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Long term hormone replacement is associated with low coronary artery calcium in a cohort of older women: The AGES-Reykjavik Study

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Abstract

Background—The long term effect of postmenopausal hormone replacement therapy (HRT) on atherosclerosis and cardiovascular health is controversial. Coronary Artery Calcium (CAC) is an established marker of atherosclerotic plaque burden.

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Conflict of Interest Disclosures:

Elements of Financial/Personal Conflicts	Adalsteinn Gudmundsson The corresponding author		6 coauthors (TA, GS, TH, LJJ, VG and HJ)					
	Yes	No	Yes	No	Yes	No	Yes	No
Employment or Affiliation		x		x				
Grants/Funds		x		x				
Honoraria		x		x				
Speaker Forum		x		x				
Consultant		x		x				
Stocks		x		x				
Royalties		x		x				
Expert Testimony		x		x				
Board Member		x		x				
Patents		x		x				
Personal Relationship		x		x				

All coauthors declare that there are no financial interest/conflicts of interest and have approved the current manuscript.

Objectives—To assess the relationship between HRT and CAC.

Design/setting—Cross sectional assessment in an established population based cohort in Reykjavik, Iceland.

Participants—2867 women (mean age 76±5 years) who had completed questionnaires on HRT use.

Measurements—The CAC by Computed Tomography was used as outcome variable and compared between women with history of HRT or had never used HRT, and was analysed according to age, length of use, and time from menopause when HRT was initiated.

Results—872 (30.4%) of the 2867 participants had used HRT and 312 (10.9%) were current users. After adjustment for age, other late life variables, and a propensity score based on midlife data for HRT use as observed in late life, the CAC showed significant negative associations with history and length of HRT use. This association was evident in all age categories. When the duration of HRT use was more than 15 years, the median coronary calcium was less than 50% of that observed in never users. The lowest CAC was observed in those who started HRT within five years after menopause. The prevalence of coronary events was comparable in both groups.

Conclusion—Long term HRT shows a strong association with lower CAC in comparison with women who had never used HRT. The negative association between HRT and CAC was linear with the duration of HRT and evident in all age groups of older women.

Keywords

Hormone replacement therapy; coronary artery calcium; older women; epidemiology

Introduction

The delayed onset of cardiac events among women in comparison to men has been linked to protective effect from estrogens.¹ Conflicting results regarding the effect of postmenopausal hormone replacement therapy (HRT) and cardiovascular mortality have emerged from several clinical trials in comparison to observational studies, where the former failed to support the presence of cardiovascular benefits previously indicated in the observational studies in postmenopausal women receiving hormone replacement.^{2–5}

Although the initial findings from the Women's Health Initiative (WHI) indicated substantial cardiovascular risks from use of HRT in postmenopausal women, an analysis of the estrogen only arm within the WHI suggested a potential lower risk of coronary heart disease if estrogen replacement therapy was initiated within 10 years after menopause.^{5–7} Another recently published randomized clinical trial of HRT for prevention of osteoporosis suggests that initiation of HRT early after menopause significantly reduces the composite endpoint of heart failure, myocardial infarction and mortality.⁸

Coronary artery calcium (CAC) score is an established marker of subclinical atherosclerosis and it has been shown that CAC assessment can improve risk predictions for coronary events after adjustment for traditional risk factors.^{9,10} In a sub study of the WHI project, women 50–59 years old at time of randomisation had their coronary artery calcium assessed after

trial completion. The women randomized to the conjugated estrogen only arm had significantly lower coronary calcium compared to the placebo arm after a mean of 7.4 years of treatment.¹¹ In contrast, the KEEPS trial did not show effect of up to 4 years of HRT (initiated within 3 years after last menses) on the progression of coronary artery calcium.¹²

Cardiovascular disease is a major cause of death in women older than 65 years of age.¹³ During the 10 years since the publication of the first WHI report, a substantial decrease in the use of HRT has been observed world-wide.¹⁴ The early discontinuation of the WHI study limits the possibility of answering the question of whether long-term therapy will reduce the eventual risk of CHD as women grow older. Currently, there are insufficient data to assess the benefits and risk of long term hormone replacement initiated in the perimenopausal years.¹⁵

In this study we used the ongoing Age, Gene\Environment Susceptibility-Reykjavik Study (AGES-Reykjavik Study), a large population-based cohort study of older Icelanders to analyse the relationship between timing of initiation and duration of HRT on coronary artery calcium.

Methods

The study population included 67–93 year old women who participated in the AGES-Reykjavik Study between 2002 and 2006. This is an ongoing population-based study of Icelandic men and women continuing the Reykjavik Study, an epidemiological study of cardiovascular and other diseases that took place between 1967 and 1997.¹⁶ The design of the AGES-Reykjavik study has been published previously.^{17,18} Data were derived from the AGES-Reykjavik study, the Reykjavik Study midlife exams and a national registry maintained by the Icelandic Heart Association. The AGES-Reykjavik examination was completed in three clinic visits, with a participant's full examination finished within a 4- to 6-week time window.

The participants responded to a detailed questionnaire during the AGES-Reykjavik first clinic visit, which included medical history, age at menopause (MP) and detailed questions about use of hormone replacement therapies, including age at initiation, route of administration and when stopped. Additional questionnaire information included family history of myocardial infarction, marital status and physical activity. Past and present physical activity was recorded on scale based on the number of hours of exercise reported per week.¹⁹

Of the 3287 women in the study, 2959 had a measurement of coronary artery calcium (CAC) at the study site, determined by computed tomographic (CT) images acquired with a single Siemens Sensation 4 detector scanner, using sequential scanning mode and prospective ECG triggering in a breath hold with the following imaging parameters; 2.5 mm thick slices, 140 KVp, 50mAS and 0.361 second scan time. Calcium in the coronary arteries was quantified using calcium scoring software and results expressed in Agatston scores.²⁰ In this group, there was insufficient questionnaire information in 24 cases, leaving 2935 women. The sample was further restricted to those women who entered the midlife exam at age 65 or

younger, resulting in a final study sample of 2867 women. This was done to use the information from the Reykjavik Study midlife data to create a propensity score for HRT use, as observed in late life. This approach gives an opportunity to adjust for and reduce the effect of selection bias. The advantage of using propensity scores is that they allow observational studies to be designed similar to randomized experiments.²¹ The covariates from the midlife data selected for use in this analysis contained: birth year (to account for cohort effect), work status (outside of home or not), raised in the Reykjavik capital area (yes/no), smoking (never, previous, current), education (primary, secondary, college, and university), participation in regular physical activity (yes/no), BMI, total cholesterol, triglycerides, and systolic blood pressure.

Missing data in late life variables were imputed using regression methods (regression or multinomial logistic) with age, birth year, and midlife data for same variables as predictors, except for late life hs-CRP, where the predictors were late life BMI, total cholesterol, LDL cholesterol, triglycerides, age and birth year. Late life BMI was imputed for 1 woman, pulse pressure for 1 woman, smoking status for 2 women, family history of MI for 3 women, late life education imputed for 17 women (based on midlife education), and hs-CRP for 1 woman.

Information about history of coronary events was based on a national registry in Iceland for all cases of myocardial infarction and procedures including percutaneous angioplasty and coronary bypass surgery.¹⁷

Statistical analysis

All statistical analysis was performed with Stata version 13 (StataCorp. 2013, College Station, TX). Imputations of late life values were performed using the *mi* procedure in STATA. A propensity score for ever use of HRT (as measured in late life) was created using the *psmatch2* procedure in STATA, with ever use of HRT as a binary response and midlife variables as predictors.²² In other words, the propensity score was defined as the predicted probability of HRT treatment, $e=P(Z=1|X)$, from a logistic regression model for HRT use on the midlife variables X . Here $Z=1$ denotes HRT treatment, and $Z=0$ denotes absence of treatment. The inverse probability of treatment weight was defined as $w=Z/e + (1-Z)/(1-e)$. The propensity score is a balancing score, participants with a similar propensity score will have similar values of the midlife covariates.²²

Balance assessment of the midlife covariates between treatment groups was performed by inspecting standardized differences of variables in the score between treated and untreated, using the inverse probability of treatment weights, based on the propensity scores, in the *pbalchk* procedure in STATA. The analysis of late life CAC was then performed using inverse probability of treatment weighting (IPTW). First unadjusted median values of CAC by age-group and HRT use were presented. Then the CAC scores were analysed using multiple quantile regression to estimate the median CAC score using IPTW. This was done both according to duration of HRT use (never HRT, 0–5 years, 6–15 years, and 16+ years); and according to initiation of HRT in relation to menopause (never HRT, before MP, within 1 year after last menses (MP year), 1–5 years after MP, >5 years after MP). Further adjustment to the IPTW analysis of CAC was made by using the late life variables: age at

entry into the AGES-Reykjavik Study, the age squared, age-interaction with HRT use, BMI, pulse pressure, total cholesterol, LDL cholesterol, hs-CRP, smoking status, education, family history of myocardial infarction, marital status, statin use, and use of medication for hypertension.

Age adjusted estimates reflect the cohort's middle age group of 75–79 year old.

The study protocol was approved by the National Bioethics Committee in Iceland as well as the Institutional Review Board of the Intramural Research Program of the National Institute on Aging (NIH, Bethesda, Maryland, USA). All participants in the AGES-Reykjavik Study gave informed consent.

Results

Prevalence of HRT use and late life characteristics

Of the 2867 participants, 872 (30.4%) had used HRT, including 312 (10.9%) who were current users. A total of 773 reported having used hormone pills and 168 had used hormone patches at some time.

The prevalence of current HRT decreased with age of subjects (69=19.5%; 70–74=15.1%; 75–79=9.0; 80–84=5.34%; 85=4.3%). Table 1 shows comparison of the characteristics between women grouped by current use, previous use of HRT and without history of HRT. The HRT groups (current and previous) were on average 2.6 years younger than the group never using HRT ($p<0.001$). After age adjustment, as shown by the adjusted p -values, the levels of LDL cholesterol and BMI remained significantly lower in HRT groups but the hs-CRP levels were higher. The rate of history of coronary events was comparable in both groups. The HRT groups were more often married, more likely to use antihypertension medication and tended to report more family history of myocardial infarctions. Participants' reported physical activity was higher in the HRT groups.

Propensity scores and inverse probability of treatment weights

All the midlife covariates were used to create a propensity score for HRT treatment. The covariates associated with HRT use were birthyear, systolic blood pressure, cholesterol, BMI, participation in physical activity, and higher education status. Women with history of HRT use were born later, had lower blood pressure, lower cholesterol, lower BMI, participated more in physical activity, and had higher education level. Covariates not associated were working outside of the home, smoking status, triglycerides, and being raised up in the Reykjavik capital area. Inverse probability of treatment weighting (IPTW), based on the propensity scores for HRT treatment, successfully balanced the HRT and the non-HRT groups with respect to the midlife covariates. A balance diagnostic graph is shown in Figure 1. No extremes were found in the estimated weights.

CAC scores by HRT use in different age groups

There was a strong positive non-linear (quadratic) association between age and CAC, despite the relatively high age of the study group. The average increase in CAC by per year, at the median age of 76, was 24 Agatston units (95%CI: 21 to 27). Figure 2 shows the steep age

related increase in CAC with age and illustrates the relationship between the groups of never HRT use, previous HRT use and current HRT use, showing consistently lower CAC scores in the current HRT users in all age categories.

CAC scores by duration of HRT treatment

Figure 3 illustrates the relationship between CAC and duration of HRT use and shows a negative linear association between these variables with a difference in median CAC of approximately 50% between the groups of never HRT and 16 or more years of HRT ($p<0.001$).

Total cholesterol and LDL cholesterol also showed a significant negative correlation with the duration of HRT after adjustment for age. For cholesterol: partial correlation = -0.06 ($p=0.003$); for LDL: partial correlation = -0.07 ($p<0.001$). The levels of hs-CRP did not correlate with the duration of HRT after age adjustment ($p=0.08$).

CAC and timing of HRT in relation to menopause

The relationship between CAC and the initiation of HRT compared with years from menopause is shown in Figure 4. Women who started HRT in the menopausal year had the lowest CAC scores and significantly lower CAC scores than women who had never used HRT or 87 Agatston units (95%CI: 42 to 132) $p=0.0001$. Women who initiated HRT treatment later also had lower CAC scores than never users or 56 Agatston units (95%CI: 13 to 98) $p=0.009$.

Discussion

In this population-based study of 2867 elderly Icelandic women we observed a strong negative association between the duration of HRT use and coronary calcium scores. This association was linear with the duration of HRT. When the duration of HRT use was more than 15 years, the median coronary calcium was approximately 50% of that found in women who had never used HRT. The lowest CAC scores were observed in those starting HRT at menopause, but even those starting HRT later had lower CAC scores than never users

The literature on estrogen and its effect on the cardiovascular system remains complex. Study results have varied by hormone preparation, coadministration of progesterone, length of observation or treatment trial, time interval since menopause and whether cardiovascular disease was present at onset of hormone replacement or not.^{9,23–25} To date, the main criticism of most randomized clinical trials of HRT using clinical cardiovascular endpoints relates to the fact that the women enrolled were well past menopause at an average age of 63–64 years old and more than 10 years beyond menopause.²⁶ Timing and duration of HRT in postmenopausal women are factors affecting cardiovascular outcomes central to the controversy of the so called “timing hypothesis” which suggests beneficial effects of HRT if initiated early after menopause.^{27,28} Another component of the hypothesis is that the beneficial effects of HRT will be lost if initiated several years after menopause.²⁹ Following the early termination of the WHI and its controversy over HRT and cardiovascular health, evidence started to accumulate in support of the hypothesis that the timing of initiation of HRT in relation to menopause onset may affect the association between this therapy and risk

of coronary artery disease.³⁰ Experimental studies in animals have also provided support for this association.^{31,32} Although, the mechanism is largely unknown whereby aging and longer periods of estrogen deprivation will affect HRT responses, there are suggestions of estrogen having more proinflammatory effect with aging.³³

It remains difficult to interpret our findings in context of the timing hypothesis as we use a surrogate marker of atherosclerosis and compare event rate through a cross sectional approach. However, our findings suggest that continuing early initiated HRT for more than 15 years, an association with low coronary calcium will remain. This requires further testing in clinical trials but research has been lacking where a upper limit of age or duration of treatment has been assessed in terms of efficacy or safety relating to cardiovascular disease or other outcomes.²⁷ In a randomized controlled trial of more than 1.000 Danish women who had recently entered menopause, Schierbeck et al. found that >10 years of HRT started early after menopause significantly reduced risk of all cause mortality, heart failure, or myocardial infarction but without apparent increase of cancer, venous thromboembolism or stroke.⁸ Different dosing regimens and preparation of HRT limit the ability to make comparisons between studies done at different time periods and geographic regions. Estradiol has been the most common estrogen compound used for HRT in Iceland and the conjugated equine estrogen used in the WHI has not been on the market.

The gender specific differences of cardiovascular disease have received increased attention in recent years.³³ The higher prevalence of myocardial ischemia among women in the presence of normal cardiac catheterization has lead to the discussion of microvascular disease being a more common condition among women.³⁴ A similar ratio of past history of coronary events in our group of HRT users is in contrast with several recent clinical trials reporting lower composites of cardiovascular outcomes when HRT is initiated early after menopause.^{7,8} There is no simple explanation for the equal rate of cardiac events. Although the lower cholesterol levels in the HRT group may reflect favourable altering of lipoprotein profile through HRT, they did not seem to affect the principal conclusions of the current study. HRT users were also more likely to be married and have a family history of myocardial infarctions. A complex situation of different indications and possible dropout due to mortality or other reasons are among possible explanations for the similar prevalence of cardiovascular events in the study. Prospective studies are needed to clarify this issue.

The use of propensity score methodology in analysis of health outcomes data in observational studies has evolved rapidly in recent years.²¹ It is evident from Figure 1 that balancing the available midlife covariates using propensity scoring may lead to better matching between the HRT groups for statistical comparisons. On the other hand, it must be borne in mind that the propensity score itself is limited by the available information and there may still exist some residual confounding by factors that are not included in the score.

The main weaknesses of our findings relate to the cross sectional nature of the data collection. Also, as the average age in our study is more than 75 years it is possible that women at higher risk for cardiovascular disease had dropped out from the cohort due to death or other reasons. It is also likely that various other indications than menopausal symptoms are behind HRT in the study group but at the turn of the century, HRT was

commonly prescribed to prevent age associated diseases such as osteoporosis and cardiovascular disease.³⁷ There is also a possibility of a memory bias, particularly among the older section of our cohort.

Additional issues include lack of accurate information whether the estrogen was opposed by progesterone or not, the dose and estrogen preparation, potential interruptions of therapy and the wide age range of the cohort. On the other hand, the large population based sample of women, the quality of the data and the very long observational window of reported HRT use reflected through the age of the cohort give a unique insight into the potential long term effects of HRT on coronary calcifications. The age span of the study sample exceeds previous large epidemiological studies of CAC but for the overlapping age groups, the CAC values seem comparable with results for women in the Framingham and MESA cohorts.³⁸

The lower coronary calcium in the HRT group in our cohort converges with a growing body of clinical trials and observational studies indicating that HRT related cardiovascular outcomes vary according to age or time since menopause.³⁶ A recent meta-analysis comparing results from observational studies vs randomized controlled trials indicates that there is little evidence of significant effect estimate differences in health outcomes.³⁹ Our finding also underscores the importance of further research on the long term role of HRT related changes in cardiovascular disease risk factors and outcomes. The AGES Reykjavik study has been ongoing and further prospective analysis of the association between HRT and cardiovascular outcomes and mortality may provide further information.

In conclusion, our results support the hypothesis that hormone replacement initiated early after menopause and taken long term, may delay or slow the progression of coronary calcification.

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References

1. Colditz GA, Willett WC, Stampfer MJ, et al. Menopause and the risk of coronary heart disease in women. *N Engl J Med*. 1987; 316:1105–1110. [PubMed: 3574358]
2. Grodstein F, Manson JE, Colditz GA, et al. A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. *Ann Intern Med*. 2000; 133:933–941. [PubMed: 11119394]
3. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. *JAMA*. 1998; 280:605–613. [PubMed: 9718051]
4. Rossouw JE, Anderson GL, Prentice RL, et al. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA*. 2002; 288:321–333. [PubMed: 12117397]

5. Anderson GL, Limacher M, Assaf AR, et al. Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: The Women's Health Initiative randomized controlled trial. *JAMA*. 2004; 291:1701–1712. [PubMed: 15082697]
6. Prentice RL, Langer R, Stefanick ML, Howard BV, Pettinger M, Anderson G, Barad D, Curb JD, Kotchen J, Kuller L, Limacher M, Wactawski-Wende J. Women's Health Initiative Investigators. Combined postmenopausal hormone therapy and cardiovascular disease: toward resolving the discrepancy between observational studies and the Women's Health Initiative clinical trial. *Am J Epidemiol*. 2005; 162:404–414. [PubMed: 16033876]
7. Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA*. 2007; 297:1465–1477. [PubMed: 17405972]
8. Schierbeck LL, Rejnmark L, Tofteng CL, et al. Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial. *BMJ*. 2012; 345:e6409. [PubMed: 23048011]
9. Pletcher MJ, Tice JA, Pignone M, et al. Using the Coronary Artery Calcium Score to Predict Coronary Heart Disease Events. A Systematic Review and Meta-analysis. *Arch Intern Med*. 2004; 164:1285–1292. [PubMed: 15226161]
10. Kara K, Mahabadi AA, Berg MH, et al. Predicting risk of coronary events and all-cause mortality: role of B-type natriuretic peptide above traditional risk factors and coronary artery calcium scoring in the general population: the Heinz Nixdorf Recall Study. *Eur J Prev Cardiol*. 2014; 21:1171–9. [PubMed: 23674833]
11. Manson JE, Allison MA, Rossouw JE, et al. Estrogen therapy and coronary-artery calcification. *N Engl J Med*. 2007; 356:2591–2602. [PubMed: 17582069]
12. Harman SM, Black DM, Naftolin F, et al. Arterial imaging outcomes and cardiovascular risk factors in recently menopausal women: a randomized trial. *Ann Intern Med*. 2014; 161:249–260. [PubMed: 25069991]
13. Maas A, van der Schouw YT, Regitz-Zagrosek V, et al. Red alert for women's heart: the urgent need for a more research and knowledge on cardiovascular disease in women. *Eur Heart J*. 2011; 32:1362–1368. [PubMed: 21406440]
14. Gompel A, Santen RJ. Hormone therapy and breast cancer risk 10 years after the WHI. *Climacteric*. 2012; 15:241–249. [PubMed: 22612610]
15. Marjoribanks J, Farquhar C, Roberts H, et al. Long term hormone therapy for perimenopausal and postmenopausal women. *Cochrane Database of Systematic Reviews*. 2012; 7:CD004143.
16. Andresdottir MB, Sigfusson N, Sigvaldason H, et al. Erythrocyte Sedimentation Rate, an Independent Predictor of Coronary Heart Disease in Men and Women; The Reykjavik Study. *Am J Epidemiol*. 2003; 158:844–851. [PubMed: 14585762]
17. Harris TB, Launer LJ, Eiriksdottir G, et al. Age, Gene/Environment Susceptibility-Reykjavik Study: multidisciplinary applied phenomics. *Am J Epidemiol*. 2007; 165:1076–1087. [PubMed: 17351290]
18. Sigurdsson G, Aspelund T, Chang M, et al. Increasing sex difference in bone strength in old age: The Age, Gene/Environment Susceptibility-Reykjavik study (AGES-REYKJAVIK). *Bone*. 2006; 39:644–651. [PubMed: 16790372]
19. Chang M, Saczynski JS, Snaedal J, et al. Midlife physical activity preserves lower extremity function in older adults: Age Gene/Environment Susceptibility-Reykjavik study. *J Am Geriatr Soc*. 2013; 61:237–242. [PubMed: 23320618]
20. Agatston AS, Janowitz WR, Hildner FJ, et al. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol*. 1990; 15:827–832. [PubMed: 2407762]
21. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med*. 2015 Aug 3. doi: 10.1002/sim.6607
22. Leuven, E., Sianesi, B. PSMATCH2: Stata module to perform full Mahalanobis and propensity score matching, common support graphing, and covariate imbalance testing. 2003. <http://ideas.repec.org/c/boc/bocode/s432001.html>, version. This version 4.0.11 22 oct 2014

23. Sturdee DW, MacLennan AH. The pendulum swings back; estrogen is now beneficial if started at the right time. *Climacteric*. 2006; 9:73–74. [PubMed: 16698654]
24. Christian RC, Harrington S, Edwards WD, et al. Estrogen status correlates with the calcium content of coronary atherosclerotic plaques in women. *J Clin Endocrin Metab*. 2002; 87:1062–1067.
25. Mendelson ME, Karas RH. HRT and the Young at Heart. *N Engl J Med*. 2007; 356:2639–264. [PubMed: 17582075]
26. The 2012 Hormone therapy position statement of: The North American Menopause Society. *Menopause*. 2012; 19:257–271. [PubMed: 22367731]
27. Harman SM, Vittinghof E, Brinton EA, et al. Timing and Duration of Menopausal Hormone Treatment May Affect Cardiovascular Outcomes. *Am J Med*. 2011; 124:199–205. [PubMed: 21396500]
28. Lenfant F, Trémollières F, Gourdy P, et al. Timing of the vascular actions of estrogens in experimental and human studies: why protective early, and not when delayed? *Maturitas*. 2011; 68:165–173. [PubMed: 21167666]
29. Clarkson TB, Meléndez GC, Appt SE. Timing hypothesis for postmenopausal hormone therapy: its origin, current status, and future. *Menopause*. 2013; 20:342–353. [PubMed: 23435033]
30. Manson JE, Bassuk SS. Invited commentary: hormone therapy and risk of coronary heart disease why renew the focus on the early years of menopause? *Am J Epidemiol*. 2007; 166:511–517. [PubMed: 17646204]
31. Pinna C, Cignarella A, Sanvito P, et al. Prolonged ovarian hormone deprivation impairs the protective vascular actions of estrogen receptor alpha agonists. *Hypertension*. 2008; 51:1210–1217. [PubMed: 18259018]
32. Sophonsritsuk A, Appt SE, Clarkson TB, et al. Differential effects of estradiol on carotid artery inflammation when administered early versus late after surgical menopause. *Menopause*. 2013; 20:540–547. [PubMed: 23615645]
33. Novella S, Heras M, Hermenegildo C, et al. Effects of estrogen on vascular inflammation: A matter of timing. *Arterioscler Thromb Vasc Biol*. 2012; 32:2035–42. [PubMed: 22679310]
34. Regitz-Zagrosek V. Therapeutic implications of the gender-specific aspects of cardiovascular disease. *Nat Rev Drug Discov*. 2006; 5:425–439. [PubMed: 16672926]
35. Buchthal SD, Den Hollander JA, Merz CN, et al. Abnormal Myocardial Phosphorus-31 Nuclear Magnetic Resonance Spectroscopy in Women with Chest Pain but Normal Coronary Angiograms. *N Engl J Med*. 2000; 342:829–835. [PubMed: 10727587]
36. Hodis HN, Mack WJ. The timing hypothesis and hormone replacement therapy: A paradigm shift in the primary prevention of coronary heart disease in women. Part 1: Comparison of therapeutic efficacy. *J Am Geriatr Soc*. 2013; 61:1005–1010. [PubMed: 23414520]
37. Nelson HD, Humphrey LL, Nygren P, et al. Postmenopausal Hormone Replacement Therapy: Scientific Review. *JAMA*. 2002; 288:872–881. [PubMed: 12186605]
38. Gudmundsson EF, Gudnason V, Sigurdsson S, et al. Coronary artery calcium distributions in older persons in the AGES-Reykjavik study. *Eur J Epidemiol*. 2012; 27:673–687. [PubMed: 22990371]
39. Anglemyer A, Horvath HT, Bero L. Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials. *Cochrane Database Syst Rev*. 2014 Apr 29;4:MR000034.doi: 10.1002/14651858.MR000034.pub2

Figure 1.

A balance diagnostic graph showing the standardized differences of midlife variables for the HRT versus the non HRT group before and after propensity score weighting based on the midlife covariates.

Figure 2.

Coronary artery calcium (CAC) scores and the relationship between the groups of never HRT use, previous HRT use and current HRT use in different age groups. Number of participants within age group and use of HRT is shown over each bar.

Figure 3.

The relationship between duration of HRT and coronary calcium (CAC) score expressed as Agatston scores. The CAC score was adjusted for late life variables and the inverse probability of treatment weighting for HRT use.

Figure 4. Coronary artery calcium (CAC) score expressed as Agatston scores and the initiation of HRT in relation to menopause (MP) compared with never HRT users. The CAC score was adjusted for late life variables and inverse probability of treatment weighting for HRT use.

Table 1

Late life characteristics and cardiovascular risk factor status according to groups of women with current history of hormone replacement (current HRT), previous history of HRT (previous HRT) or without history of HRT (never HRT).

	Current HRT (N=312)	Previous HRT (N=560)	Never HRT (N=1995)	Difference/OR (95% CI) Ever HRT vs Never HRT	P value	P value after age adjustment
Age	73.7 (4.8)	74.8 (4.9)	77.0 (5.4)	-3.2 (-3.9 to -2.6)	<0.001	
Age of menopause	48.7 (6.9)	48.5 (5.9)	49.2(7.1)	-0.6 (-1.1 to -0.1)	0.03	0.15
HRT years	10.9 (9.9)					
Body Mass Index (kg/m ²)	27.0 (4.6)	27.2 (4.5)	27.3 (4.9)	-0.1 (-0.5 to 0.3)	0.50	0.03
Pulse pressure (mmHg)	67.3 (18.4)	68.1 (17.)	70.7 (19.1)	-2.9 (-4.4 to -1.4)	<0.001	0.37
Cholesterol (mmol/l)	5.8 (1.0)	6.0 (1.1)	6.0 (1.1)	-0.1 (-0.2 to -0.01)	0.03	0.03
LDL Cholesterol (mmol/l)	3.52 (0.98)	3.64 (1.06)	3.71 (1.05)	-0.12 (-0.21 to -0.041)	0.006	0.005
HDL (mmol/l)	1.70 (0.49)	1.74 (0.44)	1.72 (0.44)	0.01 (-0.02 to 0.06)	0.30	0.21
Triglyceride (mmol/l)	1.02 (0.76)	1.08 (0.65)	1.08 (0.64)	-0.02 (-0.07 to 0.03)	0.41	0.08
C-reactive protein (mg/L)	2.10 (3.00)	2.10 (3.40)	1.90 (2.90)	0.20 (-0.01 to 0.41)	0.07	0.008
Ever smoker	49.4%(154)	55.9%(313)	48.3%(963)	1.24 (1.05 to 1.45)	0.009	0.24
History of cardiac events	12.8% (40)	14.6%(82)	14.1% (282)	1.00 (0.79 to 1.24)	0.92	0.23
Currently married	59.3%(185)	54.6%(306)	43.3% (864)	1.69 (1.43 to 1.98)	<0.001	0.005
Family history of myocardial infarction	41.7%(130)	45.0%(252)	38.2 (761)	1.26 (1.08 to 1.49)	0.004	0.044
Education (college or higher)	26.6%(83)	22.0%(123)	23.2%(463)	1.02 (0.84 to 1.23)	0.81	0.83
Statin medication use	16.7% (52)	20.2% (113)	18.9% (374)	1.01 (0.82 to 1.24)	0.91	0.90
Anti-hypertension medication use	66.0% (206)	64.3 (360)	64.2 (1281)	1.03 (0.87 to 1.22)	0.72	0.04
Physical activity at least occasionally	59.0% (184)	58.6% (328)	47.8%(953)	1.56 (1.32 to 1.83)	<0.001	0.001

Values for continuous variables are expressed by mean (SD) for approximately normally distributed variables, and median and inter quartile range (IQR) for skewed variables (CRP, and Triglycerides). Percentages and counts are presented for binary variables. Effect sizes are presented as differences in means or medians for continuous variables and odds ratios for binary variables. The groups of current and previous HRT (ever HRT) were compared with the never HRT group. P-values are expressed with and without adjustment for age by a general linear model for approximately normally distributed variables, quintile regression for CRP and triglycerides, and by logistic regression for the binary variables.