Effect of Oral Postmenopausal Hormone Replacement on Progression of Atherosclerosis
A Randomized, Controlled Trial

Peter Angerer, Stefan Störk, Wolfgang Kothny, Philip Schmitt, Clemens von Schacky

Abstract—Postmenopausal hormone replacement therapy (HRT) is associated with low cardiovascular morbidity and mortality in epidemiological studies. Yet, no randomized trial has examined whether HRT is effective for prevention of coronary heart disease (CHD) in women with increased risk. The objective of this study was to determine whether HRT can slow progression of atherosclerosis, measured as intima-media thickness (IMT) in carotid arteries. Carotid IMT is an appropriate intermediate end point to investigate clinically relevant effects on atherogenesis. This randomized, controlled, observer-blind, clinical, single-center trial enrolled 321 healthy postmenopausal women with increased IMT in ≥1 segment of the carotid arteries. For a period of 48 weeks, subjects received either 1 mg/d 17β-estradiol continuously plus 0.025 mg gestodene for 12 days every month (standard-progestin group), or 1 mg 17β-estradiol plus 0.025 mg gestodene for 12 days every third month (low-progestin group), or no HRT. Maximum IMT in 6 carotid artery segments (common, bifurcation, and internal, both sides) was measured by B-mode ultrasound before and after intervention. HRT did not slow IMT progression in carotid arteries. Mean maximum IMT in the carotid arteries increased by 0.02±0.05 mm in the no HRT group and by 0.03±0.05 and 0.03±0.05 mm, respectively, in the HRT groups (P>0.2). HRT significantly decreased LDL cholesterol, fibrinogen, and follicle-stimulating hormone. In conclusion, 1 year of HRT was not effective in slowing progression of subclinical atherosclerosis in postmenopausal women at increased risk. (Arterioscler Thromb Vasc Biol. 2001;21:262-268.)

Key Words: atherosclerosis ■ carotid arteries ■ hormones ■ prevention ■ women

Observational studies consistently found a 30% to 35% decreased risk of coronary heart disease (CHD) among postmenopausal women who use hormone replacement therapy (HRT).1,2 There is no evidence that HRT influences the risk of stroke.3 Several effects of estrogen on the cardiovascular system suggest a potential for protection.4 The only randomized trial with clinical end points (Heart and Estrogen/ progestin Replacement Study, HERS) failed to demonstrate the efficacy of estrogen plus medroxyprogesterone for secondary prevention in women with CHD.5 Among other reasons, medroxyprogesterone acetate, which is known to attenuate some of the beneficial effects of estrogen,6–9 has been discussed as a cause for the unexpected results of HERS.10 Initiation of HRT after myocardial infarction is no longer recommended.11 To date, no randomized trial has addressed the efficacy of HRT for women with increased risk for CHD who potentially benefit most, as indicated by epidemiological data.1,12

Intima-media thickness (IMT) of the carotid arteries correlates with the presence, extent, and severity of atherosclerosis in coronary and other arteries.13–17 IMT of the carotid arteries consistently and partially independently of traditional risk factors predicts future myocardial infarction and stroke.18–22 Change of carotid IMT is currently an established intermediate end point for clinical trials that study the inhibitory effect of an intervention on atherogenesis.23,24

The present randomized, controlled, observer-blind trial investigated the hypothesis that HRT with estrogen and progestin inhibits progression of carotid artery IMT in postmenopausal women with increased IMT as a sign of subclinical disease and increased risk for CHD and stroke. It was further hypothesized that the inhibitory effect of estrogen balanced with low-dose progestin would be superior to the combination with high-dose progestin.

Methods

Subjects
Between March 1995 and September 1996, women living in the greater Munich area who heard about the study through the local media contacted us for more detailed information (Figure). They were eligible if they had passed natural (cessation of bleeding) or surgical menopause for ≥1 year or, in case of hysterectomy, had follicle-stimulating hormone (FSH) levels >40 IU/L, were between 40 and 70 years old, had >1 mm IMT in ≥1 of the predefined segments of the carotid arteries, and gave informed consent. (For exclusion criteria, please see supplemental Methods section at http://atvb.ahajournals.org).
Subjects were randomized if they gave informed consent ≥24 hours after the screening visit. The study was approved by the local ethics committee of the faculty of medicine of the University of Munich. It was conducted according to the International Conference for Harmonisation—Guidelines for Good Clinical Practice (ICH-GCP). An independent clinical research organization (Biometrisches Zentrum für Therapiestudien, Munich, Germany) monitored adherence to the study protocol, verified all source data, and provided the verified database. It also ensured blinding of the ultrasound reader.

Study Design and Treatment

Postmenopausal HORMone REPLacement against Atherosclerosis (PHOREA) was a randomized, controlled, observer-blind, single-center trial in the setting of a university hospital outpatient center. Subjects were randomized to 3 groups: The HRT group with standard (high)-dose progestin (HRT 1) received tablets containing 1 mg of 17β-estradiol per day continuously, with addition of 0.025 mg gestodene on days 17 to 28 of each 4-week cycle. The HRT group with low-dose progestin (HRT 2) differed from HRT 1 in that gestodene was added in each third cycle only. The no-HRT group received no estrogen or progestin, also excluding topical application. General health advice and treatment of hypertension and of elevated LDL followed the guidelines of the American Heart Association.

Randomization and Blinding

To ensure even distribution of major cardiovascular risk factors (hypertension, diabetes mellitus, smoking, LDL >150 mg/dL), subjects were allocated to 1 of 2 strata: 0 to 2 risk factors or ≥3 risk factors. Subjects were then randomized within the stratum. The clinical research organization provided and maintained computer software for randomization at the trial center. To ensure blindness of sonographers with respect to treatment, their contact with the participant was limited to the ultrasound examination. On all recordings, a 5-digit random number replaced the name of the subject and the date of examination. The keyed list containing names, dates, and 5-digit numbers was stored at the clinical research organization until the closing of the file.

Ultrasound Outcome Measures

Atherosclerosis was measured as thickness of the intimal and medial layers of the carotid artery on both sides, visualized by high-resolution 7.5-MHz ultrasound (Apogee CX Color, ATL). An MRI 413 tissue-mimicking phantom was used to monitor instrument performance. Three segments were defined: the distal 10 mm of the common carotid artery, the carotid bifurcation from the widening of the artery up to the flow divider, and the proximal 10 mm of the internal carotid artery. Only measurements of the wall far from the probe were considered for calculation of outcome measures, for 2 reasons: ultrasound measurement of the near wall underestimates the true histological thickness, and the visualization of the near wall was often not possible in sufficient quality, as has been reported from other trials.

Subjects were examined supine with a small pillow under the neck. At baseline, the sonographer first scanned the complete circumference of each segment by transverse and longitudinal interrogation. The optimal longitudinal view of the maximum IMT in sufficient quality, ie, clear blood-intima and media-adventitia boundaries over the full length of the segment, was recorded digitally, and the angle of interrogation was noted. After 48 weeks, the scan was repeated following the same protocol, with special attention to the optimal angle previously defined. Only segments visualized on both occasions were used for calculated variables.

Sonographers (W.K. and P.A.) had completed a training program with >1000 scans of carotid arteries before the trial. All readings were done by W.K. In addition, to assess reproducibility, rescans were performed in 30 subjects within 1 week after the baseline or follow-up scan and evaluated blindly, as described above. In Table 1, reproducibility is expressed as the mean difference between 2 measurements and its SD.

IMT was measured from the digitized image twice and averaged at the site of its maximum extent within each segment by means of the software NIH-Image (National Institutes of Health) on a Power Macintosh 8100/80 with a high-resolution screen. The intima-media area was measured over the full length of the carotid bifurcation and reported as mean area of the right and left sides. The mean of maximum far wall IMT values for all segments was calculated as mean maximum IMT per subject. The highest IMT of all carotid far wall segments is presented as single maximum IMT per subject. The change of carotid mean maximum IMT during treatment in the intention-to-treat population was the primary outcome measure, and the changes of the other ultrasound variables were secondary outcome measures.

Other Outcome Measures and Variables

At baseline, a complete history was taken and a clinical examination performed, including a gynecological examination by the subjects' personal gynecologists, which was repeated at follow-up. For the HRT 2 group, a transvaginal ultrasound of the endometrium before and after the trial was required for safety reasons. At each visit, blood pressure was measured semiautomatically (Dinamap, Johnson & Johnson Medical Inc), with the subject recumbent after 5 minutes of rest, and an extended laboratory workup was carried out. LDL was calculated according to the Friedewald formula. Changes of LDL and HDL were secondary outcome measures. At each visit, medication and behavioral risk factors, and at each follow-up visit, all adverse events were documented. (For definitions, please see http://atvb.ahajournals.org).

The study medication was dispensed at each visit, and all blister packages and all remaining tablets were collected during the subsequent visits. Subjects documented daily intake of the study drug and vaginal bleeding in a diary.

Statistical Analysis

Sample size was estimated for the primary intention-to-treat analysis to achieve a power of 90% and a value of $P=0.05$. Based on the assumption of 50% less progression in the carotid mean maximum
TABLE 2. Reasons for Study Discontinuation

<table>
<thead>
<tr>
<th>Reason</th>
<th>No HRT</th>
<th>HRT 1</th>
<th>HRT 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assumed side effects of HRT (mastalgia, abdominal pain, headache, weight gain, nausea, vaginal bleeding)</td>
<td>9</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Menopausal complaints (hot flushes, night sweats)</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject’s decision</td>
<td>2</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>New occurrence of a disease defined as exclusion criterion (breast cancer, leukemia, depression)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Violation of inclusion criteria (not postmenopausal)</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Additional HRT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death (intracerebral bleeding)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
<td>21</td>
<td>23</td>
</tr>
</tbody>
</table>

Values are numbers of subjects.

IMT under HRT, given that the progression is 0.05±0.05 mm/y without HRT (mean of 2 published progression rates32,33), 80 subjects per group were required, resulting in 320 subjects altogether after addition of the estimated dropout rate of 33%.

The intention-to-treat population was defined as all randomized subjects. The valid case population included only subjects who did not violate any eligibility criteria at randomization or during the study, took $\geq 91.7\%$ (11 cycles) of the study medication, and did not use any additional HRT preparations (including topical application) during the trial.

Normality and homogeneity of variances of the outcome measures were assessed by Lilliefors test and Levene’s test, respectively. Differences between HRT 1 and no HRT and between HRT 2 and no HRT were examined by independent sample $t$ test or $\chi^2$ test, according to the nature of the data. For the analysis of the primary outcome measure, the $P$ value was adjusted for multiple comparisons according to the Bonferroni-Holm method. For secondary outcome measures, no adjustment was made, because the analysis was exploratory. All calculations were performed on a Power Macintosh 7600/120 using SPSS 6.1.1 (SPSS Inc).

Results

Baseline Data

Of 321 randomized subjects, 264 remained in the study and had a second ultrasound examination after 48 weeks (Figure). Fifty-seven subjects ended participation prematurely; their reasons are given in Table 2.

Subjects who ended participation prematurely resembled subjects who completed the trial in most characteristics, with the exception of a higher number of hysterectomies and longer duration of previous HRT use in subjects in the no HRT group who stopped and lower values for these characteristics in subjects in the HRT 2 group who stopped (Table I, please see http://atvb.ahajournals.org).

Among the 264 subjects who completed participation, there was no difference between treatment groups except for fewer previous hysterectomies in the no HRT and HRT 2 group compared with HRT 1 and a lower number of subjects with a family history of CHD in the HRT 1 group compared with HRT 2 (Table I, please see http://atvb.ahajournals.org). All the following results apply to the 264 subjects who completed participation.

Ultrasound Outcome Measures

Mean maximum IMT in the carotid arteries increased in all groups, by 0.03±0.05 mm (mean of all groups±SD). The increase in both HRT groups was greater than in the no HRT group. None of the differences in ultrasound primary and secondary outcome measures were statistically significant (Table 3).

Other Outcome Measures

LDL and fibrinogen decreased in both HRT groups and increased slightly in the no HRT group, the difference in change between HRT and no HRT groups being statistically significant. HDL decreased slightly in all groups, with the smallest change in the HRT 2 group (Table 4).

Other Characteristics

Changes of factors that potentially influence IMT (plasma glucose, blood pressure, weight, physical activity, and lipid-lowering medication) were distributed similarly among treatment groups across follow-up (Table 4). The number of current smokers remained lower in the HRT groups ($P=0.033$ for comparison between no HRT and HRT 1).

Compliance, Valid Case Analysis, and Subgroup Analysis

FSH decreased by $\approx 33\%$ in the HRT groups, whereas it increased slightly in the no HRT group. According to entries in the diary, 97.5% of the HRT 1 and 97.6% of the HRT 2 group took the study medication in $\geq 44$ of 48 weeks. Among subjects randomized to no HRT, 10.8% used systemic or topical hormones at some time during the trial. In the no HRT group, 72 subjects were considered valid cases; in the HRT 1 group, 69; and in the HRT 2 group, 73 (ie, 214 of 264). Valid case analysis of the ultrasound outcome measures yielded results very similar to the intention-to-treat analysis (Table 3, bottom).

To detect any influence of uneven distribution of baseline characteristics on ultrasound outcome measures, exploratory analysis was performed in subgroups defined by previous hysterectomy (yes/no), family history of CHD (yes/no), and current smoking (yes/no). The potential influence of previous HRT was also examined by subgroup analysis (HRT in the previous 6 months: yes/no). There was no difference between HRT groups and the no HRT group in any subgroup.
Thus, the lack of an effect of HRT on IMT in the present randomized investigation indicates that HRT does not inhibit atherogenesis to the extent that one would have expected from observational studies.

A lower dose of progesterin (HRT 2) did not result in a more beneficial effect on IMT. An advantage of minimizing the progesterin dose necessary to balance estrogen in women with intact uterus has been suggested on the basis of observational studies, animal experiments, and trials on lipid metabolism. Our results, however, do not support this assumption.

Systematic bias in epidemiological studies on HRT may have resulted in an overestimation of its benefit in preventing cardiovascular disease. To date, only very few randomized studies on postmenopausal women have dealt with the effect of HRT on cardiovascular and cerebrovascular events, all with negative results: In HERS, treatment with oral estrogen plus progesterin did not reduce the overall rate of coronary events in postmenopausal women with CHD during an average follow-up of 4.1 years. Pooled data on cardiovascular events from published randomized trials that studied other outcome measures (mostly bone-related) showed a nonsignificantly higher odds ratio for women taking HRT than for those not taking HRT.

An observational study compared postmenopausal women with and without HRT in the placebo group of the Asymptomatic Carotid Atherosclerotic Progression Study (ACAPS), which investigated the effect of lovastatin and warfarin in a randomized, factorial design. HRT use was associated with regression and no HRT use with progression of carotid IMT. If this difference in progression rate had been due to HRT and not explained by unmeasured risk factors or chance, would we have been able to detect it? Using the observed

Exclusion of subjects who took lipid-lowering medication during the trial did not alter the results.

### Adverse Events

Serious adverse events are listed in Table 5: 1 death of intracerebral bleeding occurred in the HRT 2 group. Breast cancer was diagnosed in 1 subject in the no HRT group. There was 1 hysterectomy in the no HRT group (due to a descensus uteri). There was no incident of deep venous thrombosis, thrombophlebitis, or thromboembolism.

Breast tenderness and spotting was significantly more frequent in both HRT groups than the no HRT group. Abdominal pain occurred more frequently in the HRT 1 group but not in the HRT 2 group compared with no HRT.

### Discussion

The present randomized, controlled trial examined the influence of 2 HRT regimens balanced with standard and with low-dose progesterin against no HRT on progression of IMT in carotid arteries. Among postmenopausal women with increased IMT as a sign of subclinical atherosclerosis and an above-average number of risk factors, neither HRT regimen slowed IMT progression within 1 year. As expected, HRT decreased LDL and fibrinogen but had no effect on HDL.

Progression of carotid IMT is diminished by lipid-lowering drugs. At the same time, there is clear evidence that these drugs decrease cardiovascular morbidity and mortality in men and women without CHD, in the same magnitude as the decrease attributed to HRT by observational data. Thus, the lack of an effect of HRT on IMT in the present randomized investigation indicates that HRT does not inhibit

### Table 4. Other Outcome Measures: Absolute Change From Baseline During Treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>No HRT (n=93)</th>
<th>HRT 1 (n=86)</th>
<th>HRT 2 (n=85)</th>
<th>P Value 1†</th>
<th>P Value 2‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>0.08±0.55</td>
<td>−0.34±0.61</td>
<td>−0.33±0.73</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(3.0±21.4)</td>
<td>(−13.3±23.4)</td>
<td>(−12.9±28.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>−0.09±0.21</td>
<td>−0.07±0.32</td>
<td>0.00±0.27</td>
<td>&gt;0.2</td>
<td>&gt;0.028</td>
</tr>
<tr>
<td>(−3.5±8.2)</td>
<td>(−2.67±12.4)</td>
<td>(−0.2±11.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>0.07±0.89</td>
<td>−0.21±2.34</td>
<td>0.02±0.82</td>
<td>&gt;0.2</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>(6.4±79.1)</td>
<td>(−18.9±207.0)</td>
<td>(1.8±72.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrinogen (mg/L)</td>
<td>0.07±0.41</td>
<td>−0.21±0.48</td>
<td>−0.20±0.43</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(7±41)</td>
<td>(−21±48)</td>
<td>(−20±43)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose (mg/L)</td>
<td>−0.21±2.19</td>
<td>−0.13±1.49</td>
<td>−0.05±1.02</td>
<td>&gt;0.2</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>(−3.9±39.4)</td>
<td>(−2.3±26.8)</td>
<td>(−0.9±18.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSH (IU/L)</td>
<td>5±23</td>
<td>−24±27</td>
<td>−17±26</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>0.9±3.3</td>
<td>−0.0±3.3</td>
<td>−0.2±3.9</td>
<td>0.061</td>
<td>0.042</td>
</tr>
<tr>
<td>Blood pressure systolic (mm Hg)</td>
<td>−6.5±11.0</td>
<td>−6.1±12.4</td>
<td>−9.2±11.3</td>
<td>&gt;0.2</td>
<td>0.106</td>
</tr>
<tr>
<td>Blood pressure diastolic (mm Hg)</td>
<td>−1.5±8.0</td>
<td>−2.8±7.7</td>
<td>−3.2±8.4</td>
<td>&gt;0.2</td>
<td>0.164</td>
</tr>
<tr>
<td>Physical activity, h/wk</td>
<td>−0.3±2.0</td>
<td>−0.3±1.9</td>
<td>−0.6±2.4</td>
<td>&gt;0.2</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>Current smokers at last follow-up, n (%)</td>
<td>21 (22.6)</td>
<td>9 (10.6)</td>
<td>10 (11.8)</td>
<td>0.033</td>
<td>0.057</td>
</tr>
<tr>
<td>Subjects on lipid-lowering medication during follow-up, n (%)</td>
<td>14 (15.1)</td>
<td>11 (12.8)</td>
<td>11 (12.9)</td>
<td>&gt;0.2</td>
<td>&gt;0.2</td>
</tr>
</tbody>
</table>

†P indicates plasma; S, serum.

*Mean of all follow-up visits minus baseline unless otherwise indicated (positive values indicate increase). Plus-minus values are mean±SD.

‡P value 1: no HRT vs HRT 1.

‡P value 2: no HRT vs HRT 2.
progression (0.025±0.051 mm) of mean maximum IMT in the carotid arteries and the given sample size (n=264), we would have detected a minimal difference between groups of 0.024 mm with a power of 90%. Thus, it is very unlikely that we would have missed any regression in the HRT groups. In ACAPS, the difference between HRT users and nonusers appeared after 6 months and was significant on an annual basis. Effects of lipid-lowering therapy on carotid IMT appeared after 6 months and was significant on an annual basis. To the best of our knowledge, there are no data indicating that the biological effects of the HRT in the present trial are comparable to those of standard therapy.

The variability of IMT measurements in our study is within the lower range of reported studies. The correlation of IMT measured by the technique used in this trial and in the Atherosclerosis Risk in Communities (ARIC) study, ie, mean maximum IMT of 6 far wall sites in carotid arteries, to concurrent coronary atherosclerosis and to future CHD incidence is good. Potentially atheroprotective actions of estrogens are only partly elucidated but seem to be largely independent of effects on cholesterol metabolism. In animal studies, an attenuated response to injury and a diminished progression of atherosclerosis in coronary arteries were observed. By contrast, recent studies in women indicated a proinflammatory potential of HRT by increased C-reactive protein concentration, which in turn predicts atherosclerotic complications. Thus, the net effect on atherosclerosis may be insignificant, as found in our study. Conversely, there is evidence of rapid and long-term vasodilatory actions of estrogens from experimental studies. Controlled trials examining other surrogate cardiovascular parameters demonstrated (although not uniformly) beneficial effects of HRT on endothelial function and systemic vascular compliance in healthy women and exercise capacity in women with CHD. Thus, the decrease of cardiovascular mortality observed in epidemiological studies may well be mediated by other mechanisms than inhibition of atherogenesis.

### Limitations

Subjects and their physicians were not blinded with respect to treatment, because HRT is frequently accompanied by minor side effects that hamper valid blinding. Furthermore, vaginal bleeding requires different treatment depending on whether it occurs while on or off HRT. Because IMT can be measured independently of the subjects’ awareness, bias seems very unlikely but cannot be completely excluded. Blinding of the sonographer and the reader of IMT images was ensured by a meticulous protocol monitored by an external institution. Because epidemiological studies observed beneficial effects mainly in women on oral HRT, we used this route of administration. Although the influence of oral versus transdermal estrogen on cholesterol, blood coagulation factors, and hemodynamic variables is similar to or superior, only transdermal estrogen lowered triglycerides. Thus, different routes of administration may influence atherosclerosis differently. On the basis of IMT measurements, we can draw a conclusion on atherogenesis but not on other mechanisms by which HRT may lower the risk for myocardial infarction and stroke. Findings from a recent observational study indicate that HRT reduces the risk of sudden cardiac death. This awaits further study.

### Conclusions

The present trial showed that in a population of clinically healthy postmenopausal women with increased IMT as a sign of subclinical atherosclerotic disease and increased risk for
CHD and stroke, HRT did not slow progression of atherosclerosis.

Acknowledgments

This trial was supported by a grant from the Münchener Univer-

sitätsgesellschaft, München, made possible by Schering AG, Berlin. The study medication was also provided by Schering AG.

References


Effect of Oral Postmenopausal Hormone Replacement on Progression of Atherosclerosis: A Randomized, Controlled Trial

Peter Angerer, Stefan Störk, Wolfgang Kothny, Philip Schmitt and Clemens von Schacky

doi: 10.1161/01.ATV.21.2.262

*Arteriosclerosis, Thrombosis, and Vascular Biology* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/21/2/262

Data Supplement (unedited) at:
http://atvb.ahajournals.org/content/suppl/2001/01/18/21.2.262.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Arteriosclerosis, Thrombosis, and Vascular Biology* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Arteriosclerosis, Thrombosis, and Vascular Biology* is online at:
http://atvb.ahajournals.org//subscriptions/