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Placebo-controlled trial of transdermal estrogen therapy alone in postmenopausal women: effects on arterial compliance and endothelial function

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Key words: SYSTEMIC ARTERIAL COMPLIANCE, PULSE WAVE VELOCITY, FLOW-MEDIATED VASODILATATION, ENDOTHELIAL FUNCTION, LIPIDS, BLOOD PRESSURE

ABSTRACT

Background The cardiovascular effects of hormone replacement therapy (HRT) are controversial. Improvement in vascular function, potentially mediated, at least in part, via improvements in lipid profiles, is a proposed mechanism of estrogen action; however, there are few controlled human trials. We have studied the effects of HRT, independent of changes in lipid profile, with transdermal estrogen therapy, focusing on blood pressure, lipid profiles and vascular function, encompassing both biomechanical arterial properties (systemic arterial compliance and pulse wave velocity) and endothelial function (flow-mediated vasodilatation).

Methods In this 2-year, double-blind, placebo-controlled, cross-over study, 34 healthy postmenopausal women were randomized to transdermal estrogen alone (Menorest®, 50 μg) or placebo. After withdrawals, 25 women completed measurements at baseline, 6 weeks, 6 months and 12 months during both treatment phases.

Results Transdermal estrogen did not improve blood pressure, lipid profiles or arterial function, compared with placebo.

Conclusion From this randomized, controlled trial, it appears that transdermal estrogen alone, in healthy postmenopausal women, does not improve lipid profiles or a spectrum of indices of arterial function, compared with placebo. These results would suggest that there might not be a beneficial effect of transdermal HRT on the vasculature in postmenopausal women.

INTRODUCTION

The role of hormone replacement therapy (HRT) in the prevention of cardiovascular disease remains controversial. While observational human data and interventional data in animals and humans suggest significant cardiovascular risk reduction with the use of HRT, this has been challenged in recent years. The results of the secondary prevention Heart and Estrogen/
The progestin Replacement Study (HERS), the only controlled study adequately powered to examine the effects of HRT on clinical cardiovascular end-points in women, showed no benefit of HRT over 4.1 years and suggested an early increase in events. Also, the Estrogen Replacement in Atherosclerosis (ERA) study noted no effect of HRT with either oral estrogen alone or combined estrogen and progestin on the progression of coronary atherosclerotic plaques, observed on angiography in postmenopausal women. These findings have been limited to the secondary prevention setting, and we await the results of the ongoing primary prevention studies with interest. It is notable, however, that the safety board has released a statement to patients in the large Women’s Health Initiative (WHI) primary prevention trial, noting an increased rate of cardiovascular events in the HRT group. These findings from recent human interventional studies highlight the shortcomings of previous observational and inadequately powered interventional studies, and emphasize the need for well-designed, controlled, human interventional trials on the effects of HRT on the vascular system.

Observational data have shown that women on HRT have healthier arterial function than those not on therapy. This is supported by animal data demonstrating that HRT has direct effects on the blood vessel wall, including improved endothelial function with up-regulation of the vasodilator, nitric oxide, as well as inhibition of smooth muscle proliferation and, ultimately, reduction in atherosclerosis. To date, few controlled human interventional studies have addressed the effects of HRT on vascular function.

Human trials focusing on the effects of HRT on vascular function have been hampered by the lack of availability of reliable, accurate non-invasive techniques. Recently, non-invasive techniques to evaluate arterial biomechanical properties and endothelial function have been developed. These methods both within our laboratory and in other international settings are established as accurate and repeatable. They have been used extensively to monitor the natural history of vascular disease and to study the effects of specific interventions on blood vessel function.

The aim of this 2-year, double-blind, randomized, cross-over, placebo-controlled study was to examine the vascular functional effects of transdermal estrogen alone in 34 healthy postmenopausal women. Seventeen participants were randomized to active therapy and 17 to placebo therapy for the first 12 months, after which the treatments were crossed over. The time points for data collection were baseline, 6 weeks, 6 months and 12 months in both treatment phases. End-points included blood pressure, lipid profiles (total, low-density lipoprotein and high-density lipoprotein cholesterol, and triglycerides) and indices of arterial function (system arterial compliance, pulse wave velocity and flow-mediated vasodilatation). Hormone profiles were measured at baseline.

**METHODS**

The study was approved by the Human Research and Ethics Committee, Southern Health Care Network (Melbourne, Australia). Written informed consent was obtained from all subjects. All participants were recruited from a series of advertisements in local newspapers and in a widely distributed women’s health newsletter.

**Study design**

Thirty-four healthy postmenopausal women were enrolled in a double-blind, randomized, cross-over, placebo-controlled trial with measurements made over 2 years. At baseline, 17 women were randomized to HRT and 17 to placebo. Cross-over occurred after 12 months of therapy. Women commenced either transdermal 17β-estradiol (Menorest, 50 g; Rhone-Poulenc Rorer, Melbourne, Australia) or identically appearing placebo patches.

Subjects were healthy as assessed from a medical review consisting of a detailed history and physical examination. Inclusion criteria included age between 50 and 75 years, previous hysterectomy, intact ovaries and not taking HRT in the past 2 years. Exclusion criteria included breast cancer in a first-degree relative, uncontrolled hypertension (>160/100 mmHg), a history of thromboembolic disease, cardiovascular or cerebrovascular disease, >80% carotid stenosis (on baseline ultrasound scanning), serious illness, uncontrolled migraine, undiagnosed genital bleeding, previous oophorectomy and smoking (non-smokers were defined as complete non-smokers for at least 12 months prior to the study). Pap smears and screening mammograms were organized at baseline, if not completed within the past 2 years. A questionnaire based on the National Heart Foundation of Australia Risk Factor Prevalence Study was completed by each participant to assess cardiovascular risk factors.
At each subsequent visit, this questionnaire was repeated, along with a medical review and breast examination. Medication adherence was checked by counting returned patches and by questionnaire. All medical problems identified throughout the study, including the detection of significant atherosclerotic plaques seen on ultrasound and abnormal lipid profiles, were referred for appropriate follow-up via a woman’s local medical practitioner. No medical therapy was withheld during the study.

Randomization of subjects to the treatment arms was completed by an experienced researcher, not otherwise involved in the study, using computer-generated random numbers. All other researchers were blinded. Participants were advised against consuming food and caffeine-containing drinks for 8 h prior to ultrasound measurements, which were performed in a quiet, air-conditioned clinical laboratory (temperature 25°C). At each visit, subjects rested while they filled out a questionnaire on any alterations to lifestyle, illnesses or medications. They then rested in a quiet, darkened room in a supine position for at least 10 min. Electrocardiography recording-dots were applied to the chest wall for continuous monitoring, and an appropriately sized blood-pressure cuff was applied to the upper left arm.

Height, weight, waist/hip ratio, heart rate and blood pressure readings were obtained in all participants. Six brachial arterial blood pressure readings were recorded over 15 min on a Dinamap device ( Critikon 1846 SX, Tampa, FL, USA), with the woman in a recumbent position, after 10 min rest. The first reading was discarded and the remaining values averaged.

Systemic arterial compliance
In all subjects, systemic arterial compliance (SAC) was estimated with computerized calculations based on the ‘area method’ of Liu and colleagues as previously described. This ‘area method’ requires measurement of volumetric blood flow and associated driving pressure to derive an estimated compliance over the total systemic arterial tree. Specifically, a 3.5-MHz continuous-wave Doppler flow velocimeter (Multidoplex MD1; Huntsleigh Technology, Cardiff, UK) was placed on the suprasternal notch to record ascending aortic blood flow. Aortic driving pressure was estimated by applanation tonometry of the carotid artery using a non-invasive pressure transducer (Millar Mikro-tip; Millar Instruments, Houston, TX, USA). The pressures obtained by this method were calibrated against brachial artery pressure measurements using a Dinamap device (Critikon 1846 SX).

The formula used for calculation of SAC was as follows:

$$\text{SAC} = \frac{A_d}{R(P_s - P_d)}$$

where $R$ is the total peripheral resistance calculated as mean arterial blood pressure/mean blood flow and $A_d$ is the area under the blood pressure diastolic decay curve from end-systole to end-diastole; $P_s$ is the end-systolic blood pressure (carotid); and $P_d$ is the end-diastolic blood pressure (carotid). Mean blood flow was calculated as mean velocity multiplied by aortic root area. Aortic root area was derived from body surface area, as previously described.

Pulse wave velocity
Subjects underwent simultaneous tonometry (requiring two operators), first over the carotid and femoral arteries (aorto-femoral; A–F), then femoral and dorsalis pedis arteries (femoro-dorsalis pedis; F–D), to obtain arterial pressure waveforms. The velocity of the pulse wave (PWV) was measured from the computer-generated pulse transit time and the measured distance along the respective arterial segments from surface measurements.

Endothelial function
All participants were assessed for brachial artery flow-mediated vasodilatation (FMD) using methods described by Celermajer and colleagues. Resting brachial artery baseline diameter (RBD) was measured from B-mode ultrasound images captured on a Diasonics machine (DGF-400; Sydney, Australia) using a hand-held 10-MHz mechanical sector transducer, while an electrocardiogram (ECG) trace was simultaneously recorded. The clearest image of the brachial artery was obtained following longitudinal scanning, 1–6 cm above the elbow, and this image was held while transient ischemia was induced via a pneumatic tourniquet inflated around the upper arm (above the point of imaging) to 40 mmHg above systolic pressure for 4 min. Scanning was continuous for 30 s prior and 4 min after ischemia, as previously described by our group. A single operator performed all scans and was blinded to the treatment status of all participants.
Image analysis

Images were recorded on videotape for analysis. The same single operator as performed the scans completed the analysis, with this operator remaining blinded to treatment status throughout. Measurements of vessel diameter were taken during both systole (incident with recorded T waves) and diastole (incident with recorded R waves), and averaged over five cardiac cycles. The parameters reported included baseline brachial artery diameter and FMD, the latter determined as the percentage change from baseline to 60 s post-ischemia, the time point of maximum vasodilatation noted in a previous repeatability study by our group.9

Blood samples

Blood samples were collected prior to midday, after a minimum 8-h fast, by non-traumatic phlebotomy with venipuncture performed using a 19-gauge needle directly into plain tubes (Vacutainer; Becton Dickinson, Melbourne, Australia). Specimens were collected for measurement of lipoprotein profiles, and levels of follicle stimulating hormone (FSH) and luteinizing hormone (LH). Samples were centrifuged at 2500 g for 12 min, and plasma was separated into 200-μl aliquots, stored at −80°C and thawed immediately prior to analysis.

Gonadotropin and estradiol levels were measured only at baseline to establish postmenopausal status. Gonadotropins were measured by radioimmunoassay performed on an automated MEIA using the Abbott AxSYM immunoassay analyzer (Abbott Diagnostics Division, Illinois, USA). Standardization was done against the World Health Organization (WHO) 2nd International Reference Preparation (78/549) and (80/552) for FSH and LH, respectively. Estradiol was measured by standard automated immunoassay ACS180 (Chiron Diagnostics, Massachusetts, USA).

Total cholesterol and triglyceride levels were measured using enzymatic reagents (DADE Diagnostics, Brisbane, Australia); high-density lipoprotein (HDL) cholesterol was measured by homogeneous assay techniques (HDLC-Plus; DADE Diagnostics) adapted to a DADE Dimension RXL chemistry analyzer (DADE Diagnostics). Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation (LDL cholesterol = (total cholesterol − HDL cholesterol) − (triglycerides × 0.20)), adapted to SI units. All parameters were measured at each time point except for hormone profiles, which were measured at baseline only to confirm menopausal status.

Statistics

The principal basis for the data analysis was repeated-measures analysis of variance (ANOVA), using the Greenhouse–Geisser adjustment for multisample asphericity (autocorrelation).15 The independent variable was ‘treatment’ (placebo or active). The repeated measurements were made at the start of the trial and at 6 weeks and at 6 and 12 months with each intervention. The null hypothesis of parallel profiles of values over time according to treatment was tested by the within-subjects interaction term (treatment × time).

The outcome variables were divided into three sets: blood pressure (BP) variables (systolic, diastolic and mean BP); plasma lipid variables (cholesterol, triglycerides, HDL, LDL, LDL/HDL ratio); and vascular functional variables (PWV(A–F), PWV(F–D), SAC, RBD, FMD). The p values resulting from the multiple hypotheses tested within each set were adjusted by means of the Ryan–Holm stepdown Bonferroni procedure, with corrected p values denoted as p′. This provides protection against an excessive type I error-rate (false-positive inferences), while retaining excellent power.16

There were some missing values for all the outcome variables scattered randomly among treatments, ranging from 3 to 10% of the time points for individual variables. To overcome this, the missing values were imputed using the regression technique with SYSTAT version 9 (SPSS Inc., Chicago, USA). When missing values were systematically distributed (for instance, all values missing for a given subject and treatment), the corresponding cases were eliminated from the repeated-measures ANOVA.

Only data from participants compliant with medication for the full duration of the study (n = 25) were included in the analyses. Two-sided p ≤ 0.05 was regarded as statistically significant. Data are summarized as means ± standard error (between-subjects). The statistical analyses were performed using SYSTAT version 9 (SPSS Inc., Chicago, USA).

RESULTS

Baseline characteristics including blood pressure, lipid profiles and vascular function are summarized in Tables 1–3. Additional baseline
characteristics include mean age (60 ± 14 years), weight (71 ± 3.4 kg), body mass index (26.7 ± 1.2 kg/m²), waist/hip ratio (0.88 ± 0.01) and heart rate (63 beats/min).

Nine women withdrew during the 2-year study, three during the active phase and six during the placebo phase. Of those, three women withdrew within the first 6 weeks (one active, two placebo). Between 6 weeks and 6 months, three women withdrew (one active, two placebo), and between 6 and 12 months of the treatment phase, three women withdrew (one active, two placebo). All those who withdrew were not included in the data analysis; therefore, analysis was not performed on an intention-to-treat basis. The women who withdrew did not differ in baseline characteristics from those who completed the study. Reasons for withdrawal included breast tenderness (two active), menopausal symptoms (one placebo), weight gain (one active), lung cancer diagnosed (one placebo), non-specific illness (one placebo) and unrelated personal reasons (three placebo).

### Table 1  Blood pressure (BP) readings during active (transdermal estrogen alone) and placebo treatment phases at baseline, 6 weeks, 6 months and 12 months

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>Baseline</th>
<th>6 weeks</th>
<th>6 months</th>
<th>12 months</th>
<th>p’ value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean BP (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>active</td>
<td>89 ± 2</td>
<td>88 ± 2</td>
<td>87 ± 2</td>
<td>90 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>placebo</td>
<td>90 ± 2</td>
<td>91 ± 2</td>
<td>93 ± 2</td>
<td>90 ± 2</td>
<td></td>
</tr>
<tr>
<td><strong>Systolic BP (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>active</td>
<td>130 ± 4</td>
<td>128 ± 4</td>
<td>125 ± 3</td>
<td>128 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>placebo</td>
<td>128 ± 3</td>
<td>131 ± 3</td>
<td>131 ± 3</td>
<td>128 ± 3</td>
<td></td>
</tr>
<tr>
<td><strong>Diastolic BP (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>active</td>
<td>73 ± 1</td>
<td>73 ± 2</td>
<td>71 ± 1</td>
<td>72 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>placebo</td>
<td>73 ± 1</td>
<td>74 ± 1</td>
<td>75 ± 1</td>
<td>73 ± 2</td>
<td></td>
</tr>
</tbody>
</table>

*By repeated-measures analysis of variance; NS, not significant

### Table 2  Lipid profiles during active (transdermal estrogen alone) and placebo treatment phases at baseline, 6 weeks, 6 months and 12 months

<table>
<thead>
<tr>
<th>Lipid parameter</th>
<th>Baseline</th>
<th>6 weeks</th>
<th>6 months</th>
<th>12 months</th>
<th>p’ value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>active</td>
<td>6.0 ± 0.2</td>
<td>5.8 ± 0.1</td>
<td>5.6 ± 0.1</td>
<td>6.0 ± 0.1</td>
<td>NS</td>
</tr>
<tr>
<td>placebo</td>
<td>6.0 ± 0.1</td>
<td>5.9 ± 0.2</td>
<td>5.9 ± 0.2</td>
<td>5.8 ± 0.1</td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>active</td>
<td>3.9 ± 0.2</td>
<td>3.6 ± 0.1</td>
<td>3.6 ± 0.2</td>
<td>4.0 ± 0.1</td>
<td>NS</td>
</tr>
<tr>
<td>placebo</td>
<td>3.9 ± 0.1</td>
<td>3.8 ± 0.2</td>
<td>3.8 ± 0.2</td>
<td>3.7 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>active</td>
<td>1.6 ± 0.1</td>
<td>1.8 ± 0.1</td>
<td>1.5 ± 0.1</td>
<td>1.5 ± 0.1</td>
<td>NS</td>
</tr>
<tr>
<td>placebo</td>
<td>1.6 ± 0.1</td>
<td>1.6 ± 0.1</td>
<td>1.6 ± 0.1</td>
<td>1.6 ± 0.1</td>
<td></td>
</tr>
<tr>
<td>LDL/HDL ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>active</td>
<td>2.7 ± 0.2</td>
<td>2.4 ± 0.2</td>
<td>2.5 ± 0.2</td>
<td>2.8 ± 0.2</td>
<td>NS</td>
</tr>
<tr>
<td>placebo</td>
<td>2.7 ± 0.2</td>
<td>2.6 ± 0.2</td>
<td>2.5 ± 0.2</td>
<td>2.6 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>active</td>
<td>1.2 ± 0.2</td>
<td>1.0 ± 0.1</td>
<td>1.1 ± 0.1</td>
<td>1.2 ± 0.2</td>
<td>NS</td>
</tr>
<tr>
<td>placebo</td>
<td>1.2 ± 0.1</td>
<td>1.2 ± 0.1</td>
<td>1.1 ± 0.1</td>
<td>1.2 ± 0.2</td>
<td></td>
</tr>
</tbody>
</table>

*By repeated-measures analysis of variance; LDL, low-density lipoprotein; HDL, high-density lipoprotein; NS, not significant
Blood pressure and lipid profiles

There was no significant difference in mean, systolic or diastolic blood pressure during the active treatment arm, compared with placebo, on ANOVA of repeated measures (Table 1).

On corrected ANOVA of repeated measures, no significant effect of HRT was noted on total cholesterol, LDL, HDL, LDL/HDL ratio or triglycerides (Table 2). There was no significant difference in change in body weight observed between the two treatment phases (∼0.2 ± 3.0 kg vs. 1.1 ± 3.0 kg, p = 0.16).

Vascular compliance and endothelial function

Table 3 lists changes in SAC, PWV(A–F) and PWV(F–D), RBD and FMD. On ANOVA of repeated measures over the four visits, no individual parameter was noted as being significantly different between the HRT and placebo groups.

DISCUSSION

This controlled interventional human trial on the effects of transdermal HRT on arterial function suggests that transdermal estrogen alone does not improve blood pressure, lipid profiles or an array of markers of vascular function in postmenopausal women.

From the present study, it appears that transdermal estrogen alone does not influence blood pressure over the longer term. This is consistent with the majority of published literature, suggesting that neither combined HRT nor estrogen alone, administered orally or transdermally, increases blood pressure\textsuperscript{18–20}, with some studies even suggesting a small reduction in blood pressure with HRT\textsuperscript{18}. In accordance with the stability observed in blood pressure in the present study, we noted no change in resting brachial artery diameter (RBD) over the treatment periods and no change in PWV(F–D), a parameter reflecting vasoconstriction in peripheral resistance vessels.

Transdermal estrogen alone did not significantly change lipids. This study was only 70% powered (based on the 25 women who completed the protocol) to detect significant changes in lipid parameters. However, the lack of effects of transdermal therapy are consistent with previous reports suggesting no changes in the lipid profile\textsuperscript{20,21}, related potentially to the absence of a high first-pass hepatic effect, as the liver appears to be the key site for estrogen-induced lipid changes.

<table>
<thead>
<tr>
<th>Vascular parameter</th>
<th>Baseline</th>
<th>6 weeks</th>
<th>6 months</th>
<th>12 months</th>
<th>p’ value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAC (units/mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>active</td>
<td>0.50 ± 0.04</td>
<td>0.51 ± 0.04</td>
<td>0.51 ± 0.04</td>
<td>0.49 ± 0.05</td>
<td>NS</td>
</tr>
<tr>
<td>placebo</td>
<td>0.46 ± 0.03</td>
<td>0.48 ± 0.04</td>
<td>0.50 ± 0.04</td>
<td>0.50 ± 0.04</td>
<td></td>
</tr>
<tr>
<td>PWV(A–F) (m/s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>active</td>
<td>9.8 ± 0.4</td>
<td>9.9 ± 0.4</td>
<td>9.7 ± 0.4</td>
<td>9.7 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>placebo</td>
<td>9.6 ± 0.4</td>
<td>9.8 ± 0.4</td>
<td>10.0 ± 0.4</td>
<td>10.1 ± 0.5</td>
<td></td>
</tr>
<tr>
<td>PWV(F–D) (m/s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>active</td>
<td>10.4 ± 0.4</td>
<td>10.3 ± 0.3</td>
<td>9.9 ± 0.4</td>
<td>9.9 ± 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>placebo</td>
<td>10.3 ± 0.3</td>
<td>10.2 ± 0.3</td>
<td>10.2 ± 0.4</td>
<td>10.2 ± 0.4</td>
<td></td>
</tr>
<tr>
<td>RBD (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>active</td>
<td>0.43 ± 0.01</td>
<td>0.42 ± 0.01</td>
<td>0.42 ± 0.01</td>
<td>0.44 ± 0.01</td>
<td>NS</td>
</tr>
<tr>
<td>placebo</td>
<td>0.43 ± 0.01</td>
<td>0.42 ± 0.01</td>
<td>0.42 ± 0.01</td>
<td>0.44 ± 0.01</td>
<td></td>
</tr>
<tr>
<td>FMD (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>active</td>
<td>6.0 ± 0.5</td>
<td>7.2 ± 0.6</td>
<td>6.8 ± 0.6</td>
<td>6.7 ± 0.7</td>
<td>NS</td>
</tr>
<tr>
<td>placebo</td>
<td>7.9 ± 0.7</td>
<td>8.8 ± 0.8</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*By repeated-measures analysis of variance; SAC, systemic arterial compliance; PWV, pulse wave velocity; A–F, aorto-femoral; F–D, femoro-dorsalis pedis; RBD, resting baseline diameter; FMD, flow-mediated vasodilatation; NS, not significant
Systemic arterial compliance (SAC), a measure of central conduit artery mechanical properties, reflects the ability of the proximal vascular system to convert pulsatile ventricular flow into smooth continuous peripheral blood flow, with less compliant atherosclerotic vessels causing elevated systolic pressures, increasing shear stress and thus atherosclerosis, while lower diastolic pressures reduce coronary arterial perfusion. SAC is related to the elasticity of the vessels and is influenced by age, hypertension, atherosclerotic vascular disease, exercise training, and lipid-lowering and antihypertensive drugs.

We have shown that changes in SAC were no different with transdermal estrogen alone, compared with placebo. These findings are consistent with our previous work demonstrating no effect of long-term oral combined HRT on SAC in 59 healthy menopausal women. It is, however, in contrast to two recent reports from limited short-term non-randomized studies. The HRT regimens in both studies were variable, with limited numbers taking a variety of progestins. In the first study in 11 postmenopausal women, examined before and 4 weeks after cessation of HRT, SAC fell by 22%. The second study, by the same group, examined both withdrawal and subsequent re-institution of HRT in 17 postmenopausal women, who had been on stable HRT, compared with a matched control group (17 women) receiving no HRT. Controls remained unchanged, yet the HRT group demonstrated a 17% fall in SAC after therapy withdrawal, which increased to baseline levels after re-institution of therapy.

Pulse wave velocity (PWV) is a measure of the stiffness of arteries. Increasingly, it appears to be a robust measure of arterial dysfunction and a predictor of clinical cardiovascular events. It is derived from the time delay occurring in the arterial pulse wave as it dissipates from the proximal to the distal vessels, and can be studied over various vascular beds (aorto-femoral PWV(A–F) or distal femoro-dorsalis pedis PWV(F–D)), PWV, is also related to cardiovascular risk factors including exercise, lipid levels, age, hypertension, diabetes, coronary artery disease and renal disease.

PWV, is also related to cardiovascular risk factors including exercise, lipid levels, age, hypertension, diabetes, coronary artery disease and renal disease. There are only a very limited number of interventional studies; however, antihypertensive therapy does appear to improve PWV.

The present study is one of few focusing on the effects of sex steroids on PWV. We found no effect of transdermal estrogen alone, compared with placebo, despite the fact that the study had multiple sampling times and was powered to detect small changes in PWV. This is consistent with our previous placebo-controlled study using oral combined HRT. It is also consistent with several other uncontrolled studies focusing on the impact of HRT on PWV, mostly with negative results. A cross-sectional study in 18 HRT users and 16 controls did not find any differences in PWV between the two groups. Our results are also consistent with those of a recent cross-over study in 14 diabetic women, which noted no significant change in PWV after 6 months of HRT, compared with placebo. A single interventional study in 17 postmenopausal women, outlined above, noted a significant fall in femoropopliteal PWV, 4 weeks after HRT cessation, yet not in aorto-femoral PWV.

Endothelial dysfunction is an early step in the process of vascular disease. Endothelial dysfunction is an early step in the process of vascular disease. It can be assessed in vivo, based on flow-mediated vasodilation (FMD). FMD, mediated by nitric oxide release, can be induced by shear stress following transient ischemia. It has a 95% positive-predictive value for coronary artery endothelial dysfunction, while impaired FMD is positively associated with cardiovascular risk factor status. Limitations of the technique include less than ideal repeatability, operator dependence and external influences including exercise and food ingestion.

In the present study, FMD was performed by a single experienced operator under controlled conditions with all participants fasting for 8 h and resting for 30 min prior to each scan.

Flow-mediated vasodilatation has been increasingly used to assess the effects of HRT on endothelial function, in vivo. HRT appears to improve FMD in cross-sectional studies. Also, acute short-term estrogen administration appears to improve FMD responses in postmenopausal women, compared with placebo, with the effect being dose dependent.

These results suggest that longer-term transdermal estrogen alone in postmenopausal women does not alter endothelial function, reflected by brachial artery FMD, compared with placebo. Furthermore, no change in resting brachial artery baseline diameter (RBD) was noted. Interventional data on the longer-term effects of HRT on FMD have been contradictory. Cagnacci and colleagues studied the effects of transdermal 17β-estradiol in an uncontrolled trial in 15 women over 8 weeks, and reported no significant changes in mean FMD. In contrast, Gerhard and co-workers in a double-blind, placebo-controlled, short-term study noted an improvement in FMD in 17 women over 14 weeks with transdermal estradiol and micronized progesterone.
interest, a recent trial assessing endothelial function based on acetylcholine-induced brachial artery dilatation compared oral estradiol, transdermal estradiol and placebo, and noted no change in lipids or endothelial function in the transdermal or the placebo group, but a significant improvement in the oral estradiol group. However, the conflicting data on the effects of HRT on FMD are unlikely to be explained simply by variation in the effects of estrogen administration via different routes, as the literature on the effects of oral estrogens on FMD is also conflicting. Several large, long-term, controlled studies, both blinded and open label, have noted no effect of oral combined HRT on FMD. This is in contrast to several short-term, smaller, controlled studies, which have noted beneficial effects of oral HRT on FMD. Potentially, transdermal therapy without the documented first-pass effects of oral estrogens, including alteration of lipid profiles, may not alter endothelial function. Also, oral estrogens may improve endothelial function in the short term but not in the longer term. However, further research is required to clarify these issues.

There are several limitations that require consideration when interpreting the present data. Although well designed as a double-blind, placebo-controlled cross-over trial, a 25% withdrawal rate was noted over 2 years. Also, unavoidably, some values were missing at random time points, owing to factors that included transient travel of participants (largely a retired population) and blood samples unable to be obtained on some occasions, a problem overcome by imputation prior to analysis using a specifically designed SYSTAT program. Also, these women appeared to represent a healthy group of community-dwelling postmenopausal women with good baseline PWV and FMD, reflecting low cardiovascular risk. Potentially, improvement in vascular function may have been more difficult to detect in this group. Despite these issues, this controlled cross-over trial was adequately powered, based on a previous repeatability study published by our group, to detect small changes that were less than the differences noted earlier in observational studies comparing HRT users and non-users, for the primary end-points of vascular and endothelial function. In this setting we have not demonstrated that transdermal ERT had any beneficial effects on the vascular system.

From the present long-term, randomized, cross-over, placebo-controlled study, it appears that transdermal estrogen alone, in healthy postmenopausal women, does not alter blood pressure or lipid profiles or improve a spectrum of indices of arterial function, including endothelial function, compared with placebo. These results are consistent with a previous long-term controlled study completed by our group, using oral combined continuous HRT, focusing on similar end-points, which also suggested no beneficial effects of oral HRT on vascular function in postmenopausal women.

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Conflict of interest Nil.

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