Actonel Publication Planning Dilemma and some follow-up

- Dr Aubrey Blumsohn
- Follow-up on 3rd Annual Meeting of ISMPP

- This week
  - NMT Medical and Dr Peter Wilmshurst
    - (Google: NMT Wilmshurst)
- What is the problem?
  - Failure to learn
  - Operation outside of the rules of science
  - “Groupthink”

"Well, ladies and gentlemen, we skimped on maintenance a tiny bit, and look what happened: our wings fell off, and we're going to crash. We've learned from this experience, and we'll apply what we've learned to improve the flying experience for our future passengers."

THE BANNER OF SCIENCE

Ghosting

- Ability to connect knowledge to people "who made it" is part of how we quality control the enterprise
- Ambiguity about "who made it" leads to ambiguity about what we know
- Legitimate scientific authors
  - Have intimate acquaintance with raw data
  - Have analysed it
  - Would willingly defend "their" findings if challenged
  - Would provide raw data if asked

Medical writing professionals

The Abilene Paradox

- Paradox in which a **group** of people **somehow** decide on a course of action that is counter to the preferences (and long-term interests) of any of the individuals in the group
- Each member mistakenly believes that their own preferences are counter to the group's and do not raise objections
- Challenger Space Shuttle disaster (1986)
- A dysfunctional form of decision making
- Medical writing can facilitate dysfunctional decisions (GSK study 329)

Idiocy

None of us is as dumb as all of us

- In three commercial “scientific manuscripts” there was a problematical relationship between data and company depiction of those same data
- Raw data were hidden from “authors”. This was deliberate and repeated
- Authors made false declarations to a journal
- Nothing here should be taken to imply deliberate intent to misrepresent
- On the basis of the evidence, you can decide whether intent can be ruled out with a high degree of confidence

- http://www.slate.com/id/2133061/
- http://scientific-misconduct.blogspot.com
- http://www.thejabberwock.org/presshw.htm
- http://www.aaas.org/spp/sfrl/per/per46.pdf
- BBC: http://www.bbc.co.uk/radio4/youandyours/items/01/2006_08_thu.shtml

P&G's publication plan

Original 3 key placebo controlled fracture trials of Actonel


Article

.andomized Trial of the Effects of Risedr
n Women with Established Postmenopausa

J.-Y. Reginster[1], H. W. Minne[2], O. H. Sorensen[3], M. Hooper[4], D. Ethgen[5], S. Pack[6], I. Roumagnac[7], R. Eastell,[9] on behalf of t
Therapy (VERT) Study Group[8]

[1]Centre Universitaire d'Investigation du Métabolisme Osseux et du Cartilage Ar
Metabolic Bone Disease, Bad Pyrmont, Germany; [3]Copenhagen Municipal He
Sydney and Concord Repatriation General Hospital, Sydney, Australia; [8]Coo
ance; [8]University of Florence, Florence, Italy; [9]Copenhagen, Denmark; [9]P
; and [9]University of Sheffield, Sheffield, UK

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trolled study was to determin


EFFECT OF RISEDRONATE ON THE RISK OF
IN ELDERLY WOMEN

VERT-MN

VERT-NA

HIP

A

B

C

VMN VNA HIP A

JOURNAL OF BONE AND MINERAL RESEARCH
Volume 18, Number 6, 2003

Relationship of Early Changes in Bone Resorption to the Reduction in Fracture Risk With Risedronate*

R EASTELL,[1] I BARTON,[2] RA HANNON,[1] A CHINES,[2] P GARNERO,[3,4] and PD DELMAS[3]

ABSTRACT

Changes in the level of biochemical markers of bone resorption with risedronate treatment for osteoporosis were examined as a surrogate for the decrease in fracture risk. Greater decreases in bone resorption markers were associated with greater decreases in vertebral (and nonvertebral) fractures.

Antifracture efficacy of antiresorptive therapies is only partially explained by increases in bone mineral density. Early decreases in bone resorption may also play a role. We tested this hypothesis by measuring two bone resorption markers, the C-telopeptide of type I collagen (CTX) and the N-telopeptide of type I collagen (NTX), in osteoporotic patients in risedronate vertebral fracture trials. We studied 693 women with at least one vertebral deformity (mean age, 69 ± 7 years) who received calcium (and vitamin D if required) and placebo or risedronate 5 mg daily for 3 years. The reductions in urinary CTX (median, 60%) and NTX (51%) at 3–6 months with risedronate therapy were significantly associated ($p < 0.05$) with the reduction in vertebral fracture risk (75% over 1 year and 50% over 3 years). The changes in both CTX and NTX accounted for approximately one-half (CTX, 55%; NTX, 49%) of risedronate's effect in reducing the risk of vertebral fractures in the first year and approximately two-thirds (CTX, 67%; NTX, 66%) over 3 years compared with placebo. The changes in CTX and NTX accounted for 77% and 54%, respectively, of risedronate's effect in reducing the risk of nonvertebral fractures over 3 years compared with placebo. The relationships between vertebral fracture risk and changes from baseline in CTX and NTX were not linear ($p < 0.05$). There was little further improvement in fracture benefit below a decrease of 55–60% for CTX and 35–40% for NTX. The decrease in bone resorption in patients taking risedronate accounts for a large proportion of the reduction in fracture risk. There may be a level of bone resorption reduction below which there is no further fracture benefit. (J Bone Miner Res 2003 [illegible] 1056)

Received in original form May 1, 2002

I Approached the JBMR long long ago

- Only holding replies to correspondence for 1 year
- Editor refused to open evidence bundle
- Altered a (very mild) letter for publication requesting dissociation from 2 abstracts to remove all content

- Lawyers!

www.thejabberwock.org/jbmrs.htm

% change CTX
% change NTX

VMN VNA HIP A

JBMR ONLINE

ASBMR

A publication of the American Society for Bone and Mineral Research

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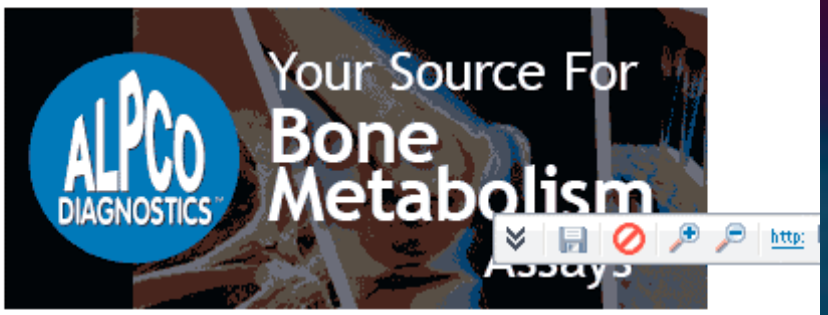


JBMR issues Statement of Concern.

The Journal of Bone and Mineral Research (JBMR), now in its 21st year of publication, provides a forum for papers of the highest quality pertaining to all areas of the biology and physiology of bone, the hormones that regulate bone and mineral metabolism, and the pathophysiology and treatment of disorders of bone and mineral metabolism. The JBMR is the top-ranked journal in its field, with an impact factor of **6.527**.

Statement of concern

- It has come to the attention of the *Journal of Bone and Mineral Research (JBMR)* that questions have been raised about an article published in the *JBMR* (*ref*). Upon reviewing these questions with the authors of the article, the authors have agreed to a statistical reanalysis of the data, upon which the article was based.

% change PINP
% change NTX

VMN VNA HIP B

- Abstract 2003
- Draft publication never published
  - First author declined to proceed

F338

Relationship of Early Changes in Bone Turnover to the Reduction in Vertebral Fracture Risk with Risedronate – The HIP Study.

A. Blumsohn[1], I. P. Barton*[2], A. Chines[3], R. Eastell[1]. [1]University of Sheffield, Sheffield, United Kingdom, [2]Procter & Gamble Pharmaceuticals, Egham, United Kingdom, [3]Procter & Gamble Pharmaceuticals, Mason, OH, USA.

Anti-fracture efficacy of antiresorptive therapies is only partially explained by increases in bone mineral density (BMD). Early decreases in bone turnover may also play a role. We tested this hypothesis by measuring 2 bone turnover markers, the N-telopeptide of type I collagen (NTX) and procollagen type I N-propeptide (PINP), in osteoporotic patients in the risedronate HIP fracture trial. We studied 938 women with a femoral neck BMD T-score

% change NTX

VMN VNA HIP C

- Abstract 2003
- Draft publication never published
  - First author declined to proceed

SA337

Relative Contributions of the Early Changes in Bone Resorption and Later Changes in Hip Bone Mineral Density to the Reduction in Vertebral Fracture Risk with Risedronate. A. Blumsohn[1], I. P. Barton*[2], A. Chines[3], R. Eastell[1]. [1]University of Sheffield, Sheffield, United Kingdom, [2]Procter & Gamble Pharmaceuticals, Egham, United Kingdom, [3]Procter & Gamble Pharmaceuticals, Mason, OH, USA.

Anti-fracture efficacy of antiresorptive therapies is partially explained by increases in bone mineral density (BMD) and partially by decreases in bone resorption markers. The relative importance of these two factors and whether or not their effects are independent is

% change CTX
% change NTX

VMN VNA HIP A

Three manuscripts = same message

- **A**: "The relationship between vertebral fracture risk and **changes from baseline in CTX and NTX** were non linear ($P<0.05$). There was little further improvement in fracture benefit below a decrease of 55-60**%** for CTX and 35-40**%** for NTX."
  "There may be a level of bone resorption reduction below which there is no further fracture benefit."

% change NTX VMN VNA HIP B

Three manuscripts = same message

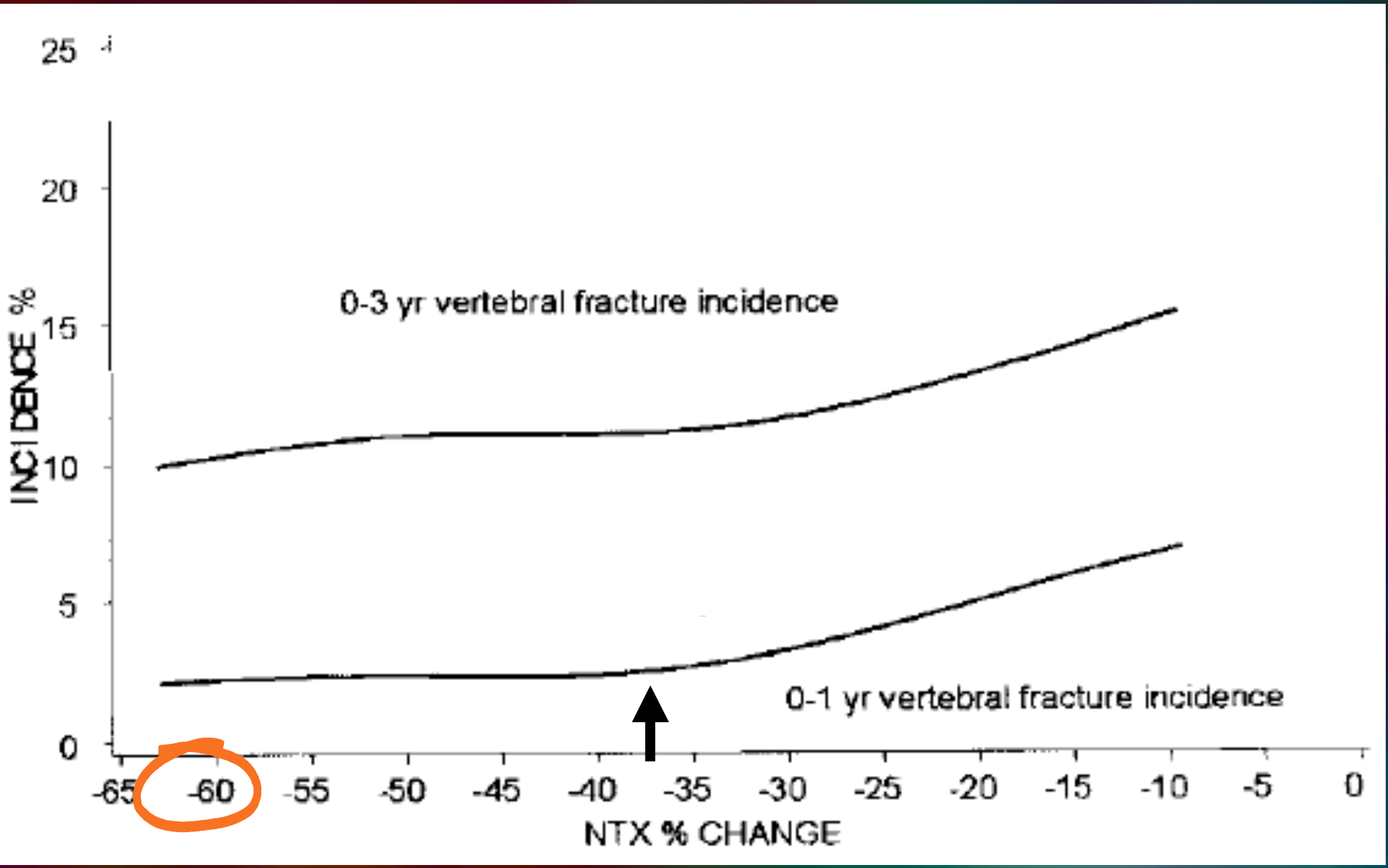
- **B**: "Consistent with findings from the VERT trial, a non-linear function was more appropriate than a linear function for modeling the relationship between early **changes** in NTX and vertebral fracture risk over 3-years (5mg Risedronate, p=0.008).
- There was little further improvement in fracture benefit below a decrease of 30 to 35**%** for NTX."....
- "In conclusion, ...there may be a level of bone resorption reduction below which there is no further fracture benefit." ...
- "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."

% change NTX VMN VNA HIP C

Three manuscripts = same message

- **C**: 5mg Risedronate showed an apparent "threshold" (i.e. fracture incidence is not continually decreased).

- "Statistically, a non-linear function was more appropriate than a linear function for modelling the relationship between vertebral fracture incidence and **NTX changes**".


25
20
15
10
5
0
INCIDENCE %
0-3 yr vertebral fracture incidence
0-1 yr vertebral fracture incidence
-65
-60
-55
-50
-45
-40
-35
-30
-25
-20
-15
-10
-5
0
NTX % CHANGE

Do other bisphosphonates show the same thing

- Merck – investigated in Alendronate studies
  - No such effect found
- Roche – Investigated in Ibandronate studies
  - No such effect found

This is a major issue of science

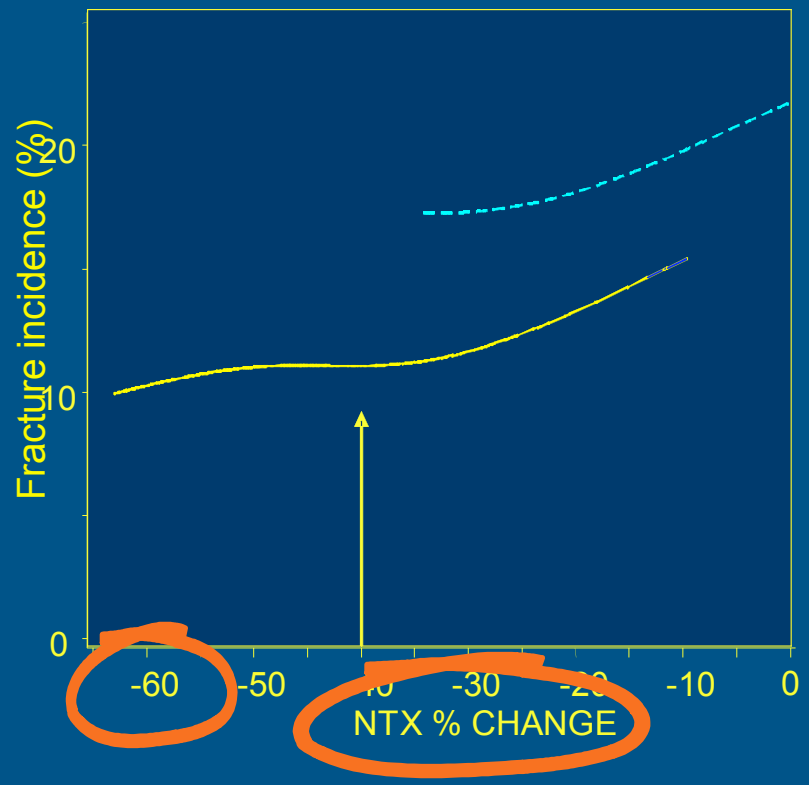
- Determines how drugs is used in practice
- Critical to monitoring of therapy for all bisphosphonates
- If we are ever going to have a chance of using surrogates as an endpoint in registration trials for these drugs, we have to understand how these surrogates work (honestly)

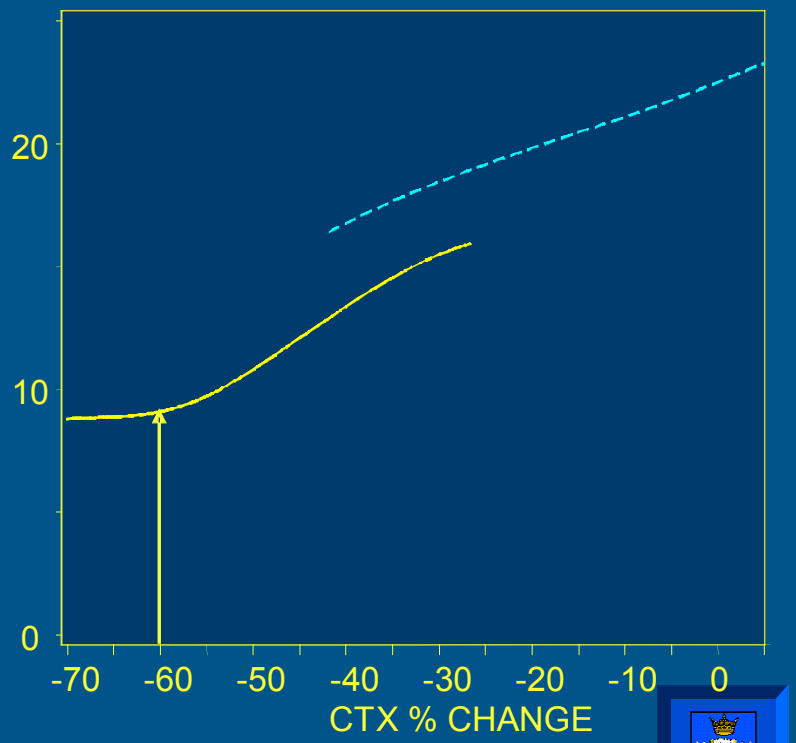
Conclusions re %change and fracture threshold widely discussed

- P&G Press statements
- Educational material
- Prominent in brochures produced by manufacturer of NTX diagnostic test (later bought out by P&G for $400 million)
- Rebuttal to a Merck study in the literature
- Widely discussed by other scientists

New Vertebral Fracture Incidence over 3 Years, vs. 3 to 6 Month Marker % Change From Baseline

Eastell et al, J Bone Miner Res, in press





TREATMENT: ---------- Control ———— Risedronate 5mg

MEDICAL CROSSFIRE®

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SPECIAL EDITION

The FACT Study

Assessing its Applications in the Treatment of Osteoporosis

CME-Certified Activity

PANELISTS

Richard Eastell, MD, FRCP, FRCPath, FMedSci
University of Sheffield;
Northern General Hospital

Robert Lindsay, MD, PhD
Columbia-Presbyterian Medical Center;
Helen Hayes Hospital

Nelson B. Watts, MD
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MODERATOR

Peter L. Salgo, MD
National Television Medical Correspondent;
Columbia University College of Physicians and Surgeons

Jointly Sponsored by

Release Date: February 2005 • Expiration Date: June 30, 2006

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VOL 6 • NO 3 • FEBRUARY 2005

9. At what point does suppressing bone turnover provide no additional benefit?

a. suppression of more than 90%
b. suppression of more than 75%
c. suppression of more than 60% to 70%
d. suppression of more than 40% to 50%

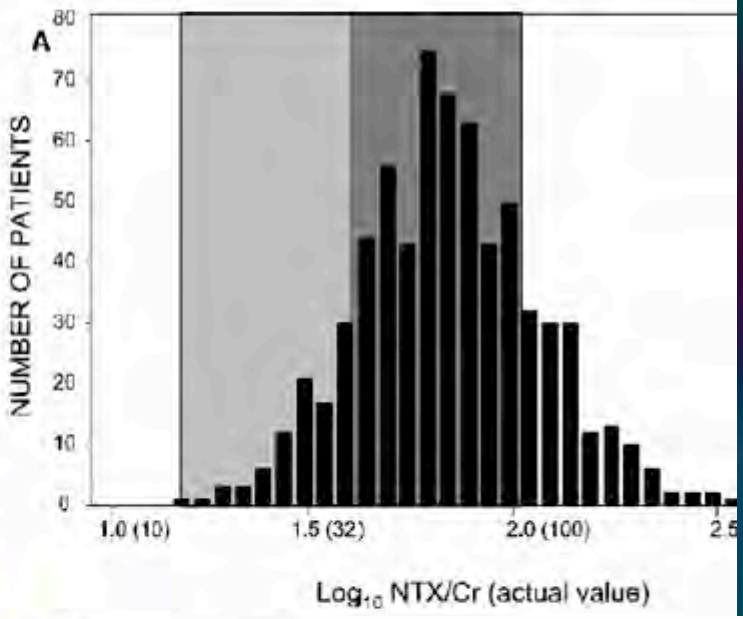
JOURNAL OF BONE AND MINERAL RESEARCH
Volume 20, Number 7, 2005
Published online on February 28, 2005; doi: 10.1359/JBMR.050217

Letter to the Editor

How to Interpret Surrogate Markers of Efficacy in Osteoporosis

To the Editor:

Rosen et al.[1] have made the important point that it is important to compare the efficacy of treatments for osteoporosis in head-to-head studies. They claim that this cannot be done with fracture as the primary endpoint, because it would require samples sizes of around 50,000. The alternative is to compare changes in BMD and bone turnover markers. This is an attractive alternative, but we have learned a lot about the use of these surrogates in the last few years, and so the interpretation of this paper needs further consideration. The first issue is that the change in bone turnover markers is at least as informative as the change in BMD.[2] The authors have focused their analyses on change in BMD. The second is that the relationship between change in these surrogates and fracture risk is not linear: for BMD, a gain of up to 3% is associated with the same fracture risk reduction as a gain of >3%[3,4]; for bone turnover markers, there may be no further benefit from further suppression of NTx/Cr <40%.[2] The authors have evaluated various BMD cut-points but not the cut-points in bone turnover markers. The third issue is that suppression



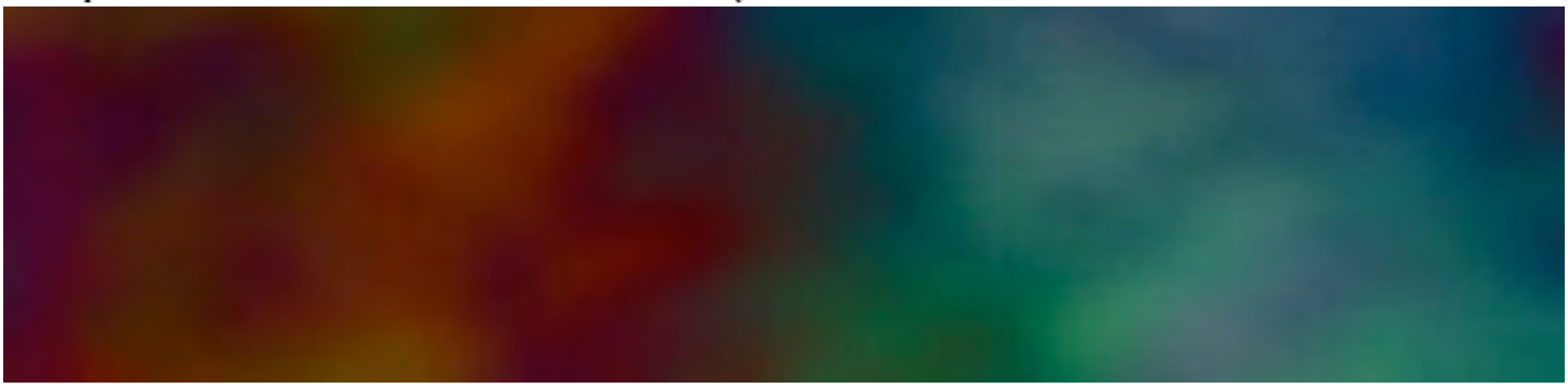
Richard Eastell[1] *and Pierre D Delmas*[2]
[1]*Division of Clinical Sciences (North)*
University of Sheffield
Sheffield, United Kingdom
[2]*INSERM Unit 403*
University Claude Bernard
Lyon, France

JOURNAL OF BONE AND MINERAL RESEARCH
Volume 20, Number 1, 2005
Published online on September 29, 2004; doi: 10.1359/JBMR.040920

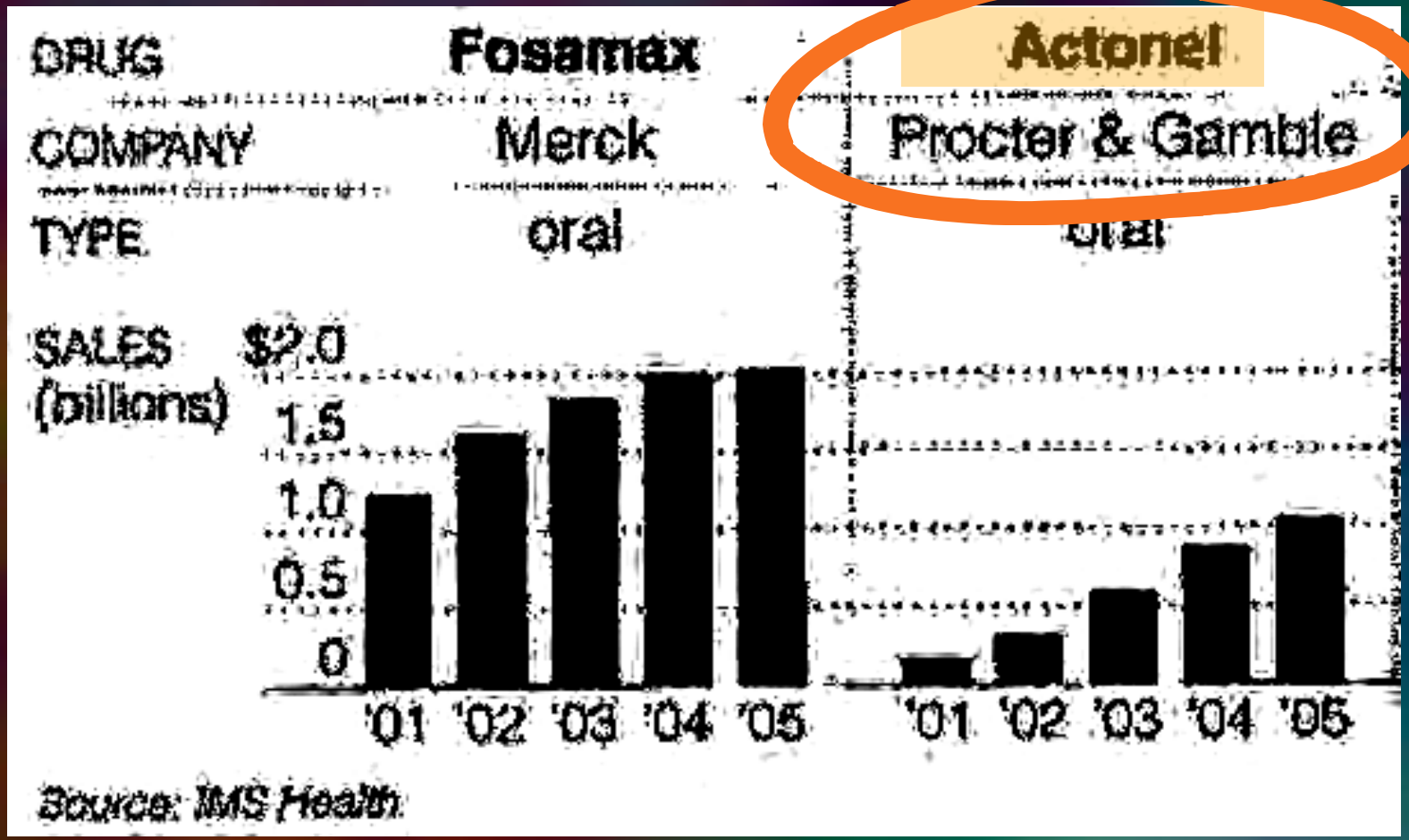
Treatment With Once-Weekly Alendronate 70 mg Compared With Once-Weekly Risedronate 35 mg in Women With Postmenopausal Osteoporosis: A Randomized Double-Blind Study

Clifford J Rosen,[1] Marc C Hochberg,[2] Sydney L Bonnick,[3] Michael McClung,[4] Paul Miller,[5] Susan Broy,[6] Risa Kagan,[7] Erluo Chen,[8] Richard A Petruschke,[8] Desmond E Thompson,[8] and Anne E de Papp,[8] for the Fosamax Actonel Comparison Trial Investigators

ABSTRACT: Once-weekly alendronate 70 mg and once-weekly risedronate 35 mg are indicated for the treatment of postmenopausal osteoporosis. These two agents were compared in a 12-month head-to-head trial. Greater gains in BMD and greater reductions in markers of bone turnover were seen with alendronate compared with risedronate with similar tolerability.



Bisphosphonate Market



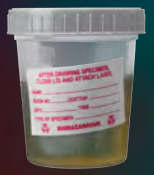
In the case of bone

Treatment

?

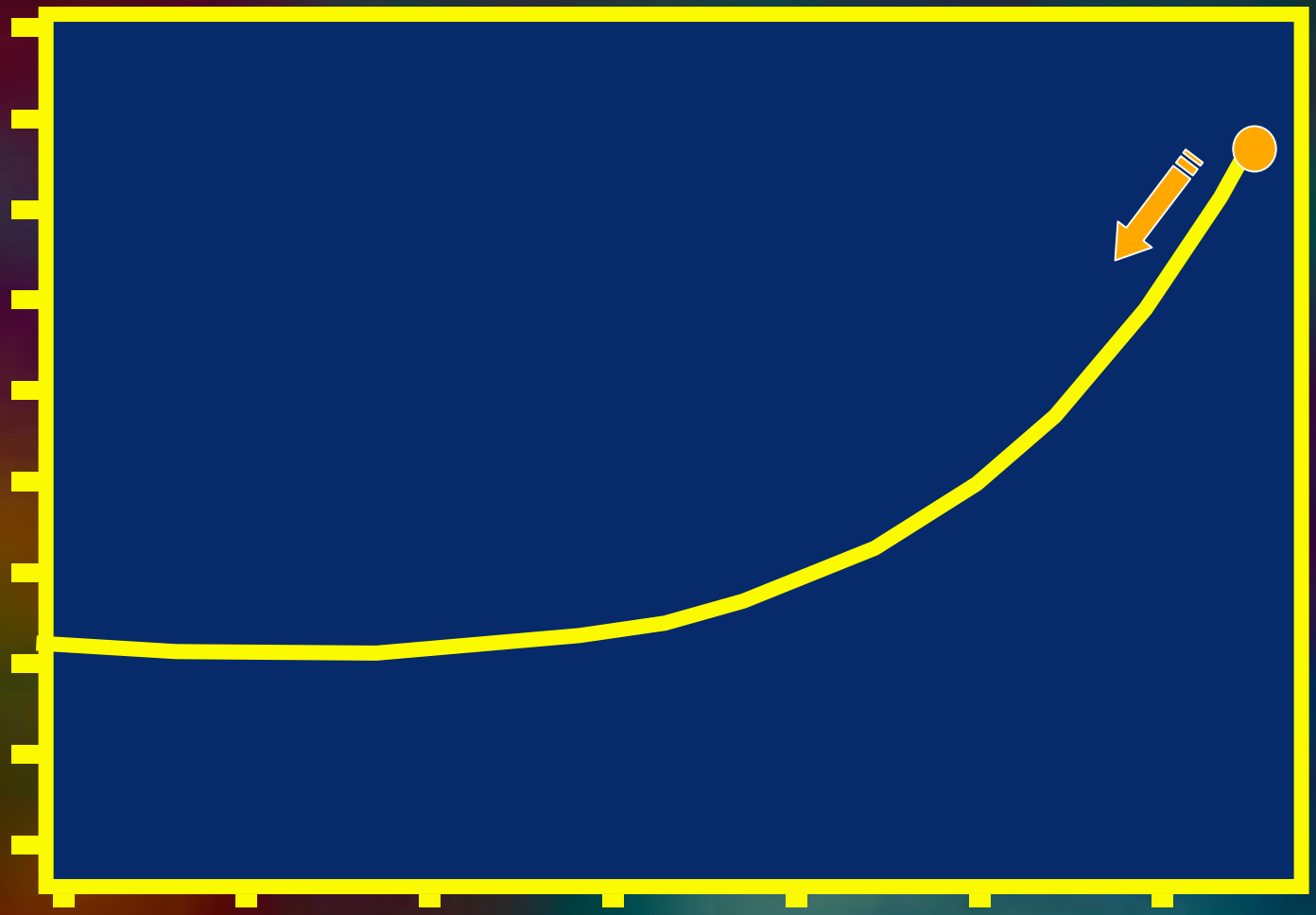
Bone Fractures

Bone Resorption

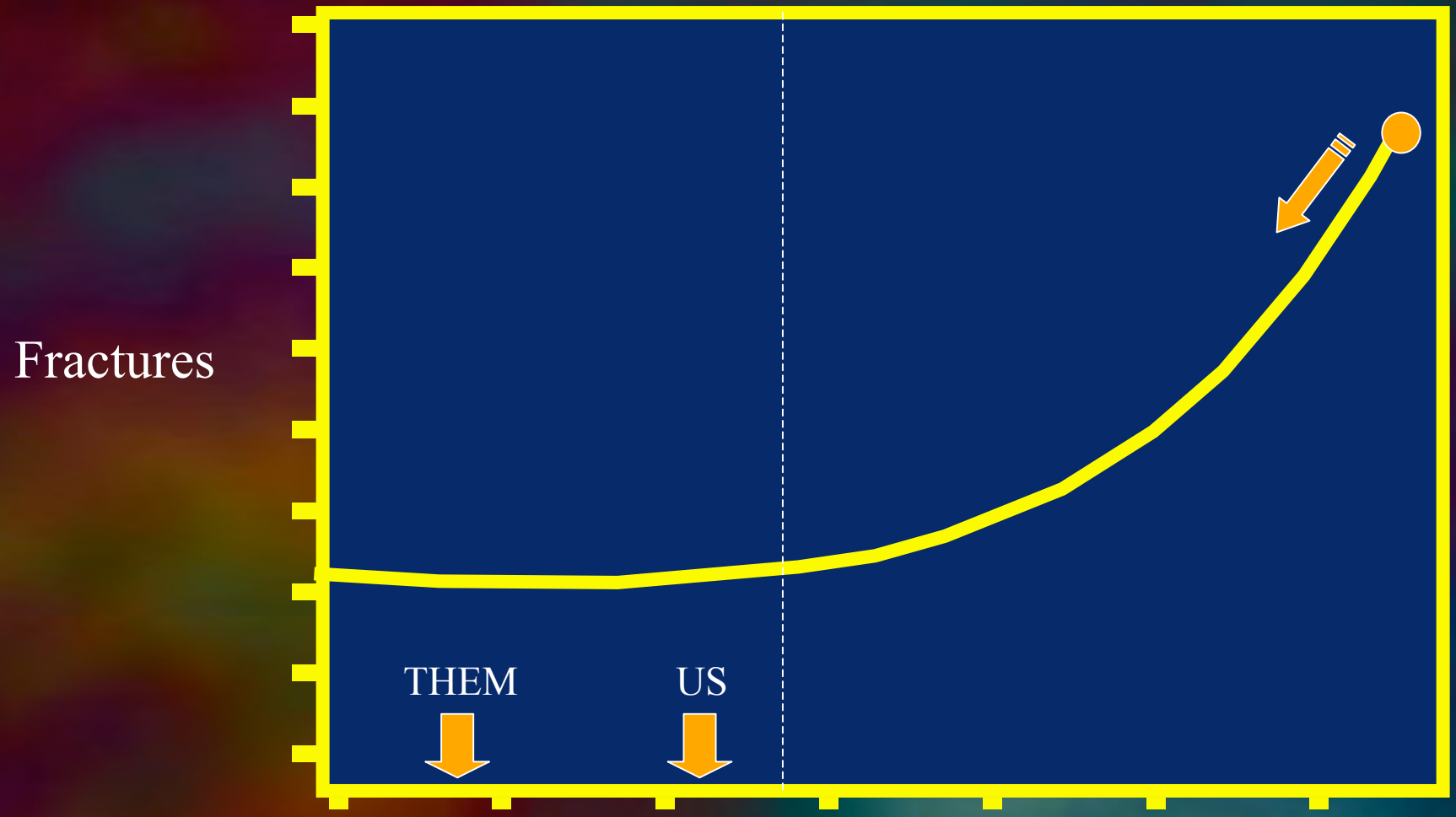


P&G Product weaker

Wouldn't it be lovely if .....



Wouldn't it be lovely if .....



THE PROBLEM

- We were generating the data blind to randomisation in the FDA registration study
- To interpret our own data would need
  - Randomisation codes (who got drug/placebo)
  - Event codes (who had a fracture)
- These data were held by the company
- The expectation as that they would give these to us

From: "Richard Eastell" <r.eastell@sheffield.ac.uk>
To: barton.ip@pg.com
CC: "Aubrey" <ablumsohn@sheffield.ac.uk>
Subject: RE: NTX/CTX data
Date: Mon, 27 May 2002 09:17:04 +0100
Message-ID: <NAEDLHFPJIKKALPANFLPOEDNDCAA.r.eastell@sheffield.ac.uk>

I was discussing our work with a US investigator (who will remain anonymous) who was really surprised when I told him that all the analyses for the IOF presentation were done by P&G employees. I told him that I had worked with you and Simon extensively on the Risedronate database and that I thought you adhered to the highest principles. However, I think that to avoid criticism in the future it would be good if we could say that we had done the analyses independently. I couldn't possible do these, but I think that Aubrey Blumsohn could

From: barton.ip@pg.com [mailto:barton.ip@pg.com]

Sent: 14 June 2002 13:37

To: Richard Eastell

Subject: Re: HIP analyses

No, we do not intend for someone else to the analysis. As far as I'm aware, the Alliance is very transparent in the analyses we perform. We always clearly explain what statistical methods have been undertaken and are happy to share with as many external people as possible. …... Also, the FDA never perform our primary analyses and write our clinical reports.

Please don't take the last point the wrong way. I just feel that we're being very clear in what we are doing and don't need to ask an independent person to analyse the data just to make a few people happy.

From: manhart.md@pg.com [mailto:manhart.md@pg.com]

Sent: 08 July 2002 15:02

To: Richard Eastell

Subject: Re: HIP data analysis

Richard

I think we should look carefully at the pros and cons of Dr. Blumshon conducting the analysis you refer to. One the plus side it does add an extra layer of external "credibility". With this however, Industry looses the opportunity to demonstrate its ability to be a true partner in scientific endeavours. Beyond this, the practical issues to training up a new statistician and the corresponding delay in "time to result" may make the option difficult.

Finally, transferring databases which the Compnay has invested hundreds of millions of dollars to obtain is not something to be taken lightly. That's not to say it can't be done, but the reasons must be sufficiently important to justify it.

*This study was previously presented in abstract form at the 23rd Annual Meeting of the American Society for Bone and Mineral Research, Phoenix, Arizona, USA, October 12–16, 2001.

Dr Eastell has received research funding from Aventis and Procter & Gamble Co. Drs Barton and Chines are full-time employees of Procter & Gamble Co. All other authors have no conflict of interest.

We would like to acknowledge the help of Dr Simon Pack and Lisa Bosch of Procter & Gamble Pharmaceuticals, as well as the help of Oldham Hospital Clinical Chemistry Department for measuring urinary CTX and creatinine. This study was supported by grants from Procter & Gamble Pharmaceuticals, Inc. (Cincinnati, OH) and Aventis Pharma, Bridgewater, NJ. Employees of Procter & Gamble Pharmaceuticals and Aventis Pharma participated in the design and execution of the study, the analysis of the data, and the preparation of the manuscript. All authors had full access to the data and analyses.

Can I have my data?

No

I personally would like us all to solely concentrate on getting publication briefs for the two manuscripts written by end of June. These briefs would have to go through internal review and will result in additional questions/analyses. Therefore, in terms of writing the actual manuscripts this will not happen until July. I think we should concentrate on each manuscript separately.

I agree with you that we should explore the data more. I would be interested in receiving detail on your thoughts in terms of trying to understand the data more. I'm happy to perform additional analyses etc. However, this shouldn't delay writing the publication briefs. We do have all data available in one dataset (i.e. treatment group, fracture data, BTM data, BMD data, baseline data, ...).

In terms of NTX conversion factor, this should only relate to publication 3 (i.e. does baseline NTX predict fracture incidence and treatment effects). With regard to publication 2 (i.e. BMD and BTM data) the analyses do take into account the variability of the measurements and I don't think we need to worry about the conversion factor as the Z.Li model looks at the treatment effect (i.e. mean difference between treatments for both NTX and BMD).

If you would find it easier to talk via phone, please let me know your availability. As you can tell, I really want to get these manuscripts written and submitted before a) we move onto other projects, b) our competitors pip us to the post and c) ASBMR. We have really interesting and unique data and I don't want us to be delayed/distracted.

Subject: Re:HIP Trial: BTM vs Fx
To: Aubrey Blumsohn <ablumsohn@sheffield.ac.uk>
CC: Richard Eastell <r.eastell@sheffield.ac.uk>
From: barton.ip@pg.com
Date: Thu, 19 Jun 2003 09:31:42 +0100

Dear Aubrey

Hope all is well. I've just spoken to Richard about you wanting to gain more of an insight into the data prior to writing a pub brief. I explained that 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. However, I don't want to be seen as hiding any of the data so we agreed that you should come down for 2-3 days to our R&D site where you and I can a) look at the data in more detail, b) perform the analyses you require and c) write up the publication briefs.

It would be good if this could happen as soon as possible, definitely within the next 4-5 weeks. Below I've listed dates which I am available.

I also note that you disagree with the approach we have taken to data analysis. You will realise that when we submit the manuscript to a journal that you will need to sign an authorship agreement form stating that you are in full agreement with the work. If you wish to be a coauthor then you need to work towards a resolution of the issues we described in our letter.

You mention the issue of probity and from your previous e-mails I understand that your major concern is that you have not had access to the original data. I have checked with Aventis and with other pharmaceutical companies in the field of osteoporosis for their guidelines to publication. They state that they take the approach described in the PhRMA guidelines and that in these guidelines there is not access to the data (other than those from your centre) for investigators. I think that the approach we have taken for this manuscript of working closely with the statisticians to identify the best approach to analyse the data is an example of best practice.

Please let us know whether you still wish to be co-author on this manuscript,

Yours sincerely

R Eastell

Richard Eastell
Professor of Bone Metabolism

RadcliffesLeBrasseur

Messrs McKay Law
Solicitors
41 St Paul's Street
LEEDS
LS1 2JG

9 June 2005

Our Ref: CJW2/MD/900100.87

Your Ref: SM DO

L 250363 v1

Dear Sirs

Re: Our Clients - Professor R Eastell

We act for the Medical Protection Society on behalf of its member Professor Eastell. We have been passed a copy of your letter to Professor Eastell dated 25th May, asking for certain raw data underlying certain abstracts, which you identify.

As you say, your client has asked for this information before. But it is not information to which Professor Eastell has access. It belongs to the pharmaceutical companies. As your client knows, Professor Eastell has already requested the data from the Pharmaceutical companies. (Profesor Eastell explained this in a letter to your client dated 13th December 2004, a copy of which is enclosed). Therefore Professor Eastell regrets that he is unable to help.

Yours faithfully,

RadcliffesLeBrasseur

- Various evidence emerged that the findings could not be correct, particularly at that stage in study B where it turned out that:
  - no fractures at all with NTX change bigger than -60%
  - This constituted about 40% of the treated arm
  - All these would have fallen off the left hand end of the plots
- Tape recorded much of the process
- Eventually went to the press

THURSDAY, FEBRUARY 23, 2006

THE WALL STREET JOURNAL.

Scientist Presses Claim P&G Misrepresented Actonel Data

By Sarah Ellison

A scientist hired by **Procter & Gamble** Co. who alleges his data were misrepresented in P&G research abstracts for the osteoporosis drug Actonel is meeting with congressional staffers and the National Institutes of Health this week to press his case.

Aubrey Blumsohn, a senior lecturer and bone-metabolism specialist at the University of Sheffield in the United Kingdom, says P&G misrepresented the author was one of Dr. Blumsohn's colleagues, that prompted Dr. Blumsohn's complaints after his analysis of similar data found different results. Dr. Blumsohn was suspended from his research position last fall after he aired his complaints in the U.K. media.

Tom Milliken, a P&G spokesman, said the company would provide its data for independent review, but it believes the review will validate its statistical approach.

P&G said in a statement, "In hindsight, we should have dedicated more


Health
Watch Dog
Teal

Bland: 'strange analysis'

He tells *You and Yours*: "It is a strange analysis because they say they're not going to do what you'd think of as a normal statistical analysis, but something that doesn't allow them to actually test whether anything is happening."

Asked about a plateau effect, Professor Bland [illegible] "Well their statistics don't demonstrate it — it is just a pict[illegible] effect. There's not[illegible] how they got it [illegible] You just have to ta[illegible]

He says he w[illegible] passed the paper [illegible] Jane Hutton, cha[illegible] University's statisti[illegible] told *The Times Hi*[illegible]

"We stand by our conclusions published in the *JBMR*... Any conclusions reached in exploratory analysis are, and should be, open to legitimate academic and scientific debate and further study. In fact, an independent review of the data is ongoing, which we believe will confirm the validity of the statistical approach

THE TIMES HIGHER FEBRUARY 24 2006

Experts cast doubt over scientists' claims for Actonel

Significant doubts over scientific claims made about Procter & Gamble's osteoporosis drug Actonel were raised this week after a report by *The Times Higher* last year that Sheffield University researchers had put their names to findings without having carried out independent analyses of the drug-trial data.

In interviews due to be broadcast this week on *You and Yours*, the Radio 4 consumer affairs programme, and in others given to *The Times Higher*, experts argue that there is insufficient evidence to warrant the conclusions on Actonel published by Sheffield's Bone Metabolism Research Unit. The claims have helped boost the drug's standing against its main rival, Fosamax, which is made by Merck and Co.

Actonel and Fosamax act to reduce the risk of fractures by increasing bone mineral density and reducing bone "turnover" — the rate at which bones break down and repair themselves. It is generally understood that Fosamax, the market leader, reduces bone turnover most effectively. But research authored by Richard Eastell, head of the Bone Metabolism Unit, has claimed that there is a "plateau effect" — a point beyond which any reduction in turnover does not lower fracture risk — which suggests that Actonel is not necessarily less effective than its rival.

Professor Eastell reported the conclusions, which P&G disseminated widely, at the 2001 conference of the American Society for Bone and Mineral Research, then again a year later at the annual meeting of the International Osteoporosis Foundation. In 2003, they were published in the *Journal of Bone Mineral Research* (*JBMR*). Now, senior academics have expressed concern over the conclusions.

Bill Fraser, head of the metabolic bone disease department at the Royal Liverpool University Hospital, was at the 2001 meeting. He tells Radio 4: "When I first saw the data, I wondered if there was a problem with the measurements. I was concerned that the blood and urine tests weren't sensitive enough, not good enough to be able to make the conclusions that Richard had come to."

Martin Bland, professor of health statistics at York University, analysed the *JBMR* paper.

Bland: 'strange analysis'

He tells *You and Yours*: "It is a strange analysis because they say they're not going to do what you'd think of as a normal statistical analysis, but something that doesn't allow them to actually test whether anything is happening."

Asked about a plateau effect, Professor Bland says: "Well, their statistics don't demonstrate it — it is just a picture of a plateau effect. There's nothing to tell you how they got it from the data. You just have to take it on trust."

He says he would not have passed the paper for publication. Jane Hutton, chair of Warwick University's statistics department, told *The Times Higher*: "There is no evidence in this paper to justify the claim that there is a threshold for decrease in bone resorption [turnover] and the associated risk of fractures."

This week P&G said: "This is not about our product's safety or fracture-reduction benefits, which have been proven in one of the largest clinical trials programmes for an osteoporosis therapy.

"We stand by our conclusions published in the *JBMR*... Any conclusions reached in exploratory analysis are, and should be, open to legitimate academic and scientific debate and further study. In fact, an independent review of the data is ongoing, which we believe will confirm the validity of the statistical approach used, and the conclusions reached, on the basis of the database studied."

Professor Eastell declined to comment, but he had indicated to colleagues that he had worked closely with the P&G statisticians to identify the best approach to analysing the data.

www.bbc.co.uk/radio4/youandyours

"P&G has a very legitimate proprietary interest in these clinical trial data. It is standard industry practice to limit access to the raw data by external researchers. Typically, analyses developed by or in collaboration with external researchers will be performed by company statisticians, and the results shared with the researcher. Occasionally, the researcher is given temporary and limited access to the data, to perform the analyses directly.

"Our policy is to allow external researchers sufficient access to the data and to perform those analyses necessary for them to be confident and comfortable with the conclusions they state in scientific communications.

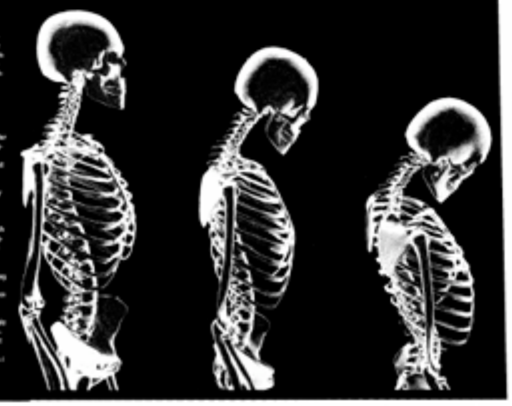
"Dr Blumsohn

The Observer 4 December 2005

How the drugs giant and a lone academic went to war

Worrying power games are at the heart of Procter and Gamble's relationship with academics, alleges the scientist investigating its billion-dollar osteoporosis treatment. **Jo Revill** reports

Osteoporosis: the facts



The battleground: the medicine, the HQ and the scientist

The Ohio headquarters of Procter & Gamble, which ... says Dr Aubrey Blumsohn, right, omitted crucial data from his research on Acto...

'If a research partnership is to be a genuine one, there has to be complete openness,' said a senior professor

'I thought I'd never walk again'

Read on...

Researchers to get a bill of rights from P&G

THE TIMES HIGHER FEBRUARY 24 2006

Revelations that academics had published findings on a drug without full access to trial data have led Procter & Gamble to make a commitment to transparency and integrity. **Phil Baty** reports

Pharmaceutical giant Procter &

practice" to limit external access

? Threats

- 1 month after the Bill of Rights, P&G lawyers apparently approached the University
  - I had acquired partial data which they "owned" without their consent
  - I had to return it
  - University states P&G may sue if not returned

- Resigned from Academic post April 2006 (after being suspended for 6 months)
- P&G supplied all the data underlying the three publications

Questions/Allegations?

1. Authors denied proper (or any) access to raw data. Declaration to journal false.
2. All graphs scaled so as to omit around 45% of data (on the left side) in treated arm
3. There is no evidence for a threshold or plateau for NTX change as stated
4. [There is no evidence of a threshold or Plateau for CTX change as stated – paper A only)
5. Unclear what “smoothing factor” applied to nice curves - it is possible to make them take any shape one wishes

Several approaches to analysis
1 – test for plateau at -35% change

- Test for plateau at region stated by P&G (-35%)
  - Cox regression splitting NTX change into two variables
    - a if X>-35 then a=x else a=-35
    - b if X>-35 then b=0 else b=X+35
- Conclusion
  - No evidence for a plateau (in any study)

Several approaches to analysis
2 – open analysis

- Open analysis
  - Model relationship between time to fracture and NTX change on active treatment
  - As many models as you like
- Conclusion
  - No evidence for a plateau (in any study)

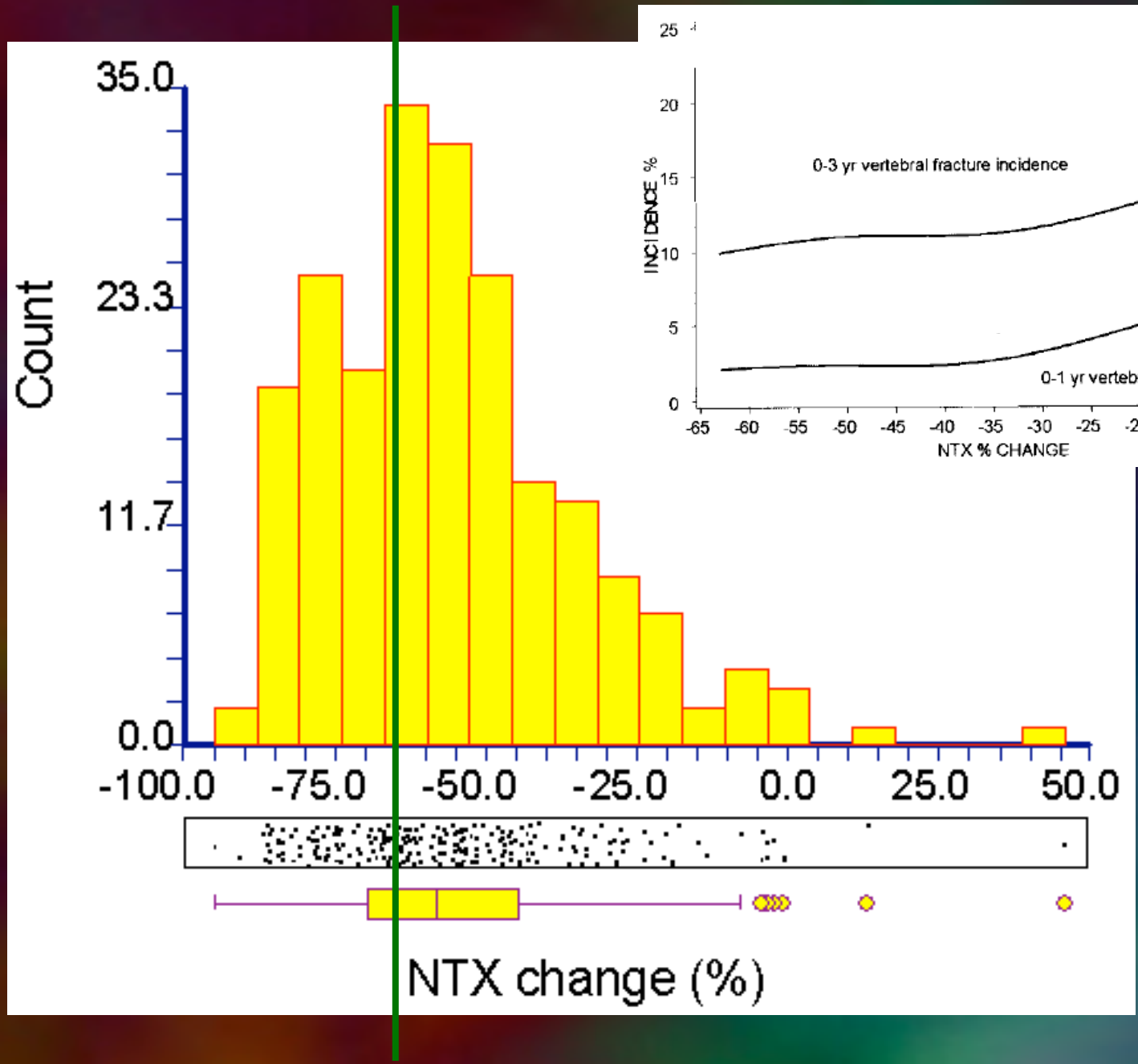
Several approaches to analysis

3 – simple visual inspection raw data plots

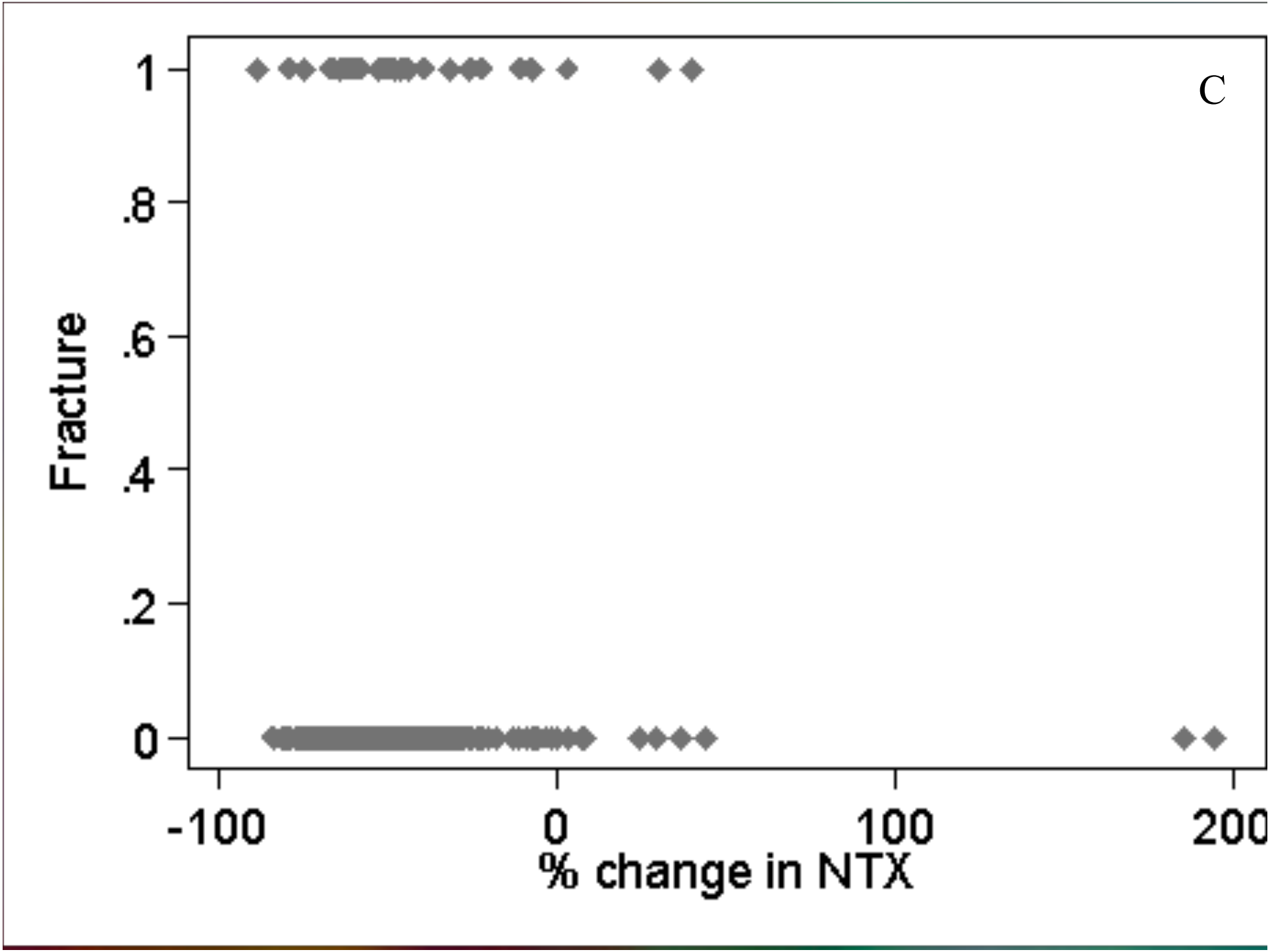
- Conclusion
  - No inkling of a plateau (in any study)

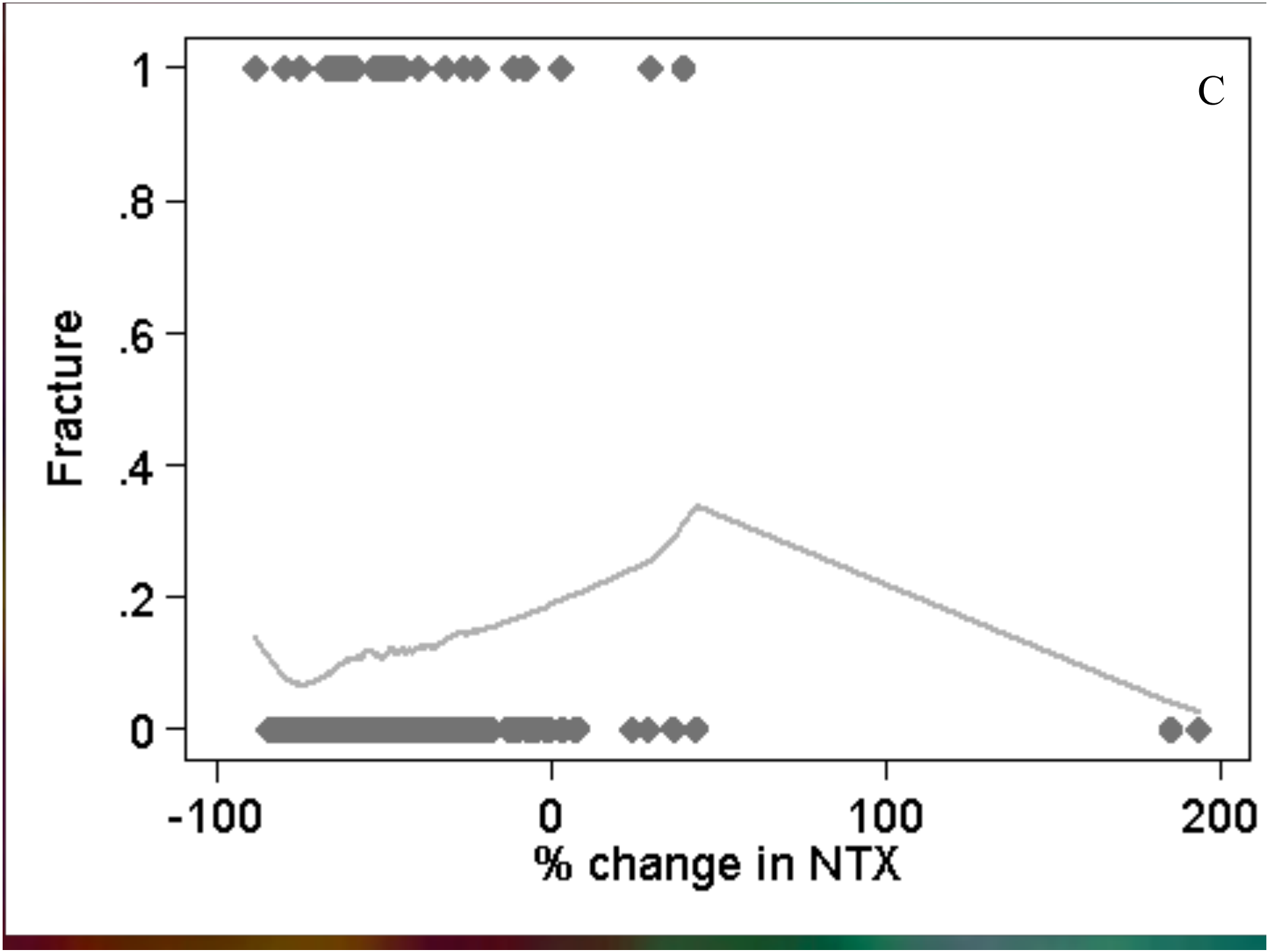
Several approaches to analysis
4 – Graphical analysis

- Try to reproduce P&G graphs
  - Impossible


35.0
23.3
11.7
0.0
Count
-100.0
-75.0
-50.0
-25.0
0.0
25.0
50.0
NTX change (%)

25
20
15
10
5
0
INCIDENCE %
0-3 yr vertebral fracture incidence
0-1 yr vertebral fracture incidence
-65
-60
-55
-50
-45
-40
-35
-30
-25
-20
-15
-10
-5
0
NTX % CHANGE


C
Fracture
1
.8
.6
.4
.2
0
-100
0
100
200
% change in NTX


C
Fracture
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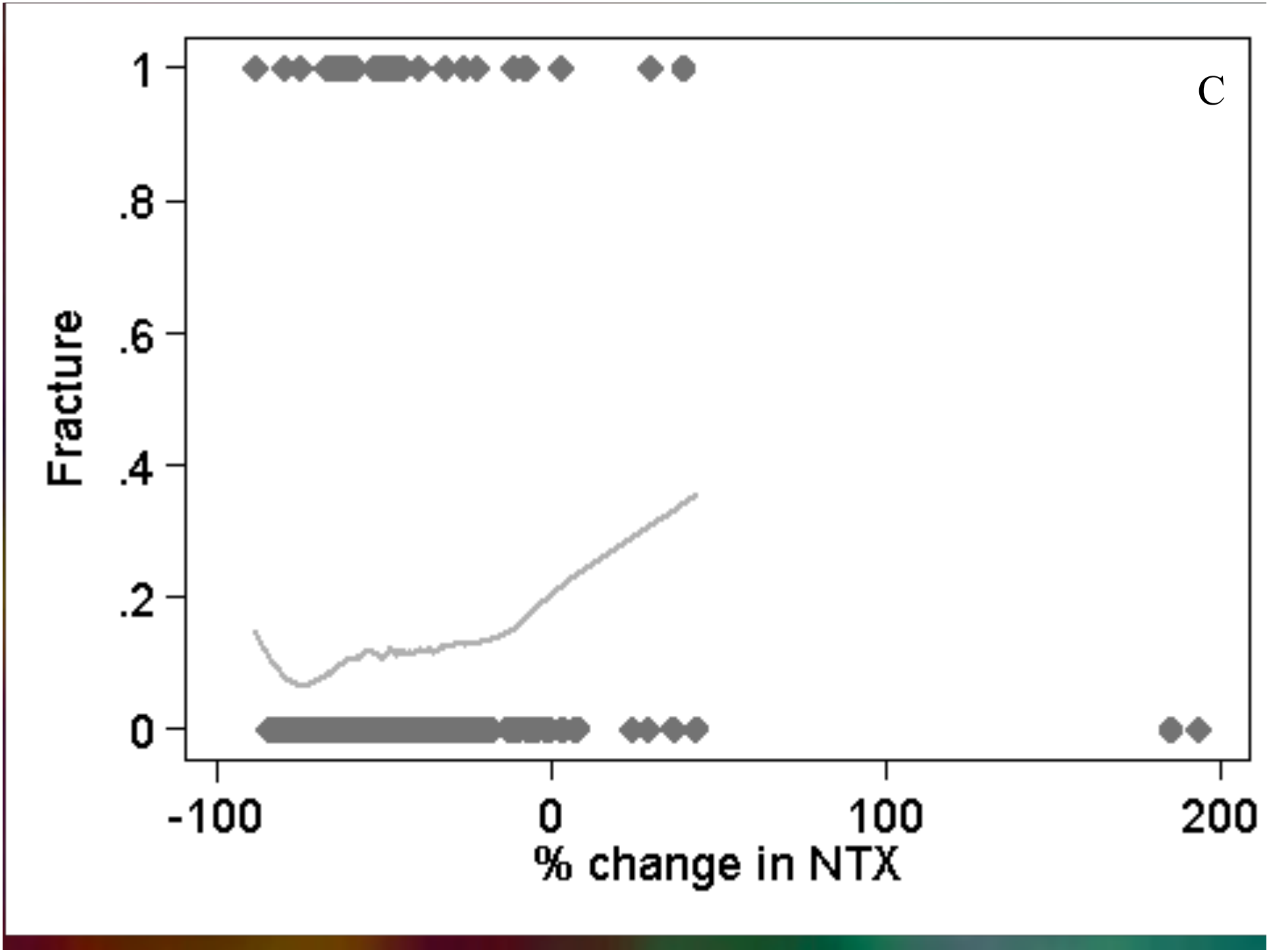
.4
.2
0
-100
0
100
200
% change in NTX


C
Fracture
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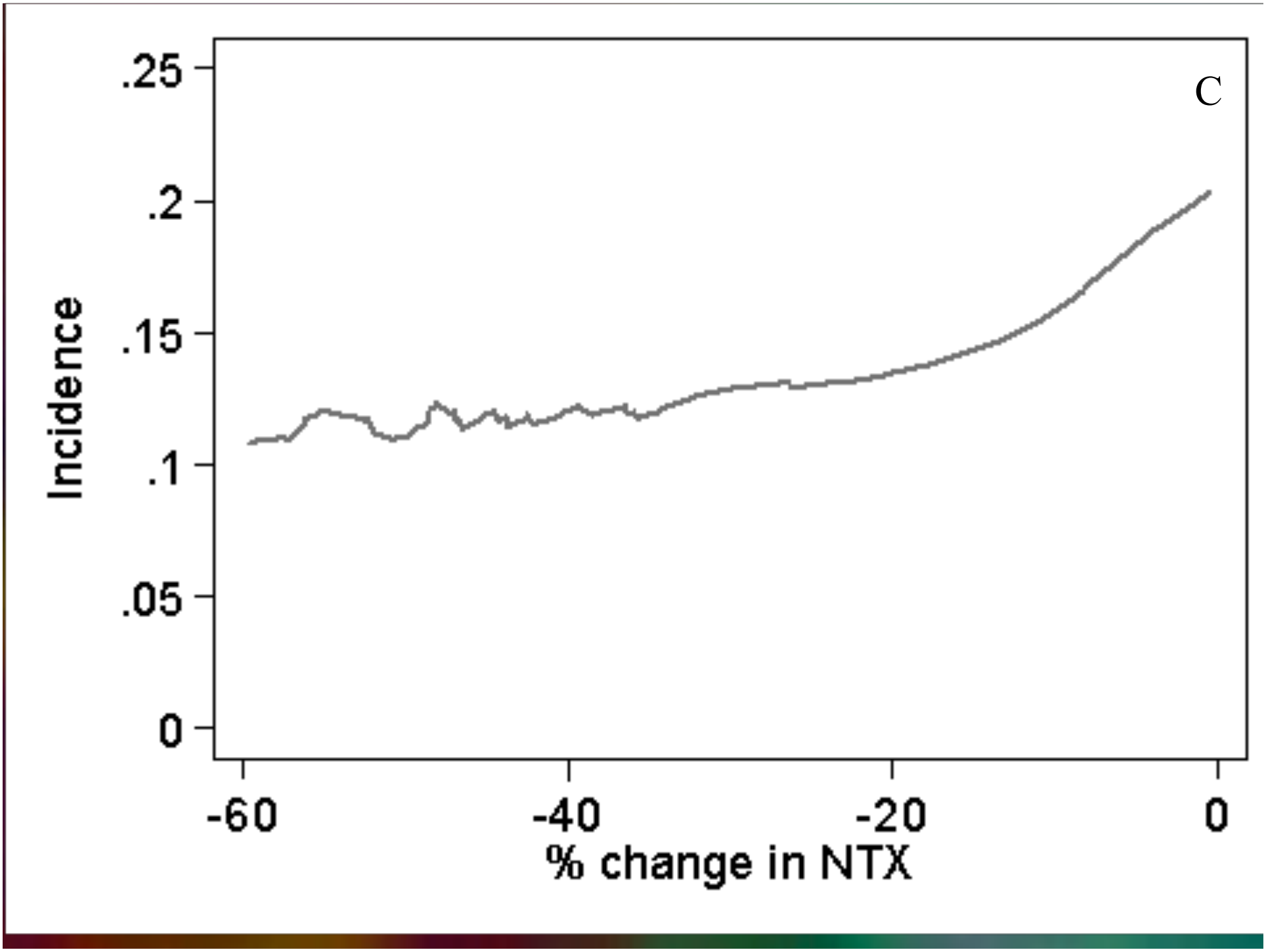
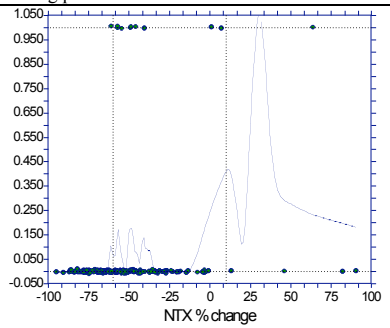
.8
.6
.4
.2
0
-100
0
100
200
% change in NTX

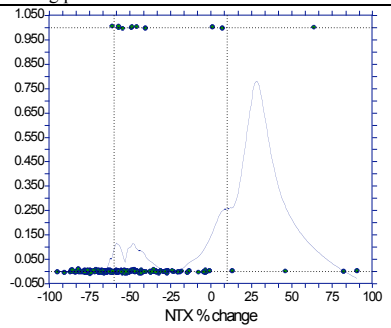

C
.25
.2
.15
.1
.05
0
Incidence
-60
-40
-20
0
% change in NTX

B

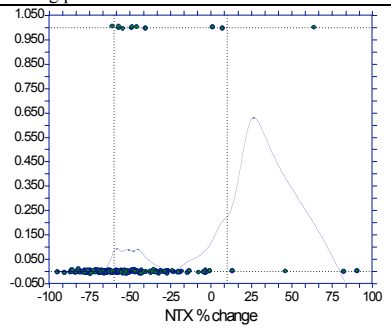
Smoothing parameter 10%



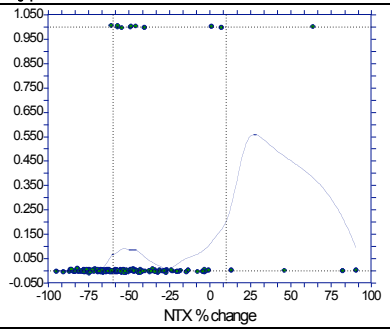
Smoothing parameter 20%



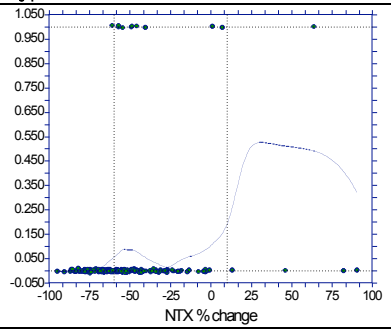
Smoothing parameter 30%



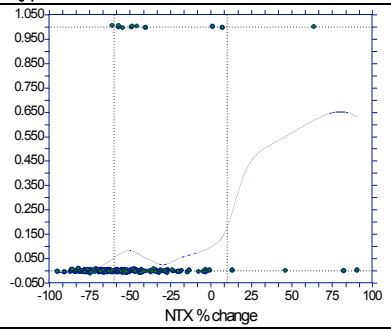
Smoothing parameter 40%



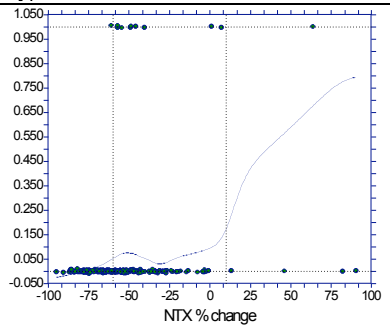
Smoothing parameter 50%



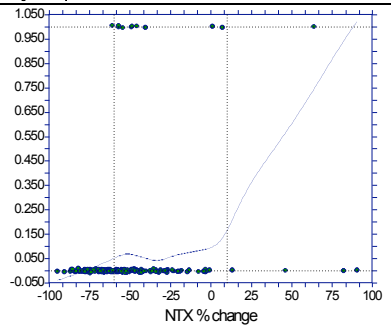
Smoothing parameter 60%



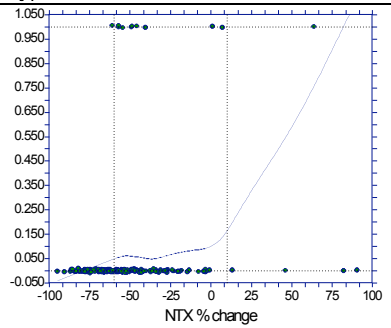
Smoothing parameter 70%



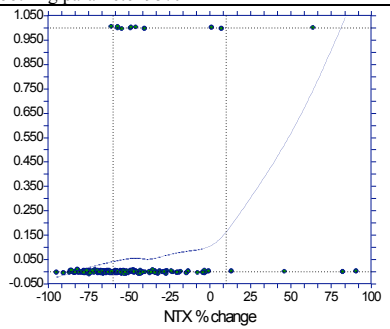
Smoothing parameter 80%



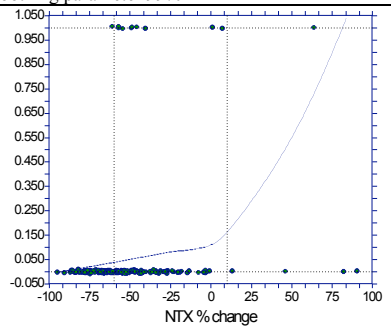
Smoothing parameter 90%



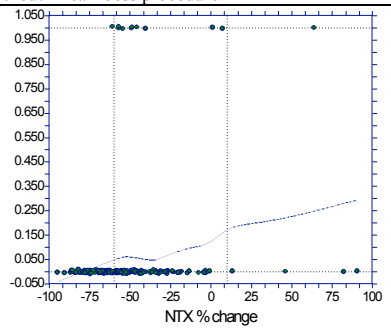
Smoothing parameter 95%



Smoothing parameter 99%



90% but linear loess procedure



B

Relationship of fracture risk to change in bone resorption with risedronate in the HIP study - is there a plateau response?

Authors: A. Blumsohn[1], J. L. Hutton[2]
[1]Sheffield Teaching Hospitals, Sheffield, UNITED KINGDOM,
[2]Department of Statistics, University of Warwick, Coventry, UNITED KINGDOM.

Understanding the determinants of bisphosphonate-induced change in fracture risk is a prerequisite [illegible] previous abstract (Blumsohn, Barton, Chi[illegible]. JBMR 2003;18 S2:S89), and draft publications [illegible] light on the relationship between change in bone resorption (uNTX/Cr) and fracture risk in the [illegible] 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[illegible]asing when NTX decreases beyond -30% (%ΔNTX < -30%), and the relation[illegible]tion linear [illegible] 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 unlicensed (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 data plots presented to authors by the sponsor). However 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[illegible]ediction for fracture by %ΔNTX on [illegible]ther for a -30% threshold ([illegible]33/255 events) or a -40% thr[illegible]0.013, 19/314 events). No significant relationship between %ΔN[illegible]V# [illegible]und by comparison of medians or regression models (all P >0.22).

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

Author Disclosure Block: A. Blumsohn: Study funded by Procter & Gamble Pharmaceutical[illegible]

Dr Purple incident

- Enter **Dr C Purple** at P&G
- Wrote to meeting organizers in background asking for our COI statement to be removed
- Meeting organizers did this
- Later restored
  - "we were misled" by P&G.

Patient consent

- Declined to supply a copy of the wording of patient consent forms
  - “a very unusual request”
  - “The research did not directly involve clinical research in patients”
- Were trial participants aware that the data derived from their risk was not open to scrutiny
  - By authors
  - By regulators
- Would they have participated had they known this?
- Did they consent to these measurements?

Can I place the raw data in public domain?

- Refusal

Can I have the confounding variables?

- Not supplied

% change CTX
% change NTX

VMN VNA HIP A

JBMR ONLINE

ASBMR

A publication of the American Society for Bone and Mineral Research

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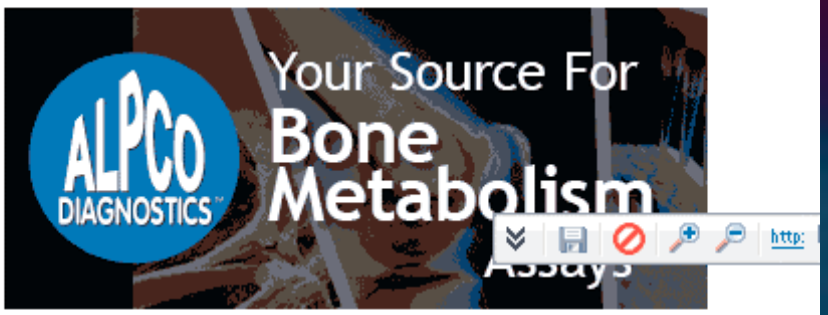


JBMR issues Statement of Concern.

The Journal of Bone and Mineral Research (JBMR), now in its 21st year of publication, provides a forum for papers of the highest quality pertaining to all areas of the biology and physiology of bone, the hormones that regulate bone and mineral metabolism, and the pathophysiology and treatment of disorders of bone and mineral metabolism. The JBMR is the top-ranked journal in its field, with an impact factor of **6.527**.

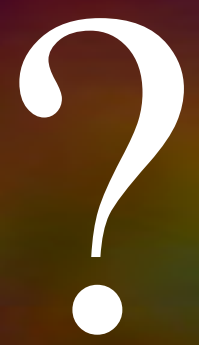
Input (data)

Specific hypotheses

Defined statistical method

Specific outputs

Report honestly



“If they can get you answering the wrong questions, the answers don't matter”

(Pynchon T, 1995 Gravity's Rainbow. ISBN 140188592)

- When Public relations people get involved in science – they make things worse

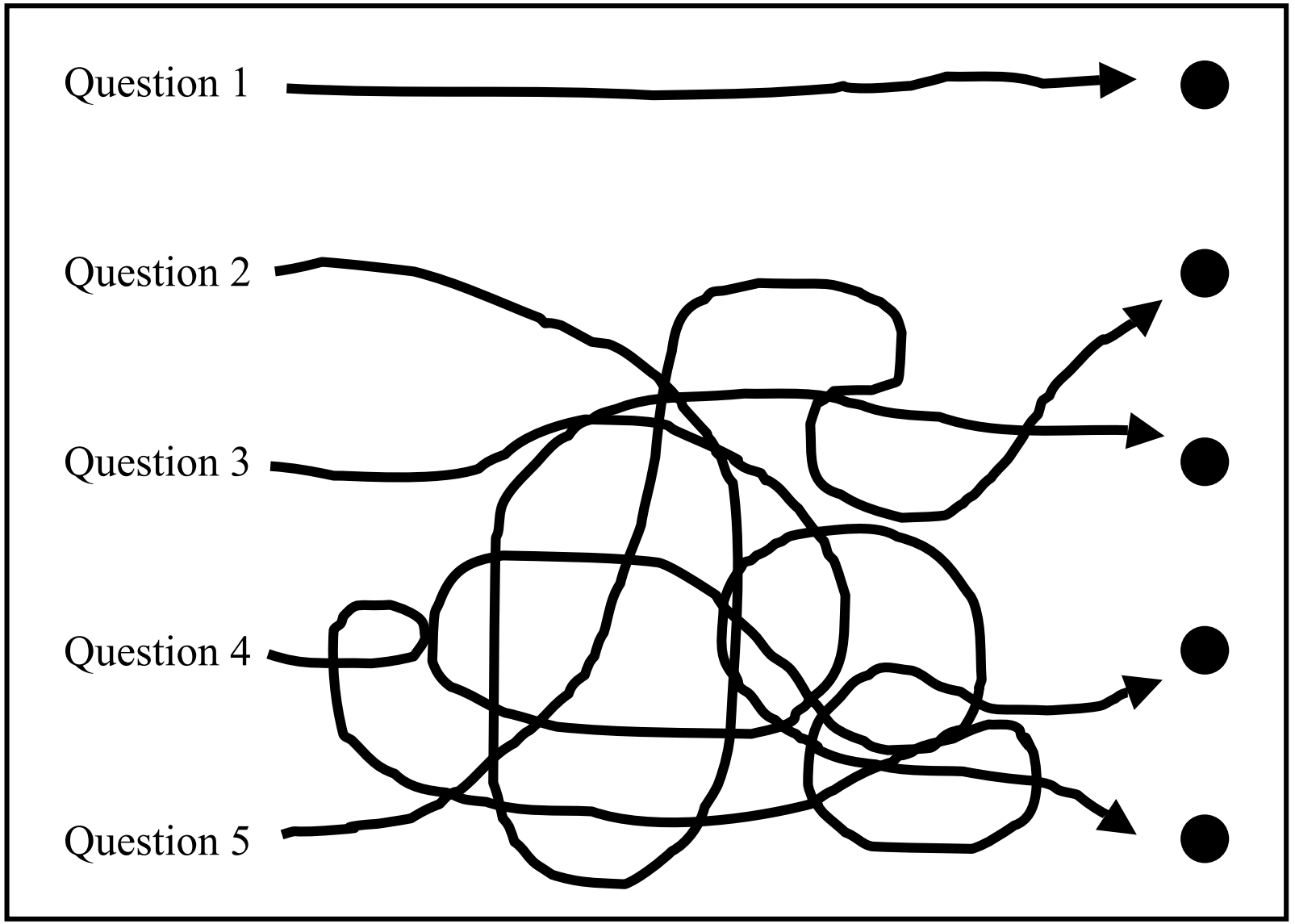
Admissions

1. Authors denied access to raw data – yes
   Declaration to journal false - yes
2. Graphs scaled to omit 45% of data - yes
3. No evidence for the stated plateau for NTX change on treatment as stated - yes
4. No evidence for the stated plateau for CTX change on treatment as stated - yes
5. "Smoothing factor" on graphs – not discussed

Official answering session

A

Follow the arrow to the appropriate dot



Official answering session

B

Follow the arrow to the appropriate dot

Question 1

Question 2

Question 3

Question 4

Question 5

Official answering session

C

Follow the arrow to the appropriate dot

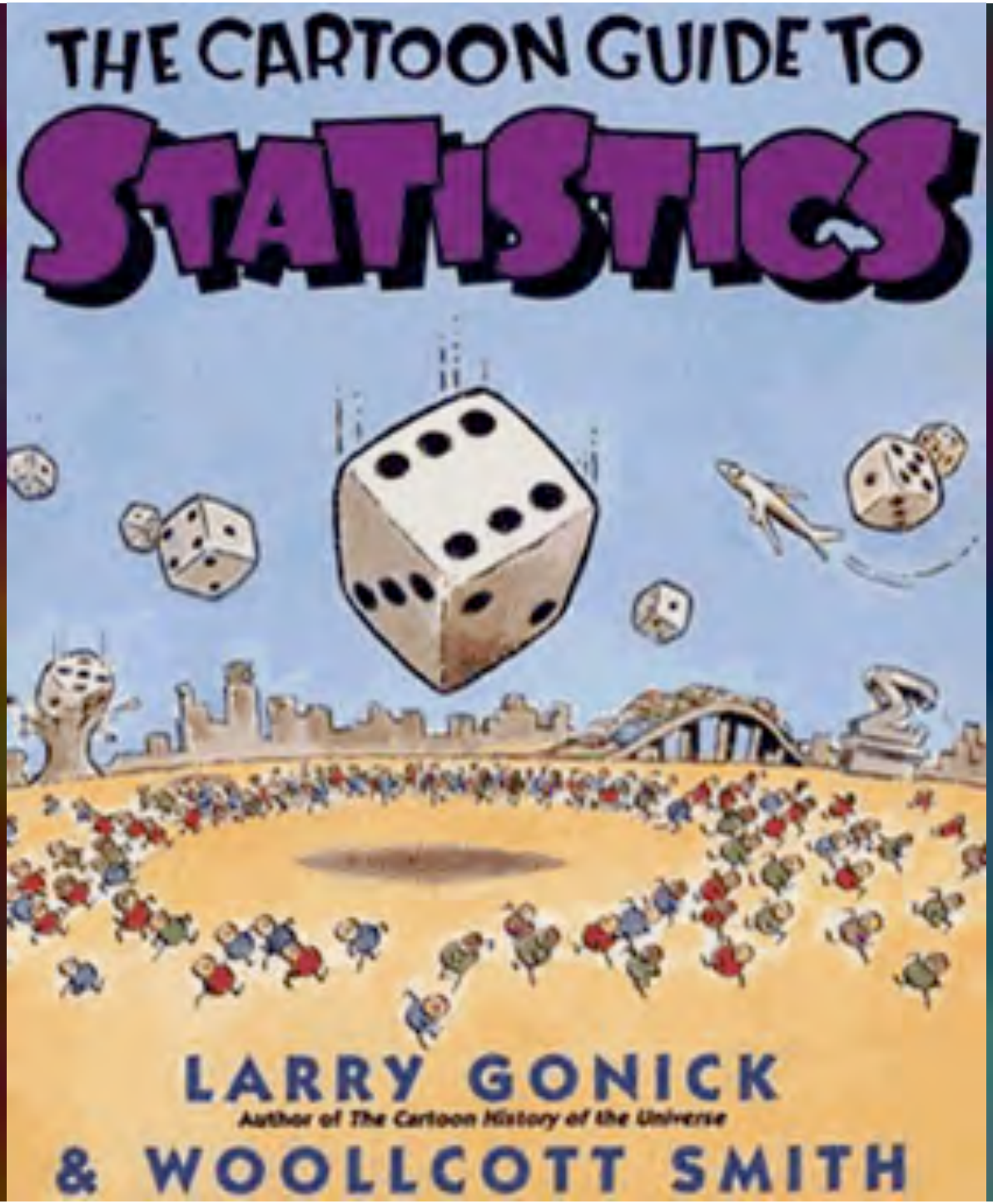
Question 1

Question 2

Question 3

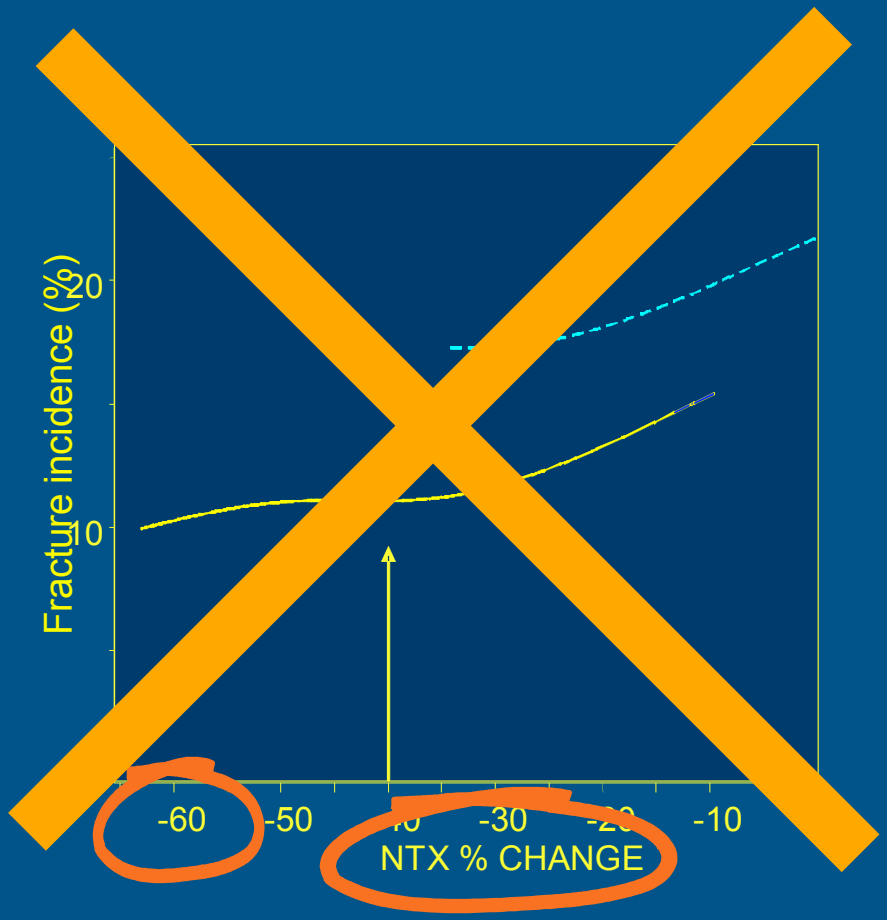
Question 4

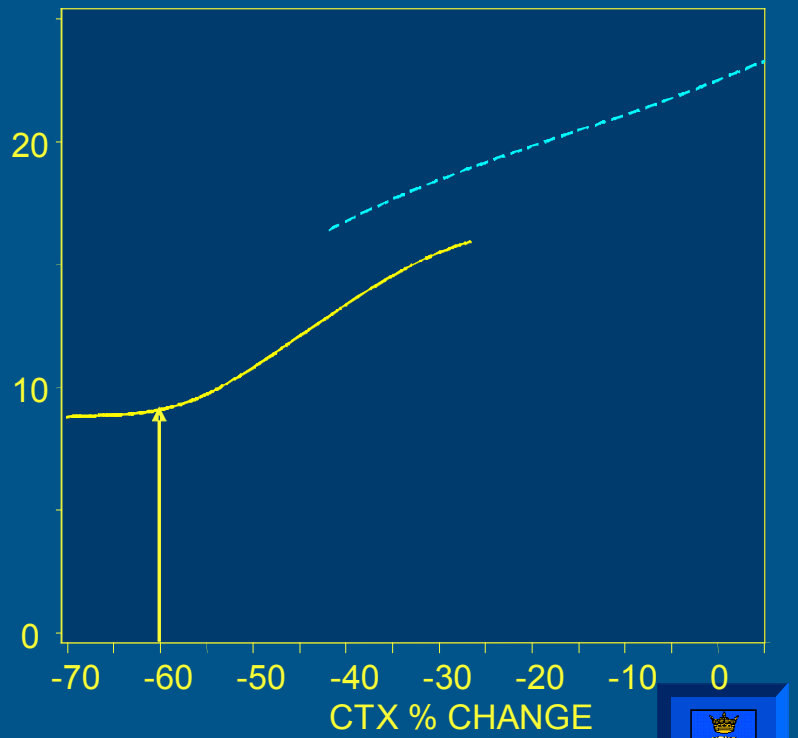
Question 5


THE CARTOON GUIDE TO
STATISTICS
LARRY GONICK
Author of The Cartoon History of the Universe
& WOOLLCOTT SMITH

New Vertebral Fracture Incidence over 3 Years, vs. 3 to 6 Month Marker % Change From Baseline

Eastell et al, J Bone Miner Res, in press

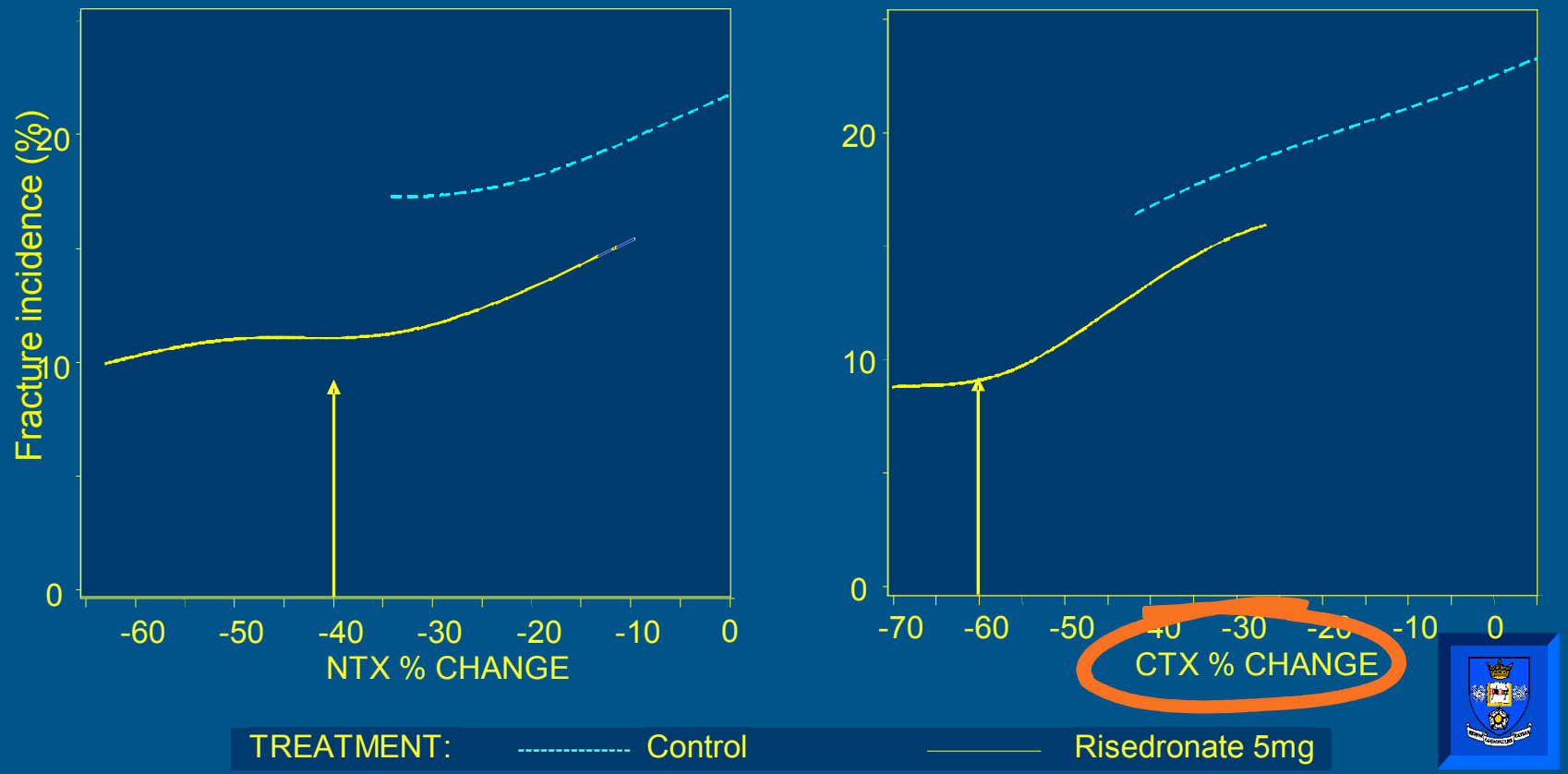




TREATMENT: ---------- Control ———— Risedronate 5mg

New Vertebral Fracture Incidence over 3 Years, vs. 3 to 6 Month Marker % Change From Baseline

Eastell et al, J Bone Miner Res, in press



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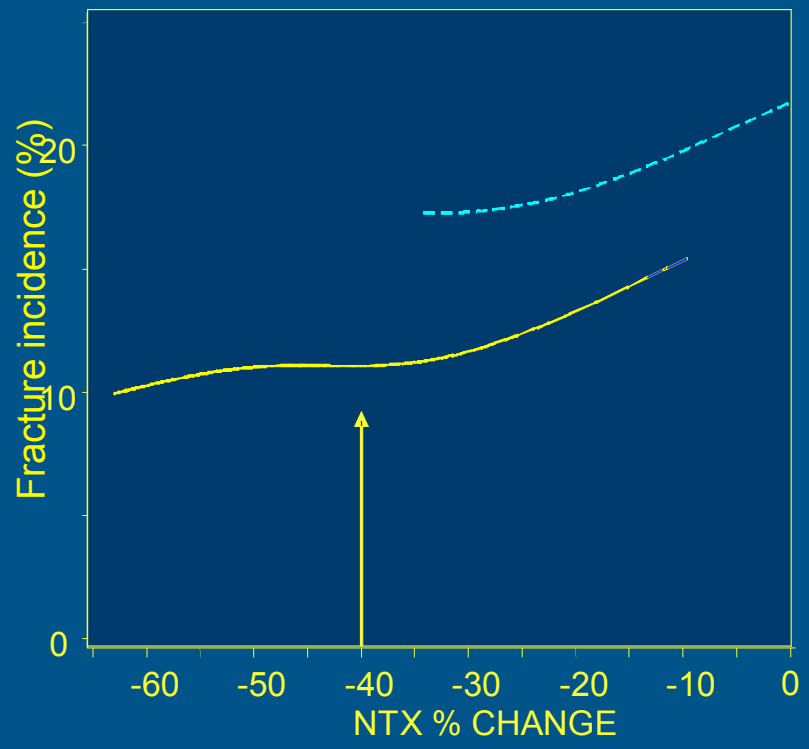

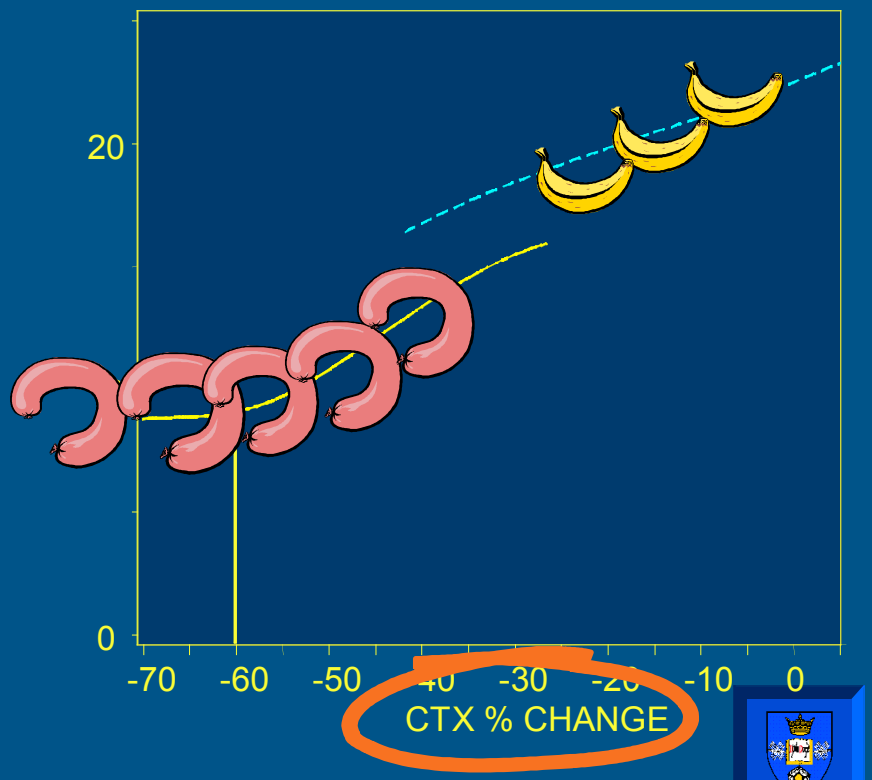

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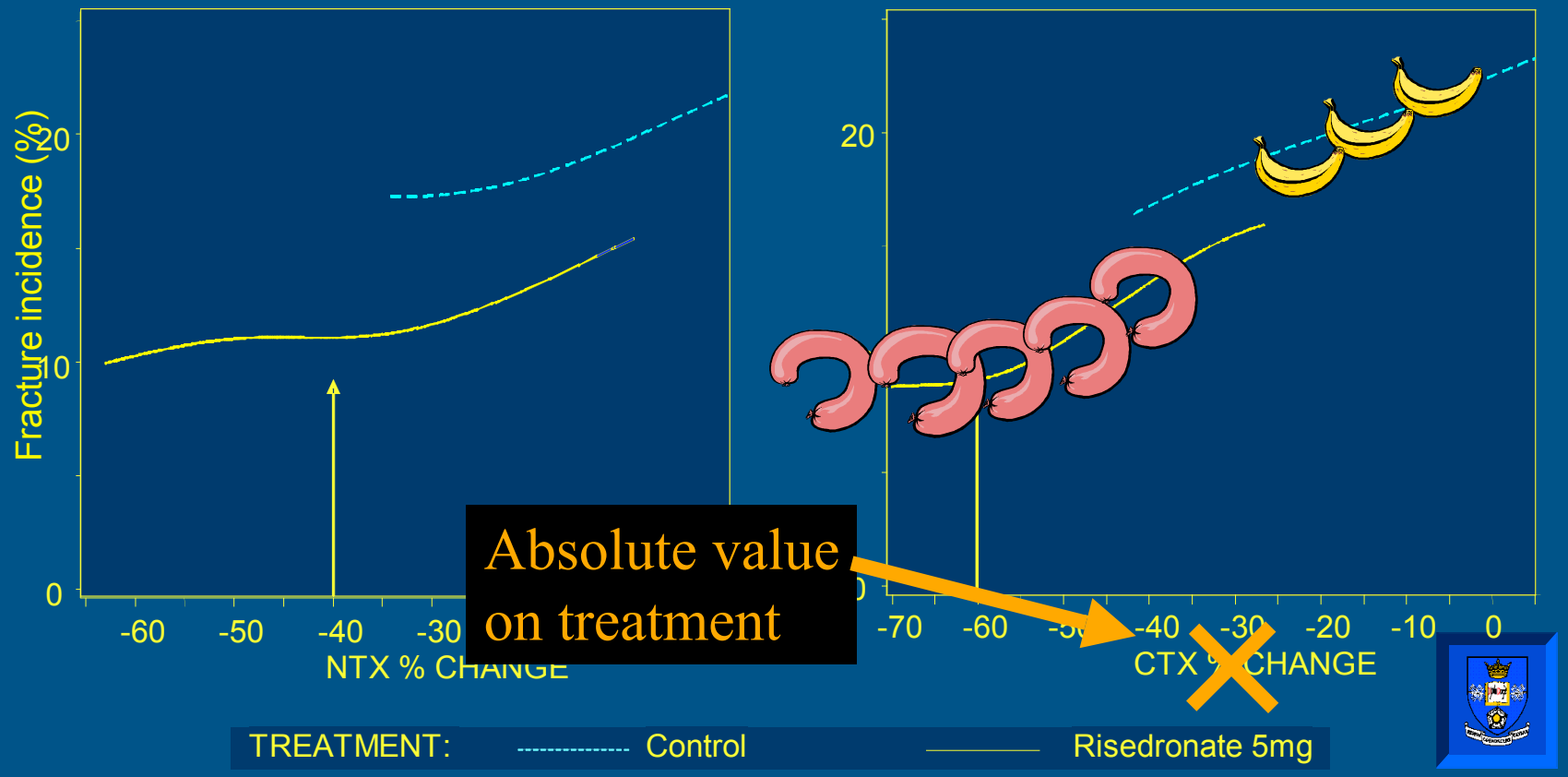

New Vertebral Fracture Incidence over 3 Years, vs. 3 to 6 Month Marker % Change From Baseline

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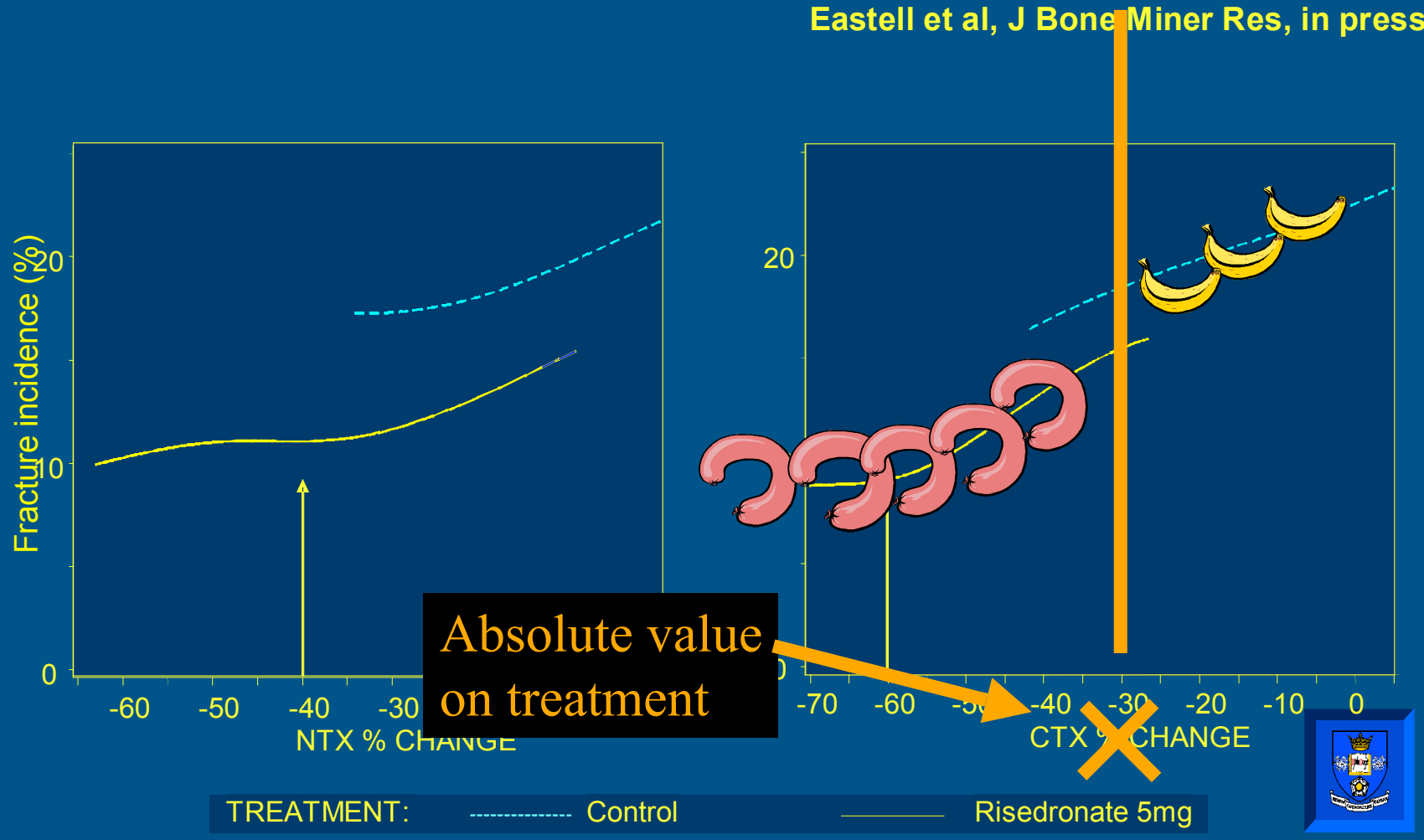

eclaration on research paper was wrong, reports **Phil Baty**

rt admits he did not full access to data

THE TIMES HIGHER OCTOBER 12 2007

ation

One of the world's leading bone experts has confirmed that he signed an incorrect declaration for a research paper that presented some erroneous findings about a leading osteoporosis drug.

Almost two years after *The Times Higher* first reported concerns about the validity of a paper by Richard Eastell on the effects of Procter & Gamble's multi-million-pound drug Actonel, the Sheffield University professor has published a peer-reviewed letter addressing the concerns raised.

In a letter to *The Journal of Bone and Mineral Research* (*JBMR*), which published the original contested paper in 2003, Professor Eastell this week accepted that he had incorrectly signed a declaration stating that he and other authors had had "full access" to the Actonel drug-trial data held by P&G.

The data analysis for the paper was carried out by P&G, which paid for the research and which did not release the data to Professor Eastell.

In the letter, published by the *JBMR* following an independent analysis of P&G's drug-trial data, Professor Eastell also conceded that the original article to which he put his name contained "some errors and some poor practice".

The editor-in-chief of the *JBMR*, John Eisman, said in the journal this week that as a result of the case, the American Society for Bone and Mineral Research (ASBMR) had agreed new publication procedures.

These insist that "authors sign that they have had full access to the underlying data for all manuscripts", which "should help reinforce the independent role of the academic researcher" in working with pharmaceutical companies.

The Times Higher was the first to report concerns about the work in November 2005, after a whistleblower in Professor Eastell's Sheffield team raised the alarm. Aubrey Blumsohn was suspended and threatened with the sack by Sheffield for co-operating with *The Times Higher*, but he later agreed a settlement understood to be worth six figures.

The work of Professor Eastell, who runs Sheffield University's Bone Metabolism Research Unit, had helped to change the understanding of the treatment of osteoporosis.

P&G's Actonel and its market rival Fosamax both reduce the risk of bone fractures by increasing bone density and reducing the "turnover" of bones — the rate at which they break down and regenerate. It had been generally understood that Fosamax was more effective at doing this.

But Professor Eastell's research suggested that Actonel's inferior potency did not mean that it was less effective at reducing the risk of fractures. He had suggested that there was a "threshold effect" — a point beyond which any further reduction in bone turnover did not affect fracture risk.

Professor Eastell reported this threshold effect in an article published in June 2003 in the *JBMR*: "Relationship of early changes in bone resorption to the reduction in fracture risk with risedronate [Actonel's generic name]."

On the paper, a declaration by the authors confirmed that Professor Eastell had received research funding from P&G and that two co-authors were full-time employees of P&G, but it concluded with the statement that "all authors had full access to the data and analyses".

Professor Eastell writes in his letter to the *JBMR*: "In the original paper one of the authors, a statistician working for P&G [Ian Barton] had full access to all data." He said that P&G applied pharmaceutical industry guidelines at the time, which restricted the release of original data to investigators.

He added that the P&G statistician "worked closely with all of the authors of the original report on the data analysis... and responded to all requests for further analyses. Thus, the authors had full access to the analyses they had requested... but not all had direct access to the raw data.

'Professor Eastell's letter to the *JBMR* acknowledges that the independent analysis of the data "identified some errors and some poor practice"'

"At the time of writing (2002-03), not all the original authors were given access to the raw data."

An e-mail exchange between Professor Eastell and P&G's statistician Ian Barton, seen by *The Times Higher*, shows Professor Eastell's requests for the raw data were rejected by P&G.

In May 2002, Professor Eastell wrote that a colleague "was really surprised when I told him that all the analyses" for a presentation of research findings "were done by P&G employees".

"I think that to avoid criticism in the future it would be good if we could say that we had done the analyses independently," he said. But P&G declined, saying that while this would "add an extra layer of external credibility" to the research, the data itself was the result of an investment of "hundreds of millions of dollars" and belonged to the company.

Professor Eastell's letter to the *JBMR* also acknowledges that the independent analysis of the data "identified some errors and some poor practice" in the original paper published under his name.

An incorrect statistical test had been used and, in particular, a graph in the original paper had been "cropped extensively and in an asymmetric manner".

"In the original paper we should have given a rationale for the approach used in cropping [lines on a graph], and stated how much data were cropped. However, we were unaware that the cropping procedure was carried out in an asymmetric way at the time we wrote the original manuscript and therefore that was not indicated." The original graph "excludes between 34 per cent and 49 per cent" of the data.

Dr Blumsohn said this week that the new independent analysis of the data showed that all his concerns had been validated. He added that "the authors have been unable to replicate the analysis as originally reported" now that they have all the data.

But Professor Eastell said the conclusion of the original *JBMR* paper that there was "a level of bone turnover reduction below which no further fracture benefit is observed" — the so-called threshold effect — could "still be supported based on the new analysis".

He told *The Times Higher* that his letter was "the final word on the topic" and had been through a thorough scientific peer review.

A spokesman for P&G said: "We agree with the corrections noted by the independent researchers... and we are pleased that the re-analysis supports the original conclusions drawn in 2003. While the mistakes in the original paper did not affect the scientific conclusions, we recognise the need for consistent and robust scientific analysis.

"It is important to note this work was not related to the safety, efficacy or approval of Actonel. This research also did not directly involve clinical research in patients."

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Press statement

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The internet will not listen

- www.scientific-misconduct.blogspot.com
- http://dcscience.net/?p=193
- http://www.6minutes.com.au/michael_blog/blogposts.asp?postid=541
- http://www.i-sis.org.uk/Actone.php
- http://www.pharmalot.com/2007/10/boning-up-medical-journal-bolsters-disclosure-policy/

They could
have done better

The Economist

JANUARY 22ND–28TH 2005 www.economist.com

The good company

A sceptical look at corporate social responsibility

Doctors as lapdogs to drug firms

The beast is ourselves

EDITOR—Fugh-Berman is correct that we need to bite something tender and to get out of that lap.[1] But we are fighting the wrong beast. The beast is not the pharmaceutical industry—it is ourselves.

Pharmaceutical companies sell products under the banner of science. But their only raison d'être is to make money. Industry has to balance genuine hypothesis testing and transparency against commercial interests and the financial consequences of dishonesty. This is not in itself a criticism—it is a simple fact.

It is also of course true that the industry provides products which are often beneficial to our patients. It is equally evident that many actions of industry have not resulted in benefit, and have instead caused harm. More importantly, we are often completely unable to assess the degree of harm, because information is hidden by gag clauses, the threat of litigation, and cosy commercial arrangements between the regulators and industry.[1 2]

We, as doctors, have created the atmosphere which has allowed companies to malfunction. We have allowed industry to subvert the rules of science.[3] We have watched quietly as governments and academics have colluded with industry to hide information critical to our patients. We have remained silent as our medical schools have churned out graduates who have no knowledge of the dilemmas and scandals of medicine. We have allowed many of our medical journals to become corrupted and timid. The soft parts that need biting may well be our own.

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Competing interests: AB is involved in a dispute with Procter and Gamble Pharmaceuticals over hiding of research data and research integrity. www.slate.com/id/2133061/

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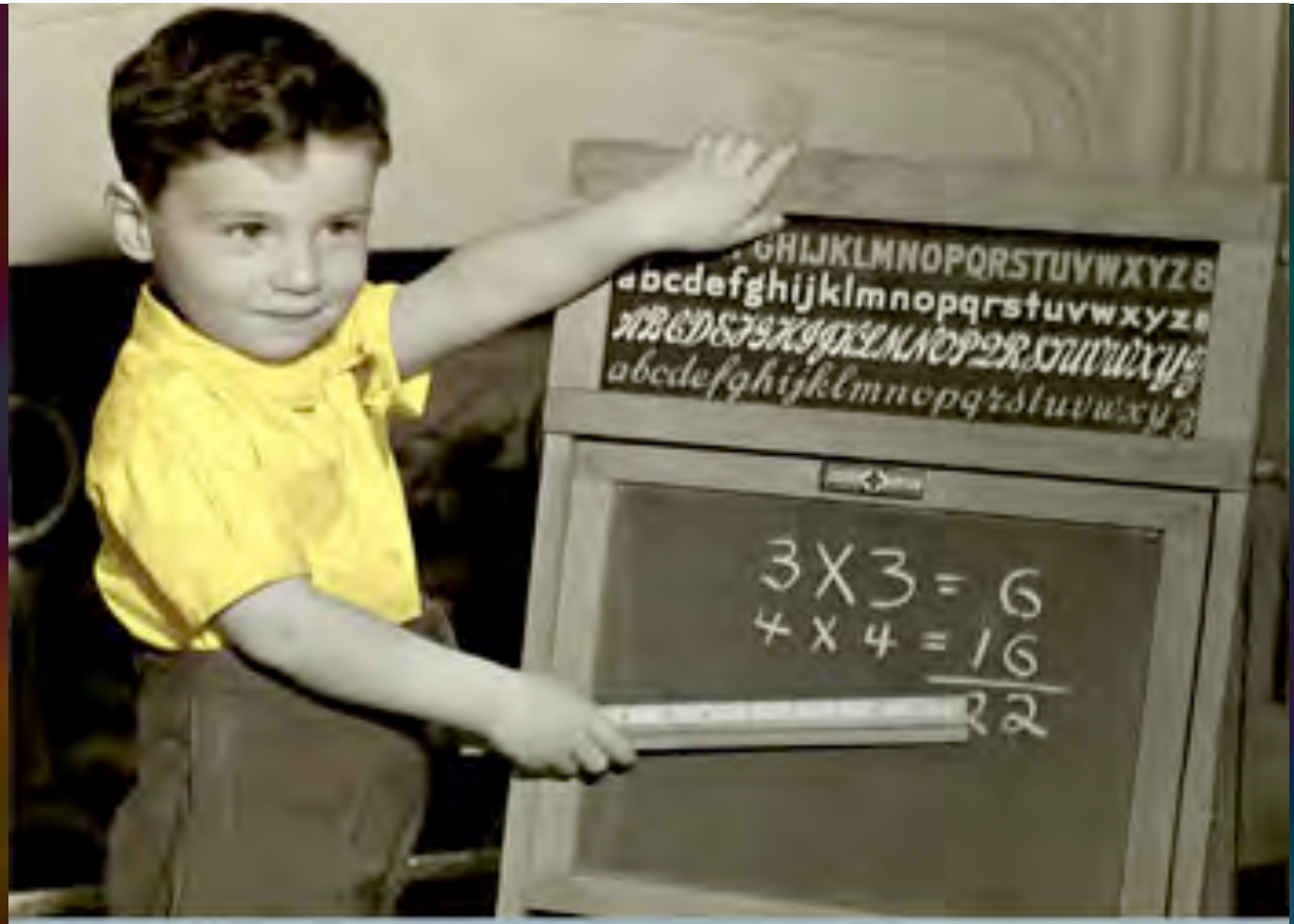

There are

NO STUPID QUESTIONS

or stupid answers.