

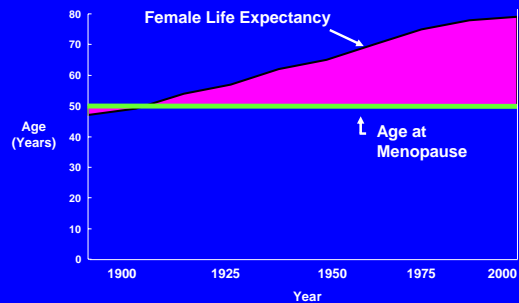
## The Trudy Bush Lecture

### Hormone Therapy: Making Sense of the Evidence

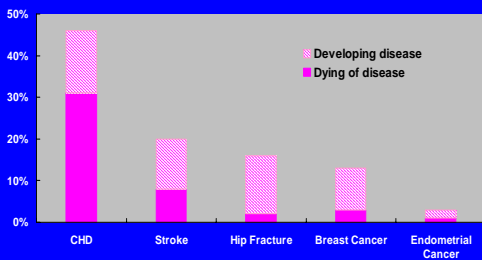
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Disclosures: None

### Female Life Expectancy, U.S., 1900-2000



### Lifetime Probabilities of U.S. Women Developing Or Dying from Various Diseases

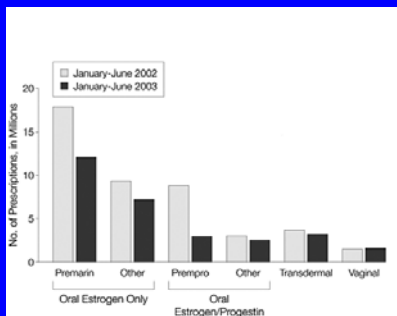


Grady D et al. *Ann Intern Med* 1992; 117:1016-1037

### Case Vignettes

- 52-year-old woman at usual risk of breast cancer and osteoporosis who is experiencing menopause-related hot flashes and disturbed sleep.
- 58-year-old woman with osteopenia whose mother had breast cancer.
- 65-year-old woman with a history of coronary revascularization and documented osteoporosis.

### Number of U.S. Prescriptions for Hormone Therapy between January-June 2002 and January-June 2003 by Formulation



Data are from the National Prescription Audit Plus, IMS HEALTH.

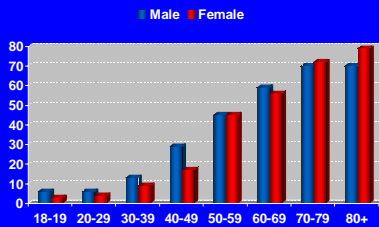
Source: *JAMA* 2004; 291

### The great tragedy of science:

Beautiful hypotheses  
slain by ugly facts.

Thomas Henry Huxley  
*Collected Essays, 1893-1894*

### Prevalence of CVD by Age and Sex



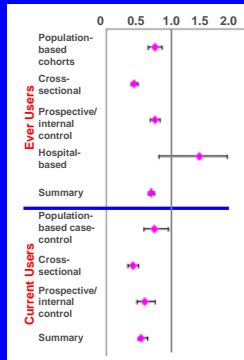
### “Feminine Forever” Mystique (1966)

- Dr. Robert Wilson wrote:  
“At age 50, there are no ova, ... no estrogen ... a galloping catastrophe”

Estrogen can save women:  
“Breasts and genitals will not shrivel. Such women will be much more pleasant to live with and will not become dull and unattractive”.

### HT and CHD: Meta-Analysis of Observational Studies

Based on more than 40 observational studies of HT and CHD, the summary relative risks for CHD were 0.64 (95% CI, 0.59-0.68) among women who ever used HT and 0.50 (95% CI, 0.45-0.59) among current users, when compared with never users.



From: Grodstein F, Stampfer MJ. *Prog Cardiovasc Dis* 1995; 38:199-210

### Limitations of Observational Studies of HT

- Women who take hormones for an extended time differ from those who don't take hormones in many ways besides hormone use.
- In observational studies, estrogen users were leaner, less likely to smoke, more physically active, more likely to see doctors regularly, and more highly educated.

*These differences could contribute to the lower rates of heart disease among hormone users in observational studies.*

### Potential Beneficial Effects of Estrogen on CHD Risk Factors

- Improvement in lipid profile
- Improvement in insulin sensitivity
- Antioxidant effects
- Direct effects on vessel wall

### Potential Adverse Effects of Estrogen on CHD Risk Factors

- Increase in thrombotic factors (factor VII, prothrombin fragment 1+2, fibrinopeptide A, D-dimer) and decrease in antithrombin
- Increase in triglycerides
- Increase in hepatic synthesis of inflammatory markers such as C-reactive protein and MMP

### Randomized Trials of HRT and CVD

**Secondary Prevention:**

- Heart and Estrogen/Progestin Replacement Study (HERS)
- Estrogen Replacement and Atherosclerosis Trial (ERA)
- Papworth HRT Atherosclerosis Study\*
- Women's Estrogen for Stroke Trial (WEST)†
- Estrogen in the Prevention of ReInfarction Trial (ESPRIT)†
- Women's Angiographic Vitamin and Estrogen (WAVE) Trial

**Primary Prevention:**

- Women's Health Initiative (WHI) Estrogen+Progestin Trial
- Estrogen-Alone Trial

CEE=MPA except: \* transdermal estradiol=NETA, † oral estradiol

### Women's Health Initiative (WHI), Ages 50-79 Hormone Program Design

### WHI Estrogen+Progestin Trial Findings, July 2002 (N=16,608; mean age 63 yrs; mean follow-up 5.2 yrs)

**Risks**

- Coronary Heart Disease 29% ↑
- Stroke 41% ↑
- Pulmonary Embolism 113% ↑
- Breast Cancer 26% ↑

**Benefits**

- Hip Fracture 34% ↓
- Colorectal Cancer 34% ↓

Threshold Level

STOPPED Early, Clear Harm

Stopped 3.3 years early

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

### Estrogen+Progestin Therapy and Risk of CHD in WHI: Results According to Time Since Menopause

*Women's Health Initiative – E+P trial*

- Women <10 years since menopause: RR=0.89
- Women 10-19 yrs since menopause: RR=1.22
- Women 20+ years since menopause: RR=1.71

Source: Manson JE, et al. NEJM 2003.

### Attributable Risk Summary

- Excess risk per 10,000 person-years on E+P
  - 7 more women with CHD
  - 8 more women with stroke
  - 8 more women with PE
  - 8 more women with breast cancer
- Risk reduction per 10,000 person-years on E+P
  - 6 fewer colorectal cancer
  - 5 fewer hip fractures
- Summary: 19 additional adverse events per 10,000 person-years on E+P; 1 in 101 "number needed to harm" for 5 years E+P use

Source: WHI Writing Group. JAMA 2002.

### WHI Estrogen-Alone and Health Outcomes (N=10,739; mean age 63.6 yrs; mean follow-up 6.8 yrs)

**Risks**

- Stroke 39% ↑

**Null**

- CHD (0.91)
- Pulm Emb (1.34)
- Breast Cancer (0.77)
- Colorectal Cancer (1.08)
- Total Mortality (1.04)
- Global Index (1.01)

**Benefits**

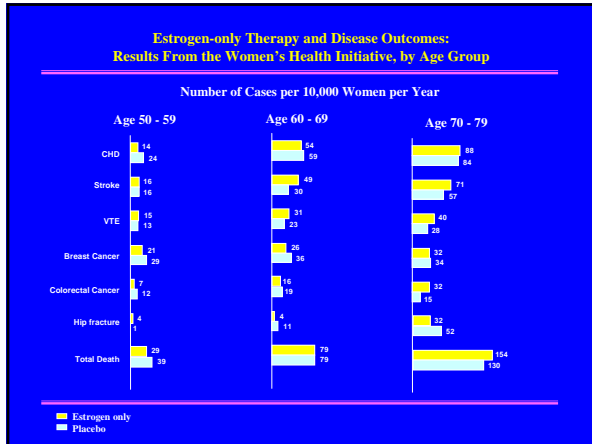
- Hip Fracture 39% ↓

Threshold Level

STOPPED Early

Stopped 1 year early

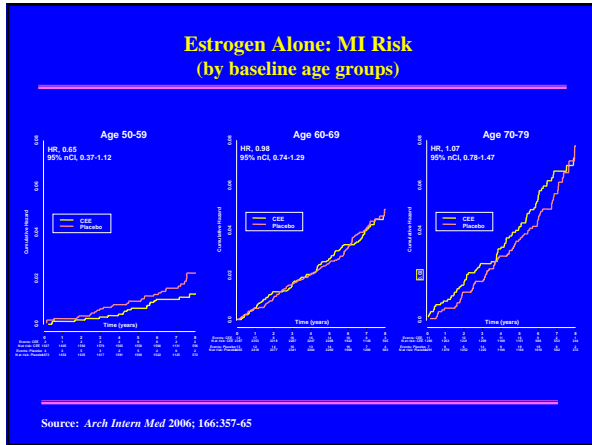
Source: JAMA 2004; 291:1701-12.



### Women's Health Initiative: Estrogen-Alone by Age Group

	50-59	60-69	70-79
<b>CHD</b>	<b>0.56</b> (0.30-1.03)	<b>0.92</b> (0.69-1.23)	<b>1.04</b> (0.75-1.44)
<b>Total Mortality</b>	<b>0.73</b> (0.47-1.13)	<b>1.01</b> (0.79-1.29)	<b>1.20</b> (0.93-1.54)
<b>Global Index</b>	<b>0.80</b> (0.62-1.03)	<b>0.98</b> (0.84-1.15)	<b>1.16</b> (0.97-1.37)

Source: JAMA 2004; 291:1701-12.



### Women's Health Initiative Estrogen-Alone Trial: Detailed CHD Results According to Age at Randomization

Outcome	50-59	60-69	70-79
<b>MI or CHD Death</b> (N=418)	<b>0.63</b> (0.36-1.08)	<b>0.94</b> (0.71-1.24)	<b>1.11</b> (0.82-1.52)
<b>CABG or PCI</b> (N=529)	<b>0.55</b> (0.35-0.86)	<b>0.99</b> (0.78-1.27)	<b>1.04</b> (0.78-1.39)
<b>Composite MI/CABG/PCI</b> (N=728)	<b>0.66</b> (0.44-0.97)	<b>1.02</b> (0.83-1.25)	<b>1.08</b> (0.85-1.38)

CEE = conjugated equine estrogens. MI = myocardial infarction. CABG = coronary artery bypass grafting. PCI = percutaneous coronary intervention

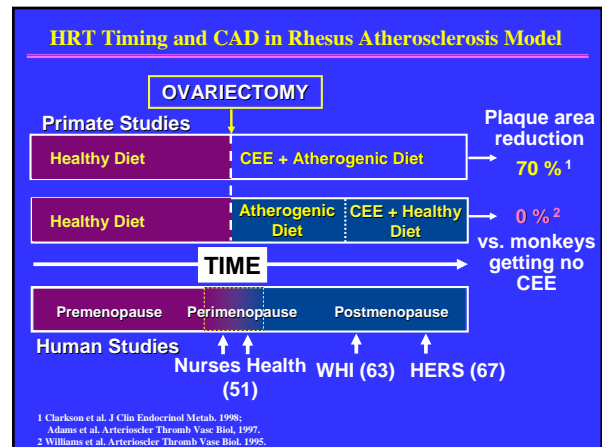
Source: J Hsia, R Langer, J Manson, et al. Arch Intern Med 2006

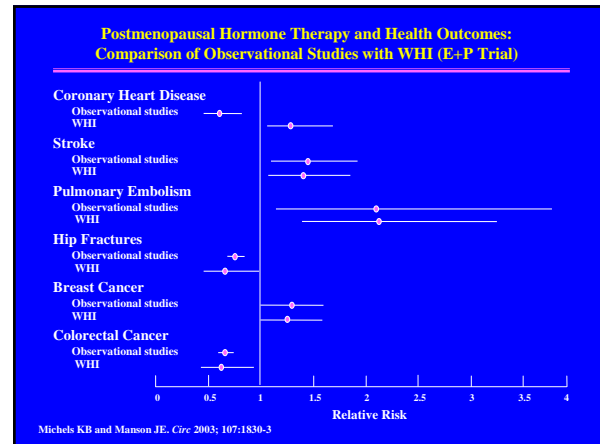
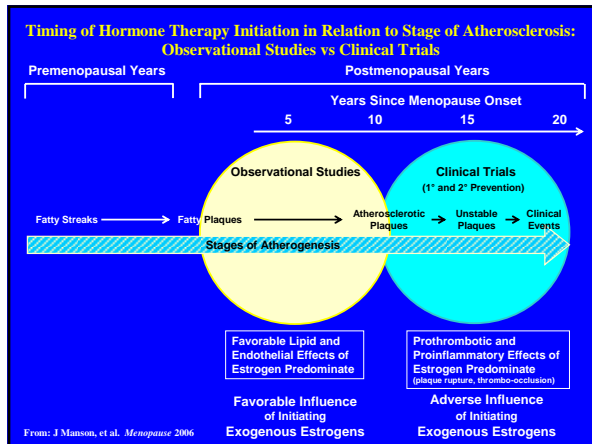
### Nurses' Health Study: Hormone Therapy (HT) and CHD According to Time Since Menopause at HT Initiation

	Estrogen-Alone RR* (95% CI)	Estrogen+Progestin RR* (95% CI)
Never users of HT	1.0 (Referent)	1.0 (Referent)
<b>HT Users: Time since Menopause at HT Initiation</b>		
Within 4 years	0.66 (0.54-0.80)	0.72 (0.56-0.92)
10 or more years†	0.87 (0.69-1.10)	0.90 (0.62-1.29)

\* Multivariate model is adjusted for age, smoking, BMI, hypertension, hypercholesterolemia, parental history of CHD, diabetes, husband's education, alcohol, physical activity, vitamin E and multivitamin supplementation, and aspirin use  
† Stimulates WHI analyses permitting inclusion of small subgroup (~6%) with prevalent CHD

Source: F Grodstein, J Manson, M Stampfer, J Women's Health 2006.





### Postmenopausal Hormone Therapy and CHD: Potential Explanations for Divergent Findings from Clinical Trials and Observational Studies

- **Methodologic Differences**
  - Confounding ("healthy user") bias
  - Compliance bias
  - Incomplete capture of early clinical events
- **Biologic Differences**
  - Hormone regimen (formulation and dose)
  - Characteristics of study population (time since menopause, stage of atherosclerosis)

Adapted from Grodstein, Clarkson, Manson. NEJM 2003; 348:645-50.

### Estrogen in the Prevention of Atherosclerosis Trial (EPAT)

**EPAT - Results (Age ≥45, mean = 61)**

- Significantly less IMT progression of carotid artery for hormone-treated group over 2 years
- **Estrogen treatment:**
  - Average rate of progression = -0.0017mm/year
- **Placebo:**
  - Average rate of progression = 0.0036mm/year
- **P=0.046**

Source: Hodis H, et al. Ann Intern Med 2001; 135:939-53.

### Rationale for Trials in Recently Menopausal Women

- A cardioprotective effect of HT initiated early in menopause is supported by:
  - Human outcomes data from large observational studies
  - Experimental data showing:
    - Benefits of early (but not late) HT in primates
    - Beneficial effects on CVD risk factors in humans
  - Data subsets from a large RCT (the WHI hormone trials)
- Known mechanisms of CVD pathogenesis and estrogen physiology provide plausible explanations for differences in HT effects with early vs. late initiation
- New clinical trials of early HT intervention are warranted (KEEPS)

### Kronos Early Estrogen Prevention Study (KEEPS)

- **Study Population:** 720 U.S. women aged 42-58 (within 3 years of last menstrual period)
- **Interventions:** Transdermal estradiol with cyclical micronized progesterone (MP) vs Low-dose CEE (0.45 mg/d) with cyclical MP vs Placebo
- **Outcomes:** Noninvasive imaging of coronary and carotid atherosclerosis: electron-beam CT or MD CT to assess coronary calcification and B-mode ultrasound to assess carotid intima-medial thickness  
Extensive assessment of quality of life and cognitive function
- **Centers:** 8 clinical centers nation-wide
- **Follow-up:** Duration 5 years

### Hormone Therapy and Menopausal Symptoms: Benefit/Risk Assessment

- Assessment of risk in newly menopausal women
  - Breast cancer—generally no increased relative risk observed with short-term use
  - CHD—absolute risk is generally low in newly postmenopausal women, dependent on background rate and risk factors<sup>1</sup>
  - Must consider other potential risks: DVT, PE, stroke
- For many newly menopausal women with moderate to severe symptoms, benefits will outweigh risks.

CHD = coronary heart disease; DVT = deep vein thrombosis; PE = pulmonary embolism.  
<sup>1</sup>Hall MJ, Owing MF. *Advance Data from Vital and Health Statistics* 329. Hyattsville, MD: National Center for Health Statistics. 2002;1-20.

### Alternative Approaches Used for Vasomotor Symptoms

- Lifestyle changes, cool environment
- Phytoestrogens, black cohosh
- Vitamin E, dong quai
- Clonidine (patch or pill)
- Antidepressant (SSRI/SNRI) therapy
- Gabapentin

SSRI/SNRI = selective serotonin reuptake inhibitor/serotonin norepinephrine reuptake inhibitor.

### Efficacy of Osteoporosis Therapies

- |   |  |
|---|--|
| • HRT   | ↓ Risk of vertebral and hip fractures by 30-40%                                |
| • Bisphosphonates<br>(alendronate, residronate) | ↓ Risk of vertebral, hip, and other fractures by 50%                           |
| • SERMS<br>(raloxifene)                         | ↓ Risk of vertebral fractures by 30%; no significant effect on other fractures |
| • Calcitonin                                    | ↓ Risk of vertebral and other fractures by 30%                                 |
| • Calcium/vitamin D/<br>exercise                | ↑ in bone density; clinical trial data on fractures are limited                |

Manson JE, Martin KA. *NEJM* 2001; 345:34-40

### Conclusions

- Postmenopausal hormone therapy (HT) should not be initiated or continued for the prevention of cardiovascular disease or other chronic diseases (at any age, in either primary or secondary prevention settings).
- HT still has a clinical role in the treatment of moderate-to-severe hot flashes and other menopausal symptoms. The lowest effective dose should be used for the shortest duration necessary.
- Additional research on the benefits and risks of HT initiated early in menopause is warranted.

### Questions & Answers

