Taking stock and looking forward

HRT
A personal view of the issues

Professor David H Barlow
Executive Dean of Medicine
Professor of Reproductive Medicine
The University of Glasgow

Perspectives on HRT

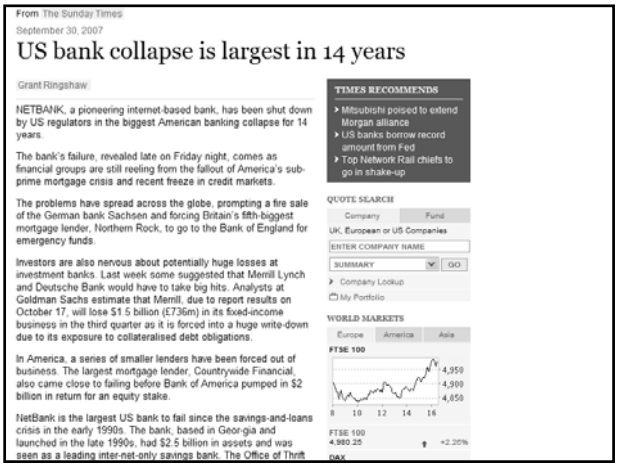
- **This meeting has reviewed the evidence across menopause research**
- **A fair appraisal of the evidence should provide a common view on clinical management**
- **Why has this been so difficult to achieve in the HRT field?**
- **Dispute and tension has been a feature of many meetings**

Perspectives on HRT

- **Reflect on…**
  - **the crisis of confidence**
  - **factors complicating the field**
  - **the solid evidence base & the uncertainties**
  - **how thinking can be so diverse**
    - **mechanisms of perception and decision making**
    - **HRT in osteoporosis**
- **Define my view on sound HRT management**

Perspective on HRT

A crisis of confidence



From The Sunday Times

September 30, 2007

US bank collapse is largest in 14 years

Grant Ringshaw

NETBANK, a pioneering internet-based bank, has been shut down by US regulators in the biggest American banking collapse for 14 years.

The bank's failure, revealed late on Friday night, comes as financial groups are still reeling from the fallout of America's sub-prime mortgage crisis and recent freeze in credit markets.

The problems have spread across the globe, prompting a fire sale of the German bank Sachsen and forcing Britain's fifth-biggest mortgage lender, Northern Rock, to go to the Bank of England for emergency funds.

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In America, a series of smaller lenders have been forced out of business. The largest mortgage lender, Countrywide Financial, also came close to failing before Bank of America pumped in $2 billion in return for an equity stake.

NetBank is the largest US bank to fail since the savings-and-loans crisis in the early 1990s. The bank, based in Geor-gia and launched in the late 1990s, had $2.5 billion in assets and was seen as a leading inter-net-only savings bank. The Office of Thrift

TIMES RECOMMENDS

- Mitsubishi poised to extend Morgan alliance
- US banks borrow record amount from Fed
- Top Network Rail chiefs to go in shake-up

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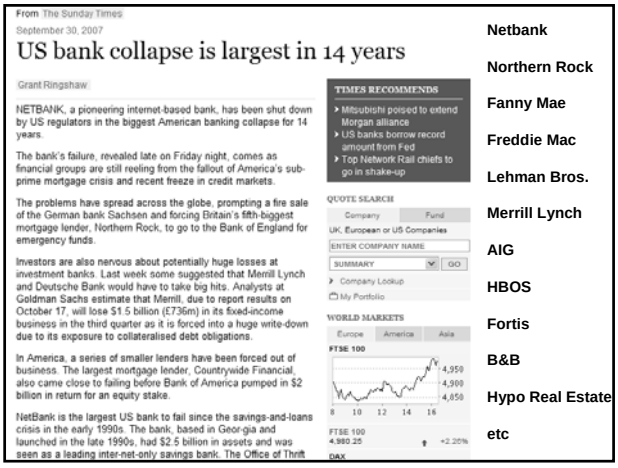

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Northern Rock

Fanny Mae

Freddie Mac

Lehman Bros.

Merrill Lynch

AIG

HBOS

Fortis

B&B

Hypo Real Estate

etc

Perspectives on HRT

- A series of events undermined the confidence of the providers and users
- There has been a resulting collapse of levels of uptake
- The correction that has occurred has affected appropriate and inappropriate activity
- After a period of consolidation can confidence in appropriate activity return?

Could there be an IVF parallel

- Scientific, clinical and sociological dimensions
- A sphere which some regard as no serious illness
- Practitioners can feel passionate about the field
- Enthusiasts may almost disregard risks/problems
- Benefits can be very positive for some patients
- Ongoing evolution of regimens and techniques
- Evidence – many gaps in the RCT evidence base
- Use of ineffective or unvalidated interventions
- Onward and upwards?

Complex factors affecting the HRT field

- Widespread use for menopausal symptoms
- Epidemiology indicated possible health benefits
- Wide-ranging claims across general health
  - Before prominence of EBM
  - Reluctance to accept need for a more rigorous evidence base
  - Issues cross specialty boundaries where sex hormones not favoured
- Criticism - medicalization of natural processes
  - marginalization of menopause problems compared to risk
- The specialist reaction to the controversy

Perspective on HRT use

- **All the different opinion groups are sure that their view is correct**
- **All approach the data in good faith**
- **Relationships can be uneasy**
- **Positions can be entrenched**
- **This need not be the case**

A common ground on HRT?

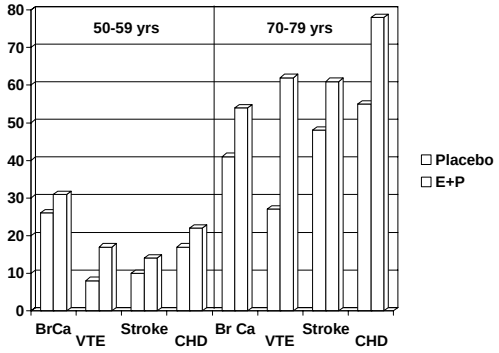
- **Most HRT use is for symptom relief**
- **HRT is highly effective for relief of symptoms in women at the menopause**
- **Most HRT use is of short duration**
- **HRT use starts in late 40s**
- **Peak HRT use has been in mid 50s and low beyond 60**
- **HRT has a bone-sparing effect on skeleton**

HRT and relief of menopausal symptoms

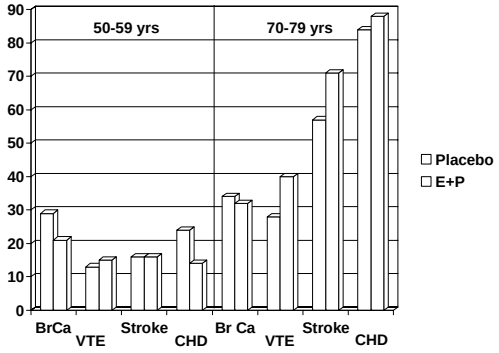
- **Predominant issue in menopausal symptom relief is anxiety around <u>side-effects and risk</u>**
  - **Side effects - good RCT data (minimized by lower dose regimens)**
  - **Risk has been the focus of attention**
    - **Was mainly observational data**
    - **RCT data from WHI**

- **WHI provides the dominant RCT evidence**
  - **Menopausal symptoms not the focus in WHI**
  - **RCTs provide best evidence for**
    - ***the specific drugs, in the specific situation, in the specific people***
  - **Trials powered for the whole population**
  - **Ten years subgroup data now published but must be used with care**

Risk events in WHI E+P study per 10,000wy



Risk events in WHI E-only study per 10,000 wy



WHI potential risk events
in **70-79** year group
excess absolute risk per 10,000 wy

	E+P/Pl	E only/Pl	Pl. risk
• **Breast Ca.**	**+13**	**-2**	**41 or 34**
• **VTE**	**+35**	**+12**	**27 or 28**
• **Stroke**	**+13**	**+14**	**48 or 57**
• **CHD**	**+23**	**+4**	**55 or 84**

Excess risk in yellow

WHI potential risk events
in **50-59** year group
excess absolute risk per 10,000 wy

	E+P/Pl	E only/Pl	Pl. risk
• **Breast Ca.**	**+5**	**-8**	**26 or 29**
• **VTE**	**+9**	**+2**	**8 or 13**
• **Stroke**	**+4**	**0**	**10 or 16**
• **CHD**	**+5**	**-10**	**17 or 24**

Excess risk in yellow

Implications of WHI reports for HRT Regimens

- **Risk events emphasise the importance of there being a clear indication for using HRT**
- **Risk events are more common >60 years and especially >70 years**
- **Risk events are uncommon <60 years and minimal <60 years in women on E alone**

- **Systemic HRT for symptom relief**
  - **Predominantly <60 years thus risk low (WHI 50-59)**
  - **Good RCT data for efficacy, lowering doses**
  - **Efficacy vs side effects soon clear to the woman**
  - **Duration of use variable, mostly no more than a few years**
  - **Positive benefit:risk balance**
- **Large numbers of symptomatic women & their clinicians anxious to use HRT even in this situation – 50% reduction in HRT use**

Current MHRA/Commission on Human Medicines (CHM) position

In December 2003, the Chairman of CHM (Professor Sir Gordon Duff) wrote to healthcare professionals in the UK to inform them of the findings of a review of the balance of risks and benefits of HRT in its licensed indications, which was initiated in response to growing safety concerns. Prof Duff explained that the WHI and MWS "and previous studies provide good evidence that use of HRT increases the risk of breast cancer, endometrial cancer and ovarian cancer in a duration-dependent manner. There is no evidence for a beneficial effect of HRT on cardiovascular disease – in fact HRT has been shown to increase the risk of myocardial infarction and VTE, especially in the first year of use, and to increase the risk of ischaemic stroke. The risk of most of these conditions increases with age, therefore increasing the overall risks the longer HRT is taken".

The review also concluded that:

- for the treatment of menopausal symptoms, HRT is beneficial for the majority of women in the short-term;
- when used in the long-term the balance of risks and benefits of HRT is such that it should be restricted to second-line therapy for the prevention of osteoporosis.

The decision to use HRT should take into consideration a woman's age, history, risk factors and personal preferences, and for all women the minimum effective dose should be used for the shortest duration. Continued use of HRT should be regularly re-assessed (eg, at least annually).

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HRT for management of osteoporosis

- **Opinion here is polarized and fragmented**
- **The EMEA/MHRA regulatory position**
- **Many in HRT field actively criticise the regulatory position**
- **Difference of approach within the field**
  - **Views on the overall management approach**
  - **Preventing osteoporosis vs. preventing fracture**
  - **Complexity of efficacy vs. cost-effectiveness**
  - **? hangover effect of treatment on bone**

Perceptions and decision-making

- **The differing perspectives may be influenced by how people from different standpoints …..**
  - **perceive the data under consideration**
  - **make their management decisions**
- **The literature on perception and decision-making provides important insights into how different people can differ in their perceptions and decisions using the same data**

Risk and uncertainty: a fallacy of large numbers
Samuelson. Scientia 1963. 98; 108-113

A colleague rejects a single gamble with an even chance of winning $200 or losing $100, but would accept a series of 100 such gambles.

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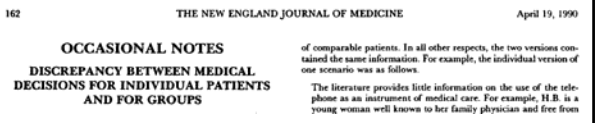
People are more likely to accept mixed gambles with positive expected values when the gambles will be played more than once.

Berartzi & Thaler 1999; DeKay & Kim 1991
Keren 1991 Kloo et al 2005
Langer & Weber 2001 Li 2003
Redelmeier & Tversky 1992 Wedell & Bockenholt 1994

We can look at the same evidence but draw quite different conclusions



162 THE NEW ENGLAND JOURNAL OF MEDICINE April 19, 1990

OCCASIONAL NOTES

DISCREPANCY BETWEEN MEDICAL DECISIONS FOR INDIVIDUAL PATIENTS AND FOR GROUPS

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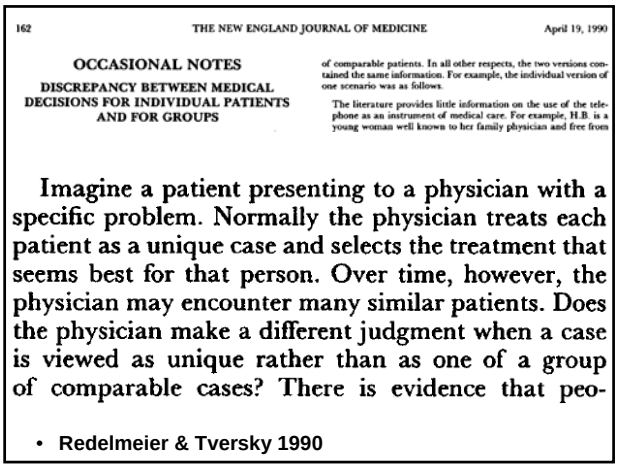
- **Redelmeier & Tversky 1990**



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Imagine a patient presenting to a physician with a specific problem. Normally the physician treats each patient as a unique case and selects the treatment that seems best for that person. Over time, however, the physician may encounter many similar patients. Does the physician make a different judgment when a case is viewed as unique rather than as one of a group of comparable cases? There is evidence that peo-

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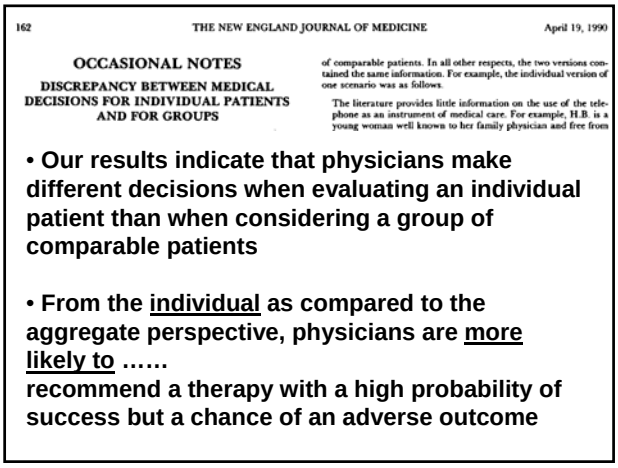

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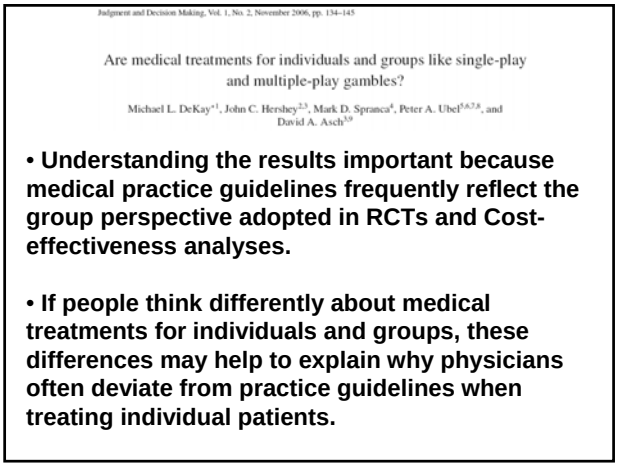
- **Our results indicate that physicians make different decisions when evaluating an individual patient than when considering a group of comparable patients**

- **From the individual as compared to the aggregate perspective, physicians are more likely to ……**
recommend a therapy with a high probability of success but a chance of an adverse outcome



Judgment and Decision Making, Vol. 1, No. 2, November 2006, pp. 134–145

Are medical treatments for individuals and groups like single-play and multiple-play gambles?

Michael L. DeKay[*1], John C. Hershey[2,3], Mark D. Spranca[4], Peter A. Ubel[5,6,7,8], and David A. Asch[3,9]

- **Understanding the results important because medical practice guidelines frequently reflect the group perspective adopted in RCTs and Cost-effectiveness analyses.**

- **If people think differently about medical treatments for individuals and groups, these differences may help to explain why physicians often deviate from practice guidelines when treating individual patients.**

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Participants read a cover story describing "a new strain of flu that is likely to sweep the region in the next few months." In the frequency frame, participants were told: "If no vaccine is administered, 600 out of every 1000 people in this region are expected to catch the flu. 400 out of every 1000 people are expected not to catch the flu. Unfortunately, there is no way to predict ahead of time who will catch the flu and who will not." The story also

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Table 1: Attributes (frequency versions) and mean ranks of treatment options, including the no-flu-shot option.

	Expected number of patients with each outcome					
Option[a]	Adverse reaction	Flu	No flu	Average quality of life	Outcome uncertainty	Mean rank[b]
No flu shot	0	600	400	70.0	24.5	8.29 (0.19)
Flu shot F	50	150	800	87.5	26.8	1.25 (0.07)
Flu shot A	50	250	700	82.5	28.6	3.38 (0.11)
Flu shot B	50	350	600	77.5	29.5	5.90 (0.14)
Flu shot G	100	100	800	85.0	32.0	2.72 (0.11)
Flu shot E	100	200	700	80.0	33.2	5.02 (0.08)
Flu shot I	100	300	600	75.0	33.5	7.61 (0.09)
Flu shot C	150	50	800	82.5	36.3	4.90 (0.17)
Flu shot H	150	150	700	77.5	37.0	6.90 (0.12)
Flu shot D	150	250	600	72.5	37.0	9.02 (0.09)

[a] Flu-shot options were assigned random letters for identification purposes.
[b] Options that were viewed more favorably have lower ranks (1 = best option, 10 = worst option). Standard errors are in parentheses.

We all look at the same evidence but draw quite different conclusions

Perception of Risk

PAUL SLOVIC

Studies of risk perception examine the judgments people make when they are asked to characterize and evaluate hazardous activities and technologies. This research aims to aid risk analysis and policy-making by (i) providing a basis for understanding and anticipating public responses to hazards and (ii) improving the communication of risk information among lay people, technical experts, and decision-makers. This work assumes that those who promote and regulate health and safety need to understand how people think about and respond to risk. Without such understanding, well-intended policies may be ineffective.

experience with hazards tends to come from the news media, which rather thoroughly document mishaps and threats occurring throughout the world. The dominant perception for most Americans (and one that contrasts sharply with the views of professional risk assessors) is that they face more risk today than in the past and that future risks will be even greater than today's (2). Similar views appear to be held by citizens of many other industrialized nations. These perceptions and the opposition to technology that accompanies them have puzzled and frustrated industrialists and regulators and have led numerous observers to argue that the American public's apparent pursuit of a "zero-risk society" threatens the nation's political and economic stability. Wildavsky (3, p. 32) commented as follows on this state of affairs.

Slovic P. Science 1987 236; 280

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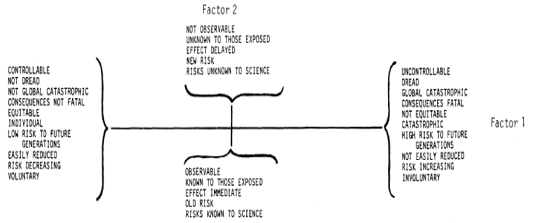

Fig. 1. Location of 81 hazards on factors 1 and 2 derived from the relationships among 18 risk characteristics. Each factor is made up of a combination o characteristics, as indicated by the lower diagram (*25*).

Slovic P. Science 1987 236; 280

$$\begin{aligned}
&Information\ Favors\ Precaution_{ijk} = \gamma_0 + \gamma_1 Prefers\ Precaution\ Before(Mean)_i \\
&\quad + \gamma_2 Prefers\ Precaution\ Before(Deviation)_{ijk} + \gamma_3 Order_{ijk} + \sum_{l=1}^{4} \gamma_{4l} Information\ Item_{jl} \\
&\quad + \sum_{m=1}^{5} \gamma_{5m} Scenario_{km} + \sum_{l=1}^{4} \sum_{m=1}^{5} \gamma_{6lm} Scenario_{km} \times Information\ Item_{jl} + u_{0i} \\
&\quad + u_{2i} Prefers\ Precaution\ Before(Deviation)_{ijk} + r_{ijk},
\end{aligned}$$

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Slovik's work also found that in the United States, women saw all risks as higher than men did, and minorities saw risks as higher than whites.

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Later studies showed that minority men and women, white women, and even most white men saw risks similarly, but there is a small group of conservative, highly-educated, authoritarian white men who see all risks as very low.

We all look at the same evidence but can draw different conclusions

- **Perception and decisions are affected by ……**
  - **starting point opinion**
  - **single patient or group perspective**
  - **preparedness to consider aggregated harms – monetary loss vs medical harm**
  - **perceptions of uncertainty in the data**
  - **use of absolute numbers rather than probabilities**

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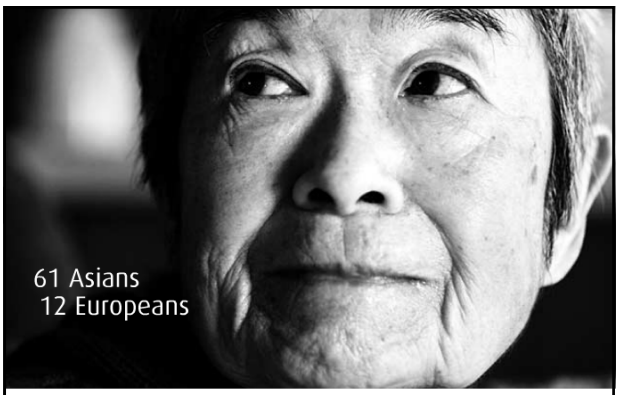
If we could turn the population
of the earth into a small community
of 100 people, keeping the same
proportions we have today,
it would be something like this...



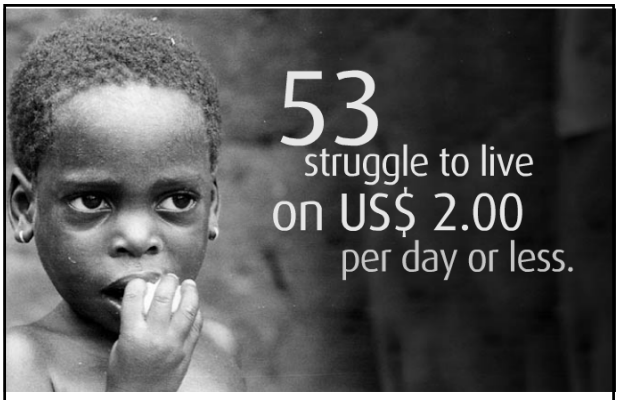

47 live in an urban area


43 live without basic sanitation


only 7 are educated at a secondary level

only 3 have an internet connection

9 ARE DISABLED



Differing perceptions and decisions are a significant issue in approaches to osteoporosis

- **Present the outcomes in absolute numbers where feasible**
- **Consider the differences in perceptions and implications for management strategy**

The range of positions on HRT and osteoporosis?

- **When to apply treatment?**
  - **Anyone who wants it**
  - **Maintaining bone density should be the goal**
  - **Anyone with osteopenia**
  - **Only those at increased fracture risk (threshold)**

The range of positions on HRT and osteoporosis?

- **Treatment in low fracture risk cases?**
  - **Justified because it maintains low risk of fracture and will last long after treatment**
  - **Will be unnecessary in most people, hangover effect not sufficient to be justification**
  - **Focus resources and treatment risks on those at increased fracture risk**

The range of positions on HRT and osteoporosis?

- **Intervention thresholds?**
  - **These are not necessary/not appropriate in clinical judgement**
  - **Use 10 year fracture risk threshold (UK NOGG = 15%)**
  - **Use a cost-effectiveness threshold (UK NICE = £20,000/QALY)**

The range of positions on HRT and osteoporosis?

- **HRT in osteoporosis?**
  - **MHRA wrong – HRT should be 1st line across the field**
    (HRT effective; Bisphosphonates over-rated)
  - **MHRA position should be revised for <60 group**
    (Risks low and HRT has best efficacy data for <60)
  - **MHRA position OK – simplifies role of HRT**
    (HRT not necessary for osteoporosis management)
    (HRT not well validated for osteoporosis indication)

A look at the numbers

- **Use the data from WHI**
- **The E+P study groups**
- **Annualized numbers per 1,000 women per year**
  - **Fracture events**
  - **Serious risk events**
- **Use of the UK FRAX absolute fracture risk estimates**
- **Use the new UK NOGG intervention threshold**
  - **15% 10 year fracture risk**
- **Aim is to provide a better feel for what really results from intervention in different situations**

Effects of Estrogen Plus Progestin on Risk of Fracture and Bone Mineral Density

The Women's Health Initiative Randomized Trial

Jane A. Cauley, DrPH
John Robbins, MD
Zhao Chen, PhD
Steven R. Cummings, MD

Context In the Women's Health Initiative trial of estrogen-plus-progestin therapy, women assigned to active treatment had fewer fractures.

Objective To test the hypothesis that the relative risk reduction of estrogen plus progestin on fractures differs according to risk factors for fractures.

Table 3. Hazard Ratio of Total Fractures by Randomization Assignment and Stratification*

Outcomes	Estrogen + Progestin, No. (%) (N = 8506)†	Placebo, No. (%) (N = 8102)†	Hazard Ratio (95% Nominal Confidence Interval)	*P* Value for Interaction
Total population	733 (1.52)	896 (1.99)	0.76 (0.69-0.83)	
Age at screening, y				
50-54	67 (1.05)	90 (1.53)	0.68 (0.49-0.93)	
55-59	124 (1.18)	126 (1.29)	0.91 (0.71-1.16)	
60-64	168 (1.53)	184 (1.85)	0.80 (0.65-0.98)	.47
65-69	161 (1.53)	238 (2.35)	0.68 (0.49-0.93)	
70-74	142 (2.11)	174 (2.61)	0.81 (0.65-1.01)	
75-79	71 (2.38)	84 (3.09)	0.73 (0.53-1.00)	
Years since menopause				
<10	187 (1.17)	221 (1.44)	0.80 (0.66-0.98)	
10-19	255 (1.55)	327 (2.03)	0.75 (0.64-0.89)	.95
≥20	200 (2.03)	257 (2.69)	0.74 (0.61-0.89)	

~~/10,000wy~~
~~E+P Pl.~~
~~111 vs 141~~ **-30**
~~153 vs 210~~ **-57**
~~226 vs 285~~ **-59**

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~~/1,000wy~~
~~E+P Pl.~~
~~11 vs 14~~ **-3**
~~15 vs 21~~ **-6**
~~23 vs 29~~ **-6**

WHI potential risk events
in **70-79** year group
excess absolute risk per 10,000 wy

	E+P/Pl	E only/Pl	Pl. risk
• **Breast Ca.**	**+13**	**-2**	**41 or 34**
• **VTE**	**+35**	**+12**	**27 or 28**
• **Stroke**	**+13**	**+14**	**48 or 57**
• **CHD**	**+23**	**+4**	**55 or 84**

Excess risk in yellow

WHI potential risk events
in **70-79** year group
excess absolute risk per 10,000 wy

	E+P/Pl	E only/Pl	Pl. risk
• **Breast Ca.**	**+13**	**-2**	**41 or 34**
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• **Stroke**	**+13**	**+14**	**48 or 57**
• **CHD**	**+23**	**+4**	**55 or 84**

84 events/10,000wy

WHI potential risk events
in **70-79** year group
excess absolute risk per 10,000 wy

	E+P/Pl	E only/Pl	Pl. risk
• **Breast Ca.**	**+13**	**-2**	**41 or 34**
• **VTE**	**+35**	**+12**	**27 or 28**
• **Stroke**	**+13**	**+14**	**48 or 57**
• **CHD**	**+23**	**+4**	**55 or 84**

8-9 events/1,000wy

The HRT conundrum

- For 1,000 **70-79** year old women given HRT there will be ….
  - approx. 6 fewer fractures per year
  - approx. 8-9 significant risk events per year (breast cancer, stroke, MI or VTE)
- Is this balance of benefit:risk acceptable if…
  - fracture prevention is the only reason for using the HRT?

The HRT conundrum

- For 1,000 **70-79** year old women given HRT each year there will be ….
  - 972 who would not have a fracture anyway
  - **6 who would avoid a fracture due to HRT**
  - 22 who would still have a fracture
  - approx. 8-9 significant risk events per year (breast cancer, stroke, MI or VTE)
- **Is this balance of benefit:risk acceptable?**

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/1,000wy E+P Pl.
11 vs 14 -3
15 vs 21 -6
23 vs 29 -6

WHI potential risk events in **50-59** year group excess absolute risk per 10,000 wy

	E+P/Pl	E only/Pl	Pl. risk
• **Breast Ca.**	**+5**	**-8**	**26 or 29**
• **VTE**	**+9**	**+2**	**8 or 13**
• **Stroke**	**+4**	**0**	**10 or 16**
• **CHD**	**+5**	**-10**	**17 or 24**

Excess risk in yellow

WHI potential risk events
in **50-59** year group
excess absolute risk per 10,000 wy

	E+P/Pl	E only/Pl	Pl. risk
• **Breast Ca.**	**+5**	**-8**	**26 or 29**
• **VTE**	**+9**	**+2**	**8 or 13**
• **Stroke**	**+4**	**0**	**10 or 16**
• **CHD**	**+5**	**-10**	**17 or 24**

23 events/10,000wy

WHI potential risk events
in **50-59** year group
excess absolute risk per 10,000 wy

	E+P/Pl	E only/Pl	Pl. risk
• **Breast Ca.**	**+5**	**-8**	**26 or 29**
• **VTE**	**+9**	**+2**	**8 or 13**
• **Stroke**	**+4**	**0**	**10 or 16**
• **CHD**	**+5**	**-10**	**17 or 24**

2-3 events/1,000wy

The HRT conundrum

- For 1,000 **50-59** year old women given HRT there will be ….
  - approx. 3 fewer fractures per year
  - approx. 2-3 significant risk events per year (breast cancer, stroke, MI or VTE)
- Is this balance of benefit:risk acceptable if…
  - there are also troublesome menopausal symptoms?
  - fracture prevention is the only reason for using the HRT?

The HRT conundrum

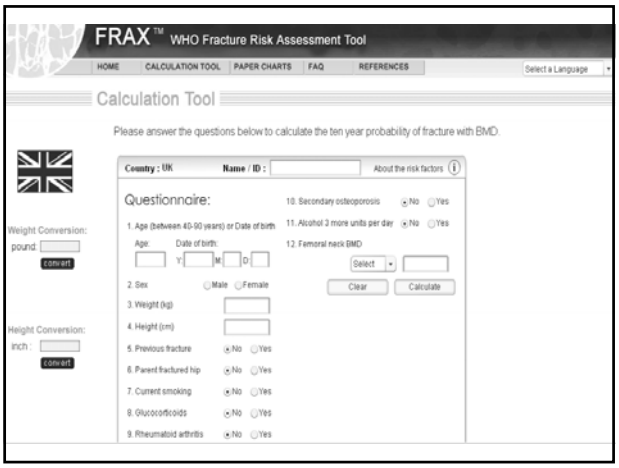
- For 1,000 **50-59** year old women given HRT each year there will be ….
  - 986 who would not have a fracture anyway
  - **3 who would avoid a fracture due to HRT**
  - 11 who would still have a fracture
  - approx. 2-3 significant risk events per year (breast cancer, stroke, MI or VTE)
- **Is this balance of benefit:risk acceptable?**

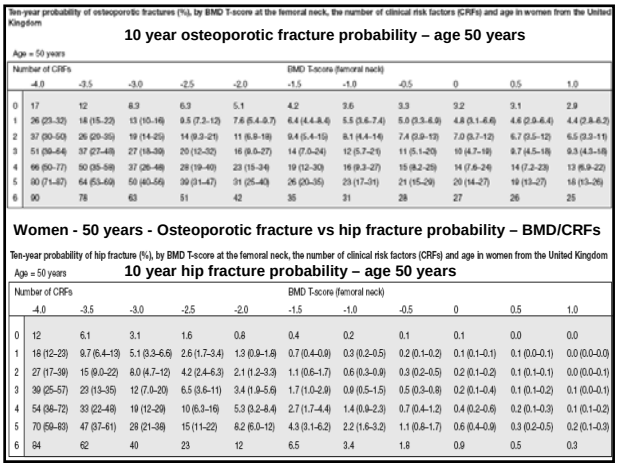
The HRT conundrum

- To provide a stronger benefit:risk ratio
- Intervene to prevent bone loss in women at much higher risk than the average
- How can I identify them?

The HRT conundrum

- To provide a stronger benefit:risk ratio
- Intervene to prevent bone loss in women at much higher risk than the average
- How can I identify them?
- **FRAX**





Ten-year probability of osteoporotic fractures (%), by BMD T-score at the femoral neck, the number of clinical risk factors (CRFs) and age in women from the United Kingdom

10 year osteoporotic fracture probability – age 50 years

Age = 50 years

Number of CRFs	BMD T-score (femoral neck)										
	-4.0	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0
0	17	12	8.3	6.3	5.1	4.2	3.6	3.3	3.2	3.1	2.9
1	26 (23–32)	18 (15–22)	13 (10–16)	9.5 (7.2–12)	7.6 (5.4–9.7)	6.4 (4.4–8.4)	5.5 (3.6–7.4)	5.0 (3.3–6.9)	4.8 (3.1–6.6)	4.6 (2.9–6.4)	4.4 (2.8–6.2)
2	37 (30–50)	26 (20–35)	19 (14–25)	14 (9.3–21)	11 (6.9–16)	9.4 (5.4–15)	8.1 (4.4–14)	7.4 (3.9–13)	7.0 (3.7–12)	6.7 (3.5–12)	6.5 (3.3–11)
3	51 (39–64)	37 (27–48)	27 (18–39)	20 (12–32)	16 (9.0–27)	14 (7.0–24)	12 (5.7–21)	11 (5.1–20)	10 (4.7–18)	9.7 (4.5–18)	9.3 (4.3–18)
4	66 (50–77)	50 (35–58)	37 (26–48)	28 (19–40)	23 (15–34)	19 (12–30)	16 (9.3–27)	15 (8.2–25)	14 (7.6–24)	14 (7.2–23)	13 (6.9–22)
5	80 (71–87)	64 (53–69)	50 (40–56)	39 (31–47)	31 (25–40)	26 (20–35)	23 (17–31)	21 (15–29)	20 (14–27)	19 (13–27)	18 (13–26)
6	90	78	63	51	42	35	31	28	27	26	25

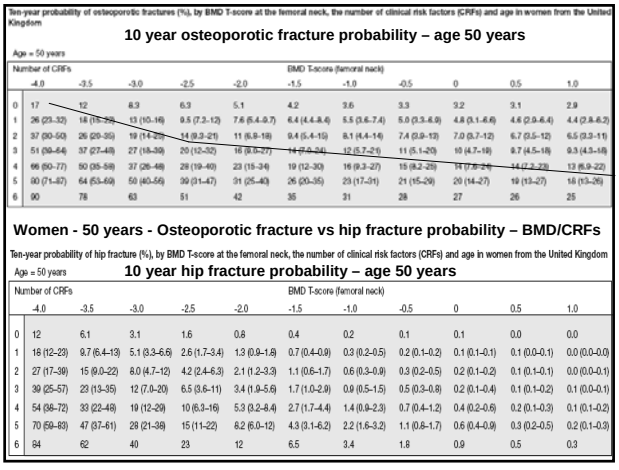
Women - 50 years - Osteoporotic fracture vs hip fracture probability – BMD/CRFs

Ten-year probability of hip fracture (%), by BMD T-score at the femoral neck, the number of clinical risk factors (CRFs) and age in women from the United Kingdom

Age = 50 years

10 year hip fracture probability – age 50 years

Number of CRFs	BMD T-score (femoral neck)										
	-4.0	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0
0	12	6.1	3.1	1.6	0.8	0.4	0.2	0.1	0.1	0.0	0.0
1	18 (12–23)	9.7 (6.4–13)	5.1 (3.3–6.6)	2.6 (1.7–3.4)	1.3 (0.9–1.8)	0.7 (0.4–0.9)	0.3 (0.2–0.5)	0.2 (0.1–0.2)	0.1 (0.1–0.1)	0.1 (0.0–0.1)	0.0 (0.0–0.0)
2	27 (17–39)	15 (9.0–22)	8.0 (4.7–12)	4.2 (2.4–6.3)	2.1 (1.2–3.3)	1.1 (0.6–1.7)	0.6 (0.3–0.9)	0.3 (0.2–0.5)	0.2 (0.1–0.2)	0.1 (0.1–0.1)	0.0 (0.0–0.1)
3	39 (25–57)	23 (13–35)	12 (7.0–20)	6.5 (3.6–11)	3.4 (1.9–5.6)	1.7 (1.0–2.9)	0.9 (0.5–1.5)	0.5 (0.3–0.8)	0.2 (0.1–0.4)	0.1 (0.1–0.2)	0.1 (0.0–0.1)
4	54 (38–72)	33 (22–48)	19 (12–29)	10 (6.3–16)	5.3 (3.2–8.4)	2.7 (1.7–4.4)	1.4 (0.9–2.3)	0.7 (0.4–1.2)	0.4 (0.2–0.6)	0.2 (0.1–0.3)	0.1 (0.1–0.2)
5	70 (59–83)	47 (37–61)	28 (21–38)	15 (11–22)	8.2 (6.0–12)	4.3 (3.1–6.2)	2.2 (1.6–3.2)	1.1 (0.8–1.7)	0.6 (0.4–0.9)	0.3 (0.2–0.5)	0.2 (0.1–0.3)
6	84	62	40	23	12	6.5	3.4	1.8	0.9	0.5	0.3



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10 year osteoporotic fracture probability – age 50 years

Age = 50 years

Number of CRFs	BMD T-score (femoral neck)										
	-4.0	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0
0	17	12	8.3	6.3	5.1	4.2	3.6	3.3	3.2	3.1	2.9
1	26 (23–32)	18 (15–22)	13 (10–16)	9.5 (7.2–12)	7.6 (5.4–9.7)	6.4 (4.4–8.4)	5.5 (3.6–7.4)	5.0 (3.3–6.9)	4.8 (3.1–6.6)	4.6 (2.9–6.4)	4.4 (2.8–6.2)
2	37 (30–50)	26 (20–35)	19 (14–25)	14 (9.3–21)	11 (6.9–16)	9.4 (5.4–15)	8.1 (4.4–14)	7.4 (3.9–13)	7.0 (3.7–12)	6.7 (3.5–12)	6.5 (3.3–11)
3	51 (39–64)	37 (27–48)	27 (18–39)	20 (12–32)	16 (9.0–27)	14 (7.0–24)	12 (5.7–21)	11 (5.1–20)	10 (4.7–18)	9.7 (4.5–18)	9.3 (4.3–18)
4	66 (50–77)	50 (35–58)	37 (26–48)	28 (19–40)	23 (15–34)	19 (12–30)	16 (9.3–27)	15 (8.2–25)	14 (7.6–24)	14 (7.2–23)	13 (6.9–22)
5	80 (71–87)	64 (53–69)	50 (40–56)	39 (31–47)	31 (25–40)	26 (20–35)	23 (17–31)	21 (15–29)	20 (14–27)	19 (13–27)	18 (13–26)
6	90	78	63	51	42	35	31	28	27	26	25

Women - 50 years - Osteoporotic fracture vs hip fracture probability – BMD/CRFs

Ten-year probability of hip fracture (%), by BMD T-score at the femoral neck, the number of clinical risk factors (CRFs) and age in women from the United Kingdom

Age = 50 years

10 year hip fracture probability – age 50 years

Number of CRFs	BMD T-score (femoral neck)										
	-4.0	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0	0.5	1.0
0	12	6.1	3.1	1.6	0.8	0.4	0.2	0.1	0.1	0.0	0.0
1	18 (12–23)	9.7 (6.4–13)	5.1 (3.3–6.6)	2.6 (1.7–3.4)	1.3 (0.9–1.8)	0.7 (0.4–0.9)	0.3 (0.2–0.5)	0.2 (0.1–0.2)	0.1 (0.1–0.1)	0.1 (0.0–0.1)	0.0 (0.0–0.0)
2	27 (17–39)	15 (9.0–22)	8.0 (4.7–12)	4.2 (2.4–6.3)	2.1 (1.2–3.3)	1.1 (0.6–1.7)	0.6 (0.3–0.9)	0.3 (0.2–0.5)	0.2 (0.1–0.2)	0.1 (0.1–0.1)	0.0 (0.0–0.1)
3	39 (25–57)	23 (13–35)	12 (7.0–20)	6.5 (3.6–11)	3.4 (1.9–5.6)	1.7 (1.0–2.9)	0.9 (0.5–1.5)	0.5 (0.3–0.8)	0.2 (0.1–0.4)	0.1 (0.1–0.2)	0.1 (0.0–0.1)
4	54 (38–72)	33 (22–48)	19 (12–29)	10 (6.3–16)	5.3 (3.2–8.4)	2.7 (1.7–4.4)	1.4 (0.9–2.3)	0.7 (0.4–1.2)	0.4 (0.2–0.6)	0.2 (0.1–0.3)	0.1 (0.1–0.2)
5	70 (59–83)	47 (37–61)	28 (21–38)	15 (11–22)	8.2 (6.0–12)	4.3 (3.1–6.2)	2.2 (1.6–3.2)	1.1 (0.8–1.7)	0.6 (0.4–0.9)	0.3 (0.2–0.5)	0.2 (0.1–0.3)
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2	37 (30–50)	26 (20–35)	19 (14–25)	14 (9.3–21)	11 (6.9–18)	9.4 (5.4–15)	8.1 (4.4–14)	7.4 (3.9–13)	7.0 (3.7–12)	6.7 (3.5–12)	6.5 (3.3–11)
3	51 (39–64)	37 (27–48)	27 (18–39)	20 (12–32)	16 (8.0–27)	14 (7.0–24)	12 (5.7–21)	11 (5.1–20)	10 (4.7–18)	8.7 (4.5–16)	9.3 (4.3–16)
4	66 (50–77)	50 (35–58)	37 (26–48)	28 (19–40)	23 (15–34)	19 (12–30)	16 (9.3–27)	15 (8.2–25)	14 (7.8–24)	14 (7.2–23)	13 (6.9–22)
5	80 (71–87)	64 (53–69)	50 (40–56)	39 (31–47)	31 (25–40)	26 (20–35)	23 (17–31)	21 (15–29)	20 (14–27)	19 (13–27)	18 (13–26)
6	90	78	63	51	42	35	31	28	27	26	25

T score -4.0 -3.5 -3.0 -2.5 -2.0 -1.5 -1.0

15% ○CRFs 0 1 2 3 3 4 4

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0	17	12	8.3	6.3	5.1	4.2	3.6	3.3	3.2	3.1	2.9
1	26 (23–32)	18 (15–23)	13 (10–16)	9.5 (7.2–12)	7.6 (5.4–9.7)	6.4 (4.4–8.4)	5.5 (3.6–7.4)	5.0 (3.3–6.9)	4.8 (3.1–6.6)	4.6 (2.9–6.4)	4.4 (2.8–6.2)
2	37 (30–50)	26 (20–35)	19 (14–25)	14 (9.3–21)	11 (6.9–18)	9.4 (5.4–15)	8.1 (4.4–14)	7.4 (3.9–13)	7.0 (3.7–12)	6.7 (3.5–12)	6.5 (3.3–11)
3	51 (39–64)	37 (27–48)	27 (18–39)	20 (12–32)	16 (8.0–27)	14 (7.0–24)	12 (5.7–21)	11 (5.1–20)	10 (4.7–18)	8.7 (4.5–16)	9.3 (4.3–16)
4	66 (50–77)	50 (35–58)	37 (26–48)	28 (19–40)	23 (15–34)	19 (12–30)	16 (9.3–27)	15 (8.2–25)	14 (7.8–24)	14 (7.2–23)	13 (6.9–22)
5	80 (71–87)	64 (53–69)	50 (40–56)	39 (31–47)	31 (25–40)	26 (20–35)	23 (17–31)	21 (15–29)	20 (14–27)	19 (13–27)	18 (13–26)
6	90	78	63	51	42	35	31	28	27	26	25

T score -4.0 -3.5 -3.0 -2.5 -2.0 -1.5 -1.0

10% ○CRFs 0 0 1 1 2 2 2

15% ○CRFs 0 1 2 3 3 4 4

Osteoporosis management in younger postmenopausal women

- **General use of HRT for fracture prevention – fracture events saved and risks in balance**
- **Numbers low**
- **The FRAX based estimation facilitates identification of women at increased fracture risk**
- **Where 15% threshold is used women need to have osteoporosis and RFs to justify treatment**
- ***This contrasts with the concept that HRT use more generally in this group must be beneficial***

Essentials for progress to a common view

- **We need to understand**
  - **that we bring our individual thinking processes, with inherent cognitive biases to our examination of data**
  - **that in good faith there might be quite divergent views**
- **We should strive to recognise the importance of seeking the highest quality evidence and to accept the result of a fair appraisal of that evidence**

My view on place of HRT in management

- **Use of HRT in premature or surgical menopause is not challenged**
- **Place of HRT in older postmenopausal women should be limited**
  - ***?indications***
  - ***? ongoing use***
  - ***? 2nd line in osteoporosis***

My view on place of HRT in management

- **Use of HRT below 60 years for fracture prevention in asymptomatic women**
  - ***risks low***
  - ***good efficacy data***
  - ***should be at increased fracture risk***

My view on place of HRT in management

- **Use of HRT for menopausal symptom relief is solidly justified.**
  - ***Risks low***
  - ***Good efficacy***
  - ***No basis for a lack of confidence in this situation.***
  - ***Lower doses reduce side effects.***
- **Joint decision-making with woman is essential in all use of HRT**

Who should use HRT? - 2008

- **Reasons for considering using HRT**
  - **Relief of vasomotor symptoms**
  - **Relief of other menopausal symptoms**
  - **Management of of postmenopausal bone loss??**
  - **Prevention of cardiovascular disease?????**
  - **Prevention of Dementia?????**

Who should use HRT? - 2008

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  - **Prevention of Dementia?????**

Yes Limited No

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Two to three years of hormone replacement treatment in healthy women have long-term preventive effects on bone mass and osteoporotic fractures: the PERF study

Yu Z. Bagger,[a,*] László B. Tankó,[a] Peter Alexandersen,[a] Henrik Bo Hansen,[a] Anette Møllgaard,[a] Pernille Ravn,[a] Per Qvist,[b] John A. Kanis,[c] and Claus Christiansen[a]

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Study design of the four original placebo-controlled HRT trials

Trial	Study period	Exposure period (years)	Treatment	References[a]
A	1983–1985	2	2 mg estradiol + 1 mg CPA 2 mg estradiol + 1 mg NETA 3 mg estradiol p.c. + 200 mg progesterone placebo	[12–14]
B	1987–1989	2	2 mg estradiol + 0.75 μg LNG 2 mg estradiol + 10 mg MPA 2 mg estradiol + 1 mg CPA placebo	[15,16]
C	1993–1995	2	3-day cycle of 0.75 mg piperazine estrone sulphate + 0.35 mg NETA 3-day cycle of 1.5 mg piperazine estrone sulphate + 0.7 mg NETA 2 mg estradiol + 1 mg NETA placebo	[17]
D	1993–1996	3	1 mg estradiol + 25 μg gestodene 2 mg estradiol + 50 μg gestodene	[18]

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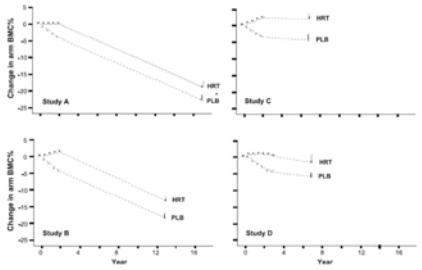

Fig. 1. Longitudinal changes in forearm bone mineral content (BMC) during 2–3 years of hormone replacement therapy (HRT) and certain years after stopping treatment. PLB denotes placebo. Data are mean ± SEM. Dashed lines indicate the period of HRT withdrawal.

fractures: the PERF study

Yu Z. Bagger,[a,*] László B. Tankó,[a] Peter Alexandersen,[a] Henrik Bo Hansen,[a] Anette Møllgaard,[a] Pernille Ravn,[a] Per Qvist,[b] John A. Kanis,[c] and Claus Christiansen[a]

Number of women who had a fracture and odds ratio (OR) of osteoporotic fractures between HRT and placebo groups at the time of follow-up

Type of fracture		Placebo (n = 108)	HRT (n = 155)	OR (95% CI)	
				Unadjusted	Adjusted[a]
Vertebral fracture	yes	26	18	0.41 (0.21–0.80)	0.47 (0.24–0.93)
	no	82	137	P = 0.008	P = 0.03
Nonvertebral fracture	yes	13	12	0.61 (0.28–1.40)	0.68 (0.30–1.60)
	no	95	143	P = 0.24	P = 0.38
All fractures	yes	36	27	0.42 (0.24–0.75)	0.48 (0.26–0.88)
	no	72	128	P = 0.003	P = 0.02

[a] Adjusted for age, baseline forearm BMC, and spine BMD.