Hormone Replacement Therapy and Distensibility of Carotid Arteries in Postmenopausal Women: A Randomized, Controlled Trial

Peter Angerer, MD, Wolfgang Kothny, MD, Stefan Störk, MD, Clemens von Schacky, MD
Munich, Germany

OBJECTIVES
The study objective was to clarify in a randomized, controlled, observer-blind trial whether hormone replacement therapy (HRT) improves elastic properties of the common carotid artery in women with signs of subclinical atherosclerosis, especially in subgroups with increased risk, and whether less progestin enhances the effect.

BACKGROUND
Previous observational studies have yielded conflicting results on the influence of HRT on central arteries. Some studies reported improvement of distensibility by estrogen alone or in the subgroup of smokers.

METHODS
A total of 321 postmenopausal women were randomized to 1 mg 17β-estradiol plus 0.025 mg gestodene for 12 days every month (HRT 1), or 1 mg 17β-estradiol plus 0.025 mg gestodene for 12 days every third month (HRT 2), or no-HRT, during 48 weeks. In 173 women, distensibility of the common carotid artery was determined before and after therapy by M-mode ultrasound and brachial blood pressure measurement.

RESULTS
Change of distensibility was small and similar in the three treatment groups. In the subgroup of current smokers, HRT 2 (low progestin) increased distensibility by 32% (HRT 2: 8.2 ± 11.7; HRT 1: 0.6 ± 6.0; no-HRT: −1.8 ± 6.8 × 10⁻³/kPa, p = 0.025 for no-HRT vs. HRT 2). In the subgroups with elevated blood pressure, high low density lipoprotein (LDL) cholesterol, or high age, no effect of HRT was detected.

CONCLUSIONS
This randomized intervention study demonstrates that long-term HRT with estrogen and progestin does not substantially influence distensibility of central arteries. Yet, in currently smoking postmenopausal women, HRT with low progestin seems to improve distensibility; this merits further study in a specifically designed trial. (J Am Coll Cardiol 2000;36:1789–96) © 2000 by the American College of Cardiology

Distensibility, the inverse of stiffness, denotes the ability of an artery to expand as a response to pulse pressure (1). Independently from established risk factors, low distensibility of central elastic arteries, mainly aorta and common carotid artery, is related to a high risk of future all-cause and cardiovascular mortality in high-risk patients (2) and the development of hypertension in the normal population (3). Furthermore, a wide pulse pressure, which is largely determined by arterial stiffness (1), is an independent predictor of coronary heart disease (CHD) morbidity, CHD mortality, and all-cause mortality in healthy populations (4,5) and in patients with CHD (6). Distensibility of central arteries can be determined noninvasively in the common carotid artery (CCA) by means of ultrasound and brachial blood pressure measurement (7,8). This method has been widely used to identify persons at risk for hypertension and CHD (3,9,10).

During menopause, distensibility of aorta and CCA decreases rapidly (11,12). The influence of hormone replacement therapy (HRT) on these arteries has been the objective of several epidemiological studies with inconsistent results (13–18). Notably, whereas studies found no difference in distensibility between HRT users and controls in the entire sample, distensibility in estrogen users was significantly higher compared to estrogen plus progestin users (14,16) and in smokers on HRT compared to smokers not on HRT (16,19).

The aim of the present randomized, controlled, one-year intervention trial was to investigate the influence of HRT on the distensibility of central arteries in postmenopausal women with increased carotid intima media thickness (IMT) as sign of preclinical atherosclerosis. Based on findings of previous studies (20,21) it was assumed that HRT beneficially influences distensibility, that HRT with low progestin has a larger effect than HRT with high progestin and that the improvement is strongest in subjects with high CHD risk (high low density lipoprotein [LDL] cholesterol, high blood pressure, older age, smokers).

METHODS
Subjects. Between March 1995 and September 1996, women living in and near Munich were informed by various media (Fig. 1) of the HRT study. They were eligible if they were between 40 and 70 years of age, had passed natural or...
surgical menopause for at least one year or had follicle stimulating hormone (FSH) levels >40 IU/liter in case they were hysterectomized, had more than 1 mm IMT in at least one of the predefined segments of the carotid arteries and gave written informed consent. Women with myocardial infarction within the last six months, CHD that required treatment for angina, or any other contraindication against HRT, as well as women with conditions requiring HRT, were not eligible. 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 Harmonization–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. Members provided and maintained computer software for randomization at the trial center and ensured blinding of the ultrasound reader.

Study design and treatment. This study was embedded in the Postmenopausal HOmone REplacement against Atherosclerosis (PHOREA) trial, which was a randomized, controlled, observer-blind, single-center study. The primary outcome measure of the present study was the change of distensibility ([DC] distensibility coefficient) within 48 weeks, comparing each of the HRT groups with the no-HRT group. Secondary outcome measures were the change of DC in the following four subgroups: age greater than median; LDL greater than median; elevated blood pressure (mean of three measurements during M-mode: either diastolic >90 or systolic >140 mm Hg); current smokers.

Subjects were randomized to three groups: The HRT group with standard (high) dose progestin (= HRT 1) received tablets containing 1 mg of 17β-estradiol daily, with addition of 0.025 mg gestodene on days 17 to 28 of each four-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. The duration of treatment was 48 weeks (12 cycles). Women were seen as outpatients at study start, and in weeks 12, 22 and 48. At each visit, history, medication, behavioral

---

**Figure 1.** Trial profile. HRT = hormone replacement therapy; IMT = intima media thickness.

---

### Abbreviations and Acronyms
- BMI = body mass index
- CCA = common carotid artery
- CHD = coronary heart disease
- DC = distensibility coefficient
- ECG = electrocardiogram
- FSH = follicle stimulating hormone
- HRT = hormone replacement therapy
- IMT = intima media thickness
- LDL = low density lipoprotein cholesterol
risk factors and adverse events were documented, and an extended laboratory workup was carried out. General health advice and treatment of hypertension and of elevated LDL followed the guidelines of the American Heart Association (22). The study medication was dispensed at each visit, and all blisters and all remaining tablets were collected during the subsequent visits. In a diary, subjects documented both daily intake of the study drug and vaginal bleeding.

**Randomization and blinding.** Subjects were randomized in two strata according to whether they had 0 to 2, or more than two, cardiovascular risk factors in order to ensure their even distribution. To ensure blindness of sonographers with respect to treatment, their contact with the participant was limited to the ultrasound examination. On all recordings a five-digit random number replaced the name of the subject limited to the ultrasound examination. On all recordings a five-digit random number replaced the name of the subject.

**Ultrasound examination.** At baseline, the carotid arteries of all subjects were visualized in B-mode and M-Mode by means of a high-resolution 7.5-MHz ultrasound (Apogee CX Color, ATL, Bothel, Washington). First, the optimal longitudinal view of the maximum IMT of each side was recorded digitally. Then, after at least 20 min in relaxed supine position, the M-mode scan of the left and right common carotid artery (CCA) 10 mm proximal to the origin of the carotid bulb was recorded simultaneously with an electrocardiogram (ECG) for 20 s on S-VHS videotape. By applying only minimal pressure, the sonographers took care not to restrict the artery’s free movement. Blood pressure was measured by a semiautomatic device (Dynamap, Johnson & Johnson Medical, Arlington, Texas) at three times during the M-mode examination. After 48 weeks, the entire examination was repeated, following the same protocol and using the same angles of interrogation. Sonographers (W. K. and P. A.) had completed a training program with more than 1,000 scans of carotid arteries before the trial. Periodically during the trial, recorded scans were checked for visual quality by a panel comprising both sonographers and one other investigator (S.S.).

**Image analysis and calculation of CCA distensibility.**

After the end of the trial a single reader evaluated the digitized pictures of all M-mode scans. This person was blinded with respect to identity of the subject, temporal order of the scans and group assignment. All studies were read in random order. Systolic and end-diastolic diameters through three cardiac cycles were measured twice by means of NIH-image 1.52 (public domain software, National Institutes of Health, Bethesda, Maryland) on a Power Macintosh 8100/80 with a high-resolution screen. All diameter measurements of one artery were averaged, as were brachial blood pressure measurements. Distensibility was calculated according to the formula:

\[
DC = \frac{2}{D_d} \times \frac{\Delta D}{\Delta P}
\]

where \(DC\) is distensibility coefficient, \(D_d\) is diastolic diameter, \(\Delta D\) is difference between systolic and diastolic diameter, and \(\Delta P\) is pulse pressure. Distensibility of the left and right CCA was averaged. A subject’s distensibility was calculated only if both carotid arteries were visualized in sufficient quality over three cardiac cycles. Maximum IMT of the far wall of the CCA was measured from the digital image. Each measurement was done twice and averaged. All segments were read by one person (W.K.).

Following the same protocol, repeatability of DC measurement was assessed in 23 women by additional ultrasound examination within one week after the follow-up scan. As has been suggested (23), repeatability is expressed as mean difference and standard deviation (SD) of the difference between the DC measurements and was 1.9 ± 7.2 \times 10^{-3}/kPa. The correlation between replicate studies was \(r = 0.76\).

**Statistical analysis.** For the outcome measures, both normality and homogeneity of variances were assessed by the Lilliefors test and Levene 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-square test according to the nature of the data.

For analysis of the primary outcome measure, the \(p\) value was adjusted for multiple comparisons according to the Bonferroni-Holm method. For the secondary outcome measures, no adjustment was made, because the analysis was exploratory.

Change of distensibility within the treatment groups was not defined as outcome measure; it was examined by paired-samples \(t\) test in order to provide additional information. Pearson correlation coefficient was used to examine the relationship between baseline distensibility and other baseline variables. Because randomization was stratified, in additional analyses of the outcome measures the stratum was controlled for by analysis of variance (ANOVA). All calculations were performed on a Power Macintosh 7600/120 using SPSS 6.1.1 (SPSS Inc., Chicago, Illinois).

At the start of the trial, no epidemiological data were available for estimation of the effect of menopause or HRT on CCA distensibility. Therefore, sample size was estimated based on the assumption that the effect of HRT on carotid artery distensibility would approximate the difference between a healthy person and someone with a mild form of CHD. The ratio of SD to difference between the means for normal and CHD subjects had been demonstrated to be 1.6 for CCA distensibility (9). To obtain a power of 90% and a \(p\) value of 0.05, 54 subjects were needed in each group, plus 18 subjects to compensate for an estimated 33% drop-out rate (24). Because preparatory ultrasound examinations showed that M-mode scans meeting the quality criteria of the protocol could not be obtained in up to one third of the subjects, it was decided to perform M-mode scans in all PHOREA subjects to ensure sufficient statistical power.
Table 1. Characteristics of All Subjects and of Smokers at Baseline

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All Subjects (n = 173)</th>
<th>Smokers (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HRT 1 (n = 58)</td>
<td>HRT 2 (n = 61)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>58.6 ± 4.0</td>
<td>59.0 ± 4.3</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.9 ± 4.2</td>
<td>25.5 ± 4.1</td>
</tr>
<tr>
<td>Pack-years of cigarettes</td>
<td>28.6 ± 22.8</td>
<td>26.3 ± 25.0</td>
</tr>
<tr>
<td>Physical activity (hours/week)</td>
<td>1.6 ± 2.5</td>
<td>2.0 ± 2.4</td>
</tr>
<tr>
<td>Family history of CHD</td>
<td>21 (36.8%)</td>
<td>36 (59.0%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>20 (34.5%)</td>
<td>28 (45.9%)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>9 (15.5%)</td>
<td>10 (16.4%)</td>
</tr>
<tr>
<td>CHD</td>
<td>1 (1.7%)</td>
<td>1 (1.6%)</td>
</tr>
<tr>
<td>Antihypertensive medication</td>
<td>15 (25.9%)</td>
<td>21 (34.4%)</td>
</tr>
<tr>
<td>Lipid-lowering medication</td>
<td>4 (6.9%)</td>
<td>4 (6.6%)</td>
</tr>
<tr>
<td>Glucose (mmol/liter)</td>
<td>5.7 ± 2.6</td>
<td>5.7 ± 1.1</td>
</tr>
<tr>
<td>LDL (mmol/liter)</td>
<td>3.93 ± 0.92</td>
<td>3.85 ± 1.15</td>
</tr>
<tr>
<td>HDL (mmol/liter)</td>
<td>1.72 ± 0.49</td>
<td>1.82 ± 0.54</td>
</tr>
<tr>
<td>Triglycerides (mmol/liter)</td>
<td>2.38 ± 3.22</td>
<td>1.78 ± 1.17</td>
</tr>
<tr>
<td>Fibrinogen (g/liter)</td>
<td>2.85 ± 0.49</td>
<td>2.88 ± 0.59</td>
</tr>
<tr>
<td>Follicle stimulating hormone (IU/liter)</td>
<td>62 ± 26</td>
<td>61 ± 33</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>152.5 ± 23.5</td>
<td>153.5 ± 26.2</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>87.9 ± 13.3</td>
<td>85.7 ± 12.2</td>
</tr>
<tr>
<td>Pulse pressure (mm Hg)</td>
<td>64.6 ± 14.8</td>
<td>67.8 ± 19.0</td>
</tr>
<tr>
<td>Pulse rate (beats/min)</td>
<td>70 ± 9</td>
<td>70 ± 10</td>
</tr>
<tr>
<td>IMT of CCA (mm)</td>
<td>1.1 ± 0.2</td>
<td>1.0 ± 0.3</td>
</tr>
<tr>
<td>Diastolic diameter of CCA (mm)</td>
<td>6.92 ± 0.78</td>
<td>6.86 ± 0.65</td>
</tr>
<tr>
<td>Difference between systolic and diastolic diameter of CCA (mm)</td>
<td>0.71 ± 0.20</td>
<td>0.74 ± 0.19</td>
</tr>
<tr>
<td>Distensibility (DC) of CCA (×10^-3/kPa)</td>
<td>25.7 ± 11.4</td>
<td>26.2 ± 11.9</td>
</tr>
</tbody>
</table>

Values are mean ± SD or numbers (percent), respectively.
p Values for differences between treatment groups are >0.05 unless otherwise indicated: *HRT 2 vs. no-HRT; p = 0.049.

RESULTS

Baseline data. Randomization resulted in an even distribution of baseline characteristics among treatment groups, with the following exceptions: a family history of CHD was more frequent in HRT 2 than in HRT 1, and in the subgroup of smokers, LDL was lower in HRT 2 than in no-HRT (Table 1).

Subjects who had a follow-up ultrasound examination including distensibility measurement after 48 weeks (n = 173), those who had complete IMT measurements, but in whom distensibility measurement was not possible (n = 91), and those who ended participation prematurely (n = 57) did not differ with respect to the baseline characteristics listed in Table 1 (data not shown, all p values > 0.2), with the following exceptions: Subjects stopping the trial prematurely were more frequently current smokers (p = 0.006). Subjects with a complete set of DC measurements differed from those without only with respect to lower weight and body mass index (BMI; p = 0.045 and p = 0.027). Failure to obtain distensibility measurements was due to technical problems in 6 of these 91 subjects. In 85 subjects the M-mode scan could not be obtained in the required quality: in 31 subjects in both carotid arteries, and in 54 in one carotid artery. In the majority of these cases visualization was a problem at baseline and at follow-up examinations.

Among all variables listed in Table 1, smokers compared to nonsmokers had lower BMI (24.1 ± 3.4 vs. 25.9 ± 4.3 kg/m², p = 0.037), lower FSH (53 ± 14 vs. 62 ± 30 IU/liter, p = 0.019) and lower LDL (3.44 ± 0.74 vs. 3.89 ± 1.05 mmol/liter, p = 0.052).

Distensibility at baseline was inversely correlated with age (r = -0.194, p = 0.011), BMI (r = -0.182, p = 0.017), blood glucose (r = -0.149, p = 0.053), LDL (r = -0.189, p = 0.017) and IMT of the CCA (r = -0.193, p = 0.011). Distensibility at baseline was not correlated with FSH levels, nor with time of previous HRT use (36.7 ± 51.7 months; mean ± SD for all subjects). This was also true in the subgroup of smokers. No difference in distensibility was observed among present users of HRT (subjects who used HRT until randomization), past users and never-users of HRT.

Follow-up. After 48 weeks, distensibility did not change significantly within groups (all p > 0.2), and change was not significantly different between HRT groups and the no-
Table 2. Outcome Measures—All Subjects

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>HRT 1 (n = 58)</th>
<th>HRT 2 (n = 61)</th>
<th>no-HRT (n = 54)</th>
<th>HRT 1 vs. no-HRT</th>
<th>HRT 2 vs. no-HRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ Distensibility of CCA (DC) (×10⁻³ kPa)*</td>
<td>0.2 ± 11.6</td>
<td>0.9 ± 11.7</td>
<td>−0.2 ± 10.4</td>
<td>p &gt; 0.2</td>
<td>p &gt; 0.2</td>
</tr>
<tr>
<td>Δ Diastolic diameter of CCA (mm)</td>
<td>0.01 ± 0.57</td>
<td>0.02 ± 0.40</td>
<td>0.01 ± 0.53</td>
<td>p &gt; 0.2</td>
<td>p &gt; 0.2</td>
</tr>
<tr>
<td>Δ Difference between systolic and diastolic diameter of CCA (mm)</td>
<td>0.02 ± 0.22</td>
<td>0.00 ± 0.26</td>
<td>0.03 ± 0.22</td>
<td>p &gt; 0.2</td>
<td>p &gt; 0.2</td>
</tr>
<tr>
<td>Δ IMT of CCA (mm)*</td>
<td>0.03 ± 0.07</td>
<td>0.02 ± 0.06</td>
<td>0.01 ± 0.07</td>
<td>p &gt; 0.2</td>
<td>p &gt; 0.2</td>
</tr>
<tr>
<td>Δ Weight (kg)*</td>
<td>−0.1 ± 2.6</td>
<td>−0.4 ± 4.3</td>
<td>0.8 ± 3.6</td>
<td>p = 0.138</td>
<td>p = 0.134</td>
</tr>
<tr>
<td>Δ Systolic BP (mm Hg)*</td>
<td>−7.9 ± 24.2</td>
<td>−7.0 ± 22.7</td>
<td>−8.4 ± 23.0</td>
<td>p &gt; 0.2</td>
<td>p &gt; 0.2</td>
</tr>
<tr>
<td>Δ Diastolic BP (mm Hg)*</td>
<td>−6.0 ± 11.8</td>
<td>−3.7 ± 12.6</td>
<td>−6.3 ± 12.3</td>
<td>p &gt; 0.2</td>
<td>p &gt; 0.2</td>
</tr>
<tr>
<td>Δ Pulse pressure (mm Hg)*</td>
<td>−1.9 ± 16.6</td>
<td>−3.3 ± 15.0</td>
<td>−2.1 ± 14.8</td>
<td>p &gt; 0.2</td>
<td>p &gt; 0.2</td>
</tr>
<tr>
<td>Δ Glucose (mmol/liter)†</td>
<td>−0.1 ± 1.7</td>
<td>−0.1 ± 0.9</td>
<td>−0.4 ± 2.8</td>
<td>p &gt; 0.2</td>
<td>p &gt; 0.2</td>
</tr>
<tr>
<td>Δ LDL (mmol/liter)†</td>
<td>−0.32 ± 0.61</td>
<td>−0.27 ± 0.71</td>
<td>0.04 ± 0.60</td>
<td>p = 0.004</td>
<td>p = 0.020</td>
</tr>
<tr>
<td>Δ HDL (mmol/liter)†</td>
<td>−0.04 ± 0.27</td>
<td>−0.02 ± 0.29</td>
<td>−0.12 ± 0.22</td>
<td>p = 0.101</td>
<td>p = 0.048</td>
</tr>
<tr>
<td>Δ Triglycerides (mmol/liter)†</td>
<td>−0.23 ± 2.39</td>
<td>−0.04 ± 0.92</td>
<td>0.06 ± 1.05</td>
<td>p &gt; 0.2</td>
<td>p &gt; 0.2</td>
</tr>
<tr>
<td>Δ Fibrinogen (g/liter)†</td>
<td>−0.23 ± 0.44</td>
<td>−0.21 ± 0.45</td>
<td>0.03 ± 0.48</td>
<td>p = 0.005</td>
<td>p = 0.009</td>
</tr>
<tr>
<td>Δ Follicle stimulating hormone (IU/liter)†</td>
<td>−22 ± 20</td>
<td>−19 ± 25</td>
<td>7 ± 24</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
</table>

*Follow-up value at 48 weeks minus baseline value; †mean follow-up values at 12, 22, and 48 weeks minus baseline value.
CCA = common carotid artery; BP = blood pressure; DC = distensibility coefficient; HDL = high-density lipoprotein cholesterol; HRT = hormone replacement therapy; IMT = intima media thickness; LDL = low-density lipoprotein cholesterol.

HRT group (Table 2). Fibrinogen, LDL, and FSH decreased in both HRT groups but increased in the no-HRT group, with a significant difference in changes among groups (Table 2).

By contrast, in the small subgroup of 26 smokers, distensibility did not change significantly in the HRT 1 and the no-HRT group, but increased in the low-progestin HRT 2 group by 32% (within-group p = 0.086; between HRT 2 and no-HRT; p = 0.025) (Table 3, Fig. 2). In both HRT groups, there was an increase in LDL, and the decrease in fibrinogen and FSH were smaller than the decrease observed in the entire sample, the changes not being significantly different among the groups (Table 3).

In the three other subgroups defined by increased LDL (>3.7 mmol/liter, n = 81)—increased blood pressure (>140 systolic or 90 diastolic, n = 78), and age over 59 (n = 74)—the change in distensibility was not significantly different among groups (all p > 0.2).

Because randomization was stratified, an additional analysis controlling for the stratum was conducted. Results
remained virtually unchanged with only the difference in change of distensibility between HRT 2 and no-HRT in smokers being significant (p = 0.029), whereas all other differences in change of distensibility among groups were not significant (all p > 0.02).

**Serious adverse events.** One death occurred in the HRT 2 group owing to intracerebral bleeding in a patient with a history of poorly controlled hypertension. Breast cancer was diagnosed in one subject in the no-HRT group. There was one hysterectomy in the no-HRT group. No incidents of deep venous thrombosis or thromboembolism occurred; there were no cases of myocardial infarction or ischemic stroke.

**DISCUSSION**

Hormone replacement therapy did not alter CCA distensibility after 48 weeks in postmenopausal women, with signs of early atherosclerosis indicated by increased carotid artery IMT, regardless whether a high or a low dose of progestin was used. In the subgroup of smokers, but not in the other three predefined subgroups, HRT with low-dose progestin significantly improved CCA distensibility, whereas the improvement by high-progestin HRT was not significant.

Our results refute our hypothesis but are in line with several previous studies—namely that no difference was found between CCA DC of HRT users and nonusers (16). Aortic size, but not aortic compliance, was influenced by HRT in a small randomized trial (25). Pausing and recomencing HRT changed pulse-wave velocity of peripheral, but not of central, arteries (17). Recently published randomized trials (26–28) did not find the beneficial cardiovascular effects of HRT that were suggested in earlier epidemiological studies (20). Potential selection bias in epidemiological research has been discussed (29).

Examining the discrepancy between the present randomized study and previous epidemiological studies (18,30), two main issues should be considered. First, did our study miss any relevant effect due to its sample size? Post hoc recalculation of the study power showed that under the given conditions a difference in change of DC of $6.5 \times 10^{-5}$ kPa corresponding to a difference of 25% could have been detected with a power of 90% and a $p < 0.05$. This is comparable to the a priori estimation. Stiffness was 21% higher in nonusers than in users of HRT in one positive study (18). The other positive study reported a 13% difference in stiffness between women with and without HRT, and a 7% increase as early as after four weeks of HRT withdrawal (30). Menopause caused a 33% decrease in aortic root distensibility within three years at maximum (11). A maximum effect of 3% increase was observed in the present study. Thus, it seems unlikely that we would have missed a change of the magnitude previously observed.

The second issue is the time of follow-up. In this study, in the cross-sectional analysis at baseline, previous long-term HRT was not related to CCA DC at the study start, which may suggest that HRT over several years did not influence CCA DC. The previously observed influence of HRT on distensibility of large arteries appeared after a short time: withdrawal of HRT changed aortic distensibility within four weeks (30), and application of intravenous estrogen changed it within 20 min (31). In peripheral arteries, distensibility was found to increase until up to one year (32). Thus, we would expect relevant effects to be detectable within one year.

**HRT and smoking.** In this study, HRT with low-dose progestin increased CCA DC in smokers by 32%. With respect to the negative results of the HERS trial (27), our finding indicates the possibility that selected subgroups of postmenopausal women with elevated risk for CHD might benefit from HRT. An epidemiological study with almost identical methodology recently observed the same phenomenon (effect only in smokers) (16). Furthermore, higher systemic arterial compliance, a measure of central conduit artery mechanical properties, has been found in smokers on HRT compared to smokers not on HRT, but not in nonsmokers on HRT (19).

Smoking cigarette reduces carotid artery distensibility by up to 33% (33–35) in both long- and short-term. Sympathetic activation, subsequent increase in arterial smooth muscle tone and impaired endothelium-dependent vasodilation may contribute to this phenomenon (33,34,36). These changes may be counteracted by HRT (21,37), by increased production of nitric oxide (38), by shifting autonomic balance from sympathetic to vagal tone (39), by increased gene expression for vasodilatory enzymes such as prostacyclin synthase and nitric oxide synthase, by inhibited proliferation of vascular smooth-muscle cells and by accelerated growth of endothelial cells (40).

**The effects of progestin.** As the present study indicates, the beneficial effect of estrogen may be lost when progestin is added to the HRT regimen. Progestin negated the inhibitory effects of estrogen on coronary atherosclerosis in a primate model, independent of any change in lipid profile. The inhibitory effects of estrogen on coronary atherosclerosis in a primate model, independent of any change in lipid profile.
The improvement of endothelial function observed after both short-term and long-term application of estrogen (21,37,42) was absent when a combined HRT regimen was given (28). In a rabbit model, estrogen but not progesterin prevented collagen synthesis in the aorta of ovariectomized animals (43). Observations in postmenopausal HRT users showed beneficial effects on distensibility only when estrogen alone was given (14,16).

**Study limitations.** Both sample size and time of follow-up have been discussed above. Furthermore, a beneficial effect on distensibility was found only in a small subgroup predefined as secondary outcome measure. Yet both the consistency with previous investigations and the biological plausibility corroborate the results. Certainly, a specifically designed study is warranted.

Compared to B-mode IMT measurements, distensibility measurements from M-mode were achieved in fewer subjects, as was expected; the vessel wall near to the probe, required only for DC calculation, was more difficult to visualize than was the far wall. Subjects for whom valid distensibility measurements could not be performed had higher BMI but did not differ from subjects with distensibility measurements in any other variable with a potential influence on arterial distensibility. Still, although there is no reason to assume selection bias, we cannot exclude it.

**Conclusions.** In postmenopausal women who are at increased risk for cardiovascular morbidity and mortality as indicated by an increased carotid IMT, HRT did not alter distensibility of the central arteries. In the context of other randomized trials, especially those with clinical end points (27), this casts doubt on the value of HRT in prevention of cardiovascular diseases. The positive result in the subgroup of smokers treated with estrogen and low-dose progesterin merits further study.

Reprint requests and correspondence: Dr. Peter Angerer, Medizinische Klinik, Klinikum der Universität München–Innenstadt, Ziemssenstr. 1, D-80336 Munich, Germany. E-mail: pangerer@medinn.med.uni-muenchen.de.

**REFERENCES**

28. Sorensen KE, Dorup I, Hermann AP, Moskilde L. Combined hormone replacement therapy does not protect women against the...