Effect of Estrogen Plus Progestin on Progression of Carotid Atherosclerosis in Postmenopausal Women With Heart Disease

HERS B-Mode Substudy

Robert P. Byington, Curt D. Furberg, David M. Herrington, J. Alan Herd, Donald Hunninghake, Maureen Lowery, Ward Riley, Timothy Craven, Lily Chaput, Christine C. Ireland, William B. Applegate, for the HERS Research Group*

Objective—The Heart and Estrogen/Progestin Replacement Study (HERS) found no overall effect of estrogen plus progestin (compared with placebo) on coronary event rates in 2763 postmenopausal women with established coronary disease (mean 4.1 years of follow-up). In addition to the events trial, a carotid ultrasound substudy was established in 1993 to be conducted concurrently to determine whether hormone therapy affects the progression of the underlying atherosclerotic process.

Methods and Results—Within the larger HERS, a subset of 362 participants underwent carotid B-mode ultrasound examinations at baseline and the end of follow-up. Progression of carotid atherosclerosis was measured as the temporal change in intimal-medial thickness (IMT).

Conclusions—IMT progressed in the hormone treatment and placebo groups, although there was no statistical difference between the rates: IMT progressed 26 μm/y (95% CI 18 to 34 μm/y) in the hormone group and 31 μm/y (95% CI 21 to 40 μm/y) in the placebo group (P=0.44). There were also no significant treatment effects when the results were examined by carotid segment or were adjusted for covariates. These data support the American Heart Association recommendation that women with established coronary disease should not initiate hormone therapy with an expectation of atherosclerotic benefit.

Key Words: women ■ secondary prevention ■ hormone therapy ■ carotid artery disease ■ atherosclerosis

Numerous observational studies have documented that compared with nonusers, users of postmenopausal hormone replacement have lower rates of coronary events and less extensive coronary and carotid atherosclerosis. Estrogen therapy can decrease LDL cholesterol (LDL-C), increase HDL cholesterol (HDL-C), improve endothelial function, and favorably affect other factors thought to play a role in the pathogenesis of atherosclerosis. Estrogen also inhibits the development of atherosclerosis in animal models.

Despite the abundance of data from observational studies suggesting that estrogen should be beneficial for the prevention of coronary heart disease (CHD), the Heart and Estrogen/Progestin Replacement Study (HERS), the first large randomized trial examining secondary prevention with hormones in women, found no effect of estrogen plus progestin (E+P) on the rate of CHD events in women with established coronary disease over an average treatment period of 4.1 years. It was originally noted that within the overall null effect, there were more coronary events in the hormone-treated group in the first year of follow-up and fewer coronary events in years 3 through 5. In an extended posttrial observational follow-up, however, there was no evidence of differences in CHD outcomes between the 2 treatment groups.

To examine the effects of estrogen plus medroxyprogesterone acetate on the progression of atherosclerotic disease, a prespecified substudy was established in 1993 in which a subset of HERS participants underwent carotid B-mode ultrasound examinations at baseline and at the end of the treatment period. This report describes changes in carotid wall thickness by treatment group in this substudy.

Methods

The trial design and baseline characteristics of the HERS cohort have been described elsewhere. Briefly, HERS was a randomized, double-masked, placebo-controlled trial designed to test the long-term efficacy and safety of E+P for the prevention of recurrent major coronary events. A total of 2763 postmenopausal women without recent hormone exposure and with an intact uterus were recruited from 18 clinical centers in the United States. To be eligible,
women had to have established CHD as evidenced by a history of myocardial infarction (MI), coronary artery bypass graft surgery, percutaneous transluminal coronary angioplasty, other mechanical revascularization, or a ≥ 50% angiographic occlusion of a major coronary artery. Participants were randomized to receive either 0.625 mg conjugated equine estrogen plus 2.5 mg medroxyprogesterone acetate in 1 tablet daily or matching placebo, and they were followed for an average of 4.1 years. The primary outcome measure for the trial was the first occurrence of new or recurrent nonfatal MI or CHD death.

The HERS B-Mode Ultrasound Substudy was designed to be conducted concurrently with the main events trial. Because of the smaller sample size requirements of an ultrasound trial (compared with an events trial), only 5 HERS clinical centers were needed for the substudy (listed in the Appendix). Eligible women in these centers who were willing to participate in the B-mode substudy had 2 ultrasound scans of the carotid arteries at baseline and 2 during the last months of follow-up. The primary measure of the extent of carotid atherosclerosis was the average maximum intimal-medial thickness (IMT) measured across 8 wall segments: the near and far walls of the common carotid and the bifurcation on the right and left sides of the neck. The methodology and quality control of the procedures used by HERS B-mode ultrasonography reading centers have been described elsewhere.18 IMT measurements were obtained by using high-resolution B-mode ultrasound with the Biosound Phase 2 system (Biosound), including an S-VHS videocassette recorder, a study flow panel, and a personal computer. Sonographers at each clinical center were centrally trained and certified. Masked readings of scans were performed by certified readers in a B-mode reading center.

The progression of carotid atherosclerosis was measured by the temporal change of the mean of the 8 maximum IMT measurements. The prespecified primary test of a treatment group effect was a simple t test of the difference in the change in mean overall IMT from baseline to follow-up. Two secondary analyses (outcomes) included t tests of treatment group differences in IMT change in the common carotid and carotid bifurcation arteries, respectively. Mirroring these simple analyses, mixed effects models were constructed to adjust for clinical center, ultrasound reader, and participant age. These models contained fixed effects for treatment, clinic, reader, age, visit (baseline versus follow-up), and visit-by-treatment interaction. Subgroup analyses were also conducted by using baseline and follow-up participant characteristics as covariates and stratifying factors in the mixed models. All analyses followed the intention-to-treat principle.

As a test of the relationship between IMT and clinical events in the women with a baseline scan, univariate and multivariate logistic models were constructed with baseline IMT as an independent variable and the primary HERS outcome measure (nonfatal MI plus fatal CHD) as the dependent variable.

**Results**

Of the 2763 women participating in the main trial, 454 (16%) had a baseline ultrasound measurement. At the end of the follow-up period, repeat scans were obtained from 362 (80%) of these women. Of the 92 women without a follow-up scan (46 in both groups), 32 women refused to come in for a clinic visit, and 18 were in nursing homes or were too sick to come to the clinic. The remaining 42 had died (25 E+P and 17 placebo subjects), and this 9.3% death rate (42 of 454 women) is similar to the 9.2% rate in the main trial.19 The mean length of follow-up for the women participating in the B-mode substudy was 3.8 years (range 3.2 to 4.7 years), or ≈ 3 months shorter than the mean for the overall trial.

The baseline characteristics of the 362 women with baseline plus follow-up scans (177 E+P and 185 placebo subjects) are described in Table 1. For comparison, the characteristics of the entire study population are also presented. There was no statistically significant difference (at P < 0.05) between the treatment groups in any baseline characteristic. IMTs progressed in the hormone and placebo groups, although this progression was primarily in the bifurcation (Table 2). The overall IMT (the primary outcome) progressed 26 μm/y (95% CI 18 to 34 μm/y) in the hormone group and 31 μm/y (95% CI 21 to 40 μm/y) in the placebo group (P = 0.44). There were no significant treatment effects when the results were examined by carotid segment (common carotid or bifurcation) or when the results were adjusted for clinical center, reader, and age of participant. However, there was a nonsignificant trend in the adjusted analyses toward slower IMT progression in the bifurcation (1 of the 2 secondary outcomes) among women on active therapy (39 μm/y for E+P group versus 57 μm/y for placebo group, P = 0.06).

The HERS investigators previously reported that hormone use among the 2763 randomized participants was associated with a 14% decrease in LDL-C and an 8% increase in HDL-C.14 Similar treatment effects were also noted among the 362 women in the B-mode substudy. In the hormone group, LDL-C dropped 16%, from 3.78 mmol/L (146.3 mg/dL) at baseline to 3.19 mmol/L (123.2 mg/dL) at 1 year; in the placebo group, LDL-C fell 3%, from 3.76 to 3.63 mmol/L (145.3 to 140.4 mg/dL, P = 0.001 for treatment group difference at 1 year). HDL-C rose 7% in the hormone group, from 1.29 mmol/L (49.9 mg/dL) at baseline to 1.38 mmol/L (53.2 mg/dL) at 1 year; in the placebo group, HDL-C fell 3%, from 1.28 to 1.23 mmol/L (49.4 to 47.7 mg/dL, P = 0.001 for treatment group difference at 1 year). Statin use also increased during follow-up among the 362 substudy participants, although statistically significant differences between the treatment groups were not noted. In the hormone group, statin use increased from 34% at baseline (Table 1) to 56% during the trial; in the placebo group, statin use increased from 39% to 62% during the trial. At the last clinic visit, 48% of the hormone group and 54% of the placebo group were on statin therapy (P = 0.30).

Because of these observations and because of the known effects of statins on the progression of IMT,20–22 the B-mode ultrasound adjusted progression rates were stratified by baseline and follow-up use of statins and baseline and follow-up LDL-C and HDL-C levels (Table 3). There was no evidence in any subgroup of a treatment group difference. There was also no evidence of a treatment group difference when the progression rates were stratified by baseline levels of Lp(a), the ratio of total cholesterol to HDL-C, non–HDL-C levels, or triglyceride levels.

Treatment group comparisons of the overall progression rates were also examined in other subgroups defined by baseline characteristics. These characteristics included age, smoking status, body mass index, exercise frequency, blood pressure level, prior use of estrogen, use of β-blockers, aspirin, or calcium channel blockers, and history of MI, diabetes, or bypass surgery. Also, in postrandomization analyses, the effect of compliance to study medication on any possible treatment effect was examined. There was no evidence of a treatment group difference in the progression of
carotid IMT in any subgroup of the HERS cohort (data not shown).

**Discussion**

In this subset of HERS participants, there was no significant effect of 3.8 years of treatment with hormone replacement on the progression of carotid atherosclerosis as measured by B-mode ultrasound. Given that previous studies have demonstrated regression of carotid atherosclerosis associated with the use of a lipid-lowering statin,20,22 the observed progression of IMT in the HERS hormone group is inconsistent with what might be expected because of the 16% reduction in LDL-C in that group. However, these results are consistent with the overall null effect of hormone replacement therapy (HRT) on clinical cardiovascular events in HERS and the lack of an apparent treatment effect of HRT on angiographic progression of existing coronary atherosclerosis in the Estrogen Replacement and Atherosclerosis (ERA) trial.23 Thus, the present study suggests that hormones may not be effective for secondary prevention of coronary atherosclerosis in postmenopausal women.

Despite the overall null results, there are patterns within the data that deserve mention. Among women not on statins during the trial, there was a nonsignificant trend toward less

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**TABLE 1. Baseline Characteristics of Participants in HERS B-Mode Substudy**

<table>
<thead>
<tr>
<th>Baseline demographics</th>
<th>Entire Cohort of Overall Trial (N=2763)</th>
<th>Women With Baseline and Follow-Up Scans (N=362)</th>
<th>Treatment Group Assignment*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean, y</td>
<td>67</td>
<td>67</td>
<td>67</td>
</tr>
<tr>
<td>White, %</td>
<td>89</td>
<td>88</td>
<td>90</td>
</tr>
<tr>
<td>Coronary heart disease risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>13</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Systolic blood pressure, mean, mm Hg</td>
<td>135</td>
<td>135</td>
<td>135</td>
</tr>
<tr>
<td>Diastolic blood pressure, mean, mm Hg</td>
<td>73</td>
<td>73</td>
<td>73</td>
</tr>
<tr>
<td>LDL-C, mean, mmol/L (mg/dL)</td>
<td>3.75 (145)</td>
<td>3.78 (146)</td>
<td>3.78 (146)</td>
</tr>
<tr>
<td>HDL-C, mean, mmol/L (mg/dL)</td>
<td>1.29 (50)</td>
<td>1.29 (50)</td>
<td>1.29 (50)</td>
</tr>
<tr>
<td>Triglyceride, mean, mmol/L (mg/dL)</td>
<td>1.87 (166)</td>
<td>1.91 (170)</td>
<td>1.87 (166)</td>
</tr>
<tr>
<td>Lp(a), mean, μmol/L (mg/dL)</td>
<td>1.21 (34)</td>
<td>1.11 (31)</td>
<td>1.11 (31)</td>
</tr>
<tr>
<td>Years since last menstrual period, mean</td>
<td>18</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>Body mass index&gt;=27 kg/m², %</td>
<td>56</td>
<td>57</td>
<td>58</td>
</tr>
</tbody>
</table>

**Coronary heart disease manifestations**

| Signs of congestive heart failure, % | 9                                       | 9                                       | 9                          |
| Percutaneous coronary revascularization, % | 45                                      | 44                                      | 47                          |
| Coronary artery bypass graft surgery, % | 41                                      | 47                                      | 45                          |
| Q wave myocardial infarction, % | 17                                      | 16                                      | 19                          |
| Self-reported MI (told by physician), % | 61                                      | 57                                      | 53                          |

**Medication use**

| Prior postmenopausal estrogen use, % | 23                                      | 21                                      | 21                          |
| Aspirin, %                           | 79                                      | 80                                      | 79                          |
| β-blockers, %                        | 33                                      | 35                                      | 36                          |
| Calcium channel blockers, %         | 55                                      | 52                                      | 49                          |
| Angiotensin-converting enzyme inhibitors, % | 17                                      | 14                                      | 15                          |
| Diuretics, %                         | 28                                      | 26                                      | 23                          |
| Lipid-lowering medications, %       | 46                                      | 44                                      | 41                          |
| Statins, %                           | 36                                      | 36                                      | 34                          |

**Carotid IMT**

<table>
<thead>
<tr>
<th>Mean of means across carotid walls, μm</th>
<th>Across all 8 Walls</th>
<th>1402</th>
<th>1403</th>
<th>1401</th>
</tr>
</thead>
<tbody>
<tr>
<td>Across 4 common carotid walls</td>
<td>–</td>
<td>1193</td>
<td>1180</td>
<td>1205</td>
</tr>
<tr>
<td>Across 4 bifurcation walls</td>
<td>–</td>
<td>1622</td>
<td>1637</td>
<td>1608</td>
</tr>
</tbody>
</table>

*No difference between the treatment groups achieved a P<0.10.
initially free of disease but not to slow the progression in animals that were minimally atherosclerotic development in animals that were recently completed carotid ultrasound trial of hormone therapy (EPAT). In the right distal far wall of the common carotid artery, the Estrogen in the Prevention of Atherosclerosis Trial recently completed carotid ultrasound trial of hormone therapy (EPAT). Among women who were treated with estrogen (the primary EPAT outcome), 2 years of oral 17β-estradiol (1 mg) slowed IMT progression compared with placebo but only in those women not on lipid-lowering (predominantly statin) therapy (P = 0.002). Among women who were treated with lipid-lowering medications, no further benefit was realized with the addition of estrogen (P > 0.2). This statistically significant treatment effect in the EPAT women not on lipid-lowering therapy was observed despite having fewer participants (122 women in this subgroup) and a shorter period of follow-up than HERS. It should be noted that EPAT was a primary prevention trial of women who at baseline likely had less subclinical atherosclerosis and a healthier endothelium than women in HERS. (Another primary prevention trial, the Postmenopausal Hormone Replacement Against Atherosclerosis [PHOREA] trial also reported that 1 year of HRT was not effective in slowing IMT progression, although they did not report subgroup findings.)

In animal models, estrogen replacement has been shown to minimize atherosclerosis development in animals that were initially free of disease but not to slow the progression in animals with established atherosclerosis. At least one of the direct effects of estrogen on the vessel wall, inhibition of LDL uptake, appears to depend on the presence of a healthy endothelium. Thus, estrogen replacement may simply be ineffective in slowing atherosclerosis in older women with established disease or abnormal endothelial function.

Other agents tested in placebo-controlled trials have been shown to be effective in slowing or reversing the progression of carotid IMT in participants with established CHD. For example, in a post hoc analysis of the Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries (PLAC)-II data, the lipid-lowering agent pravastatin slowed the 3-year progression of common carotid and carotid bifurcation IMT by 23% in 151 patients (23 women and 128 men) with documented coronary disease (P = 0.02). In the Asymptomatic Carotid Artery Progression Study (ACAPS), lovastatin reversed the 3-year progression of common carotid, carotid bifurcation, and internal carotid IMT in 919 participants (49% women) at high risk of coronary disease (P = 0.001). In a post hoc subgroup analysis, lovastatin plus warfarin significantly reversed IMT progression (P = 0.01) in 328 women in the ACAPS trial who were not on estrogen replacement therapy. Similarly, compared with placebo, the calcium channel antagonist amlodipine had a significant effect (P = 0.007) in reversing the 3-year progression of common carotid, carotid bifurcation, and internal carotid IMT in 373 patients (80% male) with documented coronary disease in PREVENT, although it also had no effect on the angiographic progression of coronary disease (P = 0.38). (The angiographic outcome was the primary outcome in PREVENT, whereas the B-mode outcome was a secondary outcome.)

HERS and PREVENT were concurrently run trials that used the same B-mode ultrasound reader center. The scanning and reading protocols were nearly identical, although the PREVENT protocol also included scanning the near and far walls of the internal carotids and required follow-up scans every 6 months for 36 months. To test whether the more frequent and comprehensive examinations might explain why PREVENT had a statistically significant result (P = 0.007) and HERS did not (P = 0.44), the extra walls and examinations were removed from the PREVENT database, and the data were reanalyzed. Amlodipine continued to have a statistically significant effect on slowing IMT progression (P = 0.05), suggesting that the larger, longer HERS substudy could have demonstrated a treatment effect if one truly existed.

There are limitations to this HERS substudy. The main HERS trial examined only 1 type, dose, and route of administration of estrogen (oral CEE 0.625 mg/d) that was...
administered with a concurrent progestin (MPA 2.5 mg/d). It is possible that other HRT regimens might be more effective. In addition, the evaluation of therapy in the HERS substudy may have been too short for an HRT effect to become apparent. Finally, perhaps the results would have been different in the setting of primary prevention or if the women were younger or closer to menopause.

In conclusion, in postmenopausal women with established coronary heart disease, treatment for 3.8 years with estrogen plus MPA had no significant effect on progression of carotid IMT. These data support the recent American Heart Association recommendation that women with established CHD should not initiate HRT with an expectation of atherosclerotic benefit. More information is needed about the potential effects of HRT and the development of atherosclerosis in healthy women. In the meantime, the mainstays of primary and secondary prevention of coronary artery disease in women should include therapies proven to slow the progression of anatomic and clinical disease, such as lipid lowering, when indicated.

### Appendix

#### Participating Investigators and Institutions in HERS B-Mode Ultrasound Substudy

HERS Clinical Centers Participating in Substudy: Baylor College of Medicine, Houston, Tex (J.A. Herd); University of Tennessee, Memphis (W. Applegate, K. Johnson, S. Satterfield, and F. Ling); University of Miami, Miami, Fla (M. Lowery); University of Minnesota Heart Disease Prevention Clinic, Minneapolis (D. Hunninghake, J. Olson, and L. Lau); and Wake Forest University School of Medicine, Winston-Salem, NC (D.M. Herrington and P.C. Sharp).

Ultrasound Reading Center: Wake Forest University School of Medicine, Department of Neurology, Winston-Salem, NC (W. Riley, T. Crotts, L. Hoots, and M. Spainhour).

Substudy Data Analysis Center: Wake Forest University School of Medicine, Department of Public Health Sciences, Winston-Salem, NC (R.P. Byington, C.D. Furberg, S. Wilmoth, G. Evans, and T. Craven).

### TABLE 3. Adjusted Annualized Change in Overall Carotid IMT by Statin Use and Level of LDL-C and HDL-C

<table>
<thead>
<tr>
<th>Statin Use</th>
<th>Across 8 Carotid Walls</th>
<th>Placebo Group</th>
<th>E+P Group</th>
<th>$P$ of Tx Grp Diff</th>
<th>$P$ for Tx×Covariate Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Across 8 carotid walls</td>
<td>23±6</td>
<td>29±6</td>
<td>0.31</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>On statin at BL</td>
<td>21±10</td>
<td>27±9</td>
<td>0.54</td>
<td>0.80</td>
<td></td>
</tr>
<tr>
<td>Not on statin at BL</td>
<td>24±7</td>
<td>30±7</td>
<td>0.43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>On statin during trial</td>
<td>22±8</td>
<td>25±8</td>
<td>0.70</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td>Never on statin</td>
<td>26±8</td>
<td>36±9</td>
<td>0.23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>On statin at last visit</td>
<td>25±8</td>
<td>24±8</td>
<td>0.89</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>Not on statin at last visit</td>
<td>23±8</td>
<td>36±9</td>
<td>0.10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BL LDL-C

≥3.70* | 27±8 | 27±8 | 0.99 | 0.054 |
<3.70 | 20±8 | 29±8 | 0.30 | |

FU LDL-C

≥3.35* | 28±8 | 28±8 | 0.91 | 0.74 |
<3.35 | 24±8 | 33±9 | 0.27 | |

BL HDL-C

≥1.24* | 28±8 | 29±8 | 0.94 | 0.78 |
<1.24 | 15±8 | 28±8 | 0.10 | |

FU HDL-C

≥1.27* | 27±8 | 33±9 | 0.66 | 0.91 |
<1.27 | 22±8 | 32±8 | 0.18 | |

Values are mean change±SE, mm/y, adjusted for clinic, reader, and age. Mean length of B-mode follow-up=3.8 years.

*Baseline and follow-up-specific cut-point values for LDL-C and HDL-C are medians for both treatment groups combined. Follow-up lipids calculated as mean of 1st and 4th annual (post-randomization) lipid values.

Lipid values presented as mmol/L: LDL-C 3.70 mmol/L = 143.2 mg/dL; LDL-C 3.35 mmol/L = 129.7 mg/dL; HDL-C 1.24 mmol/L = 48.0 mg/dL; HDL-C 1.27 mmol/L = 49.3 mg/dL.

Lipids were handled as continuous variables in interaction models.

Tx indicates treatment; BL, baseline; FU, follow-up.

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References
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