Hormone Replacement Therapy and Peripheral Arterial Disease

The Rotterdam Study

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Background: As the number of elderly women increases in Western society, peripheral arterial disease (PAD) is likely to become an increasing problem. Hormone replacement therapy, suggested to protect against coronary atherosclerosis, might also inhibit the development of PAD.

Methods: The association between hormone replacement therapy and the presence of PAD was studied in a population-based study consisting of 2196 naturally postmenopausal women aged 55 to 80 years living in a suburban area of Rotterdam, the Netherlands. Peripheral arterial disease was defined as an ankle/arm systolic blood pressure index (ratio of the systolic blood pressure at the ankle to the systolic blood pressure at the arm) lower than 0.9.

Results: Hormone replacement therapy for 1 year or longer was associated with a 52% decreased risk of PAD (odds ratio, 0.48 [95% confidence interval, 0.24-0.85]), while no association was found for therapy duration shorter than 1 year (odds ratio, 0.97 [95% confidence interval, 0.58-1.63) after adjustment for age, smoking, and socioeconomic status. Additional adjustment for body mass index, age at menopause, total cholesterol and high-density lipoprotein cholesterol, alcohol intake, and frequency of visits to health care facilities did not change the results.

Conclusion: The findings of this population-based study suggest that hormone replacement therapy given for a year or more is associated with a decreased risk of PAD among postmenopausal women.

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Peripheral arterial disease (PAD) is a growing clinical and public health issue among elderly women. Prevalence rates have been estimated to range from 6% to 25% among women older than 55 years, and increase sharply with age. With the relatively large expected increase in the number of elderly women compared with elderly men, women will make up most of the patients with PAD in the next century. Several studies have demonstrated that patients with PAD, with or without complaints of intermittent claudication, are at an increased risk of cardiovascular morbidity and mortality compared with people without PAD.1 Evidence from observational studies suggests that hormone replacement therapy (HRT) reduces morbidity and mortality from cardiovascular disease among postmenopausal women.2,3 Recently, a randomized trial involving women with coronary heart disease showed no effect of HRT on the incidence of coronary heart disease after 4 years of treatment (the Heart and Estrogen/progestin Replacement Study [HERS]).4 However, an increased risk of coronary heart disease events was found in the HRT group in the first year of the trial, and the risk decreased in subsequent years. This might be explained by an immediate prothrombotic, proarrhythmic, or proischemic effect of treatment, which is gradually outweighed by a beneficial effect on the progression of atherosclerosis. Thus, a protective effect of this treatment may be present on the development of atherosclerotic disease, but data are scarce.

We investigated the association between the use of HRT and the presence of atherosclerosis in the peripheral arteries by measuring the ankle/arm systolic blood pressure index (AAI) (ratio of the systolic blood pressure at the ankle to the systolic blood pressure at the arm) in 2196 naturally postmenopausal women, aged 55 to 80 years of age, participating in the Rotterdam Study.5
PATIENTS AND METHODS

The Rotterdam Study5 is a prospective population-based follow-up study of 7983 subjects 55 years and older designed to assess the occurrence of chronic diseases in an aging population, and to clarify their determinants. During the first survey, from 1990 to 1993, all participants were interviewed at home by a trained research assistant and visited the study center for clinical examination. A second visit to the study center took place in 1993-1994. The study was approved by the Medical Ethical Committee of Erasmus University, and all participants gave informed consent.

Interview information included medical history, current medication, smoking habits, alcohol intake, highest attained level of education, and age at last menstruation. At the study center, height and weight were measured. Serum total cholesterol and high-density lipoprotein cholesterol levels were assessed by an automated enzymatic procedure. Random and postload serum glucose levels were assessed after an oral glucose tolerance test. Ultrasonographic measurements of carotid plaques were done in all women, and measurement of the carotid artery intima-media thickness in a random subgroup of women.

The presence of PAD was assessed at baseline. Systolic blood pressure was calculated as the mean of 2 consecutive measurements at the right brachial artery while the patient was in a sitting position. A single systolic blood pressure reading was taken both at the left and the right posterior tibial artery as described previously.6 The AAI was calculated for each leg. Peripheral arterial disease was considered present when the AAI was lower than 0.9 on at least 1 side, or not measurable because the vessel could not be found, indicating low flow or occlusion of the artery.

In the baseline interview questions (1990-1993), the use of female hormones for menopausal complaints and duration of use were asked. More information on the use of female hormones was collected by a questionnaire in the first follow-up visit to the study center in 1993 and 1994, on average 2.2 years after baseline. In this questionnaire, information was collected on medication for menopausal complaints, medication after an operation of the womb/ovaries, and specific information on type and brand of medicines for menopausal complaints, medication after an operation of the womb/ovaries, and specific information on type and brand of medicines. Information from both the first and the second visit were used for classification of subjects. At baseline, 571 women reported the use of female hormones for menopausal complaints. Twenty-six women reported the use of both estrogens and progestins in addition to estrogens. Thirty-one women (9%) were recent HRT users. Twenty-six women reported use of progestins in addition to estrogens. Thirty-two women (9% of the 351 users) reported use of progestins in addition to estrogens.

Of the 2196 women in the study population, 351 reported use of female hormones in the first follow-up visit’s questionnaire, but they were not sure what type of medication this was, and they had not reported use of female hormones in the baseline interview; these women were classified as possible users. Women reporting the use of only vaginal creams or ovules were classified as nonusers. Thus, 692 (18%) of women were classified as users of female hormones. Seventy-four of these women reporting to have continued use of female hormones in the period between the baseline and the follow-up visit were classified as recent HRT users.

As data on use of HRT were mainly obtained in the second follow-up round, for this study only women participating in the second follow-up round (n=3784; 78%) were considered. Of these, women were excluded who reported reaching menopause by surgery or irradiation of the womb/ovaries (n=719) or who were older than 80 years (n=496). Thus 2569 women remained in the study. The AAI was not determined in 349 (13.6%) of these women: 128 of them did not visit the research center, and in 221, the systolic blood pressure (n=1), the systolic ankle blood pressure (n=182), or both (n=28) were not measured. These women were older, were more often current smokers, and had a lower equivalent household income.

Eight women with an AAI higher than 1.5 were excluded because this AAI usually reflects arterial rigidity preventing arterial compression, which leads to spuriously high ankle blood pressure values. Information on use of HRT was missing in 8 women. Thus, 2190 women remained for analyses.

Analysis of covariance adjusted for age was used to compare continuous variables between groups. Smokers were categorized as current, past, or never smokers, and additional adjustment was made for the number of pack-years (the number of years of smoking multiplied by the number of cigarettes smoked daily). Educational level was divided into 4 categories: primary education, lower general education and/or lower vocational education, intermediate vocational education, and higher education (university). Analyses were stratified for short-term (<1 year) and long-term (≥1 year) hormone use. For further stratification, numbers were inadequate. Logistic regression analysis was used to calculate relative risks of PAD for HRT users compared with nonusers. All odds ratios (ORs) are presented with 95% confidence intervals (CIs). The ORs derived from logistic regression analyses were used as an approximation of relative risk. Reported P values are 2 sided.

Analyses were performed using BMDP software (BMDP Statistical Software Inc, Los Angeles, Calif).

RESULTS

Of the 2196 women in the study population, 351 reported undergoing HRT (16.0%). The duration of therapy ranged from 1 to more than 15 years. Thirty-two women (9% of users) reported use of progestins in addition to estrogens. Thirty-one women (9%) were recent HRT users.

Age was comparable in the 3 study groups (Table 1). Users of HRT had a lower systolic blood pressure, were more often past smokers, and had a higher frequency of visits to health care facilities in the last month than subjects never undergoing HRT. Both short-term and long-term users were more often past smokers.

Mean (SD) AAI was 1.08 (0.19), and 284 women had an AAI lower than 0.9 (12.9%; 95% CI, 11.5-14.3). Age, systolic blood pressure, total cholesterol levels, glucose levels, the percentage of current smokers, and among smokers the number of pack-years of smoking, were all significantly higher in women with PAD (Table 2).

Of the 351 users of HRT, 34 had PAD, compared with 247 of 1837 of the subjects never undergoing the treatment. Logistic regression analysis with adjustment
for age showed that, overall, subjects undergoing HRT had a 30% lower risk of PAD (Table 3). While HRT duration of less than 1 year was not associated with a protective effect, durations of 1 year or longer were associated with a statistically significant 47% reduction of risk. Adjustment for smoking, number of pack-years smoked, and level of education increased the protective effect to 52%. Additional adjustment for body mass index, alcohol intake, age at menopause, levels of total and HDL cholesterol, or the number of visits to health care facilities in the last month did not change the risk estimates. When repeating the analyses after exclusion of women reporting recent HRT to assess the effect in past HRT users only, a similar association was found (OR, 0.39; 95% CI, 0.20-0.80). Also excluding women classified as probable or possible HRT users did not change our results (OR, 0.42; 95% CI, 0.20-0.88).

Among 31 recent users, 3 women (9%) had PAD; among the 32 HRT users taking progestins, 3 (9%) had PAD.

Our results show a lower risk of atherosclerosis in the peripheral arteries in subjects undergoing at least 1 year of HRT compared with nonusers. However, before we interpret these results, several issues need to be addressed. In a study of elderly subjects there is always the possibility of selection bias. Women had to survive until at least age 55 years to be in our study. If more women who never used female hormones died of atherosclerotic complications before the start of our study, this may have led to an underestimation of the effect. The AAI gives a good indication of atherosclerosis in the lower limbs, assessing the adequacy of blood flow through the peripheral arteries. In the Rotterdam Study, the most commonly used cutoff point of 0.9, as suggested and validated by Fowkes, is used for the definition of PAD. Low AAI and PAD have been shown to be associated with preclinical carotid atherosclerosis and to predict cardiovascular mortality in elderly women and
The mean value of the AAI in this population was 1.08. The prevalence of PAD was 12.9%. This is comparable to values reported in other studies.\textsuperscript{6,7,11-15}

The AAI was not determined in 349 women. Women without AAI measurements differed from the women with measurements in several respects. It is a frequent finding in population studies that responders are younger than nonresponders. Also, these factors may be related to reasons for missing AAI measurements, being primarily bandaged ankles in subjects with edema of the ankle. Furthermore, it cannot be excluded that, despite the strict protocol, a number of these women were accidentally misclassified as missing because of unmeasurably low flow in the peripheral arteries. However, this does not bias our results, because the use of HRT did not differ between these women and women with measurements.

Several studies\textsuperscript{16,17} have demonstrated that undergoing HRT therapy, estrogen users are healthier than never users, even prior to use of replacement therapy. This supports the hypothesis that part of the apparent benefit associated with HRT is owing to preexisting characteristics of the HRT users. We cannot exclude the possibility that some (or the whole) of our findings are based on this selection bias. In our study we dealt with the issue of confounding in the following ways. We stratified for duration of hormone use and found that among women who used female hormones for a period of less than a year (although they were similar to long-term users in several socioeconomic and risk factors), no association was found with the presence of PAD. This reduces, but does not fully exclude, the probability of selection bias. Furthermore, we adjusted for known risk factors. We measured the current status of risk factors, while the exposure to HRT had largely taken place in the past. Socioeconomic status (level of education), is a major confounder, but remains relatively stable over time. The frequency of visits to health care facilities (possibly representing health-conscious behavior now and in the past) differed between ever and never users of HRT, but adjustment did not change our results. Smoking habits might have changed over time, but misclassification of smoking habits would have given an underestimation of the effect because HRT users were more frequently smokers. Body mass index and alcohol intake may undergo changes with age, and it could be that some residual confounding remained after adjustment. We do not expect the latter to have a large effect on our results, however, because of the relatively weak associations of these factors with PAD, especially in women.\textsuperscript{8,18}

Assessment of use of HRT by interview might have led to misclassification. Goodman et al\textsuperscript{20} showed a moderate to substantial agreement between HRT patients and physicians on the use of estrogens, and no differential misclassification with disease status of the subject in women up to age 74 years.\textsuperscript{20} The reported frequency and duration of use was similar to that in studies in perimenopausal women in the Netherlands, where 12% of women between 45 and 65 years old underwent HRT and 50% of women discontinued use within 1 year.\textsuperscript{21-23} The most frequently prescribed hormone therapy in the studied period was unopposed estrogen therapy in a dose of 0.625 mg daily.\textsuperscript{24} Progestins were added in 0.9% of prescriptions in 1970, and the use of progestins gradually increased to 11% in 1986. Our observation of 9% agrees with this.

If inhibition of atherosclerosis were the mechanism through which estrogens exert their protective effect on the cardiovascular system, an association between increasing duration of HRT and decreasing risk of atherosclerosis would be expected. However, in our study this association was not found. In parallel, most, but not all other studies on atherosclerosis and cardiovascular disease did not find this association.\textsuperscript{23-30} Possibly misclassification of use of HRT can account for this, particularly in an elderly population as in the Rotterdam Study.

The finding that HRT inhibits development of atherosclerosis in the coronary arteries and aorta has been reported in several animal studies.\textsuperscript{31,32} In women, 2 of 3 angiography studies showed a lower degree of coronary atherosclerosis in HRT users compared with never users.\textsuperscript{33-35} Another study, using ultrasonographic examination, found lower degrees of atherosclerosis of the carotid arteries, aorta, and iliac arteries in 40 users of combined replacement therapy compared with never users.\textsuperscript{36} Most studies, however, focused on comparing current users with never users. The effect of past use of female hormones was studied in the Cardiovascular Health Study,\textsuperscript{25} which showed no significant differences in intima-media thickness between past users and never users.\textsuperscript{25} No tests were performed for differences in AAI between past and never users. The Cardiovascular Health Study finding that current users had a significantly lower measure of intima-media thickness than never users could not be confirmed in the Atherosclerosis Risk in Communities Study.\textsuperscript{27} In our study the number of recent users was small, but exclusion of recent users from the analysis showed that prevalence of PAD was lower in past users compared to never users. Thus, our results suggest that the advantage in levels of atherosclerosis

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### Table 3. Relative Risk of Peripheral Arterial Disease Associated With Hormone Replacement Therapy Among Postmenopausal Women With Natural Menopause Aged 55 to 80 Years\textsuperscript{*}

<table>
<thead>
<tr>
<th>HRT</th>
<th>No. of Cases</th>
<th>No. of Subjects</th>
<th>Age-Adjusted Relative Risk†</th>
<th>Multivariate-Adjusted Relative Risk‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>247</td>
<td>1837</td>
<td>1.00 (Reference)</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>Short-term (&lt;1 y)</td>
<td>20</td>
<td>157</td>
<td>0.97 (0.60-1.60)</td>
<td>0.97 (0.58-1.63)</td>
</tr>
<tr>
<td>Long-term (≥1 y)</td>
<td>13</td>
<td>169</td>
<td>0.53 (0.30-0.93)</td>
<td>0.48 (0.24-0.85)</td>
</tr>
<tr>
<td>All</td>
<td>34</td>
<td>351</td>
<td>0.70 (0.48-1.02)</td>
<td>0.65 (0.44-0.98)</td>
</tr>
</tbody>
</table>

\textsuperscript{*}Relative risks are risk (95% confidence interval). HRT indicates hormone replacement therapy.
\textsuperscript{†}Adjusted for age using the logistic regression model.
\textsuperscript{‡}Adjusted for age, smoking, and education using the logistic regression model.
rosis for women who have used HRT remains present after discontinuation of therapy. Only 1 large randomized placebo-controlled trial on the effects of HRT has been conducted. This trial in women with diagnosed cardiovascular disease showed no favorable effect of HRT on the prevention of incident coronary heart disease after 4 years of follow-up. This might indicate that bias in observational studies is larger than originally thought. On the other hand, in the trial an increased risk for coronary heart disease events was found in the HRT group in the first year of the trial, while risk decreased in subsequent years. This time trend can be explained by an immediate prothrombotic, proarrhythmic, or proischemic effect of treatment that is gradually outweighed by a beneficial effect on the progression of atherosclerosis. Thus, the results of the HERS trial support the theory that HRT can inhibit the development of atherosclerosis. Furthermore, in HERS the effect of opposed estrogen was studied, while in our study mainly unopposed estrogen was used. Progestins have been shown to have unfavorable effects on several determinants of cardiovascular disease, which may have contributed to the absence of a positive trial result. As the number of elderly women increases in Western society, PAD is likely to become an increasing problem. The results of this study suggest that the use of HRT after menopause might protect against the development of PAD later in life. Confirmation of these findings should be provided through randomized trials including PAD as an outcome measure.

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