Glycemic Effects of Postmenopausal Hormone Therapy: The Heart and Estrogen/progestin Replacement Study
A Randomized, Double-Blind, Placebo-Controlled Trial

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Background: Randomized trials of postmenopausal hormone therapy have found differing effects on fasting glucose levels. No trial has evaluated the effect of hormone therapy on diabetes incidence.

Objective: To evaluate the effect of hormone therapy on fasting glucose level and incident diabetes.

Design: Randomized, double-blind, placebo-controlled trial.

Setting: 20 U.S. clinical centers.

Participants: 2763 postmenopausal women with coronary heart disease who were followed for 4.1 years. At baseline, 734 women had diabetes, 218 women had impaired fasting glucose, and 1811 women were normoglycemic; the 2029 women without diabetes were followed for incident diabetes.

Intervention: 0.625 mg of conjugated estrogen plus 2.5 mg of medroxyprogesterone acetate daily, or placebo.

Measurements: Fasting glucose level was measured at baseline, at year 1, and at the end of the trial. Incident diabetes was defined by self-report of diabetes or disease complication, fasting glucose level of 6.9 mmol/L or greater (≥126 mg/dL), or initiation of therapy with diabetes medication.

Results: Fasting glucose levels increased significantly among women assigned to placebo but did not change among women receiving hormone therapy. The incidence of diabetes was 6.2% in the hormone therapy group and 9.5% in the placebo group (relative hazard, 0.65 [95% CI, 0.48 to 0.89]; P = 0.006). The number needed to treat for benefit to prevent one case of diabetes was 30 (CI, 18 to 103). Changes in weight and waist circumference did not mediate this effect.

Conclusions: In women with coronary disease, hormone therapy reduced the incidence of diabetes by 35%. This observation provides important insights into the metabolic effects of postmenopausal hormones but is insufficient to recommend the use of hormones for secondary prevention of heart disease.

Several clinical studies have evaluated the effect of postmenopausal hormone therapy on glucose metabolism and have had disparate results. Results from randomized, controlled trials performed primarily in women without diabetes have found decreased mean fasting glucose or insulin levels among those assigned to hormone therapy (1–5) or no difference between those assigned to hormones and those assigned to placebo (6–10). Fewer clinical trials have evaluated the effect of postmenopausal hormones on fasting glucose and insulin levels among women with type 2 diabetes mellitus, but again, the results have been mixed (11–16). Observational studies have more consistently found that postmenopausal women taking hormone therapy have lower fasting glucose or hemoglobin A1c levels than those not taking hormones (17–24). In addition, some (25, 26) but not all (24, 27) observational studies have noted a decreased incidence of diabetes among users of postmenopausal hormone therapy. No randomized, controlled trial has evaluated the long-term effect of hormone therapy on diabetes incidence.

To determine the effect of hormone therapy on subsequent diabetes, we analyzed data from the Heart and Estrogen/progestin Replacement Study (HERS), in which 2763 postmenopausal women with documented coronary heart disease (CHD) were randomly assigned to daily estrogen plus progestin therapy or to placebo. We evaluated the effect of hormone therapy on fasting glucose levels and incident diabetes over 4 years of follow-up.

METHODS
Study Setting, Participants, and Design
The design, methods, baseline characteristics (28), and main findings (29) of HERS have been published elsewhere. Briefly, HERS was a randomized, double-blind, placebo-controlled trial performed to evaluate daily doses of 0.625 mg of conjugated estrogen plus 2.5 mg of medroxyprogesterone acetate for the prevention of coronary events in postmenopausal women with established CHD. The trial enrolled 2763 women at 20 clinical centers in the United States between January 1993 and September 1994 and followed participants for a mean of 4.1 years. To be included in the trial, women had to be younger than 80 years of age and have CHD, as evidenced by previous myocardial infarction, coronary artery bypass graft surgery, mechanical revascularization, or angiographic evidence of coronary stenosis. Women who reported a CHD event within 6 months of randomization or who had used postmenopausal hormone therapy within 3 months of the initial screening were excluded. Those with serum triglyceride levels of 3.39 mmol/L or greater (≥300 mg/dL), fasting blood glucose levels of 16.5 mmol/L or greater (≥300 mg/dL), or uncontrolled hypertension (systolic blood pres-
Context
In observational studies, postmenopausal hormone therapy has been associated with lower fasting glucose levels. No prospective, controlled trial has evaluated the effect of postmenopausal hormone therapy on the development of diabetes mellitus.

Contribution
Among the 2029 women in the Heart and Estrogen/Progestin Replacement Study who had coronary disease but no diabetes at baseline, 6.2% of those receiving 0.625 mg of conjugated estrogen plus 2.5 mg of medroxyprogesterone acetate and 9.5% of those receiving placebo developed diabetes.

Implications
Recommendations about combination postmenopausal hormone therapy should consider that for every 30 women treated for 4 years, therapy might prevent one case of diabetes.

The Editors

Sure ≥ 200 mg Hg or diastolic blood pressure ≥ 105 mm Hg were also excluded.

Computer-generated random numbers were used to specify the allocation sequence. Women were randomly assigned to the two treatment groups by use of a tamper-proof blocked randomization stratified by clinical center. Participants, investigators, and staff at the clinical centers; Wyeth-Ayerst Research; and those adjudicating study outcomes were blinded to medication assignment. Additional details about sample size calculations, randomization, and blinding procedures have been published elsewhere (29).

For our analysis, women were classified as having diabetes at the baseline visit if they reported a physician diagnosis of diabetes, were taking diabetes medication, or had a fasting plasma glucose level of 6.9 mmol/L or greater (≥126 mg/dL). Women were classified as having impaired fasting glucose if they had a fasting glucose level of 6.0 to 6.9 mmol/L (110 to 125 mg/dL) at baseline. The remaining women were considered to have normal glucose metabolism.

Data Collection
At baseline, participants completed a questionnaire to ascertain age, race or ethnicity, education, smoking habits (current, former, or never), alcohol consumption (drinks per week), and exercise or walking activity. Physical examination variables measured at baseline were body weight, height, waist and hip circumference, and systolic and diastolic blood pressure. At baseline, at year 1, and at the end-of-trial visit, participants had fasting blood tests for levels of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and lipoprotein(a) measured by the Lipoprotein Analytical Laboratory at Johns Hopkins Hospital, Baltimore, Maryland. Fasting serum glucose level was measured at baseline, at year 1, and at the end-of-trial visit. Venous blood was obtained in the morning after a 12-hour fast, and Smith-Kline Beecham Clinical Laboratory, Van Nuys, California, analyzed the samples using the hexokinase enzymatic method. We determined coefficients of variation by using ChemTrac (Medical Analysis Systems, Inc., Camarillo, California) control. The coefficient of variation for serum glucose level was 1.6% at a mean value (±SD) of 4.2 ± 0.05 mmol/L (77 ± 1.0 mg/dL) and 1.1% at a mean value (±SD) of 14.6 ± 0.16 mmol/L (266 ± 3.0 mg/dL). Adherence to study medication was reassessed every 4 months, at each visit.

Ascertained of Outcomes
Diabetes incidence was not a secondary end point of the main HERS trial, but blood glucose level was prespecified as a variable that may mediate the effects of hormone therapy on CHD outcomes. We defined incident cases of diabetes by the presence of a fasting glucose level of 6.9 mmol/L or greater (≥126 mg/dL) at year 1 or at the end-of-trial visit, self-report of new diabetes or a complication directly related to diabetes, or initiation of hypoglycemic medication at any point during follow-up. Self-reported complications included diabetic neuropathy, diabetic retinopathy, diabetic foot ulcer, and diabetic renal disease. Hypoglycemia was considered a complication of diabetes if a participant taking an antidiabetic medication reported it to the study staff as an adverse event.

Table 1. Baseline Characteristics of Participants by Treatment Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hormone Therapy Group (n = 1380)</th>
<th>Placebo Group (n = 1383)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>67 ± 7</td>
<td>67 ± 7</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.6 ± 5.5</td>
<td>28.5 ± 5.5</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>92.0 ± 13.8</td>
<td>91.5 ± 13.3</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>135 ± 19</td>
<td>135 ± 19</td>
</tr>
<tr>
<td>HDL cholesterol level, mmol/L (mg/dL)</td>
<td>1.29 ± 0.34 (50 ± 13)</td>
<td>1.29 ± 0.34 (50 ± 13)</td>
</tr>
<tr>
<td>LDL cholesterol level, mmol/L (mg/dL)</td>
<td>3.75 ± 0.98 (145 ± 38)</td>
<td>3.75 ± 0.96 (145 ± 37)</td>
</tr>
<tr>
<td>Fasting serum glucose level, mmol/L (mg/dL)</td>
<td>6.2 ± 2.0 (112 ± 37)</td>
<td>6.2 ± 2.0 (112 ± 37)</td>
</tr>
<tr>
<td>Diabetes, %†</td>
<td>27.6</td>
<td>25.5</td>
</tr>
</tbody>
</table>

* Values with plus/minus signs are means ± SD. All baseline variables were balanced between groups. P > 0.2 for all between-group comparisons (determined by analysis of variance or the chi-square test, where appropriate). HDL = high-density lipoprotein; LDL = low-density lipoprotein.
† Defined as self-report of diagnosis, use of diabetes medication at baseline, or fasting glucose level ≥ 6.9 mmol/L (≥126 mg/dL).
Statistical Analysis

To compare fasting glucose levels by treatment assignment at baseline, at year 1, and at the end-of-trial visit, t-tests were used. In addition, mixed linear models for repeated measures were used to assess treatment effects on fasting glucose level measured at year 1 and at the end-of-trial visit. Since mean values changed little after the year 1 visit, treatment effects were modeled by using the interaction between treatment assignment and an indicator for follow-up compared with baseline. These analyses were repeated after stratification by baseline diabetes status (diabetes, impaired fasting glucose, or normal glucose metabolism). We calculated the number needed to treat for benefit by taking the inverse of the absolute risk reduction of incident diabetes between the treatment groups.

The effect of treatment assignment on incident diabetes was assessed by using Cox proportional hazards models. Primary analyses used unadjusted intention-to-treat models; in supplementary analyses, we adjusted first for age and then for a range of potential confounders selected a priori, including age; ethnicity; education; current smoking; alcohol use; exercise; body mass index; waist circumference; and baseline use of diuretics, β-blockers, angiotensin-converting enzyme inhibitors, and statins.

In addition to intention-to-treat analyses, we also performed “as treated” analyses to determine whether the observed effect of hormone therapy on glucose levels and incident diabetes was also seen among women who adhered to the study medication. In these analyses, follow-up was censored at the beginning of the first 2-week period in which participants did not adhere to medication. To minimize potential confounding, these analyses were adjusted for baseline variables that differed between adherent and nonadherent women.

We hypothesized that certain characteristics (body mass index, waist circumference, weight change, smoking, triglyceride level, high-density lipoprotein cholesterol level, hypertension, and certain cardiac medications) may mediate the effect of hormone therapy on fasting glucose level and diabetes incidence. To test this theory, we added post-randomization values of one or more hypothesized mediators as covariates to Cox regression models for incident diabetes. All analyses were conducted by using SAS software, version 8.02 (SAS Institute, Inc., Cary, North Carolina). A P value less than 0.05 was considered statistically significant.

Role of the Funding Sources

The funding sources had no role in the design or conduct of this analysis or in the decision to submit the paper for publication.

RESULTS

Characteristics of women enrolled in HERS did not differ substantially between the hormone therapy group and the placebo group (Table 1). At the baseline examination, 734 women (26.6%) were classified as diabetic based on self-report of diagnosis or medication use (n = 640 [87.2%]) or by a fasting serum glucose level of 6.9 mmol/L or greater (≥126 mg/dL) (n = 101 [13.8%]). Impaired fasting glucose (fasting serum glucose level, 6.0 to 6.9 mmol/L [110 to 125 mg/dL]) was noted in 218 women (7.9%), and 1811 women (65.5%) were classified as nondiabetic (Table 2). Women with diabetes had higher body mass index, waist circumference, systolic blood pressure, and triglyceride levels than women in the other two groups; in addition, they were less educated and less likely to exercise regularly. Equal proportions of women with diabetes, with impaired fasting glucose, and without diabetes were randomly assigned to hormone therapy. The Figure shows the flow of participants through the study.

Effects of treatment assignment on fasting serum glu-
Cose measurements at year 1 and at the end-of-trial visit are reported in Table 3. Women in the placebo group with and without diabetes at baseline had significant worsening of fasting glucose values compared with women receiving hormone therapy, who had no significant change in mean glucose measurements. A similar trend was seen in women with impaired fasting glucose. Analysis limited to women in both treatment groups who adhered to their assigned study medication found similar results. Baseline diabetes classification and treatment assignment had a significant interaction on glucose effect ($P = 0.001$).

Women assigned to hormone therapy had statistically significant decreases in weight (mean change, $-0.8$ kg vs. $0.2$ kg; $P < 0.001$), waist circumference (mean change, $-0.7$ cm vs. $0.3$ cm; $P < 0.001$), and waist-to-hip ratio (mean change, $-0.01$ vs. $0$; $P = 0.03$) compared with those assigned to placebo. However, these beneficial changes did not mediate the differences in fasting serum glucose level between the treatment groups (data not shown).

New diagnoses of diabetes were made in 160 women during follow-up. Cumulative incidence of diabetes for the entire cohort of women who were normoglycemic at baseline was $7.9\%$ (160 of 2029 women). Table 4 displays the participants who met criteria for diabetes at year 1 and at the end-of-trial visit. Of women with impaired fasting glucose at baseline, approximately $30\%$ were classified with diabetes by the end of the trial, compared with $5\%$ of women who were normoglycemic at baseline. Approximately $40\%$ of women with impaired fasting glucose at baseline had a fasting glucose level in the nondiabetic range at the end of the trial, while $30\%$ maintained impaired fasting glucose.

The cumulative incidence of diabetes was $6.2\%$ (62 of 999) for women assigned to hormone therapy compared with $9.5\%$ (98 of 1030) for those assigned to placebo ($P = 0.006$). The number needed to treat for benefit to prevent one case of incident diabetes was $30$ (CI, 18 to 103). Table 5 displays the cumulative incidence of diabetes by baseline classification and treatment assignment. Compared with women assigned to hormone therapy, there was a trend toward higher incidence of diabetes in both normoglycemic women and those with impaired fasting glucose who were assigned to placebo.

In Cox proportional hazards models, the relative hazard of incident diabetes for women in the hormone therapy group versus those in the placebo group was $0.65$ (CI, 0.48 to 0.89) (Table 6). This result was unchanged after adjust-
ment for baseline demographic characteristics, physical examination, and laboratory and medication variables. Pill counts showed that 56% of women assigned to placebo and 43% of women assigned to hormone therapy took more than 80% of their assigned study medication at the end of the trial. In analyses restricted to women who adhered to the study medication, the relative hazard for incident diabetes was unchanged.

We evaluated several potential mediators of treatment effect on diabetes incidence, using variables with strong biological plausibility (waist circumference, body mass index, change in weight, smoking), those that cluster with diabetes in the metabolic syndrome (dyslipidemia, hypertension), and those that have been implicated in previous studies (diuretics, \( \beta \)-blockers, angiotensin-converting enzyme inhibitors, statins). No individual variable or group of variables changed the overall treatment effect on diabetes incidence (Table 6).

**Table 3. Effect of Treatment Assignment on Fasting Serum Glucose Level**

<table>
<thead>
<tr>
<th>Diabetes Status</th>
<th>Participants</th>
<th>Visit</th>
<th>Fasting Serum Glucose Level</th>
<th>Between-Group Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hormone Therapy Group</td>
<td>Placebo Group</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>n</td>
<td>mg/dL</td>
</tr>
<tr>
<td>Normal</td>
<td>1811</td>
<td>Baseline</td>
<td>94.2 ± 7.7</td>
<td>94.6 ± 7.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Year 1</td>
<td>94.3 ± 10.0</td>
<td>96.7 ± 10.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>End of trial</td>
<td>96.3 ± 14.5</td>
<td>98.7 ± 14.3</td>
</tr>
<tr>
<td>Impaired fasting glucose</td>
<td>218</td>
<td>Baseline</td>
<td>115.6 ± 4.5</td>
<td>115.1 ± 4.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Year 1</td>
<td>111.9 ± 15.2</td>
<td>115.2 ± 30.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>End of trial</td>
<td>112.4 ± 20.3</td>
<td>125.8 ± 42.5</td>
</tr>
<tr>
<td>Diabetes</td>
<td>734</td>
<td>Baseline</td>
<td>152.7 ± 48.7</td>
<td>157.5 ± 48.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Year 1</td>
<td>154.9 ± 58.0</td>
<td>170.4 ± 64.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>End of trial</td>
<td>153.7 ± 57.9</td>
<td>165.1 ± 63.2</td>
</tr>
<tr>
<td>Overall</td>
<td>2763</td>
<td>Baseline</td>
<td>111.9 ± 36.9</td>
<td>112.4 ± 36.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Year 1</td>
<td>111.9 ± 41.1</td>
<td>117.0 ± 46.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>End of trial</td>
<td>112.4 ± 40.8</td>
<td>117.2 ± 46.4</td>
</tr>
</tbody>
</table>

* Values with plus/minus signs are means ± SD. To convert mg/dL to mmol/L, multiply by 0.0555.

**Discussion**

Women randomly assigned to hormone therapy had a 35% lower risk for diabetes than those assigned to placebo. This reduction in risk was primarily due to the fact that women in the hormone therapy group maintained a lower fasting glucose level than women in the placebo group. We found that hormone therapy prevented the increase in fasting glucose values that was seen in the placebo group over time. Characteristics commonly associated with diabetes were not responsible for the treatment effect.

Before HERS, the Postmenopausal Estrogen/Progestin Interventions (PEPI) study was the largest randomized, placebo-controlled trial to evaluate the effect of postmenopausal hormone therapy on glucose metabolism (1). Investigators followed 875 younger postmenopausal women (45 to 64 years of age) without known coronary disease for 3 years and found a statistically significant 2% to 3% decrease in fasting glucose level \((P = 0.03)\) and a 2% to 7% increase in 2-hour postchallenge glucose levels \((P = 0.01)\) in the women assigned to any of the four hormone groups compared with those assigned to placebo. In a per-protocol analysis of the PEPI results, Espeland and colleagues (2) also found decreased fasting glucose levels in women who adhered to their hormone therapy assignment. We found no change in mean fasting glucose levels over time in women assigned to hormone therapy and significant deterioration of glucose in the placebo group. Although the two study samples included primarily white women, women in the HERS sample were older; had higher body weight, body mass index, and waist-to-hip ratio; and had

**Table 4. Criteria for Diagnosis of Diabetes at Year 1 and at the End of the Study**

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Participants at Year 1</th>
<th>Participants at End of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Self-reported new diagnosis or complication*</td>
<td>2 (5.1)</td>
<td>8 (6.6)</td>
</tr>
<tr>
<td>Initiation of diabetes medication</td>
<td>7 (17.9)</td>
<td>14 (11.6)</td>
</tr>
<tr>
<td>Fasting glucose level ≥ 6.9 mmol/L (≥126 mg/dL)</td>
<td>26 (66.7)</td>
<td>62 (51.2)</td>
</tr>
<tr>
<td>New diagnosis or complication and new medication</td>
<td>1 (2.6)</td>
<td>10 (8.3)</td>
</tr>
<tr>
<td>New diagnosis or complication and fasting glucose level ≥ 6.9 mmol/L (≥126 mg/dL)</td>
<td>3 (7.7)</td>
<td>15 (12.4)</td>
</tr>
<tr>
<td>New diagnosis or complication, fasting glucose level ≥ 6.9 mmol/L (≥126 mg/dL), and new diabetes medication</td>
<td>0 (0)</td>
<td>12 (9.9)</td>
</tr>
<tr>
<td>All</td>
<td>39 (100)</td>
<td>121 (100)</td>
</tr>
</tbody>
</table>

* Complications included diabetic neuropathy, diabetic retinopathy, diabetic foot ulcer, and diabetic renal disease. Hypoglycemia was considered a complication if a participant taking an antidiabetic medication reported it to the study staff as an adverse event.
established CHD. On average, women in all hormone treatment groups in the PEPI trial as well as in the placebo group had a small increase in weight and in waist-to-hip ratio. In HERS, women assigned to hormone therapy had an overall decrease in weight and those receiving placebo had a small increase in weight. However, because changes in weight and waist circumference did not mediate the effect of hormone therapy on fasting glucose level in HERS, these differences between the study samples may not explain the disparate results.

We assessed diabetes incidence by self-report of new diagnosis or complication or initiation of new medication at every visit (that is, at 4-month intervals). Fasting serum glucose level, however, was tested only at year 1 and at the end of the trial. As a result, the differences in diabetes incidence between treatment groups became apparent only at the end of the trial, after approximately 4 years of treatment. Thus, longer treatment may explain why results from HERS differ from those of previous shorter trials (1, 3, 5–13).

In HERS, only the effect of oral daily conjugated equine estrogen and medroxyprogesterone acetate compared with placebo was examined. Several smaller short trials have examined the effect of different combinations, dosages, and routes of administration of estrogens and progestins on glucose metabolism. In studies that compared an oral preparation of estrogen with transdermal estradiol, most found no significant differences in mean fasting glucose or insulin levels within each treatment group or between the two routes of administration (15, 30–32). Moreover, the effect of estrogen plus progestin regimens on glucose metabolism is generally consistent with results of studies of estrogen-alone regimens (2, 5–7, 31, 33). Two trials with relatively long follow-up that compared estrogen alone as well as combined estrogen and progestin regimens found similar results, with small but significantly decreased fasting glucose levels in each of the treatment groups (2, 6).

Therefore, the treatment benefit of hormone therapy on fasting glucose level observed in these trials as well as in our study is probably attributable to the estrogen component and does not change substantially when progestin is added. Metabolic effects of estrogen may occur indirectly through alterations of levels of insulin, growth hormone, or catecholamines (34–37). Most clinical trials have found no change in fasting insulin level with postmenopausal hormone therapy (3, 8, 13, 15, 38). However, some studies have reported decreased fasting or 3-hour postprandial insulin levels (2, 5, 7, 39) or nonsignificant elevations in insulin levels (40). In addition, some evidence suggests that estrogen therapy may improve insulin sensitivity (3, 41, 42). However, one study found that postmenopausal estrogen therapy induces growth hormone pulses and higher basal growth hormone levels in healthy women (35). Estrogen may inhibit catecholamine uptake as well (36). Both growth hormone and catecholamines antagonize the effect of insulin, thereby retarding the uptake of glucose and increasing the mobilization of free fatty acids from

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**Table 5. Cumulative (4-Year) Incidence of Diabetes from Baseline Classification**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Diabetes Status at Baseline</th>
<th>Hormone Therapy Group</th>
<th>Placebo Group</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/n (%)</td>
<td>38/904 (4)</td>
<td>52/907 (6)</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24/95 (25)</td>
<td>46/123 (37)</td>
<td>0.06</td>
</tr>
<tr>
<td>New diagnosis of diabetes†</td>
<td></td>
<td>62/999 (6)</td>
<td>98/1030 (10)</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>Impaired fasting glucose</td>
<td>21/904 (2)</td>
<td>37/907 (4)</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>Both</td>
<td>21/95 (22)</td>
<td>42/123 (34)</td>
<td>0.05</td>
</tr>
<tr>
<td>Diabetes based on fasting glucose level ≥ 6.9 mmol/L (≥126 mg/dL) alone</td>
<td></td>
<td>42/999 (4)</td>
<td>79/1030 (8)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>26/904 (3)</td>
<td>23/907 (2)</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td></td>
<td>Impaired fasting glucose</td>
<td>11/95 (12)</td>
<td>17/123 (14)</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td></td>
<td>Both</td>
<td>37/999 (4)</td>
<td>40/1030 (4)</td>
<td>&gt;0.2</td>
</tr>
</tbody>
</table>

* Obtained by using the chi-square test.
† Fasting glucose level ≥ 6.9 mmol/L (≥126 mg/dL), new diabetes diagnosis or complication, or initiation of diabetes medication.

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**Table 6. Risk for Incident Diabetes in the Hormone Therapy Group versus the Placebo Group**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative Hazard (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted†</td>
</tr>
<tr>
<td>BMI, weight, change in weight, and waist circumference</td>
<td>0.65 (0.48–0.89)</td>
</tr>
<tr>
<td>Triglyceride and HDL levels</td>
<td>0.69 (0.50–0.95)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.65 (0.47–0.89)</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.65 (0.47–0.89)</td>
</tr>
<tr>
<td>Medications (diuretics, β-blockers, ACE inhibitors, statins)</td>
<td>0.63 (0.46–0.87)</td>
</tr>
<tr>
<td>All</td>
<td>0.67 (0.49–0.93)</td>
</tr>
</tbody>
</table>

* Diabetes was considered present if fasting glucose level was ≥6.9 mmol/L (≥126 mg/dL), if participant reported diabetes diagnosis or diabetic complication, or if a diabetes medication was initiated. ACE = angiotensin-converting enzyme; BMI = body mass index; HDL = high-density lipoprotein; statins = 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors.† Results did not change after adjustment for baseline age; ethnicity; education; alcohol use; smoking; physical activity; BMI; waist circumference; triglyceride level; HDL cholesterol level; hypertension; and use of diuretics, β-blockers, ACE inhibitors, and statins.
‡ Using time-dependent covariates.
adipocytes (43). On the basis of these physiologic changes, estrogen therapy would be expected to increase fasting and postchallenge glucose levels and increase insulin levels. We are unable to reconcile our findings with these expected physiologic changes.

Our results support the hypothesis that oral estrogen may have a beneficial effect on hepatic gluconeogenesis. It has been reported that both oral and transdermal estrogen therapies suppress hepatic glucose production (30, 34). Fasting glucose tests reflect glucose secretion by the liver, while the 2-hour postchallenge glucose test reflects muscle insulin action (44). Since we did not measure 2-hour postchallenge glucose or fasting insulin levels, we are unable to determine the effect of hormone therapy on peripheral insulin resistance. Our findings are consistent with trials of hormone therapy in postmenopausal women with type 2 diabetes mellitus that found decreased fasting glucose levels (3, 4, 12, 34) or decreased hemoglobin A1c levels (16, 45) among those randomly assigned to hormone therapy compared with those assigned to placebo.

Previous prospective studies of population-based cohorts have found that approximately 25% to 29% of persons with impaired fasting glucose progress to diabetes over a 5- to 11.5-year period (46, 47). We found that 25% of women with impaired fasting glucose assigned to hormone therapy and 37% of those assigned to placebo progressed to diabetes within 4 years of follow-up. It is likely that women enrolled in HERS had a higher risk for diabetes because of older age, higher body weight, less physical activity, concurrent metabolic disturbances, and possibly use of certain drugs associated with incident diabetes (48, 49). However, we performed separate mediation analyses for each of the four classes of cardiac medications and found that hazard ratios were almost identical for each class of agent as for the four classes combined.

Our findings were based on a post hoc analysis and therefore should be viewed with caution. Moreover, our results may not be generalizable to all postmenopausal women since HERS included only women with known CHD who had natural menopause. Repeated measurement of abnormal glucose levels is generally suggested for diagnosis of diabetes (50). We were limited to the use of three measurements of fasting glucose level during the entire study period; no oral glucose tolerance test was performed, and no 2-hour postchallenge glucose levels were obtained. A single fasting glucose test at each follow-up interval could have overestimated the incidence of diabetes. However, because no 2-hour postchallenge glucose levels were obtained during the trial, a diagnosis of diabetes could have been missed in approximately one third of our study sample (51, 52).

The strengths of our study include the large number of postmenopausal women studied; the double-blind, placebo-controlled study design; and the long follow-up (>4 years). In addition, few participants were lost to follow-up. We used a conservative approach to analyses and interpretations. Since adherence to study medication after 4 years of intervention was moderate in both the intervention and placebo groups, we analyzed the data as intention to treat as well as per protocol and found similar results using both methods.

In this 4-year clinical trial, women receiving hormone therapy had a significantly lower risk for diabetes. This difference was primarily due to prevention of the increase in fasting glucose level that occurred in women who received placebo. Postmenopausal women at high risk for incident diabetes, such as those with impaired fasting glucose, may benefit from hormone therapy. However, this potential benefit must be weighed against early risk for coronary events seen with initiation of hormone therapy (29, 53, 54), the threefold increased risk for venous thromboembolic events (55), and increased risk for breast cancer with long-term use (54, 56). For these reasons, hormone therapy is not a viable approach to diabetes prevention in women with heart disease. This finding is consistent with current clinical guidelines stating that hormone therapy should not be used for secondary prevention of CHD (57). Nevertheless, our data allude to important metabolic benefits of hormone therapy that should be studied in more detail. Greater understanding of the mechanisms by which these benefits are achieved could lead to the development of novel regimens that do not carry the risks of conventional hormone therapy.

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Acknowledgments: The authors thank members of the HERS Coordinating Center and the Executive Committee for their review and recommended revisions. They also thank Dr. Ira D. Goldfine for recommended revisions.

Grant Support: In part by the Department of Health and Human Services (Faculty Development in General Internal Medicine grant 1D08PE50109-01). The Heart and Estrogen/progesterin Replacement Study is funded by Wyeth-Ayerst Research.


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Obtaining of funding: A.M. Kanaya, D. Grady, E. Barrett-Connor.
Administrative, technical, or logistic support: A.M. Kanaya, D. Grady.