Can bone turnover markers help to define the duration of bisphosphonate drug holidays?

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Background

Good evidence for 5 years bisphosphonate (BP) treatment[1,2] but beyond this less clear

- BP long half-life; stopping treatment → wears off gradually[2]

Potential for harm

- Atypical fractures, osteonecrosis of the jaw (ONJ)
- Rare occurrence, ↑risk with increasing duration[3]

BPs impair Bone Turnover; CTX bone turnover marker (bone resorption)

- Start BP → ↓CTX
- Stop BP & CTX rises[2]

Drug holidays increasingly common - stop BP for period of time

Local practice since late 2012

- Review BP after 5 yrs
- Drug holiday
- Routine monitoring CTX at baseline, 4 months and 12 months

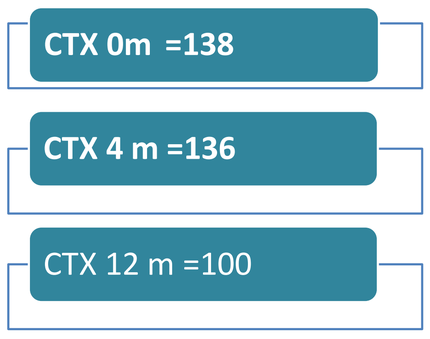
Our aim was to analyse changes in CTX on stopping long term bisphosphonate treatment to guide clinical decision-making on the duration of treatment cessation

Methods

- Patients on BP *drug holiday* via outpatient Bone Clinic identified from monitoring records
- Data extracted; patient age, sex, serum CTX levels 0, 4, 12 months, bisphosphonate and duration of use
- Excluded if baseline (0m) CTX ≥0.51 ug/L (higher fracture risk)
- Data analysis using Stata Statistics software.
- *Offset* of action defined as
  - a rise by the Least Significant Change (LSC=33%*) in CTX and CTX above the pre-menopausal mean (0.19ug/L)

$LSC=2.33xV(CVa^2)+(CVi^2)$: CVa is analytical coefficient of variation, CVi is intra-individual CV

Figure 1: All patient characteristics



Mean Patient Age	71 years
Gender	83% female; 17% male
Mean Duration BP	8 years (range 3-15 years)
Alendronic acid	59%
Risedronate	33%
Other Bisphosphonate	8%

Results

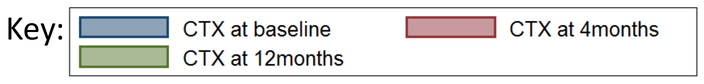
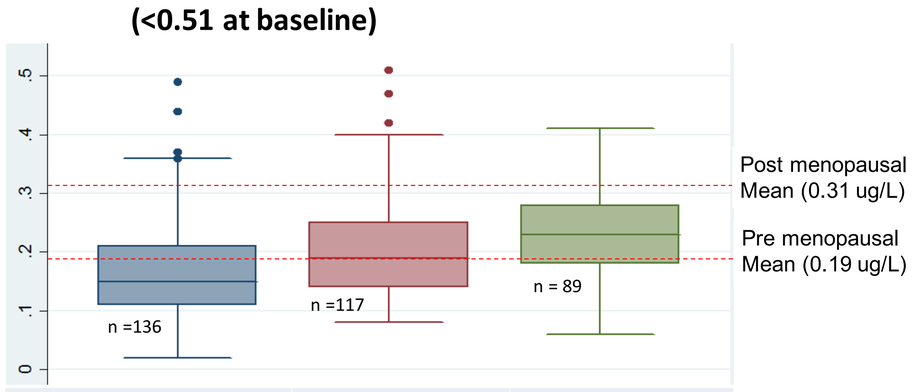


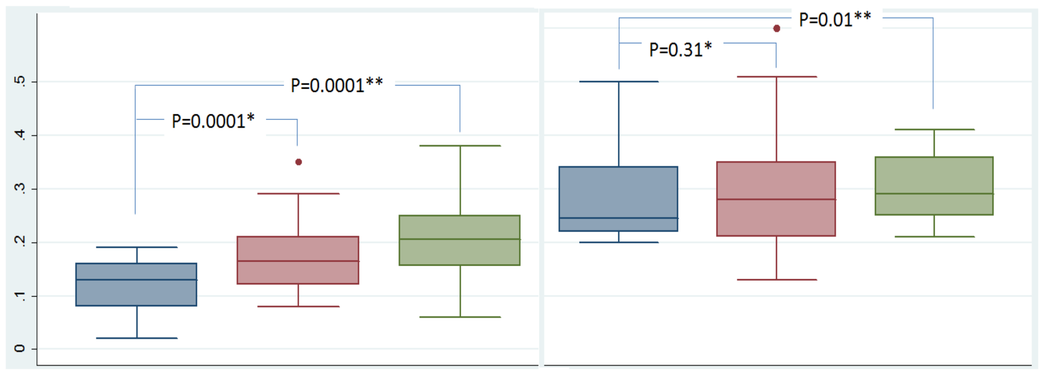
Figure 2: CTX at 0, 4, 12 months all patients (<0.51 at baseline)



Delta CTX		
Median [IQR] in ug/L	+0.04 [0.01-0.08]	+0.09 [0.04-0.12]
Mean (SD) in ug/L	+0.04 (0.06)	+0.08 (SD 0.06)
%	+42%	+80%
Significant rise (>LSC)	47%	69%

Figure 3: CTX at 0, 4, 12 months for defined populations

a) ≤ pre-menopausal mean at baseline **b) > pre-menopausal mean at baseline**



a) *0-4m mean CTX + 0.05ug/L (95% CI 0.04-0.06)
**0-12m mean CTX +0.09ug/L (95% CI 0.07-0.10)

b) *0-4m mean CTX + 0.01ug/L (95% CI -0.01-0.04)
**0-12m mean CTX +0.05ug/L (95% CI 0.01-0.09)

Overall population (figure 2):

•Detectable rise in CTX seen from as early as 4 months in 47% patients; 69% at 12 months

Subpopulations (figure 3):

•If CTX ≤ pre-menopausal mean (i.e. treatment target) at baseline, statistically significant increases in CTX seen at 4 and 12 months

•If CTX > pre-menopausal mean at baseline, no significant change at 4 months, significant by 12 months

•No significant difference between Alendronic acid and Risedronate seen (data not shown)

Monitoring outcomes using population data (figure 4):

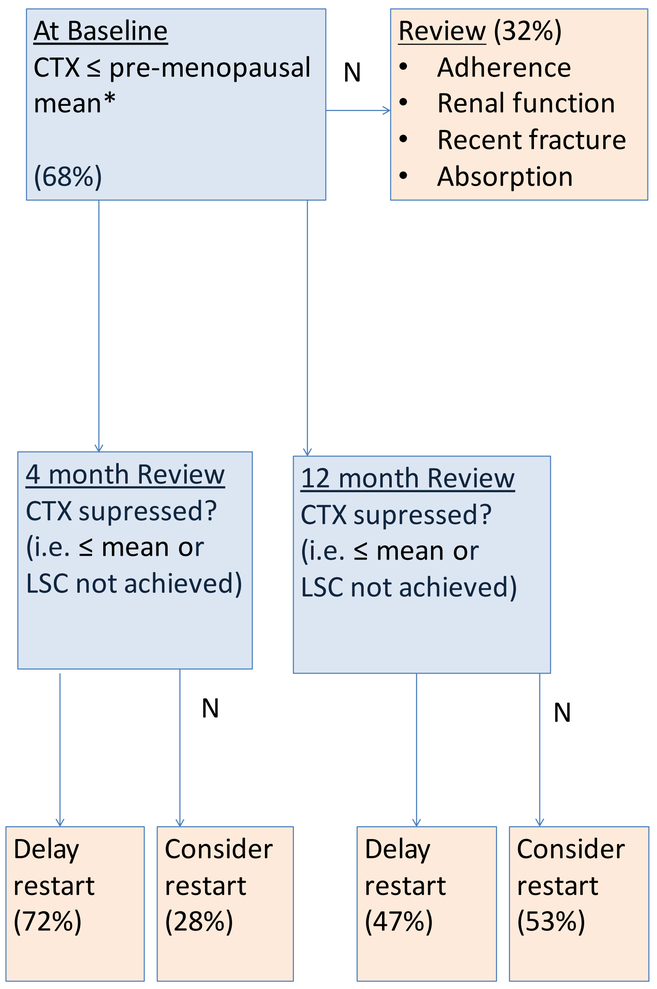
•Baseline CTX not suppressed to premenopausal mean level after 5 yrs of BP use in 32% patients

•Where CTX suppressed at baseline:

- At 4 months 28% had significant rise in CTX that was also above mean level (?consider re-start)

- At 12 months this had risen to 53%; 47% CTX still suppressed at this stage

Figure 4: CTX monitoring outcomes at baseline, 4 and 12 months



*Mean premenopausal CTX 0.19 ug/L(0.05-0.63)[4]

Conclusion

- After at least 5 years of treatment, CTX may not be adequately suppressed in a third of patients. Drug adherence and therapy choice should be reviewed in this group.
- Less significant changes in CTX seen if levels not adequately suppressed at baseline ?adherence
- Treatment effects can wear off as quickly as 4 months, but may also be maintained for 12 months
- Monitoring of CTX can potentially be used to identify these patients, some of whom may need to re-start treatment earlier

References

1.Sorensen OH *et al* (2003) Long-term efficacy of risedronate: a 5-year placebo-controlled clinical experience. Bone;32(2):120-6.; 2.Black DM et al (2006) Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. JAMA ; 296; 24;2927-2938;
3.MHRA Drug Safety Update June 2011, vol 4 issue 11: A1;
4. Gossiel F *et al* (2014) Establishing reference intervals for bone turnover markers in healthy postmenopausal women in a nonfasting state. BoneKEy Reports 3, article no: 573.

Conflicts of interest: None declared