A case–control study on the effect of hormone replacement therapy on ischaemic heart disease

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SUMMARY

Background: *Many clinicians believe that hormone replacement therapy (HRT) protects against coronary heart disease (CHD) in women. However, recent reports have cast some doubt on this because of lack of dose–response or duration–response effects. Since CHD is common in women — about half of all postmenopausal women will get it and about a third of these will die from it — the effect of HRT on CHD is of great public health importance.*

Aim: *To determine the degree of cardioprotection conferred by HRT, including the effect of duration, time since last issue, the addition of progestogens, route of administration, and dose.*

Design: *Population-based case–control study.*

Setting: *Nine general practices recruited from the Trent Focus Collaborative Research Network.*

Method: *A total of 417 female cases with CHD matched by age and practice to 2435 controls with a case–control ratio of 1:5.8 were studied. The main outcome measure was the odds ratio for CHD calculated by conditional logistic regression adjusted for diabetes, hypertension, body mass index, and smoking.*

Results: *No evidence was found, either from univariate analysis or multivariate analysis, that use of HRT was associated with reduced risk of CHD (odds ratio = 1.32; 95% confidence interval = 0.93 to 1.87). Indeed, the trend was in the opposite direction. There was no association for different types of HRT (opposed or unopposed) or routes of administration. Similarly, there was no association for current or past use and no effect for dose or duration.*

Conclusion: *This study adds to growing evidence that HRT does not confer cardioprotection. Until there is robust evidence to the contrary, general physicians need to assess risks and benefits of HRT independently of any possible reduction in risk of CHD.*

Keywords: *coronary heart disease; ischaemic heart disease; hormone replacement therapy; women; risk.*

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Introduction

HORMONE replacement therapy (HRT) is generally accepted as being protective for osteoporosis[1] and it is widely used for the treatment of menopausal symptoms, such as hot flushes and urinary problems. Many clinicians believe that HRT protects against coronary heart disease in women. The evidence for this has largely come from observational studies.[2] The largest study is the Nurses Health Study, which is a primary prevention cohort study of 70 000 postmenopausal women with 20 years of follow-up. The main consistent finding from this study (as reported in 1985, 1991, 1996[3] and 2000[4]) is that HRT is associated with a reduction in risk of coronary heart disease of around 40%. However, its most recent report[4] has cast some doubt on this benefit, since there were no demonstrable dose–response or duration–response effects. Indeed, longer duration of HRT was associated with less benefit than short-term usage (the relative risk for coronary heart disease (CHD) in users of HRT was 0.4 for the first year but only 0.7 at ten years). Although higher doses of oestrogen were associated with beneficial effects on lipids, there was no dose–response effect for reduction in coronary risk.

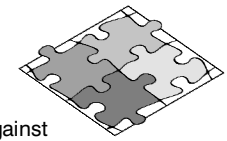
It has been suggested that apparent benefits found in such observational studies are owing to a selection bias, because there is evidence that patients who take HRT are healthier and wealthier than non-users.[5,6]

A meta-analysis of 22 randomised controlled trials reported evidence that women who take HRT were at higher risk (risk ratio = 1.39) than women who didn't.[7] This is an unlikely result if oestrogen does really reduce the risk of cardiovascular disease by between 35% and 50%.[8] A critical analysis of evidence[9] revealed that many of the trials have (a) been too short or too small to have adequate power to detect clinical events, (b) studied the impact of hormones on various physiological phenomena, symptoms or laboratory values,[10,11] or (c) lost substantial numbers to follow-up.[11]

Ongoing trials are likely to provide more robust evidence regarding the degree of cardioprotection conferred by HRT, although the full results are not expected for eight or so years. Initial results, however, have not been encouraging. The Women's Health Initiative Study is a primary prevention randomised controlled trial of 27 000 healthy women aged 50 to 79 years, designed to compare HRT with placebo.[12] After two years (out of an expected nine) they issued an interim statement that there was a small increase in the number of myocardial infarctions, strokes, and thromboses within the first two years of HRT.

The Heart and Estrogen/Progestin Replacement Study

HOW THIS FITS IN



What do we know?

Many clinicians believe that hormone replacement therapy (HRT) protects against coronary heart disease (CHD) in women. However, recent reports have cast some doubt on this because of lack of dose–response or duration–response effects.

What does this paper add?

This study adds to growing evidence that HRT does not confer cardioprotection. Until there is robust evidence to the contrary, general physicians need to assess risks and benefits of HRT independently of any possible reduction in risk of CHD.

(HERS) is a secondary prevention randomised controlled trial to compare HRT with placebo in 2763 women with established cardiovascular disease.[13] The results showed an early increase in CHD risk, followed by a later reduction within the overall null effect.

Another secondary prevention randomised placebo controlled trial (The Estrogen Replacement and Atherosclerosis Trial) investigated the effect of HRT on atherosclerosis in 300 women with established cardiovascular disease. This reported no benefit in terms of the progression of atheroma angiographically.[14]

Coronary heart disease is common in women — about half of all postmenopausal women will get it and about a third of these will die from it. Therefore, if HRT reduces risk of CHD its benefit might be substantial. But, if it is not beneficial, then adverse effects, such as breast cancer,[15] gall bladder surgery,[16] and deep vein thrombosis,[17] would require HRT to be restricted to women with menopausal symptoms and those at high risk of osteoporosis.

Aim

We conducted a large population-based case–control study to determine the degree of cardioprotection conferred by HRT, including the effect of duration, time since last script, the addition of progestogens, route of administration, and dose. We decided to use general practice computerised data, since this would not be subject to recall, non-responder or interview bias.

Method

Design and setting

The Trent Region was one of ten regional health authorities within the United Kingdom, covering a population of over five million. A matched case–control study was conducted in nine practices recruited from the Trent Focus Collaborative Research Network. The Research Network has been shown to be representative of other practices in Trent[18] and the quality of its computerised data has been validated and found to have high levels of accuracy and completeness.[19] MIQUEST[20] software was used to extract data from practice computer systems. Ethics approval was obtained from Trent Multi-Centre Research Ethics Committee.

Identification of cases

Incident cases were identified from the practice computer records from 1 January 1995 to 31 December 1999. Cases were women who had a first recorded diagnosis of CHD (including angina, myocardial infarction, and coronary artery surgery) or first prescription for nitrates.[21] Previous studies have shown that morbidity records are 80% sensitive for myocardial infarction[22] and nitrate prescriptions are 73% sensitive for angina.[23] Only cases who had been registered with the practice for more than five years before CHD was first diagnosed, and whose first recorded diagnosis was at least five years after the date on which the practice had its current computer system installed, were included. These criteria were used to ensure that the prescribing data were as complete as possible.

Selection of controls

Controls were women who had never had a recorded diagnosis of CHD. Four to six controls matched for age and practice were identified for each case, where possible. Controls were selected by finding the patients closest in age from an ordered list of all patients currently registered with the same practice. Controls had to be alive and registered with the same practice on the date that their matched cases were diagnosed with CHD and for the five years before this. The researcher who allocated the controls to the cases was blinded to the exposure status of each subject (this information was held on a separate database until the matching had been done). Each control was only allocated to one case. Where there were insufficient numbers of controls because of the age structure of the practice population, as many controls as possible were identified.

Data collection

Computerised data were extracted for cases and controls before the date of diagnosis using MIQUEST software.[20] The data comprised the name, dose, frequency, and dates of all prescriptions for HRT; Read codes and dates of onset for CHD, diabetes mellitus, and hypertension; age; sex; body mass index; most recently recorded smoking status; and registration date.

Assessment of exposure

The list of all drugs containing oestrogens or progestogens recommended for postmenopausal replacement in the *British National Formulary* (September, 2000) was used. The type of medication was grouped as follows:

- none used within the past five years;
- opposed HRT (i.e. combined oral treatment or topical oestrogen with oral progestogen); and
- unopposed HRT.

The time (in years) between the last prescription for HRT and the date of diagnosis for each case or the equivalent date for matched controls was determined. Exposure to HRT was grouped as follows:

- *non-use* — no recorded prescription for HRT within the preceding five years;

- *recent or current use* — at least one prescription for HRT within the six months before their index date; and
- *past use* — at least one prescription for HRT between six months and five years before their index date.

The route of administration was defined according to that used for the last script (oral or topical/implant). The dose was categorised according to the dose of oestrogen in the last script issued using a previously defined categorisation:[1]

- *low dose* — users of 1 mg oestradiol, 0.625 mg of oral conjugated oestrogens, 5 μg ethinyl oestradiol or 25 μg of transdermal oestradiol per day or less; and
- *high dose* — higher amounts of oestrogen.

Duration of use of HRT in the five-year period was defined by the number of prescriptions issued and categorised as follows: no scripts, 1–4 scripts, 5–8 scripts, 9–12 scripts, and >12 scripts. In general, one script was equivalent to three months of treatment.

Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using conditional multiple logistic regression. Models were adjusted for presence of diabetes, presence of hypertension, smoking status (current smoker, ex-smoker or non-smoker, not recorded) and body mass index (coded as body mass index <20 kg/m^2, 20–24.99 kg/m^2, 25-29.99 kg/m^2, 30 kg/m^2 or more, or not recorded). Missing data were coded in this way to prevent the loss of too many case–control pairs from the analysis.[25] Regression analyses were conducted with the conditional logistic procedure using STATA software (version 5.0).

Results

Characteristics of the study population

Of the 37 932 women who were currently registered at the time of the study, 1645 prevalent cases of CHD were identified (that is, women who had ever had a diagnosis of CHD recorded or more than one script for nitrates in the previous five years). Of these, 417 incident cases of CHD were identified who met our inclusion criteria. Two thousand four hundred and thirty-five age and practice-matched controls were identified (385 cases had six controls and 32 cases had fewer than six controls, giving an overall ratio of 1:5.8).

Table 1 shows the numbers of cases and controls and their baseline characteristics. As expected, cases with CHD were more likely to have risk factors recorded. Cases were more likely to have diabetes, hypertension, and to be current or ex-smokers.

Table 2 shows type, timing, route, dose, and number of scripts of the HRT in cases and controls. There were 60 cases (14.4% of 417) who had been issued with HRT in the five years before the recorded diagnosis of CHD, compared with 307 controls (12.6% of 2435).

Table 3 shows the ORs associated with HRT use and CHD before and after adjustment for diabetes, hypertension, smoking, and body mass index. In each case, comparisons have been made with patients with no recorded use of HRT in the preceding five years. There was no evidence that use of HRT was associated with reduced risk of CHD, either from univariate or multivariate analysis (adjusted OR = 1.32, 95% CI = 0.93 to 1.87). Indeed, the ORs tended to be greater than one, indicating a tendency towards an increased risk. Given the confidence intervals it is extremely unlikely that HRT reduces risk by between 35% and 50% — at best there may be a 7% reduction in risk associated with taking HRT. Specifically, there was no association for different types of HRT (opposed or unopposed) or routes of administration, no association for current or past use, and no effect for dose or duration.

Characteristics of controls who were users of HRT were compared with controls who were non-users of HRT, in order to determine whether patients who were more at risk of CHD tended to be put on HRT. This could have accounted for the increased OR observed. Users of HRT were less likely to have diabetes (2.6% versus 5.3%, $\chi^2 = 4.16$; df = 1 $P<0.04$), hypertension (22.1% versus 30.4%, $\chi^2 = 8.72$, df = 1, $P = 0.003$) and more likely to be non-smokers (53.4% versus 46.6%, $\chi^2 = 47.19$, df = 1; $P<0.0001$). There was no difference in the mean body mass index between the two groups (mean = 25.97 kg/m^2 versus 26.65 kg/m^2, $F = 3.73$, $P = 0.054$). In summary, users of HRT had better cardiovascular risk factor profiles than non-users of HRT.

Discussion

Summary of main findings

We have found no evidence to support the use of HRT in the primary prevention of CHD in women. There are theoretical reasons for expecting a cardioprotective effect for HRT in both the short and the long term. Oestrogen is an antioxidant and a calcium channel blocker and it alters lipid profile,[10] fibrinogen,[10] and vascular reactivity favourably.[8] This theoretical model has been supported by a randomised controlled trial of oestrogen alone compared with the combined HRT in terms of cholesterol reduction, but oestrogen alone was associated with a rise in triglycerides, which may have increased the risk of CHD.[11]

Strengths and limitations

Our study is based on a community population — the women were registered with nine general practices in Trent. Only those women with complete records for at least five years before the date of diagnosis (or pseudo-diagnosis date for controls) were entered into the study. The data biases inherent in retrospective case–control studies were therefore minimised. However, to ensure we had complete data that were comparable for cases and controls, we restricted the period of observation to five years before the diagnosis of CHD (or equivalent period for controls). While this may be considered a limitation, the duration of observation was still more than that of two recent secondary prevention trials, which are complete.[13,14] It was also longer than the current period of observation for which results are available for the primary prevention trial.[12] There may have been some case detection bias, since women who attend for repeat prescriptions of HRT may be more likely to have a diagnosis of CHD recorded on computer. Recall bias is not relevant here since we have used exposure data that were already entered on the clinical computer system prior to diagnosis of CHD. A limitation of our study is that we were not able to adjust for

Table 1. Baseline characteristics of 417 incident cases with CHD and 2435 age–sex matched controls without CHD.

	Cases with CHD	Percentage of 417	Controls without CHD	Percentage of 2435
Age at diagnosis/pseudodiagnosis (years)				
Mean	68.7		68.2	
Standard deviation	11.2		10.9	
Body mass index (kg/m^2)				
Valid number	268	64.3	1449	59.5
Mean	28.1		26.5	
Standard deviation	5.7		4.8	
Diabetes	58	13.9	121	5.0
Hypertension	192	46.0	714	29.3
Last recorded smoking status				
Non smoker	202	48.4	1156	47.5
Ex-smoker	69	16.5	295	12.1
Current smoker	80	19.2	385	15.8
Total with smoking status recorded	351	84.2	1836	75.4

CHD = coronary heart disease.

Table 2. Type, route, dose, and timing of HRT usage for cases and controls in the five years before the diagnosis/pseudodiagnosis date. Results are relative to a baseline of no HRT in the past five years.

Category	Cases with CHD	Percentage of 417	Controls without CHD	Percentage of 2435
Type of HRT				
No HRT in past 5 years	357	85.6	2128	87.4
Opposed HRT	46	11.0	245	10.1
Unopposed HRT	14	3.4	62	2.5
Current or past use of HRT				
Past use (6 months to 5 years)	29	7.0	146	6.0
Current use (last script within 6 months)	31	7.4	161	6.6
Years since last script				
Within past year	38	9.1	186	7.6
More than 1 and up to 2 years	6	1.4	46	1.9
More than 2 and up to 3 years	5	1.2	27	1.1
More than 3 and up to 4 years	4	1.0	16	0.7
More than 4 years	7	1.7	32	1.3
Route of administration (last script)				
Topical/implant	10	2.4	43	1.8
Oral	50	12.0	264	10.8
Dose of HRT (last script)				
Low dose	35	8.4	177	7.3
High dose	25	6.0	130	5.3
Number of scripts in five years before diagnosis/pseudodiagnosis				
1–4 scripts	24	5.8	126	5.2
5–8 scripts	8	1.9	49	2.0
9–12 scripts	10	2.4	44	1.8
>12 scripts	18	4.3	88	3.6

HRT = hormone replacement therapy.

socioeconomic status as this is poorly recorded on GP computer systems and we were not able to link census data to postcode with our method of data extraction. This could have biased our finding, if HRT usage is lower in deprived populations that are also known to have higher risk of CHD. Another strength of our study design is that there is no non-response bias, and no interview bias.

We found no evidence that patients with adverse cardiovascular risk factors were preferentially placed on HRT — indeed the converse was true. Our *post hoc* sample size calculation indicated that 413 cases (one case to six matched controls) would be able to demonstrate an OR of 0.55 for the use of HRT in the five years prior to the onset of CHD.[2,5] This is based on a 13% prevalence of use of HRT within the preceding five years. This sample size gave a 90% power at the two-sided 5% significance level and a correlation coefficient of 0.2.[24] This sample size should be sufficiently robust to detect a significant cardioprotective effect from the use of HRT in the previous five years. The fact that no such effect was shown in this population of women — indeed the non-significant trend was towards an increase in CHD with HRT used — is a strong refutation of the protective hypothesis.

Comparison with other studies

The evidence from clinical studies is mixed. While some

Table 3. Unadjusted and adjusted odds ratios for use of hormone replacement therapy and risk of ischaemic heart disease.

Category	Unadjusted odds ratios	95% CI	Adjusted odds ratios	95% CI
Use of HRT				
No HRT in past five years	1.00		1.00	
HRT used in past five years	1.25	0.89–1.74	1.32	0.93–1.87
Type of HRT				
Opposed HRT	1.20	0.83–1.73	1.27	0.87–1.86
Unopposed HRT	1.43	0.77–2.66	1.50	0.80–2.84
Current or past use of HRT				
Past use (6 months to 5 years)	1.26	0.81–1.94	1.27	0.81–2.00
Current use (last script within 6 months)	1.23	0.80–1.90	1.37	0.87–2.14
Years since last script				
Within past year	1.32	0.88–1.96	1.45	0.95–2.20
More than 1 and up to 2 years	0.83	0.35–2.00	0.90	0.37–2.18
More than 2 and up to 3 years	1.16	0.47–3.07	1.16	0.43–3.15
More than 3 and up to 4 years	1.60	0.52–4.86	1.34	0.43–4.18
More than 4 years	1.40	0.60–3.25	1.39	0.58–3.32
Route of administration (last script)				
Topical/implant	1.47	0.71–3.03	1.61	0.76–3.39
Oral	1.21	0.85–1.73	1.27	0.88–1.84
Dose of HRT (last script)				
Low dose	1.26	0.84–1.89	1.36	0.90–2.07
High dose	1.23	0.76–1.98	1.26	0.70–2.06
Number of scripts in five years before diagnosis/pseudodiagnosis				
1–4 scripts	1.20	0.75–1.92	1.32	0.81–2.16
5–8 scripts	1.05	0.49–2.28	1.18	0.54–2.60
9–12 scripts	1.45	0.71–2.97	1.46	0.69–3.08
>12 scripts	1.31	0.76–2.26	1.31	0.74–2.31

[a]Adjusted for diabetes, hypertension, body mass index, and smoking status. HRT = hormone replacement therapy.

have shown a marked reduction in coronary events in women on HRT, our findings are consistent with growing evidence that HRT is not associated with a reduction in coronary risk. This has been shown, not only from meta-analyses,[7] but also from interim results of randomised controlled trials of primary prevention[12] and secondary prevention.[13,14] Previous findings may be owing to methodological problems in the studies concerned. For example, unintended selection of healthy women may have influenced the reported beneficial effect of HRT on cardiovascular disease found in observational studies.[5,6] Other studies, where exposure status has been determined by interview or questionnaire, may have been subject to recall bias.[3]

Implications for clinical practice

Our study adds to growing evidence that HRT does not confer cardioprotection. Until there is robust evidence to the contrary, general physicians need to assess risks and benefits of HRT when recommending it for the prevention and treatment of osteoporosis and the amelioration of menopausal symptoms.

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