

Bone Turnover Markers For Monitoring Treatment of Osteoporosis



The
Mellanby
Centre
for Bone Research

Richard Eastell

Director,

The Mellanby Centre for Bone Research,
Department of Oncology and Metabolism
Faculty of Medicine, Dentistry and Health,
University of Sheffield, UK

Conflicts of Interest

- Consultant and research grants
 - Immunodiagnostic Systems
 - Roche Diagnostics
 - Nittobo
 - Amgen

Outline

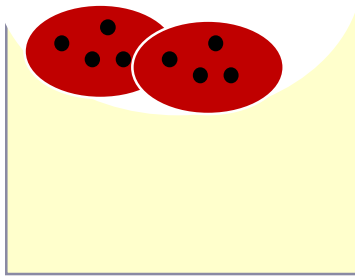
- Introduction to bone turnover markers
- Use for monitoring treatment
 - Bisphosphonates
- Use in the individual for identifying response
- Use in monitoring the offset of therapy
 - Oral bisphosphonates

Case Report

- 70 year old woman
- Osteopenia noted on spinal radiographs
- Treated with alendronate 70 mg once a week, calcium and vitamin D
- BMD T-score at the total hip and lumbar spine -3
- Bone turnover markers
 - Baseline CTX 500 ng/L, 6 months 120 ng/L
 - Baseline PINP 60 ug/L, 6 months 20 ug/L
- At review after 6 months, is she responding or not?

Bone Turnover Markers (BTM)

Resorption



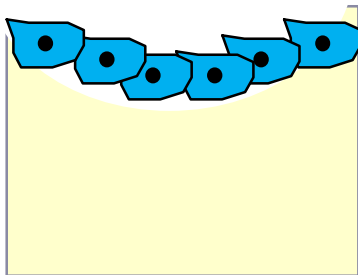
Collagen degradation products

- 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)

Sources of Variability in BTM (NBHA)

Controllable

- Circadian variation
- Food intake
- Menstrual
- Seasonal
- Exercise
- Lifestyle

Uncontrollable

- Age
- Gender
- Menopausal status
- Pregnancy and lactation
- Renal failure
- Geography
- Ethnicity
- Diseases and drugs
- Fracture

Clinical Uses of BTM

Risk assessment

- Prediction of bone loss
- Prediction of fracture
- Identification of secondary osteoporosis

Treatment

- Selection of treatment
- Monitoring of response
 - Identification of poor adherence
- Monitoring of offset of effect

Use for monitoring treatment

Anti-resorptive

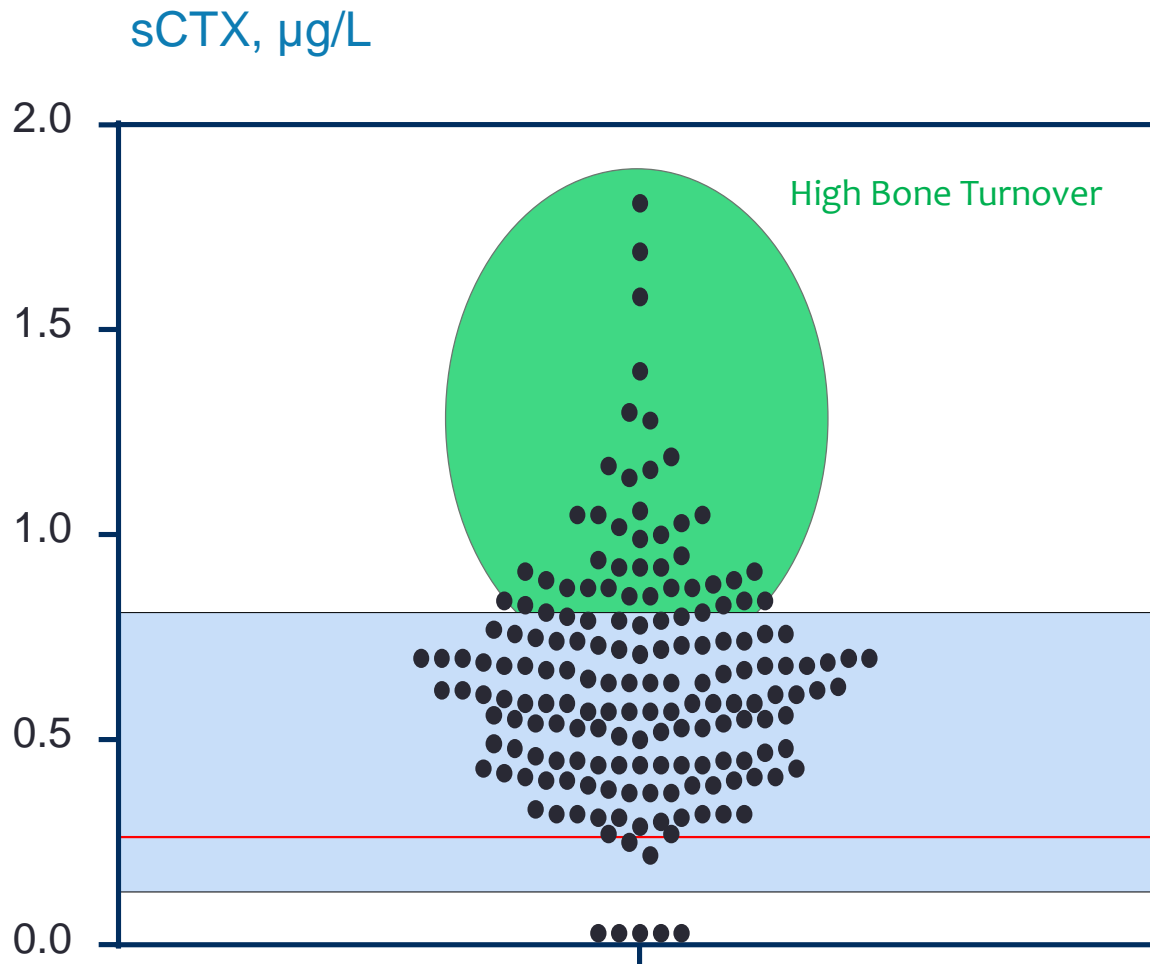
The TRIO Study



- 2-year, open-label, parallel randomised control trial of oral ibandronate, alendronate and risedronate, at their licensed dose
- Aim:- to examine and compare their effects on bone turnover and BMD
- 172 postmenopausal women (53–84 years) with osteoporosis
 - Measurements on treatment (12 and 13 weeks) allow study of variability of 5 BTMs on treatment, least significant change
- Premenopausal women (33–40 years, n=226) were concurrent controls
 - Allows calculation of reference intervals

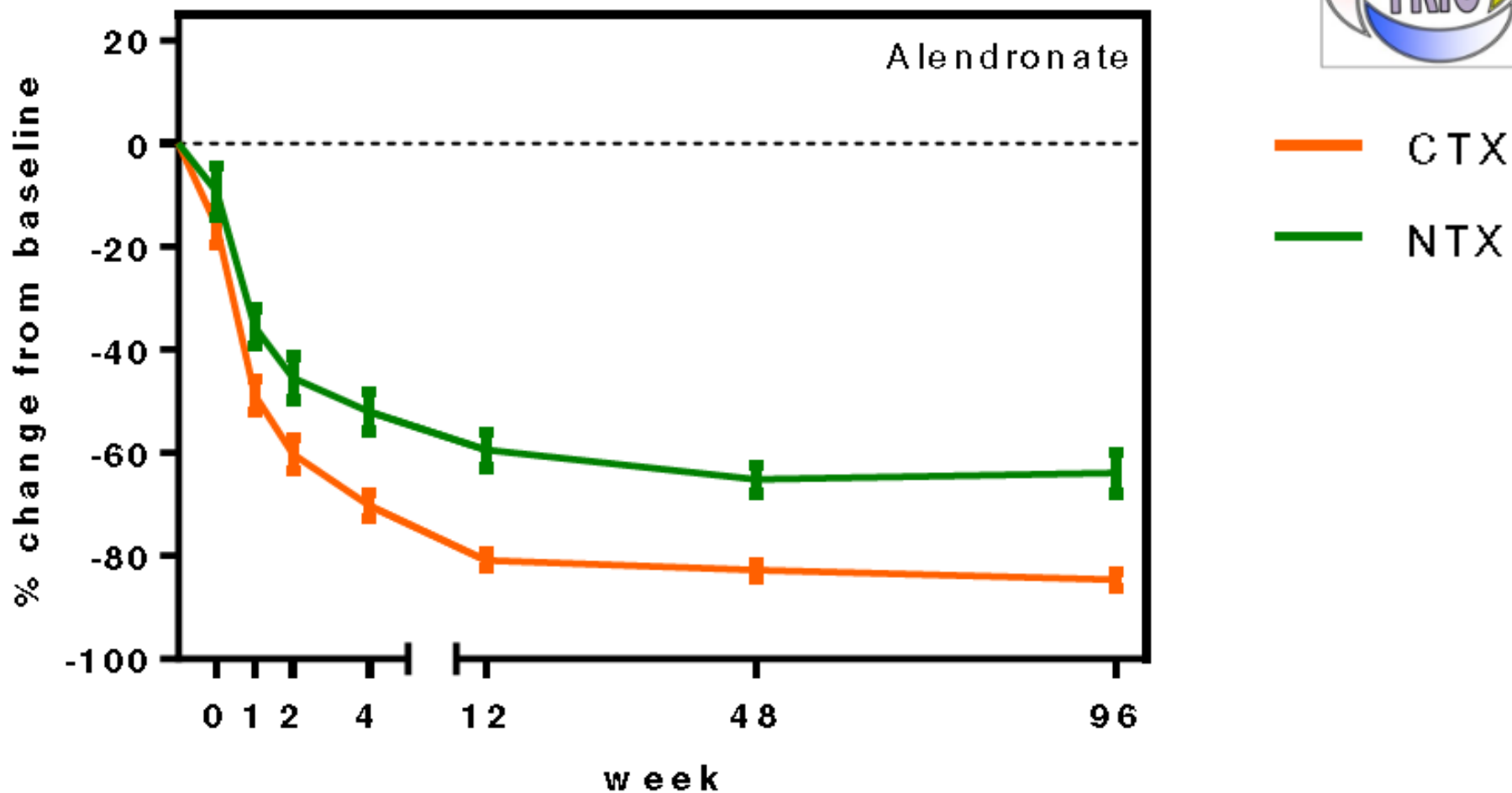
BTM is Usually 'Normal' in Osteoporosis

TRIO Study, n=172

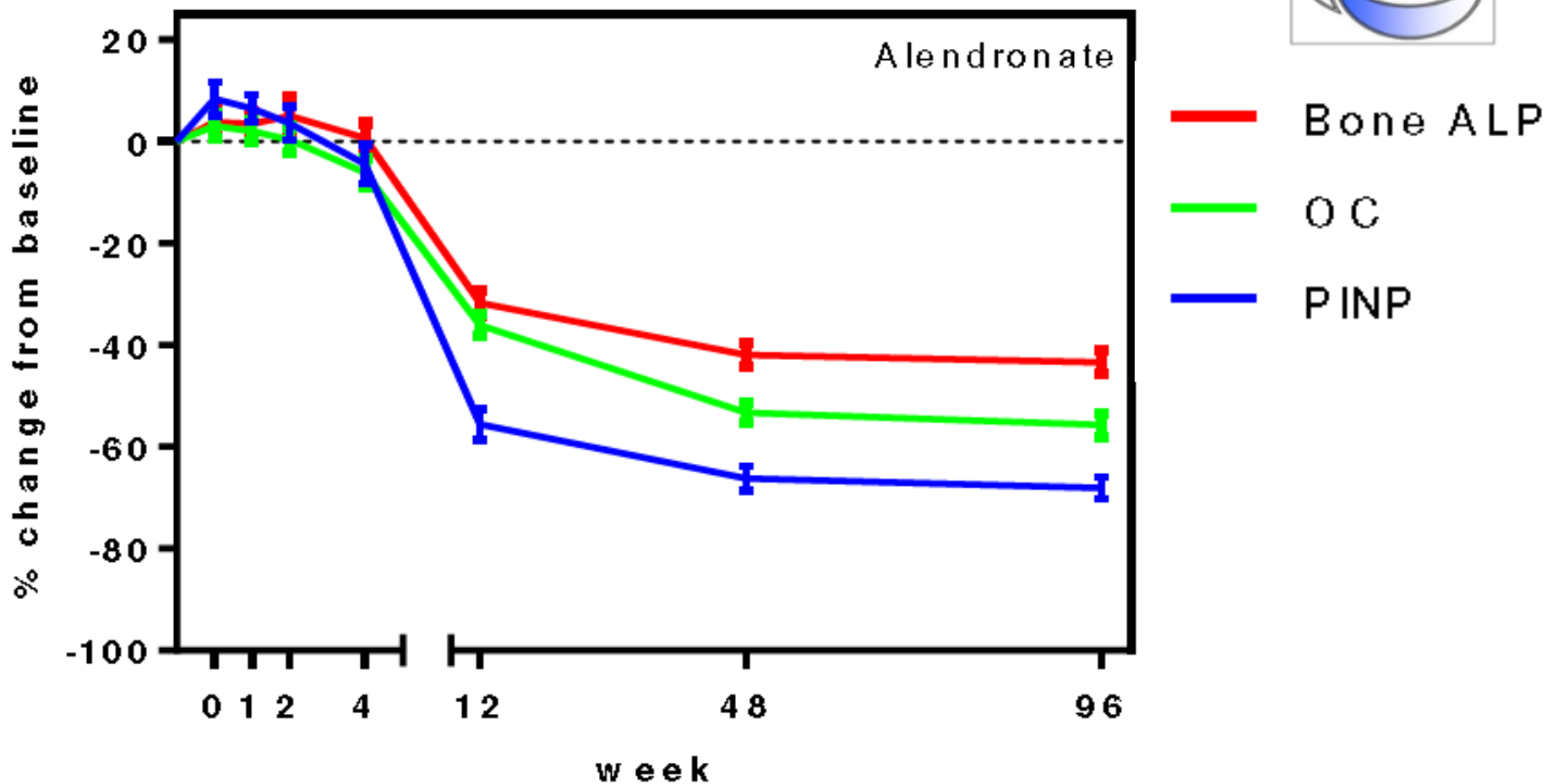


- Only 20% have high bone turnover at baseline

Effect of Alendronate Therapy in Osteoporosis: Bone Resorption Markers, TRIO Study

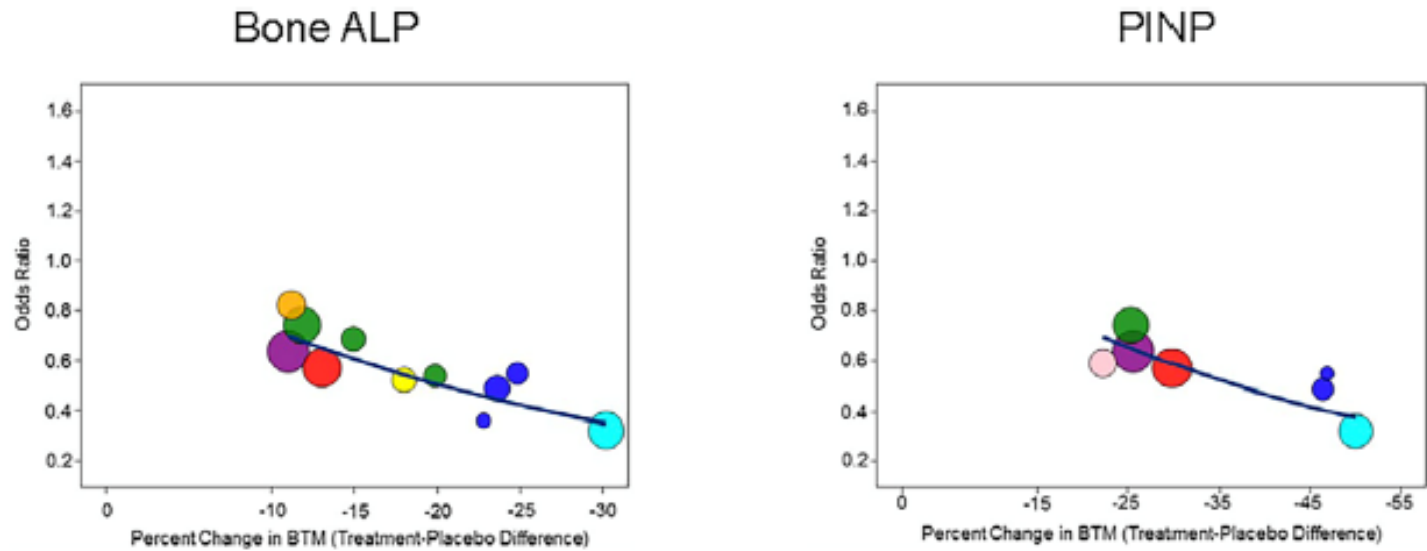


Effect of Alendronate Therapy in Osteoporosis: Bone Formation Markers, TRIO Study



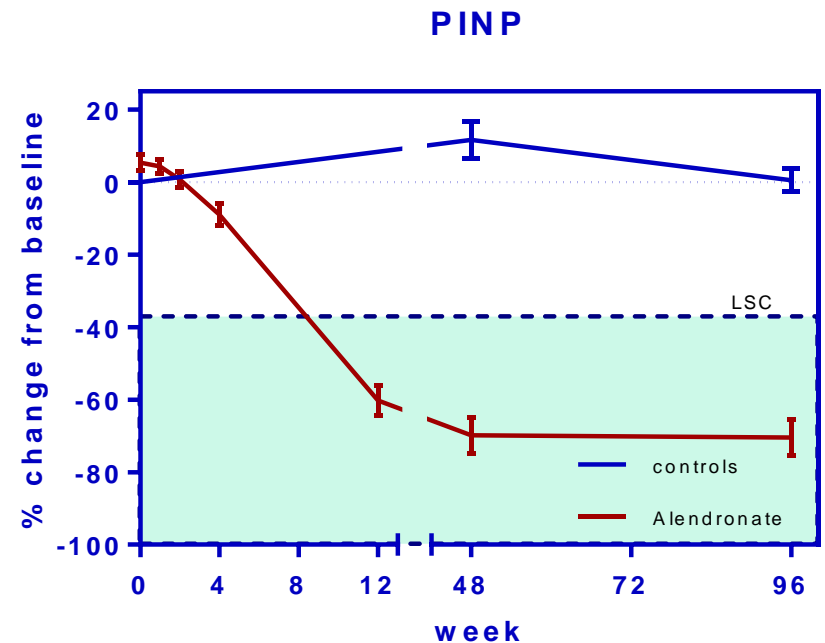
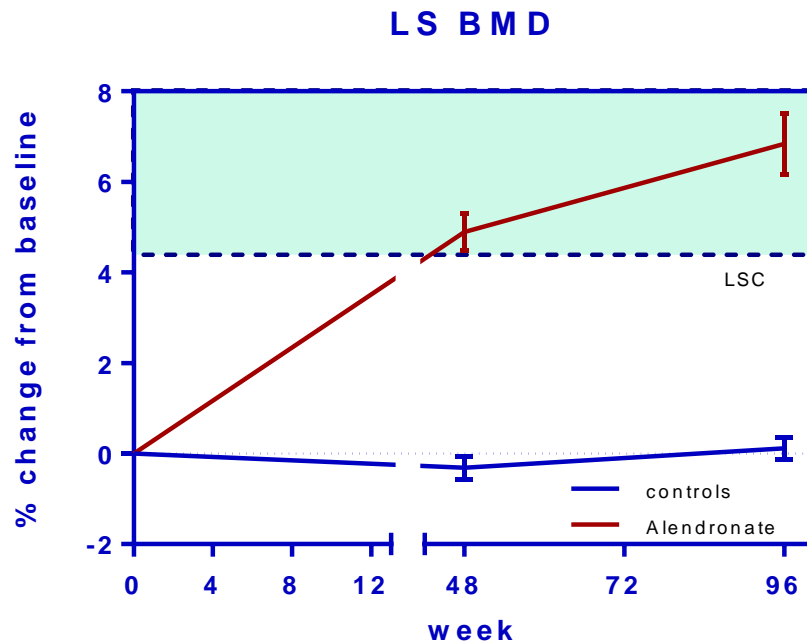
Vertebral fracture risk reduction is related to reduction in BTM: FNIH Bone Quality Study

Vertebral Fracture



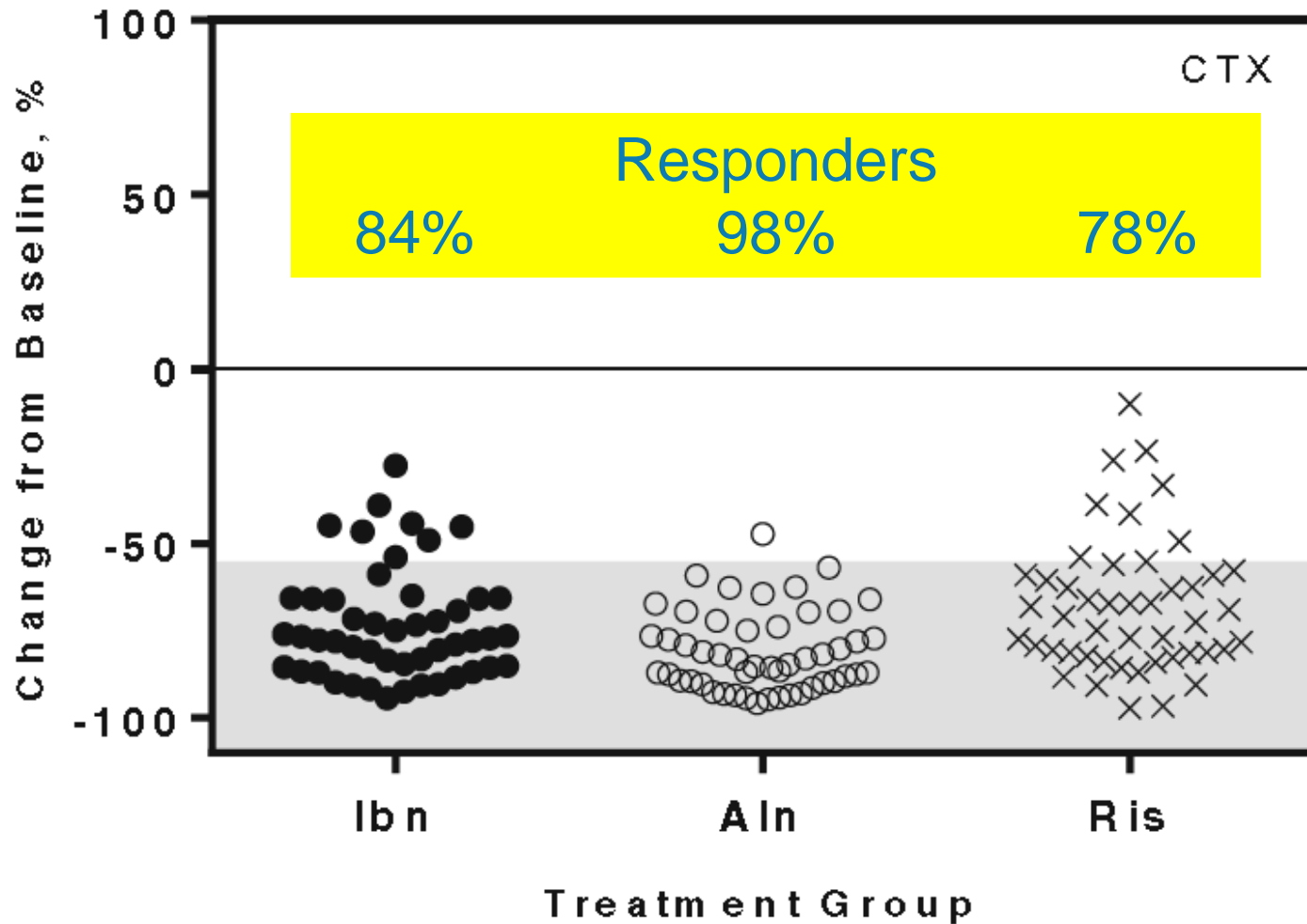
Use in the individual for identifying response

A responder is someone whose result exceeds the least significant change

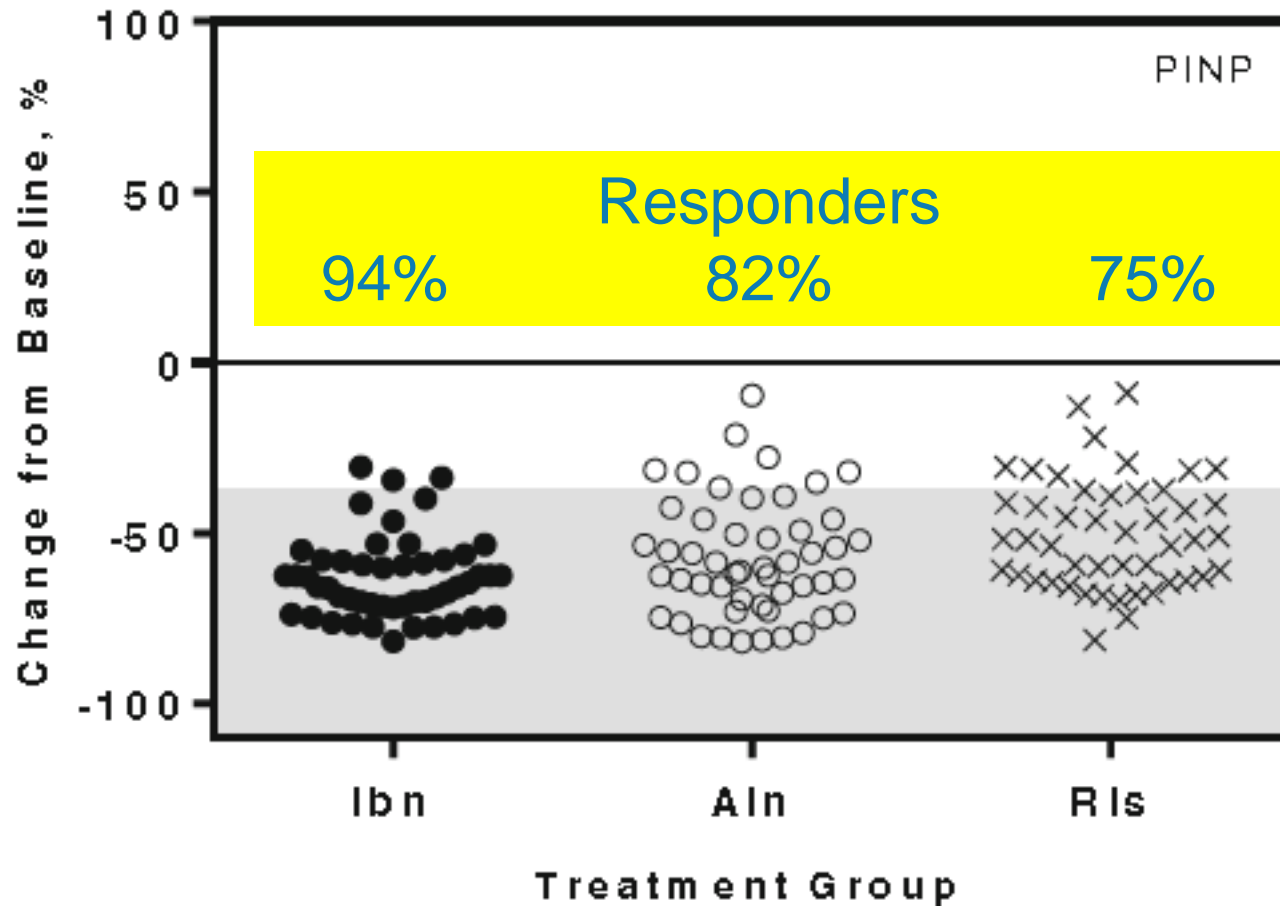


LSC = least significant change (also, RCV, reference change value)

Least significant change for CTX, 56% Change at 12 weeks

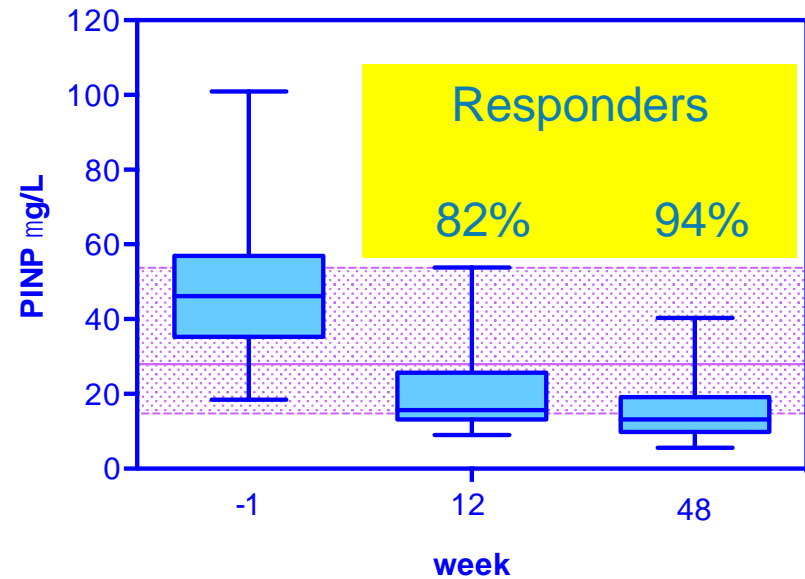
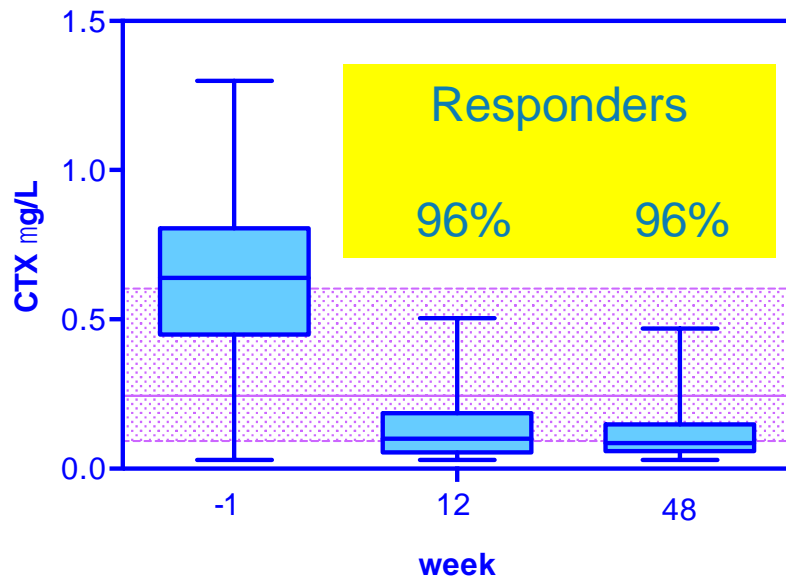


Least significant change for PINP, 38% Change at 12 weeks



Target for Treatment: Bone Turnover Marker in the Lower Half of the Reference Interval

Alendronate Therapy for Osteoporosis



Targets for Therapy

Greater than the least significant change

- Statistical approach
- Large reductions in BTM are associated with low fracture risk
- Requires BTM before and during treatment
 - Initial value may be useful
- Example: PINP reduced by 10 ug/L, or more

Below the mean value for healthy young women

- BTM level associated with minimal bone loss
- Low bone turnover is associated with low fracture risk
- Only requires a BTM on treatment
- Example: reduce PINP to below 35 ug/L

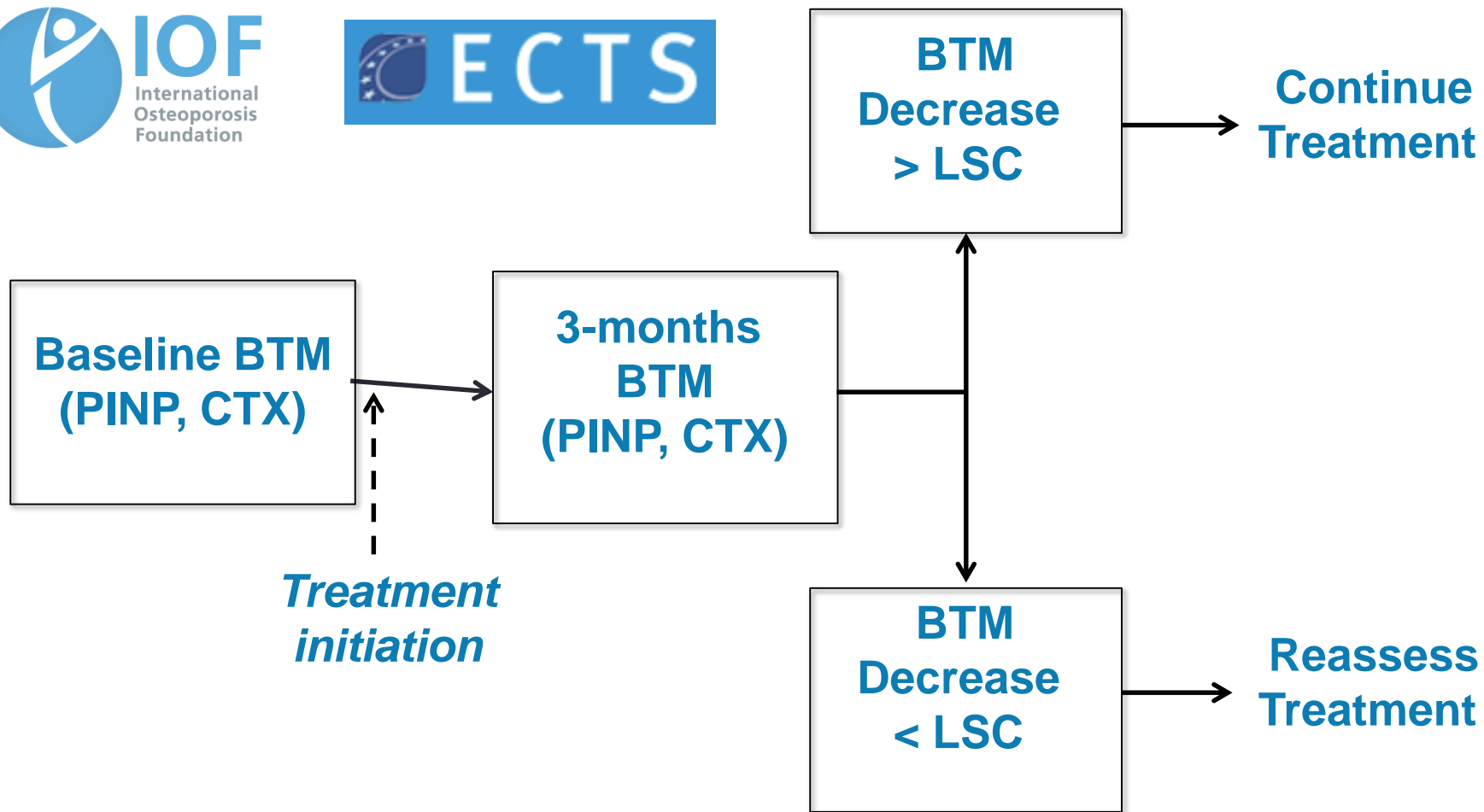
The problem of adherence



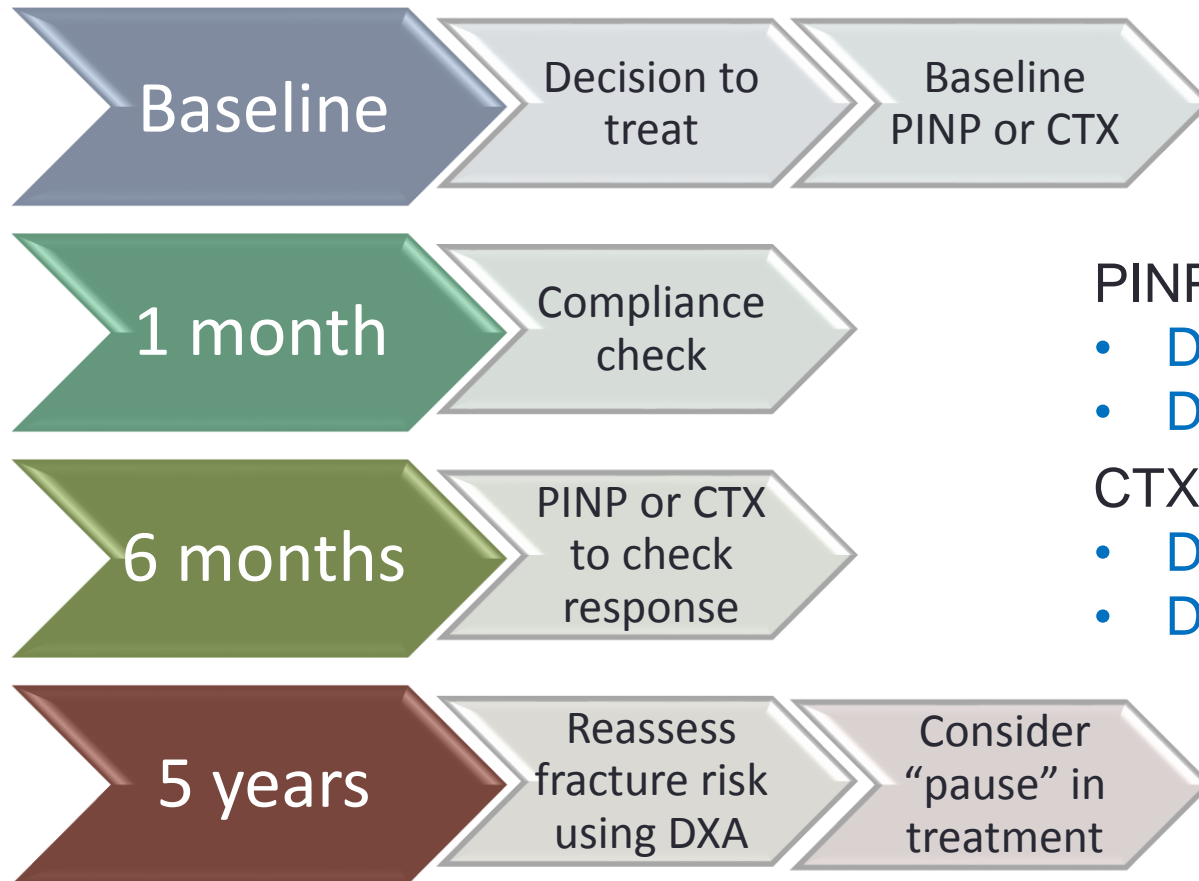
- Bisphosphonates (BPs) are considered a first-line treatment of osteoporosis
- Adherence to BPs has been reported at 50% or below after one year¹⁻³
- Low adherence results in lack of efficacy (no or limited decrease in fracture risk) and reduced cost effectiveness⁴

1. Cramer JA, et al (2007). *Osteoporos Int* 18(8):1023–1031; 2. Kothawala P, et al (2007). *Mayo Clin Proc* 82(12):1493–1501; 3. Kanis JA, et al (2012). *Osteoporos Int* 23(1):213–221; Hiligsmann M et al (2010). *Calcif Tissue Int* 86(3):202–210

Algorithm for adherence screening: International Osteoporosis Foundation and European Calcified Tissue Society



Oral bisphosphonate monitoring algorithm



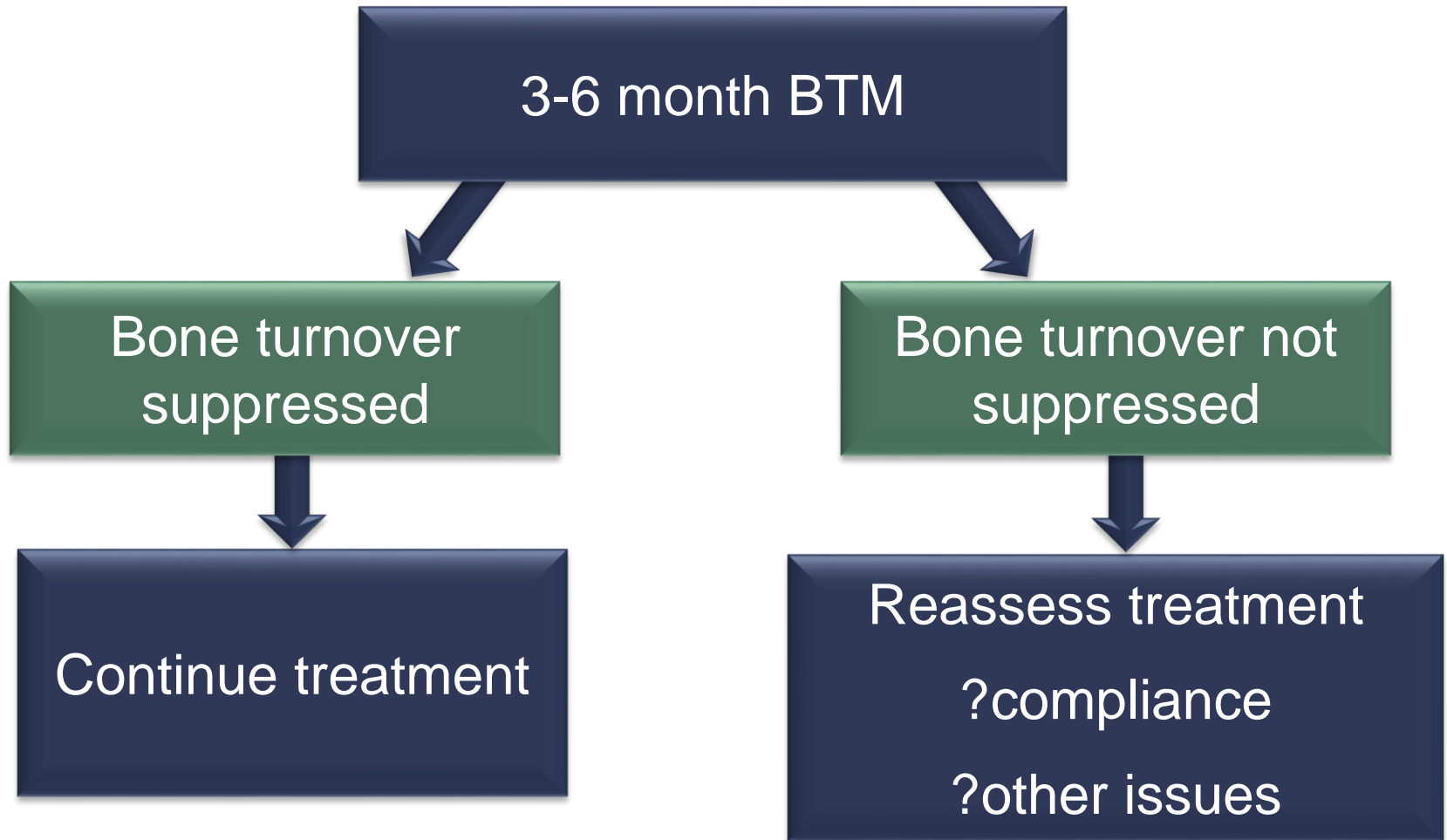
PINP response defined by:

- Decrease ≥ 10 $\mu\text{g/L}$
- Decrease to ≤ 35 $\mu\text{g/L}$

CTX response defined by:

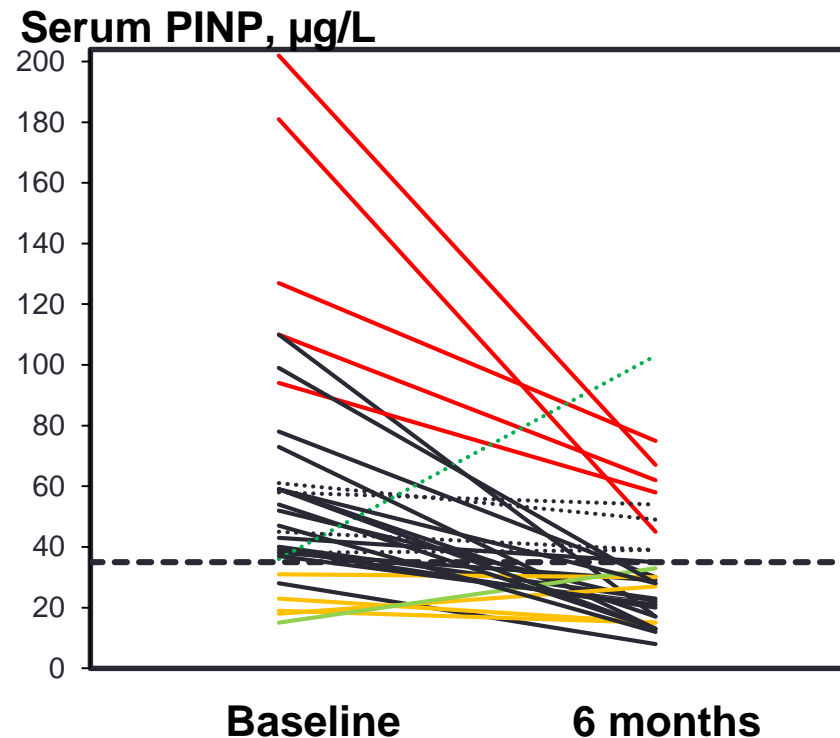
- Decrease ≥ 100 ng/L
- Decrease to ≤ 280 pg/L

Approach to non-response



Types of BTM response observed in general practice

- Response, and target
- Response, not target
- No response, target
- ⋯ No response, not target
- Increase

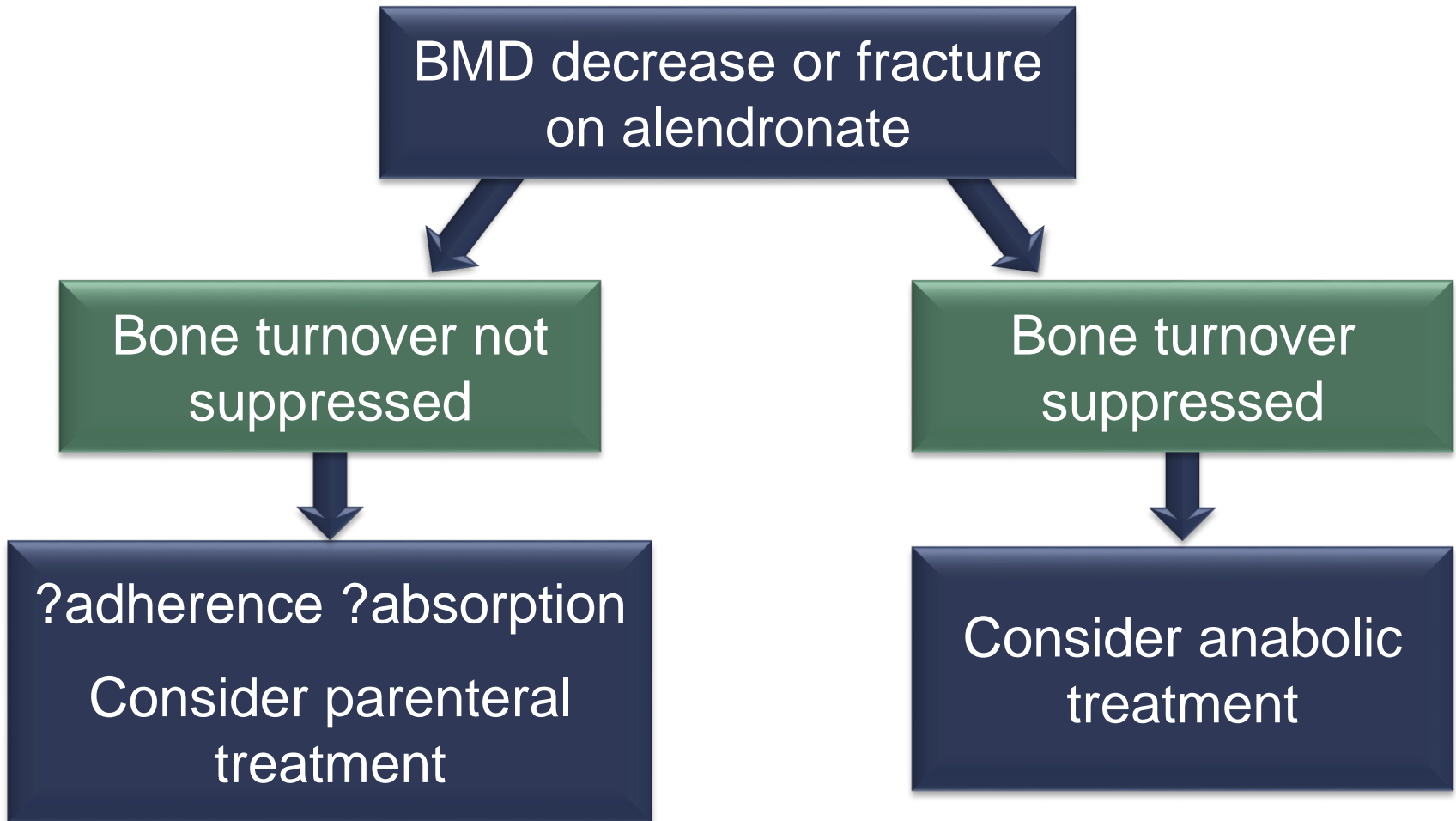


Response is decrease more than 10, target is below 35 ug/L

Case Report

- 70 year old woman
- Osteopenia noted on spinal radiographs
- Treated with alendronate 70 mg once a week, calcium and vitamin D
- BMD T-score at the total hip and lumbar spine -3
- Bone turnover markers
 - Baseline CTX 500 ng/L, 6 months 120 ng/L
 - Baseline PINP 60 ug/L, 6 months 20 ug/L
- At review after 6 months, is she responding or not?
 - YES, she is responding and she met her target

BTM to assist management decision

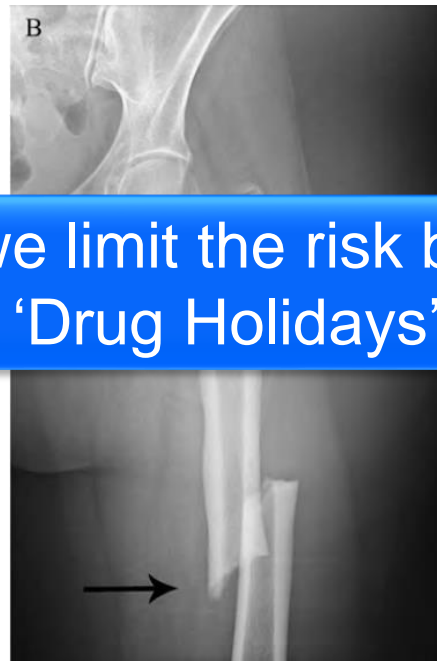


Use in monitoring the offset of therapy

Oral bisphosphonate

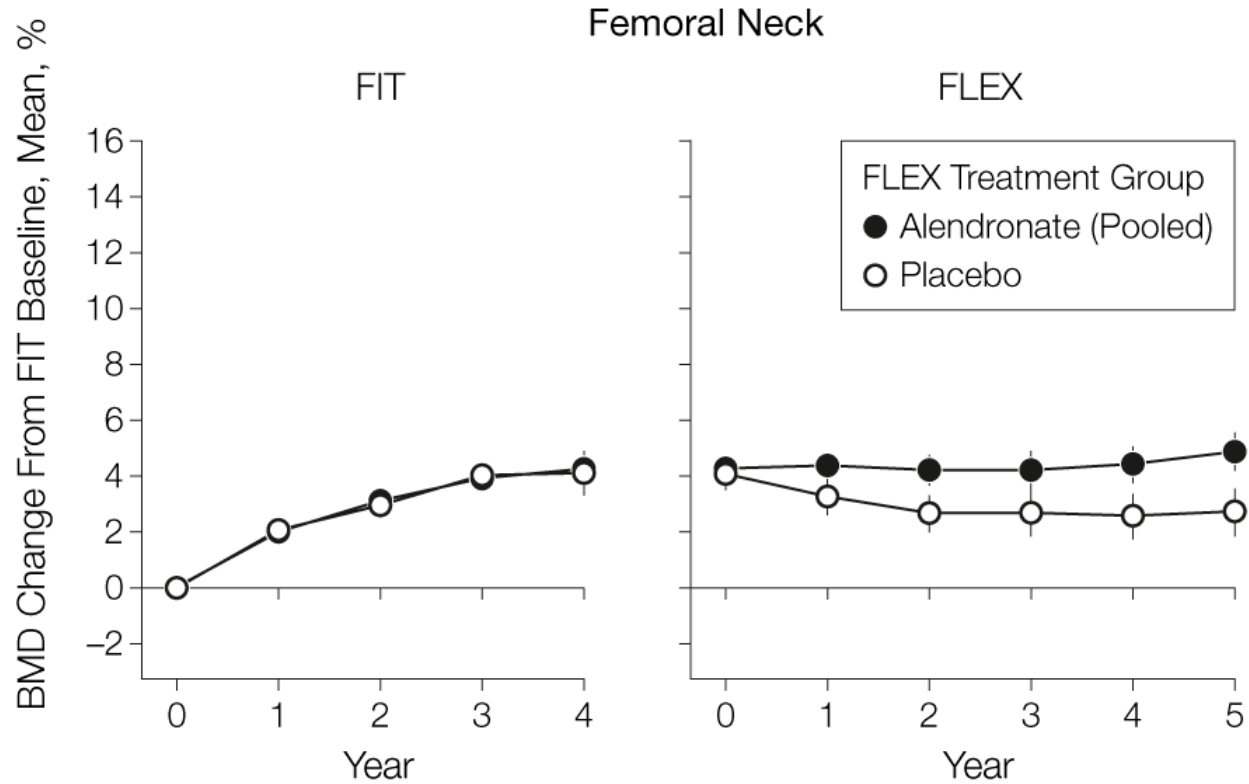
Atypical Fractures of the Femur Have Been Associated with Long-term Bisphosphonate Therapy

- Fracture of the subtrochanteric region or femoral shaft
- Transverse or short oblique orientation
- Minimal trauma
- Medial spike
- No comminution



Can we limit the risk by using
'Drug Holidays'?

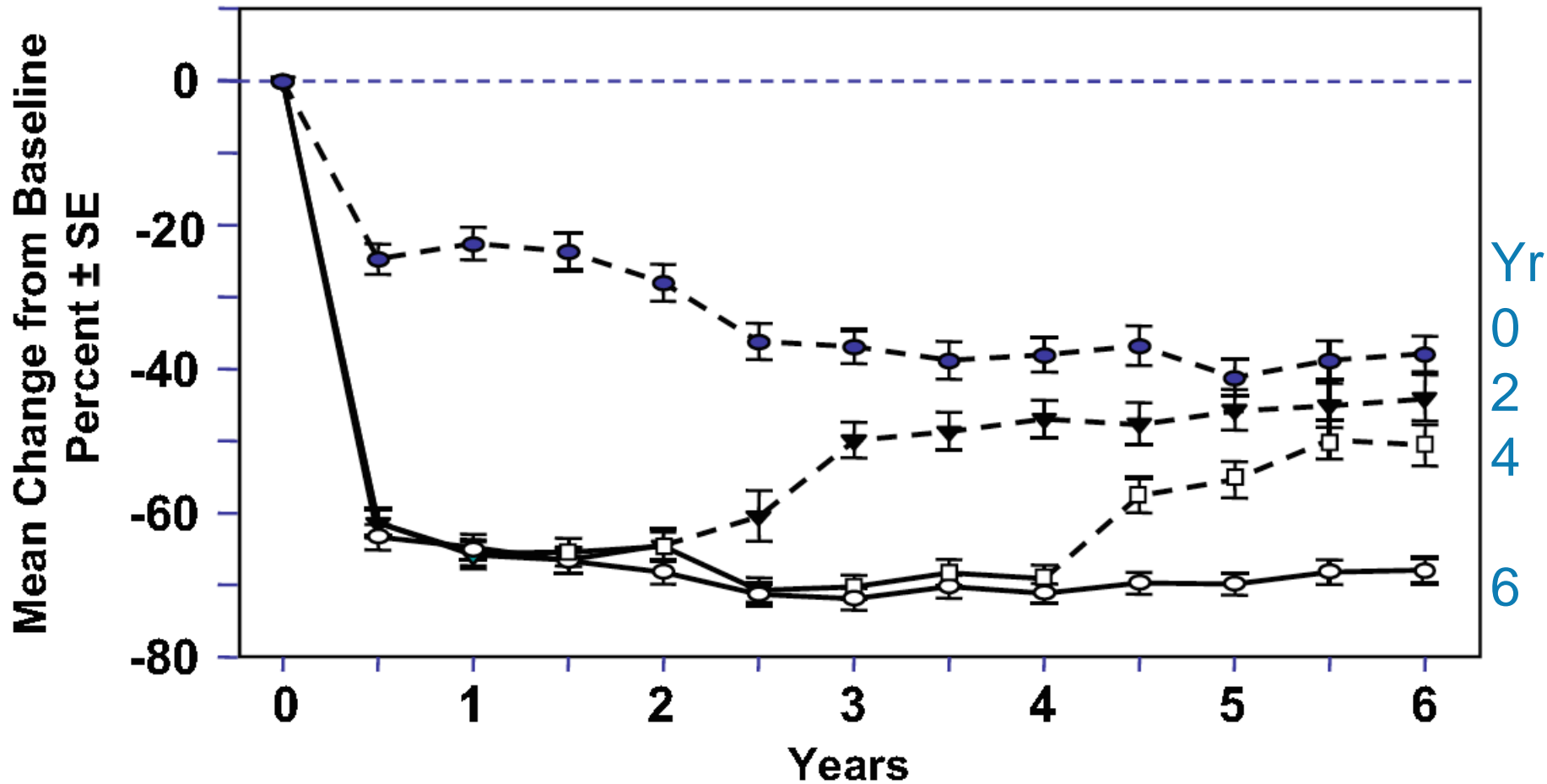
Effect of alendronate on hip BMD over 10 years: FIT and FLEX



No.	Year 0	Year 1	Year 2	Year 3	Year 4	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
Alendronate	662	660	658	656	460*	657	642	628	599	580	553
Placebo	437	435	436	432	297*	437	428	415	401	380	361

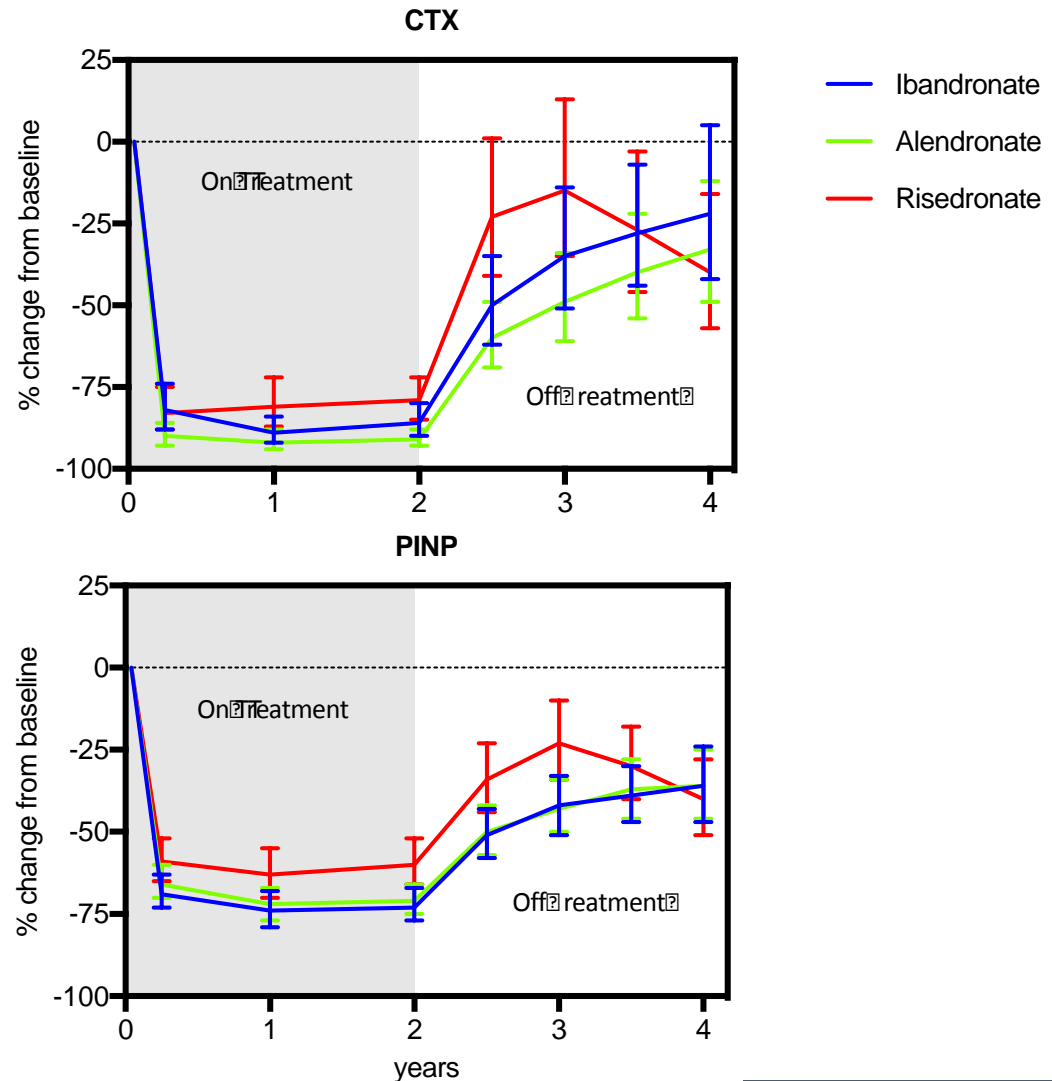
BISPHOSPHONATES

Changes in Bone Resorption (NTX/Cr) after Alendronate for 0, 2, 4 and 6 Years (EPIC)

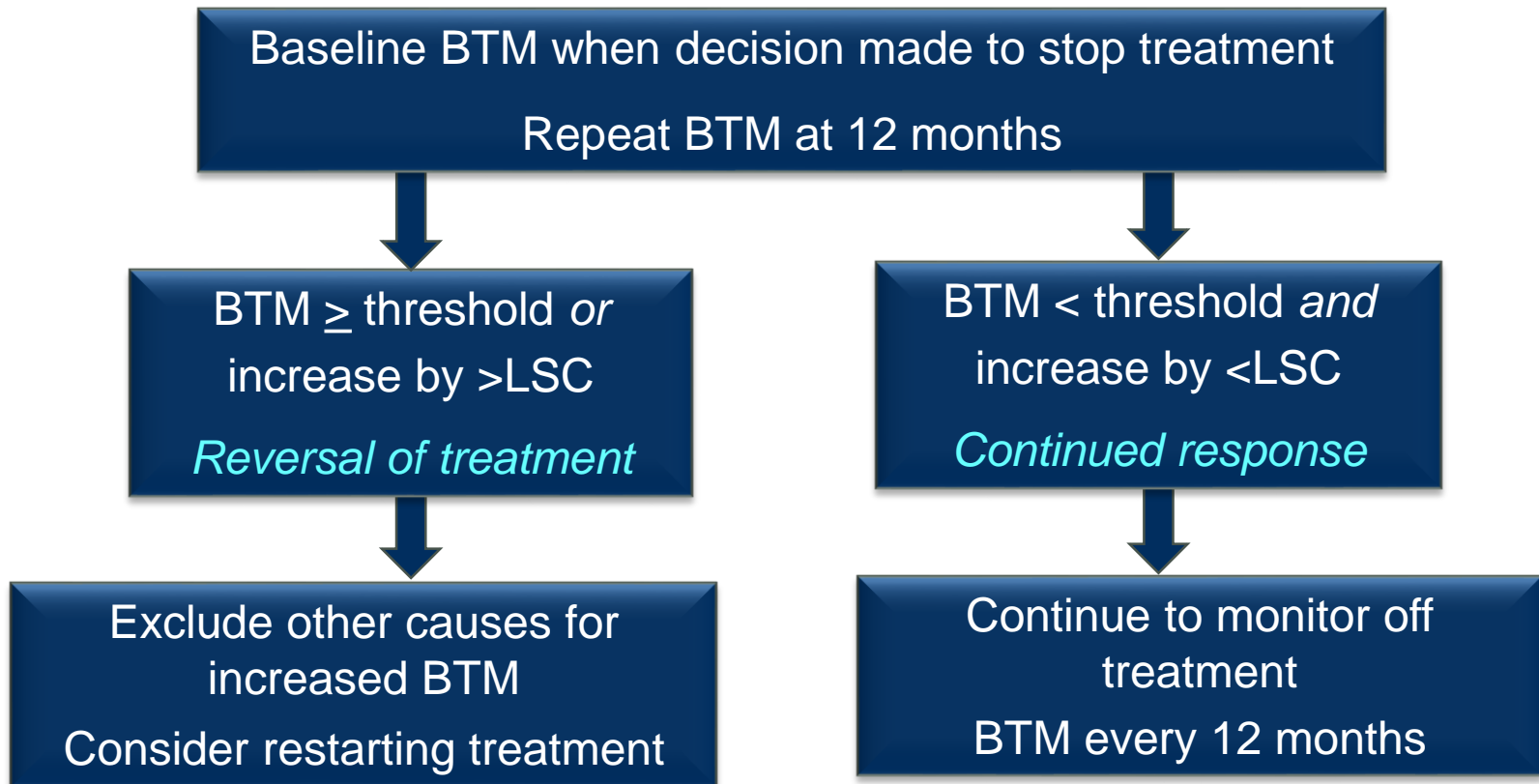


How Quickly Does Anti-resorptive Effect Wear off after Stopping Oral Bisphosphonates?

- 57 women with postmenopausal osteoporosis
- Treatments stopped for two years



BTM to monitor offset of bisphosphonate treatment



Case Report

- 70 year old woman
- Osteopenia noted on spinal radiographs
- Treated with alendronate 70 mg once a week, calcium and vitamin D
- BMD T-score at the total hip and lumbar spine -3
- Bone turnover markers; treatment stopped at 60 months
 - Baseline CTX 500 ng/L, 60 months 120 ng/L, 72 months 400 ng/L
 - Baseline PINP 60 ug/L, 60 months 20 ug/L, 72 months 40 ug/L
- She is showing signs of offset of effect with PINP increasing by more than 10, to above 35 ug/L



Case examples

Female, 87years old, clinic follow up

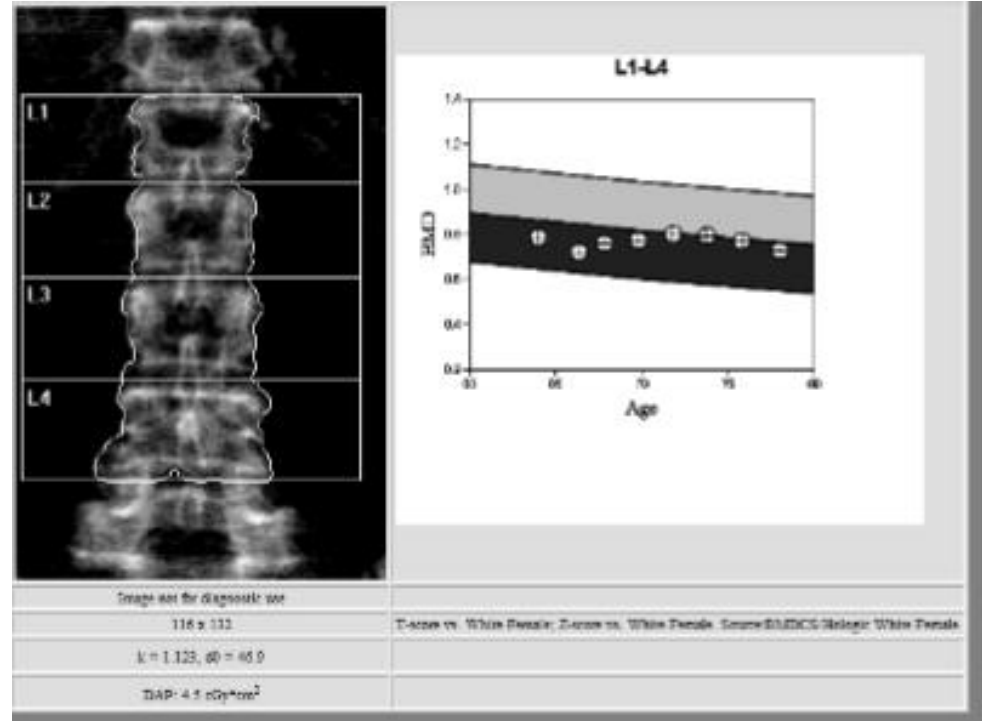
- Osteoporosis
- Previous fractures: left femur, left shoulder, right wrist, vertebral L3,L4
- Treatment: alendronate for 10 years, stopped 2017. Now on calcium and vitamin D
- Vertebral fracture assessment performed, suspicion for new fracture at L2, confirmed by radiographs
- Investigations normal
- How would you treat?

Female, 87years old, clinic follow up (cont.)

- Treatment options: teriparatide, denosumab, bisphosphonate
- PINP 140µg/L
- What treatment would you give?
- Decision
 - Treat with zoledronate

Female 78y, clinic follow up

- Osteoporosis, no fractures
- PMH: AF, Parkinson's disease
- Treatment:
 - alendronate, 2004-2008
 - zoledronate, six annual infusions 2008-2013
- BMD:
 - T score spine -2.9, hip -2.3.
 - 5% loss since 2017



- What would you do?

Female 78y, clinic follow up (cont.)

- PINP 36 μ g/L
- **Would you treat?**
- Previous result PINP 8 μ g/L in 2013
 - >10 μ g/L increase, above 35 μ g/L
- Decision: One more infusion of zoledronic acid

Summary

- Bone turnover markers show large and early response to anti-resorptive or anabolic therapy
 - Response is indicated by a decrease beyond the least significant change
 - Target is reached if beyond the mean value for young women
 - Response relates to fracture risk reduction
- Bone turnover markers are partially suppressed for several years after stopping bisphosphonate therapy, but not other therapies
 - Offset of effect may be detected earliest by bone turnover markers

Q & A

THANK YOU

On behalf of IOF, we thank you for your participation in this webinar

This webinar was supported by

