CV Aspects of Estrogen Use in Early Menopause

Thomas Dayspring, MD, FACP

Clinical Assistant Professor of Medicine

University of Medicine and Dentistry of New Jersey,
New Jersey Medical School

Diplomate of the American Board of Clinical Lipidology

Certified Menopause Practitioner: North American Menopause Society

North Jersey Institute of Menopausal Lipidology
Wayne, New Jersey

St. Joseph's Regional Medical Center Paterson, NJ

American Heart Association Guidelines

Evidence Based Guidelines for Cardiovascular Disease Prevention in Women

Free Download

www.americanheart.org

Mosca, L. et al. Circulation 2004;109:672-693

AHA Guidelines for CVD Prevention in Women

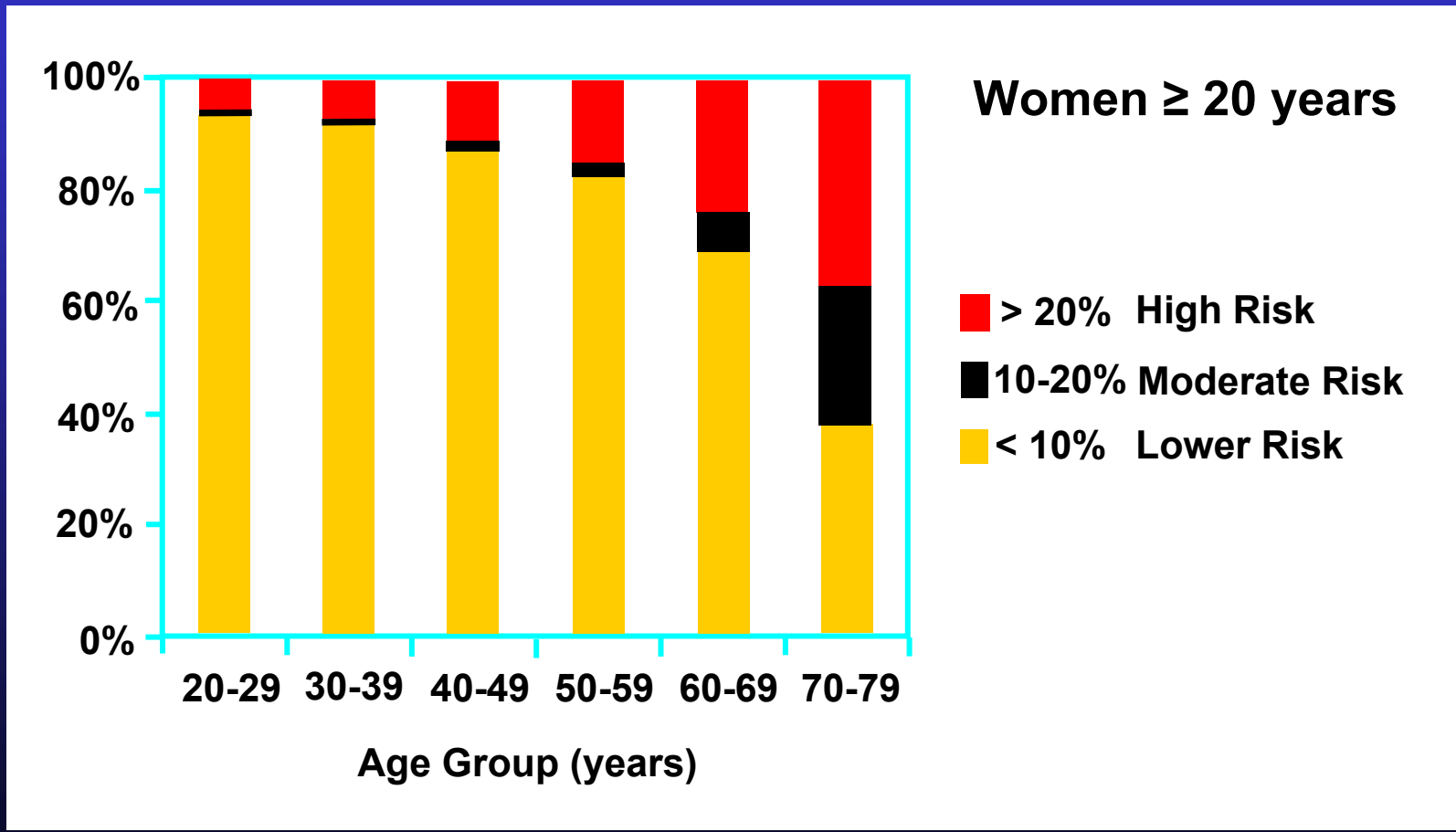
CVD Statistics

- CVD remains the **leading cause of death** in women
- > 500,000 women a year die
  - One death every minute
- 2/3 of women who die suddenly have no warning symptoms

Mosca, L. et al. Circulation 2004;109:672-693

National Health And Nutrition Examination Survey III (NHANES)

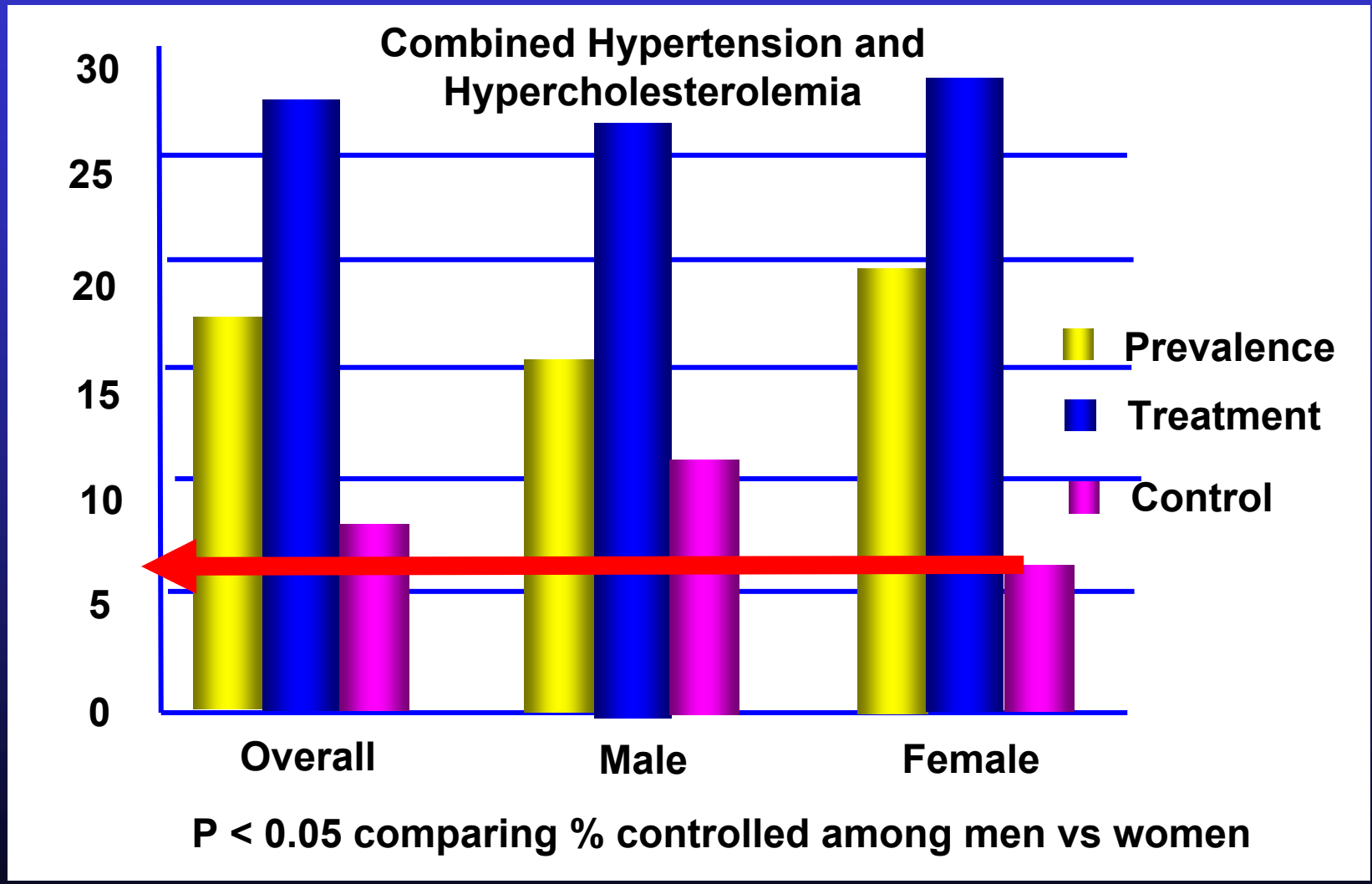
Age Specific Distribution of Ten Year Risk for CHD



NHANES III 1988-1994

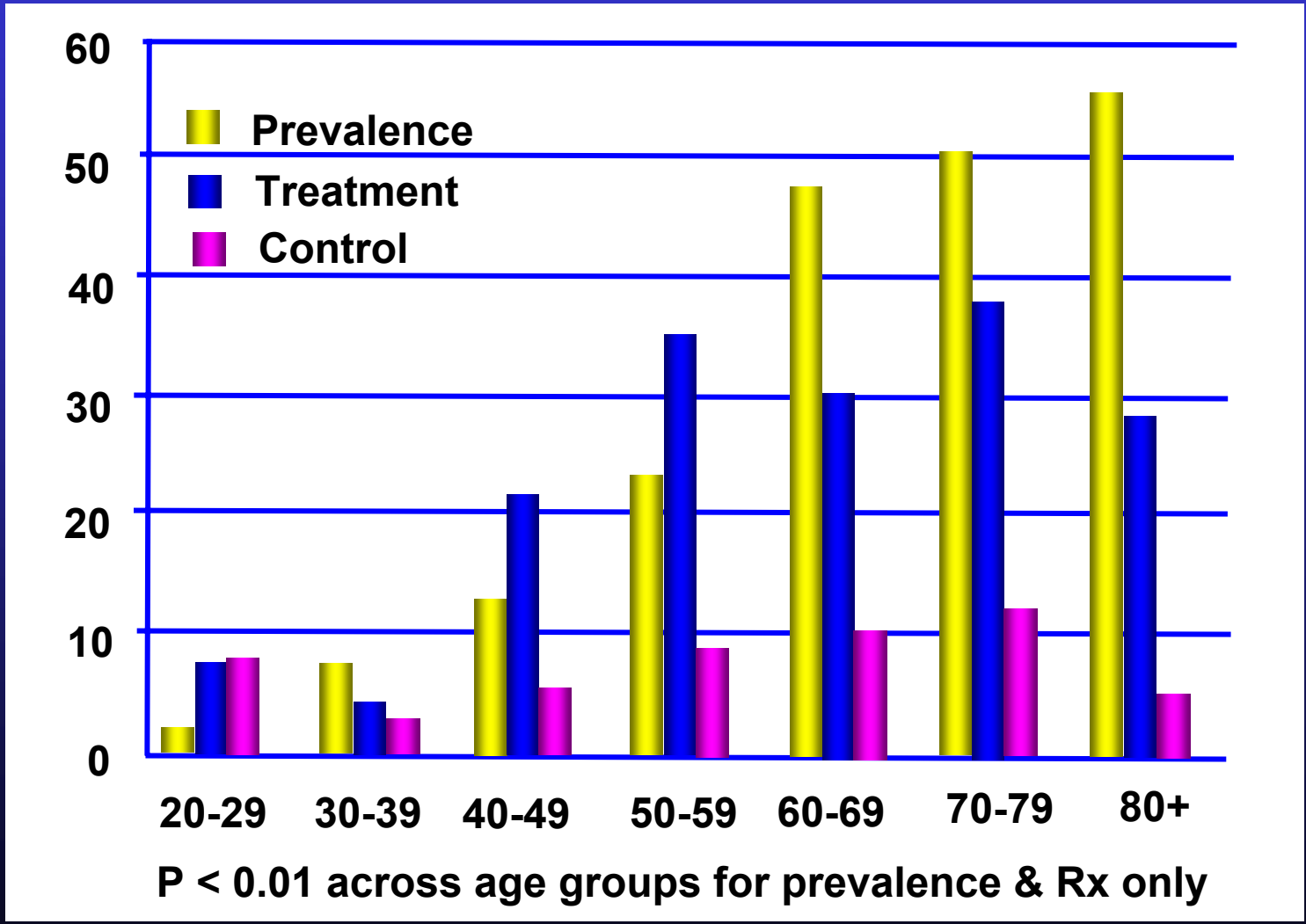
Ford ES et al. JACC 2004;43:1791-1796

Recognition and Treatment of CV Risk



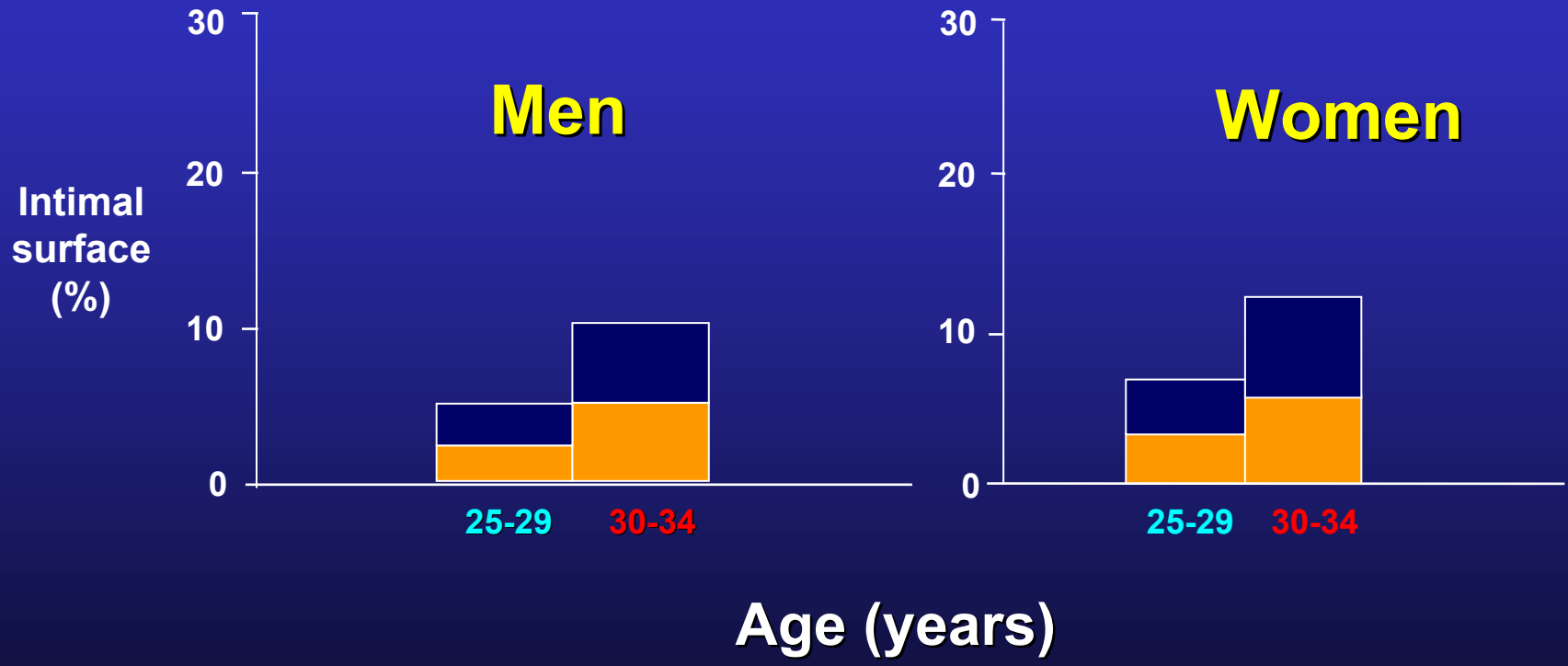
Wong ND et al. Am J Cardiol 2006;98;204-208

Recognition and Treatment of CV Risk



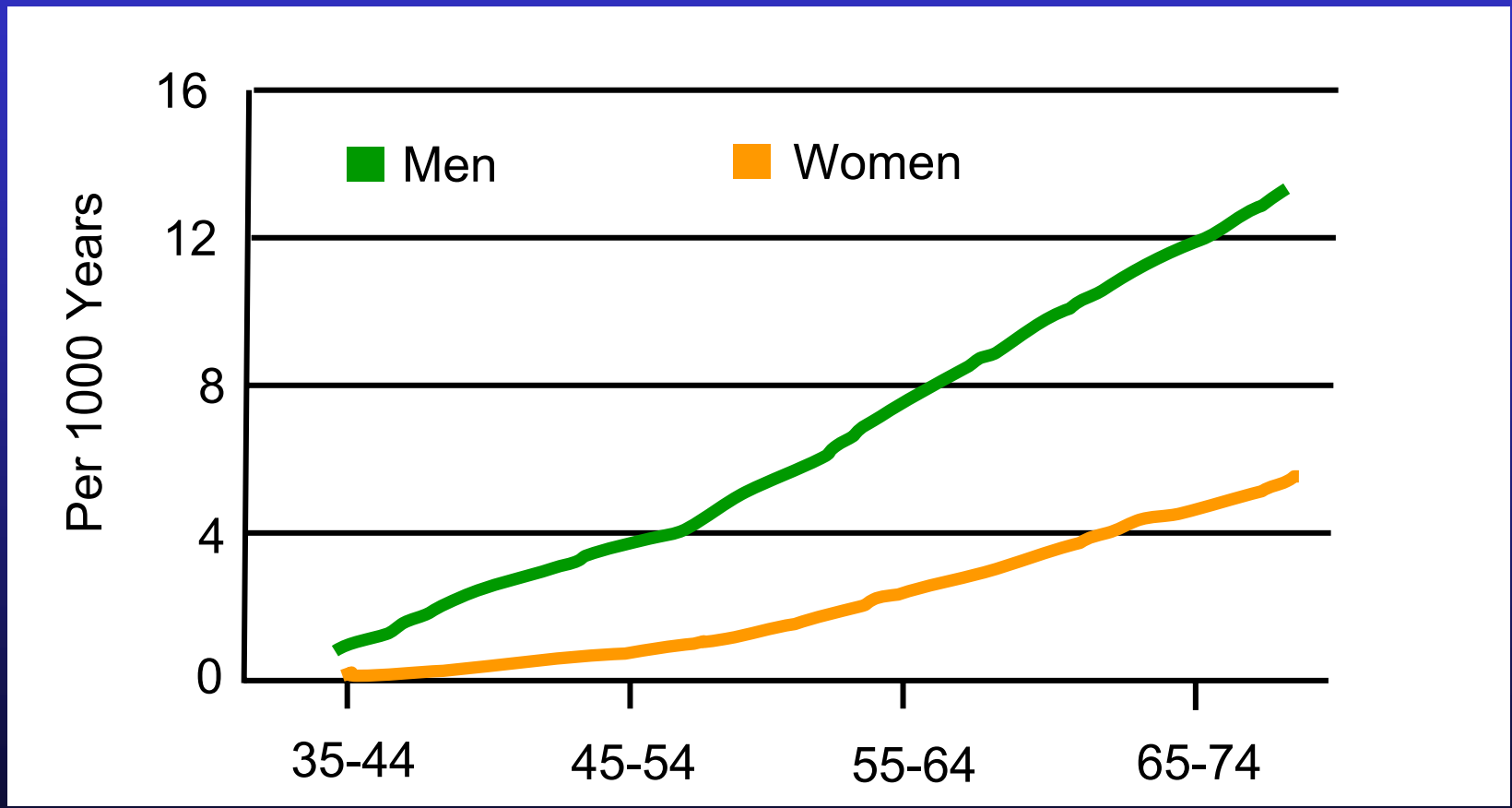
Wong ND et al. Am J Cardiol 2006;98;204-208

Pathobiological Determinants of Atherosclerosis in Youth (PDAY): Percentage of Right Coronary Artery Intimal Surface Affected With Early Atherosclerosis (Caucasians)



Strong JP, et al. *JAMA*. 1999;281:727-735.

Annual Rate of First Heart Attack by Age and Sex



Heart Disease and Stroke Statistics – 2003 Update AHA

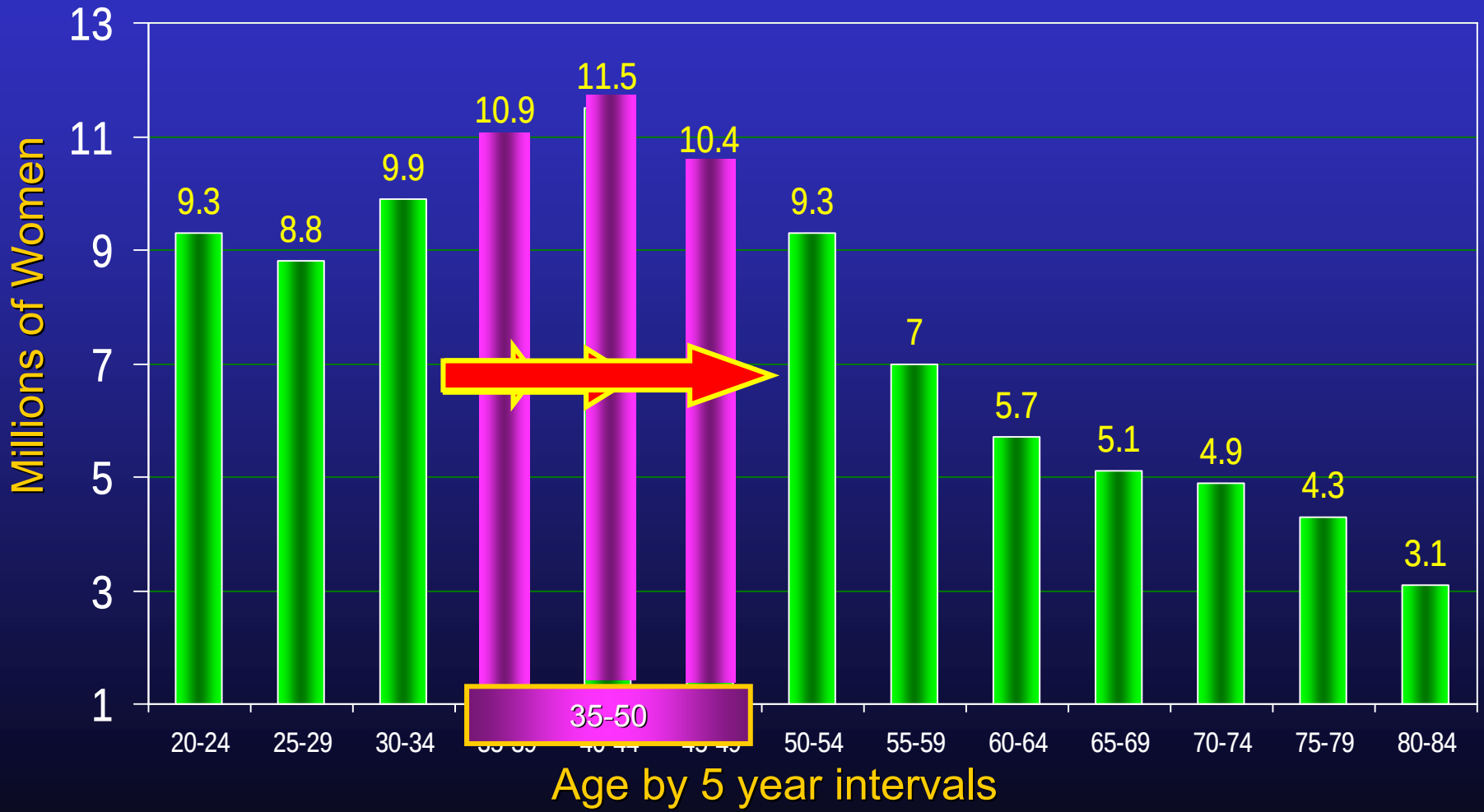
Gender Differences in CHD

- Until puberty boys and girls have similar HDL-C levels
- At puberty, with the concurrent rise in testosterone, HDL levels in young men decline to lower adult levels
- Thus, the HDL differences between genders may be an *androgenic effect, not an estrogenic effect*
- The 20% difference in HDL probably accounts for at least a 20% decrease in CHD over a lifetime which can entirely explain the gender difference

Gordon DJ et al. Circulation 1989;79:8-15
NCEP ATP III Chapter VIII Page 2
Rossouw J Cardiovascular Research 2002;53:550-557

The Incoming Wave of Baby Boomers

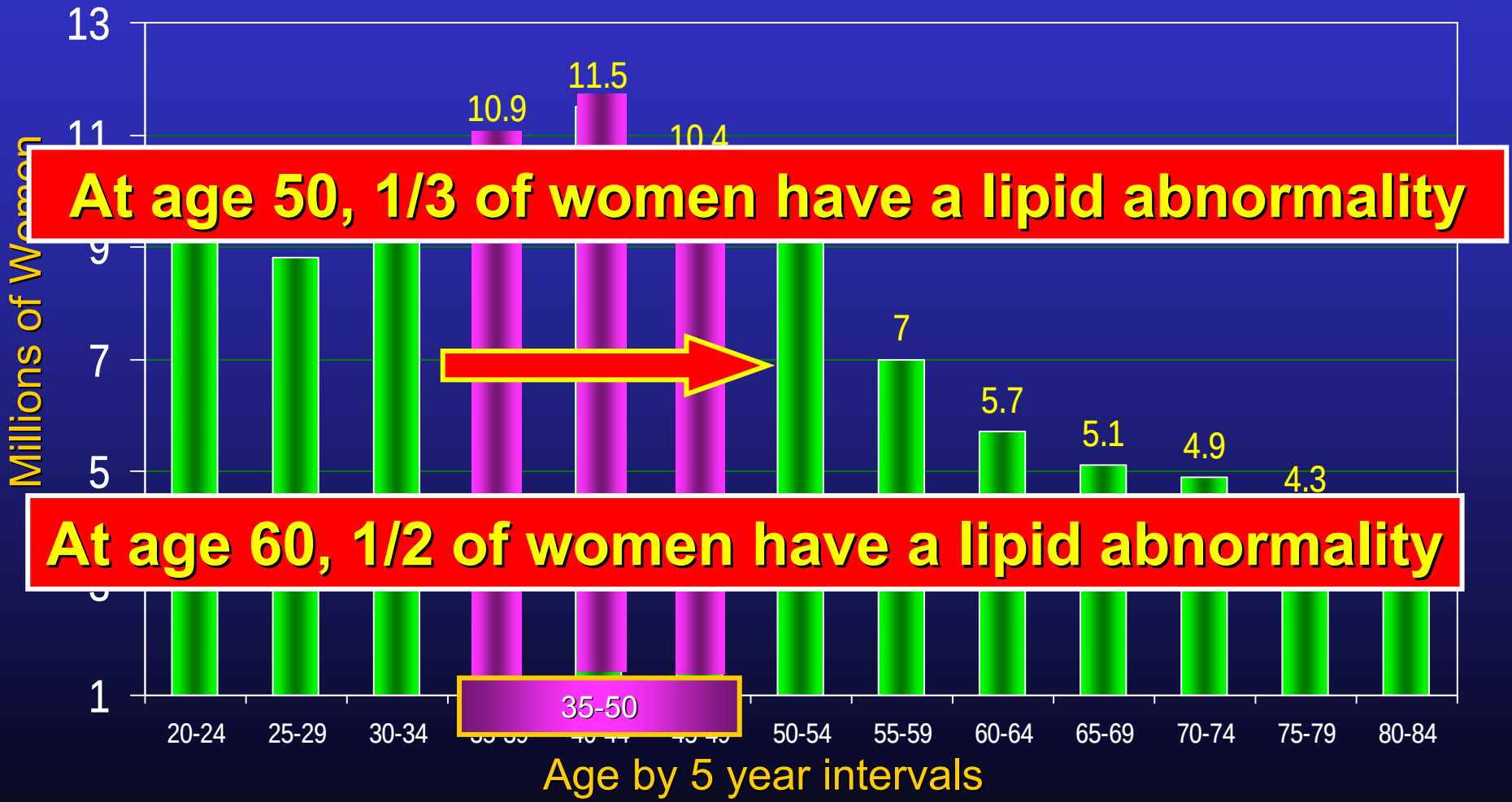
Approximately 2 million women per year (more than 5,000 women per day) will reach age 50 during the next 10 years



Source: US Census Bureau, January 13, 2000.

The Incoming Wave of Baby Boomers

Approximately 2 million women per year (more than 5,000 women per day) will reach age 50 during the next 10 years



At age 50, 1/3 of women have a lipid abnormality

At age 60, 1/2 of women have a lipid abnormality

Source: US Census Bureau, January 13, 2000.

National Cholesterol Education Program Adult Treatment Panel III NCEP-ATP III

- Start Lipid screening at age 20
- Treat high risk premenopausal women

NCEP ATPIII. *JAMA* 2001;285:2486-2497

AHA Guidelines for Women and CHD

Clinical Recommendations

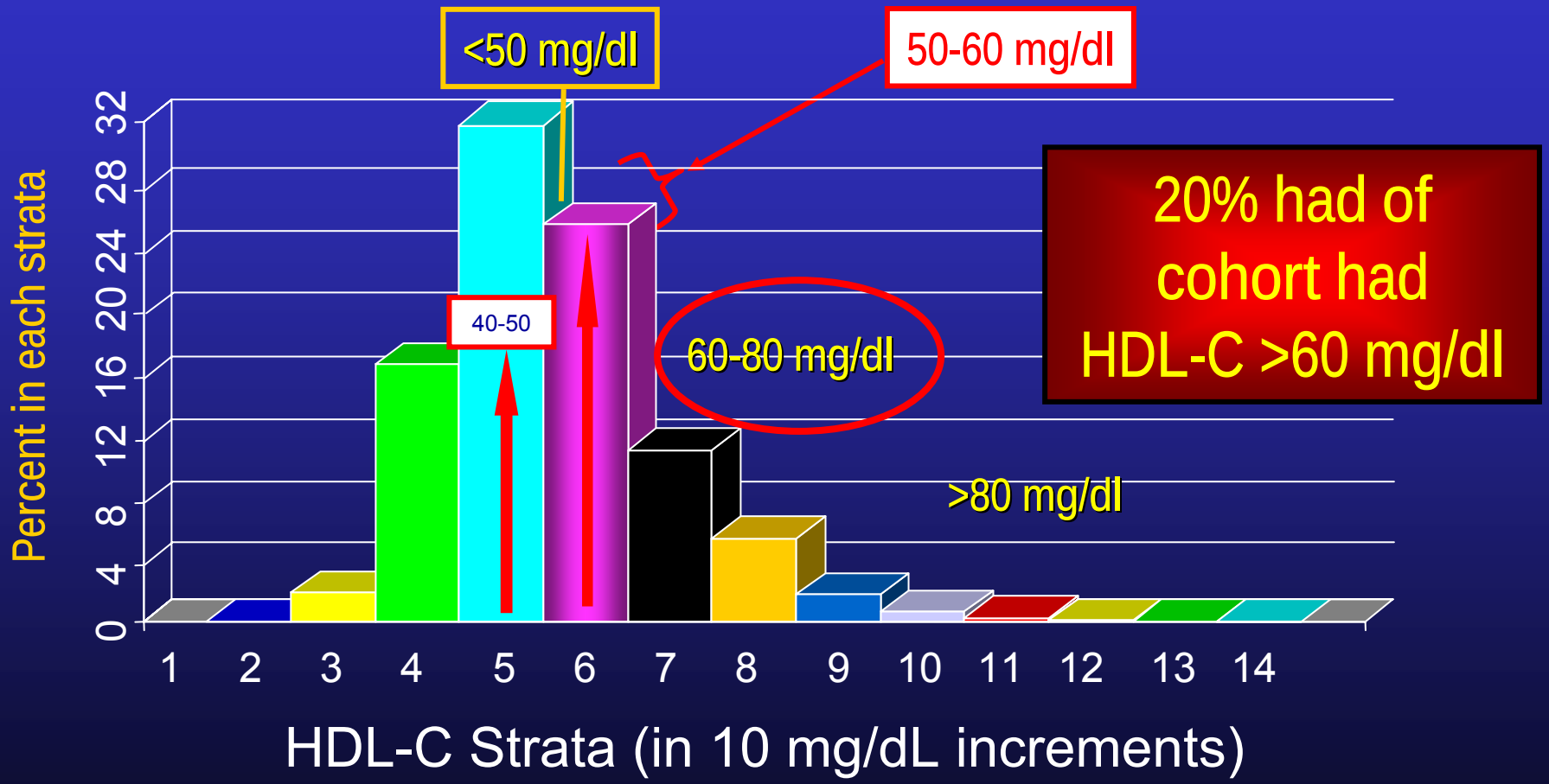
Major Risk Factor Interventions

- Lipids - Lipoproteins:
  - Optimal levels of lipids and lipoproteins in women:
    - LDL-C < 100 mg/dL
    - HDL-C > 50 mg/dL

Mosca, L. et al. Circulation 2004;109:672-693

Heart and Estrogen/Progestin Replacement Study (HERS)

HDL-C in Women with Heart Disease



Bittner V et al. Am Heart J 2000;139:288-96

AHA Guidelines for Women and CHD

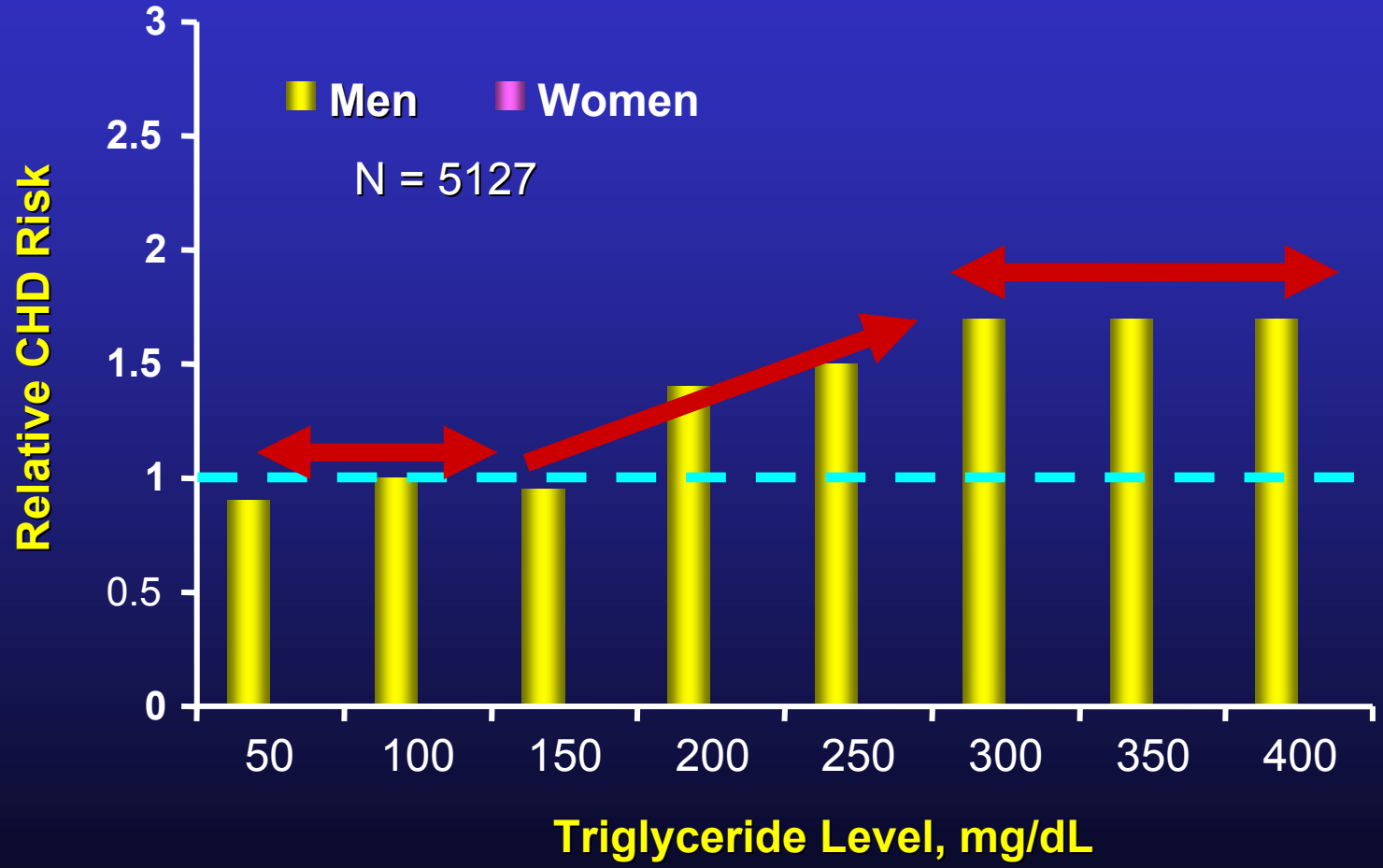
Clinical Recommendations

Major Risk Factor Interventions

- Lipids - Lipoproteins:
  - Optimal levels of lipids and lipoproteins in women:
    - LDL-C < 100 mg/dL
    - HDL-C > 50 mg/dL
    - TG < 150 mg/dL

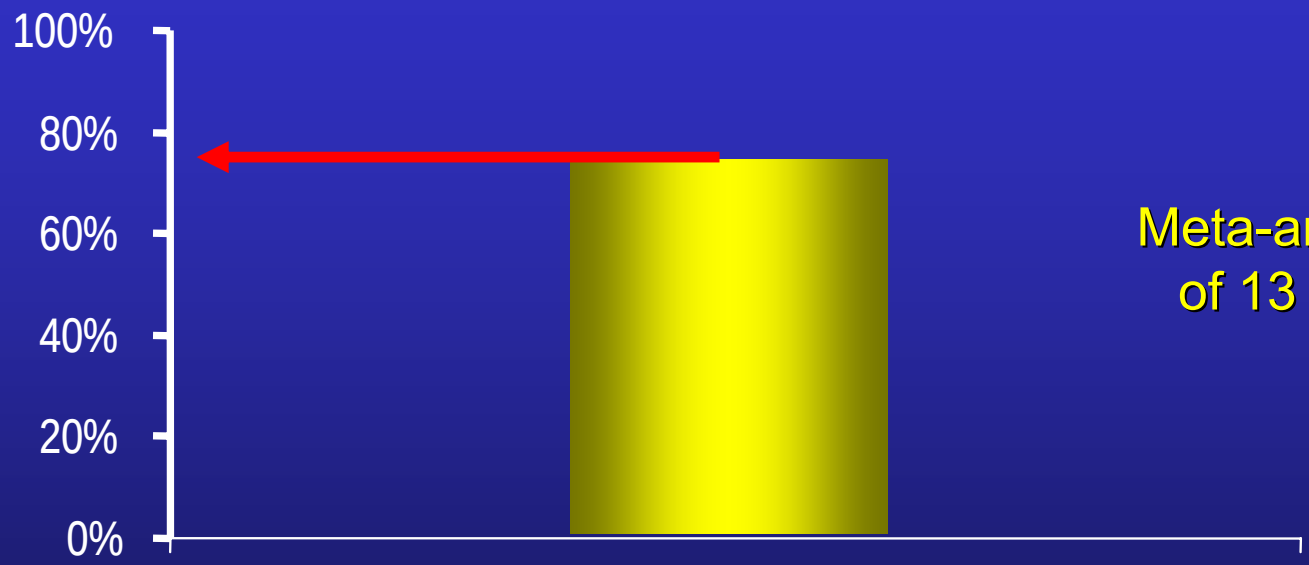
Mosca, L. et al. Circulation 2004;109:672-693

Risk of CHD by Triglyceride Level
The Framingham Heart Study



Castelli WP. *Am J Cardiol.* 1992;70:3H-9H.

Increase in CVD Risk Due to High Triglycerides: Univariate Analysis



Women n=10,864

Relative risks with respect to a 80 mg/dl increase in triglyceride

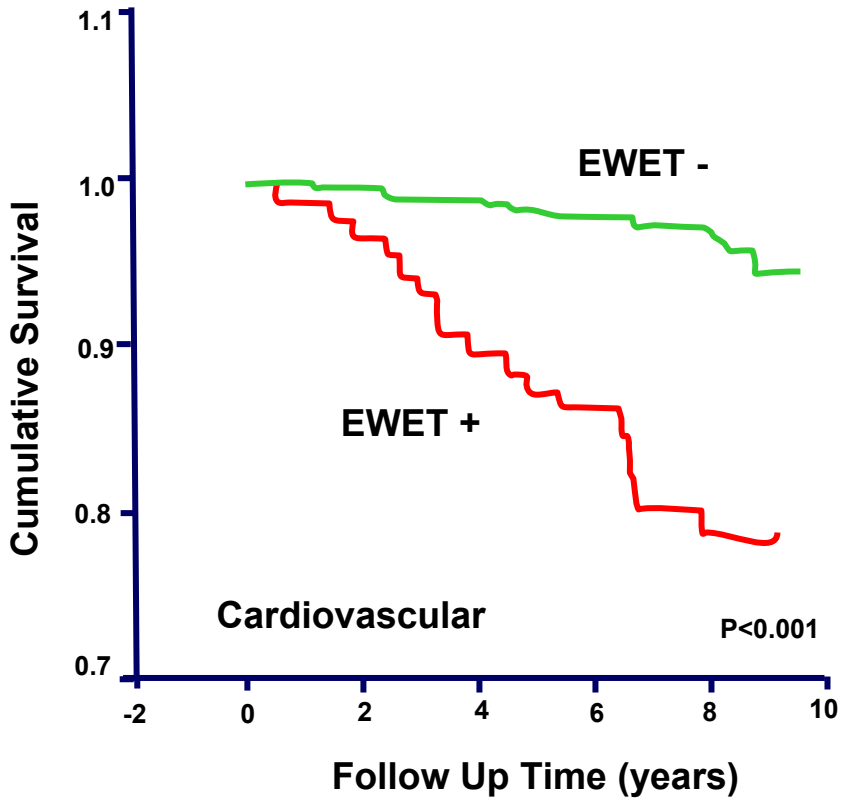
Hokanson JE, et at. *J Cardiovasc Risk.* 1996:3(2):213-219.

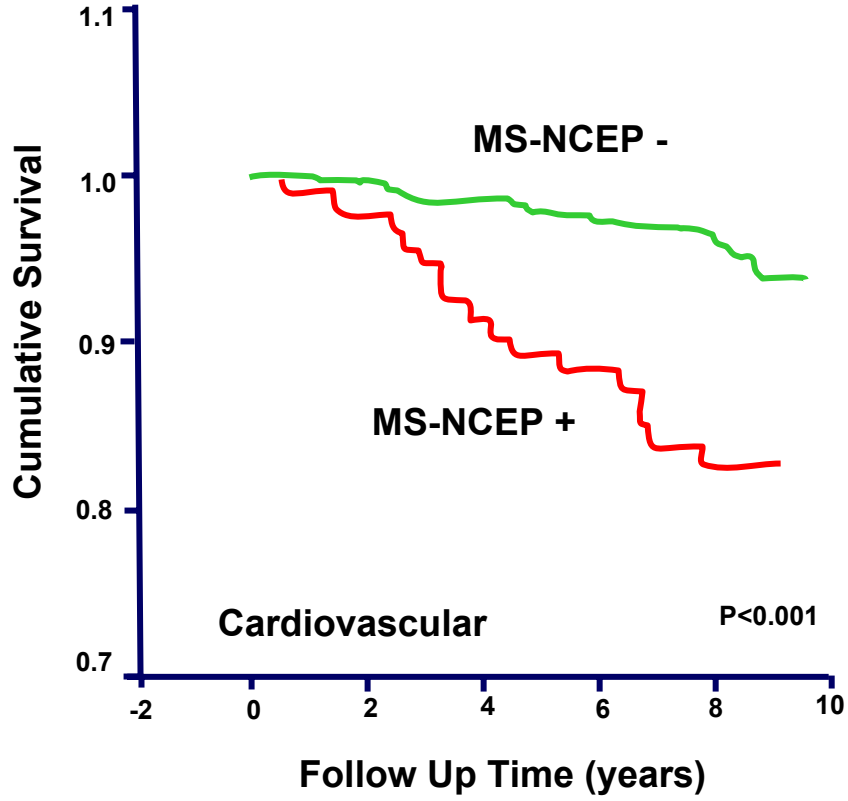
Enlarged Waist Combined With Elevated Triglyceride Is a Strong Predictor of Accelerated Atherogenesis and Related Cardiovascular Mortality in Postmenopausal Women (EWET)

- ***Conclusions:*** The combined presence of EWET may be the best indicator of cardiovascular risk in postmenopausal women.
  - The TG value of concern is 128 mg/dL
- Other components of the MS-NCEP add little medical value to screening in general practices.

***Circulation*.2005;111:1883-1890**

Enlarged Waist Combined With Elevated Triglyceride (EWET)





Kaplan-Meier curves indicating cardiovascular event rates in women with (n=88) or without (n=469) EWET or with (n=100) or without (n=433) MS-NCEP

Circulation.2005;111:1883-1890

AHA Guidelines for Women and CHD

Clinical Recommendations

Major Risk Factor Interventions

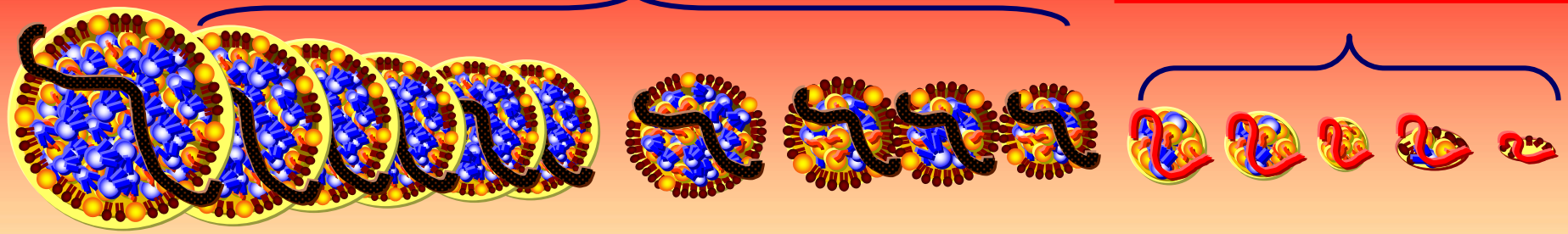
- Lipids - Lipoproteins:
  - Optimal levels of lipids and lipoproteins in women:
    - LDL-C < 100 mg/dL
    - HDL-C > 50 mg/dL
    - TG < 150 mg/dL
    - Non HDL-C < 130 mg/dL

Mosca, L. et al. Circulation 2004;109:672-693

Lipoprotein & Lipid Concentrations

ApoB-lipoproteins

ApoAI-lipoproteins



V6 V5 V4 V3 V2 V1

L3 L2 L1

H5 H4 H3 H2 H1

VLDL-C

IDL-C + LDL-C

HDL-C

Reported LDL-C

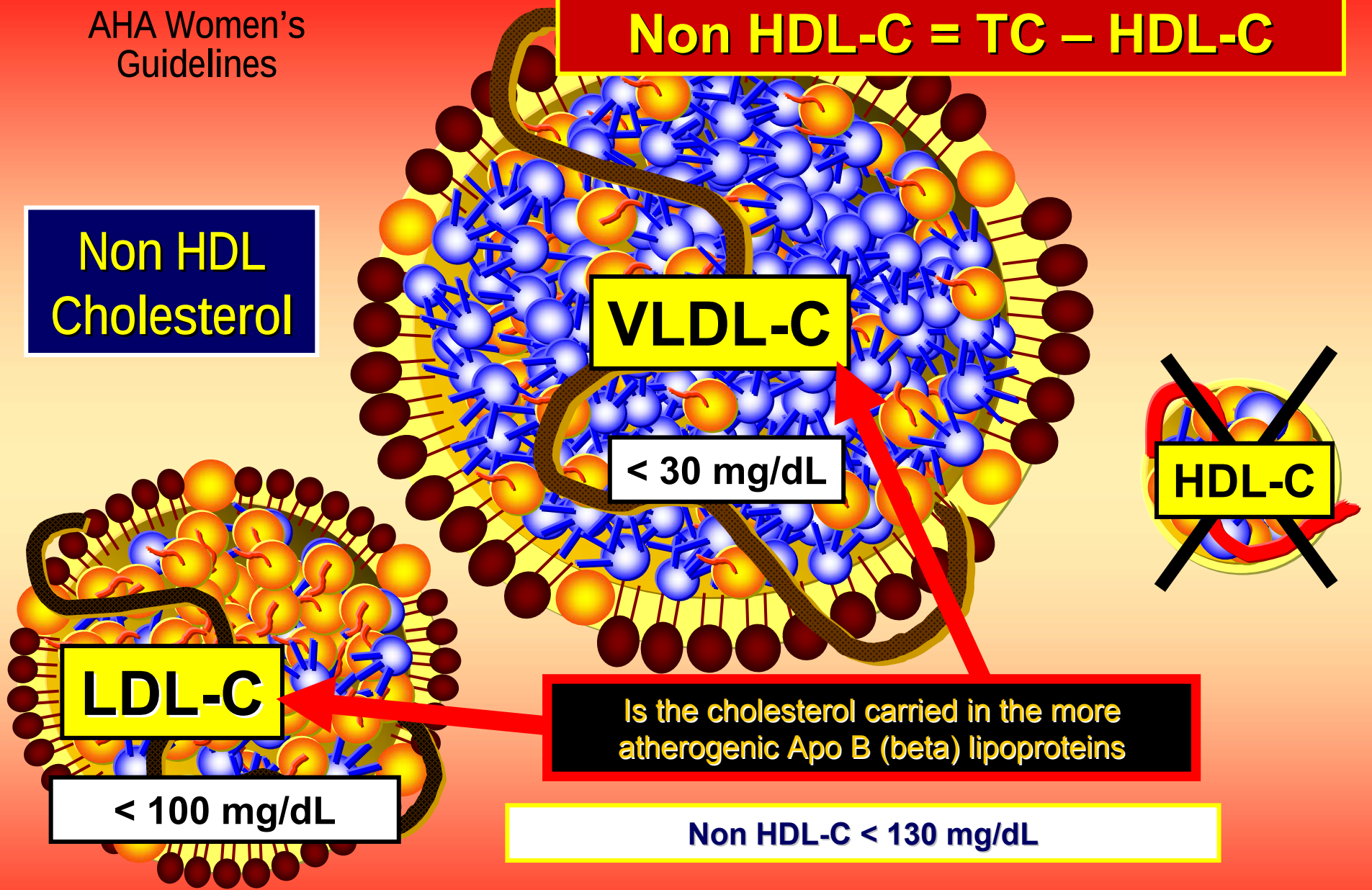
Total Cholesterol

TC = HDL-C + LDL-C + VLDL-C

AHA Women's Guidelines

Non HDL-C = TC – HDL-C

Non HDL Cholesterol



Is the cholesterol carried in the more atherogenic Apo B (beta) lipoproteins

Non HDL-C < 130 mg/dL

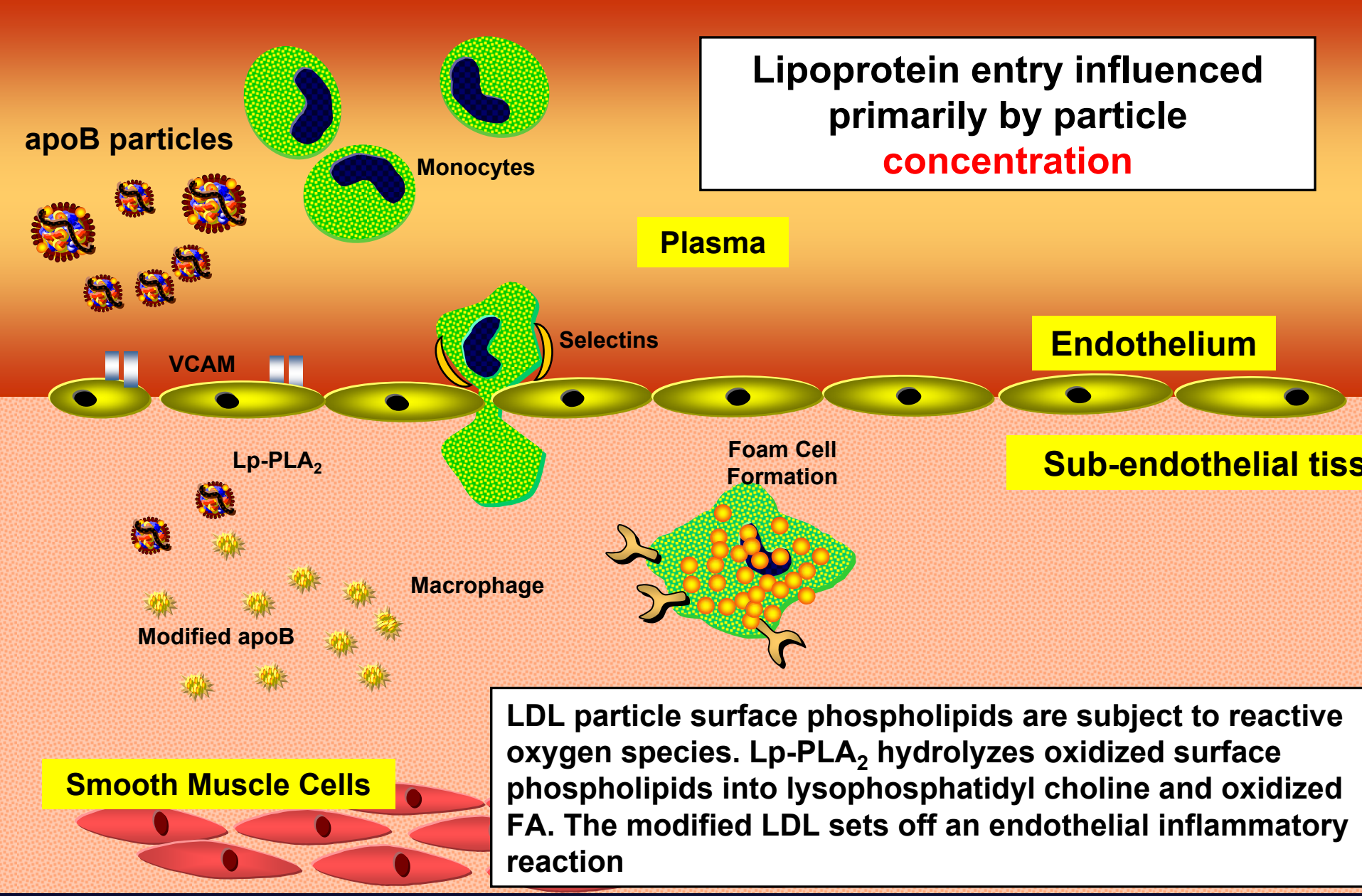
The Central Role of the Endothelium

Plays a key role in regulating vascular tone and structure.

Modulates inflammatory and thrombotic processes.

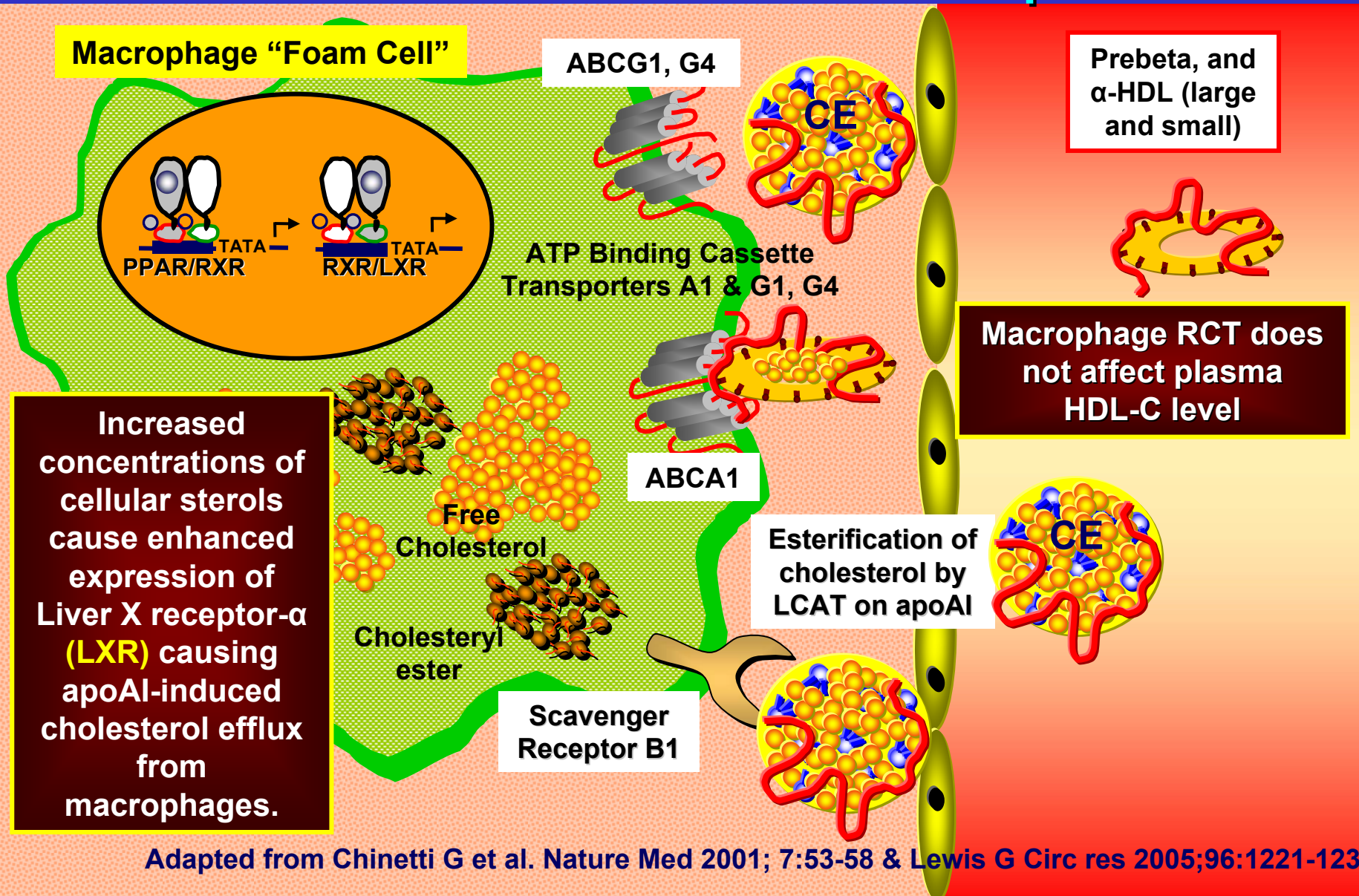
Its function is dependent on circulating and local factors.

The endothelium is a protective, one cell deep barrier lining all arteries



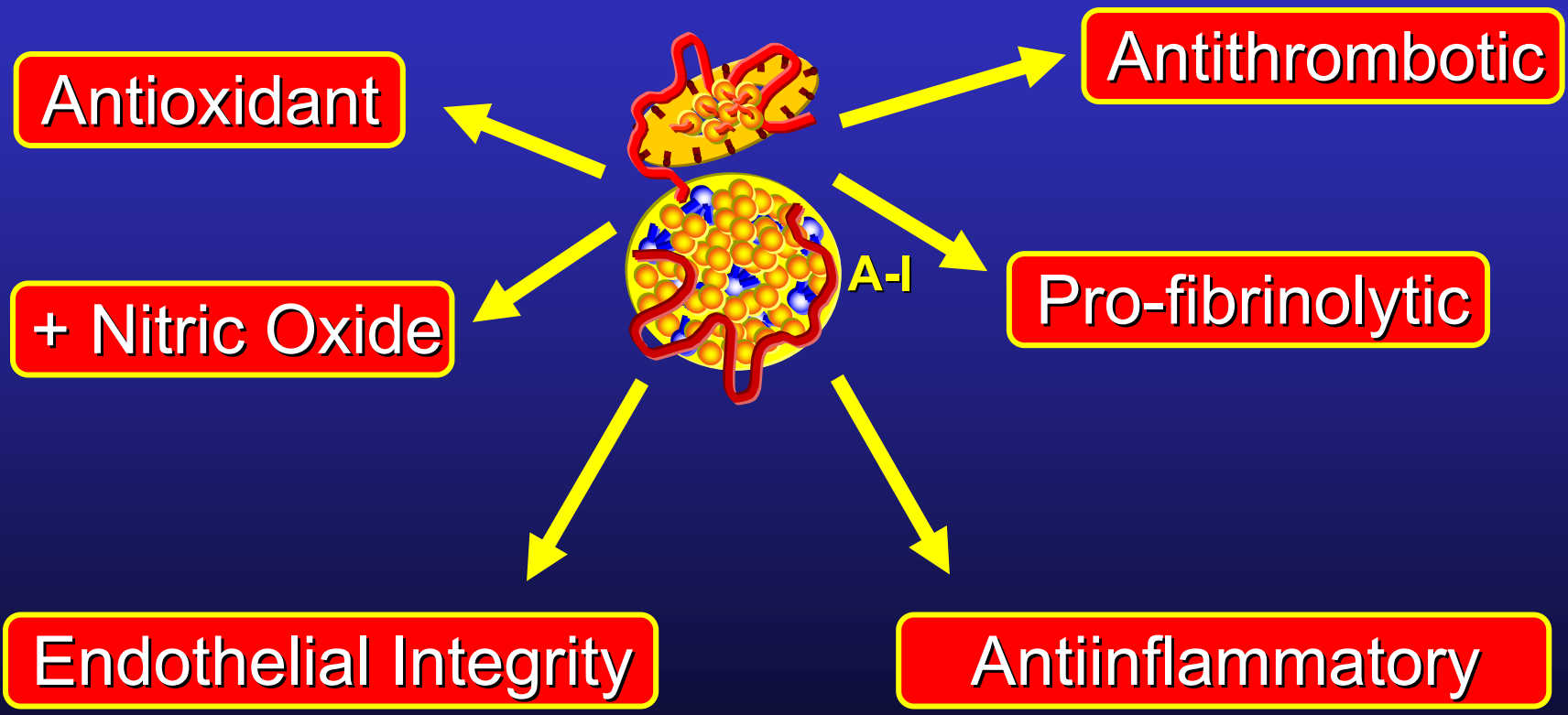
de Winther MPJ et al. *Arterioscler Thromb Vasc Biol*. 2005;25:904-914

HDL Lipidation via Macrophage Reverse Cholesterol Transport



Adapted from Chinetti G et al. Nature Med 2001; 7:53-58 & Lewis G Circ res 2005;96:1221-1232

HDL Functionality and Vascular Protection



AHA Guidelines for Women and CHD

CVD Prevention Strategies for Clinical Practice

- Assess and stratify women into high, intermediate, lower or optimal risk categories
- Lifestyle approaches (cigarette cessation, regular exercise, weight management, and heart healthy diet) to prevent CVD are Class I recommendations for all women and a **top priority** in clinical practice

Mosca, L. et al. Circulation 2004;109:672-693

AHA Guidelines for Women and CHD

Spectrum of CVD Risk in Women

Framingham Global Risk > 20%

- Established CHD
- Cerebrovascular disease
- Peripheral vascular disease
- Abdominal aortic aneurysm
- Diabetes mellitus
- Chronic kidney disease
- Subclinical CVD with > 20% Framingham risk

Mosca, L. et al. Circulation 2004;109:672-693

AHA Guidelines for CVD Prevention in Women

Spectrum of CVD Risk in Women

Framingham Global Risk > 10 - 20%

- Subclinical CVD (+ coronary calcification)
- Multiple risk factors
- Markedly elevated levels of a single risk factor
- First degree relatives with early onset atherosclerosis (< 55 in men and 65 in women)
- Metabolic Syndrome

Mosca, L. et al. Circulation 2004;109:672-693

National Cholesterol Education Program

Adult Treatment Panel III NCEP-ATP III

The Metabolic Syndrome in Women

- Diagnosis suggested by the presence of **three or more** of the following features:
  - Waist > 35 inches
  - Triglycerides >150 mg/dl
  - HDL-C <50 mg/dL
  - SBP ≥130 or DBP ≥ 85 mm Hg
  - Fasting plasma glucose >110 mg/dL

NCEP ATP III. NIH Publication 01-3670, 2001.

National Health And Nutrition Examination Survey (NHANES) Increasing Prevalence of Metabolic Syndrome Among Adults

- A total of 6,436 men and women aged 20 years from the (NHANES) III (1988–1994) and 1,677 participants from NHANES 1999–2000 were included in the analyses.
- The unadjusted prevalence of the metabolic syndrome was
  - 23.1% in NHANES III and 26.7% in NHANES IV 1999–2000 (*P*0.043),
  - The age-adjusted prevalences were 24.1 and 27.0% (*P* 0.088), respectively.
- The age-adjusted prevalence **increased by 23.5% among women** (*P* 0.021) and 2.2% among men (*P* 0.831).
- Increases in high blood pressure, waist circumference, and hypertriglyceridemia accounted for much of the increase in the prevalence of the metabolic syndrome, **particularly among women**.

Ford ES et al. Diabetes Care 2004;2444-2449

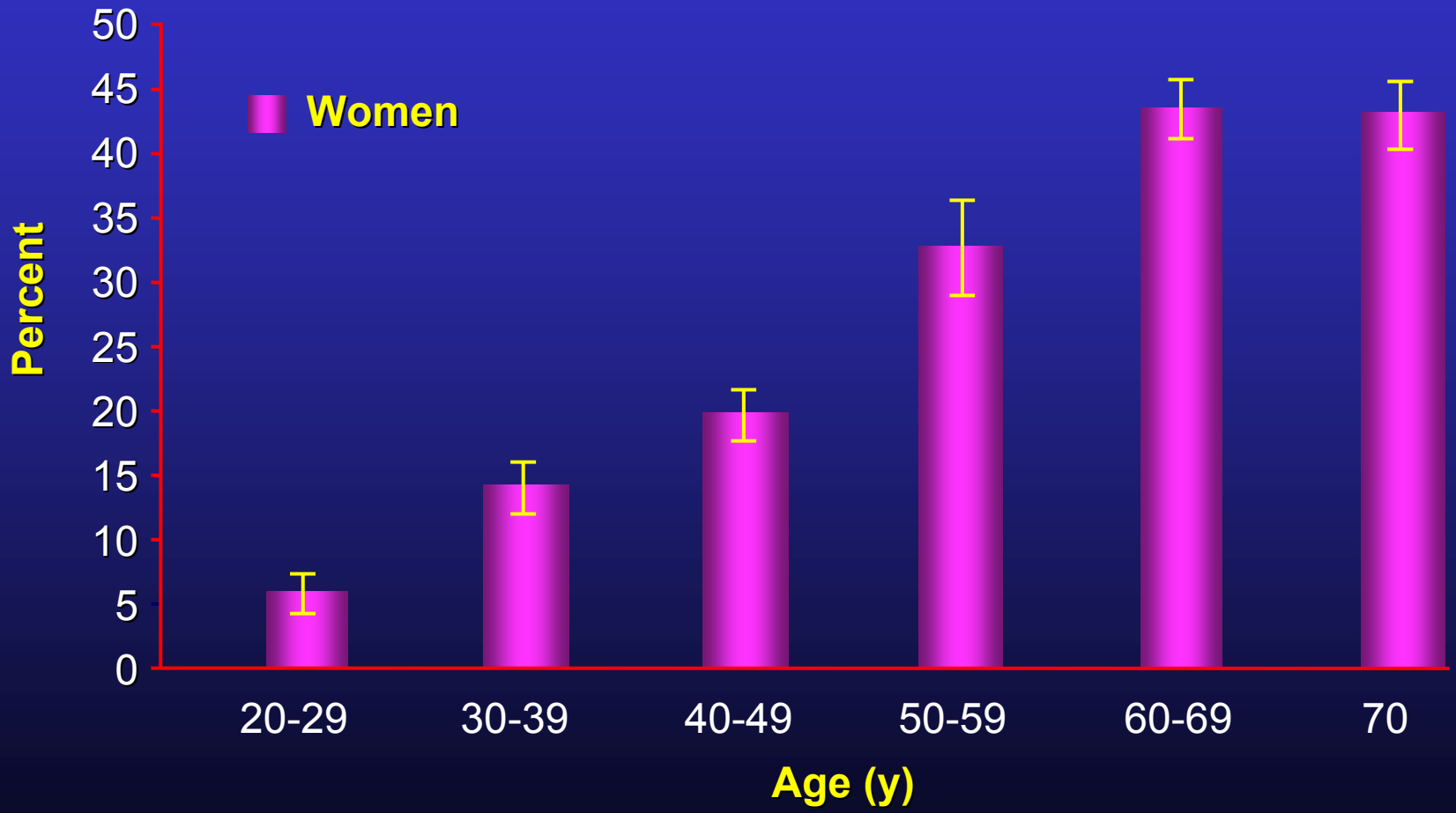
National Health And Nutrition Examination Survey II (NHANES) 1976-1980

13.3 ± 3.8 Year Follow Up Study: Impact of Metabolic Syndrome

- In those with Metabolic Syndrome, **40%** are at intermediate risk of CHD (10% to 20% 10-year risk)
- **20%** of men are at higher risk.
- Moreover, **40%** of persons with Metabolic Syndrome either are at high risk or have significant coronary calcium (75th percentile for age and sex)
- In these individuals, more aggressive risk factor management may be warranted.

Malik S. et al Circulation 2004;110:1234-1250

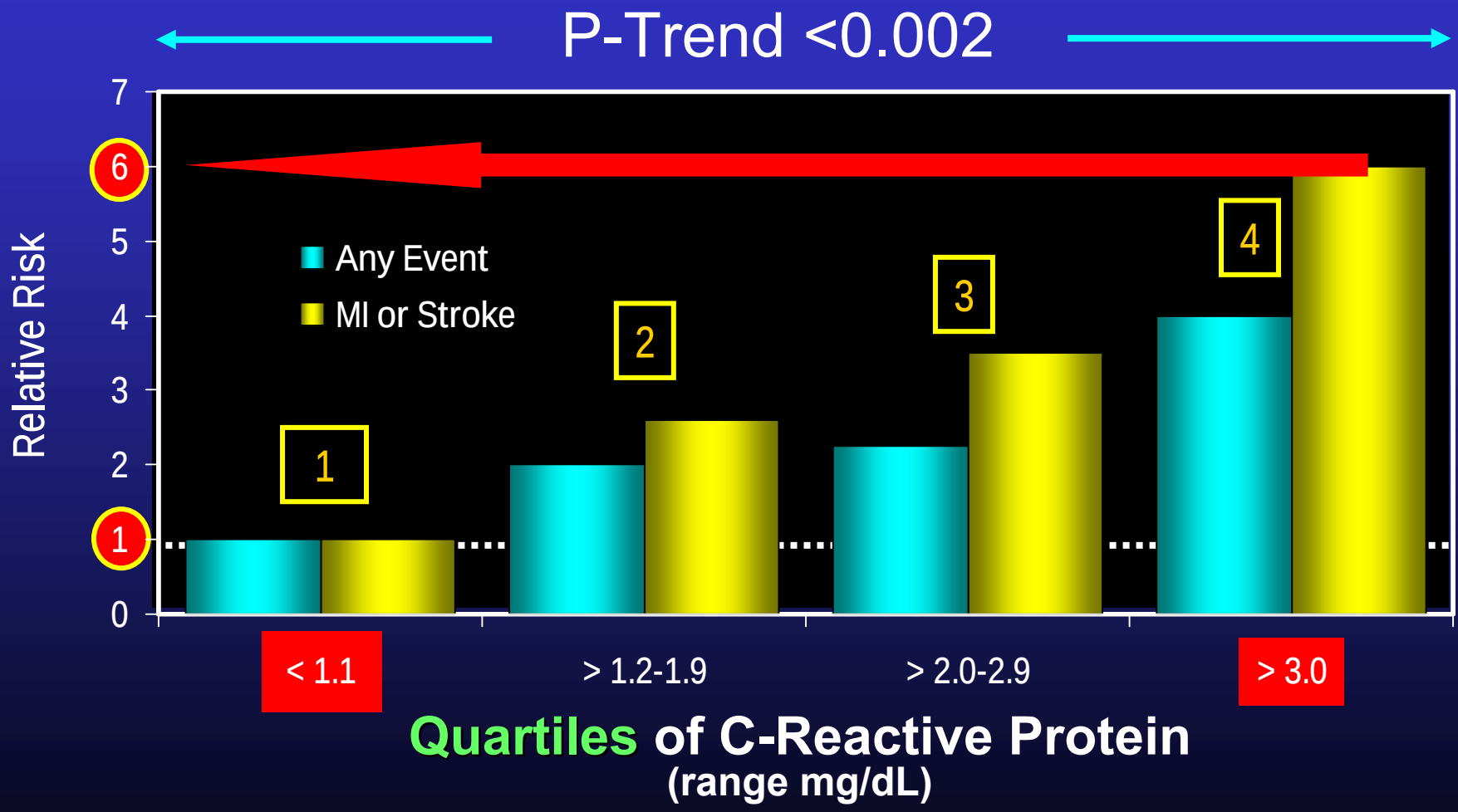
NHANES III: Age-Specific Prevalence of the Metabolic Syndrome



Data are presented as percentage (SE).

Ford ES, et al. *JAMA*. 2002;287:356-359.

CRP & Risk of Cardiovascular Events Among Apparently Healthy PM Women -The Women's Health Study-



Adapted from Ridker PM. *Circulation.* 1998;98:731-33.

AHA Guidelines for CVD Prevention in Women

Clinical Recommendations
Major Risk Factor Interventions

- Lipids: Pharmacotherapy - High risk
  - Initiate LDL-C lowering therapy (preferably a statin) simultaneously with lifestyle therapy in women with an LDL-C ≥ 100 mg/dL
  - Initiate statin therapy in **high risk** women with an LDL-C < 100 mg/dL unless contraindicated

Mosca, L. et al. Circulation 2004;109:672-693

AHA Guidelines for CVD Prevention in Women

Clinical Recommendations
Major Risk Factor Interventions

- Lipids: Pharmacotherapy - High risk
  - Initiate **niacin or fibrate** therapy when HDL-C is low or non HDL-C elevated
  - Dietary supplement niacin must not be used as a substitute for prescription niacin and OTC niacin should only be used if approved & monitored by a physician

Mosca, L. et al. Circulation 2004;109:672-693

AHA Guidelines for Women and CHD

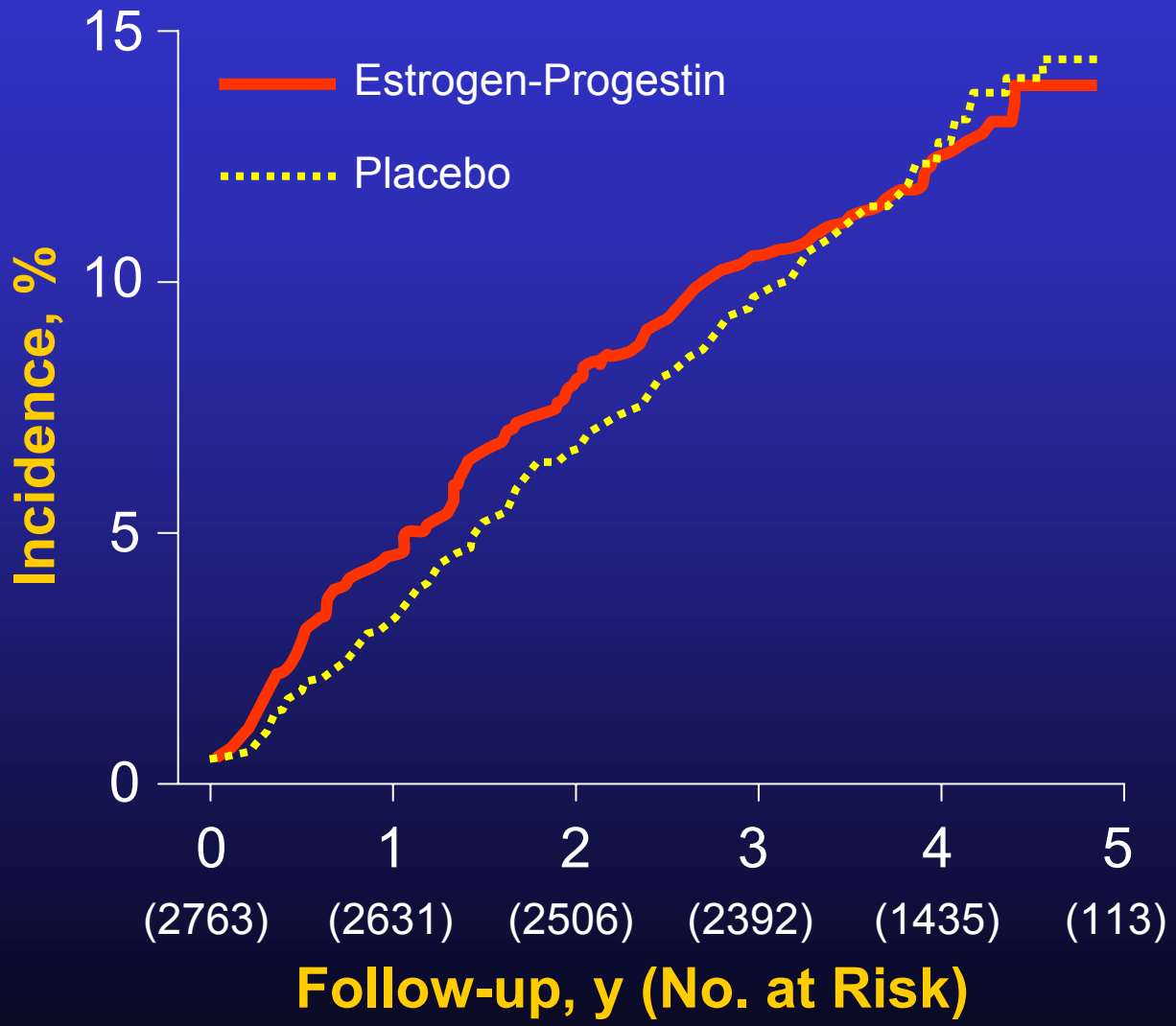
Clinical Recommendations

Class III Interventions

- Hormone Therapy (Class III, Level A)
  - Combined estrogen plus progestogen therapy **should not be initiated** to prevent CVD in postmenopausal women
  - Combined E+P should not be continued to prevent CVD in postmenopausal women
  - Other forms of menopausal hormone therapy (e.g. unopposed estrogen) should not be initiated or continued to prevent CVD pending results from ongoing trials (Class III Level C)

Mosca, L. et al. Circulation 2004;109:672-693

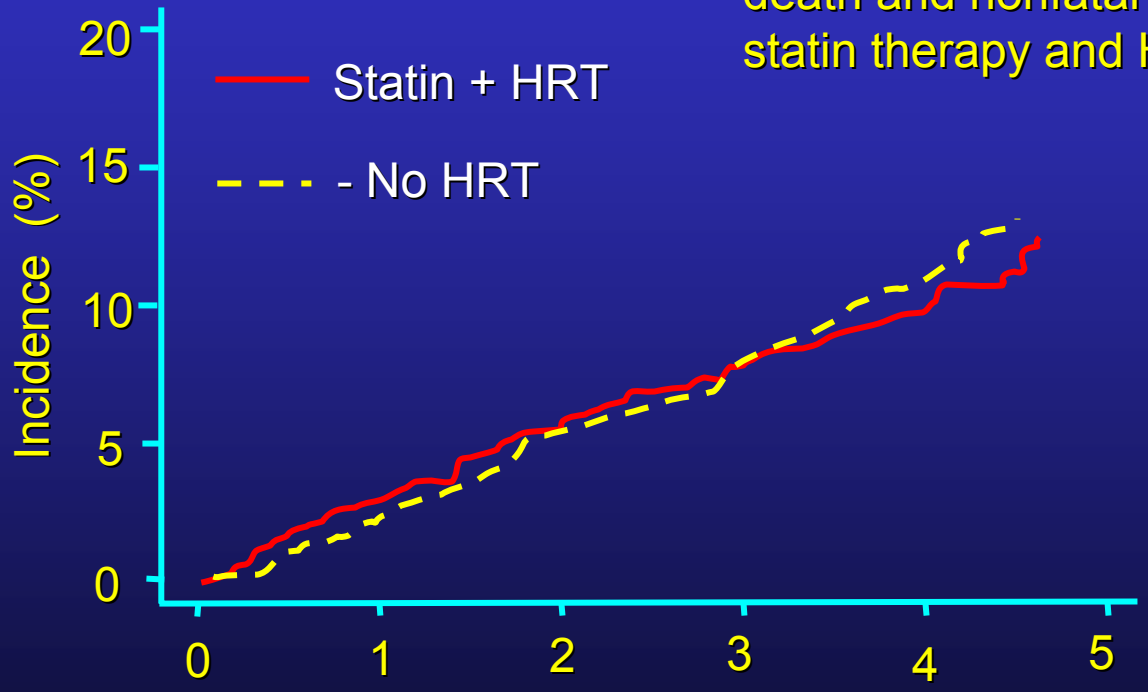
Heart and Estrogen/Progestin Replacement Study (HERS): Incidence of Nonfatal MI and CHD Death



Hulley, et el. *JAMA*. 1998; 280, 605-613.

Heart and Estrogen/Progestin Replacement Study (HERS): Statin Use

Cumulative incidence of primary events (CHD death and nonfatal MI) according to baseline statin therapy and HRT treatment assignment



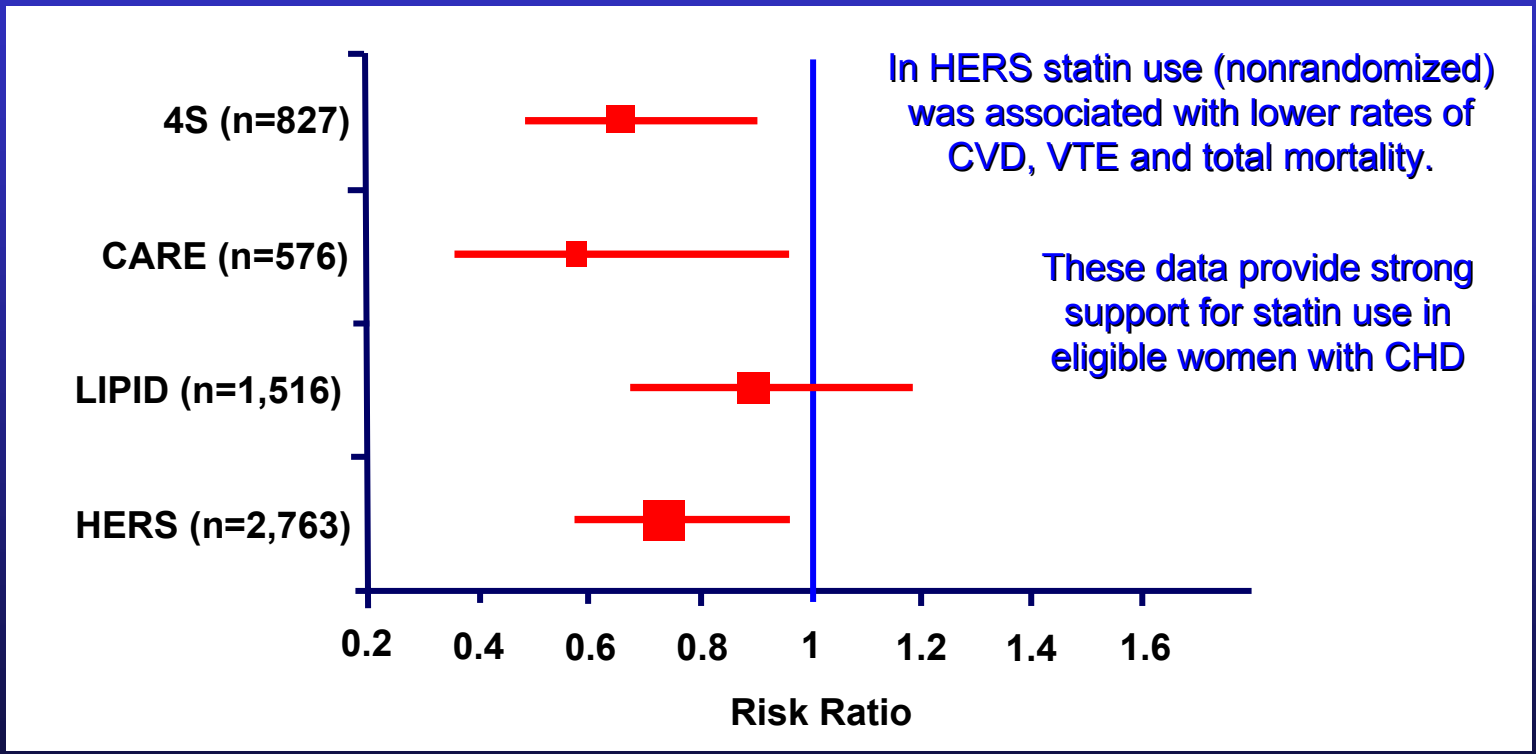
HRT use resulted in a significant increase in early risk for primary events in women not on statins but not in statin users.

Postrandomization statin use showed no effect of HRT on risk for the primary outcome

0.625 mg conjugated equine estrogens plus 2.5 mg medroxyprogesterone acetate.

Herrington, D. et al. Circulation 2002;105:2962-67

Statin Use in Women in Secondary Prevention Trials and in HERS

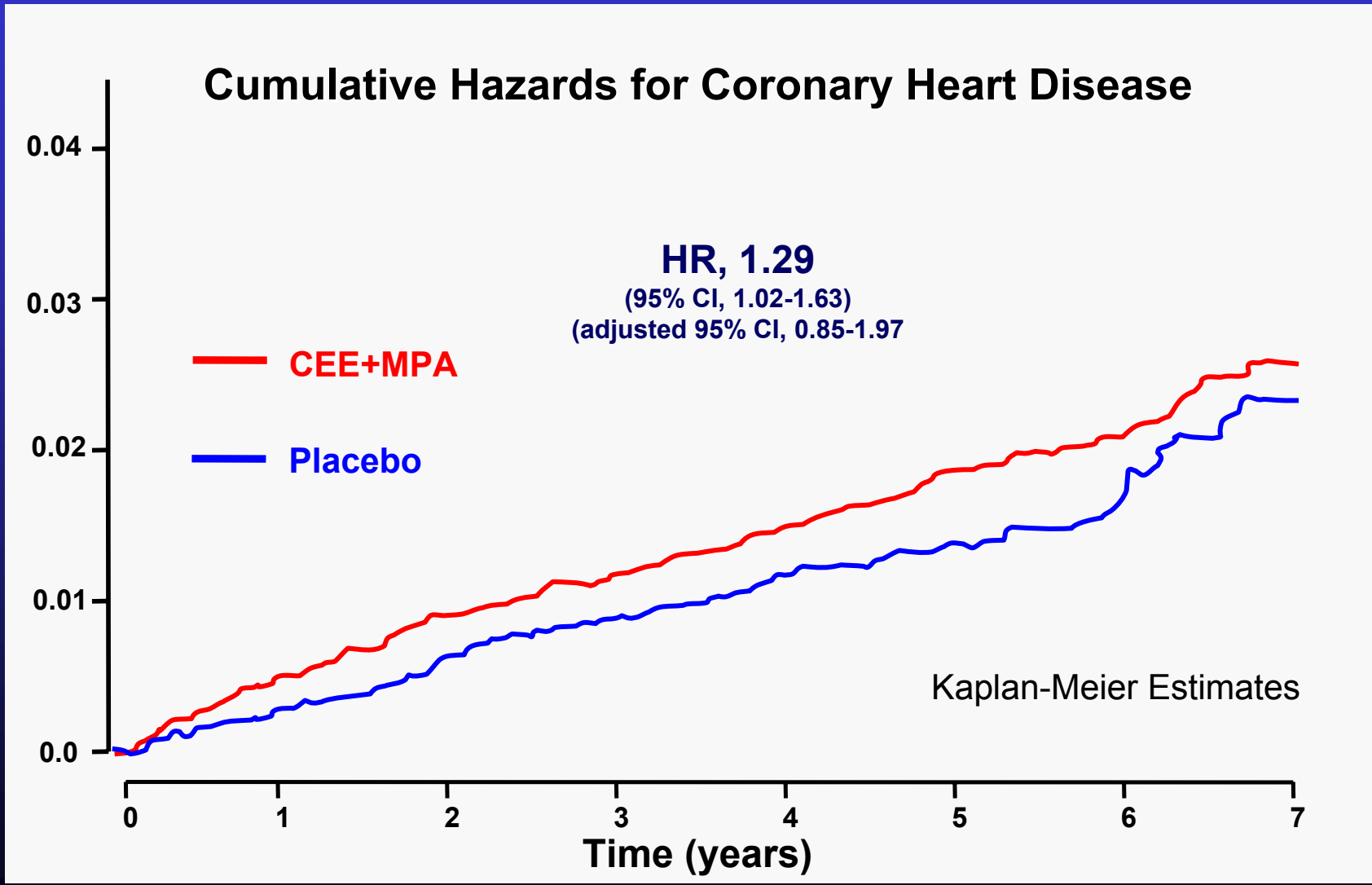


Sizes of squares are proportional to numbers of women in each study

Herrington, D. et al. Circulation 2002;105:2962-67

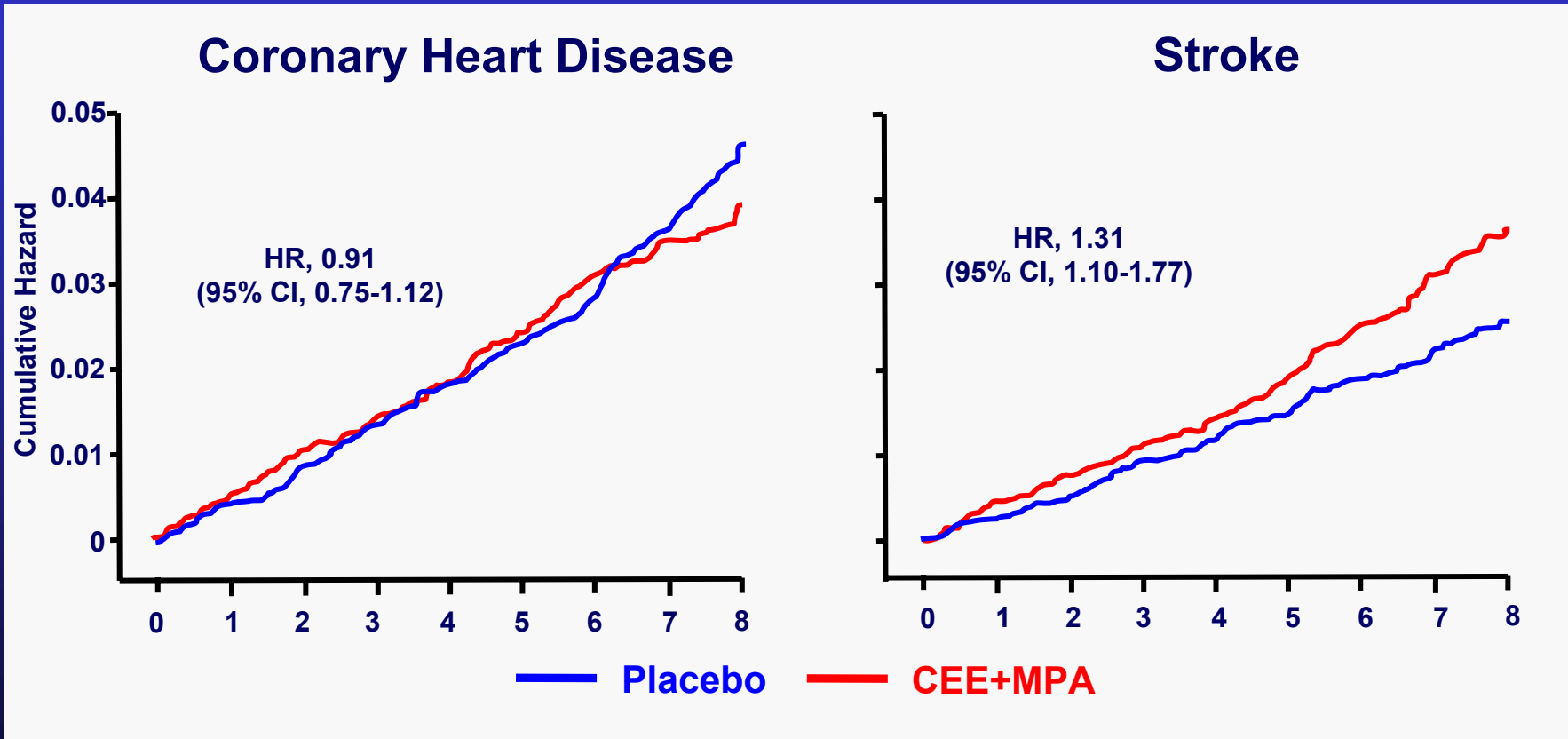
Women's Health Initiative (WHI)

CEE and MPA and CHD



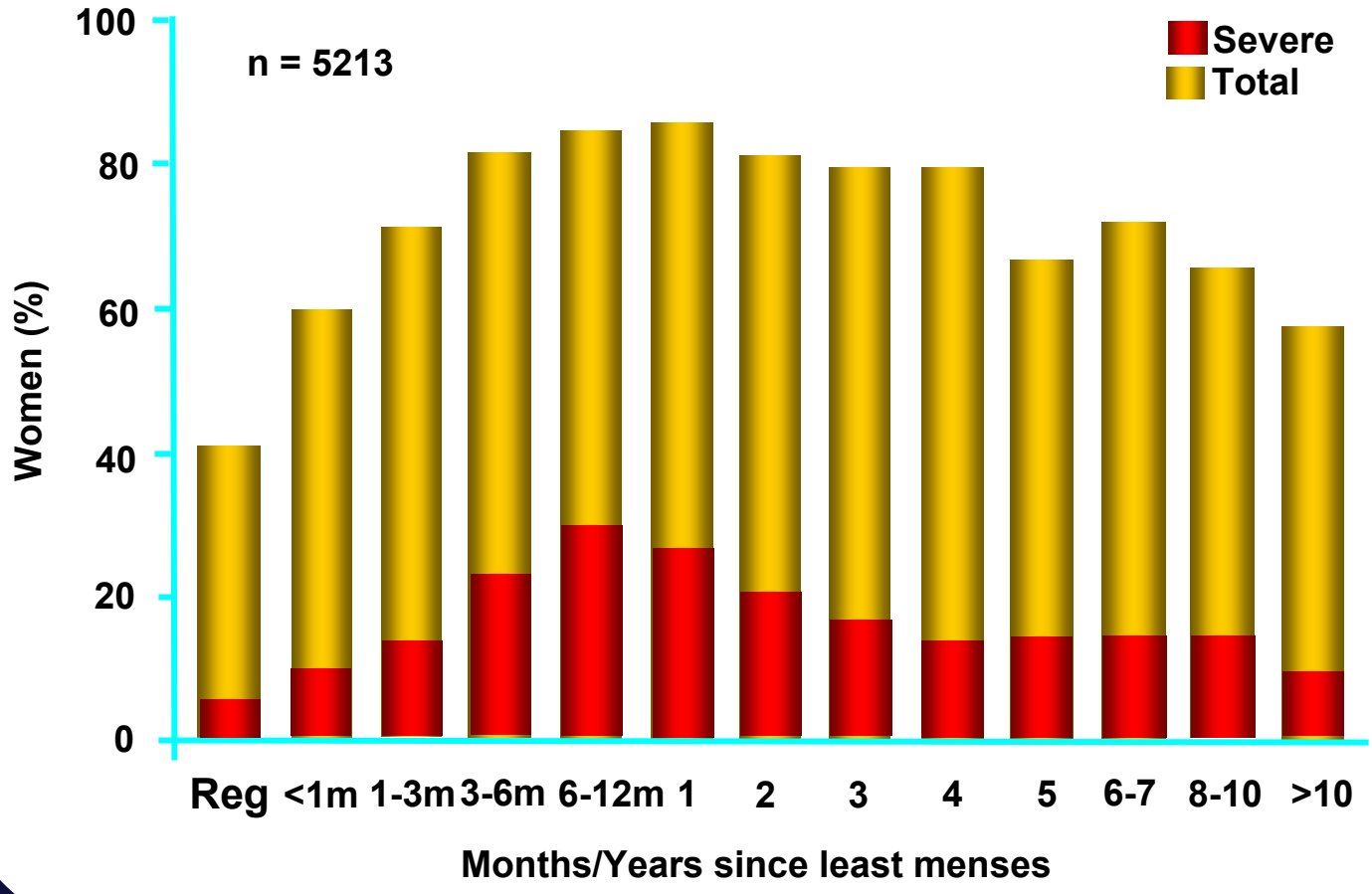
Writing Group for the WHI JAMA 2002;288:321-333

Women's Health Initiative (WHI)
Conjugated Equine Estrogens and CAD



WHI Steering Committee JAMA. 2004;291:1701-1712

Menopausal Symptoms and Age



Oldenhave et al. Am J Obstet & Gynecol193;168:772-780

North American Menopause Society Recommendations for Estrogen and Progestogen Use in Peri- and Postmenopausal Women

2004 Position Statement: Quality of Life Issues

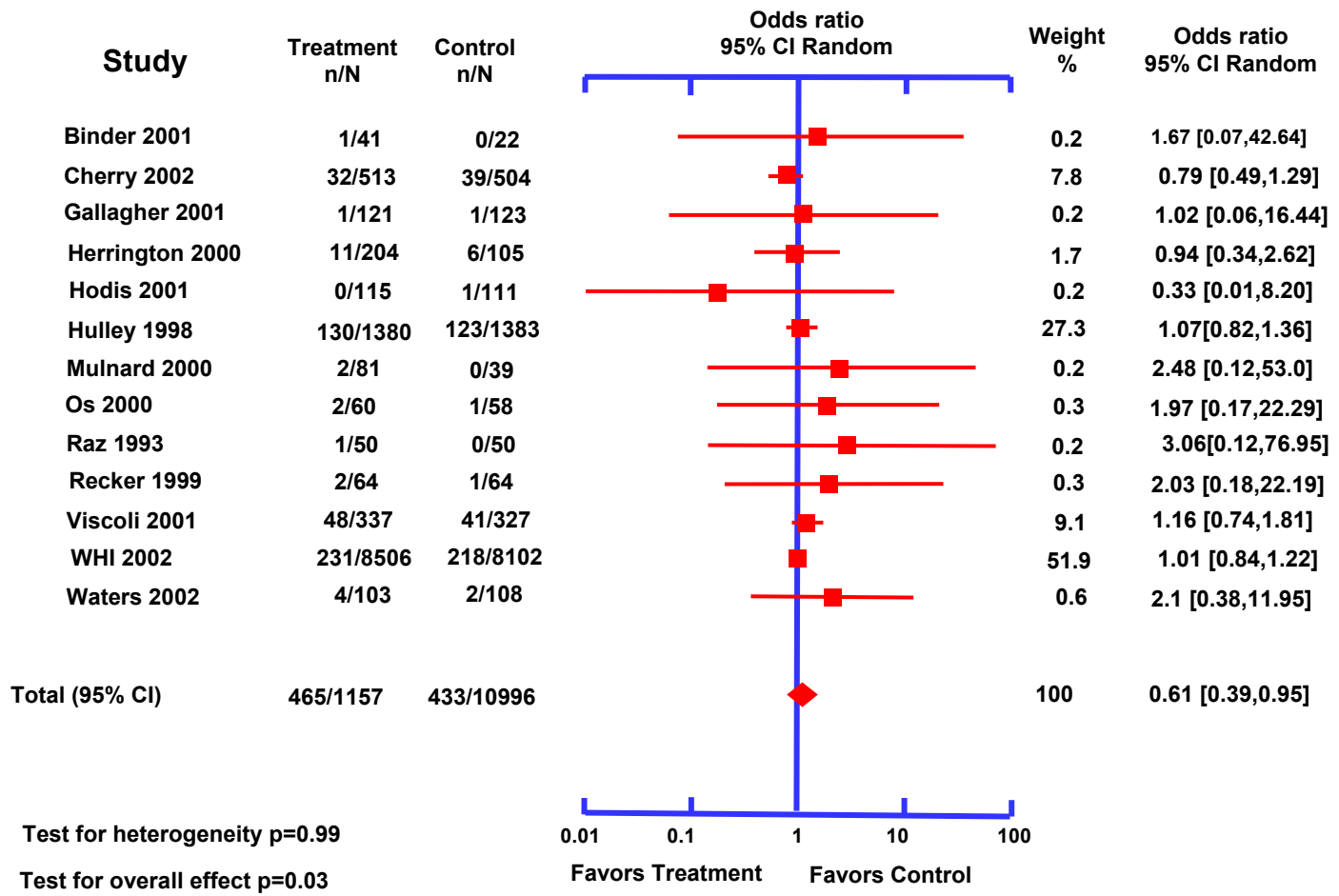
- NAMS considers treatment for moderate to severe menopause-related hot flashes to be a primary indication for systemic ET and EPT.
- Use of ET and EPT should be limited to the shortest duration consistent with treatment goals, benefits, and risks for the individual woman.

Menopause: The Journal of The North American Menopause Society

2004 Vol. 11, No. 1, pp. 11-33

Mortality Associated with Hormone Therapy

Mean age > 60 years **HT and Total Mortality**

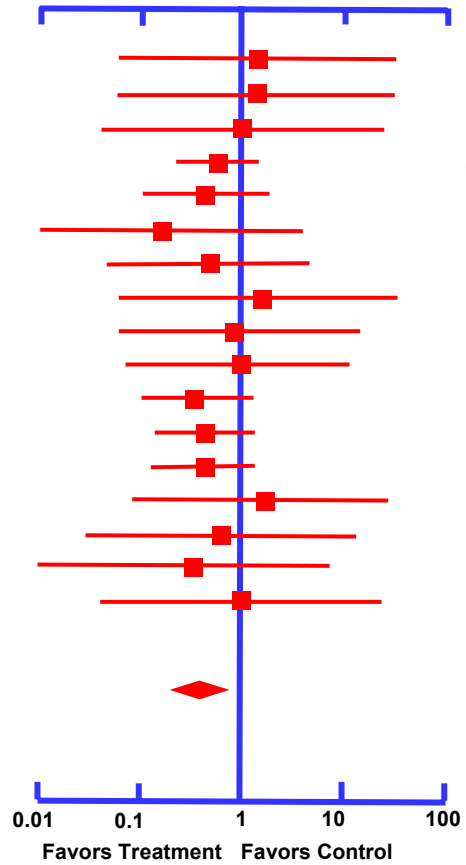


Salpeter S et al. Eur Heart JCIM 2004;19:791-804

Mortality Associated with Hormone Therapy

Mean age < 60 years — **HT and Total Mortality**

Study	Treatment n/N	Control /N	Weight %	Odds ratio 95% CI Random
Angerer 2000	1/215	0/106	1.9	1.49 [0.06,36.88]
Arrenbrecht 2002	1/108	0/53	1.9	1.49 [0.06,37.27]
Giske 2002	1/123	0/43	1.9	1.07 [0.04,25.64]
Guidozzi 1999	32/62	41/68	41.0	0.70 [0.35,1.41]
Hall 1994	3/27	3/16	6.7	0.38 [0.07,2.14]
Hall 1998	0/40	1/20	1.9	0.16[0.01,4.12]
Komulainen 1999	1/115	2/115	3.4	0.50 [0.04,5.54]
Kyllonen 1998	1/52	0/26	1.9	1.54 [0.06,39.21]
Lindsay 1976	1/63	1/57	2.5	0.90 [0.06,14.78]
MacDonald 1994	1/22	1/22	2.5	1.00[0.06,17.07]
Mijatovic 1998	0/13	1/13	1.8	0.31 [0.01,8.30]
Moosekilde 2000	4/502	9/504	14.2	0.44 [0.14,1.44]
Nachtigall 1979	3/84	7/84	10.3	0.41 [0.10,1.63]
PEPI 1995	3/701	0/174	2.3	1.75 [0.09,3401]
Perez-Jaraiz 1996	0/26	1/52	1.9	0.65 [0.03,16.45]
Raven 1999	0/110	0/109	1.9	0.33 [0.01,8.12]
Watts 2000	1/303	0/103	1.9	1.03 [0.04,25.39]
Total (95% CI)	53/2576	68/1565	100	0.61 [0.39,0.95]

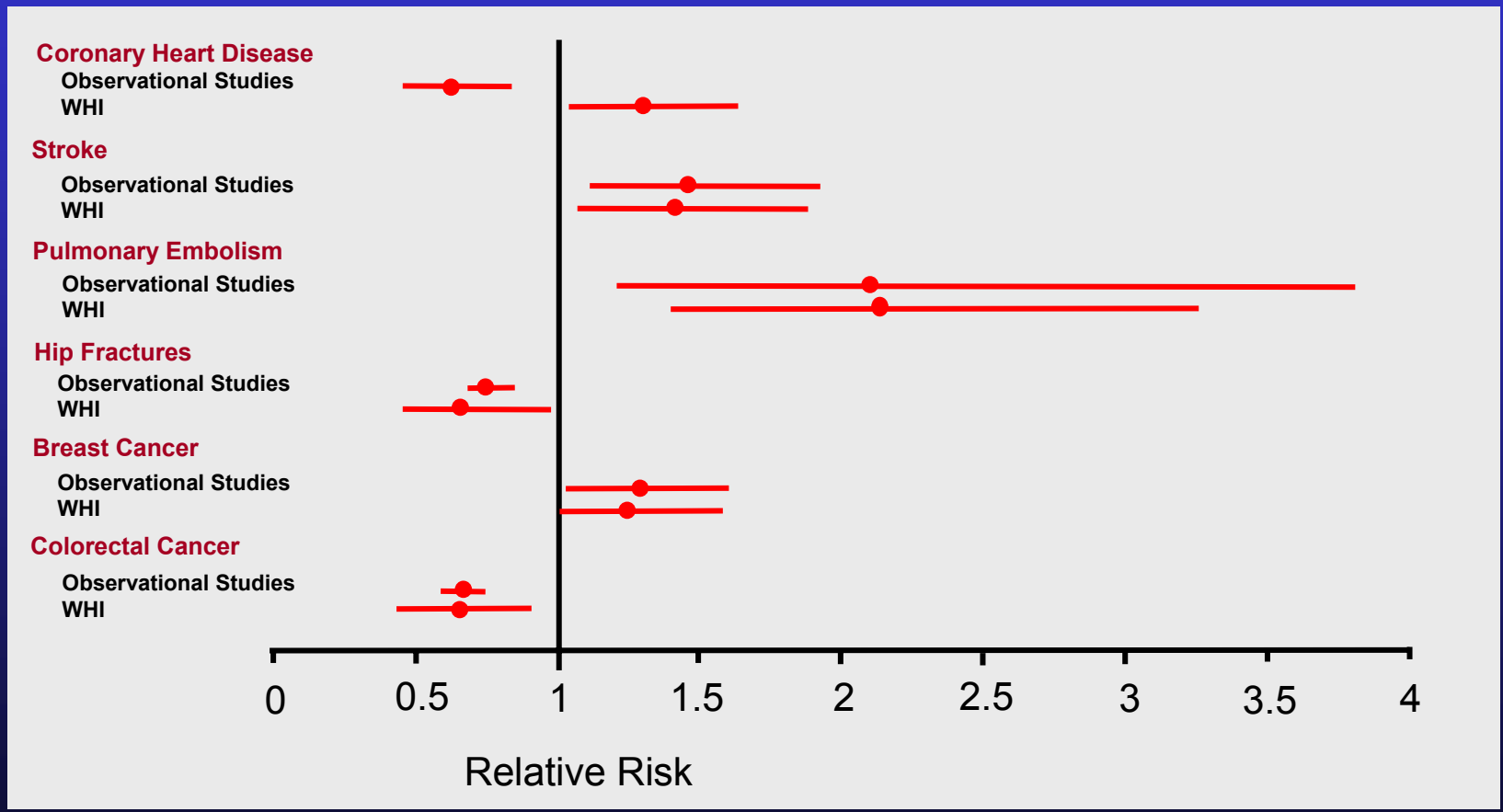


Test for heterogeneity p=0.99

Test for overall effect p=0.03

Salpeter S et al. Eur Heart JCIM 2004;19:791-804

Relationship Between HT & Clinical Endpoints in Observational Studies & WHI



Michels KB, Manson JE Circulation 2003;107:1830-1833

Relationship Between HT & Clinical Endpoints in Observational Studies & WHI

Although women in the observational studies generally initiated HT use at onset of menopause, most of the participants in the WHI started HT many years after menopause. In fact, 67% of women in WHI were age 60 years or older. It is conceivable that many of these older women already had subclinical CHD.

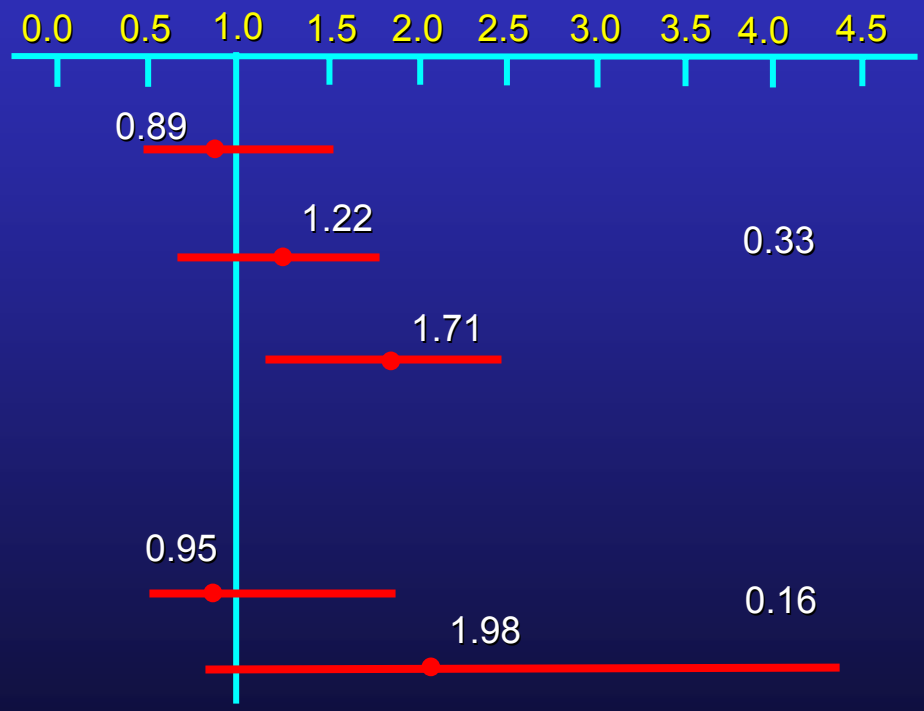
The prothrombotic effect of estrogens may manifest itself predominantly among women who initiate HT well into their menopause, whereas women who start HT early after the onset of menopause may experience cardiovascular benefit from estrogens.

This possibility derives support from nonhuman primate data.

Michels KB, Manson JE Circulation 2003;107:1830-1833

HRT and Risk of CVD: Implications of The Women's Health Initiative (WHI)

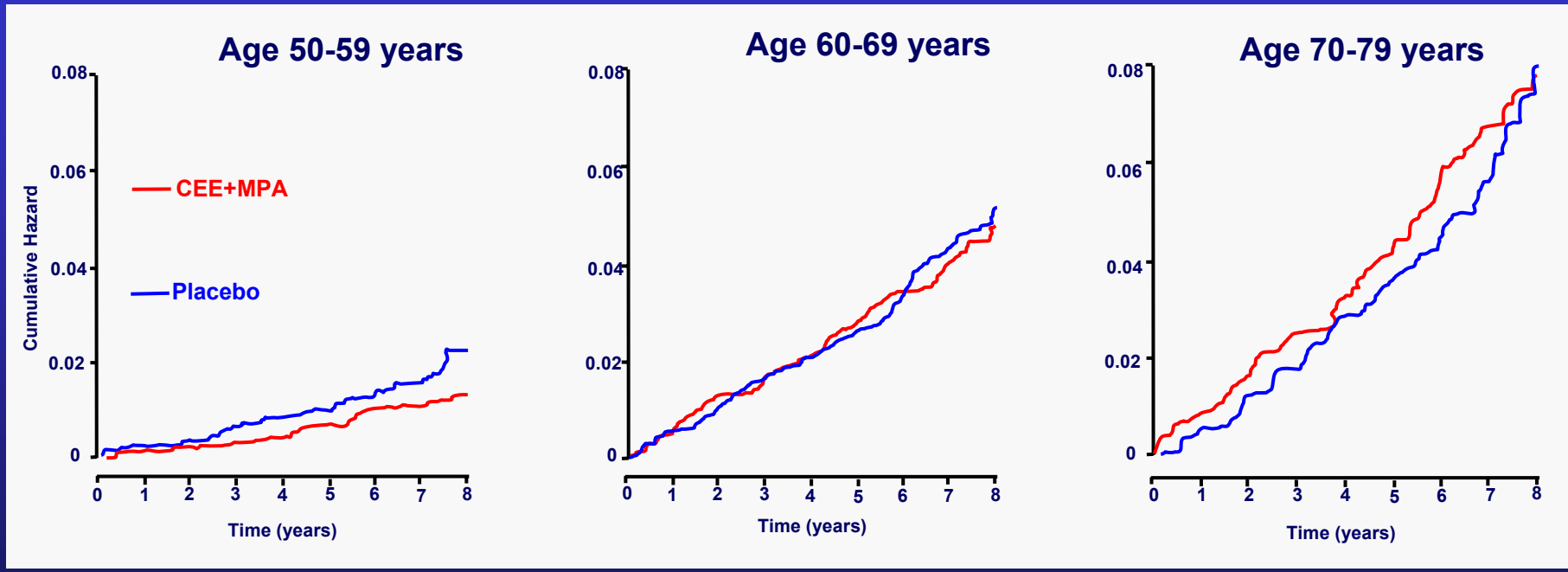
Subgroup	EPT	Placebo
Years since menopause		
< 10	31 (0.19)	34 (0.22)
10 -19	63 (0.38)	51 (0.32)
≥ 20	74 (0.75)	44 (0.46)
Hot flashes in women 50-59 yr of age		
Yes	31 (0.19)	34 (0.22)
No	31 (0.19)	34 (0.22)



No. of cases of CHD (annualized percentage)

Manson JE et al. NEJM 2003;349:523-534

Women's Health Initiative (WHI)
Conjugated Equine Estrogens and CAD



Hsia J et al. Arch Intern Med. 2006;166:357-365

CVD Severity in Women Time Since Menopause

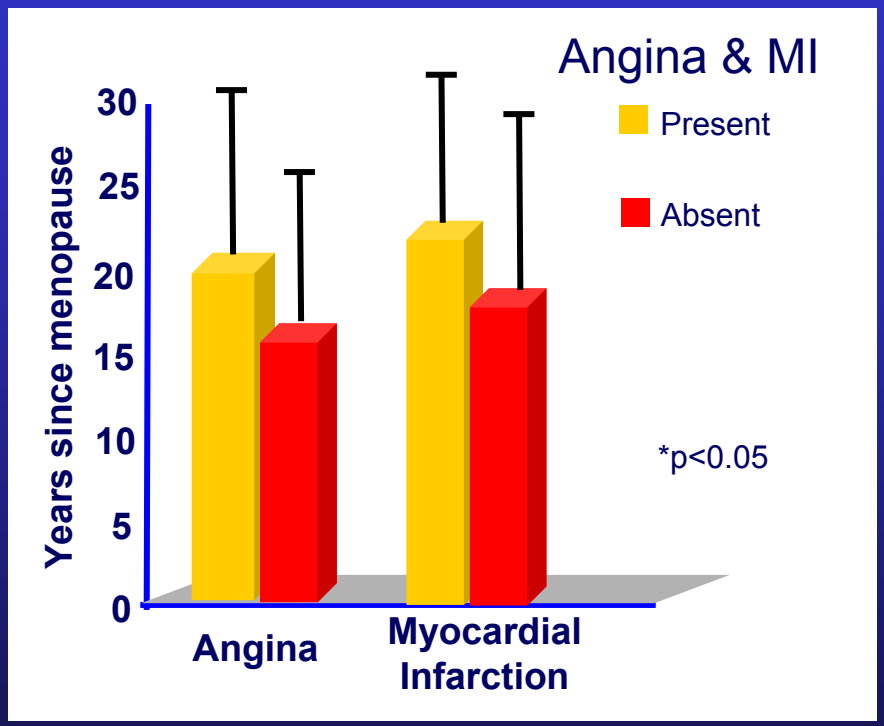
The severity of CAD in women referred for coronary angiography is correlated with measures of exposure to endogenous estrogen.

Both the time since menopause and the age at menopause are aggravating factors for MI, independently of age.

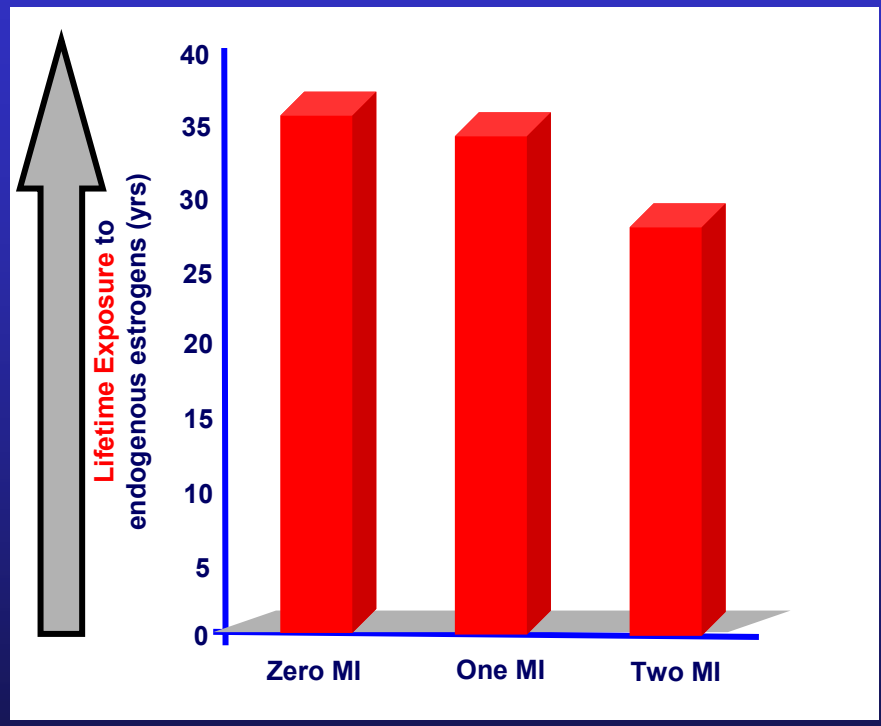
There is an independent protective effect of the duration of estrogen exposure on the number of MIs; this has not been reported before and supports the protective role of the length of exposure to endogenous estrogen, especially for the occurrence of MI in this selected group of women.

Katerina Saltiki et al. Maturitas 2006;55:51–57

CVD Severity in Women
Time Since Menopause



Women undergoing angiography: mean time since menopause in those reporting angina or MI vs those without

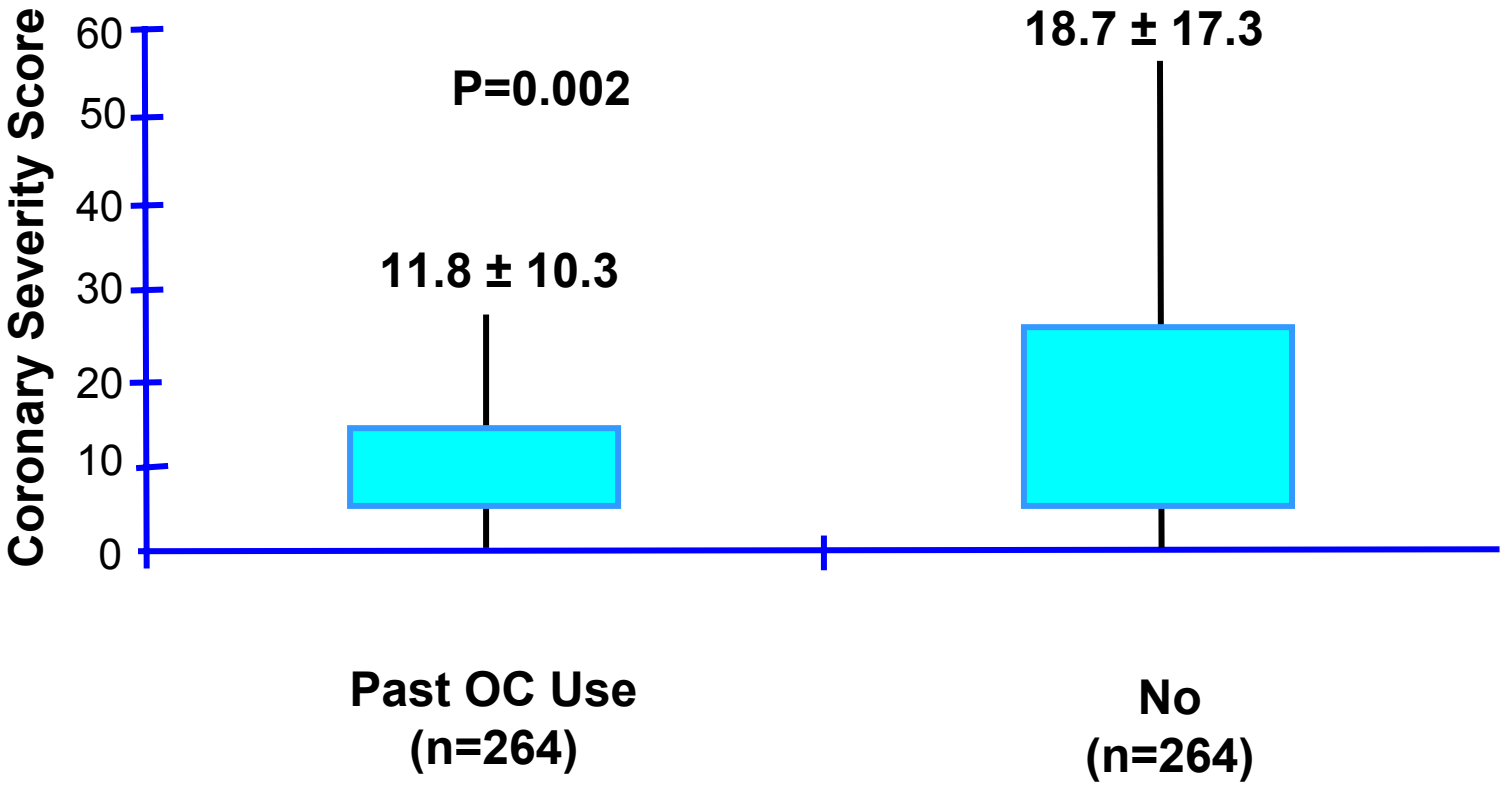


# of MIs with relation to life time exposure to endogenous estrogens (age at menopause – age at menarche) in PM women undergoing coronary angiography

Katerina Saltiki et al. Maturitas 2006;55:51–57

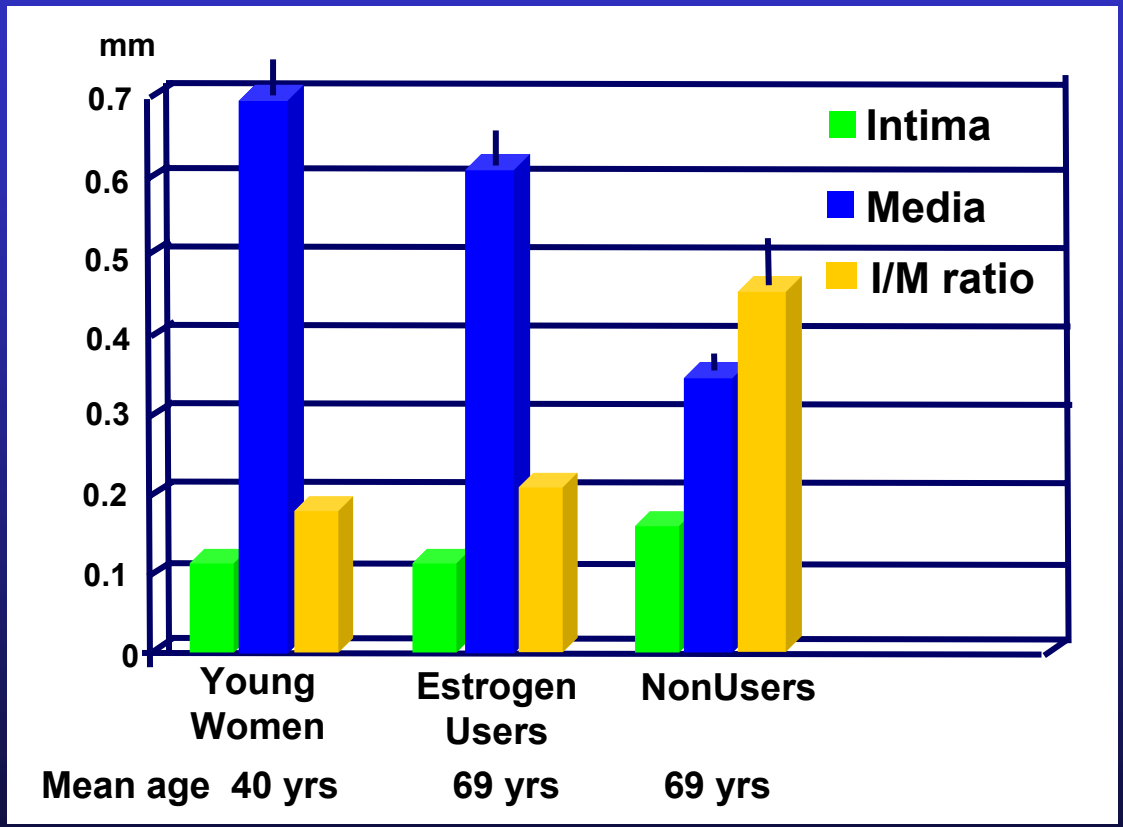
Coronary Disease & Prior OC Use

Coronary artery severity score assessed by quantitative coronary angiography stratified by prior OC use



Bairey Merz N. et al. Fertil & Ster 2006;85:1425-31

Carotid IMT and Menopausal ET



E2 users had hysterectomies

The thickness of carotid and femoral artery intima and media was assessed, using noninvasive high-frequency ultrasound (25 MHz).

Long-term estrogen (20 mg E2 implants) users (mean treatment duration 20 years) had a significantly thinner mean carotid intima layer (−25%; $P = 0.0002$), a thicker media layer (+74%; $P = 0.0002$) and a substantially lower intima/media thickness ratio (−54%; $P < 0.0001$) than 17 age-matched nonusers, with values closer to those in 20 premenopausal women.

Similar but less pronounced differences between the postmenopausal groups were found for the femoral artery.

Tord Naessen, Kenny Rodriguez-Macias Atherosclerosis 189 (2006) 387–392

Carotid IMT and Menopausal ET

Conclusions

The findings presented here suggest that long-term estrogen therapy may prevent/delay the known age-related thickening of the carotid artery intima and the thinning of the media.

The preservation of a thin intima layer and a preserved *I/M* ratio, at values similar to those in premenopausal women, could be partially responsible for the *observational* beneficial effect of long-term postmenopausal hormone therapy on the risk of cardiovascular disease, when therapy is initiated at or soon after menopause.

Tord Naessen, Kenny Rodriguez-Macias Atherosclerosis 189 (2006) 387–392

Estrogen in the Prevention of Atherosclerosis Trial (EPAT)

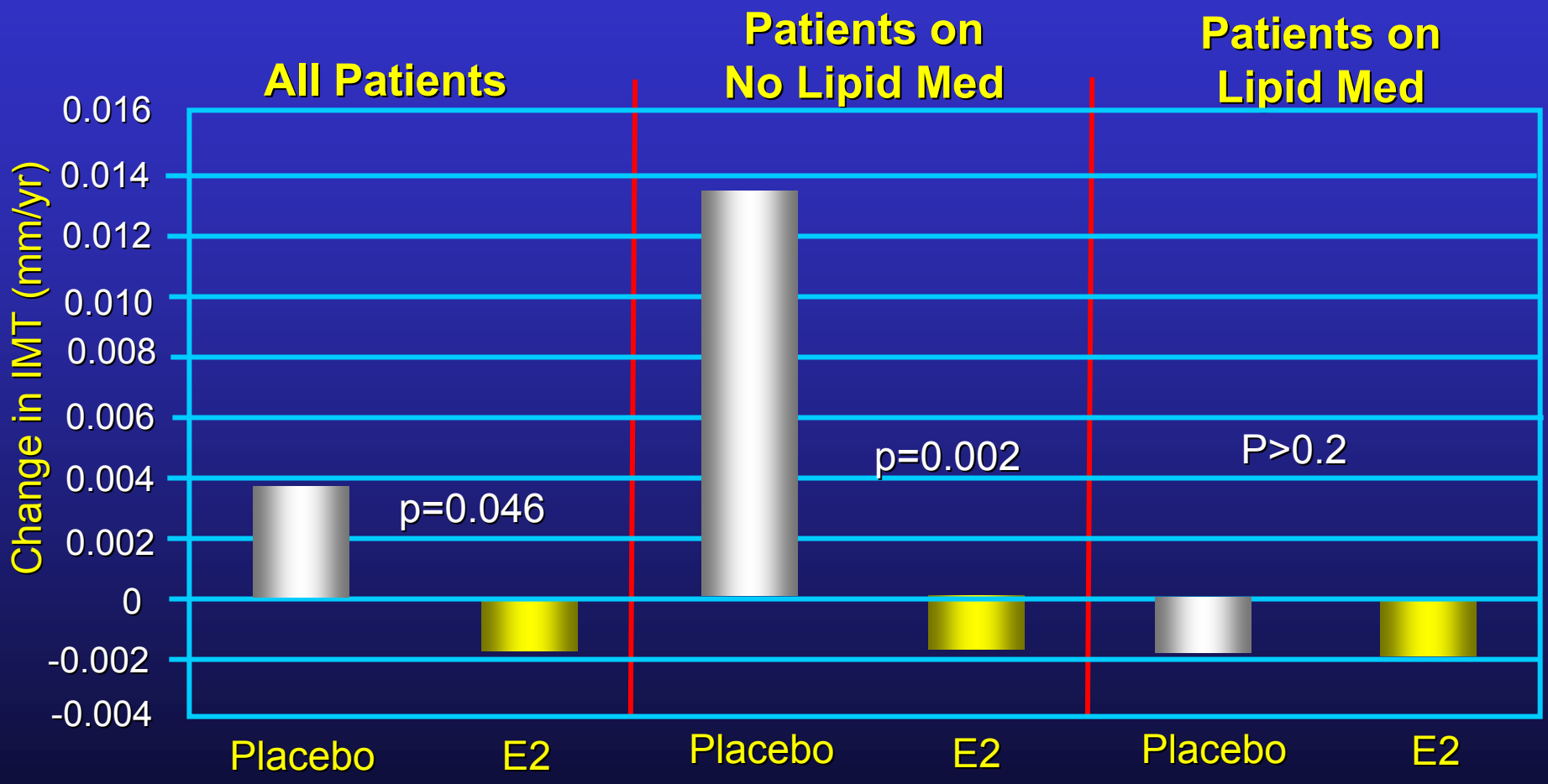
- 199 healthy PM women aged 45-81 (estradiol <20 pg/mL) with LDL-C > 130 mg/dL
- Carotid wall thickness measured.
  - Randomized to **ERT** or placebo.
    - Received uterine ultrasounds and biopsies

(1 mg micronized 17 β estradiol)

- If LDL-C >160 mg/dl statin added (n=122)
  - 61% of cohort

Hodis H et al. Ann Int Med 135:939-953

Estrogen in the Prevention of Atherosclerosis Trial (EPAT)



Hodis H et al. Circulation 2000;102:2835

Estrogen in the Prevention of Atherosclerosis Trial (EPAT)

Estradiol alone may reduce progression of atherosclerosis, but estradiol in combination with lipid lowering medication provides no benefit beyond that of lipid treatment.

Estradiol is thus the only estrogen that has been successful in a RCT looking at plaque.

EPAT was not a clinical outcome trial

Hodis H et al. Ann Int Med 2001;135:939-953

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

In older postmenopausal women with established coronary-artery atherosclerosis, 17β-estradiol either alone or with sequentially administered medroxyprogesterone acetate had no significant effect on the progression of atherosclerosis.

The rate of change in intima-media thickness was not significantly reduced in the estradiol group compared to placebo

Hodis H et al. NEJM 2003;349:535-545

Explaining the Very Different Arterial Results in EPAT vs WELL-HART

The only differences of the EPAT and WELL-HART studies are the participants characteristics

EPAT: Healthy women with no baseline carotid intimal thickening and 5 years less duration of menopause to randomization: 40% not on lipid Rx

WELL-HART: Women with established CAD (>30% stenosis) and 5 years longer duration of menopause to randomization. 100% were on lipid Rx

Hodis H et al. NEJM 2003;349:535-545

Koh KK & Sakuma I. Atheroscler Thromb Vasc Bio 2004;24:1171-1179

Effect of Hormone Therapy on Saphenous Vein Grafts & Native Coronary Arteries Women after CABG

- 83 women had coronary angiography and 42 also had IVUS within 6 months of CABG
  - 40 Randomized to HT (1 mg estradiol ± MPA 2.5 mg) and 43 to placebo
  - 27 on HT and 18 on placebo had repeat angiogram at 432 months (remaining did not as study stopped after WHI)

Ouyang P, Tardif JC, Herrington DM et al. Atherosclerosis 189 (2006) 375–386

Effect of Hormone Therapy on Saphenous Vein Grafts & Native Coronary Arteries Women after CABG

The study showed a beneficial effect of HT on SVG resulting in attenuation of atherosclerosis progression compared with accelerated disease in the native coronary arteries.

This finding would support the hypothesis that HT may provide benefit in the absence of underlying atherosclerosis.

This study does indicate that not all is known about the effect of estrogen on vascular tissue and atherosclerosis.

Ouyang P, Tardif JC, Herrington DM et al. Atherosclerosis 189 (2006) 375–386

Failure of HRT in Clinical Trials "Healthy Endothelium Hypothesis"

The favorable vascular effects of estrogen on atherosclerosis, inflammation, hemostasis, and coronary flow reserve are dependent on the integrity of the endothelium and estrogen receptor populations in endothelial cells and vascular smooth muscle cells.

These conditions were probably not met by most women in these trials because of their advanced age, multiple risk factors, and coronary atherosclerosis.

Optimization of estrogen's cardioprotective properties may depend on maintenance of a healthy endothelium.

Koh KK & Sakuma I. Atheroscler Thromb Vasc Bio 2004;24:1-10

Cardiovascular Gender Differences

The biological explanations for gender differences in cardiovascular diseases (CVDs) are complex.

The current controversy that has arisen from the Women's Health Initiative (WHI) trials of the cardiovascular effects of hormone replacement therapy (HRT) on CVD is a case in point.

This controversy is in part due to an under-appreciation of the relationship between the timing of HRT initiation and differences in the underlying vascular biology that exist between perimenopausal and older women.

Resolving this controversy will require a more complete understanding of the molecular and cellular physiology of each of the sex steroid hormones and their receptors in the cardiovascular system and a greater focus on how the extent of underlying atherosclerosis affects the response to HRT.

Michael E. Mendelsohn and Richard H. Karas. Science 2005;308:1583-1587

North American Menopause Society Recommendations for Estrogen and Progestogen Use in Peri- and Postmenopausal Women

2004 Position Statement

- ET and EPT did not reduce CHD in the WHI study.
  - The role of ET/EPT in primary prevention of CHD remains unclear when considered for peri- and early postmenopausal women if started early and continued for a number of years, and needs further evaluation.
  - Until that evidence is forthcoming, no ET or EPT regimen should be used for primary or secondary prevention of CHD

North American Menopause Society Recommendations for Estrogen and Progestogen Use in Peri- and Postmenopausal Women

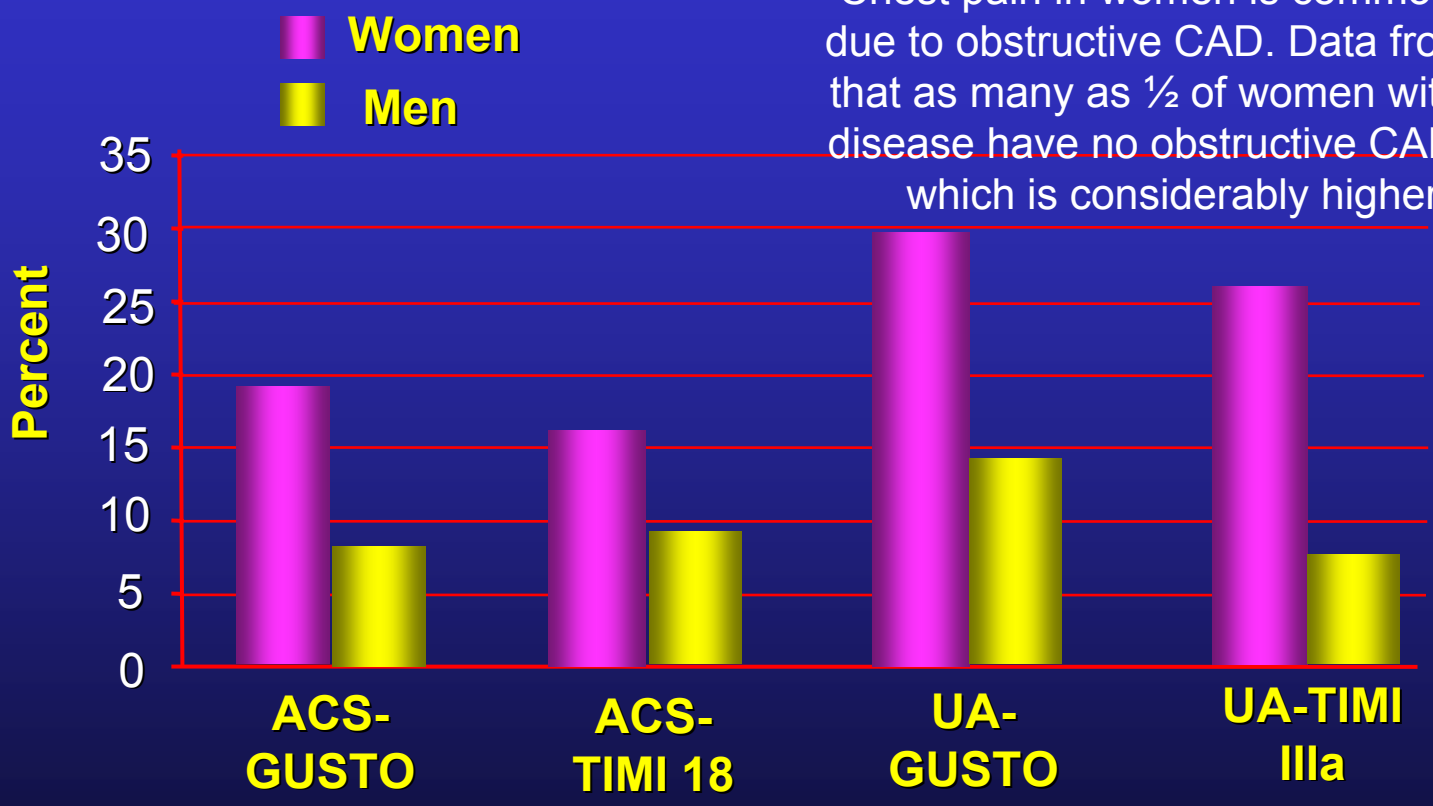
2004 Position Statement

Areas Where Panel Could Not Reach Consensus

- There is evidence that early harm within the first year of use may not pertain to healthy postmenopausal women using ET/EPT for menopausal symptom management

www.menopause.org

Prevalence of "Normal" and Nonobstructive Coronary Arteries in Women Compared with Men



Chest pain in women is common but not usually due to obstructive CAD. Data from WISE indicate that as many as ½ of women with ischemic heart disease have no obstructive CAD at angiography which is considerably higher than in men

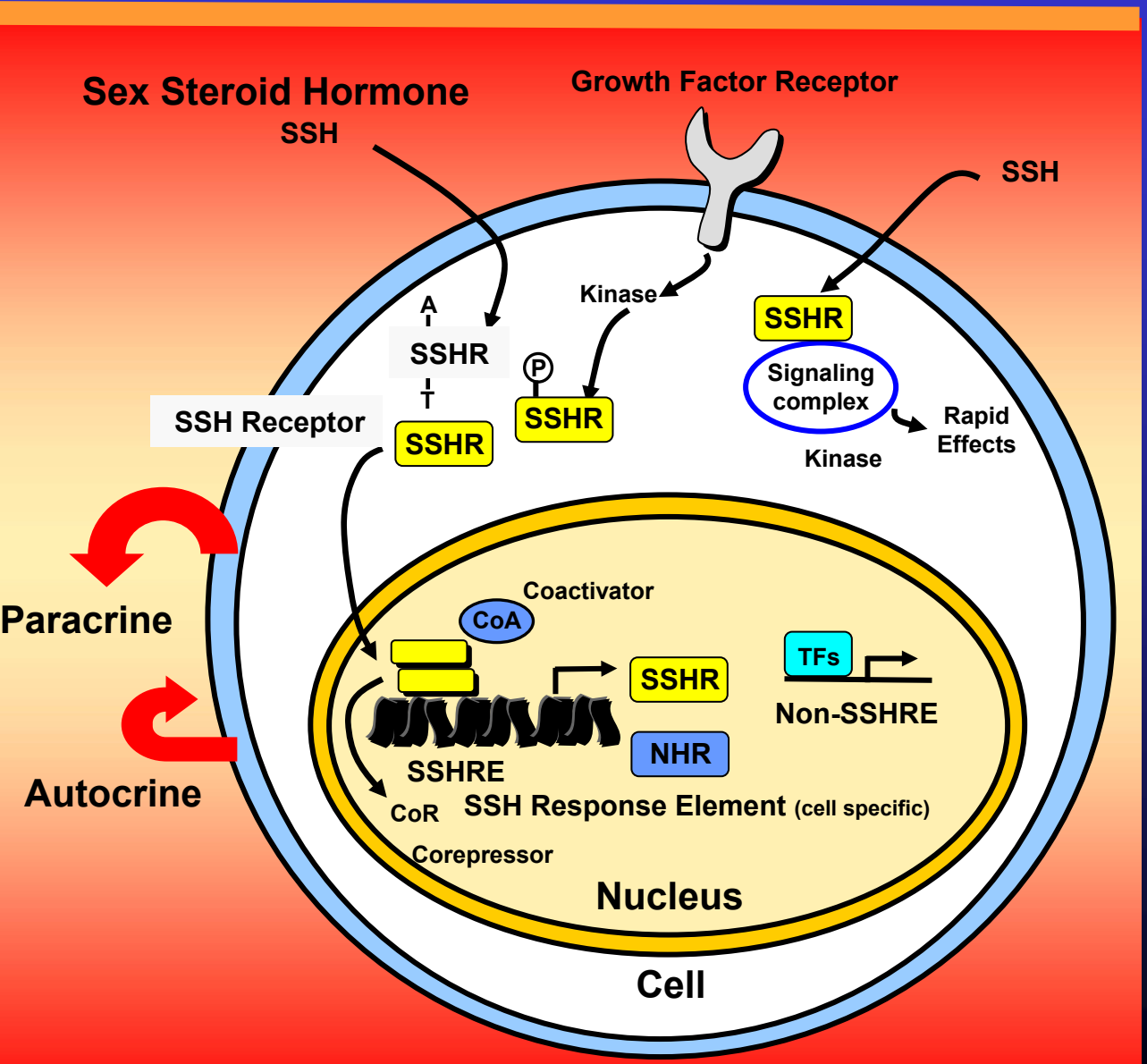
All $p < 0.001$

Endothelial dysfunction is detectable in about 1/3 of these women and is termed microvascular angina

Abrams J. Cardiosource Rev J 2006;15:30-34

The Sex Steroid Story

Sex Steroid Receptor Signaling

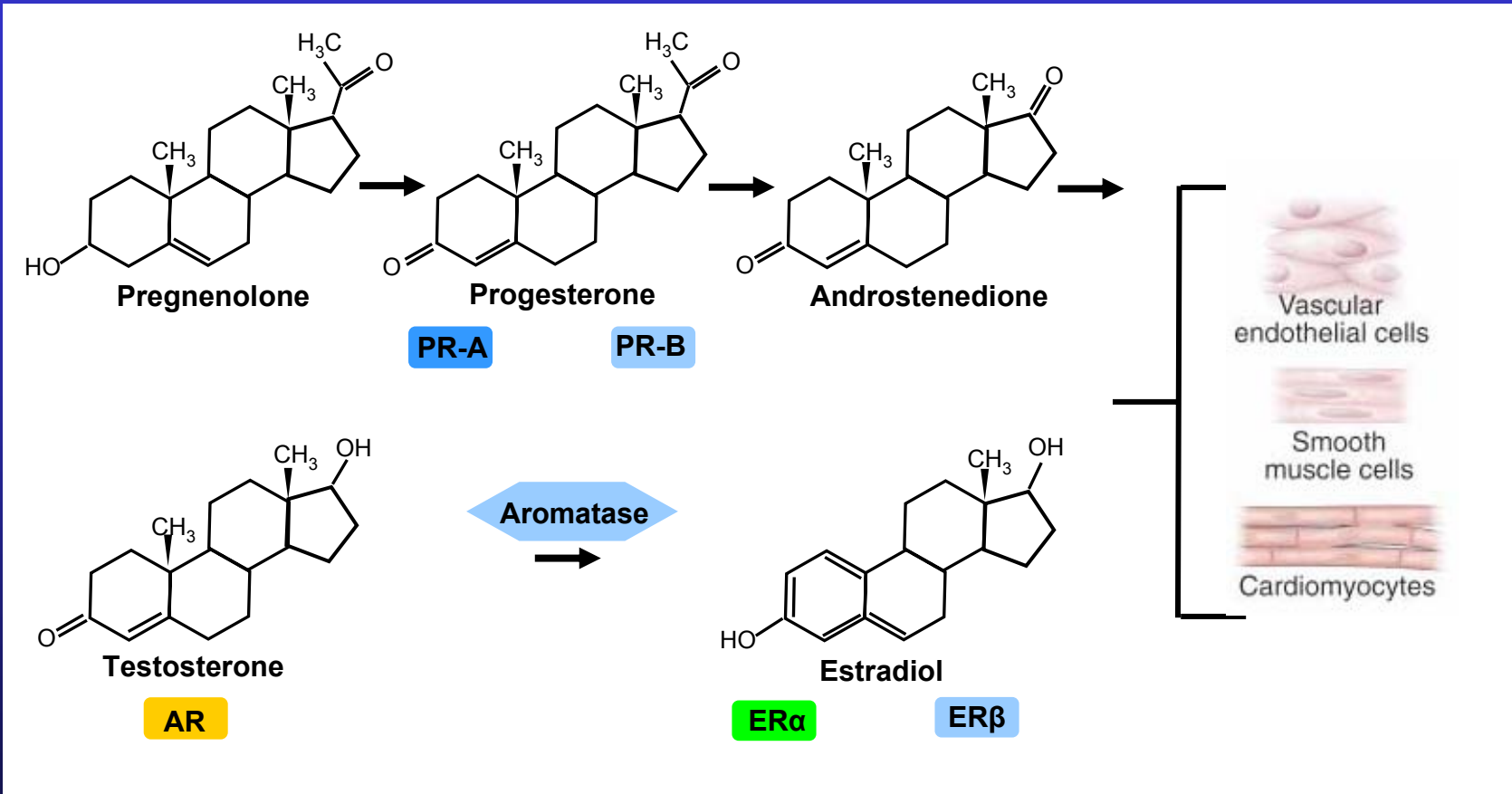


Steroid hormone receptors do not act alone, but interact with a broad array of coregulatory proteins to alter transcription.

Cell-specific expression of coactivator and corepressor proteins and their regulation by post-translational modifications allow for exquisite tissue-specific and temporal regulation of SSHR-mediated transcription

Mendelsohn & Karas. Science 2005;308:1583-1587

Cardiovascular Gender Differences



All of the sex steroid hormone receptors and the enzyme aromatase are expressed in vascular endothelial cells, vascular smooth muscle cells and cardiomyocytes

Michael E. Mendelsohn and Richard H. Karas. Science 2005;308:1583-1587

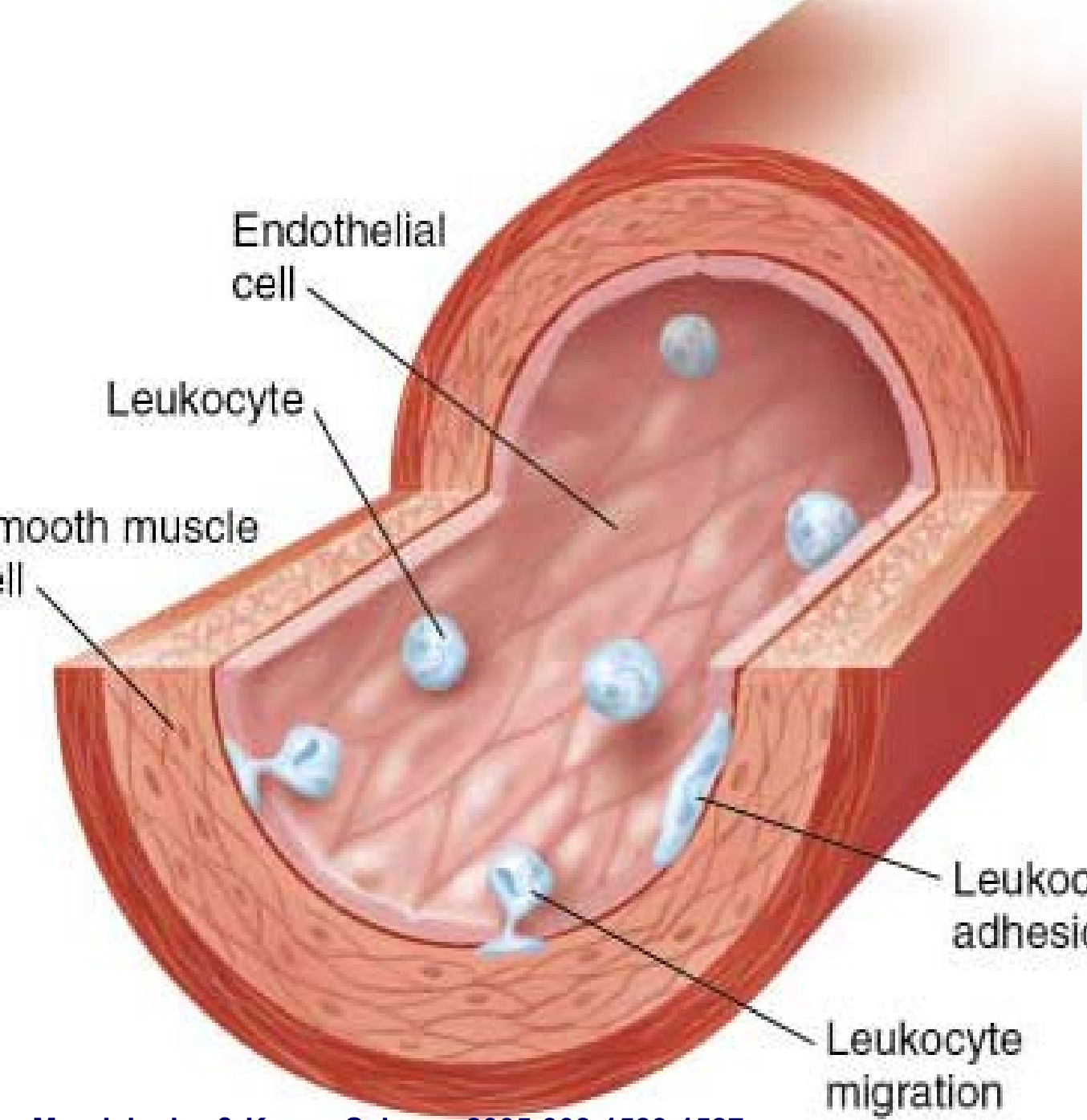
Sex Steroid Receptor Signaling

The Timing Hypothesis

Atherosclerosis is characterized by the gradual loss of vascular protective mechanisms and the emergence of advanced, unstable lesions.

SSH effects on the endometrium and its protective functions, vascular smooth muscle cells, and inflammatory cells differ, depending on the stage of atherosclerosis in the underlying blood vessel.

Mendelsohn & Karas. Science 2005;308:1583-1587



Beneficial Effects of EPT

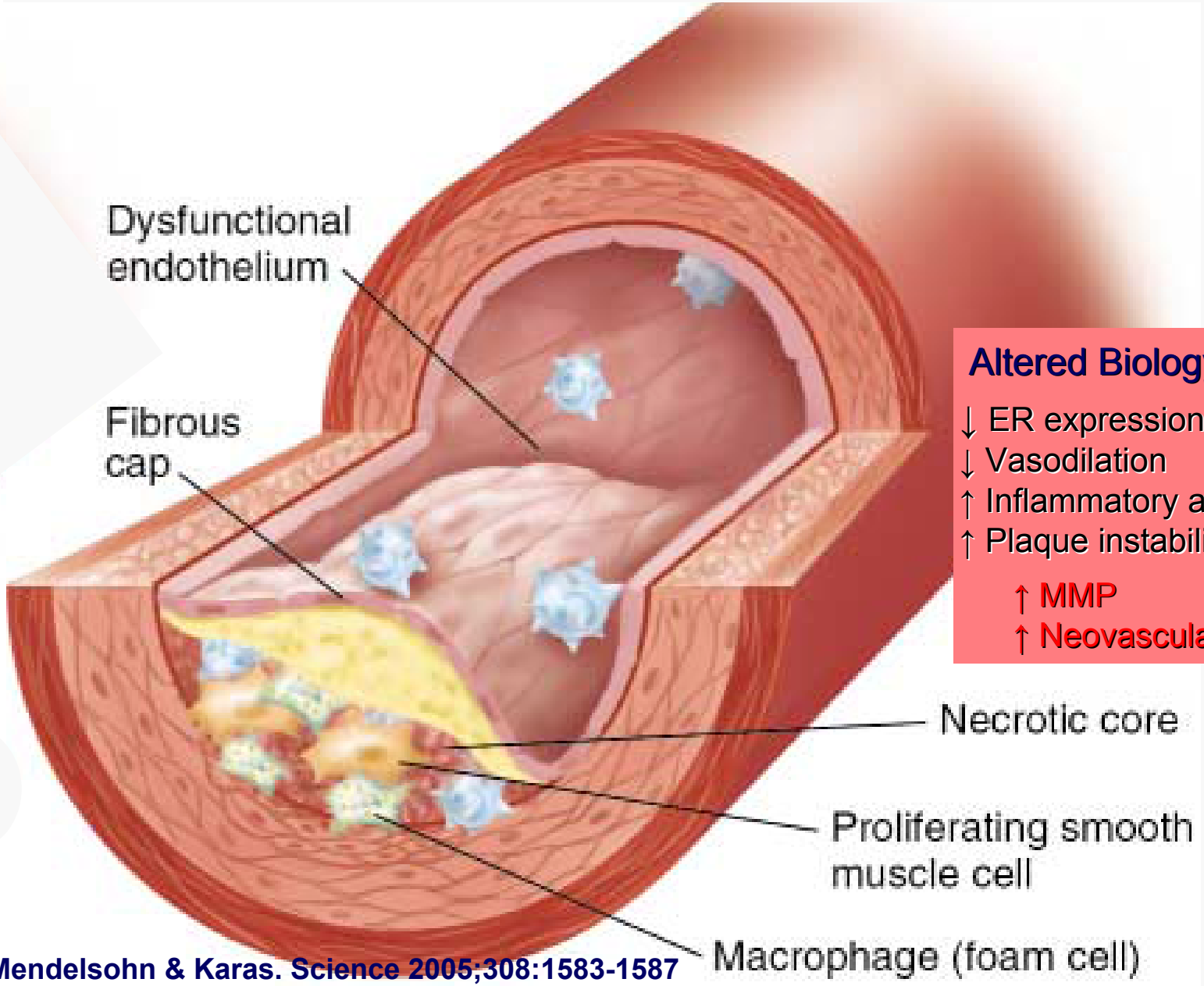
↑ Vasodilation
- ↑ Nitric Oxide
- ↓ Endothelin
- ↑Cox-2

↓ Inflammatory Activation
- ↑ Nitric Oxide
- ↓CAMs
- ↓MCP-1, TNF-α

↓ Lesion Progression
- ↑ Nitric Oxide
- ↓ Inflammatory cell adhesion
- ↓ LDL oxidation/binding
- ↓ Platelet activation
- ↓ VSMC proliferation

Mendelsohn & Karas. Science 2005;308:1583-1587

Effects of EPT on Established Atherosclerotic Disease



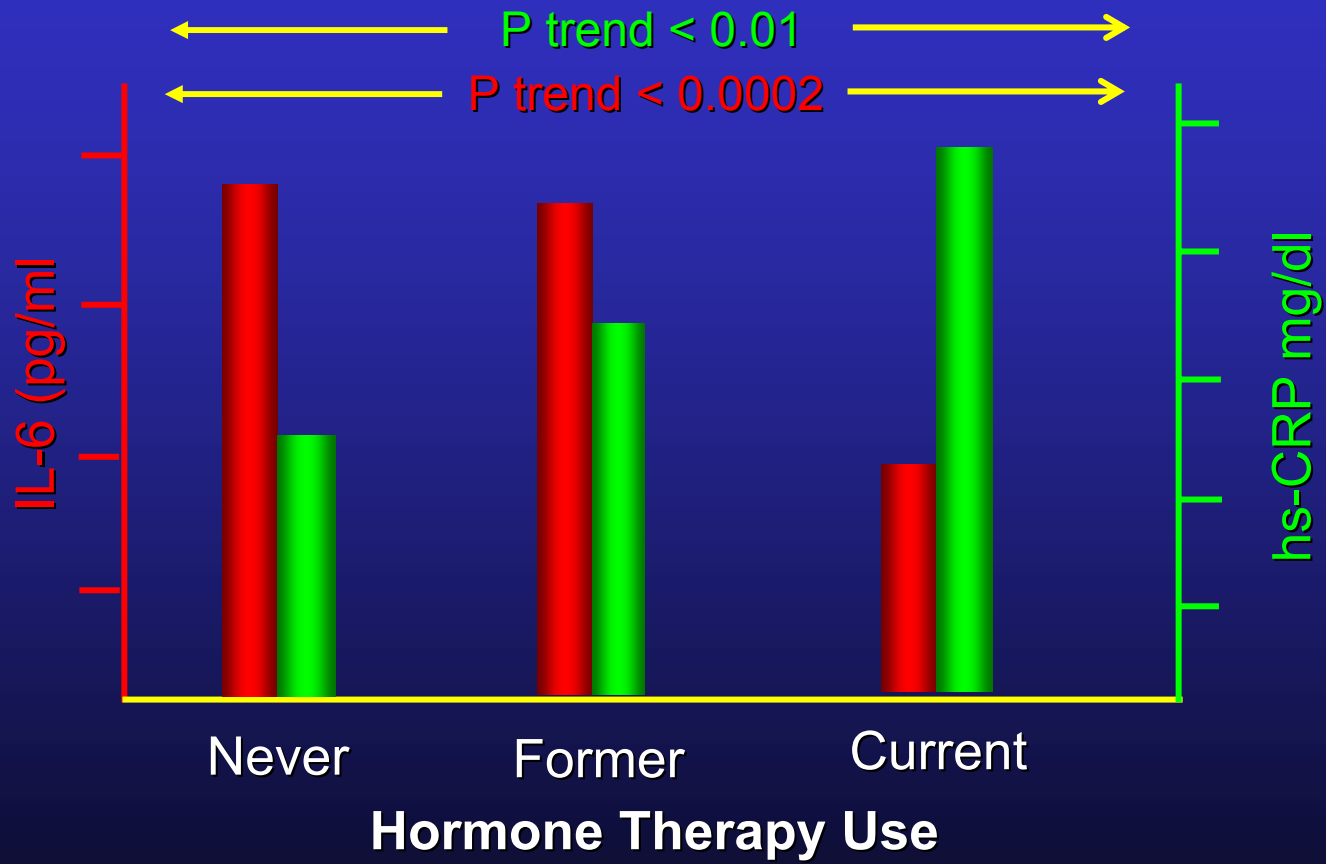
Altered Biology of EPT

↓ ER expression, function
↓ Vasodilation
↑ Inflammatory activation
↑ Plaque instability

↑ MMP
↑ Neovascularization

Mendelsohn & Karas. Science 2005;308:1583-1587

Women's Health Study
IL-6, CRP and HRT relationship



Bermudez E et al Arterioscler Thromb Vasc Biol 2002; 22:1668-1673

Women's Health Initiative Observational Study (WHI-OS)
Inflammatory Biomarkers

- Nested case control study of 75,343 healthy (no baseline CHD) PM women
  - 304 women had an MI
  - Controls matched to age, ethnicity, smoking, follow up time
- Baseline CRPs, IL-6 higher for the CHD cases
- CRP associated with risk in lean and obese women

Pradham A et al. JAMA 2002;288:980-987

Women's Health Initiative Observational Study (WHI-OS)
Inflammatory Biomarkers

- CHD Group (MI): CRP **55%** higher in HRT users vs non users (p=0.001)
- Control Group: CRP **70%** higher in HRT users vs non users (p=0.001)
- Increasing levels of CRP are associated with graded increase risk of CHD among HRT users and nonusers
- The OR (odds ratio) were similar in HRT users in low, moderate and high biomarkers tertiles

Pradham A et al. JAMA 2002;288:980-987

Women's Health Initiative Observational Study (WHI-OS)
Inflammatory Biomarkers

Baseline levels of hs-CRP and IL-6 are independently associated with a two fold risk of CHD

HRT use did elevate CRP but did not elevate IL-6 suggesting HRT does not initiate a generalized inflammatory state

Incremental increases on CRP are independently associated with future CHD risk irrespective of HRT use

Pradham A et al. JAMA 2002;288:980-987

Postmenopausal HOrmone REplacement against Atherosclerosis (PHOREA) Trial: Effect of 17β Estradiol/Gestodene on Inflammatory Markers

- 48 week trial looking at inflammatory CV markers
  - 1 mg 17 β estradiol plus 25 ug gestodene last 12 days of cycle n=65
  - 1 mg 17 β estradiol plus 25 ug gestodene every third cycle n=65
  - No HRT n=73

HRT vs Placebo

↓ ICAM - 9%

↓ VCAM-1 - 9%

↓ Selectin - 11%

↓ Fibrinogen – 12%

No affect on hs-CRP in any group

Stork S at al. Atherosclerosis 2002;165:301-307

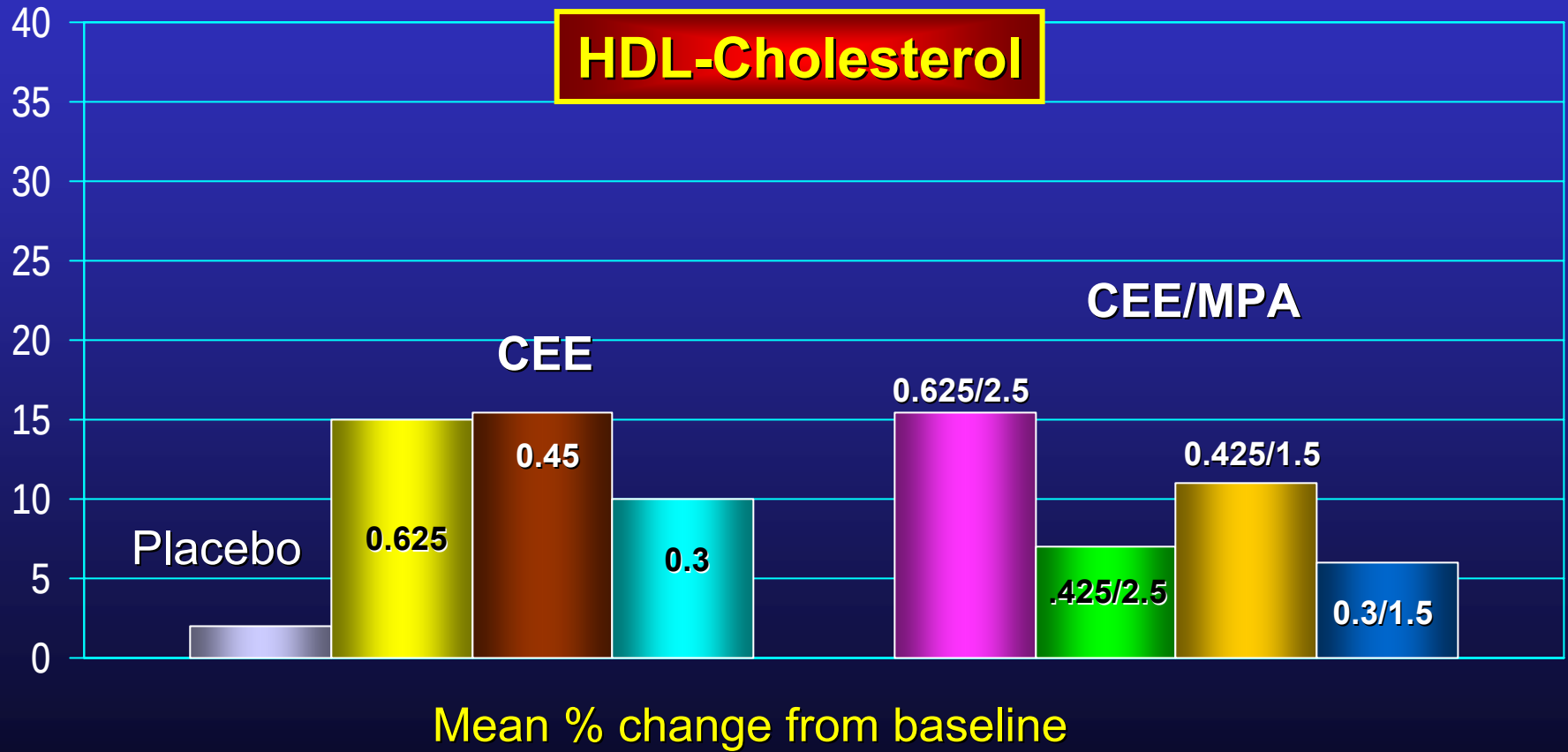
Postmenopausal HOrmone REplacement against Atherosclerosis (PHOREA) Trial: Effect of 17β Estradiol/Gestodene on Inflammatory Markers

Combination therapy with 17-β estradiol favorably affects the vascular inflammation process as indicated by neutral effects on CRP and reduction of cell adhesion molecules

Stork S at al. Atherosclerosis 2002;165:301-307

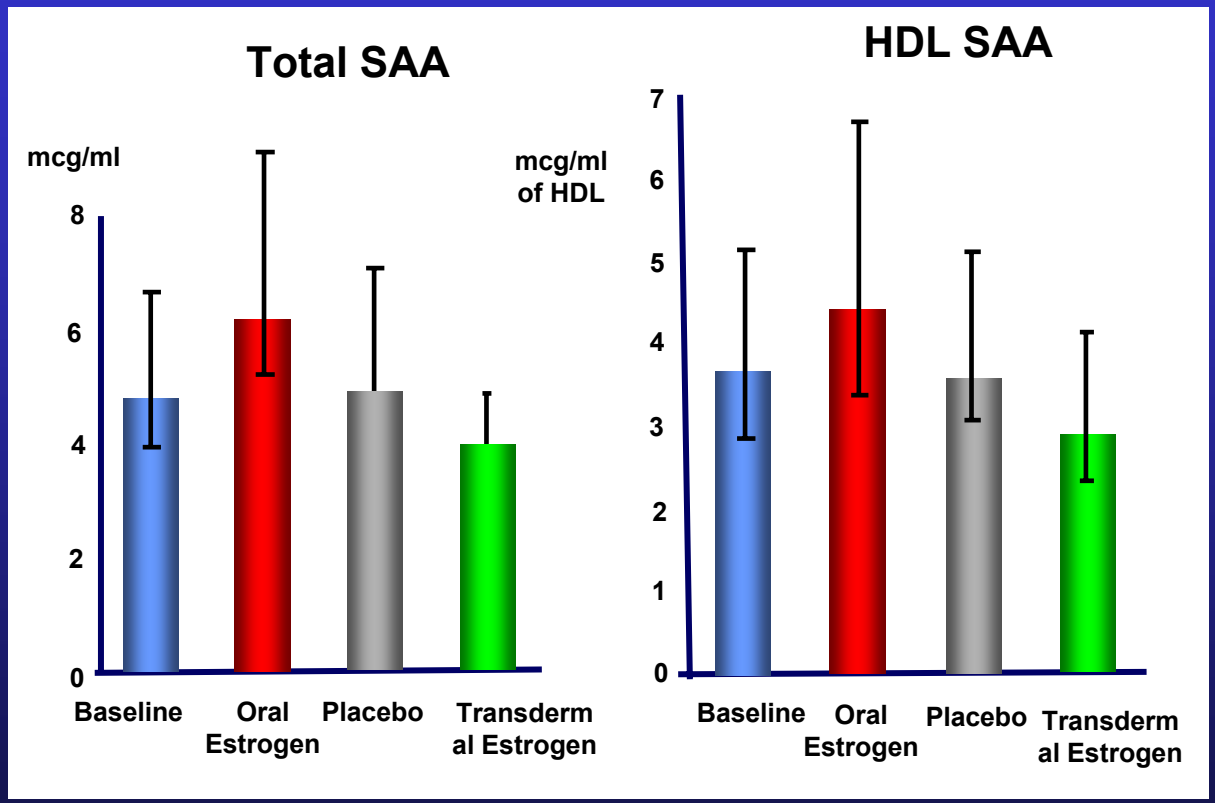
Women's Health, Osteoporosis, Progestin, Estrogen Study (HOPE)

CEE, CEE/MPA Dose Variability & Effect on Lipids



Lobo et al. Fertil & Steril 2001;76:13-24

Oral vs Transdermal Estradiol Effects on Amyloid A and HDL-Amyloid A



Oral estrogen increased SAA and altered HDL composition to contain a higher level of SAA by a first-pass hepatic mechanism.

Because elevated SAA levels predict adverse prognosis in healthy postmenopausal women, and elevated HDL-SAA levels have been shown to interfere with HDL function, the route of administration may be an important consideration in minimizing side effects of estrogen replacement therapy on cardiovascular outcomes.

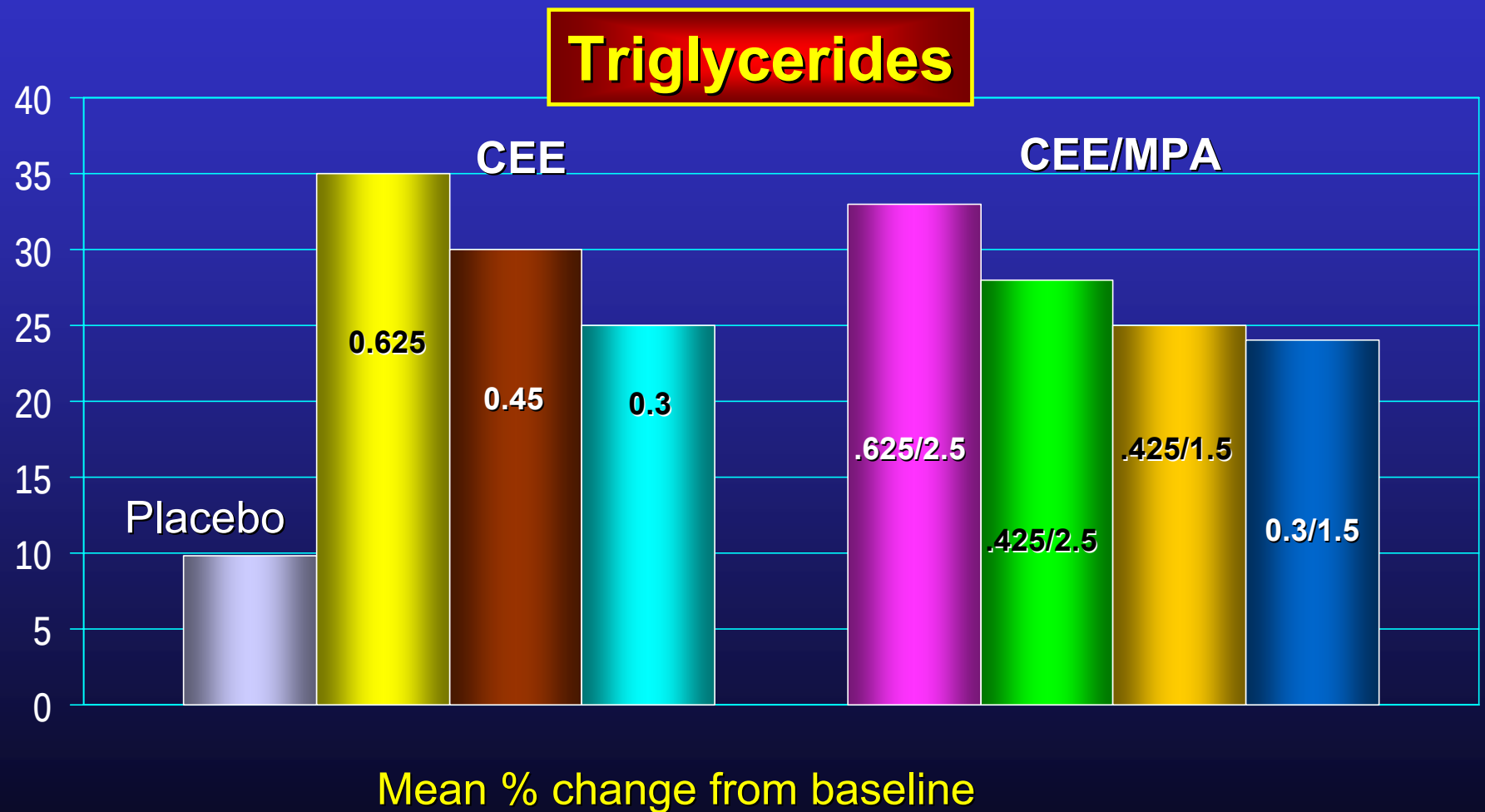
The data by emphasize the folly of relying simply on HDL cholesterol concentration to infer a clinical effect of hormone therapy.

David Herrington ATVB 2004:24:1741-42

Abbas A et al ATVB 2004;24:e164-e167

Women's Health, Osteoporosis, Progestin, Estrogen Study (HOPE)

CEE, CEE/MPA Dose Variability & Effect on Lipids

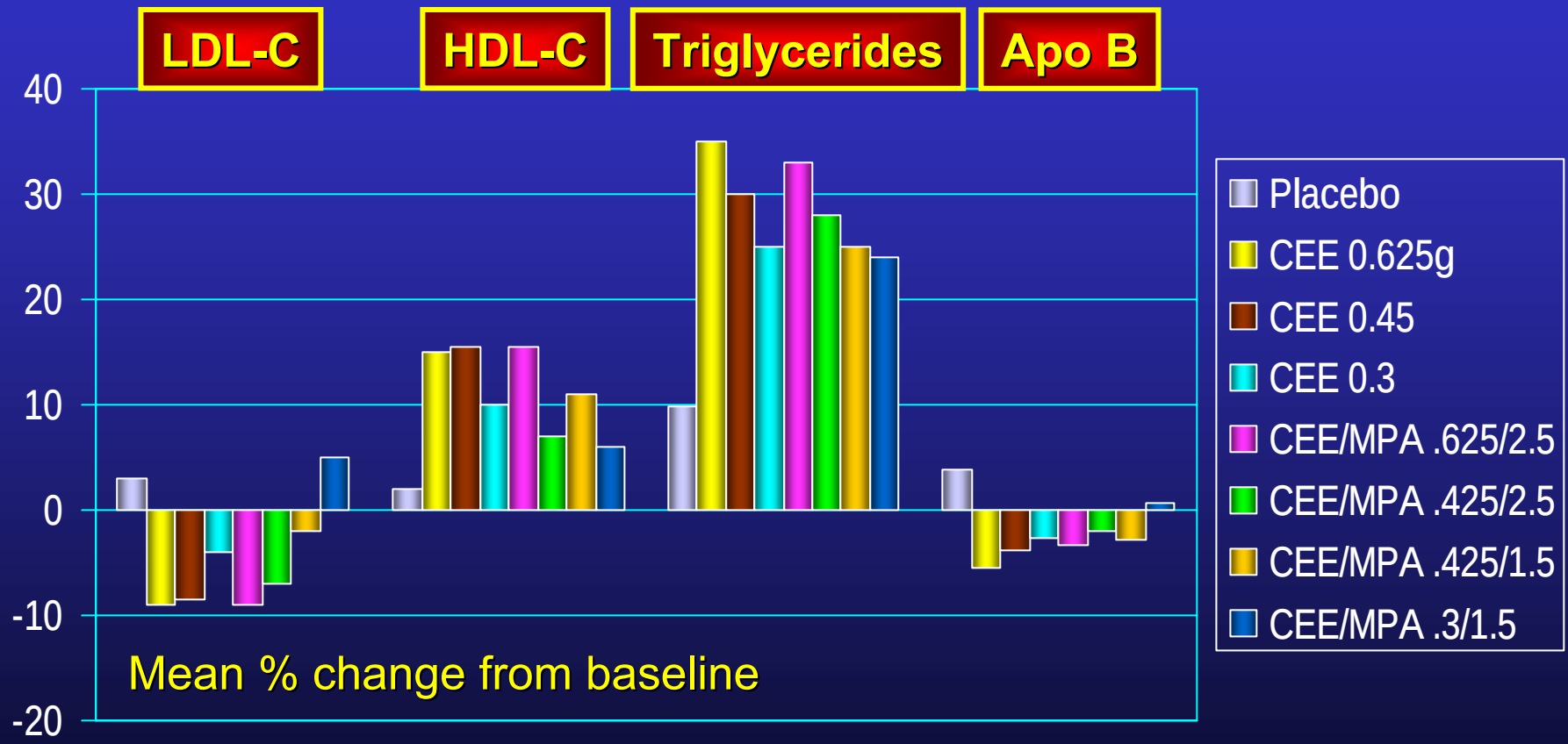


Lobo et al. Fertil & Steril 2001;76:13-24

Overall Lipid Effects of EPT Preparations

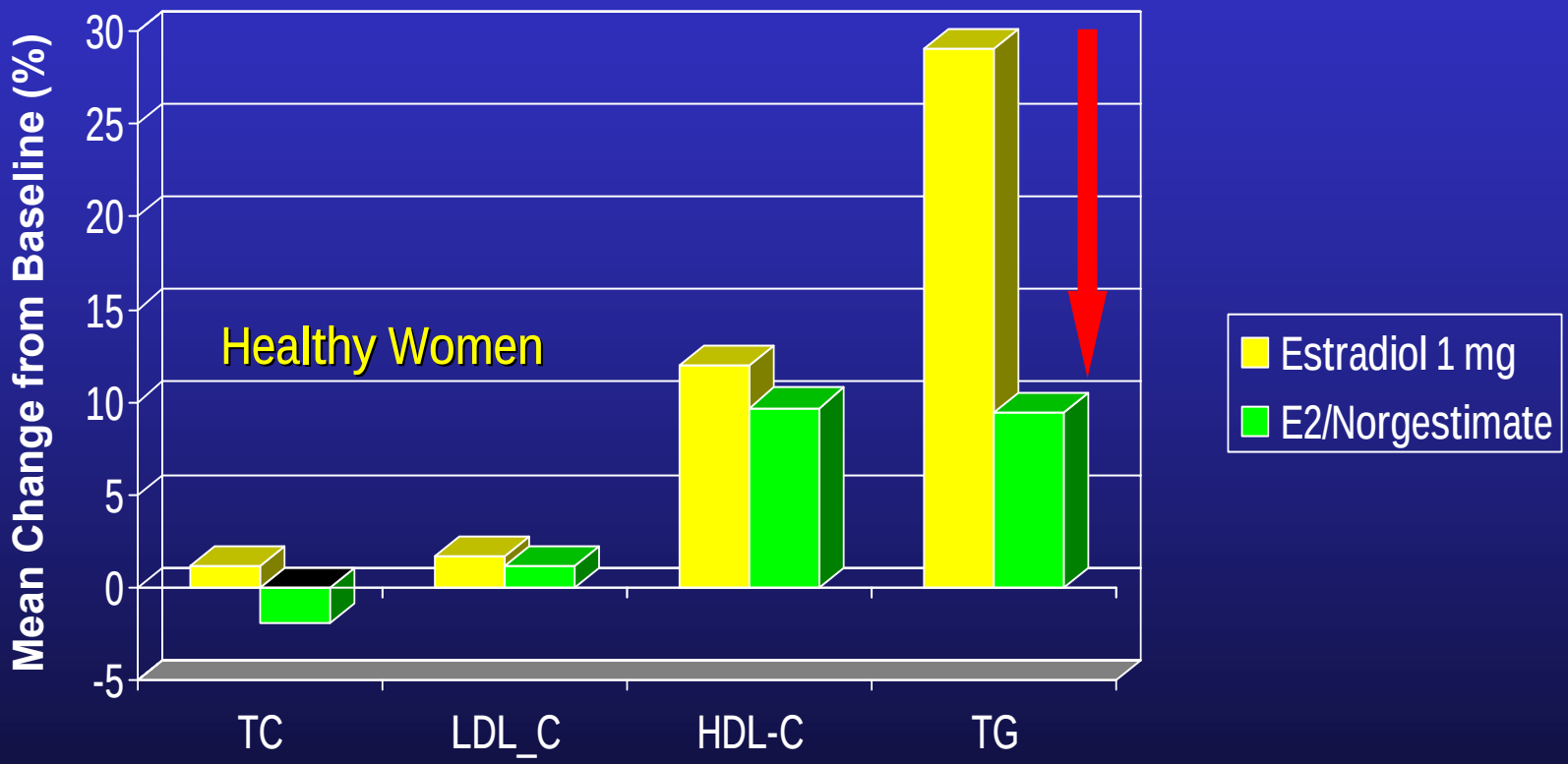
Women's Health, Osteoporosis, Progestin, Estrogen Study (HOPE)

CEE, CEE/MPA Dose Variability & Effect on Lipids



Lobo et al.
Fertil & Steril 2001;76:13-24

17B-Estradiol/Norgestimate Tabs

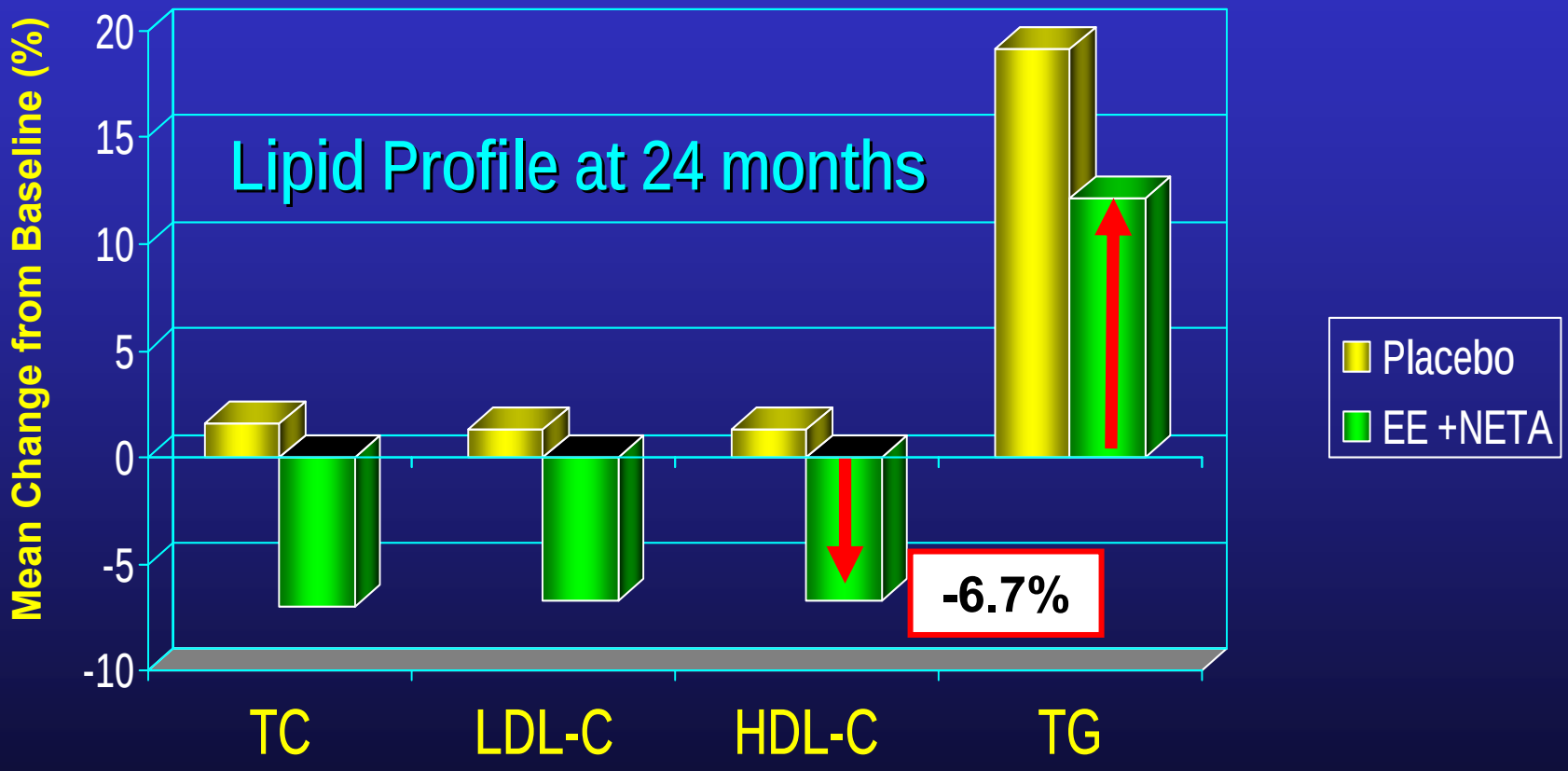


Lipid Profile at 12 months

N = 36

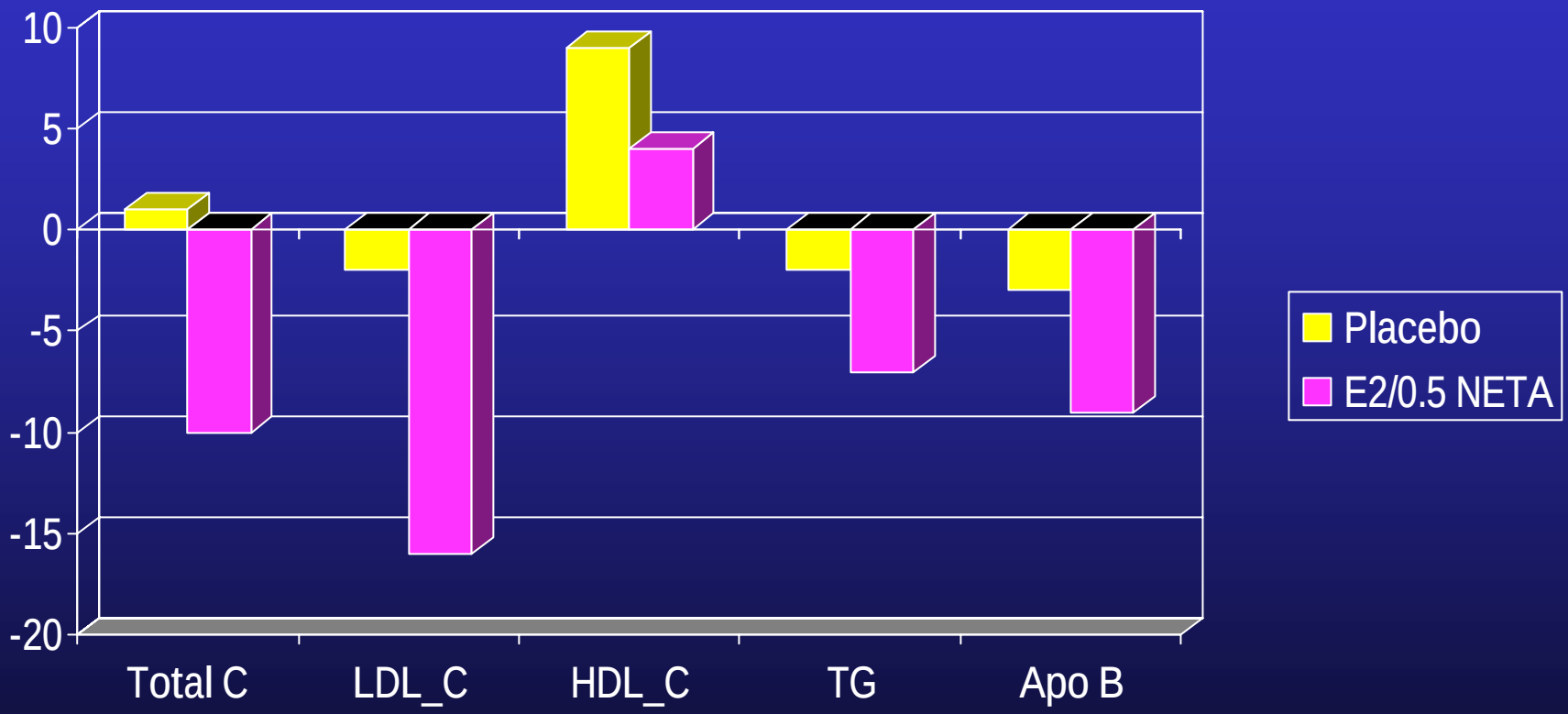
Phase 3 Clinical Trials Ortho-McNeil

Continuous Hormones As Replacement Therapy (CHART): Ethinyl Estradiol (5 mcg) / Norethindrone Acetate (1 mg)



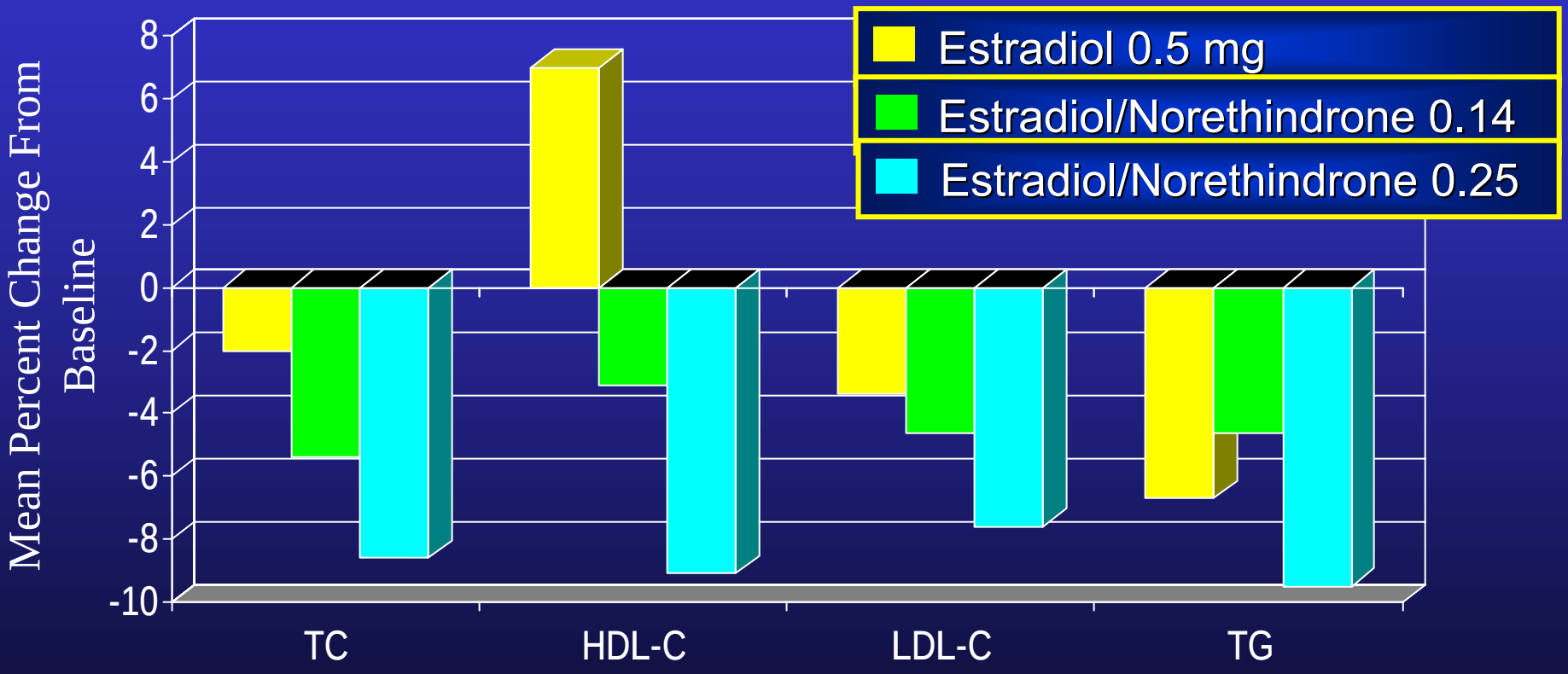
Speroff L et al. JAMA 1996;276:1397-1403

Estradiol (1 mg) / Norethindrone Acetate (0.5mg)



Davidson M. Arch Intern Med 2000;160:3315-25

Transdermal Preparations



955 PM patients at 12 months

CombiPatch PIF Jan 1999

Estrogen, progesterone, and cardiovascular health: when shall we complete the puzzle?

It is likely that the timing of the initiation of HT and the status of cardiovascular health determines in part whether HT will protect against CVD.

Understanding age-dependent changes in vascular pathology and the pharmacology of different estrogens and progestins may facilitate the development of therapeutic strategies for HT that are effective in delaying vascular remodeling leading to postmenopausal CVD.

Amnon Brzezinski, MD and Haim D. Danenberg, MD Menopause 2005;12:488-

Kronos Early Estrogen Prevention Study (KEEPS)

- Multicenter, 5 year randomized, placebo-controlled trial
  - Low-dosage oral CEE (0.45 mg/d)
  - Transdermal estradiol 50 mcg/d
  - Cyclic oral micronized progesterone 200mg/d for 12 days a month
- Endpoints
  - Progression of carotid intimal media thickness
  - Accrual of coronary calcium in women aged 42-58 who are < 3 years post-menopausal
  - QOL, cognition, metabolism, bone health

Harman SM, Brinton EA et al. Climacteric 2005;8:3-12

Early vs Late Intervention Trial with Estradiol (ELITE)

- Examines the effect of 17-estradiol on the progression of early atherosclerosis in 504 women divided into two groups:
  - Less than 6 years post-menopause
  - 10 years or more post-menopause
  - To receive either oral 17-estradiol 1 mg/d or placebo
    - Women with a uterus will receive vaginal progesterone gel 4% for last ten days of each monthly cycle
- Primary endpoint is rate of change of distal common carotid artery far wall intima-media thickness
  - Secondary endpoint: Neurocognitive function

http://www.clinicaltrials.gov/show/NCT00114517