WHI

Hormone Therapy (HT) Trials:

- **Estrogen + Progestin** (Uterus)
- **Estrogen-alone** (No uterus)

Opening Remarks; Overview of Session; Introductions

Marcia L. Stefanick, PhD
Principal Investigator
Stanford Clinical Center

Professor of Medicine
Stanford Prevention Research Center
Professor of Obstetrics and Gynecology
Stanford University
Stanford, CA

Overview of Session; Introductions

- **Background, Hypothesis, Design**
  Jacques Rossouw, MD
- **Baseline Characteristics of Hormone Program Participants**
  David Barad, MD, MS
- **Trial Monitoring and Early Stopping**
  Garnet Anderson, PhD

Overview of Session; Introductions

The Estrogen and Progestin (E+P) and Estrogen-alone (E-alone) Trials Results

- **Heart, Brain (Stroke), Blood Clots**
  Judith Hsia, MD
- **Breast and Colon**
  Rowan Chlebowski, MD, PhD
- **Bones**
  Cora E. Lewis, MD, MSPH

Overview of Session; Introductions

The E+P and E-alone Trials Results (cont.)

- **Brain (Cognitive Function, WHIMS)**
  Sally Shumaker, PhD
- **Summary**
  Marcia Stefanick, PhD

Background, Hypothesis, Design

Jacques Rossouw, MD
Project Officer
WHI Program Office

National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

Hormone

Role of Hormones* in Preventing Diseases of Aging

** approved to relieve menopausal symptoms and prevent bone loss*

Sources of Evidence at Outset of WHI (1991)

- Epidemiological studies
- Animal models
- Biological effects (e.g, blood cholesterol)
- Trials with surrogate outcomes (e.g., angiography, bone mineral density)

But: no adequate clinical trials with disease endpoints

An increasing number of asymptomatic and older women were being prescribed "HRT" to prevent diseases of aging, e.g. coronary heart disease, osteoporosis

Recommendations in the 1990s

1992 American College of Obstetricians and Gynecologists

"Probable beneficial effect of estrogen on heart disease"

1992 American College of Physicians

"Women who have coronary heart disease or who are at increased risk of coronary heart disease are likely to benefit from hormone therapy"

1996 American Heart Association

"ERT does look promising as a long-term protection against heart attack"

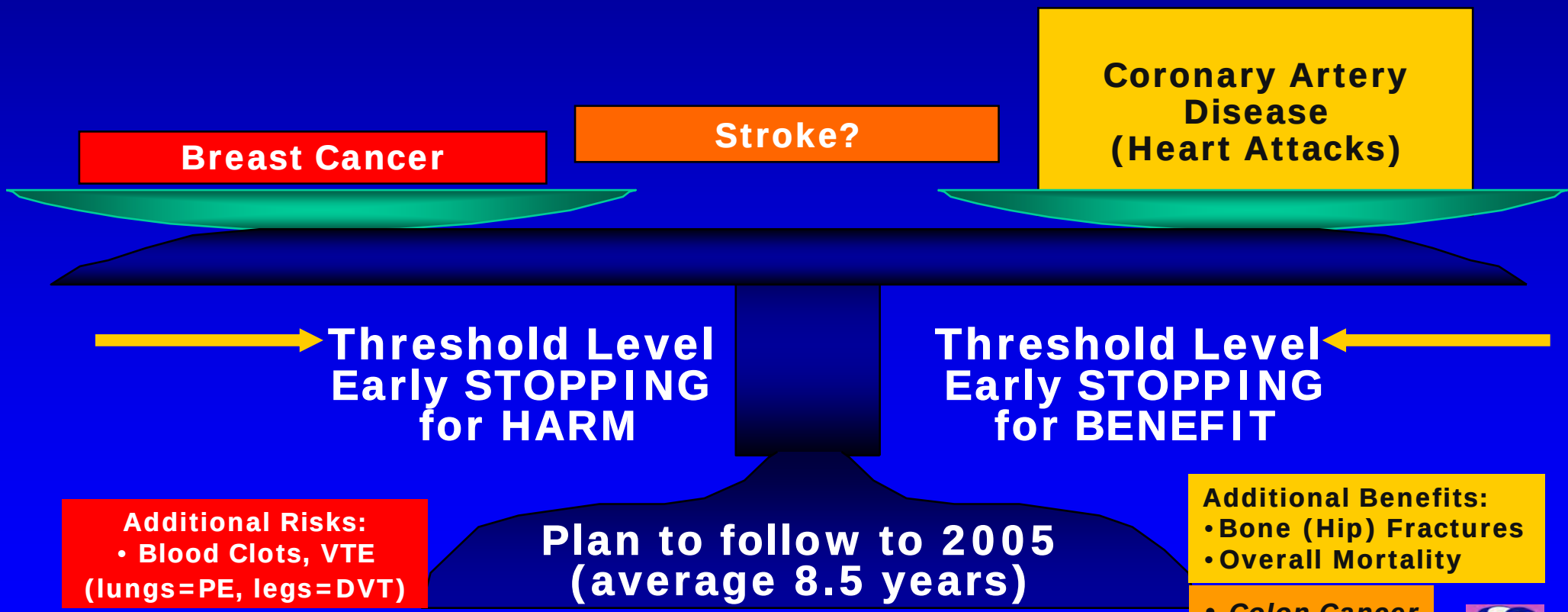
WHI Hormone Trials: Specific Aims

To test whether **Estrogen-alone (E-alone)**
- or- Estrogen + Progestin (E+P)

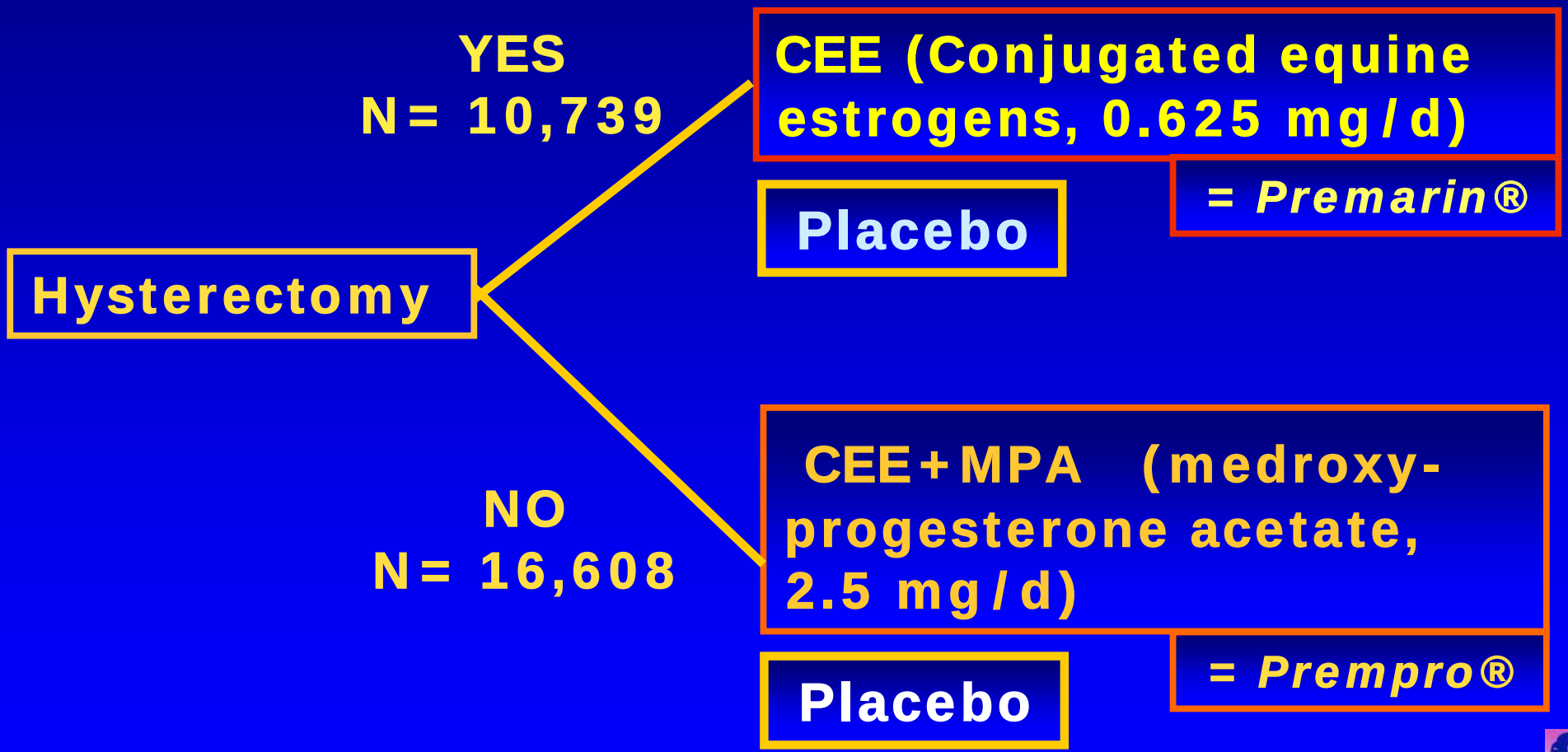
- **reduce the incidence of Coronary Heart Disease**
- **increase the risk of Breast Cancer**
- **reduce the incidence of Hip Fracture and other Osteoporosis-related fractures**

To determine the **balance of risks and benefits of menopausal hormones on the overall health** of **postmenopausal women, aged 50-79** (baseline).

WHI Hormone Trials: Baseline Hypotheses



Women's Health Initiative Hormone Trials



WHI HT Trials: Sample Size, Outcomes, Follow-up

Women, aged 50-79 **Total HT trials = 27,347**

Hormone Treatment Trials

Primary Outcome:

Coronary Heart Disease

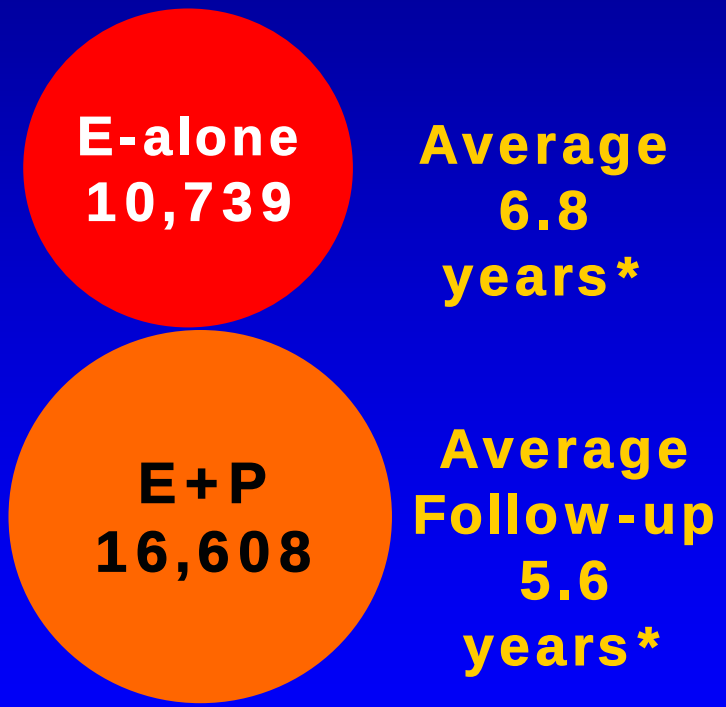
Secondary Outcomes:

Stroke, Pulmonary Emboli,
Breast & Colon Cancers
Hip Fracture; Other Deaths

WHI Memory Study (WHIMS)

***- for women aged ≥ 65*:**

Dementia



*design = 8.5 years

Hormone

Numbers by Age at Randomization

	50-59 yrs	60-69 yrs	70-79 yrs
Estrogen-alone	3310	4852	2577
Estrogen+ Progestin	5522	7510	3576
Both Trials	8832	12362	6153

Baseline Characteristics of E+P and E-alone Participants

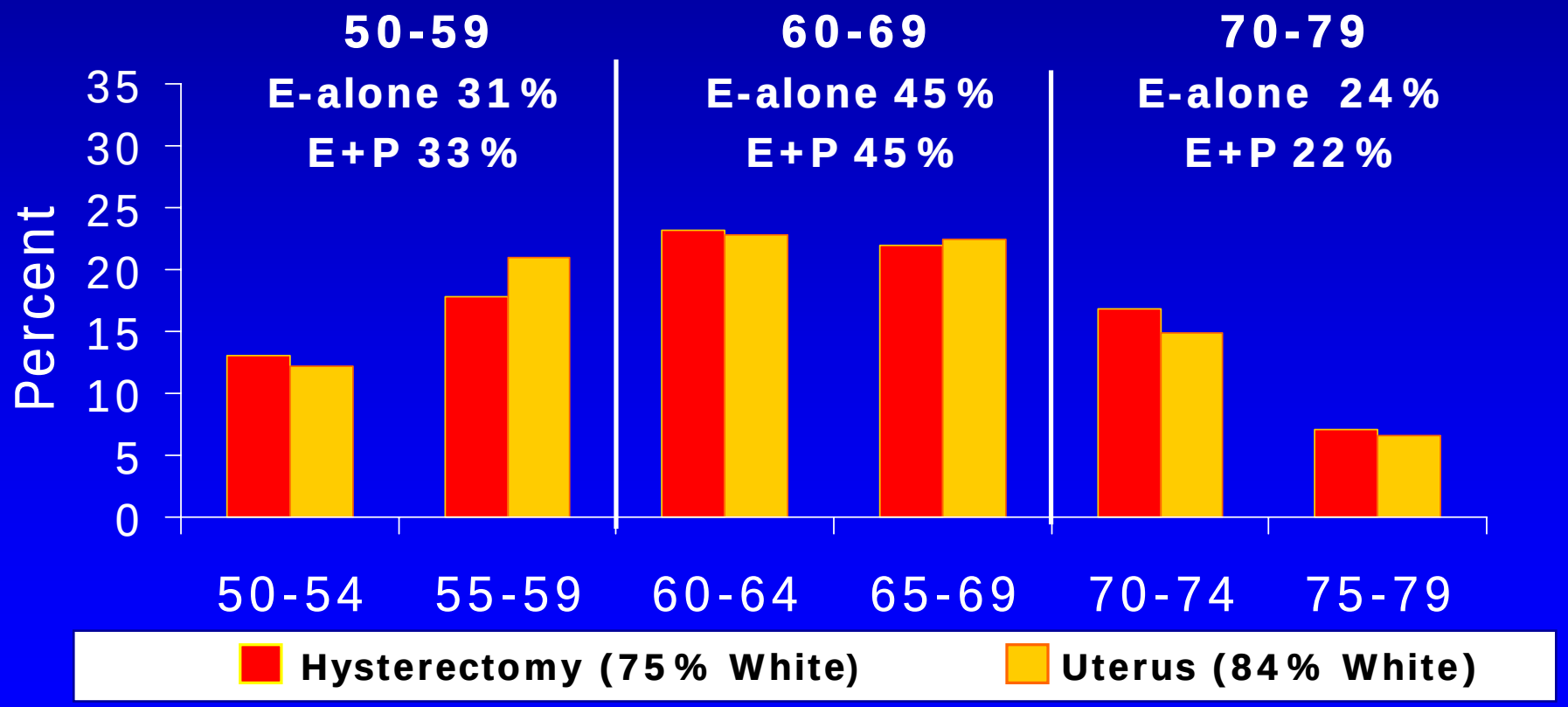
David Barad, MD, MS
Co-Investigator
New York City Clinical Center

Associate Clinical Professor
Department of Epidemiology and Social Medicine
Department of Obstetrics and Gynecology
Albert Einstein College of Medicine
Bronx, New York

WHI HT: Baseline Age Distribution

E-alone Trial = 63.6 ± 7.3 **E+P Trial = 63.3 ± 7.1**

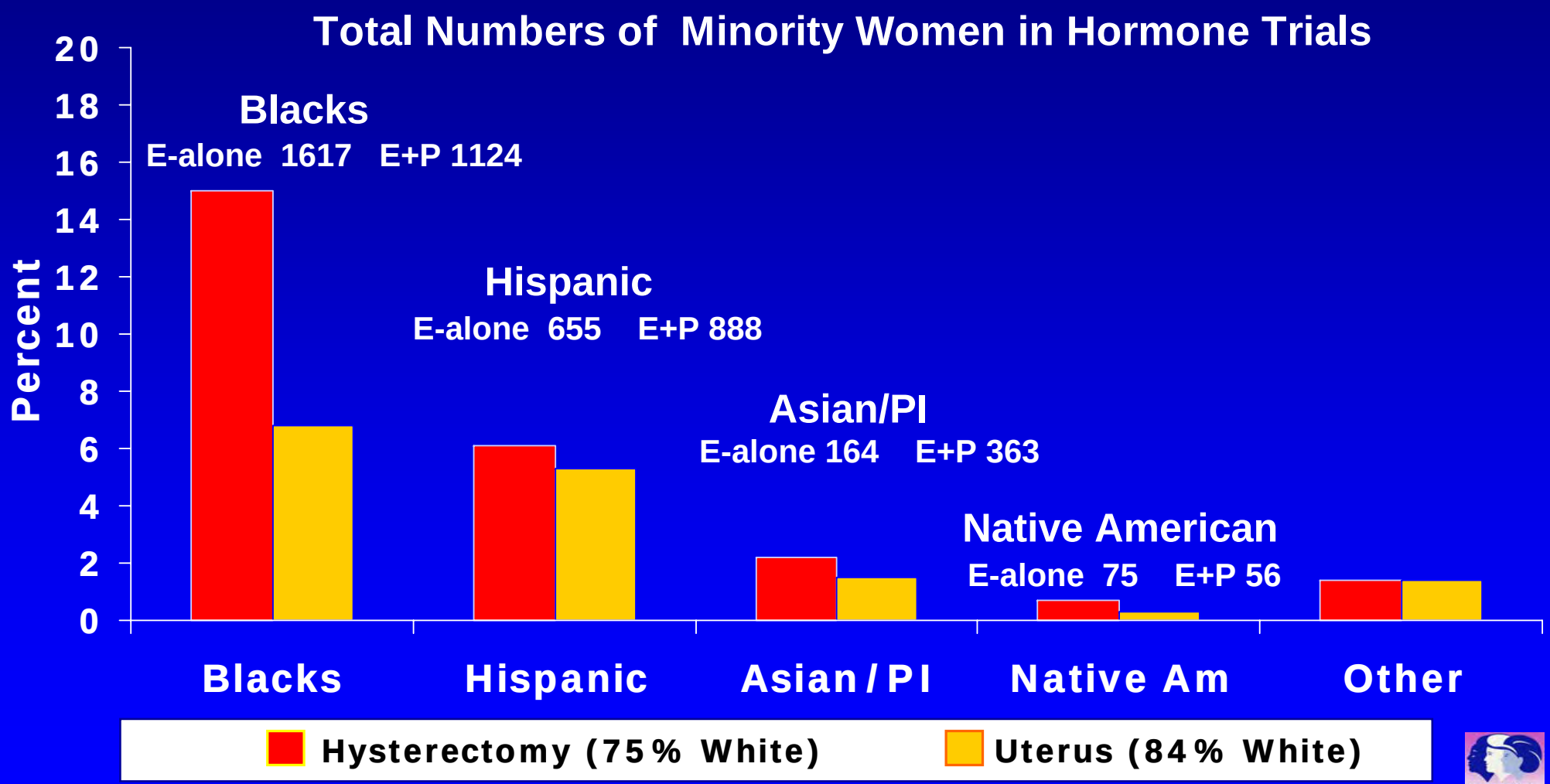
Goal: 50-54: 10%; 55-59: 20%; 60-69: 45%; 70-79: 25%



Ann Epidemiol 2003; 13: S78-S86

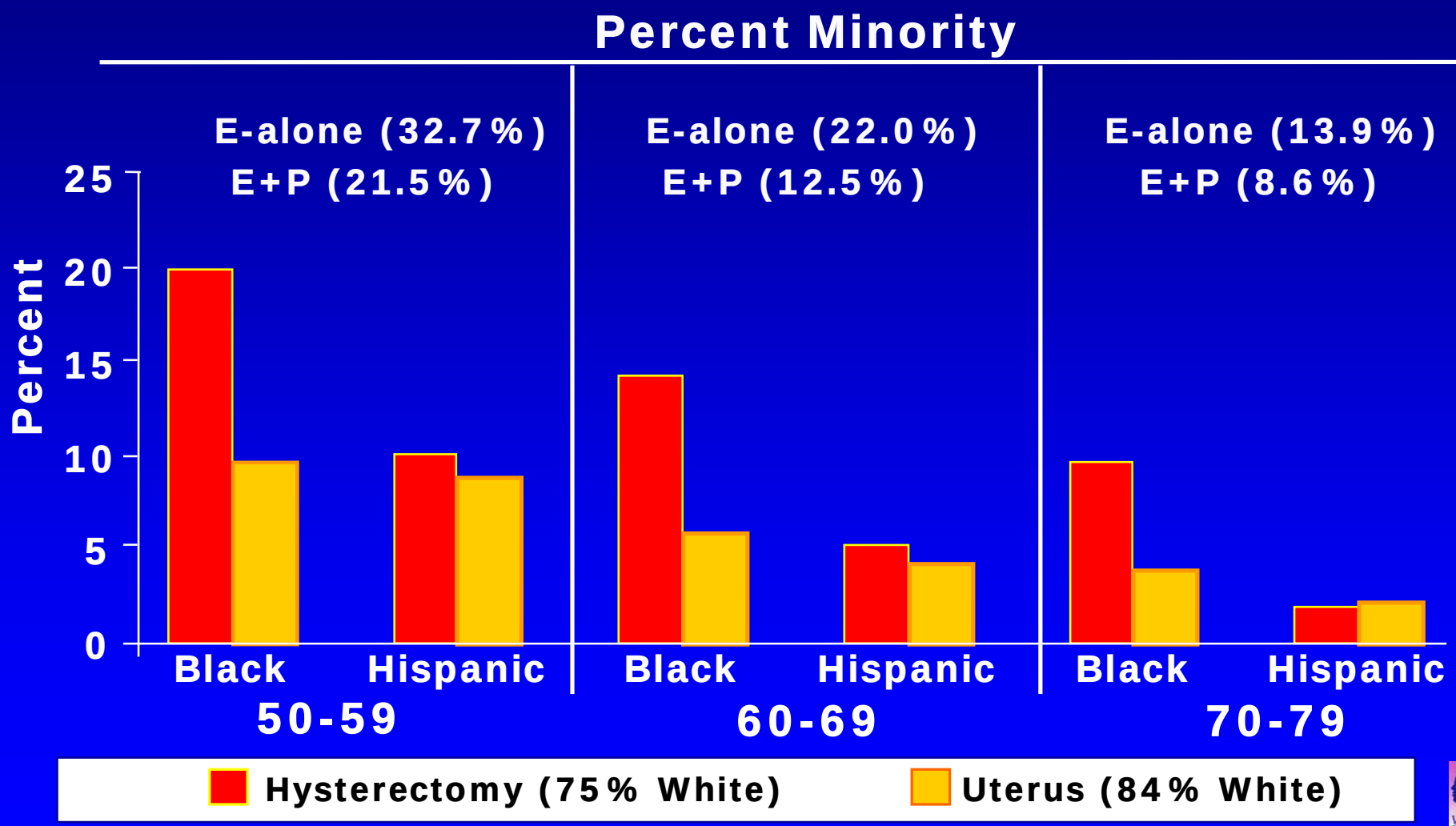
WHI Minority Distribution: Total Numbers (% of Cohort)

E-alone Trial: 2511 (23.3%) E +P Trial: 2531 (14.6%)



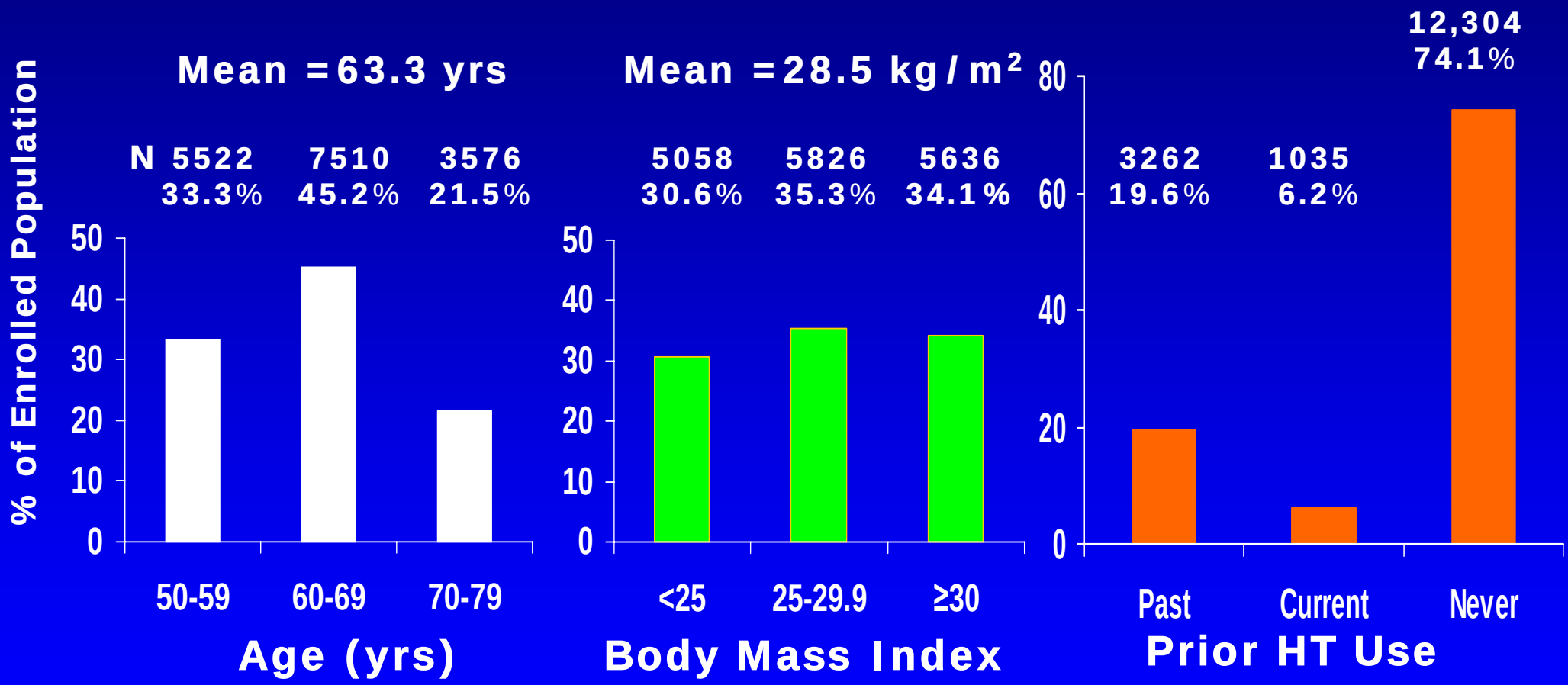
Ann Epidemiol 2003; 13: S78-S86

WHI HT: Ethnic Distribution by Baseline Age



Ann Epidemiol 2003; 13: S78-S86

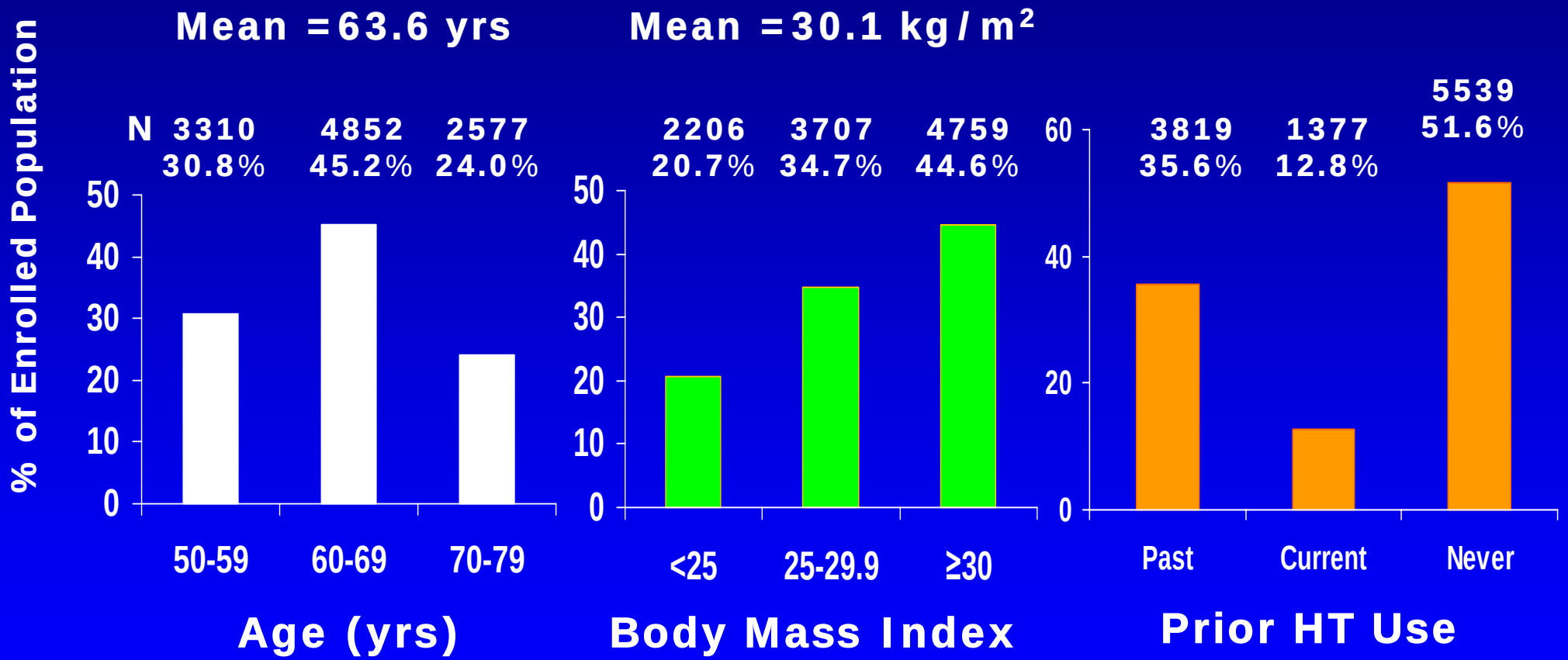
WHI E+P Trial: Baseline Age, BMI, Prior HT Use



JAMA 2002; 288: 321-33

Hormone

WHI E-alone Trial: Baseline Age, BMI, Prior HT Use



Age at Hysterectomy **< 40: 39.8%**
40-49: 42.7% **50-54: 10.0%** **55+: 7.5%**

Bilateral Oophorectomy 40.7%

JAMA 2004; 291: 1701-12

WOMEN'S HEALTH INITIATIVE

Hormone

Selected Differences in Baseline Characteristics between E+P and E-alone Trial Cohorts

	E+P	E-alone
Mean BMI (kg/m^2)	28.5	30.1
Prior HT Use	25.9%	48.4%
Caucasian African American	84.0% 6.7%	75.3% 15.0%
Fracture at age ≥ 55 y	13.6%	13.6%
Mean Gail 5-year Risk	1.5%	1.6%

Selected Differences in Baseline Characteristics between E+P and E-alone Trial Cohorts

History of Cardiovascular Disease or Hypertension

	E+P (%)	E-alone (%)
MI	1.8	3.1
Angina	2.8	5.8
CABG/PTCA	1.3	1.5
Stroke	1.9	1.6
VTE	0.9	1.5
Hypertension	36.1	47.9

Trial Monitoring and Early Stopping

Garnet Anderson, PhD
Co-Principal Investigator
Clinical Coordinating Center

Member, Public Health Sciences Division,
Fred Hutchinson Cancer Research Center

Affiliate Professor, Department of Biostatistics,
University of Washington

Study hypotheses guided trial monitoring and early stopping

Primary Outcome	Coronary Heart Disease
Primary Safety Outcome	Breast Cancer
Secondary Outcomes	Hip Fractures
	Colorectal Cancer
	Endometrial Cancer (E+P only)
	Stroke
	Pulmonary Embolism

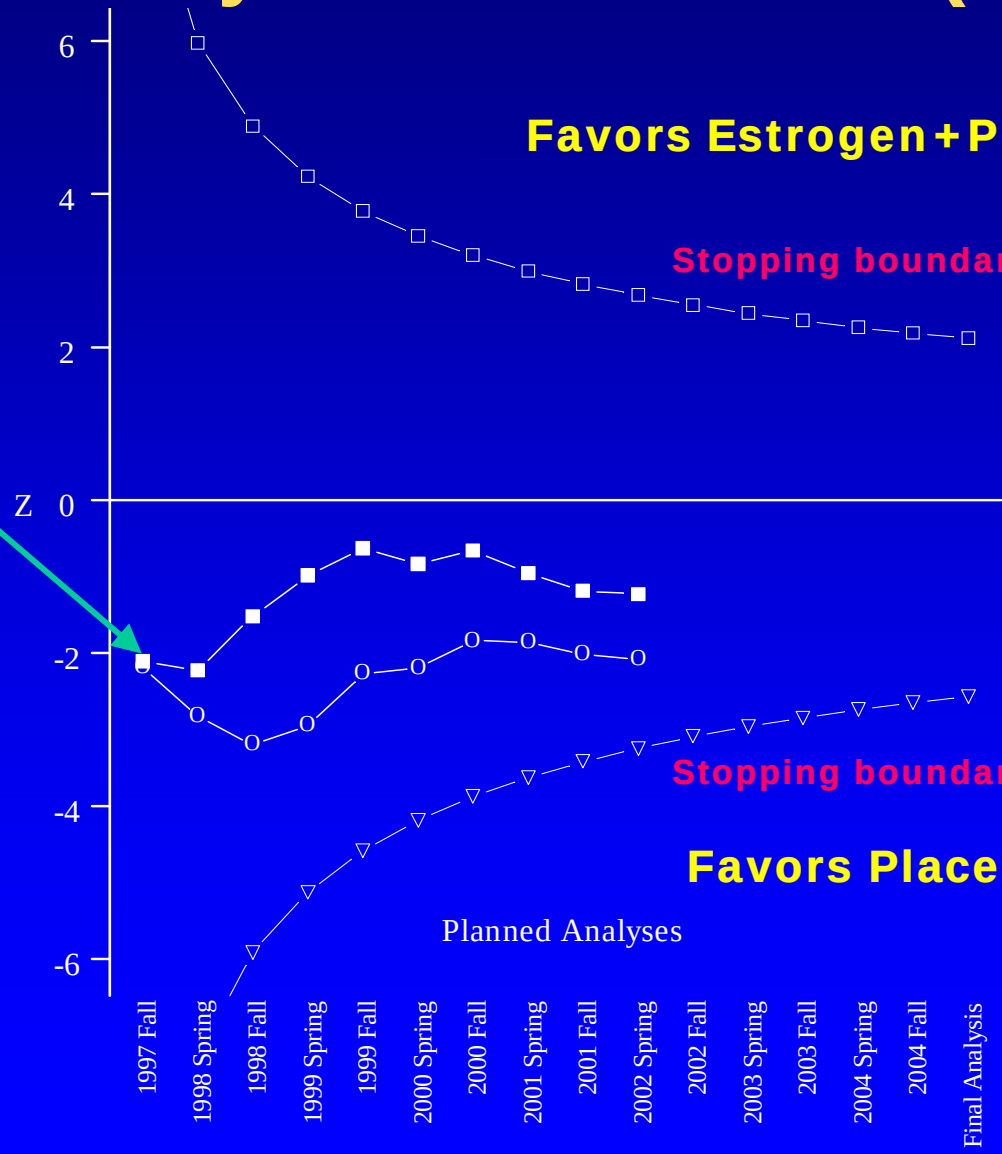
Prevention trial monitoring

- Objective: Ensure ethical conduct of the trial
- Conducted by independent Data and Safety Monitoring Board
- Specific issues in prevention trials:
  - Weighing risks versus benefits
  - Controlling potential errors associated with multiple comparisons
  - Consideration of different timeline for effects

A “Global Index” of risks and benefits

- Counted women in each group who had any of the monitored outcomes
  - Coronary heart disease
  - Stroke
  - Pulmonary embolism
  - Breast cancer
  - Colorectal cancer
  - Hip fractures
  - Endometrial cancer (E+P trial only)
  - + Deaths from other causes
- Analysis compared the global index event rates over time

Monitoring the Estrogen+Progestin Trial
Coronary Heart Disease (CHD)



Statistics comparing disease rates over time

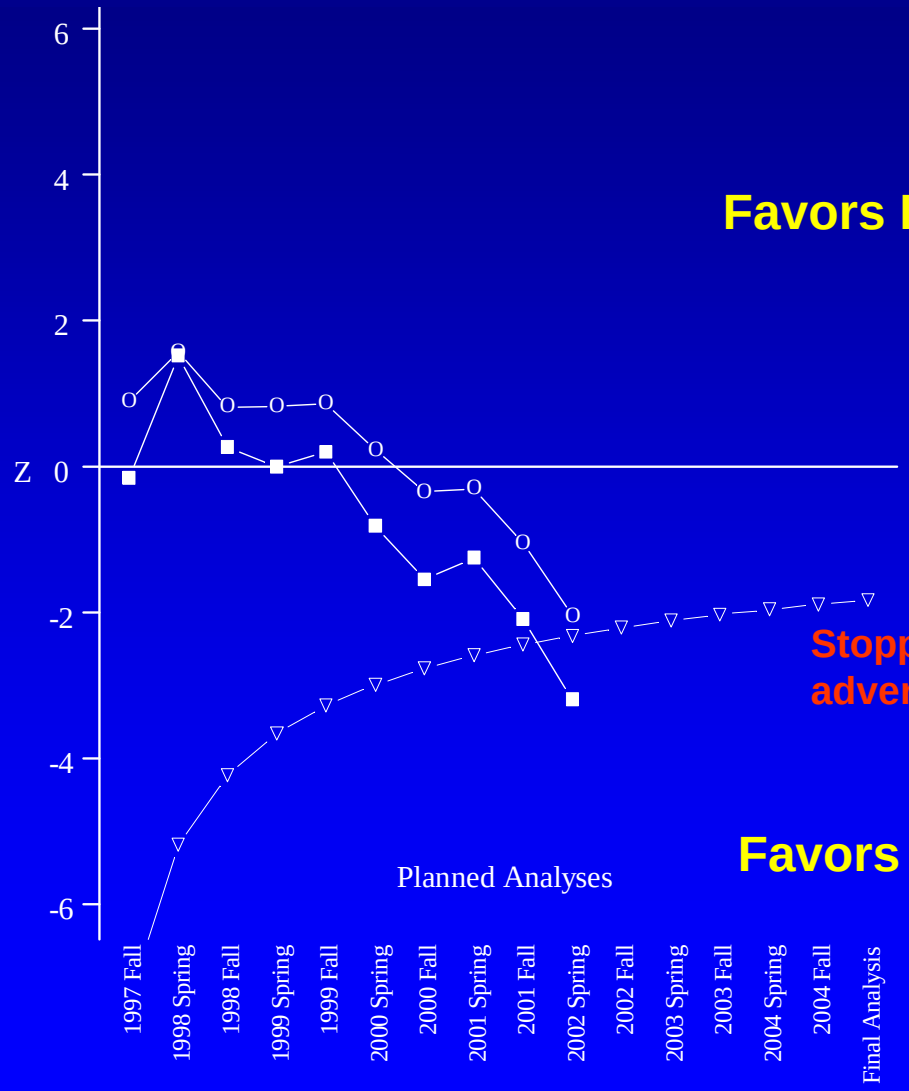
WOMEN'S HEALTH INITIATIVE

Hormone

Monitoring the E+P Trial: Stroke

Hormone

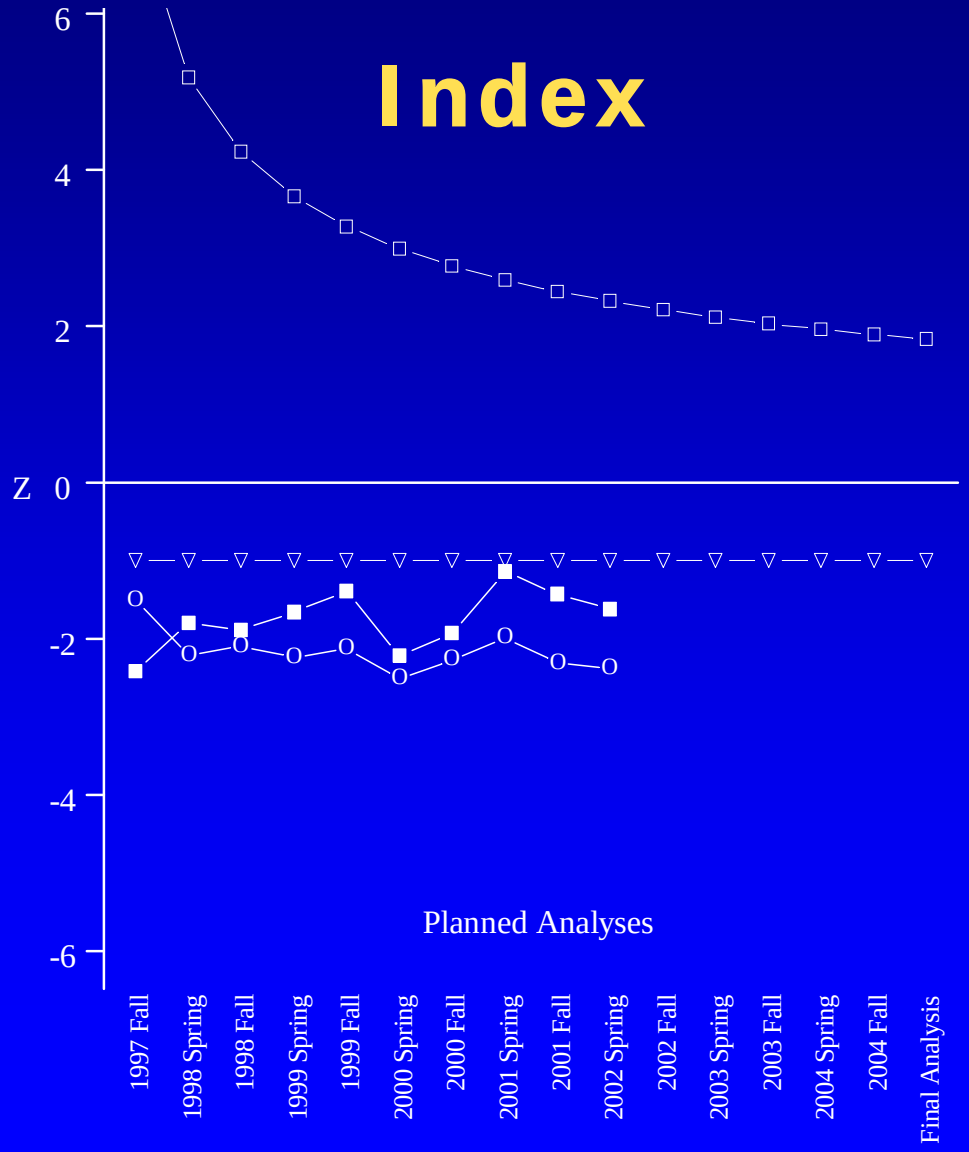
Monitoring the E+P Trial: Breast Cancer



WOMEN'S HEALTH INITIATIVE

Hormone

Monitoring the E+P Trial: Global Index



Stopping boundary for supporting an overall finding of risks exceeding benefits

WOMEN'S HEALTH INITIATIVE

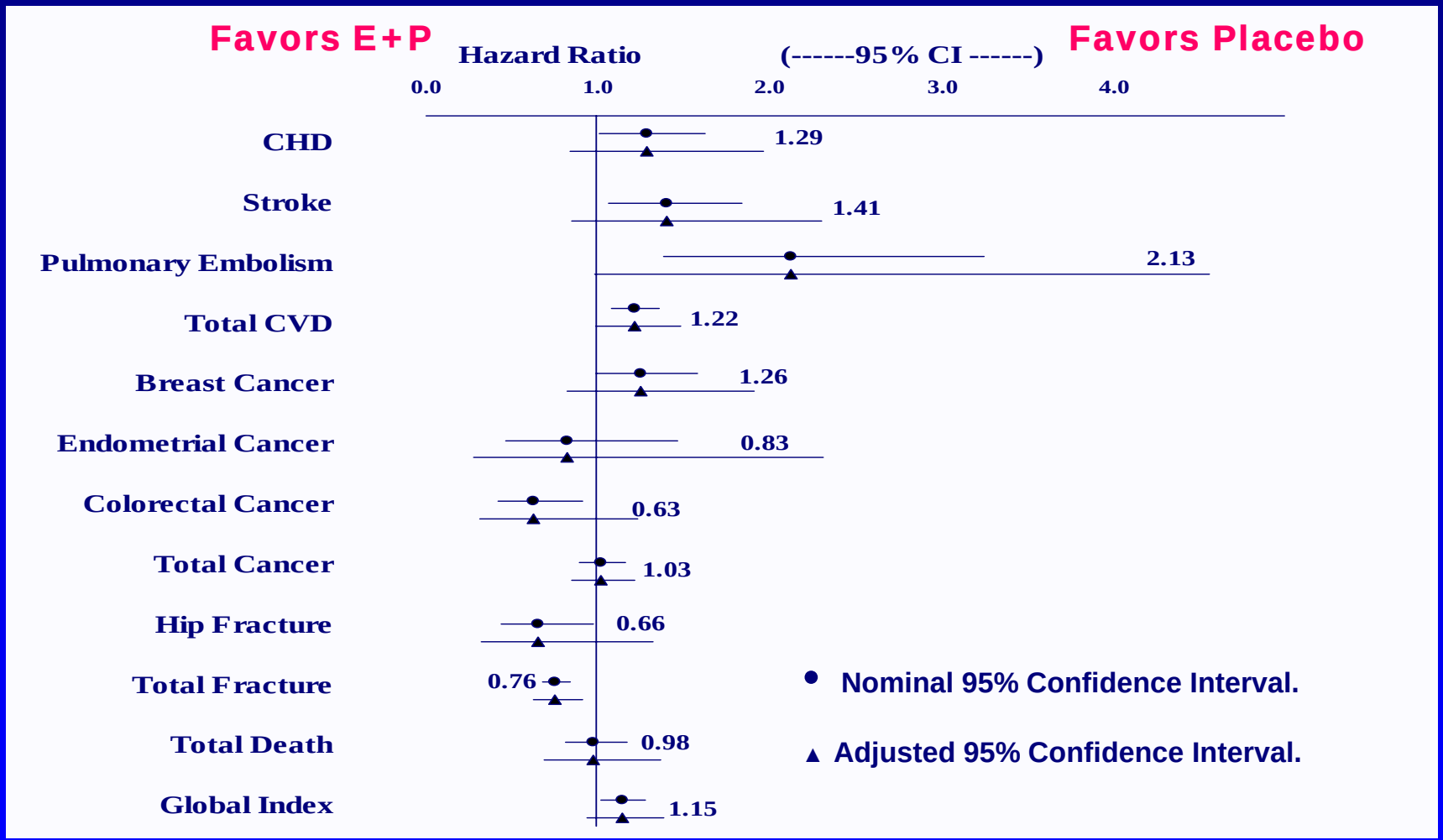
Hormone

Estrogen + Progestin Trial stopped

In May 2002, the WHI Data and Safety Monitoring Board recommended the E+P trial be stopped based on:

- Breast cancer risk significantly increased
- Global index supported harms exceeding benefits

Risks and benefits of Estrogen+Progestin

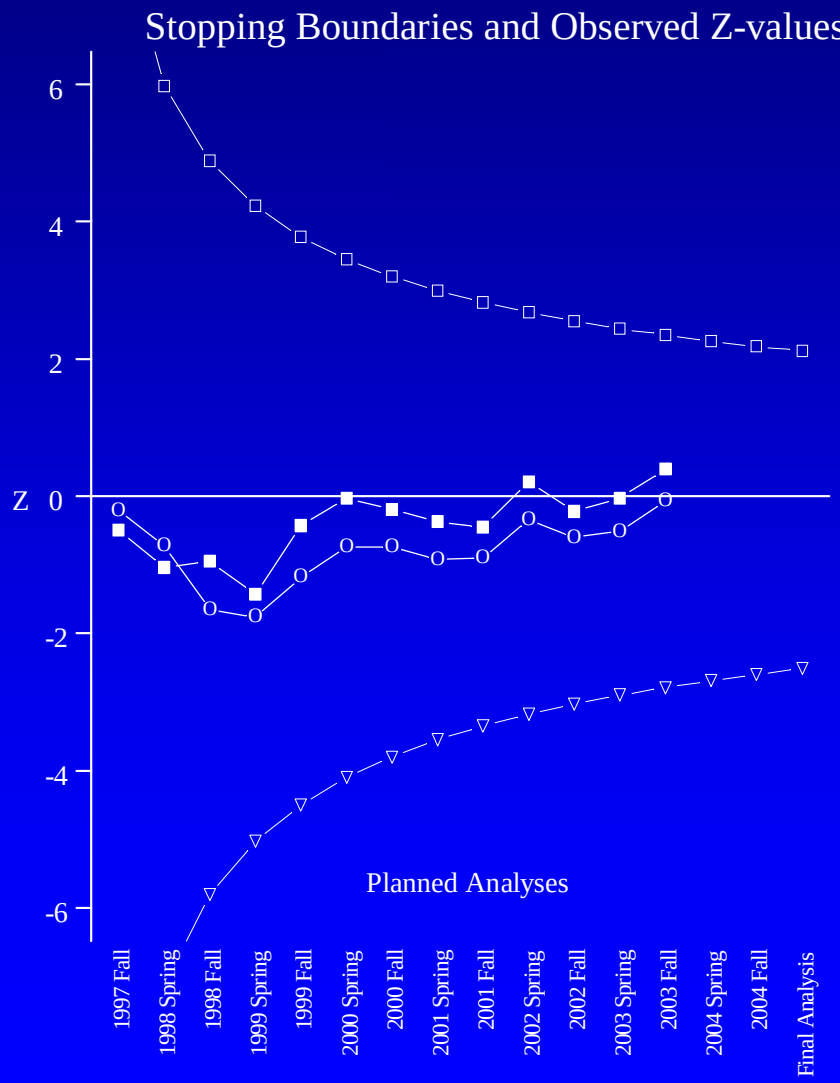


JAMA 2002; 288:321-33

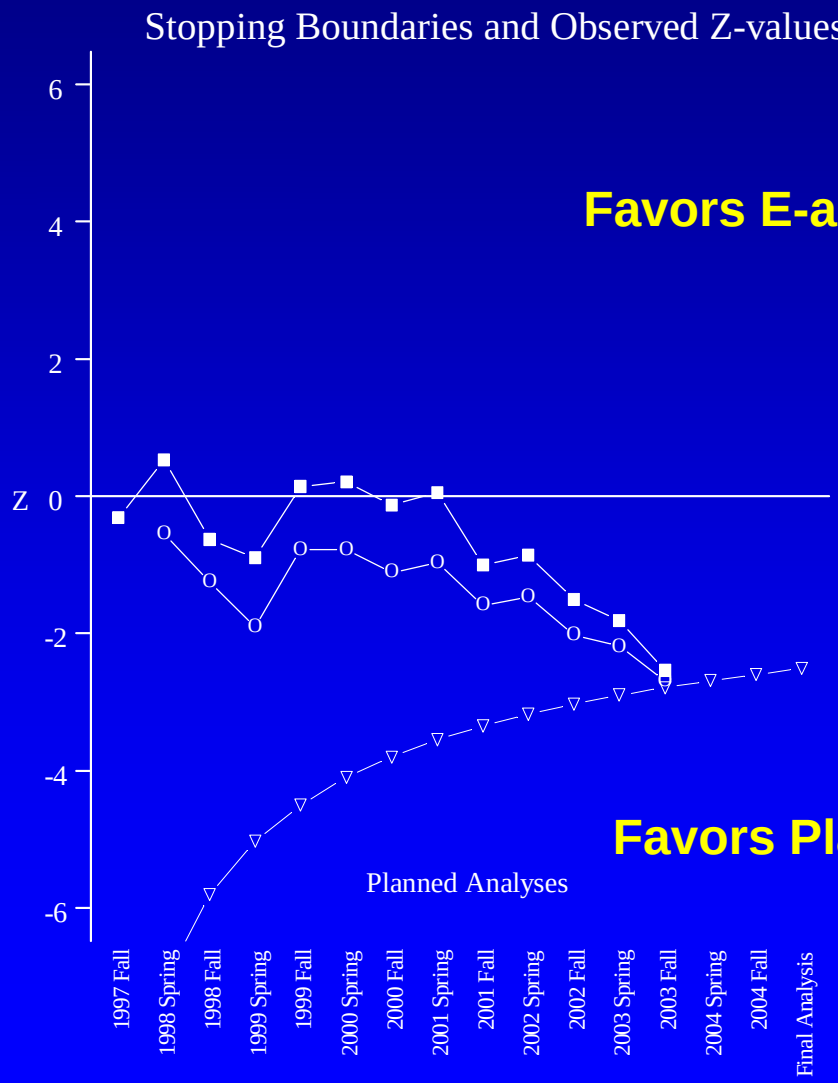
Hormone

Estrogen-alone

CHD



Stroke



Favors E-alone

Favors Placebo

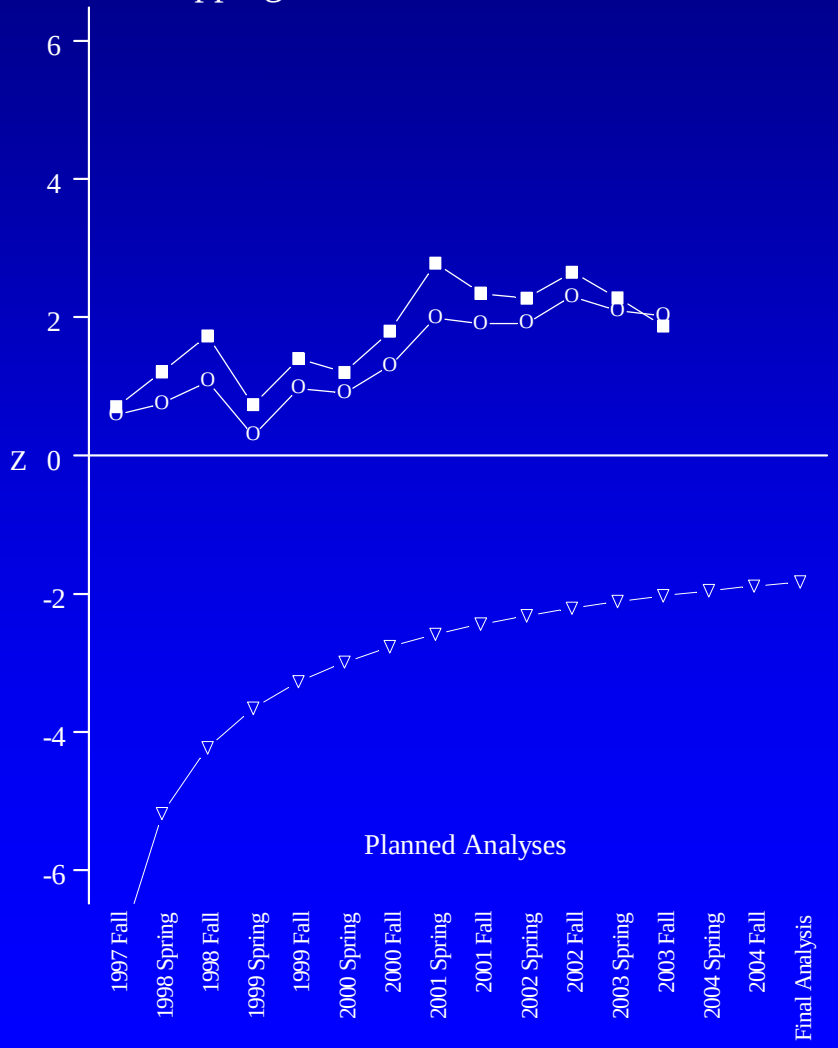
WOMEN'S HEALTH INITIATIVE

Hormone

Estrogen-alone

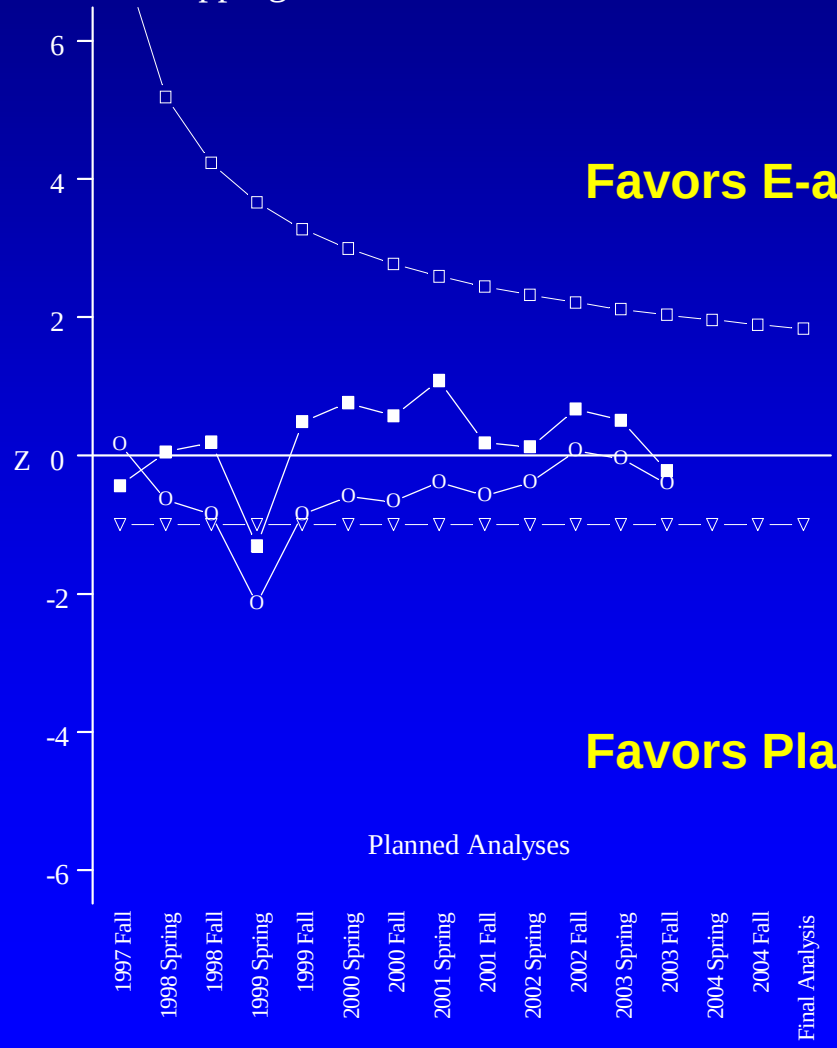
Invasive Breast Cancer

Stopping Boundaries and Observed Z-values



Global Index

Stopping Boundaries and Observed Z-values



Favors E-alone

Favors Placebo

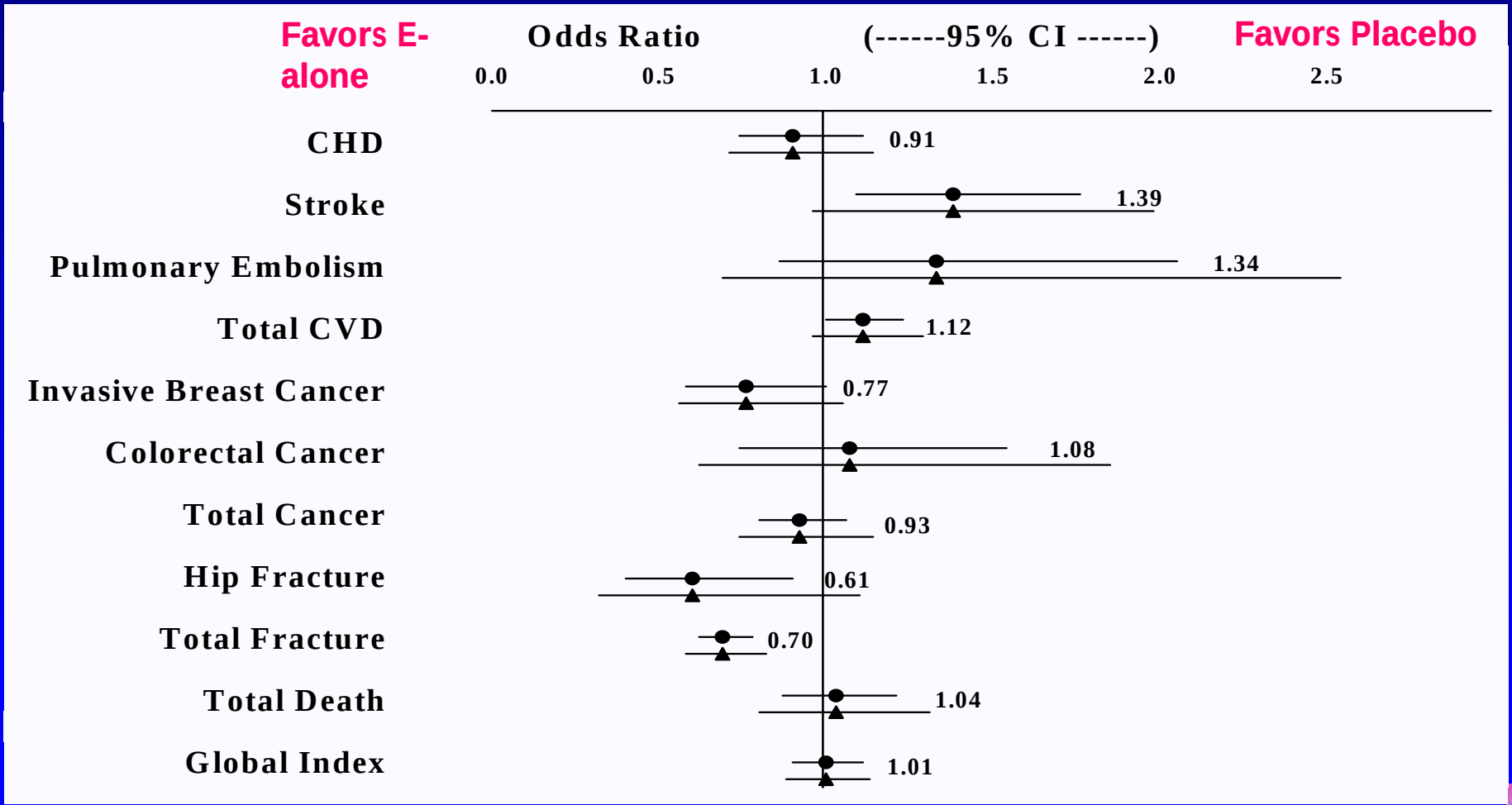
WOMEN'S HEALTH INITIATIVE

Hormone

Estrogen-alone trial stopped

- In February 2004, NIH stopped the trial after 6.6 years of intervention, based on
  - Increased risk of stroke
  - Low probability of establishing heart disease benefit
  - Low probability of showing an increased risk of breast cancer

Effects of conjugated equine estrogens



JAMA 2004; 291:1701-12

Summary

- **HT trials were stopped when the primary question was answered: Is hormone therapy an appropriate medicine for heart disease prevention?**
- **Risk benefit profile differed importantly between Estrogen plus Progestin and Estrogen-alone**

The Estrogen + Progestin (E+P) and Estrogen-alone (E-alone) Trials

Results

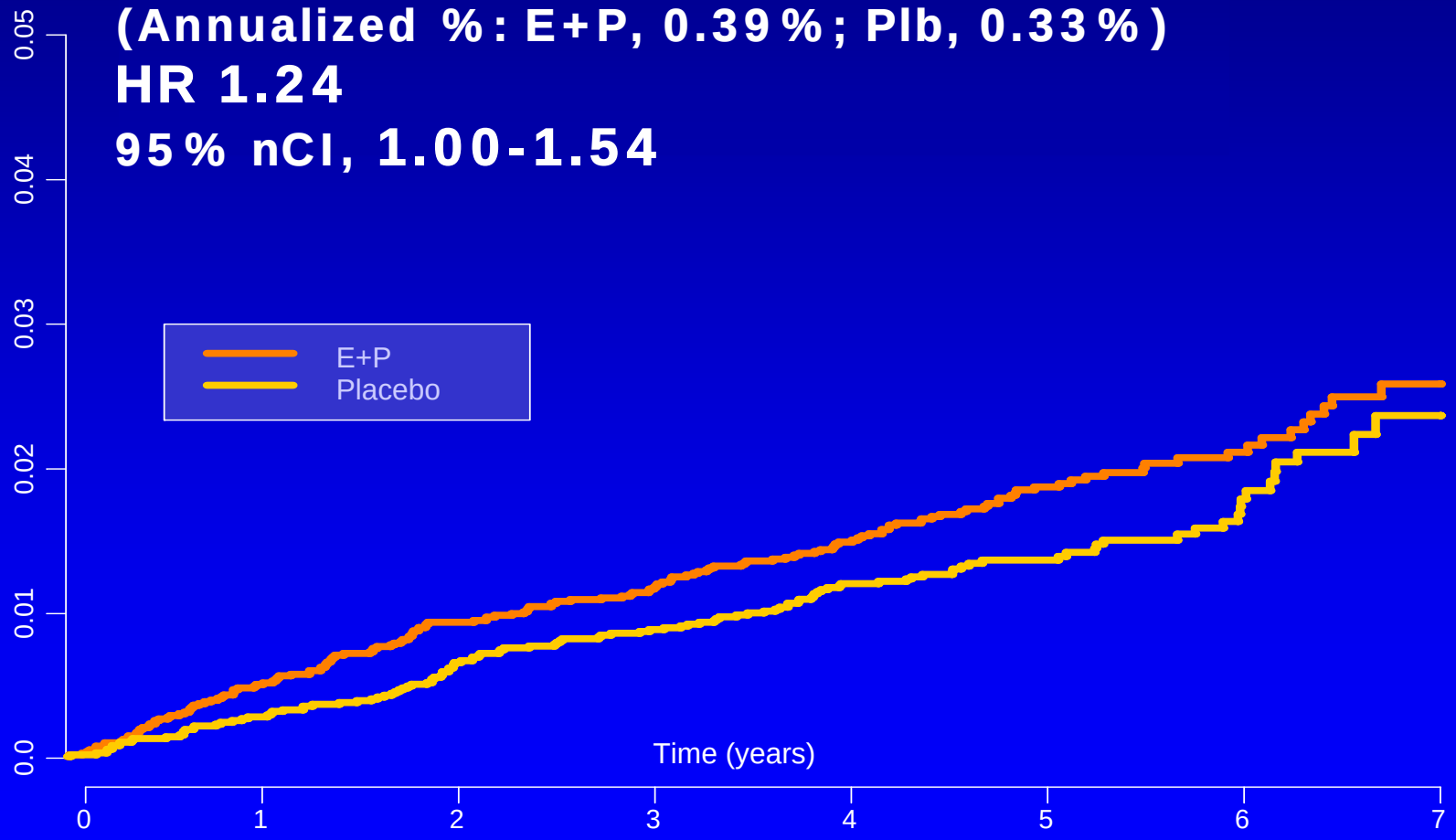
Heart, Brain (Stroke), Blood Clots

Judith Hsia, MD
Principal Investigator
George Washington University
Clinical Center

Professor of Medicine
George Washington University
Washington, DC

E+P Trial: Heart attack risk

(Annualized %: E+P, 0.39%; Plb, 0.33%)
HR 1.24
95% nCI, 1.00-1.54

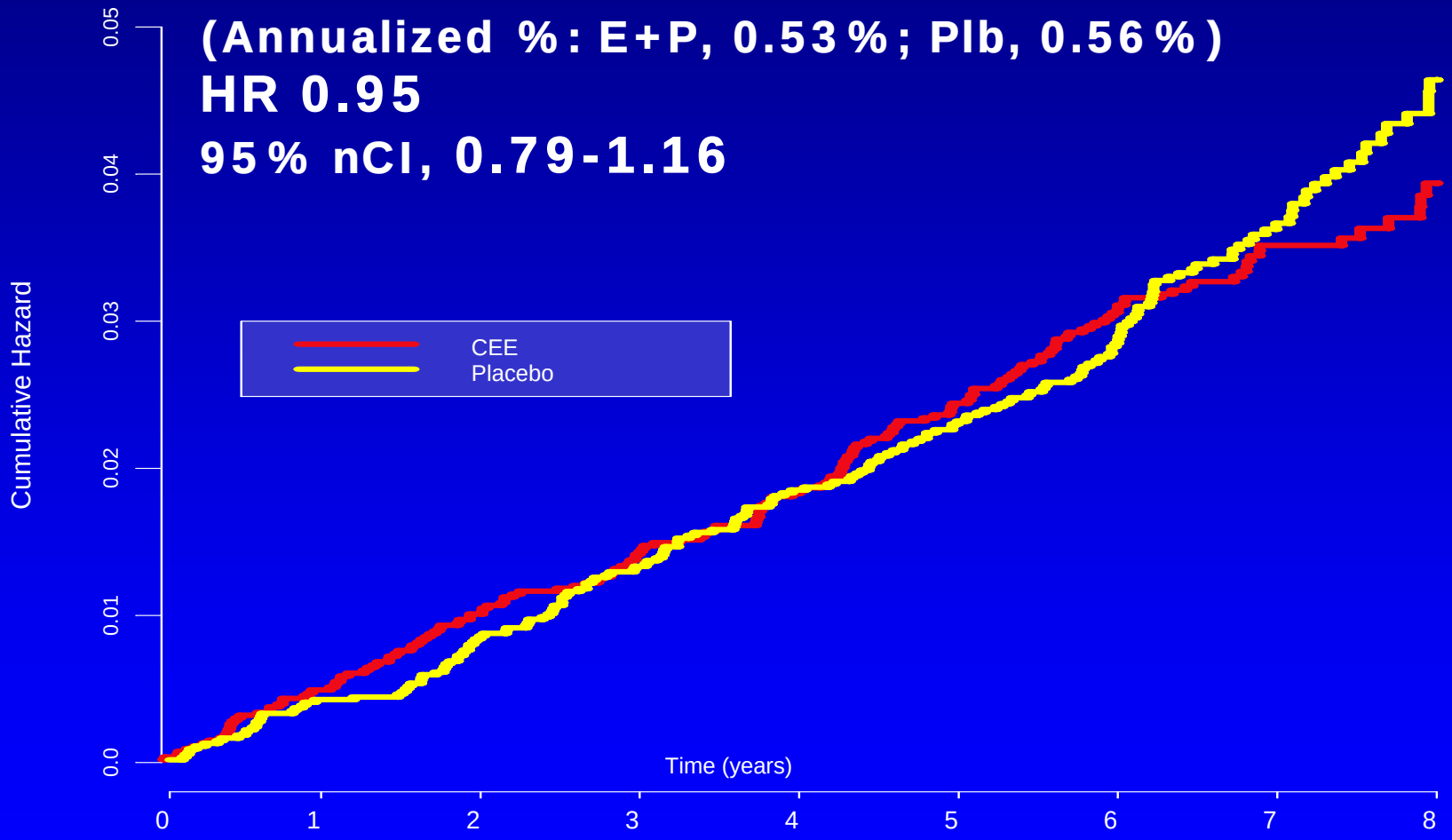


JAMA 2002; 288:321-33 ***Updated:*** **NEJM 2003; 349: 523-34**

WOMEN'S HEALTH INITIATIVE

Hormone

E-alone Trial: Heart attack risk

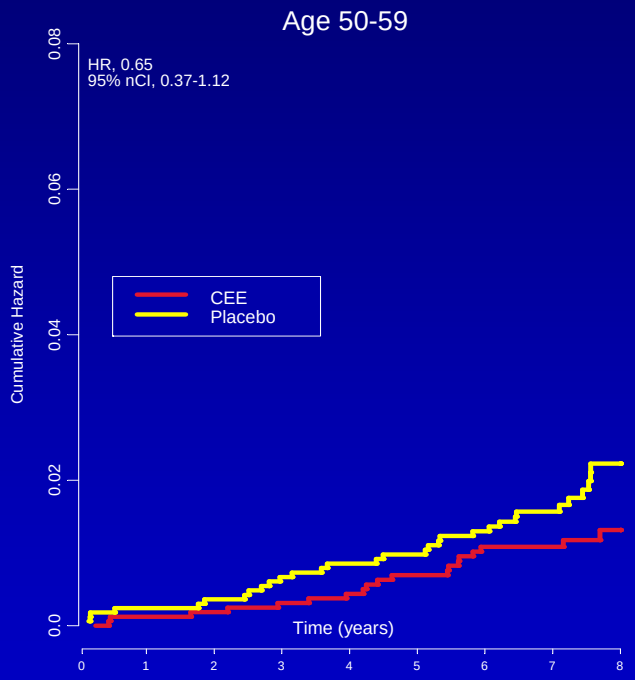


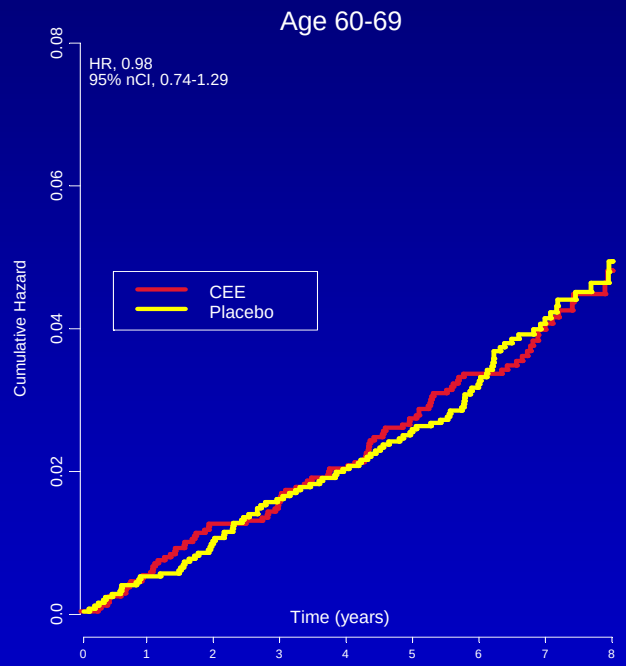
JAMA 2004; 291:1701-12; ***Updated*** **Arch Intern Med 2006; 166:357-65**

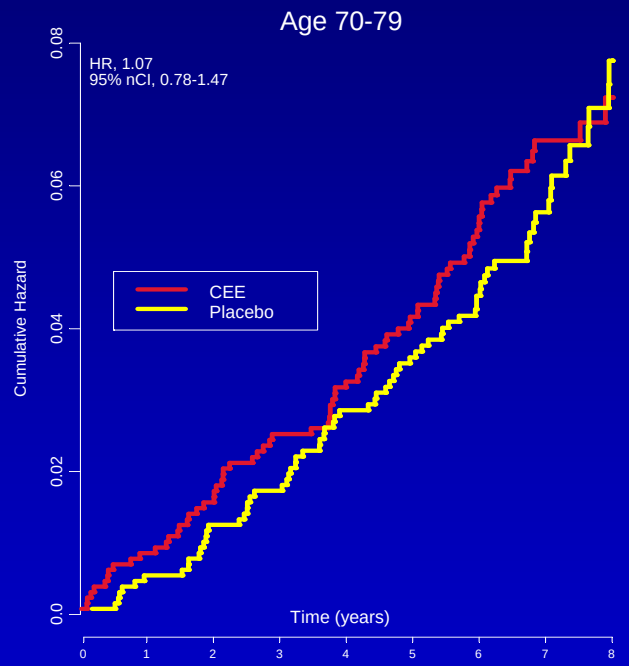
WOMEN'S HEALTH INITIATIVE

Hormone

Estrogen-alone: Heart attack risk
(by baseline age groups)







Arch Intern Med 2006; 166:357-65

WOMEN'S HEALTH INITIATIVE

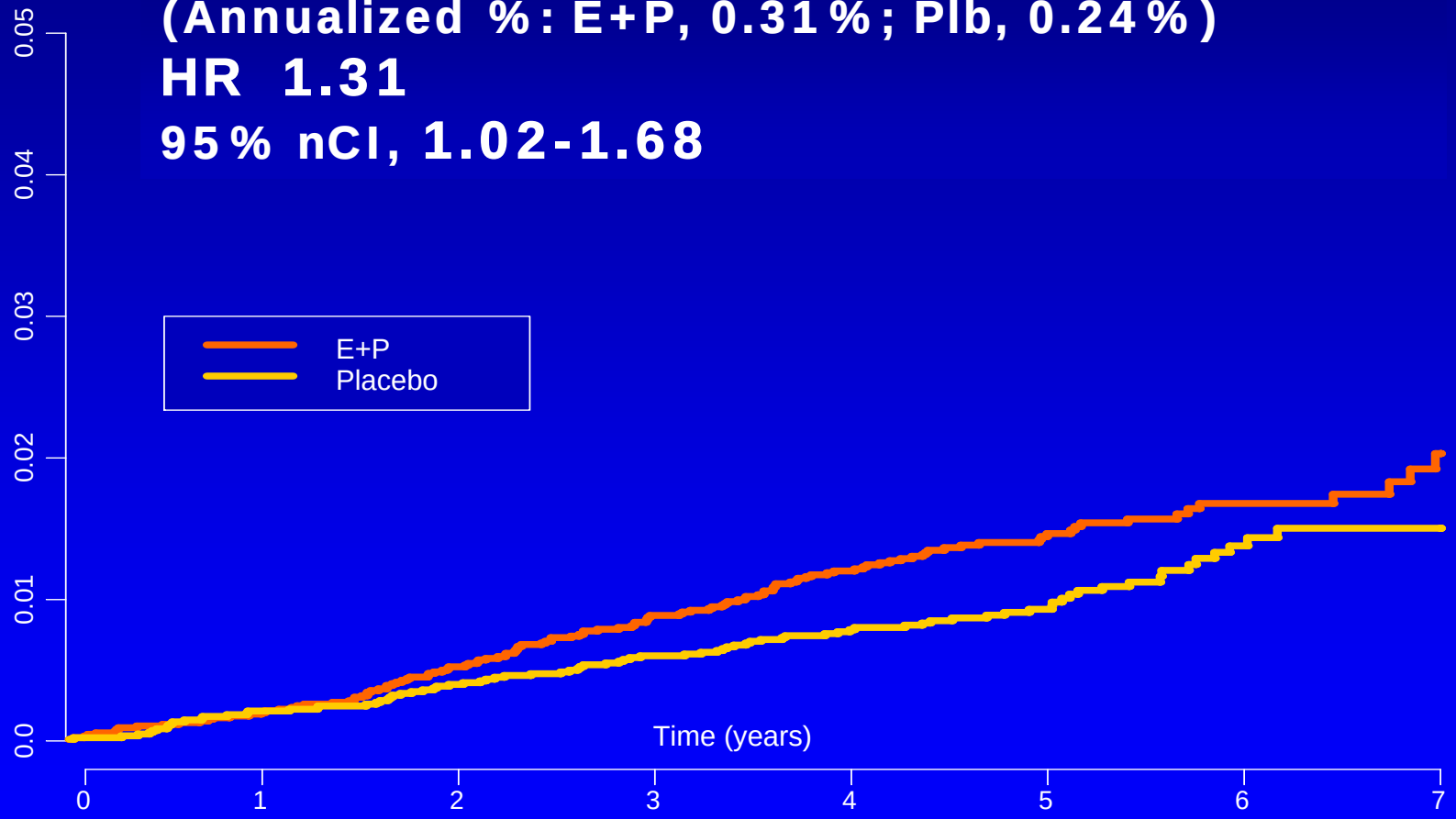
Hormone

E+P Trial: Stroke risk

(Annualized %: E+P, 0.31%; Plb, 0.24%)

HR 1.31

95% nCI, 1.02-1.68



JAMA 2002; 288:321-33 ***Updated:*** **JAMA 2003; 289:2673-84**

WOMEN'S HEALTH INITIATIVE

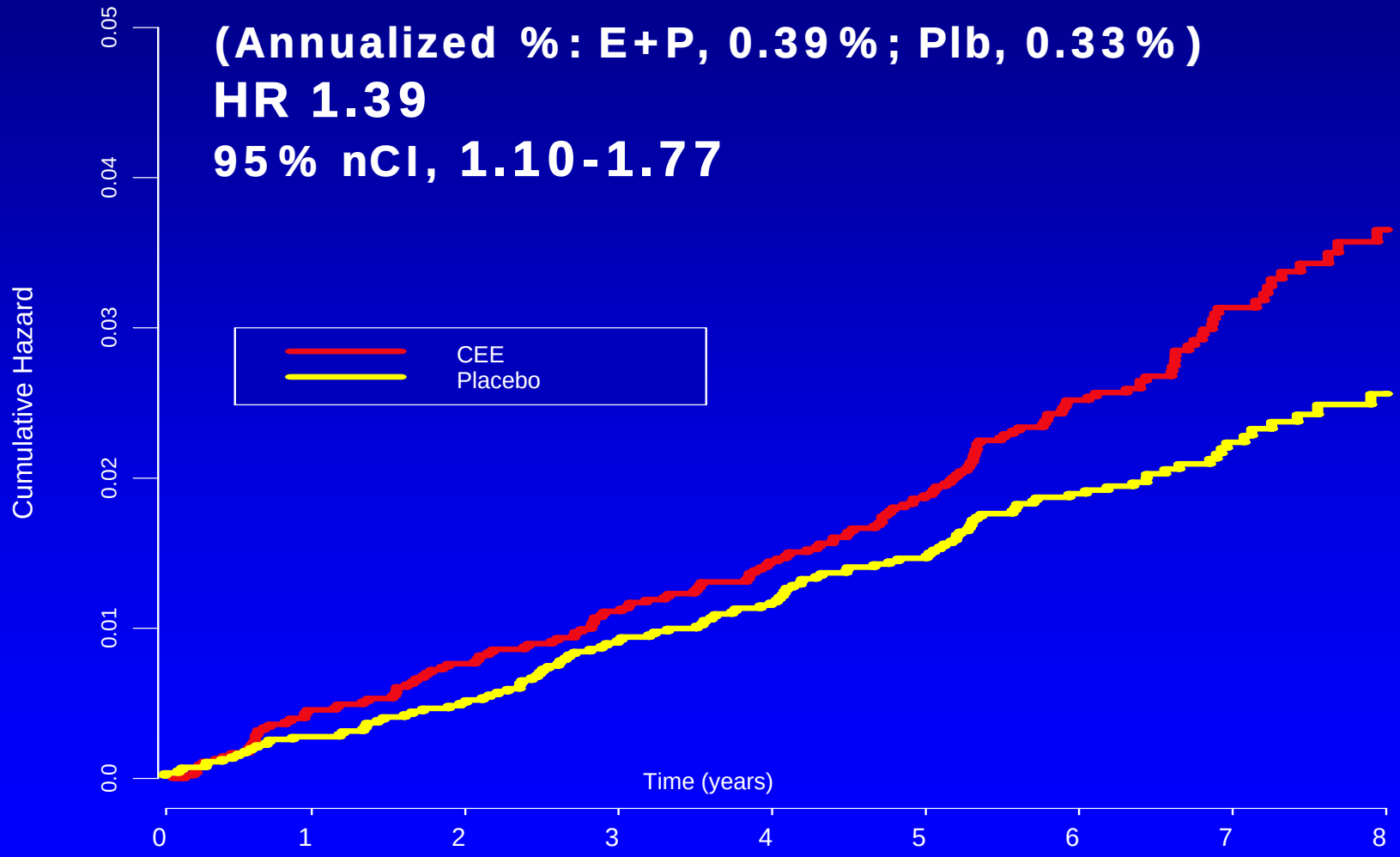
Hormone

E-alone Trial: Stroke risk

(Annualized %: E+P, 0.39%; Plb, 0.33%)

HR 1.39

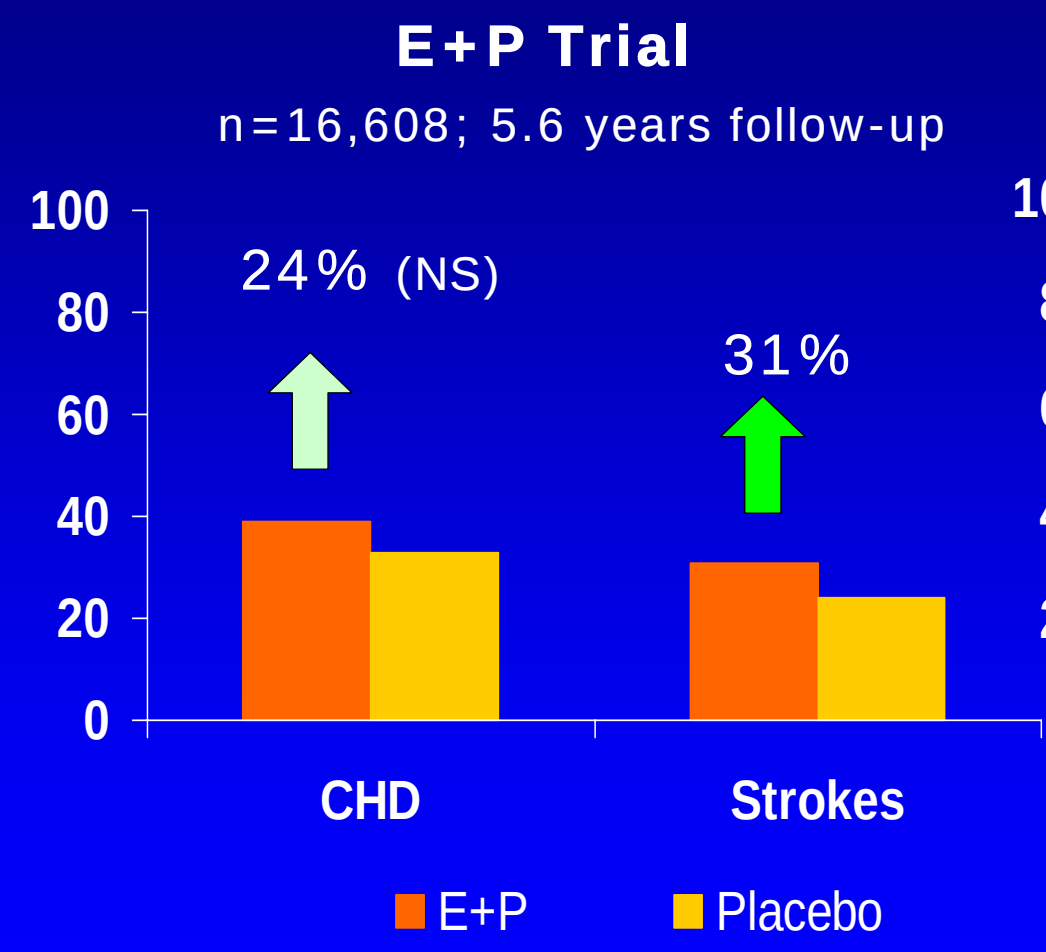
95% nCI, 1.10-1.77

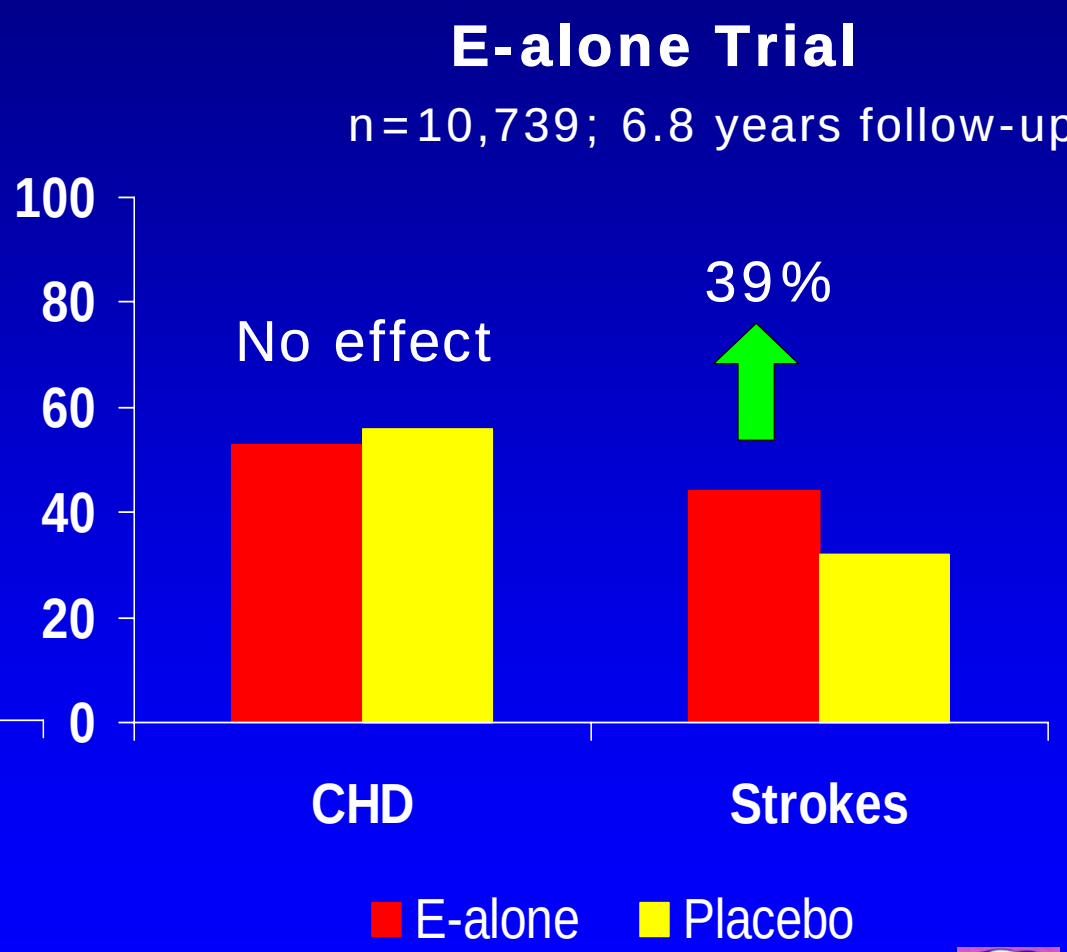


JAMA 2004; 291:1701-12

Hormone

Coronary Heart Disease and Strokes
(Rates per 10,000/Year) in E+P and E-alone



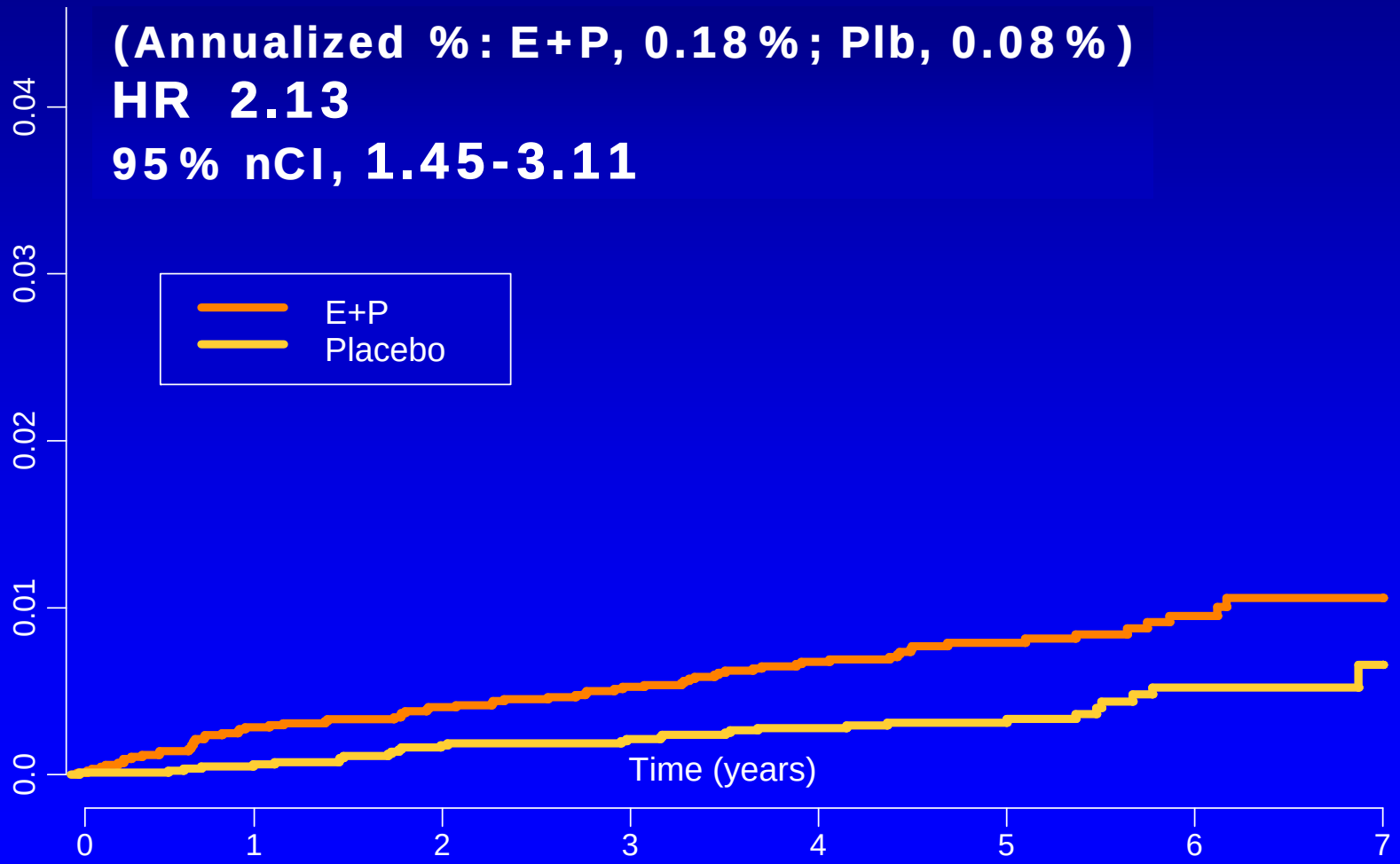


N Engl J Med. 2003; 349:523-34. JAMA. 2003; 289:2673-84.
JAMA. 2004; 291:1701-12. Arch Intern Med 2006; 166:357-65

WOMEN'S HEALTH INITIATIVE

Hormone

E+P trial: Risk of blood clots in the lung



JAMA 2002;288:321-33 ***Updated:*** **JAMA 2003; 289: 2673-84**

WOMEN'S HEALTH INITIATIVE

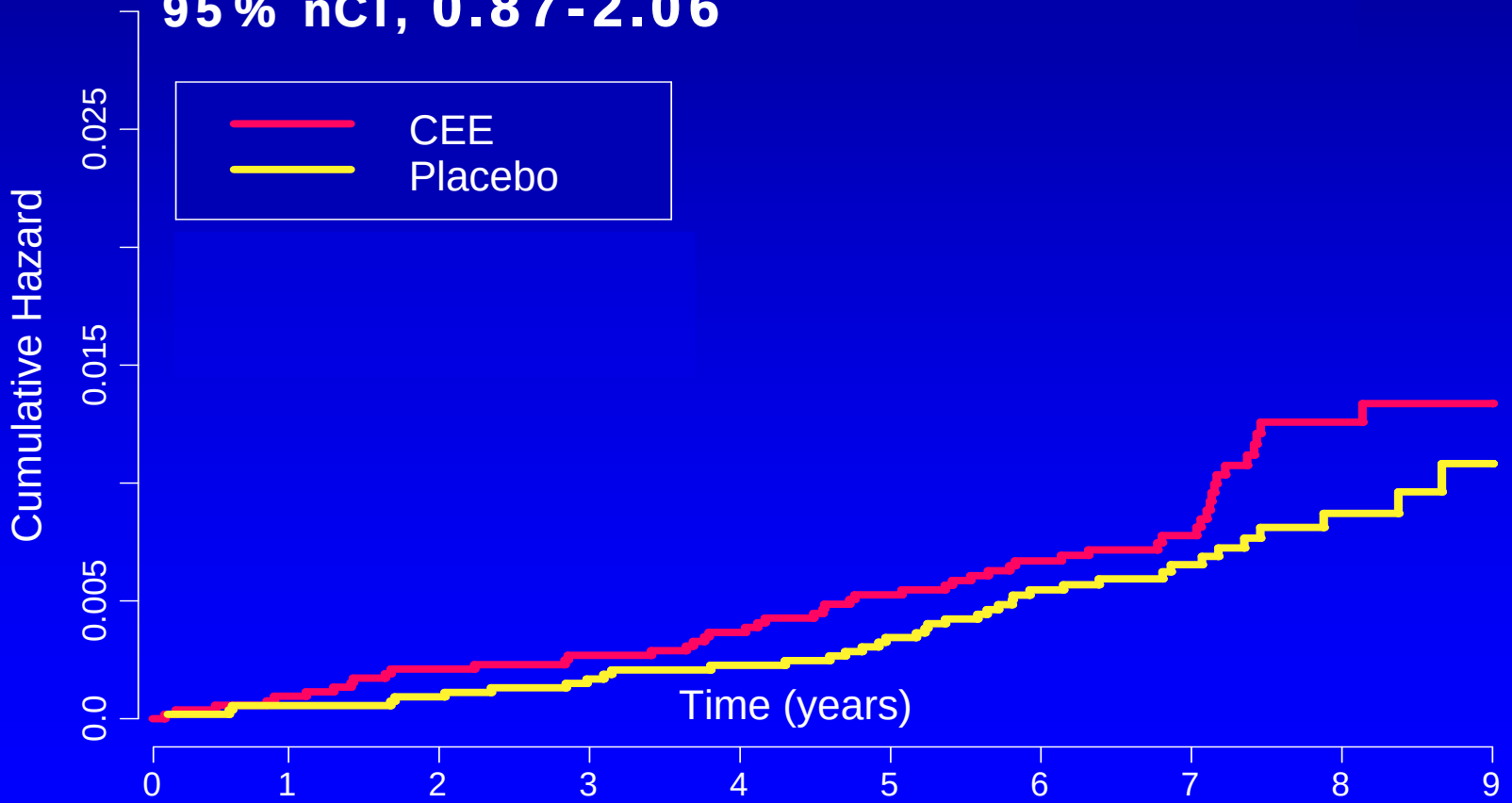
Hormone

E-alone trial: Risk of blood clots in the lung

(Annualized %: E-alone, 0.13%; Plb, 0.10%)

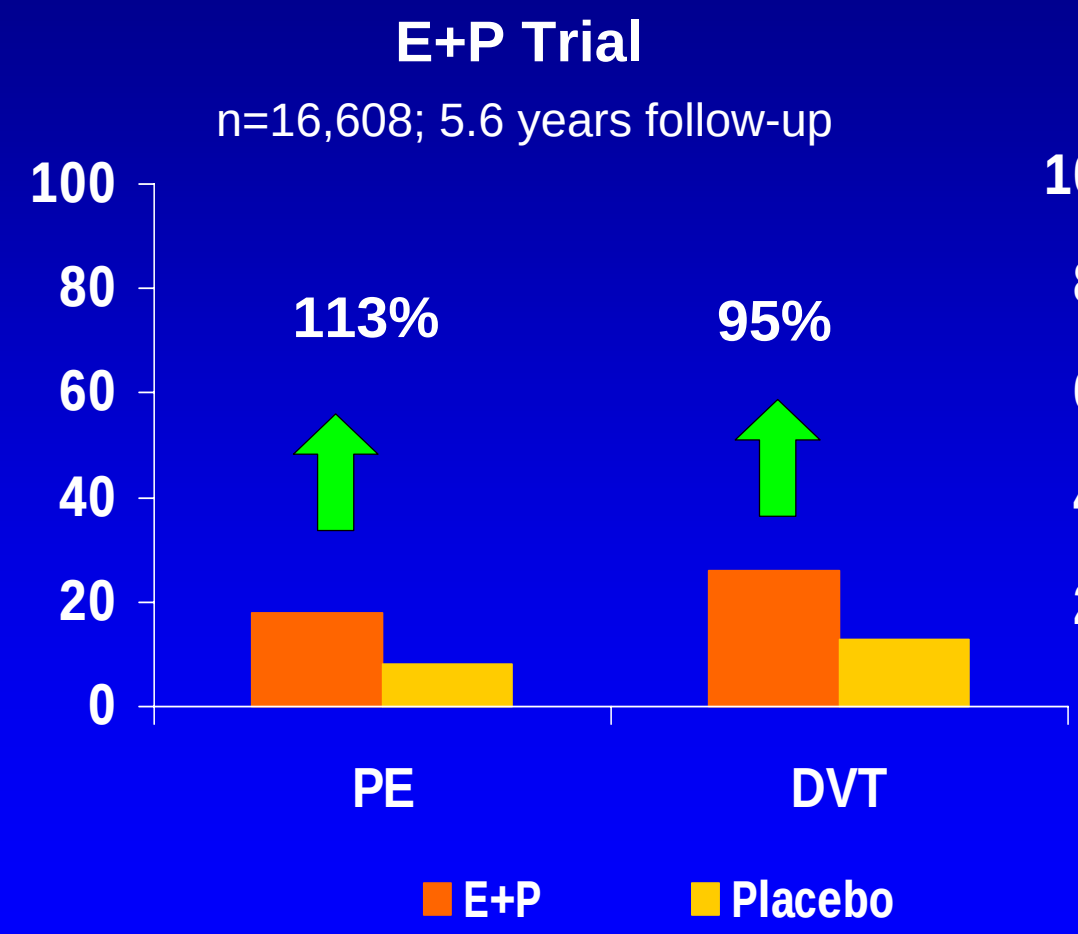
HR 1.34

95% nCI, 0.87-2.06

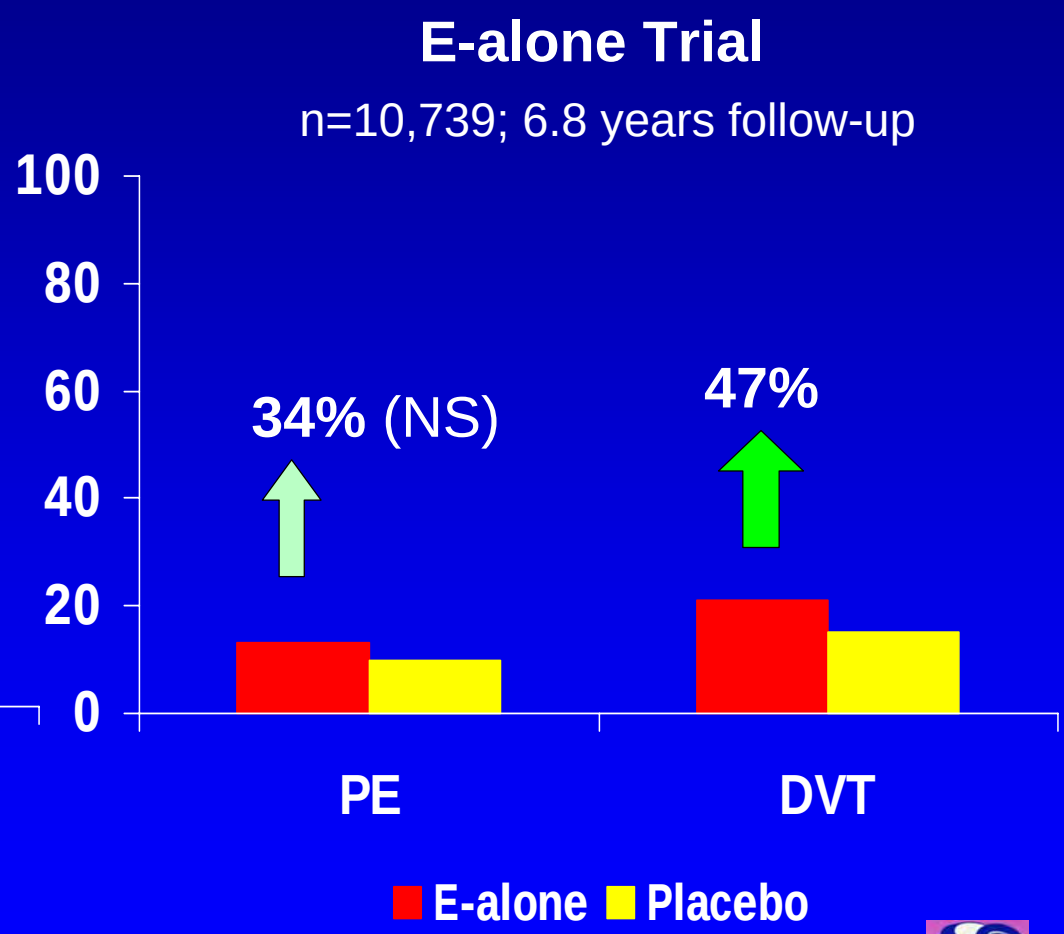


JAMA 2004; 291:1701-12

Pulmonary Emboli and Deep Vein Thrombosis (Rates per 10,000/Year) in E+P and E-alone



JAMA 2004; 292:1573-80



JAMA 2004; 291:1701-12

Conclusion: Cardiovascular Outcomes

Estrogen with progestin (E+P) Trial

- Increased stroke
- Increased venous blood clots
- No protection against heart disease and suggestion of harm (especially in 1st year)

Estrogen alone (E-alone) Trial

- Increased stroke
- Appeared to increase venous blood clots
- No protection against heart disease but a suggestion of benefit in participants aged 50-59 yrs

Menopausal estrogen therapy (with or without a progestin) should not be started or continued for the purpose of preventing cardiovascular disease

Breast and Colon Cancers

Rowan Chlebowski, MD, PhD
Principal Investigator
Torrance Clinical Center

Chief, Division of Medical Oncology and Hematology
Los Angeles Biomedical Research Institute
Harbor-UCLA Medical Center
Torrance, California

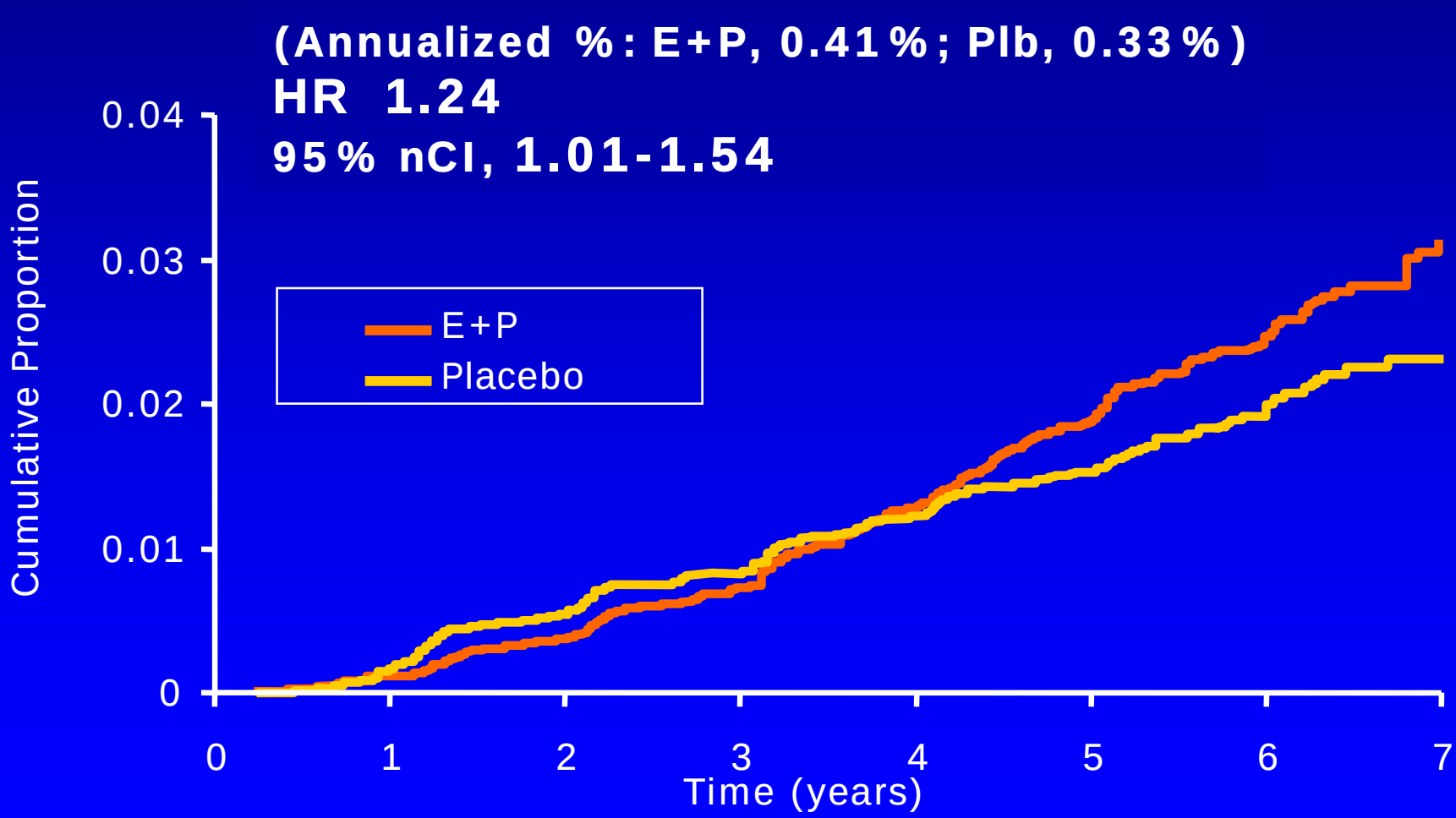
Conclusions from Preponderance of Observational Studies of HT and Breast and Colorectal Cancer

- **Breast cancer risk increased**
  - **moderately by E alone (long duration)**
  - **more on E+P for good prognosis cancers**
  - **with receptor positive preponderance**

- **Colorectal cancer risk decreased**
  - **moderately by hormone therapy (no difference for E-alone vs E+P)**

McMichael J Natl Cancer Inst 65:1201, 1980
Colditz Am J Epid 147:645, 1998
Goodstein Am J Med 106:574, 1999

E+P Trial: Invasive Breast Cancer By Group



JAMA 2003; 289:3243-53

Hormone

Breast Cancer Characteristics by Group

	E+P	Placebo	P-Value
Tumor size, cm[1]	1.7 (1.1)	1.5 (0.9)	0.038[2]
Nodes Positive[2]	25.9 %	15.8%	0.033
SEER Stage Regional / Mets	25.4%	16.0%	0.041

[1] mean (SD) for tumor with known tumor size

[2] P-values from weighted Cox proportional hazards models

More advanced stage on E+P

Mammogram Findings by Group and Time

	Baseline		Year 1		Cumulative	
	E+P	Placebo	E+P	Placebo	E+P	Placebo
Mammogram performed[1]	100%	100%	90.3%	90.5%	97.3%	97.8%
Mammogram abnormal (total)[2]	5.2%	5.0%	9.4%[3]	5.4%	31.5%[3]	21.2%

[1] % of women due for visit with mammogram in study period who had mammogram;

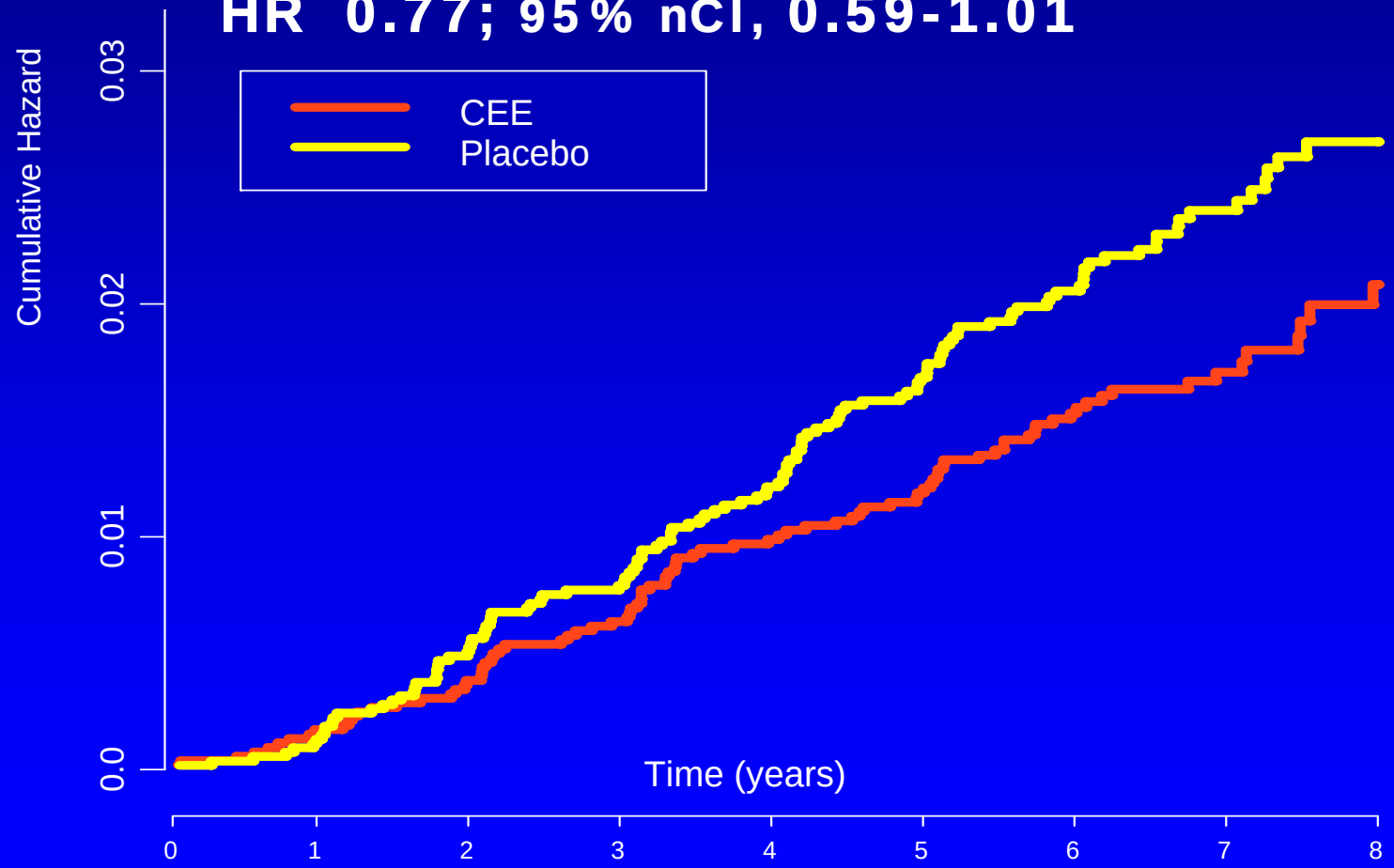
[2] % of women with any category of abnormal mammogram;

[3] $p < 0.0001$ E+P versus placebo

More mammograms with abnormalities on E+P

E-alone Trial: Invasive Breast Cancer By Group

(Annualized %: E-alone, 0.26%; Plb, 0.33%)
HR 0.77; 95% nCI, 0.59-1.01



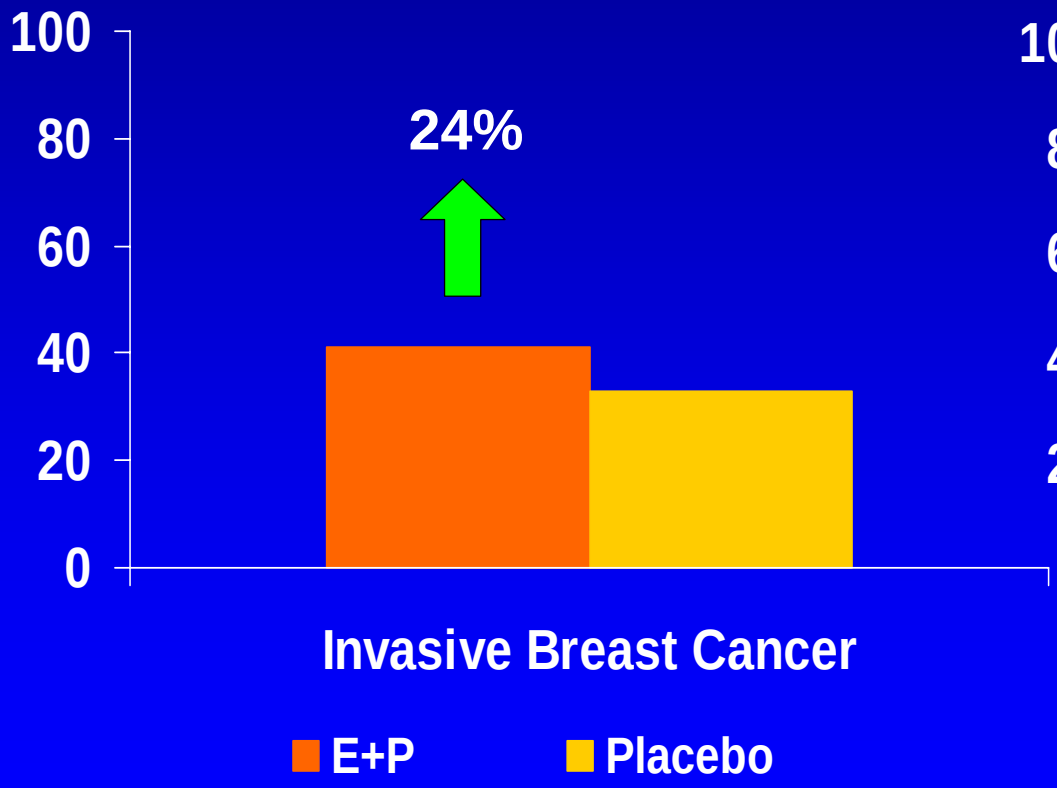
JAMA 2004; 291:1701-12

Hormone

Invasive Breast Cancer
(Rates per 10,000/Year) in E+P and E-alone

E+P Trial

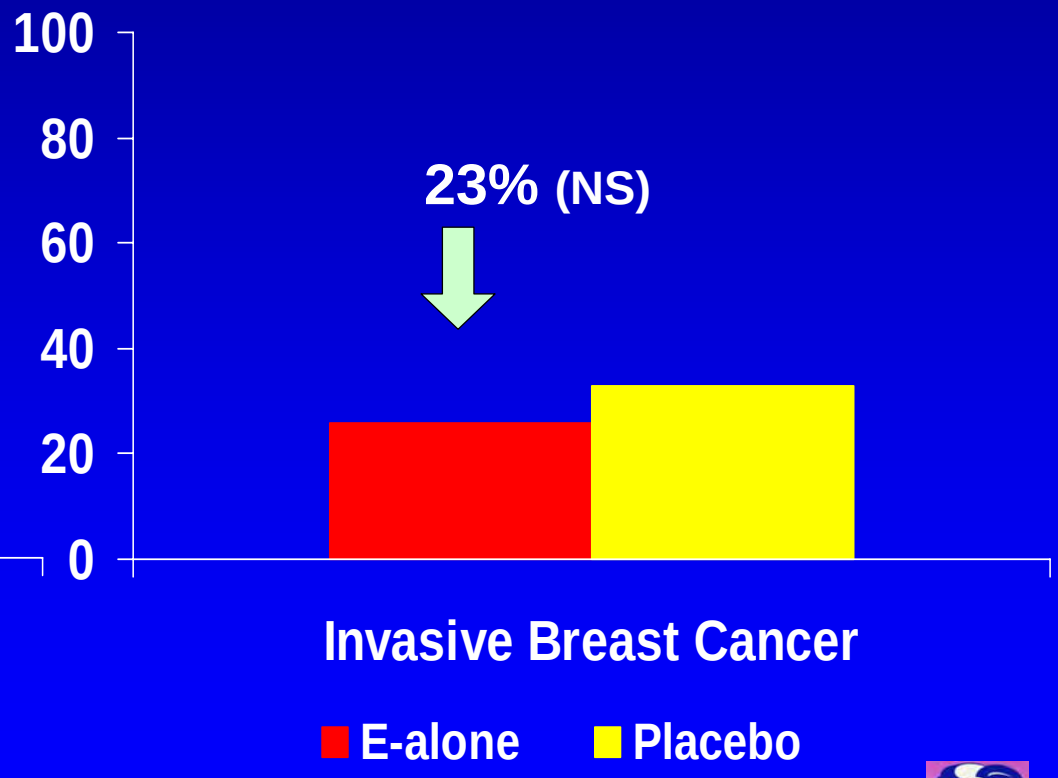
n=**16,608**; **5.6 years** follow-up



JAMA 2003; 289:3243-53

E-alone Trial

n=**10,739; 6.8 years** follow-up

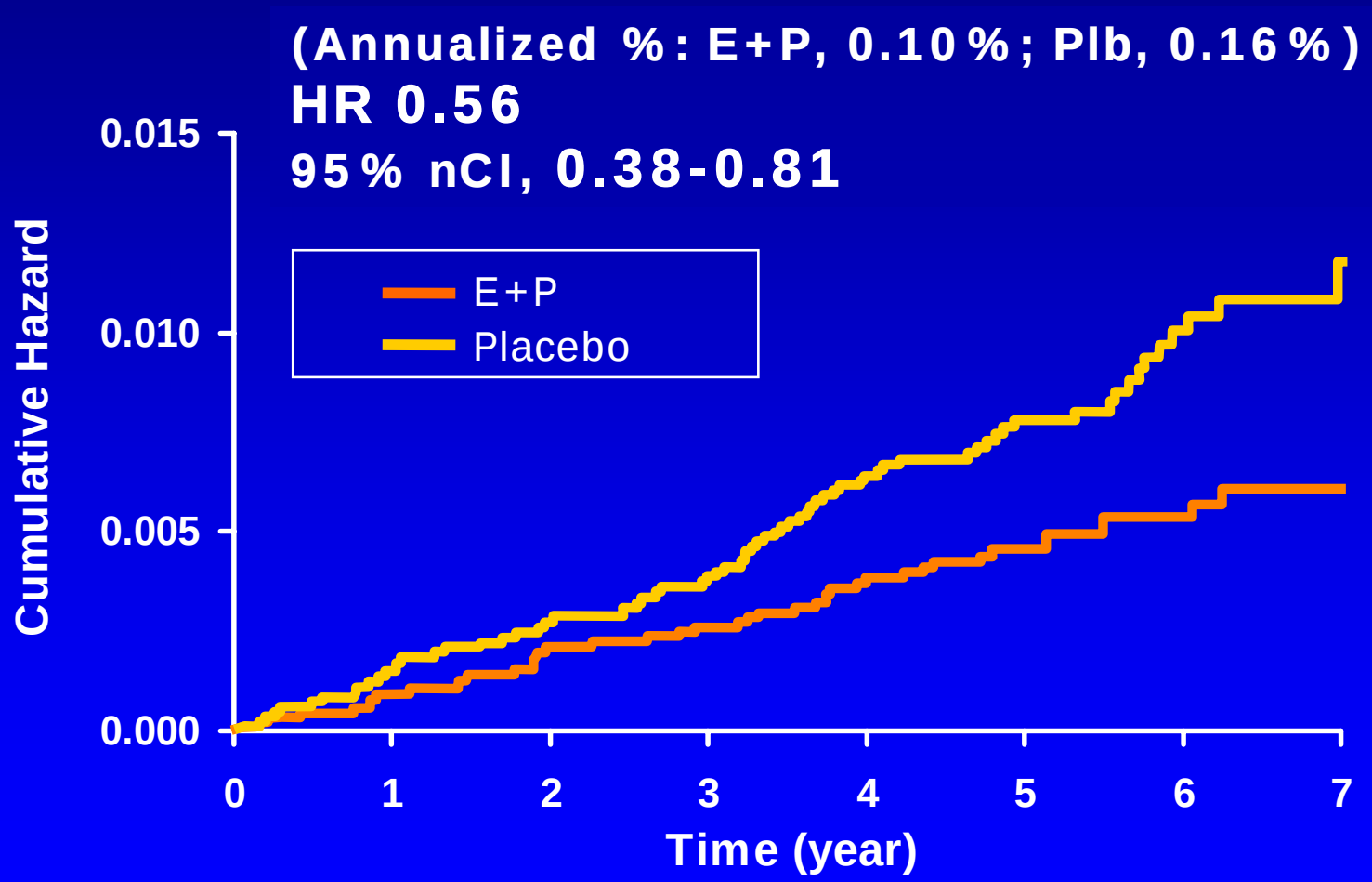


JAMA 2004; 291:1701-12

WOMEN'S HEALTH INITIATIVE

Hormone

Invasive Colorectal Cancer in E+P



N Engl J Med 2004; 350:991-1004

Colorectal Cancer Characteristics by Group

	E+P	Placebo	P-Value
Tumor Size, cm[1]	4.9 (2.5)	4.3 (2.5)	0.34
Nodes Positive[2] (%)	59.0%	29.4%	0.003
No. Positive Nodes (mean + SD)	3.2 (4.1)	0.8 (1.7)	0.002
SEER Stage Regional / Mets	76.2%	48.5%	0.004

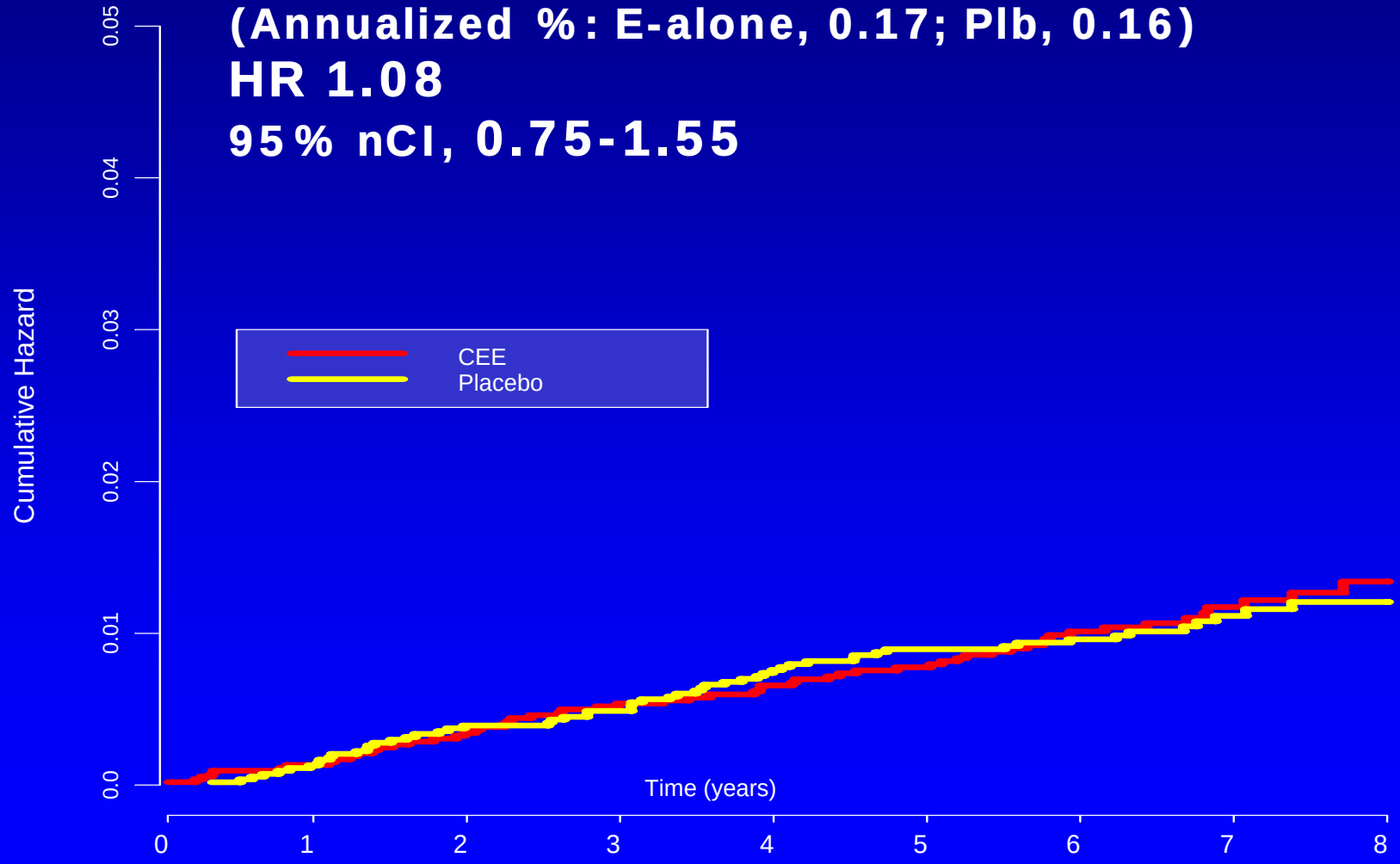
[1]Mean (SD) for tumor with known tumor size
[2]p-value from weighted Cox proportional hazards models

More advanced stage Colorectal Cancer on E+P

N Eng J Med 2004; 350: 10

E-alone Trial: Invasive Colorectal Cancer by Group

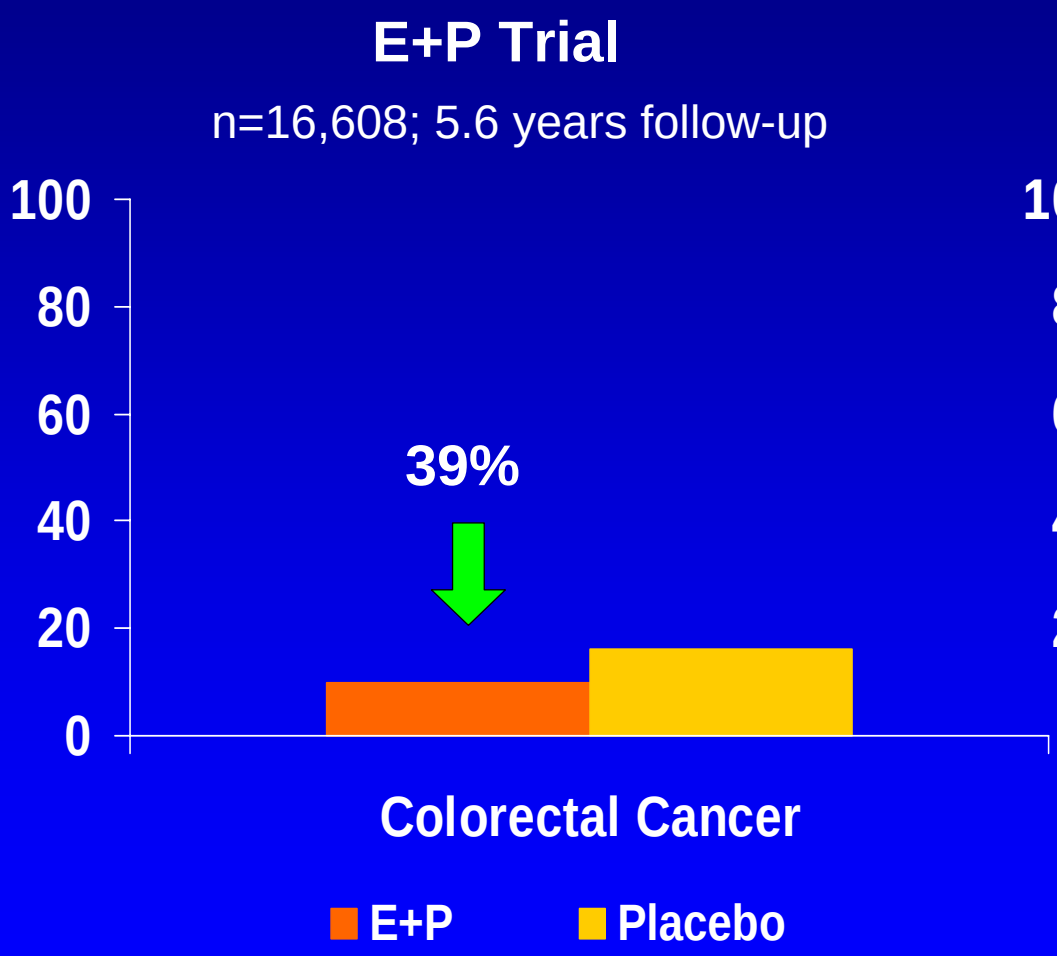
(Annualized %: E-alone, 0.17; Plb, 0.16)
HR 1.08
95% nCI, 0.75-1.55

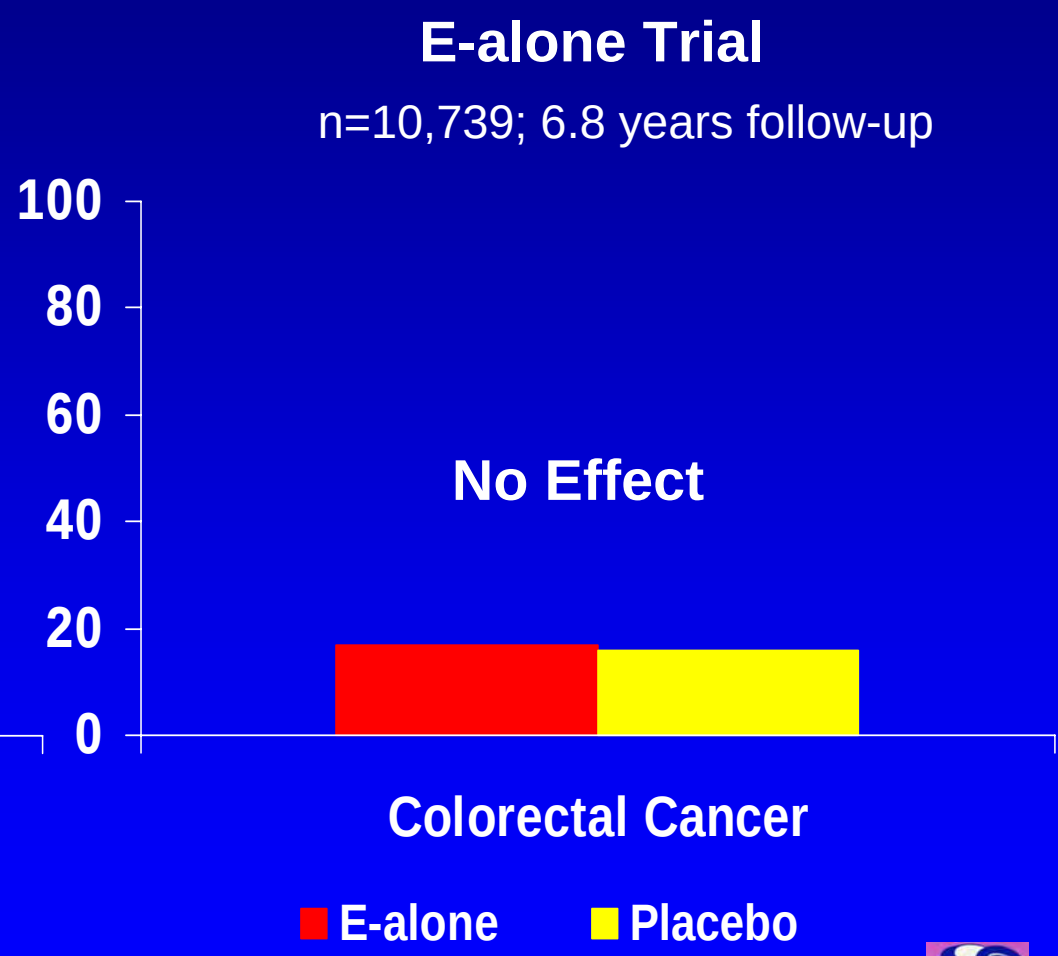


JAMA 2004; 291:1701-12

Hormone

Colorectal Cancer
(Rates per 10,000/Year) in E+P and E-alone





N Engl J Med 2004; 350:991-1004

JAMA 2004;291:1701-12

Conclusions and Additional Information: Breast and Colorectal Cancer

Estrogen with progestin (E+P) Trial

- Increased breast cancer
  - diagnosed at more advanced stage
  - increases abnormal mammograms
- Decreased colorectal cancer
  - diagnosed at more advanced stage

Estrogen alone (E-alone) Trial

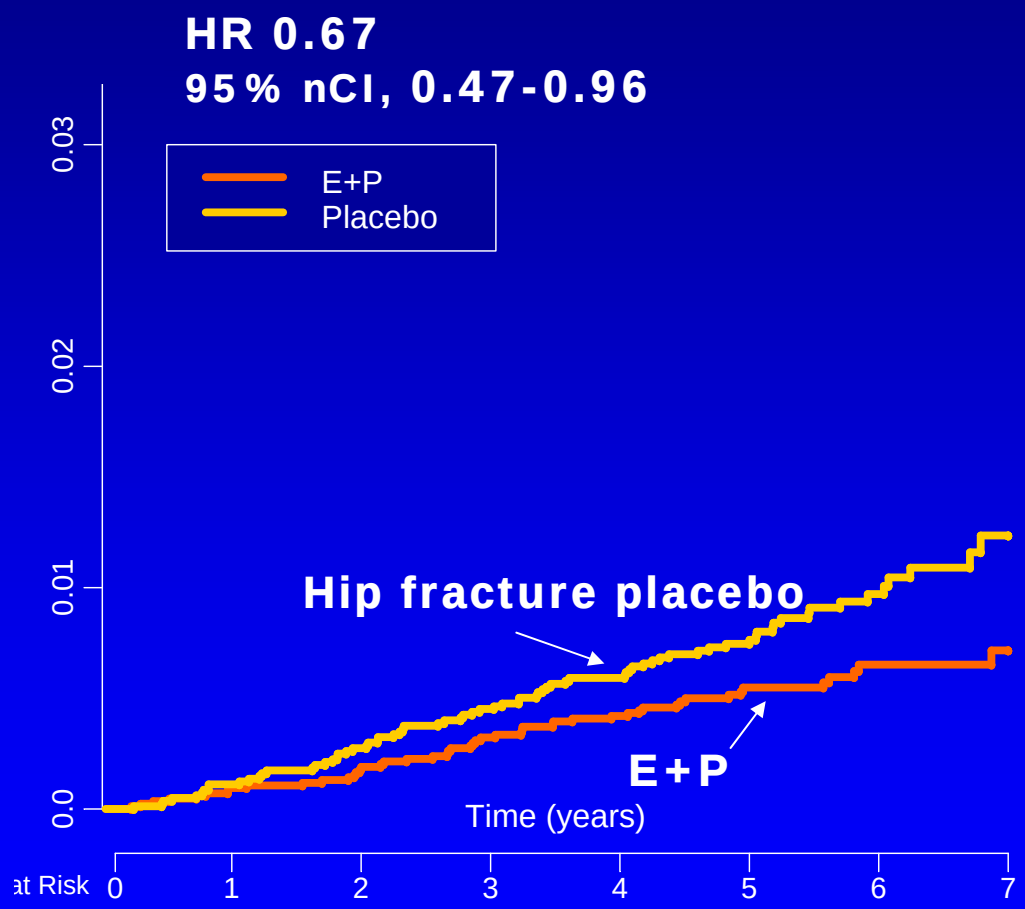
- did not increase breast cancer incidence
- did not decrease colorectal cancer incidence

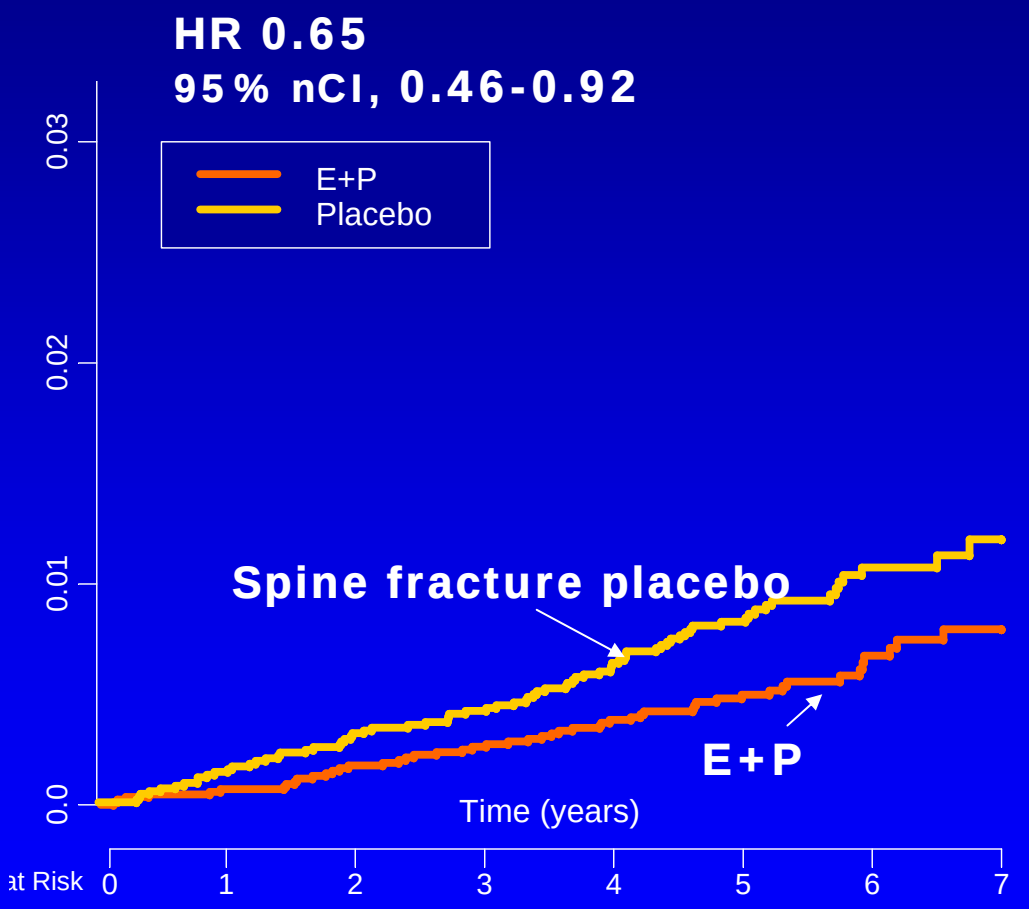
Bones

Cora E. Lewis, MD, MSPH
Principal Investigator
Birmingham Clinical Center

Professor of Medicine
Division of Preventive Medicine
Department of Medicine
University of Alabama at Birmingham
Birmingham, Alabama

E+P: Hip and Clinical Vertebral Fractures
Estimates of Cumulative Hazards



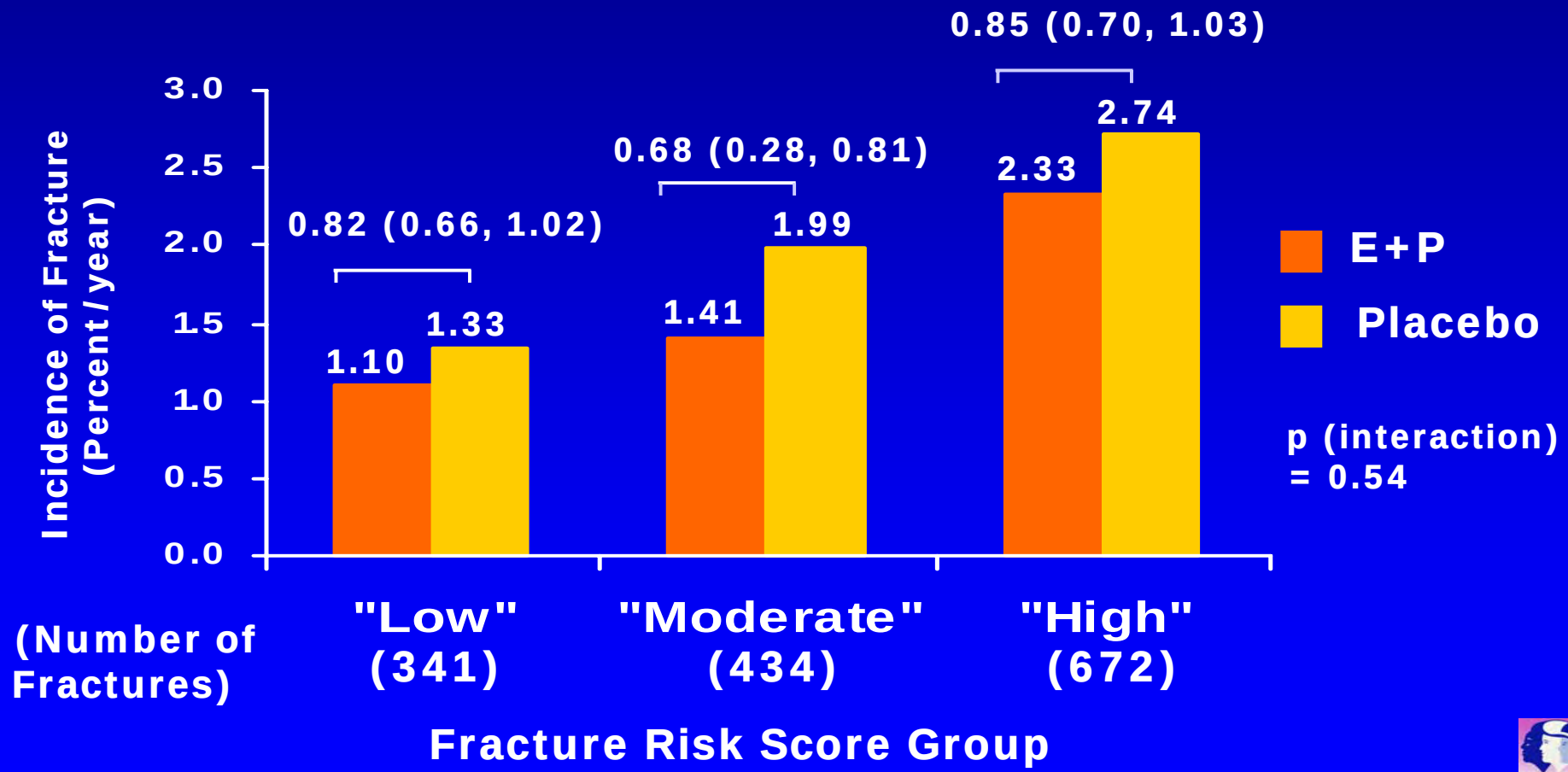


JAMA 2003; 290:1729-38

WOMEN'S HEALTH INITIATIVE

Hormone

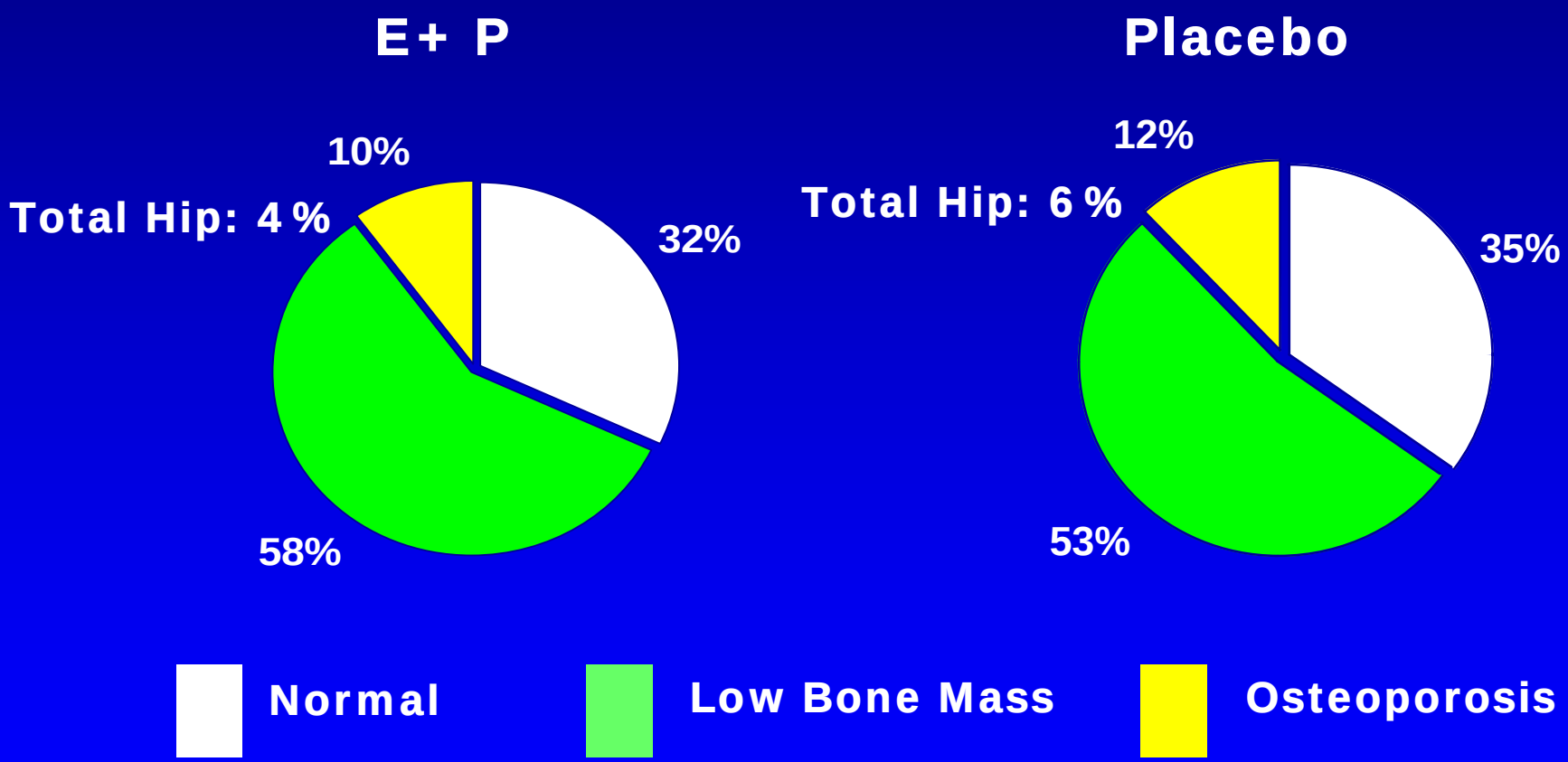
Effects of E+P on Total Fractures by Summary Fracture Risk Score



JAMA 2003; 290:1729-38

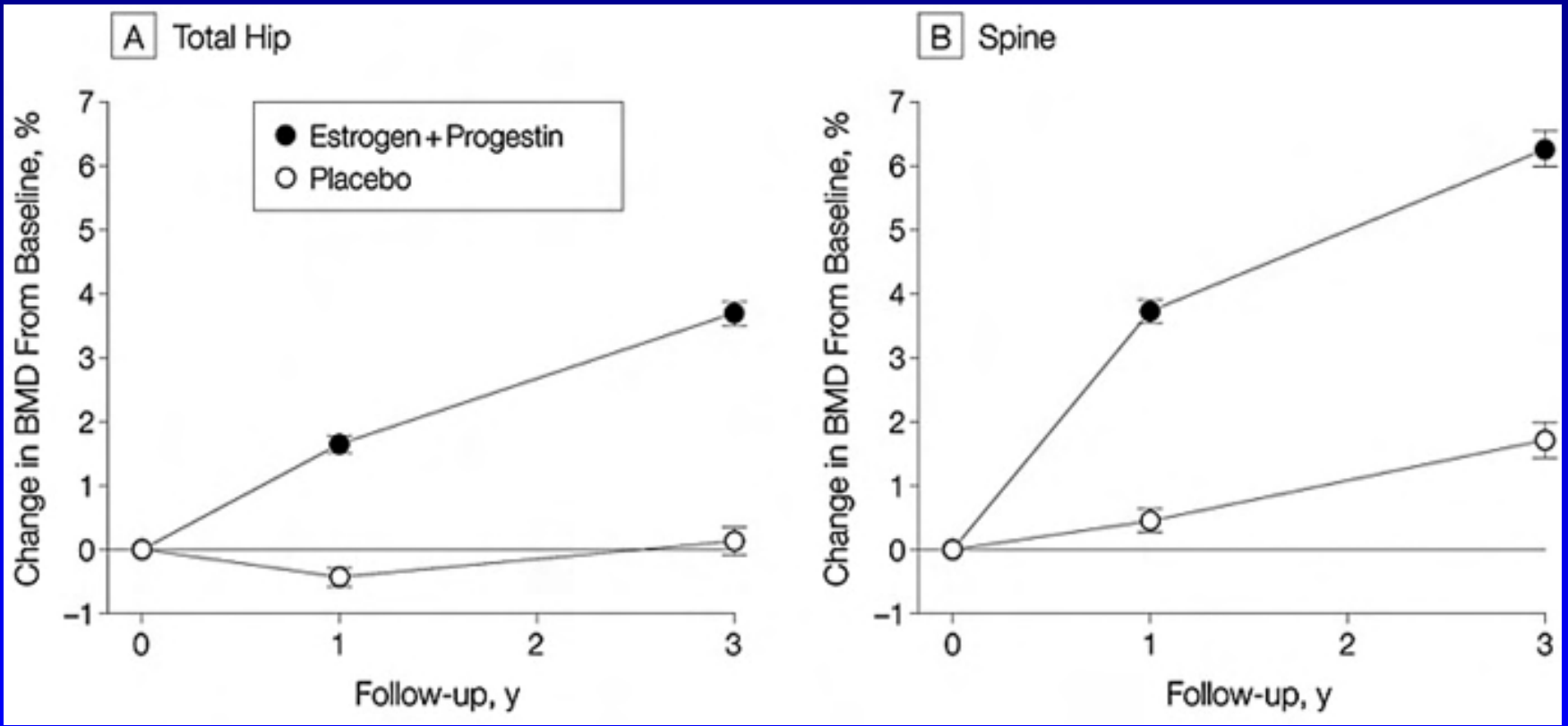
Hormone

WHI E+P BMD Cohort: Prevalence of Osteoporosis by Femoral Neck DXA (n=1024)



JAMA 2003; 290:1729-38

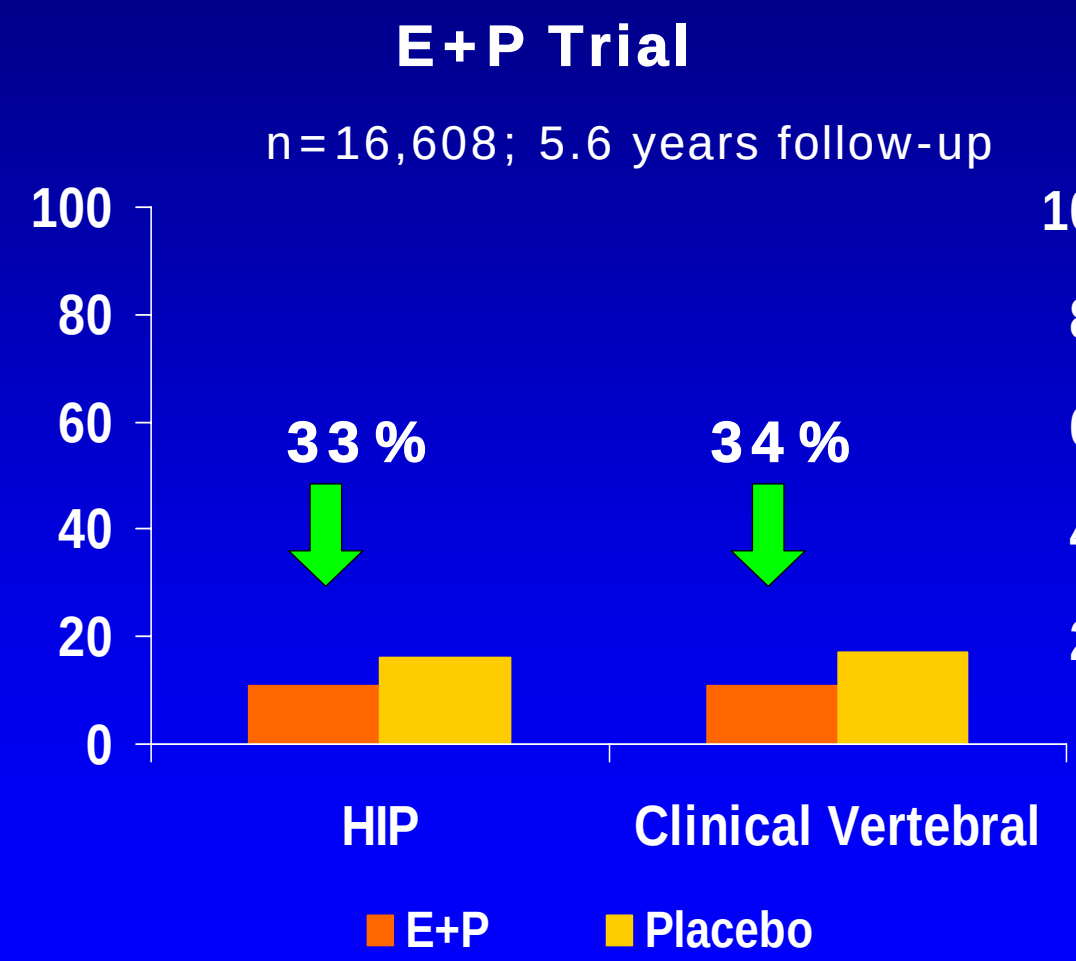
E+P Trial: Mean Percent Change in Total Hip and Spine BMD over 3 Years of Follow-up

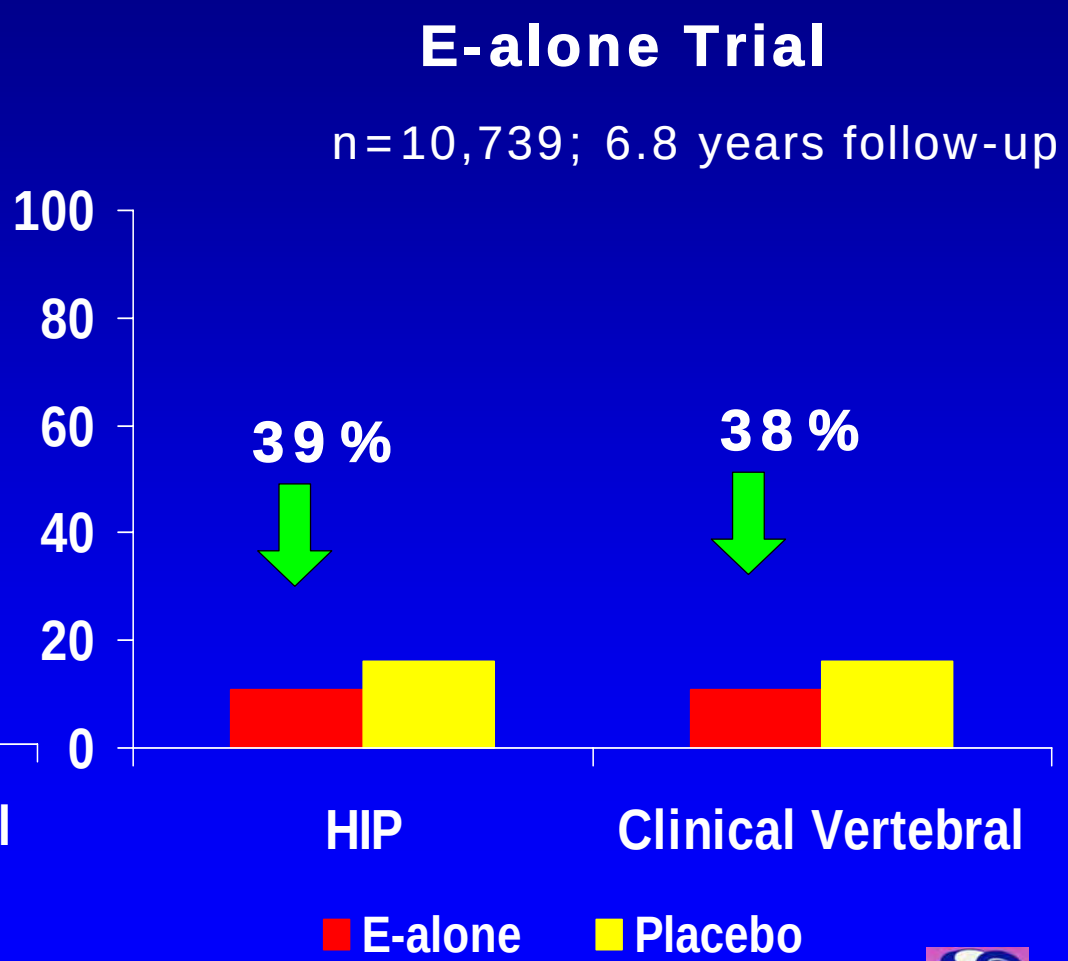


BMD indicates bone mineral density. Error bars indicate SEs.

JAMA 2003; 290:1729-38

Hip and Clinical Fractures
(Rates per 10,000/Year) in E+P and E-alone





JAMA 2002; 288:321-33

JAMA 2004; 291:1701-12

Brain (Cognitive Function)

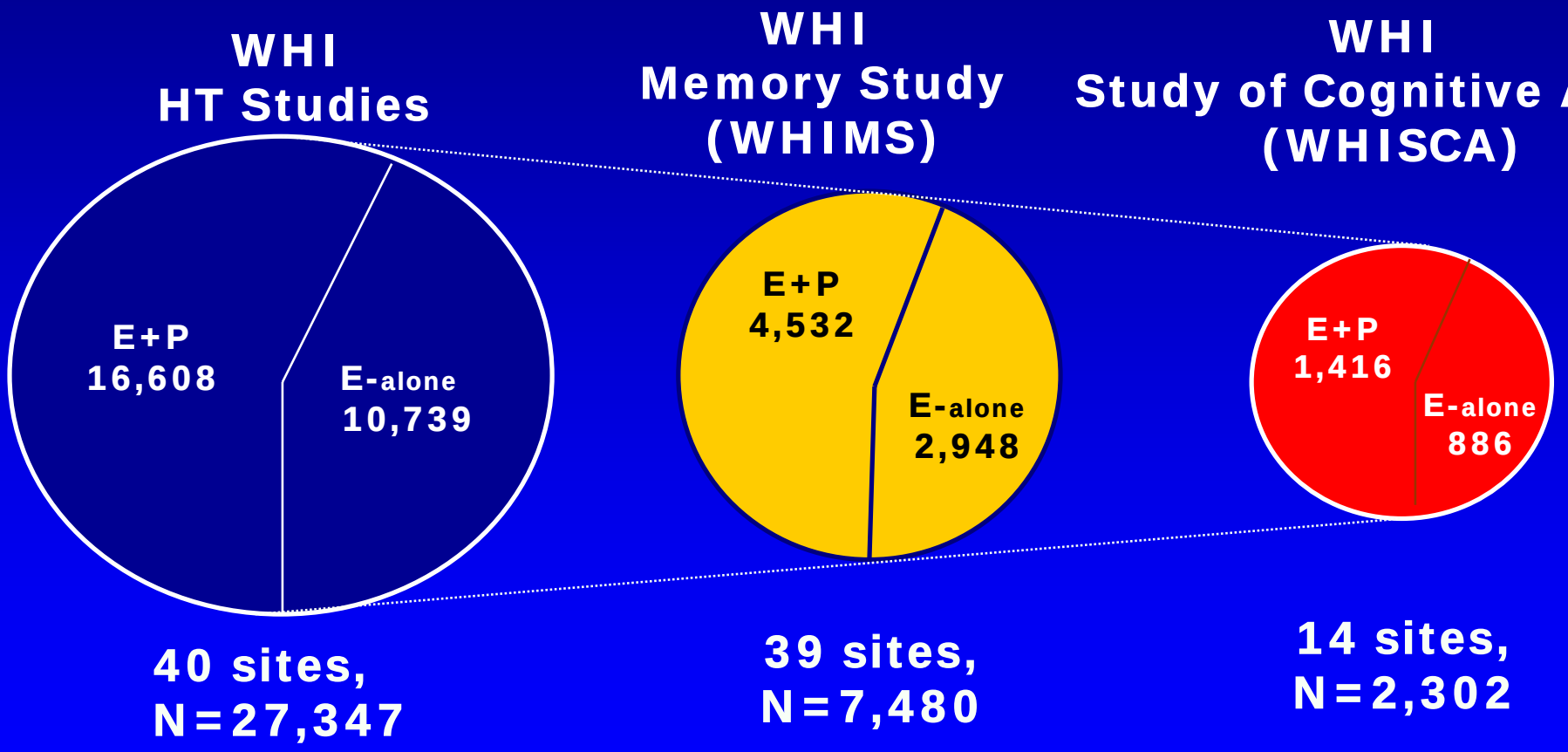
Sally Shumaker, PhD
Principal Investigator
WHIMS, WHISCA Ancillary Studies
WHI Clinical Facilitating Center

Professor and Associate Dean of Research
Department of Public Health Sciences
Wake Forest University School of Medicine
Winston-Salem, North Carolina

WHI Memory Study (WHIMS): Objectives

- To test the hypothesis that in women *65 years of age and older*, E+P and/or E-alone will reduce incidence of:
  - **Dementia (any cause)**
    - Dementia caused by Alzheimer's Disease
  - **Mild cognitive impairment**
- To measure changes in cognitive functioning over time

Relationship of WHI, WHIMS, and WHI Study of Cognitive Aging (WHISCA)



Hormone

WHI Memory Study (WHIMS) - ancillary study

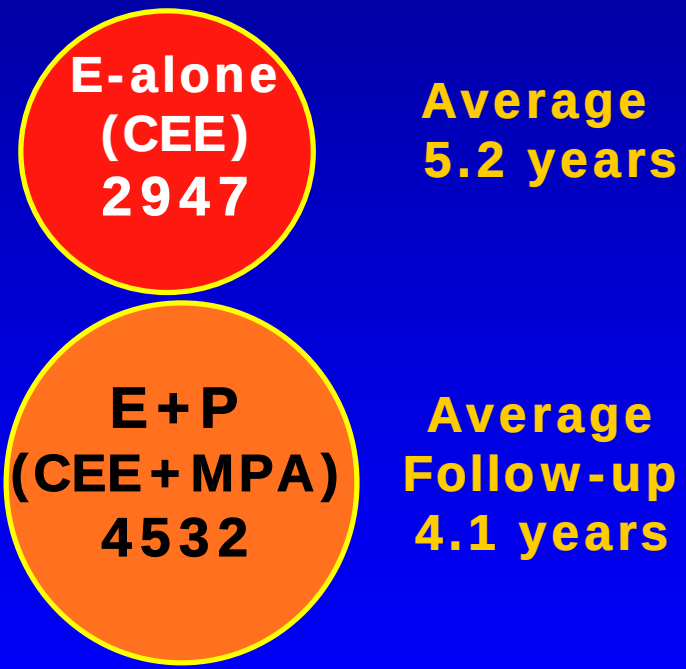
Women, aged 65-79 at baseline Total = 7479

Primary Outcome:
Probable Dementia (PD)

Secondary Outcomes:
Combined PD and Mild Cognitive Impairment (MCI)

Supporting Data:
Global Cognitive Function (by annual Modified Mini-mental State Examination, 3MSE)

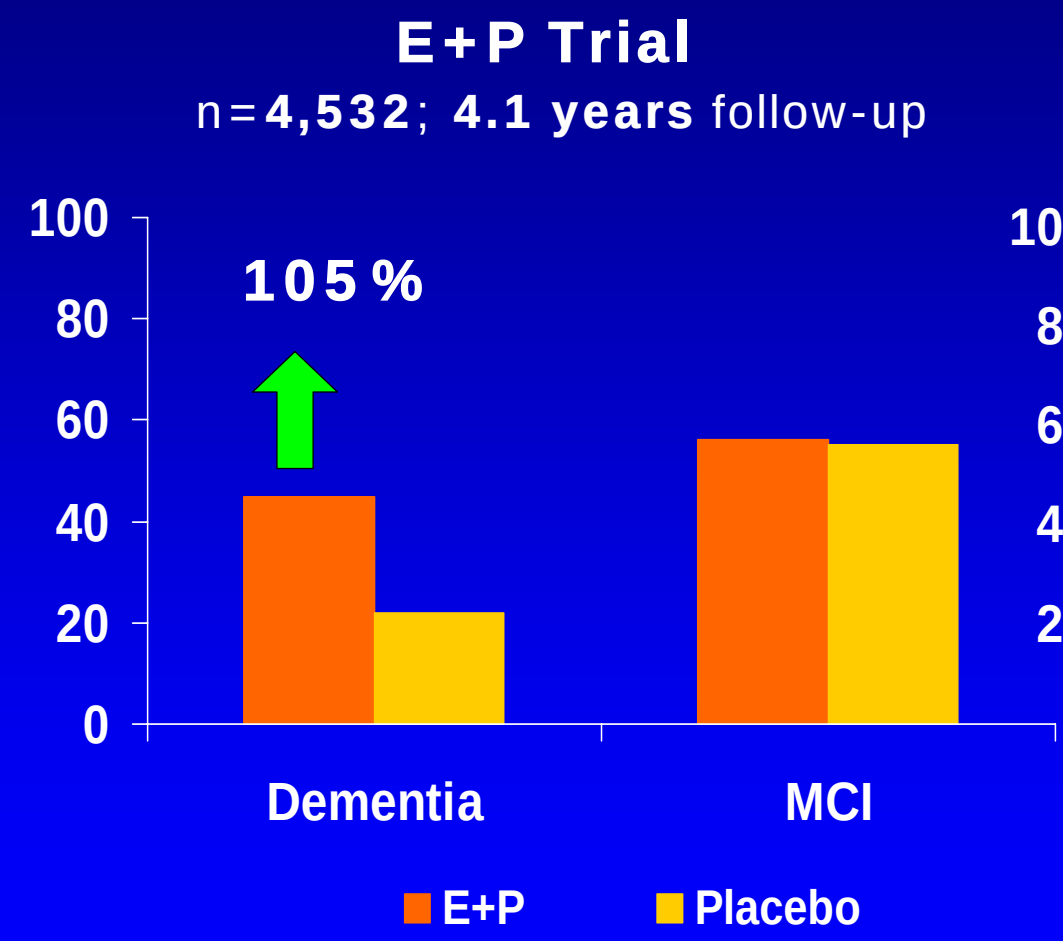
***Shumaker, Wake Forest University**

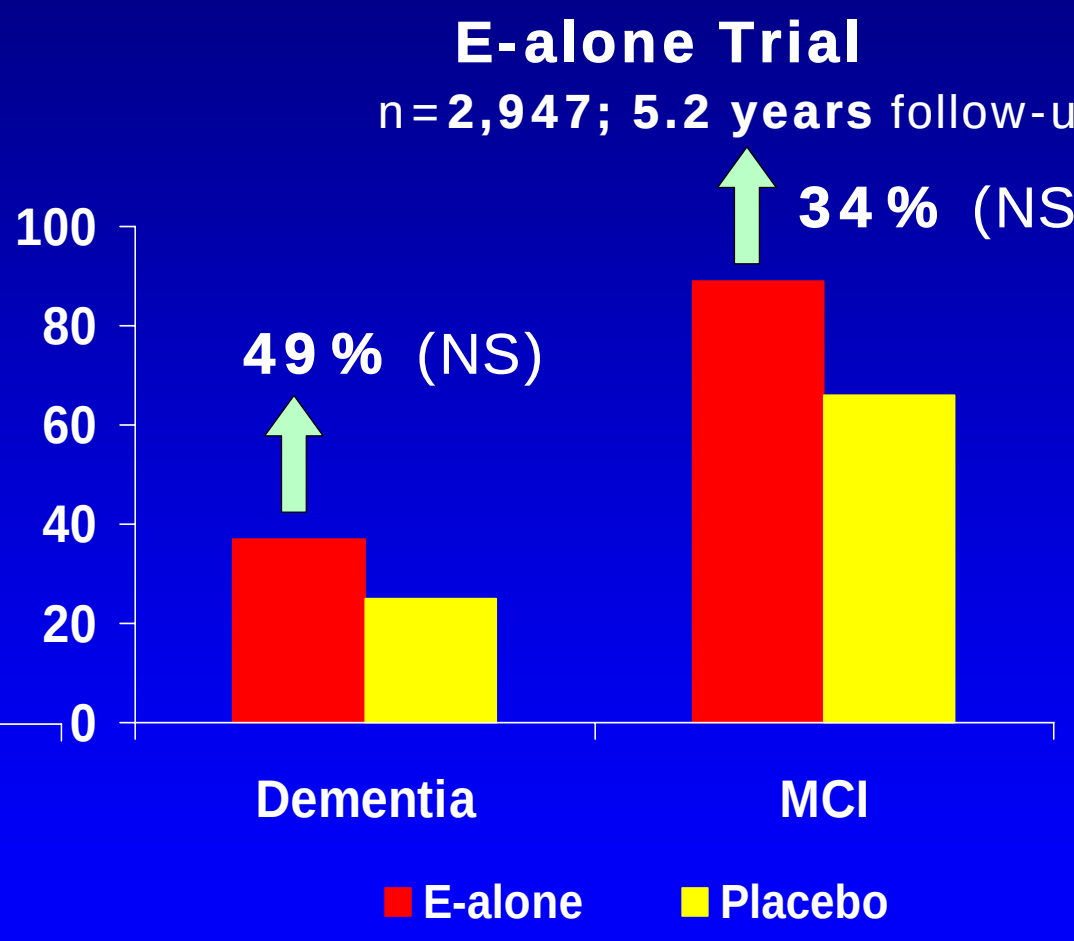


***design = 7 years**

Hormone

Probable Dementia and Mild Cognitive Impairment (Rates per 10,000/Year) in E+P and E-alone





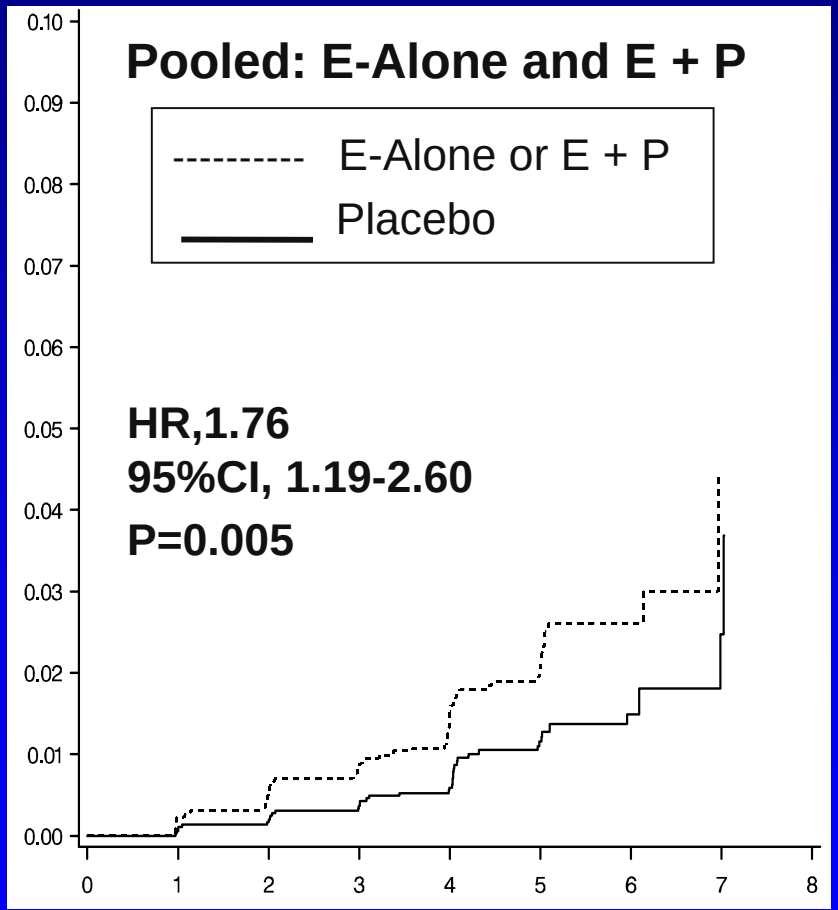
JAMA 2003; 289:2651-62

JAMA 2004; 291:2947-58

WOMEN'S HEALTH INITIATIVE

Hormone

WHIMS Overall Results for Probable Dementia



JAMA 2004; 291:2947-58

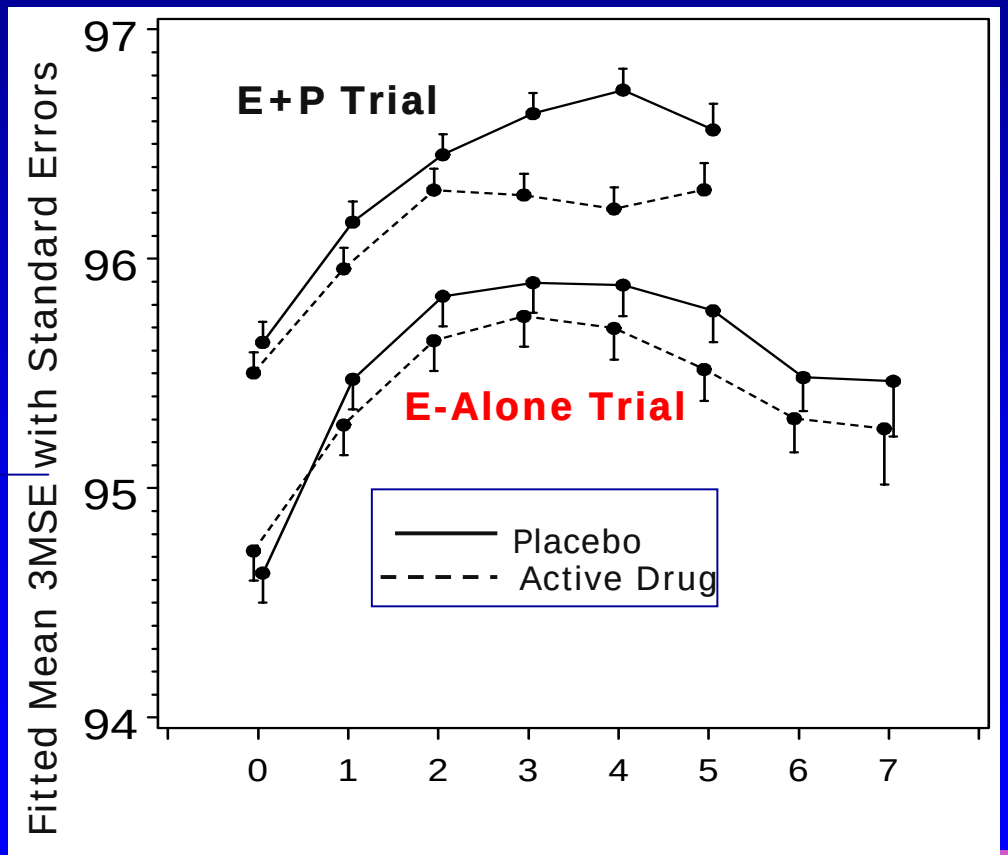
Hormone

WHIMS E-alone and E+P: Mean 3MSE

Modified Mini-mental State Examination (3MSE): Domains

- –Orientation to time
- –Orientation to place
- –Registration
- –Attention
- –Recall
- –Drawing
- –Naming
- –Repetition
- –Comprehension
- –Reading
- –Writing

Global Cognitive Function



JAMA 2004; 291:2959-68

WHIMS E+P +/or E-Alone Trial Summary of Findings

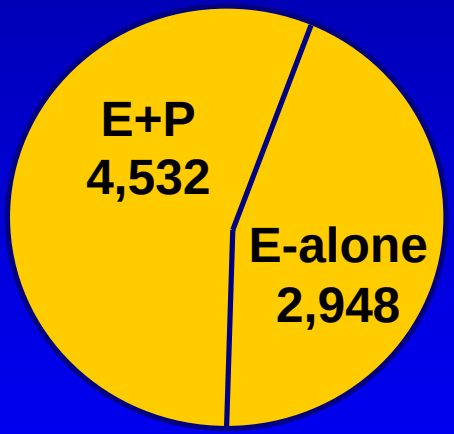
- HT did not improve global cognitive function
- Compared to women taking placebo, women taking HT:
  - performed slightly poorer overall
  - were more likely to have a sharp drop in cognitive performance
- Risk of being diagnosed with probable dementia in the HT groups was higher than that of women in the placebo group
- Risk of MCI was higher in HT groups than that of women on placebo

Questions Being Answered Now

- *What happens to cognition and risk of PD/MCI when women stop HT?*
  - ➢ WHIMS Extension Study
- *Are there subgroups of women who are more vulnerable?*
  - ➢ Continued analysis of WHIMS and WHISCA data
- *What biological effects of HT might explain the increased risk of PD?*
  - ➢ WHIMS MRI Study with assessment of micro (subclinical) infarcts and changes in cerebral structure and volume by treatment group (MRI)

Relationship of WHIMS and WHIMS-MRI (Magnetic Resonance Imaging) Study

WHI Memory Study (WHIMS)



39 sites, N=7,480

WHIMS-MRI Current

14 sites, N=2,302

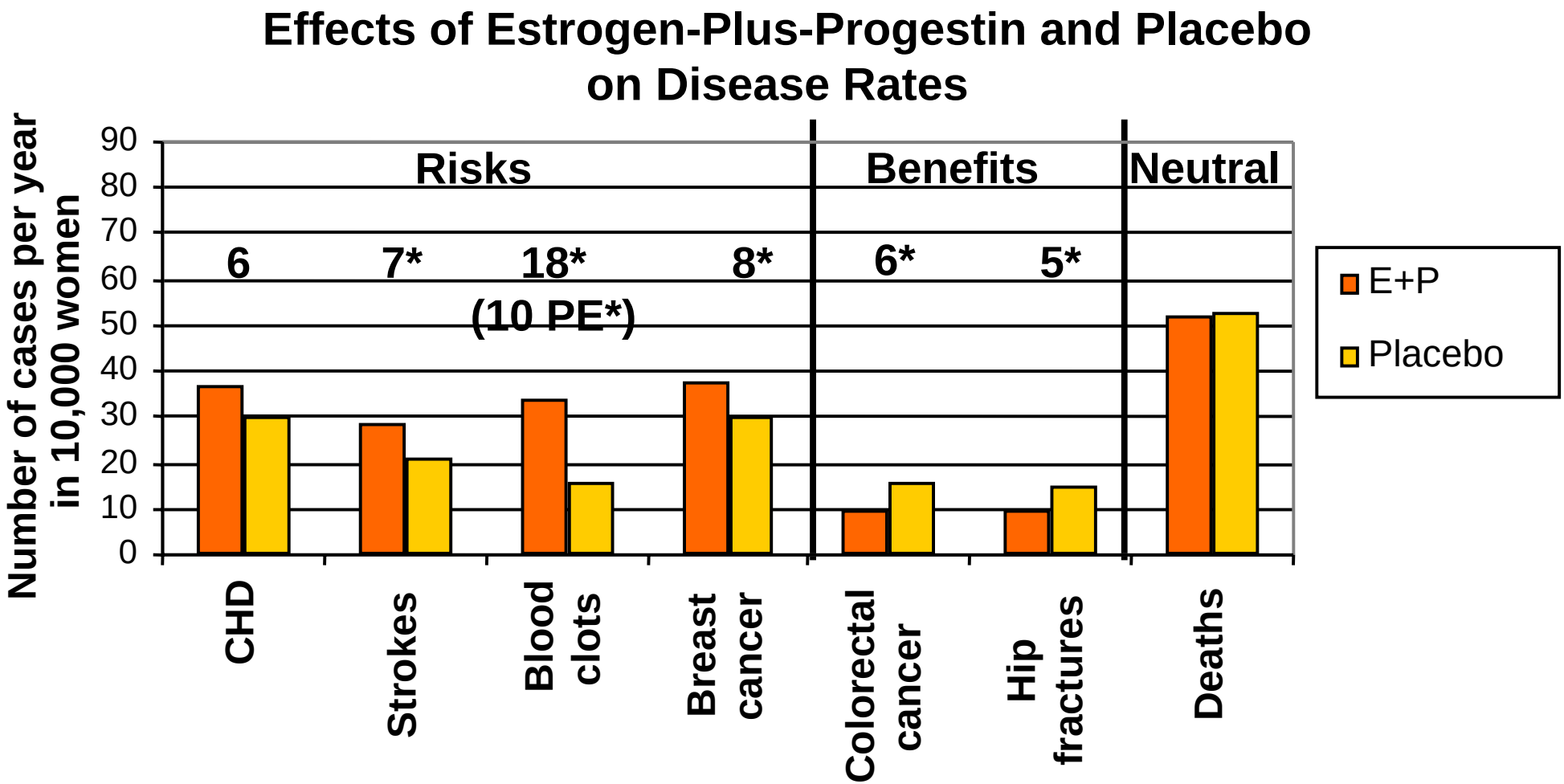
Hormone

Summary of Key Findings
Introductions (continued)

Marcia Stefanick, PhD
Principal Investigator
Stanford Clinical Center

Professor of Medicine
Stanford Prevention Research Center
Professor of Obstetrics and Gynecology
Stanford University
Stanford, CA

WHI E+P Trial: Absolute (annualized) Risk (5.6 Yrs)

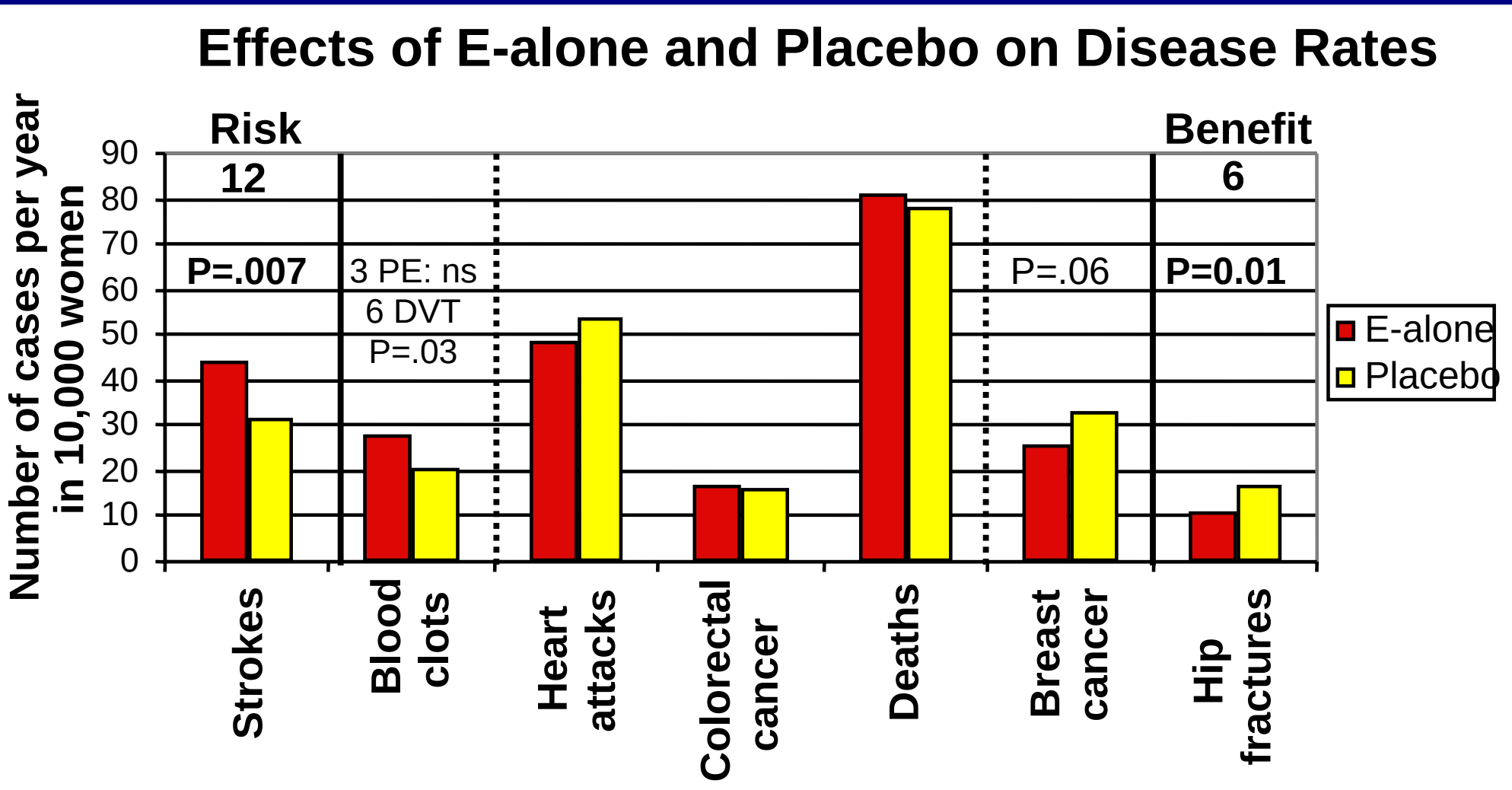


JAMA 2002; 288:321-33

*Statistically significant based on 95% nominal CI on Hazard Ratios

Hormone

WHI E-Alone Trial: Absolute (annualized) Risk (6.8 Yrs)



JAMA 2004; 291:1701-12

WOMEN'S HEALTH INITIATIVE

Hormone

Summary: Major Outcomes in E+P vs. E-Alone

- **Concordant results**
  - **Heart Disease – no benefit**
  - **Strokes, Blood Clots – harmful**
  - **Fractures – beneficial**
  - **Dementia (if ≥ 65 yrs of age) – harmful**
- **Disparate Results**
  - **Breast Cancer**
    - **Increased in E+P (CEE + MPA) Trial**
    - **Neutral in E-alone (CEE) Trial**
  - **Global Index**
    - **Increased in E+P (CEE + MPA) Trial**
    - **Neutral in E-alone (CEE) Trial**

Overview of Session; Introductions

The E+P and E-alone Trials Results (cont.)

- **Quality of Life, Symptoms, Stopping Hormones**
  Jennifer Hays, PhD
- **Diabetes, Gallbladder, Incontinence**
  Denise Bonds, MD, MPH

Overview of Session; Introductions

Special E+P and E-alone Trial Studies

- **Coronary Artery Calcium Study**
  JoAnn Manson, MD, DrPH
- **Biomarkers and Genetic Studies**
  Karen Johnson, MD, MPH

Audience Questions and Answers

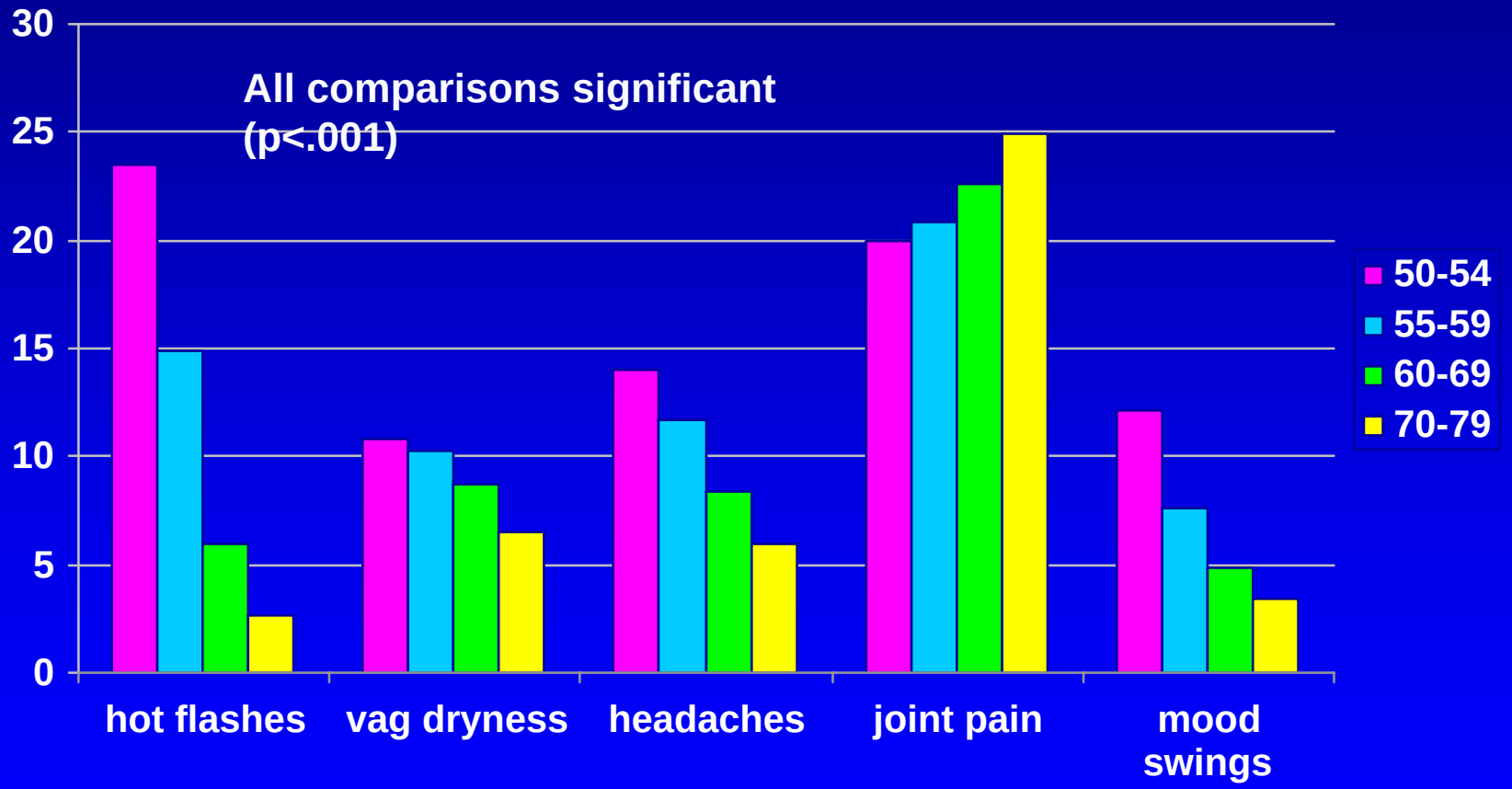
- ***Break***

Health-related Quality of Life, Symptoms, Stopping Hormones

Jennifer Hays, PhD
Principal Investigator
Houston Clinical Center

Associate Professor
Department of Medicine
Texas A&M College of Medicine
Scott & White Hospital
Temple, Texas

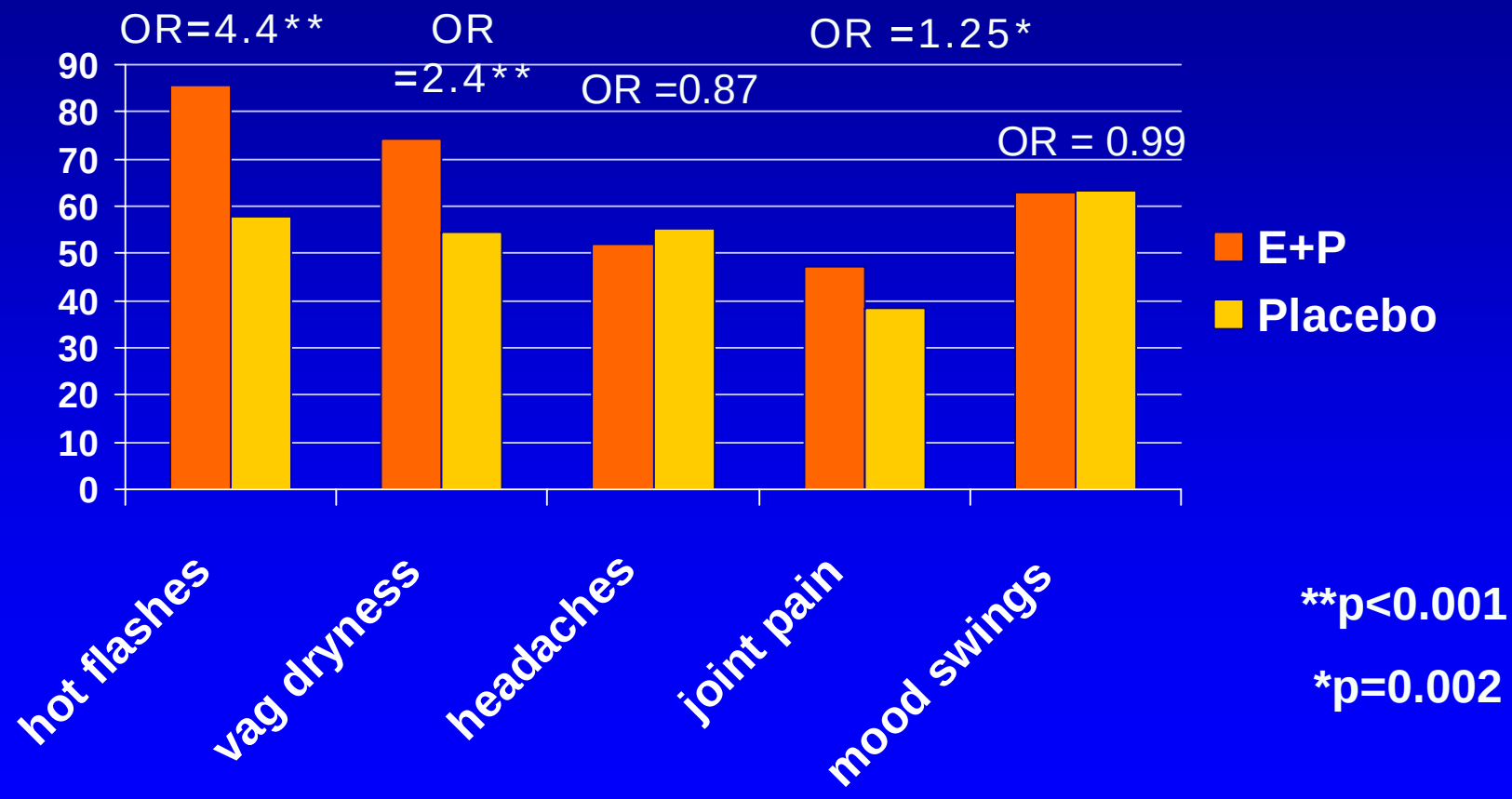
E+P: Symptoms at baseline by age



Obstet Gynecol 2005; 105:1063-73

Hormone

E+P: Symptom changes at 1 year



**p<0.001

*p=0.002

Obstet Gynecol 2005; 105:1063-73

Hormone

Purpose of WHI Quality of Life (QOL) Study

- To test the hypothesis that decreasing menopausal symptoms would increase women's perceived quality of (QOL) using valid measures of physical, mental and social functioning (including Rand-36, CES-D)
- To assess whether effects on QOL would differ by to baseline age, weight, symptoms, sleep problems, prior hormone use

E+P: Health-related QOL Primary Results

- Three of 13 measures statistically significant (between groups after 1 year)
  - **Physical functioning** (0.8 difference/100 point scale)
  - **Bodily pain** (1.9 difference/100 point scale)
  - **Sleep** (0.4 difference/20 point scale)
- None clinically significant
- 5% improvement in sleep among 50-54 year-old women with menopausal symptoms
- No differences after 3 years (n=1,511 women)

NEJM 2003; 348:1839-54.

E-alone: Health-related QOL Primary Results

- Two of 13 measures statistically significant (between groups after 1 year)
  - **Sleep** (+0.4 points/20 point scale)
  - **Social functioning** (**-**1.3 points/100 point scale)
- None clinically significant
- No differences among 50-54 year old symptomatic women
- No differences after 3 years (n=1,511 women)

Arch Intern Med 2005; 165:1976-86

Hot Flashes (HF) 8-12 months after stopping study pills by baseline symptom status

	E+P (%)	Placebo (%)
Women with HF at baseline	55.5	21.3
Women with HF prior to baseline	21.6	3.7
Never had HF	6.4	1.2

- **Women more likely to have hot flashes after stopping if:**
  - **had symptoms at baseline**: OR = 5.4 (95% CI = 4.5-6.4)
  - **were randomized to E+P**: OR = 5.8 (95% CI = 4.9-6.9)
  - **were current smokers**: OR = 1.5 (1.2-2.0)

JAMA 2005; 294:183-93

Summary of symptoms and QOL in HT trials

- **HT improved menopausal symptoms and joint pain** (particularly in younger, thinner women) but **increased breast tenderness, bleeding, headaches**
- **All symptoms except joint pain decreased with age**
- **Improvement in symptoms did not translate into clinically significant improvements in QOL**
- **Symptoms recurred in many women after stopping study pills, particularly in women with prior symptoms**
- *Caveat: WHI hormone trials did not include women unwilling to be randomized to placebo*

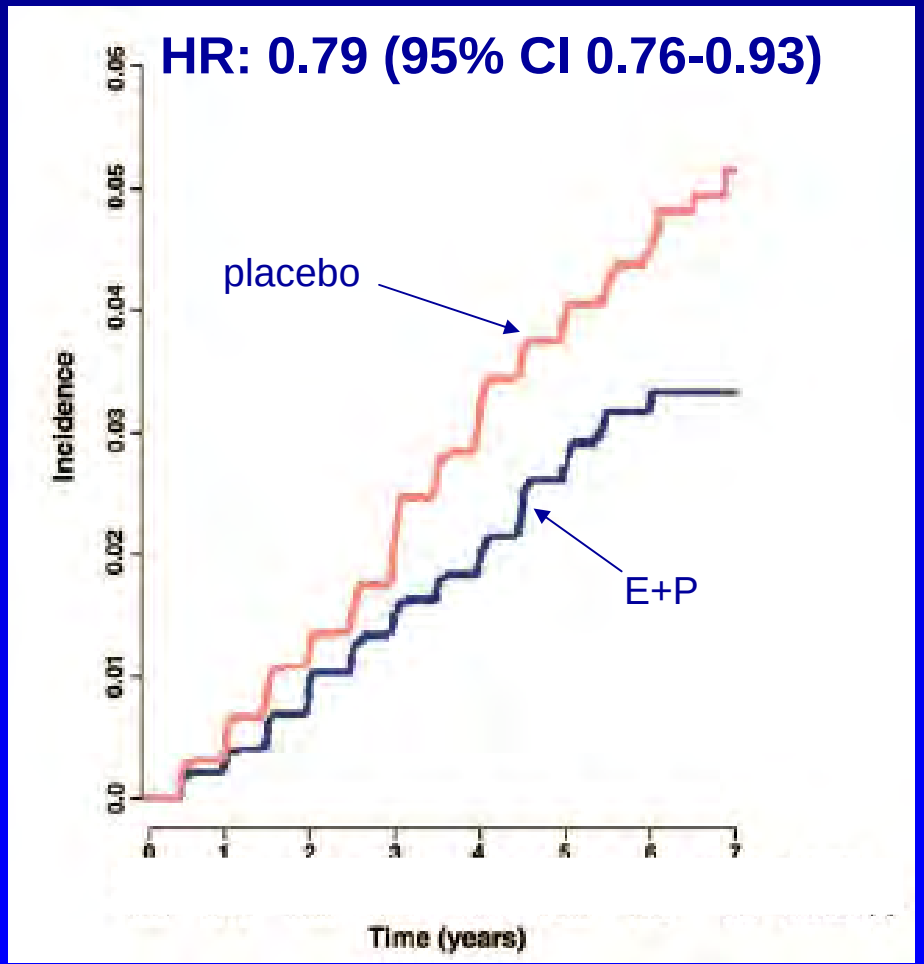
Diabetes, Gallbladder, Incontinence

Denise Bonds, MD, MPH
Principal Investigator
Winston-Salem Clinical Center

Assistant Professor
Department of Public Health Sciences
Wake Forest University School of Medicine
Winston-Salem, North Carolina

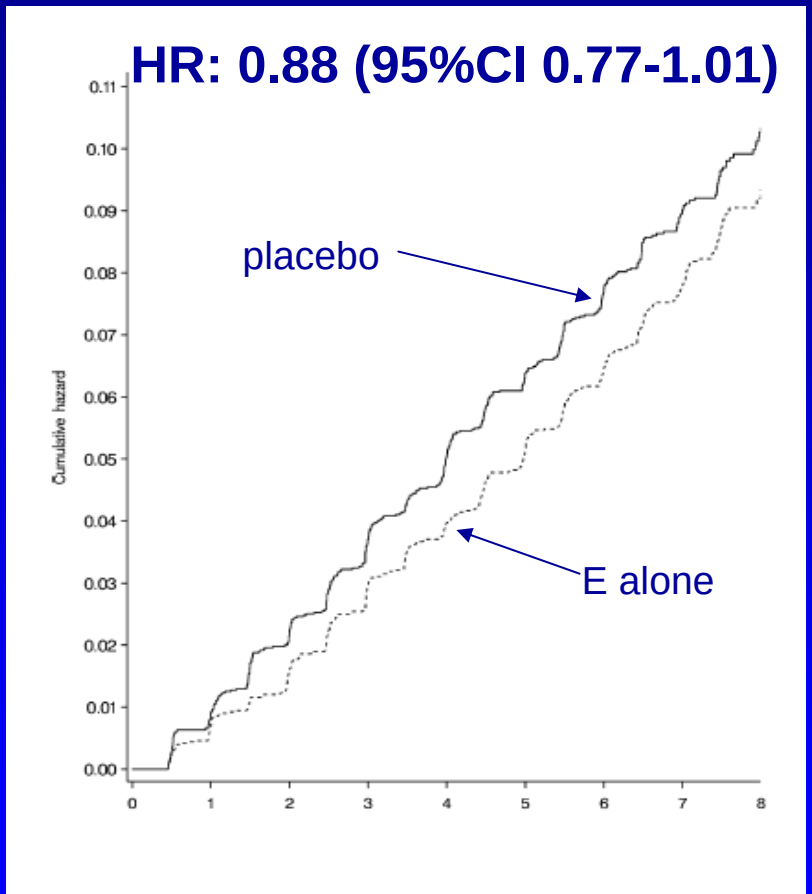
E+P: Diabetes

- **3.5%** (212/7352) of women receiving **E+P** reported treated diabetes **compared to 4.2%** (252/7352) of women receiving **placebo**
- After 1 year, both glucose and insulin significantly reduced



Hormone

E-alone: Diabetes



- **8.3%** (397/4787) of women on **E alone** reported diabetes **compared to 9.3%** (455/4887) of women on **placebo**
- Both glucose and insulin reduced after one year on estrogen

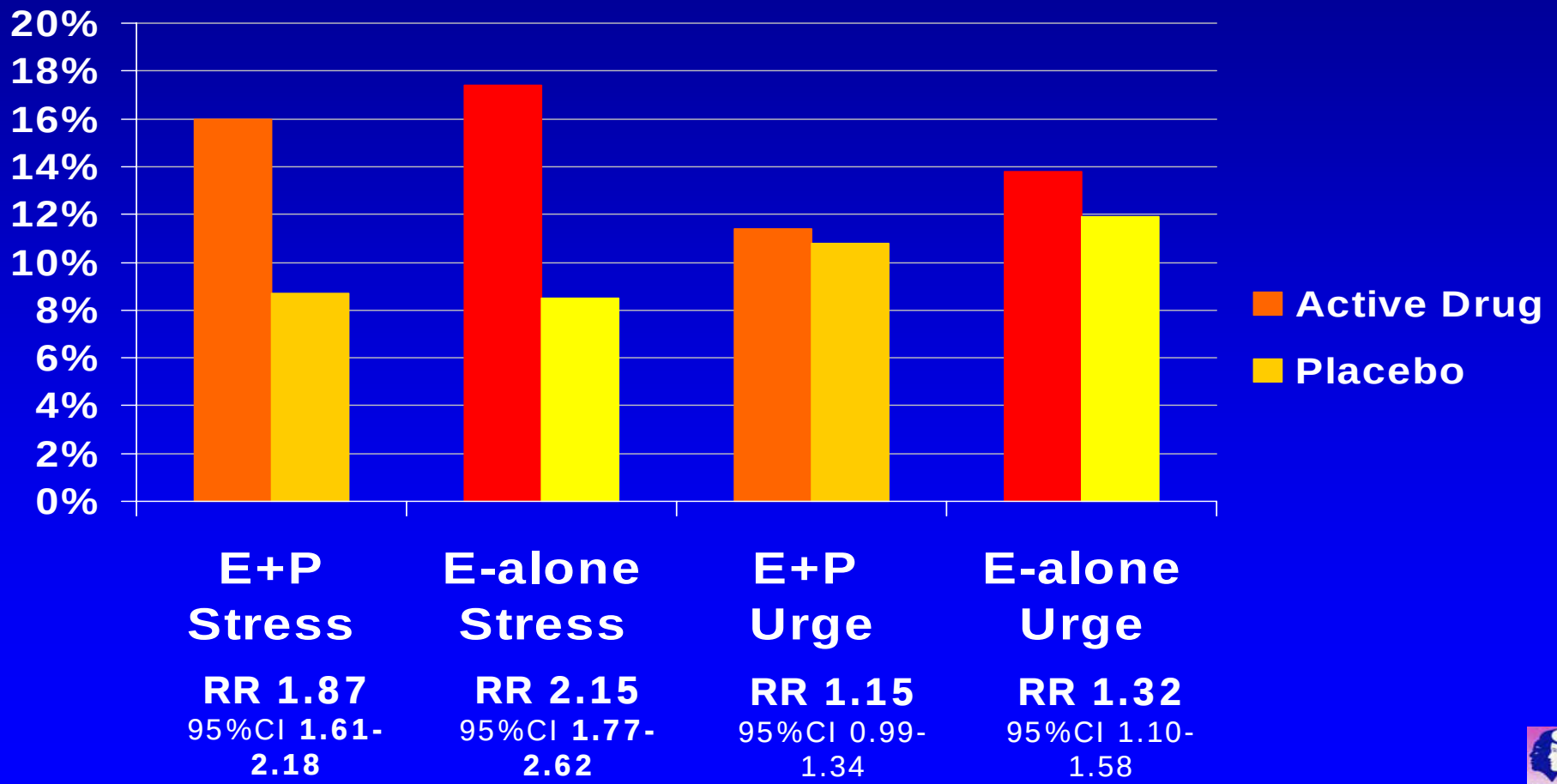
WOMEN'S HEALTH INITIATIVE

Hormone

Urinary Incontinence in Hormone Trials

- **Incontinence:**
  - "Have you ever leaked even a small amount of urine involuntarily and you couldn't control it"
  - **Stress:** "When I cough, laugh, sneeze, lift, stand up or exercise"
  - **Urge:** "When I feel the need to urinate and can't get to the toilet fast enough"
- Both effect of hormone therapy on incontinence present at baseline and the number of women with new onset incontinence examined

New onset incontinence



JAMA 2005; 293:935-48

Hormone

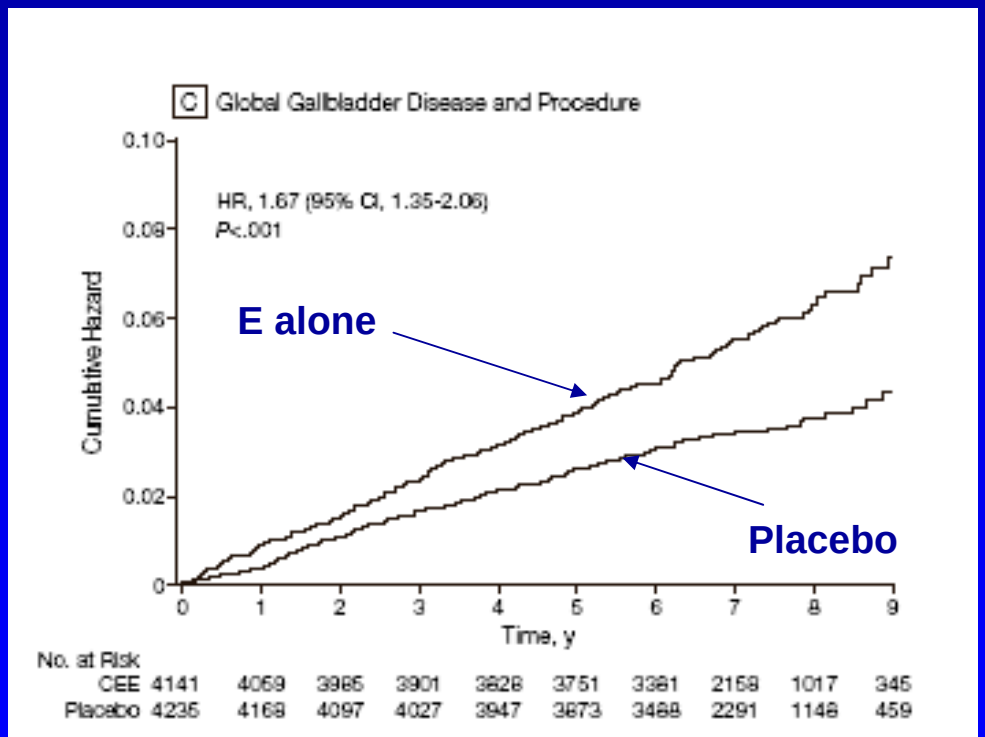
Change in Incontinence (if present at Baseline)

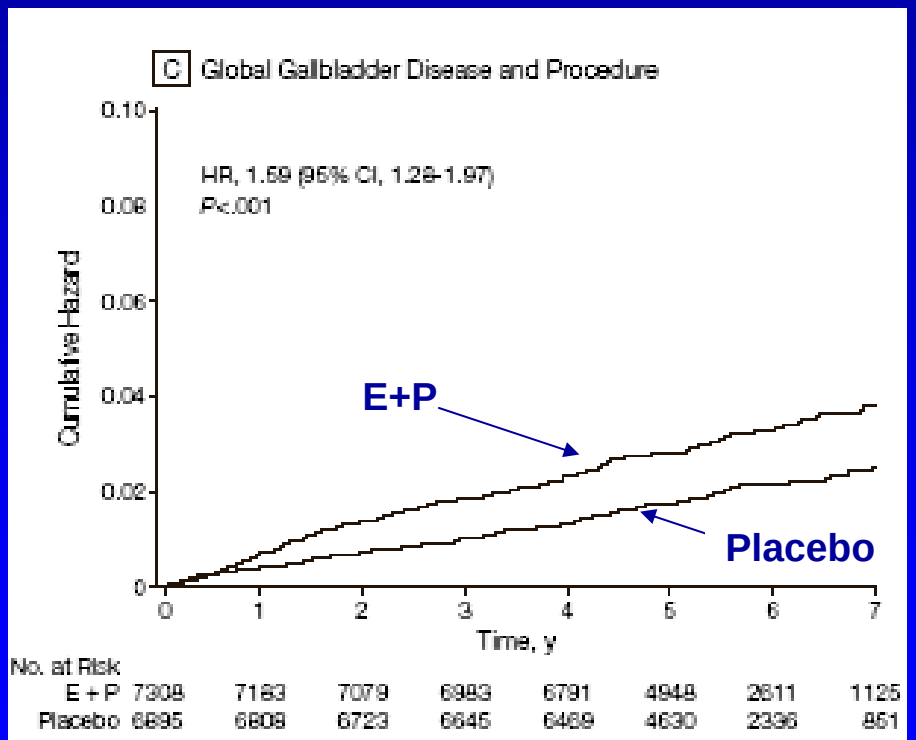
- Women who had incontinence symptoms at baseline showed an increase in severity after one year of therapy
  - Increase in amount of urine leaked, frequency of leakage, limitations in activities, and degree of bother
  - Seen in both E alone and E+P

JAMA 2005; 293:935-48

Gallbladder Disease and Hormones

- **In both E +P and E alone, women taking active drug had more gallbladder disease and gallbladder surgery**





JAMA 2005; 293:330-39

Coronary Artery Calcium Study

JoAnn Manson, MD, DrPH
Principal Investigator
Boston Clinical Center

Professor of Medicine and Elizabeth Brigham Professor of Women's Health - Harvard Medical School
Chief – Division of Preventive Medicine, Brigham and Women's Hospital
Boston, Massachusetts

The WHI Coronary Artery Calcium Study (WHI-CACS)

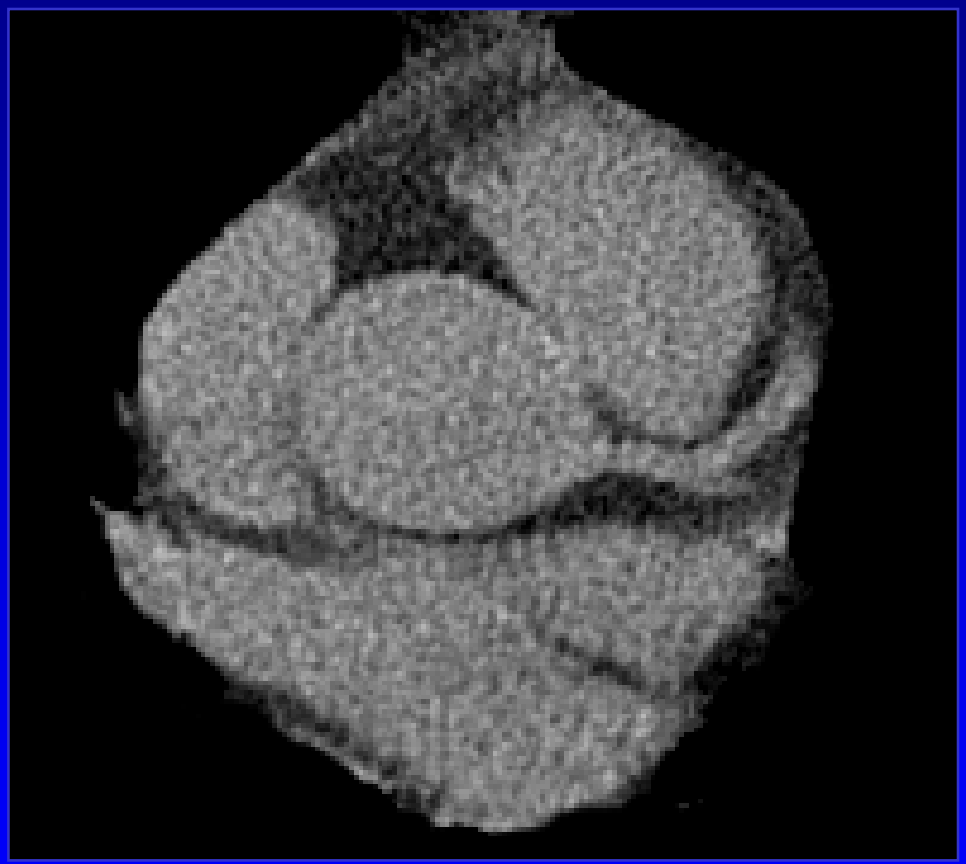
Goals:

- Obtain noninvasive measures of the amount of calcium in the coronary arteries (marker of atherosclerosis) at end of E-alone trial in women aged 50-59 at baseline.
- Develop a resource of vascular imaging measurements for WHI: opportunities to assess multiple predictors.

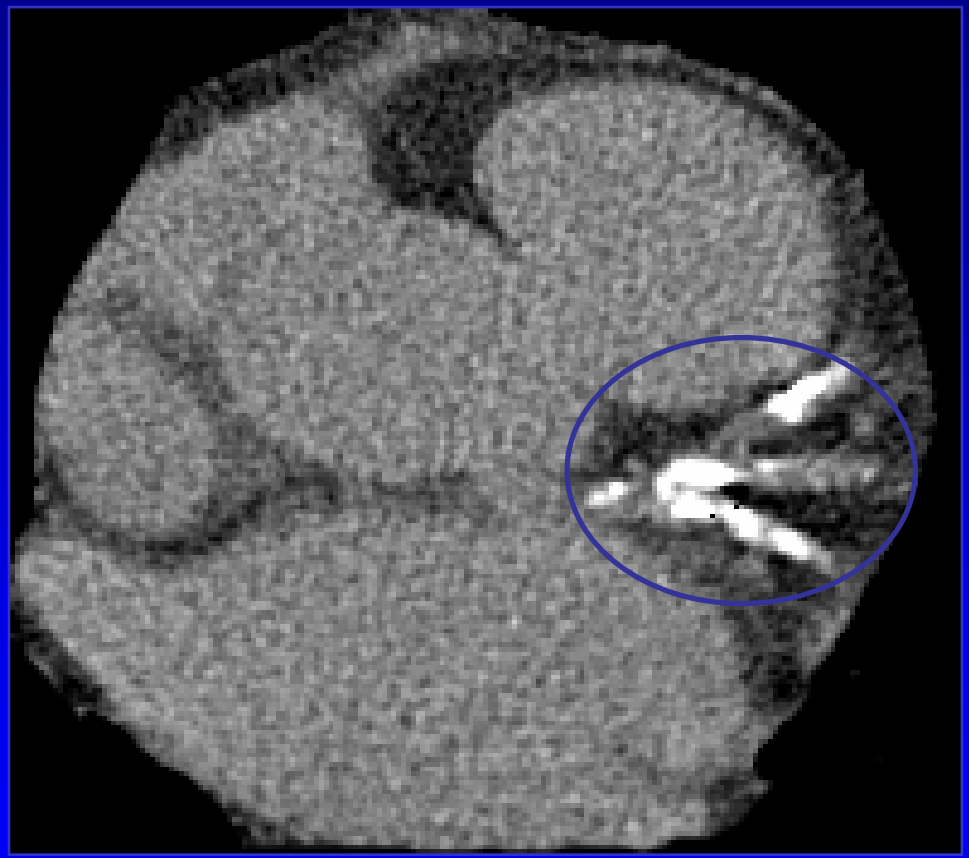
Enrollment in the Coronary Artery Calcium Study

- 28 WHI clinical centers participated.
- ~1700 women (aged 50-59 at time of randomization for the E-alone trial) were eligible and invited to participate.
- ~1100 completed scanning between May 2005 and September 2005.
- Analyses of results are in progress.

Coronary Artery Calcium



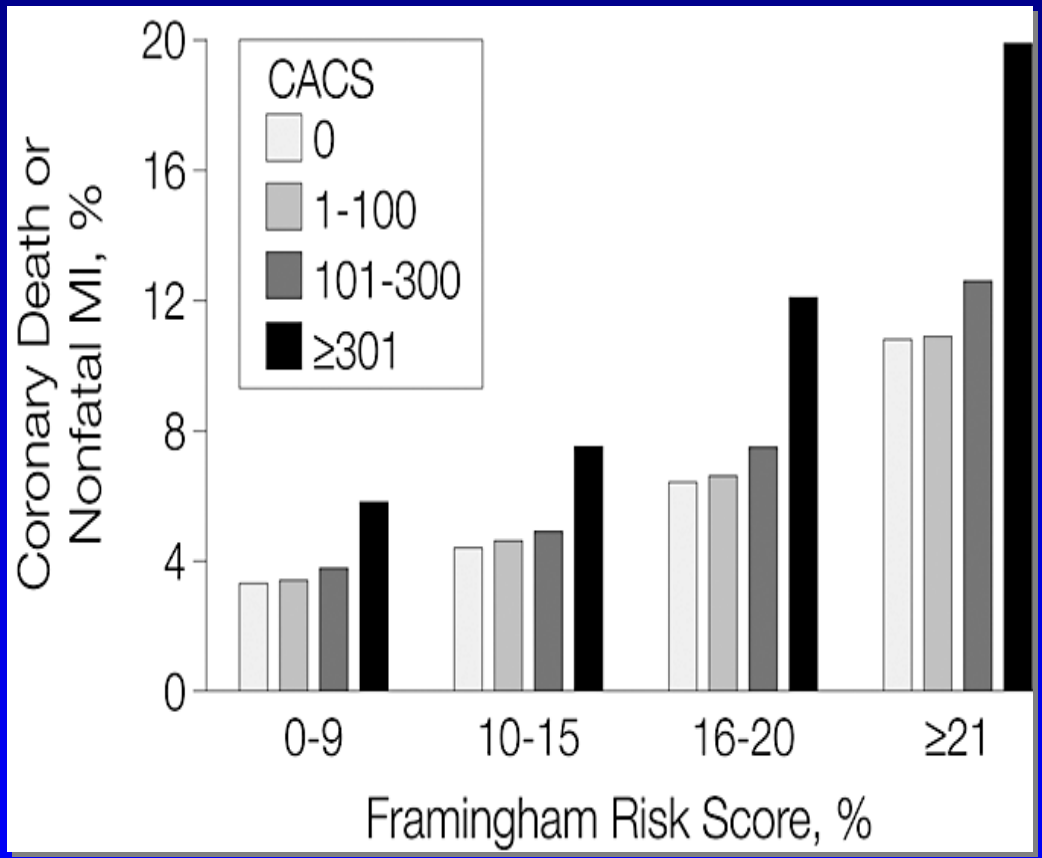
No Calcium



Severe Calcification

Hormone

CAC & Framingham Model: Risk Prediction in Asymptomatic Individuals



Predicted 7-year event rate for CHD death or MI for categories of FRS or CAC score.

JAMA 2004; 291:210-15

Other WHI-CACS Analyses Planned

To assess role of the following in predicting CAC score:

- **Clinical characteristics (age, ethnicity, time since menopause, prior hormone therapy use, blood pressure, body mass index, etc.)**
- **Lifestyle factors (physical activity, smoking, diet, alcohol use, stress, etc.)**
- **Biomarkers from stored blood samples**

Biomarkers and Genetic Studies

Karen Johnson, MD, MPH
Principal Investigator
Memphis Clinical Center

Professor with Tenure
Joint Appointment in the Departments of
Preventive Medicine and Medicine
University of Tennessee Health Science Center
Memphis, Tennessee

Laboratory Studies
(Biospecimen Repository)

Blood samples (fasting ≥ 12 hrs) collected on:

- **all CT** @ baseline & Year 1; **6% subsample,** Yrs 3, 6, 9
- **all OS** @ baseline and Year 3
- **Serum, Citrate and EDTA plasma, RBC, DNA stored**
  DNA extraction from buffy coat

DEXA Bone Mineral Density & body composition **@ 3 sites**

Urine on all CT & OS at 3 "bone sites" @ baseline **& Yr 1 & 9**

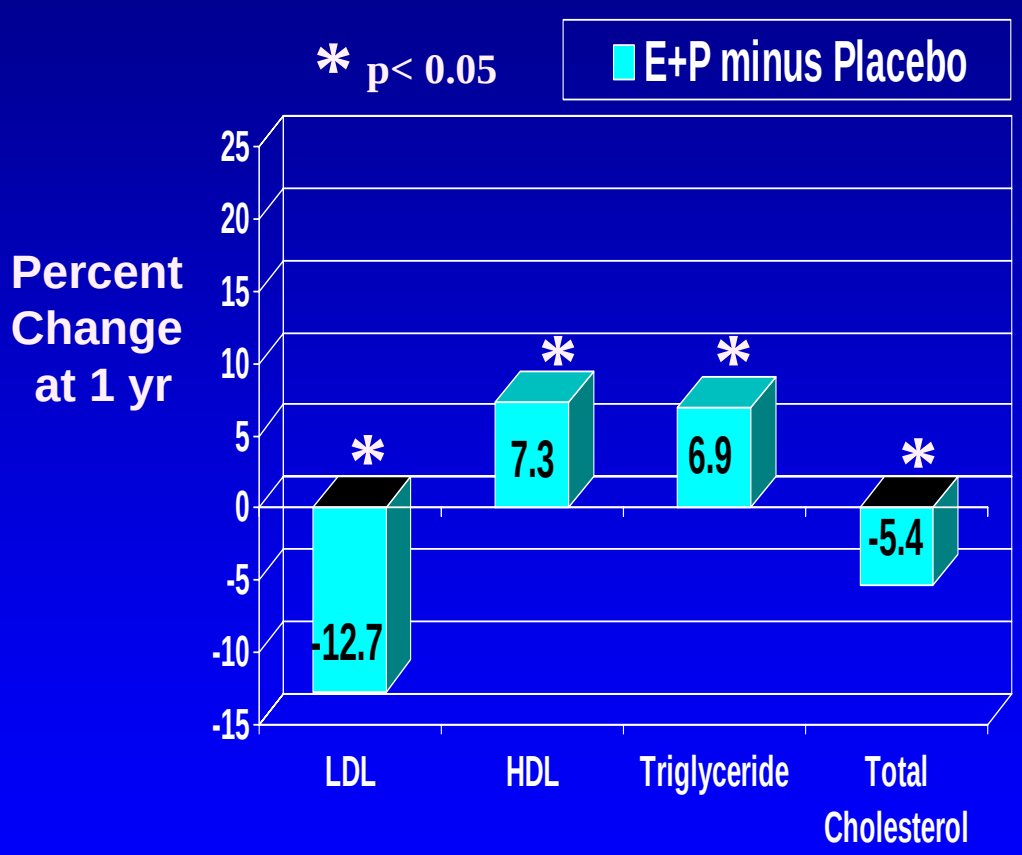
Core Analytes for 6% CT subsample

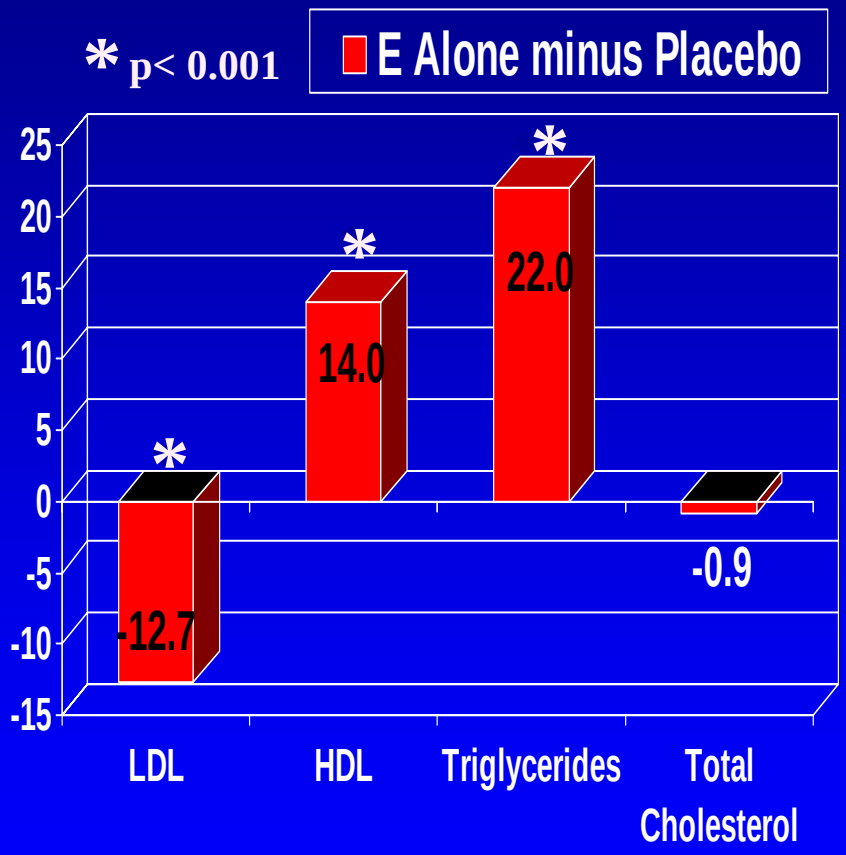
Micronutrients	Lipid Fraction	Clotting Factors	Hormones
Alpha-carotene	Triglycerides	Factor VII	Glucose
Beta-carotene	Total Cholesterol	Factor VII C	Insulin
Alpha-tocopherol	LDL-C	Fibrinogen	
Gamma-tocopherol	HDL-C		
Beta-cryptoxanthine	HDL-2		
Lycopene	HDL-3		
Lutein and zeaxanthin	Lp(a)		
Retinol			

Hormone Trial CVD Biomarker Case-control Study CHD, Stroke, VTE

Lipids	Inflammation	Thrombosis	Polymorphisms
HDL-C, HDL-2 &-3	C-reactive protein	Antithrombin III	MTHF; PAI-1
LDL-C; Lp(a)	E-selectin	D-dimer	Prothrombin 20210
LDL Particle size	Interlukin (IL)-6	Factor VIII	Prothrombin 19911
Subfractions (10)	MMP-9	Factor IX Conc	Factor XIII val34leu
Triglyceride Total Cholesterol	TFPI activity, free, total	Fibrinogen Protein C, S total, free	ERB-1730AG; GPIIIa-PIA
Other		Fragment 1+2 PAI-1; PAP	IVS1-154, -401, -1415, -1505
Homocysteine		TAFI, vWF, APC-ETP	F5LE; GPIM; HR2
Glucose		Prothrombin Ag	Intergrina2-807C/T
Insulin			EVS1 EXON 1+30

Lipid Levels in E+P and E-alone Trials





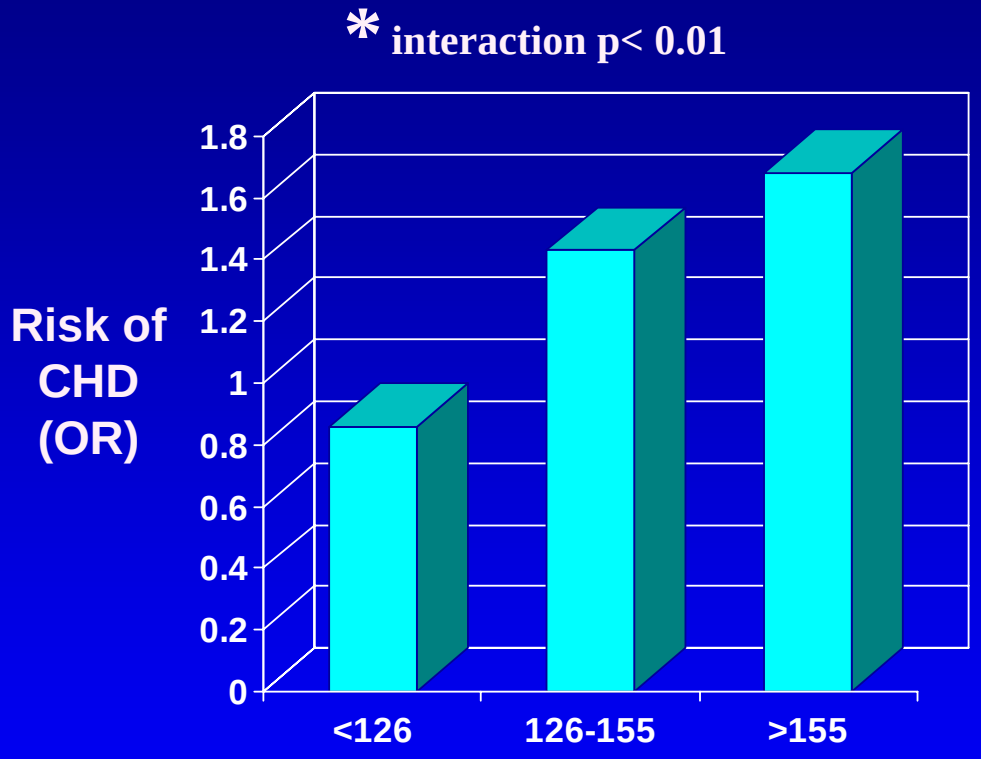
NEJM 2003; 349:523-34

Arch Intern Med 2006; 166:1-9

WOMEN'S HEALTH INITIATIVE

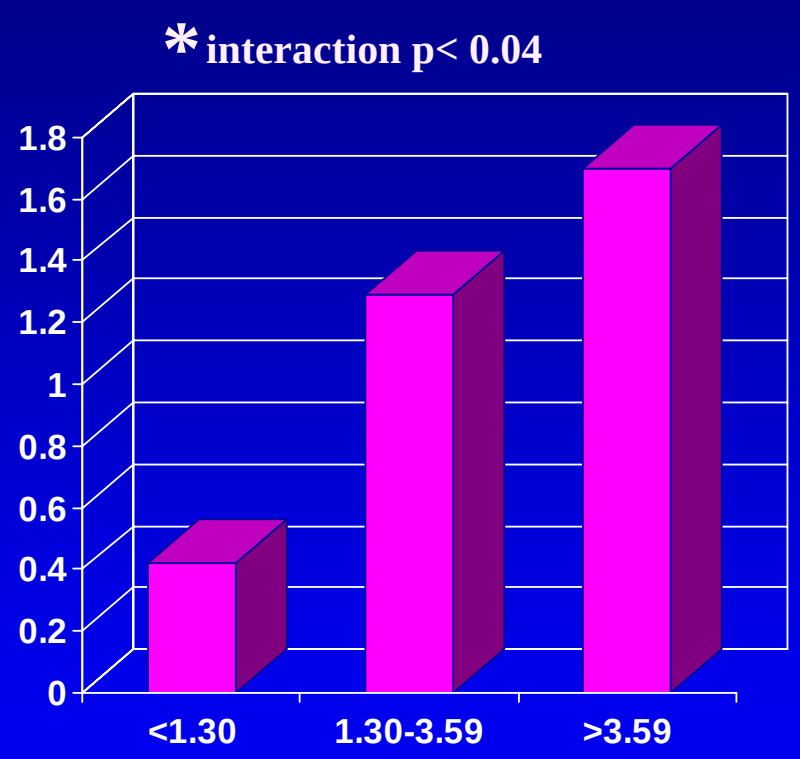
Hormone

Biomarker Interactions in E+P and E-alone Trials



E + P Trial

NEJM 2003;349:523-34



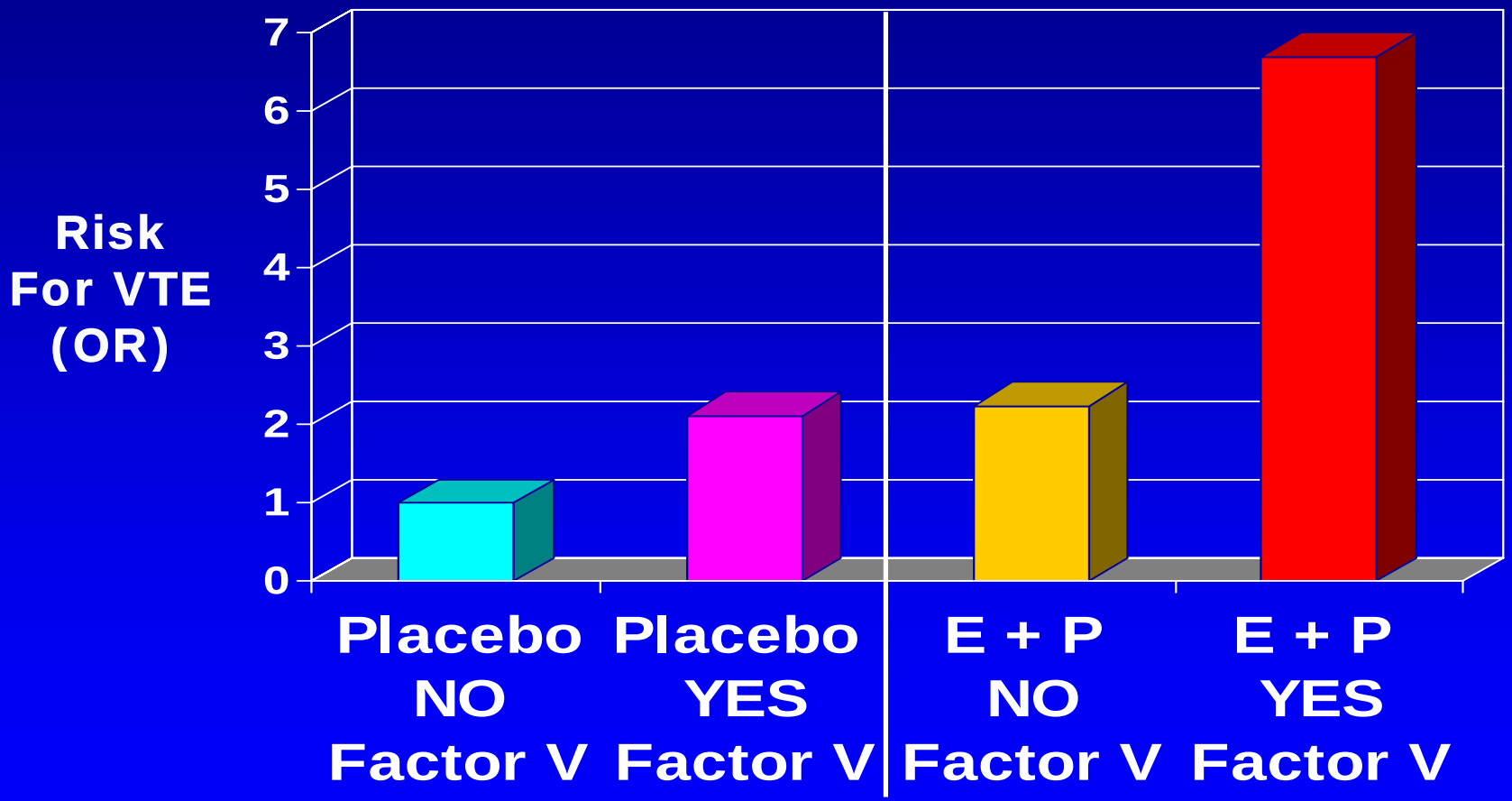
E Alone Trial

Arch Intern Med 2006;166:1-9

WOMEN'S HEALTH INITIATIVE

Hormone

Risk for Venous Thrombosis in E+P Trial by Factor V Leiden Gene Mutation Status



JAMA 2004; 292:1573-80

Future Directions for the WHI Study

- Biomarkers: HT Effects on Cardiovascular Outcomes
- Biomarkers: HT Effects on Risk of Fractures, Breast Cancer
- Proteomic Patterns in Relation to Colorectal Cancer in HT & OS
- Genome-wide Scan of Single Nucleotide Polymorphisms (SNPs) in Relation to CHD, Stroke, Breast Cancer

Audience Questions and Answers

Marcia Stefanick, PhD
Principal Investigator
Stanford Clinical Center

- ***Break***

Overview of Session; Introductions

- **Communicating Unexpected Findings to the Public**
  Barbara Alving, MD
- **Hormone Participant Panel**
  - Facilitator: James Shikany, DrPH, PA-C
  - Participants: Gene Gary-Williams, PhD
    Natalie Gordon, DSW
    Gail LaMar
    Eiko Nomura

Overview of Session; Introductions

- **Impact of HT Trials on Medical Practice**
  Margery Gass, MD
  Robert Brzyski, MD, PhD
- **Future Directions for Menopausal Hormone Research**
  Jacques Rossouw, MD
- **Audience Questions and Answers**

Challenges in Communicating Results of Large Clinical Trials

Barbara Alving, MD, MACP
Past Director,
Women's Health Initiative

Acting Director,
National Center for Research Resources
National Institutes of Health
Bethesda, Maryland

Hormone

Dissemination of Research Results

Dissemination of Information

Role of NIH in Communicating Results of Clinical Trials

- **Work with investigators to develop messages about the clinical trial results:**
- Notify and discuss with other NIH offices, Institutes, and Department Health & Human Services
- Notify FDA (NIH often registers trials under an IND with the FDA for new drugs or new indications for old drugs)
- Notify Industry that has supplied the drug and that needs to work with FDA to revise labeling information

Communicating Results of Clinical Trials to Participants/Public

- **WHI participants receive personal letters (hormone trials) or timely newsletters just as information is being released through the media**
- **Professional organizations alerted**
- **Public advocacy groups alerted**
- **News media receives information under embargo** in order to interview investigators and other experts; news reports are coordinated with publication of reports in medical journals.

Special Letters to all WHI Hormone Trial Participants

1997: HERS: risks of deep vein thrombosis & pulmonary emboli

1998: HERS: increased risk of heart disease in first year, no protection against heart disease overall

April 2000: more heart attacks, strokes, and blood clots (DVT, PE) seen in active pill groups after most were past 2 years

May 2001: higher rates of heart attacks, strokes, & blood clots persisted in active pill groups, after average of 4 years

May 2002: NIH accepted DSMB recommendation to stop Estrogen plus Progestin Trial after average of 5.2 years, because risks (breast cancer + overall harm, "Global Index") exceeded benefits

February 2004: NIH stopped WHI E-alone Trial after average of 6.6 years because of increased stroke, no heart disease benefit

Actions Following Stopping the E+P Trial

- Menopausal hormone therapy meeting: NIH, Oct 2002
- New meeting in 2005 to focus on research issues in menopause
- Lower doses of *Prempro* and *Premarin* approved by FDA
- Women taking a new approach to the prevention of heart disease, their #1 cause of death
- Women participating more in decisions about their health care

Personal Accounts of Participants

James Shikany, DrPH, PA-C
Co-Investigator and Lead Clinic Practitioner
Birmingham Clinical Center

Assistant Professor of Medicine
Division of Preventive Medicine
University of Alabama at Birmingham
Birmingham, Alabama

Personal Accounts of Participants

Facilitator: **James Shikany, DrPH, PA-C**

Participants: **Gene Gary-Williams, PhD**

Natalie Gordon, DSW

Gail LaMar

Eiko Nomura

Hormone

Impact of WHI Hormone Trials on Medical Practice

Robert Brzyski, MD, PhD
Principal Investigator
San Antonio Clinical Center

Associate Professor
Obstetrics & Gynecology
University of Texas Health Science Center – San Antonio
San Antonio, Texas

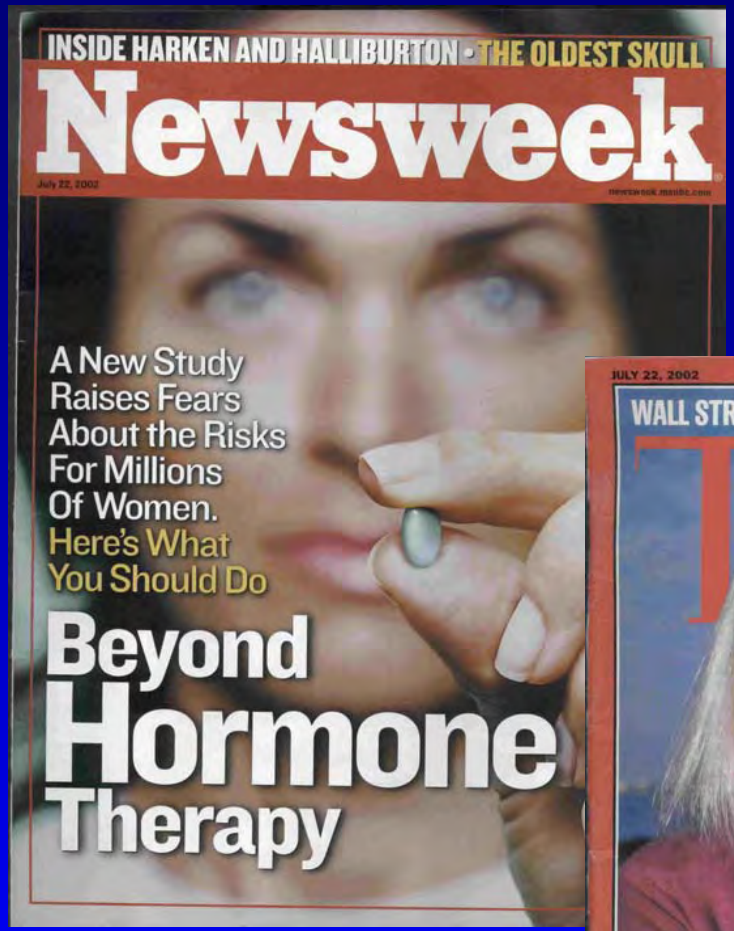
Impact of WHI Hormone Trials on Medical Practice

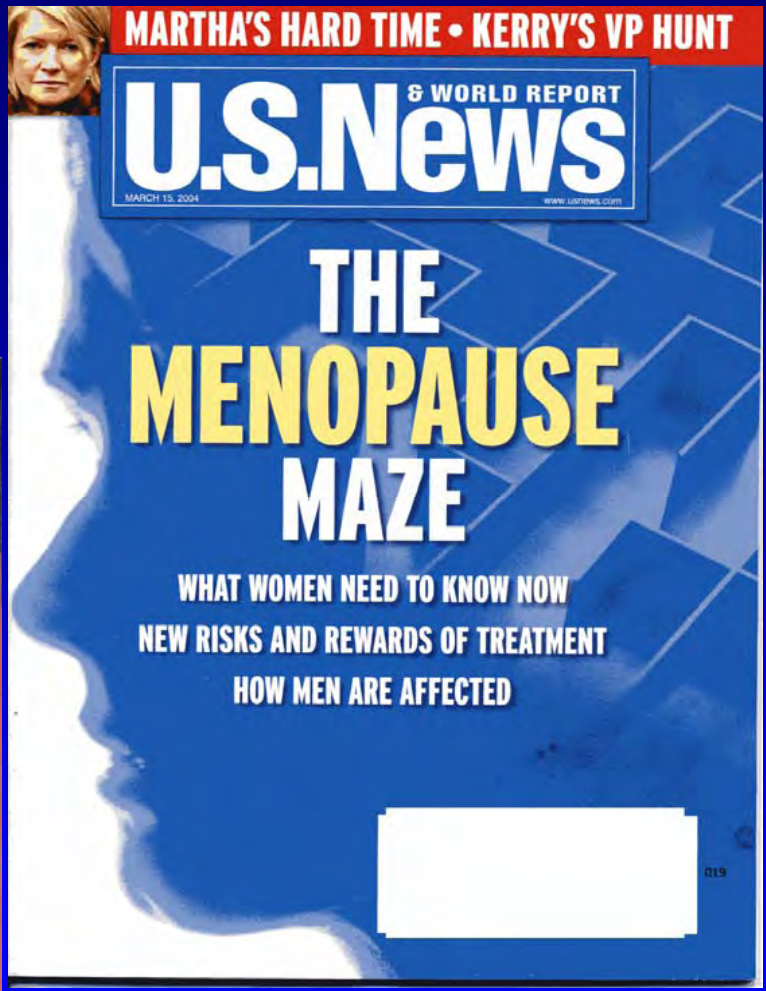
Margery Gass, MD
Principal Investigator
Cincinnati Clinical Center

Professor
Clinical Obstetrics & Gynecology
University of Cincinnati
Cincinnati, Ohio

WOMEN'S HEALTH INITIATIVE

Hormone





WOMEN'S HEALTH INITIATIVE

Hormone

FDA Response 2003

"BLACK BOX" warning on estrogen products:

Estrogens and progestins should not be used for the prevention of cardiovascular disease.

.....estrogens with or without progestins should be prescribed at lowest effective doses and for the shortest duration consistent with treatment goals and risks for individual woman.

Current Labeling for most widely prescribed Hormone Therapy: Premarin® and Prempro® or Premphase®

1. Treatment of moderate to severe vasomotor symptoms (hot flushes, night sweats) associated with the menopause.

2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause.

- When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered

Current Labeling: Indications and Usage (cont'd)

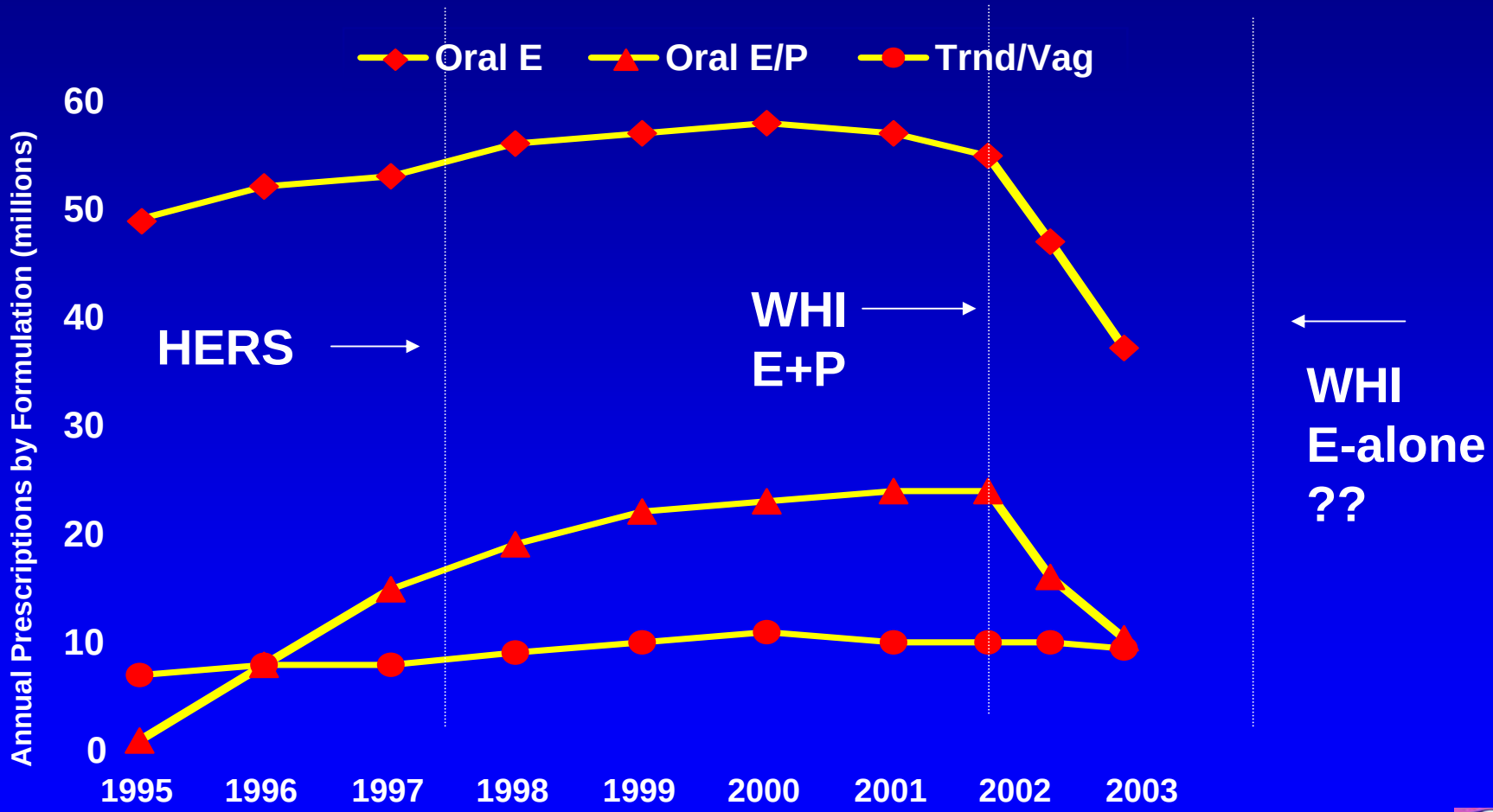
3. **Prevention of postmenopausal osteoporosis *(not treatment)***

   When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis after non-estrogen medications have been carefully considered.
   Start at 0.3 mg [+1.5 mg MPA]

FDA-approved non-estrogen medications for prevention of osteoporosis

Raloxifene (Evista®); Alendronate (Fosomax®); Risedronate (Actonel®); Calcitonin, as a nasal spray (Miacalcin®)

Annual Number of US Prescriptions for HT 1995 - Aug 2003



Source: IMS Health NPA Plus

JAMA 2004; 291:47-53

HMO Analysis

- Examination of cohort of 160,000 women in 5 HMOs across the country
- Prevalence of combined hormone therapy declined 46% and prevalence estrogen therapy declined 28% in the 6 months after WHI report
- Significant increase in discontinuation rate and significant decline in new initiations noted

Obstet Gynecol 2005; 104:1042

Hormone Discontinuation after WHI

- Kaiser-Permanente Health Plan
- Telephone survey of 670 postmenopausal women 6-8 months after WHI published
- 1000 letters mailed to explain study
- 56% tried to stop
- 44% chose not to stop
- Reasons: hot flushes, osteoporosis, mood swings, vaginal dryness, urinary incontinence, depression
- 17.7% reduced their dosage

Obstet Gynecol 2003; 102:1225

Restarting Hormone Therapy

- **Kaiser Foundation Health Plan**
- **Telephone survey of 377 postmenopausal women who tried to stop HT** after WHI results were published 2002
- **74% successfully stopped**
- **26% restarted**
- **Reasons: hot flushes, osteoporosis, mood swings, vaginal dryness, urinary incontinence, depression**

Obstet Gynecol 2003;102:1233-9

What are Doctors and Patients Doing?

- Lower doses, shorter times
- Other routes of administration (skin, vagina)
- "Bioidentical" or "natural" hormones
- Other prescription drugs
- Various supplements and herbals
- **Practical measures:** paced respirations; dressing in layers; avoiding turtleneck sweaters, down comforters, alcohol / spicy foods, bright lights, etc.

Limitations of Strategies

- Evidence of efficacy sometimes lacking
- Evidence of safety lacking
- Evidence from small studies of short duration

Bioidentical Hormones

- Safety implied or stated
- No outcome data to support claims
- Strong marketing efforts evident

Estrogen Levels and Stroke

- 2447 postmenopausal women <80 years old
- Women with estradiol levels below 10 pmol/L had only one-third the rate of strokes as those women with estradiol levels above 10 pmol/L

Lee et al. American Stroke Association 2006. Abstract

Estrogen therapy: The dangerous road to Shangri-La*

- Estrogen should be used only for vasomotor symptoms and vaginal atrophy. The lowest effective dose for the shortest amount of time.
- Estrogen may trigger high blood pressure and increase blood clotting.
- Women with high blood pressure or a family history of early heart attacks are advised not to use estrogen
- For the treatment of osteoporosis, there may be safer alternative therapies.
- Women are cautioned as to their own responsibility when taking estrogens.

*Consumer Reports 1976 Nov; 41(11):642-5

Future Directions for Menopausal Hormone Research

Jacques Rossouw, MD
Program Officer
WHI Program Office

National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

Hormone

Research Questions

Do effects vary by:

- **Age? - or - Years since Menopause?**
- **Drug? - or - Delivery Method?**
- **Dose? - or - Regimen? Duration?**

Stages of Atherosclerosis

Young adult	Initiation (endothelium, fatty streaks)	Estrogen may delay
Middle age	Progression (raised lesions)	Estrogen has no effect
Older age	Complicated lesions (erosion or rupture of unstable plaque)	Estrogen triggers events

Hormone Therapy, Coronary Heart Disease, and Age

- **For older women**: identify markers of early harm
  - Tailor therapy to risk
- **For younger women**: do hormones reduce risk of CHD?
  - Examinations of results by age in existing studies
  - Surrogate outcomes (imaging studies)
  - Definitive trial starting at younger age??
    - Very large numbers of younger women needed
    - Very long duration—will any benefit persist into older age?
    - Hormones have other adverse effects (blood clots, stroke, etc.)
    - Better prevention strategies for CHD available

Drug, Route of Administration, and Regimen

- **Transdermal estradiol**
  - Possibly less pro-thrombotic
  - Does not raise C-reactive protein
- **Progesterone**
- **Cyclic rather than continuous administration**
- Selective estrogen receptor modulators (SERMs)

Dose

- Lower dose of estrogen is effective for osteoporosis prevention
- Effect on coronary heart disease, stroke, blood clots, and breast cancer unknown

Audience Questions and Answers
Closing Hormone Session

Marcia Stefanick, PhD
Principal Investigator
Stanford Clinical Center

- ***BREAK***