Maintaining bone and cardiovascular health after the menopause

John C Stevenson
National Heart & Lung Institute
Imperial College London
Royal Brompton Hospital
London, UK

PRESENTER DISCLOSURE

Relationships with commercial interests:

- **Grants/Research Support:** Abbott, Pfizer
- **Speakers Bureau/Honoraria:** Abbott, Bayer, Gedeon Richter, Menarini, Mylan and Pfizer
- **Consulting Fees:** Abbott, Pfizer

OSTEOPOROTIC FRACTURE

- reduced bone mass
- increased bone turnover
- destruction of bone micro-architecture
- clinical consequence is fracture

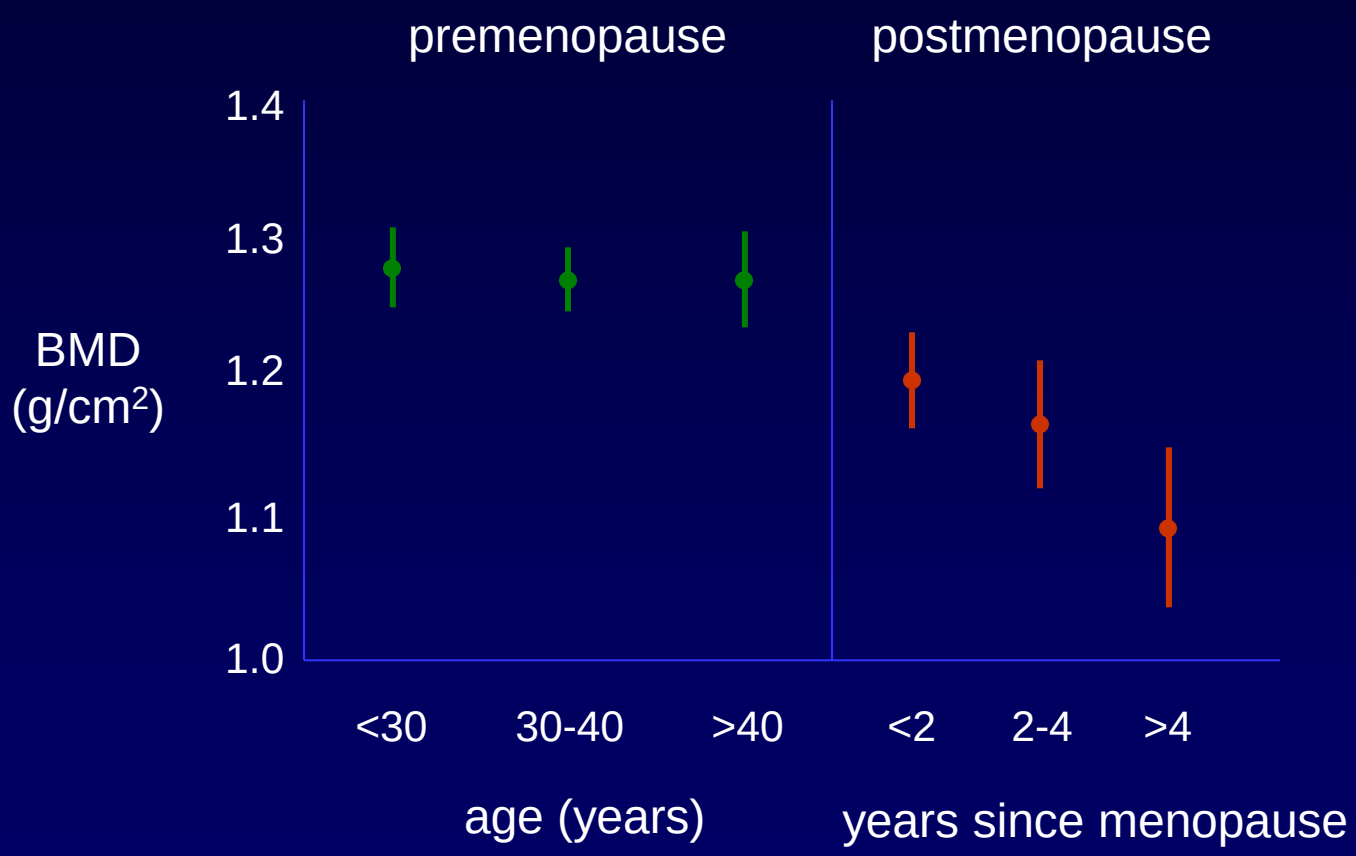
BONE DENSITY AND FRACTURE

- reduced bone density can result in osteoporotic fracture
- vertebral fracture is a common osteoporotic fracture
- reduced bone density accounts for <30% of fracture risk

MENOPAUSE

- menopause & BMD
- menopause & muscle loss
- menopause & intervertebral discs

BMD & MENOPAUSE: SPINE



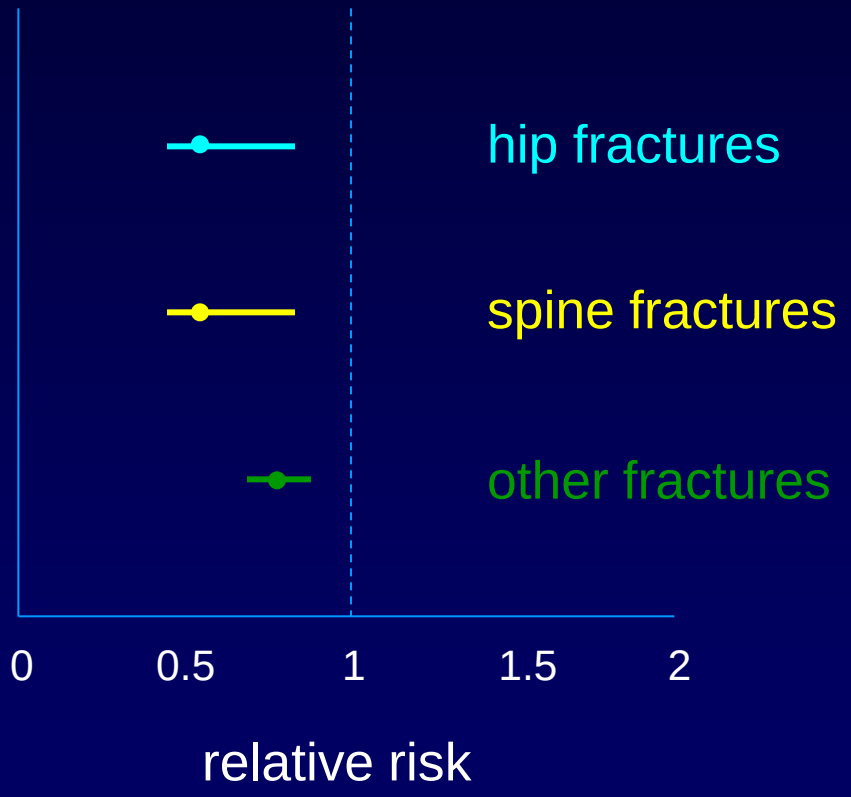
Stevenson et al. Br Med J 1989; 298: 914-28

E2/DYDRO: L_2-L_4 BMD

months

Lees & Stevenson. Osteoporosis Int 2001; 12: 251-58

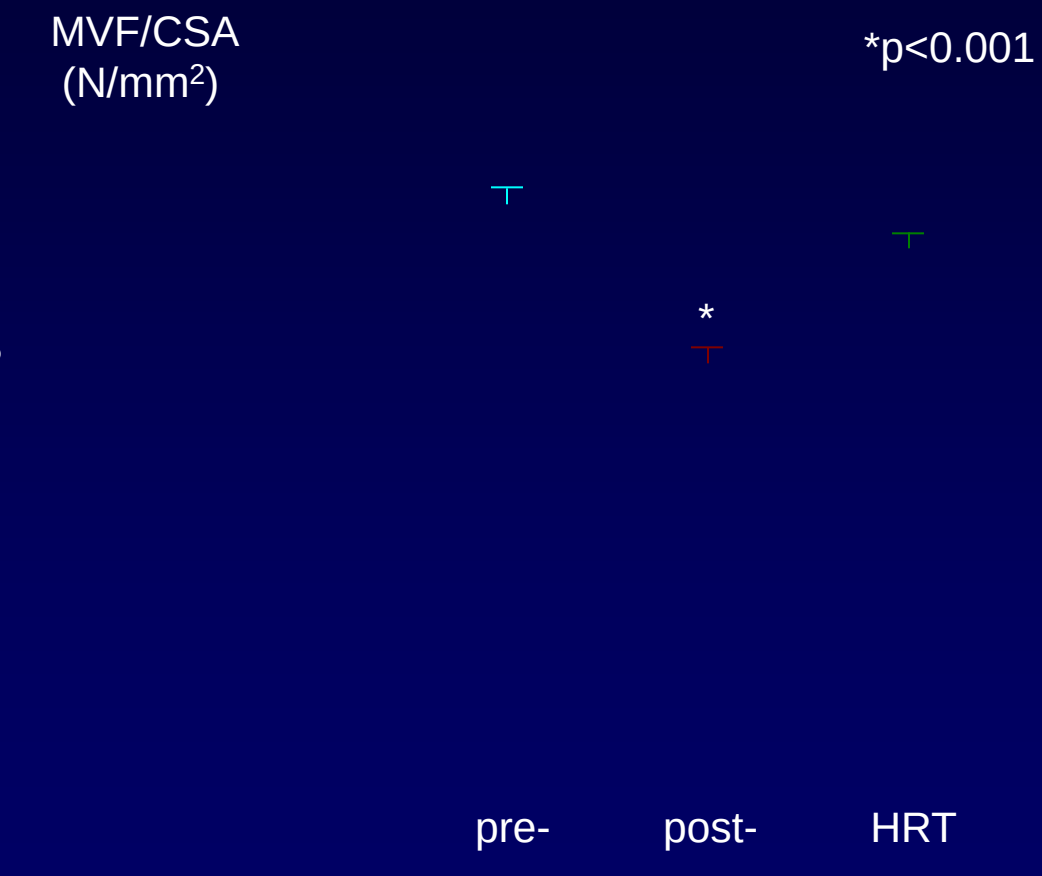
HRT AND FRACTURES



- Women's Health Initiative
- prospective randomised trial
- 16,608 postmenopausal women
- aged 50 - 80 years

Writing Group for Women's Health Initiative. JAMA 2002; 288: 321-33

MENOPAUSE: MUSCLE POWER



- locomotor effects
- muscle effects

Phillips et al. Clin Sci 1993; 84: 95-98

INTERVERTEBRAL DISCS

- intervertebral discs act as shock-absorbers in the spine
- loss of intervertebral disc height may predispose to vertebral fracture
- loss of intervertebral disc height occurs with aging
- loss of intervertebral disc height occurs with menopause

CROSS-SECTIONAL STUDIES

Muscat Baron et al. Human Reprod 2006

DISC HEIGHT: PLACEBO vs E DOSE

mean disc height

p=0.96. p=0.015 p=0.006

n=69 n=152 n=134

Stevenson et al, Climacteric 2023; 26: 110-13

MENOPAUSE AGE & CHD

- 10,533 women
- postmenopausal
- natural or surgical
- no prior CHD
- 286 CHD cases

menopause age

<40

40-45

>45

CHD

Lokkegaard et al. Maturitas 2006; 53: 226-33

MENOPAUSE: METABOLIC RISKS

- increased total cholesterol
- increased LDL cholesterol
- decreased HDL cholesterol
- increased triglycerides
- increased lipoprotein (a)
- increased small dense LDL particles
- Increased insulin resistance

MENOPAUSE: OTHER FACTORS

- altered fat distribution
- increased blood pressure
- haemostatic changes
- increased inflammatory markers
- impaired vascular endothelial function

HRT: METABOLIC EFFECTS

- oestrogen improves lipid profile - reduces LDL, increases HDL
- oral androgenic progestogens blunt HDL increase
- oral non-androgenic progestogens have little effect on lipid profile
- oestrogen improves insulin resistance - oral > transdermal
- oral androgenic progestogens worsen insulin resistance
- oral non-androgenic progestogens have little effect on insulin resistance

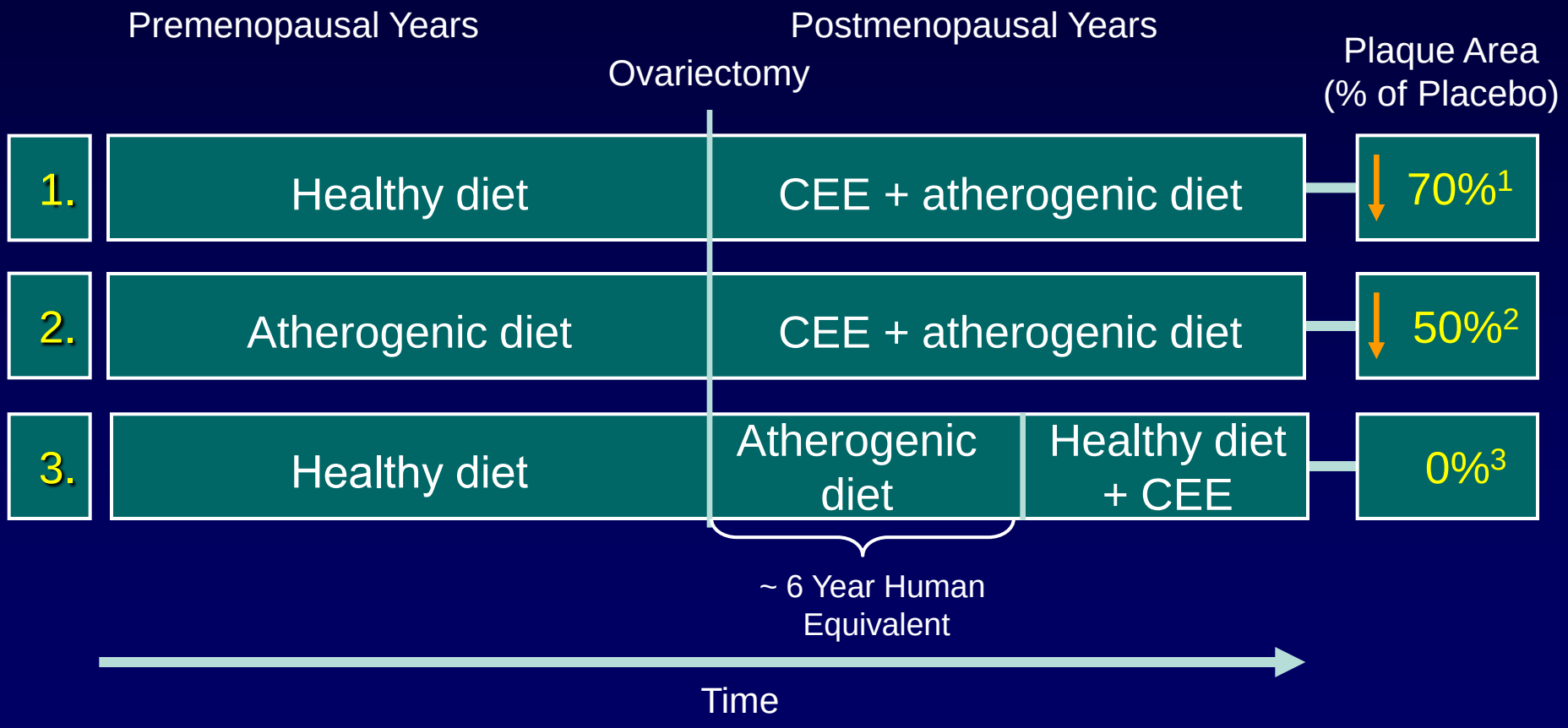
ESTROGEN: VASCULAR EFFECTS

- improves vascular function
- restores NO-dependent endothelial function
- increases endothelial NO synthase production
- reduces endothelial endothelin-1 release
- inhibits calcium channels
- enhances potassium-dependent channels
- reduces atheroma development
- androgenic progestogens blunt estrogen benefits on vascular function and atheroma development
- non-androgenic progestogens have no adverse effects

NO=nitric oxide

TIMING OF HRT INTERVENTION

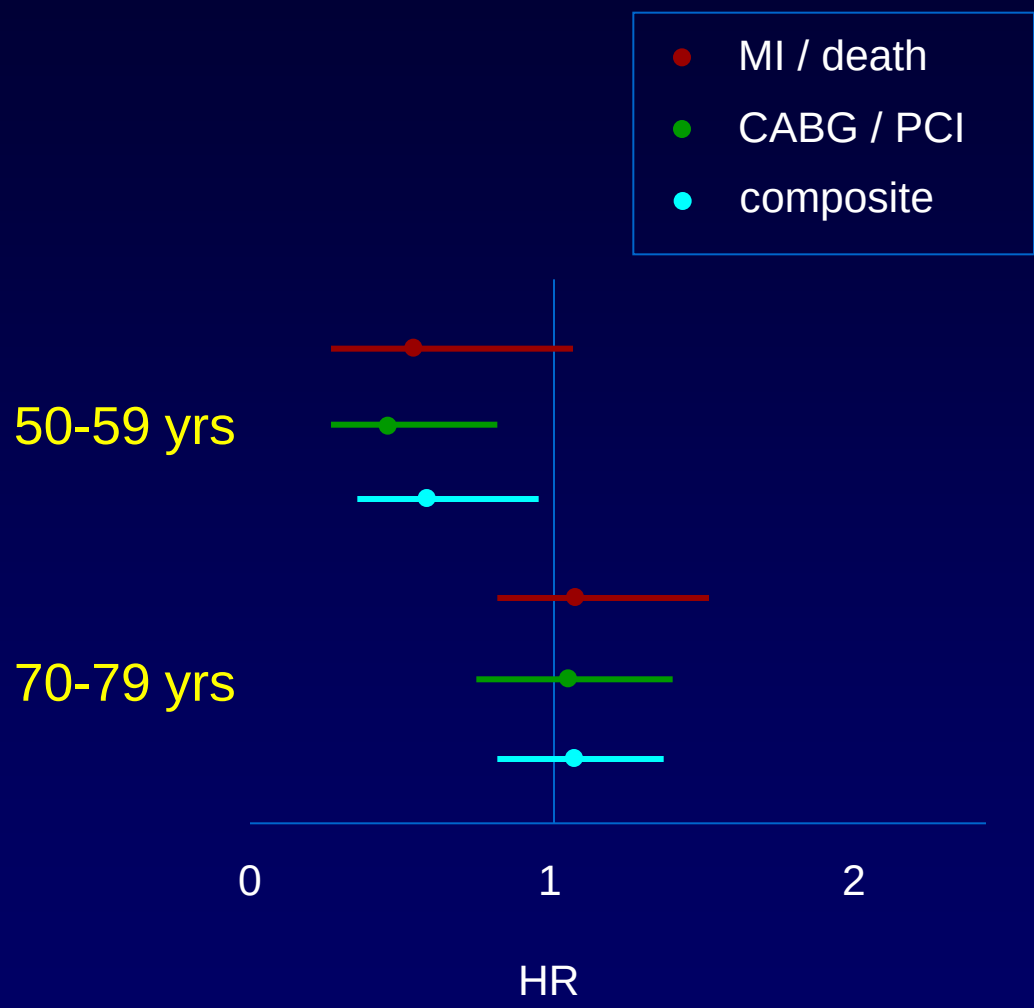
effect of estrogens on atherogenesis in non-human primates



[1]Clarkson et al. J Clin Endocrinol Metab 1998;83:721-26.
[2]Clarkson et al. J Clin Endocrinol Metab 2001;86:41.
[3]Williams et al. Arterioscler Thromb Vase Biol 1995;15:827.

WHI: CHD EVENTS (E alone)

- fewer CHD events in young women
- oestrogen dose too high for elderly women



Hsai et al. Arch Intern Med 2006; 166: 357-65

WHI AND CHD: FINAL OUTCOME

E alone treatment phase + cumulative follow-up

- age 50-59, HR 0.65 (CI 0.44-0.96)
- age 60-69, HR 1.00 (CI 0.82-1.23)
- age 70-79, HR 1.01 (CI 0.80-1.28)

Manson et al. JAMA 2013; 310: 1353-68

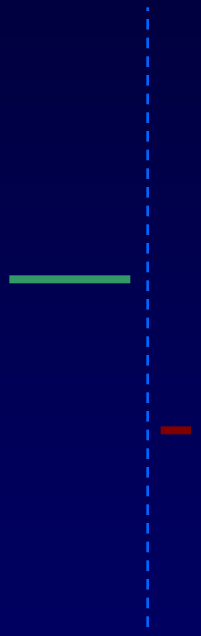
CHD: PRIMARY PREVENTION

- 1006 women aged 45-58 years, average 7 months postmenopause
- randomised to E 2 mg/1 mg/cyclical NETA 1 mg (or E 2 mg alone) or no treatment
- trial stopped after 10 years (observational follow-up for further 6 years)
- no increased risk of stroke, VTE or cancer (including breast cancer) with HRT

Schierbeck et al. BMJ 2012; 345: e64094

HRT & CHD META-ANALYSIS

- pooled results from 23 RCTs
- 39,049 postmenopausal women
- younger women aged <60 years / <10 years postmenopause
- older women aged >60 years / >10 years postmenopause
- randomised to HRT or placebo / no treatment
- followed for 191,340 patient-years
- myocardial infarction or cardiac death



Salpeter et al. J Gen Intern Med 2006; 21: 363-66

CONCLUSIONS

- menopause results in loss of bone, muscle power and intervertebral disc height, and an increase in osteoporotic fractures
- HRT reverses these losses and reduces fracture risk
- menopause results in an increase in CHD
- totality of current data indicates that HRT is beneficial for prevention of coronary events
- benefit may depend on:
  - type of hormones, particularly progestogen
  - dose of hormones
  - age at initiation of therapy