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
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

Anticipated Risk
- Breast Cancer
- Stroke?

Expected Benefit
- Coronary Artery Disease (Heart Attacks)

Threshold Level
- Early STOPPING for HARM
- Plan to follow to 2005 (average 8.5 years)

Additional Risks:
- Blood Clots, VTE (lungs=PE, legs=DVT)

Additional Benefits:
- Bone (Hip) Fractures
- Overall Mortality
- Colon Cancer
Women’s Health Initiative Hormone Trials

Hysterectomy

YES
N= 10,739

CEE (Conjugated equine estrogens, 0.625 mg/d) = Premarin®
Placebo

CEE+MPA (medroxyprogesterone acetate, 2.5 mg/d) = Prempro®
Placebo

NO
N= 16,608
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

E-alone
10,739
Average
6.8 years*

E+P
16,608
Average
Follow-up
5.6 years*

*design = 8.5 years
<table>
<thead>
<tr>
<th></th>
<th>50-59 yrs</th>
<th>60-69 yrs</th>
<th>70-79 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen-alone</td>
<td>3310</td>
<td>4852</td>
<td>2577</td>
</tr>
<tr>
<td>Estrogen+Progestin</td>
<td>5522</td>
<td>7510</td>
<td>3576</td>
</tr>
<tr>
<td>Both Trials</td>
<td>8832</td>
<td>12362</td>
<td>6153</td>
</tr>
</tbody>
</table>
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%

50-59  E-alone 31%  E+P 33%
55-59  E-alone 45%  E+P 45%
60-69  E-alone 24%  E+P 22%
70-79

Hysterectomy (75% White)  Uterus (84% White)

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%)

Total Numbers of Minority Women in Hormone Trials

Blacks
E-alone 1617  E+P 1124

Hispanic
E-alone 655  E+P 888

Asian/PI
E-alone 164  E+P 363

Native American
E-alone 75  E+P 56

Other

Hysterectomy (75% White)  Uterus (84% White)

Ann Epidemiol 2003; 13: S78-S86
WHI HT: Ethnic Distribution by Baseline Age

<table>
<thead>
<tr>
<th>Baseline Age</th>
<th>E-alone</th>
<th>E+P</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td>32.7%</td>
<td>21.5%</td>
</tr>
<tr>
<td>60-69</td>
<td>22.0%</td>
<td>12.5%</td>
</tr>
<tr>
<td>70-79</td>
<td>13.9%</td>
<td>8.6%</td>
</tr>
</tbody>
</table>

Ann Epidemiol 2003; 13: S78-S86
WHI E+P Trial: Baseline Age, BMI, Prior HT Use

Mean = 63.3 yrs

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>% of Enrolled Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td>5522 (33.3%)</td>
</tr>
<tr>
<td>60-69</td>
<td>7510 (45.2%)</td>
</tr>
<tr>
<td>70-79</td>
<td>3576 (21.5%)</td>
</tr>
</tbody>
</table>

Mean = 28.5 kg/m²

<table>
<thead>
<tr>
<th>Body Mass Index</th>
<th>% of Enrolled Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25</td>
<td>5058 (30.6%)</td>
</tr>
<tr>
<td>25-29.9</td>
<td>5826 (35.3%)</td>
</tr>
<tr>
<td>≥30</td>
<td>5636 (34.1%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior HT Use</th>
<th>% of Enrolled Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Past</td>
<td>3262 (19.6%)</td>
</tr>
<tr>
<td>Current</td>
<td>1035 (6.2%)</td>
</tr>
<tr>
<td>Never</td>
<td>12,304 (74.1%)</td>
</tr>
</tbody>
</table>

Mean = 63.3 yrs, Mean = 28.5 kg/m²

JAMA 2002; 288: 321-33
WHI E-alone Trial: Baseline Age, BMI, Prior HT Use

**Age (yrs)**

<table>
<thead>
<tr>
<th>Age</th>
<th>% of Enrolled Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td>N 3310 30.8%</td>
</tr>
<tr>
<td>60-69</td>
<td>4852 45.2%</td>
</tr>
<tr>
<td>70-79</td>
<td>2577 24.0%</td>
</tr>
</tbody>
</table>

**Body Mass Index**

<table>
<thead>
<tr>
<th>BMI</th>
<th>% of Enrolled Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25</td>
<td>2206 20.7%</td>
</tr>
<tr>
<td>25-29.9</td>
<td>3707 34.7%</td>
</tr>
<tr>
<td>≥30</td>
<td>4759 44.6%</td>
</tr>
</tbody>
</table>

**Prior HT Use**

<table>
<thead>
<tr>
<th>Use</th>
<th>% of Enrolled Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Past</td>
<td>3819 35.6%</td>
</tr>
<tr>
<td>Current</td>
<td>1377 12.8%</td>
</tr>
<tr>
<td>Never</td>
<td>5539 51.6%</td>
</tr>
</tbody>
</table>

**Mean =63.6 yrs**

**Mean =30.1 kg/m²**

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

<table>
<thead>
<tr>
<th></th>
<th>E+P</th>
<th>E-alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean BMI (kg/m²)</td>
<td>28.5</td>
<td>30.1</td>
</tr>
<tr>
<td>Prior HT Use</td>
<td>25.9%</td>
<td>48.4%</td>
</tr>
<tr>
<td>Caucasian</td>
<td>84.0%</td>
<td>75.3%</td>
</tr>
<tr>
<td>African American</td>
<td>6.7%</td>
<td>15.0%</td>
</tr>
<tr>
<td>Fracture at age ≥ 55 y</td>
<td>13.6%</td>
<td>13.6%</td>
</tr>
<tr>
<td>Mean Gail 5-year Risk</td>
<td>1.5%</td>
<td>1.6%</td>
</tr>
</tbody>
</table>
## Selected Differences in Baseline Characteristics between E+P and E-alone Trial Cohorts

### History of Cardiovascular Disease or Hypertension

<table>
<thead>
<tr>
<th></th>
<th>E+P (%)</th>
<th>E-alone (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>1.8</td>
<td>3.1</td>
</tr>
<tr>
<td>Angina</td>
<td>2.8</td>
<td>5.8</td>
</tr>
<tr>
<td>CABG/PTCA</td>
<td>1.3</td>
<td>1.5</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.9</td>
<td>1.6</td>
</tr>
<tr>
<td>VTE</td>
<td>0.9</td>
<td>1.5</td>
</tr>
<tr>
<td>Hypertension</td>
<td>36.1</td>
<td>47.9</td>
</tr>
</tbody>
</table>
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)

Favors Estrogen+Progestin

Stopping boundary for benefit

Favors Placebo

Stopping boundary for adverse effect

Statistics comparing disease rates over time

Planned Analyses
Monitoring the E+P Trial: Stroke

Stopping boundary for adverse effect

Favors Placebo
Monitoring the E+P Trial: Breast Cancer

Favors Estrogen+Progestin

Stopping boundary for adverse effect

Favors Placebo
Monitoring the E+P Trial: Global Index

Stopping boundary for supporting an overall finding of risks exceeding benefits.
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

Favors E+P                  Favors Placebo

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio</th>
<th>(------95% CI ------)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>0.0</td>
<td>1.0</td>
</tr>
<tr>
<td>CHD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary Embolism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total CVD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrial Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip Fracture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Fracture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global Index</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

• Nominal 95% Confidence Interval.
▲ Adjusted 95% Confidence Interval.

JAMA 2002; 288:321-33
Estrogen-alone

CHD
Stopping Boundaries and Observed Z-values

Stroke
Stopping Boundaries and Observed Z-values

Favors E-alone

Favors Placebo
Estrogen-alone

Invasive Breast Cancer
Stopping Boundaries and Observed Z-values

Global Index
Stopping Boundaries and Observed Z-values

Favors E-alone

Favors Placebo
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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Favors E-alone</th>
<th>Odds Ratio</th>
<th>(---95% CI ---)</th>
<th>Favors Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td></td>
<td>0.91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td>1.39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary Embolism</td>
<td></td>
<td>1.34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total CVD</td>
<td></td>
<td>1.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive Breast Cancer</td>
<td></td>
<td>0.77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal Cancer</td>
<td></td>
<td>1.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Cancer</td>
<td></td>
<td>0.93</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip Fracture</td>
<td></td>
<td>0.61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Fracture</td>
<td></td>
<td>0.70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Death</td>
<td></td>
<td>1.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global Index</td>
<td></td>
<td>1.01</td>
<td></td>
<td></td>
</tr>
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</table>

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
E-alone Trial: Heart attack risk

(Annualized %: E+P, 0.53%; Plb, 0.56%)

HR 0.95

95% nCI, 0.79-1.16

JAMA 2004; 291:1701-12; Updated Arch Intern Med 2006; 166:357-65
Estrogen-alone: Heart attack risk (by baseline age groups)

Age 50-59

CEE
Placebo

HR, 0.65
95% nCI, 0.37-1.12

Age 60-69

CEE
Placebo

HR, 0.98
95% nCI, 0.74-1.29

Age 70-79

CEE
Placebo

HR, 1.07
95% nCI, 0.78-1.47

Arch Intern Med 2006; 166:357-65
E+P Trial: Stroke risk

(Annualized %: E+P, 0.31%; Plb, 0.24%)
HR 1.31
95% nCI, 1.02-1.68
E-alone Trial: Stroke risk

(Annualized %: E+P, 0.39%; Plb, 0.33%)
HR 1.39
95% nCI, 1.10-1.77
Coronary Heart Disease and Strokes (Rates per 10,000/Year) in E+P and E-alone

**E+P Trial**
- n=16,608; 5.6 years follow-up
- CHD: 24% (NS)
- Strokes: 31%

**E-alone Trial**
- n=10,739; 6.8 years follow-up
- CHD: No effect
- Strokes: 39%

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

(Annualized %: E+P, 0.18%; Plb, 0.08%)

HR 2.13
95% nCI, 1.45-3.11

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

**E+P Trial**
- n=16,608; 5.6 years follow-up
- 113% (↑)
- 95% (↑)

**E-alone Trial**
- n=10,739; 6.8 years follow-up
- 34% (NS) (↑)
- 47% (↑)

PE and DVT rates compared to Placebo:
- E+P Trial: 113% for PE, 95% for DVT
- E-alone Trial: 34% (NS) for PE, 47% for DVT

Sources:
- 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)

Goodstein Am J Med 106:574, 1999
E+P Trial: Invasive Breast Cancer By Group

(Annualized %: E+P, 0.41%; Plb, 0.33%)

HR 1.24
95% nCI, 1.01-1.54

JAMA 2003; 289:3243-53
Breast Cancer Characteristics by Group

<table>
<thead>
<tr>
<th></th>
<th>E+P</th>
<th>Placebo</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor size, cm(^1)</td>
<td>1.7 (1.1)</td>
<td>1.5 (0.9)</td>
<td>0.038(^2)</td>
</tr>
<tr>
<td>Nodes Positive(^2)</td>
<td>25.9 %</td>
<td>15.8%</td>
<td>0.033</td>
</tr>
<tr>
<td>SEER Stage Regional / Mets</td>
<td>25.4%</td>
<td>16.0%</td>
<td>0.041</td>
</tr>
</tbody>
</table>

\(^1\) 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

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Year 1</th>
<th>Cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E+P</td>
<td>Placebo</td>
<td>E+P</td>
</tr>
<tr>
<td>Mammogram performed(^1)</td>
<td>100%</td>
<td>100%</td>
<td>90.3%</td>
</tr>
<tr>
<td>Mammogram abnormal (total)(^2)</td>
<td>5.2%</td>
<td>5.0%</td>
<td>9.4%(^3)</td>
</tr>
</tbody>
</table>

\(^1\) % 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
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
- 24% increase

**E-alone Trial**
- n=10,739; 6.8 years follow-up
- 23% (NS)

---

Invasive Breast Cancer
- E+P
- Placebo

JAMA 2003; 289:3243-53

Invasive Breast Cancer
- E-alone
- Placebo

JAMA 2004; 291:1701-12
Invasive Colorectal Cancer in E+P

(Annualized %: E+P, 0.10%; Plb, 0.16%)

HR 0.56
95% nCI, 0.38-0.81

### Colorectal Cancer Characteristics by Group

<table>
<thead>
<tr>
<th></th>
<th>E+P</th>
<th>Placebo</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor Size, cm&lt;sup&gt;1&lt;/sup&gt;</td>
<td>4.9 (2.5)</td>
<td>4.3 (2.5)</td>
<td>0.34</td>
</tr>
<tr>
<td>Nodes Positive&lt;sup&gt;2&lt;/sup&gt; (%)</td>
<td>59.0%</td>
<td>29.4%</td>
<td>0.003</td>
</tr>
<tr>
<td>No. Positive Nodes</td>
<td>3.2 (4.1)</td>
<td>0.8 (1.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>(mean + SD)</td>
<td>(mean + SD)</td>
<td>(mean + SD)</td>
<td></td>
</tr>
<tr>
<td>SEER Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regional / Mets</td>
<td>76.2%</td>
<td>48.5%</td>
<td>0.004</td>
</tr>
</tbody>
</table>

<sup>1</sup>Mean (SD) for tumor with known tumor size  
<sup>2</sup>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
Colorectal Cancer (Rates per 10,000/Year) in E+P and E-alone

**E+P Trial**
- n=16,608; 5.6 years follow-up

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

39%  

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

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

HR 0.67
95% nCI, 0.47-0.96

HR 0.65
95% nCI, 0.46-0.92

JAMA 2003; 290:1729-38
Effects of E+P on Total Fractures by Summary Fracture Risk Score

Fracture Risk Score Group

JAMA 2003; 290:1729-38
Hormone

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

E+ P

- Normal: 58%
- Low Bone Mass: 32%
- Osteoporosis: 10%
- Total Hip: 4%

Placebo

- Normal: 53%
- Low Bone Mass: 35%
- Osteoporosis: 12%
- Total Hip: 6%

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

**E+P Trial**
- n=16,608; 5.6 years follow-up

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

- HIP Clinical Vertebral
  - E+P: 33%
  - Placebo: 34%
  - E-alone: 39%
  - Placebo: 38%

**References**
- 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)

WHI HT Studies
- E+P: 16,608
- E-alone: 10,739
- 40 sites, N=27,347

WHI Memory Study (WHIMS)
- E+P: 4,532
- E-alone: 2,948
- 39 sites, N=7,480

WHI Study of Cognitive Aging (WHISCA)
- E+P: 1,416
- E-alone: 886
- 14 sites, N=2,302
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

**E-alone (CEE)**
- 2947
- Average Follow-up 5.2 years

**E+P (CEE+MPA)**
- 4532
- Average Follow-up 4.1 years

*design = 7 years
Probable Dementia and Mild Cognitive Impairment (Rates per 10,000/Year) in E+P and E-alone

**E+P Trial**
- n=4,532; 4.1 years follow-up
- **105%** (E+P) vs. Placebo

**E-alone Trial**
- n=2,947; 5.2 years follow-up
- **34%** (NS) (E-alone) vs. Placebo

JAMA 2003; 289:2651-62  
JAMA 2004; 291:2947-58
WHIMS Overall Results for Probable Dementia

Pooled: E-Alone and E + P

- E-Alone or E + P
- Placebo

HR, 1.76
95% CI, 1.19-2.60
P = 0.005

Years Since Randomization

JAMA 2004; 291:2947-58
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

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

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?
- Are there subgroups of women who are more vulnerable?
- What biological effects of HT might explain the increased risk of PD?

- WHIMS Extension Study
- Continued analysis of WHIMS and WHISCA data
- 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)

- E+P: 4,532
- E-alone: 2,948
- 39 sites, N=7,480

WHIMS-MRI Current

- E+P: 824
- E-alone: 499
- 14 sites, N=2,302
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)

Effects of Estrogen-Plus-Progestin and Placebo on Disease Rates

<table>
<thead>
<tr>
<th></th>
<th>Risks</th>
<th>Benefits</th>
<th>Neutral</th>
</tr>
</thead>
<tbody>
<tr>
<td>E+P</td>
<td>6</td>
<td>6*</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>7*</td>
<td></td>
<td>5*</td>
</tr>
<tr>
<td>(10 PE*)</td>
<td>18*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Number of cases per year in 10,000 women

- CHD
- Strokes
- Blood clots
- Breast cancer
- Colorectal cancer
- Hip fractures
- Deaths

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

JAMA 2002; 288:321-33
Effects of E-alone and Placebo on Disease Rates

- **Risk**
  - Strokes: 40 cases per year in 10,000 women (P=0.03)
  - Blood clots: 30 cases per year in 10,000 women
  - Heart attacks: 50 cases per year in 10,000 women
  - Colorectal cancer: 25 cases per year in 10,000 women
  - Deaths: 90 cases per year in 10,000 women (P=.007)

- **Benefit**
  - Breast cancer: 6 cases per year in 10,000 women (P=0.01)
  - Hip fractures: 6 cases per year in 10,000 women

**P-values**
- 3 PE: ns
- 6 DVT: P=.03
- Deaths: P=.06

**References**
JAMA 2004; 291:1701-12
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

All comparisons significant (p<.001)

- hot flashes
- vag dryness
- headaches
- joint pain
- mood swings

E+P: Symptom changes at 1 year

- OR = 4.4**
- OR = 2.4**
- OR = 0.87
- OR = 1.25*
- OR = 0.99

**p<0.001
*p=0.002

Purpose of WHI Quality of Life (QOL) Study

- To test the hypothesis that decreasing menopausal symptoms would increase women’s perceived quality of life (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

<table>
<thead>
<tr>
<th></th>
<th>E+P (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women with HF at baseline</td>
<td>55.5</td>
<td>21.3</td>
</tr>
<tr>
<td>Women with HF prior to baseline</td>
<td>21.6</td>
<td>3.7</td>
</tr>
<tr>
<td>Never had HF</td>
<td>6.4</td>
<td>1.2</td>
</tr>
</tbody>
</table>

- 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

HR: 0.79 (95% CI 0.76-0.93)
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.
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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Active Drug</th>
<th>Placebo</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>E+P Stress</td>
<td>2%</td>
<td>0%</td>
<td>1.87</td>
<td>1.61-2.18</td>
</tr>
<tr>
<td>E-alone Stress</td>
<td>18%</td>
<td>2%</td>
<td>2.15</td>
<td>1.77-2.62</td>
</tr>
<tr>
<td>E+P Urge</td>
<td>8%</td>
<td>2%</td>
<td>1.15</td>
<td>0.99-1.34</td>
</tr>
<tr>
<td>E-alone Urge</td>
<td>12%</td>
<td>0%</td>
<td>1.32</td>
<td>1.10-1.58</td>
</tr>
</tbody>
</table>

JAMA 2005; 293:935-48
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.

*References*

JAMA 2005; 293:935-48
In both E +P and E alone, women taking active drug had more gallbladder disease and gallbladder surgery.
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.
- Analyses of results are in progress.
Coronary Artery Calcium

No Calcium

Severe Calcification
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

<table>
<thead>
<tr>
<th>Micronutrients</th>
<th>Lipid Fraction</th>
<th>Clotting Factors</th>
<th>Hormones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-carotene</td>
<td>Triglycerides</td>
<td>Factor VII</td>
<td>Glucose</td>
</tr>
<tr>
<td>Beta-carotene</td>
<td>Total Cholesterol</td>
<td>Factor VII C</td>
<td>Insulin</td>
</tr>
<tr>
<td>Alpha-tocopherol</td>
<td>LDL-C</td>
<td>Fibrinogen</td>
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</tr>
<tr>
<td>Gamma-tocopherol</td>
<td>HDL-C</td>
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</tr>
<tr>
<td>Beta-cryptoxanthine</td>
<td>HDL-2</td>
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<tr>
<td>Lycopene</td>
<td>HDL-3</td>
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<tr>
<td>Lutein and zeaxanthin</td>
<td>Lp(a)</td>
<td></td>
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<tr>
<td>Retinol</td>
<td></td>
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</tr>
</tbody>
</table>
## Hormone Trial CVD Biomarker Case-control Study
### CHD, Stroke, VTE

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

**E+P minus Placebo**

- **Percent Change at 1 yr**
  - LDL: -12.7%
  - HDL: 7.3%
  - Triglyceride: 6.9%
  - Total Cholesterol: -5.4%

**E Alone minus Placebo**

- **Percent Change at 1 yr**
  - LDL: -12.7%
  - HDL: 14.0%
  - Triglycerides: 22.0%
  - Total Cholesterol: -0.9%

* p< 0.05

NEJM 2003; 349:523-34

Arch Intern Med 2006; 166:1-9
Biomarker Interactions in E+P and E-alone Trials

**E + P Trial**

Risk of CHD (OR)

- LDL Cholesterol (mg/dl)
  - <126
  - 126-155
  - >155

- C-reactive protein (mg/L)
  - <1.30
  - 1.30-3.59
  - >3.59

**E Alone Trial**

- Interaction p< 0.01
- Interaction p< 0.04

NEJM 2003;349:523-34

Arch Intern Med 2006;166:1-9

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

Risk For VTE (OR)

Placebo NO Factor V
Placebo YES Factor V
E + P NO Factor V
E + P YES Factor V

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
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
Dissemination of Research Results

Clinical Trial Result

- Academic Journals
- Pharmaceutical Industry
- Professional Organization
- Public
- Advocacy Groups
- Press/Media
- Other Government Agencies (FDA)
- Payers (Medicare, Medicaid, Insurance Co)

Physicians

Public
Dissemination of Information

Assimilation into Practice

Organizations/Physicians Digest Information

Public Reaction

Trial stops

Time
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

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Personal Accounts of Participants

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Impact of WHI Hormone Trials on Medical Practice

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Impact of WHI Hormone Trials on Medical Practice

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Beyond Hormone Therapy

The Truth About Hormones

THE MENOPAUSE MAZE

What Women Need to Know Now
New Risks and Rewards of Treatment
How Men Are Affected
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.
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.
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

- Oral E
- Oral E/P
- Trnd/Vag

HERS → WHI E+P

WHI E-alone ??

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.

Future Directions for Menopausal Hormone Research

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Research Questions

Do effects vary by:

- Age? - or - Years since Menopause?
- Drug? - or - Delivery Method?
- Dose? - or - Regimen? Duration?
Stages of Atherosclerosis

- **Initiation** (endothelium, fatty streaks)
  - Young adult
  - Estrogen may delay

- **Progression** (raised lesions)
  - Middle age
  - Estrogen has no effect

- **Complicated lesions** (erosion or rupture of unstable plaque)
  - Older age
  - 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

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