enopausal Hormone *(Replacement)* Therapy ("HRT") - Where are we now?

anaging Menopause After the Women's Health Initiative

Marcia L. Stefanick, Ph.D.

Professor of Medicine

and, Professor of Obstetrics and Gynecology

Stanford Prevention Research Center

Stanford University

WHI Principal Investigator, Stanford

Chair, WHI Steering Committee

WHAT IS MENOPAUSE?

Natural - ovarian estrogen production decreases

usually begins in a woman's late 40's/early 50's

- **irregular menstrual cycles (shorter or longer cycles, heavier or lighter bleeding, more missed periods)**
- **hot flashes, night sweats (may disrupt sleep)**
- **vaginal dryness (may cause itching, painful intercourse increased bladder infections)**

Surgical - removal of both ovaries at any age

Hysterectomy, removal of uterus, i.e. does not cause menopaus

NATURAL MENOPAUSAL TRANSITION

Perimenopausal phase (mid-late 40's, early 50's):

- irregular menstrual cycles, may go on for years
- ? - hot flashes, night sweats, vaginal dryness
- accelerated bone loss, transitory

Menopause - defined as having had no uterine (menstrual) bleeding for 12 months; average age:

Postmenopausal

- ?? - hot flashes, night sweats, vaginal dryness
- gradual bone loss, ongoing

A Brief History of Hormone Therapy

Observational Studies suggest **Benefits > Risk**

E associated with **fewer fractures; higher BMD**

OCs associated with **blood clots, heart attacks**

E associated with **lower CHD**

E associated with **higher breast cancer**

E associated with **uterine cancer**

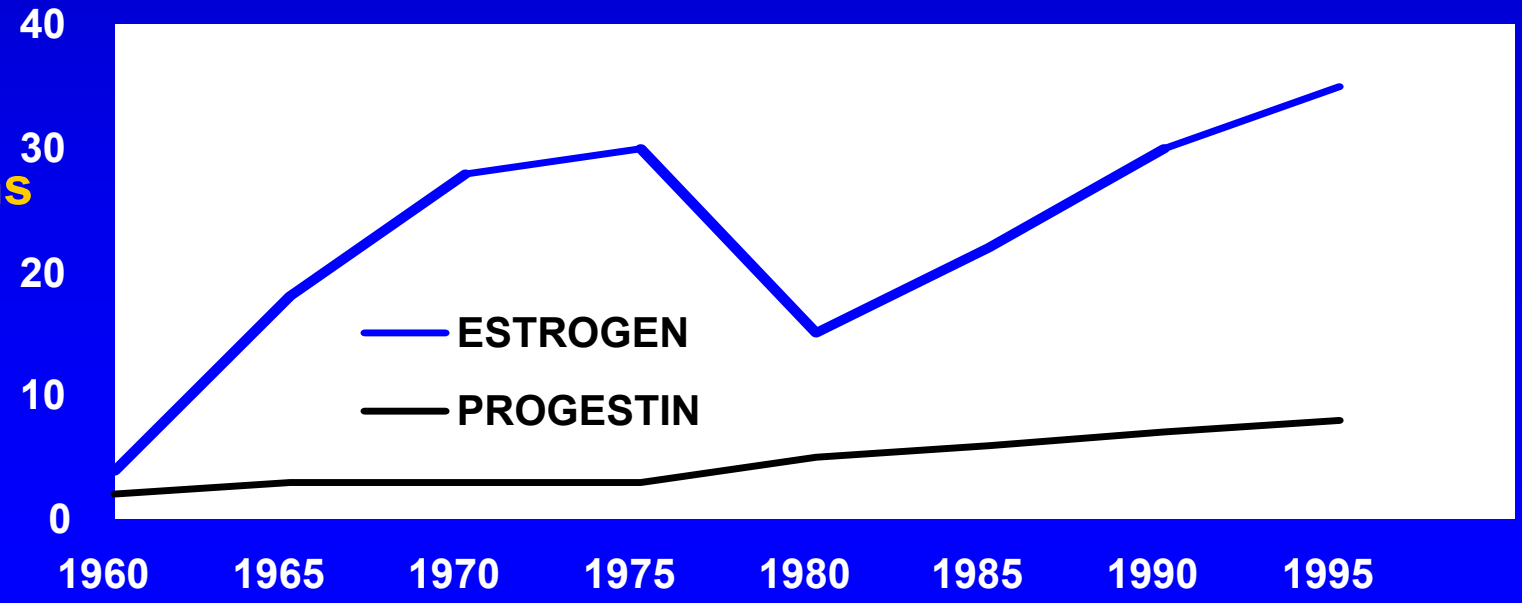
"Feminine forever"

CEE in men: blood clots, heart attacks

Progestins protect uterus

42: FDA proved rogen EE) for atment of nopausal mptoms

scriptions lions)



ple of Hormones* in Preventing Diseases of Agi

e.g. Coronary Heart Disease, Osteoporosis, (Alzheimer's D.

pproved to relieve menopausal symptoms and prevent bone lo

Sources of Evidence at Outset of WHI (1991)

Epidemiological studies, e.g. observational & **cohort studie**
(longitudinal, prospective); case-control (retrospective)

Animal models

Biological effects (surrogate markers, e.g. HDL-cholesterc

Clinical Studies (Angiographic, Bone Mineral Density, etc.)

But: no adequate clinical trials with disease endpoints

oint: An increasing number of asymptomatic and older wom
ere being prescribed "HRT" to prevent diseases of aging.

WHI Hormone Trials: **Specific Aims**

To test whether **Estrogen Only (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

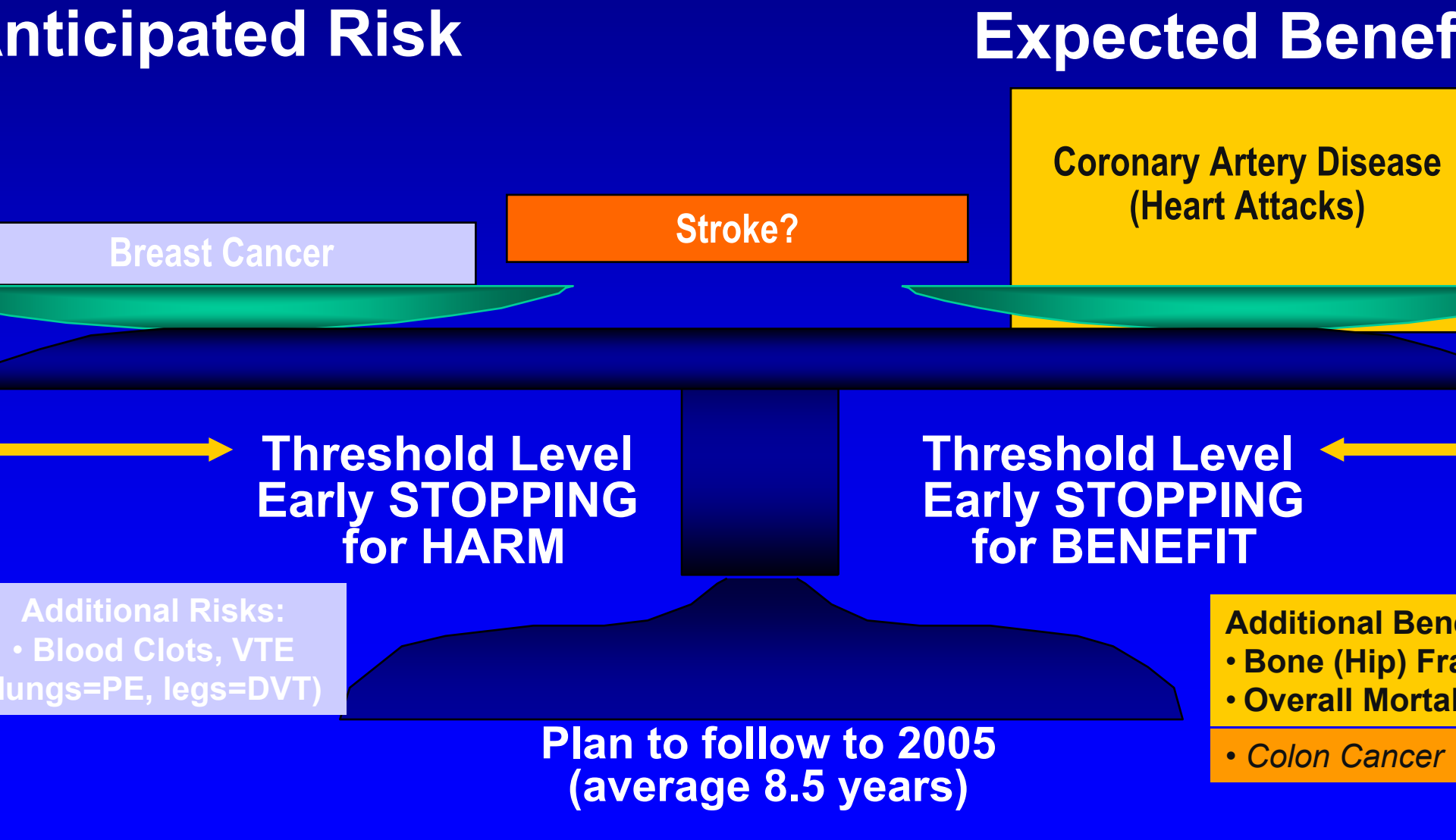
To determine the **balance of risks and benefits of menopausal hormones on the overall health** of **postmenopausal women, aged 50-79** (baseline).

WHI: Data Safety Monitoring Board Outcomes

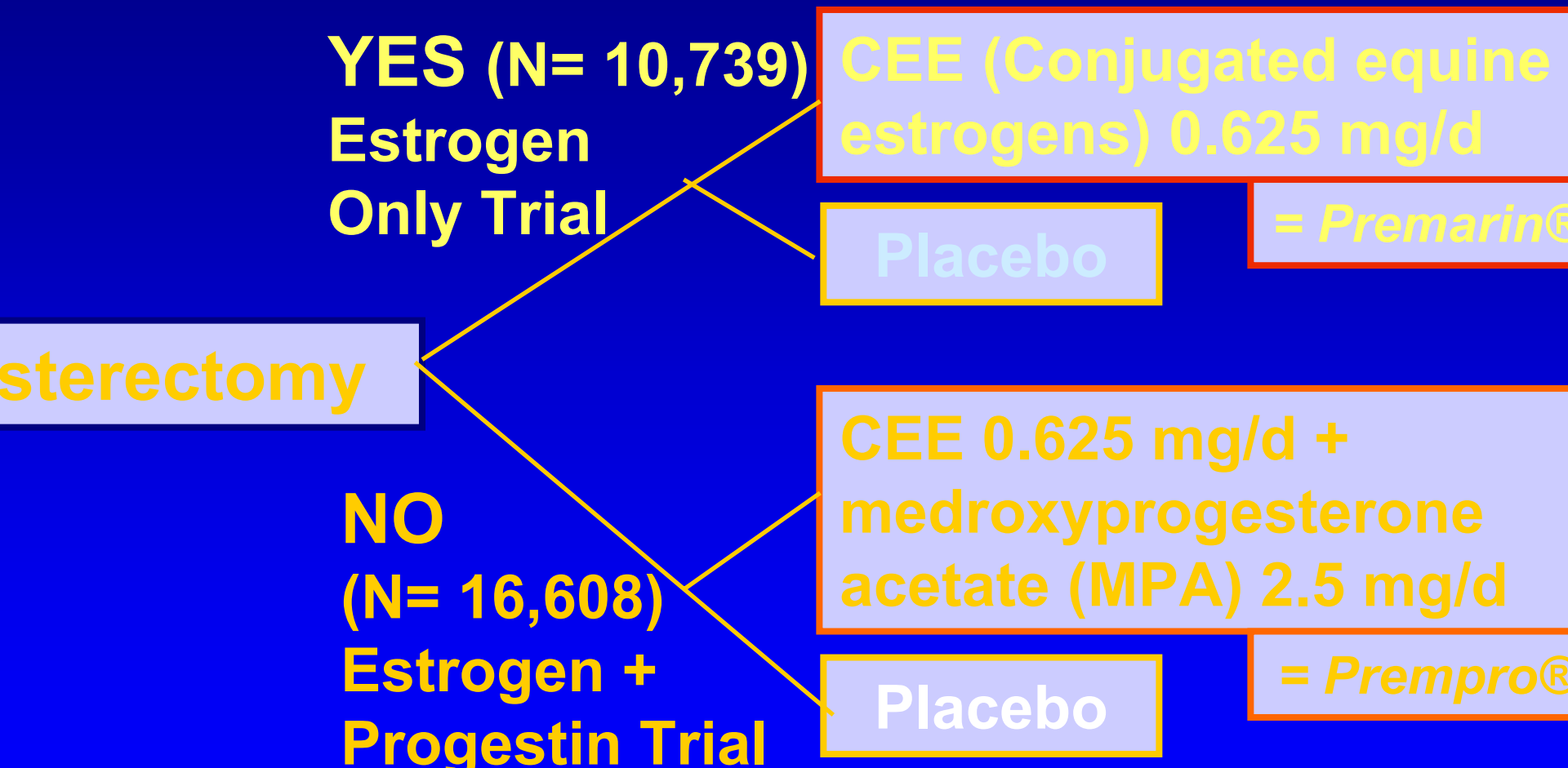
- **Cardiovascular disease**
  - **Heart attacks (Coronary Heart Disease, CHD)**
  - **Strokes**
  - **Blood Clots in the Lungs** (Pulmonary Emboli, PE)
- **Invasive Breast Cancer**
- **Colorectal Cancer**
- Endometrial (uterine) Cancer - *(for E+P Trial only)*
- **Hip Fractures**
- **Deaths from other causes**
- **Global Index: overall balance of benefits and risks**

Earliest occurrence of **CHD, Stroke, PE, Breast Cancer, Hip Fracture, Colorectal Cancer, Endometrial Cancer, Death from other causes**

WHI HT Study: Baseline Hypotheses



WHI Hormone Program Design



rent HT required 3-month wash-out before baseline testing

WHI Hormone Sample Size, Outcomes, Follow-u

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

ormone Trials

Primary Outcome:

Coronary Heart Disease

Secondary Outcomes:

Breast, **Colon, Endometrial Cancers**

Hip Fracture; Other Fractures

Stroke, Pulmonary Emboli

WHI Memory Study (WHIMS)

- ***for women aged ≥ 65*: Dementia**

E-only
CEE
10,739

Average
6.8 years*

E+P
CEE+MPA
16,608

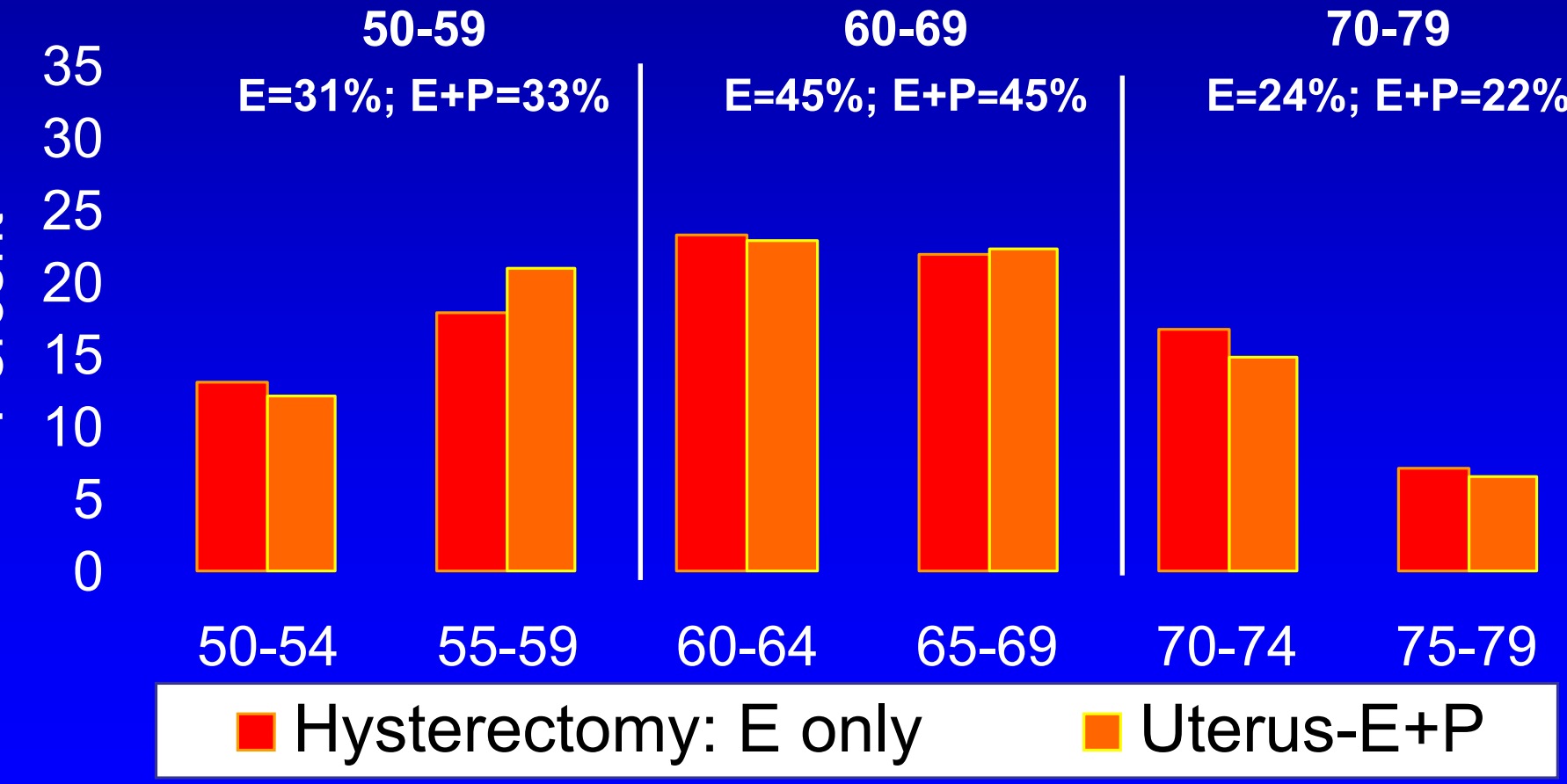
Average
Follow-up
5.6 years*

***design = 8.5 years**

WHI HT: Baseline Age Distribution

Mean± SD: **HystX-E only = 63.6**±7.3; **Uterus-E+P = 63.3**±7.

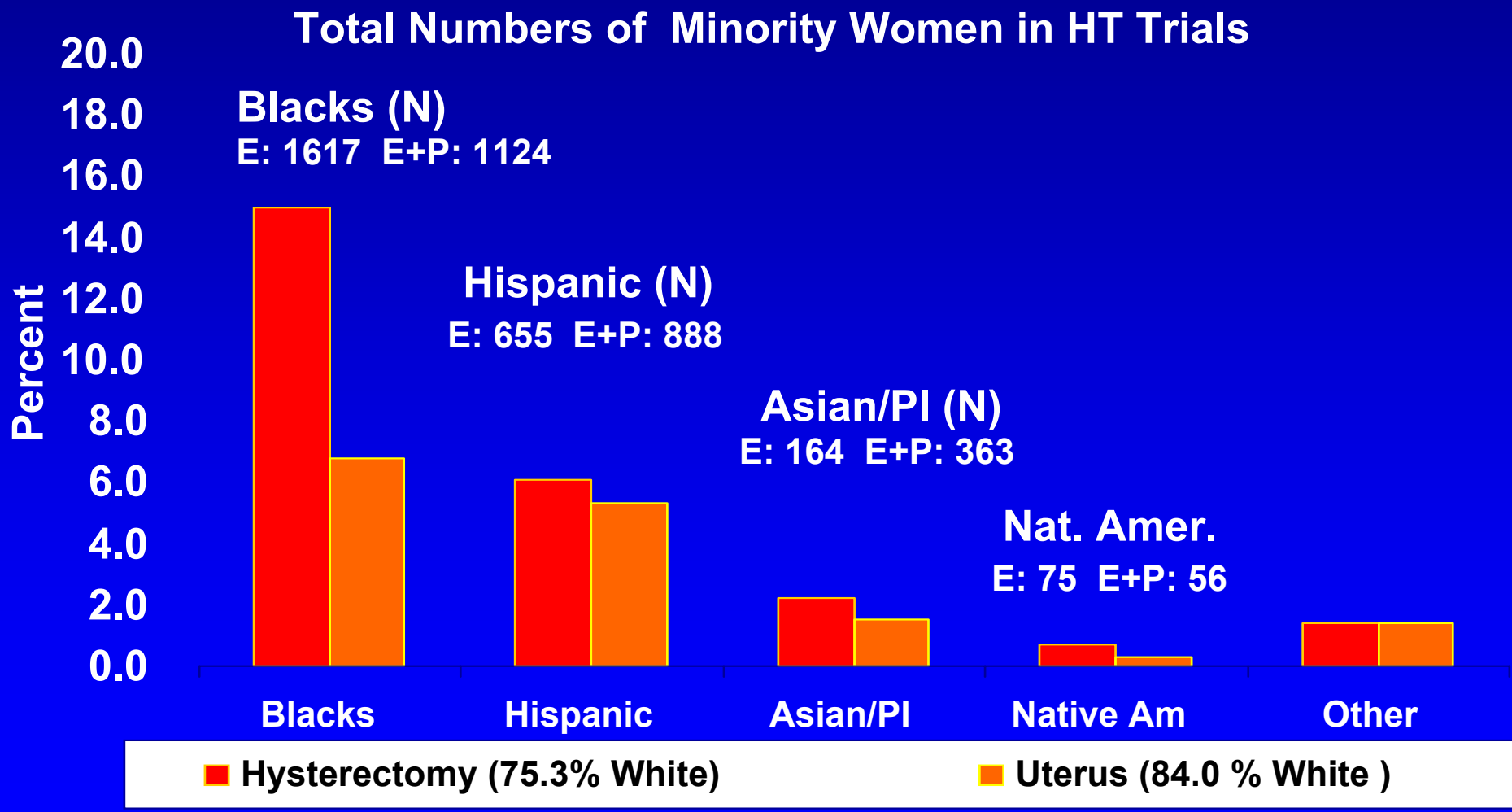
Goal: 50-54 = 10%; 55-59=20%; 60-69=45%; 70-79=25%



Stefanick, Cochrane, Hsia, Barad, Liu, Johnson Ann Epidemiol 2003; 13: S78-S86

WHI HT: Minority Distribution (% of Cohort)

HystX: 2511/10,739 (23.3%) Uterus: N = 2531/16,608 (14.6%)



Stefanick, Cochrane, Hsia, Barad, Liu, Johnson Ann Epidemiol 2003; 13: S78-S86

ay 2002: NIH accepted DSMB recommendation to stop WHI Estrogen plus Progestin Trial

y 2 years, more CVD was seen in active HT groups.

ter an average of **5.2 years**:

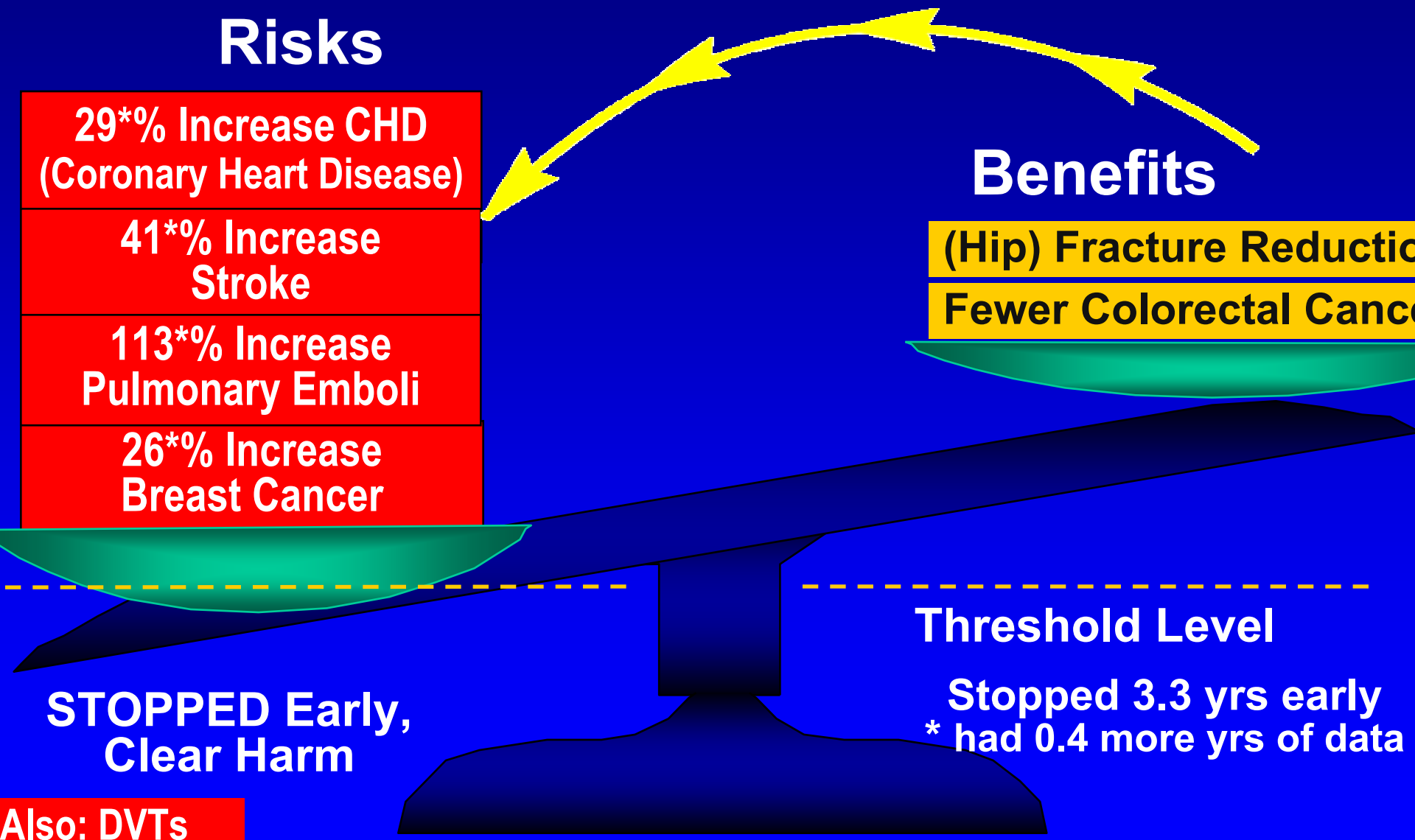
Women in **E+P trial told to stop** study pills because the **risks** of CEE+MPA **exceeded the benefits**.

- **Participants in the E+P trial continue to be monitored, to determine how long risks or benefits persist, over time**

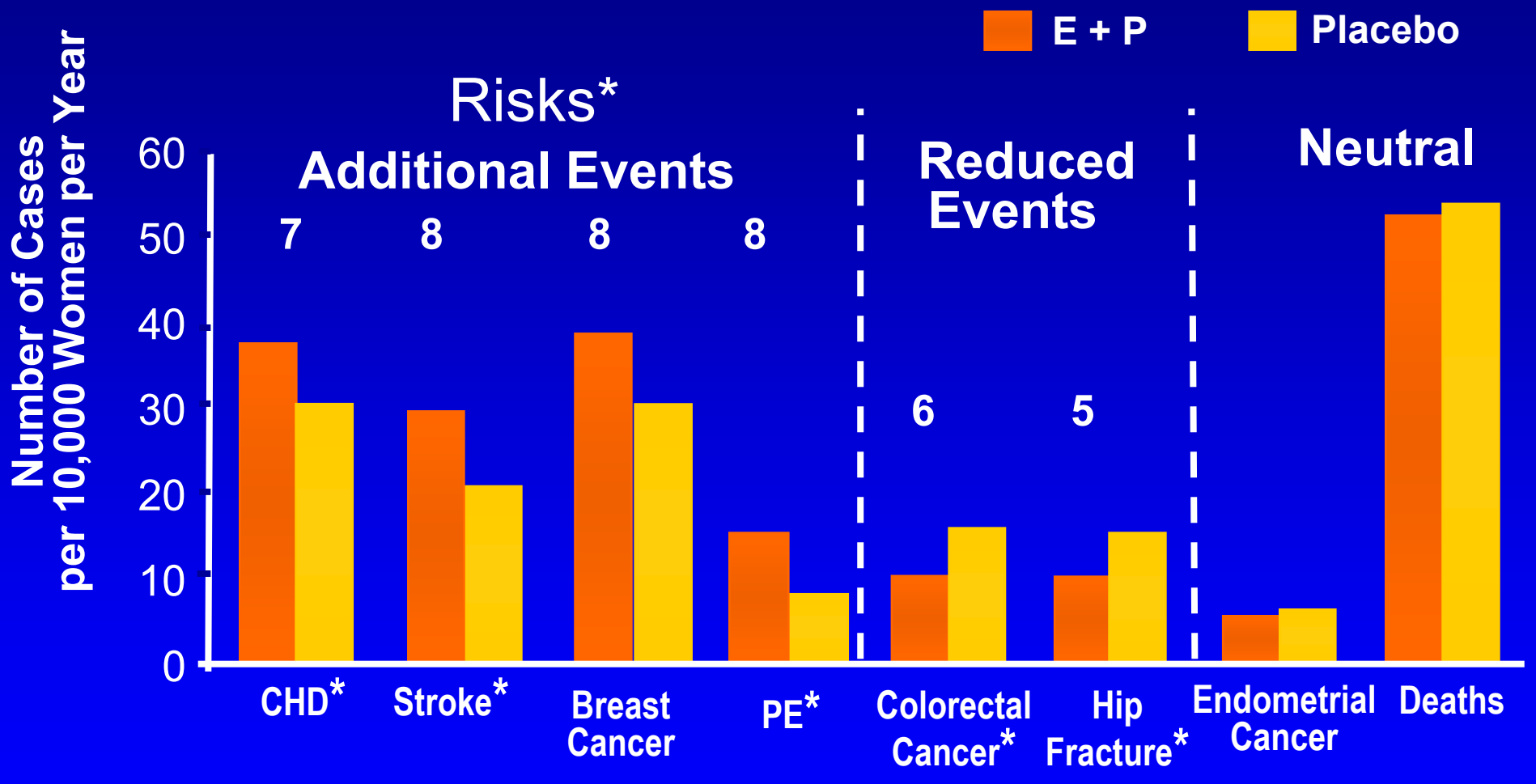
Women in Estrogen-only study asked to continue study pills: **balance of benefits and risks was unclear.**

- **no increased risk of breast cancer had been seen in women taking estrogen only vs placebo**.

WHI CEE+MPA Trial Findings, July 2002 (aver. 5.2 yr



WHI E+P Trial: Annualized Event Rates



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

Adapted from: Writing Group for the Women's Health Initiative. **JAMA. 2002;288:321-333**

WHI E+P Trial: Updated Attributable Risk Summa

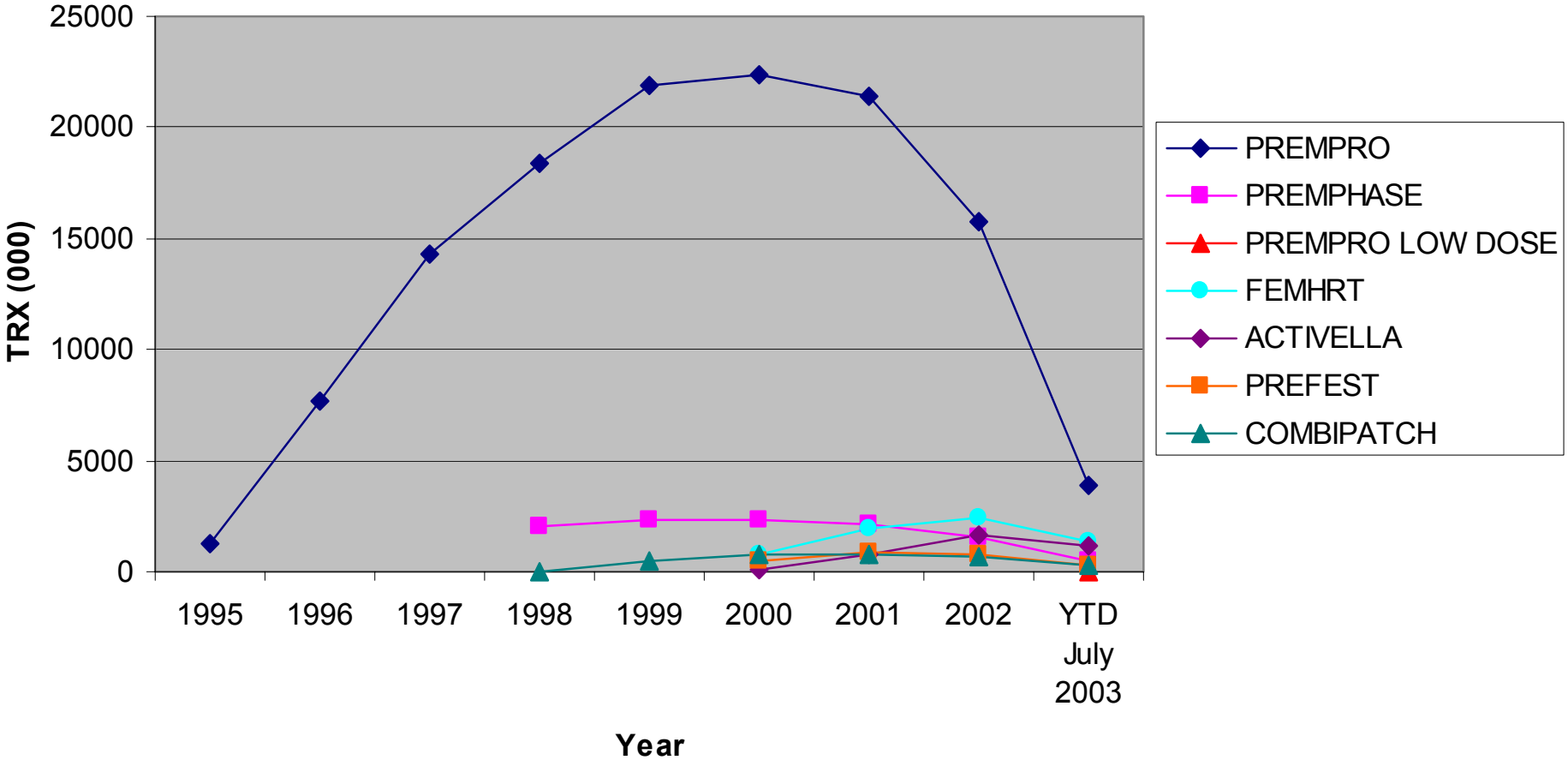
Excess risk per 10,000 women per year on E+P

- 8* breast cancers *significant (E+P: more advanced tumo
- 6* CHD *updated findings, borderline significant
- 7* strokes
- 8 PE
- Not included: 10 more DVT; (≥65 yrs of age: 23 more dementia

Risk reduction per 10,000 women per year

- 6* fewer colorectal cancer (E+P: more advanced tumors)
- 5* fewer hip fractures
- Not included: 6 fewer clinical vertebral fractures

Total Prescriptions Dispensed for Combination Estrogen/Progestin Products, 1995 - July 2003



IMS Health, National Prescription Audit *Plus*™, 1995 – July 2003, extracted August 2003.

WHI Memory Study (WHIMS) - an ancillary study

Women, aged 65-79 at baseline Total = 7479

imary Outcome:

Probable Dementia (PD)

econdary Outcomes:

Combined PD and Mild Cognitive Impairment (MCI)

upporting Data:

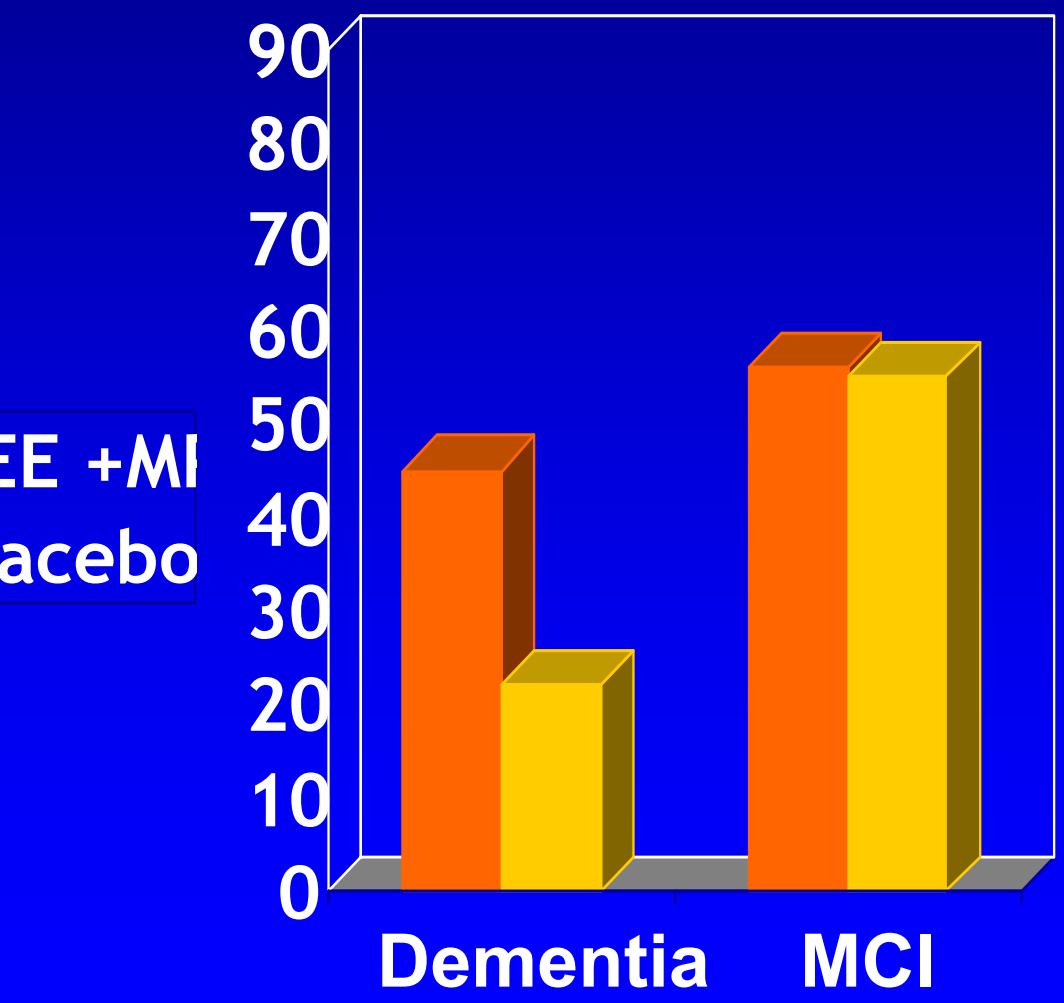
Global Cognitive Function (by annual Modified Mini-mental State Examination, 3MSE)

Average 5.2 years

Average Follow-up 4.1 years

WHIMS CEE+MPA: Rates per 10,000 women per year for Probable Dementia and Mild Cognitive Impairment Diagnosis

* Average 4.1 years of follow-up



	CEE N = 2229	Placebo N = 230
PD (N)*	40	21
Rate per 10,000 person-years	45	22

PD: Hazard Ratio (95%
2.05 (1.21-3.48)

MCI: Hazard Ratio (95%
1.07 (0.74-1.55)

Shumaker et al JAMA 2003; 289:2651-2662

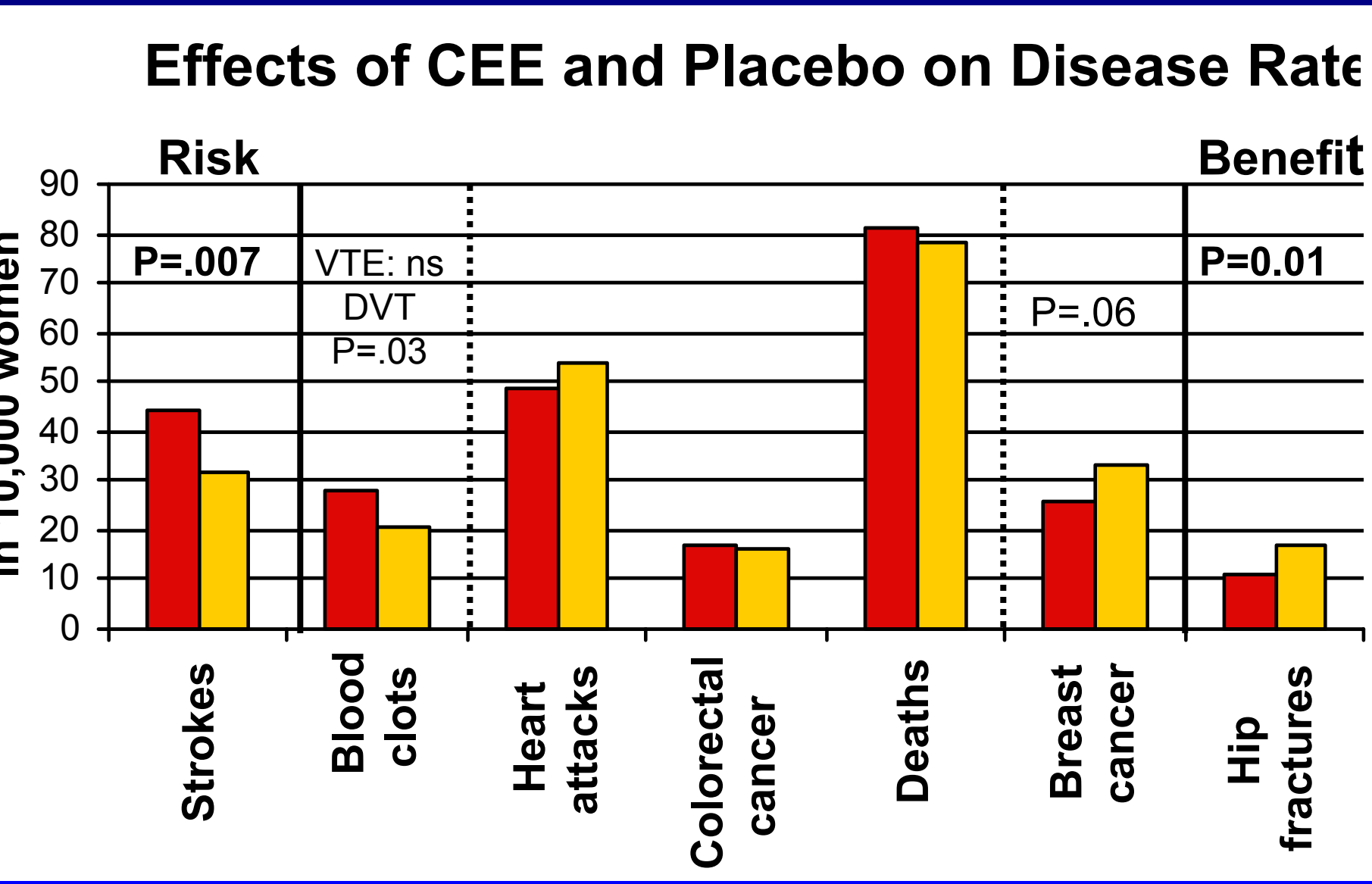
ebruary 2004: NIH stopped the WHI E-Alone Tria

After an average of **6.6 years**:

Women in Estrogen-Alone study asked to stop studi
pills and initiate a follow-up phase. NIH believed

- **increased risk of stroke was unacceptable in healthy women in absence of benefit to heart disease.**
- **enough data had been obtained to answer the main study question regarding heart disease.**
- **the balance of benefits and risks was not likely to change with an additional year of follow-up.**

HI E-Alone (CEE) Trial: Absolute (annualized) Risk (6.8



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

WHI E-Alone Trial: Attributable Risk Summary

Excess risk per 10,000 women per year on CEE

- **12** more women with **strokes**
- 6 more **Deep Vein Thrombosis (DVT)**
- **unclear:** more **total blood clots in lungs (PE) + legs (DVTs)**

Risk reduction per 10,000 women per year

- **6** fewer **hip fractures**
- 6 fewer **clinical vertebral fractures**
- **unclear:** 7 fewer **breast cancer** (Tumor characteristics unknown)

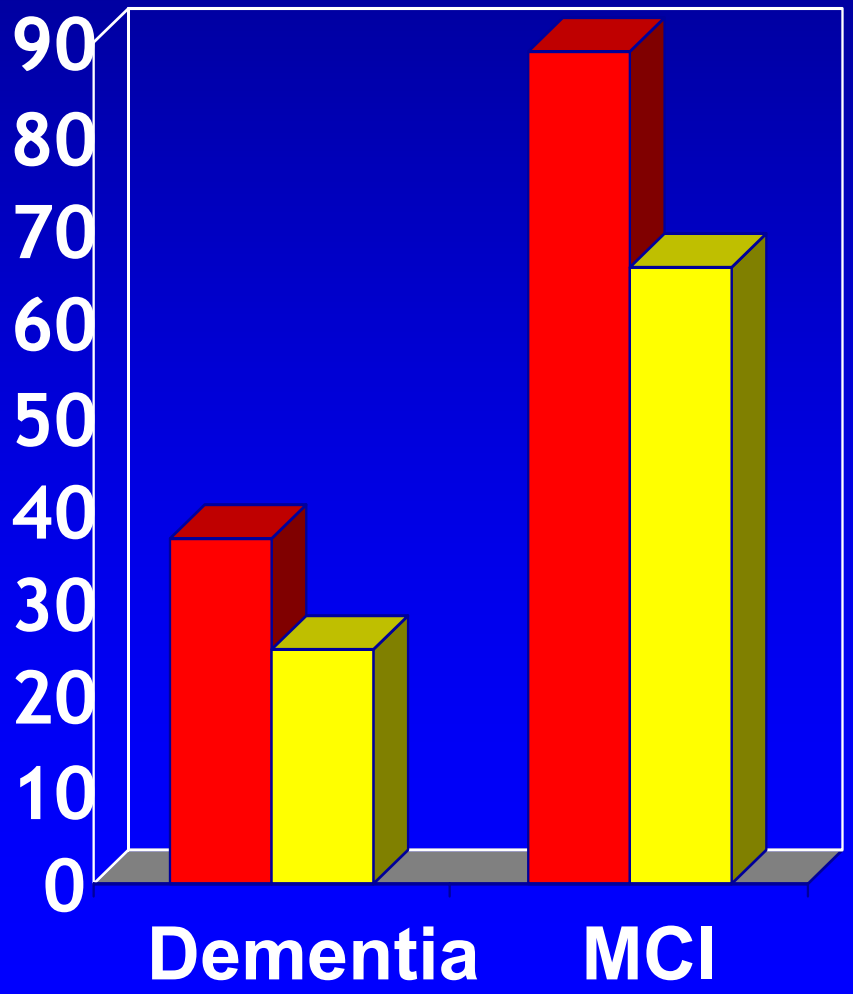
Neutral (no differences)

- **Coronary Heart Disease**
- **Colorectal cancer** (Tumor characteristics unknown)
- **Deaths**

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

WHIMS CEE: Rates per 10,000 women per year for Probable Dementia and Mild Cognitive Impairment Diagnosis

* Average 5.2 years of follow-up



EE on
aceb

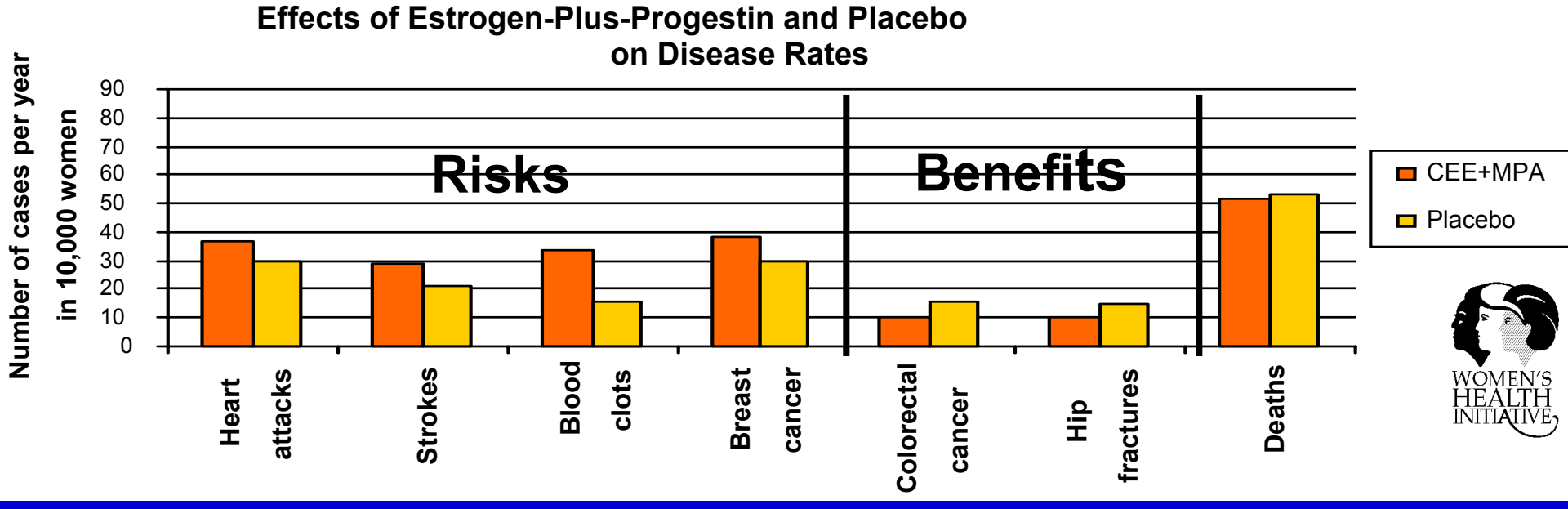
	CEE	Placebo
	N = 1464	N = 148
PD (N)*	28	19
Rate per 10,000 person-years	37	25

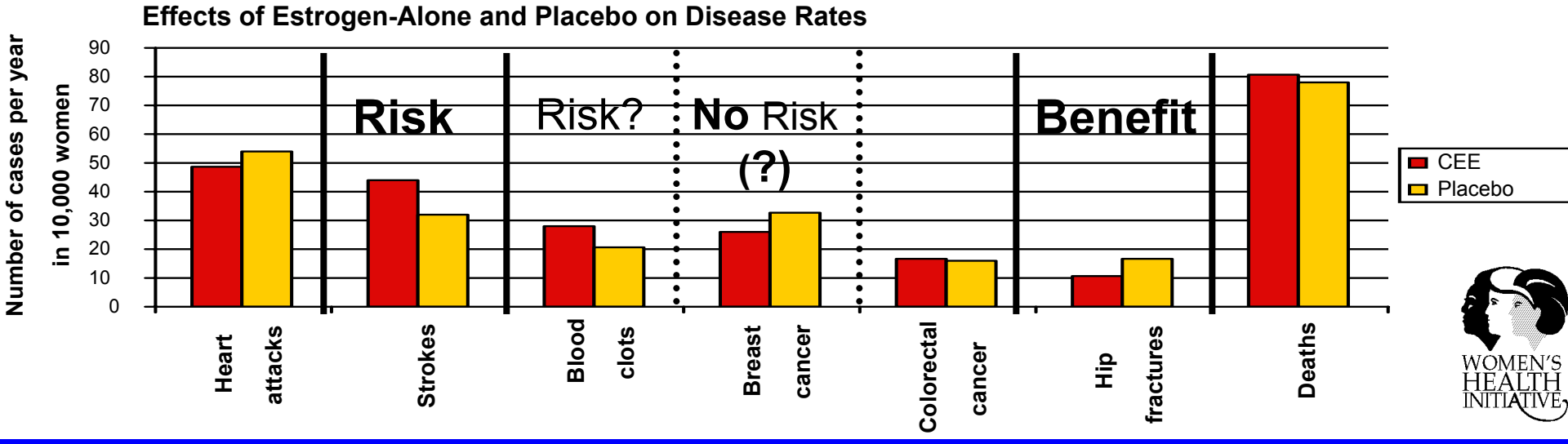
PD: Hazard Ratio (95%
1.49 (0.83-2.66)

MCI: Hazard Ratio (95%
1.34 (0.95-1.89)

Shumaker et al JAMA 2004; 291:2947-2958

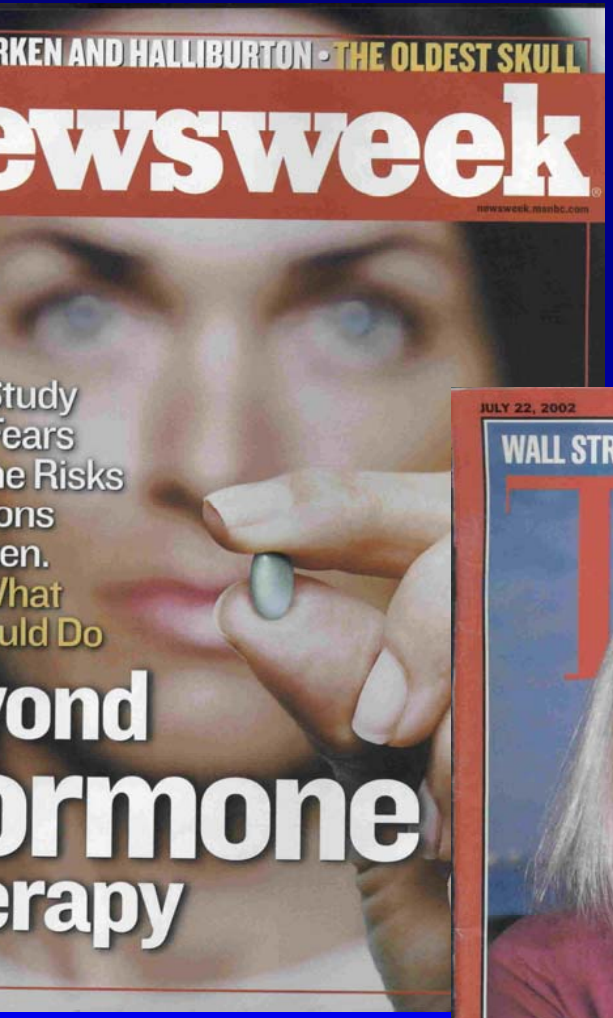
WHI E+P and E-Alone Trials: Absolute (annualized) Ris





Leading Causes of Death (%) in U.S. Women, 20

	20-39	40-59	60-79	80+	AL
aths age)	30,594 (<2.5)	127,281 (10.3)	407,204 (33.0)	646,819 (52.5)	1,233
t ases	8.8	16.6	25.1	36.2	29
cers	18.5	38.5	31.2	12.5	21
ke	2.5	4.2	6.5	10.4	8.
Lower ratory	2.0	3.1	7.4	4.4	5.
etes	2.0	3.5	4.2	2.5	3.
r (%) %	**Accidents: 21.2** **Suicide: 6.0** **Homocide: 5.9** **HIV: 4.8**	**Accidents: 5.6** Liver,Cirrhs 2.8 Suicide: 2.1	Kidney Dis 1.8 Flu/Pneum. 1.7 Accidents 1.7 Septicemia 1.6 Alzheimer's 1.5	**Alzheimer's Disease 4.9** **Flu/Pneum. 4.0** Kidney Dis. 1.7 Accidents 1.7	Alzheim Accident Flu/Pneu Kidney D Septicem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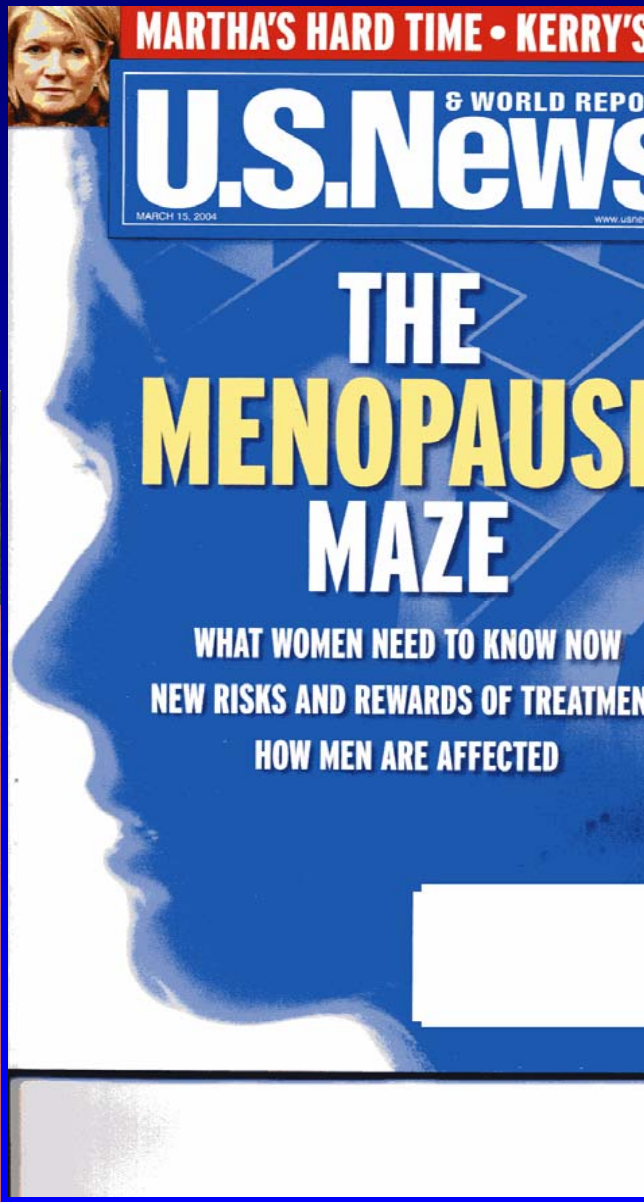
JULY 22, 2002
WALL STREET: LOSING SAVINGS—AND TRUST
TIME
IS THIS OUR FIRST ANCESTOR?
THE TRUTH ABOUT HORMONES
Susan Pierres, 60, of Miami, has been on hormones for 10 years. She is angry and confused but not yet ready to stop taking them
Hormone-replacement therapy is riskier than advertised. What's a woman to do?


MARTHA'S HARD TIME • KERRY'S
U.S.News & WORLD REPO
MARCH 15, 2004
THE MENOPAUSE MAZE
WHAT WOMEN NEED TO KNOW NOW
NEW RISKS AND REWARDS OF TREATMEN
HOW MEN ARE AFFECTED

Current Labeling for most widely prescribed Hormone Therapy: Indications and Usage

strogens with or without progestins should not be used for the preventio
rdiovascular disease.

emarin® (CEE) [and Prempro® or Premphase®, in women who have a
erus (CEE + MPA)] is indicated for the following:

- Treatment of moderate to severe vasomotor symptoms (hot flushes, nig
veats) associated with the menopause.
- Treatment of moderate to severe symptoms of vulvar and vaginal atrop
sociated with the menopause.

hen prescribing solely for the treatment of symptoms of vulvar and vagi
rophy, topical vaginal products should be considered

Management of Menopausal Symptoms
Hot Flashes and Night Sweats: Lifestyle

- **Wear layered clothing**
- **Exercise:** There is no evidence that exercise will decrease these symptoms
- **Diet:** Avoid hot spicy foods and beverages, reduce caffeine and avoid alcohol

Management of Menopausal Symptoms

Hot Flashes and Night Sweats: **Medications**

Estrogen: currently, most effective therapy

- **Oral & transdermal estrogen**: each reduce severity of vasomotor symptoms.
- **Transdermal estradiol & intranasal 17-beta estradiol spray** - as effective as oral estrogens
- **Oral CEE at doses lower than 0.625mg/day are effective**. **Women are recommended to use the lowest dose needed to relieve symptoms.**
- **Women with intact uterus are recommended not to use estrogen alone (i.e. without a progestin)**.

Managing Menopausal Hot Flashes & Night Sweats
Complementary and Alternative Therapies

None of the following have been shown to decrease vasomotor symptoms significantly better than placebo

- **Phytoestrogens** (Plant-based estrogens)

  Best single dietary source is soy.

  FDA has approved a statement that soy protein at a dose of 25 gm/day, combined with a low-fat diet, may reduce CVD risk, based on modest reduction in total cholesterol.

- **Dong quai**
- **Black Cohash**
- **Evening primrose oil** (gamma-linoleic acid)

Management of Menopausal Symptoms

Hot Flashes & Night Sweats: **Medications** (cont)

elective Serotonin Reuptake Inhibitors (SSRIs),
venlafaxine & paroxetine substantially reduce hot flushes.

eralipride (100 mg/day) - in patients on GnRH agonists

rogestogens in high daily doses, i.e. MPA 20 mg/day,
megestrol acetate 40 mg/day, reduce vasomotor symptoms.

ropanolol is no more effective than placebo.

elective Estrogen Receptor Modulators (SERMS), i.e.
raloxifene (Evista®), tamoxifen (Nalvodex@) can increase
hot flashes. [20% of women < 60 yrs old & > 2 yrs past
menopause and 10% of older women developed hot flushes o
raloxifene.] Symptoms were mild, rarely led to discontinuation.

Managing Menopausal Urogential Symptoms

Oral and transdermal estrogen and a estradiol-releasing silicone vaginal ring improve urogenital symptoms.

Vaginal Dryness and Dyspareunia can be treated with a topical estrogen cream, tablet, or vaginal ring, or with non-hormone moisturizing or lubrication products.

Topical estrogen preparations provide more effective relief of vaginal dryness than oral or transdermal estrogen, avoid high levels of estrogen in blood stream.

Incontinence- Not reduced by systemic estrogen alone or with a progestin. In HERS trial, was increased by estrogen plus progestin vs placebo; also in WHI.

Current Labeling: Indications and Usage

PREMARIN [PREMPRO or PREMPHASE in women who have a uterus]

3. Prevention* of postmenopausal osteoporosis

*(*not FDA-approved for treatment)*

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

Other Indications for Premarin *(not listed for Prempro):*

- treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure;
- treatment of breast cancer (for palliation only) in appropriately selected women and men with metastatic disease;
- treatment of advanced androgen-dependent carcinoma or the prostate (for palliation only)

Managing Menopausal Osteoporosis

Lifestyle: stop smoking; avoid extreme weight loss; add weight-bearing, muscle-building, and balance exercises; avoid sedatives; avoid excess alcohol; correct visual impairment; fall-proof the home

Diet: correct calcium deficiency; first, increase calcium-rich foods: (Each dairy portion contains approximately 300 mg; for women with lactose intolerance, calcium-supplemented orange juice or mineral water rich in calcium are useful). **The combined diet and supplement intake should be 1200 mg/day of calcium**

DA-approved medications to prevent osteoporos

- based on **Bone Mineral Density (BMD) cut-points**

Estrogens (± progestin) - wide range

Raloxifene (Evista®)
- Selective Estrogen Receptor Modulator (SERM)

Bisphosphonates:
Alendronate (Fosomax®); Risedronate (Actonel®)

Calcitonin, as a nasal spray (Miacalcin®)

FDA approved medications to prevent osteoporotic fractures (CT evidence)

Estrogens are not FDA approved to prevent fracture
despite WHI E+P and E-only trial evidence that these hormones prevent hip and other fractures.

Raloxifene (Evista®)
has been shown to reduce spine fracture risk

Bisphosponates: **Alendronate (Fosomax®); Risedronate (Actonel®),** rapid acting bone-spec effects, shown to reduce spine & non-spine fractu

Parathyroid hormone (Fortao®) by daily injection
effective in women with very severe osteoporosis who need to gain substantial bone