

# Relationship of fracture risk to change in bone resorption with risedronate in the HIP study: Is there a plateau response?

A. Blumsohn<sup>1</sup>, J. L. Hutton<sup>2</sup>

<sup>1</sup>Sheffield Teaching Hospitals, UK <sup>2</sup>Department of Statistics, University of Warwick, Coventry, UK

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## Abstract

Understanding the determinants of bisphosphonate induced change in fracture risk is a prerequisite to rational prescribing and therapeutic monitoring. A previous abstract (Blumsohn, Barton, Chines, Eastell. JBMR 2003;18 S2:S89), and draft publications failed to shed light on the true relationship between change in bone resorption (uNTX/Cr) and fracture risk in the HIP study. The study included 938 women (FN T score <-3, age 74 SD 3) who received Ca and either 5mg risedronate/day, 2.5mg or placebo for 3 years. Randomization and event codes were supplied to authors in 2006. Data did not provide evidence to support previous conclusions.

Previous reports on these data suggested risk of incident vertebral fracture (V#) was non-decreasing when NTX decreases beyond -30% (%ΔNTX < -30%), and the relationship was "non linear" with "little further improvement in fracture benefit below a decrease of 30 to 35%". It further suggested that another marker (%ΔPINP) was significantly predictive of V#.

We used several statistical models as well as visual inspection to evaluate a potential "plateau" effect at a putative threshold -30% or -40%. Cox and logistic regression models were used, with thresholds of -30% and -40%, and two transformations of NTX: %ΔNTX and Δlog(NTX). The response was allowed to take different values above and below the threshold, for both linear and quadratic functions. Conclusions were essentially the same for all models, with or without inclusion of data on the unlabeled (2.5mg) dose.

Visual inspection showed no evidence of a plateau near the putative threshold. With 5mg risedronate most (9/11) incident V# occurred with change in NTX beyond the proposed -30% threshold (median %ΔNTX with V# was -49%). No patients with %ΔNTX < -61% sustained V# (-61% was also the approximate lower limit of plots presented to authors by the sponsor). 44% of patients on 5mg had %ΔNTX < -61%.

Regression models showed no evidence for a plateau at either threshold, and significant evidence of no plateau (Cox P < 0.05). For both 2.5 and 5mg doses the risk of V# decreased significantly with greater NTX decrement. Regression models showed significant prediction for fracture by %ΔNTX on the alleged plateau either for a 30% threshold (Cox P=0.010, 23/355 events) or a -40% threshold (P=0.013, 19/314 events). No significant relationship between %ΔPINP and V# was found by comparison of medians or regression models (all P > 0.22).

In conclusion, this study provides no evidence to support a plateau relationship between %ΔNTX and fracture risk with threshold near -30% in patients on risedronate.

**Disclosure: Study funded by Procter & Gamble**

## Background

- This abstract focuses on the relationship between data and representation of that data in a previous ASBMR abstract (1) and associated draft publication (4) prepared by the sponsor in 2003. Data revealed to authors in 2006
- Similar concerns raised about representation of data in the larger HIP+VERT population (2,5) and the VERT population alone (3)

## Previously reported

Previous reports on these same data (1,4) suggested risk of V# was non-decreasing at NTX change beyond -30% (%ΔNTX < -30%), and the relationship was "non linear" with "little further improvement in fracture benefit below a decrease of 30 to 35%". Reports further suggested that %ΔPINP was significantly predictive of V#.

ASBMR abstract (1) stated:

*"In keeping with our previous findings with the VERT study, the relationship between vertebral fracture risk and change from baseline in NTX was not linear (P<0.05 in the 5mg group). There was little further improvement in fracture benefit below a decrease of 30 to 35% for NTX. In conclusion, the decrease in bone turnover in patients taking risedronate accounts for some of the reduction in vertebral fracture risk. There may be a level of bone resorption reduction below which there is no further fracture benefit".*

Draft publications (4) relating to (1) stated:

**"Summary :** Consistent with findings from the VERT trial, a non-linear function was more appropriate than a linear function for modeling the relationship between early changes in NTX and vertebral fracture risk over 3-years (5mg risedronate, p=0.008). There was little further improvement in fracture benefit below a decrease of 30 to 35% for NTX."

**"Key Message:** The relationship between early changes in NTX and longer term fracture risk for 5mg risedronate is non-linear (p=0.008), consistent with findings from the VERT trial."

**"Results:** Figure 1a clearly shows that the fracture incidence is not continually decreased as NTX is reduced."

## Brief history of events

- ± **Jan 02:** Manuscript (3) submitted to Lancet
- **1 May 02:** Manuscript (3) submitted to JBMR
- **27 May 02:** "Author" of (3) requests data "to avoid criticism in the future".
- **14 Jun 02:** Sponsor replies: "No, we do not intend for someone else to do the analysis" and we "don't need to ask an independent person to analyse the data just to make a few people happy"  
[independent persons = authors]
- **8 Jul 02:** P&G executive writes that data would not be provided as "delay to result", not "sufficiently important to justify it" and if provided "industry loses the opportunity to demonstrate its ability to be a true partner in scientific endeavours".
- **12 Dec 02:** Manuscript (3) accepted by JBMR
- **14 Apr 03:** Abstracts (1,2) transmitted to ASBMR
- **24 Apr 03:** Draft manuscript (4) from P&G pertaining to abstract (1)
- **15 Jun 03:** Manuscript (3) printed in JBMR states: "All authors had full access to the data and analyses". Author's declaration states: "Any limitation to the full access of the Authors to all material must be disclosed. This is particularly important for ..work supported in part or entirely by a pharmaceutical [company]" and "Any limitation to the full access of the Authors to all material has also been disclosed".
- **10 Jun 03:** P&G employee responds to further requests for data codes stating he would perform any analysis: "I don't want us to be delayed/distracted" while "our competitors pip us to the post"
- **12 Jun 03:** Draft manuscript (5) from P&G pertaining to abstract (2)
- **19 Jun 03:** P&G employee writes: "The Alliance has received a couple of requests from external parties to obtain the BTM/FX data and we have declined. Therefore, as we have set a precedent we would be unable to share the d/base with Sheffield."
- **Jul-Oct 03:** Several concerns raised re data analysis in (1-5). All graphs scaled to exclude ~40% of data in treated arm. Rate of incident fracture in data beyond axes appears very low.
- **1 Jan 04 to 31 Mar 04:** Company declares intention to alter mode of analysis in retrospect to investigate t-scores avoiding %ΔNTX
- **13 Dec 04:** Informed that P&G "take the approach described in the PhRMA guidelines and in these guidelines there is not access to data (other than those from your centre) for investigators"
- **Feb 05:** Information about %ΔNTX plateau used in rebuttal to Merck FACT trial in educational material, JBMR, and by NTX manufacturer
- **25 May 05:** Eastell unable to provide data underlying (1-5) in response to legal request
- **25 May 05:** Legal request to P&G to disclose data underlying (1-5)
- **9 Sep 05:** P&G respond to legal request without data: "It is not standard practice of P&GP to allow unlimited access to raw data from clinical trials to individual investigators as these data are proprietary and are generated only after the investment of substantial R&D effort and funding by P&GP"
- **14 Apr 06:** Randomization and event codes underlying (1-5) released following press exposure. Confounding variables denied

## Study Data

Same data utilized by sponsor in representing (1,4)

- Patients from group 1 of risedronate HIP trial taking either placebo or 5mg risedronate (additional analysis for 2.5mg dose)
- Incident new vertebral fractures (V#) over 3 years by quantitative and semi-quantitative methods with adjudication
- Urinary NTX/Cr (second morning void; Vitros ECi, Ortho Clinical Diagnostics) at baseline, 3+6 months. Stored at -20C
- Serum PINP at baseline, 3+6 months (Roche Elecsys)

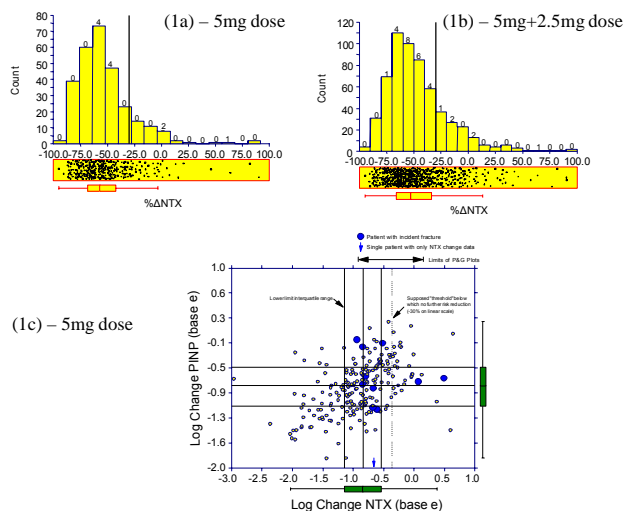
## Statistical analysis

A large number of statistical models (see abstract, full statistical report available from authors) as well as visual inspection were used to evaluate a potential "plateau" at putative threshold -30% or -40%.

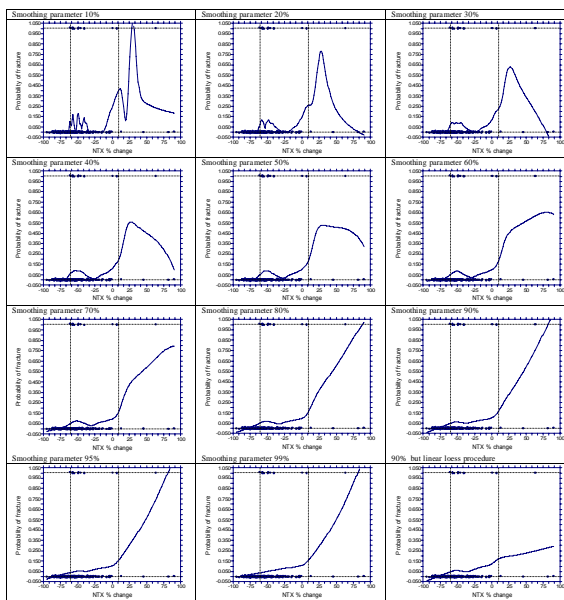
One mode of analysis (suggestion Professor Martin Bland) involved transforming % $\Delta$ NTX into two variables above and below a putative plateau, including both of them in a Cox (or logistic) model, and testing whether the variable on the plateau has any effect upon fracture-free survival. Other approaches involved testing whether incorporation of a (% $\Delta$ NTX)<sup>2</sup> term fits better than a linear model, and examining the resulting hazard ratio vs % $\Delta$ NTX.

## Results

- Simple visual inspection of data was not compatible with a plateau relationship between % $\Delta$ NTX incident V# with threshold -30% or at -40% at any dose.
- **Fig 1** shows the distribution of % $\Delta$ NTX in patients on risedronate in relation to incident V#
- All plots produced by the sponsor had been constructed with the % $\Delta$ NTX axis from 0% to -60%. 45% of patients on 5mg had % $\Delta$ NTX < -60%. These 45% patients with largest change would have "fallen off" the left hand scale of all plots. The fracture rate in these patients was zero.
- With 5mg risedronate most (9/11) incident V# occurred with change in NTX beyond the proposed -30% threshold
- At both 5mg+2.5mg doses most (23/29) incident V# occurred with change in NTX beyond the proposed -30% threshold
- No patients at 5mg with % $\Delta$ NTX < -61% sustained V# (-61% was also the approximate lower limit of plots presented to authors by the sponsor). A zero V# rate in the 44% of patients with largest NTX decrease is incompatible with the conclusions of (1,4)
- It was not possible to demonstrate a plateau at a -30% threshold or a -40% threshold using any plausible statistical method
- For combined 5mg+2.5mg doses, regression models showed no evidence for a plateau at a -30% threshold or a -40% threshold, and significant evidence of no plateau (Cox P < 0.05). Regression models showed significant prediction for V# by % $\Delta$ NTX on the alleged plateau for a 30% threshold (Cox P=0.010, 23/355 events) or a -40% threshold (P=0.013, 19/314 events).
- Attempts were made to reconstruct graphical displays as produced by the sponsor. This proved impossible without severe scale truncation, data truncation or data exclusion. It was possible to generate a wide variety of curves (some showing an apparent plateau) through random choice of smoothing parameter and scale truncation (**Fig 2**).
- **PINP**: No significant relationship between % $\Delta$ PINP and V# was found by comparison of medians or regression models (all P > 0.22). In patients on 5mg, % $\Delta$ PINP did not differ significantly between patients with incident V# (n=13) and those without V# (N=281)  
% $\Delta$ PINP -43.6% $\pm$ 5.4 vs -49.7% $\pm$ 1.3 P=0.32



**Figure 1.** Various displays of the distribution of change in NTX at 5mg or at both doses: (a,b) Distribution of % $\Delta$ NTX. The solid vertical line indicates the putative plateau threshold at -30%. Number of patients with incident V# is shown above each bar. Plots produced by the sponsor were truncated at -60% (c) Distribution of log change in NTX and PINP. Individual patients with incident V# are shown as larger filled circles.



**Figure 2.** Various data depictions generated through random choice of smoothing parameter for 5mg dose. Vertical dashed lines indicate limits of plots produced by the sponsor. Individual patients with and without incident V# are shown as individual dots.

## Conclusion

This study provides no evidence to support a plateau relationship between % $\Delta$ NTX and fracture risk with threshold near -30% in patients on risedronate.

## References

1. Blumsohn A, Barton IP, Chines A, Eastell R (2003). JBMR 18(S2):S89 #F338 [submitted April 2003]
2. Blumsohn A, Barton IP, Chines A, Eastell R (2003). JBMR 18(S2):S157 #SA337 [submitted April 2003]
3. Eastell R, Barton I, Hannon RA, Chines A, Garnero P, Delmas PD (2003). JBMR 18(6) 1051-6 [submitted May 2002]
4. Draft Publication 1: Relationship of early changes in bone resorption and formation to the risk of incident new vertebral fracture in the HIP trial. [April, May, June 2003]
5. Draft Publication 2: Relationship of early changes in bone resorption and changes in bone mineral density to the risk of incident new vertebral fracture. [June, July 2003]
6. Blumsohn A (2006), AAAS Professional Ethics Reports Volume XIX (3) for further discussion [http://www.aaas.org/spp/sfirl/per/per46.pdf] ablumsohn-3@yahoo.co.uk