

Is there really a window of opportunity?

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DECLARATION OF INTERESTS

- I have been sponsored by pharmaceutical companies to speak publicly about HRT - both for and against
- I have received grants from pharmaceutical companies that have, and have not, HRT products, and from non-commercial sources, research councils and charities, to conduct HRT research

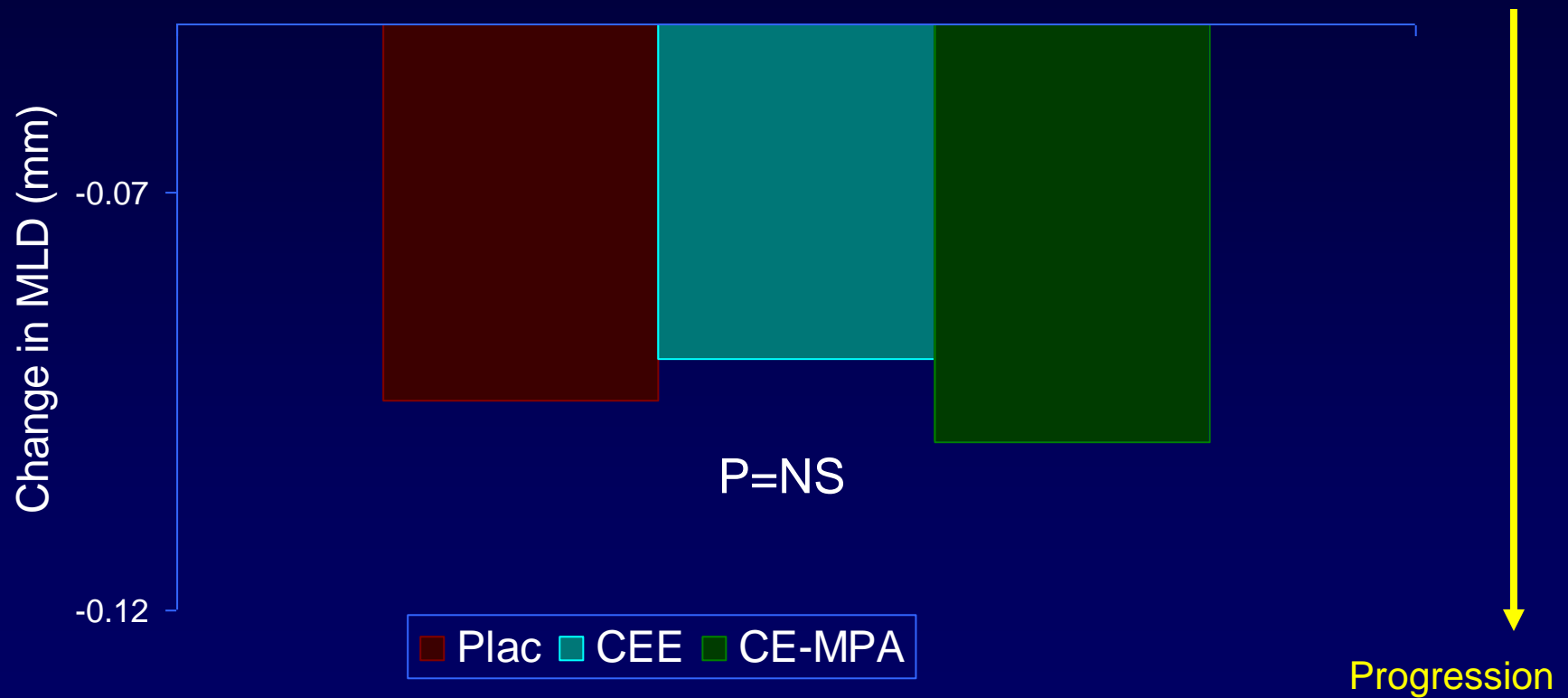
HRT & CARDIOVASCULAR SYSTEM

- lipids and lipoproteins
- glucose and insulin metabolism
- body fat distribution
- coagulation and fibrinolysis
- blood pressure
- arterial function

HRT AND CHD

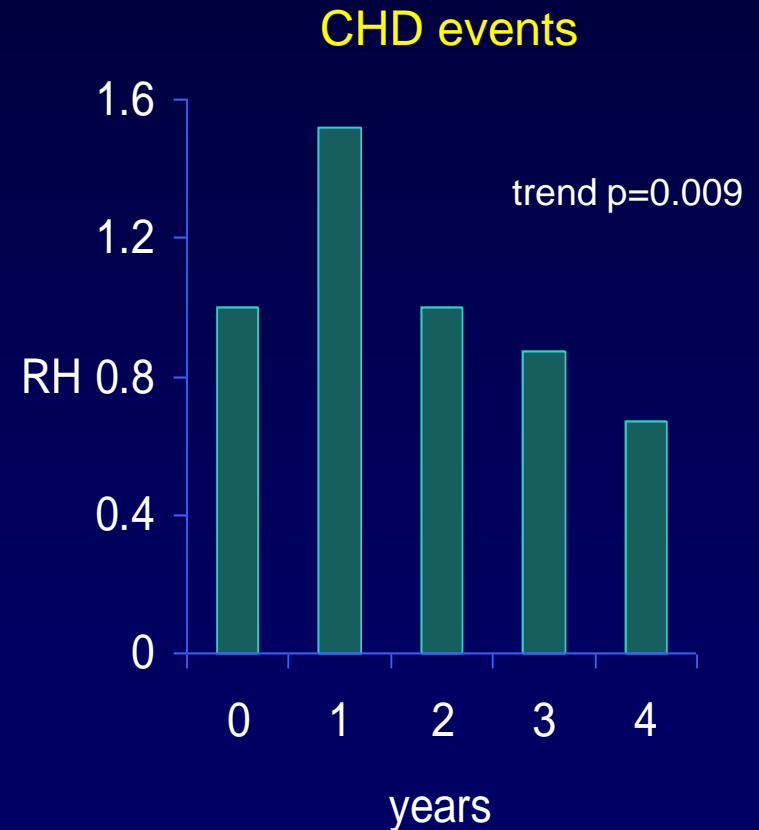
- in view of the biological effects of estrogen on the vascular system, how can HRT *not* be beneficial?

ERA STUDY



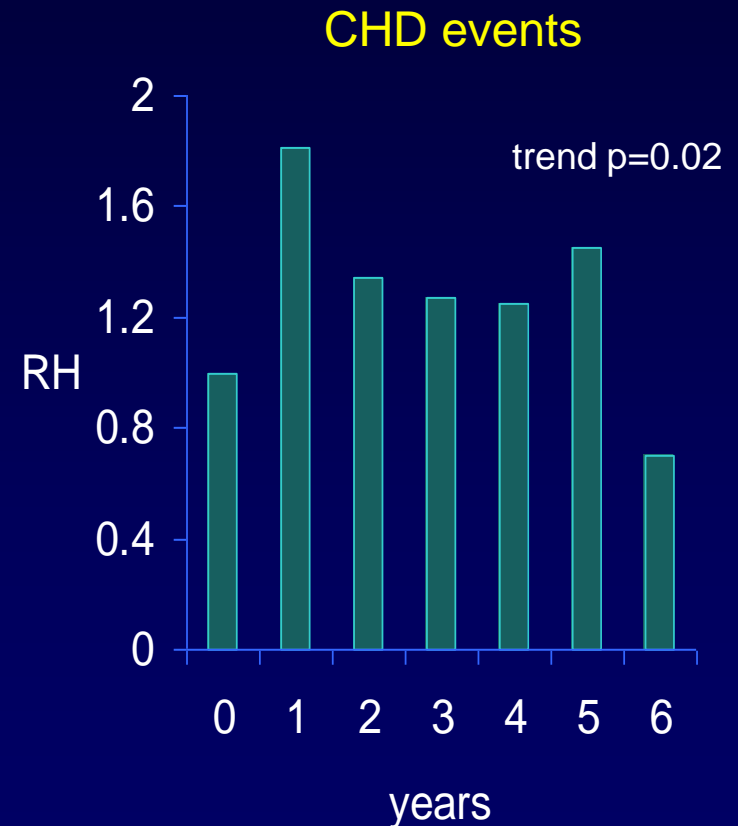
HERS TRIAL

- 2763 women
- mean age 66.7 years
- >6 months from cardiac event
- conjugated equine oestrogens 0.625 mg + MPA 2.5 mg
- event rate 3.3% (estimated 5%)
- mean follow-up 4.1 years (estimated 4.75 years)
- **no overall benefit seen**



WOMEN'S HEALTH INITIATIVE

- **no overall benefit seen**
- increased CHD events in early years
 - age skewed to older women
 - ? oestrogen dose too high
 - ? effect of MPA (E alone showed possible benefit)



HRT AND CHD

observational studies

- HRT is beneficial to CVS
 - primary prevention
 - secondary prevention
- women start HRT around menopause
- studies are not randomised
 - healthy user bias (applies to other outcomes e.g. osteoporosis)
 - data can be adjusted for potential biases

randomised trials

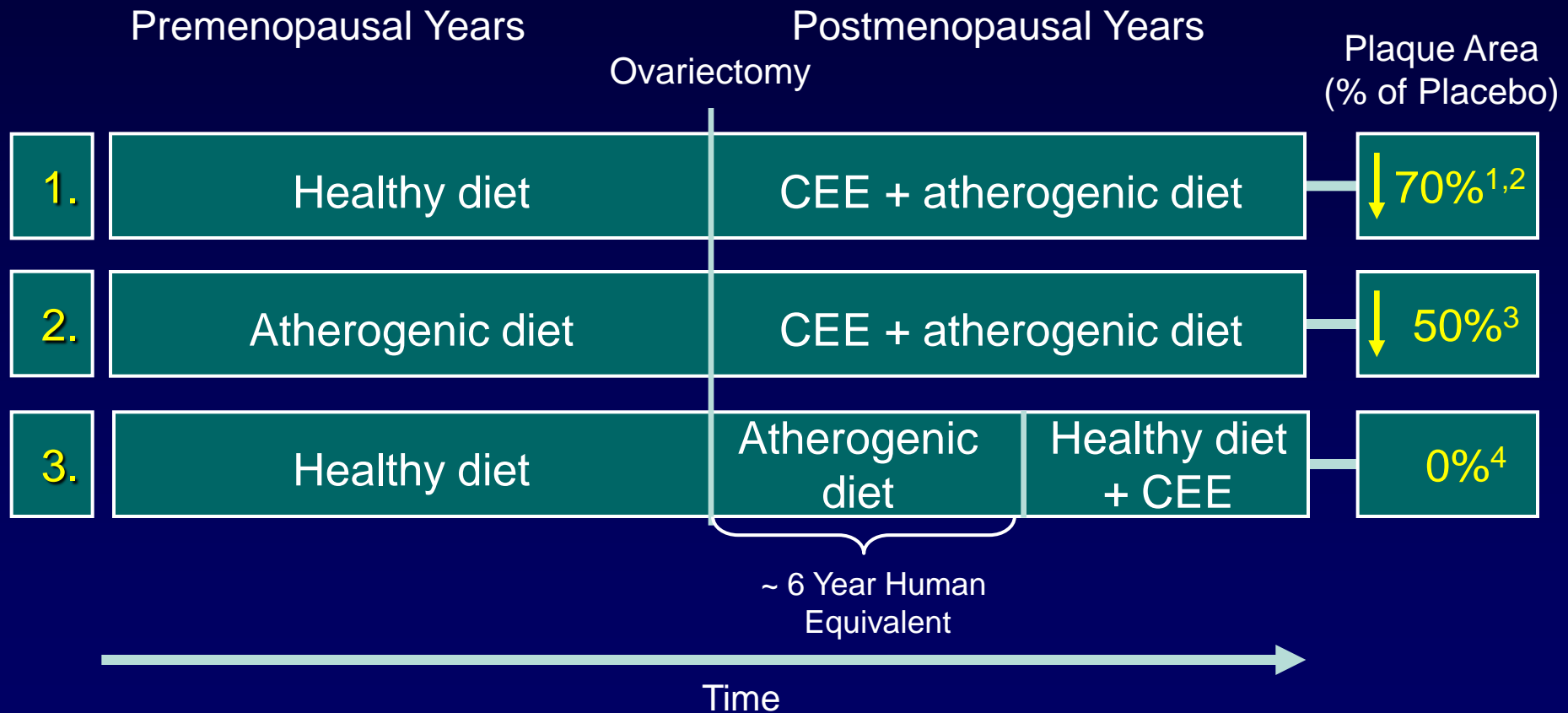
- HRT is not beneficial to CVS
 - primary prevention
 - secondary prevention
- women start HRT at later ages
- problem lies with HRT
 - dose and type of oestrogen
 - dose and type of progestogen
 - harm is due to increased thrombogenesis
 - harm is due to adverse vascular remodelling

HRT & CARDIOVASCULAR SYSTEM

- does it only work in younger / healthy women?
- does it not work in older / women with disease?
- is there just a “window of opportunity” around menopause?

TIMING OF HRT INTERVENTION

effect of estrogens on atherogenesis in non-human primates



¹Clarkson et al. J Clin Endocrinol Metab 1998;83:721.

³Clarkson et al. J Clin Endocrinol Metab 2001;86:41.

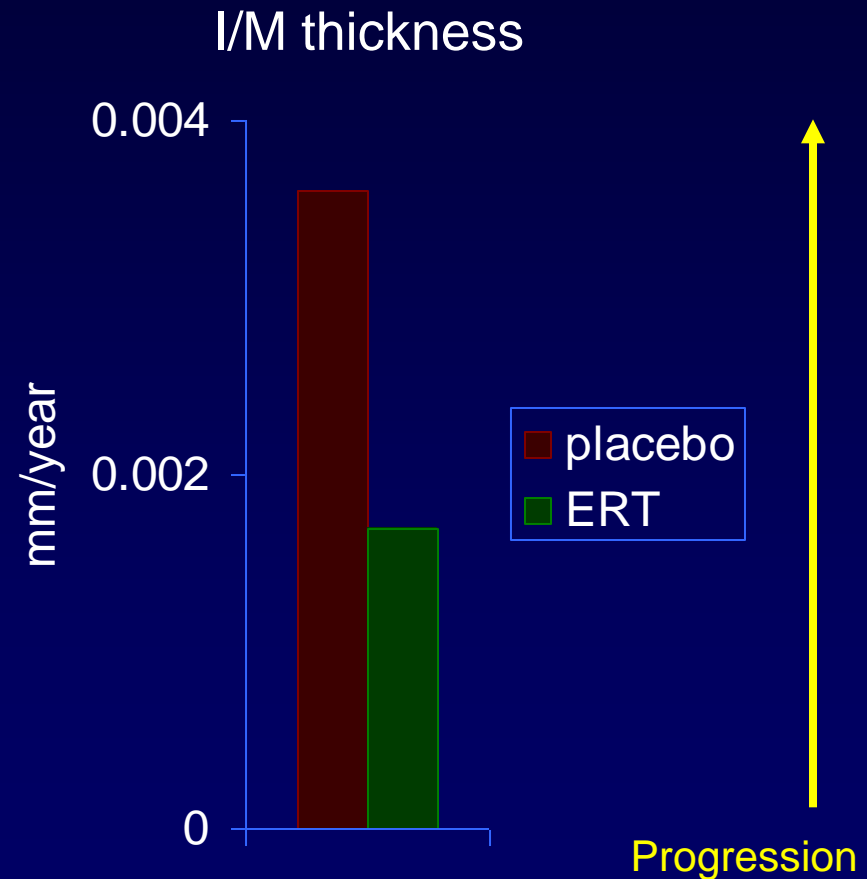
²Adams et al. Arterioscler Thromb Vase Biol 1997;17:217.

⁴Williams et al. Arterioscler Thromb Vase Biol 1995;15:827.

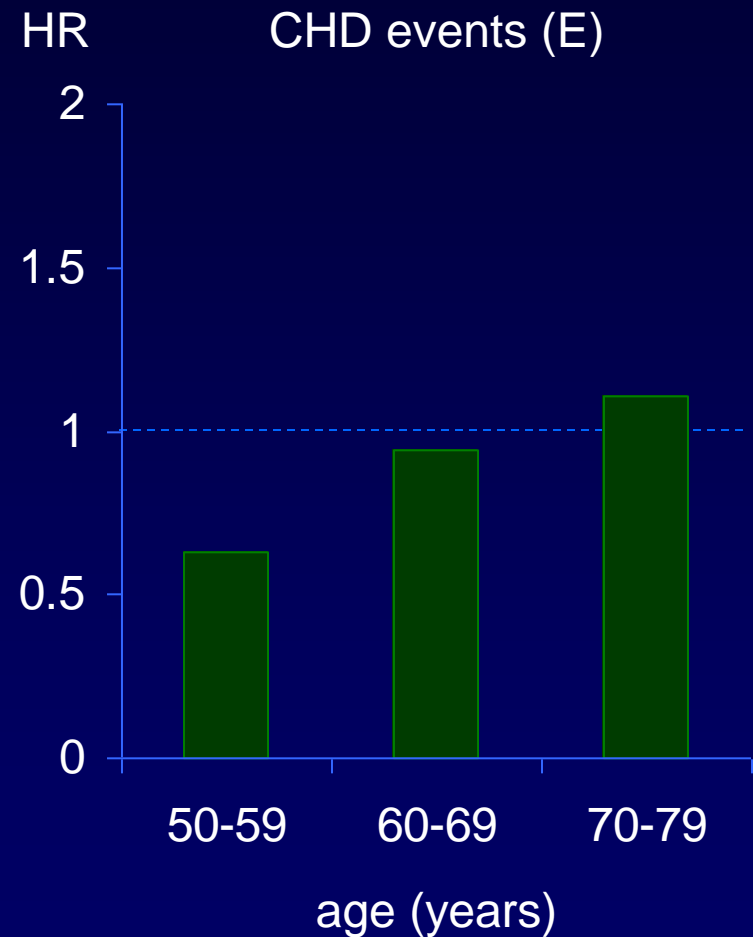
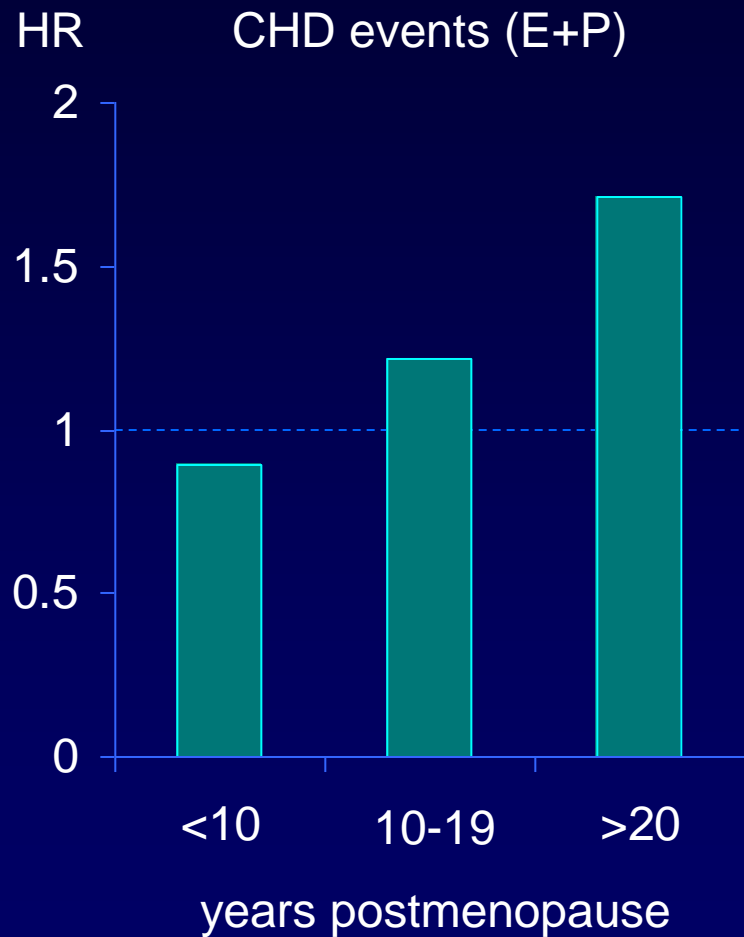
1995;15:827.

ERT AND ATHEROMA PREVENTION

- 222 healthy postmenopausal women
- oestradiol 17 β 1 mg daily vs placebo
- study duration 2 years
- carotid artery intima-media thickness by U/S

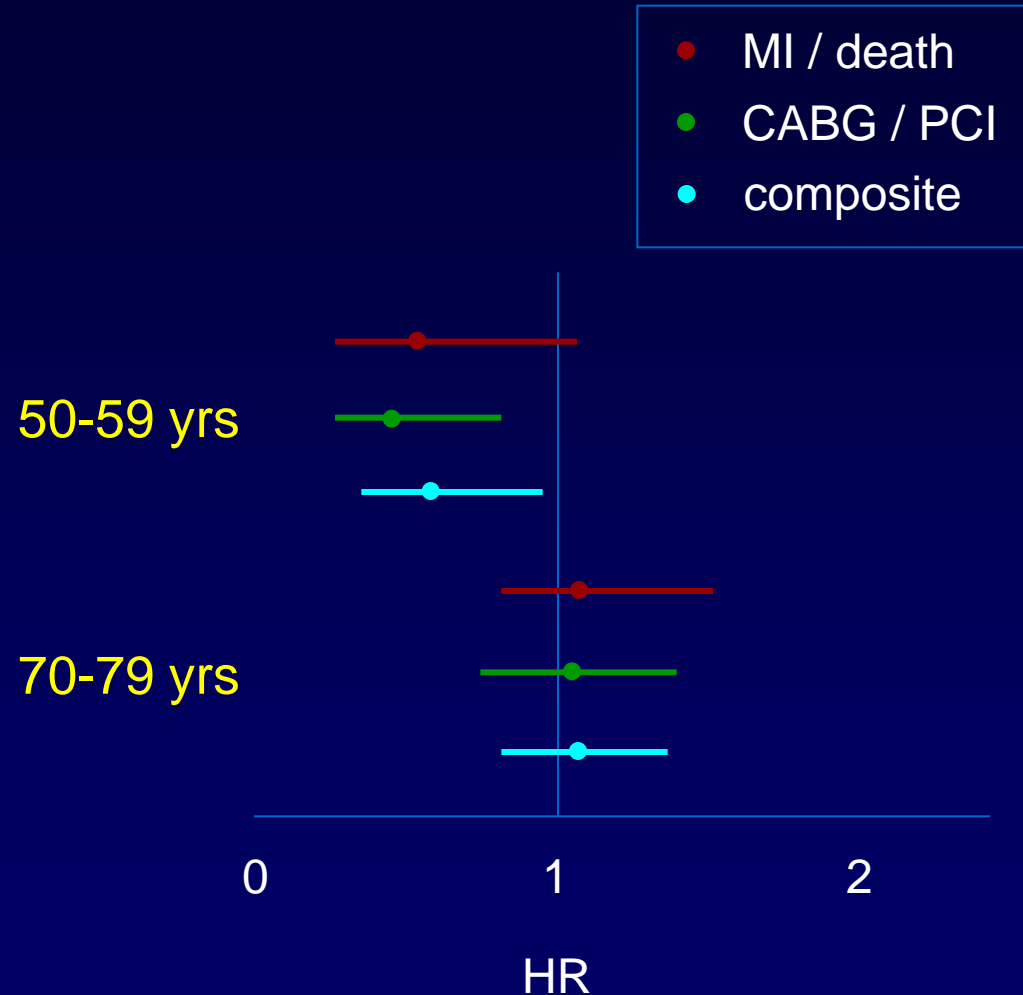


WHI: CHD RISK



HRT AND CHD EVENTS

- reduction in CHD events in young women
- no reduction in CHD events in elderly women
 - ? increased thrombogenesis / adverse remodelling
 - ? oestrogen dose too high

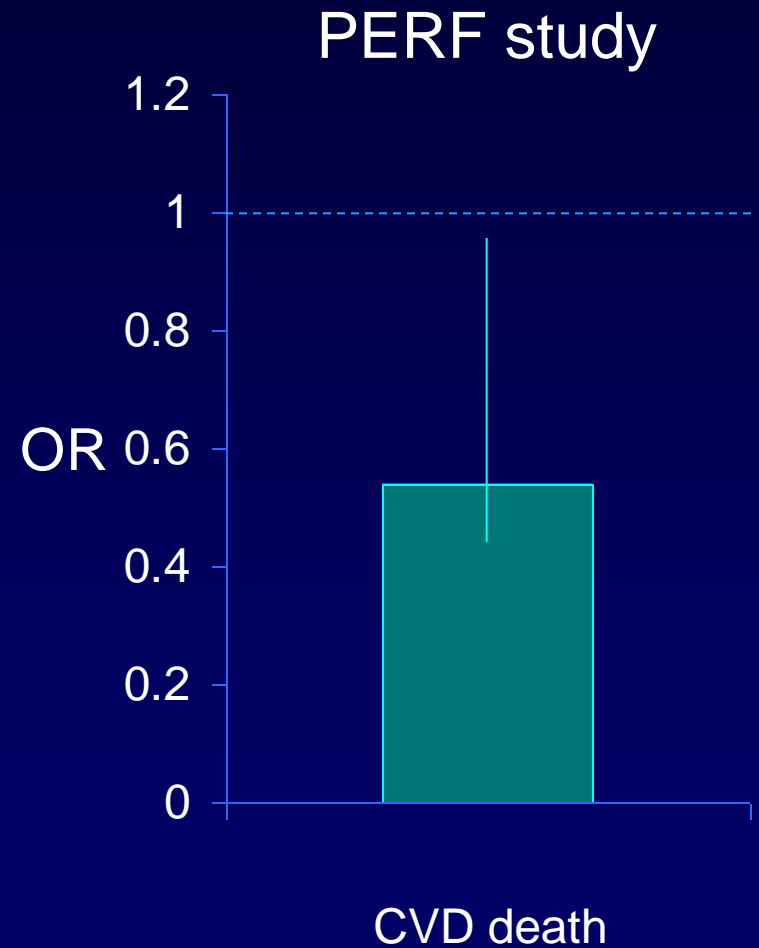


WHI - CACS

- 1064 hysterectomised women (50-59 years) now aged 64 years
- conjugated equine estrogens 0.625 mg daily or placebo for 7.5 years
- coronary artery calcification scores measured by CT 1.3 years after study termination
- 20-40% lower calcified plaque in ERT users
- 50-60% lower calcified plaque in ERT compliers

HRT AND SUBSEQUENT CHD

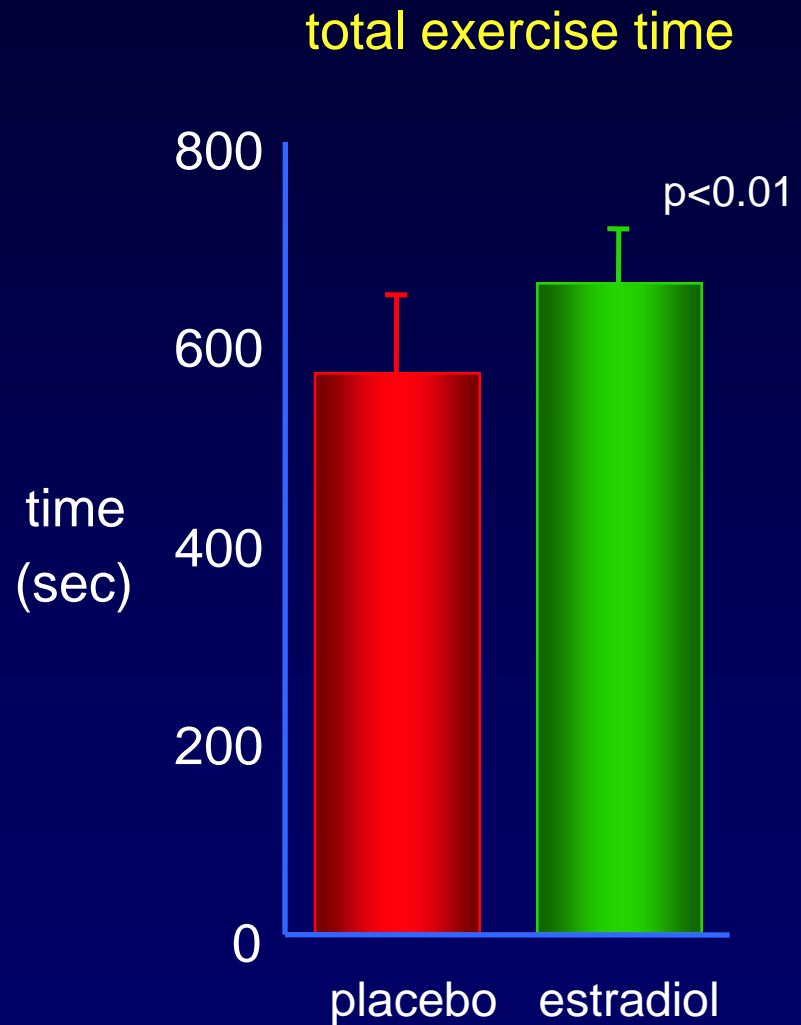
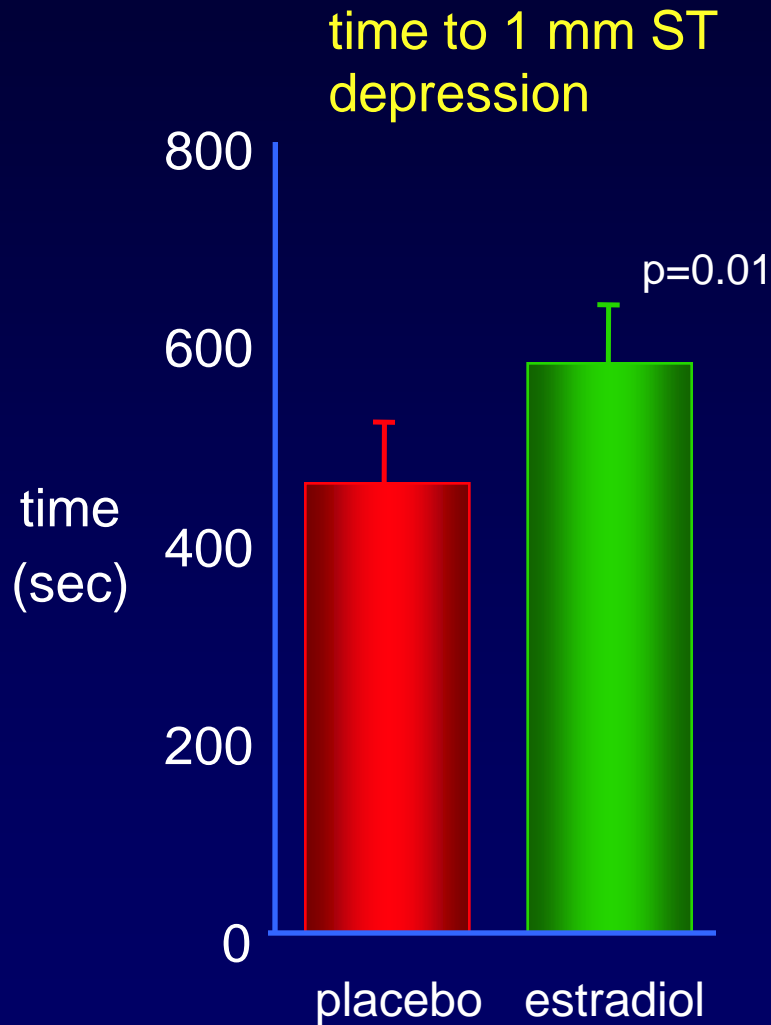
- 1,280 women
- healthy postmenopausal women
- age 65 years
- HRT or placebo for 2-3 years
- no subsequent HRT
- follow-up 5, 11 or 15 years



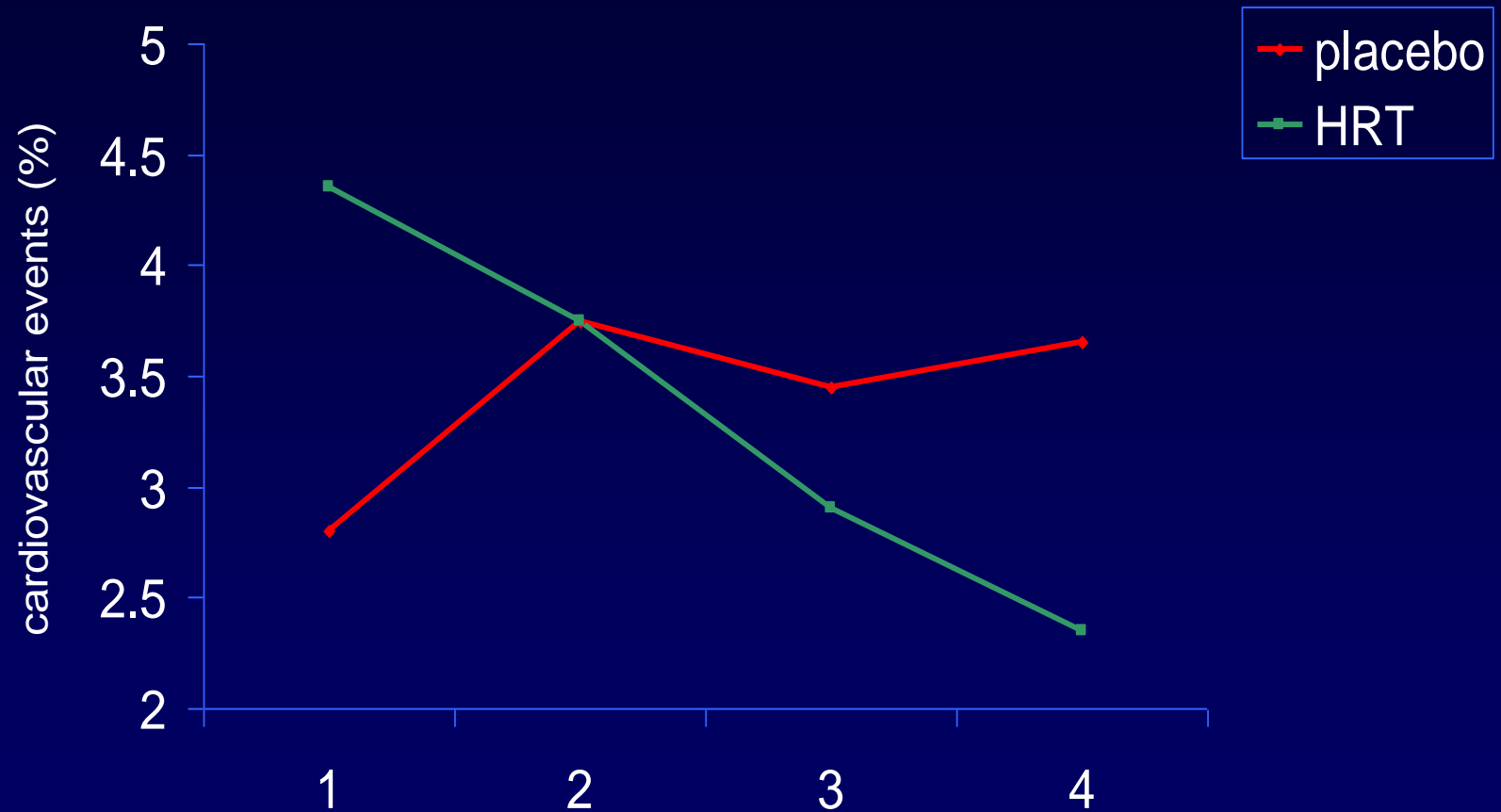
HRT & CARDIOVASCULAR SYSTEM

- it does work in younger / healthy women
- does it not work in older / women with disease?

ESTRADIOL & MYOCARDIAL ISCHAEMIA

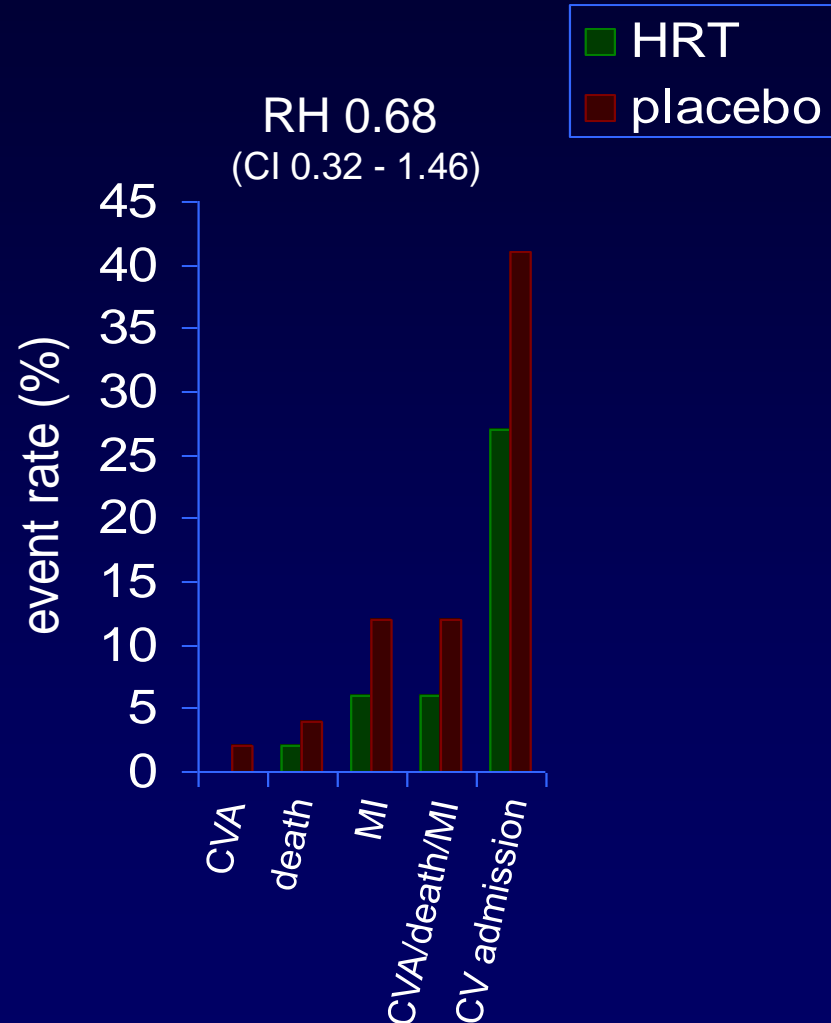


HERS TRIAL



WHISP

- 100 postmenopausal women followed up to 12 months
- acute coronary syndrome (majority MI)
- randomised to placebo or HRT 2 - 28 days post-event
- oestradiol 17 β 1 mg/NETA 0.5 mg daily
- efficacy
 - lipid parameters
 - (clinical events)
- safety
 - haemostatic parameters



CONCLUSIONS

- HRT may be beneficial for prevention of CHD
 - as yet, not an indication for HRT use
- greatest benefit may be seen in younger postmenopausal women
 - therapeutic “window of opportunity”
 - menopause is opportunity for CV risk assessment