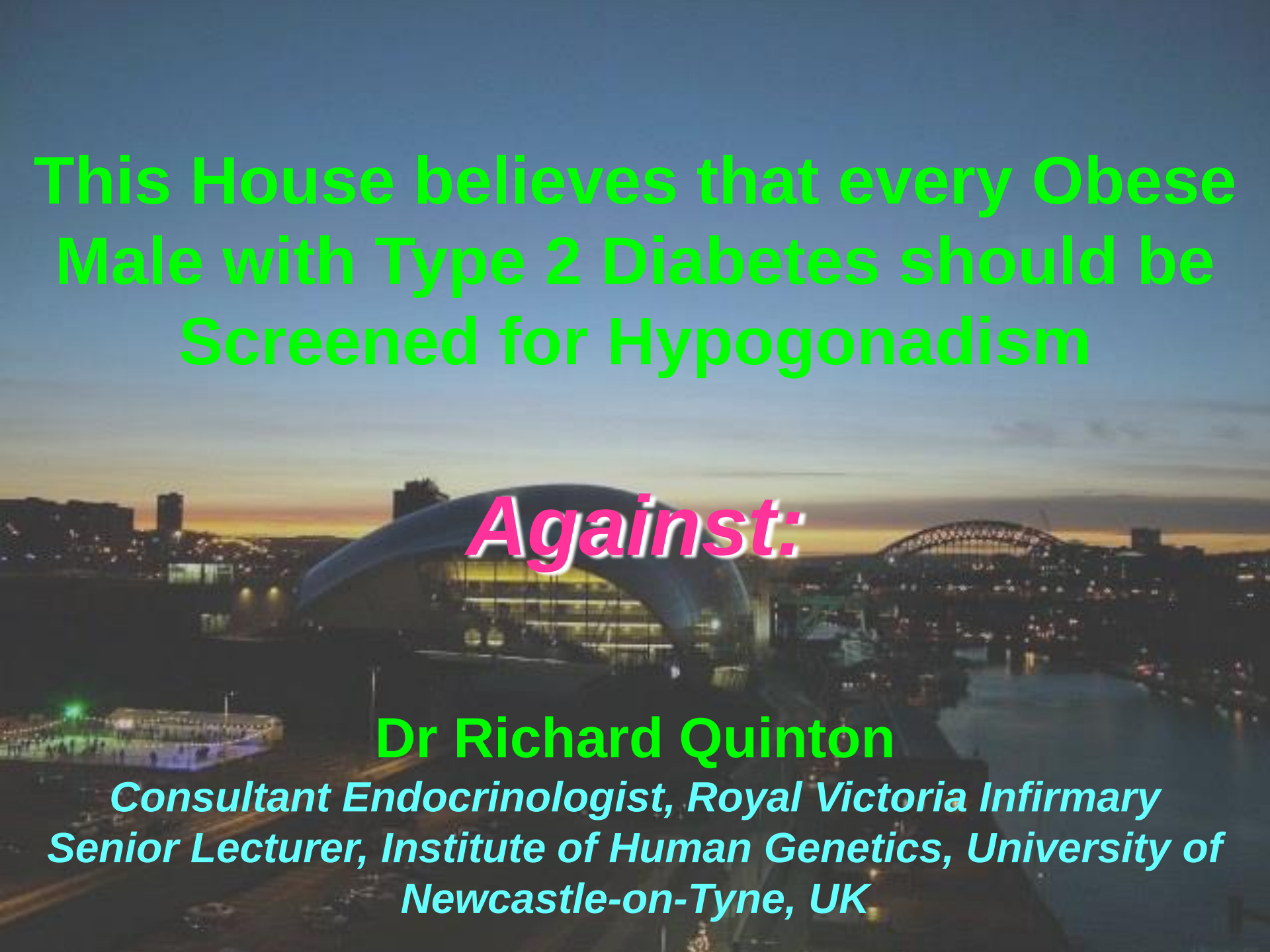
This House believes that every Obese Male with Type 2 Diabetes should be Screened for Hypogonadism

Against:



Dr Richard Quinton

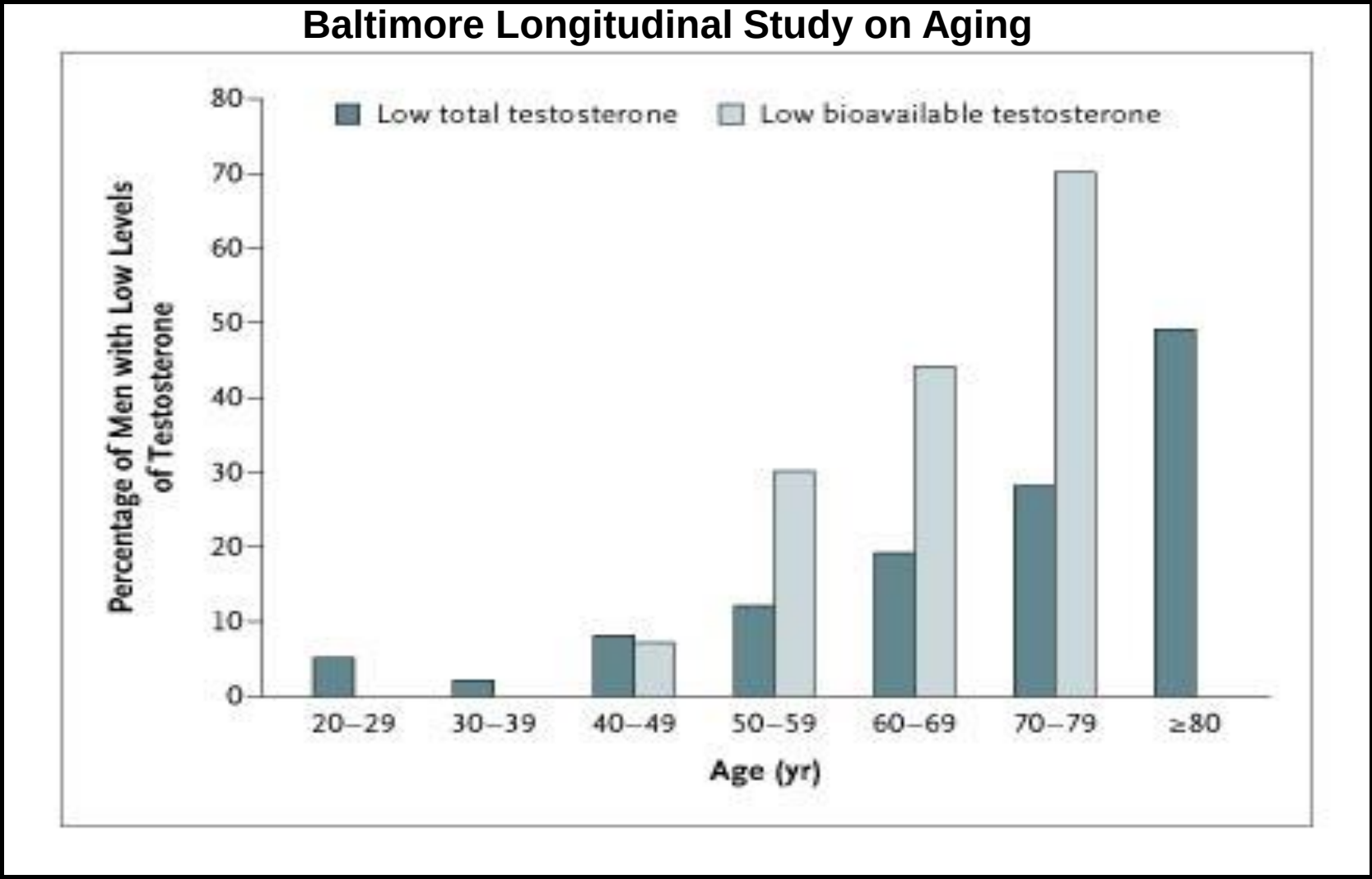
Consultant Endocrinologist, Royal Victoria Infirmary

Senior Lecturer, Institute of Human Genetics, University of Newcastle-on-Tyne, UK

Screening asymptomatic individuals is worthwhile if:

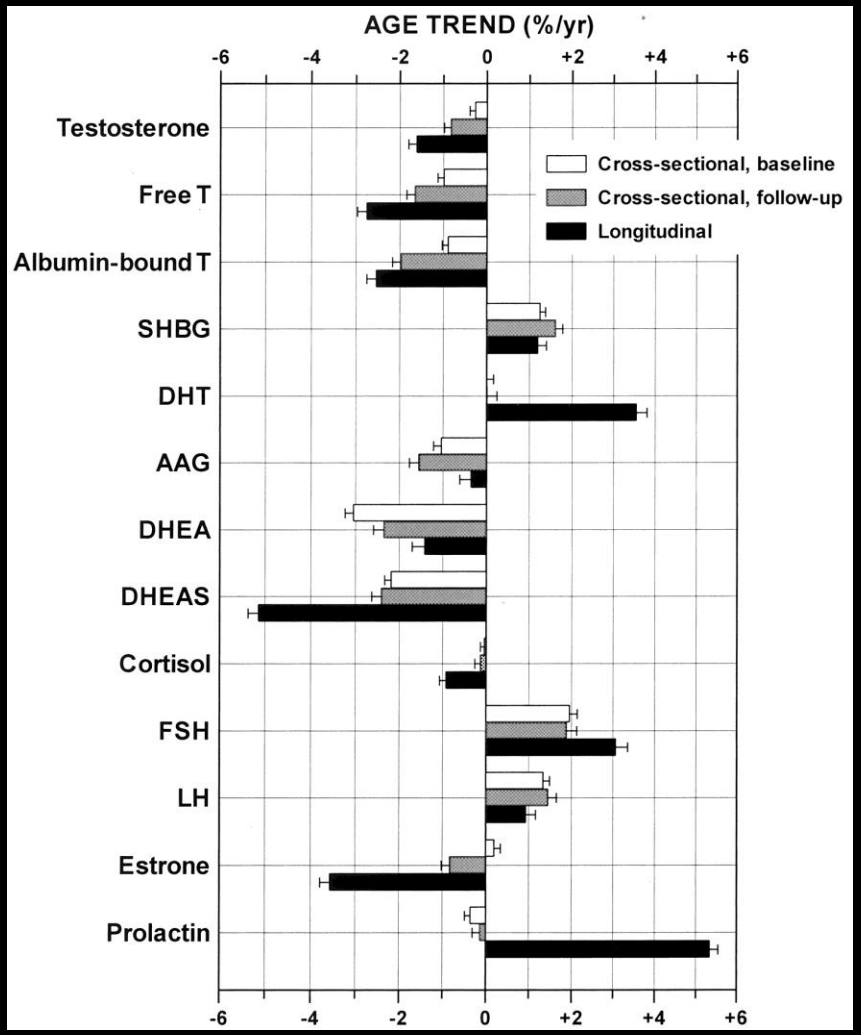
- Condition to be screened for has appreciable morbidity
- Test is reliable and cost-effective.
- There is a reasonable pick-up rate among the population to be screened.
- There is safe, effective & evidence-based treatment.

Age-Related Decline in Testosterone Levels



Decline in testosterone is both central (secondary) & peripheral (primary/testes) in origin. There is also loss of circadian rhythm of testosterone secretion & rise in sex hormone binding globulin (SHBG). ***Harman SM et al, JCEM. 2001; 86: 724-731***

Cross-sectional & longitudinal trends of Testosterone & related hormones in middle-aged men, participants in MMAS, 1987–97.



Feldman HA. et al.
J Clin Endocrinol Metab 2002;87:589-598

EMAS:

Secondary hypogonadism is associated with obesity & primary (compensated) hypogonadism…..with age.

Tajar A, et al.
J Clin Endocrinol Metab 2010;95:1810-1818

Gonadotrophin secretion is impaired with acute/critical illness & in chronic disease

- **Demonstrated for every conceivable disease state –even sleep-deprived young doctors (pre EWTD) & Norwegian soldiers in simulated arctic warfare conditions.**
- **Analagous to non-thyroidal illness syndrome =sick euthyroid.**
- **Is it adaptive or maladaptive? –intervention studies lacking.**
- **Not analogous to Hypothalamic Amenorrhoea in women, which is almost certainly an adaptive evolutionary response to avoiding pregnancy under famine/stress conditions.**

Aakvag A, et al. Eur J Appl Physiol, 1978; 39: 283-291.
Turner HE & Wass JA. Clin Endocrinol, 1997
Ball SG & Boudoin SV. Core Topics Endocrinol, Anaethesia & Crit Care, 2010

Frustrations in managing glycaemic control in patients with diabetes

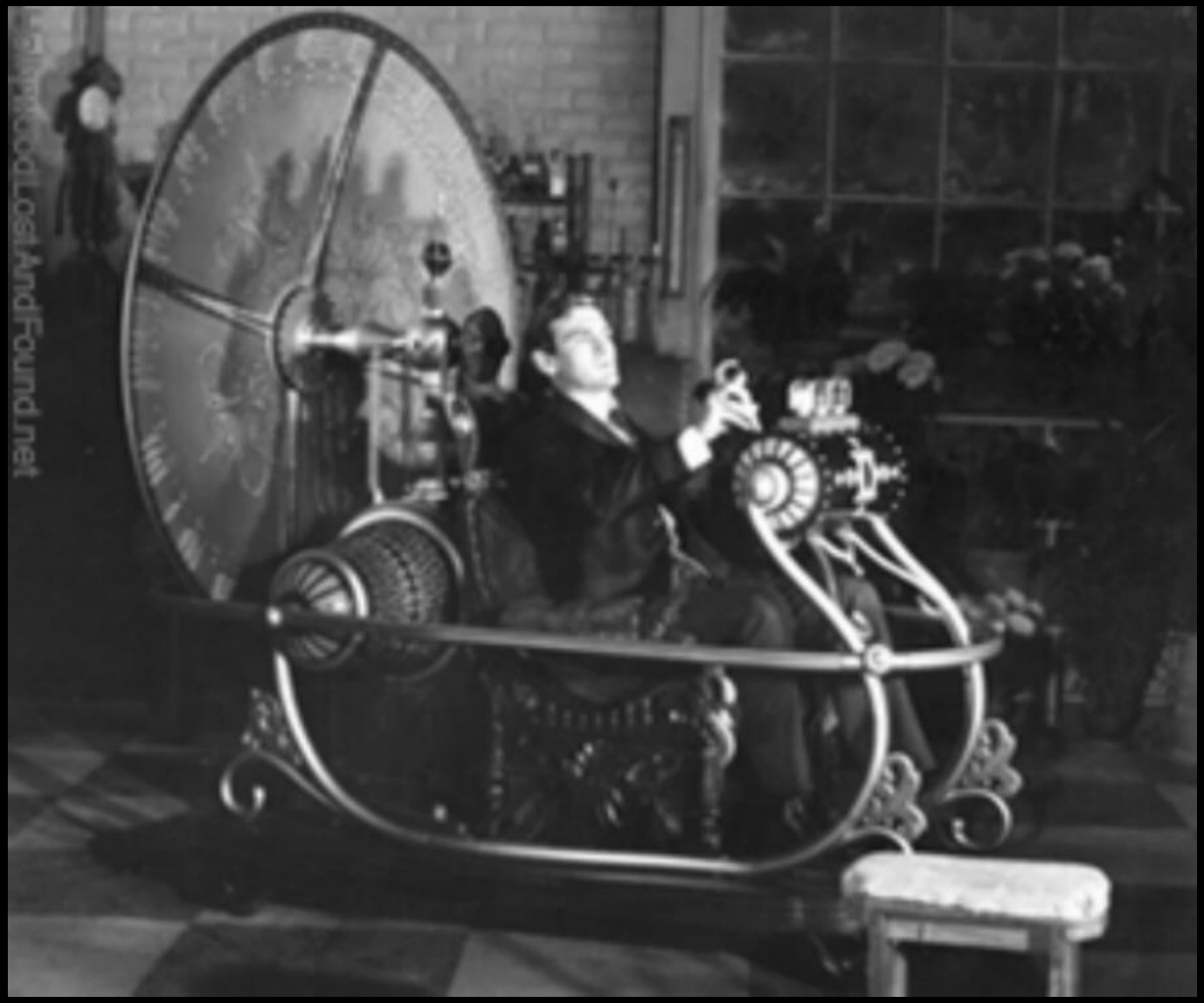
- Cardiovascular risk takes off with development of IGT.
- Microvascular risk takes off with progression to frank DM.
- Apart from diet/lifestyle adjustments ±Metformin, interventions aimed at reducing HbA1c much <7% result in adverse outcomes, hypoglycaemia, weight gain, *etc.*
- So given that we can't safely normalise HbA1c, can we do anything else to improve outcomes in Diabetes?

Tight BP control?	Yes, but no benefit from <120 *vs* <140 target.
Statins?	Yes (and the more the better?).
Aspirin?	Good idea, but remarkably NO!
HRT in women?	……we'll come back to that one later.
HRT in men?	Promising science & small-scale clinical trials.

Time to take a Lesson from The History Man:

Anthony Sher plays Howard Kirk, the lecherous Sociology lecturer at Waterhouse University in the BBC series of Malcolm Bradbury's novel

Let’s go back to 1997



What we used to think we knew

- **Menopause is a deficiency state & E_2 therapy restores the premenopausal endocrine milieu.**
- **E_2 therapy reduces the risk of cardiovascular disease, osteoporosis & Altzheimer's disease.**
- **Although its immediate effect is to alleviate climacteric symptoms, the major therapeutic benefit of E_2 seems to be cardiovascular disease prevention.**

Prelevic GM & Jacobs HS. Baillière's Clin Endocrinol Metab. 1997; 11: 311-340.

Cardiovascular disease protection (I)

- **Protection against CVD is the major benefit of menopausal hormone replacement therapy (HRT) [1].**
- **E_2 replacement therapy reduces morbidity & mortality from CHD by approximately 50% in normal post-menopausal women [2-4] & in those with established CHD [5].**
- **E_2 therapy is also associated with a reduction in the risk of death from stroke [6].**

[1] Stampfer & Colditz, 1991
Barrett-Connor & Laakso, 1990
Stampfer et al, 1990

[4] Barrett-Connor & Bush, 1991 *2*
[5] Henderson et al, 1991 *3*
[6] Paganini-Hill et al, 1988

Cardiovascular disease protection (II)

- **Angiographic studies have provided particularly strong evidence for the benefits of E_2 [1-4].)**
- **E_2 therapy reduces coronary stenosis, as documented by a repeat coronary angiogram [2-3].**
- **E_2 treatment also improves survival after coronary bypass surgery [5].**
- **Women with risk factors for CVD such as smoking, hypertension or history of myocardial infarction seem to be those who have the most to gain from HRT [6].**

[1] Gruchow et al, 1988
[2] Sullivan et al, 1988
[3] MacFarland et al, 1989
[4] Hong et al, 1992
[5] Sullivan et al, 1994
[6] Barrett-Connor & Bush, 1991

Effects on lipids & lipoproteins

- **E_2 therapy reduces serum total & LDL cholesterol [1-2].**
- **Cholesterol falls even more markedly in women with hypercholesterolaemia than in those with "normal » cholesterol concentrations [3].**
- **Oral E_2 therapy reduces LDL cholesterol by 10-15% [4].**
- **Transdermal (but not oral) E_2 causes a reduction in triglycerides by 15-20% [5].**

[1] Campos et al, 1993
[2] Crook et al, 1996
[3] Tonstad et al, 1995
[4] Rijpkema et al, 1990
[5] Crook et al, 1992

All the above observations remain true today, though the "beneficial" effect of E_2 on lipid profile are blunted by Progestin co-treatment.

Effects on Endothelial & Vascular Function

- **E_2 causes arterial relaxation via stimulation of nitric oxide (NO), inhibition of endothelin-1 production & direct non-genomic calcium-antagonist-like effects [1-3].**
- **In post-menopausal women with atherosclerosis both acute E_2 administration & long-term E_2 replacement therapy improve or enhance endothelium-dependent relaxation in response to acethylcholine [4-6].**

[1] Miller et al, 1988
[2] Collins et al, 1993
[3] Ylikorkala et al, 1995
[4] Williams et al, 1990
[5] Williams et al, 1992
[6] Gilligan et al, 1994

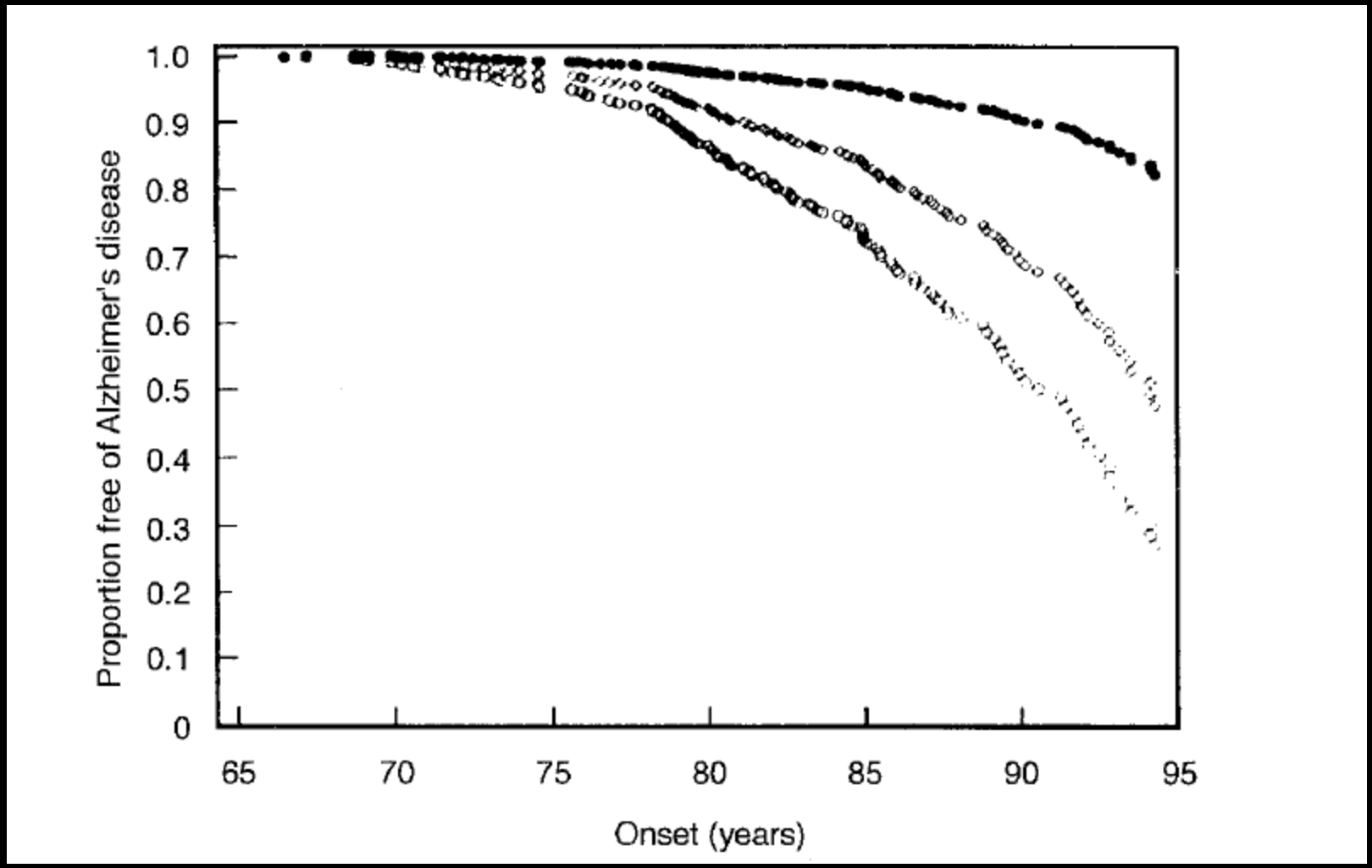
Effects on cardiac output & blood flow

- **E_2 increases blood flow in several vascular compartments, including uterus, skeletal muscle, brain & heart [1-4].**
- **E_2 replacement increases stroke volume, cardiac output & flow velocity over the aortic valve in healthy post-menopausal women [3-4].**
- **Both acute [5] & chronic [6] administration of E_2 increases peripheral blood flow in post-menopausal women.**

[1] Bourne et al, 1990
[2] Gangar et al, 1991
[3] Pines et al, 1991
[4] Prelevic & Beljic, 1994
[5] Volterrani et al, 1995
[6] Ginsburg & Hardiman, 1990

Effect on Altzheimer's disease age of onset

Nurses' Health Study



○ > 1yr ◆ ≤ 1 yr ● Never used

Table 1. **Age-Standardized Distribution of Characteristics of Women with Previous Coronary Disease in the Nurses' Health Study (1976–1996), according to Postmenopausal Hormone Use**

Characteristic	Hormone Use		
	Never	Current	Past
Parental myocardial infarction before 60 years of age, %	25.6	25.1	24.6
Hypertension, %	64.7	61.2	60.4
Diabetes mellitus, %	19.1	13.6	18.7
High serum cholesterol level, %	55.8	63.3	58.8
Current cigarette smoker, %	22.5	15.2	22.1
Mean age at entry, *y**	57.4	57.7	60.0
Mean age at menopause, *y*	48.4	45.0	45.0
Mean body mass index, kg/m^2	27.6	26.1	26.8

* For mean age at entry, information on hormone use at entry was used.

Grodstein F et al. Ann Intern Med. 2001; 135: 1-8

Table 2. **Risk for Major Coronary Heart Disease among Current Postmenopausal Hormone Users and Nonusers, Nurses' Health Study, 1976–1996**

Hormone Use	Person-Years of Follow-up	Cases, *n*	Age-Adjusted Relative Risk (95% CI)	Multivariate-Adjusted Relative Risk (95% CI)*
Never	358 125	662	1.0 (referent)	1.0 (referent)
Past	185 497	337	0.88 (0.77–1.00)	0.82 (0.72–0.94)
Current	265 203	259	0.54 (0.46–0.62)	0.61 (0.52–0.71)
<1 y†	20 091	9	0.30 (0.16–0.58)	0.40 (0.21–0.77)
1–1.9 y†	19 155	9	0.32 (0.16–0.61)	0.41 (0.21–0.80)
2–4.9 y†	78 928	60	0.47 (0.36–0.61)	0.53 (0.41–0.70)
5–9.9 y†	77 435	74	0.51 (0.40–0.65)	0.58 (0.45–0.74)
≥10 y†	69 594	107	0.69 (0.56–0.85)	0.74 (0.59–0.91)

* Adjusted for age, body mass index, history of diabetes, hypertension, high cholesterol level, age at menopause, cigarette smoking, and parental history of premature heart disease.
† Duration of use is underestimated by an average of 1 year, since duration during each 2-year follow-up period was established at the start of each period.

Grodstein F et al. Ann Intern Med. 2000; 133: 933-941.

Trend to lower stroke risk among women who used HRT for up to 2 years, compared with never used

Table 3. Risk for Stroke among Postmenopausal Current Users of Hormone Therapy and Nonusers by Duration of Therapy, Nurses' Health Study, 1976–1996

Hormone Use	Person-Years of Follow-up	All Stroke			Ischemic Stroke			Hemorrhagic Stroke		
		Cases, *n*	Age-Adjusted Relative Risk (95% CI)	Multivariate-Adjusted Relative Risk (95% CI)*	Cases, *n*	Age-Adjusted Relative Risk (95% CI)	Multivariate-Adjusted Relative Risk (95% CI)*	Cases, *n*	Age-Adjusted Relative Risk (95% CI)	Multivariate-Adjusted Relative Risk (95% CI)*
Never	358 125	312	1.0 (referent)		170	1.0 (referent)		79	1.0 (referent)	
Past	185 497	217	1.11 (0.93–1.33)	1.02 (0.85–1.24)	120	1.06 (0.84–1.34)	1.01 (0.79–1.30)	45	1.07 (0.74–1.55)	0.95 (0.65–1.40)
Current	265 203	238	1.03 (0.87–1.22)	1.13 (0.94–1.35)	142	1.13 (0.90–1.41)	1.26 (1.00–1.61)	50	0.89 (0.62–1.27)	0.93 (0.64–1.34)
<1 y†	20 091	13	1.05 (0.60–1.85)	1.32 (0.76–2.32)	6	0.94 (0.40–2.20)	1.07 (0.44–2.61)	5	1.39 (0.57–3.38)	1.56 (0.63–3.90)
1–1.9 y†	19 155	10	0.85 (0.45–1.60)	1.04 (0.55–1.97)	6	1.03 (0.46–2.32)	1.32 (0.58–3.00)	2	0.54 (0.13–2.28)	0.63 (0.15–2.59)
2–4.9 y†	78 928	61	1.08 (0.82–1.43)	1.14 (0.86–1.52)	36	1.25 (0.87–1.79)	1.31 (0.90–1.92)	14	0.87 (0.49–1.55)	0.95 (0.54–1.67)
5–9.9 y†	77 435	63	0.94 (0.71–1.23)	1.05 (0.79–1.38)	42	1.14 (0.81–1.60)	1.36 (0.96–1.92)	12	0.73 (0.40–1.34)	0.74 (0.40–1.36)
≥10 y†	69 594	91	1.09 (0.85–1.39)	1.17 (0.91–1.49)	52	1.02 (0.74–1.39)	1.17 (0.84–1.63)	17	1.11 (0.66–1.87)	1.03 (0.59–1.78)

* Adjusted for age, body mass index, history of diabetes, hypertension, high cholesterol level, age at menopause, cigarette smoking, and parental history of premature heart disease.
† Duration of use is underestimated by an average of 1 year, since duration during each 2-year follow-up period is established at the start of each period.

Grodstein F et al. Ann Intern Med. 2000; 133: 933-941

HERS RCT shows no benefit of E_2+Prog HRT in the 2^0 prevention of CHD

Table 2. Cardiovascular Events During Heart and Estrogen/Progestin Replacement Study (HERS), HERS II, and Overall

Outcome	Hormone		Placebo		Relative Hazard (95% Confidence Interval)*	*P* Value†	*P* Value‡
	No. of Events	Events/ 1000 Person-Years	No. of Events	Events/ 1000 Person-Years			
Primary Event							
CHD							
HERS	179	34.0	182	34.3	0.99 (0.81-1.22)	.94	.99
HERS II	111	41.8	111	42.1	1.00 (0.77-1.29)	.97	
Overall	290	36.6	293	36.8	0.99 (0.84-1.17)	.93	
CHD death							
HERS	70	12.7	59	10.6	1.20 (0.85-1.69)	.31	.46
HERS II	62	20.6	63	20.7	0.99 (0.70-1.41)	.96	
Overall	132	15.5	122	14.2	1.09 (0.85-1.39)	.49	
Nonfatal myocardial infarction							
HERS	122	23.2	134	25.2	0.92 (0.72-1.17)	.49	.76
HERS II	61	23.1	62	23.5	0.98 (0.69-1.40)	.91	
Overall	183	23.1	196	24.7	0.94 (0.77-1.15)	.54	

Hulley S, et al. JAMA. 1998; 280: 605-613

What did the HERS trial show? *

- **Taking estrogen plus progestin for up to 4 years did not prevent further heart attacks or death from previous heart disease in postmenopausal women who already had a previous heart attack or known heart disease.**
- **This neutral finding occurred even though there was a good effect of treatment on cholesterol.**
- **For the entire four-year HERS trial period, there were no significant differences in heart problems between the active hormone & the placebo groups.**
- **In the first year of HERS, the active hormone group did have somewhat more heart problems than the placebo group, but after 2 or more years the active hormone group had somewhat fewer heart problems.**

**** Information given to participants in the WHI study***

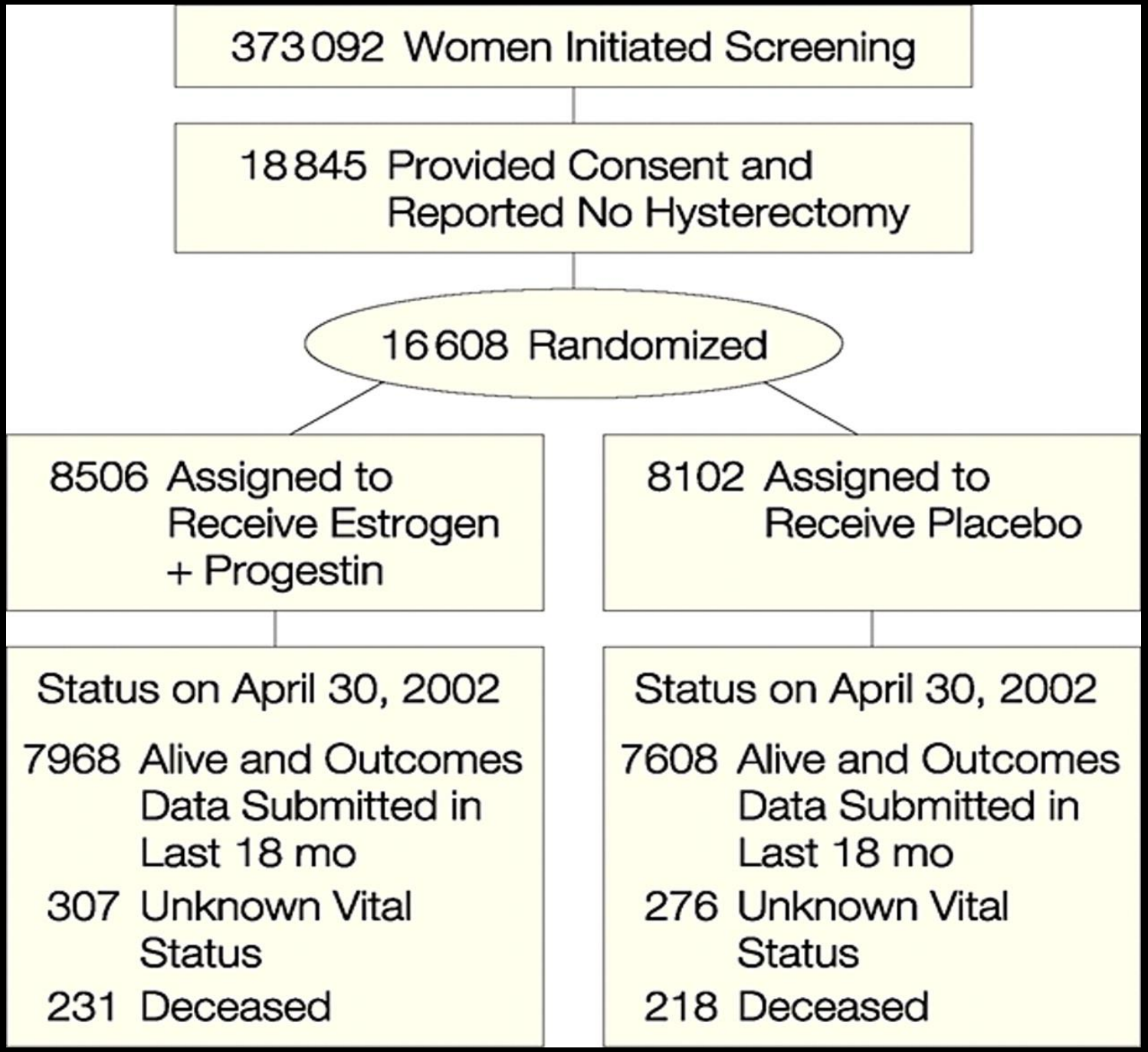
http://www.nhlbi.nih.gov/whi/update_hers1998.pdf

Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women

Principal Results From the Women's Health Initiative Randomized Controlled Trial

Women's Health Initiative Study

- RCT 1993-1998; 40 centres in USA..
- 16608 women aged 50-79 with intact uterus
- Low fat dietary pattern, Ca+D supplementation.
- Once daily E_2+progestin or placebo.
- Primary outcomes: occurrence of CAD events (non fatal MI & CAD related death) & invasive breast Ca.
- Secondary outcomes: osteoporotic fractures, CVD other than CAD, endometrial & colorectal Ca.


373 092 Women Initiated Screening
18 845 Provided Consent and Reported No Hysterectomy
16 608 Randomized
8506 Assigned to Receive Estrogen + Progestin
8102 Assigned to Receive Placebo
Status on April 30, 2002
7968 Alive and Outcomes Data Submitted in Last 18 mo
307 Unknown Vital Status
231 Deceased
Status on April 30, 2002
7608 Alive and Outcomes Data Submitted in Last 18 mo
276 Unknown Vital Status
218 Deceased

WHI: key findings after five years

Early study termination based on increased risk of:

- **Breast cancer (from 30 to 38 cases per 10,000 women)**
- **Coronary heart disease (from 30 to 37 cases per 10,000)**
- **Stroke (from 21 to 29 cases per 10,000 women)**

WHI Clinical Outcomes

Outcomes	No. of Patients (Annualized %) Estrogen + Progestin (n = 8506)	Placebo (n = 8102)	Hazard Ratio	Nominal 95% CI	Adjusted 95% CI
Follow-up time, mean (SD), mo	62.2 (16.1)	61.2 (15.0)	NA	NA	NA
Cardiovascular disease†					
CHD	164 (0.37)	122 (0.30)	1.29	1.02-1.63	0.85-1.97
CHD death	33 (0.07)	26 (0.06)	1.18	0.70-1.97	0.47-2.98
Nonfatal MI	133 (0.30)	96 (0.23)	1.32	1.02-1.72	0.82-2.13
CABG/PTCA	183 (0.42)	171 (0.41)	1.04	0.84-1.28	0.71-1.51
Stroke	127 (0.29)	85 (0.21)	1.41	1.07-1.85	0.86-2.31
Fatal	16 (0.04)	13 (0.03)	1.20	0.58-2.50	0.32-4.49
Nonfatal	94 (0.21)	59 (0.14)	1.50	1.08-2.08	0.83-2.70
Venous thromboembolic disease	151 (0.34)	67 (0.16)	2.11	1.58-2.82	1.26-3.55
Deep vein thrombosis	115 (0.26)	52 (0.13)	2.07	1.49-2.87	1.14-3.74
Pulmonary embolism	70 (0.16)	31 (0.08)	2.13	1.39-3.25	0.99-4.56
Total cardiovascular disease	694 (1.57)	546 (1.32)	1.22	1.09-1.36	1.00-1.49
Cancer					
Invasive breast	166 (0.38)	124 (0.30)	1.26	1.00-1.59	0.83-1.92
Endometrial	22 (0.05)	25 (0.06)	0.83	0.47-1.47	0.29-2.32
Colorectal	45 (0.10)	67 (0.16)	0.63	0.43-0.92	0.32-1.24
Total	502 (1.14)	458 (1.11)	1.03	0.90-1.17	0.86-1.22
Fractures					
Hip	44 (0.10)	62 (0.15)	0.66	0.45-0.98	0.33-1.33
Vertebral	41 (0.09)	60 (0.15)	0.66	0.44-0.98	0.32-1.34
Other osteoporotic‡	579 (1.31)	701 (1.70)	0.77	0.69-0.86	0.63-0.94
Total	650 (1.47)	788 (1.91)	0.76	0.69-0.85	0.63-0.92
Death					
Due to other causes	165 (0.37)	166 (0.40)	0.92	0.74-1.14	0.62-1.35
Total	231 (0.52)	218 (0.53)	0.98	0.82-1.18	0.70-1.37
Global index§	751 (1.70)	623 (1.51)	1.15	1.03-1.28	0.95-1.39

UK Million Women Study

- **Pilot 1994 to 1997:- 6,000 women**
- **Launched in 1997:- prospective study**
- **1.3 million postmenopausal women**
- **Aged 50-64 at recruitment, with average age of 56 years**
  - 1 in 2 women had taken the oral contraceptive pill
  - 1 in 2 women had tried HRT
  - 1 in 3 women was currently using HRT
  - 1 in 4 had had a hysterectomy
  - 1 in 11 had a close female relative with breast cancer
  - 1 in 70 had had breast cancer in the past

Million Women Study
Ovarian cancer & HRT

- **Women who use HRT are at an increased risk of both incident & fatal ovarian cancer.**
- **Since 1991, use of HRT has resulted in some 1300 additional ovarian cancers & 1000 additional deaths from the malignancy in the UK.**

Million Women Study

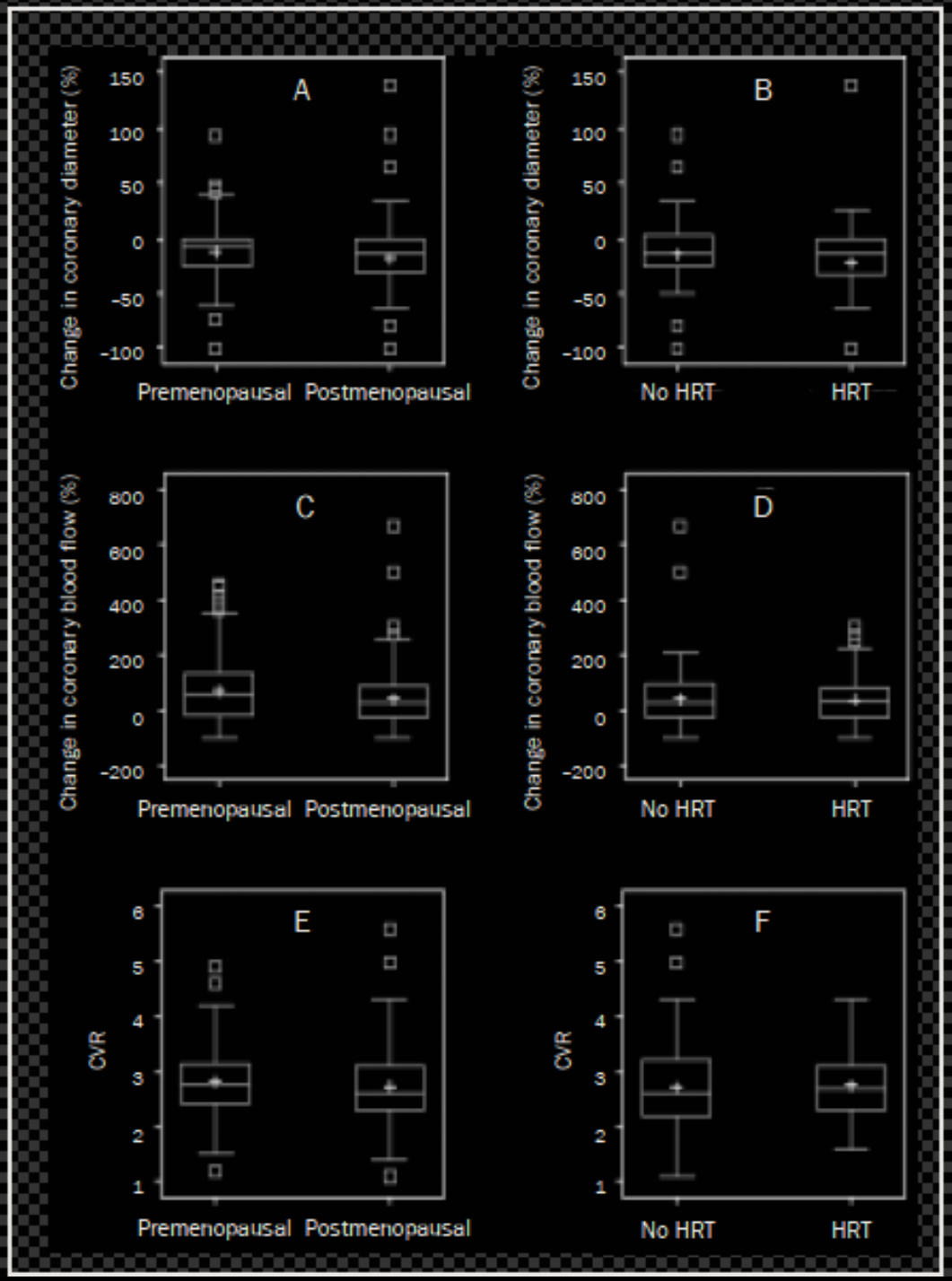
HRT & Breast Cancer

- HRT are more likely to develop breast cancer than those who are not using HRT.
- Past users are not at increased risk.
- Effect is substantially greater for combined HRT than for E_2-only HRT.
- Current users of combined HRT were at 2 fold increased risk of developing breast cancer.
- Current users of E_2-only HRT at 1.3 fold risk.
- Use of HRT by women aged 50-64 in the UK in the decade from 1993-2003 resulted in an estimated 20,000 extra breast cancers…albeit no demonstrable mortality excess.

Effect of Long-term Hormone Replacement Therapy on coronary Endothelial Function in Postmenopausal Women

Halligan SC, et al. Mayo Clinic Proc. 2004; 79: 1514-20

A total of 270 women (89 premenopausal & 181 postmenopausal) participated in the study. Endothelium-dependent coronary blood flow change (baseline to peak flow) in response to acetylcholine (10–6, 10–5, & 10–4 mol/L) was lower in postmenopausal women compared with premenopausal Women (39.7% vs 72.9%, P=.03). There was no significant difference between the postmenopausal women receiving & not receiving HRT with regard to percent change in coronary diameter (–21.8% vs –13.9%, P=.15), percent change in coronary blood flow (37.3% vs 42.7%, P=.74), or coronary velocity reserve (2.7 vs 2.7,P=.82)


A
Change in coronary diameter (%)
150
100
50
0
-50
-100
Premenopausal
Postmenopausal
B
Change in coronary diameter (%)
150
100
50
0
-50
-100
No HRT
HRT
C
Change in coronary blood flow (%)
800
600
400
200
0
-200
Premenopausal
Postmenopausal
D
Change in coronary blood flow (%)
800
600
400
200
0
-200
No HRT
HRT
E
CVR
6
5
4
3
2
1
Premenopausal
Postmenopausal
F
CVR
6
5
4
3
2
1
No HRT
HRT

Committee on Safety of Medicines

HRT should not be used to prevent coronary artery disease.

For menopausal symptoms or osteoporosis is important for women to discuss risks & benefits with their GP.

Trends in Endocrinology and Metabolism **2010 Apr 6 [epub ahead of print]**

Testosterone deficiency: a risk factor for cardiovascular disease?

T.H. Jones[1,2]

[1] Robert Hague Centre for Diabetes and Endocrinology, Barnsley Hospital NHS Foundation Trust, Barnsley, UK
[2] Academic Unit of Diabetes, Endocrinology and Metabolism, University of Sheffield, Sheffield, UK

The second question is whether testosterone therapy has a beneficial effect on cardiovascular risk and reduces cardiovascular events and mortality. A number of short-term studies support the notion that testosterone therapy improves independent cardiovascular risk factors (summarized in Figure 2), but there is no clear answer as to whether testosterone treatment reduces mortality. Accumulating evidence strongly supports a role of testosterone as an immunomodulatory and atheroprotective hormone and certainly warrants further scientific and clinical research. There is increasing interest not only in the scientific and clinical community but also in the media and general public especially in relation to diabetes. Although testosterone is now mainly administered as a natural hormone with the aim of replacing it to normal levels, we need to be careful with the diagnosis of hypogonadism and determine whether it is a safe mode of therapy in the longer term.

The major challenge would be to prove whether or not normalization of testosterone status by appropriate replacement therapy protects against and/or impedes the progression of atherosclerosis. Clinically, any beneficial or adverse effects of testosterone replacement therapy in men with cardiovascular disease could only be conclusively confirmed by a large multi-center randomized trial over 5 years. This trial would have to have a combined measure of cardiovascular events and death as the primary outcome. The safety of testosterone replacement therapy with regard to specific concerns about heart failure, prostate safety and polycythemia will require a full assessment.

I agree with Hugh, let's wait for the trial

Check 9am Testosterone in men with diabetes &

- **ED refractory to PDE_5 inhibitors.**
- **Evidence of osteoporotic # (but don't forget 25OHD!).**
- **Iron overload.**
- **Clinical features of hypogonadism.**

Acknowledgements

- **Dr Arif Ullah, Registrar in Diabetes & Endocrinology, RVI, for his contribution to these slides.**
- **Dr Gordana Prelevic & Prof Howard Jacobs for pointing me towards the evidence basis for HRT in post-menopausal women pre -WHI / MWS.**
- **Prof Hugh Jones for his mentorship over the years.**