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Timing of Hormone Therapy, Type of Menopause, and Coronary Disease in Women: Data from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE)

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Abstract

Objective—To assess the relationship of timing of hormone therapy (HT) use with angiographic coronary artery disease (CAD) and cardiovascular disease (CVD) events in women with natural versus surgical menopause.

Methods—We studied 654 postmenopausal women undergoing coronary angiography for evaluation of suspected ischemia. Timing and type of menopause, HT use, and quantitative angiographic evaluations were obtained at baseline, and the women were followed for a median of 6 years for CVD events.

Results—Ever users of HT had a significantly lower prevalence of obstructive CAD compared to never users (age-adjusted OR=0.41 [0.28, 0.60]). Naturally menopausal women initiating HT at age <55 years had lower CAD severity compared to never users (age-adjusted beta [SE] = −6.23 [1.50], p<0.0001) while those initiating HT age ≥55 years did not differ statistically from never users (−3.34 [2.13], p=0.12). HT use remained a significant predictor of obstructive CAD when adjusting for a "healthy user" model OR 0.44 [0.30, 0.73] (p=0.002). An association between HT and fewer CVD events was observed only in the natural menopause group (HR [95%CI] =

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0.60[0.41, 0.88], p=0.009) but became non-significant when adjusting for presence or severity of obstructive CAD.

Conclusions—Using quantitative measurements of timing and type of menopause and HT use, earlier initiation of HT was associated with less angiographic CAD in women with natural but not surgical menopause. Our data suggest that the effect of HT use on reduced cardiovascular event rates is mediated by the presence or absence of angiographic obstructive atherosclerosis.

Keywords

cardiovascular disease; menopause; hormone therapy; atherosclerosis

Introduction

Women have a relatively lower risk of cardiovascular disease (CVD) compared to age matched men[1], suggesting that endogenous reproductive hormones play a protective role against coronary artery disease(CAD). Indeed, animal models[2] and human epidemiological studies[3] suggest that oophorectomy is a risk factor for accelerated CAD. Exogenous reproductive hormones have also been proposed to play a role in CAD.[4] In animal oophorectomy models, hormone therapy (HT) has anti-atherosclerotic effects when initiated early after oophorectomy,[5] and observational epidemiological studies in humans have demonstrated protective effects for CAD among postmenopausal HT users.[6–7] Clinical trials, however, have demonstrated overall no benefit and early adverse effects in women following menopause randomized to a variety of forms of HT, using angiographic[8–9] or clinical outcomes.[10–12] This discrepancy has called into question the validity of the endogenous estrogen protection hypothesis, as well as the prior animal and human epidemiological exogenous HT studies.

Recent data have shed light on this controversy. In the observational Nurses Health Study, younger women without coronary heart disease had a reduction of adverse events with HT[6] but older women with known disease had an initial increase in adverse events followed by a reduction after several years of treatment,[13] which was similar to what was seen with older women in the Women's Health Initiative (WHI) trials. In the pooled WHI trials, women who started HT within 10 years of menopause had less relative risk for adverse events compared with those who started HT greater than 10 years from menopause.[14] Pooled data from randomized trials including the WHI found a statistical trend in lower relative risk, suggesting that HT when started closer to the age of menopause may reduce adverse events compared to HT started at an older age.[14–15] Prior studies have also not been able to assess directly the putative mechanism of HT benefit, e.g. coronary atherosclerosis.

The Women's Ischemia Syndrome Evaluation (WISE) is a prospective, multi-center NHLBI-sponsored study designed to explore female-specific CVD pathophysiology in a large sample of women undergoing coronary angiography for suspected ischemic heart disease.[16] We undertook a detailed study to examine the relationship between timing and type of menopause and the timing of HT use with CAD, measured by quantitative coronary angiography and prospective adverse CVD events, to shed additional light on this controversy.

Methods

Women undergoing coronary angiography due to suspected ischemia underwent a one time baseline evaluation that included collection of demographic, medical history, detailed reproductive history and exogenous hormone use, psychosocial and symptom data from 1998–2002, as described previously[16] (cross-sectional phase). These women have been

followed annually for major adverse CVD events for a median of six years (prospective phase). Blood for reproductive hormone determinations was drawn at baseline following an overnight fast in close temporal proximity to the WISE testing. The study was approved by all involved sites' Institutional Review Boards.

Reproductive Status Questionnaire

The WISE reproductive status algorithm has been validated to be an accurate assessment of menopausal status and current HT use using both a detailed questionnaire and blood reproductive hormone levels.[17] The WISE reproductive status questionnaire includes a detailed history of menarche, date of last menstrual period, current and prior menstrual cycling patterns, prior reproductive events (pregnancy, hysterectomy, uni- and bilateral oophorectomy), current and prior perimenopausal symptoms, and current and prior oral contraceptive or HT use.[17] Reproductive hormone levels were assessed using validated steroid and protein assay methods for total estradiol, bioavailable estradiol, estrone, progesterone, follicle-stimulating hormone (FSH) and luteinizing hormone (LH).[18] Documentation of type of gynecological surgery was obtained when the blood reproductive hormone levels were not consistent with the reported status during expert consensus review for menopausal status determination.

A total of 654 postmenopausal WISE women were included in the current analysis. Among those without a history of hysterectomy or oophorectomy, the mean age of the last menstrual cycle was 49 years in smokers compared to 51 years in non-smokers, thus we imputed these menopausal ages for cessation of ovarian cycling in women with a pre-menopausal hysterectomy (with and without unilateral oophorectomy)(n=27). Because 95% of women are postmenopausal by age 55 years,[19] we used a conservative threshold of 55 years to define initiation of HT use before versus after menopause. Surgical menopause was defined as bilateral oophorectomy performed within less than one year after last menstrual period.

Measurement of Coronary Artery Disease

Coronary angiography was assessed at baseline by a core laboratory (blinded to historical or clinical data) used in previous NHLBI-sponsored multi-center trials.[20] Measurements included quantitative assessment of the presence of obstructive CAD, defined as ≥ 70% luminal diameter stenosis in ≥1 epicardial coronary artery and the WISE CAD severity score, using previously published methods.[20] The WISE CAD severity score was based on percent stenosis adjusted for any complete collaterals with the possible range of score being 5 (no detectable stenosis) to 100 (multiple severe lesions), and the actual range in the WISE was 5–78.

Adverse Cardiovascular Events

Major adverse CVD events were defined as CVD-related mortality, myocardial infarction, congestive heart failure, or stroke. Patients were contacted by telephone annually by experienced study coordinators completing a scripted interview about adverse CVD events or hospitalizations up to 9 years (median 6.0 [IQR 3.8–7.1]). If a patient was no longer living, we obtained a death certificate where available, records of any related CVD hospitalizations during the preceding follow-up time period, and/or description by a primary relative regarding the circumstances surrounding the death. The cause of death was reviewed by two cardiologist investigators blinded to the clinical and angiographic data; a third reviewer was used in discrepant death classification. For non-fatal major events (myocardial infarction, stroke, or heart failure), one WISE clinical site examined hospital and clinic records from 113 WISE women and only 1.8% of the self-reported events required reclassification, suggesting high accuracy in self-reported morbidity rates.

Statistical Methods

Values are expressed as raw means ± standard deviations or percentages as indicated. Because of the strong association of age with predictors and outcomes, we age-adjusted all p-values, odds ratios (OR) and 95% confidence intervals (CI), as well as beta coefficients and standard errors throughout this report. We used logistic regression when comparing women with obstructive CAD versus those without obstructive CAD (Tables 2 and 3) or women with natural versus surgical menopause (Table 4). We used linear regression when the dependent variable was the continuous CAD severity score rather than the dichotomous variable of obstructive CAD presence. For Table 5, we performed a two-factor ANOVA that assessed demographic and health risk variables according to HT use and menopause type (surgical versus natural), as well as their interaction terms, with p-values again adjusted for age (Table 5).

To assess the degree to which HT use provided incremental prediction of the presence versus absence of obstructive CAD over and above available healthy user variables, we performed logistic regression modeling in three steps. The first step evaluated the unadjusted odds ratios (OR) and 95% confidence intervals (CI) of history of HT use in predicting the presence of obstructive CAD. In the second step we developed a multivariate model of selected lifestyle and risk factor variables. These variables included traditional risk factors (diabetes, chronic disease, functional limitation [DASI], aspirin use) as well as those that were associated with either menopausal type or HT use with a $p \leq 0.05$. To avoid over-fitting, we included metabolic syndrome and the ATP III risk score that combine several traditional risk factors. This model included all variables listed in Table 5 with the exception of depression (which was collinear with antidepressant use), menopause, or HT use. In the third step we added HT use to this model. We then used the log rank test to estimate the incremental predictive power of HT use over and above that provided by the multivariate model. The same sequence of steps was repeated using linear regression when the outcome was the continuous log-transformed CAD severity score. In this latter case we used the F-test to estimate the significance of the incremental R^2 obtained when HT was added to the multivariate model.

Unadjusted Kaplan-Meier curves were used to compare event-free survival from CVD events among women with no history of HT use, those who initiated their HT use prior to age 55, and those initiating HT use at age 55 or older. We then used Cox proportional hazards regression to adjust for important covariates. The proportional hazards assumption of invariant relative risk was tested and found to be satisfactory for all models constructed. For all analyses a p-value of <0.05 was considered statistically significant. All analyses were performed using the SAS 9.1 software (Cary, N.C.).

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Results

The demographics and clinical profile for the 654 postmenopausal women with complete reproductive hormone variables and coronary angiography results are shown in Table 1. The women represent a broad age range (36–86 yrs), 17% were non-white (primarily African American), and the majority had at least one cardiac risk factor. A total of 134 (20%) had undergone surgical menopause. These women were younger than the naturally menopausal women (58 vs. 63 years, $p<0.0001$) and were more than twice as likely to use HT (age-adjusted OR 2.52 [1.59, 4.01]).

Menopause, Gynecological Surgery and Angiographic Coronary Artery Disease

Women with angiographic obstructive CAD (n=167) were older compared to those without obstructive CAD (n=487). Following age-adjustment, there were no significant differences between the two groups in age of menopause (Table 2). There was an inverse relationship between presence of obstructive CAD and history of menopausal symptoms (OR [95% CI] 0.58 [0.40, 0.84]), and bilateral oophorectomy before the age of 55 (0.57 [0.37, 0.86])(Table 2). Sensitivity analyses using the CAD severity score as the dependent variable demonstrated similar differences (age-adjusted beta coefficient [standard error] for menopausal symptoms = −4.08 [1.21], p=0.0008; for any gynecological surgery = −3.67 [1.18], p=0.002). Repeat age-adjusted analyses excluding the women with imputed menopausal age attenuated the effect of menopausal symptoms (p=0.19) but not of any gynecological surgery (OR [95% CI] = 0.40 [0.26, 0.61], p<0.0001).

Hormone Therapy (HT) Use and Obstructive Coronary Artery Disease

We evaluated relationships between HT use and obstructive CAD in the total population. After adjusting for age, historical ever users of HT had a significantly lower prevalence of CAD compared to never users (0.41 [0.28, 0.60]) (Table 3). Similarly, women with current HT use were less likely to have obstructive CAD (0.51 [0.34, 0.75]). Initiation of HT use at a younger age was marginally associated with lower prevalence of angiographic CAD in the overall population. A majority of the HT users were taking unopposed estrogen (Table 3).

HT Use in Surgical and Natural Menopause

Women who had undergone surgical menopause were significantly younger than naturally menopausal women (Table 4). Compared to women with natural menopause, those with surgical menopause were more than twice as likely to use HT (age-adjusted OR 2.52 [1.59, 4.01]), consisting almost exclusively of unopposed estrogen (Table 4). Notably, a relatively high proportion of naturally menopausal women also used unopposed estrogen, likely related to the relatively high hysterectomy rate (Table 2).

Association of HT Use with Coronary Artery Disease in Surgical and Natural Menopause

We compared the angiographic CAD severity score across HT subgroups stratified by natural versus surgical menopause (Figure 1). Among the surgical menopause women, there was no statistical difference among those who never used HT, those who initiated HT prior to age 55, and those initiating HT after age 55 (age-adjusted p=0.12), although there were very few women in the latter group. In contrast, among the naturally menopausal women the overall difference among the three HT subgroups was statistically significant (age-adjusted p=0.0002). Among the natural menopause subgroups, women initiating HT prior to age 55 had significantly lower CAD severity compared to never HT users (age-adjusted beta [SE] = −6.23 [1.50], p<0.0001) while those initiating HT after age 55 did not differ statistically from never HT users (−3.34 [2.13], p=0.12). The interaction term between type of menopause and HT subgroup was significant (p=0.010), suggesting a differential HT effect by surgical vs natural menopause.

In further sensitivity analyses, we stratified the obstructive CAD results according to no HT use, initiation of HT use before 2 years following menopause, and initiation after 2 years of reaching menopause. This was repeated for 5 years and 10 years, according to more recently published thresholds (14). The p-values for the menopause type by HT group interaction term were 0.025, 0.026, and 0.036 for 2, 5 and 10 year thresholds, respectively, when the outcome was presence vs. absence of obstructive CAD, and 0.06, 0.07, and 0.07, respectively, when the outcome was the log transformed CAD severity score. While naturally menopausal women showed the same relations in angiographic CAD severity

across HT groups as shown in Figure 1 (all p-values <0.0001), the differences were non-significant in surgically menopausal women (p-value range = 0.72 to 0.91).

Exploration of "Healthy User" Effects

Initiating HT use before and after the age of 55 years in women with natural and surgical menopause differed from non-HT users by both traditional and non-traditional risk factors including physical activity, nutritional and psychosocial variables (Table 5). When pooling the women with natural and surgical menopause, the HT subgroups (no HT, initiating HT before age 55, and after age 55), showed significant differences in both traditional and non-traditional risk factors that included physical activity and psychosocial variables (Table 5). At the time of WISE enrollment, HT users were younger, had a higher income, were less likely to smoke, were less obese and had a lower Framingham Risk Score, however had more frequent depression, lower usage of aspirin, and an earlier onset of menopause (Table 5). We used a "healthy user" risk model that included all the factors listed in Table 5, with the exception of history of depression, which was collinear with antidepressant use, or the menopausal status or HT variables such as age at menopause, duration of HT use, etc. Unadjusted, a history of HT use was strongly associated with a lower incidence of CAD (OR [95% CI] = 0.34 [0.24, 0.48], p<0.0001) and explained 8% of the total variance in CAD. When HT use was added to the full "healthy user" model, the OR [95% CI] for HT use was attenuated to 0.44 [0.30, 0.73] (p=0.002) and the contribution of HT use to the total variance dropped to 2% which still provided a statistically significant increment (p=0.0003) over and above the healthy user model for predicting presence or absence of CAD. When the outcome was the CAD severity score, history of HT use became non-significant when added to the healthy user model (from beta [SE] = −6.46 [1.16] p<0.0001 to −2.35 [1.36], p=0.08).

Association of HT Use with Adverse CVD Events in Surgical and Natural Menopause

After adjusting for age, historical ever users of HT had a trend toward lower incidence of adverse CVD events compared to never users (hazard ratio [95% CI]=0.72 [0.50, 1.04)], p<0.08). When stratified by surgical versus natural menopause, there was no difference in event rates among the surgical menopause subgroups (p=0.51), but a significant difference among the natural menopause subgroups (p=0.012) (Figure 2). Parallel to the finding for angiographic CAD, HT use was associated with fewer CVD events in women with natural menopause, with the women initiating HT prior to 55 years having the lowest CVD event rate.

Because the number of women in the surgical menopause subgroups was relatively low thus limiting statistical power to detect event differences within this stratum, we collapsed the two HT groups into type of menopause (natural/surgical) and HT history (no HT vs. HT use). This strengthened the association between HT and adverse CVD events in the natural menopause group (HR [95%CI] = 0.60[0.41, 0.88], p=0.009) but not in the surgical menopause group (1.55 [0.46, 5.17], p=0.48). When the relationships between HT use and adverse CVD events were adjusted for angiographic CAD, these findings became non-significant (0.76 [0.51, 1.14], p=0.18 in the natural menopause group and 1.52 [0.46, 5.10] in the surgical menopause group).

Discussion

To our knowledge, our findings represent the first observation evaluating HT use to core-laboratory assessment of angiographic CAD, and adverse CVD events in women. The current results link HT use with less angiographic CAD events particularly with an earlier onset of HT use. A significant but small residual beneficial association remained even after

statistical adjustment for a multitude of variables measured in the WISE study attributable to a "healthy user" effect. HT use, and particularly earlier initiation of HT use was also associated with a lower incidence of adverse CVD events. However, this effect became non-significant after adjusting for the presence or severity of obstructive CAD. This type of a pattern is suggestive of a mediating effect, such that the beneficial association between HT use and reduced CVD event rates appears to be mediated via the mechanism of less atherosclerosis.

The current results further suggest that HT initiated at a relatively early age (<55 years) in natural menopause is associated with a benefit, consistent with recent studies using an intermediate cardiovascular disease marker in relatively young women,[21–22] as well as subgroup analyses of the Women's Health Initiative.[14, 23] The current results are also consistent with recent clinical trials that have failed to show benefit either for angiographic coronary disease,[8–9] or cardiac events[10–12] in older women, and suggest the anti-atherosclerotic HT effect, if present, may be age-dependent.

Early prior observational human studies[3, 18, 21–22, 24–25] failed to distinguish premature surgical menopause (removal of ovaries prior to the time natural menopause would have occurred) from other forms of surgical menopause (hysterectomy or postmenopausal oophorectomy), or separate hysterectomy (cessation of menstrual periods with persistent ovulatory function) from bilateral oophorectomy (cessation of ovulatory function), while contemporary studies do not have this failing. [24, 26] Stampfer and colleagues indicated that the magnitude of observed HT protection was greater among those with surgical menopause compared to natural menopause in 5 of the 7 studies that addressed this,[27] however these data are similarly limited by the failure to accurately define type of menopause. Notably, our current results, using a specific definition of surgical menopause that includes the age of surgery relative to the age of menopause, are consistent with more recent studies using carotid intimal-medial thickness (IMT), which found no association with HT in surgically menopausal women.[28] Additional studies also failed to find an adverse association between surgical menopause and carotid IMT,[29] or hysterectomy and future cardiovascular events.[30] Finally, our results are consistent with a prior study that evaluated arteriosclerotic heart disease in women defined as documented myocardial infarction, positive ischemic stress test or angina and demonstrated the same prevalence of arteriosclerosis among 267 women with bilateral oophorectomy and 385 hysterectomized women.[31]

The mechanism(s) behind this apparent differential association between HT use and CAD by surgical versus natural menopause are unknown. Because HT use following surgical menopause was routinely prescribed, we had very few women in the surgical menopause group with either HT initiation after 55 years, or non-HT use. Thus limited statistical power is potentially a leading explanation for the lack of association of HT use in surgically menopausal women. It is also possible that the residual beneficial HT association observed in the natural menopause women can be explained by unadjusted additional healthy user variables (residual confounding), for example prescribing physician decision-making. Alternatively, physiological differences between surgical and natural menopause may account for these findings. Surgical oophorectomy, for example, reduces both blood estrogens and androgens, compared to natural menopause in which the ovaries continue to produce androgens that are converted to estrogens in peripheral tissue,[32] with a resulting endogenous estrogen and androgen hormonal milieu that may shape a differential HT response. Bilateral oophorectomy is performed for a variety of reasons in humans, including polycystic ovary syndrome where oophorectomy might theoretically lower subsequent CAD risk. Our results demonstrating a lower angiography CAD severity score in our surgical menopause non-HT users compared to the natural menopause non-HT users supports this

possibility. Finally, these results suggest that animal oophorectomy-HT models may not accurately reflect human physiology.[2, 5, 33–34]

Limitations

The current study results are limited by the observational design that precludes determination of causality. Our results obtained from a patient population of women undergoing coronary angiography for suspected ischemia may not be generalizable to a healthy population with regard to referral bias due to cardiac risk factor status. Statistical power to detect relations between HT use, CAD and adverse CVD events in our surgical menopause women was limited, due to the low prevalence of no HT use in this group. Moreover, it is inherently difficult to pinpoint age of onset of HT use and duration of HT therapy that rely on patient recollection. A larger dataset with a greater distribution of HT duration in early and late users could help further evaluate this. Also, the cross-sectional component of our study design is unable to detect early adverse cardiac events due to HT, as have been observed in prospective, randomized trials.[10, 12] Finally, our choice of the age cut-point for initiating HT use of 55 years may be questioned. This age was chosen because this is the age at which 95% of the population has reached menopause. In subsequent sensitivity analyses (reported above), we looked at other possible cut-points which yielded very similar results, suggesting that the distinction between earlier vs. later HT initiation is robust and not dependent on the specific age selected.

Conclusion

Recent HT trials[8–12] have consistently demonstrated overall no benefit and early adverse effects in older postmenopausal women, and have questioned the validity of the prior animal[2, 5] and human epidemiological results.[5–7] The current study results combined with recent publications evaluating younger women and early onset of HT use[13–15] suggest that the beneficial association between HT and CAD in natural menopause women observed in prior studies is attributable to both “healthy user” effect and a residual anti-atherosclerotic effect, particularly among those starting HT at a relatively earlier age (<55 years). Because menopausal symptoms requiring treatment remain common,[35] further investigation to document the presence or absence of these putative anti-atherosclerotic benefits, as well as improve the safety of HT regimens is clearly warranted. The current analysis sheds light on prior data discrepancies, and may be useful for prospective HT clinical trial planning.

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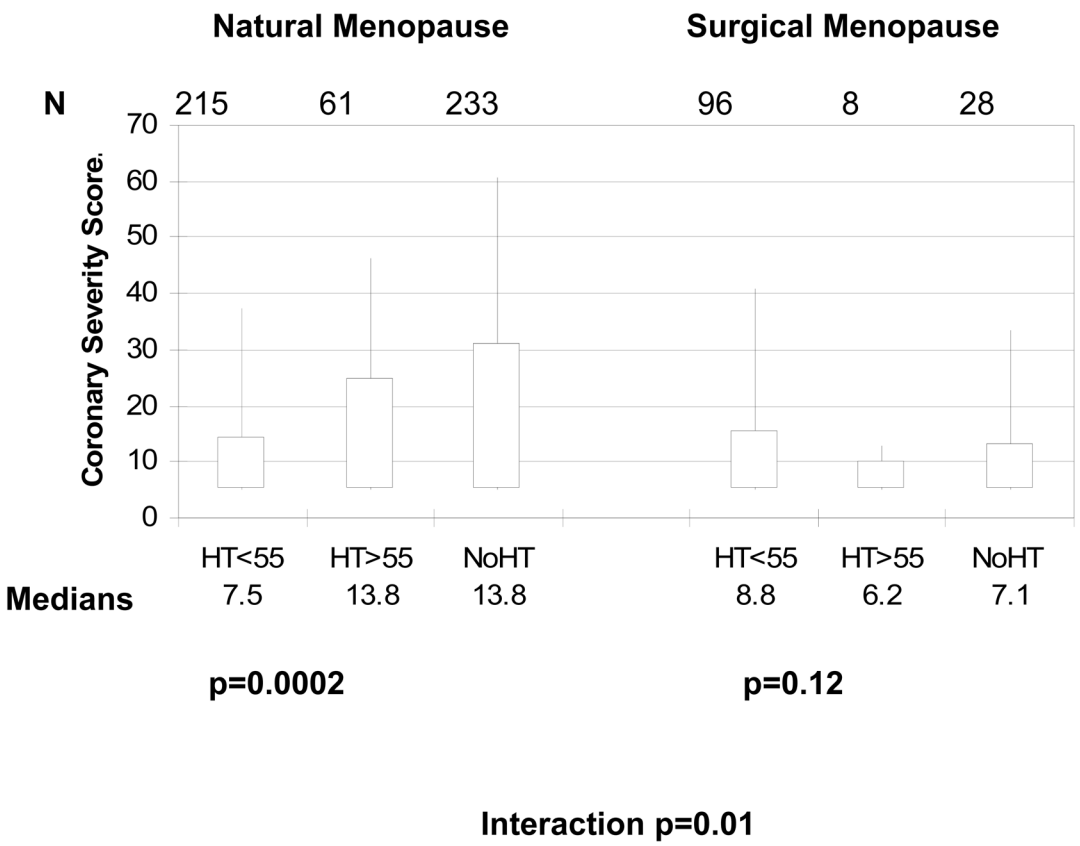

FIG. 1. Surgical versus natural menopause, HT, and angiographic CAD severity

CAD severity score box plots according to HT use in surgical versus natural menopause and age of HT use onset. The upper and lower edges of the boxes represent the interquartile range, and the whiskers represent the 95th percentile. *P* values are age adjusted. CAD, coronary artery disease; HT, hormone therapy.

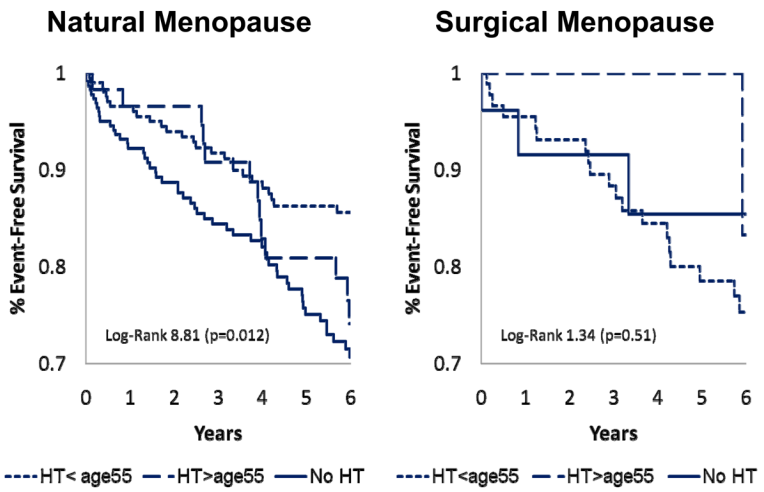

FIG. 2. Surgical versus natural menopause, HT, and freedom from major adverse cardiovascular events

Unadjusted Kaplan-Meier curves and *P* values for natural menopause HT less than 55 years (n = 215), HT 55 years or more (n = 61), and no HT (n = 233) as well as surgical menopause HT less than 55 years (n = 96), HT 55 years or more (n = 8), and no HT (n = 28). Major events defined as CVD mortality or nonfatal myocardial infarction, heart failure, or stroke. HT, hormone therapy; CVD, cardiovascular disease.

Table 1

Baseline Demographic and Clinical Variables (n=654)

Age (yrs)(±SD)	62±10
Race (% white)	83%
Hypertension (%)	61%
Diabetes Mellitus (%)	26%
Current Smoking (%)	18%
Lipid Lowering Rx (%)	33%
Current Postmenopausal HT Use (%)	44%
Coronary Artery Disease (% ≥1 coronary ≥70%)	26%
CAD Severity Score (± SD)	15.8±14.8

HT=hormone therapy, Rx=therapy, SD=standard deviation

Table 2

Menarche, Menopause, Gynecological Surgery and Coronary Artery Disease

	No Coronary Disease (n=487)	Coronary Disease (n=167)	OR (95% CI)	p
Age (yrs±SD)	61±9	66±9	1.05 (1.03,1.08)	<0.0001
Menopausal age (yrs±SD)	44±9	46±8	1.02 (0.99,1.04)	0.24
“ (No hysterectomy, yrs±SD)	48±5	49±5	1.02 (0.97,1.07)	0.49
“ (Natural menopause, yrs±SD)	46±8	48±6	1.02 (0.99,1.05)	0.25
“ (Surgical menopause, yrs±SD)	38±8	37±10	0.96 (0.90,1.02)	0.22
Menopausal symptoms (%)	71	55	0.58 (0.40,0.84)	0.004
Any gynecological surgery (%)	70	47	0.44 (0.30,0.63)	<0.0001
Surgical menopause (%)	23	13	0.62 (0.38,1.04)	0.07
Bilateral oophorectomy (BO) (%)	41	23	0.53 (0.35,0.80)	0.003
BO before age 55 (%)	39	22	0.57 (0.37,0.86)	0.008
Hysterectomy only (%)	19	17	0.80 (0.55,1.28)	0.35
Hysterectomy before age 55 (%)	17	16	0.84 (0.51,1.36)	0.47
Unilateral oophorectomy (UO) (%)	10	6	0.64 (0.32,1.28)	0.64
Hysterectomy with UO (%)	8	5	0.66 (0.31,1.40)	0.28
Hysterectomy with BO (%)	41	23	0.53 (0.35,0.80)	0.003
Hysterectomy with or without UO/BO before age 55 (%)	64	42	0.49 (0.34,0.72)	0.0002

BO=bilateral oophorectomy, SD=standard deviation, UO, unilateral oophorectomy, OR=odds ratio, CI=confidence interval.

CAD defined as ≥70% luminal diameter stenosis in ≥ one epicardial coronary artery. Surgical menopause defined as bilateral oophorectomy performed less than one year after last menstrual period. All ORs, CIs, and p values are age-adjusted except age.

Table 3

Hormone Therapy Use and Angiographic Coronary Artery Disease

	No Coronary Disease (n=487)	Coronary Disease (n=167)	OR (95% CI)	P
Overall:				
History of HT use (%)	66	39	0.41 (0.28,0.60)	<0.0001
Current HT use (%)	49	29	0.51 (0.34,0.75)	0.0007
Among Ever HT Users:	*(n=319)*	*(n=65)*		
Age onset of HT (yrs±SD)	46±11	55±11	1.03 (1.00,1.06)	0.052
Duration of HT use (yrs±SD)	10.4±10.0	8.7±10.2	0.98 (0.95,1.003)	0.08
Among Current HT Users:	*(n=241)*	(n=48)		
Unopposed estrogen (%)	74	75	1.03 (0.55,2.11)	0.93

Abbreviations and definitions as previously.

All ORs, CIs, and p values are age-adjusted.

Table 4

HT Use in Women with Natural versus Surgical Menopause

	Natural Menopause (n=520)	Surgical Menopause (n=134)	OR (95% CI)	p
Overall:				
Age (yrs±SD)	63 ± 9	58 ± 10	0.95 (0.93,0.97)	<0.0001
History of HT use (%)	54	78	2.52 (1.59,4.01)	<0.0001
Current HT use (%)	42	53	1.25 (0.84,1.86)	0.27
Among Ever HT Users:	*(n=279)*	*(n=105)*		
Age onset of HT (yrs±SD)	48±11	42±10	0.96 (0.93,0.98)	0.0003
Duration of HT use (yrs±SD)	10±10	11±10	1.02 (0.997,1.04)	0.09
Among Current HT Users:	*(n=218)*	(n=71)		
Unopposed estrogen (%)	68	93	1.03 (0.55,2.11)	0.93

Abbreviations and definitions as previously.

All ORs, CIs, and p values are age-adjusted.

Table 5

Demographic and Health Risk Profiles in Surgical vs Natural Menopause According to HT Use

	Natural Menopause			Surgical Menopause				
	HT≤55 yrs	*HT>55 yrs*	*No HT*	*HT≤55 yrs*	*HT>55 yrs*	*No HT*		
	(n=218)	*(n=62)*	*(n=234)*	*(n=97)*	*(n=8)*	*(n=28)*	*p(HT)*	*p(MP)*
Age (±SD)(yrs)	59(8)	66(5)	66(9)	57(10)	65(7)	60(12)	<.0001	0.001
Income ≥35K (%)	44	34	29	43	38	35	0.02	0.98
High School+ Ed. (%)	84	71	73	81	75	78	0.03	0.84
Non-White Race (%)	16	23	18	16	25	11	0.27	0.56
Hx Diabetes (%)	19	29	34	27	0	18	0.10	0.94
Chronic Disease (%)	39	55	52	42	0	56	0.11	0.92
Current Smoke (%)	16	13	18	26	12	32	0.005	0.07
BMI (±SD)	29(6)	29(6)	30(6)	30(8)	29(6)	31(6)	0.03	0.26
Metabolic Synd (%)	23	31	32	28	12	48	0.02	0.36
ATP III Risk (±SD)	4(4)	5(4)	7(6)	4(4)	4(2)	6(7)	0.0006	0.06
DASI (±SD)	20(15)	22(15)	18(12)	19(16)	26(10)	14(14)	0.15	0.17
Hx Depression (%)	33	18	12	34	25	36	0.04	0.22
Hx Cancer (%)	12	10	17	14	0	32	0.03	0.22
Antidepressants (%)	26	18	10	24	0	18	0.004	0.65
Vitamins C, E, A (%)	32	35	26	28	38	11	0.02	0.29
Aspirin Use (%)	58	68	71	61	100	71	0.15	0.17
Age at menopause	45(8)	49(5)	47(6)	39(8)	35(8)	35(9)	0.008	<.0001
Years since menopause	14(10)	17(7)	19(10)	19(9)	30(7)	25(11)	<.0001	<.0001
Yrs since initiating HT	16(11)	4(4)	-	17(10)	3(2)	-	<.0001	0.44
Duration of HT use	12(10)	3(4)	-	12(10)	2(1)	-	<.0001	0.99

p(HT)=p values for HT group across the entire sample after adjusting for natural vs. surgical menopause and age. p(MP)=p value for type of menopause from the same model, after adjusting for HT group and age.

BMI=body mass index, DASI=Duke Activity Status Inventory, a measure of functional capacity and physical activity habits, Hx=history of, ATP III Risk=National Cholesterol Education Program, Adult Treatment Panel III Global Coronary Heart Disease Risk Score (see Methods), Chronic Disease includes diabetes, COPD, renal disease, autoimmune disease, anorexia, or >25 drinks/week.

Non-significant variables included: marital status, Hx hypertension, Hx dyslipidemia, Hx smoking, Family Hx CAD, systolic and diastolic blood pressure, waist circumference, waist/hip ratio, prior CAD, lipid lowering therapy, antihypertensive therapy, anxiolytics, ACE inhibitors and nitrates. There were significant menopause type * HT group interaction terms for diabetes (p=0.01), Vitamins C, E, A (p=0.04), other chronic disease (p=0.01), age at menopause (p<0.0001), years since menopause (p=0.04). All other interactions were non-significant.