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RESEARCH

Discontinuation of hormone replacement therapy after myocardial infarction and short term risk of adverse cardiovascular events: nationwide cohort study


OPEN ACCESS

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Abstract

Objective To assess the risk of adverse cardiovascular events in women who discontinue hormone replacement therapy after myocardial infarction compared with those who continue.

Design Nationwide register based cohort study.

Setting All hospitals in Denmark.

Population All 3322 women aged 40 years or over who survived 30 days after a myocardial infarction and were prescribed hormone replacement therapy at the time of myocardial infarction in the period 1997 to 2008.

Main outcome measures Reinfarction, cardiovascular mortality, and all cause mortality 30 to 360 days after discharge.

Results A total of 282 (8.5%) women had a reinfarction, 218 (6.6%) died of cardiovascular causes, and 357 (10.7%) died of any cause during follow-up. Women who discontinued overall hormone replacement therapy in the first year after myocardial infarction did not have a significantly different risk of reinfarction (hazard ratio 0.90, 95% confidence interval 0.68 to 1.19), cardiovascular mortality (1.21, 0.90 to 1.62), or all cause mortality (1.22, 0.97 to 1.53) than women who continued use. However, discontinuation of vaginal oestrogen was associated with a lower risk of reinfarction (hazard ratio 0.54, 0.34 to 0.86).

Conclusion No certain conclusions can be drawn regarding increased or decreased risk of adverse cardiovascular events with continuing hormone replacement therapy after myocardial infarction. The results rule out neither a modest benefit nor a worrisome increase in risk. These figures may be valuable when a possible cardiovascular risk of hormone replacement therapy needs to be balanced with menopausal symptoms for the individual patient.

Introduction

Hormone replacement therapy (HRT) was recommended for prevention of coronary artery disease until the end of the 1990s because several observational studies had shown a cardioprotective effect of HRT.[1-3] However, in 1998 the Heart and Estrogen Replacement Study evaluated the role of HRT compared with placebo for secondary prevention of coronary artery disease and found no significant differences in the primary outcome of cardiac death or myocardial infarction, and in 2001 the Women's Health Initiative study of HRT for primary prevention was stopped prematurely when an increased risk of coronary artery disease in women using HRT was found.[4 5] As a result, guidelines now recommend that HRT should not be used for primary or secondary prevention of coronary artery disease.[6-8]

Oestrogen has favourable effects on endothelial function, as well as inflammatory and haemostatic mechanisms.[9] However, these effects and the blood concentrations of respective hormones differ between different types of HRT and routes of administration, and they disappear rapidly after discontinuation of HRT.[10-17] Discontinuation of HRT can be troublesome owing to rebound climacteric symptoms, and this is particularly problematic in women diagnosed as having coronary artery disease while using HRT, as guidelines for this situation recommend discontinuation of HRT although evidence on the risk-benefit of this strategy is lacking.[18-21] Indeed, the period after a myocardial infarction is a pathophysiologically vulnerable time, with endothelial dysfunction, elevated inflammatory markers, and so on, and potential rebound effects on these mechanisms of discontinuation of HRT may be more prone to cause adverse cardiovascular events in this period.[22-24] We have

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previously shown that in spite of current recommendations for discontinuation of HRT after myocardial infarction, around 80% of women in Denmark using HRT at the time of myocardial infarction continue HRT after discharge.[25]

The aim of this study was therefore to assess whether women who discontinue HRT after myocardial infarction have a lower risk of reinfarction, cardiovascular death, or all cause death in the first year after myocardial infarction than do women who continue HRT.

Methods

All citizens in Denmark have a unique civil registration number that enables linkage of nationwide registers at an individual level. The Danish national patient register holds information on all admissions to Danish hospitals since 1978 registered by diagnoses according to the World Health Organization's international classification of diseases (ICD). Operations are classified according to the Danish classification of operation until 1996 and according to the Nordic Medico-Statistical Committee's classification of surgical procedures from 1997.[26] The Danish national prescription register holds information on all prescriptions dispensed by Danish pharmacies since 1995. Prescriptions are coded according to the anatomic therapeutical chemical (ATC) system. All residents in Denmark are covered by a national health security system and have the cost of drugs partially reimbursed.[27] All pharmacies are therefore required to register all dispensed prescriptions. All deaths are registered in the central population register within 14 days of occurrence.

Population

We identified all women who were aged 40 years or older on 1 January 1997 and discharged with a diagnosis of myocardial infarction (ICD-8 code 410, ICD-10 codes I21 to I22) in the period 1997 to 2008 in the national patient register. The diagnosis of myocardial infarction in this register has previously been validated and has a sensitivity of 91% and a positive predictive value of 93%.[28] We included women who were still alive 30 days after discharge (fig 1⇓). As a measure of socioeconomic status, we calculated the yearly household income as an average of the income in the five years before admission, where possible, and divided it into thirds of income. We excluded all women who migrated to or from Denmark in the study period 1997 to 2008.

Use of hormone replacement therapy

We identified all claimed prescriptions for HRT in the Danish register of medicinal product statistics (ATC codes G03C, G03D, G03F, G03XC and G02BA03) in the study period. We did not include drugs usually used for contraceptive purposes, except for a progesterone intrauterine device which is commonly used by postmenopausal women. HRT covers a broad spectrum of chemical compounds, formulations, routes of administration, and dosages. We divided this pharmacological multiplicity into four categories (table 1⇓): oestrogen alone, combinations of oestrogen and progestogen, vaginal oestrogen alone, and "other HRT." These categories were mutually exclusive. We used the "other HRT" category to ensure that all treatment intervals could be included in the analyses, not because of similarities of the treatments in this group.

The register includes information about dispensing date, strength, and quantity of the prescription. Indication and daily drug dosage are not included in the register, so we estimated the daily drug dose by calculating the average drug dose of up to three consecutive prescriptions before the actual prescription and not using information on future prescriptions in the calculations. This method has previously been described in detail.[29] On the basis of these assumptions, we calculated periods when HRT was available and we defined patients as receiving HRT if it was available. Similarly, we defined discontinuation of any of the four categories if no treatment was available in the specific category of HRT. We defined discontinuation of overall HRT if no treatment was available in any of the four categories. Thus, each woman could contribute with HRT treatment or discontinuation periods several times. For analyses of the four HRT categories, we followed women as long as they did not change to a different category of HRT. We calculated exposure to and discontinuation of HRT for all prescriptions in the entire period from 1 January 1996 to 31 December 2008. This means that any discontinuation beginning in the first 30 days after discharge was registered and included in the analysis as a discontinuation if it continued beyond the first 30 days after discharge (which was the beginning of the follow-up time).

Concomitant drugs and comorbidity

We defined concomitant drugs as claimed prescriptions within 180 days before or 30 days after the myocardial infarction for β blockers (ATC code C07), angiotensin converting enzyme inhibitors/angiotensin II receptor blockers (ATC code C09), statins (ATC code C10AA), and clopidogrel (ATC code B01AC04). We defined comorbidity with the modified Ontario acute myocardial infarction prediction rules by diagnosis from the index admission and one year before admission.[30 31] The national registers have a low sensitivity for the diagnosis of heart failure, and they hold no information about left ventricle ejection fraction.[32] We therefore used prescriptions for loop diuretics (ATC code C03C) as a proxy for heart failure, as previously done.[33] Similarly, we used prescriptions for glucose lowering drugs (ATC code A10) as a proxy for drug treated diabetes. We also obtained information about previous myocardial infarction, revascularisation (percutaneous coronary intervention (operation codes 30350, 30354, and KFNG) and coronary artery bypass graft surgery (operation codes 30009 to 30199 and KFNA to KFNE)).

Outcomes

We defined reinfarction as fatal or non-fatal myocardial infarction (ICD-10 codes I21 to I22) at least 30 days after discharge for the index myocardial infarction as done previously.[34] We defined cardiovascular death as death due to a disease of the circulatory system (ICD10-code I00 to I99) and all cause death as death of any cause. Follow-up was from day 30 until 1 year after discharge.

Statistical analysis

We present baseline characteristics of the different groups of women as numbers with percentages or medians with interquartile ranges and compared them by using χ^2 tests and analysis of variance. We categorised age into groups of 40-59 years, 60-69 years, 70-79 years, and 80 years and above (table 2⇓).

We calculated unadjusted incidence rates for reinfarction, cardiovascular mortality, and all cause mortality for discontinuation of and continued treatment with overall HRT and the four categories of HRT. We divided duration of discontinuation of HRT into 1-90 days, 91-180 days, 181-360 days, and 1-360 days. We did calculations and analyses for the periods 30-90 days, 91-180 days, 181-360 days, and 30-360

days after discharge. We used a multivariable Cox proportional hazards model to calculate hazard ratios for reinfarction, cardiovascular mortality, and all cause mortality for various periods of discontinuation. We did this for both overall HRT and the four HRT categories, using continued treatment as the reference. The multivariable Cox model was adjusted for age group, year of myocardial infarction, comorbidity (previous myocardial infarction, revascularisation within 30 days of myocardial infarction, cerebrovascular disease, congestive heart failure, malignancy, cardiac dysrhythmias, chronic renal failure, acute renal failure, diabetes with complications, pulmonary oedema, shock), concomitant use of drugs (β blockers, angiotensin converting enzyme inhibitors, statins, loop diuretics, clopidogrel, glucose lowering drugs), and income group. We tested the model assumptions and found them to be valid. We did tests for interactions for the various periods of discontinuation of the HRT groups and age groups, year of myocardial infarction, revascularisation within 30 days after myocardial infarction, comorbidity, previous myocardial infarction, and concomitant drugs and for year of myocardial infarction and age groups. No interactions were evident, so we included no interactions in the final Cox model.

For all statistical analyses, we considered a level of 5% to be statistically significant. We used SAS statistical software version 9.2 and Stata version 11 for all analyses. The study was conducted and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations.[35]

Sensitivity analyses

To make sure that the exclusion of women who died during the first 30 days after discharge did not seriously affect our results, we did sensitivity analyses of cardiovascular death and all cause death including these women and beginning follow-up at the day of discharge. We estimated the effect of an unmeasured confounder according to the "rule out" approach for the relevant reported results.[36]

Results

A total of 44 099 women aged 40 or over on 1 January 1997 had a myocardial infarction in the period 1997 to 2008, but 10 494 of these women died during the first 30 days after discharge and were therefore excluded, as were the 71 women lost to follow-up (fig 1⇓). Among the remaining 33 534 women, 3322 (9.9%) were using HRT at the time of myocardial infarction, and these women constituted the population of this study. The number of reinfarctions during follow-up was 282 (8.5%), 357 (10.7%) women died of all causes, and 218 (6.6%) died of cardiovascular causes.

Most women used the combination of systemic oestrogen and progestogen (1100; 33.1%), followed by vaginal oestrogen (977, 29.4%) and systemic oestrogen alone (954, 28.7%). Only 291 (8.8%) women used HRT belonging to the category "other HRT" (table 2⇓). Baseline characteristics of women using different categories of HRT were very different, as is evident from table 2⇓ and as we have previously found.[25]

Analyses of discontinuation in the first 30-360 days after myocardial infarction showed an association between discontinuation of vaginal oestrogen and a decreased risk of reinfarction (hazard ratio 0.54, 95% confidence interval 0.34 to 0.86), as well as an insignificant association for discontinuation of systemic oestrogen (0.56, 0.28 to 1.11) and overall HRT (0.90, 0.68 to 1.19) (table 3⇓). We also found a statistically insignificant increase in cardiovascular mortality (hazard ratio 1.39, 0.73 to 2.66, for discontinuation of systemic oestrogen; 1.15, 0.78 to 1.72, for vaginal oestrogen; and 1.21, 0.90 to 1.62, for overall HRT) and all cause mortality (hazard ratio 1.17, 0.70 to 1.94, for discontinuation of systemic oestrogen; 1.31, 0.95 to 1.83, for vaginal oestrogen; and 1.22, 0.97 to 1.53, for overall HRT).

When analysing the different durations of discontinuation, we found that discontinuation of overall HRT for 1-90 days was associated with an increased risk of cardiovascular mortality and all cause mortality but no increased risk of reinfarction (fig 2⇓). This increased risk was apparent for cardiovascular mortality only when discontinuation occurred in the period 30-90 days after discharge (hazard ratio 1.90, 1.15 to 3.12) and for all cause mortality in both the periods 30-90 days (1.58, 1.04 to 2.39) and 91-180 days after discharge (1.76, 1.08 to 2.87). For 1-90 days of discontinuation of systemic oestrogen alone, we found increased cardiovascular mortality (hazard ratio 6.14, 1.95 to 19.3) and all cause mortality (3.23, 1.30 to 8.07) during the first 30-90 days after discharge (fig 2⇓). Again, we found a statistically insignificant lower risk of reinfarction. For 1-90 days of discontinuation of vaginal oestrogen, we found a decreased risk of reinfarction during the first 30-90 days after discharge (hazard ratio 0.36, 0.16 to 0.82) (fig 2⇓). For all the above, the corresponding unadjusted incidence rates of continued and discontinued treatment were equivalent to the proportional hazard analyses (tables 3⇓, 4⇓, 5⇓, and 6⇓). For discontinuation of combinations of oestrogen and progestogen and for the category "other HRT," calculations were limited owing to very few endpoints (table 3⇓, fig 2⇓).

Tables 7⇓ and 8⇓ show the results of the sensitivity analyses. The associations between discontinuation and the endpoints did not change significantly after inclusion of the first 30 days in the analyses or after postponement of the time of discontinuation by seven or 14 days.

Unmeasured confounding

To test whether the low risk of reinfarction after discontinuation of vaginal oestrogen found in both the first year and the first 30-90 days after myocardial infarction could be due to unmeasured confounding, we tried to estimate the hypothetical size of such an unmeasured confounder, assuming a 20% prevalence of an unmeasured confounder in the population and a prevalence of discontinuation of 20%.[36] The results indicate that an unmeasured confounder would be very unevenly distributed between the groups and have a very strong association with continued treatment (fig 3⇓ and fig 4⇓). A confounder or combination of confounders that could decrease the risk of reinfarction from 1.00 to 0.54 for discontinuation in the first year after myocardial infarction would have to increase the risk fivefold (fig 3⇓) and thereby exceed the effects of any measured confounder in the study, such as diabetes or age 80 or over. However, to render the results statistically insignificant, a confounder would have to increase the risk only twofold. In the case of discontinuation of vaginal oestrogen in the first 30-90 days after myocardial infarction, a confounder would have to increase the risk less than twofold to make the result statistically insignificant (fig 4⇓).

Discussion

This study is to our knowledge the first to look at whether women in a real life population who discontinue hormone replacement therapy after myocardial infarction have a lower risk of adverse cardiovascular events than do women who continue using HRT and whether discontinuation of different

categories of HRT might carry different risks. Our main finding was that in women with myocardial infarction who followed treatment guidelines and discontinued HRT overall, we could not detect a decreased or increased risk of reinfarction, cardiovascular mortality, or all cause mortality during the first year after the index myocardial infarction. Discontinuation of vaginal oestrogen after myocardial infarction was associated with a decrease in risk of reinfarction in the first year and the first 30-90 days after discharge. Women in the vaginal oestrogen group had very different baseline characteristics and higher incidence rates compared with women in the other HRT categories, which is relevant in interpreting these results.

Comparison with other studies

Most trials of the cardiovascular efficacy and safety of HRT have used oral conjugated equine oestrogens with or without medroxyprogesterone acetate depending on whether the woman had an intact uterus, but the use of conjugated equine oestrogens in our population was very limited.[4 5 25] HRT covers a multitude of hormones, formulations, doses, and routes of administration and has favourable effects on endothelial function, serum lipids, lipoproteins, and markers of fibrinolysis, inflammation, and coagulation.[9 37] These effects differ, however, between oral and transdermal oestrogen, probably because of the hepatic first pass effect with oral oestrogen.[10-13] Vaginal oestrogen treatment was previously believed to have only local effects, but a recent study showed a fivefold increase in serum oestradiol after one week of vaginal treatment.[14] Interestingly, a recent observational study in Denmark found no overall effect of oral HRT on risk of coronary artery disease, but both transdermal and vaginal HRT were associated with decreased risk.[38] Our results, too, seem to imply that vaginal oestrogen has a systemic effect or, alternatively, that some unmeasured confounder is responsible for the observed difference. As this is an observational study, we can only speculate about, and not explain, what causes the observed lower risk of reinfarction in women who discontinue vaginal oestrogen.

We have previously found in a population of women using HRT at the time of myocardial infarction in the period 1997 to 2005 that more than 80% of women who survived one year after myocardial infarction claimed a new prescription for HRT in the first year after discharge.[25] The vast majority of women continued use of the same category of HRT that they used at the time of myocardial infarction. This low rate of discontinuation might be because most women who discontinue HRT experience serious discomfort such as hot flushes and sleep disorders, which have a negative effect on their quality of life. Likewise, discontinuation of HRT can be especially difficult for women on long term HRT or for those who previously had severe climacteric symptoms.[18-20 39] Discontinuation of long term HRT may lead to increases in plasminogen activator inhibitor 1 and to augmented endothelial dysfunction in women with coronary artery disease. Also, blood concentrations of low density lipoprotein cholesterol and total cholesterol increase in women who discontinue HRT.[17] These findings suggest that discontinuation of HRT might cause a detrimental rebound effect that may contribute to adverse cardiovascular events. The period immediately after myocardial infarction is a pathophysiologically vulnerable time window, with endothelial dysfunction and elevated inflammatory markers. Hence, a possible rebound effect of discontinuation of HRT on these mechanisms might be especially detrimental during this period.[22-24] That the post-infarction period may not be the optimal time to discontinue HRT would therefore seem plausible. The results reported here, in which discontinuation seems to have a greater effect in the first 30-90 days after myocardial infarction, suggest that this line of reasoning may be true.

Only a few studies have examined the effect of HRT on prognosis after myocardial infarction. An observational study of women admitted with myocardial infarction found that women using HRT at the time of admission had significantly lower in-hospital mortality than did women who did not use HRT and concluded that this could be explained by therapeutic effects of HRT, selection bias, or both.[40] Among women who used HRT at the time of coronary artery stenting, repeat revascularisation has also been reported to be significantly reduced.[41] Our study illustrates the importance of future randomised studies in this area concerning the use and discontinuation of HRT; however, adequately powered studies of this sort seem unlikely ever to be done.

Strengths and limitations

The main strength of this study is the complete and nationwide cohort of unselected women using HRT at the time of myocardial infarction, including information about concomitant drugs and comorbidity. The required registration by the Danish pharmacies and the reimbursement of medical expenses ensure that all social classes and women both in and out of the labour market were represented. Moreover, we were able to include women using all the formulations of HRT available on the market.

The study has several limitations inherent to its observational nature. We have no information on clinical parameters such as obesity and smoking status, and although the incorporation of, for example, concomitant drugs, comorbidity, and income in our analyses might capture some effects of the important cardiovascular risk factors that we lack information about in this study, we cannot rule out unmeasured confounding. The significantly lower risk of reinfarction seen after discontinuation of vaginal oestrogen might be due to unmeasured confounding even though such a confounder or combination of confounders would have to be highly prevalent and carry a great risk. The HRT doses and treatment durations were calculated approximations, and the true dates of beginning and discontinuing a treatment may differ from the calculated dates. The sensitivity analyses in which discontinuation was postponed for seven and 14 days did not alter the direction of the results, and discontinuation has previously been assessed using prescriptions and the same algorithm for calculating treatment intervals and discontinuation as in our study.[42] However, we cannot rule out the possibility of unmeasured factors influencing our calculations, as the accuracy of assessment of discontinuation by monitoring of prescriptions is unknown. We lack information about the precise indications for use or discontinuation of HRT and about symptoms that may be a confounder, as hot flushes may be a marker of increased cardiovascular risk.[43] Furthermore, the well known observation that discontinuation of drugs as well as of placebo is associated with increased mortality must clearly be considered for a balanced interpretation of our results.[44 45]

Conclusion

The main result of this study is that we found no certain increased or a decreased risk of reinfarction or death with continuing HRT after a myocardial infarction. The 95% confidence limits rule out neither a modest benefit nor a worrisome increase in risk. These figures are valuable when a possible cardiovascular risk needs to be balanced with menopausal symptoms for the individual patient.

What is already known on this topic

Guidelines recommend discontinuation of HRT after myocardial infarction, even though randomised trials have not found an increase in cardiovascular risk in women with coronary heart disease

However, around 80% of women do not follow these guidelines

What this study adds

No certain increased or decreased risk of reinfarction or death with continuing HRT after a myocardial infarction was found

These figures are valuable when a possible cardiovascular risk needs to be balanced with menopausal symptoms for the individual patient

Contributors: D-MB, PRH, SZA, CT-P, and GHG were involved in the study conception and design. D-MB and PRH obtained funding. D-MB, JL, CT-P, and GHG were involved in acquisition of data. D-MB, PRH, RS, JL, OA, CA, CT-P, and GHG were responsible for analysis and interpretation of data. DMB, JL, OA, CT-P, and GHG did the statistical analysis. D-MB drafted the manuscript, and all authors critically revised it for important intellectual content. D-MB, CT-P provided administrative, technical, or material support. PRH, SZA, CT-P, and GHG supervised the study. D-MB and GHG are the guarantors.

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Ethical approval: The Danish Data Protection Agency approved the study (No 2007-41-1667). Retrospective register studies do not require ethical approval in Denmark.

Data sharing: No additional data available.

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Tables

Table 1| Categories of hormone replacement therapy (HRT)

HRT category	Anatomical therapeutic chemical system codes
1. Systemic oestrogen (oral, intramuscular, nasal, or transdermal administration)	G03C A03, G03C A04, G03C A53, G03C A57
2. Systemic oestrogen and progestogen, continuous or cyclic* (oestrogen: oral, intramuscular, nasal, or transdermal administration; progestogen: intrauterine, transdermal, or oral administration)	Continuous: G03F A01, G03F A11, G03F A12, G03F A15, G0F A17; cyclic: G03F B01 , G03F B05, G03F B06, G03F B09, G03F B11, G03H B01. Or oestrogen from category 1 + progestogen from category 4
3. Vaginal oestrogen	Vaginal tablet: G03C A03, G03C A04, G03C A57, G03C B01; vaginal ring: G03C A03; vaginal cream: G03C A04
4. Other HRT	Progestogen intrauterine device: G02B A03; raloxifene: G03X C01; tibolone: G03D C05, G03C X01; progestogen alone: G03D A02, G03D A04, G03D B01, G03D C02, G03D C03. Or any combination of categories 1 and 3 or 2 and 3

*Continuous combined oestrogen/progestogen: daily doses of both oestrogen and progestogen; cyclic combined oestrogen/progestogen: daily doses of oestrogen and intermittent periods with daily doses of progestogen.

Table 2| Baseline characteristics. Values are numbers (percentages) unless stated otherwise

Characteristic	Overall HRT at time of MI	Systemic oestrogen at time of MI	Systemic oestrogen and progestogen at time of MI	Vaginal oestrogen at time of MI	Other HRT at time of MI	P value for difference between groups*
No of women	3322	954 (28.7)	1100 (33.1)	977 (29.4)	291 (8.8)	
Median (interquartile range) age (years)	70 (61-79)	71 (63-79)	63 (57-71)	79 (72-84)	68 (58-77)	<0.001
Age group (years):						
40-59	683 (20.6)	175 (18.3)	386 (35.1)	40 (4.1)	82 (28.2)	<0.001
60-69	891 (26.8)	251 (26.3)	411 (37.4)	155 (15.9)	74 (25.4)	
70-79	963 (29.0)	314 (32.9)	242 (22.0)	325 (33.3)	83 (28.5)	
≥80	784 (23.6)	214 (22.4)	61 (5.6)	457 (46.8)	52 (17.9)	
Year of MI:						
1997-9	872 (26.3)	276 (28.9)	348 (31.6)	202 (20.7)	46 (15.8)	<0.001
2000-2	1097 (33.0)	323 (33.9)	388 (35.3)	274 (28.1)	112 (38.5)	
2003-5	889 (26.8)	247 (25.9)	266 (24.2)	293 (30.0)	83 (25.8)	
2006-8	464 (14.0)	108 (11.3)	98 (8.9)	208 (21.3)	50 (17.2)	
Comorbidity:						
Previous MI	309 (9.3)	99 (10.4)	75 (6.8)	113 (11.6)	22 (7.6)	0.001
Revascularisation within 30 days	862 (26.0)	221 (23.2)	351 (31.9)	202 (20.7)	88 (30.2)	<0.001
Cerebrovascular disease†	101 (3.0)	28 (2.9)	17 (1.6)	49 (5.0)	7 (2.4)	<0.001
Congestive heart failure†	106 (3.2)	35 (3.7)	22 (2.0)	43 (4.4)	6 (2.1)	0.009
Malignancy†	60 (1.8)	16 (1.7)	15 (1.4)	23 (2.4)	6 (2.1)	0.38
Cardiac dysrhythmias†	134 (4.0)	41 (4.3)	28 (2.6)	56 (5.7)	9 (3.1)	0.002
Chronic renal failure†	16 (0.5)	1 (0.1)	3 (0.3)	11 (1.1)	1 (0.3)	0.006‡
Acute renal failure†	6 (0.2)	1 (0.1)	1 (0.1)	4 (0.4)	0 (0.0)	0.25‡
Diabetes with complications†	27 (0.8)	6 (0.6)	6 (0.6)	11 (1.1)	4 (1.4)	0.30
Pulmonary oedema†	12 (0.4)	1 (0.1)	6 (0.6)	3 (0.3)	2 (0.7)	0.29‡
Shock†	13 (0.4)	1 (0.1)	2 (0.2)	9 (0.9)	1 (0.3)	0.02‡
Concomitant drugs:						
β blockers	1985 (59.8)	563 (59.0)	670 (60.9)	576 (59.0)	176 (60.5)	0.77
ACE inhibitors	1399 (42.1)	405 (42.5)	428 (38.9)	432 (44.2)	134 (46.1)	0.04
Statins	1356 (40.8)	389 (40.8)	468 (42.6)	365 (37.4)	134 (46.1)	0.02
Loop diuretics	1216 (36.6)	364 (38.2)	306 (27.8)	447 (45.8)	99 (34.0)	<0.001
Clopidogrel	995 (30.0)	269 (28.2)	345 (31.4)	278 (28.5)	103 (35.4)	0.06
Glucose lowering drugs	311 (9.4)	87 (9.1)	74 (6.7)	122 (12.5)	28 (9.6)	<0.001
Income group:						
1	725 (21.8)	199 (20.9)	164 (14.9)	304 (31.1)	58 (19.9)	
2	961 (28.9)	296 (31.0)	264 (24.0)	328 (33.6)	73 (25.1)	<0.001
3	1636 (49.3)	459 (48.1)	672 (61.1)	345 (35.3)	160 (55.0)	

ACE=angiotensin converting enzyme; HRT=hormone replacement therapy; MI=myocardial infarction.

*χ^2 test for categorical variables and analysis of variance for continuous variables.

†According to modified Ontario acute myocardial infarction prediction rules.

‡χ^2 test may not be valid owing to very few observations.

Table 3| **Hazard ratios and unadjusted incidence rates for discontinuation in first year after myocardial infarction**

	Reinfarction		Cardiovascular death		All cause death	
	Discontinuation	Continued treatment	Discontinuation	Continued treatment	Discontinuation	Continued treatment
Hormone replacement therapy overall						
Hazard ratio* (95% CI)	0.90 (0.68 to 1.19)	Reference	1.21 (0.90 to 1.62)	Reference	1.22 (0.97 to 1.53)	Reference
Incidence rate†	90.9	112.9	91.9	74.2	156.3	119.2
No of events	66	216	70	148	119	238
Person years	725.7	1912.5	761.6	1995.8	761.6	1995.8
Systemic oestrogen						
Hazard ratio* (95% CI)	0.56 (0.28 to 1.11)	Reference	1.39 (0.73 to 2.66)	Reference	1.17 (0.70 to 1.94)	Reference
Incidence rate†	58.7	116.1	80.3	60.6	126.2	111.1
No of events	10	66	14	36	22	66
Person years	170.5	568.5	174.3	594.0	174.3	594.0
Systemic oestrogen and progestogen						
Hazard ratio* (95% CI)	0.30 (0.09 to 0.96)	Reference	0.94 (0.37 to 2.39)	Reference	0.96 (0.53 to 1.75)	Reference
Incidence rate†	16.9	85.9	43.4	33.4	89.0	83.7
No of events	3	59	6	31	16	60
Person years	177.9	686.8	179.8	716.8	179.8	716.8
Vaginal oestrogen						
Hazard ratio* (95% CI)	0.54 (0.34 to 0.86)	Reference	1.15 (0.78 to 1.72)	Reference	1.31 (0.95 to 1.83)	Reference
Incidence rate†	78.1	168.4	139.7	136.8	212.5	189.4
No of events	26	68	47	59	73	80
Person years	332.8	403.8	343.5	422.3	343.5	422.3
Other hormone replacement therapy						
Hazard ratio* (95% CI)	0.11 (0.01 to 2.20)	Reference	0.60 (0.03 to 11.8)	Reference	1.00 (0.24 to 4.28)	Reference
Incidence rate†	26.3	105.7	63.9	25.5	101.2	115.0
No of events	1	16	1	10	4	18
Person years	38.0	151.3	39.2	156.5	39.2	156.5

*Multivariable Cox proportional hazards analysis adjusted for age group, year of myocardial infarction (MI), comorbidity (previous MI, revascularisation within 30 days of MI, cerebrovascular disease, congestive heart failure, malignancy, cardiac dysrhythmias, chronic renal failure, acute renal failure, diabetes with complications, pulmonary oedema, shock), concomitant use of drugs (β blockers, angiotensin converting enzyme inhibitors, statins, loop diuretics, clopidogrel, glucose lowering drugs), and income; no interactions were found or included in the model.

†Unadjusted event rates per 1000 person years.

Table 4| Unadjusted incidence rates of reinfarction, cardiovascular mortality, and all cause mortality for discontinuation of HRT overall

	Reinfarction				Cardiovascular mortality				All cause mortality			
		HRT discontinued				HRT discontinued				HRT discontinued		
	Continued HRT	1-90 days	91-180 days	181-360 days	Continued HRT	1-90 days	91-180 days	181-360 days	Continued HRT	1-90 days	91-180 days	181-360 days
30-90 days after myocardial infarction												
Incidence rate*	237.7	198.5	–	–	116.7	257.3	–	–	180.8	349.9	–	–
Failures	102	19	–	–	51	25	–	–	79	34	–	–
Person years	429.2	95.7	–	–	436.9	97.2	–	–	436.9	97.2	–	–
91-180 days after myocardial infarction												
Incidence rate*	108.9	157.1	63.4	–	80.3	105.4	97.7	–	104.7	210.8	171.0	–
Failures	60	17	5	–	46	12	8	–	60	24	14	–
Person years	551.2	108.2	78.9	–	573.0	113.9	81.9	–	573.0	113.9	81.9	–
181-360 days after myocardial infarction												
Incidence rate*	57.9	69.4	80.4	31.8	51.7	51.0	60.5	50.2	100.4	87.4	105.8	105.5
Failures	54	9	10	6	51	7	8	10	99	12	14	21
Person years	932.1	129.7	124.4	188.8	986.0	137.3	132.3	199.1	986.0	137.3	132.3	199.1

HRT=hormone replacement therapy.

*Unadjusted incidence rates per 1000 person years.

Table 5| Unadjusted incidence rates of reinfarction, cardiovascular mortality and all cause mortality for discontinuation of systemic oestrogen

	Reinfarction				Cardiovascular mortality				All cause mortality			
		HRT discontinued				HRT discontinued				HRT discontinued		
	Continued HRT	1-90 days	91-180 days	181-360 days	Continued HRT	1-90 days	91-180 days	181-360 days	Continued HRT	1-90 days	91-180 days	181-360 days
30-90 days after myocardial infarction												
Incidence rate*	184.5	109.7	–	–	75.5	327.4	–	–	151.1	382.0	–	–
Failures	24	2	–	–	10	6	–	–	20	7	–	–
Person years	130.1	18.2	–	–	132.3	18.3	–	–	132.3	18.3	–	–
91-180 days after myocardial infarction												
Incidence rate*	116.0	36.0	NA	–	88.3	69.5	59.9	–	117.8	173.7	59.9	–
Failures	19	1	0	–	15	2	1	–	20	5	1	–
Person years	163.8	27.8	16.6	–	169.8	28.8	16.7	–	169.8	28.8	16.7	–
181-360 days after myocardial infarction												
Incidence rate*	83.8	65.8	125.0	22.0	37.7	31.5	60.5	43.7	89.1	63.0	90.8	87.5
Failures	23	2	4	1	11	1	2	2	26	2	3	4
Person years	274.5	30.4	32.0	45.4	291.9	31.8	33.0	45.7	291.9	31.8	33.0	45.7

HRT=hormone replacement therapy.

*Unadjusted incidence rates per 1000 person years.

	Reinfarction				Cardiovascular mortality				All cause mortality			
		HRT discontinued				HRT discontinued				HRT discontinued		
	Continued HRT	1-90 days	91-180 days	181-360 days	Continued HRT	1-90 days	91-180 days	181-360 days	Continued HRT	1-90 days	91-180 days	181-360 days
30-90 days after myocardial infarction												
Incidence rate*	343.0	124.2	–	–	213.5	282.9	–	–	284.7	371.2	–	–
Failures	33	7	–	–	21	16	–	–	28	21	–	–
Person years	96.2	56.4	–	–	98.4	56.6	–	–	98.4	56.6	–	–
91 to 180 days after myocardial infarction												
Incidence rate*	184.9	90.9	107.7	–	160.7	173.4	128.9	–	200.9	260.1	236.3	–
Failures	22	4	5	–	20	8	6	–	25	12	11	–
Person years	119.0	44.0	46.4	–	124.4	46.1	46.5	–	124.4	46.1	46.5	–
181 to 360 days after myocardial infarction												
Incidence rate*	68.9	42.7	88.9	42.4	90.2	79.3	104.1	83.5	135.3	119.0	187.4	146.2
Failures	13	2	4	4	18	4	5	8	27	6	9	14
Person years	188.6	46.8	45.0	94.3	199.5	50.4	48.0	95.8	199.5	50.4	48.0	95.8

Table 6 Unadjusted incidence rates of reinfarction, cardiovascular mortality, and all cause mortality for discontinuation of vaginal oestrogen

HRT=hormone replacement therapy.

*Unadjusted incidence rates per 1000 person years.

Table 7| **Sensitivity analysis: hazard ratios (95% CI) for discontinuation* after inclusion in analyses of women who died in first 30 days after myocardial infarction**

Death	HRT overall	Systemic oestrogen	Systemic oestrogen and progestogen	Vaginal oestrogen
Cardiovascular death	1.24 (0.96 to 1.62)	1.47 (0.86 to 2.52)	1.01 (0.48 to 2.14)	1.17 (0.83 to 1.65)
All cause death	1.26 (1.02 to 1.54)	1.30 (0.85 to 2.00)	1.02 (0.61 to 1.70)	1.30 (0.98 to 1.73)

HRT=hormone replacement therapy.

*Discontinuation 1-360 days after MI myocardial infarction.

Table 8| Sensitivity analysis: hazard ratios (95% CI) for discontinuation* after postponement of discontinuation date by 7 and 14 days

Postponement	Reinfarction	Cardiovascular death	All cause death
HRT overall:			
7 days	0.91 (0.69 to 1.22)	1.09 (0.80 to 1.48)	1.14 (0.90 to 1.44)
14 days	0.86 (0.63 to 1.15)	1.02 (0.74 to 1.39)	1.12 (0.89 to 1.43)
Systemic oestrogen:			
7 days	0.54 (0.26 to 1.11)	1.34 (0.69 to 2.61)	1.17 (0.70 to 1.97)
14 days	0.51 (0.24 to 1.09)	1.30 (0.66 to 2.69)	1.18 (0.70 to 2.00)
Vaginal oestrogen:			
7 days	0.50 (0.31 to 0.80)	0.94 (0.62 to 1.41)	1.14 (0.82 to 1.60)
14 days	0.48 (0.30 to 0.79)	0.86 (0.56 to 1.30)	1.11 (0.79 to 1.53)

HRT=hormone replacement therapy.

*Discontinuation in 1-360 days after MI myocardial infarction.

Figures

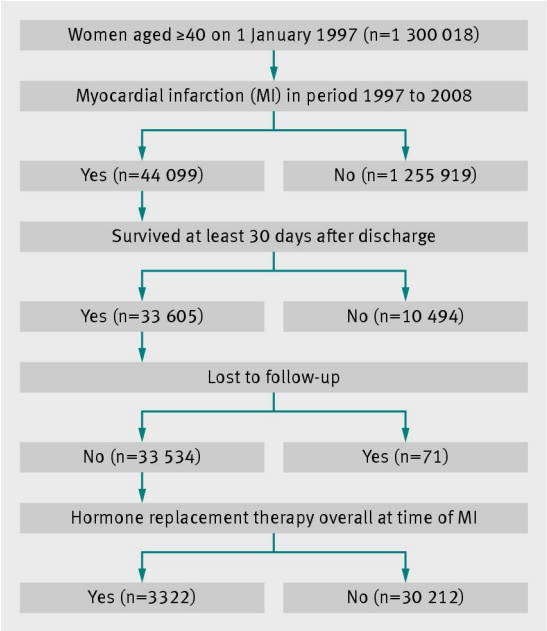

Fig 1 Study population

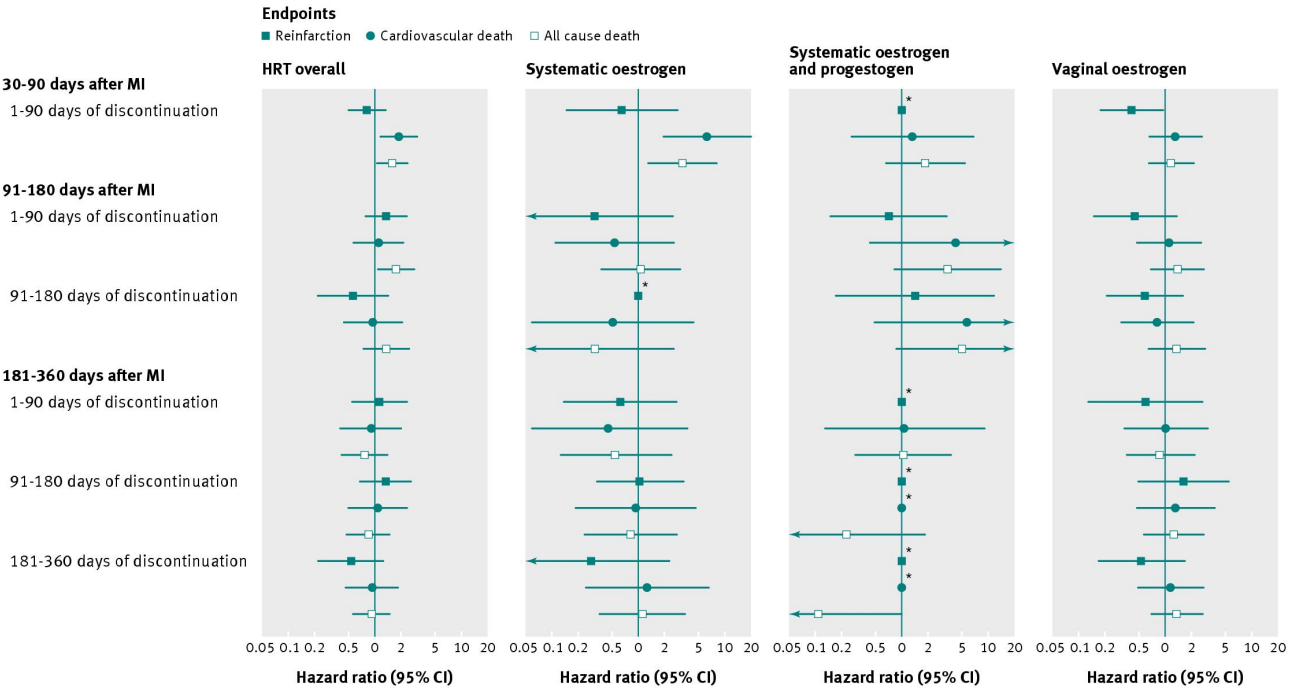

Fig 2 Hazard ratios (95% CI) for reinfarction, cardiovascular mortality, and all cause mortality for discontinuation of hormone replacement therapy (HRT) overall and HRT categories. Hazard ratios are for discontinuation with continued use as reference. Multivariable Cox proportional hazards analysis was adjusted for age group, year of myocardial infarction (MI), comorbidity (previous MI, revascularisation within 30 days of MI, cerebrovascular disease, congestive heart failure, malignancy, cardiac dysrhythmias, chronic renal failure, acute renal failure, diabetes with complications, pulmonary oedema, shock), concomitant drug use (β blockers, angiotensin converting enzyme inhibitors, statins, loop diuretics, clopidogrel, glucose lowering drugs), and income. No interactions were found or included in model

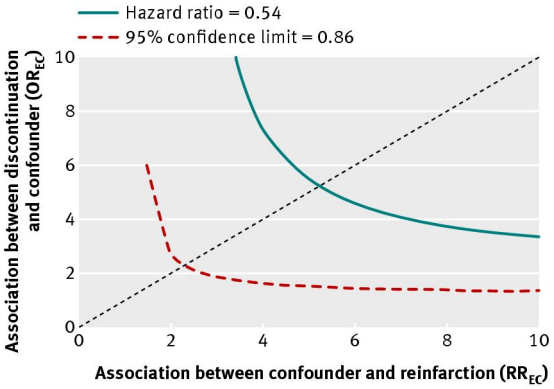

Fig 3 Required size of unmeasured confounder to fully explain decrease in risk from 1.00 to 0.54 (solid blue line) and to render results statistically insignificant (dashed red line), assuming prevalence of confounder of 20% in population and prevalence of discontinuation of 20%

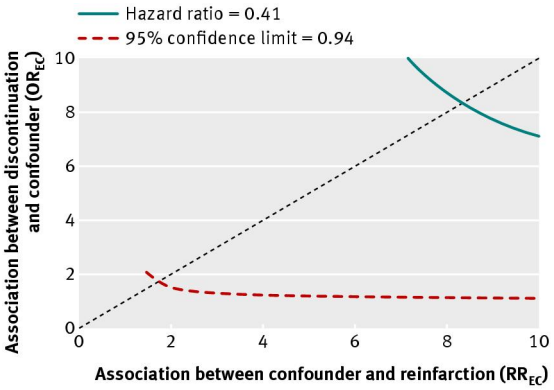

Fig 4 Required size of unmeasured confounder to fully explain decrease in risk from 1.00 to 0.41 (solid blue line) and to render results statistically insignificant (dashed red line), assuming prevalence of confounder of 20% in population and prevalence of discontinuation of 20%