The science behind HRT

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HRT: ESTROGENS

natural estrogens

- conjugated equine estrogens
- estradiol 17β
- estrone sulphate

synthetic estrogens

- ethinyl estradiol
- mestranol

HRT: PROGESTOGENS

19 nor-testosterone derivatives
- norgestrel
- norethisterone acetate
- desogestrel

19 nor-pregnane derivatives
- promogestone
- trimogestone

C-21 progestogens
- medroxyprogesterone acetate
- dydrogesterone
- progesterone

spironolactone derivatives
- drospirenone

PROGESTINS: RECEPTOR EFFECTS

19 nor-testosterone derivatives

Progestogen	E	A-E	AND	A-A	GLU	A-M
norethisterone	(+)	+	+	-	-	-
levonorgestrel	-	+	+	-	-	-
norgestimate	-	+	+	-	-	-
desogestrel	-	+	+	-	-	-
gestodene	-	+	+	-	(+)	+
dienogest	-	+	-	+	-	-

PROGESTINS: RECEPTOR EFFECTS

progesterone derivatives

Progestogen	EST	A-E	AND	A-A	GLU	A-M
progesterone	-	+	-	(+)	(+)	+
medroxyprogesterone	-	+	(+)	-	+	-
dydrogesterone	-	+	-	-	-	(+)
chlormadinone acetate	-	+	-	+	+	-
medrogestone	-	+	-	(+)	-	-
cyproterone acetate	-	+	-	+	+	-
drospirenone	-	+	-	+	-	+

HRT: ROUTES

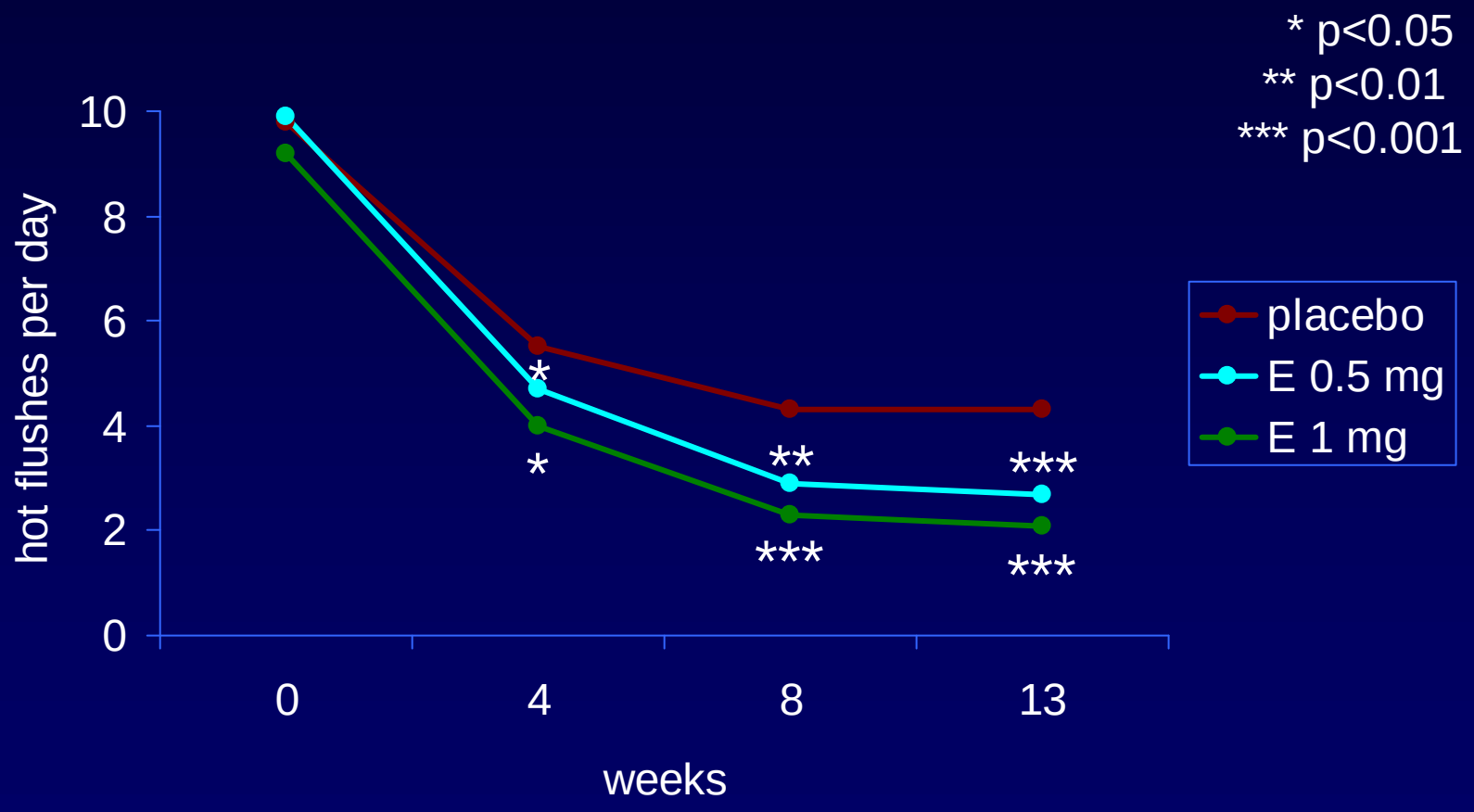
- oral
- impregnated pessary / ring
- percutaneous gel
- intranasal spray
- subcutaneous implants
- transdermal patches

BENEFITS OF HRT

- symptom relief
- osteoporosis
- cardiovascular
- neuro-cognitive
- colo-rectal cancer

Stevenson JC. Plenary Lecture. 9th IMS World Congress, Yokohama, Japan 1999

ULTRA-LOW DOSE HRT & FLUSHES



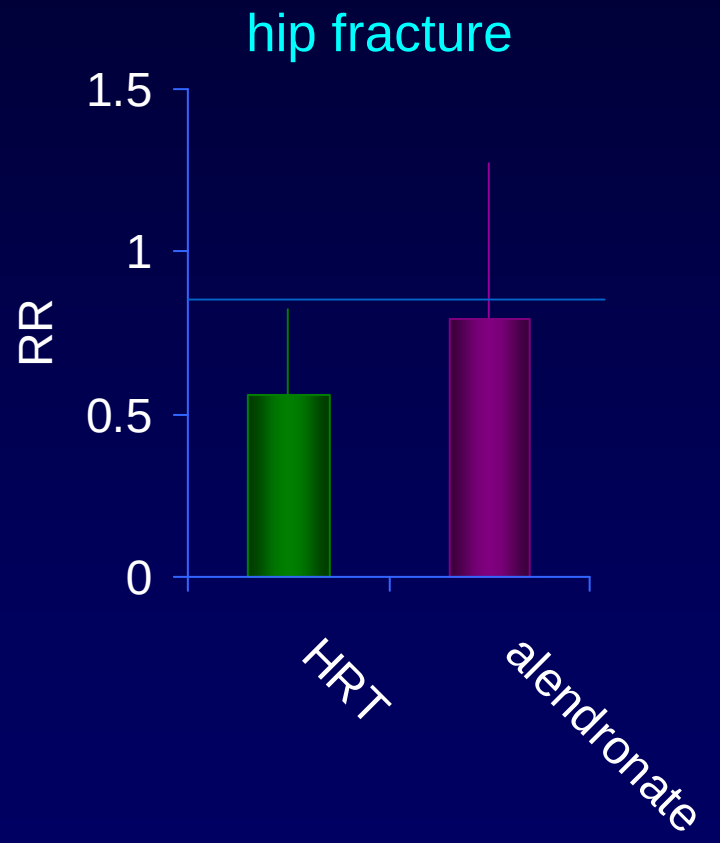
Stevenson et al. Maturitas 2010; 67: 227-32

ESTROGEN AND BONE

- mechanisms
  - cellular
  - local cytokines and growth factors
  - circulating hormones

HRT & OSTEOPOROSIS

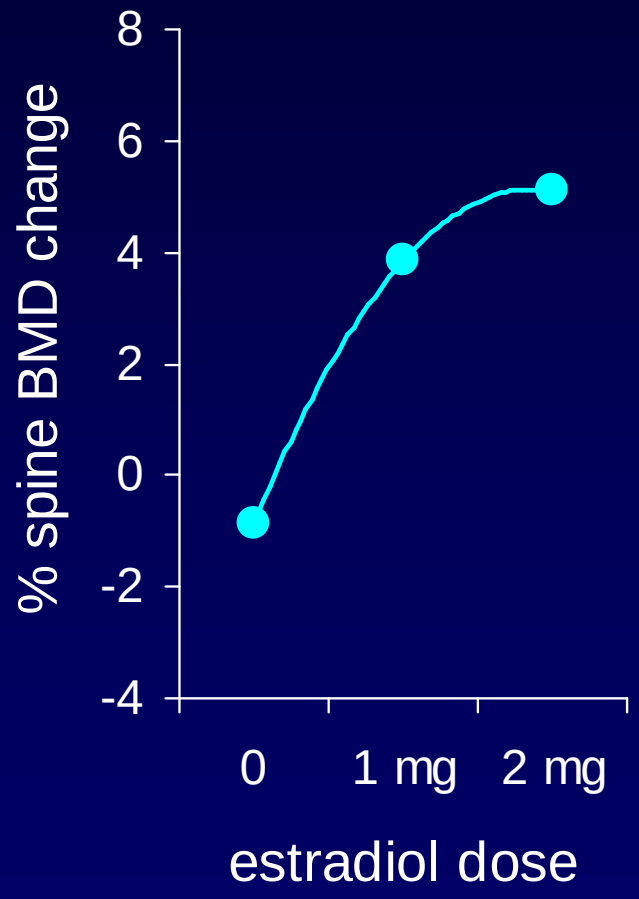
- prevents postmenopausal bone loss
- increases bone mass
- reduces bone turnover
- reduces osteoporotic fracture incidence
- effective at all skeletal sites
- as effective as any other current treatment



Cauley et al. JAMA 2003; 290: 1729-38

Cummings et al. JAMA 1998; 280: 2077-82

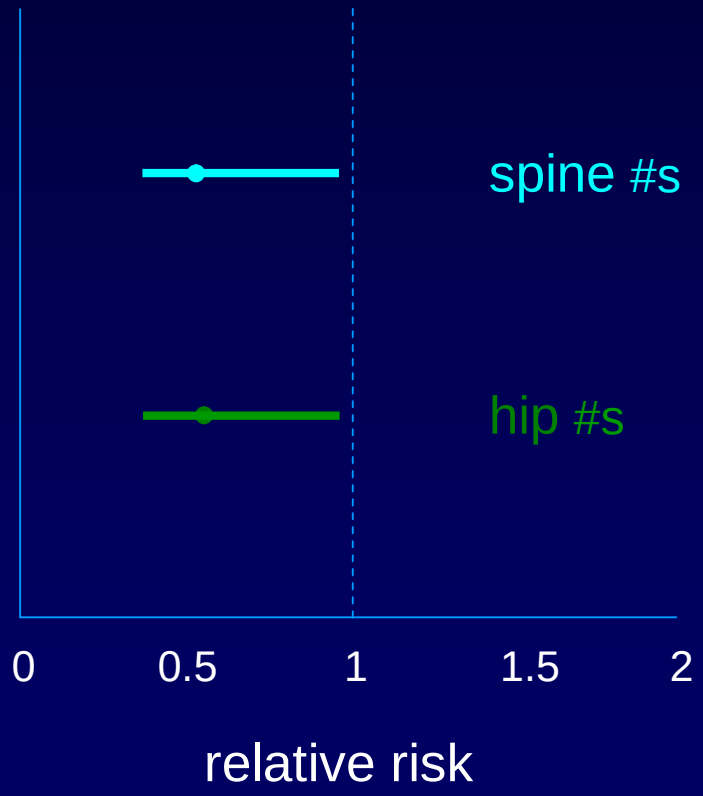
DOSE-RESPONSE CURVE



1 year treatment

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

HRT & FRACTURE: NORMALS



- prospective randomised trial
- placebo-controlled
- 16.608 postmenopausal women
- 101 new vertebral #s
- 106 new hip #s

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

ULTRA-LOW DOSE HRT

transdermal estradiol 0.014 mg daily

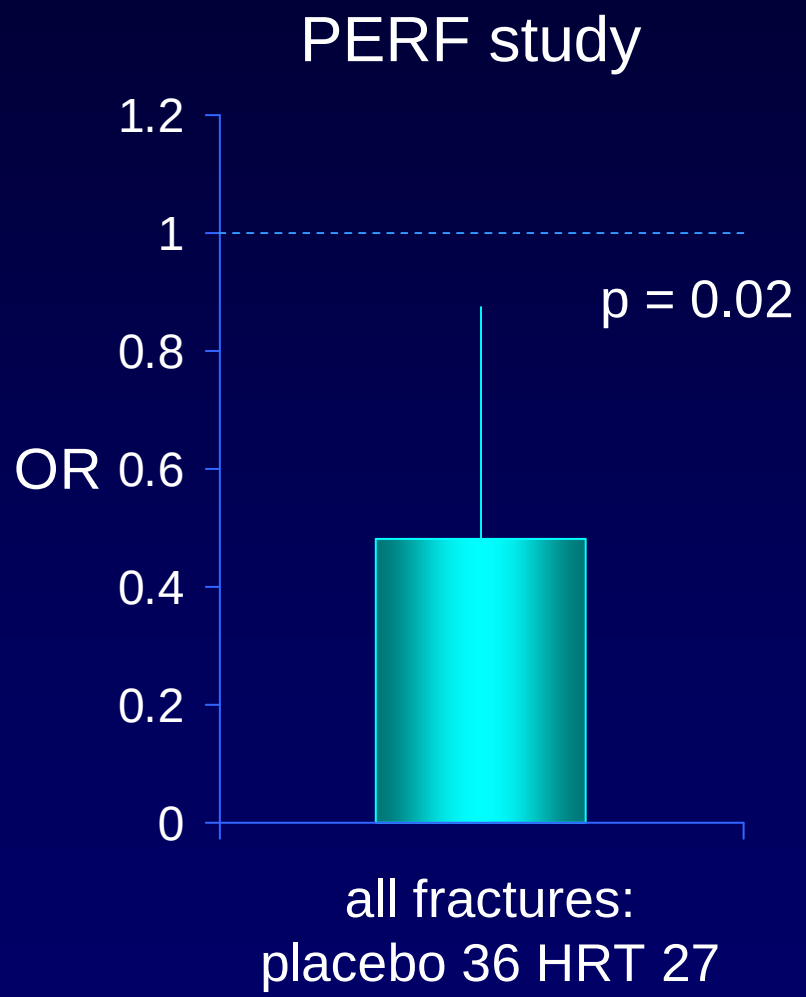
	Ultra Low E2	Placebo
ULTRA	4	10
Prestwood et al*	2	6
Combined**	6	16

* Prestwood et al. JAMA 2003; 290: 1042-48

** S. Cummings, RR = 0.4; p = 0.04

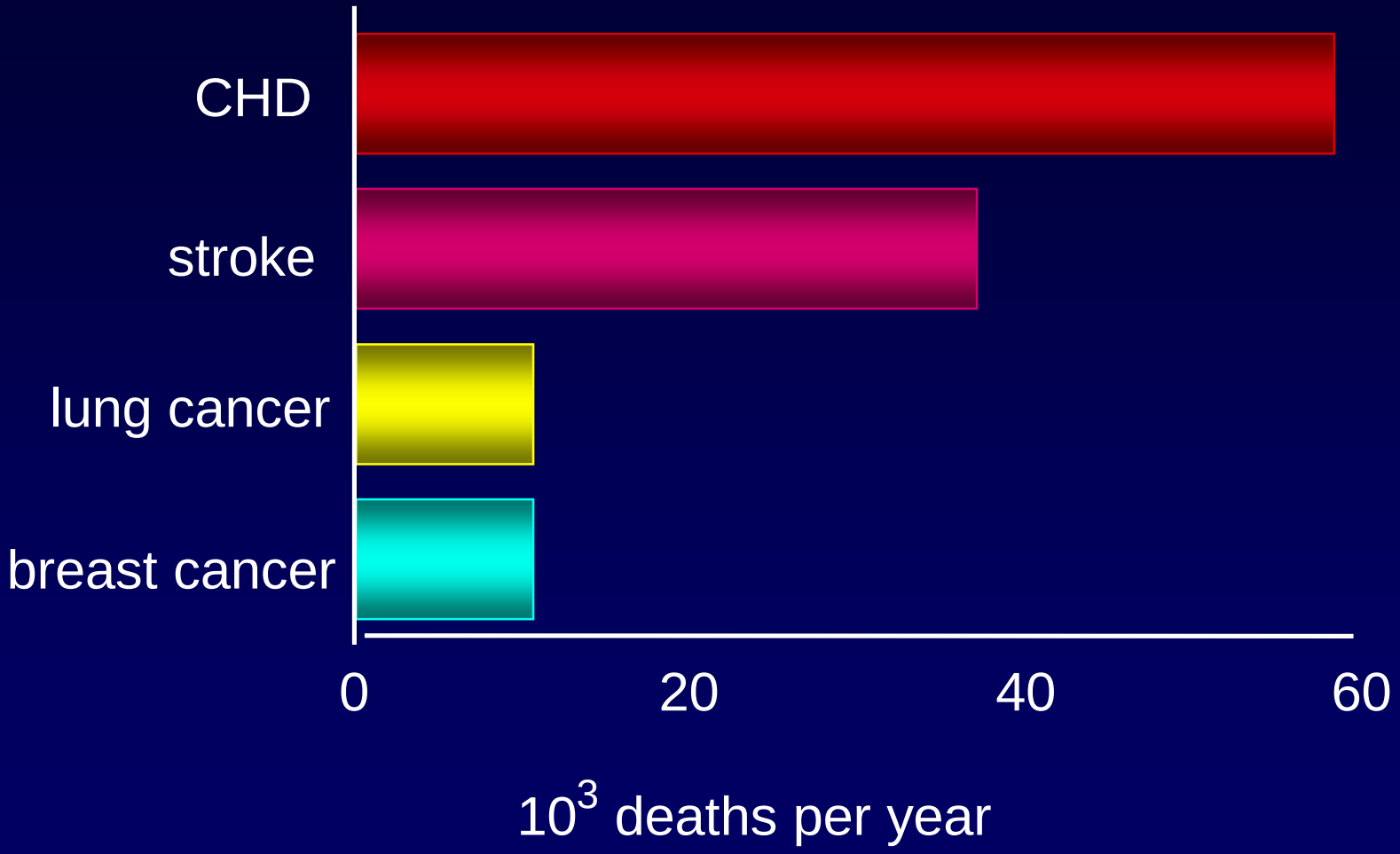
HRT & SUBSEQUENT FRACTURES

- healthy postmenopausal women
- age 65 years
- HRT or placebo for 2-3 years
- follow-up 5, 11 or 15 years
- placebo n=108
- HRT n=155
- all fractures OR 0.48 (CI 0.26-0.88)
- spine fractures OR 0.47 (0.24-0.93)
- NNT to prevent any fracture = 7



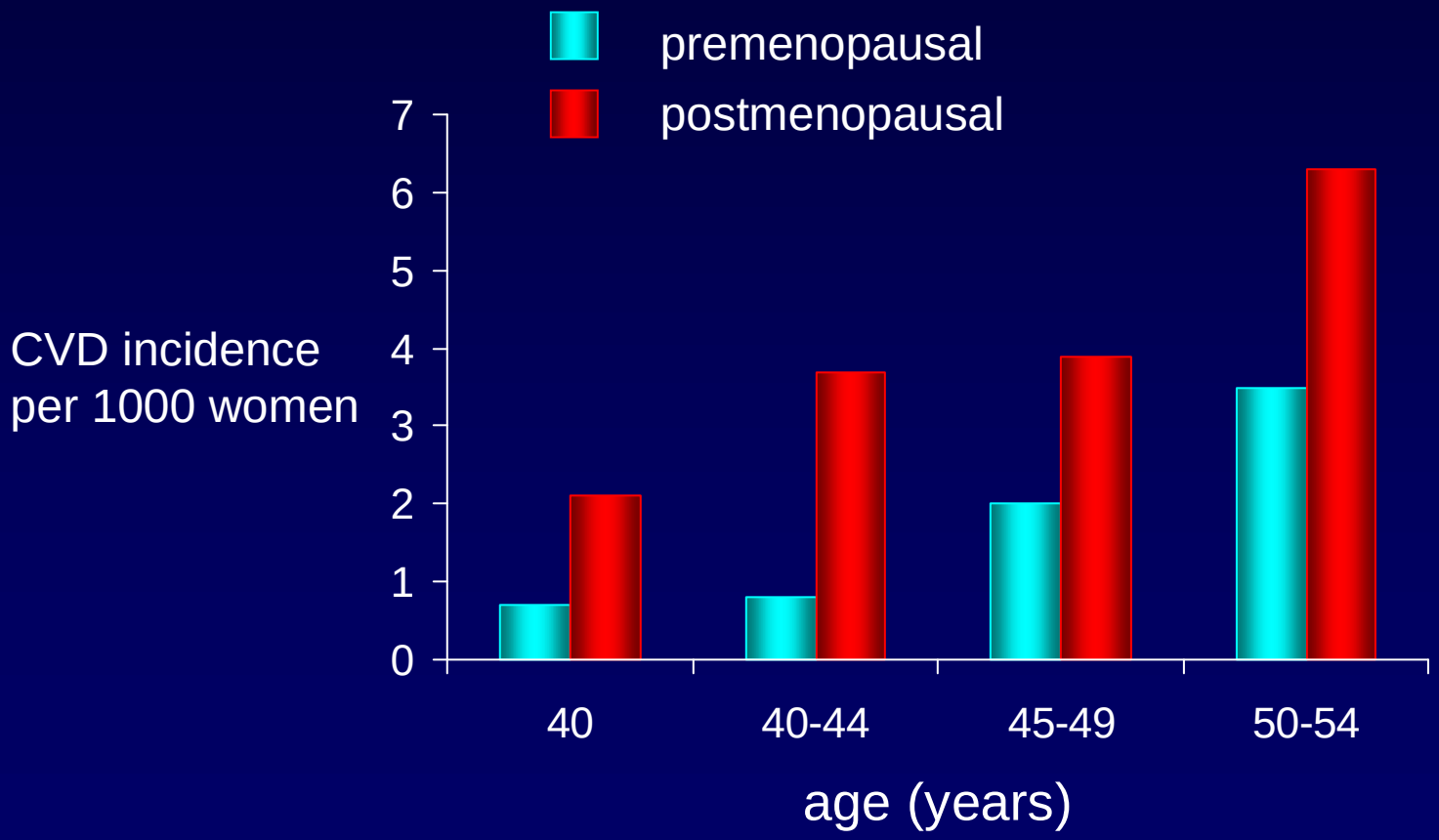
Bagger et al. Bone 2004; 34: 728-35

FEMALE DEATHS: LEADING CAUSES



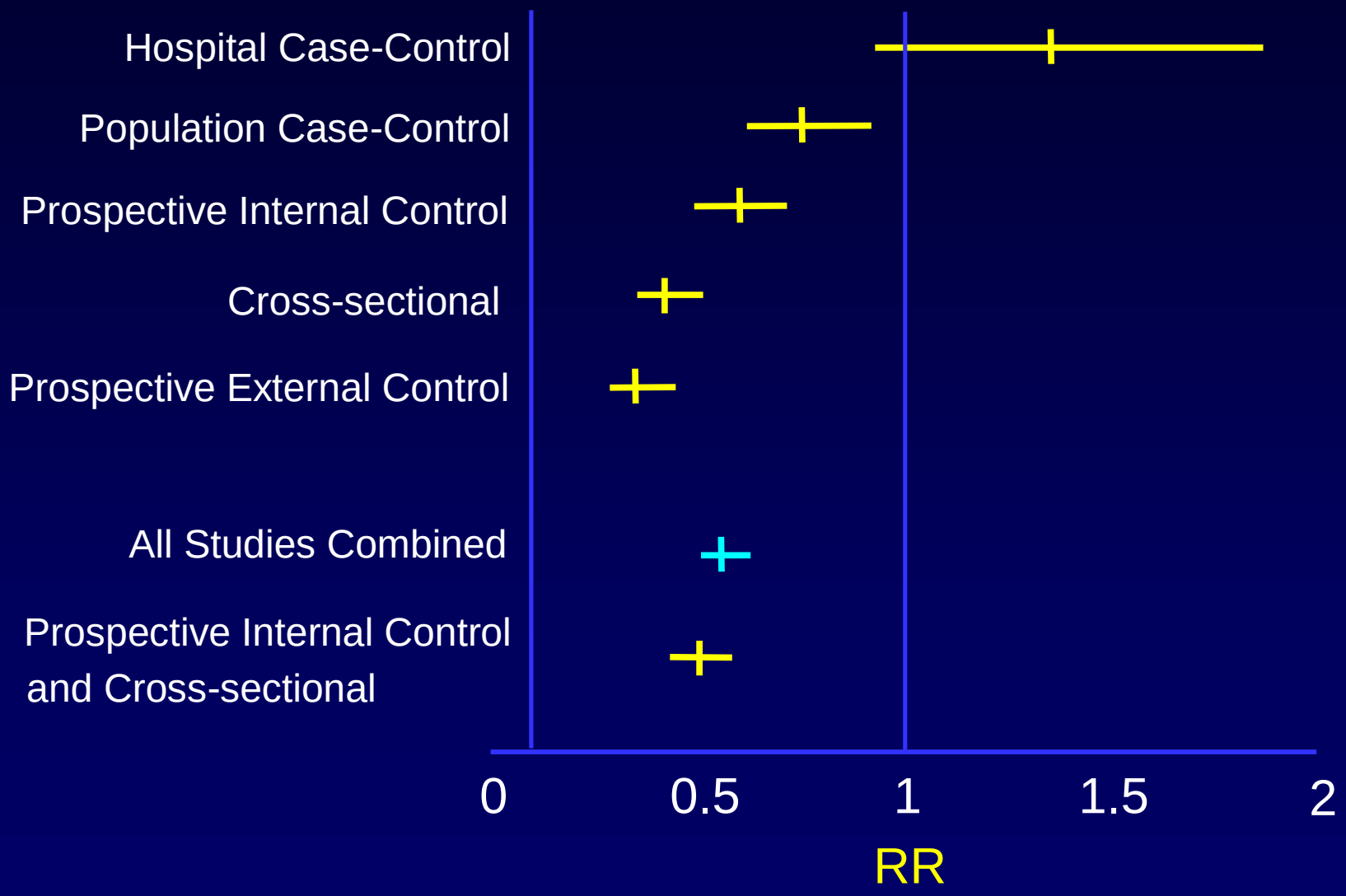
Registered deaths - England and Wales, Office for National Statistics, 1996

CVD AND MENOPAUSAL STATUS



Adapted from the Framingham Study, DHEW No 74, 1974

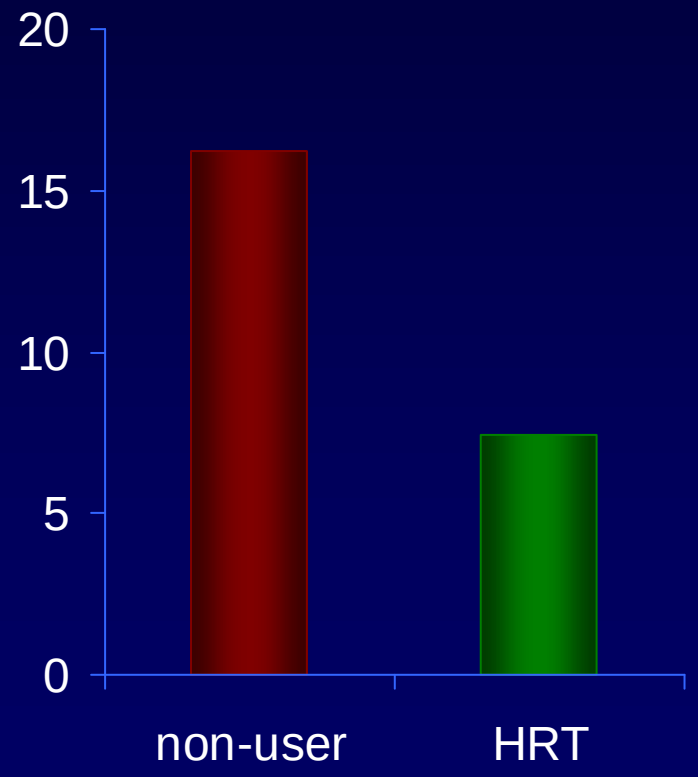
HRT & CVD: META-ANALYSIS



Stampfer and Grodstein. Raven Press, 1994

HRT & MI SURVIVAL

- 114,724 women with confirmed MI
- age >55 years
- 7,353 (6.4%) on HRT
- adjusted OR 0.65 (CI 0.59-0.72)



Schlipak et al. Circulation 2001; 104: 2300-09

HRT & CARDIOVASCULAR SYSTEM

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

HRT AND LIPOPROTEINS

- decreased total cholesterol
- decreased LDL cholesterol
- increased or decreased HDL and triglycerides
- decreased lipoprotein (a)
- increased small dense LDL clearance
- increased postprandial lipid clearance
- decreased LDL oxidation

HRT & GLUCOSE / INSULIN

- CEE normal / impaired glucose tolerance
- oral / transdermal E_2 normal / improved glucose tolerance
- CEE increased insulin response
- oral / transdermal E_2 normal / decreased insulin response
- androgenic progestogens increase insulin resistance

CEE=conjugated equine estrogen

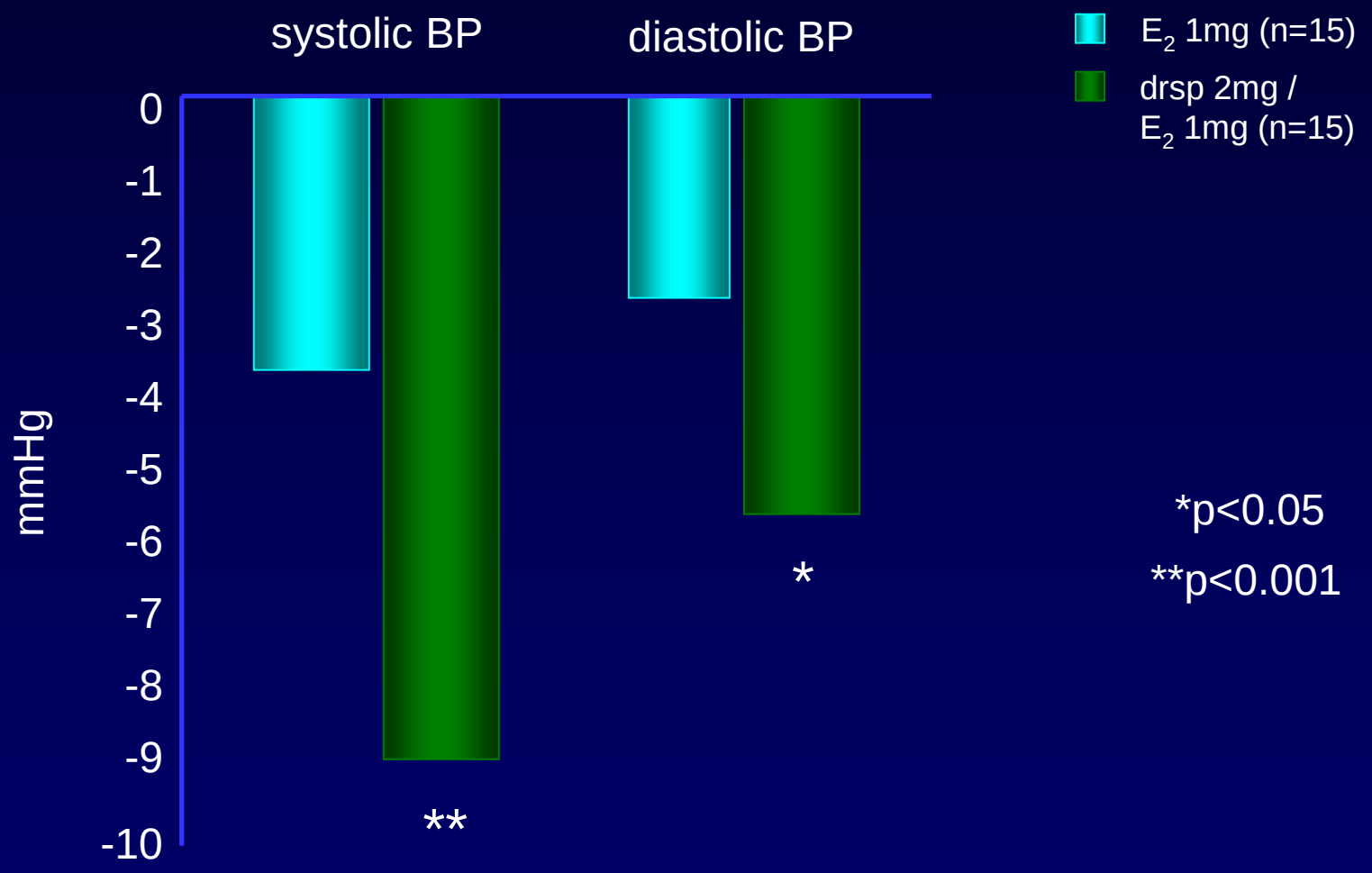
HRT AND BODY COMPOSITION

- no increase in total fat
- relative decrease in android fat
- android fat related to adverse metabolic changes
- android fat related to increased CHD risk

HRT AND HEMOSTASIS

- oral oestrogen reduces fibrinogen / factor VII
- oral oestrogen reduces PAI-1
- oral oestrogen increases thrombogenesis
  - low dose neutral effect
- transdermal oestrogen neutral effect

E_2 + DSRP: BLOOD PRESSURE



Archer et al. Menopause 2005; 12: 716

METABOLIC SUMMARY

- different forms of HRT have different metabolic effects
- metabolic effects have their major impact on the cardiovascular system
- different HRT regimens may have different cardiovascular effects

HRT AND INCIDENT DIABETES

- WHI E + P study
- 15,641 postmenopausal women
- mean age 63.2 years
- follow-up 5.6 years
- diabetes incidence
  - HR 0.79 (CI 0.67-0.93)
- >80% compliant
  - HR 0.67 (CI 0.54-0.82)

Margolis et al. Diabetologia 2004; 47: 1175-87

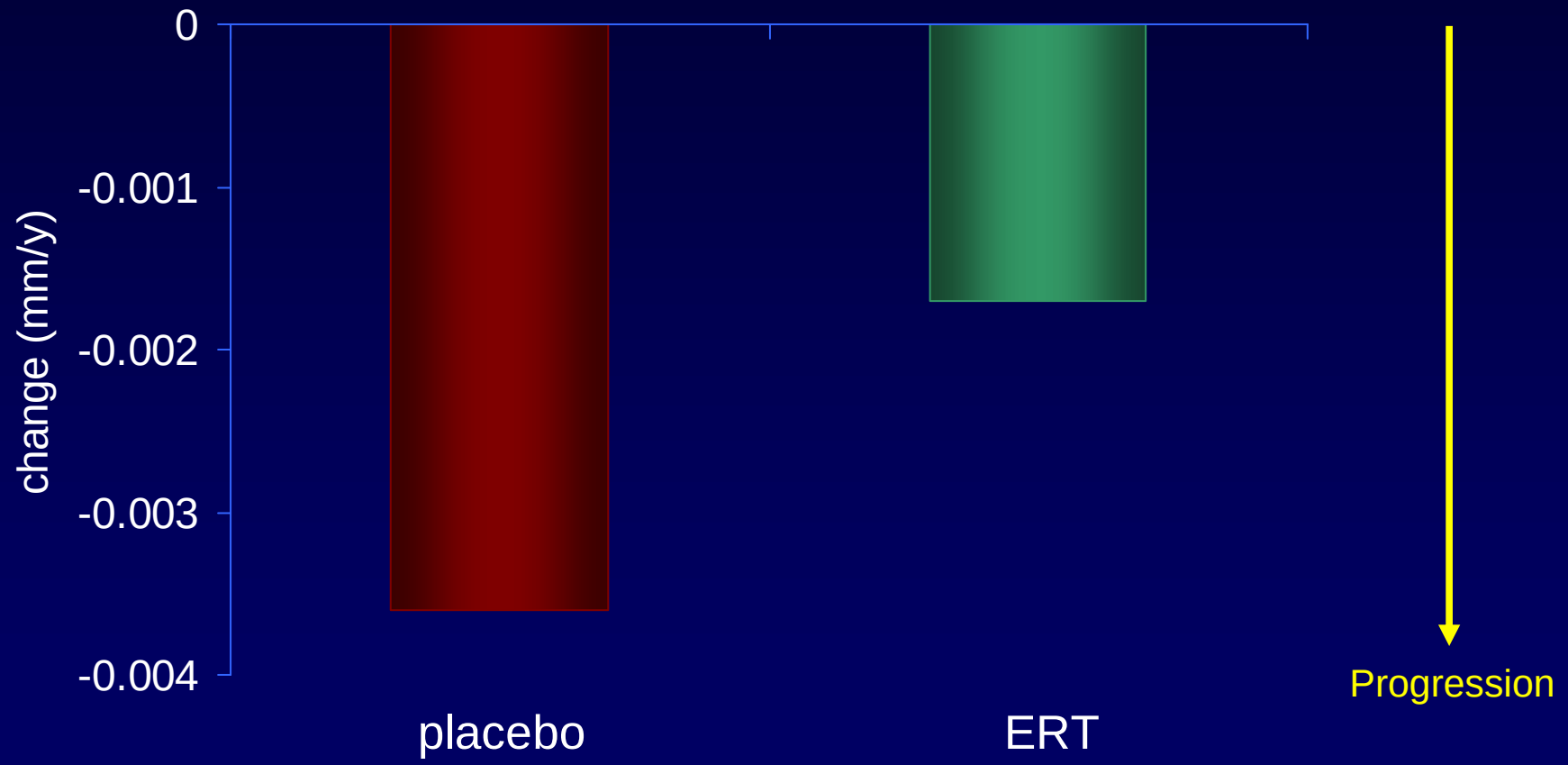
ESTROGEN & ARTERIAL FUNCTION

- restores NO-dependent endothelial function
- increase endothelial NO synthase production
- reduces endothelial endothelin-1 release
- inhibits calcium channels
- enhances potassium-dependent channels
- reduces ACE activity
- reduces smooth muscle cell proliferation
- ? improves vascular remodelling processes

NO=nitric oxide

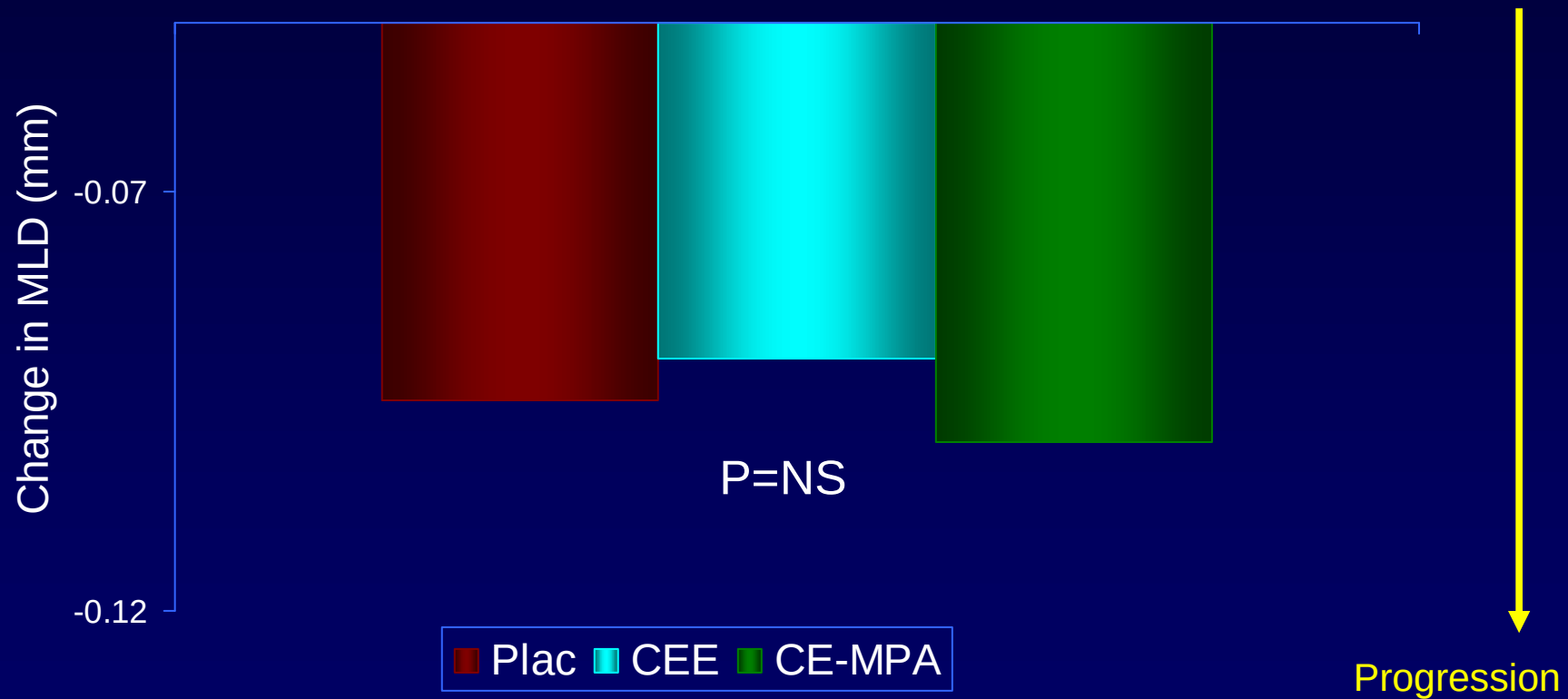
ACE=angiotensin converting enzyme

ERT & INTIMA-MEDIA THICKNESS



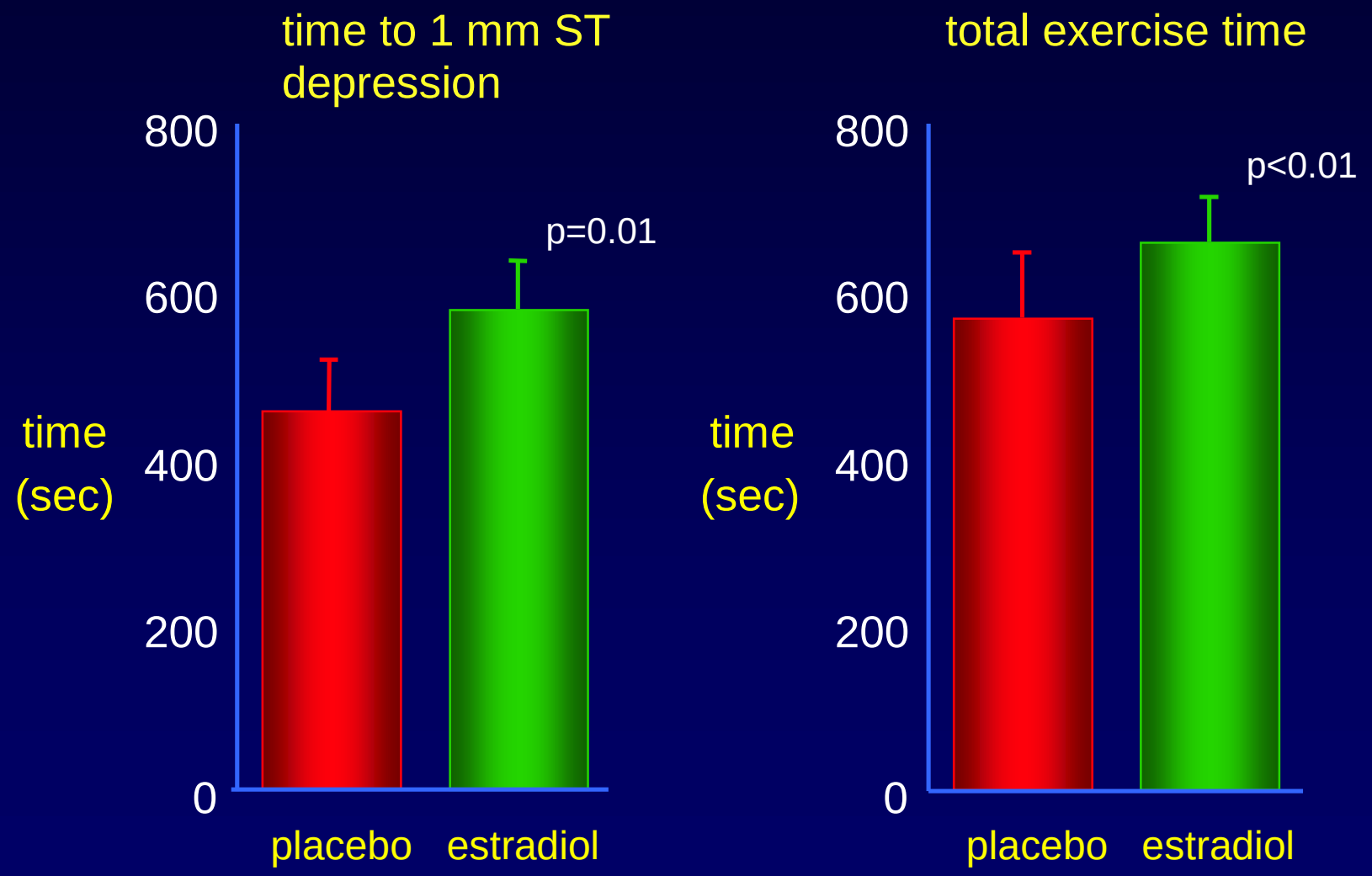
Hodis et al. Ann Intern Med 2001;135: 939-53

ERA STUDY



Herrington DM et al. N Engl J Med 2000

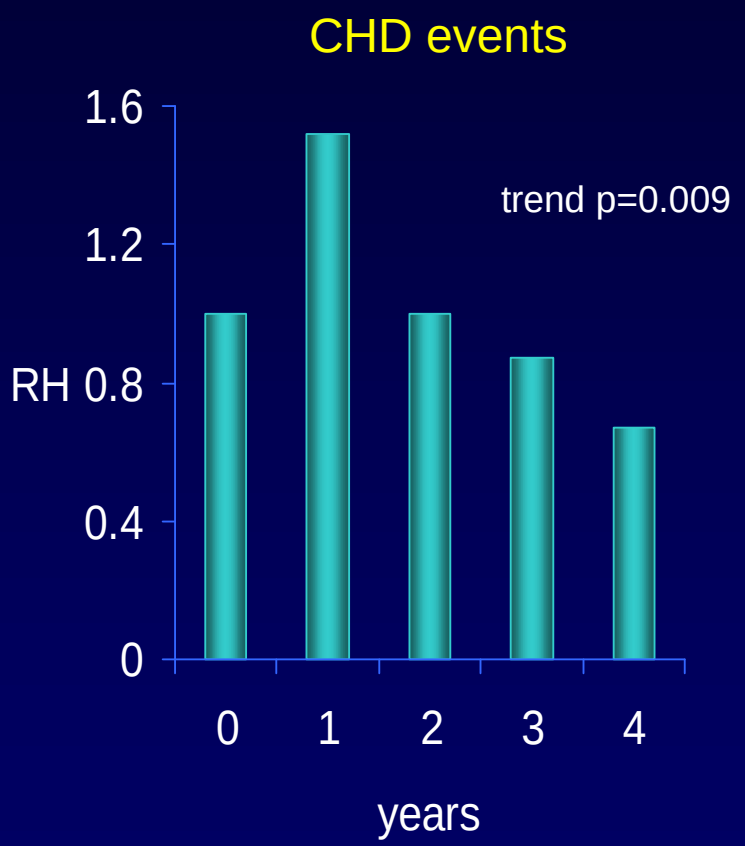
ESTRADIOL & MYOCARDIAL ISCHAEMIA



Rosano et al. Lancet 1993; 342: 133-36

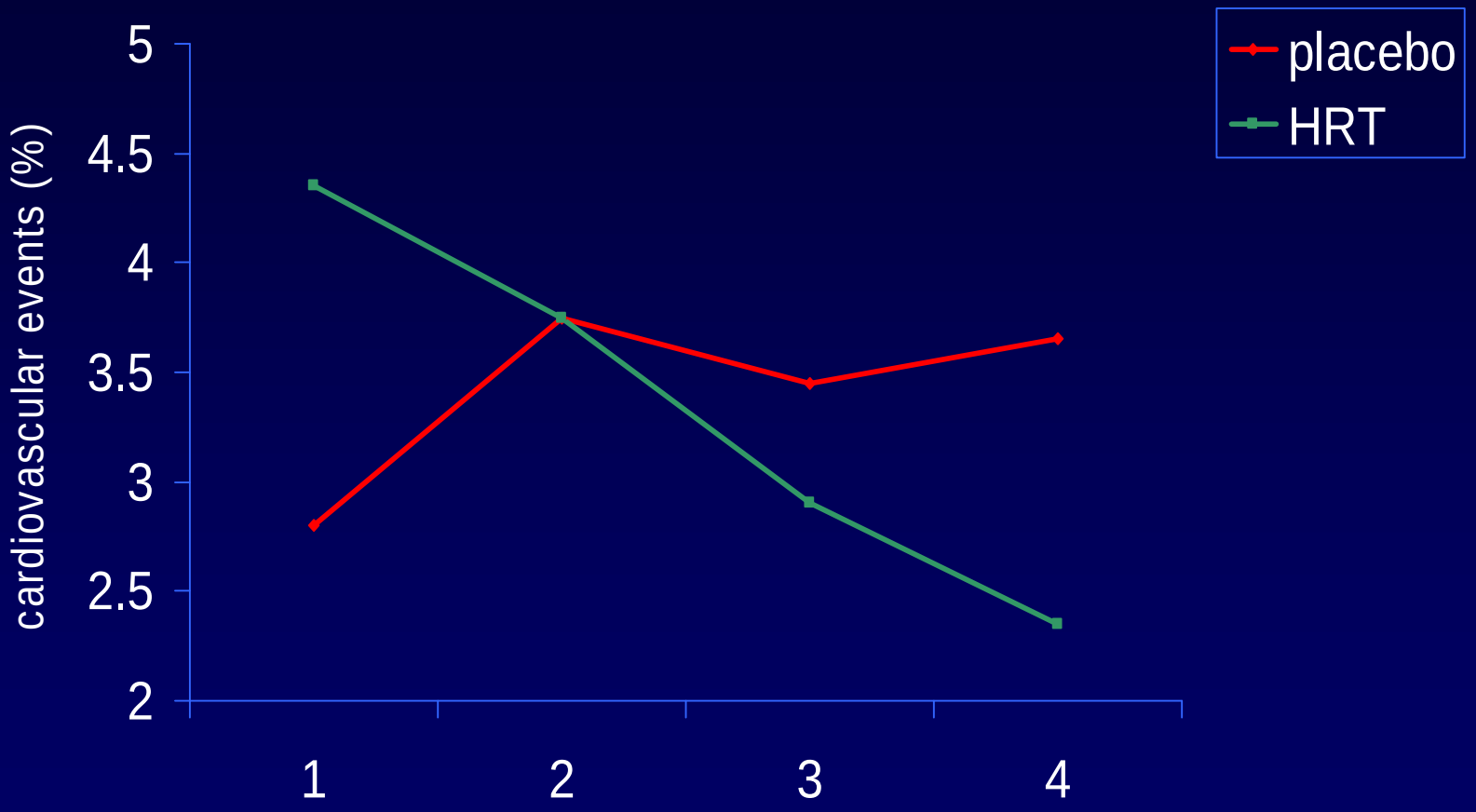
HERS TRIAL

- 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



Hulley et al. J Am Med Assoc 1998; 260: 605-13

HERS TRIAL



Hulley et al. J Am Med Assoc 1998; 260: 605-13

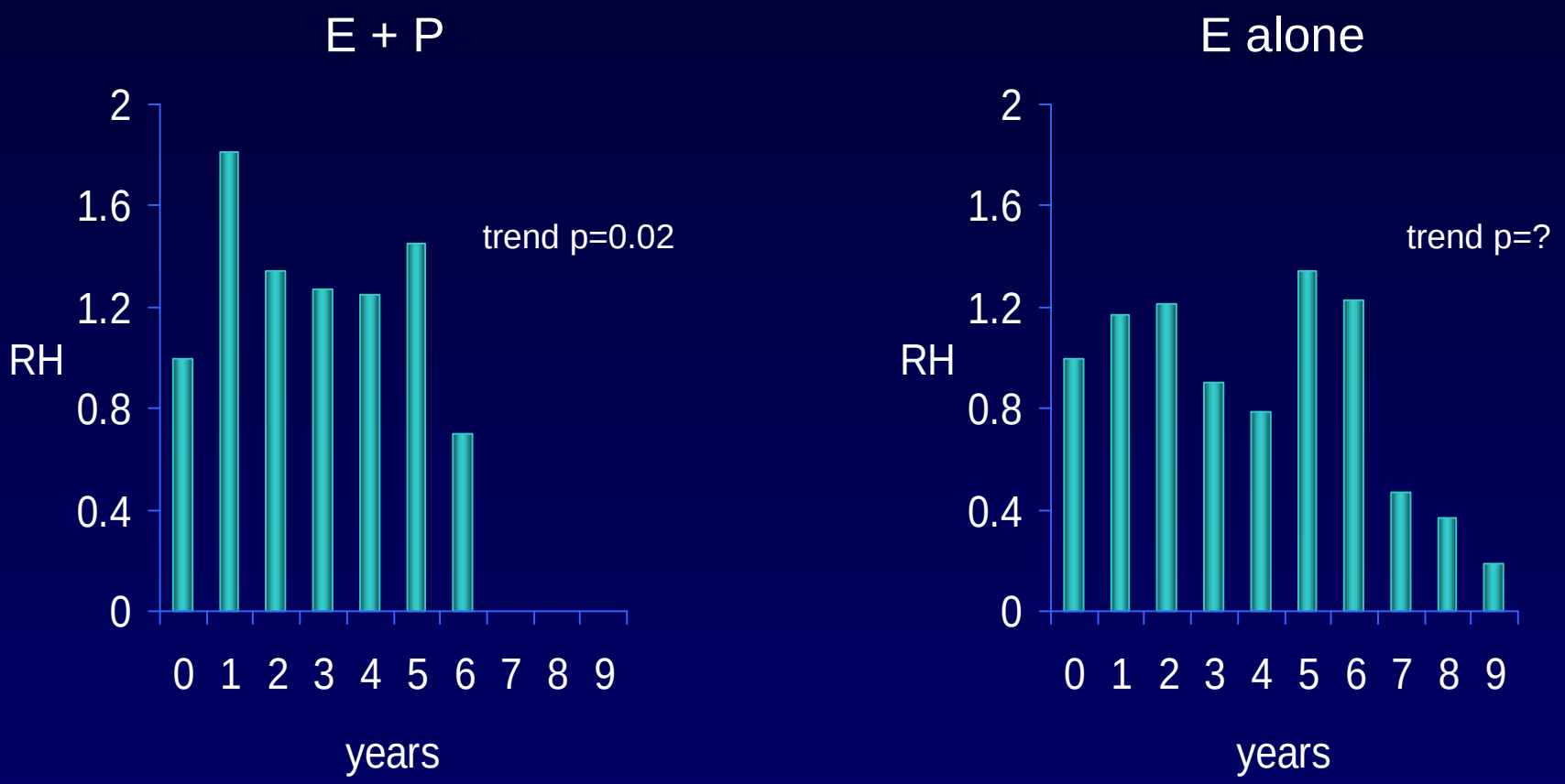
WOMEN'S HEALTH INITIATIVE

- 16,608 "healthy" postmenopausal women (E+P)
- 10,739 "healthy" postmenopausal women (E)
- age 50 - 79 years
- CEE 0.625 mg (E) / + MPA 2.5 mg (E+P)
- duration 5.2 years (E+P) / 6.8 years (E)
  (planned 8.5 years)
- primary benefit: CHD events
- primary adverse event: breast cancer

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

The Women's Health Initiative Steering Committee. JAMA 2004; 291: 1701-12

WHI: CHD EVENTS



Manson et al. N Engl J Med 2003; 349: 523-34

The Women's Health Initiative Steering Committee. JAMA 2004; 291: 1701-12

HRT AND CHD

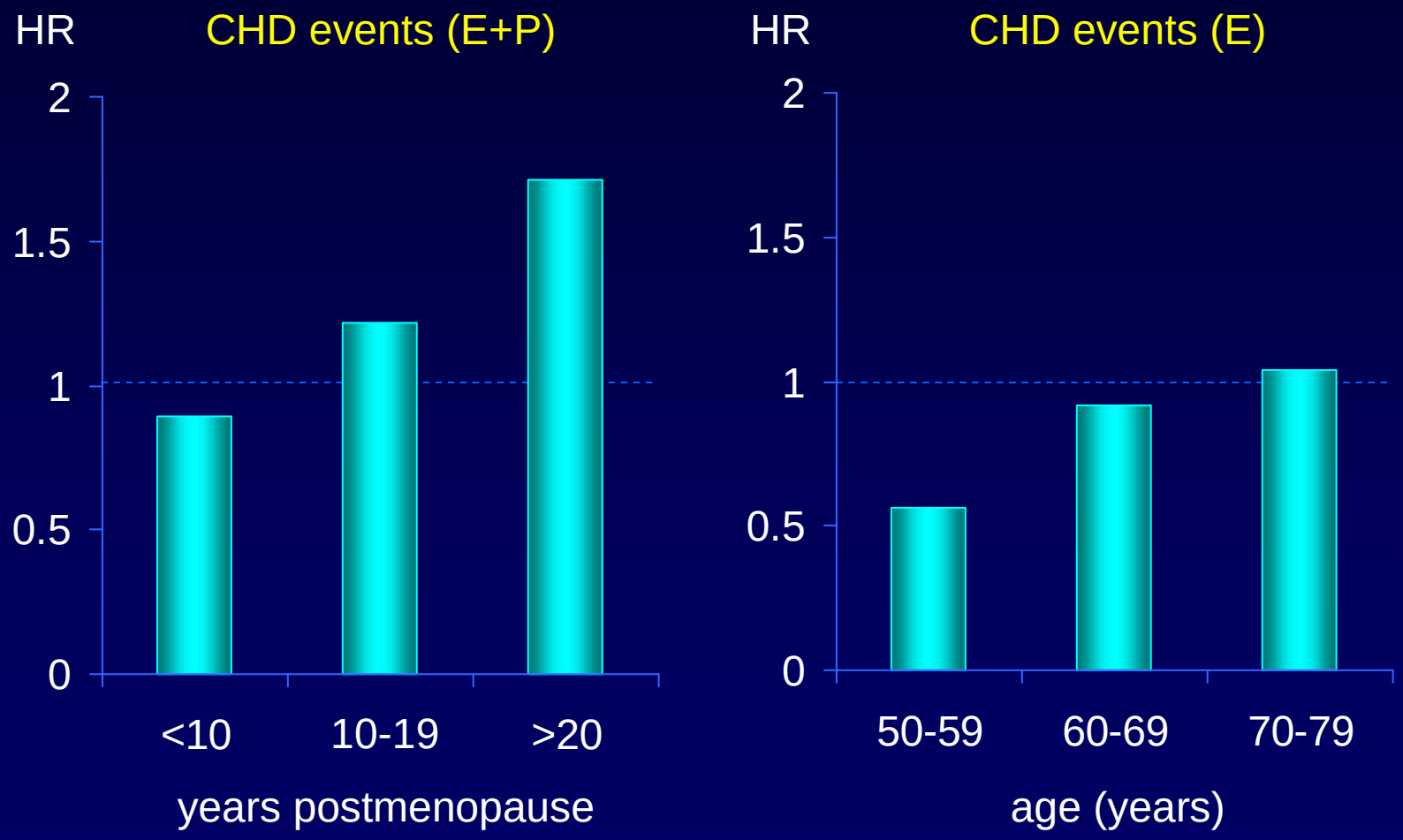
observational studies

- 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

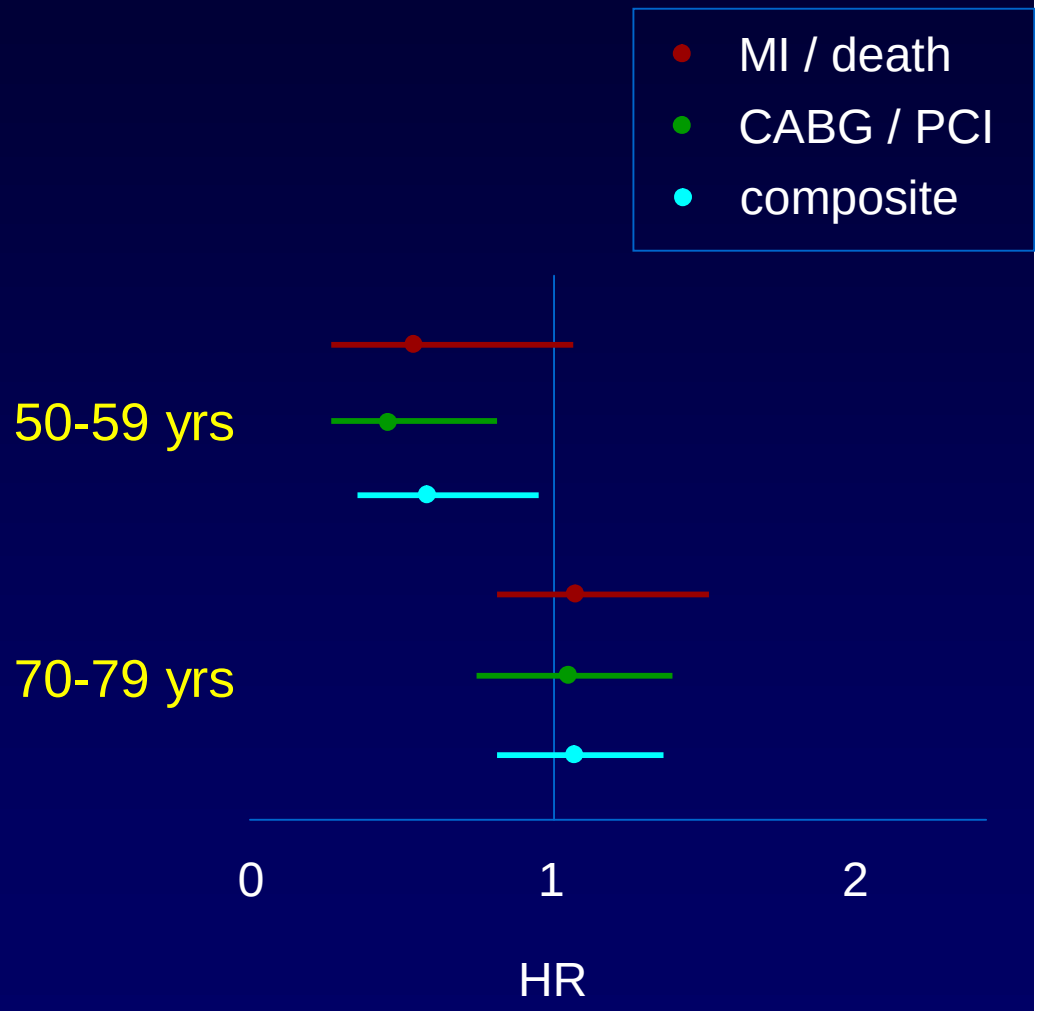
WHI: CHD RISK



Writing Group for the Women's Health Initiative Investigators. JAMA 2002; 288: 321-33
The Women's Health Initiative Steering Committee. JAMA 2004; 291: 1701-12

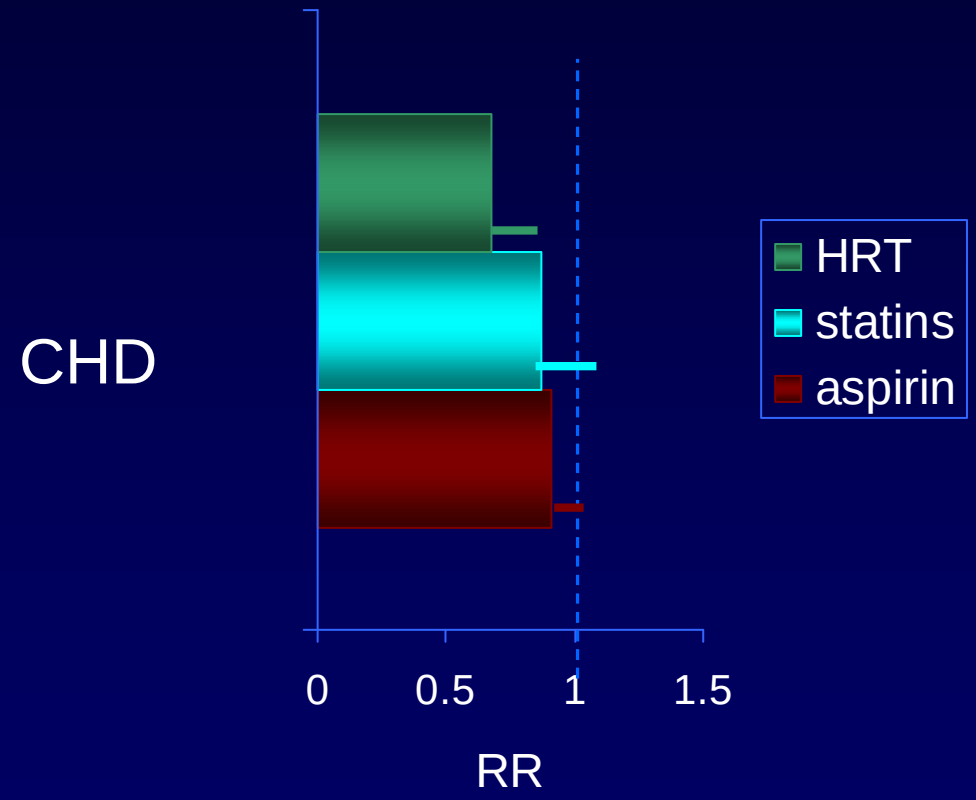
HRT AND CHD EVENTS

- increased CHD events in elderly women
  - ? increased thrombogenesis / adverse remodelling
  - age skewed to older women
  - ? oestrogen dose too high



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

HRT AND CHD EVENTS



Hodis and Mack. Menopause 2007; 14: 1-14

RISKS OF HRT

- breast cancer
- endometrial cancer
- thrombo-embolism
- stroke
- gallbladder disease
- myths and legends

Stevenson JC. Plenary Lecture. 9th IMS World Congress, Yokohama, Japan 1999

MILLION WOMEN STUDY

- can a million women be wrong?
- not even one woman can be wrong!

Stevenson BM – personal communication

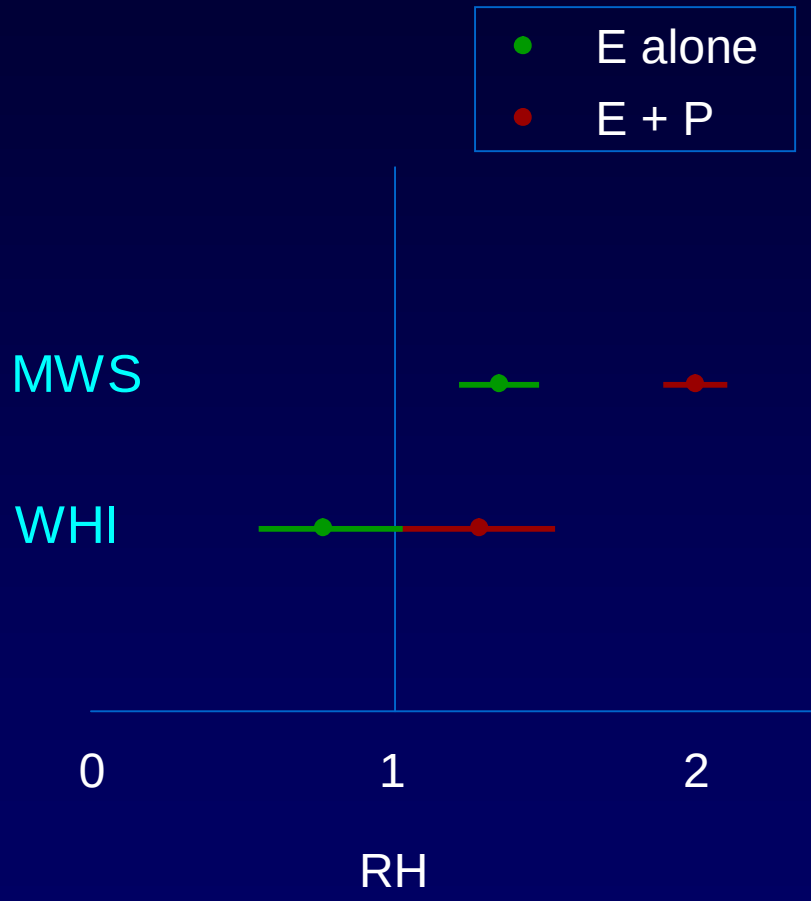
HRT AND BREAST CANCER

- Million Women Study (MWS)
  - observational study of women undergoing routine mammography in UK NHS programme
- study biases
  - inclusion bias
  - surveillance bias
  - treatment misclassification
- biological plausibility
  - “new” tumours detected after 1.2 years
  - risk disappears 14 months after discontinuation

Million Women Study Collaborators. Lancet 2003; 362: 419-427

HRT AND BREAST CANCER

- Million Women Study (MWS) showed RR 2.00 for combined HRT, 1.30 for oestrogen alone or 1.45 for tibolone
- WHI shows *no* increased risk (RR 0.77) for oestrogen alone
- MWS has *overestimated* risk
- will other progestogens show same risk?



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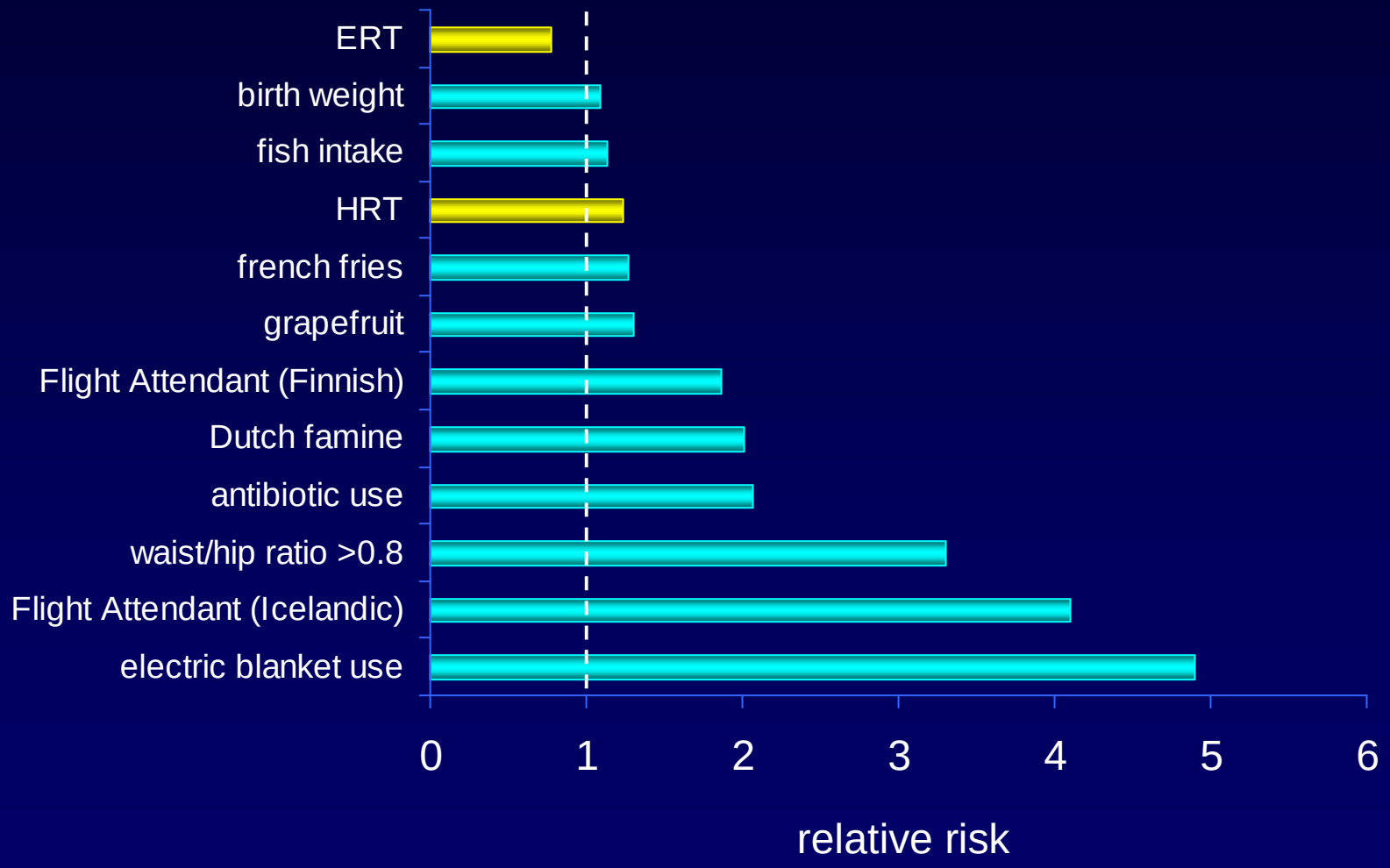
Million Women Study Collaborators. Lancet 2003; 362: 419-427

RISKS FOR BREAST CANCER



Bluming & Tavris. Cancer J 2009; 15: 93-104

RISKS FOR BREAST CANCER

- living in cities
- being left handed
- asymmetrical breasts
- using aerosol deodorants
- drinking 1 glass of wine per day
- eating 2 oz red meat per day
- living in the countryside

VTE & OESTROGEN DOSE

- 8 - 12 additional PE cases in 10,000 women/years
- no increased risk with non-oral administration
- possible risk decrease with lowering the dose of estrogens:

  - CEE 1.25 mg RR 6.9
  - CEE 0.625 mg RR 3.3
  - CEE 0.3 mg RR 2.1

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

Jick et al. 1996

STROKE & HRT: DOSE EFFECT

- CEE 1.25 mg RR 1.58 (1.16-2.15)
- CEE 0.625 mg RR 1.11 (0.90-1.37)
- CEE 0.3 mg RR 0.43 (0.22-0.83)

Grodstein et al 2000

FUTURE THERAPIES: TSEC

- some SERMs have anti-estrogenic effect on endometrium
- combine estrogen with a SERM instead of a progestogen
- forms tissue selective estrogen complex (TSEC)
- complete amenorrhoea and endometrial protection
- symptom relief and bone protection
- ? protection against breast cancer

CONCLUSIONS

- benefits of HRT established
  - symptoms, QoL, osteoporosis
- risks of HRT established
  - VTE (transient)
- benefits/risks *not* established
  - CHD, stroke
  - breast cancer
- start with low doses
- other progestogens / SERMs