Hormonal Replacement Therapy in Women

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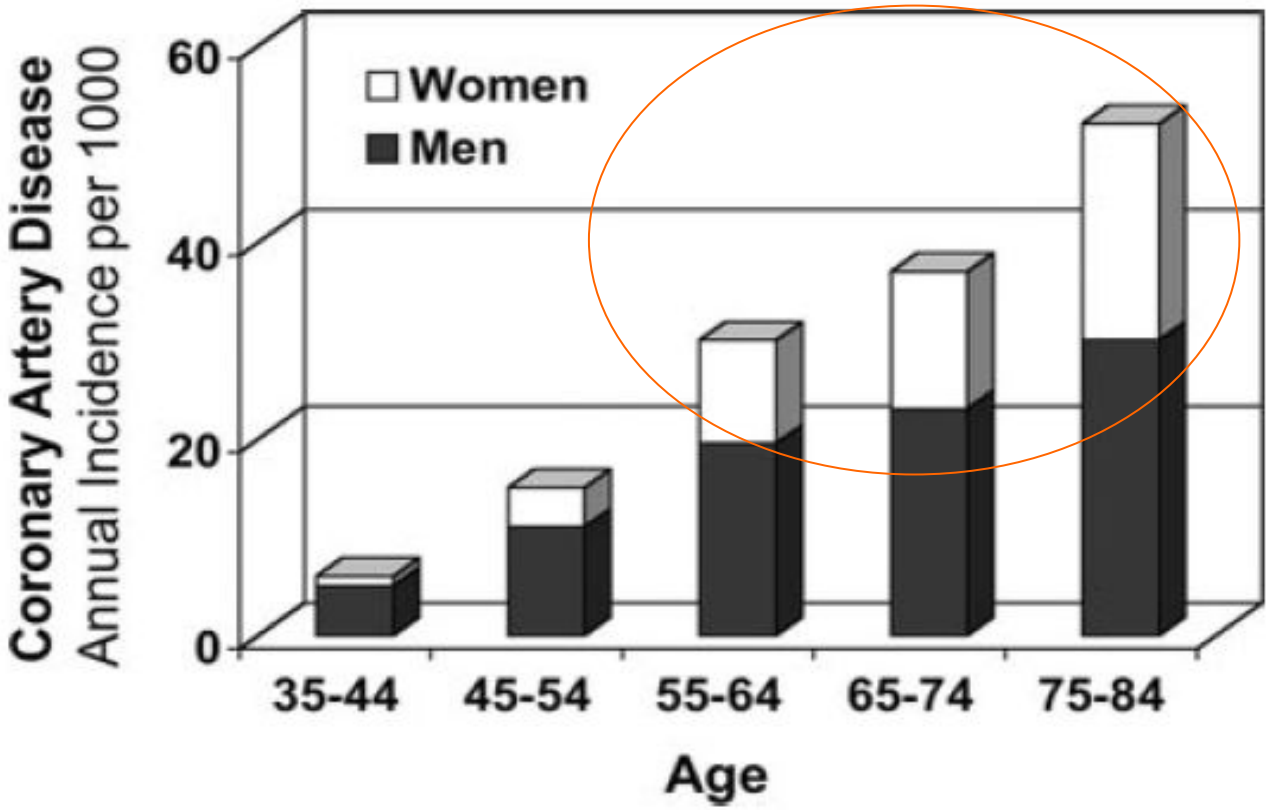
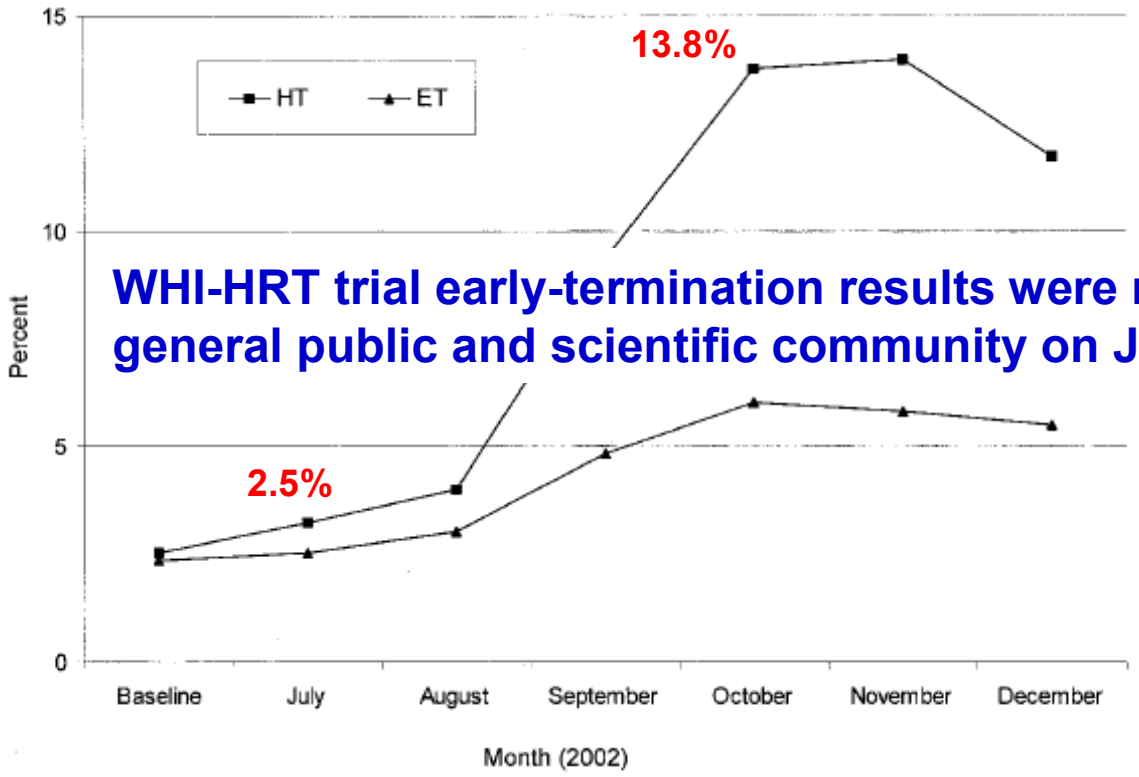
20071012

Age-dependent Incidence of Coronary Artery Disease in Men and Women (Framingham Heart Study).



Circulation. 1997;95:252.

Percentage of HRT(HT) and Estrogen Therapy (ET) Users Who Discontinued by WHI Study Month.

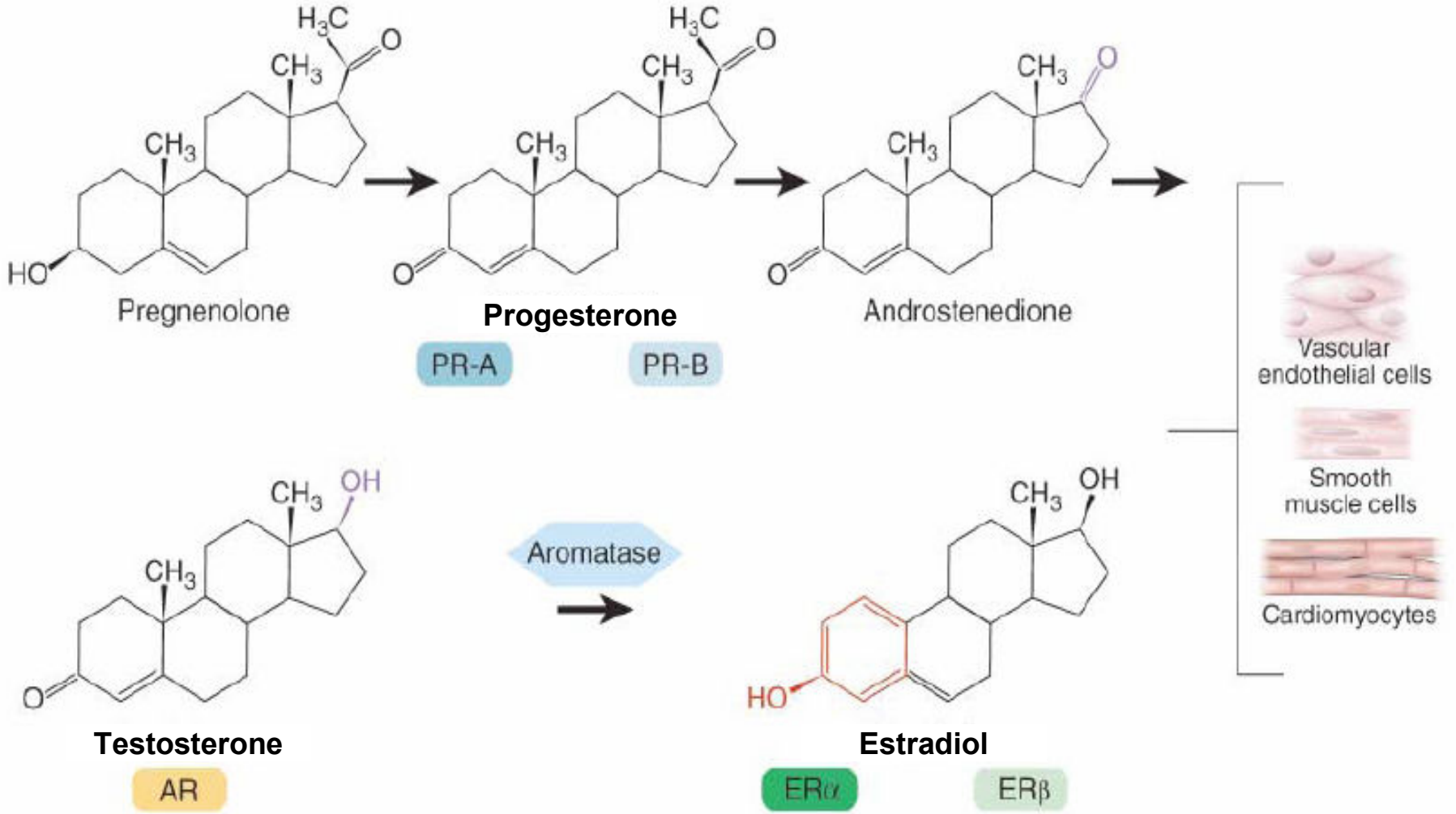


WHI-HRT trial early-termination results were released to the general public and scientific community on July 9, 2002.

Baseline includes combined data from September 1999 to June 2002 Hormone therapy: estrogen plus progestin. Estrogen therapy: estrogen alone.

Buist. HT Prescribing Patterns in the United States. Obstet Gynecol 2004.

Sex Steroid Hormones And Sex Steroid Hormone Receptors

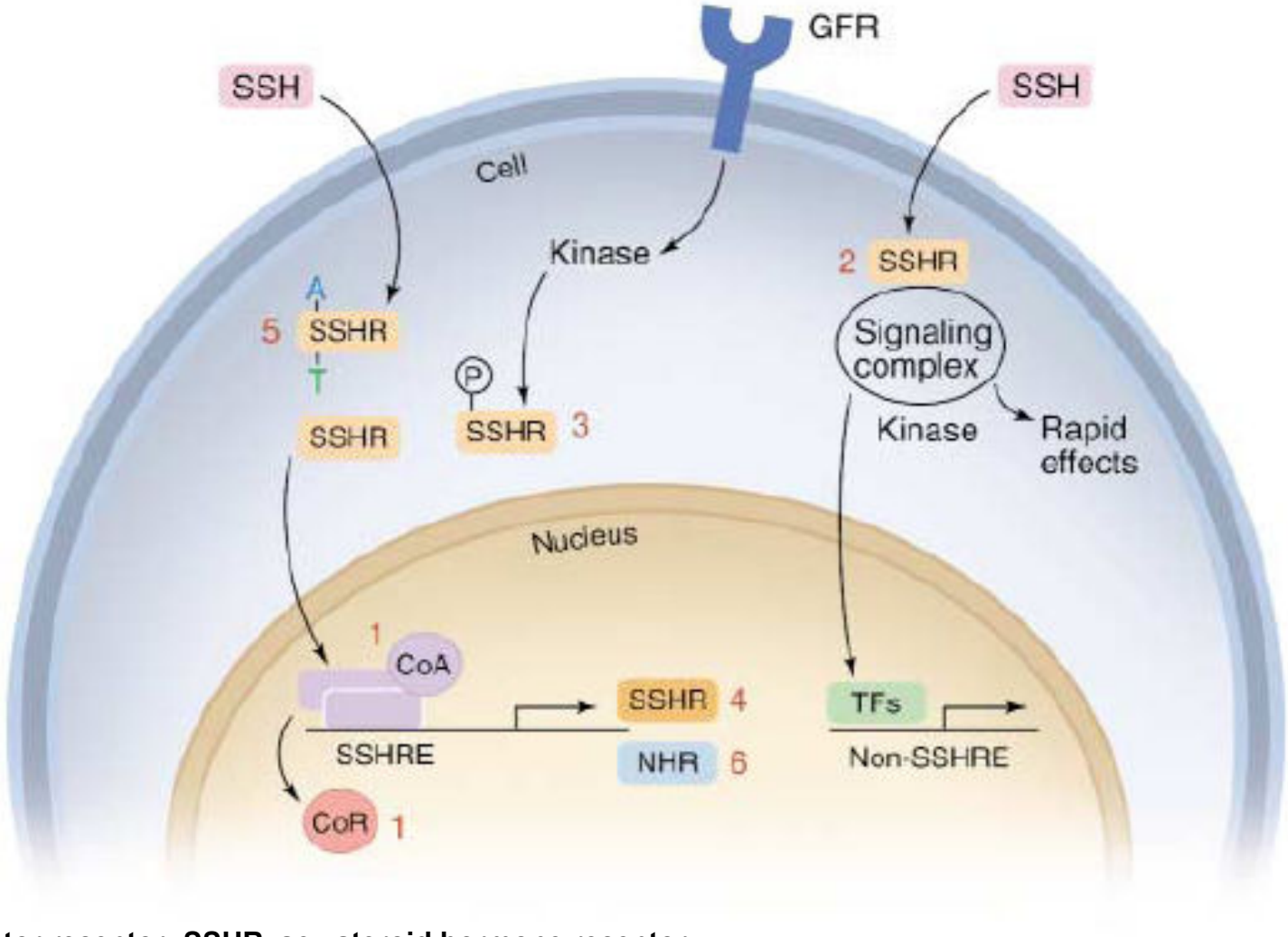


Science 2005; 308,1583

Constituents of Drug Treatments ("Conjugated Equine Estrogens") Used in Large-Scale Prospective Hormone Replacement Trials (HERS, WHI) in Postmenopausal Women

Estrogens
Sodium-estrone sulfate
Sodium-equilinsulfate
Sodium-17α-dihydroequilinsulfate
Sodium-17α-estradiolsulfate
Sodium-17β-dihydroequilinsulfate
Sodium-17α-dihydroequileninsulfate
Sodium-17β-hydroequileninsulfate
Sodium-equileninsulfate
Sodium-17β-estradiolsulfate
Sodium-delta 8,9-dehydroestronsulfate
Progestins
5α-Pregnane-3β, 20β-diol
5α-Pregnane-3β, 16α, 20β-triol
5α-Preg-16-en-3β-ol-20-one
5α-Pregnane-3β-ol-20-one
Sodium-4-pregene-20-ol-3-one-sulfate
3β-Hydroxy-5(10), 7-estradiene 17-one-3-sulfate
Androgens
5α-Androstane-3β, 17α-diol
5α-Androstane-3β, 16η-diol
5α-Androstane-3β, 16α-diol
5α-Androstane-3β-ol, 16-one
Other substances
5,7,9 (10) Estratriene-3β, 17β-diol
17α-Dihydro-delta 8,9-dehydroestrone
17β-Dihydro-delta 8,9-dehydroestrone
5,7,9,(10) Estratriene-3β-ol-17-one
2-Hydroxyestrone
2-Methoxyestrone

Emerging Concepts in Sex Steroid Hormone Receptor Signaling of Potential Importance in Cardiovascular Physiology



GFR, growth factor receptor; SSHR, sex steroid hormone receptor; SSHRE, SSH response element; CoA, coactivator; CoR, corepressor; NHR, non-SSHR nuclear receptors; TFs, transcription factors

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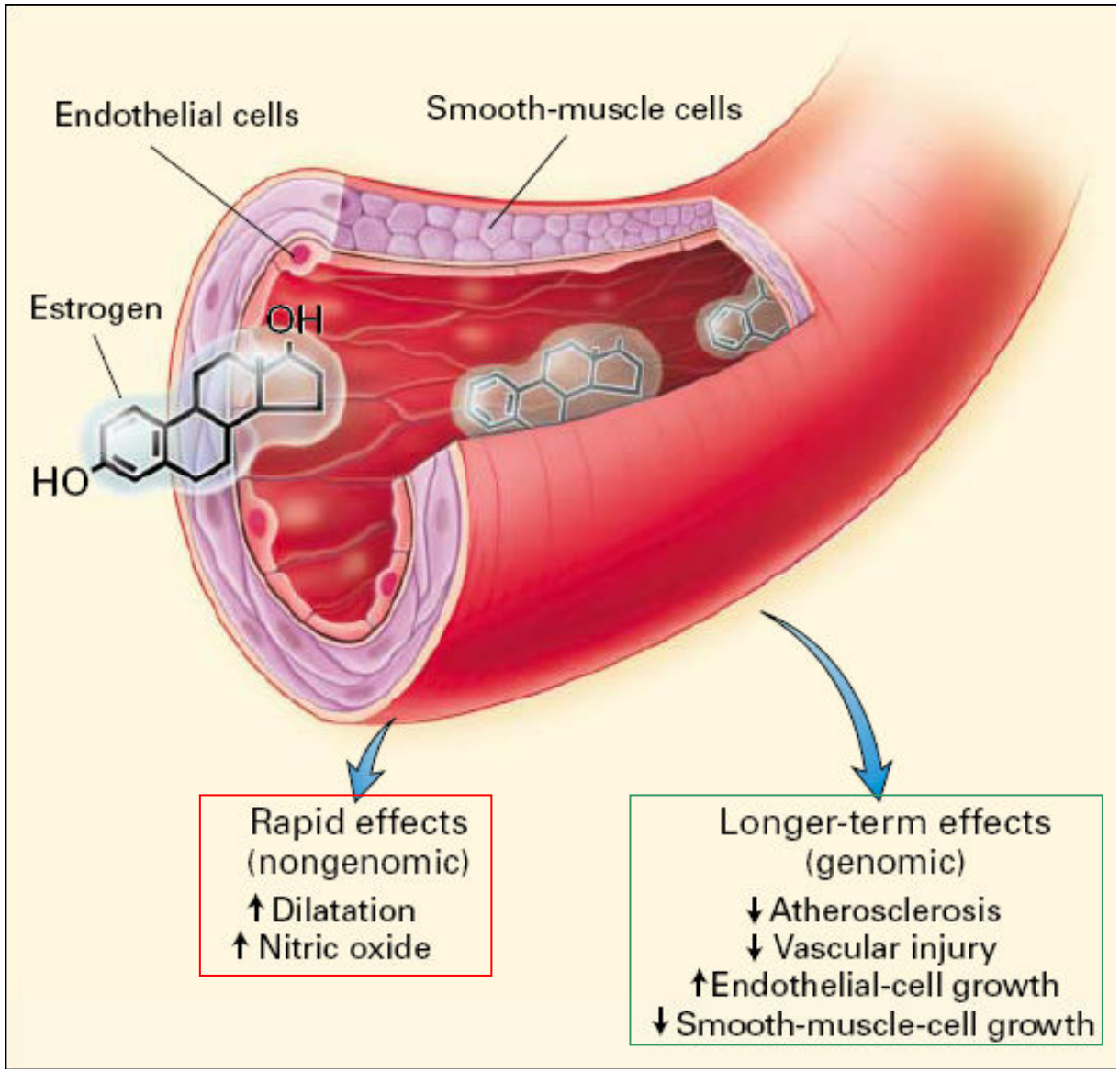
Direct Effects of Estrogen on Blood Vessels



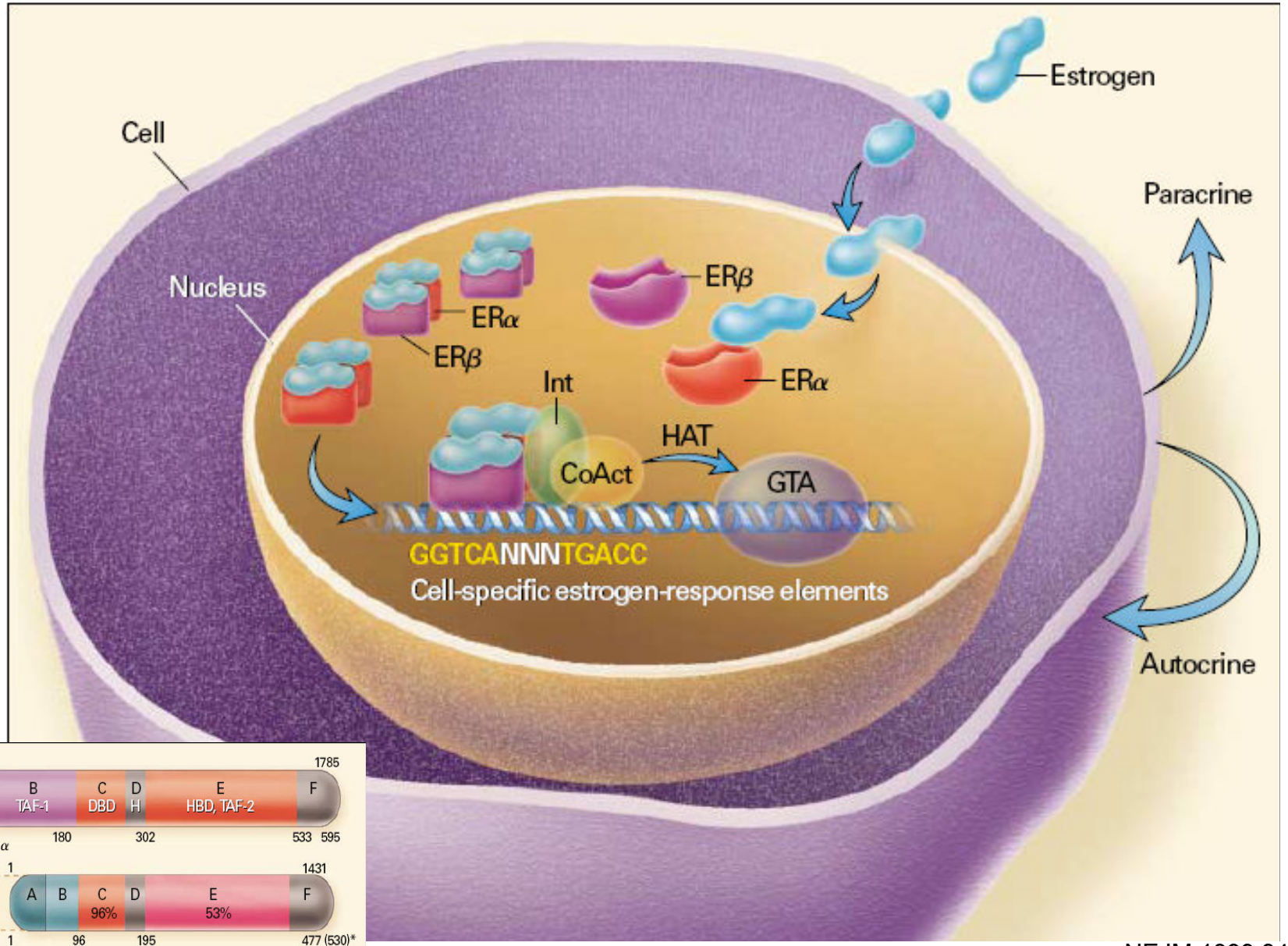
NEJM 1999;340:1801

Estrogen-regulated Genes of Potential Importance in Vascular Physiology and Disease

GENE PRODUCT	PHYSIOLOGIC OR PATHOPHYSIOLOGIC ROLE*
Candidate estrogen-regulated genes (vascular cells)	
Prostacyclin synthase	Vasodilatation
Endothelial nitric oxide synthase	Vasodilatation
Inducible nitric oxide synthase	Vasodilatation in response to vascular injury
Endothelin-1	Vasoconstriction
Collagen	Vascular-matrix formation
Matrix metalloproteinase 2[23]	Vascular-matrix remodeling
E-selectin	Cell adhesion
Vascular-cell adhesion molecule	Cell adhesion
Vascular endothelial growth factor	Angiogenesis and endothelial-cell proliferation
Candidate estrogen-regulated genes (nonvascular cells)	
Growth- and development-related genes	
Transforming growth factor β_1[24]	Wound healing
Epidermal growth factor receptor	Cell growth in response to vascular injury
Platelet-derived growth factor[25]	Cell growth in response to vascular injury
flt-4 tyrosine kinase	Angiogenesis and endothelial-cell proliferation
Coagulation- and fibrinolysis-related genes	
Tissue factor[26]	Hemostasis in response to thrombosis
Fibrinogen	Hemostasis in response to thrombosis
Protein S	Hemostasis in response to thrombosis
Coagulation factor VII	Hemostasis in response to thrombosis
Coagulation factor XII[27]	Hemostasis in response to thrombosis
Plasminogen-activator inhibitor 1	Hemostasis in response to thrombosis
Tissue plasminogen activator[28]	Fibrinolysis
Antithrombin III	Anticoagulation
Signaling-related and miscellaneous genes	
Estrogen receptor α	Hormonal regulation and gene expression
Estrogen receptor β	Hormonal regulation and gene expression
Monocyte chemotactic protein 1[29]	Monocyte recruitment and atherosclerosis
I_{SK} and HK2 (cardiac potassium channels)[30]	Cardiac conduction
Connexin 43	Cardiac conduction
Leptin[31]	Fat metabolism and obesity
Apolipoproteins A, B, D, and E and Lp(a)	Lipid metabolism and atherosclerosis
Angiotensin-converting enzyme	Vasoconstriction
Angiotensin II receptor, type 1	Vasoconstriction

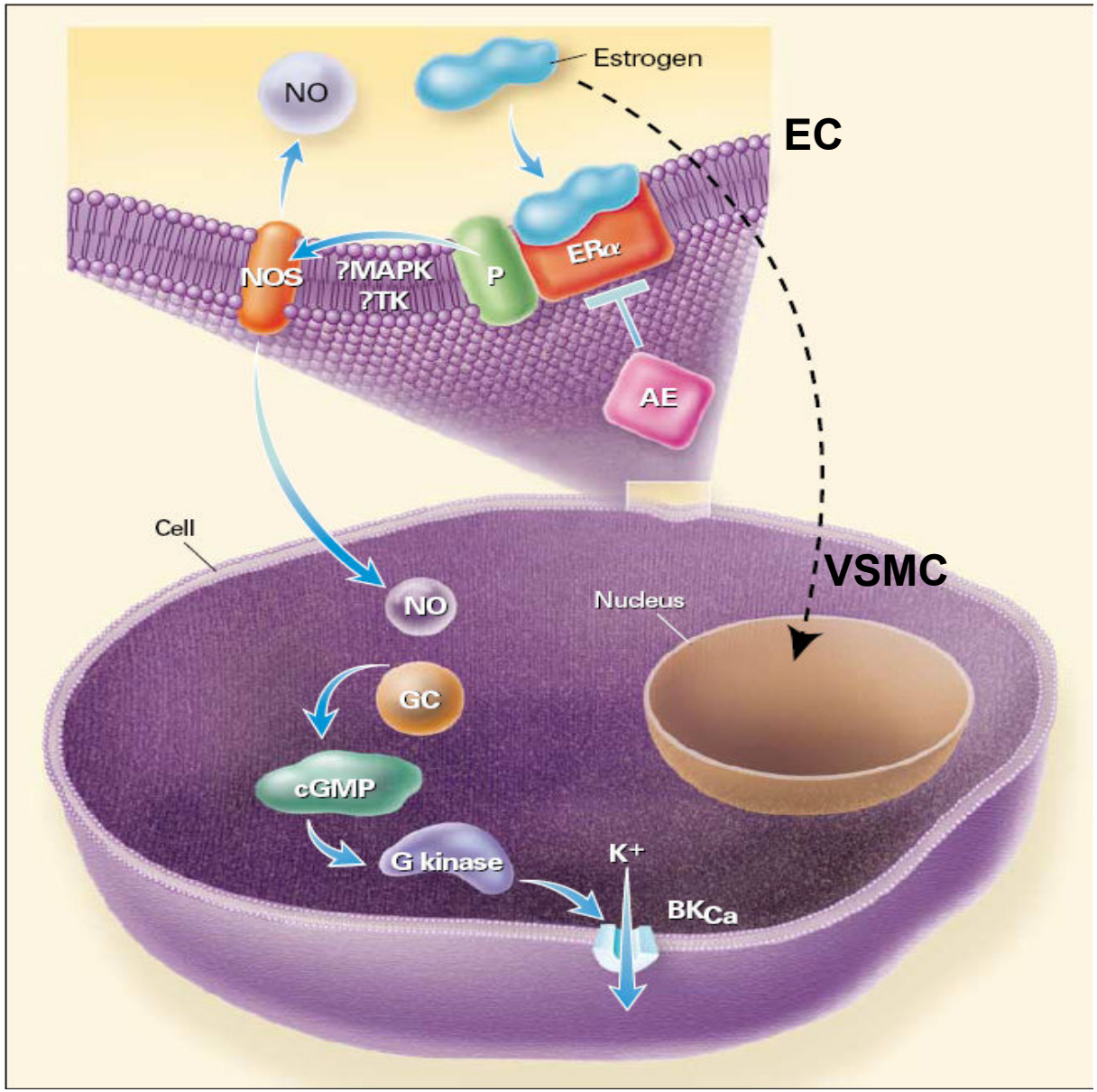
NEJM 1999;340:1801

Mechanism of Estrogen-Receptor Activation of Gene Expression



NEJM 1999;340:1801

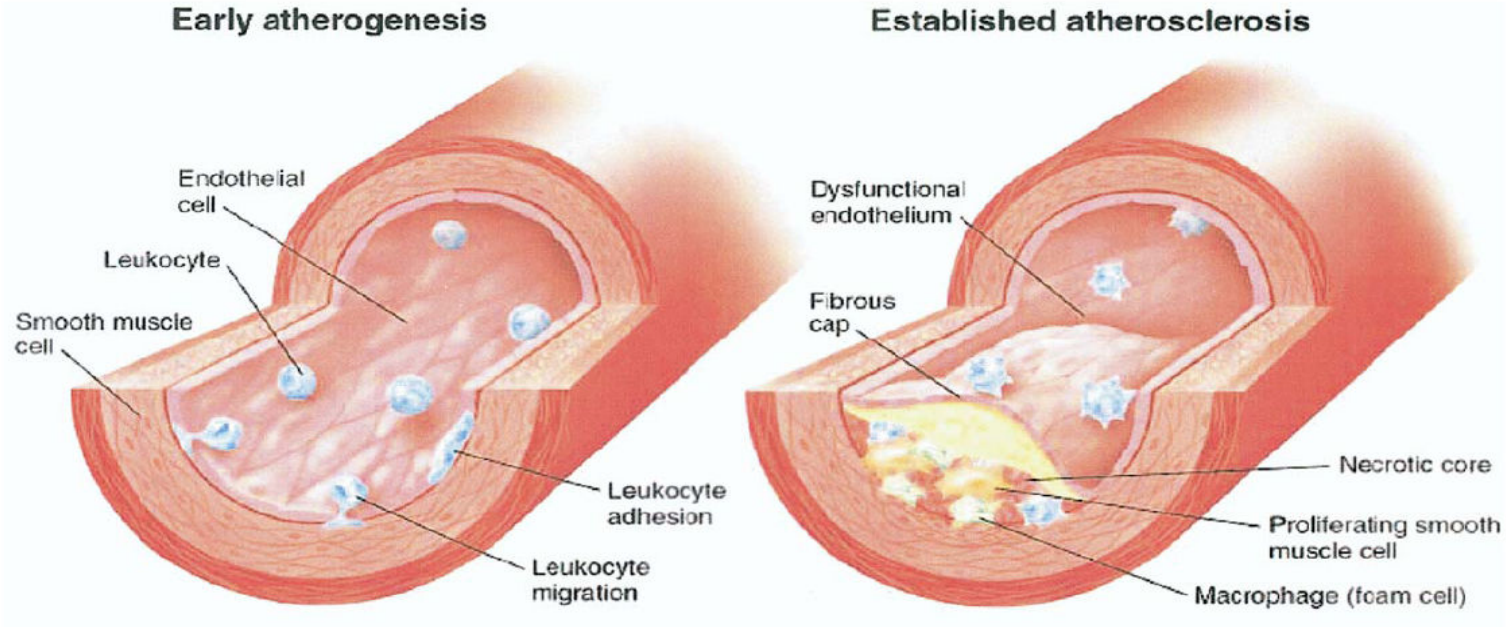
Mechanism of Rapid, Nongenomic Activation of NO Synthase by Estrogen in Endothelial Cells and Vascular Smooth-Muscle Cells



AE: antiestrogens
BKCa: Ca-activated K-channels

NEJM 1999;340:1801

The Timing Hypothesis: Differential Effects of HRT on Early and Later Stages of Atherosclerotic Disease.



Beneficial effects of HRT

- ↑ Vasodilation
  - ↑ Nitric oxide
  - ↓ Endothelin
  - ↑ Cox-2
- ↓ Inflammatory activation
  - ↑ Nitric oxide
  - ↓ CAMs
  - ↓ MCP-1, TNF-α
- ↓ Lesion progression
  - ↑ Nitric oxide
  - ↓ Inflammatory cell adhesion
  - ↓ LDL oxidation/binding
  - ↓ Platelet activation
  - ↓ VSMC proliferation

Altered biology of HRT

- ↓ ER expression, function
- ↓ Vasodilation
- ↑ Inflammatory activation
- ↑ Plaque instability
  - ↑ MMP
  - ↑ Neovascularization

Science 2005; 308,1583

Impact of Disease State on the Cardiovascular Effects of Estrogen

- There is growing evidence showing that the effects of estrogen on the vasculature depend in part on the extent to which atherosclerosis has become established.

- Estrogen receptor expression is markedly diminished in atherosclerotic arteries, and thus, to the extent that direct, receptor-dependent effects on the vasculature contribute to the potential for anti-atherosclerotic effects, this will be diminished or absent in diseased arteries.

- The effects of estrogen on a given pathway may have different consequences depending on the state of health of the underlying vessel.

- Estrogen up-regulates specific members of the MMP family such as MMP-9.
- The MMPs degrade the ECM with the arterial wall.
  - in a non-diseased artery, an estrogen-induced increase in MMP-9 may have little or no consequences,
  - in an atherosclerotic artery, where MMP-9 is expressed in the shoulder region of an atherosclerotic plaque,
  - an increase in MMP-9 activity could conceivably be associated with an increased risk of plaque rupture and thus ACS.

Impact of Disease State on the Cardiovascular Effects of Estrogen

- **Estrogen-mediated up-regulation of COX-2 plays an important role in retarding atherosclerosis in a hypercholesterolemic mouse model.**

  - atherosclerotic arteries with impaired COX-2 responses may also lose this potentially beneficial effect of hormone treatment.

- **More direct support for the hypothesis that the effects of estrogen on CV risk depend on the timing of initiation of therapy in relation to the extent of underlying atherosclerosis.**

- **Using a monkey model of atherosclerosis, the antiatherosclerotic effects of oral CEE are apparent only in monkeys with minimal underlying atherosclerosis at the time that therapy is initiated.**

Cardiovascular Disease and Menopause

- In 1976 the Framingham investigators
  - a 2.6-fold higher incidence of CV events in age-matched postmenopausal women compared with premenopausal women.
  - a 2.7-fold higher surgical menopause compared with premenopausal women of the same age ($p<0.01$)
  - a 2.2-fold higher compared with women with a natural menopause.

  This excess risk seemed to be prevented by ERT.

- Plasma lipoproteins were thought to play a role in the increased CHD risk that menopause confers
  - TC, LDL-C, and TG levels all increase in women after menopause,
  - HRT seemed to counter these unfavorable effects of lipids, although the HDL-C levels also decreased.
  - There is an age-associated increase in the incidence of CVD for both pre- and post-menopausal women independent of the effects of HRT.

- Withdrawal of estrogen during menopause is associated with an increased risk of heart disease above that seen for premenopausal women.

- This led to interest in the potential CV benefit from postmenopausal ERT.

Animal Studies of Hormone Replacement

In animal studies, estrogens exert vasodilator, antiinflammatory, and antiatherosclerotic properties, as well as favorably affecting lipid profiles.

In a study of randomized ovariectomized hypercholesterolemic rabbits, estradiol significantly reduced atherosclerosis progression compared with levonorgestrel or no hormones.

A series of studies have also shown that estradiol significantly lessens the response to vascular injury in mice and further implicate ER as the specific estrogen receptor that mediates this vasculoprotective effect.

Similarly in ovariectomized monkeys, 17-estradiol or CEE reduced coronary artery atherosclerosis compared with control animals by 50% ($p<0.05$) to 72% ($p<0.04$).

Although the role of estrogen replacement seemed promising in the animal studies, the data regarding progesterone were more conflicting.

Observational and Case-Controlled Studies of Hormone Therapy

Investigator/ Year	Type of Study	Population	Hormone Preparation	Primary End Point	Results	Conclusions
Rosenberg et al. (40)/1993	Case-controlled	858 women age 45–60 yrs with first MI compared with 858 age-matched control subjects.	Estrogen (E) alone: 21% of both cases and control subjects used E; most using CEE.	First MI	OR of 0.9 (0.7–1.2) with history of E use. For >5 yrs of use OR of 0.6 ($p = 0.08$).	Nonsignificant trend toward reduced first MI in E users, longer-term use was stronger than recent use ($p < 0.05$) and compared with past use ($p = 0.08$).
Mann et al. (41)/1994	Case-controlled	Database within British National Health Service. Women age 45–64 yrs (n = 567,096), with 1,521 cases of MI matched with 6,084 control subjects.	Any E or E+ progestin (P): 117 cases and 562 control subjects used HT. Approximately 2/3 on E+P and 1/3 on E.	First MI (fatal or nonfatal)	OR 0.83 (0.66–1.03), $p = 0.089$ with HT use. Nonsmokers on HT, OR 0.70 (0.49–1), smokers on HT, OR 1.05 (0.71–1.53).	Nonsignificant trend toward reduced first MI with any form of HT. However, protective effect seems to be confined to nonsmokers.
Psaty et al. (42)/1994	Case-controlled	Group Health Cooperative of Puget Sound, WA. Postmenopausal women, 502 cases of MI and 1,193 control subjects.	Any E or E+P. Among cases, HT use was E (n = 45) and E+P (n = 16); among control subjects use was E (n = 157) and E+P (n = 74). Majority used cyclical 0.625 CEE and 10 mg MPA.	First MI (fatal or nonfatal)	OR 0.69 (0.47–1.02) with E alone. OR 0.68 (0.38–1.22) with E+P.	Nonsignificant trend toward reduced risk of MI.
Jonas et al. (48)/1996	Cross-sectional, nonrandomized	2,962 women in the Cardiovascular Health Study.	E formulation not specified. Past users (n = 787), current E alone (n = 280), current E+P (n = 73).	Carotid IMT Carotid stenosis	IMT was 0.22 mm less in E ($p = 0.003$) and 0.09 mm less in E+P ($p = 0.05$) vs. in nonusers. Adjusted OR for carotid stenosis of 0.61 (0.36–1.01) for E and OR 0.91 (0.67–1.25) for E+P.	Both E+P and E alone were associated with decreased measures of carotid atherosclerosis.
Grodstein et al. (4)/1996	Prospective observational	59,337 women from Nurses' Health Study ages 30–55 yrs at baseline. 770 cases of MI/ CHD death and 572 cases of stroke over 16-yr follow-up.	Past users (n = 12,503), current E alone (n = 7,776), and E+P (n = 6,224).	MI or CHD death	For MI/CHD events, RR 0.39 (0.19–0.78) in E+P, 0.60 (0.43–0.83) in E alone. For stroke, RR 1.09 (0.66–1.8) in E+P and 1.27 (0.95–1.69) for E alone.	These data support a reduced risk of hard CHD events in women on HT that is not attenuated by the addition of progestin. However, there was a nonsignificant trend toward increased strokes.

Investigator/ Year	Type of Study	Population	Hormone Preparation	Primary End Point	Results	Conclusions
Grodstein et al. (51)/2000	Prospective, observational	Nurses' Health Study. 70,533 postmenopausal women with 1,258 fatal/nonfatal MI and 767 strokes over 20-yr follow-up.	Any HT including CEE 0.3 mg, 0.625 mg, and >1.25 mg either alone or in combination with progestin.	Fatal or nonfatal MI and stroke	CHD events: RR in current E users of 0.61 (0.52–0.71); 0.54 (0.44–0.67) with CEE 0.625 mg and 0.58 (0.37–0.92) with CEE 0.3 mg. Stroke: RR 1.35 (1.08–1.68) with CEE 0.625 mg, 1.63 (1.18–2.26) for >1.25 mg, and 1.45 (1.10–1.92) for E+P.	CEE seemed to decrease the risk of CHD events with similar reduction for 0.3 mg and 0.625 mg CEE. However, CEE ≥0.625 mg or in combination with progestin may increase risk of stroke.
Varas-Lorenzo et al. (46)/ 2000	Case-controlled	General Practice Research Database (n = 164,769), with 1,242 cases of first MI and 5,000 age-matched control subjects.	Any HT including oral (79%) and transdermal (21%) formulations.	MI	Current HT users had OR 0.72 (0.59–0.89), OR 0.52 (0.35–0.78) for E, and OR 0.79 (0.59–1.08) for E+P.	Data showed an association between HT and reduced incidence of acute MI. This was similar in users of oral and transdermal formulations.
Ferrara et al. (72)/2003	Observational	Kaiser database. Diabetic women age >50 yrs (mean age 65 yrs, n = 25,000).	Low-, medium-, or high-dose E alone or combined E+P. There were 2,526 (10%) women on E alone and 2,088 (9%) on E+P.	3-yr MI risk	In those without a recent MI, RH for MI for combined HT was 0.77 (0.61–0.97); unopposed estrogen was 0.88 (0.73–1.05). In those with a recent MI, RH was 1.78 (1.06–2.98).	In diabetic women without a recent MI, use of HT was associated with decreased risk of MI in women on <0.625 mg CEE but not a higher dose. However, HT was associated with an increased risk of MI in women with a history of recent MI, especially for HT use <1 yr.

Investigator/ Year	Type of Study	Population	Hormone Preparation	Primary End Point	Results	Conclusions
Grodstein et al. (50)/1997	Prospective observational	Postmenopausal women of Nurses' Health Study. 3,637 cases and 34,625 control subjects over 18-yr follow-up.	Any hormone replacement.	Mortality	RR 0.63 (0.56–0.70) in current HT users, decreasing after 10 years of use (RR 0.80, 0.67–0.96). Benefit seen in HT users with CHD risk factors (RR 0.51, 0.45–0.57), not in those at low risk (RR 0.89, 0.62–1.28).	Mortality is lower among current HT users; however, survival benefit diminishes over time and is lower for women at low risk for CHD.
Heckbert et al. (47)/1997	Case-controlled	Group Health Cooperative of Puget Sound, WA enrollees. Postmenopausal women; 850 cases with MI and 1,974 control subjects.	E alone or E+P. 229 cases and 700 control subjects used HT, most commonly CEE with or without MPA.	Fatal or nonfatal MI	For categories of duration of E use, OR 1.0 for never (ref), 0.91 for <1.8 yrs, 0.70 for 1.8–4.2 yrs, 0.64 for 4.2–8.2 yrs, and 0.55 for >8.2 yrs. $p = 0.05$ for the trend.	A longer duration of HT among current users was associated with a reduced risk of first MI.
Sidney et al. (43)/1997	Case-controlled	Kaiser database. Post-menopausal women age 45–74 yrs; 438 cases with MI and 438 age-matched control subjects.	E or E+P. In women s/p hysterectomy 51% used E, 1.2% used E+P. In women with a uterus 18.4% used E+P, 3% used E.	MI	OR 0.96 (0.66–1.49) in current HT users compared with nonusers, OR 1.07 (0.72–1.58) in past users.	No statistically significant decrease in OR for MI in current or past users of HT.
Petitti et al. (44)/2000	Case-controlled	Same population of Kaiser database as above.	As above.	MI	OR 0.9 (0.5–1.6) in current HT users without CHD risk factors, 0.8 (0.5–1.8) with 1 risk factor and 1.1 (0.5–2.2) with 2 risk factors.	No decrease in risk of MI in current users of HT who had 0, 1, 2, or 3 major CHD risk factors.
Grodstein et al. (45)/1999	Case-controlled	Sweden. Postmenopausal women with 213 cases of MI and 289 strokes matched to control subjects.	Medium-potency compared with low-potency or short-term E or E+P use.	MI and stroke	For MI, OR 0.75 (0.56–0.99) for medium-potency compared with low-potency E and OR 0.69 (0.45–0.90) for combined E+P. For stroke, OR 0.91 (0.71–1.17) for medium-potency E and 0.81 (0.61–1.10) for E+P.	Decreased risk of MI for medium potency E or E+P. No effect was seen on stroke risk.

Summary of the Randomized Trials of Hormone Therapy

Investigator/ Year	Study Design	Subjects	Intervention	Median Follow-Up	End Point	Results	Conclusions
Angerer et al. (59)/2001 (PHOREA)	Randomized, double-blind, placebo-controlled, secondary prevention	321 healthy postmenopausal women with increased carotid IMT	17 β-estradiol 1 mg + 0.025 mg gestodone for 12 days/months vs. every 3 months (low-progestin) vs. no HT	48 weeks	IMT: maximum carotid IMT thickness	HT did not slow carotid IMT progression	1 yr of HT did not slow progression of subclinical atherosclerosis in postmenopausal women at increased risk.
Hodis et al. (52)/2001 (EPAT)	Randomized, double-blind, placebo-controlled, primary prevention trial	222 healthy postmenopausal women without CHD	Unopposed 17 β-estradiol (1 mg) (n = 111) or placebo (n = 111)	2 yrs	IMT: rate of change in carotid artery IMT every 6 mo	−0.0017 mm/yr in E arm vs. 0.0036 mm/yr, placebo-estradiol difference in progression was 0.0053 mm/yr (0.0001–0.0105 mm/yr, p = 0.046)	Progression of subclinical atherosclerosis was slower in healthy postmenopausal women taking unopposed E, compared with placebo.
Byington et al. (58)/2002 (HERS B-Mode substudy)	Randomized, double-blind, placebo-controlled secondary prevention trial	362 postmenopausal women with CHD (subset of HERS trial)	CEE 0.625 + MPA 2.5 mg (n = 177) or placebo (n = 185)	Mean 3.8 yrs	IMT: temporal change in mean of 8 maximum IMT measurements	IMT progressed 26 μm/yr (18–34) in CEE+MPA group and 31 μm/yr (21–40) in placebo group, p = 0.44	IMT progressed in both groups without significant difference.
Schulman et al. (60)/2001	Randomized, double-blind, placebo-controlled trial	293 postmenopausal women presenting with unstable angina enrolled within 24 h of symptom onset	IV 1.25 mg bolus then oral CEE 1.25 mg + MPA 2.5 mg × 21 days vs. IV bolus then oral CEE 1.25 mg + placebo vs. IV then oral placebo	48 h	ECG evidence of ischemia by continuous ambulatory monitoring (first 48 h) and repeated after 21 days of study drug	ECG ischemia did not differ among the three groups	Acute HT does not reduce ischemia in postmenopausal women with unstable angina when added to standard anti-ischemia therapy.
Viscoli et al. (61)/2001 (Women's Estrogen for Stroke Trial)	Randomized, double-blind, placebo-controlled secondary prevention trial	664 postmenopausal women (mean age 71 yrs) with recent stroke or TIA	17 β-estradiol 1 mg	Mean 2.8 yrs	CV events: recurrent stroke or death	Combined events: RR 1.1 (0.8–1.4) in E vs. placebo. Death alone RR 1.2 (0.8–1.8). Nonfatal stroke RR 1.0 (0.7–1.4). Fatal stroke RR 2.0, (0.9–9.0) in E users. Nonfatal strokes had slightly worse neurologic outcome in E users.	Estradiol does not reduce mortality or recurrent stroke in postmenopausal women with cerebrovascular disease.

Investigator/ Year	Study Design	Subjects	Intervention	Median Follow-Up	End Point	Results	Conclusions
Herrington et al. (54)/2000 (ERA)	Randomized, double-blind, placebo-controlled secondary prevention trial	309 postmenopausal women with coronary stenosis >30%, mean age 65.8 yrs	CEE 0.625 mg only (n = 100), CEE 0.625+MPA 2.5 mg daily (n = 104), or placebo (n = 100)	3.2 yrs	Quantitative coronary angiography: adjusted change in mean luminal diameter	−0.09 ± 0.02 mm for E, −0.12 ± 0.02 for combined E+P, and −0.09 ± 0.02 for placebo, p = 0.38	Neither E alone nor E+P affected the progression of coronary atherosclerosis.
Waters et al. (55)/2002 (WAVE)	Randomized, double-blind, placebo-controlled secondary prevention trial	423 postmenopausal women with at least 1 coronary stenosis 15% to 75%, mean age 65 yrs	CEE 0.625 mg ± MPA 2.5 mg daily (n = 210) vs. placebo (n = 213), and vitamins vs. placebo	2.8 yrs	Quantitative coronary angiography: annualized mean change in minimum lumen diameter	Coronary progression worsened with HT by 0.047 (0.15) mm/yr and by 0.024 (0.015) in control subjects, p = 0.17. Death, nonfatal MI, or stroke HR was 1.9 (95% CI 0.97–3.6) in HT compared with control subjects.	No significant change in progression of atherosclerosis. Neither HT (nor antioxidant supplements) provided CV benefit. Instead a potential for harm was suggested.
Hodis et al. (56)/2003 (WELL-HART)	Randomized, double-blind, placebo-controlled	226 postmenopausal women with CHD, mean age 63.5 yrs	Oral 17 β-estradiol (1 mg/day) alone (n = 76), +5 mg MPA (n = 74), or placebo (n = 76)	3.3 yrs	Quantitative coronary angiography: average per-participant change in percent stenosis	Mean change in stenosis was 1.89 ± 0.78 in placebo, 2.18 ± 0.76 in E, 1.24 ± 0.80 in E+P; p = 0.66 for comparison	Estrogen alone or with progesterone had no significant effect on the progression of atherosclerosis.
de Kleijn et al. (53)/2001	Randomized, double-blind, placebo-controlled primary prevention trial	105 healthy postmenopausal women	Tibolone (n = 35), CEE+MPA (n = 35), or placebo (n = 35)	3 months	Brachial reactivity: % flow-mediated lumen diameter change after 3 months	CEE+MPA vs. placebo had 2.5% change (0.3–4.6). Tibolone vs. placebo was 0.6% (−1.6–2.8).	HT with CEE+MPA (but not tibolone) increases endothelium-dependent flow-mediated dilation.

Investigator/ Year	Study Design	Subjects	Intervention	Median Follow-Up	End Point	Results	Conclusions
Hulley et al. (5)/1998 (HERS)	Randomized, double-blind, placebo-controlled secondary prevention trial	2,763 postmenopausal women with CHD, mean age 66.7 yrs	CEE 0.625 + MPA 2.5 mg (n = 1,380) or placebo (n = 1,383)	Mean 4.1 yrs	CV events: occurrence of nonfatal MI or CHD death	RR of 0.99 (0.80–1.22). Trend to increased events in first year with fewer events at years 4–5.	No overall CV benefit. Possible divergence at 4–5 yrs. HT increased the rate of thromboembolic disease.
Grady et al. (62)/2002 (HERS II)	As above	As above	As above	Mean 6.8 yrs	CV events: as above	Unadjusted RR of 0.99 (0.81–1.22), adjusted 0.99 (0.84–1.17)	Lower rates of CHD events at 4–5 yrs among women on HT in HERS did n ot persist during additional years of follow-up.
Clarke et al. (57)/2002 (PHASE)	Randomized, prospective secondary prevention trial	255 postmenopausal women with ≥1 coronary stenosis >50%, mean age 66.5 yrs	Transdermal E+P (n = 134) vs. placebo (n = 121)	30.8 mo	CV events: MI, cardiac death, or admission to hospital with unstable angina	Event ratio 1.29 (0.84–1.95, p = 0.24)	HT group had a not statistically significantly higher event rate compared with control subjects.
Rousouw et al. (6)/2002 (WHI CEE and MPA)	Randomized, double-blind, placebo-controlled primary prevention trial	16,608 postmenopausal women	CEE 0.625 mg + MPA 2.5 mg (n = 8,506) vs. placebo (n = 8,102)	5.2 yrs (planned 8.5 yrs)	CV events: primary CHD outcome of nonfatal MI, and CHD death; adverse risk score included invasive breast cancer	HR: CHD 1.29 (1.02–1.63), breast cancer 1.26 (1.0–1.59), stroke 1.41 (1.07–1.85), PE 2.13 (1.39–3.25), colon cancer 0.63 (0.43 –0.92), endometrial cancer 0.83 (0.47–1.47), hip fracture 0.66 (0.45–0.98), total mortality 0.98 (0.82–1.18)	Stopped early for absolute excess risks. For 10,000 person-years attributed to HRT were 7 more CHD events, 8 more PEs, 8 more asive breast cancers; whereas 6 fewer colon cancers and 5 fewer hip fractures were seen.
Anderson et al. (63)/2004 (WHI-CEE alone)	Randomized, double-blind, placebo-controlled trial primary prevention	10,379 postmenopausal women with prior hysterectomy	CEE 0.625 alone (n = 5,310) vs. placebo (n = 5,429)	6.8 yrs	CV events: as above	HR for CHD events 0.91 (0.75–1.12), breast cancer 0.77 (0.59–1.01), stroke 1.39 (1.10–1.77), PE 1.34 (0.87–2.06), colorectal cancer 1.08 (0.75–1.55), hip fracture 0.61 (0.41–0.91), total mortality 1.04 (0.88–1.22)	The use of CEE increases the risk of stroke, decreases the risk of hip fracture, and does not affect CHD incidence.

Abbreviations as in Table 1.

Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women
WHI Randomized Controlled Trial

Estrogen + Progestin Component of the WHI

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

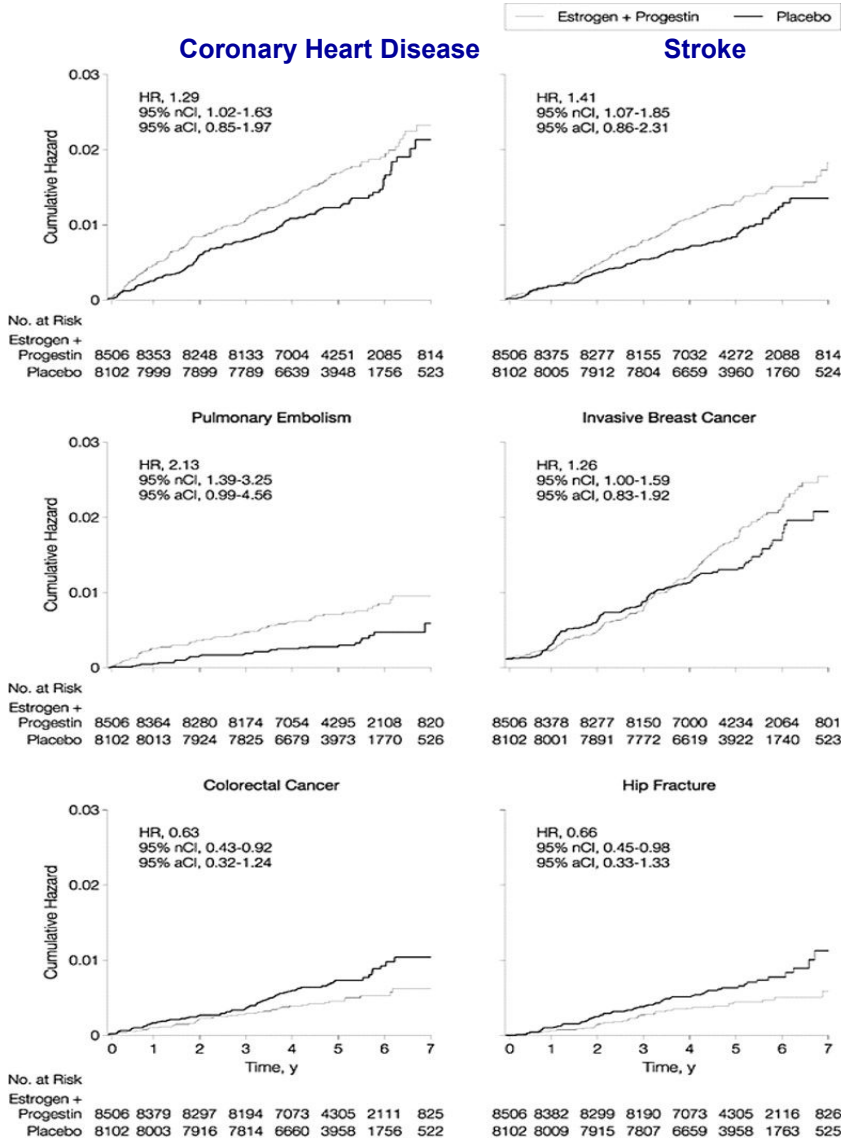
231 Deceased

Status on April 30, 2002

7608 Alive and Outcomes Data Submitted in Last 18 mo

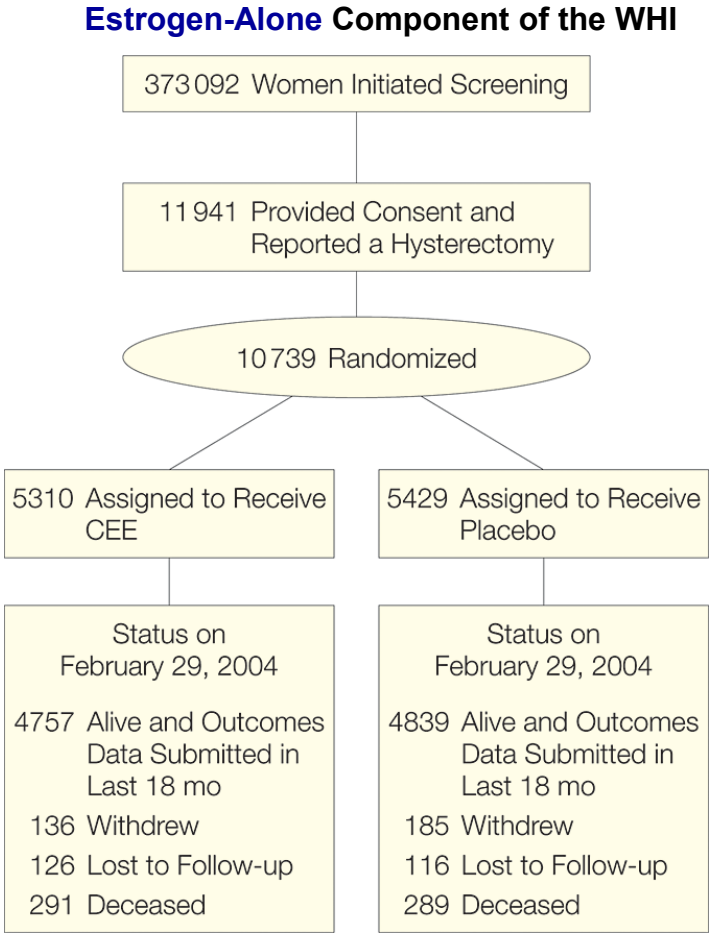
276 Unknown Vital Status

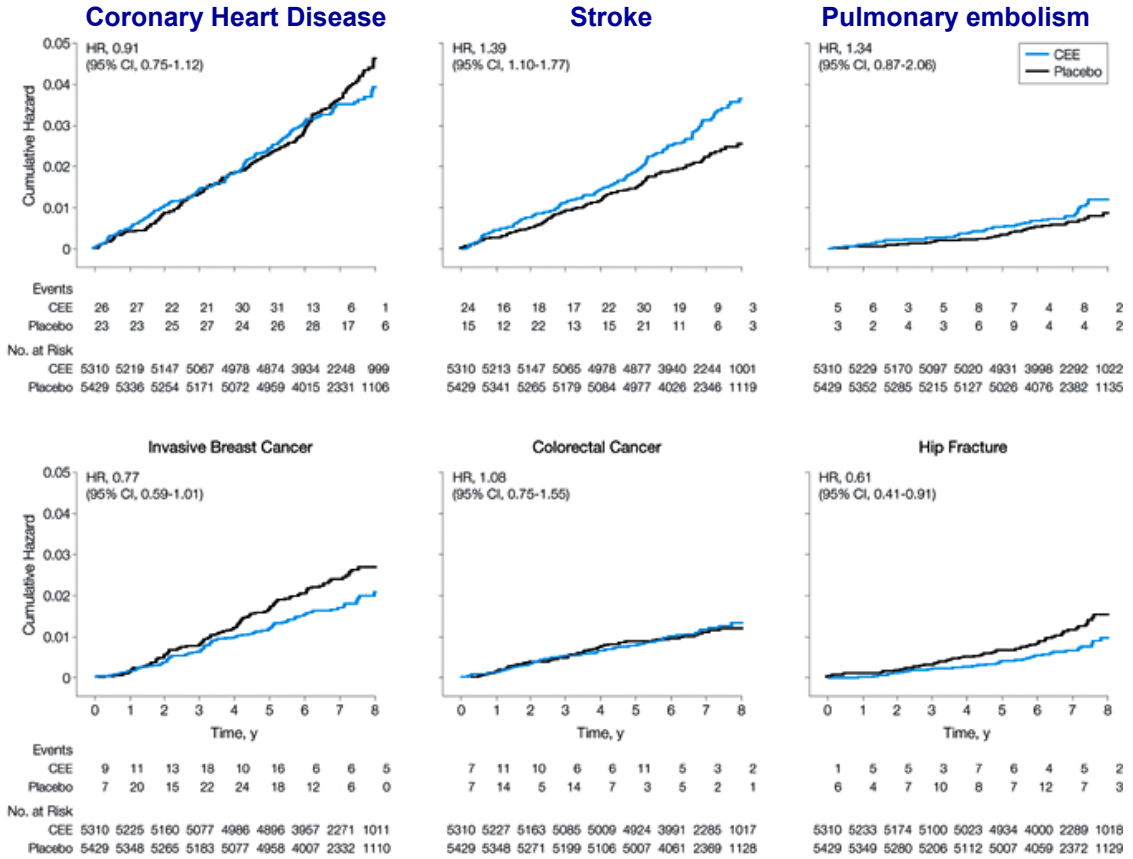
218 Deceased



Writing Group for the Women's Health Initiative Investigators, JAMA 2002;288:321-333.

Effects of Conjugated Equine Estrogen in Postmenopausal Women With Hysterectomy: WHI Randomized Controlled Trial





The Women's Health Initiative Steering Committee, JAMA 2004;291:1701-1712.

The WHI Estrogen-Alone Trial— Do Things Look Any Better?

Hazard Ratios From 3 Hormone Therapy Trials

Clinical Event	Hazard Ratio (95% Confidence Interval)		
	HERS (Estrogen + Progestin)[5,7]	WHI (Estrogen + Progestin)[6]	WHI Estrogen Alone[14]
CHD events	0.99 (0.80-1.22)	1.29 (1.02-1.63)	0.91 (0.75-1.12)
Stroke	1.23 (0.89-1.70)	1.41 (1.07-1.85)	1.39 (1.10-1.77)
Pulmonary embolism	2.79 (0.89-8.75)	2.13 (1.39-3.25)	1.34 (0.87-2.06)
Breast cancer	1.30 (0.77-2.19)	1.26 (1.00-1.59)	0.77 (0.59-1.01)
Colon cancer	0.69 (0.32-1.49)	0.63 (0.43-0.92)	1.08 (0.75-1.55)
Hip fracture	1.10 (0.49-2.50)	0.66 (0.45-0.98)	0.61 (0.41-0.91)
Death	1.08 (0.84-1.38)	0.98 (0.82-1.18)	1.04 (0.88-1.22)
Global index†	. . .	1.15 (1.03-1.28)	1.01 (0.91-1.12)

Abbreviations: CHD, coronary heart disease; HERS, Heart and Estrogen/progestin Replacement Study; WHI, Women's Health Initiative; ellipses, not calculated.
*Data are based on the intent-to-treat analyses. For the primary CHD events outcome (myocardial infarction plus CHD death), the 3 trials had similar numbers of events and thus similar power. For other outcomes the smaller HERS trial had fewer events and less precise hazard ratios.
†The global index was composed of the first occurrence of any of the events listed in the table.

JAMA 2004;291:1769

Hazard Ratios For Various Outcomes For Women 50 To 79 Years

Outcome	Hazard ratio (95% confidence interval)	
	Combined oestrogen and progestogen	Oestrogen only
Stroke (mainly ischaemic)	1.41 (1.07 to 1.85)	1.39 (1.10 to 1.77)
Breast cancer (final results)	1.24 (1.01 to 1.54)	0.77 (0.59 to 1.01)
Deep vein thrombosis	1.95 (1.43 to 2.67)	1.47 (1.06 to 2.06)
Coronary heart disease (final results)	1.24 (1.00 to 1.54)	0.95 (0.70 to 1.16)
Dementia (women ≥65 years)	2.05 (1.21 to 3.48)	1.49 (0.83 to 2.66)
Gall bladder disease and procedure	1.59 (1.20 to 1.97)	1.67 (1.35 to 2.06)
Hip fracture	0.66 (0.45 to 0.98)	0.61 (0.41 to 0.91)
Total fracture	0.76 (0.69 to 0.85)	0.70 (0.63 to 0.79)
Colorectal cancer	0.63 (0.43 to 0.92)	1.08 (0.75 to 1.55)
Total mortality	0.98 (0.82 to 1.18)	1.04 (0.88 to 1.22)

BMJ 2007:334:736-41.

Questions To Be Answered

Given the findings of the HERS and of WHI trials,
is the HRT discussion ended for good?

Questions To Be Answered

Given the findings of the HERS and of WHI trials,
is the HRT discussion ended for good?
Hardly.

The conflicting results from animal/observational studies compared with the RCT raise many unanswered questions.

These include whether some of the discrepancy is related to
- the age of the women in the studies,
- the timing of initiation (perimenopausal or postmenopausal),
- the amount of atherosclerosis at the time of initiation (1˚ vs. 2 ˚ prevention),
- the dosage,
- the preparation form (transdermal, oral, or intravenous with or without progesterone),
- whether there are genetic aspects to benefit or harm from HT.

Timing of Initiation

Because atherosclerosis accelerates after estrogen deficiency, it would seem logical that estrogen replacement would have the most benefit when starting early in perimenopausal women.

Most women in the observational trials such as the Nurses' Health Study, which suggested a protective effect of estrogen, started HRT during the perimenopausal transition,

In the WHI trial the average age was 10 years after menopause, an age at which subclinical atherosclerosis has developed in many women.

In support of the notion that timing of initiation is critical,

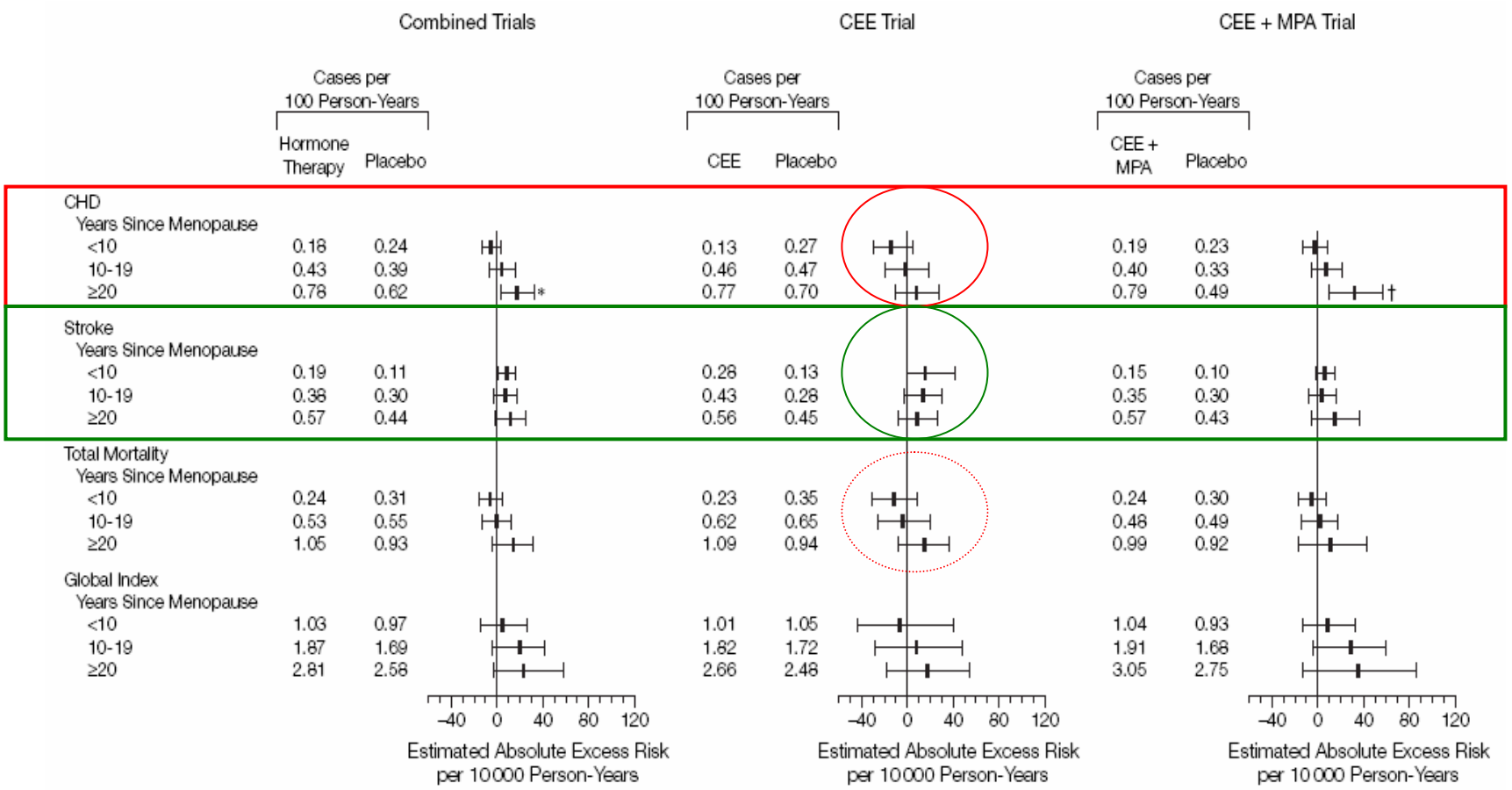
animal studies also showed no benefit of estrogen in animals that already had artery damage, either from balloon injury or from atherosclerotic diet, before initiation of HRT.

These animal studies are consistent with the findings of the secondary prevention (i.e., HERS) trials.

In postmenopausal women in the CV Health Study, ERT only caused vasodilation of the brachial artery in younger women without clinical or subclinical CV disease, suggesting that the favorable effects of estrogen may be limited to only those in whom atherosclerotic vascular disease has not yet developed.

Postmenopausal HRT and Risk of CVD by Age and Years Since Menopause

Estimated Absolute Excess Risk per 10 000 Person-Years by Years Since Menopause at Baseline



JAMA. 2007;297:1465-1477

Estrogen Therapy and Coronary-Artery Calcification: WHI Coronary-Artery Calcium Study (WHI-CACS)

1064 women aged 50 to 59 years at randomization
Imaging was conducted after a mean of 7.4 years of treatment and 1.3 years after the trial was completed (8.7 years after randomization).

Odds Ratios for Various Categories of Elevation in the Coronary-Artery Calcium Score.*

Coronary-Artery Calcium Score	Conjugated Equine Estrogens		Placebo	Odds Ratio (95% CI)		Multivariate P Value
				Unadjusted	Multivariate	
	no. (%)					
Intention-to-treat analyses†	N=537		N=527			
<10 (referent)	348 (64.8)		302 (57.3)	1.00	1.00	
10–100	100 (18.6)		106 (20.1)	0.82 (0.60–1.12)	0.82 (0.57–1.18)	
>100–300	48 (8.9)		61 (11.6)	0.68 (0.45–1.03)	0.72 (0.44–1.17)	
>300	41 (7.6)	<	58 (11.0)	0.61 (0.40–0.94)	0.58 (0.35–0.95)	0.03
Analyses restricted to participants with ≥80% adherence to study medication‡	N=387		N=352			
<10 (referent)	262 (67.7)		191 (54.3)	1.00	1.00	
10–100	71 (18.3)		78 (22.2)	0.66 (0.46–0.96)	0.67 (0.44–1.02)	
>100–300	29 (7.5)		45 (12.8)	0.47 (0.28–0.78)	0.43 (0.23–0.80)	
>300	25 (6.5)	<	38 (10.8)	0.48 (0.28–0.82)	0.39 (0.21–0.73)	0.004

* Higher calcium scores indicate greater calcification.

N Engl J Med 2007;356:2591.

Timing of Initiation

- **Kronos Early Estrogen Prevention Study (KEEPS),**

a multicenter randomized placebo-controlled clinical trial that will evaluate the effectiveness of 0.45 mg CEE or 50 g transdermal estradiol (in combination with 200 mg progesterone) in preventing the progression of carotid IMT or coronary calcium in women who are within 36 months of their final menstrual period.

It is hoped that the KEEPS trial will provide some answers to the important question of whether HRT will have a beneficial role if started early, although a relatively small sample size and the use of a surrogate end point represent limitations of this study.

- **Early vs. Late Intervention Trial with Estrogen (ELITE),**

focused on examining the potential importance of time since menopause on the cardiovascular effects of HRT.

In the ELITE study, the effects of oral 17-estradiol on carotid IMT will be compared directly in perimenopausal women v.s. those 6 years after menopause.

Dose

- Although 0.625 mg CEE clearly showed no CV benefit in the HERS and WHI trials, the observational Nurses' Health Study found the protective effect of CEE only in the lower doses of 0.3 mg and 0.625 mg, whereas 1.25 mg and higher doses were not protective.

- In postmenopausal diabetic women without a recent MI among the Kaiser Permanente database, low-dose or medium-dose estrogen (0.625 mg) decreased the risk of MI, which was not seen with a higher dose.

- Whether a lower dose of estrogen such as 0.3 mg CEE would provide cardioprotection without increasing thromboembolism remains to be seen.

Route of Delivery

The formulation of estrogen used in the large clinical trials and in the majority of the smaller studies was CEE with or without MPA.

When estrogen is given orally, it has first-pass effects on the liver.

Transdermal estrogen delivery

- **provides sustained release of estrogens and more constant blood levels than oral administration.**
- **avoid the first-pass effects on the liver and have less effection the lipoprotein profile.**

Estradiol-to-estrone conversion is slower in parental administration, but transdermal delivery more commonly facilitates an estradiol-estrone ratio of about 1, which is similar to the physiological ratio in the pre-menopausal state.

Other differences that favor the transdermal approach include a neutral effect on CRP, a decrease in factor VII and fibrinogen, and a reduction in BP. Because the first pass through the liver is avoided, there may be less induction of a prothrombotic state with the transdermal preparation.

Route of Delivery

The Estrogen and Thromboembolism Risk study Group (ESTHER) case controlled trial found that oral estrogen but not a transdermal formulation increased the risk of VTE in postmenopausal women on HRT compared with control subjects.

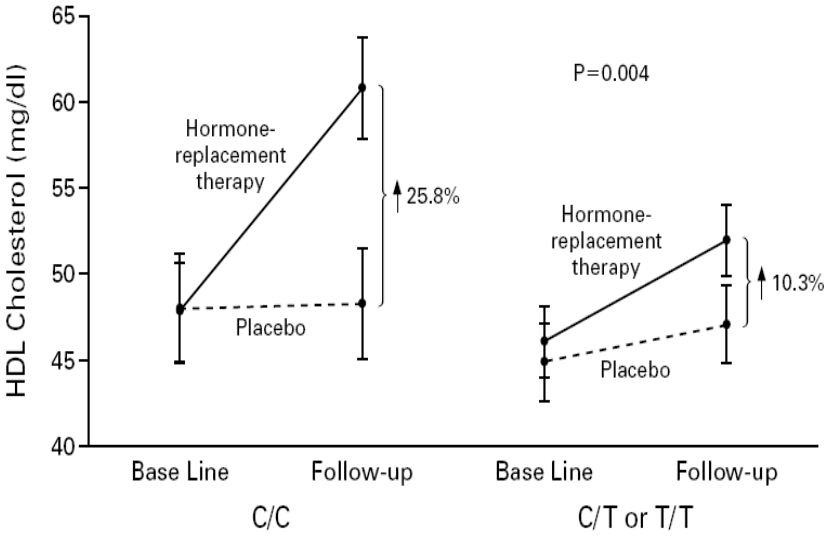
In a case-controlled study, transdermal users seemed to have similar level of cardioprotective effects as those receiving oral preparations.
These effects are not significant, but this may be attributable to small sample size.
However, an animal study using transdermal estradiol did not find inhibition of aortic atherosclerosis.

Overall, the benefits of a transdermal estrogen preparation over an oral one Seem encouraging, but further randomized trials are warranted.
It is hoped that the KEEPS trial, which will randomize healthy perimenopausal women to oral versus transdermal hormone replacement, will provide information on this important question.

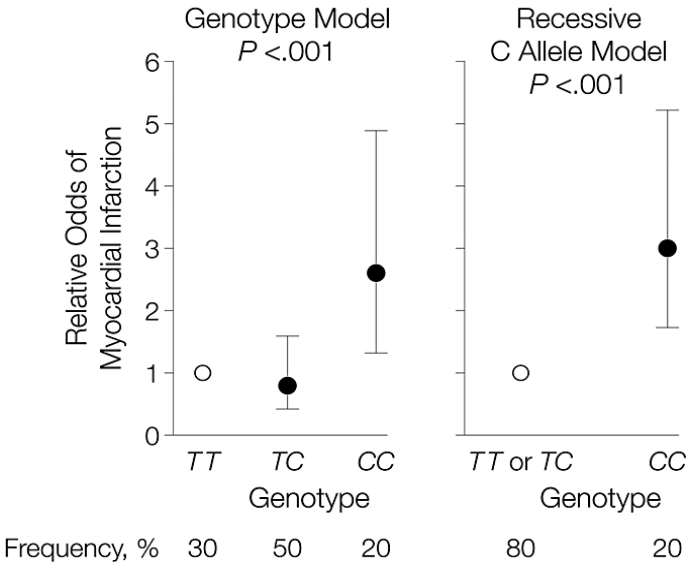
Genetics

It is possible that genetically determined subgroups of women may benefit by or be harmed from HRT.

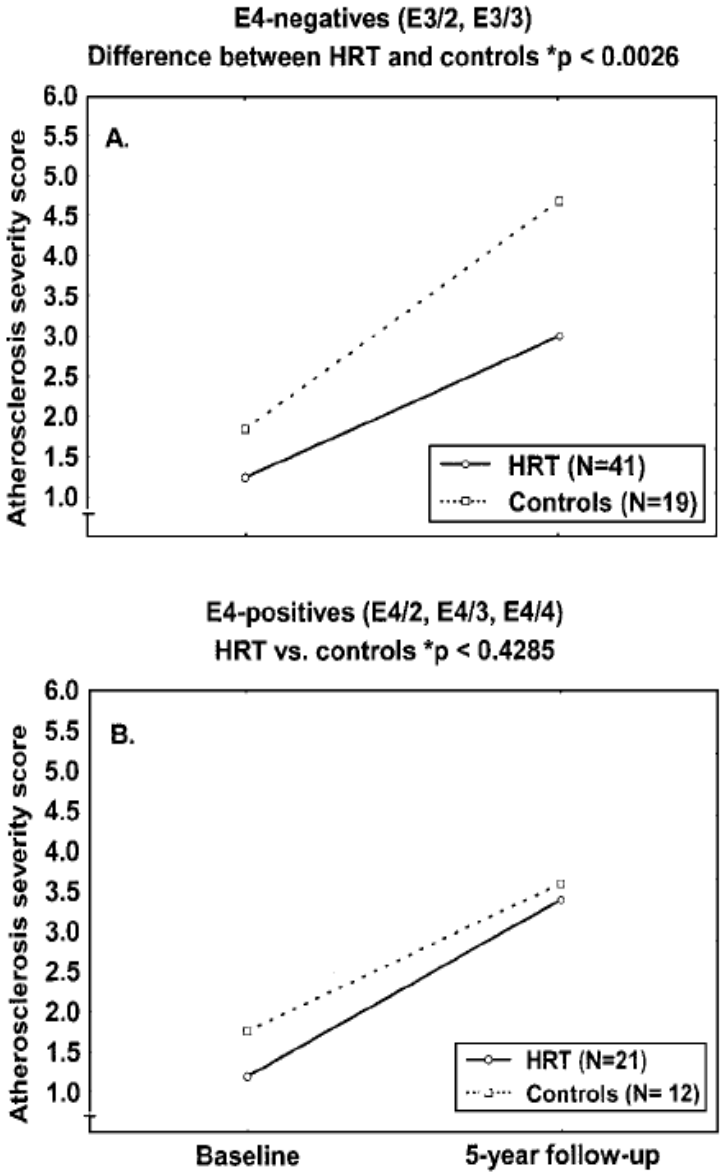
Human Estrogen Receptor *a* IVS1¡401 Genotype

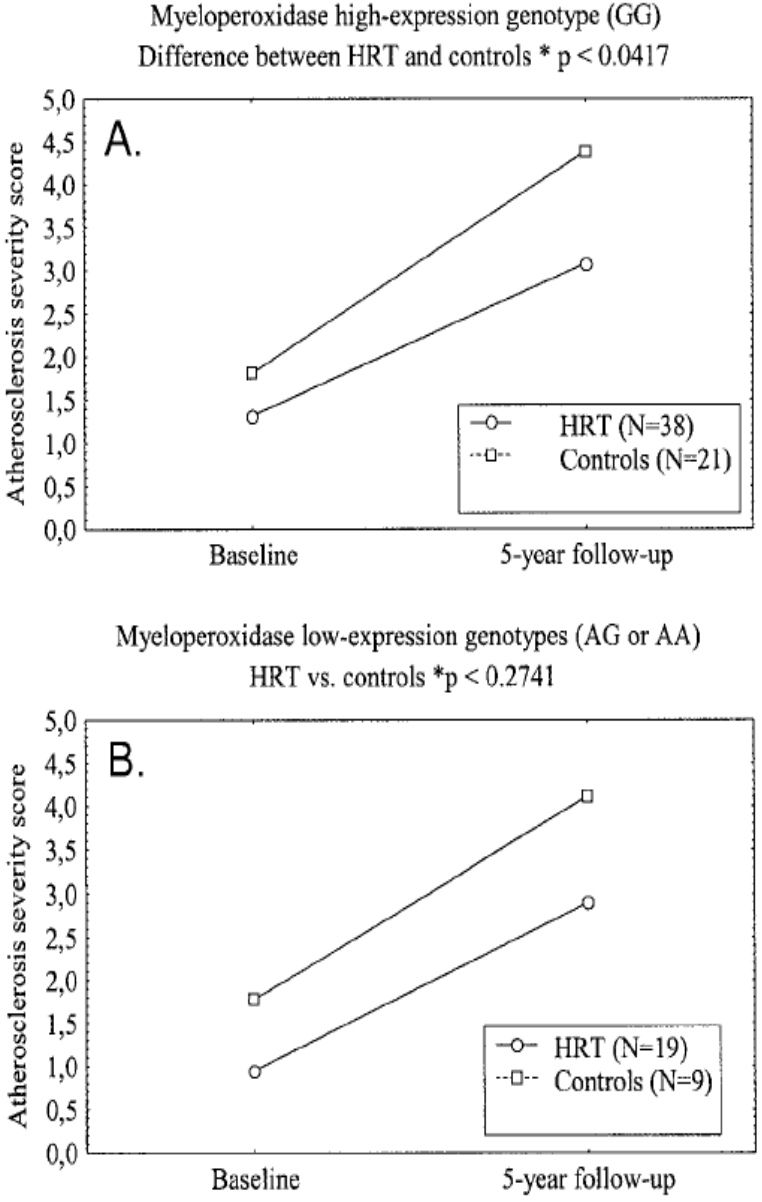


ER Polymorphisms and Effects of Estrogen Replacement on HDL-cholesterol in Women with CAD

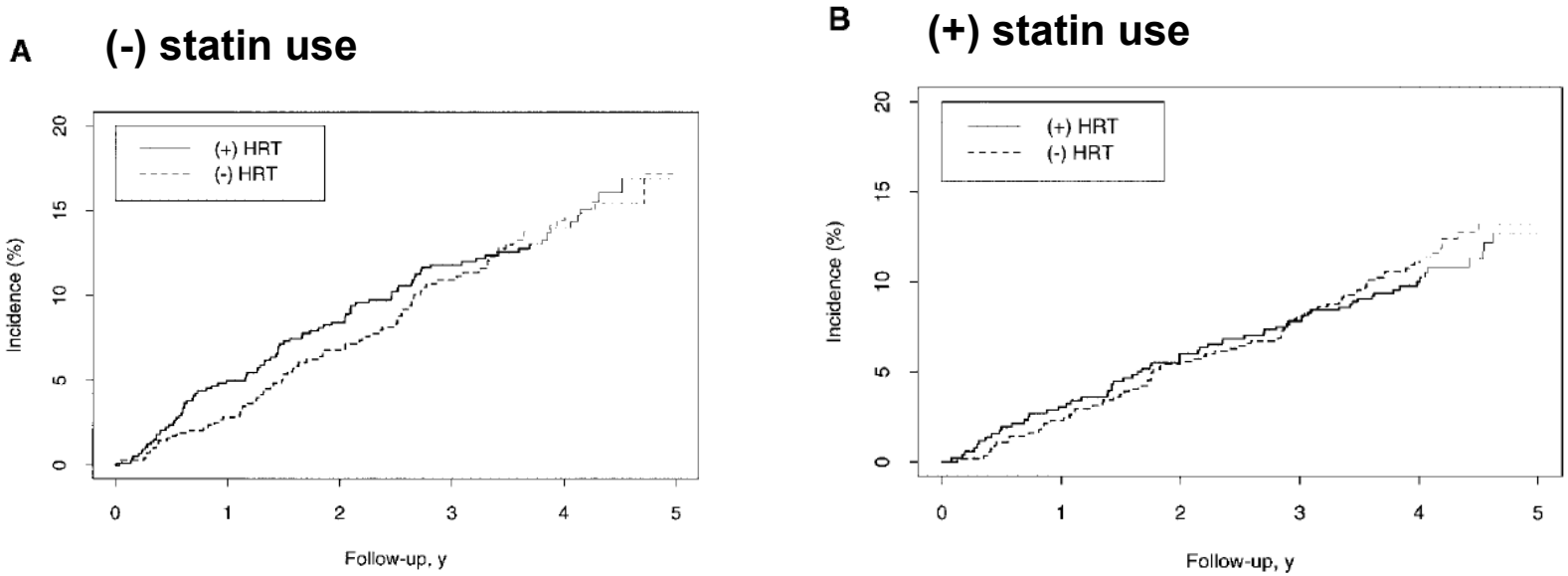


Association of ESR1 c.454-397T>C Genotype with Risk of MI in 1739 Unrelated Men and Women from the Framingham Heart Study

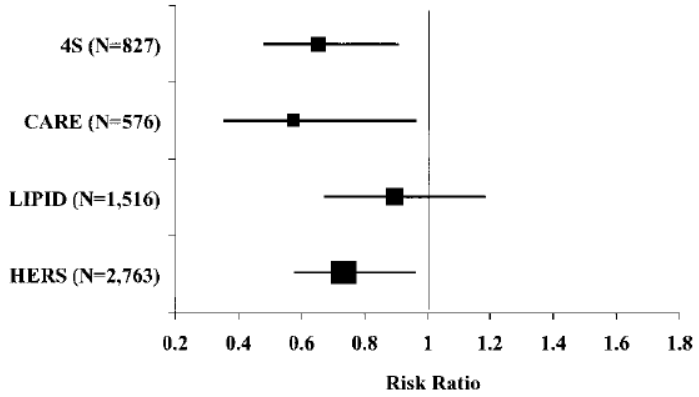

E4-negatives (E3/2, E3/3)
Difference between HRT and controls *p < 0.0026
A.
Atherosclerosis severity score
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
HRT (N=41)
Controls (N=19)
E4-positives (E4/2, E4/3, E4/4)
HRT vs. controls *p < 0.4285
B.
Atherosclerosis severity score
HRT (N=21)
Controls (N= 12)
Baseline
5-year follow-up


Myeloperoxidase high-expression genotype (GG)
Difference between HRT and controls * p < 0.0417
A.
Atherosclerosis severity score
5,0
4,5
4,0
3,5
3,0
2,5
2,0
1,5
1,0
0,5
0,0
HRT (N=38)
Controls (N=21)
Baseline
5-year follow-up
Myeloperoxidase low-expression genotypes (AG or AA)
HRT vs. controls *p < 0.2741
B.
Atherosclerosis severity score
HRT (N=19)
Controls (N=9)
Baseline
5-year follow-up

Statin Therapy, Cardiovascular Events, and Total Mortality in the Heart and Estrogen/Progestin Replacement Study (HERS)



Cumulative incidence of primary events (nonfatal MI and CHD deaths) according to baseline use of statin therapy and treatment assignment.



Risk ratios and 95% CIs for CV events (MI or CHD death) associated with statin use in women enrolled in major secondary prevention trials of statin therapy and in HERS. Sizes of squares are proportional to numbers of women in each study.

Circulation. 2002;105:2962

Summary

- The HRT controversy has not yet been laid to rest.
- Current randomized clinical trial data support the AHA/ACC guidelines that HRT should not be prescribed for prevention of cardiovascular disease.
- However, it remains possible that some formulations and doses of HRT may have favorable cardiovascular benefits when initiated earlier in the premenopausal or perimenopausal period in women without pre-existing atherosclerotic disease.