Articles

Oestrogen therapy for prevention of reinfarction in postmenopausal women: a randomised placebo controlled trial

*The ESPRIT team**

Summary

Background Results of observational studies suggest that hormone replacement therapy (HRT) could reduce the risk of coronary heart disease (CHD), but those of randomised trials do not indicate a lower risk in women who use oestrogen plus progestagen. The aim of this study was to ascertain whether or not unopposed oestrogen reduces the risk of further cardiac events in postmenopausal women who survive a first myocardial infarction.

Methods The study was a randomised, blinded, placebo controlled, secondary prevention trial of postmenopausal women, age 50–69 years (n=1017) who had survived a first myocardial infarction. Individuals were recruited from 35 hospitals in England and Wales. Women received either one tablet of oestradiol valerate (2 mg; n=513) or placebo (n=504), daily for 2 years. Primary outcomes were reinfarction or cardiac death, and all-cause mortality. Analyses were by intention-to-treat. Secondary outcomes were uterine bleeding, endometrial cancer, stroke or other embolic events, and fractures.

Findings Frequency of reinfarction or cardiac death did not differ between treatment groups at 24 months (rate ratio 0·99, 95% CI 0·70–1·41, p=0·97). Similarly, the reduction in all-cause mortality between those who took oestrogen and those on placebo was not significant (0·79, 0·50–1·27, p=0·34). The relative risk of any death (0·56, 0·23–1·33) and cardiac death (0·33, 0·11–1·01) was lowest at 3 months post-recruitment.

Interpretation Oestradiol valerate does not reduce the overall risk of further cardiac events in postmenopausal women who have survived a myocardial infarction.

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Introduction

Data from observational studies suggest that hormone replacement therapy (HRT) reduces the risk of coronary heart disease. Results of a meta-analysis[1] indicate a relative risk of 0·70 for ever users of oestrogen as HRT, with a slightly lower risk (0·66) for users of combined therapy (oestrogen plus progestagen). Such risk reductions seem plausible, since studies show potentially advantageous changes in lipid profiles,[2,3] vessel walls,[4] fibrinogen and antithrombin III concentrations,[5,6] and insulin secretion[7] in women on HRT. However, possibly unfavourable effects, such as altered triglyceride[8] and factor VII concentrations,[9] have also been reported. Studies that used angiography or carotid ultrasonography have provided contradictory evidence. Increased survival in ever users of oestrogen with greater than 70% coronary artery stenosis was noted in one observational study.[10] Findings of three randomised trials,[11–14] however, showed no beneficial effect on progression of coronary arteriosclerosis, although those of another trial[15] indicated a slower rate of progression in healthy postmenopausal women who took unopposed oestrogen (17β oestradiol) rather than placebo. Results of a small trial[16] indicate no effect of conjugated oestrogen on recurrence of ischaemic events.

The results of the Heart and Estrogen/progestin Replacement Study (HERS), a randomised controlled trial[17] of HRT in women with coronary heart disease that used the clinical end-points of non-fatal myocardial infarction or cardiac death, indicate no overall difference between intervention groups. HERS compared 2763 women with coronary disease allocated to either conjugated equine oestrogen plus medroxyprogesterone acetate or placebo. A significantly increased risk of cardiac events in the first year of treatment was noted in women given active treatment, followed by a reduced risk in years 3–5 that was not sustained with further follow-up.[18] Results of smaller trials of women with ischaemic heart disease,[19] or who had recently had a cerebrovascular event,[20] also showed no cardiac benefit from HRT.

The Women's Health Initiative randomised controlled trials of primary prevention assessed two hormonal components—namely, oestrogen alone in women who had undergone hysterectomy, and oestrogen plus progestagen in those who had not. The combined treatment component, which was stopped early, showed a significantly increased risk of coronary heart disease, an effect that was greatest in the first year.[21] Results are not yet available for the unopposed oestrogen component, which is still being assessed.[22]

Almost all randomised trials with clinical cardiac endpoints have investigated combined hormone therapies. The oEStrogen in the Prevention of

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ReInfarction Trial (ESPRIT) was, therefore, designed to assess the effect of unopposed oestradiol valerate on risk of another cardiac event or death in postmenopausal women who had just survived their first myocardial infarction.

Methods

Participants

All women aged 50–69 years admitted to coronary care units or general medical wards in participating hospitals in England and Wales between July, 1996, and February, 2000, were eligible for inclusion provided that they met the diagnostic criteria for myocardial infarction, they were discharged alive from hospital within 31 days of admission, and they had not had a previous documented myocardial infarction or any other exclusion condition—ie, use of HRT or vaginal bleeding in the 12 months before admission; history of breast, ovarian, or endometrial carcinoma; or active thrombophlebitis or a history of deep-vein thrombosis or pulmonary embolism, acute or chronic liver disease, Rotor syndrome, Dubin-Johnson syndrome, or severe renal disease.

Myocardial infarction was defined as two or more of: typical chest pain; ST elevation of 0.1 mV or more in at least one standard, or two precordial, leads of a 12-lead ECG; or biochemical marker indicative of myocardial infarction (serum concentrations of creatinine kinase or aspartate transaminase greater than twice the normal laboratory value, or serum troponin concentration greater than the locally defined threshold for myocardial infarction).

To identify eligible women, trained research nurses visited hospital wards at least twice a week to inspect ward admission lists and lists of patients, and to speak to ward nursing staff and cardiac rehabilitation nurses. The research nurses were instructed to investigate the eligibility of any woman in the target age group admitted with, or developing while in hospital, chest pain, angina, suspected myocardial infarction, or confirmed myocardial infarction. The hospital case notes of all such women were examined for the presence of criteria for myocardial infarction. If enzyme concentrations had not been assessed or ECG investigations had not been done, or if the results did not meet the diagnostic criteria initially, the case notes were reinspected at regular intervals. The research nurses were trained to interpret test results by the cardiology clinical lecturer (MAK), to whom they referred any ambiguous cases. If the diagnostic criteria were met, the woman's family doctor was asked by MAK whether he or she would be willing to collaborate with follow-up procedures. When agreement was obtained, the research nurse approached the woman with information about the trial. At every stage—ie, case note, family doctor, patient—evidence of the exclusion conditions was sought; if found, the nurse did not proceed with the remainder of the recruitment process.

At the first meeting with the patient, the nurse gave detailed verbal and written information about the trial to the woman, who was encouraged to discuss the trial with her family, friends, or medical care providers. At a second meeting, at least 24 h later, those agreeing to participate provided written consent. Women whose judgment was considered by the research nurse to be impaired were not included in the trial. Women without good understanding of English were recruited with the help of an interpreter, provided that a close female relative was able to emphasise the importance of reporting vaginal bleeding. At recruitment, the research nurse recorded information from the woman about height, weight, smoking habits, alcohol use, age when fulltime education finished, last occupation, ethnic group, ever use of oral contraceptives or HRT, age at last menstrual period, history of hysterectomy, ever been told she had angina, high blood pressure, stroke or diabetes, and fractures in the previous 10 years.

Most women were recruited in hospital, and were instructed to start the trial medication on the day of discharge (the date when these women were deemed to have formally entered the study). Delays at the preinterview stages sometimes meant that the recruitment interview(s) took place in the woman's home, in which instance participants were asked to start trial medication on the date of the second interview (and were deemed to have entered the study on that day).

The process of screening hospital records and approaching general practitioners before speaking to potential participants was undertaken to avoid disturbing women ineligible for the trial. However, in two hospitals, the ethics committees required that consent be obtained from patients before their case notes were inspected or their family doctor contacted, or both.

The trial was approved by the central ethics committee of the Royal College of General Practitioners, UK, the research ethics committee of the University of Manchester, UK, and the local research ethics committees of the 35 collaborating hospitals in the northwest of England and Wales.

Protocol

Women were randomly allocated to receive either 2 mg oestradiol valerate or placebo, taken as one tablet daily for 2 years. Randomisation was stratified by hospital. For each hospital, the trial statistician (RMcN) used a restricted randomisation scheme based on a block size of four to generate a list of treatment allocations. Consecutive study numbers were then attached to the allocations. The lists were sent to Schering AG who prepared numbered packages that contained the corresponding treatments. The two treatments were of identical appearance and were supplied in identical packaging.

On giving consent, each woman was assigned the next available study number for her hospital and received a 12-week supply of medication from the recruiting research nurse. Thereafter she was requested, by letters sent close to the relevant date, to see her family doctor at 12, 24, 48, and 72 weeks after recruitment to receive further supplies of medication previously dispatched from the trial office.

The randomisation lists were held in a locked room separate from the main trial office, accessible only by RMcN. Early notification of the ESPRIT treatment allocation, that is before the entry date plus 2 years, was made to a participant's family doctor if the information was required by a doctor treating her; if unblinded, the trial medication was discontinued. Allocation was also disclosed if a participant who had not had a hysterectomy chose to withdraw early from ESPRIT treatment, to ensure that appropriate gynaecological investigations could be arranged as soon as possible. In the early stages of the study, women who had had a hysterectomy and who withdrew early from treatment were also notified. Individuals involved in outcome assessment remained unaware of allocation throughout the trial.

Women in either group were allowed to receive any additional treatments, besides HRT, deemed appropriate by their medical carers.

The primary end-points were first non-fatal reinfarction, cardiac death, or death from another cause within 2 years of study entry. Surveillance of participants was for 2 years from randomisation, irrespective of whether or not they took the ESPRIT treatment for the full period. Follow-up of the final recruit ended on Feb 2, 2002.

All participants were flagged at the NHS Central Register in Southport, England, by the Office for National Statistics for notification of deaths that occurred between August, 1996, and February, 2002, and a search was made on the NHS-Wide Clearing Service for hospital consultant episodes between July, 1996, and August, 2001, using all codes that might have been rationally used to classify individuals with myocardial infarction.

We also obtained data on participants by follow-up questionnaires sent to their family doctors at about 3, 6, 12, and 18 months after study entry, to be completed after the woman visited to collect supplies of ESPRIT medication, and at 24 months after finishing treatment. The questionnaire enquired about vital status and reinfarction, and about secondary events and compliance with treatment. Reminders were sent to doctors who did not return the follow-up questionnaire, with one additional reminder at 24 months. For a small number of women, the doctor withdrew from the trial after treatment had started, although the women themselves wished to continue participating; in these circumstances the women were contacted directly by a trial physician (MAK or PH) and follow-up questionnaires were completed by telephone.

Suspected myocardial infarction or death was also reported by the research nurses if encountered while routinely investigating admissions in collaborating hospitals for possible new participants; this type of ascertainment stopped when recruitment ceased in February, 2000.

Finally, a fax was sent (and followed up by telephone calls if necessary) to the family doctors of all women still in the trial after May, 2001, to ascertain whether an unreported reinfarction or death had occurred between May, 2001, and the end of her follow-up.

Deaths and reinfarctions reported by relatives or participants in telephone calls or letters to the centre were also investigated, as were those noted in hospital records reviewed by MAK.

Irrespective of the original source of information, the medical records of all individuals who had potential reinfarctions were retrieved and, using the same criteria as for the original myocardial infarction, MAK or the research nurse ascertained, blind to treatment group, whether or not a reinfarction had actually occurred. In the instance of reported deaths, medical records, death certificates, and autopsy reports (where applicable) were retrieved and presented by MAK. The records were reviewed, without knowledge of treatment group, by a committee of five cardiologists who assessed whether or not the death was very unlikely, unlikely, possible, likely, or confirmed as cardiac. In the statistical analysis, those described as confirmed or likely were classified as cardiac deaths, with all others classified as other deaths.

Other outcomes of interest were uterine bleeding, endometrial cancer, breast cancer, stroke, other embolic events, fractures, and compliance with treatment. Information was obtained from the questionnaires completed by family doctors and, for cancers registered with a cancer registry, from the Office for National Statistics. No attempt was made to verify reports from these sources, except in the instance of uterine bleeding. In view of the possibility of malignant endometrial changes in women who had not had a hysterectomy and who received active treatment, additional procedures were adopted to maximise the notification of all episodes of vaginal bleeding. The information leaflet given to patients details the possibility of endometrial changes (hyperplasia and cancer). At recruitment and at each follow-up contact, both the woman and her family doctor were reminded of the importance of reporting any vaginal bleeding to the ESPRIT team. After a report of bleeding, the trial gynaecology research fellow (KG), using a predetermined protocol, contacted the patient and assessed, by telephone, whether the episode required further investigation. In most instances, where the history did not suggest a withdrawal bleed, a pipelle endometrial biopsy was done by KG, usually at the woman's local surgery but, if required, at her local hospital or a tertiary centre. After the biopsy, the woman started a 14-day course of medroxyprogesterone acetate 20 mg daily. If complex hyperplasia was noted, two further 14-day courses of medroxyprogesterone acetate were given. ESPRIT treatment was continued concurrently. Any woman whose biopsy showed atypical hyperplasia was withdrawn from ESPRIT treatment and immediately started on 3 months of cyclical medroxyprogesterone acetate. All women with atypical hyperplasia had their endometrium assessed by hysteroscopy with further endometrial biopsy and, in some instances, pelvic ultrasound scanning.

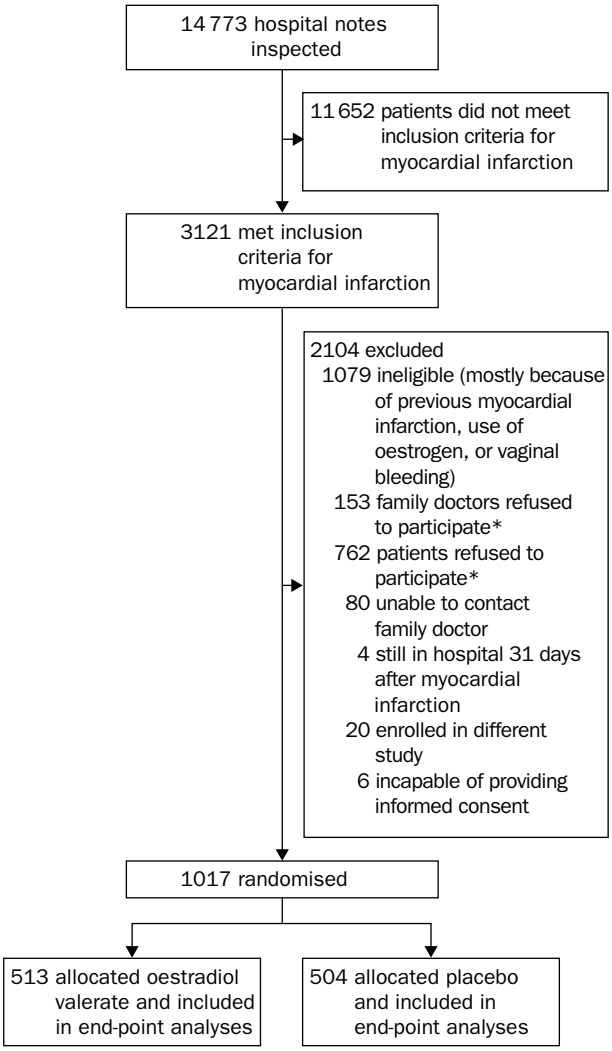
If simple, complex, or atypical hyperplasia was found, repeat endometrial biopsies were done every 6 months until complete resolution of the endometrial abnormalities. A histopathologist (HB) who was unaware of treatment assignment interpreted all biopsy specimens.

The team investigating uterine bleeding was separate from that investigating cardiac outcomes, to ensure that the knowledge of bleeding (suggesting active treatment) should not influence outcome assessment.

When women who had not had a hysterectomy stopped taking active drug or placebo, either at 2 years after study entry as scheduled or earlier, those who had not been previously investigated for endometrial bleeding (or who had continued treatment after the last investigation) were offered an endometrial biopsy. Women with endometrial abnormalities identified at the end of the 24 month period were managed in the same way as those with problems detected during treatment.

After 2-years of follow-up, or after early withdrawal, all women who had not had a hysterectomy and who had taken active treatment were sent annual reminders that they had received unopposed oestrogen and that any vaginal bleeding should be fully investigated. A similar letter was sent to their family doctor. This procedure will be continued for each of these women until 5 years after the end of ESPRIT medication.

Formal methods to check compliance were considered unfeasible, but family doctors were asked to report on patients' compliance at 3, 6, 12, 18, and 24 months. At 6 weeks after entry to the study, each woman was contacted by a study clinician or nurse to check progress and asked about compliance. Additionally, whenever a participant was in contact



Trial profile
*Excluded without eligibility being fully established.

with ESPRIT clinicians for any reason, attempts were made to gain information about regularity of tablet use.

Statistical analysis

The cumulative incidence rate for non-fatal reinfarction or cardiac death in a population not receiving oestrogen was estimated as 13% from results of previous studies, and we postulated, on the basis of findings from observational studies, that oestrogen would reduce this rate by a third. On the basis of these figures, about 1700 participants would need to be recruited to achieve 80% power with a two-sided test and a 5% significance level. A study with 500 in each group would have a power of 56%. These figures assume full compliance with treatment; non-compliance in the active group would reduce the effect of oestrogen and hence the power of the study.

Recruitment of participants was slower than anticipated, with fewer myocardial infarctions taking place in the recruitment areas than predicted from hospital statistics. Audit of hospital discharge records indicated that the research nurses identified more than 90% of eligible cases. Substantial increases in funding would have been required to recruit the number of participants needed for optimum power. In discussion with the data monitoring committee and later with an advisory committee convened by the UK National Health Service Research and Development Programme, we decided that, even with reduced power, the study would provide important information about the use of unopposed oestrogen for secondary cardiac prevention. Recruitment to the trial was terminated when a revised target of 1000 women had been reached.

All primary analyses were by intention-to-treat. The main analysis compared the rates of non-fatal reinfarction or cardiac death in the 2 years after study entry, with observation time censored at reinfarction, death, or 24 months, whichever arose first. If a woman had a non-fatal reinfarction and later a cardiac death, only the reinfarction contributed to the rate numerator. Crude and adjusted rate ratios were estimated from Cox's proportional hazards model as implemented in STATA (version 7). The variables for which adjustments were made were chosen, before inspection of the data, as potential confounders on the basis of their likely relation with the primary end-points. They were: reported history of diabetes, high blood pressure, hysterectomy, body-mass index (BMI; <30 kg/m^2 *vs* ≥ 30 kg/m^2), smoking habit at recruitment (never, ex-smoker, intending to give up, or current smoker), and age at entry (treated as a continuous variable). The adjusted and unadjusted

	Oestradiol valerate		Placebo	
	Number*	Mean (SD) or number (%)	Number*	Mean (SD) or number (%)
Age at admission to hospital (years)	513	62·3 (5.2)	504	62·9 (4·9)
Age at finishing full-time education (years)	498	14·9 (1·2)	479	14·9 (1·2)
Age at last menstrual period (years)	487	46·3 (5·8)	476	46·6 (5·7)
BMI (kg/m²)	507	26·8 (5·1)	500	26·7 (5·3)
Last occupation manual	499	286 (57%)	483	292 (60%)
Smoker at time of admission	513	276 (54%)	503	264 (52%)
Normally drinks >1 unit of alcohol per week	513	197 (38%)	504	177 (35%)
White	511	496 (97%)	503	489 (97%)
Ever had				
Angina	512	140 (27%)	504	136 (27%)
High blood pressure	513	237 (46%)	504	211 (42%)
Stroke	513	39 (8%)	504	36 (7%)
Diabetes	513	79 (15%)	503	74 15%)
History of				
Fracture in previous 10 years	512	71 (14%)	503	97 (19%)
Hysterectomy	513	140 (27%)	504	105 (21%)
Oral contraceptive use	509	187 (37%)	497	185 (37%)
Used HRT >12 months before admission	512	62 (12%)	502	51 (10%)

*Number for whom information available.

Table 1: **Baseline characteristics**

	Number (%) not complying		
	Oestradiol valerate (n=513)	Placebo (n=504)	Total (n=1017)
Time since entry (months)			
3	149 (29%)	118 (23%)	267 (26%)
6	212 (41%)	134 (27%)	346 (34%)
12	259 (51%)	157 (31%)	416 (41%)
18	279 (54%)	171 (34%)	450 (44%)
24	294 (57%)	184 (37%)	478 (47%)

Table 2: **Rate of known non-compliance in the two treatment groups by time since study entry**

results yielded similar findings. We have presented mainly unadjusted rate ratios but have also given adjusted rates for the primary end points. Analyses were also done that excluded women randomised to treatment but who reported that they never took ESPRIT medication. A p value of less than 0·05 was judged significant.

Rate ratios for non-fatal reinfarctions, and for cardiac deaths ignoring earlier reinfarctions, are reported. To allow for the possibility that a reduction in cardiac deaths might be offset by an increase in other deaths, all-cause mortality rate ratios were also estimated. Analyses were undertaken for the 24 months as a whole and, as a secondary analysis, to examine time trends by follow-up period within the 2 years of assigned treatment. To test for linear trend in the log rate ratios as time from entry to study increased, the significance of a regression term, representing the interaction between treatment group and time, was calculated.

Interim analyses of the primary outcomes, secondary events (including uterine bleeding), and recruitment rates were done by RMcN in August, 1998, October, 1999, and October, 2000. The data monitoring committee reviewed these results and on each occasion recommended continuation of the trial. No formal statistical criteria were recorded for stopping the trial early. The present analyses do not allow for this sequential testing.

Role of the funding source

Schering AG provided all trial medication (active and placebo). The sponsors of the study had no role in study design (other than the decision to curtail the sample size because of financial limitations), data collection, data analysis, data interpretation, or writing of the report.

Results

The figure shows the trial profile. 1017 women were randomly assigned to active treatment (n=513) or placebo (n=504). At the time of admission the mean age of participants was 62·6 years, 97% (n=985) were white, 53% (n=540) were smokers, 24% (n=245) reported having had a hysterectomy, and 15% (n=153) had been told they had diabetes (table 1). Both groups had similar baseline characteristics, including those identified a priori as potential confounders.

Compliance with treatment was poor, and was lower in the active group than in the placebo group (table 2). The proportion not complying in the active group was higher than that in the placebo group because of the high rate of vaginal bleeding seen in individuals taking oestradiol valerate. 238 women reported such bleeding at some point during the trial: 56% (208 of 373) and 7% (26 of 399) of non-hysterectomised women in the active and placebo groups, respectively, and four of 245 women who had had a hysterectomy. Even in women who had had a hysterectomy non-compliance was higher (39%, n=54) in the active than in the placebo group (31%, n=32).

	Oestradiol valerate (n=513)	Placebo (n=504)	Rate ratio (95% CI)	p
Reinfarction or cardiac death	62	61	0·99 (0·70–1·41)	0·97
Cardiac death	21	30	0·68 (0·39–1·19)	0·17
Death from any cause	32	39	0·79 (0·50–1·27)	0·34

Table 3: **Rate ratios for reinfarction, cardiac death, or any death by 24 months**

91 patients had a reinfarction, of whom 20 subsequently died within 24 months of study entry. In all, 71 women died during the 24 months of follow-up, of whom 38 were classified as confirmed cardiac deaths, 13 as likely, five as possible, and 15 as very unlikely to be cardiac deaths; for the analysis, 51 were classified as cardiac and 20 as other deaths. Of the 51 cardiac deaths, 32 were in patients who had not had a previous reinfarction. The primary outcome was thus confirmed in 123 women (12%), 62 in the active group and 61 in the placebo group (table 3).

Of those taking oestradiol valerate, 41 had one or more reinfarctions, but were still alive at the end of follow-up, six had a reinfarction and subsequent cardiac death, 15 died from cardiac causes without a previous reinfarction, and 11 died from other causes. In the placebo group, the figures were: 30 surviving reinfarction, 13 with reinfarction and subsequent cardiac death, 17 with cardiac death only, and eight who died from other causes. Additionally, one participant on placebo had a reinfarction and died from a non-cardiac cause. No difference between groups was seen in the overall rate of primary outcome, whether compared as a crude rate ratio (table 3) or after adjustment for potential confounders (rate ratio 0·98, 95% CI 0·68–1·40).

The risk of death from any cause by 24 months was less in those on active treatment, but this finding was non-significant (table 3). After adjustment for potential confounders the rate ratio was unchanged (0·79, 0·49–1·27). The reduction in cardiac death (by about one third) was greater than that for mortality from all causes, but was still not significant (table 3).

Table 4 shows the rate of all-cause and cardiac deaths in the first 3, 6, 12, and 18 months of treatment. A smaller risk of cardiac death in the active compared with the placebo groups by 24 months (0·68, 0·39–1·19, p=0·17) was noted to be lower at the other time points (although none of the rate ratios were significant). For cardiac deaths, the trend towards higher rate ratios with increased time in the trial was of borderline significance (p=0·10).

100 women (43 active, 57 placebo) reported that they had never taken any ESPRIT tablets (shown as non-compliant within the first 3 months in table 2). Inclusion of these women in the analysis would be expected to dilute any effect of oestrogen. This trend was not observed. The rate ratio for reinfarction or cardiac death was 0·99 (0·70–1·41, p=0·97) before these women were excluded from analysis compared with 1·04 (0·72–1·51, p=0·83) after.

Table 5 shows secondary outcome events reported

	Any death				Cardiac death			
	Oestradiol valerate	Placebo	Rate ratio (95% CI)	p	Oestradiol valerate	Placebo	Rate ratio (95% CI)	p
Time to events (months)								
3	8	14	0·56 (0·23–1·33)	0·19	4	12	0·33 (0·11–1·01)	0·052
6	14	20	0·68 (0·34–1·35)	0·27	9	18	0·49 (0·22–1·09)	0·079
12	20	30	0·65 (0·37–1·14)	0·13	14	25	0·54 (0·28–1·05)	0·059
18	27	39	0·67 (0·41–1·10)	0·11	19	30	0·61 (0·35–1·09)	0·096

Table 4: **Rate ratio of any death or a cardiac death at 3, 6, 12, and 18 months' follow up**

during the 24 months of treatment. Unadjusted relative risks were calculated for all women. The number of events was small. No instance of endometrial cancer was reported. Fractures arose less frequently in those on active treatment than on placebo, and both stroke and deep-vein thrombosis more frequently, although none of the risk ratios were significant.

In women taking oestradiol valerate, 208 of 373 who had not had a hysterectomy had vaginal bleeding while on treatment. Endometrial biopsies were obtained in 189 of these instances. Some women declined biopsy (14 at first bleed) or did not require a biopsy because of their medical history (five). When usable tissue was unobtainable, the endometrium was assessed by ultrasound. Eight of the 189 women had atypical hyperplasia, 12 complex hyperplasia, and 57 simple hyperplasia as their most abnormal biopsy, and 112 had a negative biopsy result. The endometrium of all women who had an abnormal biopsy result reverted to normal after treatment with medroxyprogesterone acetate (and in the instance of atypical hyperplasia, cessation of oestrogen). None of the women needed a hysterectomy because of bleeding or endometrial histology.

Of the women in the active group who had not had a hysterectomy and who did not bleed (n=165), 35 had not taken any medication and 13 had died before being offered biopsy (none from a gynaecological cause). All other women were offered endometrial biopsy, but only 27% (32 of 117) accepted. One woman was diagnosed with atypical hyperplasia and three with simple hyperplasia. These abnormalities all reverted to normal after a course of medroxyprogesterone acetate. In ten women, usable tissue was unobtainable, since the uterus could not be cannulated. Other procedures were initiated to investigate the endometrium.

	Oestradiol valerate (n=513)	Placebo (n=504)	Risk ratio (95% CI)	p
Stroke (number, %)	10 (2%)	6 (1%)	1·64 (0·60–4·47)	0·45
Transient ischaemic attack (number, %)	15 (3%)	13 (3%)	1·13 (0·54–2·36)	0·85
Deep-vein thrombosis (number, %)	2 (0·4%)	1 (0·2%)	1·96 (0·18–21·60)	1·00
Pulmonary embolism (number, %)	3 (1%)	3 (1%)	0·98 (0·20–4·84)	1·00
Breast cancer (number, %)	4 (1%)	4 (1%)	0·98 (0·25–3·91)	1·00
Endometrial cancer (number, %)	0	0	. .	. .
Fracture (number, %)	11 (2%)	18 (4%)	0·60 (0·29–1·26)	0·19

*Multiple events of the same type were counted only once.

Table 5: **Secondary outcome events by 24 months***

Discussion

The findings of ESPRIT indicate no overall difference in the frequency of reinfarction or cardiac death between individuals treated with unopposed oestrogen or placebo. Furthermore, although the rate of death from all causes was lower at 24 months in the active treatment group than in the placebo group, because of the slightly lower rate of cardiac deaths, this finding was not significant. The results of ESPRIT, showing no clear benefit of oestrogen for clinical cardiac outcomes, are consistent with those of other studies, which largely assessed combined treatments.[19,23]

Conjugated equine oestrogen has been used as the oestrogen in most studies, rather than 17β oestradiol, which was used in this study. The effects of the two forms of oestrogen might not be identical. One trial[20] that did show favourable effects on progression of atherosclerosis used oestradiol rather than conjugated equine oestrogen,[15] but oestradiol gave no protection from cardiac death in women admitted to hospital after a stroke or transient ischaemic attack.

ESPRIT had several strengths. All participants were followed-up for 24 months post recruitment (or to death if earlier). Endpoints were assessed from multiple sources with almost all reinfarctions and all deaths being ascertained blind to knowledge of treatment. Primary endpoints were assessed with standardised criteria, also blind to treatment allocation. Thorough procedures for following up vaginal bleeding enabled us to test the efficacy of unopposed oestrogen without increased detection of endometrial cancer. The power of the study, however, was less than planned, and known non-compliance was high. Furthermore, non-compliance was probably under-reported. Finally, the length of follow-up was too short to identify delayed effects of treatment; participants continue to be monitored for cancer (including breast and endometrium) and death.

Analyses by time within the 24-month period were done for two reasons. First, the results of HERS[17] showed a higher frequency of cardiac events during the early months in which women receive combined HRT, a similar time trend to that recorded in the combined HRT component of the Women's Health Initiative randomised trials.[21] Several other investigators have re-examined data from observational studies[24–26] to examine this pattern. Second, our limited compliance data suggested that any effect of oestrogen would be more apparent during the early months of treatment, when most women in both intervention groups were still taking their allocated medication. The risk of all-cause mortality and cardiac mortality was non-significantly lower in the active treatment group during the first 3 months after entering the trial.

When designing ESPRIT, we felt that we should use unopposed oestrogen, to avoid the use of progestagen in women at high risk of ischaemic events.[27–28] At that time there was little direct evidence of the effect of combined HRT on cardiovascular disease. However, since

progestagens had been shown to adversely affect serum lipid profiles we thought that, at best, any cardioprotective effect of oestrogen would be attenuated by the concurrent use of progestagen.[29–30] Thus, in women recovering from a myocardial infarction, the balance of likely risks and benefits would shift in favour of unopposed oestrogen, even in women who had not had a hysterectomy.

Vaginal bleeding was frequent in ESPRIT. A high rate of bleeding[21] or endometrial hyperplasia[2] has also been reported in other trials. In ESPRIT, the absence of endometrial cancer, and of hysterectomy resulting from bleeding, suggests that the risk of endometrial pathology is low, although bleeding resulted in poor compliance. Other secondary outcomes were rare, with wide CIs around the risk ratios. These results suggest than the decision to use unopposed oestrogen in a randomised clinical trial, with careful management of bleeding, was not inappropriate, even in women with an intact uterus. This decision does not, however, endorse the use of unopposed oestrogen in other circumstances in women who have not had a hysterectomy.

This trial did not have the power to detect small differences in risk, hence limiting the inferences that can be drawn. However, the value of a point estimate, the most plausible single value in light of the observed data, is consistent with a small beneficial effect of unopposed oestrogen (oestradiol) in postmenopausal women when taken immediately after a first myocardial infarction. The point estimate for the combined outcome of reinfarction or cardiac death, however, indicates no benefit. Thus, ESPRIT provides insufficient evidence of benefit to alter current guidance against the use of HRT for the secondary prevention of cardiovascular disease.[31]

The Esprit team

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Contributors

N Cherry contributed to the conception and design of the study, to the establishment of the team, to all aspects of study management, to the planning of the analysis, and to the drafting and revision of the report. She was principal investigator and is guarantor for the report. K Gilmour did endometrial biopsies, and was responsible for the management of gynaecological problems reported by patients and doctors, for liaison with histopathology, and for compiling a database. He contributed to the report. P Hannaford contributed to study design, to obtaining ethical review, to all aspects of management of the study, particularly those related to general practice, and to the drafting and revision of the report. A Heagerty contributed to study design, established and chaired the cardiac endpoints committee, and contributed to decision making in cardiac aspects of the study and to the final report. M A Khan contributedto study design, ethical review, and general management procedures. He had lead responsibility for cardiology issues within the study, for ascertaining eligibility, and for clinical management issues. He contributed to the report. H Kitchener contributed to the design of the study's gynaecological protocol and took responsibility for ensuring the quality of gynaecological care. He contributed to decision making on gynaecological aspects of the study and to the final report. R McNamee contributed to the conception and design of the study, to many aspects of study management, particularly in methods of data capture and quality control. She was responsible for establishing randomisation procedures and for unblinding, and she did the statistical analysis. She contributed to the drafting and revision of the report. M Elstein contributed to study design and to the supply of trial medication. C Kay contributed to study design and management. M Seif supervised the clinical work of the gynaecological fellow and contributed to the design of the gynaecological protocol. H Buckley contributed to the design of the gynaecological protocol and provided expert opinion on all endometrial histopathology specimens.

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Conflict of interest statement

CK, ME, and PH have received research grants from Schering AG; CK and PH have received hospitality and speaker fees from Schering Health Care Limited and Schering AG; ME served on the research advisory board of Schering AG as a paid consultant.

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