VASOMOTOR SYMPTOMS AND CORONARY ARTERY CALCIUM IN POSTMENOPAUSAL WOMEN

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Abstract

Objective—We assessed whether vasomotor symptoms (VMS) were associated with coronary artery calcium (CAC) and how hormone therapy may influence this association.

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Methods—Subjects were a subset of women aged 50 to 59 and a history of hysterectomy that enrolled in the Women's Health Initiative (WHI) clinical trial of estrogen alone and underwent a computed tomography scan of the chest at the end of the trial to determine CAC. Participants provided information about VMS (hot flashes and/or night sweats), as well as HT use, on self-administered questionnaires at trial baseline.

Results—The sample consisted of 918 women with a mean (SD) age of 55.1 (2.8) years at WHI randomization and 64.8 (2.9) years at CAC ascertainment. The prevalence of a CAC score > 0 was 46%, while the prevalence of a CAC score ≥ 10 and > 100 was 39 and 19%, respectively. At randomization, 77% reported a history of any VMS at any time prior to or at enrollment in the WHI while 20% reported any VMS only present at enrollment. Compared to those without a history of any VMS and after adjustment for potential confounders, a history of any VMS at any time up to and including WHI enrollment was associated with a significantly reduced odds for CAC > 0 (Odds Ratio 0.66, 95% CI 0.45 – 0.98). Moreover, as duration of HT increased the inverse association between any VMS and CAC moved toward the null.

Conclusion—A history of any VMS was significantly associated with a *reduced* odds for CAC independent of traditional CVD risk factors and other relevant covariates. This association appears to be influenced by duration of hormone therapy.

INTRODUCTION

Vasomotor symptoms (VMS), including hot flashes and night sweats, are relatively common and cause significant morbidity in women.[1] The prevalence of these symptoms varies in relation to the menopausal transition with the lowest levels typically being found in premenopausal women (14 – 51%), and higher levels in both perimenopausal (35 – 50%) and postmenopausal women (30 – 80%).[2] Although VMS have been shown to be responsive to hormone therapy,[3, 4] their specific etiology is uncertain. In this regard, VMS in women of middle age have been associated with lower serum estradiol and inhibin levels but higher FSH concentrations.[5] Since this pattern of reproductive hormones has been shown to be associated with higher levels of CVD risk factors[6] we hypothesize that women with vasomotor symptoms would be at increased risk for coronary artery disease.

In a regulated process similar to skeletal bone formation,[7] calcium is deposited in atherosclerotic plaques.[8] With the advent of computed tomography, these calcified atheromatous plaques can be detected throughout the vasculature,[9] including the coronary arteries.[10] The extent of coronary artery calcium (CAC) is highly correlated with both the total atheromatous plaque burden[11] and the percent stenosis in that vascular bed.[12] Moreover, several studies have shown CAC to be a strong and independent predictor of incident coronary heart disease (CHD) events in both men and women.[13, 14]

Use of CAC as marker of coronary atherosclerosis is increasingly advocated as a component of individual cardiovascular disease (CVD) risk stratification procedures.[15] Accordingly, the aim of this study was to determine the magnitude of the associations between VMS and CAC in women with a history of hysterectomy that were between the ages of 50 and 59 years at the time of their enrollment in the Women's Health Initiative (WHI).

METHODS

Subjects

This study examined a subset of participants in the WHI Conjugated Equine Estrogen trial (ET). These women were postmenopausal and aged 50 to 79 years at randomization with a history of hysterectomy prior to enrollment. The women were randomized (N = 10,739) to receive CEE, 0.625 mg/d (Premarin; Wyeth Pharmaceuticals, St Davids, PA) or a matching placebo. Women enrolled in the ET agreed to not take hormone therapy, beyond that provided in the clinical trial. Methods for data collection, management, and quality assurance have been published previously.[16] The ET trial was ended after an average of 6.8 years follow-up.

The Women's Health Initiative Coronary Artery Calcium Study (WHI-CACS) was a substudy of the WHI ET trial, conducted approximately 1.3 years after its completion (8.7 years after the baseline WHI visit). All WHI clinical sites were asked to participate in this substudy and 28 agreed. Reasons for site non-participation included lack of suitable equipment and logistical concerns. Women who were between 50 to 59 years old at the time of their randomization into the ET trial were invited to enroll. Invitations were mailed to these women (N=1742) requesting them to undergo a one-time cardiac computed tomography (CT) scan to determine CAC by electron beam or multidetector-row computed tomography. Exclusion criteria were a last measured or reported weight of 300 lbs or higher (due to technical and equipment-related restrictions), participant request for no further contact or clinic visits, or participant lost to follow-up or deceased since randomization (30.4% of participants were excluded for one or more of these reasons). Informed consent for WHI-CACS was provided by 1,079 women (61.6% of those eligible at the 28 clinical centers).

The Human Subjects Review Committee at each participating institution approved the WHI study protocols. In accordance with institutional guidelines, all subjects provided written informed consent.

Data Collection

Trial participants provided data on a wide range of factors at the ET study baseline clinic visit. Ethnicity was determined by self-report with the following categories: non-Hispanic white, African-American/black (non-Hispanic), Hispanic, Asian/Pacific Islander, American Indian/Alaska Native, or unknown (women who indicated "other" ethnicity or did not answer the question). Education and income were ascertained by self-report from a range of categories. The presence of high cholesterol or diabetes was identified by self-reported use of a medication for these conditions. Smoking was categorized as current, former or none. Use of postmenopausal hormone therapy before WHI CEE trial enrollment was ascertained via an in-person interview at the baseline clinic visit.

Vasomotor symptom data was collected at baseline by a questionnaire specifically designed to ascertain the participant's reproductive history. In this questionnaire, participants were asked their age at the time of their last regular menstrual period, their age at time they had their last menstrual bleeding of any kind and for a history of any oophorectomy and their age at the time of this procedure. The questionnaire included items on menopausal symptoms (i.e. "Have you ever had menopausal symptoms, such as hot flashes or night sweats?"), and, if these had occurred, participants were asked to provide their age when these symptoms started (i.e. "How old were you when you first had symptoms such as hot flashes or night sweats?") and ended (i.e. "How old were you when you last had symptoms such as hot flashes or night sweats? If you are still having symptoms such as hot flashes or night sweats, enter your current age.") Presence of vasomotor symptoms at baseline, as well

as other menopausal symptoms, was assessed by self report at baseline on a different questionnaire.

Anthropomorphic measurements were obtained at baseline. Body mass index was calculated as weight (kg) / height (m^2). Waist and hip circumferences (in cm) were obtained using a standardized measuring tape. After a 5-minute rest and using a conventional mercury sphygmomanometer and appropriately sized cuffs, blood pressure was measured twice at baseline and then at each clinic visit until the end of the CEE trial.

Coronary Artery Calcified Plaque Measurements

A standardized protocol was developed based on prior multi-center experience with cardiac CT[17]. Phantom scan and test images were obtained from each CT system to verify technical parameters and CT system performance. Analyses of the measurements were performed by certified staff at the central reading center at Wake Forest University who were masked to participants' treatment assignment. The Agatston score was calculated on a computer workstation (TeraRecon Inc, San Mateo, CA) by experienced image analysts using established parameters (lesion size of >1 mm^2, adjustment for slice thickness, and threshold of 130 HU).[18] After the scan was scored, the participants were provided with a letter documenting their calcium score, which could be reviewed with their health care provider (if desired).

Women with a history of coronary revascularization (CABG or PTCA) prior to randomization were excluded from the analysis. Also, the reading protocol specified exclusion of coronary stents, pacemakers, metallic clips, and other surgical remnants from the analysis process. Three women with incomplete scans were excluded. After excluding these women and accounting for missing data, the final dataset included 918 participants. If participant had missing age at menopause data, we used age at oophorectomy (as applicable or available) or age at hysterectomy as a surrogate.

Statistical Analyses

The primary outcome variable was a CAC score > 0 while CAC severity (CAC = 0, 0 < CAC ≤ 100 and CAC > 100) was treated as a secondary outcome. The primary exposure variable was a history of ever having vasomotor symptoms. Secondary analysis investigated duration of vasomotor symptoms and the interaction between self-report of HT use and VMS (yes/no).

Using baseline measurements, hypertension was defined as a systolic blood pressure ≥ 140 or a diastolic blood pressure ≥ 90 or use of a blood pressure lowering medication. Diabetes and hypercholesterolemia were defined as physician prescribed current use of medications for these conditions. Cigarette smoking covariate adjustment was by pack years.

Baseline characteristics were compared between participants with a CAC score of zero versus greater than zero. Differences between the groups were assessed using age adjusted logistic regression models. For the main analysis, logistic regression models were used to evaluate the association between the presence of any CAC and the exposure variables a) VMS ever (yes/no) and b) VMS timing (prior to WHI enrollment/prior to and present at WHI enrollment/no VMS). Nominal multinomial logistic regression models were used to evaluate the association between the primary exposure variables and the severity of CAC. To control for potential confounding, we adjusted for baseline values of age (categorical and linear), race/ethnicity (White/Black/Hispanic/Other), diabetes, dyslipidemia, smoking, BMI (categorical and linear), systolic blood pressure, diastolic blood pressure (linear and quadratic), family history of CHD, education, income, pre-enrollment HT use, bilateral oophorectomy and CEE randomization assignment; unless specified categorical variables

were coded as shown in Table 2 and continuous variables were fit linearly. A two-sided p-value < 0.05 was considered statistically significant.

We also investigated the interaction of VMS ever (yes/no) with a) HT duration (self-report of hormone therapy use prior to WHI enrollment) and b) timing of HT initiation (<= 2 years after menopause, > 2 years after menopause). For b) HT use includes HT use prior to WHI enrollment, as well as CEE use in the WHI clinical trial. Statistical significance of this subgroup analyses was based on Wald tests of the multiplicative interactions. The main statistical analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary, NC).

RESULTS

The characteristics of the cohort stratified by the presence and absence of CAC are presented in Table 1. Those who had any CAC were significantly older. After adjustment for age, the CAC positive group had significantly higher levels of body mass index, hip and waist circumference, hypertension, cholesterol medication use, diabetes medication use and pack-years cigarette smoking while having significantly lower levels of physical activity, annual income and education. In this analysis, a history of any VMS, VMS severity and VMS duration were not significantly different by CAC status.

Seven-hundred and one women had any VMS

Table 2 shows the distributions of the cohort characteristics stratified by the presence/absence of ever having vasomotor symptoms. Compared to those with *no* history of VMS, women with a history of *any* VMS had a significantly lower body mass index, waist circumference and were more likely to report current or former use of hormone therapy. Those with any VMS were also more likely to be African American and less likely to be Hispanic or non-Hispanic White. The prevalence of any CAC in those with a history of any VMS was 45.1% while the prevalence in those without a history of VMS was 50.5% (p = 0.17). Adjustment for age at enrollment in the WHI did not change the significance of the associations listed above.

The results of multivariable logistic regression analyses for the association between a history of any VMS and the presence of a CAC score greater than zero are presented in Figure 1. With adjustment for age and ethnicity and compared to those without a history of VMS, women with a history of any VMS had a 29% lower odds for any CAC (p = 0.06). Additional adjustment for income, education and smoking (model 2), these variables plus diabetes, dyslipidemia, BMI, systolic blood pressure, diastolic blood pressure and family history of myocardial infarction (model 3), and then model 3 plus CEE randomization status (model 4) minimally accentuated the magnitudes of the associations (OR: 0.70, 95% CI: 0.49 – 1.01, p = 0.06; 0.69, 0.47 – 1.01, p = 0.05; 0.68, 0.47 – 1.00, p = 0.05; respectively). Addition of both a history of bilateral oophorectomy and any hormone therapy use prior to WHI enrollment to the multivariable models (model 5) further accentuated the association (0.66, 0.45 – 0.98, p=0.04). Addition of 1) time from the baseline WHI visit to the time of CT scan and 2) physical activity did not change these results. Moreover, the results did not differ by severity of CAC. Specifically and after complete multivariable adjustment, the OR for the presence of severe CAC (>100) was 0.67 (0.41 – 1.12) compared to 0.66 (0.43 – 1.02) for moderate CAC (<= 100).

Since the variable "any VMS" is rather crude and duration of VMS may be relevant to the presence of CAC, we conducted analyses to determine if there were differences in the odds for CAC *between* those who had a history of any VMS, but *did not* report VMS at WHI enrollment (i.e. VMS were absent at enrollment), and those who had a history of any VMS and *did* report VMS at enrollment (i.e. VMS were present at enrollment). Twenty percent of

the sample had a history of any VMS present at WHI enrollment. Utilizing the same analytic strategy employed in the previous paragraph and using the group with no history of VMS as the reference category, those with a history of any VMS, but that were absent at baseline, had a lower odds for the presence of any CAC than those with a history of any VMS that were also present at WHI enrollment (p=0.06, Figure 2).

When we examined the association between severity of VMS and CAC, there was no significant associations found. Specifically, compared to those with no VMS, the odds of CAC among those with moderate to severe VMS was 0.99 (0.65 – 1.50) while the odds were 0.95 (0.66 – 1.37) among those with mild VMS.

As HT has been used to treat VMS, and HT may be associated with CAC in women of the age group studied,[19] we postulated that use of HT may modify the association between VMS and CAC. Accordingly, we conducted analyses testing the association between CAC and VMS, with the latter being contingent on the reported duration of HT use. In these analyses, as duration of HT increased the inverse association between VMS and CAC moved toward the null (Figure 3). A test for interaction between VMS and HT (as a linear function of time) for CAC was of borderline significance (p = 0.06) and the results were unchanged when "age at starting HT" was included in the models. Model diagnostics suggested that the linear fit of HT was reasonable and the association was not influenced by any extreme values.

We then explored whether the timing of starting HT, relative to menopause, modified the association between VMS and CAC. Specifically, we created 3 HT groups (no HT use, HT use starting within 2 years of menopause and HT use starting 2 or more years after menopause) and tested the interaction of this categorization with VMS and CAC. In this analysis and compared to no VMS, the presence of any VMS among those who reported no history of taking HT or who started HT within 2 years of menopause resulted in the same odds for any CAC (0.48, 0.23 – 1.03 and 0.48, 0.26 – 0.89; respectively). Conversely, the odds for any CAC among those with any VMS and who started HT 2 or more years after menopause was 1.40 (0.71 – 2.75). The p-value for interaction was significant (0.04) indicating a significant difference in odds for CAC by when HT use was initiated relative to menopause. Similar results were found when the HT use variable was defined by 5 years after menopause [results not shown].

We also conducted analyses where the type of VMS was based on self-report of bilateral oophorectomy. Here, VMS was coded as "none", "Natural VMS" (no self-report of bilateral oophorectomy or VMS occurred before bilateral-oophorectomy) or "Other VMS" (VMS occurred after bilateral oophorectomy). After multivariable adjustment, the results did not demonstrate differences in the magnitudes of the associations for the presence of any CAC by type of VMS. That is, with adjustment for the covariates listed in model 5 of figures 1, 2 or 3, the odds (95% CI) for the presence of any CAC were 0.73 (0.50 – 1.08) for those with a history of Natural VMS and 0.76 (0.47 – 1.21) for those with a history of Other VMS. As before, the odds ratios did not differ by severity of CAC.

DISCUSSION

In this study of women with a history of hysterectomy and between the age of 50 and 59 at enrollment in the WHI, a history of vasomotor symptoms was associated with a *reduced* odds for the presence and extent of coronary artery calcium independent of the traditional CVD risk factors and other relevant covariates. This association was stronger among those who did *not* have VMS that persisted until enrollment in the WHI suggesting that shorter duration of symptoms is associated with a lower odds for having any CAC. The association

between VMS and CAC may be influenced by hormone therapy use such that longer HT use may attenuate the inverse association between VMS and CAC. Moreover, the timing of when HT use is started appears to modify this association in that those who either did not take HT or took it within 2 years of menopause had a lower odds for any CAC while those who took HT more than 2 years after menopause had a higher odds for any CAC. Taken together, the results presented indicate complex relationships between vasomotor symptoms, hormone therapy and calcification of atherosclerotic plaques.

Atherosclerosis is a systemic[20] inflammatory process[21, 22] that is typically initiated at arterial branch points.[23] Calcium is actively deposited in the lipid core of atherosclerotic plaques via an organized and regulated process[24–26] analogous to embryonic cortical bone formation.[7, 27] In this regard, previous studies have shown different phases of bone formation in these plaques to include acellular matrix, calcified matrix, osteoid and mature skeletal bone.[7] Since previous studies have demonstrated either very weak or null associations between plasma lipid levels and calcified atherosclerosis,[28, 29] it seems plausible that the formation of skeletal bone in atherosclerotic plaques may be regulated by metabolic processes relatively distinct from the endothelial function, lipid deposition and smooth muscle infiltration characteristic of the atherosclerotic process.[24] If true, pathophysiologic processes (such as VMS) could have differential effects on calcified atherosclerotic plaques depending on which 'component' (i.e. atherosclerosis or calcification) is influenced by that process at the stage of disease that exists when the process occurs.

The pathophysiology of VMS is not clearly delineated. Previous studies are mixed on the association between estradiol levels and the presence of hot flashes. Similarly, luteinizing hormone (LH) levels have not consistently been shown to be associated with VMS such that symptomatic women can have normal LH levels.[30] Interestingly, recent research suggests that frequent vasomotor symptoms and bone loss is linked to follicle stimulating hormone (FSH) levels and not necessarily estradiol levels.[31, 32] In animal models, higher FSH levels result in increased osteoclast formation and activity.[33] Clinical studies extend these findings by demonstrating increased bone turnover with higher FSH levels.[34] In this context, estrogen supplementation would reduce the level of FSH resulting in lower osteoclast activity and thereby lower bone turnover resulting in a slower loss of bone (i.e. more bone relative to those who don't supplement with HT).

Using data from the Eindhoven Perimenopausal Osteoporosis study, Gast and colleagues examined the association between VMS (flushing and/or night sweats) and bone mineral density (BMD) of the lumbar spine by dual energy x-ray absorptiometry (DEXA). In this study, women with a higher frequency of VMS symptoms were found to have significantly lower BMD values independent of age, body mass index, menopause status, smoking, education, exercise and hormone therapy use.[32] Similarly, results from the Study of Women's Health Across the Nation (SWAN) indicate a lower BMD by DEXA for women with VMS regardless of whether the VMS occurred pre-, peri- or postmenopausally.[31] These results support the thesis of either lower bone formation or higher levels of bone resorption among those with VMS. However, results from the Rancho Bernardo Study (RBS) did not find a significant association between VMS and BMD.[35] Importantly, the women in the RBS were significantly older (mean age: 73 years) than in our study (as well as those cited above) and had a higher prevalence of HT use, which was on average for over 12 years.

Contrary to their findings on VMS and BMD, the SWAN published results showing current (i.e. within 2 weeks) VMS being associated with higher levels of both coronary and aortic calcified atherosclerosis, with the latter association being independent of CVD risk factors

and estradiol levels.[36] From this, the authors suggest that hot flashes may mark adverse underlying vascular changes among midlife women. Of note, women enrolled in the SWAN were younger (mean age: ~47 years) and over half were either pre- or perimenopausal. Also, night sweats was not part of the definition of VMS. Since our definition of VMS was based on ever having VMS and included night sweats, and our population was composed entirely of postemenopausal women with a history of hysterectomy, direct comparisons of our results to those from the SWAN are difficult, as they are likely confounded by the issues described above.

The lack of association between VMS and BMD in the RBS raises the question of whether HT use could modify the association between VMS and calcium deposits in atherosclerotic plaques. Estrogen is important for maintaining higher levels of BMD in both men[37] and women.[38] Clinically, trial data from the WHI indicate a significantly lower risk for incident fractures among women without a uterus who received estrogen alone[39], as well as women with a uterus who received estrogen plus progestin,[40] further substantiating the association between HT and higher levels of BMD. The results from our study are in agreement with these findings in that women with VMS who reported either no HT use or a shorter duration of HT use had significantly lower odds of having any calcified atherosclerotic plaques.

The finding of an attenuation of the odds between VMS and CAC with longer HT use appears to be disparate from previous findings in the WHI-CACS cohort of lower CAC among those who received estrogen alone.[19] In this regard, although the previous and current analyses utilized the WHI-CACS cohort, it is important to note that the results presented from the current analysis are within the context of VMS, whereas the previous analysis were conducted independently of VMS. Also, the duration of HT use may be relevant. In the WHI-CACS trial of ET, the mean duration of estrogen alone treatment was 7.4 years, which corresponded to a 22% lower odds of a CAC score greater than zero. Odds of CAC for shorter durations of treatment are not available. In our study, the odds for a CAC score greater than zero were 38% lower for those who took HT for 6 years and 27% lower for those who took HT for 8 years. Clearly, these results are similar to those for the WHI-CACS trial and suggest that among women of the same relative age (50 – 59 years), use of HT for less than 10 years is likely to be associated with a reduced odds for CAC.

Results from our study also indicate that the timing of starting HT may result in differences in the magnitudes (and direction) of the association between VMS and CAC. That is, women with VMS who started HT relatively shortly after menopause (i.e. < 2 years) had a reduced odds for having any CAC; however, their odds for any CAC did not differ from those who did not take HT within 2 years. On the other hand, those with VMS who start HT later than 2 years had a significantly higher odds for any CAC. These results are in agreement with previous studies that tend to have fewer incident CHD events among those who begin HT shortly after menopause while those who take HT later are at higher risk for incident CHD, especially if they also reported vasomotor symptoms at baseline.[41] Because inflammatory changes are believed to precede the development of atheroma, and calcification of atherosclerotic plaques (i.e. CAC) is a relatively late development of this process[42, 43], the lack of association in women with VMS who started HT within 2 years of menopause may reflect protection from this early process, limiting or delaying the subsequent stages leading to calcification.

Vasomotor symptoms in women of middle age have been associated with lower serum estradiol and inhibin levels but higher FSH.[5] This pattern of reproductive hormones has been shown to be associated with higher levels of CVD risk factors.[6] In this regard, the results from the SWAN study (discussed above) suggest that VMS are associated with an increased risk for CVD. However, a recent report from the RBS demonstrated a reduced risk

for incident CVD among women with a history of VMS.[44] This, combined with the results we present, are contrary to those from the SWAN and indicate the need for further study on the association between VMS and risk of cardiovascular disease.

Although the WHI-CACS study was conducted using women enrolled in a randomized clinical trial, the current analysis was observational and cross-sectional in nature and conducted using a subset of women in the WHI ET clinical trial. Therefore, there could be residual confounding or bias affecting the results. We have attempted to address this issue by considering as many potential confounding variables as possible in the analysis. Also, as the measures for coronary calcium were obtained at the end of the WHI-ET trial, there is the possibility of survival bias. As the presence and extent of coronary calcium is significantly associated with incident morbidity and mortality, the bias in this case would result in an attenuation of the magnitude of the effect. Also, since the average age of the cohort at baseline and time of CT scan was less than 65 years, the likelihood for a significant number of incident CHD deaths in this study population is relatively small. History of VMS was ascertained retrospectively by questionnaire, which may result in recall bias for this exposure. Similarly, self-report of oophorectomy may have resulted in some misclassification. Finally, the results of this study are limited to those women who are recently postmenopausal and with a history of a hysterectomy.

CONCLUSION

The presence of any VMS was associated with a lower odds for the presence of calcified coronary atherosclerosis. This association appears to differ by the duration of VMS, as well as the duration and timing of HT use, with the latter associations indicating shorter duration and more immediate use after menopause being associated with a reduced odds for CAC.

Acknowledgments

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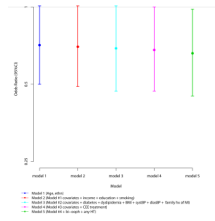
Figure 1. Multivariable Associations between the History of Any Vasomotor Symptoms and the Presence of Coronary Artery Calcium
316 (45.1%) of participants with a history of any VMS had a CAC score > 0.
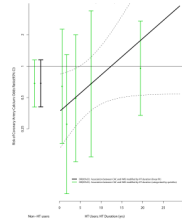105(50.5%) of participants with no history of any VMS had a CAC score > 0.
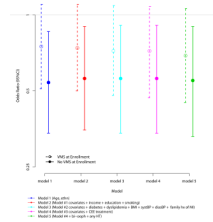
Figure 2. Multivariable Associations between History of Any Vasomotor Symptoms for Women with and without Vasomotor Symptoms at Enrollment and the Presence of Any Coronary Artery Calcium

246 (45.2%) of participants with a history of any VMS and did report VMS at enrollment had a CAC score > 0.

80 (43.7%) of participants with a history of any VMS and reported no VMS at enrollment had a CAC score > 0.

92 (51.1%) of participants with no history of any VMS and reported no VMS at enrollment had a CAC score > 0.

Note that 28 participants reported VMS at enrollment had either missing(n=5) or reported "no" to ever having VMS (n=25). For this analysis, these women were coded as a history of any VMS and reporting VMS at enrollment

Figure 3. Multivariable Association between the Presence of Any Vasomotor Symptoms and the Presence of Coronary Artery Calcium (Modified by Hormone Therapy Duration)
Adjusted for age, ethnicity, ethnicity, income, education, smoking, diabetes, dyslipidemia, BMI, SBP, DBP, family history of MI, CEE treatment, bilateral oophorectomy and hormone therapy use

129 (43.7%) of participants with a history of any VMS and no prior HT use had a CAC score > 0.

62 (49.2%) of participants with no history of any VMS and no prior HT use had a CAC score > 0.

187 (46.1%) of participants with a history of any VMS and prior HT use had a CAC score > 0.

43(52.4%) of participants with no history of any VMS and prior HT use had a CAC score > 0.

TABLE 1

Cohort Characteristics by Coronary Calcium Status

Characteristic	CAC > 0 (n = 423)	CAC = 0 (n = 495)	P-value[*]
Age at screening[†] (years)	55.6 (2.7)	54.8 (2.9)	<0.01
Age at menopause[†] (years)	43.4 (7.7)	43.8 (7.2)	0.30
Body Mass Index (kg/m^2)	31.6 (6.2)	29.8 (6.1)	<0.01
Waist circumference[†] (cm)	95.1 (13.7)	88.7 (14.2)	<0.01
Hip circumference[†] (cm)	113.3 (13.0)	110.4 (13.1)	<0.01
Pack years of smoking[†]	13.6 (19.5)	7.5 (14.7)	<0.01
Hypertension[‡]	44.4	30.5	<0.01
Dyslipidemia[‡]	14.2	6.7	<0.01
Diabetes[‡]	6.9	3.0	0.01
Family history of CHD[‡]	48.7	46.0	0.52
Physical Activity[†] (MET-hours/week)	8.9 (12.2)	11.0 (13.8)	0.04
History of any VMS[†]	51.5	56.7	0.24
VMS severity at baseline			0.75
- None	41.4	39.2	
- Mild	33.6	36.1	
- Moderate/Severe	25.0	24.7	
Duration of VMS[‡]			0.87
- < 5 years	18.2	22.7	
- 5 to <10 years	25.5	25.9	
- 10 to < 15 years	20.8	21.1	
- ≥ 15 years	35.5	30.3	
HRT use status[‡]			1.00
- Never used	45.4	47.3	
- Past user	32.6	30.5	
- Current user	22.0	22.2	
Bilateral oophorectomy[‡]	39.8	37.2	0.72

[*] Adjusted for age;

[†] Mean (SD),

[†]Percent (Frequency)

TABLE 2

Distribution of Study Variables by the Presence/Absence of Vasomotor Symptoms

Continuous Variables	VMS (Yes)	VMS (No)	
	Mean (SD)	Mean (SD)	p-value[*]
Age at screening (years)	55.1 (2.9)	55.3 (2.8)	0.35
Body-mass index (kg/m^2)	30.4 (6.1)	31.4 (6.6)	0.04
Waist circumference (cm)	91.1 (14.1)	93.3 (14.9)	0.05
Hip circumference (cm)	111.3 (13.2)	112.8 (12.9)	0.15
Systolic BP (mm Hg)	124.8 (15.5)	123.4 (16.6)	0.21
Diastolic BP (mm Hg)	77.7(8.7)	77.1 (9.6)	0.35
Pack years of smoking	10.6 (17.8)	9.7 (16.1)	0.5
Total energy expenditure/wk (MET-hours)	10.0 (12.3)	9.9 (15.5)	0.96
Categorical Variables	VMS (Yes)	VMS (No)	
	% (N)	% (N)	p-value[*]
Agatston score > 0	54.9 (385)	49.5 (103)	0.21
Race/ethnicity			0.009
- White	73.8 (517)	76.9 (160)	
- Black	18.8 (132)	10.6 (22	
- Hispanic	5.4 (38)	9.6 (20)	
- American Indian	0.9 (6)	1.0 (2)	
- Asian/Pacific Islander	0.3 (2)	0.0 (0)	
- Unknown	0.9 (6)	1.9 (4)	
Baseline income (< $35,000)	38.8 (262)	39.5 (77)	0.86
Education			0.59
- High school/GED or less	26.2 (182)	24.2 (50)	
- School after high school	43.5 (302)	47.3 (98)	
- College degree or higher	30.4 (211)	28.5 (59)	
HRT arm (CEE group)	50.2 (352)	51.9 (108)	0.67
HRT use status			<0.01
- Never used	42.1 (295)	60.6 (126)	
- Past user	34.5 (242)	21.6 (45)	
- Current user	23.4 (164)	17.8 (37)	
Bilateral oophorectomy	38 (257)	39.3 (75)	0.79
Alcohol consumption			0.32
- Non Drinker	45.1 (315)	51.0 (106)	
- <= 1 drink/day	45.6 (318)	40.4 (84)	
- > 1 drink/day	9.3 (65)	8.7 (18)	
Antihypertensive medication use at Baseline	26.0 (182)	20.7 (43)	0.11
Baseline hypertension			0.4
- Normotensive: < 120/80 and no meds	28.7 (201)	33.2 (69)	

Continuous Variables	VMS (Yes)	VMS (No)	
	Mean (SD)	Mean (SD)	p-value[*]
- Prehypertensive: [120,140)/[80,90) and no meds	33.4 (234)	32.7 (68)	
- Hypertensive: >= 140/90 or on medication	37.9 (266)	34.1 (71)	
History high cholesterol or taking lipid-lowering med	9.8 (69)	11.1 (23)	0.66
Antihyperlipidemic use (including statins)	4.9 (34)	6.3 (13)	0.47
History treated diabetes or taking anti-diabetic med	5.0 (35)	4.3 (9)	0.66
Family History of MI	47.2 (317)	47.4 (93)	0.98

[*] Adjusted for age