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부산, 2010. 4.16

Can a Healthy Endothelium Influence the Cardiovascular Effects of Hormone Replacement Therapy?

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Cardiology

Gachon University Gil Medical Center

Incheon, Korea

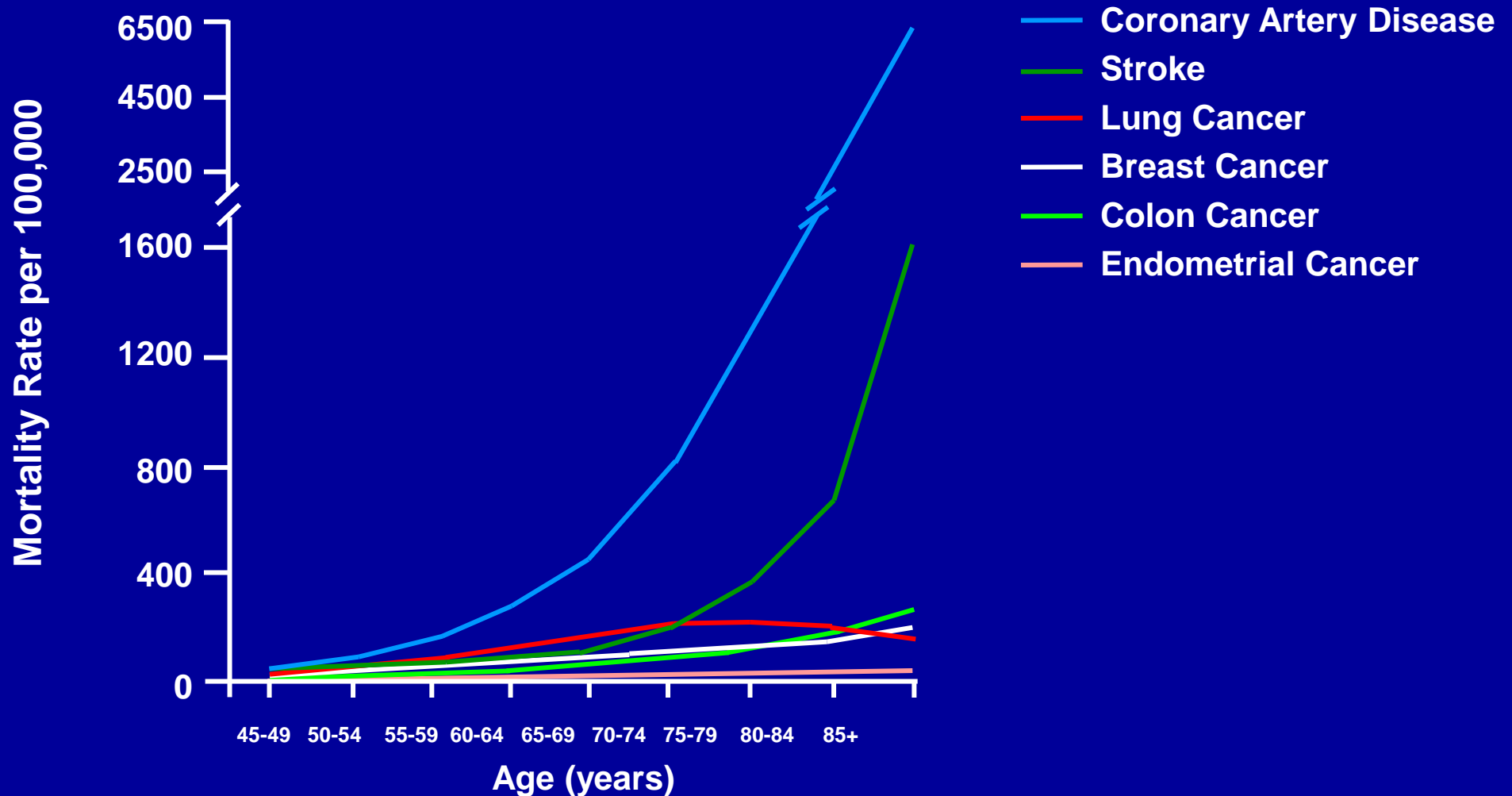


American Heart Association
scientific sessions 2008



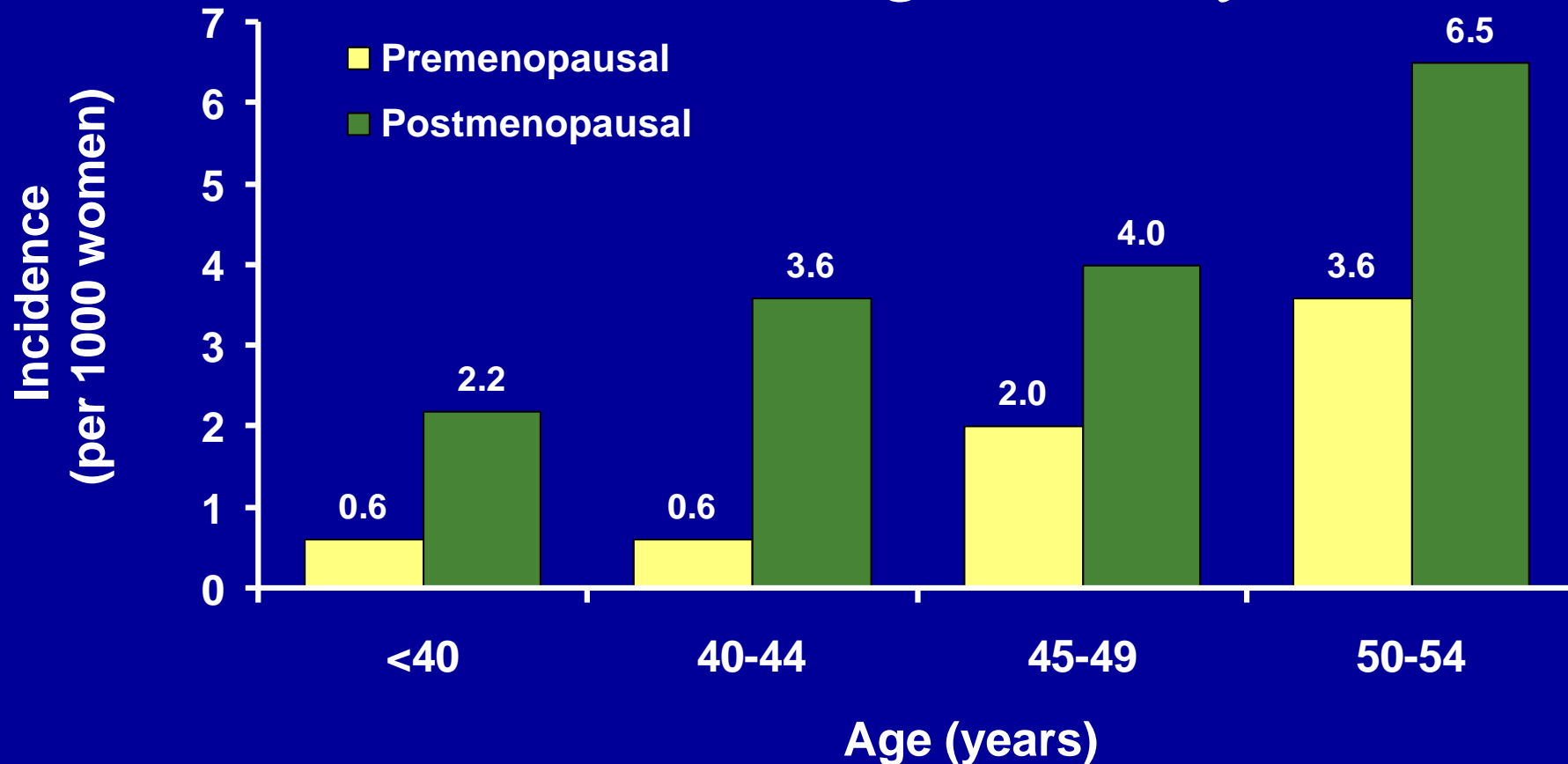
Mortality Rates in Women

At Every Age, More Women Die of Heart Disease Than Breast Cancer



Incidence of Cardiovascular Disease: Relation to Menopause Status

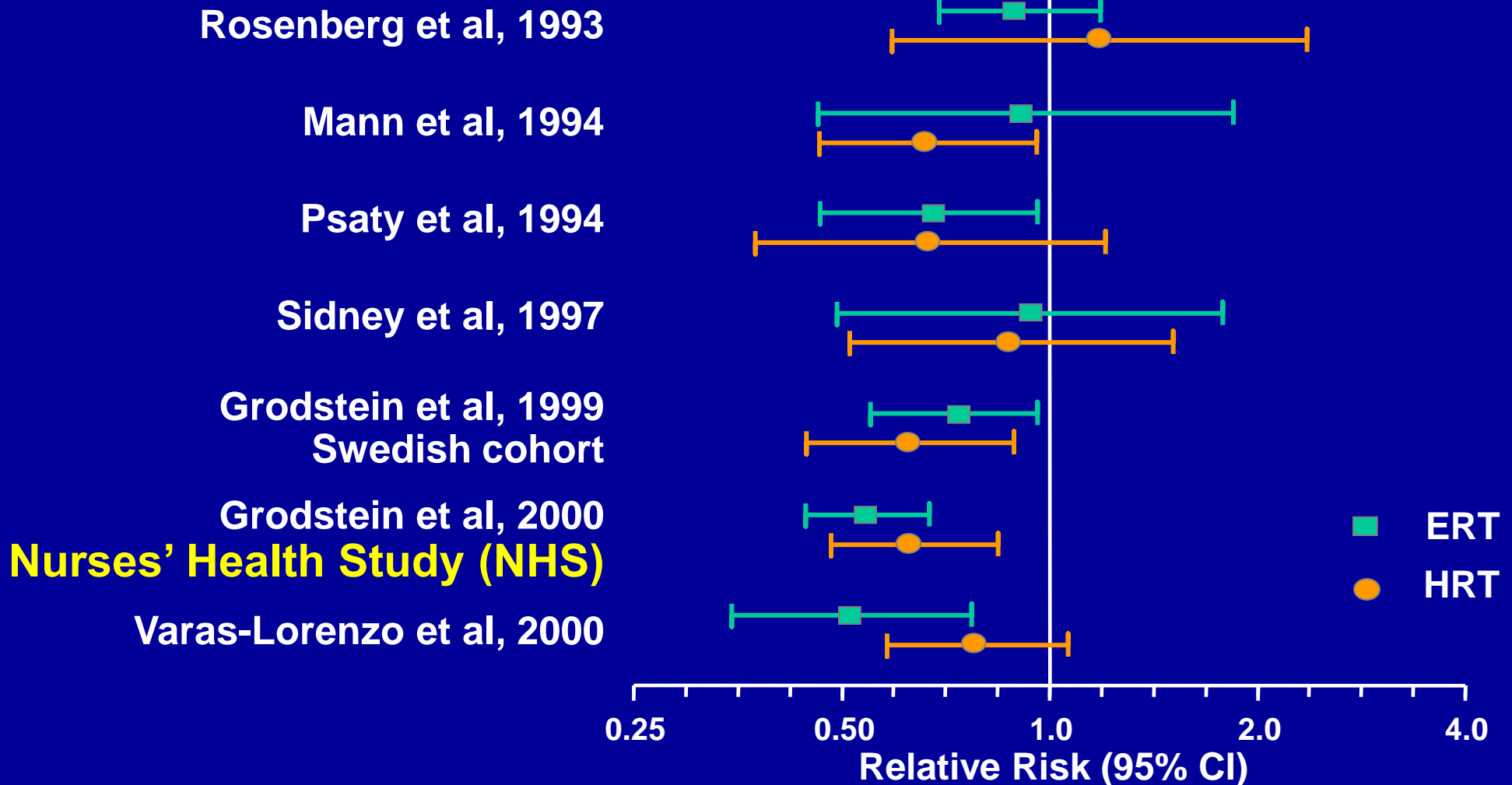
The Framingham Study



n = 2873.

Kannel WB, et al. *Ann Intern Med.* 1976;85:447-52.

Observational Studies of CVD Risk: ERT Compared With HRT



CVD = cardiovascular disease; ERT = estrogen replacement therapy (estrogen only);
HRT = hormone replacement therapy (estrogen plus a progestin).

Potential Mechanisms of Estrogen Benefit to CVD Risk

- Human Studies:

- ↑ HDL
- ↓ LDL
- ↓ Lp(a)
- Antioxidant
- ↑ nitric oxide
- ↓ inflammation (CAM etc)
- ↑ fibrinolysis
- ↓ endothelin-1

- Animal Studies:

- ↓ proliferative response to arterial injury
- ↓ extent of atherosclerosis

Koh KK, Int J Cardiol 2003;87;1 (Review)

Koh KK & Sakuma I, ATVB 2004;24:1171 (Review)

Koh & Yoon B-K, Cardiovas Res 2006;70;22 (Review)

Heart and Estrogen/progestin Replacement Study (HERS)

Study design: Randomized, double-blind, placebo-controlled, secondary prevention

Subjects: 2763 postmenopausal women, <80 years old (mean age, 66.7 years) with CAD

Intervention: CEE 0.625 mg + MPA 2.5 mg daily or placebo

Follow-up: HERS I 4.1 years
HERS II open-label 2.7 years

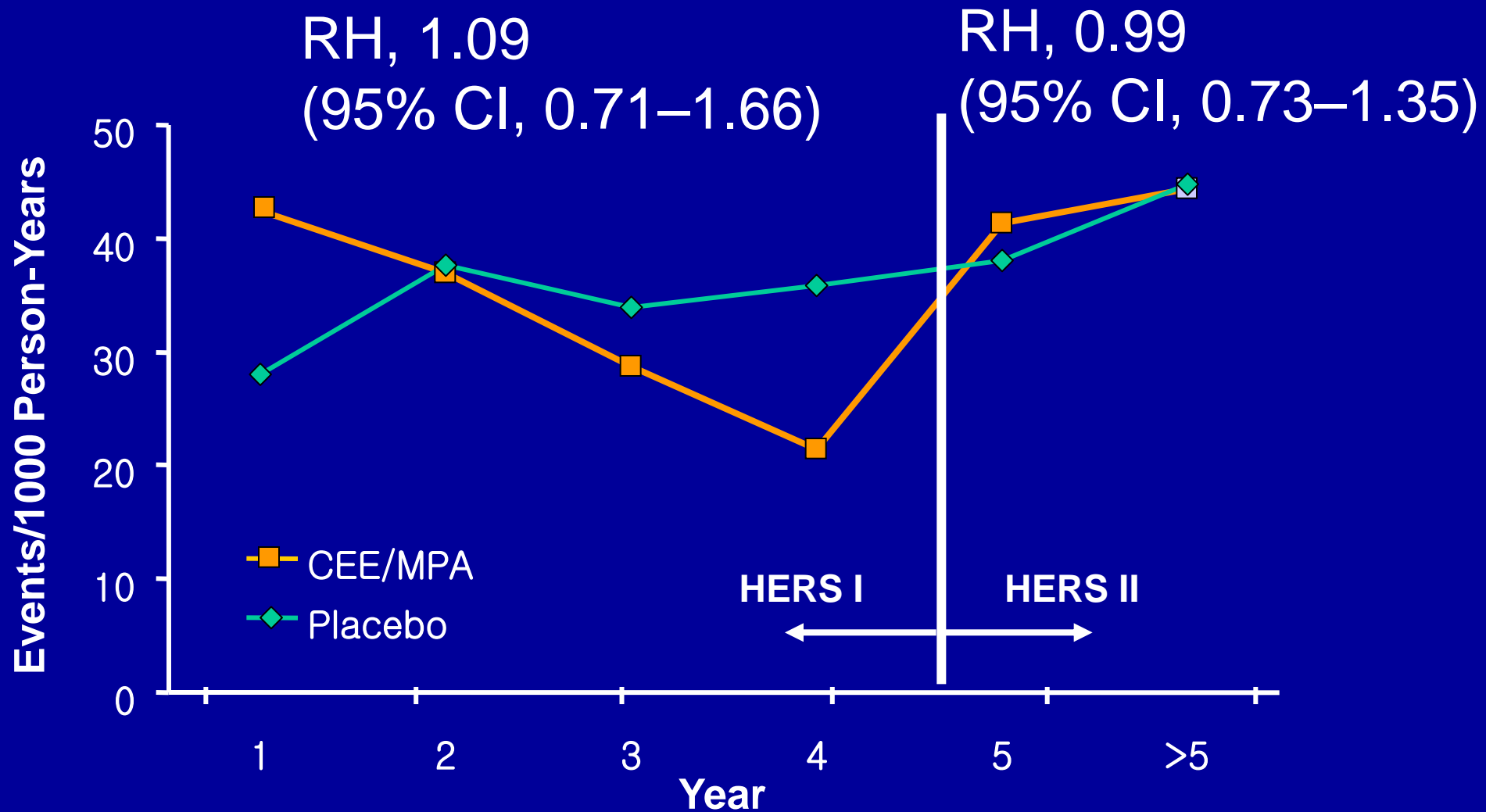
1° end point: Nonfatal MI or CHD death

CAD = coronary artery disease; MI = myocardial infarction; CHD = coronary heart disease.

Hulley S, et al. *JAMA*. 1998;280:605-13.

Grady D, et al. *JAMA*. 2002;288:49-57.

HERS: CHD Events by Year



Estrogen in the Prevention of Atherosclerosis Trial (EPAT)

Study Design

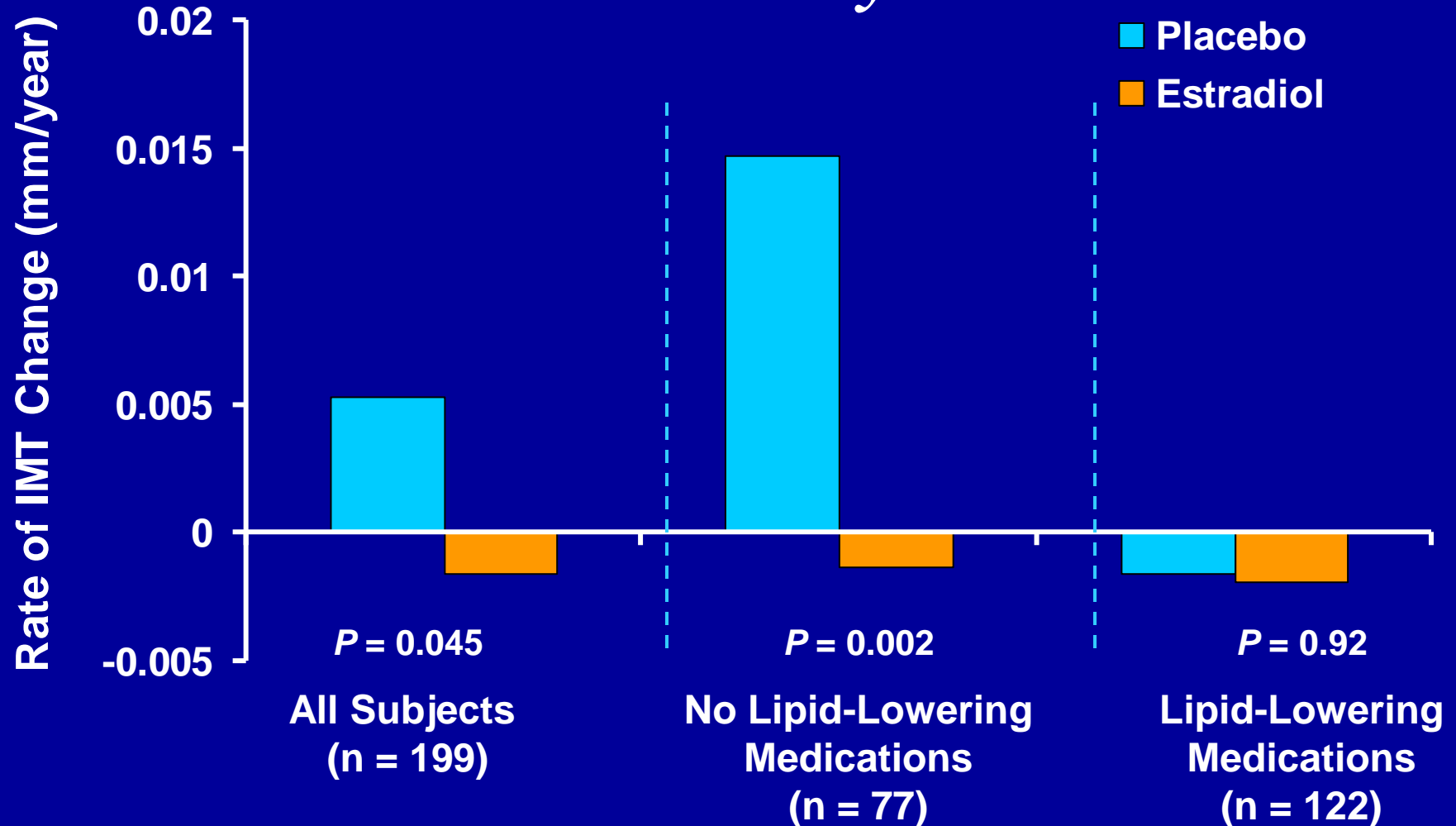
- ❖ Randomized, double-blind, placebo-controlled
- ❖ 222 apparently healthy postmenopausal women (mean age, ~61 years)
- ❖ No pre-existing CVD and LDL-C levels ≥ 130 mg/dL
- ❖ Micronized 17 β -estradiol (1 mg/d) or placebo for 2 years
- ❖ Lipid-lowering drugs given if LDL-C exceeded 160 mg/dL

Primary Outcome

- ❖ Rate of change in carotid artery IMT every 6 months

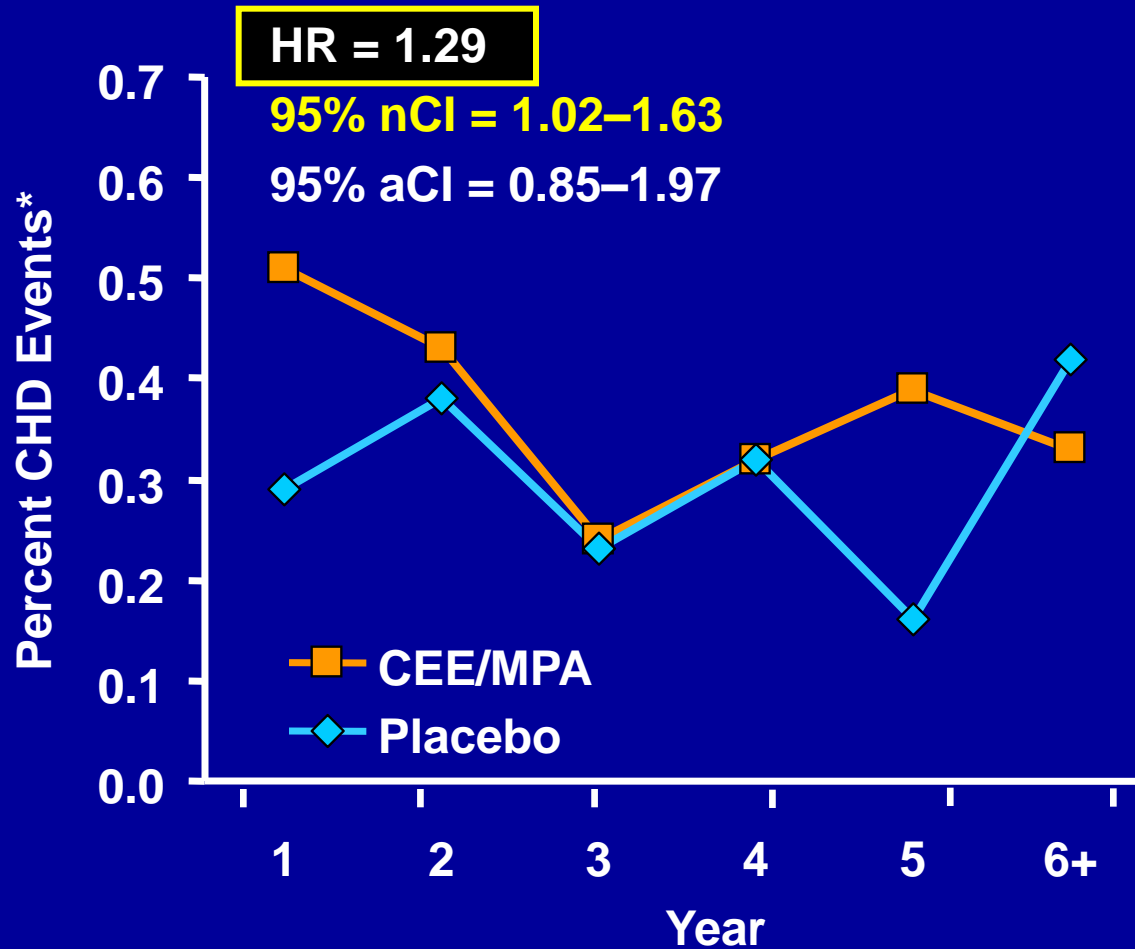
Effect of Estrogens on Carotid IMT

EPAT Study



WHI Results

Annualized Percent CHD Events by Year



Year	Hazard Ratio
1	1.78
2	1.15
3	1.06
4	0.99
5	2.38
6+	0.78

P = NS for trend over time.

*Includes 8 silent MIs.

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

CVD Outcomes: Risk Comparison of WHI and NHS

	<i>Relative Risk (95% CI)</i>	
	<i>NHS*</i>	<i>WHI¹</i>
CHD	0.61 (0.52–0.71)²	1.29 (1.02–1.63)
Stroke	1.13 (0.94–1.35)²	1.41 (1.07–1.85)
PE	2.10 (1.20–3.80)³	2.13 (1.39–3.25)

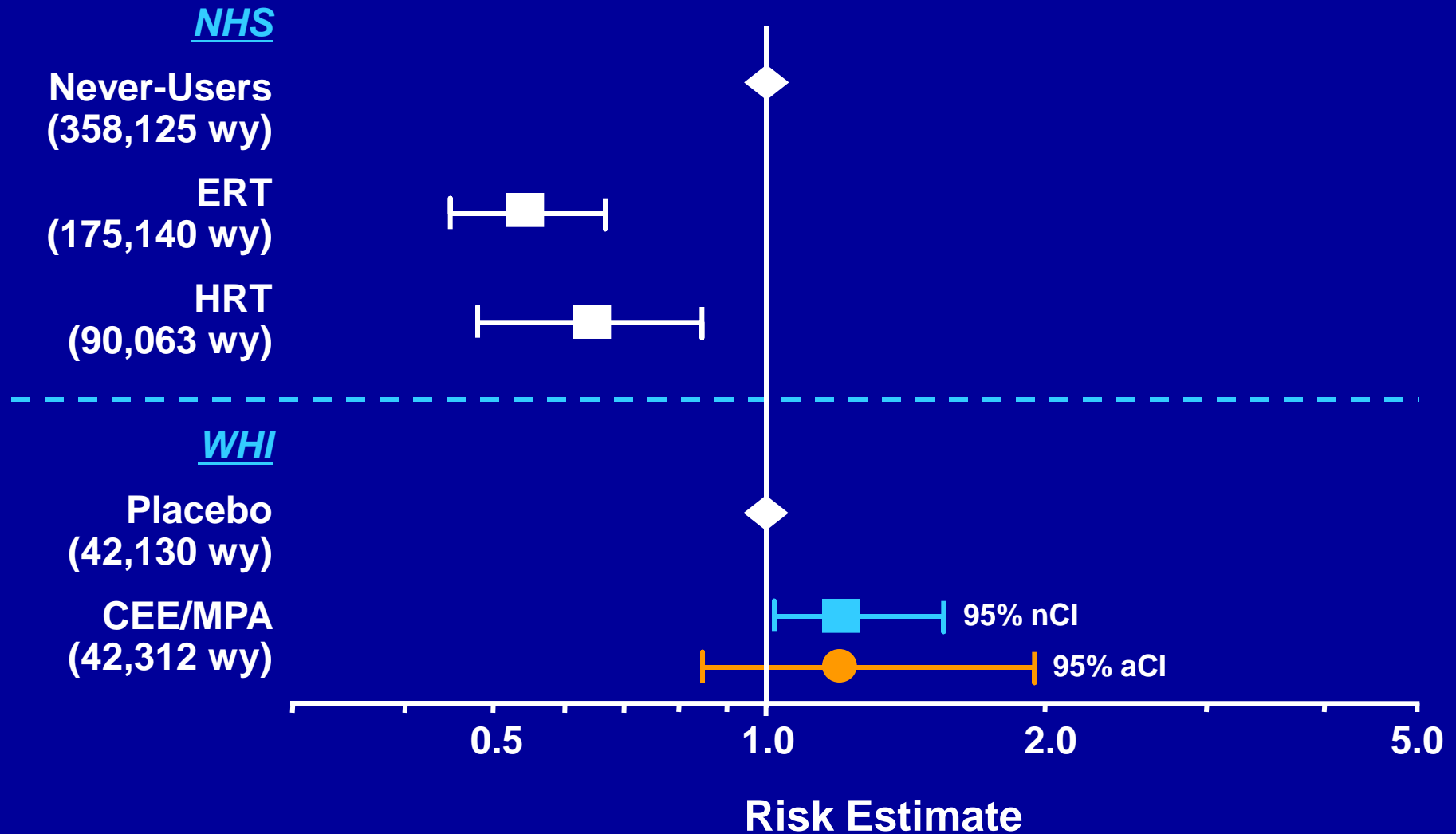
*Among current users of ERT/HRT.

¹Writing Group for the Women's Health Initiative Investigators. *JAMA*. 2002;288:321-33.

²Grodstein F, et al. *Ann Intern Med*. 2000;133:933-41.

³Grodstein F, et al. *Lancet*. 1996;348:983-7.

Relative Risk of CHD: NHS Versus WHI



wy = woman-years; nCI = nominal confidence interval; aCI = adjusted confidence interval.

Grodstein F, et al. *Ann Intern Med.* 2000;133:933-41.

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

Baseline Characteristics: NHS Versus WHI

	<i>NHS</i> ^{1,2}	<i>WHI</i> ³
Mean age or age range at enrollment (years)	30-55	63
Smokers (past and current)	6.9%	49.9%
BMI (mean)	25.1 kg/m ²	28.5 kg/m ² *
Aspirin users	43.9%	19.1%
HRT regimen	unopposed sequential	continuous combined
Menopausal symptoms (flushing)	predominant	excluded

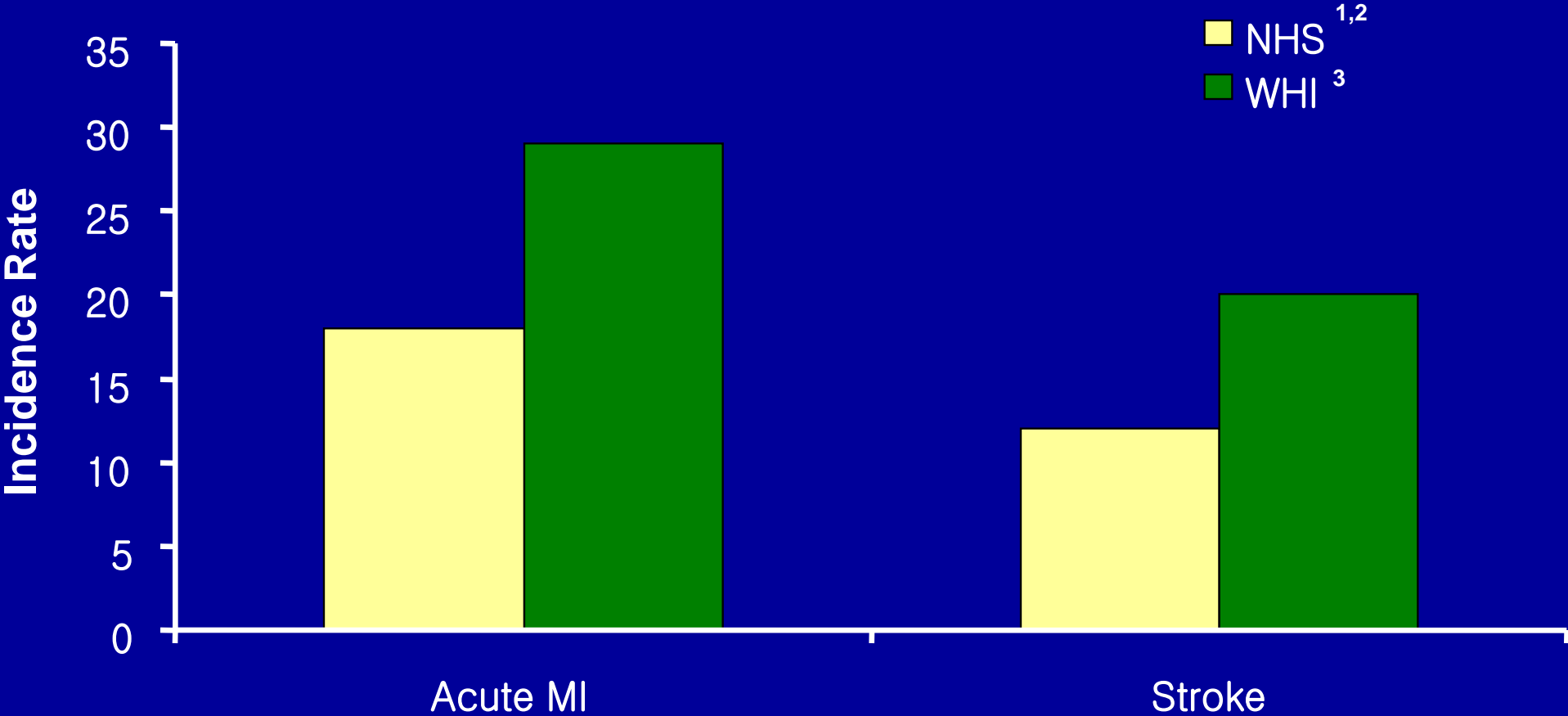
*34.1% had BMI \geq 30 kg/m².

¹Grodstein F et al. *Ann Intern Med.* 2000;133:933-41.

²Grodstein F et al. *N Engl J Med.* 1996;335:453-61.

³Writing Group for the Women's Health Initiative Investigators. *JAMA.* 2002;288:321-33.

Disease Incidence* Among HRT Nonusers From Recent Studies



*Incidence rates are expressed as events per 10,000 person-years.

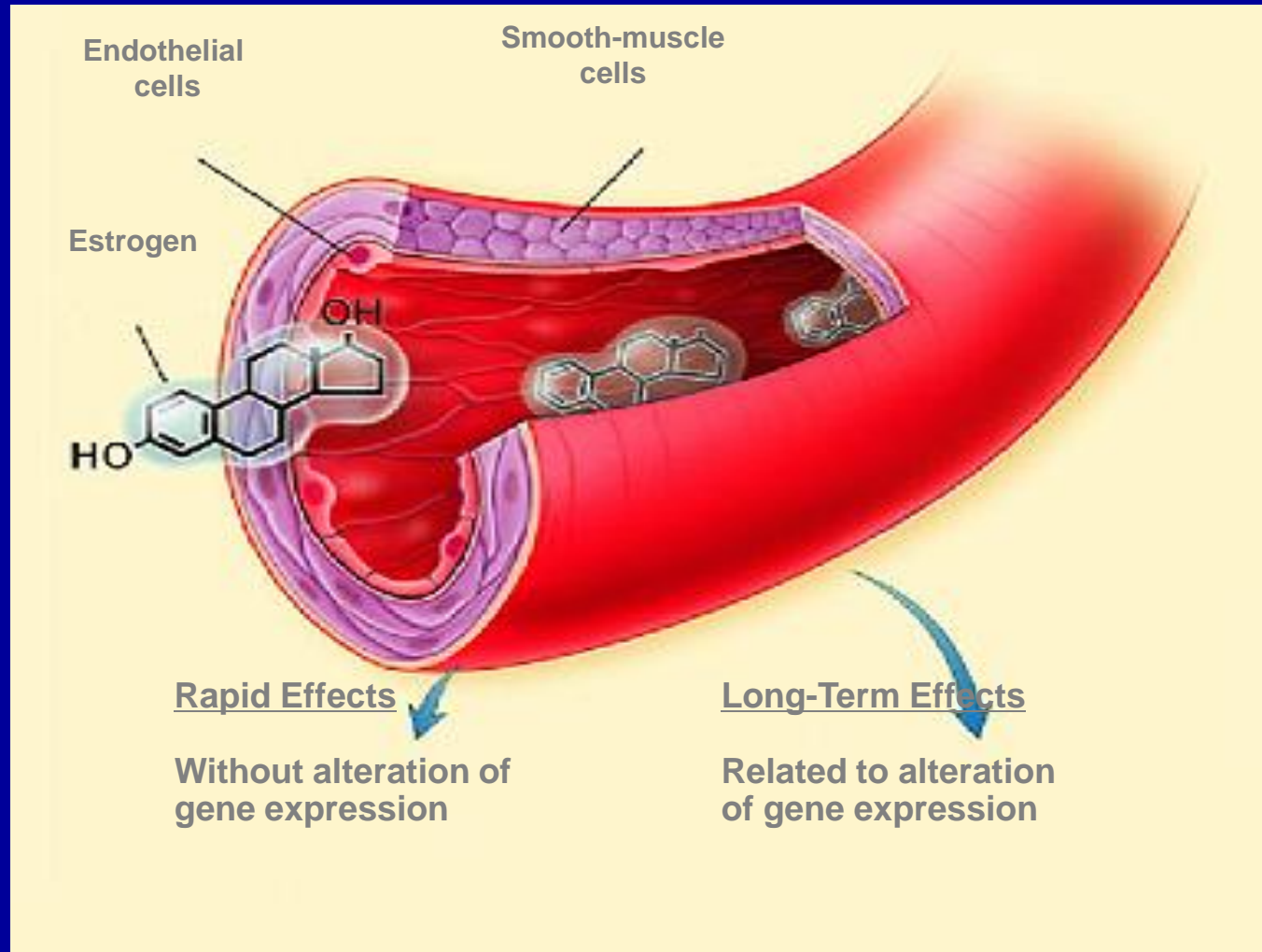
¹Grodstein F, et al. *Ann Intern Med.* 2000;133:933-41; ²Grodstein F, et al. *Lancet.* 1996;348:983-7;

³Writing Group for the Women's Health Initiative Investigators. *JAMA.* 2002;288:321-33.

The Challenge !!

How can we integrate the findings of all of the published studies into one consistent concept?

Direct Effects of Estrogen on Arterial Vessels



Mendelsohn ME, Karas RH. *N Engl J Med.* 1999;340:1801-11.
Science. 2005;308:1583-1587.

Healthy Endothelium and Estrogen Therapy (I)

- Many of the anti-atherogenic and other favorable vascular effects of estrogen are **receptor-mediated** and **endothelium-dependent**.
- Consequently, endothelial injury or declines in vascular estrogen receptor (ER) populations can diminish the anti-inflammatory, antithrombotic, and other cardioprotective benefits of this reproductive hormone.

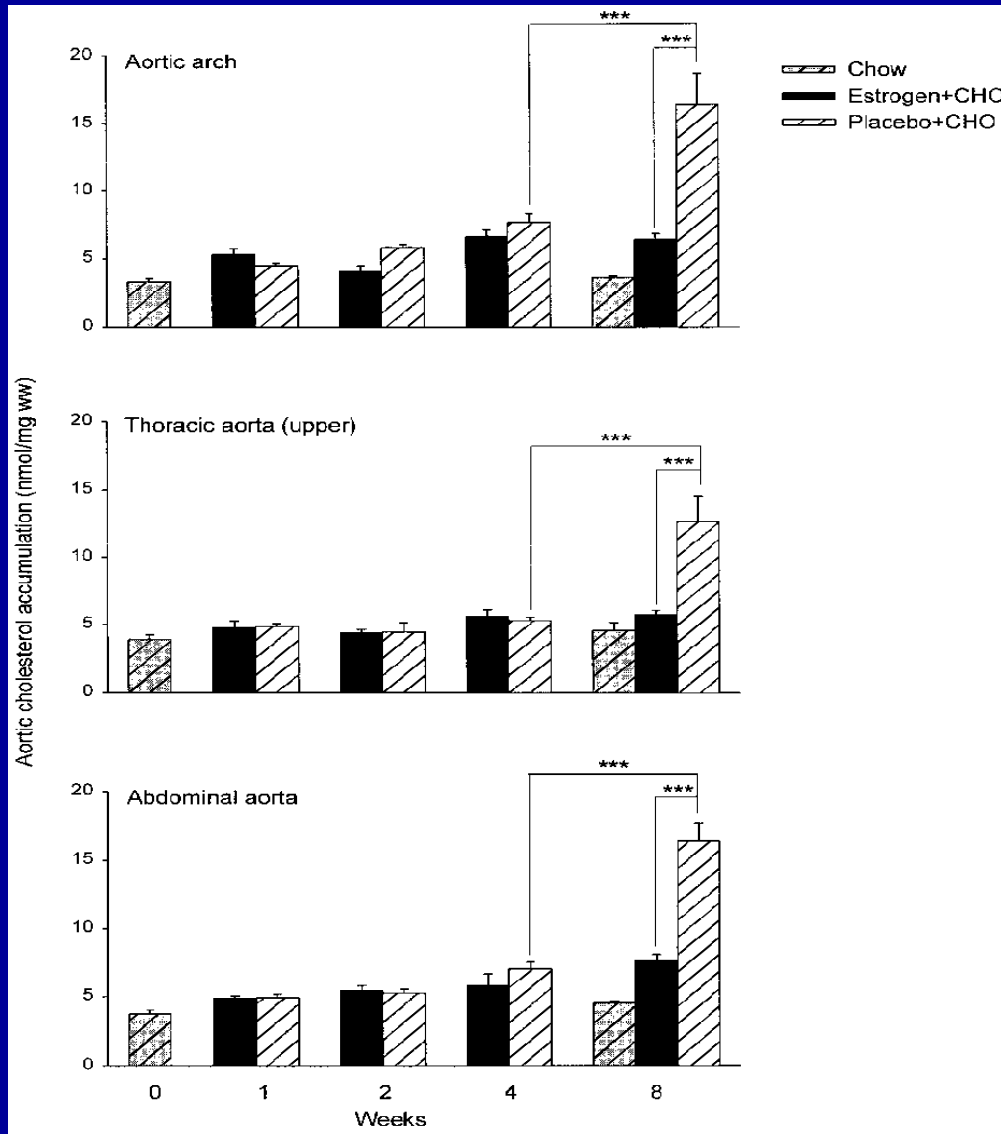
Koh KK. Cardiovasc Res 2002;55:714-26 (Review).

Koh KK. Int J Cardiol. 2003;87:1 (Review).

Mendelsohn ME, et al. N Engl J Med 1999;340:1801-11.

Losordo et al, Circulation 1994;89:1501.

Direct Antiatherogenic Effect of Estrogen: Present Depending on State of Endothelium

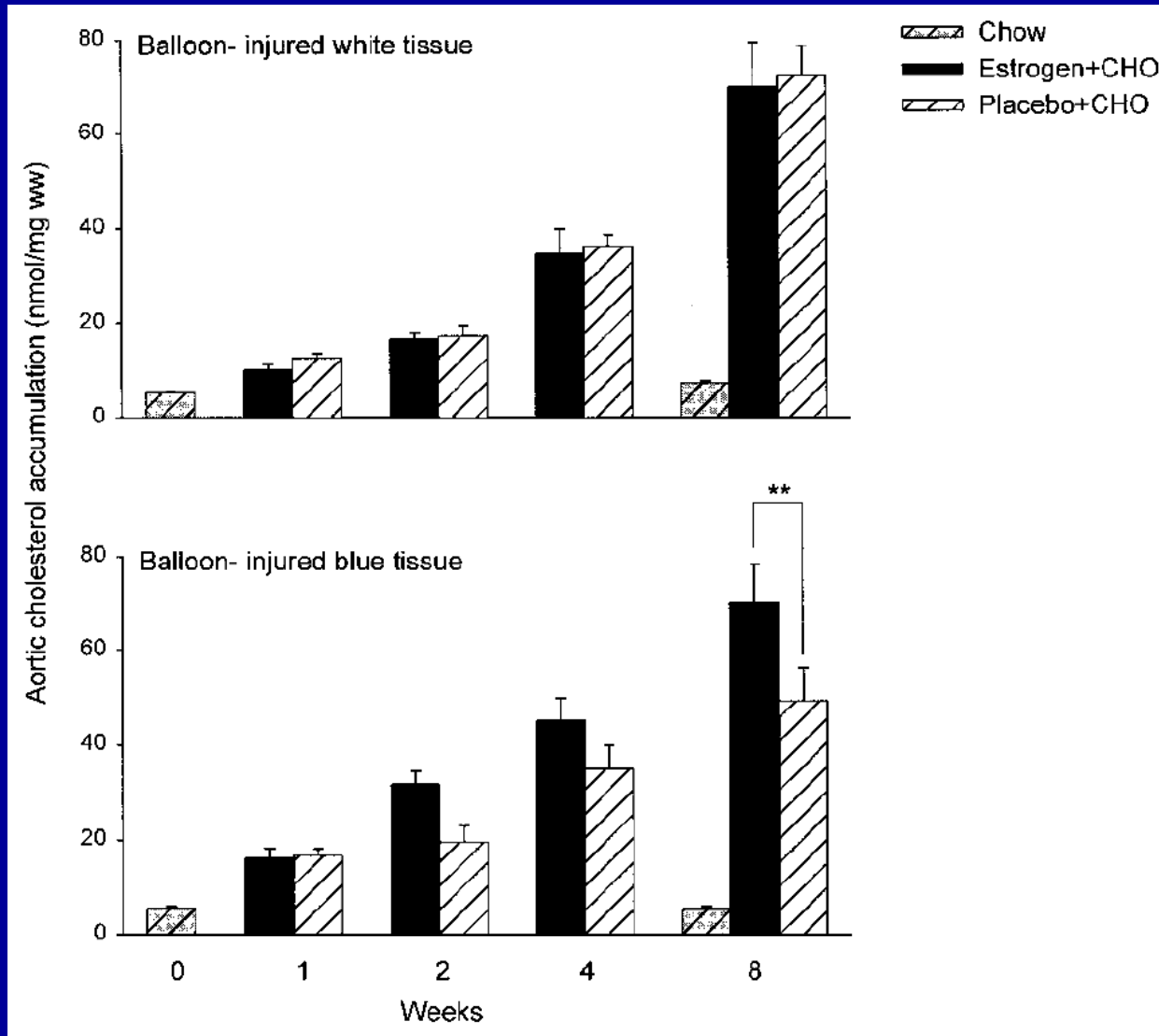


Intact Endothelium

- Time course study in cholesterol-clamped rabbits
- Extent of *aortic cholesterol accumulation* for 3 *undamaged regions of aorta*

Holm et al, Circulation 1999;100:1727

Direct Antiatherogenic Effect of Estrogen: Absent or Reversed Depending on State of Endothelium



Re-endothelialized

De-endothelialized

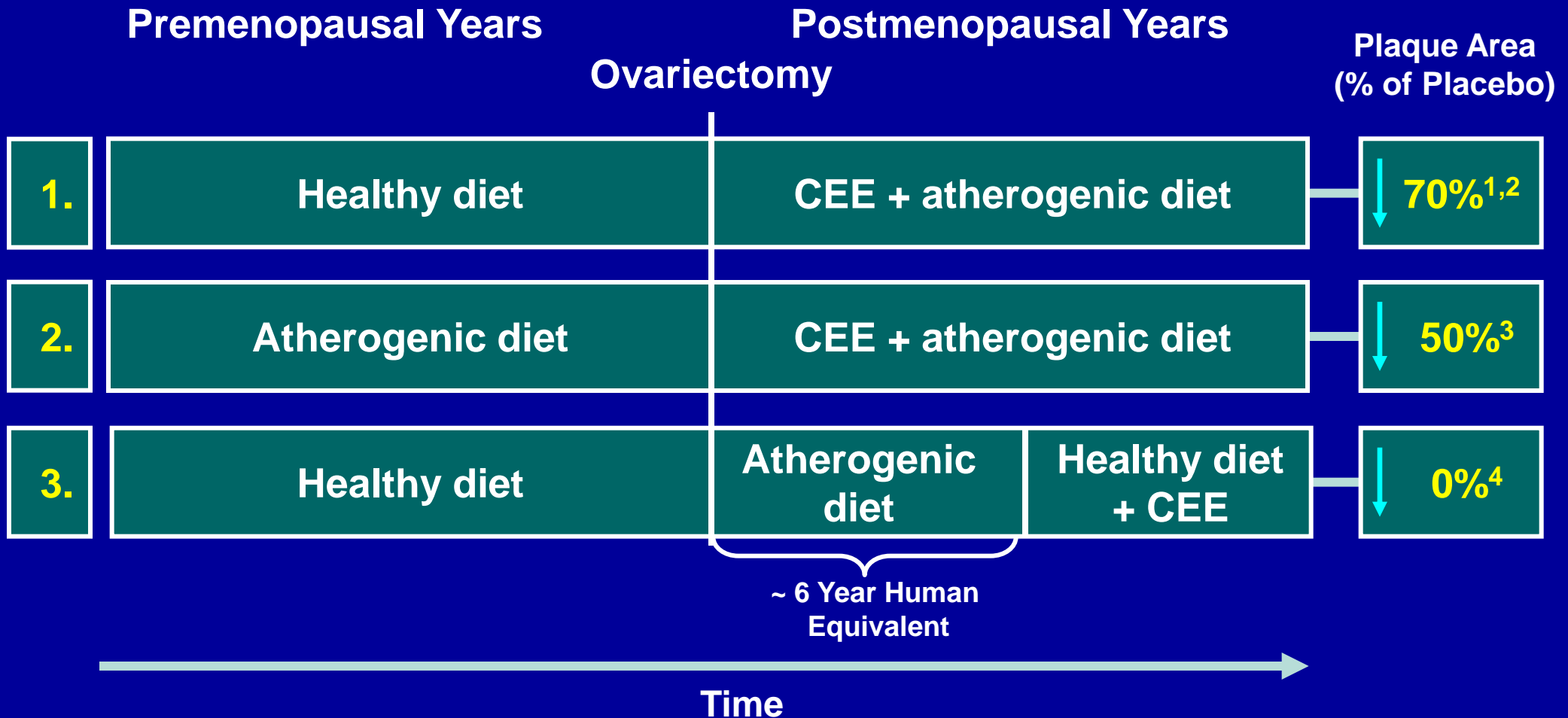
Holm et al,
Circulation 1999;100:1727

Healthy Endothelium and Estrogen Therapy (II)

- **Randomized, controlled studies**
Relevant only to postmenopausal women initiating HRT at an average of >20 years after menopause
- **Generalizability has been questioned:**
the relevance of angiographic end points, the drug regimen, multiple risk factors, and coronary atherosclerosis

Mendelsohn and Karas. Circulation. 2001;104:2256-9.

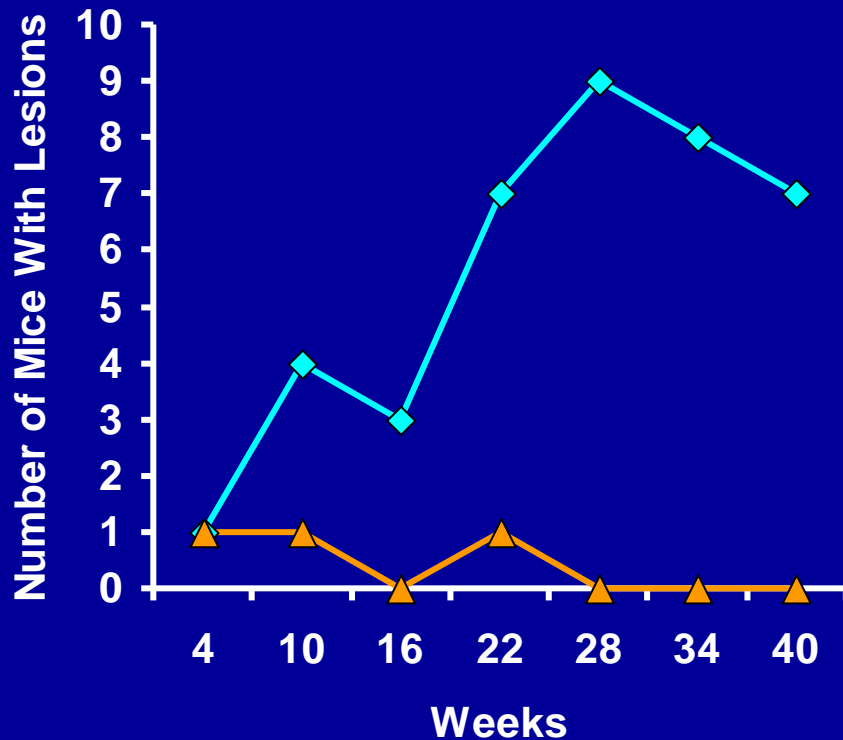
Effect of ERT on Coronary Atherosclerosis in Monkeys: Timing of Initiation



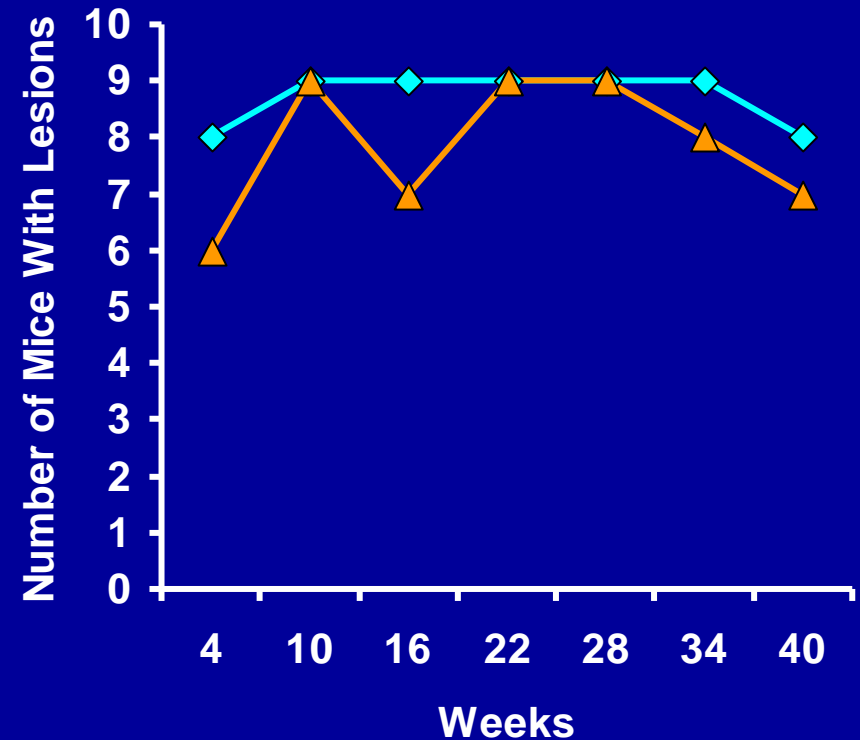
¹Clarkson TB, et al. *J Clin Endocrinol Metab.* 1998;83:721-6; ²Adams MR, et al. *Arterioscler Thromb Vasc Biol.* 1997;17:217-21; ³Clarkson TB, et al. *J Clin Endocrinol Metab.* 2001;86:41-47; ⁴Williams JK, et al. *Arterioscler Thromb Vas Biol.* 1995;15:827-36.

Estrogen Inhibits Initiation but not Progression of Established Lesions in Mice

New Lesions



Established Lesions



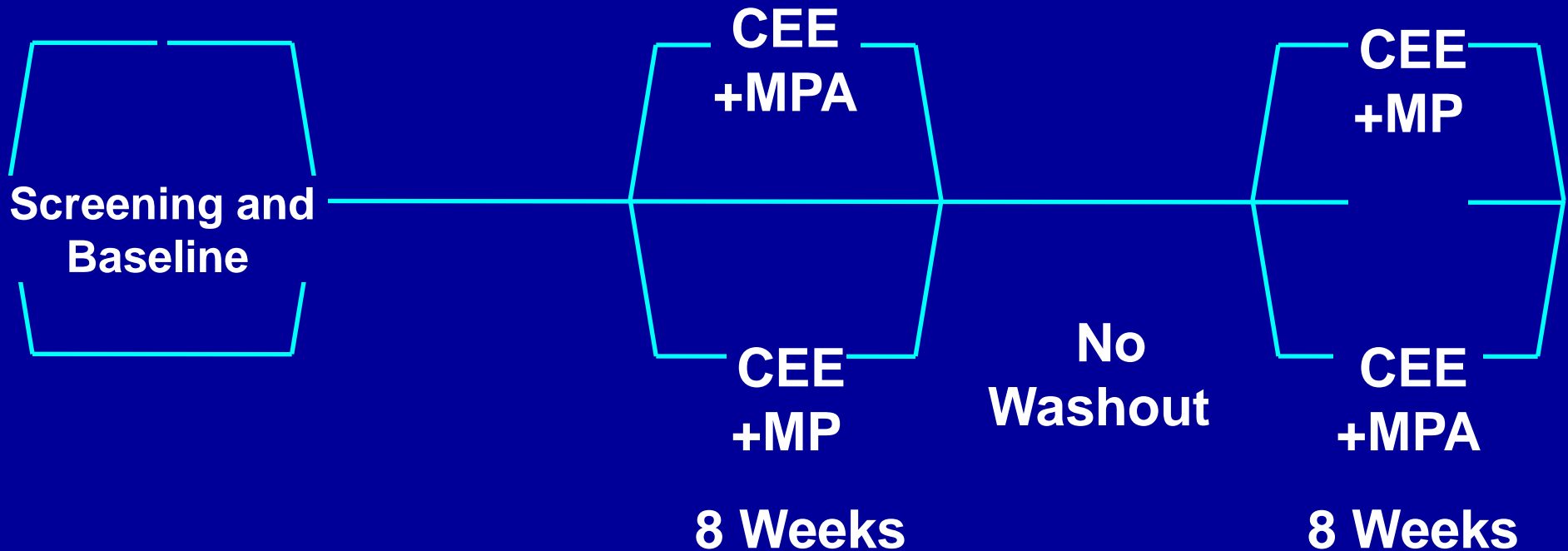
◆ Iliac -E2

▲ Iliac +E2

◆ Carotid -E2

▲ Carotid +E2

Study Design

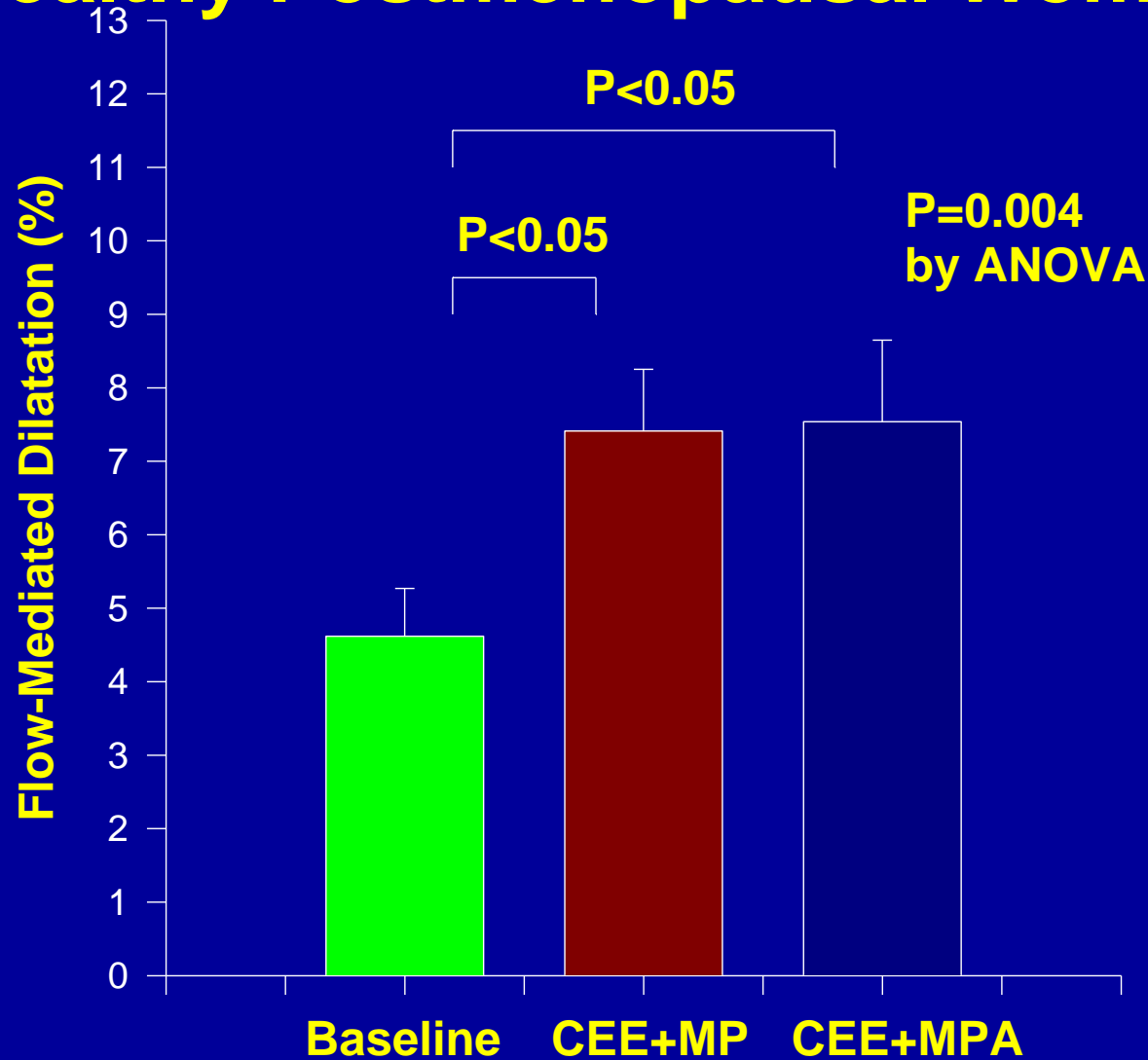


20 healthy postmenopausal women

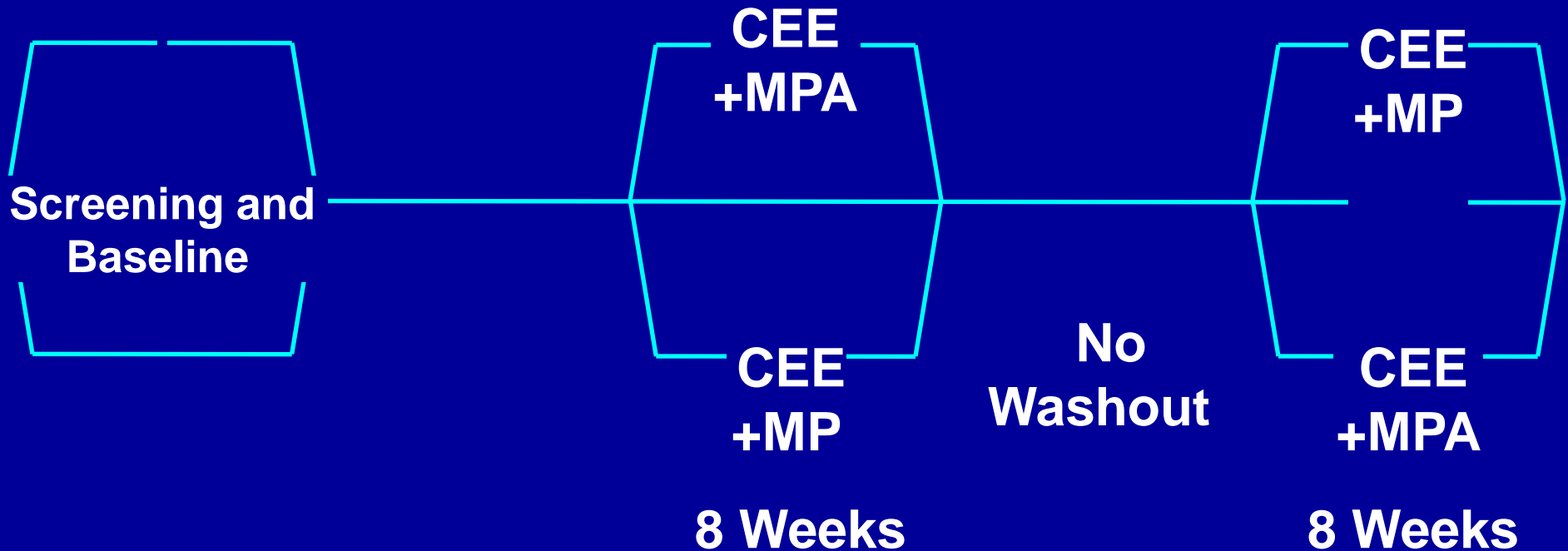
Mean age 55 ± 8

- CEE 0.625 mg and MPA 10 mg cyclically
- CEE 0.625 mg and MP 200 mg cyclically

Effect of HRT on Flow-Mediated Dilatation in Healthy Postmenopausal Women



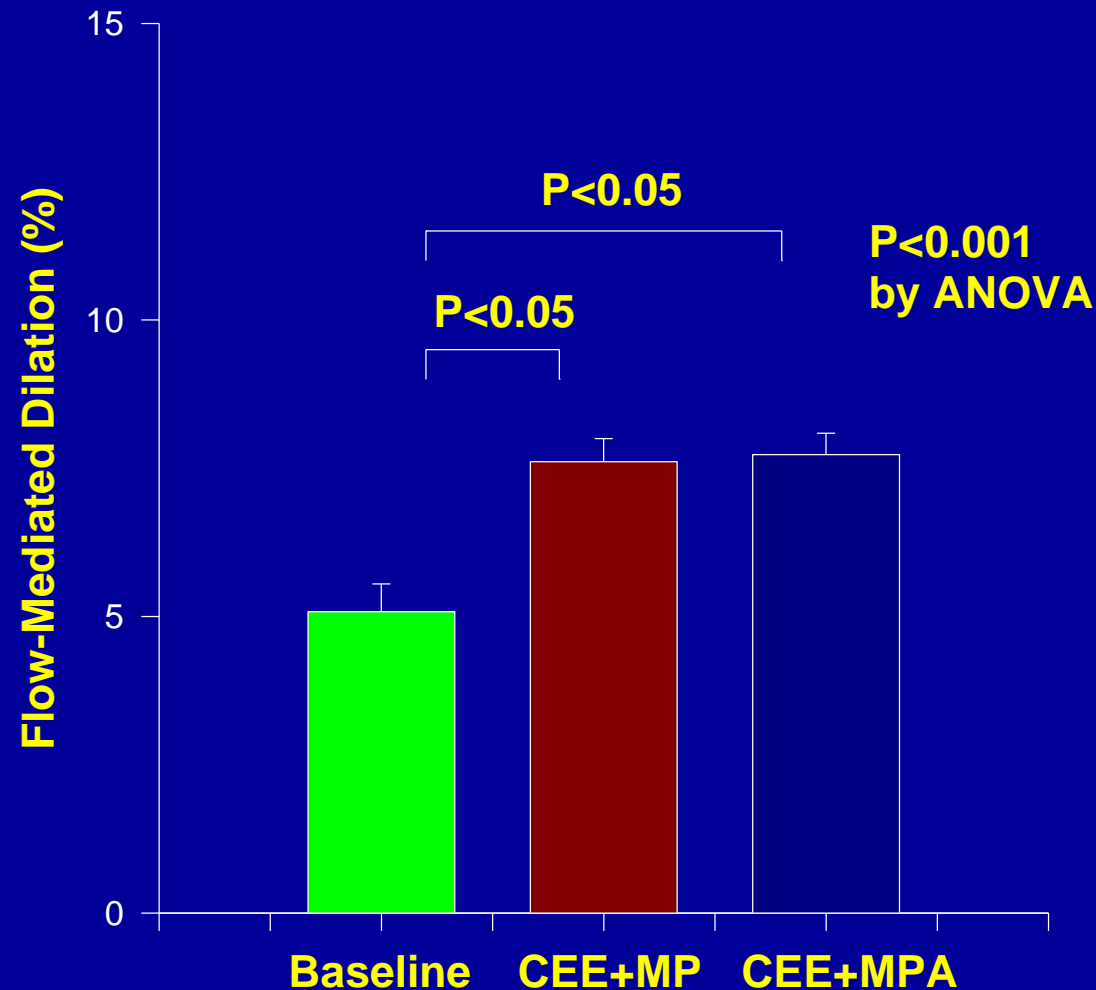
Study Design



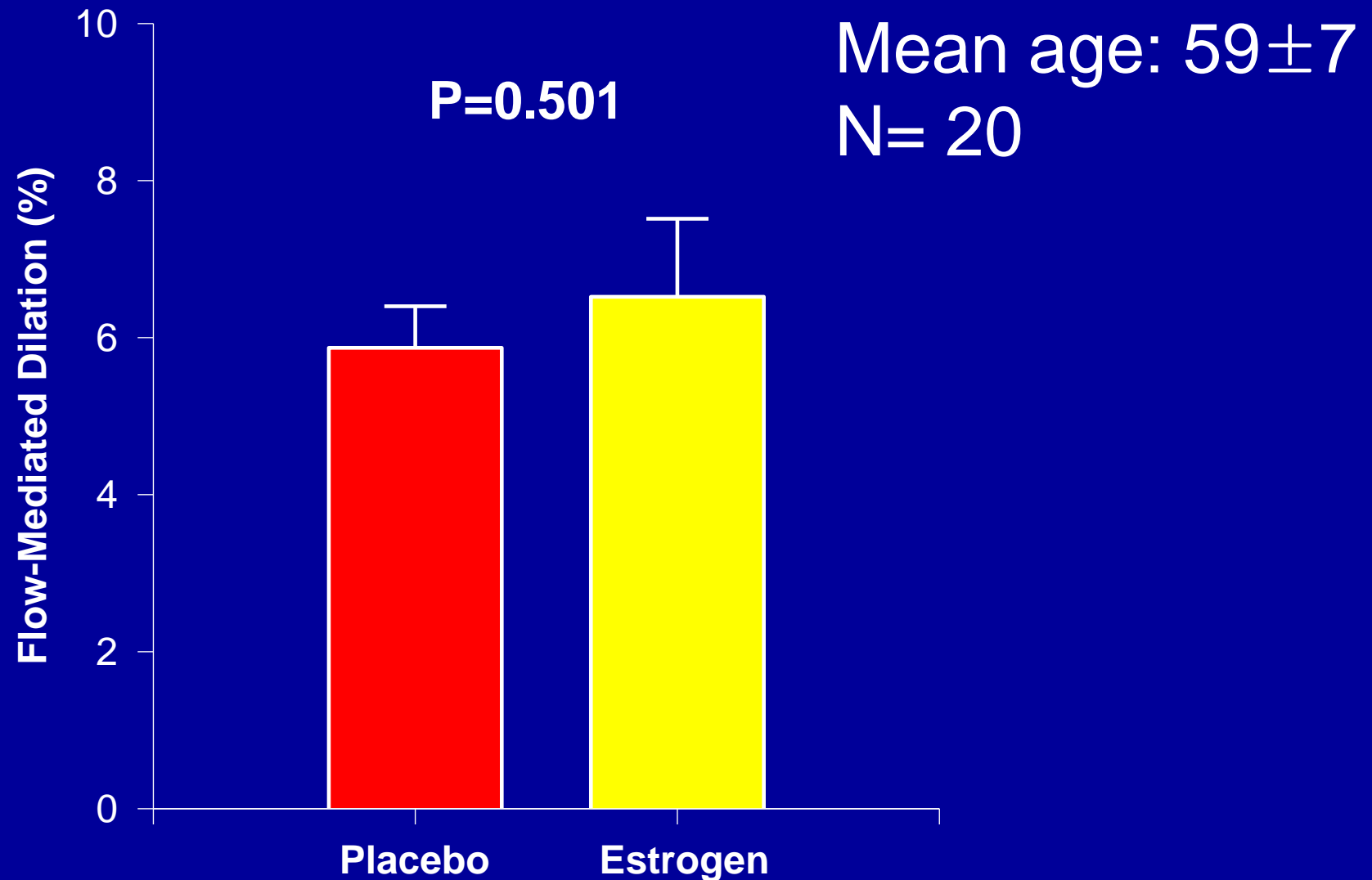
**35 Hypertensive and/or overweight
postmenopausal women, mean age 58 ± 1**

- CEE 0.625 mg and MPA 2.5 mg daily
- CEE 0.625 mg and MP 100 mg daily

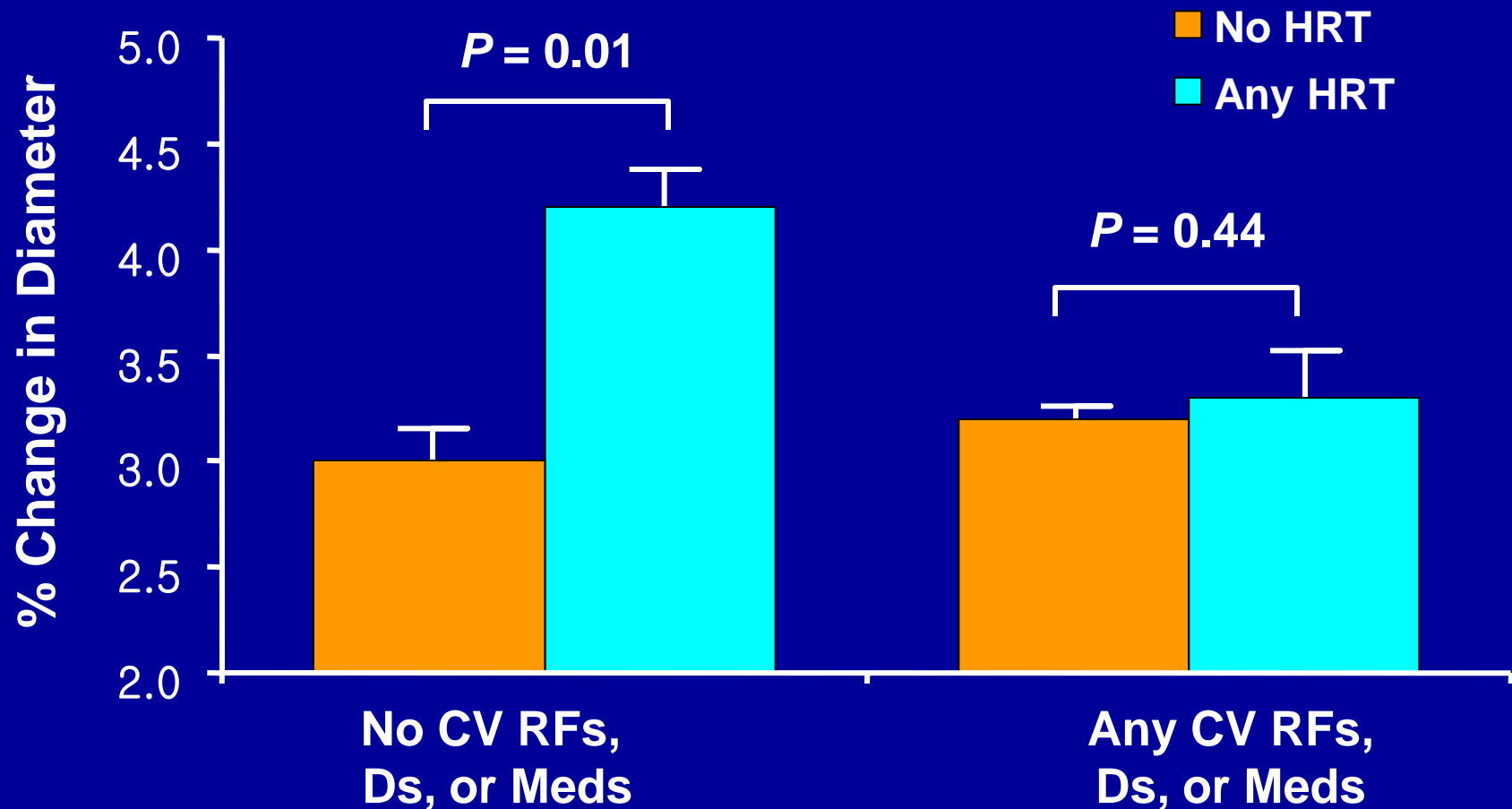
Effect of HRT on Flow-Mediated Dilatation in HT and/or Overweight Postmenopausal Women



Effects of ERT on FMD in Type 2 Diabetes



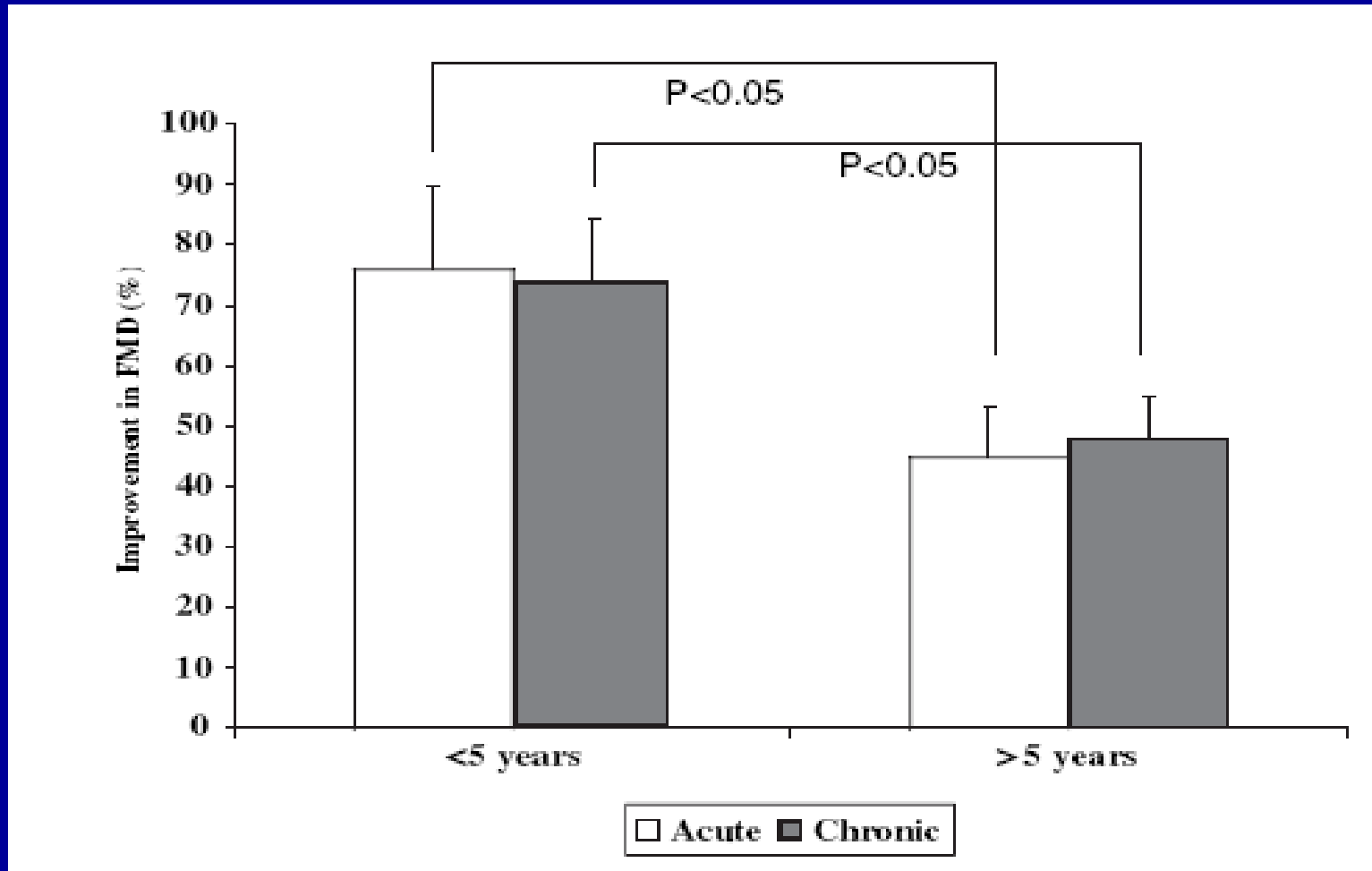
HRT Vasodilates Only in Women Without Cardiovascular Risk Factors

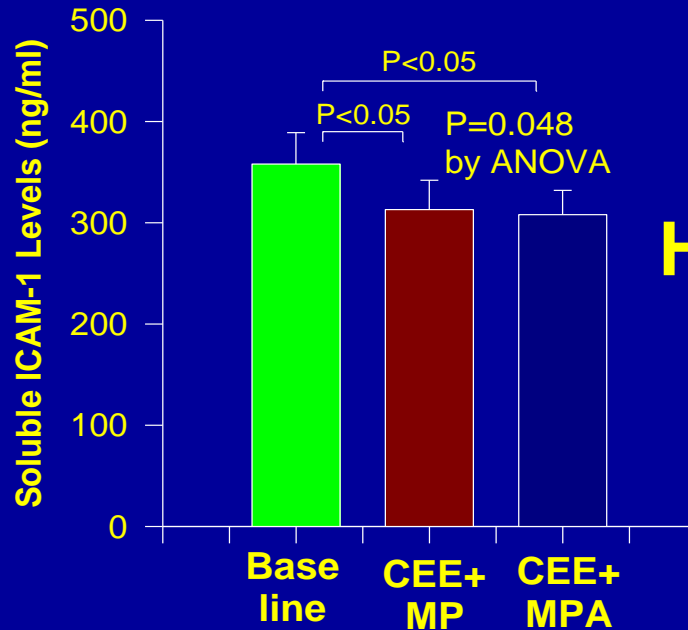
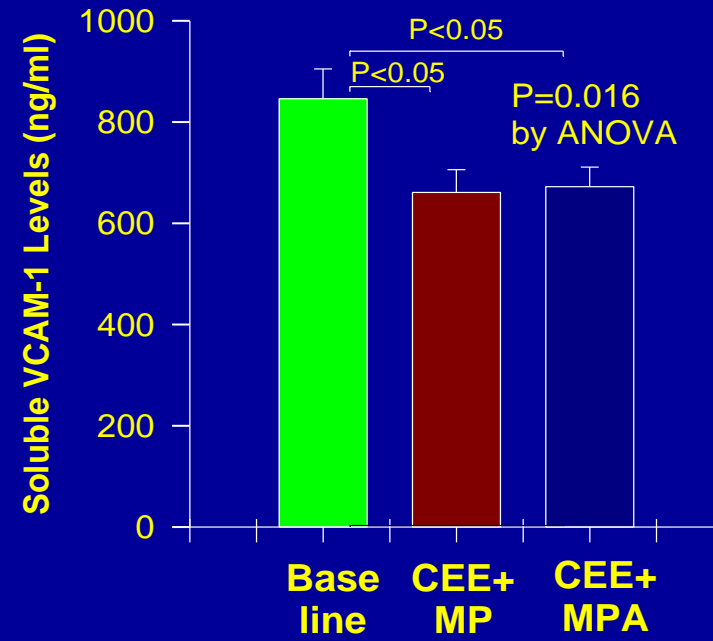
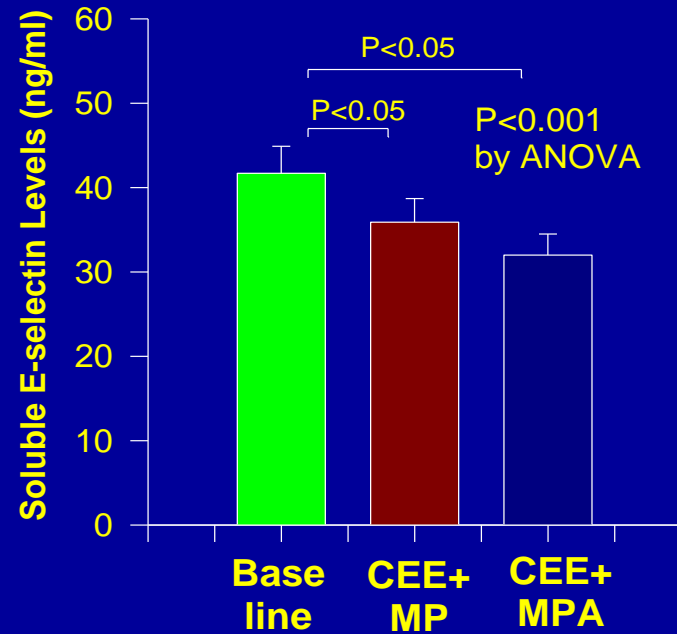


RFs = risk factors; Ds = diseases; Meds = medications.
Herrington DM, et al. *Arterioscler Thromb Vasc Biol.* 2001;21:1955-61.

Cardiovascular Health Study

Estradiol Effect on FMD in PMW Between <5 years and >5 years since Menopause

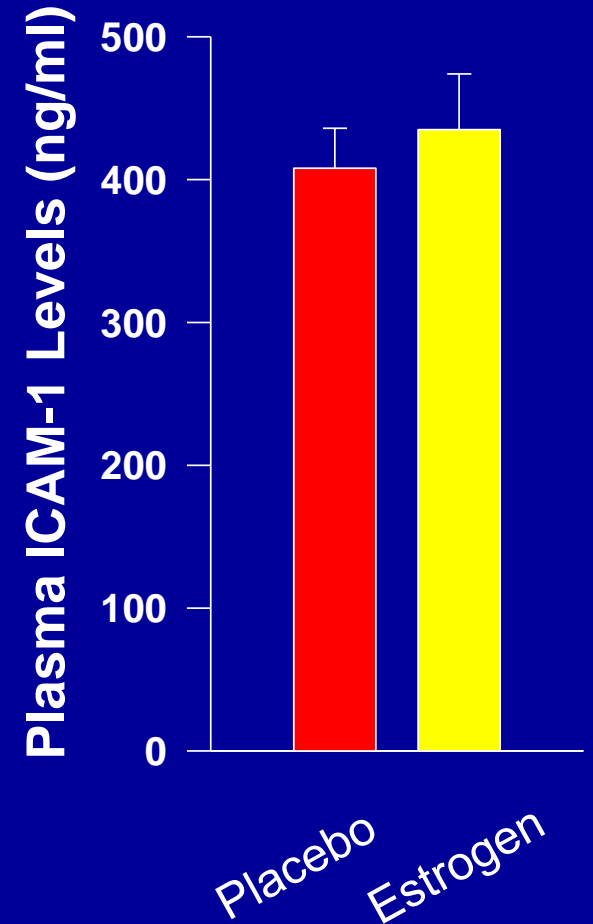
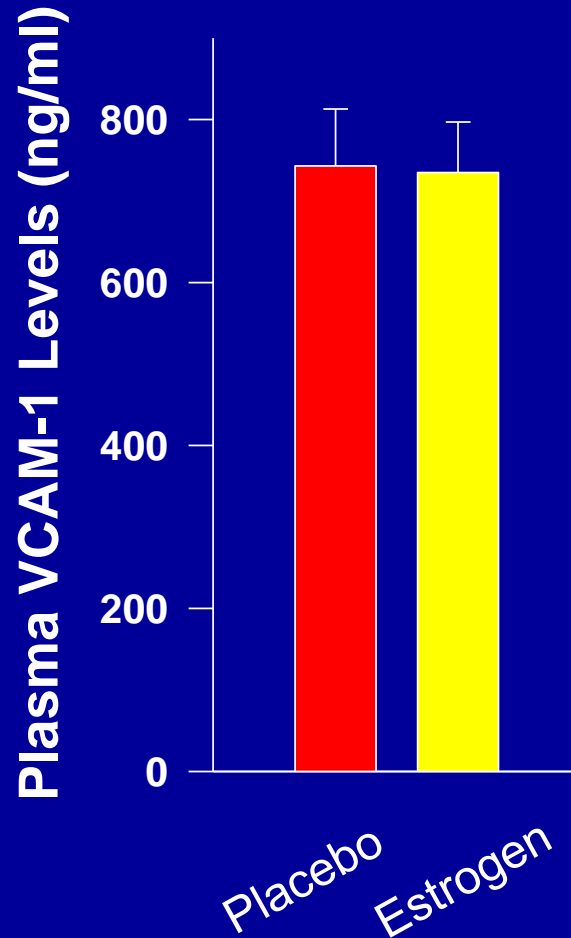
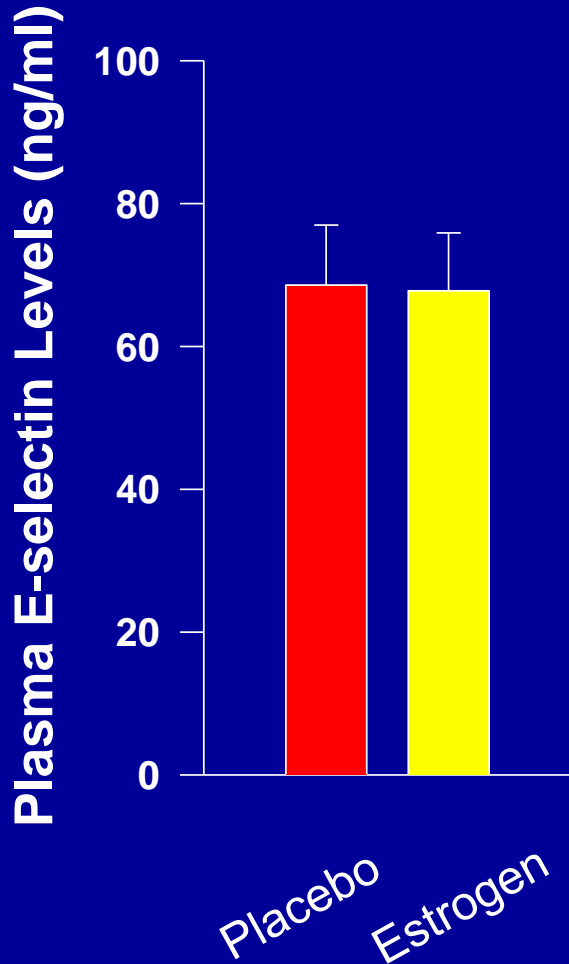




Effect of HRT on CAMs in Healthy Postmenopausal Women

Koh KK, et al. Circulation. 2001;103:1961-6.

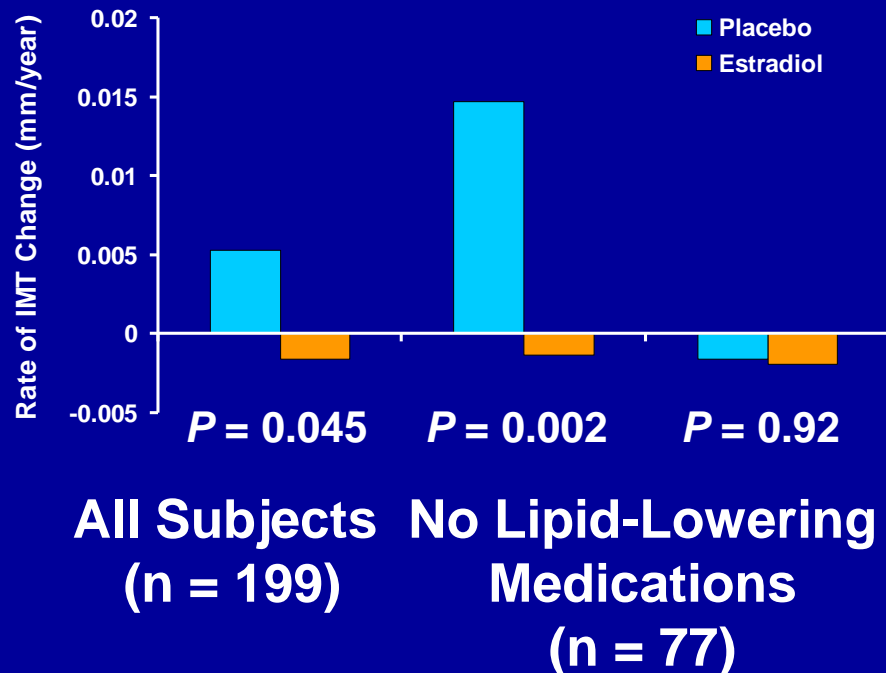
Effects of ERT on CAMs in Type 2 Diabetes



Koh KK, et al. J Am Coll Cardiol 2001;38:1409-15.

Effect of Estrogens on Carotid IMT

Estrogen in the Prevention of Atherosclerosis Trial (EPAT)



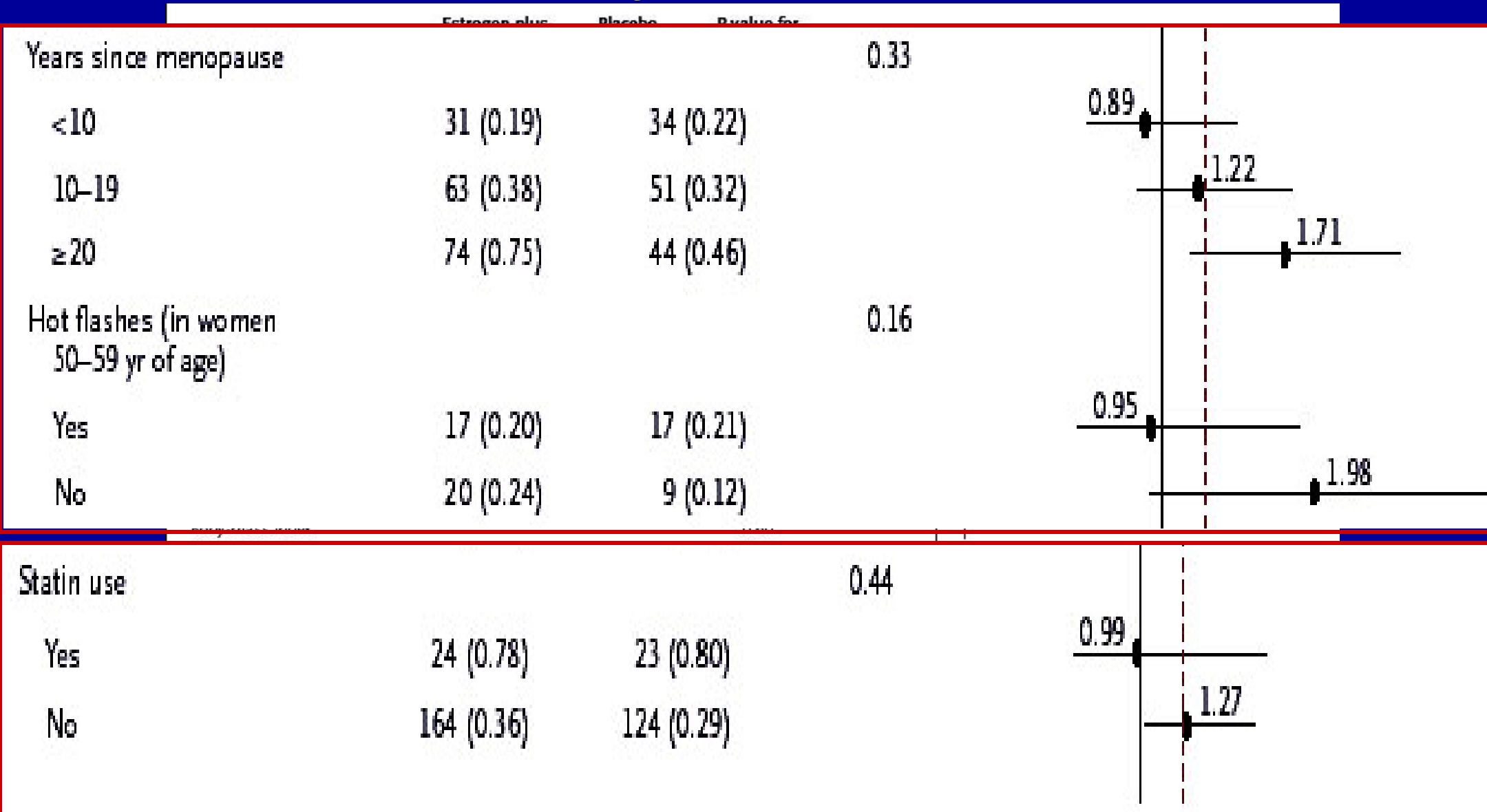
Women's Estrogen-Progestin Lipid-Lowering Hormone Atherosclerosis Regression Trial (WELL-HART)

- Women with CAD (>30% st.)
- 5 years longer menopause to randomization
- No effect of ERT or HRT and no differences

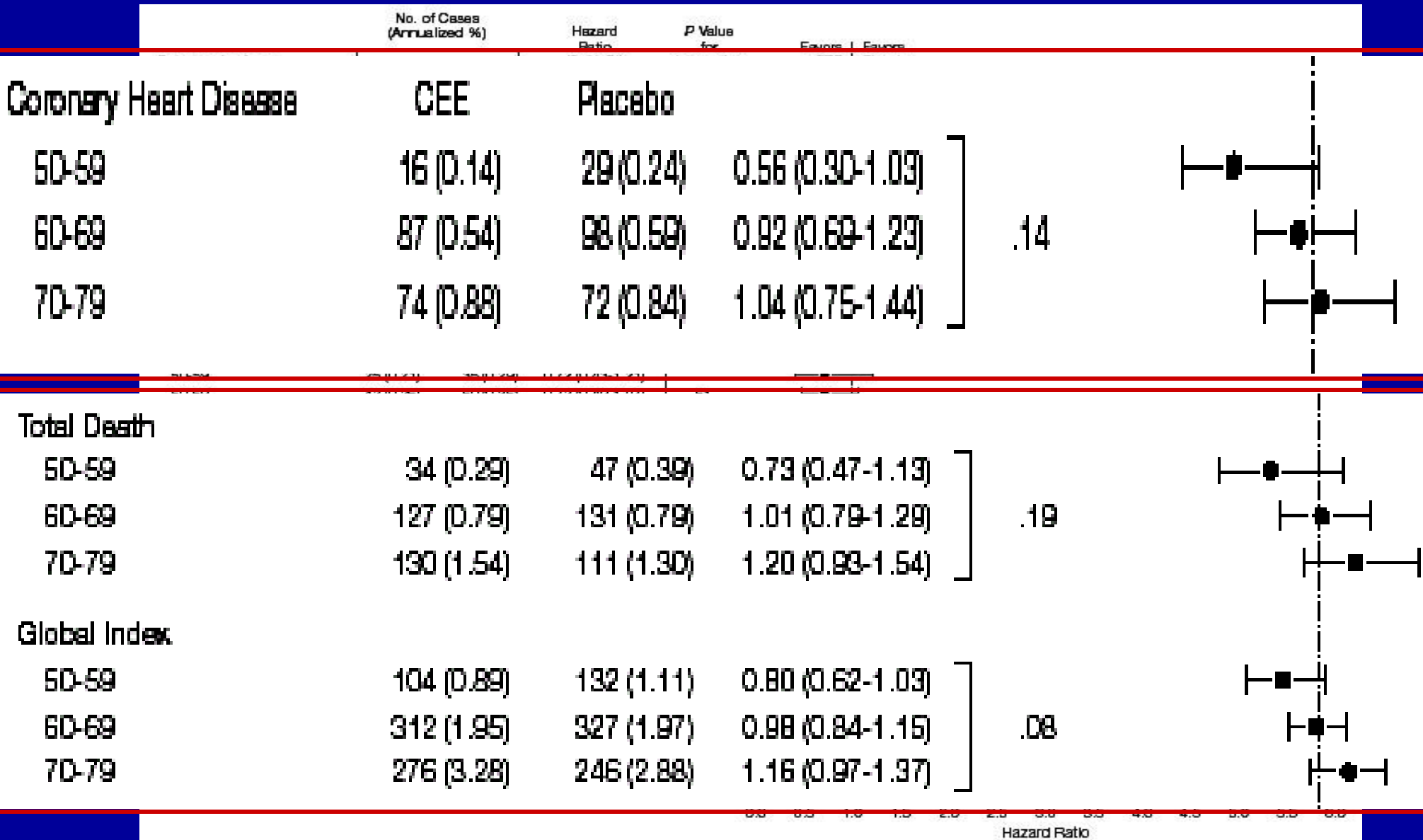
Hodis HN, et al. *Ann Intern Med.* 2001;135:939.

Hodis HN, et al. *N Engl J Med.* 2003;349:535.

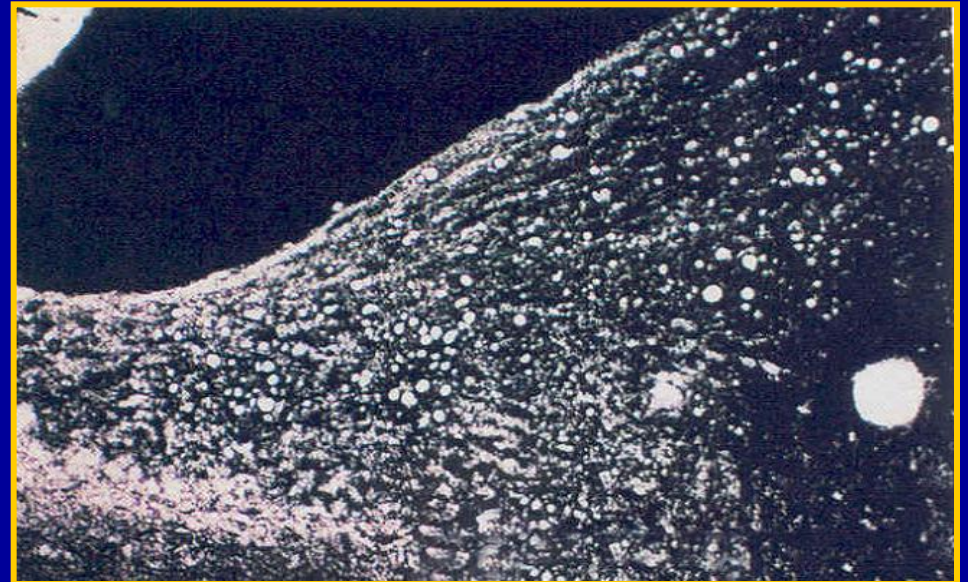
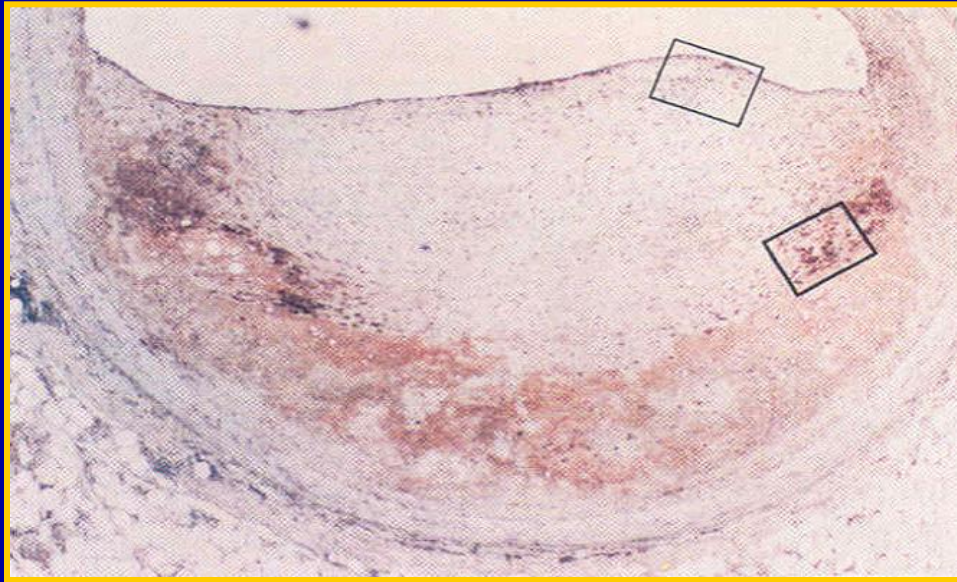
Hormone Therapy and Risk of CHD in WHI



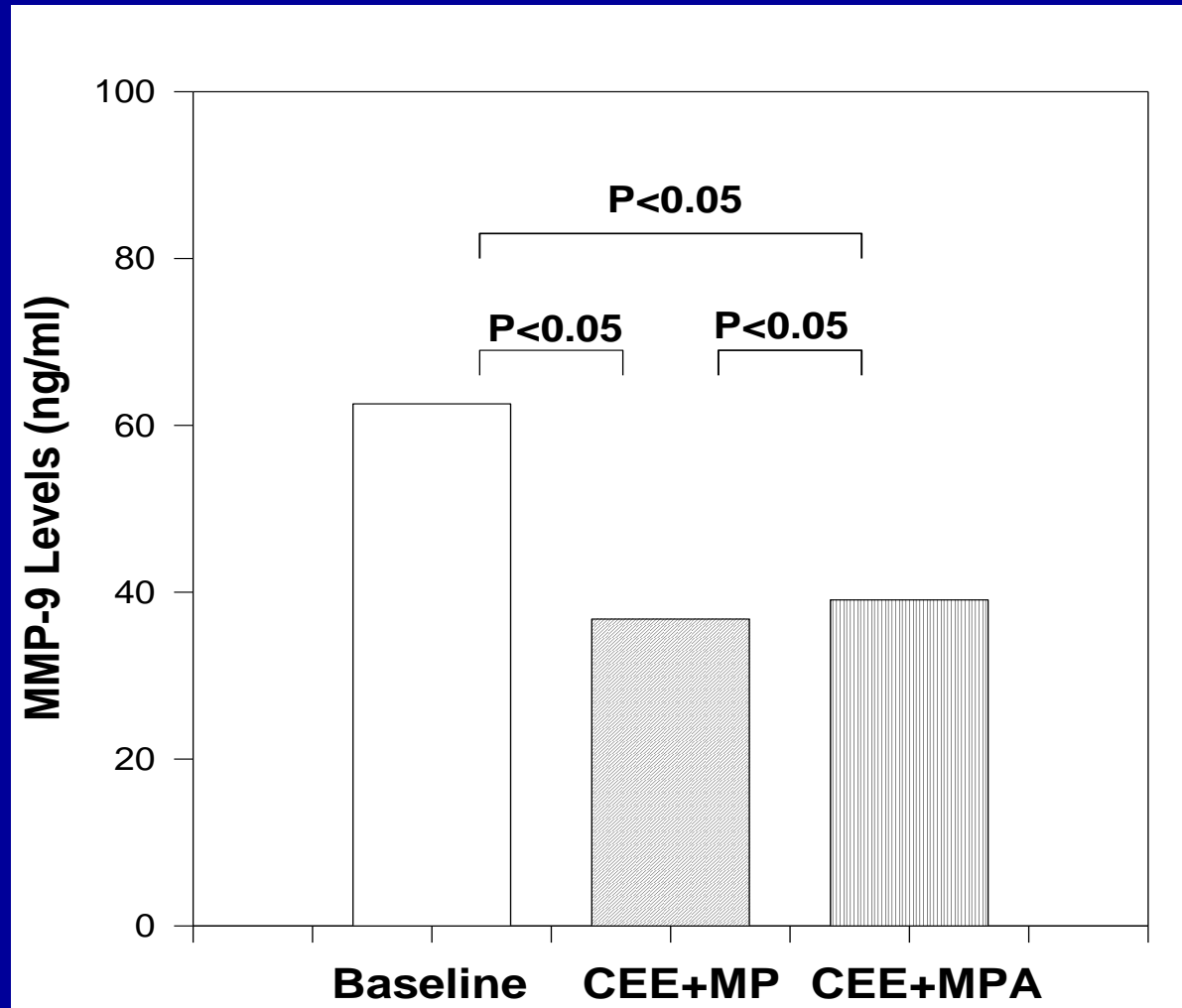
ERT and Risk of CHD in WHI



Metalloproteinase Staining and Gelatinolytic Activity of Human Coronary Artery Atherosclerotic Plaques

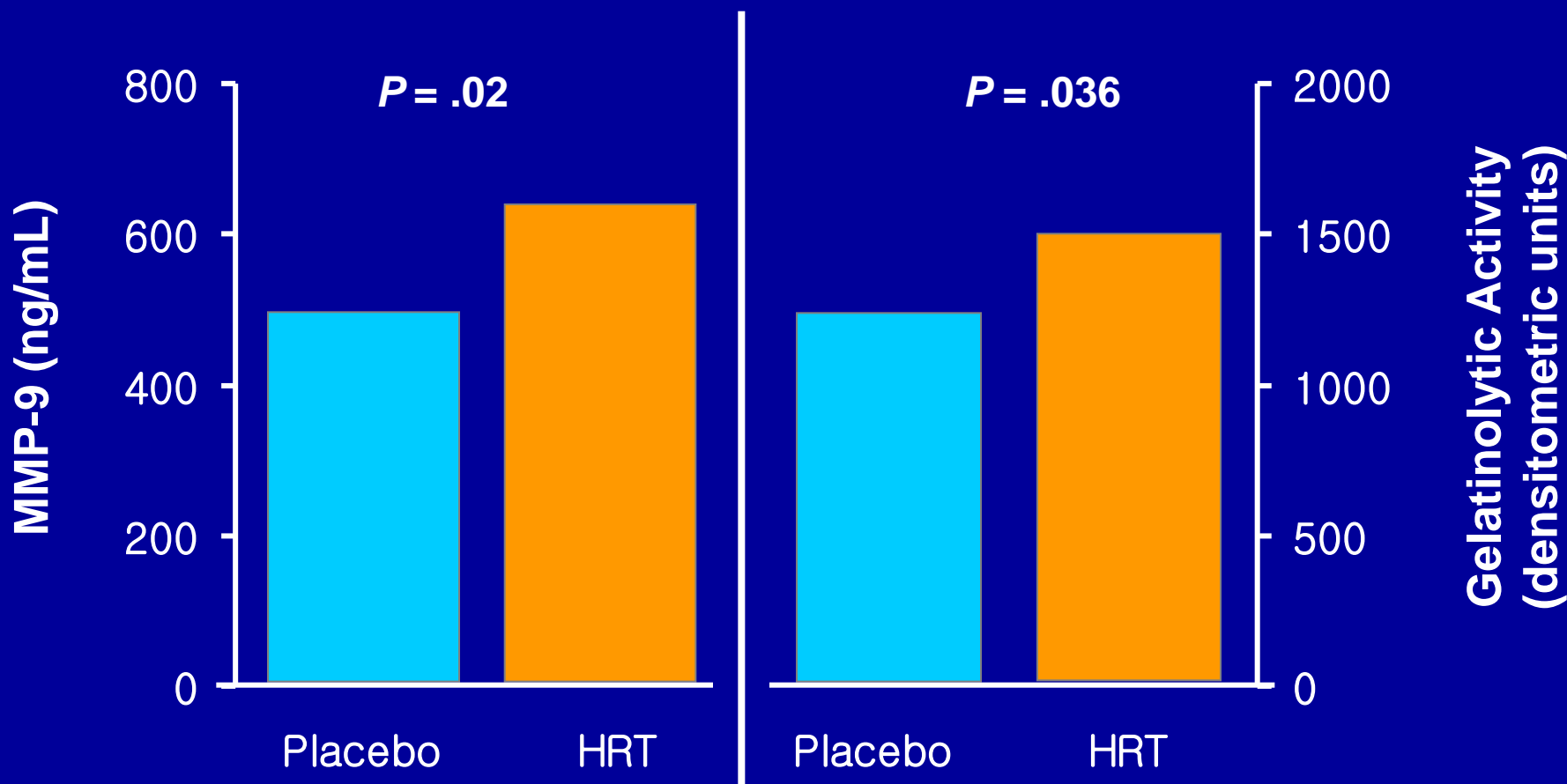


Effect of HRT on Plaque Stability in HT and/or Overweight Postmenopausal Women



mean age
 60 ± 7
N=20

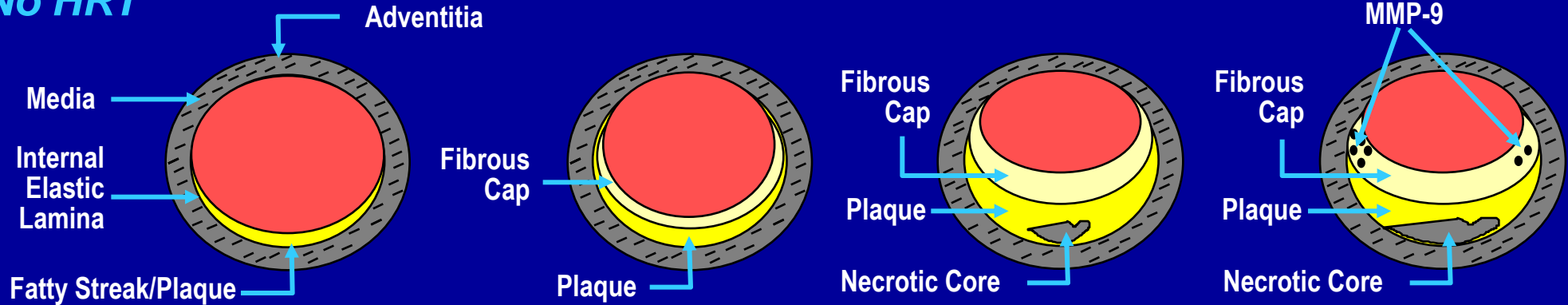
Plasma Expression of Matrix Metalloproteinase-9 (MMP-9) and Gelatinolytic Activity of Women with CAD (Average Age, 66 Years) Treated With either Placebo or HRT*



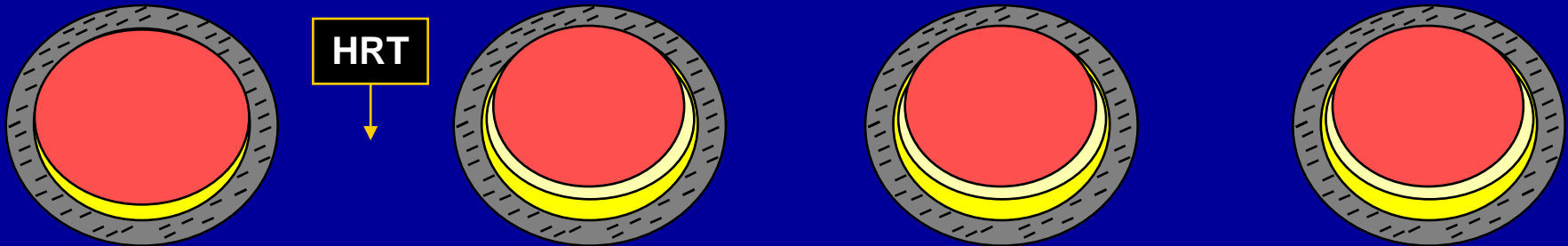
*0.625 mg CEE and 2.5 mg MPA per day
Zanger D, et al. *J Am Coll Cardiol.* 2000;36:1797-802.

Hypothetical Pathogenetic Sequence

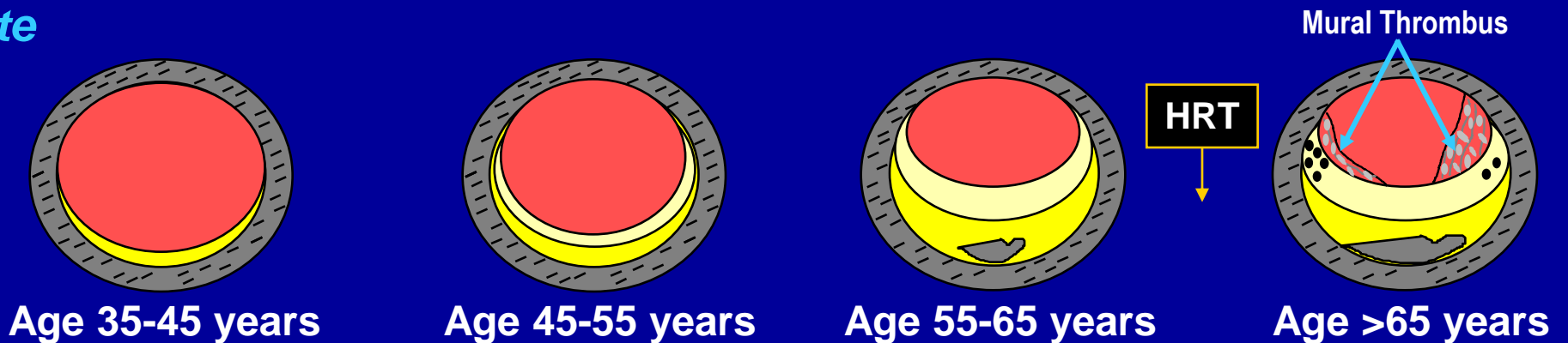
No HRT



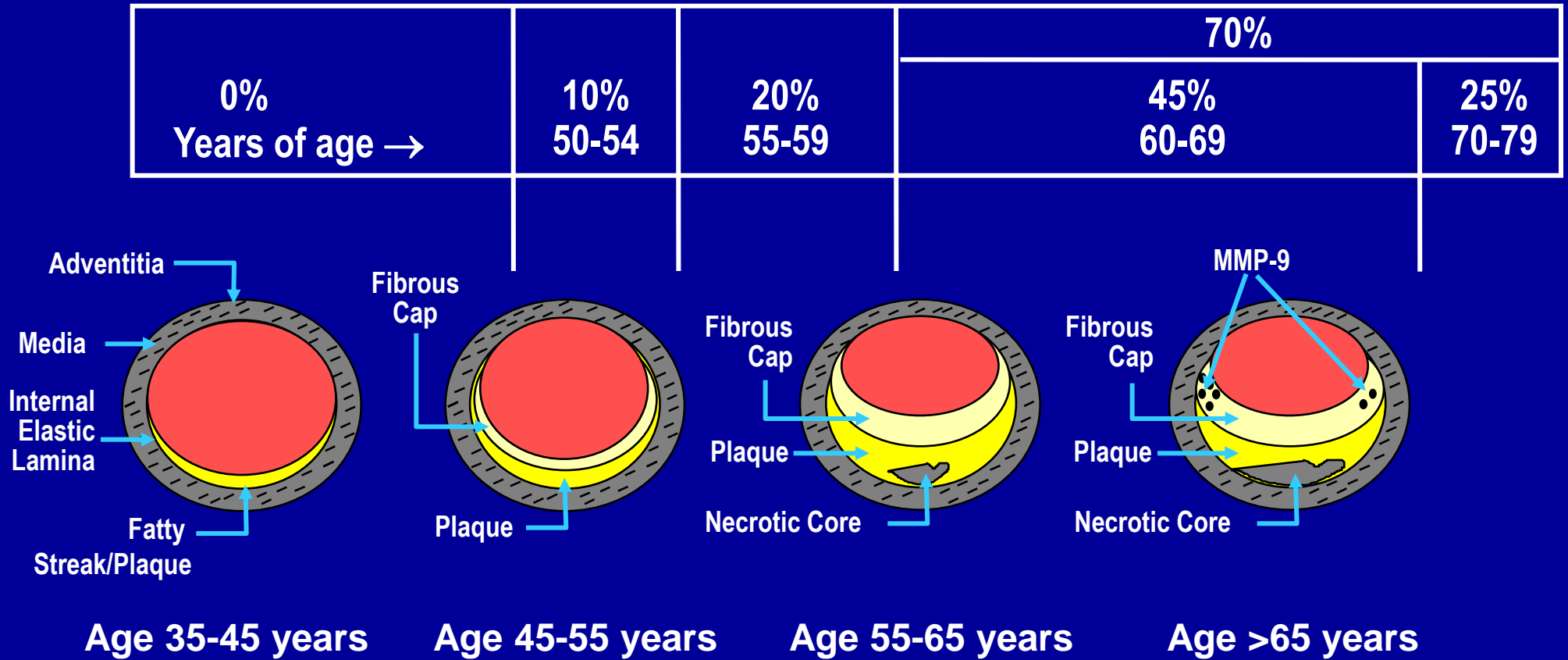
HRT Early & Continued



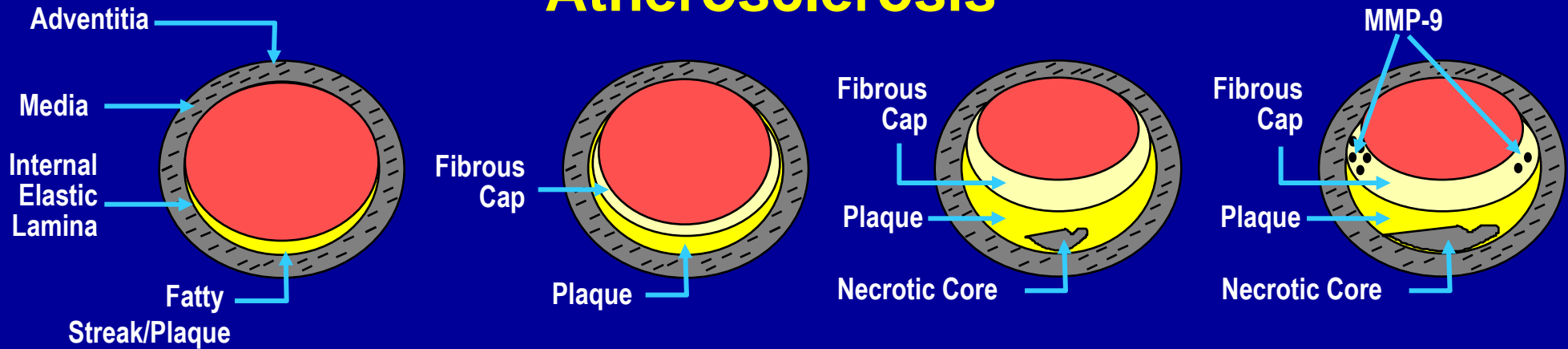
HRT Late



Relation of Age Distribution in WHI to Stage Progression of Coronary Artery Atherosclerosis



Estrogen Effects on the Natural History of Atherosclerosis



•Estrogen Effects in Atherogenesis

- ↓LDL oxidation ⇒ ↓LDL atherogenicity
- ↓LDL binding/accum ⇒ ↓lesion progression
- ↓CAMs ⇒ ↓monocyte adhesion/
↓macrophage accumulation
- ↓ MCP-1 and $TNF\alpha$
- ↓SMC proliferation ⇒ ↓lesion progression
- ↑Endothelial function ⇒ ↑vasodilation

***Benefits of estrogen
on atherosclerosis***

•Estrogen Effects in Established Plaques

- ↑MMP expression ⇒ ↑PQ instability/rupture
- ↑Neovascularization ⇒ ↑PQ hemorrhage

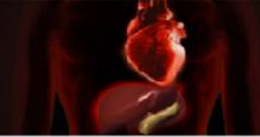
•Loss of Estrogen Benefits

- ↓ Expression of estrogen receptors
- ↓ Vascular responsivity

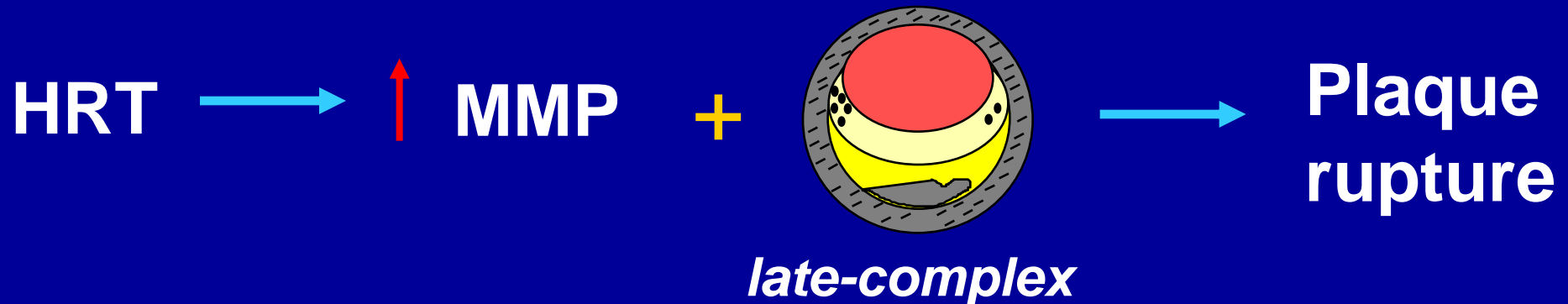
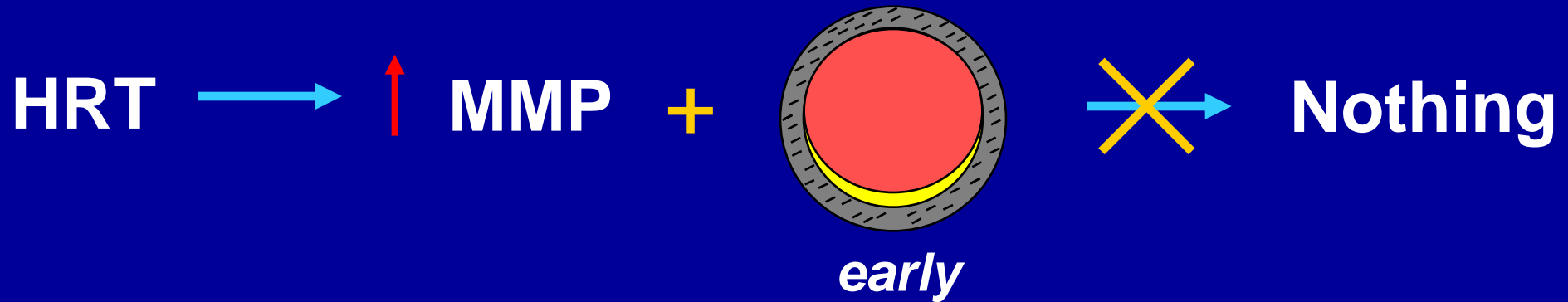
***Potentially adverse effects of
estrogen on atherosclerosis/CHD***

Summary of CV Effects of HRT

- ❖ Large deficit in public awareness that heart disease is leading cause of mortality in women (**Go Red for Women**)
- ❖ More than 20 observational studies in younger postmenopausal women support the conclusion that HRT has cardiovascular benefit in postmenopausal women
- ❖ Data from the randomized controlled trials of older postmenopausal women have not supported the observational data
- ❖ Optimizing the clinical benefits of these regimens in postmenopausal women depends largely on promoting a healthy endothelium through **life-style modifications** that diminish coronary risk.



HRT and Plaque Rupture Susceptible Substrate



Incitant

Catalyst Substrate

Reaction