Clinical research
Coronary heart disease

Randomized trial of effects of continuous combined HRT on markers of lipids and coagulation in women with acute coronary syndromes: WHISP Pilot Study

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Aims Randomized trials have not demonstrated coronary heart disease benefit from hormone replacement therapy (HRT). We hypothesized that low-dose HRT may avoid harm.

Methods and results We studied the effects of HRT on lipids and coagulation in women with acute coronary syndromes. A total of 100 post-menopausal women, 55 years were enrolled between 2 and 28 days after an acute coronary syndrome and randomized to oral oestradiol-17β 1 mg plus norethisterone acetate 0.5 mg daily, or matching placebo, and followed for up to 12 months. Levels of lipids, lipoproteins, and haemostasis markers were measured at baseline, 3, and 6 months. There were no significant differences in lipid levels between the two groups, probably due to concomitant statin use. Antithrombin and factor VII levels were significantly lower in the HRT group, whereas fibrinogen was significantly decreased in the placebo group. No evidence of increased coagulation activation was observed, nor of adverse cardiovascular outcomes [odds ratio (OR) 0.63 (95% confidence intervals 0.31–1.31)].

Conclusion Low-dose HRT may give cardiovascular benefit. These findings require confirmation in a full clinical trial with evaluation of cardiovascular outcomes as the primary objective.

KEYWORDS
CHD; HRT; Lipids; Haemostasis

Introduction

Coronary heart disease (CHD) is a major cause of morbidity and mortality in women. Loss of ovarian steroid hormones at the menopause appears to be linked to the increased risk of CHD,¹ generating the hypothesis that hormone replacement therapy (HRT) could potentially be of benefit in preventing CHD. The HRT modifies many metabolic risk factors for CHD,³ which would decrease the risk of atherogenesis, and oestrogen has direct effects on blood vessels which are potentially beneficial.⁴ Protective effects of hormone therapy have been reported in numerous observational studies.⁵,⁶ However, clinical trials of HRT have not shown a benefit on cardiovascular events in post-menopausal women, either with prior CHD⁷ or without prior CHD.⁸ Most of these studies have used conjugated equine oestrogens (CEEs) 0.625 mg daily, combined with medroxyprogesterone acetate (MPA), and have observed an early increase in CHD events, albeit with a later decrease. Different doses and types of oestrogens and progestogens have different metabolic effects, some of which may be less favourable than others for the cardiovascular system. Higher doses of oral oestrogens have the potential to increase coagulation activation and adversely affect vascular remodelling, both of which could produce early harm.⁹ We hypothesized that the use of low-dose oestrogen combined with a different progestogen may have a beneficial effect in acute coronary syndromes by avoiding early harm. We therefore evaluated the effects of a continuous combined low-dose HRT on lipids and markers of haemostasis, as well as overall safety and feasibility, as a prelude to a larger study to assess effects of HRT on clinical outcomes.

Methods

Patients

Details of inclusion and exclusion criteria are given in Table 1. At the start of the study, eligibility criteria restricted enrolment to post-menopausal women with a confirmed myocardial infarction (MI) between 2 and 7 days of presentation, but after 34 patients had been enrolled, eligibility was extended to include patients with...
non-ST elevation acute coronary syndrome up to 28 days after presentation. The main reason for modifying eligibility part way through the study was to improve enrolment. Ethical approval was obtained from the North Thames Multicentre Research Ethics Committee and the Local Research Ethics Committee at each centre. Written informed consent was obtained from all patients.

Patients were randomized to HRT [continuous combined oral oestradiol-17β 1 mg and oral norethisterone acetate (NETA) 0.5 mg daily (Klovance™, Novo Nordisk)] or placebo by telephone call to the co-ordinating centre. A blinded treatment pack was allocated to the patient. Study treatment was stratified by centre (blocks of four) and provided for a maximum of 12 months. WHISP was a multi-centre, prospective, randomized, double-blind, placebo-controlled pilot study. Seventeen hospitals throughout the UK participated in the study (see list of investigators and centres at end of this report).

Outcome measures

The aim of the study was to examine the (1) effects of HRT on lipids, and markers of coagulation and fibrinolysis, (2) feasibility of enrolment, patients, and (3) safety and tolerability of HRT. Patients were followed-up at 3, 6, 9, and 12 months after the date of randomization (minimum follow-up 3 months). At each follow-up visit, clinical events, compliance to medication, possible side effects of the trial treatment, and general symptoms were recorded. Fasting blood samples for lipid and coagulation markers were collected at 3 and 6 months. Study treatment was discontinued for any of the following: suspected breast or endometrial cancer, clinical suspicion of thromboembolism, unacceptable side effects, or at the patient’s request. Patients who had discontinued treatment were requested to continue with follow-up.

Laboratory analyses

An overnight fasting blood sample was taken for analysis of lipid (EDTA plasma) and coagulation markers (citrated plasma). Coagulation samples were separated into polypropylene cryovials prior to storage. Chilled tubes (4°C) were used to collect samples for prothrombin fragment 1-2 (F1-2) analysis. Samples were centrifuged at 4°C (3000 rpm) within 30 min, plasma were stored at −20°C prior to transportation to the central laboratory for subsequent assay. Plasma total cholesterol and triglycerides were measured using enzymatic procedures (ABX Diagnostics). HDL cholesterol was measured following heparin manganese precipitation of other lipoproteins. HDL sub-fraction 3 (HDL3) cholesterol was measured following further precipitation with dextran sulphate. HDL subfraction 2 (HDL2) cholesterol was calculated as the difference between HDL and HDL3 cholesterol. LDL cholesterol was calculated using the Friedewald formula. Apolipoproteins Al and B were measured with commercial immunonunoturbidometric kits (Wako). Lipid assay performance was monitored using lyophilized human sera. Within- and between-assay percentage coefficients of variation were 0.9 and 1.5 (total cholesterol), 1.3 and 2.1 (triglycerides), 0.9 and 2.3 (HDL cholesterol), 1.6 and 4.2 (HDL3 cholesterol), 0.9 and 2.4 (apolipoprotein Al), and 1.5 and 2.0 (apolipoprotein B).

Samples for factor VII coagulation (VIIc) activity were thawed in a water bath (37°C) and then left at room temperature prior to analysis for a period not greater than 30 min prior to analysis. Plasma fibrinogen, factor VIIc activity and activated protein C (APC) resistance were measured by an ACL coagulometer (materials supplied by Instrumentation Laboratories). Plasma antithrombin activity was measured by chromogenic assay (Chromogenix). F1-2 and fibrin D-dimer were measured using commercial ELISA kits (Dade-Behring and Quadratach Ltd, IE). Coagulation assay performance was monitored using lyophilized and frozen human plasmas. Within- and between-assay percentage coefficients of variation were 3.2 and 6.5 (fibrinogen), 3.2 and 5.0 (factor VIIc), 0.8 and 3.2 (APC resistance), 0.9 and 4.4 (antithrombin), 6.0 and 7.5 (F1-2), 4.7 and 9.8 (fibrin D-dimer).

Statistical analysis

The sample size was determined from the observed LDL-cholesterol decreases with a continuous combined oestradiol-17β/NETA (2 mg/1 mg) regimen in older healthy post-menopausal women.12 We assumed that there could be a lesser effect with the lower dose used in our study. Allowing for a 33% drop-out, a study of 50 patients per group would have 96% power to detect a difference of 0.3 mmol/L in LDL cholesterol between treatment and placebo after 3 months of treatment, assuming a standard deviation of 0.4 mmol/L, a correlation with baseline of r = 0.5, and an alpha of 0.05.

For the blood results analyses, the distribution of each parameter was examined and normalized if necessary by logarithmic
transformation. ANOVA was performed to examine treatment effects on laboratory parameters between the groups, using baseline values and statin use as covariates. We performed the comparisons of blood results using patients with complete values at baseline and 6 months. Imputation of missing values was performed using the last observation carried forward (LOCF) method. Pearson $\chi^2$ analyses and Kaplan–Meier survival plots were used to examine treatment differences in events and treatment compliance.

Results

Between October 1999 and October 2001, 1851 women were screened for entry and 100 patients were randomized to HRT (49 patients) or matching placebo (51 patients; Figure 1). There were no significant differences in any of the baseline characteristics between the two groups (Table 2). The majority of patients were admitted with anterior (30.6% in HRT group vs. 35.3% in placebo group) or inferior (42.9 vs.
Table 2  Baseline characteristics

<table>
<thead>
<tr>
<th>Description</th>
<th>HRT (n = 49)</th>
<th>Placebo (n = 51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at randomization (years)</td>
<td>69.4 ± 8.6</td>
<td>68.3 ± 9.0</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.0 ± 3.9</td>
<td>26.4 ± 4.7</td>
</tr>
<tr>
<td>Treatment for hypertension</td>
<td>34 ± 69.4</td>
<td>26 ± 51.0</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current (%)</td>
<td>17 (34.7)</td>
<td>13 (25.5)</td>
</tr>
<tr>
<td>Ex (%)</td>
<td>14 (28.6)</td>
<td>19 (37.2)</td>
</tr>
<tr>
<td>Never (%)</td>
<td>18 (36.7)</td>
<td>19 (37.2)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDDM (%)</td>
<td>5 (10.2)</td>
<td>4 (7.8)</td>
</tr>
<tr>
<td>NIDDM (%)</td>
<td>7 (14.3)</td>
<td>7 (13.7)</td>
</tr>
<tr>
<td>No (%)</td>
<td>37 (75.5)</td>
<td>40 (78.4)</td>
</tr>
<tr>
<td>Time since menopause (years)</td>
<td>21.6</td>
<td>23.9</td>
</tr>
<tr>
<td>Time from onset of symptoms to randomization (days)</td>
<td>4 (3, 7)</td>
<td>4 (3, 7)</td>
</tr>
</tbody>
</table>

Values are mean ± SD, or n (%), or median (inter-quartile range).

The number of patients admitted with unstable angina was 14.3% of patients in HRT group vs. 15.7% in placebo group. There were no differences in statin use at baseline or follow-up (22.4 vs. 25.5% on admission, 79.6 vs. 82.4% at discharge). There were also no differences at baseline between HRT and placebo groups in aspirin or other anti-platelet medication (37 vs. 29%), beta-blockers (22 vs. 25%), nitrates (22 vs. 24%), calcium antagonists (18 vs. 12%), ACE-inhibitors (12 vs. 14%), or diuretics (24 vs. 24%). Median (inter-quartile range) follow-up was 7 (3, 12) months representing a total of 61 person years of follow-up. In total, 14 patients (29%) in the treatment group and 3 (6%) in the placebo group discontinued treatment for clinical reasons (Figure 1). Other reasons for withdrawal are presented in Figure 1. Thirty percent of patients underwent coronary angiography during the study, 16% underwent angioplasty, and 6% underwent coronary artery by-pass grafting. There were no significant differences between the treatment groups for these procedures.

Effects on lipids

Table 3 shows the absolute values and differences between groups adjusted for baseline and statin use for each of the lipid markers, respectively. There were no significant differences between groups in lipid markers. Both groups showed reductions from baseline in total cholesterol and triglycerides, LDL cholesterol, and apolipoprotein B concentrations. Increases in HDL cholesterol and apolipoprotein A1 were observed in both groups.

Markers of coagulation and fibrinolysis

Table 4 shows absolute values and differences between groups adjusted for baseline and statin use for each marker of coagulation and fibrinolysis. A significant difference in fibrinogen was observed between the two groups at 3 months due to a fall from baseline in the placebo group with no change in the HRT group. This difference had disappeared by 6 months. Significant differences in factor VII concentrations between the two groups were observed at both 3 and 6 months, with a decrease from baseline with HRT at 3 months. There was a significant difference between the two groups in antithrombin at 3 and 6 months due to a decrease with HRT group. No differences were observed in APC resistance, F 1 + 2, or fibrin D-dimer between the two groups.

Clinical events, feasibility of enrolment, and safety

Table 5 shows the number of patients who had experienced an adverse event at 12 months post randomization. The rate of the composite outcome of death, MI, stroke was 8 and 16%, respectively for HRT and placebo and for death, MI, stroke, or cardiovascular hospital admissions it was 24 and 31%, respectively (HR 0.63, CI 0.31–1.31). There was no significant difference between any of the other adverse events (HR 0.59, CI 0.32–1.06). Figure 1 summarizes the reasons for discontinuation of study drug. The main reason for stopping treatment was at the patient’s request rather than a recognized side effect. Of the 39 patients who stopped taking the treatment before the end of the study, 20 (51%) still attended all follow-up sessions, 12 from the treatment group and 8 from the control group. Therefore, 19 patients were lost to follow-up before the end of the trial. There was a significant difference between the discontinuation rates in the two groups. Patients in the HRT group were more likely to discontinue compared with those in the placebo group [HR 2.16 (1.11, 4.22) P = 0.02]. Figure 2 shows the Kaplan–Meier estimates of the discontinuation rates for the two treatment groups.

Discussion

Our results show that a low-dose continuous combined HRT regimen appears safe when given to post-menopausal women at high risk for cardiac events. There was no evidence of increased coagulation activation, but a reduction in the risk of a composite of cardiovascular events was shown although this was not significant.

In the Heart and Estrogen/progestogen Replacement Study (HERS), women assigned to daily oral CEE 0.625 mg plus MPA 2.5 mg experienced a higher rate of CHD events than those receiving placebo in the first year. Post-hoc analysis found a significant trend towards decreased risk in the treatment group thereafter. Over the entire 4.1-year study, no difference was found between the groups. The estrogen–progestogen arm of the Women’s Health Initiative (WHI) conducted by the National Institutes of Health in the United States randomized to either combined continuous oestrogen (CEE 0.625 mg) and progestogen (MPA 2.5 mg) or placebo to evaluate the impact of HRT in the primary prevention of CHD. This arm of the study was stopped early due to the finding of a lack of overall benefit in selected clinical outcomes after a pre-specified safety limit on increased risk of breast cancer was breached. There was also an increase in cerebrovascular events, but the pattern of CHD events was similar to HERS, with early harm being followed by possible later benefit. The oestrogen-alone arm of WHI randomized 12 000 women to either CEE 0.625 mg or placebo. Overall, there was no significant reduction in CHD events with this treatment, although there was a significant decrease in a composite of MI and coronary interventions.
<table>
<thead>
<tr>
<th>Lipid markers</th>
<th>Baseline: mean (SD), n</th>
<th>3-month visit: mean (SD), n</th>
<th>6-month visit: mean (SD), n</th>
<th>Treatment effect (95% CI)</th>
<th>P-value</th>
<th>Treatment effect (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HRT</td>
<td>Placebo</td>
<td>HRT</td>
<td>Placebo</td>
<td>HRT</td>
<td>Placebo</td>
<td>HRT</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>5.14 (1.08)</td>
<td>n = 47</td>
<td>5.11 (1.07)</td>
<td>n = 51</td>
<td>4.73 (0.93)</td>
<td>n = 48</td>
<td>4.63 (0.88)</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.99 (1.13)</td>
<td>n = 46</td>
<td>1.91 (1.24)</td>
<td>n = 51</td>
<td>1.68 (1.05)</td>
<td>n = 47</td>
<td>1.72 (1.23)</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>1.47 (0.36)</td>
<td>n = 46</td>
<td>1.50 (0.34)</td>
<td>n = 49</td>
<td>1.49 (0.33)</td>
<td>n = 47</td>
<td>1.51 (0.36)</td>
</tr>
<tr>
<td>HDL3 (mmol/L)</td>
<td>0.90 (0.17)</td>
<td>n = 46</td>
<td>0.93 (0.20)</td>
<td>n = 49</td>
<td>0.96 (0.19)</td>
<td>n = 47</td>
<td>0.97 (0.22)</td>
</tr>
<tr>
<td>HDL2 (mmol/L)</td>
<td>0.57 (0.25)</td>
<td>n = 46</td>
<td>0.56 (0.23)</td>
<td>n = 49</td>
<td>0.53 (0.25)</td>
<td>n = 47</td>
<td>0.54 (0.23)</td>
</tr>
<tr>
<td>LDL (mmol/L)</td>
<td>2.84 (1.07)</td>
<td>n = 41</td>
<td>2.87 (1.01)</td>
<td>n = 47</td>
<td>2.49 (0.99)</td>
<td>n = 44</td>
<td>2.36 (0.74)</td>
</tr>
<tr>
<td>Apo A1 (mg/dL)</td>
<td>121.66 (19.22)</td>
<td>n = 47</td>
<td>122.96 (19.32)</td>
<td>n = 51</td>
<td>126.08 (17.46)</td>
<td>n = 47</td>
<td>130.29 (20.30)</td>
</tr>
<tr>
<td>Apo B (mg/dL)</td>
<td>91.51 (18.59)</td>
<td>n = 47</td>
<td>91.82 (16.99)</td>
<td>n = 51</td>
<td>84.88 (18.46)</td>
<td>n = 48</td>
<td>80.63 (14.92)</td>
</tr>
</tbody>
</table>

*Values have undergone logarithmic transformation prior to analysis.*
Table 4 Markers of coagulation and fibrinolysis

<table>
<thead>
<tr>
<th>Baseline: mean (SD), n</th>
<th>3-month visit 1: mean (SD), n</th>
<th>6-month visit: mean (SD), n</th>
<th>3-month visit, adjusted for baseline and statin use</th>
<th>6-month visit, adjusted for baseline and statin use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HRT</td>
<td>Placebo</td>
<td>HRT</td>
<td>Placebo</td>
</tr>
<tr>
<td>Antithrombin (%)</td>
<td>105.02 (16.47)</td>
<td>107.51 (13.21)</td>
<td>101.83 (15.19)</td>
<td>109.40 (12.67)</td>
</tr>
<tr>
<td></td>
<td>n = 45</td>
<td>n = 49</td>
<td>n = 47</td>
<td>n = 50</td>
</tr>
<tr>
<td>APC resistance (ratio)</td>
<td>2.45 (0.50)</td>
<td>2.38 (0.38)</td>
<td>2.34 (0.46)</td>
<td>2.37 (0.46)</td>
</tr>
<tr>
<td></td>
<td>n = 47</td>
<td>n = 47</td>
<td>n = 48</td>
<td>n = 50</td>
</tr>
<tr>
<td>Factor VII (%)</td>
<td>130.86 (66.25)</td>
<td>138.65 (54.35)</td>
<td>109 (30.02)</td>
<td>131.84 (45.68)</td>
</tr>
<tr>
<td></td>
<td>n = 44</td>
<td>n = 44</td>
<td>n = 46</td>
<td>n = 49</td>
</tr>
<tr>
<td>Fibrinogen (mg/dL)</td>
<td>461.33 (140.71)</td>
<td>454.76 (143.84)</td>
<td>446.40 (109.79)</td>
<td>404.94 (107.89)</td>
</tr>
<tr>
<td></td>
<td>n = 45</td>
<td>n = 51</td>
<td>n = 47</td>
<td>n = 51</td>
</tr>
<tr>
<td>D-dimer (μg/L)+</td>
<td>322.70 (239.01)</td>
<td>276.94 (173.37)</td>
<td>310.53 (200.45)</td>
<td>244.18 (159.29)</td>
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<td></td>
<td>n = 44</td>
<td>n = 49</td>
<td>n = 47</td>
<td>n = 50</td>
</tr>
<tr>
<td>Prothrombin F1&amp;2</td>
<td>1.67 (1.18)</td>
<td>1.83 (1.78)</td>
<td>1.58 (1.37)</td>
<td>1.76 (1.89)</td>
</tr>
<tr>
<td>(mmol/L)+</td>
<td>n = 41</td>
<td>n = 50</td>
<td>n = 44</td>
<td>n = 51</td>
</tr>
</tbody>
</table>

Values in bold signify statistically significant differences.

*Values have undergone logarithmic transformation prior to analysis.

Why are our findings different from those of HERS? The metabolic effects of HRT differ from those of HERS. The large dose of oestrogen and progestogens used in HERS resulted in a large reduction in HDL cholesterol, which would be regarded as beneficial for atheroma in the cardiovascular system. CEEs with MPA produce symptoms or on the skeleton, but are clearly important for bone health.

Figure 2: Kaplan-Meier plot of discontinuation rates.

Table 5 Adverse events

<table>
<thead>
<tr>
<th>Cardiovascular events</th>
<th>Stroke</th>
<th>Death cardiac</th>
<th>Death non-cardiac</th>
<th>MI</th>
<th>Composite of death, stroke, and MI</th>
<th>Hospitalization</th>
<th>Other elective procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>n = 49</td>
<td>n = 51</td>
<td>n = 49</td>
<td>n</td>
<td>n = 51</td>
<td>n = 49</td>
<td>n = 51</td>
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</table>

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in F1r and fibrin D-dimers. The transient fall in antithrombin levels with HRT has been noted previously, as has a fall in factor VII.\textsuperscript{15} Of importance, there were no increases seen with HRT in the other markers of susceptibility to venous thrombosis, such as APC resistance and fibrin D-dimers. This was reflected by the equal numbers of venous thrombo-embolic events seen with both HRT and placebo. One concern with some HRT regimens is that there may be an increase in venous, and possibly arterial, thromboembolism. This is usually an early event, and other studies of a different HRT regimen have suggested early harm.\textsuperscript{7,8} These studies used a relatively high starting dose of HRT for the patients’ age and found an increase in cardiovascular events in the first year of treatment with HRT, even though the incidence of these events has tended to decline in later years. This dose of oestrogen could be of initial harm to older women but of benefit to younger women.\textsuperscript{16} It is therefore of interest that those women in WHI on active treatment who were either closest to menopause or in the youngest age decade showed a decrease in events compared with the older groups.\textsuperscript{8,13} In our pilot study, we do not see any evidence of such an increase in events. We chose a low dose of a different oestrogen because adverse effects of HRT on coagulation activation appear to be dose-dependent and may vary with the type of oestrogen,\textsuperscript{17,18} and we appear to have avoided this risk. We did not measure inflammatory markers in our study. However, although oral HRT has been shown to increase CRP concentrations, the relevance of this is unclear because it also reduces the levels of various other inflammatory markers.\textsuperscript{19} The choice of progestogen may also be important for the cardiovascular system. MPA has been shown to negate the beneficial effects of oestrogen on vascular function,\textsuperscript{20,21} whereas our chosen progestogen, NETA, appears to have a much smaller negative effect.\textsuperscript{22} We observed a smaller number of cardiovascular events in the HRT group, although this reduction was not statistically significant. The CHD events in the WHI studies were fewer in those on CEE alone than in those on combined CEE plus MPA. The number of events in our study was much higher than those seen in the HERS secondary prevention study, probably reflecting the higher risk population we chose to study. Our WHISP patients were all within 1 month of an acute coronary syndrome, whereas the HERS population were all at least 6 months beyond their last cardiac event. Obviously, the HERS trial was a full study rather than a pilot study, with a much greater patient population studied over a longer time period.

Another randomized trial of transdermal oestradiol-17β with or without transdermal NETA also failed to show benefit in women with CHD,\textsuperscript{23} but again the dose of oestradiol used (80 μg per day) was high for the age of the patients. In contrast, a randomized trial using the relatively lower dose of oral oestradiol 1 mg daily showed a non-significant reduction in coronary deaths during the first 12 months of study.\textsuperscript{24} It has been suggested that only relatively healthy arteries will respond to HRT, and this could explain the apparent benefit in younger women but lack of response in older women.\textsuperscript{25} This concept is supported by primate data,\textsuperscript{26} but there are findings in humans, which show that diseased arteries can respond to oestrogen.\textsuperscript{27,28} Our study would support these findings.

Two main difficulties with our study were encountered. First, it proved to be difficult to recruit patients into the trial. Only 5% of patients screened were eventually enrolled in the study. Sixty percent of patients screened were ineligible for the study, and of those eligible only 13% were actually enrolled. However, this compares favourably with the published recruitment rates of other randomized trials of women with CHD. For example, the Estrogen Replacement and Atherosclerosis trial screened 73,327 women to recruit 309,\textsuperscript{29} an uptake rate of <1%. The main reason for low recruitment was refusal to take part in the trial. Secondly, the adherence to therapy was relatively poor. In the HRT group, 22% of patients discontinued because of side effects. These difficulties could be in part due to the unfamiliarity of local investigators with HRT, as they were not experienced in menopause and HRT management. Future studies may benefit from the involvement of local menopause clinicians with the cardiac teams, helping to improve both study uptake and treatment adherence.

In conclusion, the WHISP study has demonstrated that a low-dose HRT regimen can be given safely to post-menopausal women with acute coronary syndromes. No adverse effects on coagulation activation were observed. The lack of an early increase in cardiovascular events was in contrast to that seen in a previous secondary prevention study using a different HRT regimen, suggesting that the dose and type of HRT regimen may be critical in determining benefit or harm for the cardiovascular system. Full clinical trials of alternative HRT regimens are clearly needed.

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References