REVIEW ARTICLE

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Hormone Replacement Therapy and Risk of Acute Myocardial Infarction

A Review of the Literature

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Abstract

Many animal studies and studies on intermediate clinical endpoints have shown hormone replacement therapy (HRT) to be associated with both favourable and unfavourable cardiovascular effects. We reviewed the literature regarding HRT and the distinct endpoint of acute myocardial infarction (AMI) in peri- and postmenopausal women.

Searches of the MEDLINE and EMBASE databases were conducted. Fifty papers were identified as eligible for inclusion: eight randomised controlled trials, 18 cohort studies, 23 case-control studies and one case-control and cohort study.

The single large primary prevention randomised controlled trial on HRT and the risk of AMI in generally healthy women (Women's Health Initiative trial) reported a small yet significantly increased risk of AMI in postmenopausal women receiving combined HRT. This contrasts with a large number of observational studies that suggested a protective effect, although in many of these studies

the results were not statistically significant. Inconclusive evidence on the effect of duration of use does not support the notion that a possible protective association is causal. Detection bias and residual confounding are alternative explanations for the associations observed in the randomised controlled trial and observational studies. No studies on groups of women with existing cardiovascular disease or with diabetes mellitus, including the only large secondary prevention trial (Heart and Estrogen/Progestin Replacement Study), reported a significant change in AMI risk between HRT users and non-users.

There is insufficient evidence to suggest that HRT is associated with a change in the risk of AMI in the majority of women. However, certain subgroups of women with specific genetic polymorphisms may be more susceptible to a change in the risk of AMI with HRT use.

Hormone replacement therapy (HRT) is indicated for the alleviation of climacteric symptoms and for the prevention of osteoporosis in postmenopausal women.[1] Much attention has been given to other potential benefits of HRT as well as the potential risks, most notably the increased risk of breast cancer.[2] Opinion remains divided on whether HRT affects the risk of acute myocardial infarction (AMI). Because AMI is a relatively frequent clinical event in women of postmenopausal age, this issue is of great public health interest.

Evidence from animal studies and from clinical studies of intermediate endpoints has shown HRT to be associated with both favourable[3-7] and unfavourable[8-10] cardiovascular effects. However, this is only relevant to clinical practice if it translates into actual changes in the numbers of clinical events. We reviewed the literature regarding the association between the use of HRT and the risk of AMI.

1. Methods

Searches of the MEDLINE (1966–April 2004) and EMBASE (1988–April 2004) databases were conducted using the keywords 'myocardial infarct*', 'hormone*', 'postmenopausal', 'estrogen*', 'estrogen replacement therapy', 'hormone replacement therapy', 'infarction' and 'coronary heart disease'. The inclusion criteria for studies in this review were:

- The study must include original research on postmenopausal/perimenopausal women who received estrogen replacement therapy with or without added progestogens.
- The endpoint(s) of the study must be fatal or nonfatal AMI, or AMI otherwise not defined.
- The endpoint must be distinct – studies presenting results for AMI within another diagnostic category, for example coronary heart disease (CHD), without presenting results for AMI separately were excluded.
- The study must be published in English.

The bibliographies of relevant papers were searched for other potentially relevant papers not identified from the database searches.

2. Results

Forty-seven papers were identified from the database searches as being potentially eligible for inclusion. Nine of these were excluded: seven because AMI was included only within a broader category of CHD, one because the risk was calculated for AMI and stroke combined, and one because risk was calculated for death from any cause and not specifically from AMI. A further 12 papers were identified after searching the bibliographies of relevant papers, bringing the total number of papers included in this review to 50. Of these, there were eight randomised controlled trials, 18 cohort studies, 23 case-control studies and one case-control and cohort study. Risk estimates presented refer to comparison with HRT non-users unless otherwise specified.

2.1 Primary Prevention Studies

2.1.1 Randomised Controlled Trials (RCTs)

The WHI (Women's Health Initiative) trial was a double-blind, randomised, controlled trial designed to evaluate the benefits and risks of a specific combined-continuous HRT regimen in women with an intact uterus[11] and of conjugated equine estrogens (CEE) in women without a uterus (table I).[12] In the combined HRT arm of the trial, 16 608 postmenopausal women aged between 50 and 79 years at baseline (mean age 63.3 years in the CEE arm and 63.3 years in the placebo arm) were randomly assigned to receive either CEE 0.625mg combined with medroxyprogesterone (MPA) 2.5mg or placebo. There were no significant differences in the characteristics of the two study groups at baseline. Both the combined and estrogen-only arms of the trial were stopped prematurely; the CEE/MPA arm was stopped because of a significant increase in overall morbidity relating to the trial endpoints, whereas the CEE-only arm was stopped because of a significant increase in the risk of stroke. 133 cases of nonfatal AMI occurred in the CEE/MPA group compared with 96 in the placebo group, giving a hazard ratio (HR) of 1.32 with nominal 95% CI 1.02, 1.72 from an 'intention-to-treat' analysis and adjusted 95% CI 0.82, 2.13. These results were from an analysis including endpoints through April 2002.[11]

In the CEE-only arm, 132 cases of nonfatal AMI occurred compared with 153 in the placebo arm (HR 0.89 with nominal 95% CI 0.70, 1.12 and adjusted 95% CI 0.63, 1.26).[12] In both arms, the mean age of the women at study entry was 63.6 years. At the time of study termination, 53.8% of women had stopped taking the study medication. During the study, 5.7% of women in the CEE arm initiated HRT use outside the trial compared with 9.1% of women in the placebo arm. There was no differential unblinding of gynaecologists in these arms of the trial: 100 women in the CEE arm versus 83 women in the placebo arm ($p = 0.16$).

No significant change in the results was reported from a later final analysis on endpoints reached through July 2002 in the combined arm.[13] In this trial, a greater number of women in the HRT group (3444) were unblinded to HRT status compared with

Table I. Primary prevention: randomised controlled trials

Study	Setting	Description of cohort	Length of follow-up (y)	Endpoint	Data source	Age at baseline (y) [mean]	Cases in TG	Cases in PG	Risk estimate (95% CI)
Writing Group for the Women's Health Initiative Investigators, 2002[11]	40 US clinical centres	16 608 postmenopausal women with intact uterus	Mean of 5.2	Nonfatal AMI	Biannual in-clinic visits comprising interview and self-administered questionnaire. ECGs collected at baseline and after 3 and 6 years of follow-up	50–79 [63.3]	133	96	1.32 (nominal CI 1.02, 1.72), (adjusted CI 0.82, 2.13)
The Women's Health Initiative Steering Committee, 2004[12]	40 US clinical centres	10 739 postmenopausal women with prior hysterectomy	Average of 6.8	Nonfatal AMI	Biannual in-clinic visits comprising interview and self-administered questionnaire. ECGs collected at baseline and after 3, 6 and 9 years of follow-up	50–79 [63.6]	132	153	0.89 (nominal CI 0.70, 1.12), (adjusted CI 0.63, 1.26)
Manson et al., 2003[13]	40 US clinical centres	16 608 postmenopausal women with intact uterus	Mean of 5.2	Nonfatal AMI	Biannual in-clinic visits comprising interview and self-administered questionnaire. ECGs collected at baseline and after 3 and 6 years of follow-up	50–79 [63.3]	151	114	1.28 (nominal CI 1.00, 1.63), (adjusted CI 0.96, 1.70)
Nachtigall et al.,1997[14]	US chronic disease hospital	168 postmenopausal inpatients	Up to 10	AMI	Annual physical examination (including ECG, chest x-ray and blood tests) and medical record review	Mean 55.3 in TG, 54.9 in PG	1	3	0.33 (0.006, 4.15)

AMI = acute myocardial infarction; **PG** = placebo group; **TG** = treatment group.

those assigned to placebo (548). In addition, after about 2.5 years, a warning was issued to all participants about a possible association between HRT and an increased risk of CHD. This combination of differential unblinding and potential increased awareness of risk could have led to higher detection rates of atypical or mild AMIs among women in the HRT group, which would have resulted in an overestimated risk.[15]

A much smaller trial conducted by Nachtigall et al.[14] on 168 postmenopausal women in a chronic disease hospital reported a non-significant unadjusted risk estimate for fatal and nonfatal AMI of 0.33 (95% CI 0.006, 4.15) associated with combined HRT compared with placebo. This was based on only one AMI case in the treatment group and three cases in the placebo group.

2.1.2 Cohort Studies

Studies Reporting Decreased Risk Estimates

After following a cohort of postmenopausal women (median age 74 years) for up to 7.5 years, Henderson et al.[16] reported a protective effect against fatal AMI associated with ever use of HRT (age-adjusted relative risk [RR_{ageadj}] 0.60 $p < 0.05$; CIs not stated) [table II]. Statistically significant trends of an increasing protective effect with both increasing duration of use ($p < 0.05$) and with increased recency of use ($p < 0.05$) were also reported. Previous analyses on this cohort, after shorter follow-up, had also provided decreased risk estimates associated with HRT use, most of which were statistically significant.[17,18] In these studies, significantly decreased risk estimates were reported for both medium- and high-dose estrogen and for longer and shorter duration of use, although these did not differ significantly from each other.[18]

Stampfer et al.[19] studied 32 317 married postmenopausal nurses from 11 US states (Nurses Health Study) aged between 30 and 55 years and without prior CHD at baseline. After up to 4 years of follow-up, 65 cases of nonfatal AMI occurred within 105 786 women-years, yielding significantly reduced risk estimates for AMI associated with current HRT use, RR_{adj} 0.34 (95% CI 0.14, 0.82) but not with past use, RR_{adj} 0.65 (95% CI 0.33, 1.28). HRT use was recorded during follow-up, thereby accounting for changes in use over time. Confounding by lifestyle factors was thought to be at least partially controlled in this allegedly homogenous group of women.

Falkeborn et al.[20] studied 23 247 women from Uppsala, Sweden who had ever been prescribed HRT within a 3-year period for an average of 5.8 years. 227 cases of AMI were identified. Comparison of AMI incidence rates in the HRT cohort with the expected rates in the general female population of Uppsala gave a significantly decreased risk estimate for AMI associated with ever use of HRT: RR 0.81 (95% CI 0.71, 0.92). While lower risk estimates were reported with increasing duration of follow-up (RR 0.96; 95% CI 0.44, 1.83 and RR 0.76; 95% CI 0.55, 1.02, during the first and last years of follow-up, respectively), these were not significant and do not necessarily relate to increasing duration of HRT use. Adjustments were not made for several potential confounders. However, in a later sub-analysis, Grodstein et al.[21] reported little difference in the risk estimate for AMI after adjusting for several risk factors. Again, a lower risk estimate was reported with increasing follow-up, this being significant after >7 years. Information on HRT use was not updated during follow-up, which may have led to misclassification of exposure.

Three other large studies reported decreased but non-significant risk estimates for AMI associated with HRT use. Hernandez-Avila et al.[22] followed a cohort of female enrollees of the Group Health Cooperative, Puget Sound, aged 50–64 years for up to 6 years. 120 women discharged from hospital with a diagnosis of AMI were identified during 128 484 women-years of follow-up (RR_{adj} 0.7; 95% CI 0.3, 1.3 for current HRT use, after adjustment for age and calendar year). In a study of 13 084 postmenopausal nurses, Løkkegaard et al.[23] reported a risk estimate for AMI of HR_{adj} 0.97 (95% CI 0.57, 1.65) associated with current HRT use. This was based on 108 cases of AMI. Similar estimates were reported for past and ever HRT use. In a cohort of 7944 Finnish women aged between 57 and 65 years, with up to 8 years of follow-up, Sourander et al.[24] presented incidence rates for AMI corresponding to risk estimates of 0.77 (95% CI 0.42, 1.32) for current users. Three small cohort studies also yielded decreased but non-significant risk estimates,[25-27] which ranged from 0.16 to 0.34. However, these

Table II. Primary prevention: cohort studies

Study	Description of cohort	Length of follow-up (y)	Endpoint	Data source	Age at baseline (y)	No. of cases	Risk estimate (95% CI)
Henderson et al., 1991[16]	8881 women from Leisure World Retirement Community, California, USA	Up to 7.5	Fatal AMI	Biennual questionnaires medical records, hospital data	44–101	78	Ever users 0.60 (CI not stated)
Henderson et al., 1986[17]	8881 women from Leisure World Retirement Community, California, USA	Up to 3.2	Fatal AMI	Biannual questionnaires, medical records, hospital data	Median 74	84	Ever users 0.54 (0.33, 0.87)
Henderson et al., 1988[18]	8881 women from Leisure World Retirement Community, California, USA	Up to 7.4	Fatal AMI	Biennual questionnaires medical records, hospital data	44–101	139	Current users 0.47 (0.20, 1.08) Past users 0.62 (0.43, 0.90) Ever users 0.59 (0.42, 0.82)
Stampfer et al., 1985[19]	32 317 nurses from 11 US states	Up to 4	Nonfatal AMI	Postal questionnaires in 1976, 1978 and 1980	30–55	65	Current users 0.34 (0.14, 0.82) Past users 0.65 (0.33, 1.28)
Falkeborn et al., 1992[20]	23 247 entire female population of Uppsala Healthcare Region of Sweden	Average of 5.8	AMI	Pharmacy records, records linkage to registers	35+	227	Current users any HRT 0.74 (0.61, 0.88) OV+LNG 0.50 (0.28, 0.80) OD/CEE 0.90 (0.74, 1.08) Women <60y 0.69 (0.54, 0.86) Women ≥60y 0.84 (0.61, 1.13)
Grodstein et al., 1999[21]	9236 HRT users from female population of Uppsala Healthcare Region of Sweden[a]	Up to 16	Nonfatal AMI	Pharmacy records and records linkage to registers and postal questionnaire	30–55	213	Recent use 0.69 (0.48, 0.98) Past use 0.78 (0.57, 1.07) Ever use 0.75 (0.56, 0.99) unopposed HRT 0.86 (0.63, 1.19) opposed HRT 0.64 (0.45, 0.90)

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Table II. Contd

Study	Description of cohort	Length of follow-up (y)	Endpoint	Data source	Age at baseline (y)	No. of cases	Risk estimate (95% CI)
Hernandez-Avila et al., 1990[22]	128 484 enrollees of health maintenance organisation (GHC, Puget Sound, WA, USA)	Up to 6	Nonfatal AMI	Pharmacy database and linkage to other GHC databases	50–64	120	Current users 0.7 (0.3, 1.3)
Løkkegaard et al., 2003[23]	13 084 postmenopausal nurses	Up to 5	Fatal and nonfatal AMI	Postal questionnaire and National Registers of Death, Hospital Discharges and Central Persons	≥45	108	Current users 0.97 (0.57, 1.65) unopposed 0.97 (0.49, 1.93) combined 1.09 (0.54, 2.21) Past users 0.93 (0.54, 1.60) Ever users 0.95 (0.63, 1.44)
Sourander et al., 1998[24]	7944 participants in a mammography screening for breast cancer	Up to 8	Fatal and nonfatal AMI	Biennial questionnaires and record linkage to registers	57–65	196	Crude incident rate ratio 0.77 (0.42, 1.32)[b]
Petitti et al., 1987[25]	6093 enrollees of the KPMCP: Walnut Creek facility, USA	12–15 for mortality, 5–9 for HRT and other factors	Fatal AMI	Medical examinations and interviews or postal interview	18–54	11	Ever users 0.3 (0.1, 1.3)
Lafferty and Helmuth, 1985[26]	124 women from a single general practice	3–16 (mean 8.6)	AMI	Annual/biannual physical examinations	43–60	7	Current users 0.16 (0.003, 1.29)
Lafferty and Fiske, 1994[27]	157 women from a single general practice	3–19	AMI	Annual/biannual physical examinations	43–60	6	Current users 0.34 (0.09, 1.34)
Wilson et al., 1985[28]	1234 women from Framingham, MA, USA	Up to 8	Nonfatal MI	Interview + medical records	50–83	51	Ever users 1.87 (CI not stated)

a Medium potency estrogen for at least 1 year (compared with use of low-dose estrogen or short-term users).

b Incidence per 1000 person-years: current users = 2.0 (1.1, 3.2); never users = 2.6 (2.2, 3.1).

AMI = acute myocardial infarction; **GHC** = Group Health Co-operative; **HRT** = hormone replacement therapy; **KPMCP** = Kaiser Permanente Medical Care Program; **OV+LNG** = estradiol valerate combined with levonorgestrel; **OD/CEE** = estradiol or conjugated equine estrogens with or without progestogen.

estimates had wide CIs and were based on a maximum of 11 cases.

Studies Reporting Increased Risk Estimates

The only primary prevention cohort study to find an increased, albeit non-significant, risk of AMI associated with postmenopausal exposure to exogenous estrogens (RR_{adj} 1.87; CIs and p-value not stated) was the Framingham Study,[28] which included 1234 postmenopausal women aged between 50 and 83 years with up to 8 years of follow-up (table II). The risk estimate was based on 51 AMI cases. Misclassification of exposure will have occurred because information on HRT use was not updated during follow-up and the risk estimates may have been diluted by the inclusion of older women, who would have been less likely to be exposed.

2.1.3 Population-Based Case-Control Studies

All of the identified population-based case-control studies reported neutral or decreased risk estimates for AMI associated with HRT use (table III). Varas-Lorenzo et al.[29] performed a nested case-control study within a cohort of postmenopausal women aged between 50 and 74 years, registered on the General Practice Research Database (GPRD). 1013 cases of fatal and nonfatal AMI were identified and age-frequency matched to 5000 controls. A decreased risk of HRT associated with AMI risk was reported (OR_{adj} 0.72; 95% CI 0.59, 0.89 and OR_{adj} 0.73; 95% CI 0.51, 1.03 for current and past use, respectively). Among current/recent users, lower risk estimates were reported for >3 years of HRT use (OR_{adj} 0.59; 95% CI 0.42, 0.85). No difference in AMI risk was reported between unopposed and opposed therapy, oral and transdermal therapy or with varying HRT dose. Decreased risk estimates were observed among most subgroups of women with varying levels of coronary risk factors.

In a study of postmenopausal women aged between 30 and 79 years, Heckbert et al.[30] reported reduced risk estimates for AMI associated with current and past HRT use (OR_{adj} 0.70; 95% CI 0.55, 0.89 and OR_{adj} 0.74; 95% CI 0.57, 0.96, respectively). These estimates were based on 850 cases of first fatal and nonfatal AMI and 1974 controls, matched by calendar year and the age-frequency of the cases. Previous analyses on this study population, with fewer cases, had provided similar but non-significant risk estimates.[31] The authors also reported a trend of decreasing AMI risk with longer duration of use among current but not past users (p = 0.05).

In a study of women in the UK aged between 35 and 65 years, Chilvers et al.[32] reported a decreased risk for nonfatal AMI associated with ever use of HRT (OR_{adj} 0.74; 95% CI 0.55, 0.99). This was based on 559 cases, each age-matched to two community controls from the same geographical area. When duration of HRT use was analysed, only use for >60 months was associated with a significant risk reduction (OR_{adj} 0.42; 95% CI 0.24, 0.73). No differences were seen between use of unopposed or combined therapy or between route of HRT delivery. Similar results were reported on 198 identified cases of fatal AMI.

Sidney et al.[33] reported no association between AMI risk and HRT use: OR_{adj} 0.96 (95% CI 0.66, 1.40) and OR_{adj} 1.07 (95% CI 0.72, 1.58) for current and past use, respectively. In this study of postmenopausal women aged between 45 and 74 years, 438 cases of women hospitalised for AMI were matched by year of birth and health centre facility to one control. Among current HRT users, no trend of decreasing risk was seen with increasing duration of use. A further analysis reported statistically significant results with combined HRT (OR_{adj} 0.6; 95% CI 0.4, 0.9) but not with unopposed estrogen (OR_{adj} 0.8; 95% CI 0.6, 1.2).[34]

Mann et al.[35] conducted a study among women aged between 45 and 64 years who were registered on the GPRD. 1521 cases of fatal and nonfatal AMI were identified and each was matched to four controls by 5-year age group. Of these, 117 (7.7%) cases and 562 (9.2%) controls had received HRT within the 6 months before the index date: OR_{adj} 0.83 (95% CI 0.66, 1.03).

Rosenberg et al.[36] conducted a study among postmenopausal women aged between 45 and 69 years. 858 cases of nonfatal AMI were identified from hospital coronary care units and were interviewed and matched to one control by 5-year age group and residential area. No association was found between the risk of AMI and ever use of unopposed estrogen: OR_{adj} 0.9 (95% CI 0.7, 1.2) or combined HRT OR_{adj} 1.2 (95% CI 0.6, 2.4). A statistically significant trend for a decrease in AMI

Table III. Primary prevention: population-based case-control studies

Study	Setting	Outcome studied	Data source	Age range (y)	No. of cases	No. of controls	Risk estimate (95% CI)
Varas-Lorenzo et al., 2000[29]	UK GPRD	Fatal and nonfatal AMI	GP medical records	50–74	1013	5000	Current users all HRT 0.72 (0.59, 0.89) opposed 0.79 (0.59, 1.08) unopposed 0.52 (0.35, 0.78) Past users all HRT 0.73 (0.51, 1.03)
Heckbert et al., 1997[30]	Enrollees of health maintenance organisation (GHC, Puget Sound, WA, USA)	Incident fatal and nonfatal AMI	Pharmacy database, medical records, telephone interview	30–79	850	1974	Current use 0.70 (0.55, 0.89) Ever use 0.72 (0.59, 0.88) Past use 0.74 (0.57, 0.96)
Psaty et al., 1994[31]	Enrollees of health maintenance organisation (GHC, Puget Sound, WA, USA)	Incident fatal and nonfatal AMI	Pharmacy database, medical records, telephone interviews (for survivors)	30–79	502	1193	Current users unopposed HRT 0.69 (0.47, 1.02) opposed HRT 0.68 (0.38, 1.22) Past users unopposed 0.69 (0.44, 1.07) opposed 1.04 (0.53, 2.05)
Chilvers et al., 2003[32]	East Midlands region of the UK	Nonfatal AMI	Interview and general practice records	35–65	559	1118	Ever use any HRT 0.74 (0.55, 0.99) unopposed only 0.82 (0.53, 1.28) combined only 0.76 (0.53, 1.10)
		Fatal AMI			198	393	Ever use any HRT 0.41 (0.27, 0.61) unopposed only 0.47 (0.26, 0.85) combined only 0.40 (0.23, 0.68)
Sidney et al., 1997[33]	Medical Centres of KPMCP	Incident AMI	In-person interview and medical records	45–74	438	438	Current users 0.96 (0.66, 1.40) Women who had not had a hysterectomy 0.89 (0.52, 1.53) Unopposed in women without a uterus 0.95 (0.50, 1.80) Past users all HRT 1.07 (0.72, 1.58)

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Table III. Contd

Study	Setting	Outcome studied	Data source	Age range (y)	No. of cases	No. of controls	Risk estimate (95% CI)
Petitti et al., 2000[34]	KPMCP	Incident AMI	In-person interview and medical records	45–74	410	411	Current users unopposed 0.8 (0.6, 1.2) opposed 0.6 (0.4, 0.9) By number of major CHD risk factors[a] none – 0.9 (0.5, 1.6) 1 – 0.8 (0.5, 1.8) 2 – 1.1 (0.5, 2.2) Past users 1.0 (0.7, 1.4)
Mann et al., 1994[35]	General practices	Fatal and nonfatal AMI	VAMP database	45–64	1521	6084	Current user 0.83 (0.66, 1.03) opposed HRT 0.68 (0.47, 0.97) unopposed HRT 0.93 (0.47, 1.86)
Rosenberg et al., 1993[36]	Residents of Massachusetts, USA	Nonfatal AMI	Interview, in-person or telephone, hospital discharge summaries	45–69	858	858	Ever use unopposed 0.9 (0.7, 1.2) combined 1.2 (0.6, 2.4) past use 0.9 (0.7, 1.3)
Hernandez-Avila et al., 1990[22]	Members of GHC (Puget Sound, WA, USA)	Nonfatal AMI	Pharmacy database and linkage to other GHC databases	50–64	103	721	Current users 0.7 (0.4, 1.4) Past users 0.6 (0.1, 2.1)
Pfeffer et al., 1978[37]	Retirement community in California, USA	Fatal and nonfatal AMI	Pharmacy records, medical charts	57–98	171	454	Current users 0.68 (0.32, 1.42) Ever users 0.86 (0.54, 1.37)
Bain et al., 1981[38]	Married nurses from 11 US states	Nonfatal AMI	Postal questionnaires	33–55	123	2438	Current users all women 0.7 (0.4, 1.1) bilateral oophorectomy 0.4 (0.2, 0.8) natural menopause 1.3 (0.5, 3.4) Ever users 0.8 (0.6, 1.3)
Croft and Hannaford, 1989[39]	UK general practices	Fatal and nonfatal AMI	General practitioners	Not stated	158	474	Ever users 0.8 (0.3, 1.8)
Petitti et al., 1979[40]	KPMCP: Walnut Creek facility, USA	Fatal and nonfatal AMI	Medical examinations, postal questionnaire, hospital discharge records, death certificates	18–54	26	On average 200 controls per case	Ever users 1.2 (90% CI 0.6, 2.3)
Adam et al., 1981[41]	General practices in England and Wales	Fatal AMI	Questionnaire filled in by GP by reference to medical records, death certificates	50–59	76	151	Current users 0.79 (0.08, 4.82) Ever users 0.65 (0.27, 1.42)

a Reference group for these ORs is non-current users of estrogen and estrogen-progestin.

AMI = acute myocardial infarction; **CHD** = coronary heart disease; **GHC** = Group Health Co-operative; **GP** = general practitioner; **GPRD** = General Practice Research Database; **HRT** = hormone replacement therapy; **KPMCP** = Kaiser Permanente Medical Care Program; **VAMP** = Value Added Medical Products.

risk with increasing duration of unopposed estrogen use was observed in recent ($p < 0.05$) but not past ($p = 0.86$) users. However, none of the risk estimates for these various durations were statistically significant.

After performing a case-control analysis on the same study population as in their cohort study (previously described in section 2.1.2), Hernandez-Avila et al.[22] reported similar risk estimates for AMI to that previously reported: OR_{adj} 0.7 (95% CI 0.4, 1.4) and OR_{adj} 0.6 (95% CI 0.1, 2.1) for current and past use, respectively. These estimates were based on 103 cases matched to seven controls by year of birth (±2 years). No association with dose or increasing duration of use was found, which may have been as a result of the small numbers. Lack of adjustment for several AMI risk factors and the possible inclusion of premenopausal women in this study may have distorted the results.

Two other studies reported decreased but non-statistically significant risk estimates for AMI associated with HRT.[37,38] These results were based on 171 and 123 cases of AMI, respectively. Bain et al.[38] reported a significantly reduced risk estimate associated with current HRT use among the 16 women who had had a bilateral oophorectomy (OR_{adj} 0.4; 95% CI 0.2, 0.8) but not among women who had had a natural menopause (OR_{adj} 1.3; 95% CI 0.5, 3.4). The study by Pfeffer et al.[37] was seriously flawed as it was later found that estrogen exposure had been significantly underestimated.[42] Three other small studies also reported non-significant risk estimates.[39-41]

2.1.4 Hospital-Based Case-Control Studies

Studies Reporting Decreased Risk Estimates

Two studies reported decreased but non-statistically significant risk estimates for AMI associated with HRT use (table IV). Rosenberg et al.[43] conducted a study on 336 postmenopausal women aged between 40 and 75 years who were hospitalised with nonfatal AMI. A stratified analysis, comparing cases with the 6730 'reference patients' who had similar cardiovascular risk profiles, gave an overall risk estimate for nonfatal AMI of 0.97 (95% CI 0.48, 1.95) associated with regular recent estrogen use. A smaller study by Szklo et al.[44] on 84 postmenopausal women reported a non-significant decrease in risk for the first nonfatal AMI (OR_{adj} 0.61; 95% CI 0.20, 1.88) associated with past HRT use. In this study, controls but not patients were excluded if they had gallbladder or gynaecological disorders, and this would have biased the results in favour of HRT if women without these conditions were preferentially prescribed HRT.

Studies Reporting Increased Risk Estimates

Three studies reported statistically significant increased risk estimates of AMI.[45,46,48] Women included in the study population had to be considered eligible for HRT and free from conditions predisposing to AMI and from contraindications to estrogen use. The first study[45] reported an OR for nonfatal AMI of 7.5 (90% CI 2.4, 24.0) for women aged between 39 and 45 years after stratification as follows: (a) women who had received a natural menopause or hysterectomy; or (b) women who had received a tubal ligation or whose husband had received a vasectomy. Of the 17 cases, 16 were current cigarette smokers compared with 16 of the 34 controls, which was not adjusted for. The second study[46] (using more data) reported a risk estimate of 9.3 (95% CI 3.1, upper limit not stated) after a similar analysis based on 19 cases and 39 controls.

After initial results from La Vecchia et al.[47] had suggested that HRT was associated with an increased, albeit non-statistically significant, risk of AMI (OR_{adj} 2.95; 95% CI 0.80, 10.8),[45] Fioretti et al.[48] reported a statistically significant increased risk of nonfatal AMI after an extra 8 years of data collection and an increased upper age limit of 74 years: crude OR 1.88 (95% CI 1.20, 2.92). However, potential confounders were not adjusted for and 50% of cases were pre-menopausal compared with 33% of controls. Bias may have resulted from the exclusion from controls (but not cases) of women with a primary diagnosis associated with cigarette smoking or alcohol consumption in the preceding year.

In a large study by Rosenberg et al.,[49] an OR of 1.2 (95% CI 0.8, 1.8) was reported for risk of nonfatal AMI associated with past HRT use. The association with recent use was OR_{adj} 1.0 (95% CI 0.6, 1.7). No trend in AMI risk was seen with increasing duration of use. Elimination of those predisposed to AMI from the analysis did not alter

Table IV. Primary prevention: hospital-based case-control studies

Study	Setting	Outcome studied	Data source	Age range (y)	No. of cases	No. of controls	Risk estimate (95% CI)
Rosenberg et al., 1976[43]	Hospitals from seven different countries	Nonfatal AMI	Patient interviews and hospital discharge diagnosis records	40–75	336	6730	Current use all HRT 0.97 (0.48, 1.95) unopposed 0.85 (0.38, 1.91)
Szklo et al., 1984[44]	Five general hospitals in MD, USA	Nonfatal AMI	Hospital records and patient interview	35–64	39	45	Past use all women 0.61 (0.20, 1.88) surgical menopause 0.37 (0.04, 3.23) natural menopause 0.29 (0.04, 1.94)
Jick et al., 1978[45]	Hospitals throughout the US	Nonfatal AMI	Hospital discharge summaries, telephone interviews	39–45	17	34	Ever use 7.5 (90% CI 2.4, 24.0)
Jick et al., 1978[46]	Hospitals throughout the US	Nonfatal AMI	Hospital discharge summaries, telephone interviews	39–45	19	39	Ever use 9.3 (3.1, upper limit not stated)
La Vecchia et al., 1987[47]	Women admitted to coronary care units of 30 hospitals in the Lombardy region of Italy	Nonfatal AMI	Interview	23–54	168	251	Current use 2.95 (0.80, 10.8) Past use 0.77 (0.16, 3.60)
Fioretti et al., 2000[48]	Women admitted to coronary care units of 30 hospitals in the Lombardy region of Italy	Nonfatal AMI	Interview	<75	429	863	Past use 1.88 (1.20, 2.92)
Rosenberg et al., 1980[49]	155 hospitals with coronary care units in Long Island, USA	Nonfatal AMI	Hospital records and patient interviews	30–49	477	1832	Recent use (within month prior to event) 1.0 (0.6, 1.7) Past use 1.2 (0.8, 1.8)

AMI = acute myocardial infarction; **HRT** = hormone replacement therapy.

the risk estimates. Since this study was primarily designed to evaluate the effects of oral contraceptives and other factors on AMI risk among young women, only 21% of cases and 20% of controls were postmenopausal.

2.2 Studies Looking at Groups of Women at High Risk

2.2.1 Secondary Prevention Studies: RCTs

In the HERS (Heart and Estrogen/Progestin Replacement Study) trial, Hulley et al.[50] randomised 2763 postmenopausal women aged <80 years with an intact uterus and established CHD to receive either CEE 0.625mg plus MPA 2.5mg or placebo (table V). There were no statistically significant differences in the baseline characteristics of the women in the two study groups and all analyses were based on the 'intention-to-treat' principle. After an average follow-up of 4.1 years, no significant change in the risk of nonfatal AMI was observed (RR 0.91; 95% CI 0.71, 1.17) based on 116 events in the hormone group and 129 events in the placebo group. An increased risk estimate was reported during the first year of treatment but this was not statistically significant (RR 1.47; 95% CI 0.91, 2.36). However, a statistically significant trend of decreasing risk with each subsequent year of the trial ($p = 0.01$) was also reported. After an additional unblinded 2.7 years of follow-up (HERS II),[51] the overall risk estimate did not change significantly, nor was there a continued trend towards lower risk estimates with longer duration of HRT use. A later analysis[52] reported that the overall risk estimate did not change after stratification by lipoprotein(a) level (a putative risk factor for CHD in women) at baseline. Although there was a greater use of HMG-CoA reductase inhibitors (statins) in the placebo group, a subsequent analysis found that risk estimates did not change significantly after adjusting for statin use both at baseline and post-randomisation (this analysis used the combined endpoint of nonfatal AMI and CHD death).[53]

In the ESPRIT (Evaluation of Subcutaneous Proleukin in a Randomized International Trial) study,[54] 1017 postmenopausal women aged between 50 and 69 years (mean age 62.6 years) who had survived a first AMI were randomised to estradiol valerate or placebo and followed up for 2 years in a study of reinfarction and cardiac death. No differences were found between the two treatment arms (RR 0.99; 95% CI 0.70, 1.41). The study only had statistical power to detect large differences between HRT and placebo and non-compliance was 57% in the HRT and 37% in the placebo arm of the trial. Unlike in HERS, there was no increase in risk in the first year; in fact, risk estimates were lowest in the first few months of follow-up.

Two other small trials among postmenopausal women with angiographically defined coronary artery disease[55] or ischaemic heart disease[56] at baseline reported no significant difference in the risk of nonfatal AMI between the different treatment groups.

2.2.2 Secondary Prevention Studies: Cohort Studies

Alexander et al.[57] conducted a study of 1857 postmenopausal women who had experienced a previous AMI and were receiving daily aspirin (acetylsalicylic acid) and warfarin (table VI). After a median follow-up of 15 months, no difference was found in the rates of recurrent infarction among current/recent users (HR_{adj} 0.88; 95% CI 0.58, 1.33). 'New HRT users' (began HRT after their AMI) were significantly less likely to experience a second infarct ($p = 0.03$); however, there were only four recurrences among this group.

In a retrospective cohort study, Newton et al.[58] evaluated 726 postmenopausal women who had survived a first AMI to hospital discharge, for up to 13 years. Based on 135 cases, risk estimates for recurrent AMI of RR_{adj} 0.72 (95% CI 0.35, 1.46) and RR_{adj} 0.83 (95% CI 0.56, 1.22) associated with current and past HRT use, respectively, were reported. Based on more limited numbers, three other secondary prevention cohort studies also reported a non-statistically significant change in AMI risk associated with HRT use.[59-61]

2.2.3 Diabetic Women: Cohort Studies

Ferrara et al.[62] evaluated 25 000 diabetic women aged >49 years, for up to 3 years (table VII). Among the 24 420 women without a prior AMI, a decreased risk of AMI with HRT use was reported: HR_{adj} 0.84 (95% CI 0.72, 0.98) based on 1110 cases of AMI. The risk estimates for unopposed and combined HRT did not significantly differ from each other

Table V. Secondary prevention: randomised controlled trials

Study	Setting	Description of cohort	Length of follow-up (y)	Endpoint	Data source	Age at baseline (y)	Cases in treatment group	Cases in placebo/ control group	Risk estimate (95% CI)
Hulley et al., (HERS) 1998[50]	20 US clinical centres	2763 postmenopausal women with intact uterus and established coronary disease	Mean of 4.1	Nonfatal AMI	In-person examination (including ECG) and interview	<80, mean 67	116	129	0.91 (0.71, 1.17)
Grady et al., (HERS II) 2002[51]	20 US clinical centres	2763 postmenopausal women with intact uterus and established coronary disease	Mean of 6.8	Nonfatal AMI	Telephone interview	<80, mean 67	183	196	0.98 (0.69, 1.40) Overall (HERS + HERS II) 0.94 (0.77, 1.15)
Shlipak et al., (HERS) 2000[52]	20 US clinical centres	2763 postmenopausal women with intact uterus and established coronary disease	Mean of 4.1	Nonfatal AMI	In-person examination (including ECG) and interview	44–79, mean 66.7	122	134	0.92 (0.72, 1.17) By lipoprotein(a) quartile first 1.35 (0.84, 2.17) second 0.88 (0.50, 1.54) third 0.71 (0.42, 1.20) fourth 0.85 (0.55, 1.31)
The ESPRIT team, 2002[54]	35 hospitals in England and Wales	1017 postmenopausal women who had survived a first AMI	Up to 2	Reinfarction or cardiac death	Regular follow-up visits to the family doctor	50–69, mean 62.6	62	61	0.99 (0.70, 1.41)
Herrington et al., (ERA) 2000[55]	Five US clinical sites	309 postmenopausal women with angiographically verified coronary disease	Mean of 3.2	Nonfatal AMI	6-month in-clinic visits, coronary angiograms, ECGs, cardiac enzyme values, hospital discharge notes, data from cardiovascular testing	41–79	6 (unopposed group) 6 (combined HRT group)	7	Unopposed 0.90 (0.25, 3.13) Opposed 0.87 (0.24, 3.01)
Clarke et al., (Papworth HRT Atherosclerosis Study) 2002[56]	A UK regional cardiac unit	255 postmenopausal women with angiographically proven ischaemic heart disease	Up to 4, mean of 30.8 months	Nonfatal AMI	Regular visits to hospital outpatient clinic for questioning by a research nurse	Mean age 66	1	4	Only stated as being non-significant

AMI = acute myocardial infarction; **ESPRIT** = Evaluation of Subcutaneous Proleukin in a Randomized International Trial; **HERS** = Heart and Estrogen/Progestin Replacement Study; **HERS II** = Heart and Estrogen/Progestin Replacement Study follow-up; **HRT** = hormone replacement therapy.

Table VI. Secondary prevention: cohort studies

Study	Description of cohort	Length of follow-up (y)	Endpoint	Data source	Age range (y)	No. of cases	Risk estimate (95% CI)
Alexander et al., 2001[57]	1857 women who had sustained an AMI	8–23 months, median of 15 months	AMI	Interview, medication records	Not stated	157	Prior/current use 0.88 (0.58, 1.33)
Newton et al., 1997[58]	Enrollees of health maintenance organisation (GHC, Puget Sound, WA, USA)	Up to 13	Re-infarction (incident fatal and nonfatal MI)	Pharmacy database, medical records, telephone interview	<80	135	Current use all HRT 0.72 (0.35, 1.46) unopposed 0.64 (0.28, 1.49) Ever use 0.83 (0.56, 1.22)
O'Keefe et al., 1997[59]	Patients who underwent elective coronary angioplasty at Mid America Heart Institute, USA	Mean of 5.4	MI	Database, chart review, patient/family interviews and postal questionnaire	Not stated	22	Current use 0.68 (0.23, 1.78)
Khan et al., 2000[60]	Women who underwent successful single coronary artery stenting	Up to 5	MI	Questionnaire, hospital and clinical charts	Not stated	5	Current use 1.71 (0.2, 20.6)
Shlipak et al., 2001[61]	114 724 women with a documented AMI	Not stated	Recurrent AMI	National Registry of Myocardial Infarction	≥55	4	Prior use p = 0.74

AMI = acute myocardial infarction; **GHC** = Group Health Co-operative; **HRT** = hormone replacement therapy.

Table VII. Studies on diabetic women

Study	Study type	Study population	Endpoint	Data source	Age range (y)	Number of cases	Risk estimate (95% CI)
Ferrara et al., 2003[62]	Cohort	24 420 women with diabetes mellitus registered with the KPMCP	Fatal and nonfatal AMI	Health Plan's computerised pharmacy hospitalisation and membership files and also postal/telephone questionnaire	≥50, mean 64.9	1110	Current use all HRT 0.84 (0.72, 0.98) Unopposed 0.88 (0.73, 1.05) Combined 0.77 (0.61, 0.97)
		580 women with diabetes and with a recent MI registered with the KPMCP	Fatal and nonfatal recurrent AMI	Health Plan's computerised pharmacy hospitalisation and membership files and also postal/telephone questionnaire	≥50, mean 69.2	89	Current use 1.78 (1.06, 2.98)
Løkkegaard et al., 2003[23]	Cohort	47 postmenopausal nurses with diabetes	Fatal and nonfatal AMI	Postal questionnaire and National Registers of Death, Hospital Discharges and Central Persons	≥45	13	Current use 9.15 (2.02, 41.4) Past use 1.17 (0.12, 11.3)
Kaplan et al., 1998[63]	Case-control	Pharmacologically treated diabetic female enrollees of GHC, Puget Sound, WA, USA	Fatal and nonfatal AMI	Computerised pharmacy data + medical records	30–79	212	Current use 0.51 (0.22, 1.15) Past use 1.22 (0.71, 2.09)
Varas-Lorenzo et al., 2000[29]	Case-control	256 women with diabetes registered on the UK GPRD	Fatal and nonfatal AMI	GP Medical records	50–74	86	Current use 1.4 (0.6, 3.3)

AMI = acute myocardial infarction; **GHC** = Group Health Co-operative; **GPRD** = General Practice Research Database; **KPMCP** = Kaiser Permanente Medical Care Program.

(p = 0.35). A decreased risk of AMI was observed with use of low- or medium-dose estrogen but not with high-dose estrogen. Additionally, a decreased risk of AMI was reported after 1 year of HRT use but not during the first year of use. However, among the 580 women who had experienced a recent AMI, an increased risk of recurrent AMI was reported associated with current HRT use: HR_{adj} 1.78 (95% CI 1.06, 2.98) based on 89 events. This increased risk was evident in women currently using HRT for <1 year (HR_{adj} 3.84; 95% CI 1.60, 9.2) but not among those using HRT for >1 year (HR_{adj} 0.87; 95% CI 0.36, 2.15).

Although originally reporting non-significant risk estimates among a population of Danish nurses, Løkkegaard et al.[23] reported that a subgroup analysis of only those with diabetes mellitus showed a significantly increased risk of AMI associated with current HRT (HR_{adj} 9.15; 95% CI 2.02, 41.4) but not past use (HR_{adj} 1.17; 95% CI 0.12, 11.3). Judging by the confidence intervals, these risk estimates were unstable.

2.2.4 Diabetic Women: Case-Control Studies

A smaller study by Kaplan et al.[63] among women with treated diabetes reported non-significant risk estimates for AMI (OR_{adj} 0.51; 95% CI 0.22, 1.15 and OR_{adj} 1.22; 95% CI 0.71, 2.09, respectively) associated with current and past use of HRT (table VII). However, a significantly decreased risk of AMI was reported among current users with >6 years of use (OR_{adj} 0.18; 95% CI 0.04, 0.83). No changes in risk were reported in relation to time since cessation of use. A subgroup analysis by Varas-Lorenzo et al.[29] also reported no risk of AMI with HRT use among diabetic women (OR_{adj} 1.4; 95% CI 0.6, 3.3). Again, numbers were limited.

2.2.5 Women with Specific Genetic Variants

In a subgroup analysis of their previous case-control study,[31] Psaty et al.[64] reported that women with hypertension who had the prothrombin 20210 G→A genetic variant allele had no change in risk of AMI (OR 1.45; 95% CI 0.28, 7.66). However, compared with non-HRT users with the wild-type genotype, women with the prothrombin variant who were current HRT users had an 11-fold increase in risk (OR 10.9; 95% CI 2.15, 55.2); the width of the CI suggests that this risk estimate was unstable. This interaction was not evident among non-hypertensive women or among women with a factor V Leiden genetic variant, either with or without hypertension (table VIII).

In a further subgroup analysis of the same study population, Reiner et al.[65] reported no significant change in risk of nonfatal AMI among current HRT users who were carriers of either the coagulation factor XIIIA Leu34 or XIIIB Arg95 variants compared with non-HRT users who were homozygous for the wild-type allele. In contrast, women who had at least two copies of the variant factor XIII alleles and were current HRT users had a 70% significant lower risk of AMI compared with HRT non-users with fewer than two factor XIII variant alleles (OR_{adj} 0.33; 95% CI 0.13, 0.85).

3. Discussion

From this comprehensive literature review evaluating the association between HRT use and AMI risk from observational studies and randomised controlled trials, there is insufficient evidence to suggest that HRT is associated with a change in the risk of AMI in the majority of women. However, certain subgroups of women may be more susceptible to a change in the risk associated with HRT use.

3.1 Primary Prevention

The only large randomised controlled trial of HRT and the association with AMI risk in generally healthy women, the WHI, reported a small early increase in AMI risk associated with combined, but not estrogen-only, HRT in older postmenopausal women. It has been suggested that this increased risk could result from detection bias;[15] it contrasts with a large number of observational studies, of which all but four were neutral or suggested a protective association with HRT. Among those presenting significantly decreased risk estimates, the point estimates ranged from approximately 0.3 to 0.8.

Animal studies have shown that if HRT was initiated immediately following surgical menopause in monkeys without pre-existing atherosclerosis, there was an average inhibition of coronary artery sclerosis of approximately 70%. However, if initiation of estrogen replacement was delayed for 2 years (equivalent to 6 years in humans) then no inhibition

Table VIII. Case-control studies on women with specific genetic polymorphisms

Study	Study population	Endpoint	Data source	Age range (y)	Number of cases	Risk estimate (95% CI)
Psaty et al., 2001[64]	Enrollees of health maintenance organization (GHC, Puget Sound, WA, USA)	Nonfatal AMI	Pharmacy database, medical records, telephone interviews and venous blood sample	30–79	6	Hypertensive women + prothrombin variant 10.9 (2.15, 55.2)
					0	Non-hypertensive women + prothrombin variant 0 (no cases)
					1	Hypertensive women + factor V Leiden variant 0.51 (0.06, 4.19)
					1	Non-hypertensive women + factor V Leiden variant 0.41 (0.05, 3.44)
Reiner et al., 2003[65]	Enrollees of health maintenance organization (GHC, Puget Sound, WA, USA)	Nonfatal AMI	Pharmacy database, medical records, telephone interviews and venous blood sample	30–79	234	Women with XIIIA Leu34 variant allele 0.82 (0.41, 1.64) Women with XIIIB Arg95 variant allele 0.62 (0.32, 1.56) Women with two or more copies of the variant factor XIII alleles OR 0.33 (0.13, 0.85)

AMI = acute myocardial infarction; **GHC** = Group Health Co-operative.

in coronary artery atherosclerosis was observed. The average age at study entry of women in the WHI was 63 years. It has been suggested that the women included in the trial had been postmenopausal for too long before starting HRT and could therefore have developed at least a moderate amount of atherosclerosis. If the animal studies are a good model of these effects in humans, women who delayed the HRT treatment would be less likely to obtain any benefit than those women who started HRT immediately at the start of their menopause.[66]

3.2 Groups of Women at High Risk

The only large secondary prevention randomised controlled trial of HRT and AMI risk found no statistically significant change in the risk of AMI with HRT use compared with placebo. Two smaller trials and five cohort studies also reported no significant changes in risk. The evidence for a change in risk of AMI with HRT is inconclusive among diabetic women. However, two studies on women with specific genetic variants suggest that among some women, estrogen may be associated with a change in AMI risk.[63,64]

3.3 Progestogen Supplementation

Clinical studies on intermediate endpoints and experimental studies on non-human primates suggest that MPA, but not natural progesterone, may antagonise the potential beneficial effects of estrogen.[67-69] The results of the WHI and HERS trials, in which the progestogen component was MPA, would be in line herewith were it not for the recently published estrogen-only arm of the WHI, which reported no association of estrogen-alone with AMI. In observational studies that looked at both unopposed and combined regimens, some reported lower risk estimates with opposed HRT and others reported lower risk estimates with combined. In none of the studies was there a significant difference between the two. The parallel WHI trial of unopposed estrogen in 10 739 postmenopausal women who had previously had a hysterectomy has recently been terminated[12] and found no increase in the risk of CHD or cardiovascular death.

3.4 Biological Plausibility

A relationship with duration of use, time since cessation of use or a dose-response effect would lend support to a hypothesis of a causal association between HRT and risk of AMI. The WHI trial did not provide data specifically for AMI with duration of HRT use while the HERS trial reported no association. Some observational studies reported lower risk estimates with increasing duration of use, with three studies[16,30,36] reporting a significant trend of decreasing risk with increasing duration of use. However, overall the data are inconclusive. The few studies that evaluated the effect of dose,[18,22,29,61] recency of use[16,29,32,62] and mode of administration[29,32] also provide inconclusive results.

3.5 Chance, Bias and Confounding

Careful consideration must be given to the interpretation of these studies since chance, bias and confounding are all possible alternative explanations for at least part of any observed association. The size of the study must be considered – many small studies in this review lacked the power to detect a moderate change in AMI risk between users and non-users of HRT if there was one.

Several sources of confounding and bias may have created spurious protective results in observational studies. In observational studies, unlike randomised controlled trials, HRT is not randomly assigned and there is evidence to suggest that women prescribed HRT exhibit more health-conscious behaviour,[70] have fewer cardiovascular risk factors[71-74] and are more compliant[75] than those not using HRT. Although several observational studies endeavoured to adjust for such differences, residual confounding may have occurred and this may be more pertinent in earlier studies (conducted when estrogen treatment was considered to increase coronary disease[76]) if those perceived at being at high risk were prescribed HRT less frequently than those perceived to be at low risk.

Sturgeon et al.[77] proposed that a healthy-survivor cohort effect could explain at least part of the protective effect suggested by most observational studies. This theory is based on the notion that the characteristics of the individual are likely to determine not only whether HRT is initiated in the first place but also how long use continues. There is some suggestion that subgroups of women with genetic polymorphisms may be more susceptible to the pro-coagulant effects of estrogen. These women, and those who are less compliant and health conscious, are more likely to discontinue treatment earlier, leaving an increasingly healthier cohort of users as time progresses. This could explain the lower risk estimates reported with increasing duration of use found in some of the studies.[16]

Although randomised controlled trials have the advantage of minimising confounding at baseline, they are not immune from bias and it has been argued that the WHI trial, because of the extent of unblinding in the course of the study (44.4%), acquired the characteristics of an observational study. As a result, the possibility that the increased, albeit small, risk of AMI seen in the WHI trial could be an artefact due to detection bias cannot be ruled out.[15]

Misclassification of HRT use must also be considered as a potential source of bias in all study types. Some studies did not account for changes in HRT use during follow-up or were unable to obtain previous HRT use. Such misclassification would bias the risk estimate towards 1.0.

3.6 Generalisability

The study population and the HRT regimen(s) examined must be taken into account when considering how generalisable a study's findings are to the general HRT-using population. The average age of the women in the WHI and HERS trials was 63 and 67 years, respectively. This is much older than, and therefore not representative of, the age that most women take HRT (in their 50s).[73] Similarly, several observational studies included women not representative of HRT users in the general population.

The results of the WHI and HERS trials, which compared the same regimen of combined HRT with placebo, do not necessarily apply to different HRT formulations, modes of administration or doses. The HRT preparations examined in the observational studies varied according to whether the study was conducted in the US or in Europe. Preparations containing CEE either alone or combined with a progestogen (often MPA) are far more prevalent in the US[78] than in Europe, where preparations con-

taining 17β-estradiol, either alone or combined with 19-nortestosterone progestogens, are also commonly used.[73]

No studies have examined the association of the synthetic HRT preparation tibolone[79] with risk of AMI, although clinical studies suggest that it may be associated with factors that affect AMI risk.[79-81] One trial has shown the selective estrogen receptor modulator raloxifene (an alternative to conventional HRT for osteoporosis prophylaxis and treatment) to have no significant effect on the risk of nonfatal AMI and coronary death in postmenopausal women with osteoporosis after 4 years, despite having favourable effects on cardiovascular risk factors.[82-84] However, raloxifene reduced cardiovascular risk in women with osteoporosis and a high cardiovascular risk.

Although the majority of studies in this review are neutral or suggest that HRT is associated with a decreased AMI risk, the effect of residual confounding and several potential biases cannot be ruled out. The lack of a dose-response effect and lack of support from the two large-scale randomised controlled trials that have been conducted lead to hesitancy in concluding that HRT has a protective effect. Similarly, in our view, the possibility of detection bias in the combined arm of the WHI, together with the results from the estrogen-only arm and the HERS, suggests the WHI's reported small increase in AMI risk associated with combined HRT might be because of bias and does not necessarily prove causality.

4. Conclusion

There is insufficient evidence at present to suggest that HRT is causally associated with a change in the risk of AMI in the majority of women. Certain subgroups, especially early menopausal women, may be more susceptible to a decreased risk. Furthermore, specific genetic polymorphisms may render women more susceptible to an increased or decreased risk of AMI with HRT use.

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