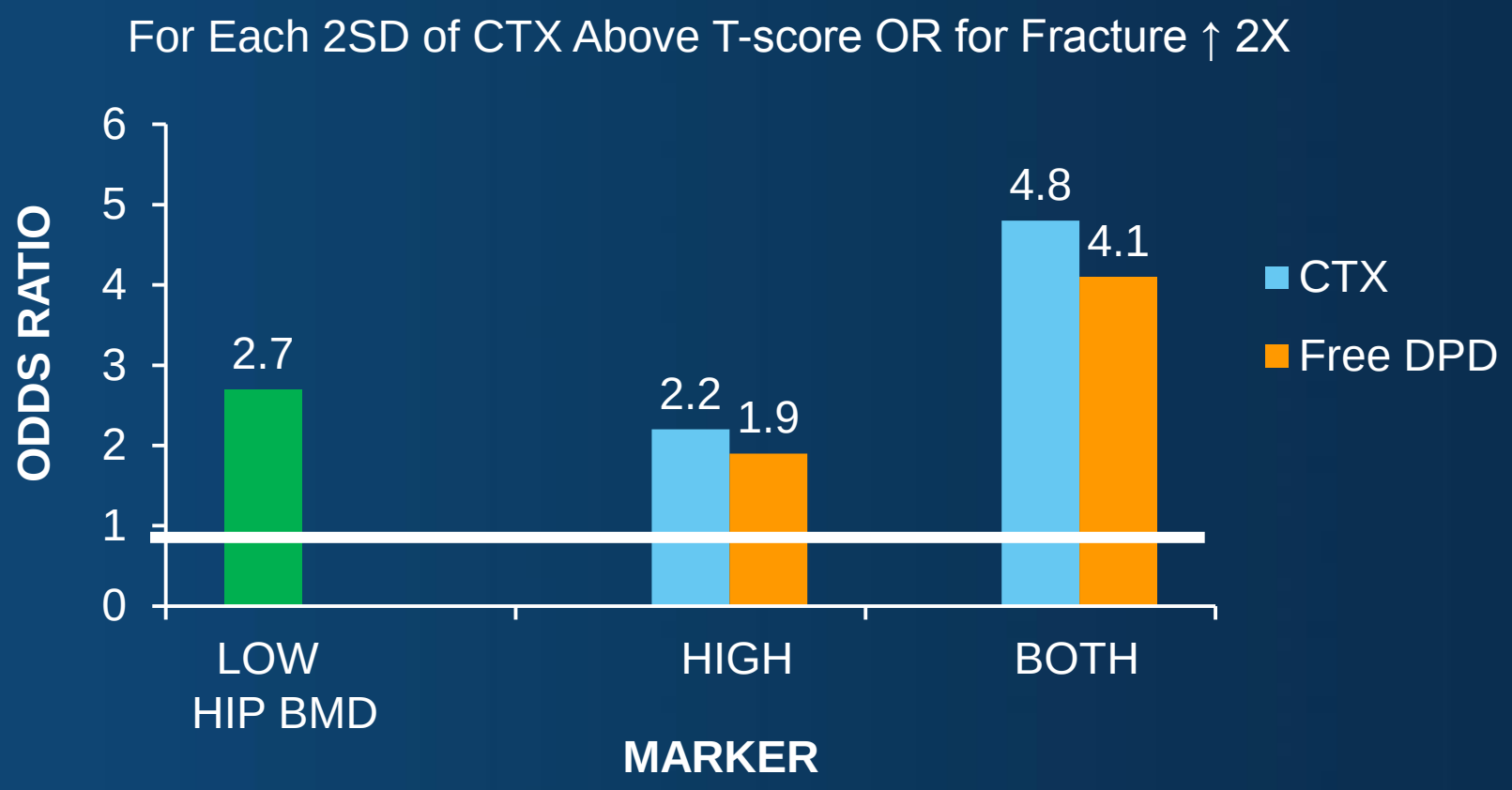
In Untreated Subjects

Population Studies: Elevated Biomarkers Increase Fracture Risk in Untreated Patients

A Risk Factor Not Captured in FRAX*

* Fracture Risk Assessment Tool

BMD and Markers Predict Hip Fracture the Epidos Study



Garnero P, et al. JBMR 1996;11:1531

Bone Turnover Markers Predict a Higher Risk for Fractures 9 years Later in Elderly (75 yrs +) Untreated Women

Baseline sCTX
Highest tertile
≥ 2, 810 pg/mL

9 years later

Had HRs (1.32) of all clinical fractures by tertiles not adjusted for age (mean = 75 yrs.) increase adjusted for baseline BMD

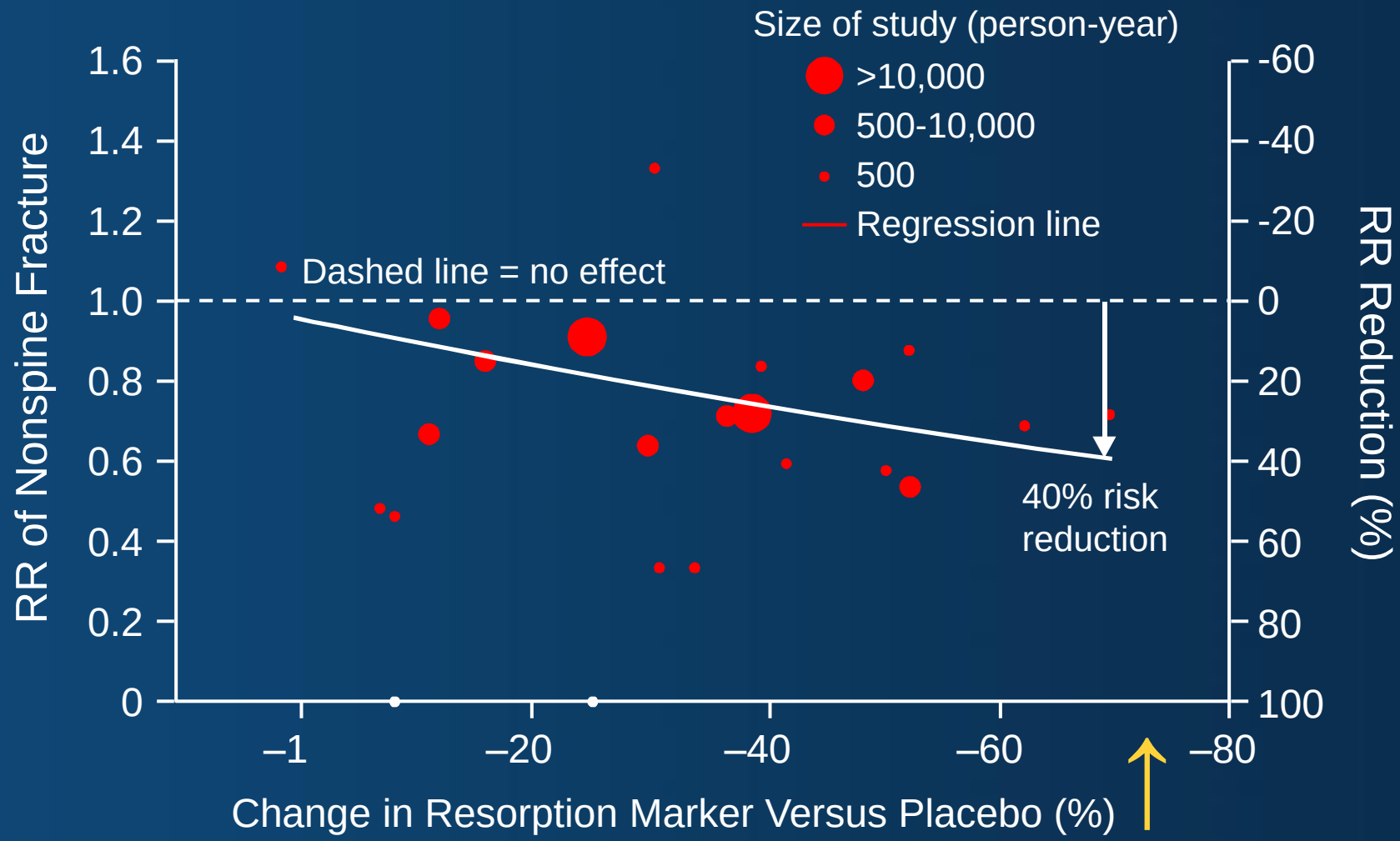
Population sample size : 1,040
Fracture number : 363 fractures including 116 hip fractures

Ivaskaa KK et al JBMR 2010 Malmo, Sweden

Predictor of Increased Fracture Risk

In Treated Patients (Groups)

OP Therapies: Greater Decrease in Bone Resorption Predicts Greater Reduction in Non-spine Fracture Risk

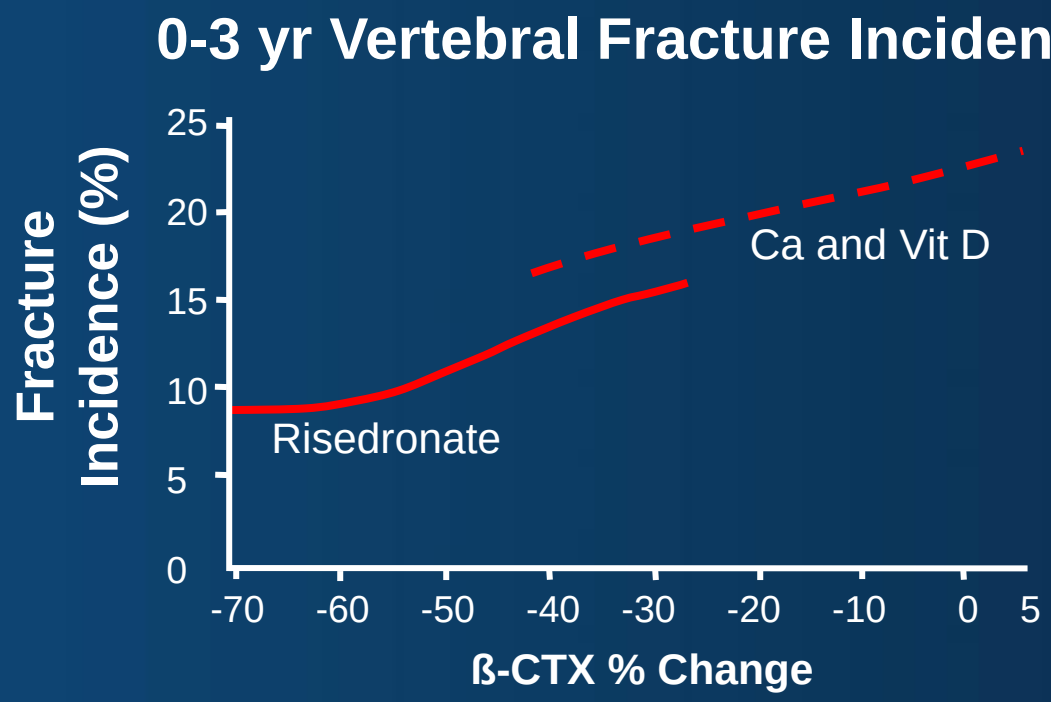


RR= Relative risk

Hochberg MC et al. J Clin Endocrinol Metab. 2002;87:1586–1592

Bone Marker Reduction Correlates to Fracture Risk Reduction

- CTX reduction after 3-6 months correlates to fracture risk reduction.
- When 60% reduction is achieved, there is no greater reduction in fracture risk.



Source: *Eastell et al* (2003), J Bone Miner Res.18

The Association of Marker Changes (ALP and P1NP) after 1 Year and Fracture Risk Reduction with Alendronate Treatment for 3 years.

Cutpoint (% of women)	Spine fracture (N=118) OR (95% CI)*	Non-spine fracture (N=225) RH (95% CI)*
>15% reduction bone ALP	0.63 (0.42,0.95)	0.79 (0.58,1.08)
>30% reduction bone ALP	0.90 (0.62,1.33)	0.72 (0.55,0.92)
>50% reduction bone ALP	0.52 (0.29,0.94)	0.84 (0.60,1.19)
>30% reduction in P1NP	0.45 (0.30,0.70)	1.02 (0.70,1.49)
>50% reduction in P1NP	0.66 (0.49,0.99)	0.86 (0.65,1.15)
>70% reduction in P1NP	0.79 (0.50,1.25)	0.63 (0.46,0.88)

*OR or RH for fracture among alendronate-treated women with specified 1-year reduction in marker compared with women without specified reduction in marker

Bauer DC et al. J Bone Miner Res. 2004;19:1250-1259.

Short-term Changes in Bone Turnover Markers and Bone Mineral Density Response to PTH in PMOP

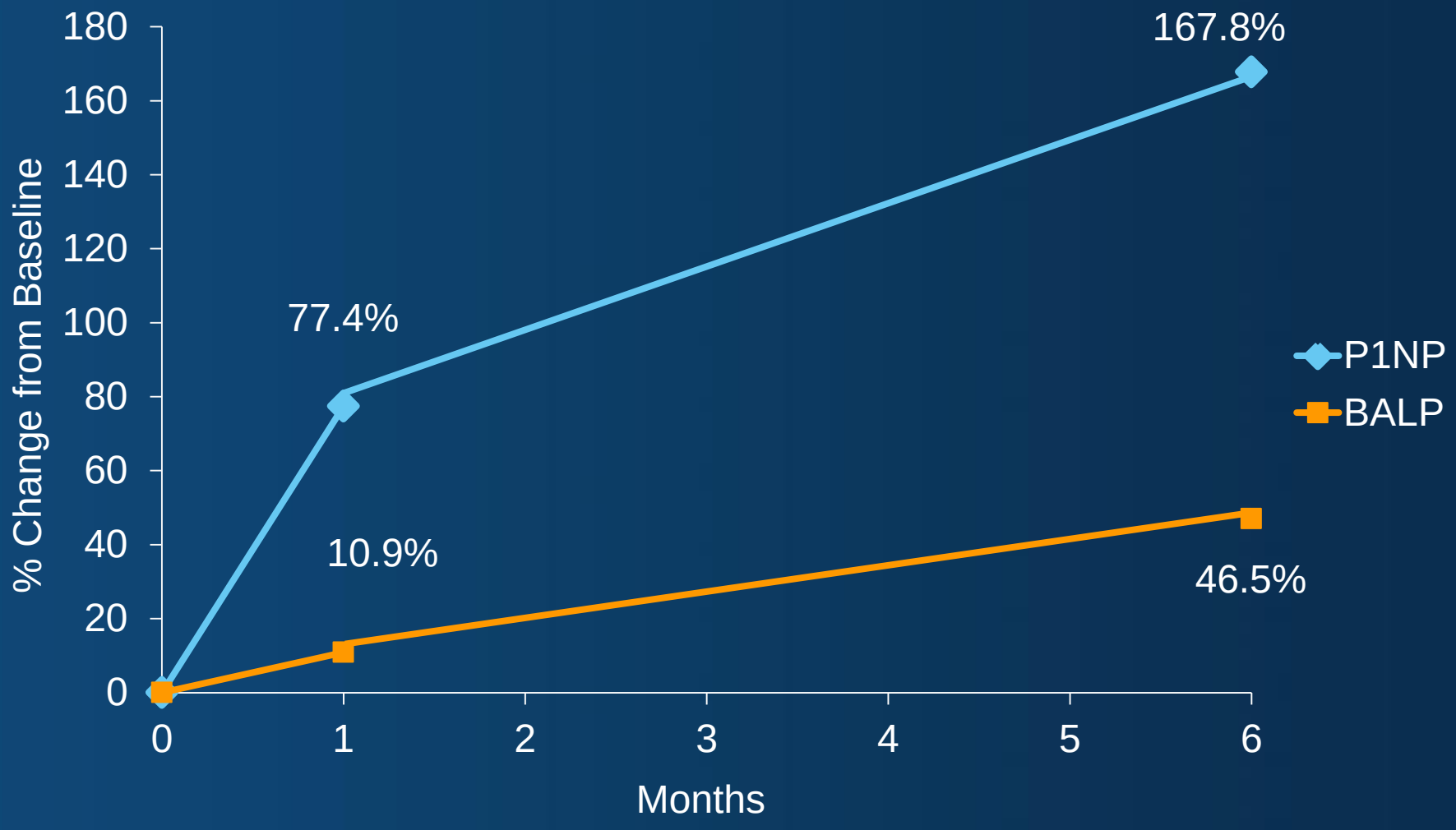
Baseline and Follow-up BTM Among 119 Subjects

Variable	0 mth	1 mth	3 mth	1 yr
P1NP (bg/mL)	58.0 ± 35	111.9±77	171.6±147.5	180.5±143
Bone ALP	18.1 ±8	23.2±13.3	29.0±21.1	32.2± 19.6 (ng/mL)
sCTX	392 ±203	400 ± 252	722 ± 550	882 ± 559 (pg/mL)

Bauer DC et al. J Bone Miner Res. 2004;19:1250-1259.

Anabolic Data

Changes in P1NP and BALP with Teriparatide



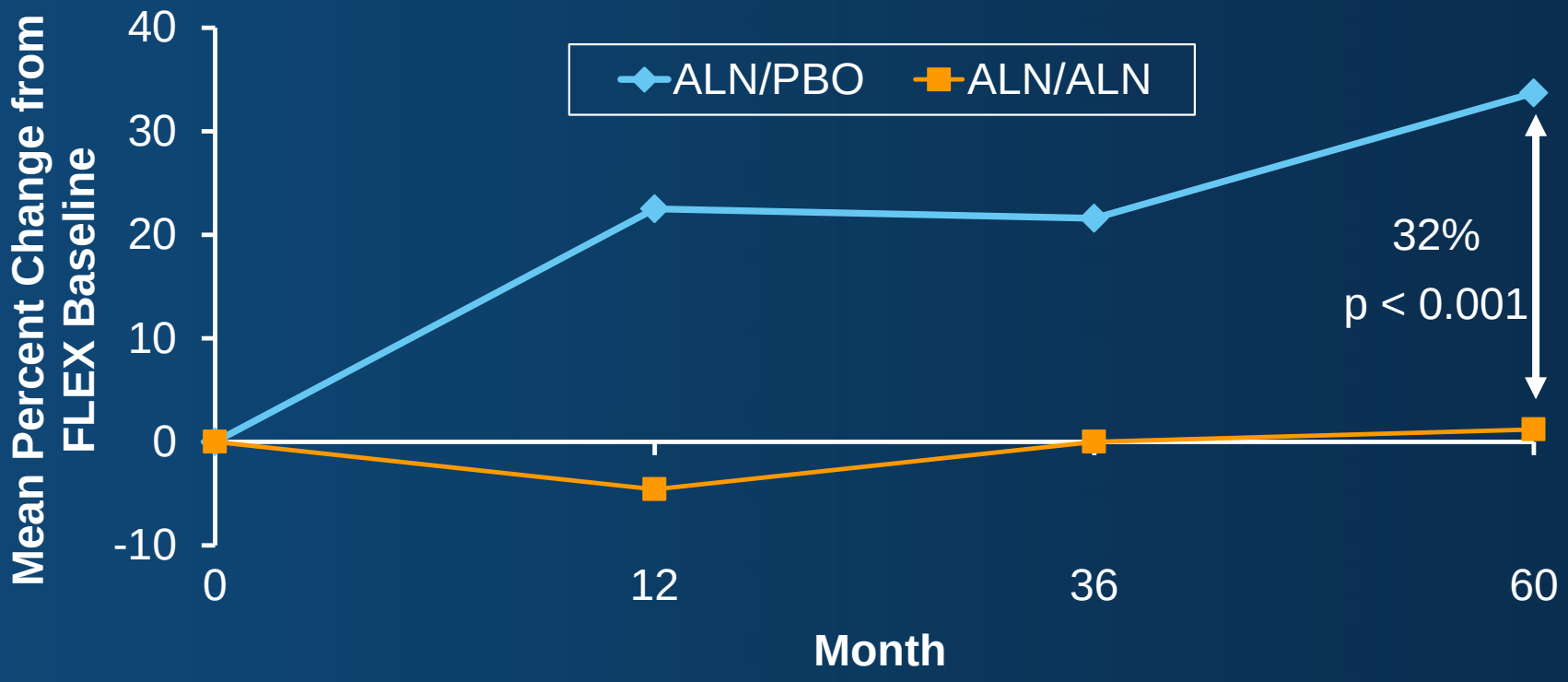
Blumsohn A, et al. Osteoporos Int 2011;22:1935-1946.

Bone Turnover Markers

- Bone turnover markers…
  - Predict bone loss and fracture risk in untreated patients
- With treatment…
  - Change sooner than BMD
  - Identify more “responders” than BMD
  - Explain a greater proportion of fracture reduction than change in BMD
- Can be useful in monitoring the response to treatment

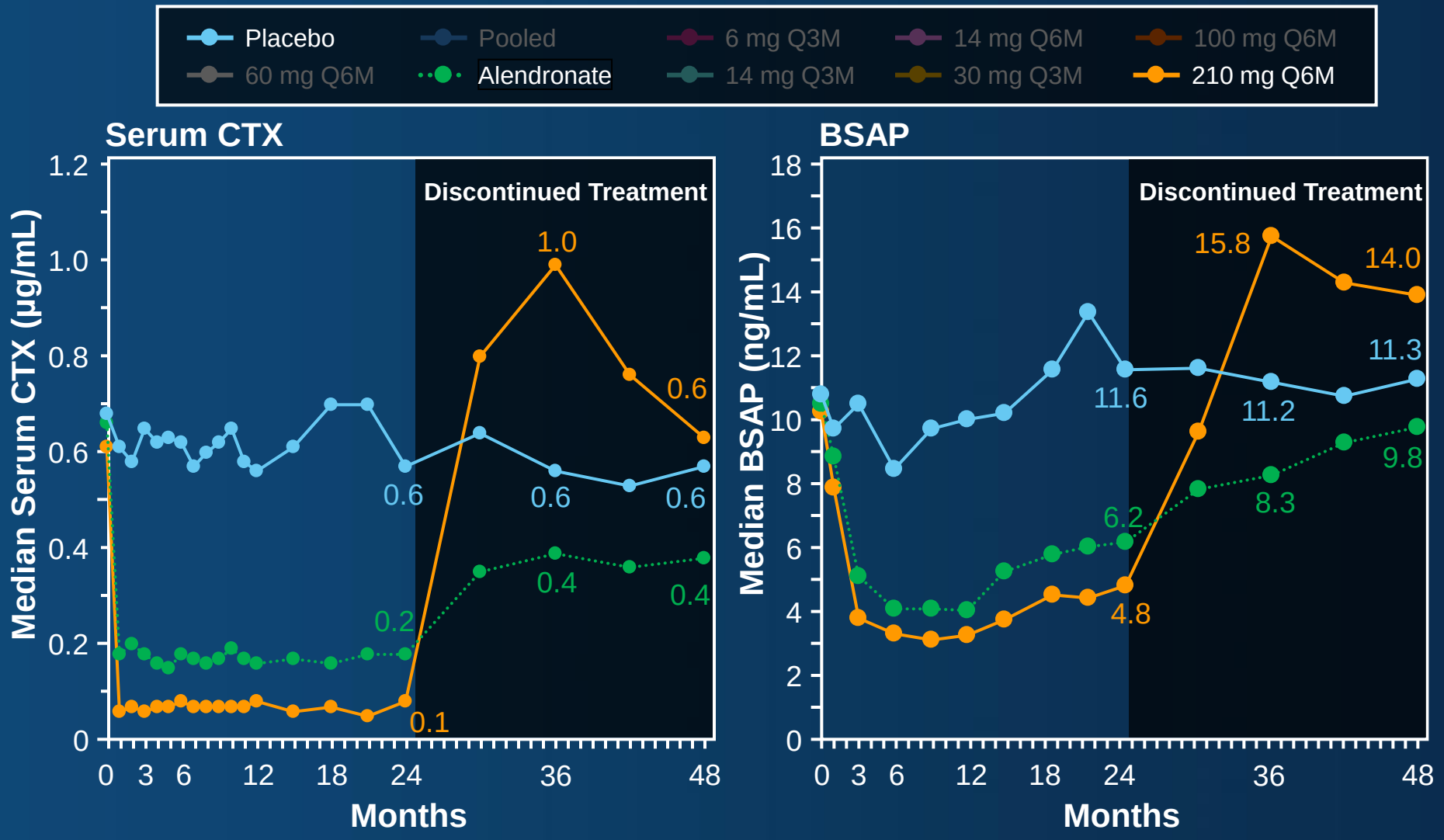
Drug Holidays

Change in Urinary ntx: Creatinine Ratio From Flex Baseline to Flex Month 60 in Women Receiving Alendronate or Placebo



Black DM et al, *J Bone Miner Res* 2004; 19 (suppl 1): 1174
Ensrud K et al, *J Bone Miner Res* 2004;19:1259-1269

Effect of Denosumab on Serum CTX and BSAP – Discontinued Treatment



FDA NEJM Perspective

- Recommend treatment with bisphosphonates for 3-5 years and consider discontinuation in “lower risk” patients but consider continuation in “higher risk” patients (prior fracture, older, BMD criteria for osteoporosis).
- Weak and inconclusive recommendations on what to do when discontinuation is begun.

Whitaker M et al; *Bisphosphontes for OP*; NEJM 2012; 366:2048-2051

Bisphosphonate (BP) Drug Holidays: A Perspective from a Clinician

1. Most patients don't stay on therapy very long.
2. In USA, patients stop on their own; Docs are afraid to treat.
3. The legal threat is there if a patient fractures on or off a bisphosphonate.
4. The "skeletal load" of BP may differ greatly from patient to patient on the same BP or among different BPs.
5. If BPs are stopped, serial BMD and BTM are the only clinical tools we have to "monitor."

Khosla S et al JCEM 2012
Boonen S et al JBMR 2012

How I Use Markers

1. In untreated patients with high baseline values-think beyond PMO “rapid losers.”
2. In untreated patients high values may “tip the scale” in those with borderline risk.
3. In treated patients-values above clinical trial treatment group suggests poor compliance, poor absorption or poor bone biological effect
4. In treated patients a change (decline with anti-resorptive or increase with anabolic) from baseline is encouraging (me and the patient)
5. Holiday or retirement?