Cardiovascular Disease in Women

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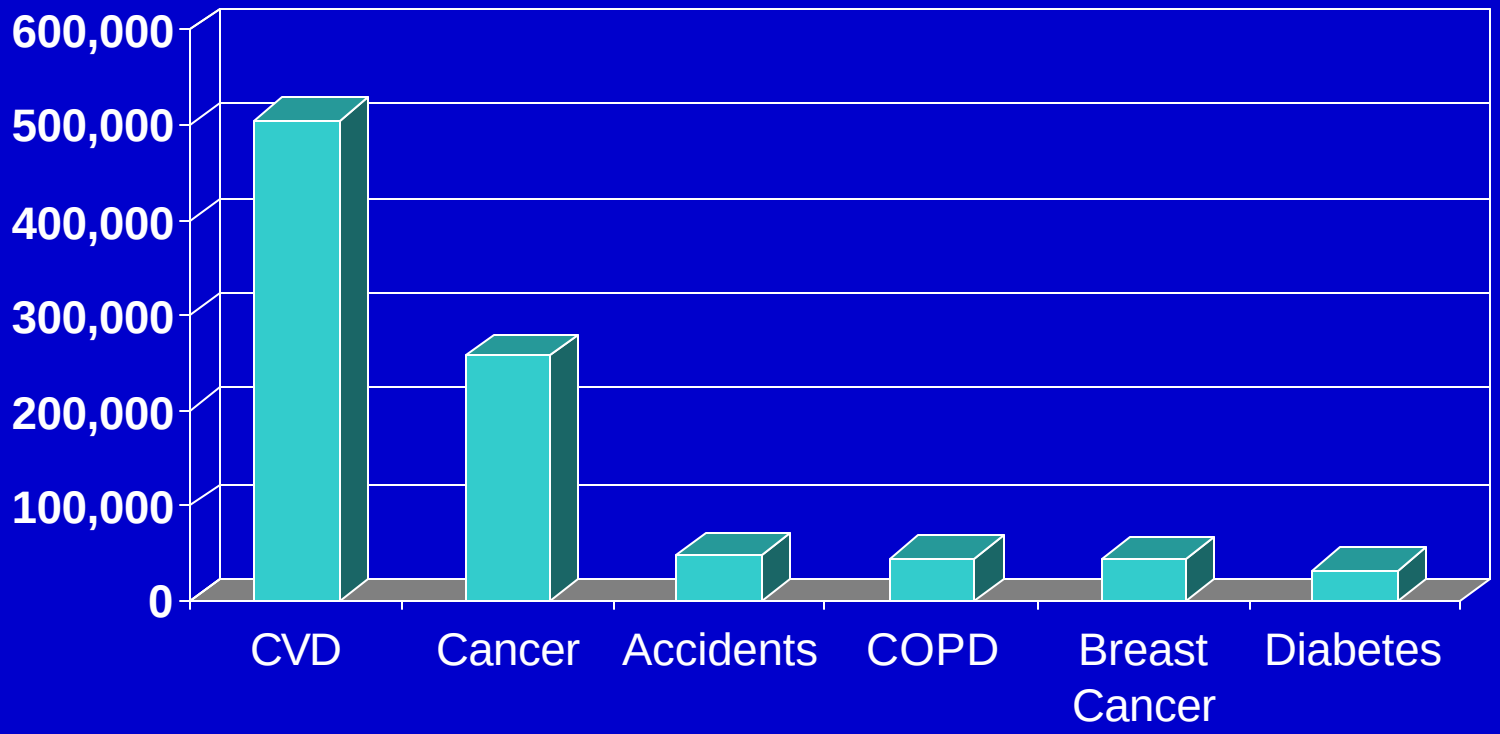
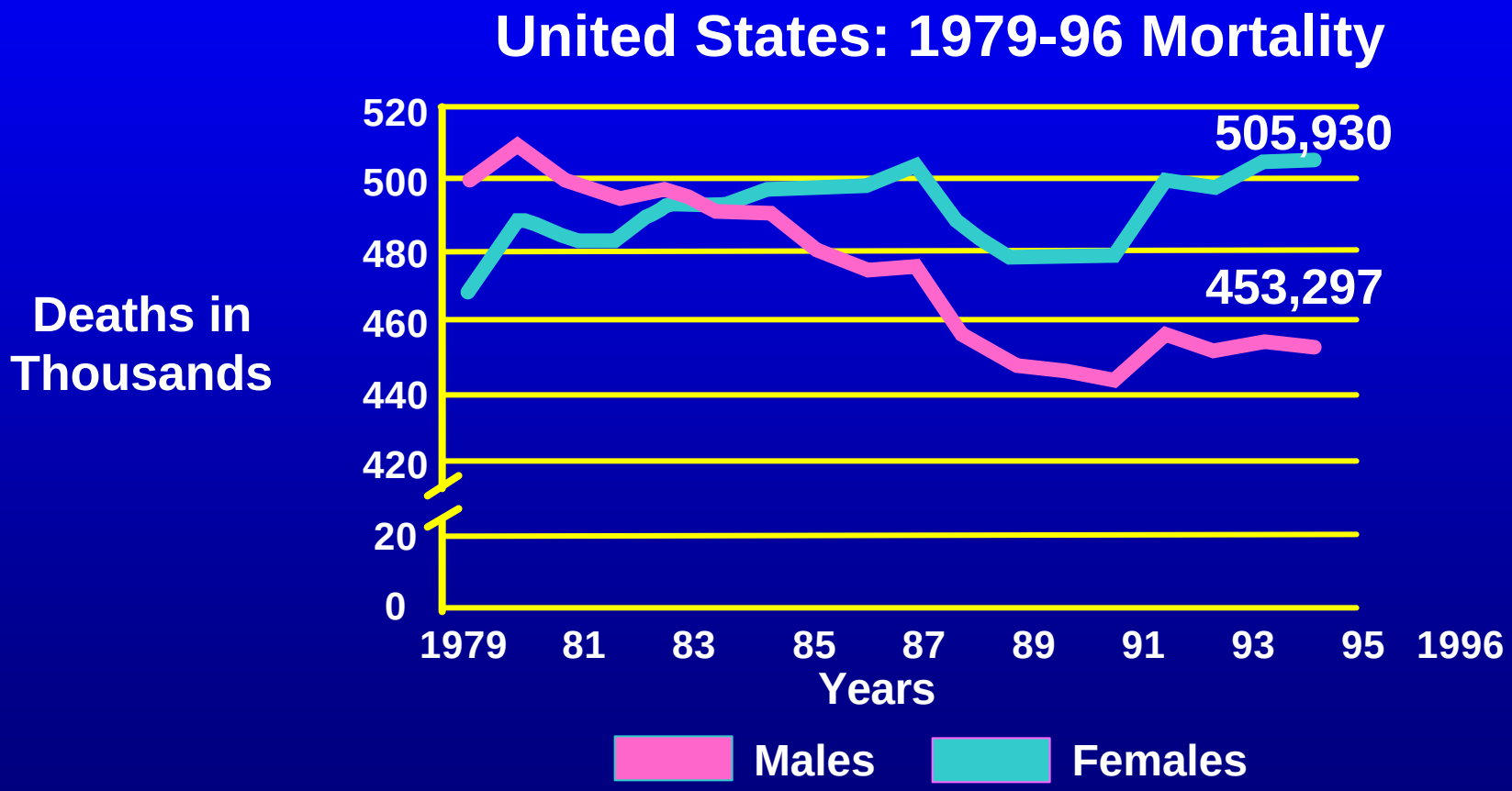
Leading Causes of Death in Women

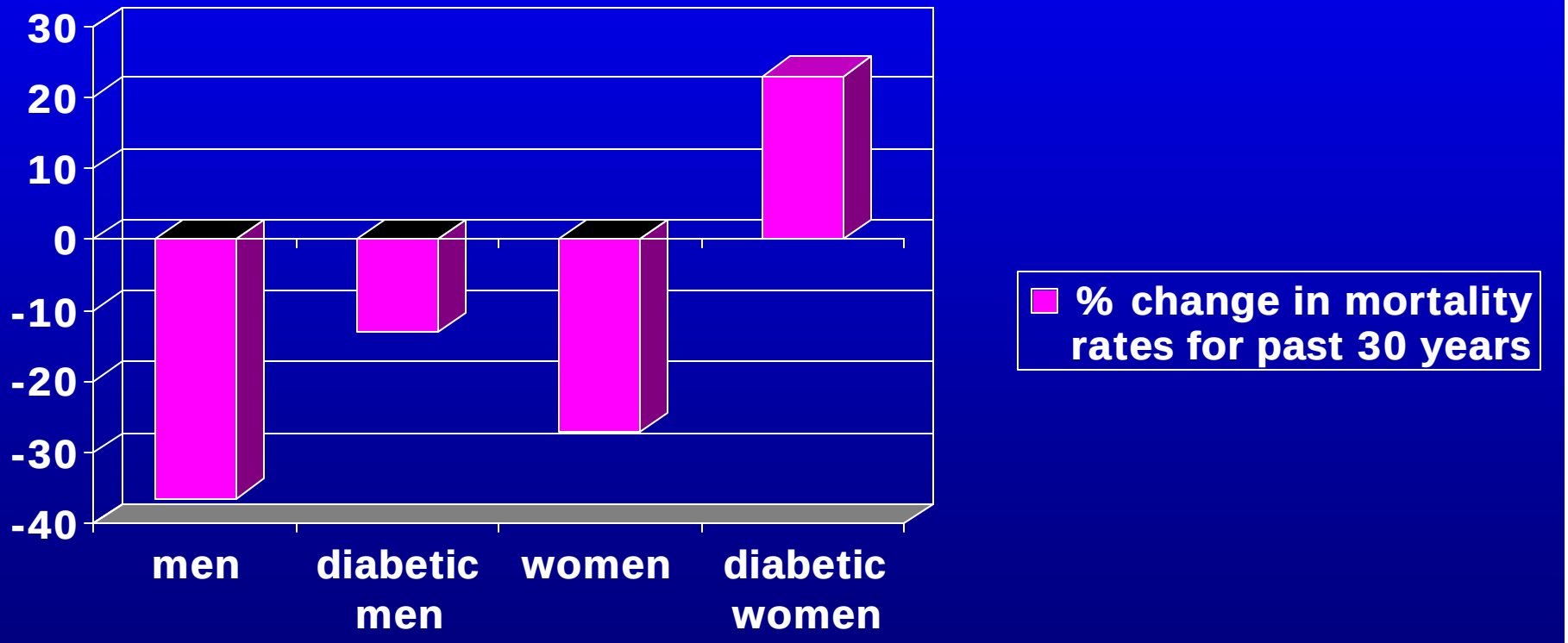


Cardiovascular Disease Mortality Trends



American Heart Association 1999 Heart and Stroke Statistical Update

Time trends in mortality for CHD



Gu JAMA 1999

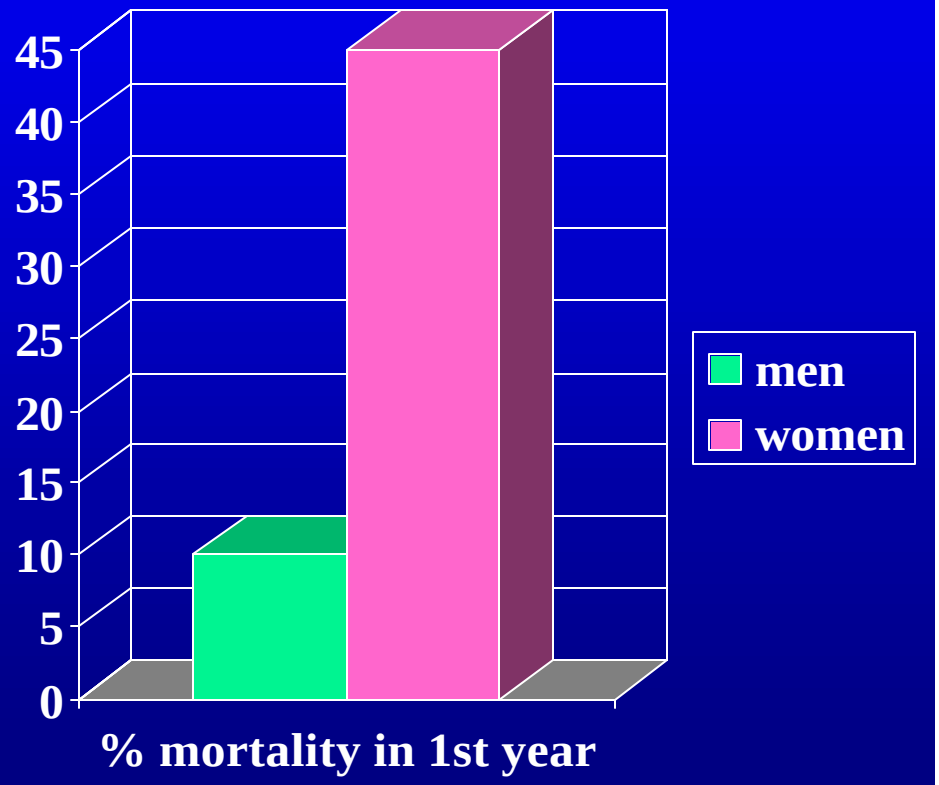
One year mortality after MI

Mortality:

10% men

Vs.

45% women



AHA, 2000

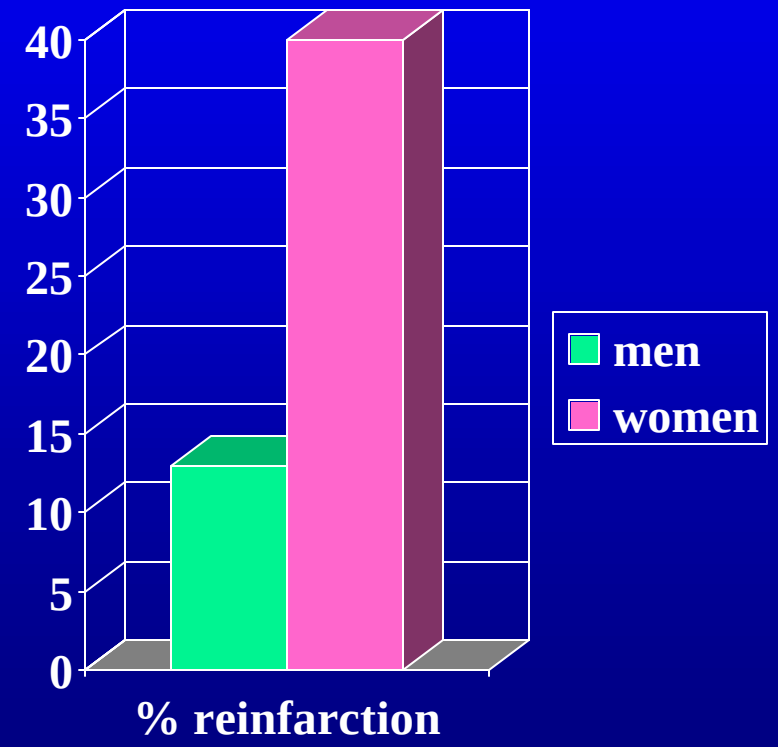
In the 1st year after MI….

Rate of reinfarction:

40% of women

Vs.

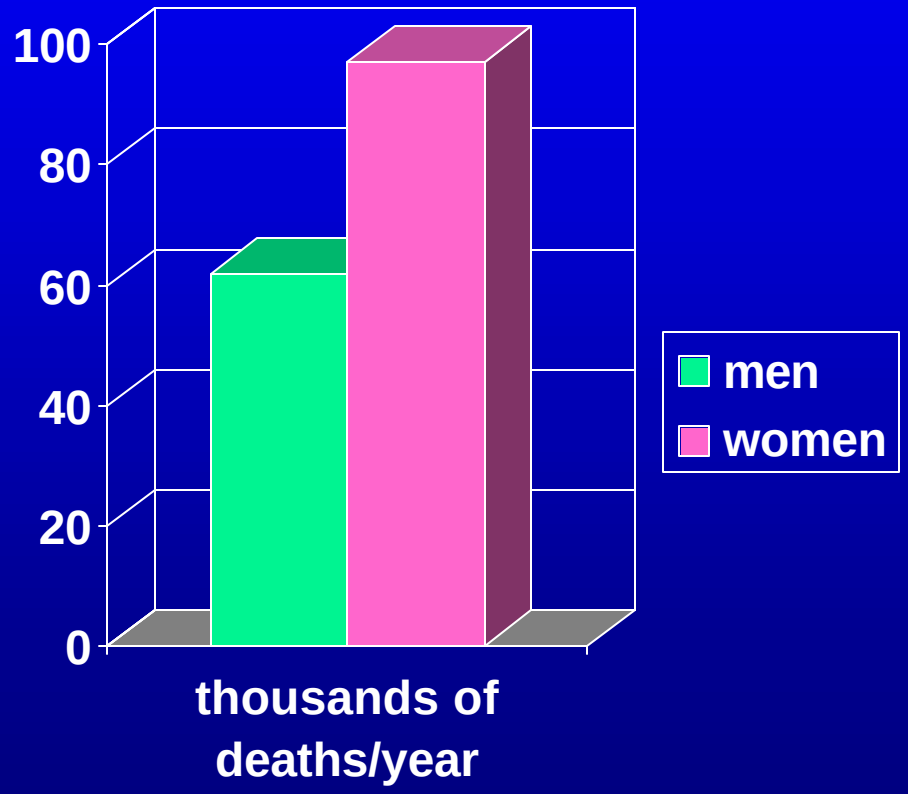
13% of men



AHA

Stroke mortality

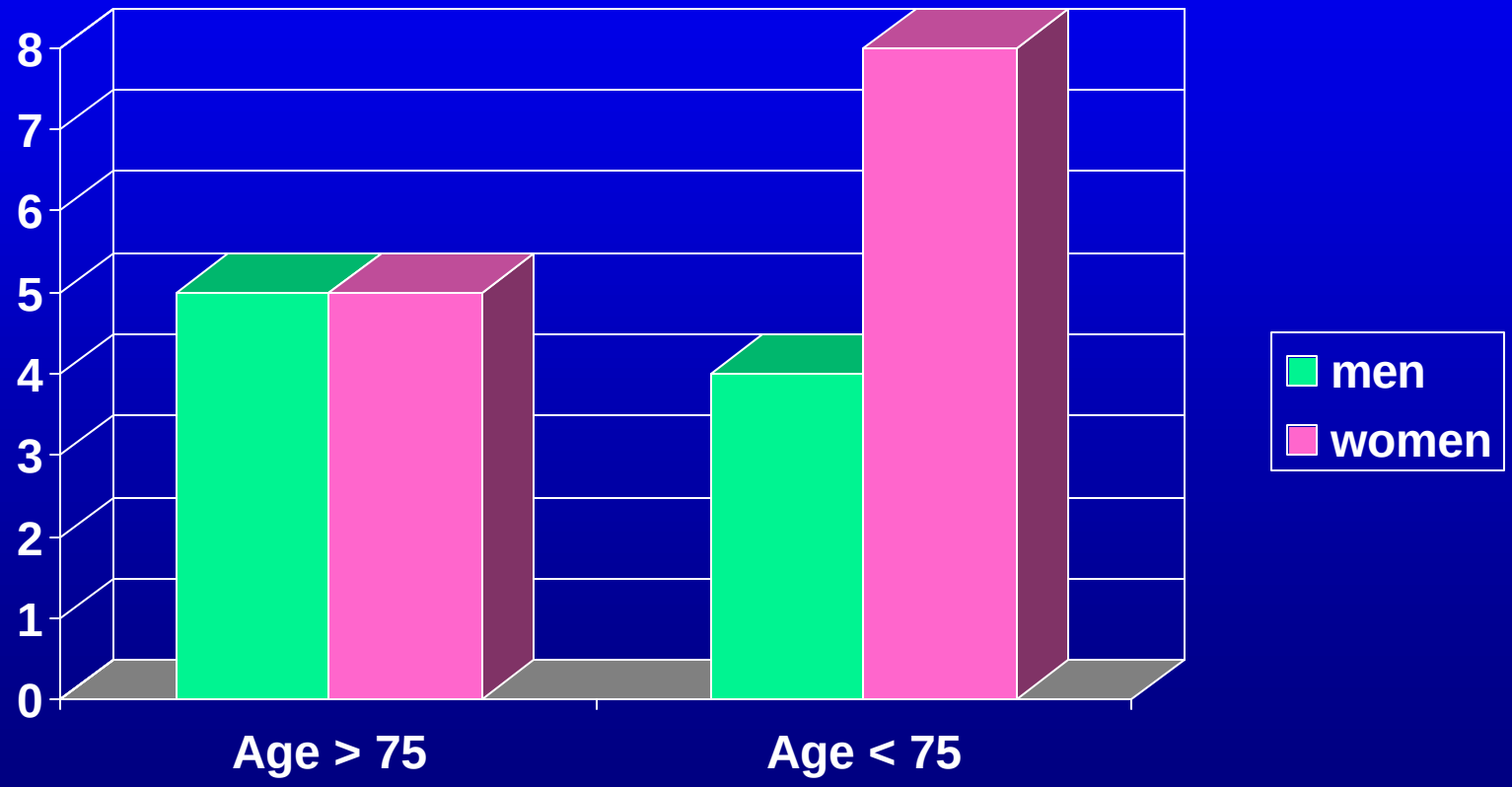
- Mortality
  - **62,000** men vs. **97,000** women
  - AA women 4x's higher
- Prevalence
  - AA women 3x's higher



Why Do Women Do Worse?

- Women are *older* at 1st MI
- Women are *sicker* at 1st MI
- Management less aggressive
- Confusion about diagnostic studies
- Lack of knowledge
- Less awareness of risk factors

Age, sex and death from MI



Vaccarino NEJM 1998, 2000

Why Do Women Do Worse?

- Women are sicker at 1st MI
- Women are older at 1st MI
- Management less ***aggressive***
- Less awareness of risk factors
- Lack of knowledge
- Confusion about diagnostic studies

Bias in management

Women are less likely to get…

- Catheterizations after an abnormal stress test
- Stents to keep vessels open
- Clot-busting drugs
- Aspirin in the emergency room

Tobin, JACC, 1987, Schulman NEJM, 1999

Why Do Women Do Worse?

- Women are older at 1st MI
- Women are sicker at 1st MI
- Management less aggressive
- ***Confusion*** about diagnostic studies
- Lack of ***knowledge***
- Less awareness of risk factors

Diagnostic Challenge

- Women present with “atypical” symptoms
- The ECG is affected by menstrual cycle and estrogen
- Lower exercise capacity therefore the stress test is less useful

Physiologic Sex Differences

- More non-Q wave MI's
- Plaque shape and size
- Smaller vessels
- LVH more common $\rightarrow$ CHF more common
- Longer QT interval

Why Do Women Do Worse?

- Women are older at 1st MI
- Women are sicker at 1st MI
- Management less aggressive
- Confusion about diagnostic studies
- Lack of knowledge
- Less ***awareness*** of risk factors

Women underestimate CVD risk

- Only 14% think that they will have MI
- 1 in 4 women are overweight
- 1 in 3 women has hypertension
- 1 in 4 women smokes
- 2 in 3 women are sedentary
- 70% don’t know cholesterol….
  - …….But ***1 in 4*** has hyperlipidemia

Physicians underestimate CV risk

Physicians….

.... *do not* discuss CV risk factors in

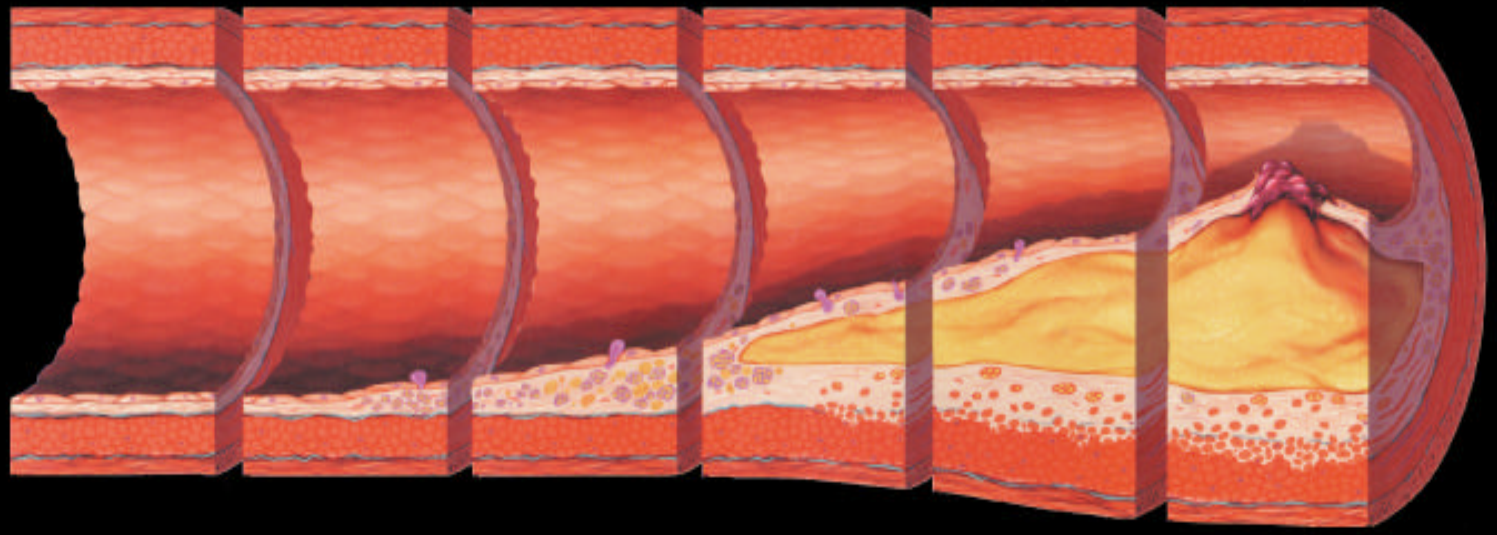
59% of all women patients

44% of women patients > 55

….*do not* check lipids in 50% women

VBWG

Atherosclerosis timeline



Endothelial dysfunction

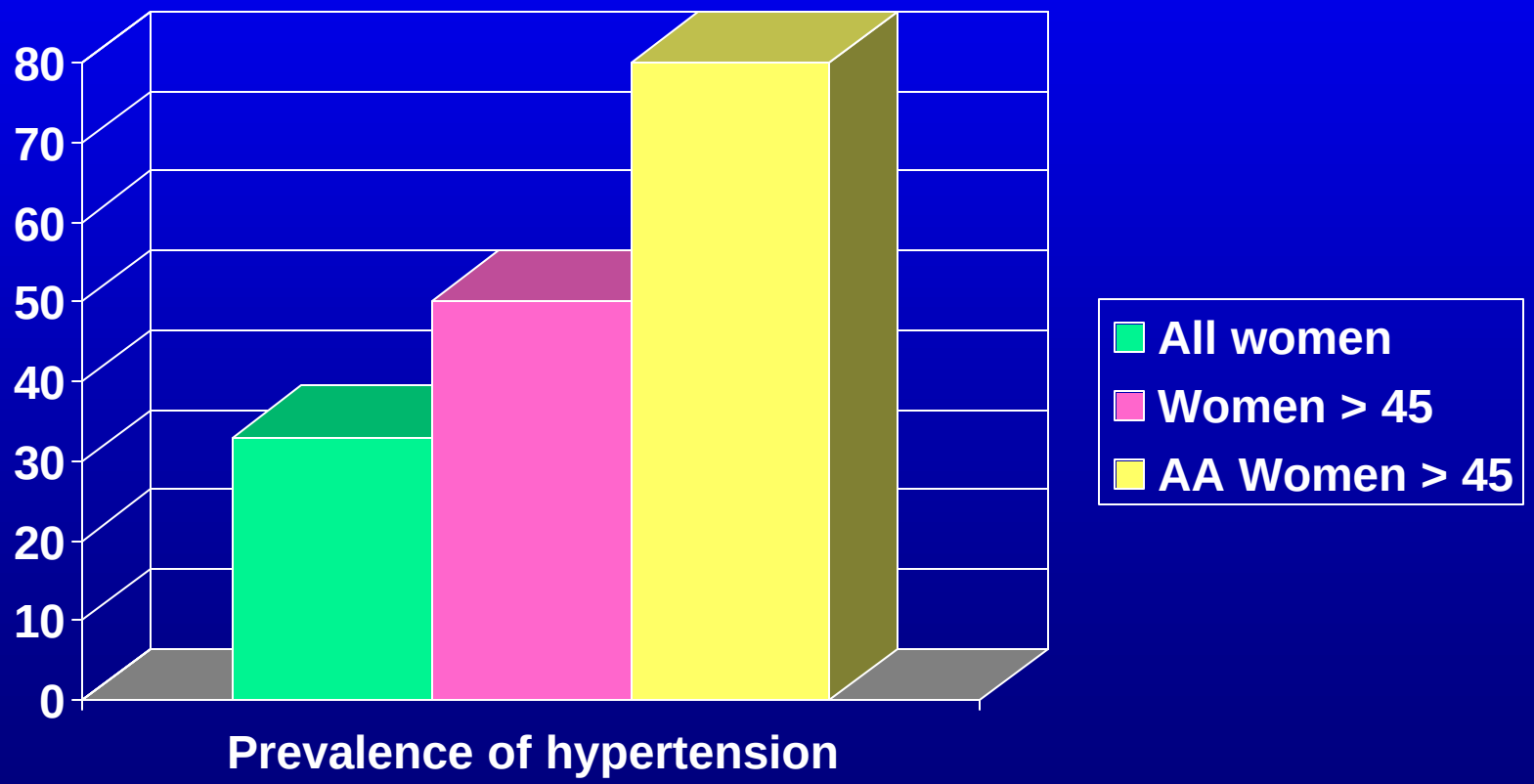
From first decade	From third decade	From fourth decade	
Growth mainly by lipid accumulation		Smooth muscle and collagen	Thrombosis, hematoma

Adapted from Pepine CJ. *Am J Cardiol.* 1998;82(suppl 104).

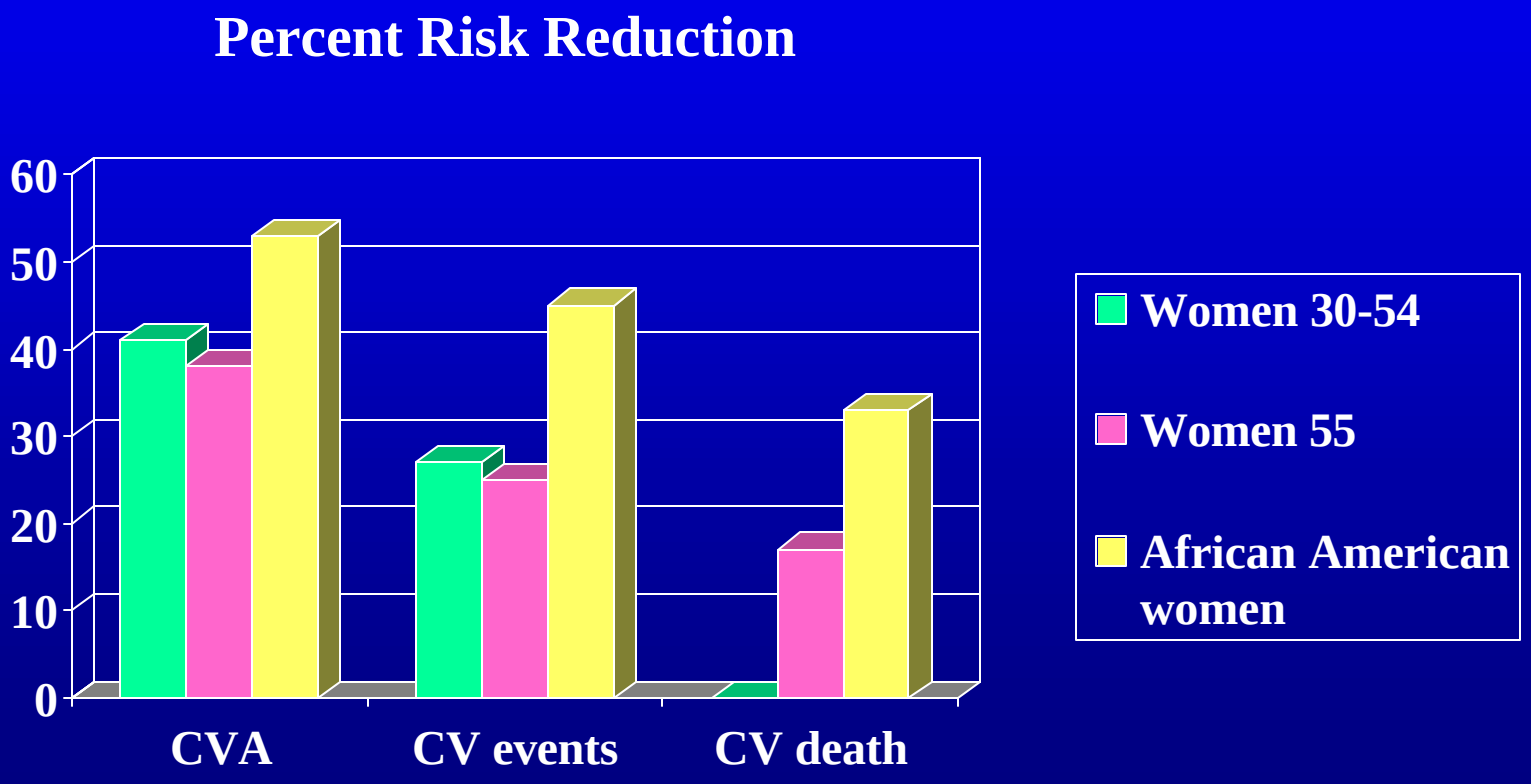
Traditional risk factors

- **Positive Risk Factors**
  - **Family History**
  - **Age: Women ≥ 55 years or early menopause**
  - **Smoker**
  - **Hypertension**
  - **Diabetes**
  - **Hyperlipidemia**
  - **Overweight**
- **Negative Risk Factors**
  - **If HDL is > 60 mg/dl, subtract one risk factor**

Prevalence of Hypertension



Efficacy of treating hypertension in women



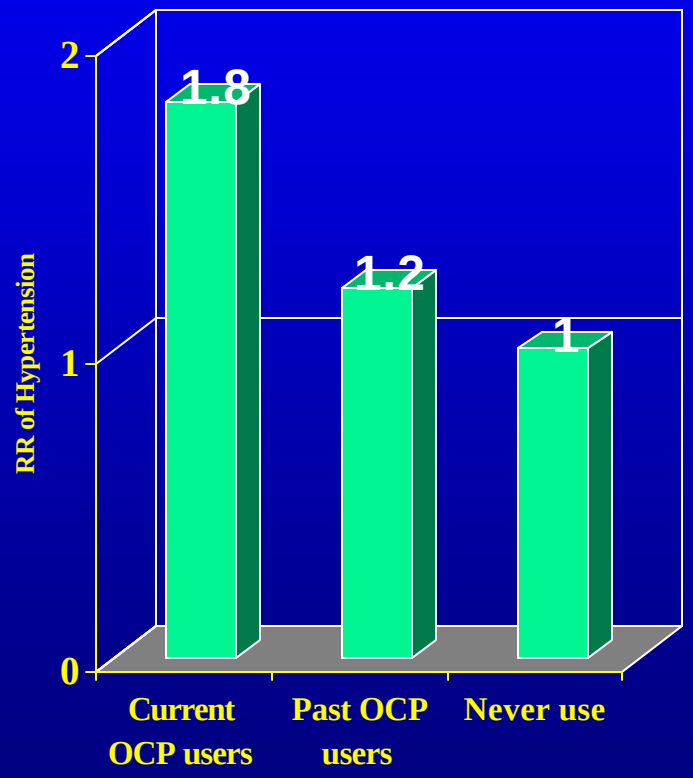
Quan et al. *J Gen Int Med* 12:718, 1999

Common Misconceptions

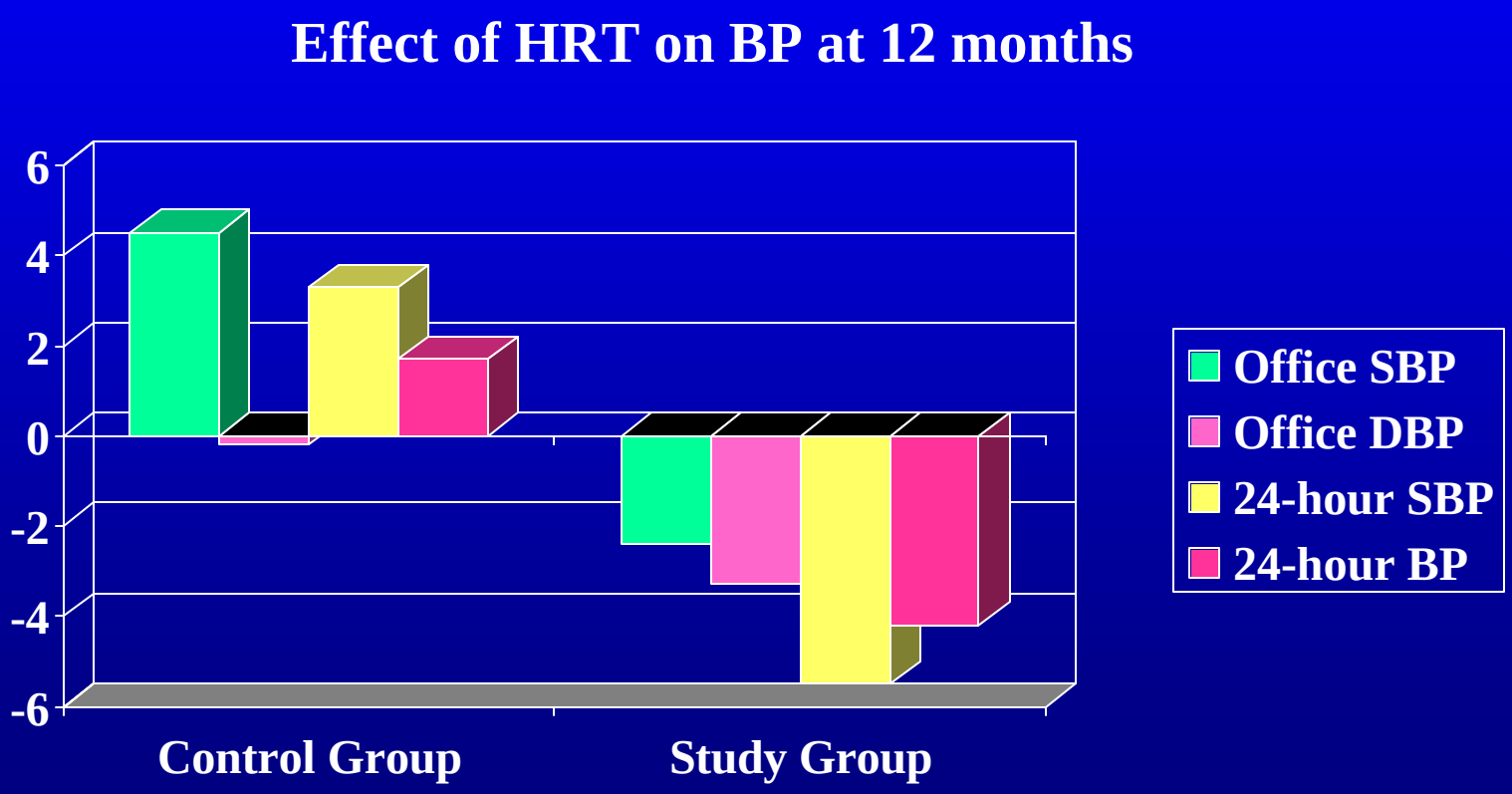
"It is not clear whether white women benefit at all from therapy, or, if in fact, they are harmed by pharmacologic therapy."

Anastos, *Ann Intern Med* 1991;115:287-293

NHS: Low-dose OCPs ↑ the RR of developing hypertension



HRT decreases BP in normotensive women



Am J Hypertens 11:1147, 1998

Hypertension in Women

There are no sex-specific ranges !

Diabetes

- more powerful risk factor in women
- doubles risk of 2nd MI
- quadruples risk of congestive heart failure
- confers the same CHD risk as a prior MI

Hu NEJM 1998

Smoking

- 1 in 4 women smokes
- higher risk of MI than males (RR 1.5)
- significant contributor to sudden death in young women
- OCP use increases risk of MI by a factor of 30
- ↓ HDL, ↑fibrinogen and ↑platelet stickiness
- ↓ age of menopause by 1-2 years
- lowers age of first heart attack

Hyperlipidemia – A key risk factor

- 25% of all American women
- 50% of all postmenopausal women
- HIGH RISK:
  - Hypothyroidism
  - Diabetes
  - Family history of cardiovascular disease
  - Polycystic ovarian syndrome
  - Smokers

Screening for Hyperlipidemia

- Lipid profile
  - Total cholesterol
  - LDL
  - HDL
  - Triglycerides
  - Total cholesterol/HDL ratio
- NCEP: screen every 5 years after age 20
- USPSTF & ACP: screen after age 45
- Fasting or non-fasting lipid profile?

NCEP Risk Stratification

LDL Level	Classification
< 130	Desirable
130 – 159	Borderline high-risk
≥160	High risk

NCEP Treatment Guidelines

	LDL GOAL
• 0 - 1 Risk Factor	<160
• 2 or more risk factors	<130
• CAD or diabetes	<100

NCEP-defined strata of HDL

Low HDL	< 40 mg/dL
Normal HDL	35-59 mg/dL
High HDL	> 60 mg/dL

"High" = 85th percentile….

...but 60 = 85th percentile in ***men***

60 = **75th** percentile in women

☞ Reference ranges need to be sex-specific ☜

HDL & TG: independent predictors

If TC > 200, mortality is significantly higher if:

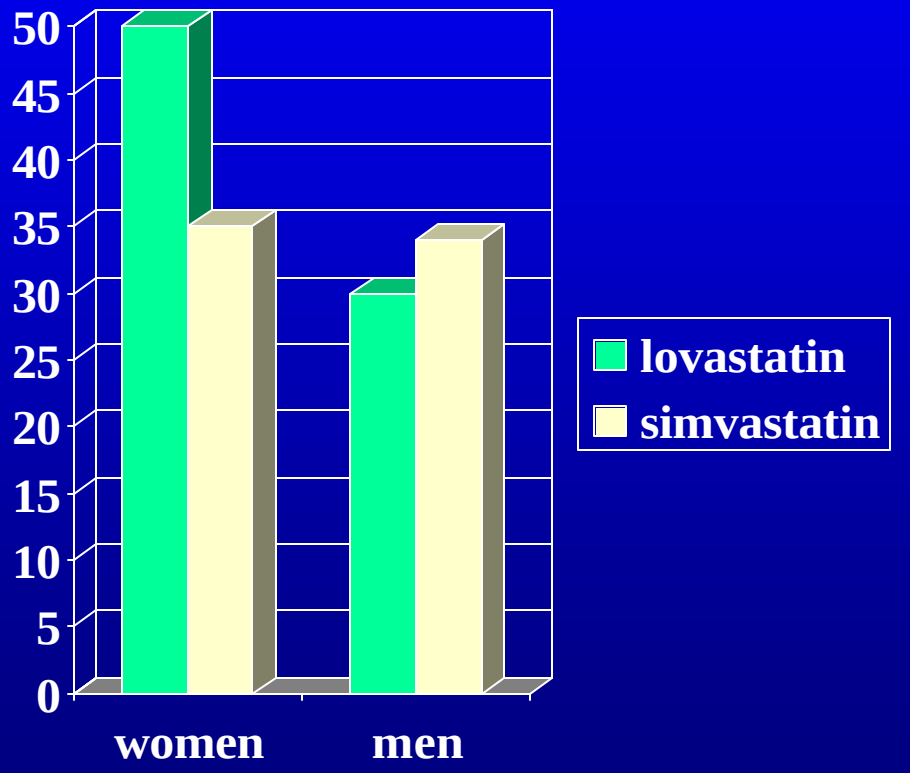
HDL <50 vs. **HDL of > 50**

At any LDL

Miller Bass, LRC, Arch Int Med 1993

Risk reduction in statin survival studies

- AFCAPS/TexCAPS 1997
  - 1º Prevention with lovastatin
  - Endpoint: 1st cardiac event
- 4S 1994
  - 2º Prevention with simvastatin
  - Endpoint: major coronary event

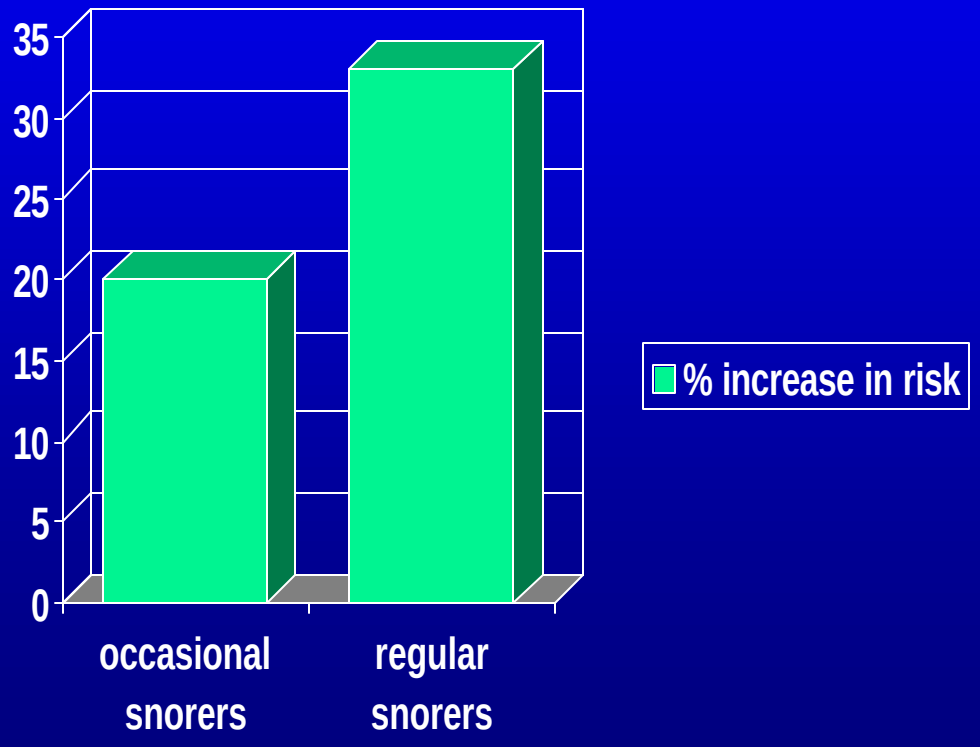


Non-traditional risk factors

- Premature menopause/surgical menopause
- History of gestational diabetes
- Obstructive sleep apnea
- Hypothyroidism
- Homocysteine
- Lipoprotein (a)
- Chronic renal insufficiency
- Fasting plasma glucose in elderly women
- Heterozygosity for hemochromatosis
- Polycystic Ovary Syndrome

Snoring & CVD Risk

- Nurses' Health Study
- 72,000 women
- 45 – 65 years old
- 8 year follow-up



JACC 2000

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Subclinical Hypothyroidism

TSH **high**, free T4 **normal**

- Attributable risk percentage is 50% compared to cardiac risk conferred by:
  - hyperlipidemia 58%
  - hypertension 38%
  - diabetes 58%

Subclinical Hypothyroidism

TSH **high**, free T4 **normal**

- **Attributable risk percentage is 50%** compared to cardiac risk conferred by:
  - hyperlipidemia 58%
  - hypertension 38%
  - diabetes 58%

- Rotterdam study: 12% of 1000 women had subclinical hypothyroidism.
- Twice as likely to have cardiac disease. If thyroid peroxidase antibody positive, the odds ratio for MI increased to 3.1

Non-traditional risk factors

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Homocysteine

- Stronger link with CAD in women
- Serum homocysteine higher in women with diabetes, rheumatoid arthritis, lupus, end-stage renal disease patients and eclampsia
- Reference ranges ARE sex-specific

Non-traditional risk factors

- Premature menopause/surgical menopause
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Lipoprotein (a)

- Independent risk factor for both men and women; may be more predictive in women.

  Bostom, Circulation 1994

- Lp(a) is linked with homocysteine in young African American women.

  Sherif, Am J Hypertens 1999

Non-traditional risk factors

- Premature menopause/surgical menopause
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PCOS has been viewed as a purely reproductive disorder…..

Chronic anovulation with oligomenorrhea

Irregular periods

Infertility

Dysfunctional uterine bleeding

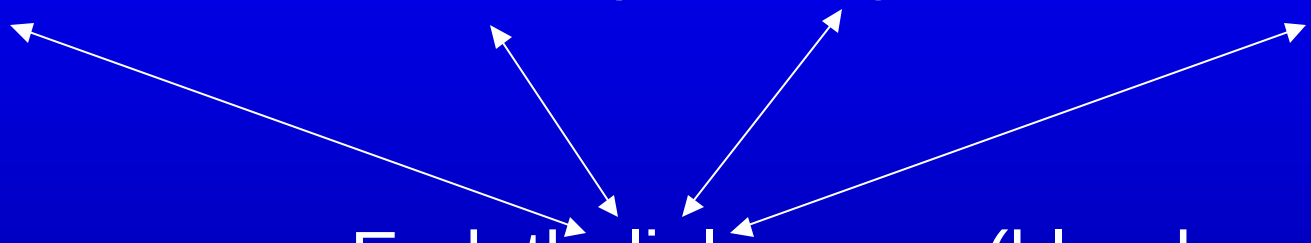
Pregnancy loss

Polycystic ovaries

Endometrial carcinoma

….PCOS is primarily a metabolic disorder affecting the ENTIRE cardiovascular system

Diabetes/IR Abnormal lipids High BP Clotting Disorders



Endothelial Dysfunction (blood vessels)

Early Atherosclerosis

Higher rates of MI and Stroke at younger ages

Conclusions

- **Learn sex-associated risks**
- **Have a high index of suspicion**
- ***SCREEN* aggressively**
- ***TREAT* aggressively**

Menopause: Physiologic Changes

- ↑ LDL
- ↑ Triglycerides
- ↑ Insulin resistance
- ↑ Central Fat
- ↓ Endothelial Dysfunction
- Arteries are stiffer → BP increases
- ↓ Bone Density

Sex hormones confer a protective effect

- Risk factors *increase* after menopause
- *Incidence* of CVD increases after menopause
- *Premature* menopause increases risk
- *Surgical* menopause increases risk
- Diabetes (hyperandrogenemic state) increases risk ***3-7 times***

Hormone replacement therapy

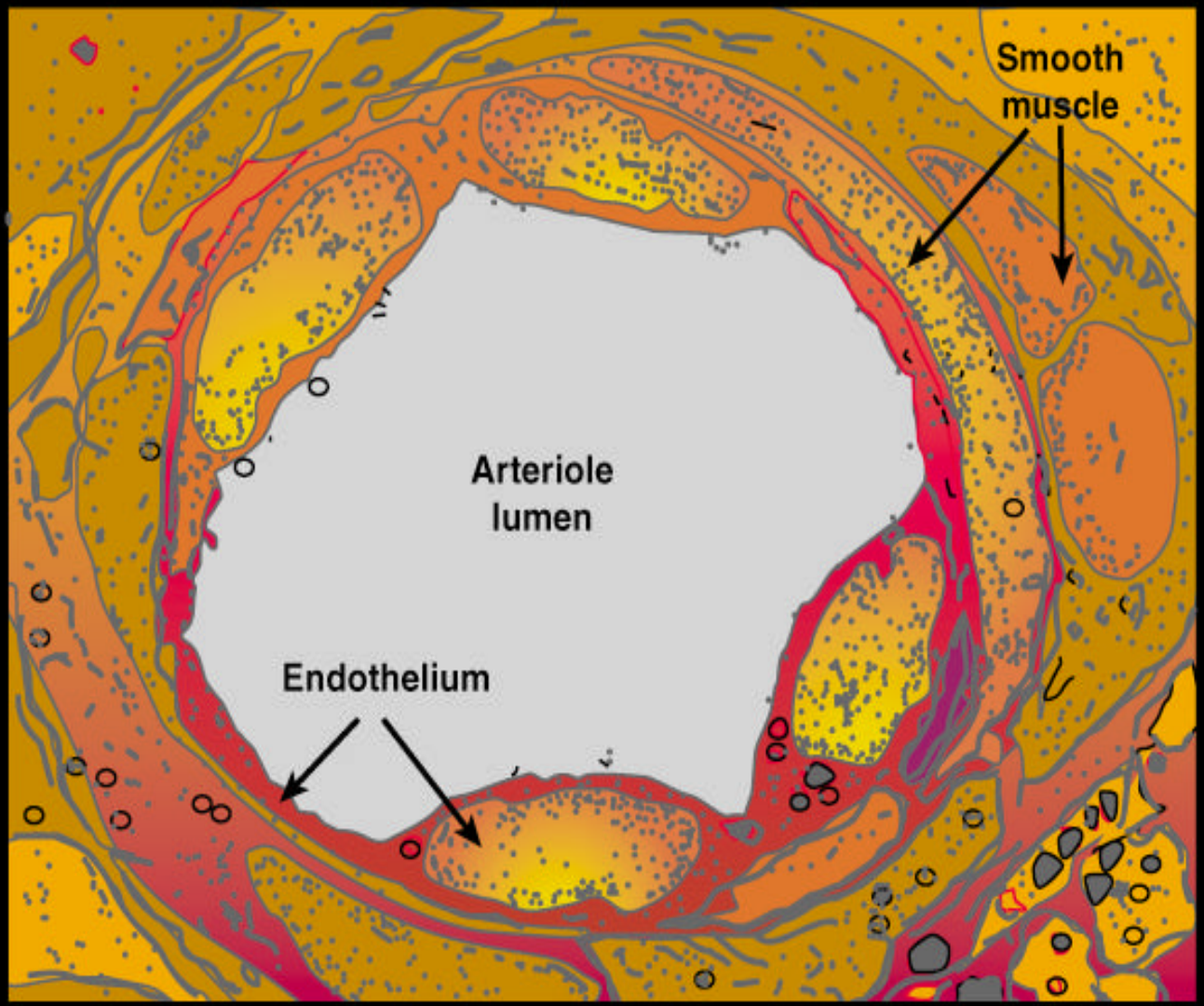
- PEPI trial JAMA 273:199-208, 1995
  - primary prevention
  - examined BP, glucose, fibrinogen, HDL
- HERS trial JAMA 280(7):605-613, 1999
  - secondary prevention
  - examined clinical outcomes

Estrogen's Lipid Effects

- ↑ HDL
- ↑ Triglycerides
- ↓ LDL
- ↓ Total cholesterol (and ratio)
- ↓ Apolipoprotein B
- ↓ Lipoprotein (a)

VBWG

The endothelium: A living organ



The endothelium maintains vascular health

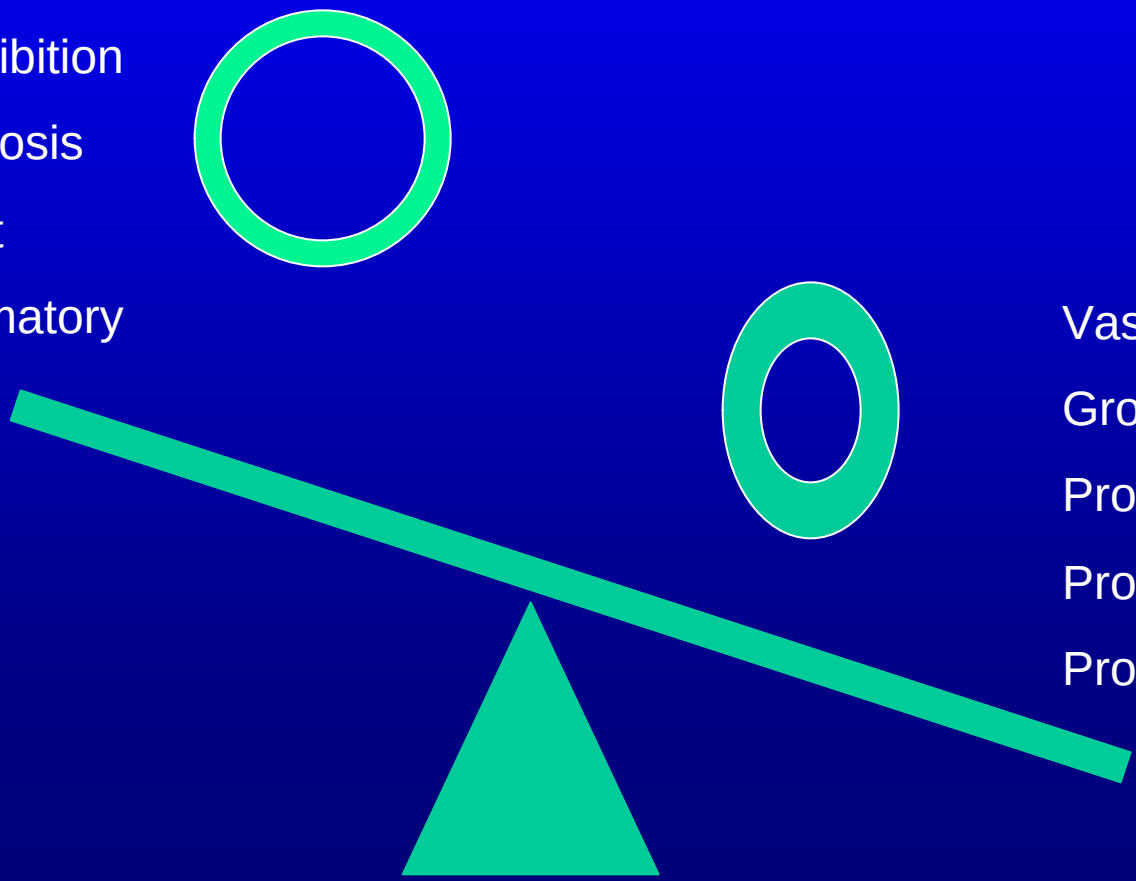
Vasodilation

Growth inhibition

Antithrombosis

Antioxidant

Antiinflammatory



Vasoconstriction

Growth Promotion

Prothombosis

Prooxidant

Proinflammatory

Endothelial Dysfunction

Elevated BP, diabetes, smoking, hyperlipidemia

Endothelial dysfunction

↓NO ↑ PAI-1 ↑ Angiotensin II ↑Endothelin

AT_1

vasoconstriction, thrombosis, inflammation, smooth muscle cell growth, plaque rupture

Substances that improve endothelial function

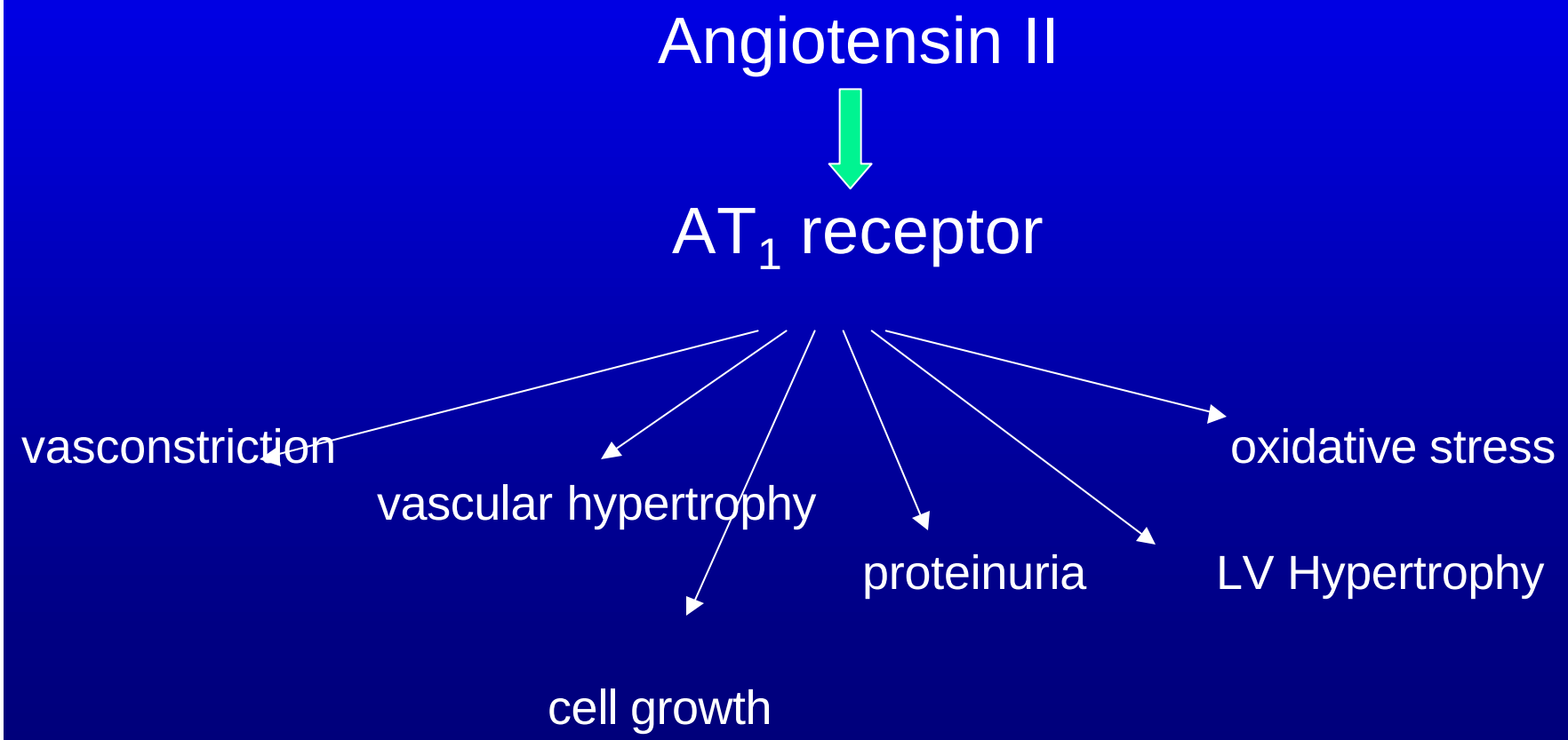
- Statins
- ACE inhibitors
- Ascorbic Acid
- Thiazolidinediones
- Vitamin E
- Estrogen

Estrogen's Endothelial Effects

- ↓ endothelin-1, ↓ PAI-1, ↓ homocysteine
- ↑ prostacyclin
- ↑ vasodilatation by ↑ NO and NOS
- ↑ vascular smooth muscle cell sensitivity to NO
- ↑ calcium transport out of vascular smooth muscle
- Antioxidant by ↓ LDL uptake and ↑ degradation
- **Downregulates the AT_1 receptor**

Nickenig et al., *Circ* 102:1828, 1000

Role of the AT_1 receptor



Angiotensin II type-1 and type-2 receptors

AT_1 receptor

- Vasoconstriction
- Growth stimulation
- Anti-apoptotic
- Prothrombotic
- Profibrotic
- Prooxidant

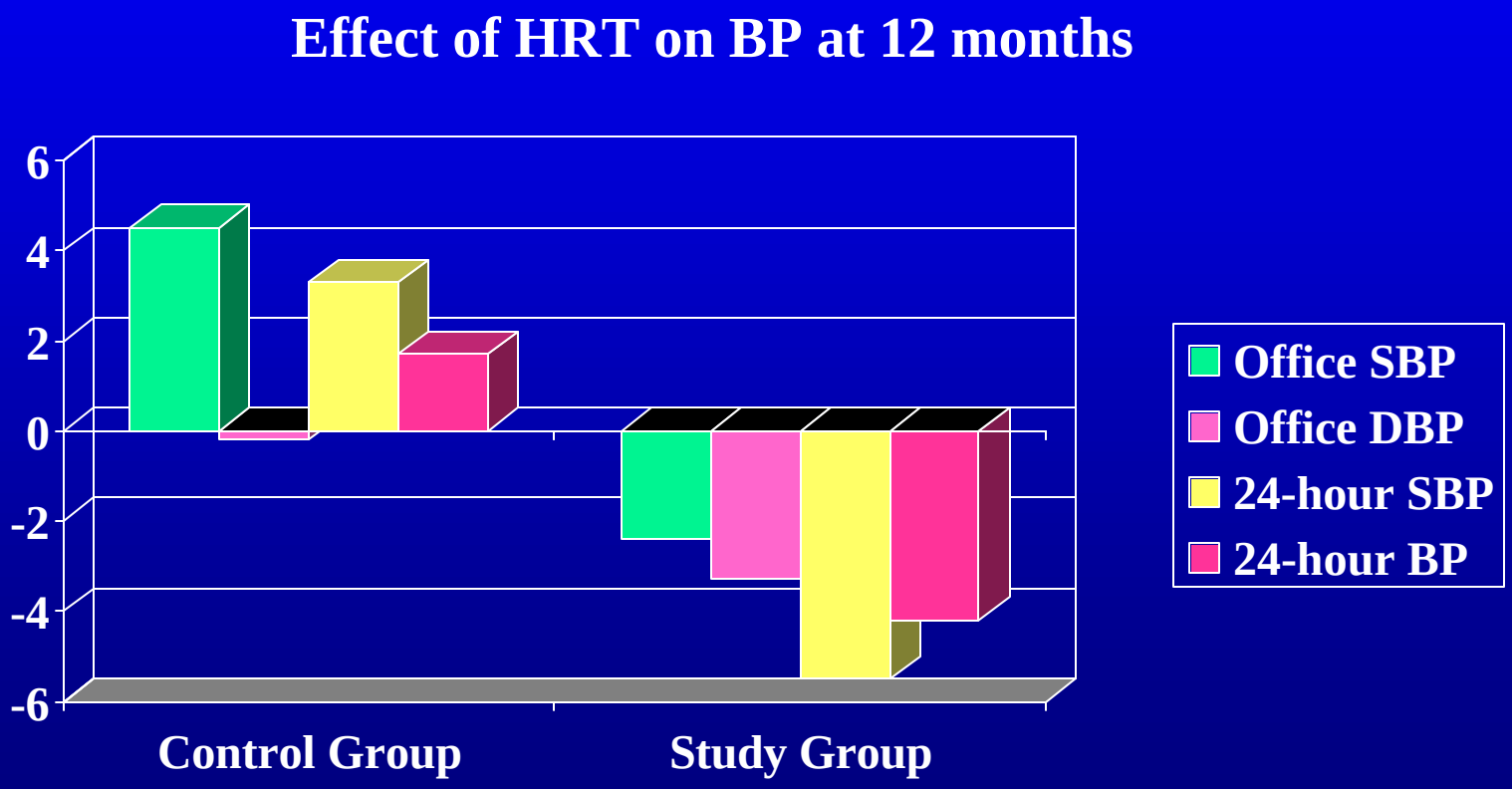
AT_2 receptor

- Vasodilation
- Growth inhibition
- Pro-apoptotic
- ? Fibrosis
- ? Thrombosis
- ? Redox

Effect of HRT on BP in hypertensives

- Acute estradiol ↓ BP
  - Both oral and transdermal administration
- Acute estradiol ↑ LV diastolic function
- Estradiol converts non-dippers to dippers
- Estradiol ↓ LVM and the incidence of LVH
- Estradiol ↓ proteinuria

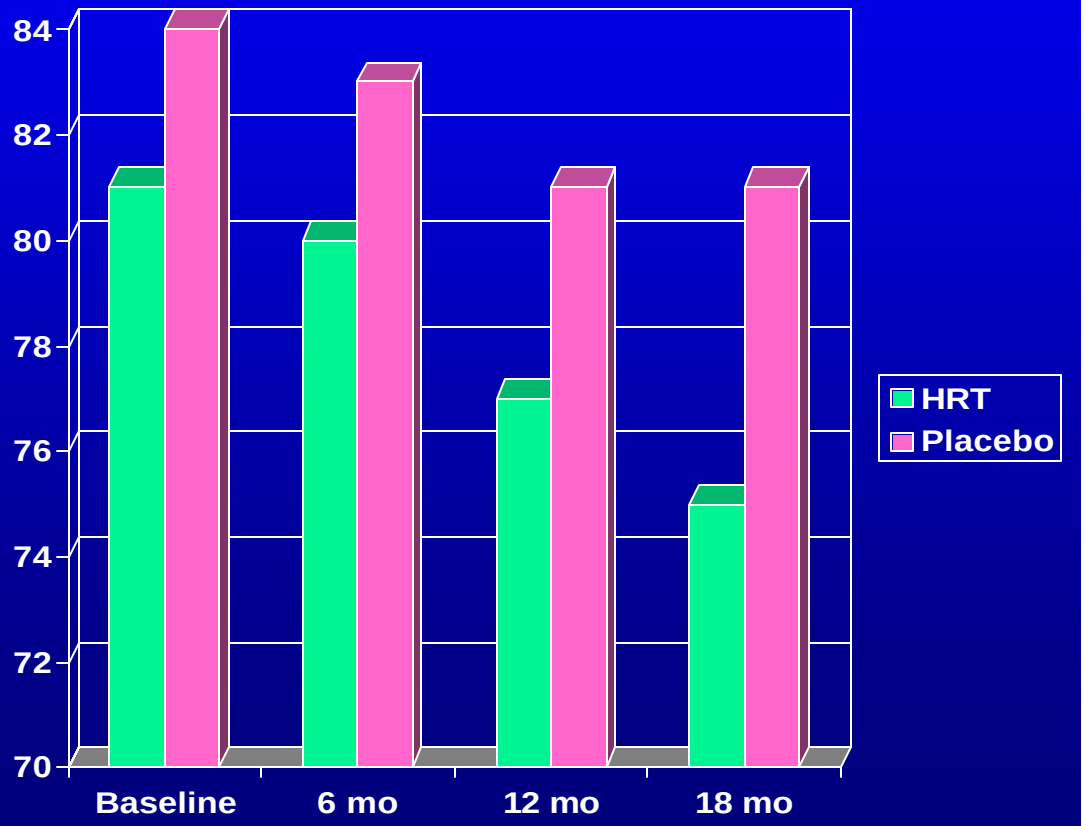
HRT decreases BP in normotensives



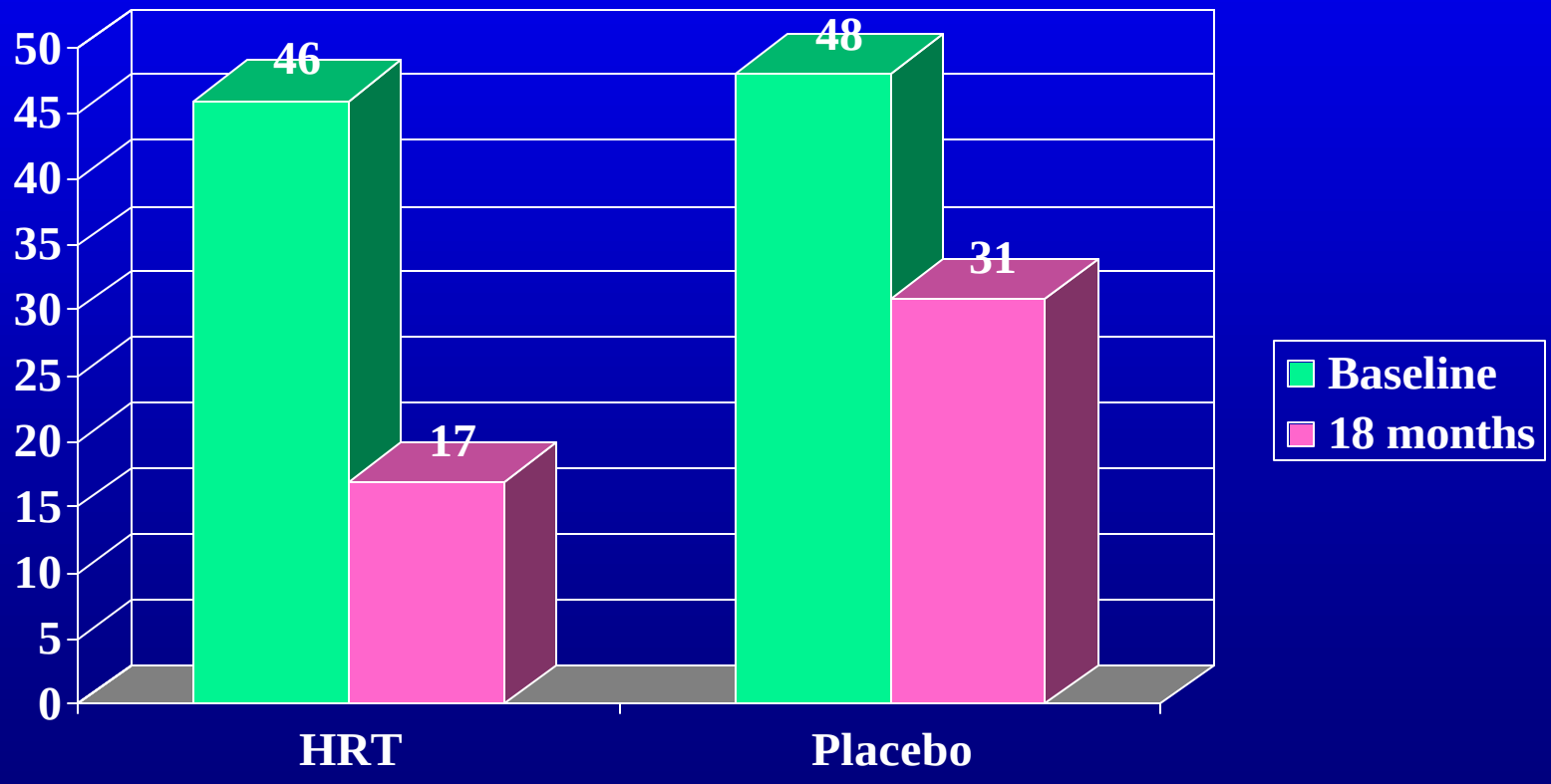
Am J Hypertens 11:1147, 1998

HRT decreases left ventricular mass

- **200 hypertensives**
- **HRT or placebo**
- **2-D echo**
- **BP 120/80 with tx**
- ***P* = .031**



HRT reduces incidence of LVH



Modena *Am J Hypertens* 1999

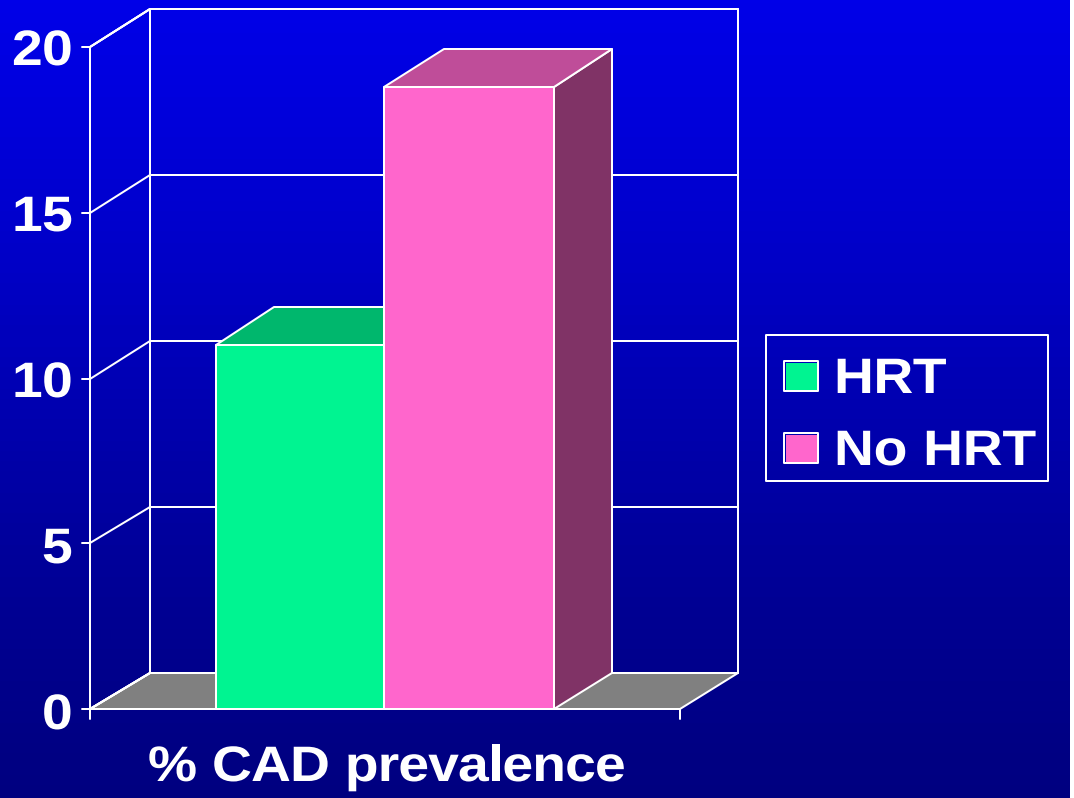
Observational Studies: HRT confers a 50% risk reduction

- Over 45 population studies in healthy women and women with CAD
- RR Reduction with HRT ranges from 30-80%
- Nurses' Health Study: 50% risk reduction

RR of MI in a Medicaid Population

RR 58%, (95% CI 53-63%)

P < .0001



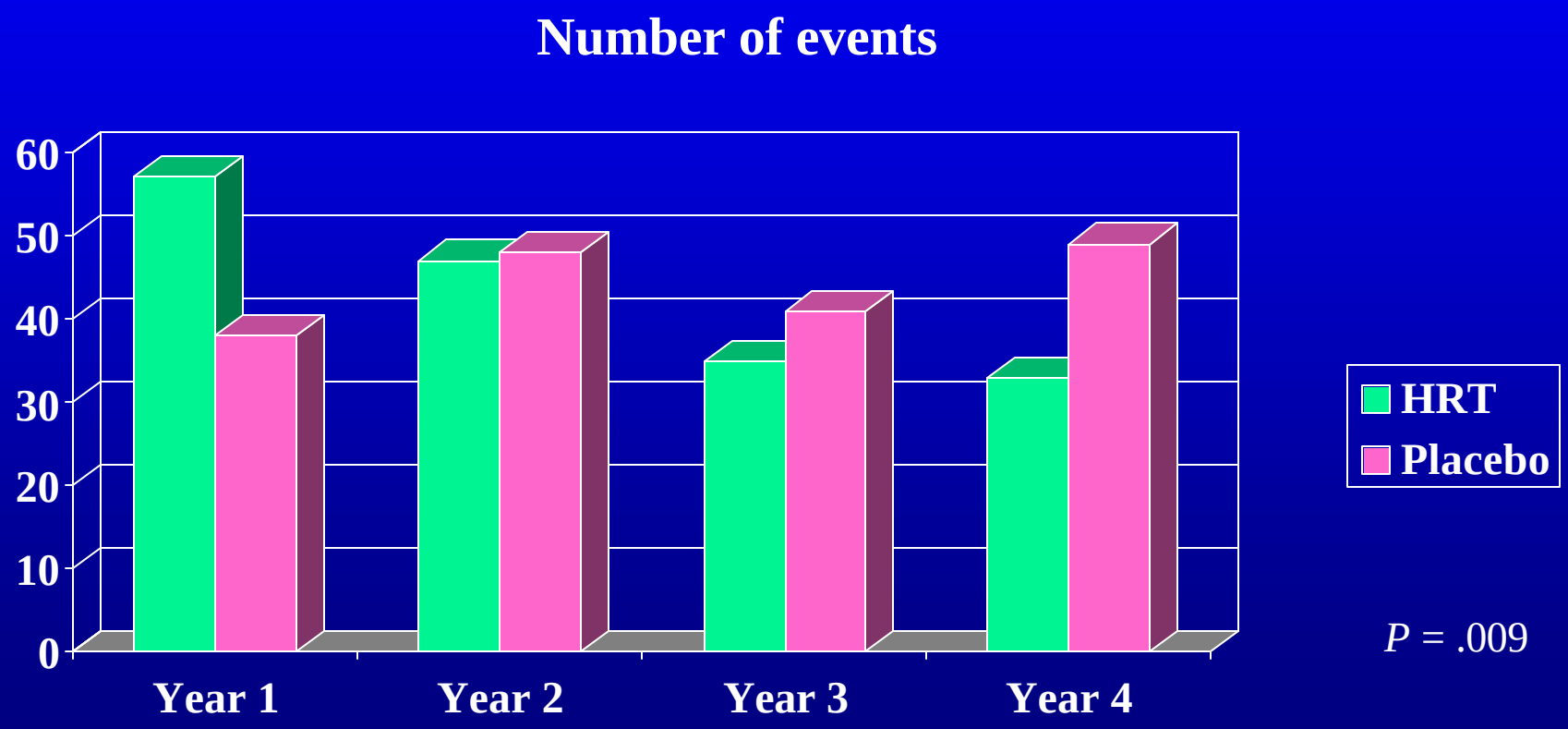
Sherif 2001

Heart & Estrogen/Progestin Replacement Study

- 2763 women with CAD
- Equine estrogen + continuous MPA vs. placebo
- End points: nonfatal and fatal cardiac effects
- Increased risk of events in 1st year with HRT

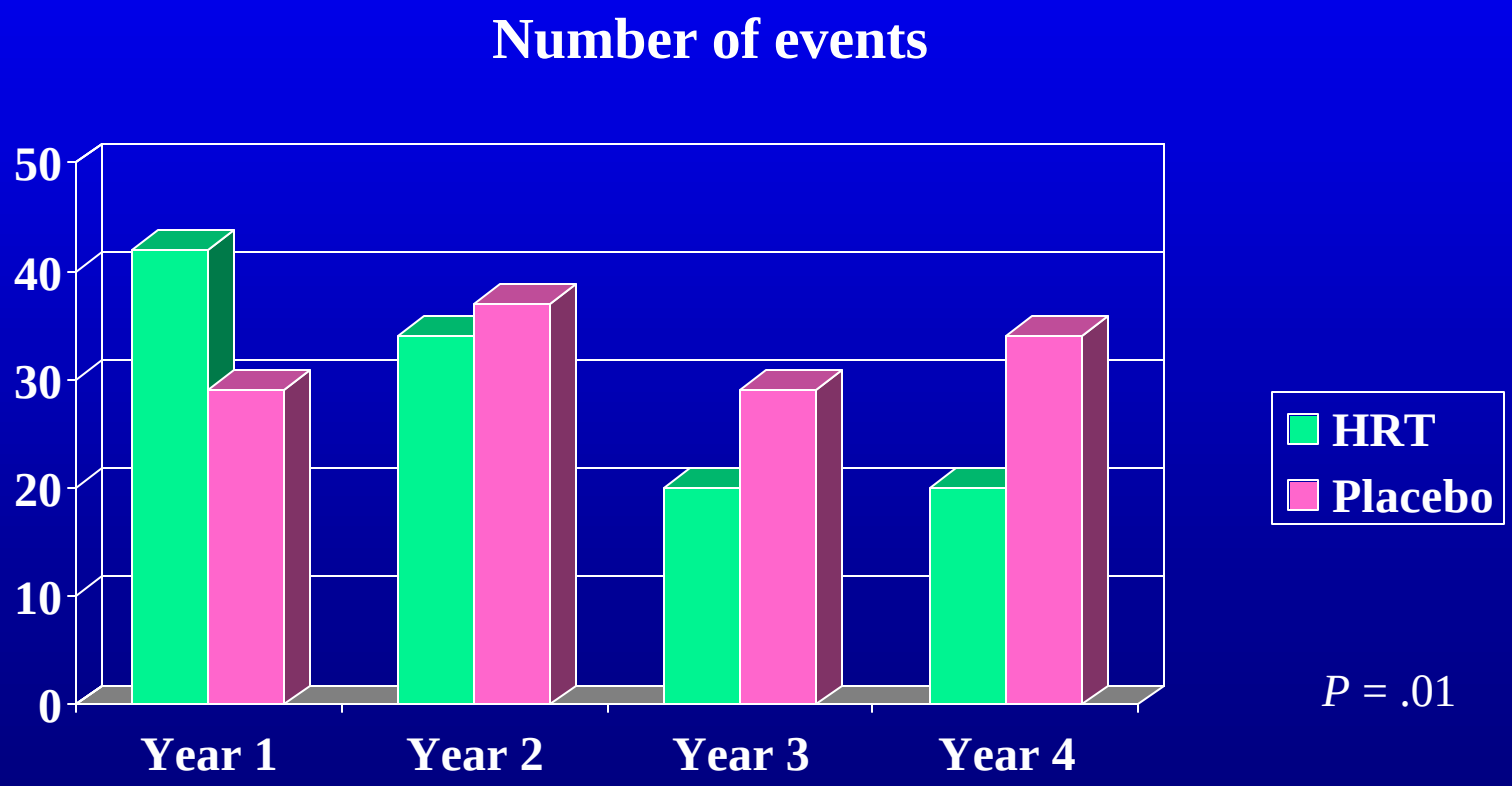
JAMA 280(7):605-613, 1999

HERS: nonfatal MI & CHD death



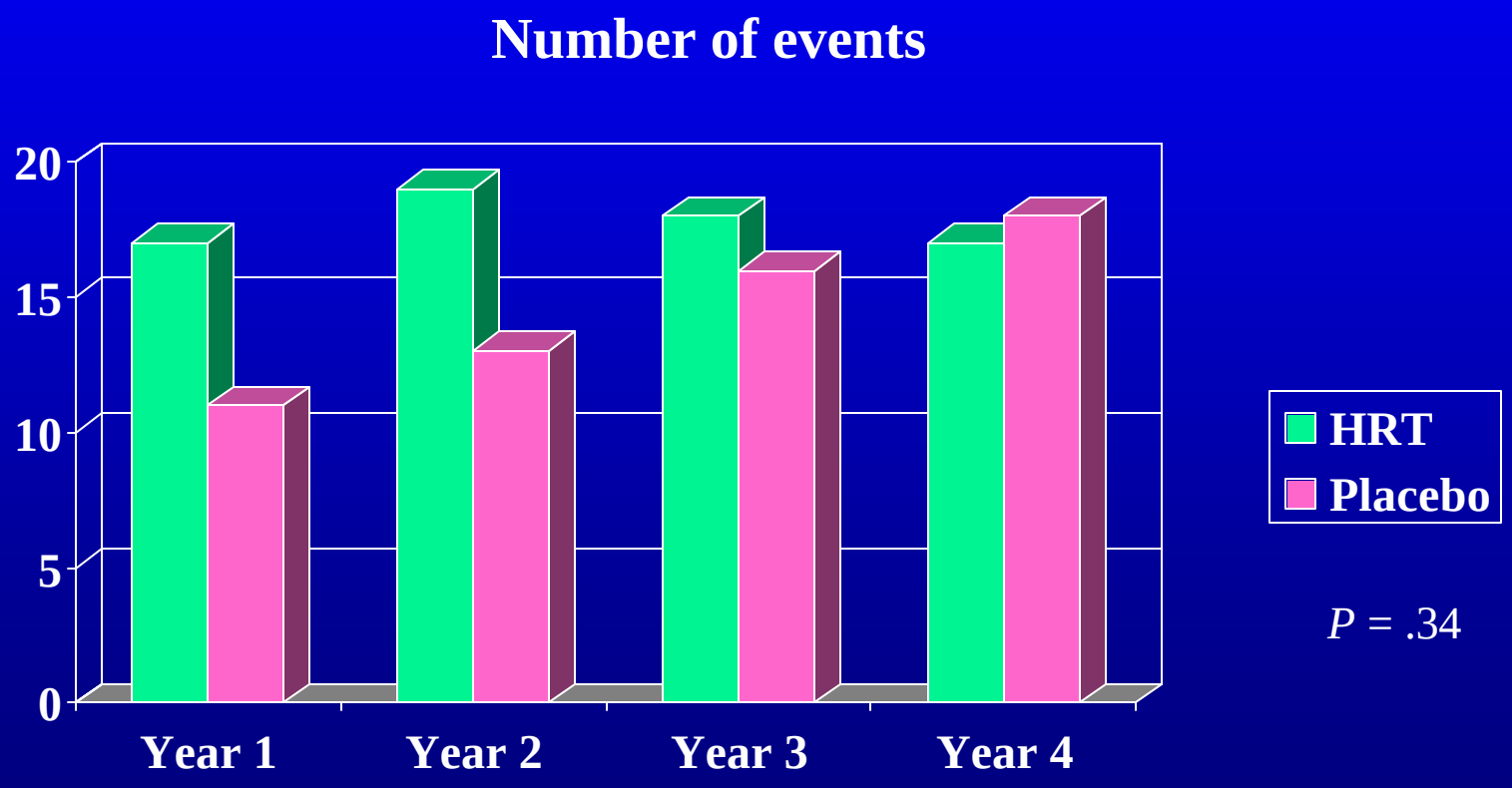
P = .009

HERS: nonfatal MI

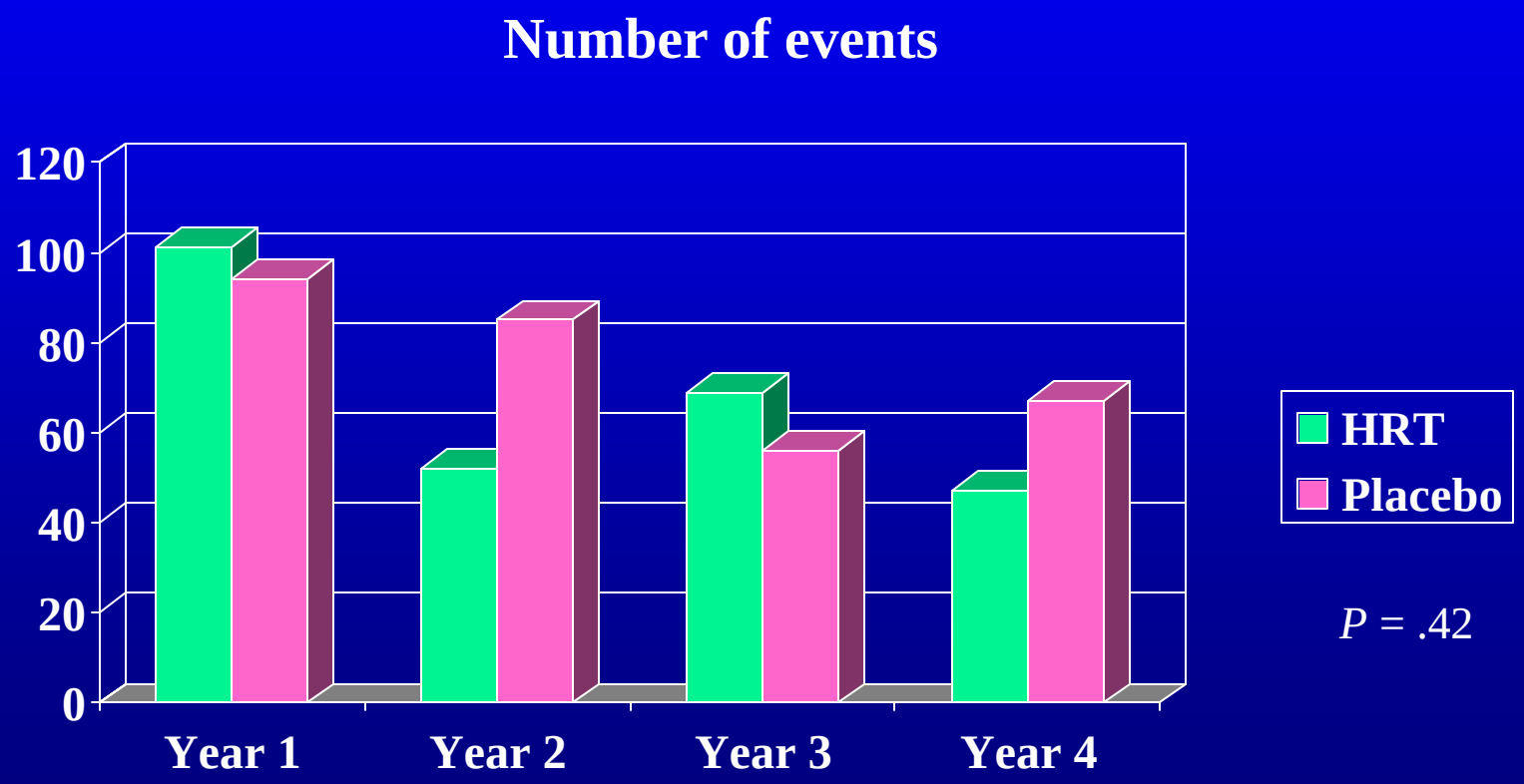


P = .01

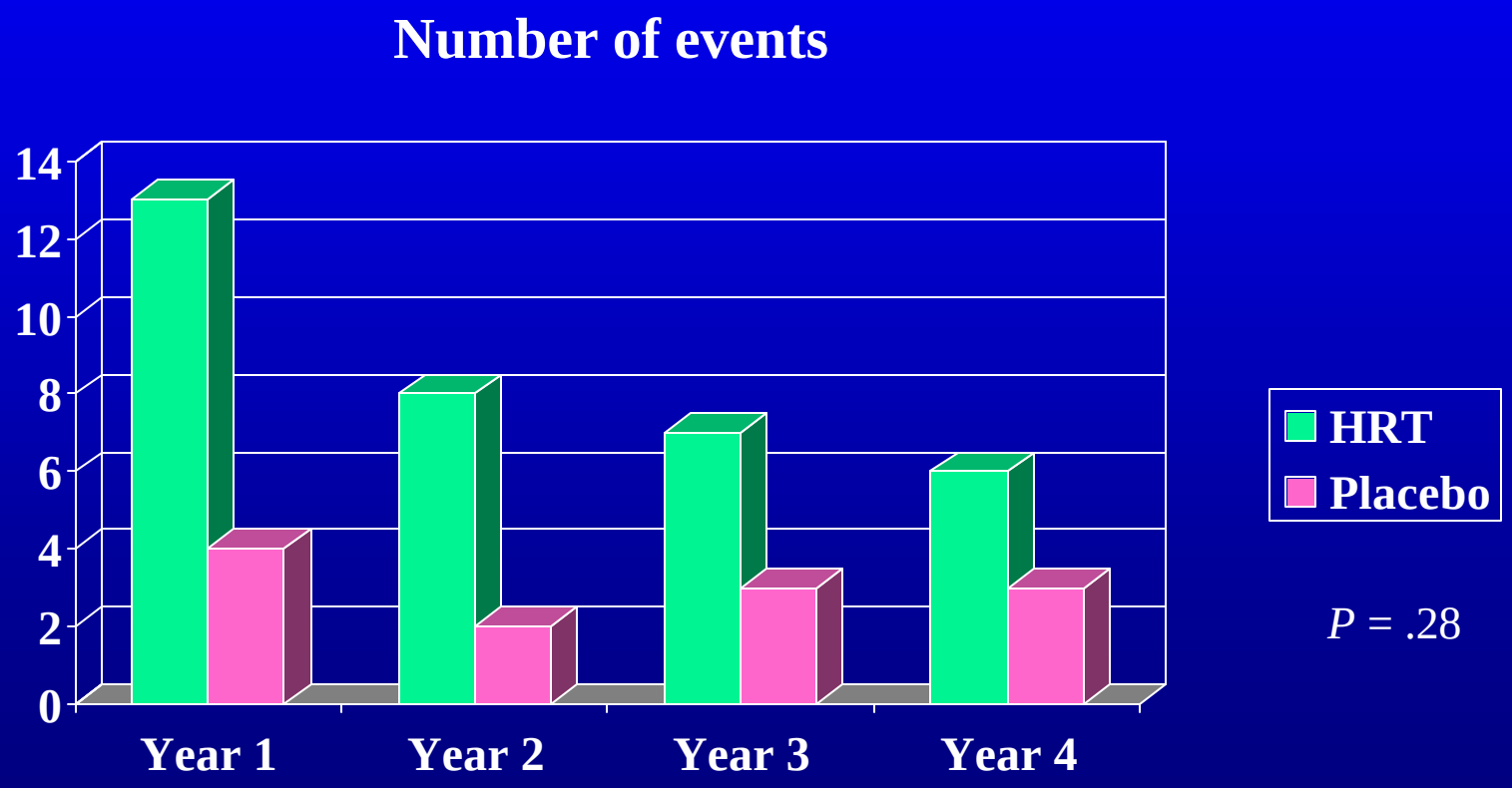
HERS: CHD death



HERS: unstable angina, CABG, PCI



HERS: Venous thromboembolism

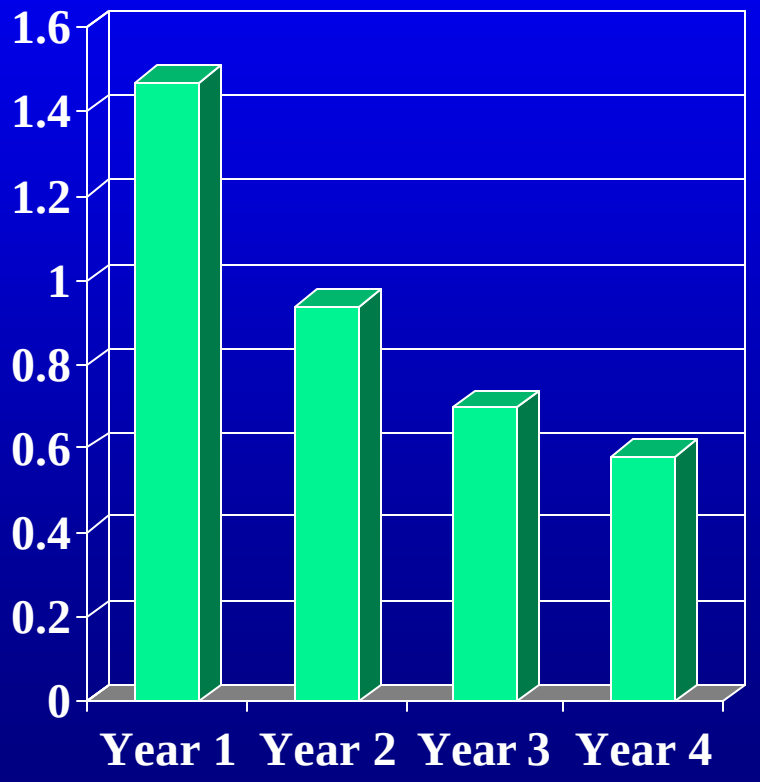


HERS: RR of nonfatal MI with HRT

Relative Risk

Year 1	1.47
Year 2	0.94
Year 3	0.70
Year 4	0.58

P = 0.009



Medication use in HERS subjects

- Only 33% were on beta blockers
- Only 45% were on lipid medications
- Only 17% were on ACE inhibitors
- Only 30% were on vitamins

At the end of one year….

- LDL was 125 in the treatment group
- LDL was 140 in the placebo group
- Only 9% of women were at goal LDL

Explanations of the HERS results

- The type of estrogen: CEE
- The type of progestin: MPA
- Prevalence of clotting disorders in a very high-risk population
- Prevalence of homocysteinemia in a very high-risk population
- The interaction of MPA with diseased arteries

Summary

- Cardiovascular disease
  - is very common
  - increases after menopause
  - Results in worse outcomes in women
  - Can be prevented with aggressive risk reduction
- Estrogen has beneficial *lipid* effects
- Estrogen exerts beneficial *endothelial* effects

Is CAD a different disease…..?

- Morbidity & mortality are higher
- Physiologic sex differences
- Differences in risk factors

Or, is it managed differently?

- Diagnosis is made later
- Management is less aggressive

Atherosclerosis is **preventable** in women

- Strategies under the **patient's** control
  - normalize weight, improve diet, stop smoking, exercise
- Strategies under the **physician's** control:
  - Lower lipids aggressively & aim for a higher HDL
  - Screen for diabetes and other risk factors
  - Discuss hormone replacement therapy
  - Start aspirin

Conclusions

- Estrogen has interesting effects on the vascular endothelium
- Estrogen has beneficial effects on risk factors
- The effect of HRT on 1°prevention is unknown
- The effect of HRT on 2°prevention is unknown
- In the HERS trial, CEE & MPA did not prevent cardiac deaths in the first year