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Hot flushes, coronary heart disease, and hormone therapy in postmenopausal women

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Abstract

Objective—The aim of this study was to examine interactions between hot flushes, estrogen plus progestogen therapy (EPT), and coronary heart disease (CHD) events in postmenopausal women with CHD.

Methods—We analyzed data from the Heart and Estrogen/Progestin Replacement Study, a randomized, placebo-controlled trial of 0.625 mg conjugated equine estrogens plus 2.5 mg medroxyprogesterone acetate in 2,763 postmenopausal women with CHD. Hot flushes were assessed at baseline using self-administered questionnaires; women reporting bothersome hot flushes “some” to ”all” of the time were considered to have clinically significant flushing. Cox regression models were used to examine the effect of EPT on risk of CHD events among women with and without significant flushing at baseline.

Results—The mean age of participants was 66.7 ± 6.8 years, and 89% (n = 2,448) were white. Sixteen percent (n = 434) of participants reported clinically significant hot flushes at baseline. Among women with baseline flushing, EPT increased risk of CHD events nine-fold in the first year compared with placebo (hazard ratio = 9.01; 95% CI, 1.15-70.35); among women without baseline flushing, treatment did not significantly affect CHD event risk in the first year (hazard ratio = 1.32; 95% CI, 0.86-2.03; *P* = 0.07 for interaction of hot flushes with treatment). The trend toward differential effects of EPT on risk for CHD among women with and without baseline flushing did not persist after the first year of treatment.

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Conclusions—Among older postmenopausal women with CHD, EPT may increase risk of CHD events substantially in the first year of treatment among women with clinically significant hot flushes but not among those without hot flushes.

Keywords

Hot flushes; Coronary heart disease; Hormone therapy; Menopause; Estrogen

Hot flushes affect up to 80% of women during the menopausal transition[1,2] and persist for 5 or more years past menopause in up to a third of women.[3,4] The etiology of these common symptoms is currently unknown, although alterations in thermoregulation probably play arole.[5,6] Several recent studies have suggested that hot flushes may be associated with higher levels of oxidative stress[7] as well as adverse vascular changes[8-10] during menopause. As a result, there has been interest in hot flushes as a possible marker of risk of coronary heart disease (CHD) as well as other vascular complications in postmenopausal women.[10,11]

Estrogen therapy decreases the frequency of hot flushes associated with menopause and is currently the most effective treatment for these symptoms.[12] When given in standard oral doses and combined with a progestogen, however, estrogen therapy has been shown to increase CHD risk, particularly in older postmenopausal women.[13,14] Furthermore, a recent analysis of data from the combined Women's Health Initiative (WHI) clinical trials found that the increased risk for CHD events associated with estrogen therapy was disproportionately concentrated in older postmenopausal women who reported hot flushes before treatment.[14] However, the relationships between hot flushes, CHD, and hormone therapy in postmenopausal women are still poorly understood.

We examined the interactions between hot flushes, estrogen plus progestogen therapy (EPT), and CHD events in the Heart Estrogen/Progestin Replacement Study (HERS), a randomized, placebo-controlled trial of 0.625 mg oral conjugated equine estrogens plus 2.5 mg medroxyprogesterone acetate in postmenopausal women with CHD. As has been reported, the HERS trial found that EPT was associated with an increased risk of CHD events in the first year of therapy, although not in subsequent years.[15,16] We sought to determine whether the effects of EPT on incidence of CHD events in this population differed for women with and without baseline hot flushes.

METHODS

HERS was a randomized, placebo-controlled clinical trial of EPT in 2,763 postmenopausal women aged 55 to 80 years with CHD. Details on inclusion and exclusion criteria have been described elsewhere.[15,16] Briefly, women were considered to be postmenopausal if they had no natural menses for 5 years or more, no natural menses for 1 year or more plus follicle-stimulating hormone levels greater than 40 IU/L, or documented bilateral oophorectomy. Women were considered to have CHD if they had a history of myocardial infarction (MI), coronary artery bypass graft surgery, percutaneous coronary revascularization, or angiographic evidence of 50% or greater occlusion of one or more coronary arteries.[15,16]

The primary outcome of the HERS trial was time to first major CHD event, defined as either nonfatal MI or CHD death.[15,16] Diagnosis of nonfatal MI was based on an algorithm that took into account ischemic symptoms, electrocardiogram abnormalities, and elevated cardiac enzyme levels at the time of the event. CHD death was defined as a fatal documented MI, sudden death within 1 hour of onset of ischemic symptoms, unobserved death out of the hospital in the absence of other known cause, or death due to a coronary revascularization procedure or congestive heart failure.

Hot flushes were assessed at baseline using self-administered questionnaires, in which women described the degree of bother associated with their symptoms. Specifically, women were asked, "How often do hot flushes bother you?" with response options including "none," "a little," "some," "a good bit," "most," or "all of the time." For the purposes of analysis, we decided a priori to categorize women who were bothered by hot flushes "some" to "all" of the time as having "clinically significant" hot flushes.

Demographic characteristics, medical history, medication use, and health-related habits were also assessed by self-report questionnaires at baseline. Participants' height and weight were measured at a baseline visit, and body mass index was calculated as weight in kilograms divided by height in meters squared. Fasting total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein cholesterol, and triglyceride levels were determined by the Lipoprotein Analytical Laboratory at Johns Hopkins Hospital.[15,16]

We first examined bivariate associations between potential CHD risk factors and the presence of "clinically significant" hot flushes among participants at baseline using χ^2 or analysis of variance tests, as appropriate. We then identified CHD risk factors that were independently associated with baseline flushing using backward elimination multivariate logistic regression. We then developed Cox proportional hazards models to examine the effect of EPT on risk of first CHD event, stratified by baseline hot flush status. Tests for interaction were used to assess potential differences in treatment effects among women with and without clinically significant flushing at baseline. In the main HERS trial, the effect of EPT on CHD risk was found to differ by year, in that treatment increased risk in the first year of treatment but not thereafter.[15,16] As a result, we decided a priori to examine the effects of hormone therapy in each year of treatment separately. Finally, we included selective interaction terms in our models to assess whether any differences in treatment effects by hot flush status could be explained by interactions with other CHD risk factors that were associated with hot flushes at baseline. All analyses were preformed using SAS software, version 9.1 (SAS Institute, Inc, Cary, NC). The HERS trial was approved by the institutional review board of the University of California San Francisco.

RESULTS

Of the 2,759 participants who provided data on hot flushes at baseline, 16% (n = 434) reported clinically significant hot flushes, defined as hot flushes that were bothersome "some" to "all" of the time. The remaining 84% of women (n = 2,325) were bothered by hot flushes "a little" or "none of the time." The proportion of women with clinically significant hot flushes at baseline did not differ significantly between the EPT and placebo groups (15% vs 17%; $P = 0.16$).

Participants with clinically significant hot flushes at baseline tended to be younger, nonwhite, less educated, and more recently postmenopausal, as well as to have higher diastolic blood pressure, higher LDL cholesterol levels, higher triglyceride levels, higher body mass index, worse self-reported overall health, higher rates of prior estrogen use, and greater prevalence of prior MI (Table 1). In multivariable analysis, clinically significant flushing was independently associated with younger age, nonwhite race, fewer years of education, fewer years since menopause, higher diastolic blood pressure, body mass index greater than 27 kg/m^2, poor or fair self-reported health, prior estrogen use, and prior MI (Table 2). Adherence to the study medication during the course of the trial did not differ substantially among women with and without clinically significant flushing at baseline (71% of women without flushing and 70% of women with flushing demonstrated ≥80% adherence to study medications for 4 years based on pill counts; $P = 0.66$).

Among participants reporting clinically significant hot flushes at baseline, women randomized to placebo had somewhat higher average triglyceride levels at baseline compared with those randomized to EPT (mean [±SD] triglyceride levels = 185 [±64] mg/dL vs 160 [±61] mg/dL; $P = 0.01$), but did not differ with regard to other CHD risk factors ($P > 0.05$ for age, race, education, smoking, diabetes, blood pressure, LDL cholesterol, high-density lipoprotein cholesterol, years since menopause, body mass index, exercise, alcohol use, overall health, prior estrogen use, history of congestive heart failure, prior percutaneous coronary revascularization, prior coronary artery bypass graft surgery, and prior MI). Among participants without flushing at baseline, no significant differences in baseline CHD risk factors were observed among those randomized to placebo versus EPT ($P > 0.05$ for all).

Among the 2,325 women reporting no significant hot flushes at baseline, 84 CHD events were observed during the first year of treatment, and a total of 305 events were observed during the entire trial period (Table 3). Forty-seven of the first-year events occurred in those randomized to EPT and 37 in those randomized to placebo (hazard ratio [HR] for the effects of EPT in the first year = 1.32; 95% CI, 0.86-2.03; $P = 0.21$; Table 4). Among the 434 women reporting clinically significant hot flushes at baseline, 11 CHD events occurred in the first year of treatment and a total of 56 events during the entire trial period. Of the 11 first-year events, 10 events occurred among women in the EPT group versus ony 1 in the placebo group (HR for the effects of EPT = 9.01; 95% CI, 1.15-70.35; $P = 0.04$) ($P = 0.07$ for interaction between hot flushes and treatment). There was no evidence of an interaction of hot flushes and treatment assignment after the first year of treatment ($P > 0.10$ for all).

The interaction between hot flushes and hormone therapy in the first year of treatment was not diminished and, in some cases, became even more significant after adjustment for potential competing interactions with other CHD risk factors found to be associated with flushing at baseline, including age, race, years of education, years since menopause, diastolic blood pressure, body mass index, self-reported health, prior estrogen use, and prior MI ($P = 0.03$ for interaction to 0.08 for all).

DISCUSSION

These analyses from the HERS randomized, controlled trial of EPT for secondary prevention of CHD point to potentially interesting interactions between hot flushes, hormone therapy, and CHD events in postmenopausal women. Our results suggest that older postmenopausal women with clinically significant hot flushes at baseline may be at substantially increased risk for CHD events in the first year after treatment initiation. In contrast, among those without significant flushing at baseline, we did not find that hormone therapy was associated with a substantially increased risk of early CHD events.

These findings should be viewed with caution because the research hypotheses were not prespecified, the number of CHD events observed in women with baseline hot flushes was small, the statistical test for interaction with hot flush status was borderline significant, and the interaction occurred only during the first year of treatment. Further research is necessary to confirm whether the observed interaction between EPT and hot flushes represents a true relationship versus a chance finding. However, our results are consistent with recent findings from the WHI clinical trials, in which an increased risk of CHD events associated with hormone therapy was observed primarily in those older postmenopausal women (>20 y postmenopausal, or 70 y or older) who had baseline hot flushes.[14] In light of those results, our study may offer additional evidence that the adverse effects of hormone therapy on CHD may be disproportionately concentrated in those older postmenopausal women who continue to experience hot flushes.

Given that the pathophysiology of hot flushes is still unknown, we cannot explain with confidence why the effects of EPT might differ between women with and without these symptoms. Consistent with previous research,[13,17,18] we found that certain cardiovascular risk factors such as higher body mass index and higher diastolic blood pressure were more prevalent in women with clinically significant flushing at baseline. Nevertheless, the observed interaction with EPT in the first year did not change substantially when we accounted for interactions with these and other risk factors in our analyses, indicating that hot flushes were not simply a marker for other CHD risk factors.

One possible explanation is that postmenopausal women with ongoing hot flushes may differ with regard to estrogen function in ways that might make them more susceptible to the negative cardiovascular effects of systemic hormone therapy. Several recent studies have pointed to differences in polymorphisms in genes encoding estrogen-metabolizing enzymes and estrogen receptors among older women with and without hot flushes.[19,20] Genetic variations in estrogenmetabolizing enzymes and receptors have also been implicated in risk of CHD and the effects of estrogen therapy on CHD in older women.[21-23] It is possible that hot flushes may be a marker for differences in the metabolism of estrogen or the activity of estrogen receptors in response to both endogenous and exogenous estrogens.

Several clinical studies have suggested that women who experience severe hot flushes during menopause may have lower levels of plasma antioxidant activity,[7,24] which has been linked with progression of atherosclerosis. Furthermore, a recent large community-based study of middle-aged women found that women reporting hot flushes in the previous 2 weeks had greater coronary artery and aortic calcification suggestive of subclinical cardiovascular disease compared with women without recent hot flushes.[10] Among participants in the HERS trial, however, we did not find that hot flushes were predictive of subsequent CHD events among those not taking hormone therapy; in fact, the reverse trend was seen in the first year of the trial, with hot flushes seeming to be protective against CHD events among those randomized to placebo (age-adjusted HR = 0.13; 95% CI, 0.02-0.94; $P = 0.03$).

Unlike previous hot flush studies that have tended to focus on perimenopausal or younger postmenopausal women, most participants in HERS were older postmenopausal women. At this time, it is not clear whether pathophysiologic mechanisms underlying hot flushes in early menopause play the same role in flushing experienced by women 10, 15, or 20 years after cessation of menses. Participants in HERS were not asked to describe the age of onset of their hot flushes, and thus, we cannot assess whether their hot flushes were persistent from the early menopausal transition or emerged de novo during the late postmenopausal years. As a result, our findings cannot necessarily be extrapolated to women initiating hormone therapy for flushing experienced during the immediate menopausal transition. Further research is needed to explore the relationships between hot flushes and CHD, as well as potential interactions with hormone therapy, among women in different menopausal stages.

Several additional limitations of this research should be acknowledged. First, HERS was a secondary prevention trial of hormone therapy, and our findings may not be generalizable to postmenopausal women without CHD. As we have previously noted, however, similar findings were noted in the WHI primary prevention trials involving older postmenopausal women who did not have documented CHD upon enrollment. Second, hot flushes were assessed in HERS using a single self-report severity measure only. Further research should examine interactions between hot flushes, hormone therapy, and CVD risk using measures that allow more detailed characterization of hot flushes.

CONCLUSIONS

In these analyses from a large randomized trial of EPT in postmenopausal women with CHD, we found that EPT was associated with a substantially increased risk of early CHD events among women with hot flushes but not among women without hot flushes. Further research may help assess whether hormone therapy may selectively increase the risk of CHD events in older postmenopausal women who are most likely to use it to treat persistent hot flushes.

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TABLE 1

Baseline characteristics of participants by hot flush status

Risk factor	No significant hot flushes (n = 2,325)	Clinically significant hot flushes[a] (n = 434)	*P*
Age, mean (SD), y	67.3 (6.3)	63.0 (7.3)	0.001
White, n (%)	2,110 (90.8%)	338 (77.9%)	0.001
Education, mean (SD), y	12.8 (2.7)	12.1 (2.5)	0.001
Years since last menses, mean (SD)	18.7 (7.8)	13.7 (8.0)	0.001
Current smoker, n (%)	291 (12.5%)	68 (15.7%)	0.07
Diabetes mellitus, n (%)	528 (22.8%)	106 (24.5%)	0.42
Systolic blood pressure, mean (SD), mm Hg	135.0 (19.0)	135.6 (19.3)	0.56
Diastolic blood pressure, mean (SD), mm Hg	72.7 (9.7)	75.7 (9.6)	0.001
LDL cholesterol, mean (SD), mg/dL	144.1 (37.4)	149.9 (39.5)	0.001
HDL cholesterol, mean (SD), mg/dL	50.4 (13.3)	49.7 (12.8)	0.29
Triglyceride, mean (SD), mg/dL	165.0 (63.5)	172.1 (63.6)	0.03
Body mass index, mean (SD), kg/m^2	28.4 (5.5)	29.6 (5.6)	0.001
Aerobic exercise >3 times/wk, n (%)	916 (39.4%)	150 (34.6%)	0.06
Alcoholic drinks/wk, mean (SD)	1.4 (3.8)	1.2 (2.9)	0.17
Fair or poor overall health, n (%)	520 (22.4%)	145 (33.4%)	0.001
Prior postmenopausal estrogen use, n (%)	510 (22.3%)	135 (31.5%)	0.001
History of congestive heart failure, n (%)	291 (12.5%)	54 (12.4%)	0.97
Prior percutaneous coronary angioplasty, n (%)	999 (43.0%)	187 (43.1%)	0.96
Prior coronary artery bypass surgery, n (%)	959 (41.3%)	172 (39.6%)	0.53
Prior myocardial infarction, n (%)	1,161 (49.9%)	244 (56.21%)	0.02

LDL, low-density lipoprotein; HDL, high-density lipoprotein.

[a]Defined as hot flushes that were bothersome all, most, a good bit, or some of the time.

TABLE 2

Cardiovascular risk factors associated with hot flushes at baseline

Risk factor	Adjusted OR (95% CI)[a]
Age (per 5-y increase)	0.80 (0.70-0.92)
Nonwhite race	2.04 (1.51-2.76)
Less than high school education	1.50 (1.16-1.95)
Years since last menses (per 5-y increase)	0.79 (0.70-0.89)
Diastolic blood pressure (per 5-mm Hg increase)	1.12 (1.05-1.18)
Body mass index >27 kg/m^2	1.35 (1.07-1.70)
Poor/fair self-reported health	1.47 (1.15-1.89)
Prior estrogen therapy use	2.14 (1.68-2.74)
Prior myocardial infarction	1.26 (1.01, 1.57)

[a]Odds ratio (OR) and CIs estimates were obtained through backward elimination logistic regression and are adjusted for all variables included in the table.

TABLE 3

Coronary heart disease events by treatment assignment, baseline hot flush status, and year of study

Study year	Estrogen + progestogen group (n = 1,387)		Placebo group (n = 1,382)	
	No significant hot flushes (n = 1,147)	Significant hot flushes[a] (n = 230)	No significant hot flushes (n = 1,178)	Significant hot flushes[a] (n = 204)
Year 1	47	10	37	1
Year 2	36	11	40	9
Year 3	31	4	33	9
Year 4+	36	4	45	8
Total	150	29	155	27

[a] Defined as hot flushes that were bothersome all, most, a good bit, or some of the time.

TABLE 4

The effect of estrogen + progestin treatment on risk of coronary heart disease events, by baseline hot flush status

	No significant hot flushes (n = 2,325)		Clinically significant hot flushes[a] (n = 434)		Total participants (N = 2,763)[b]	
Study year	**HR (95% CI)[b]**	***P***	**HR (95% CI)[c]**	***P***	**HR (95% CI)[b]**	***P***
Year 1	1.32 (0.86-2.03)	0.21	9.01 (1.15-70.4)	0.04	1.52 (1.01-2.29)	0.05
Year 2	0.94 (0.60-1.47)	0.79	1.11 (0.46-2.68)	0.82	0.98 (0.66-1.46)	0.91
Year 3	0.98 (0.60-1.60)	0.93	0.40 (0.12-1.29)	0.12	0.85 (0.54-1.33)	0.47
Year 4+	0.81 (0.52-1.25)	0.34	0.44 (0.13-1.45)	0.18	0.75 (0.49-1.12)	0.16
Total	1.00 (0.80-1.25)	0.99	0.96 (0.57-1.62)	0.88	0.99 (0.81-1.22)	0.94

HR, hazard ratio.

[a] Defined as hot flushes that were bothersome all, most, a good bit, or some of the time.

[b] Data on baseline hot flush severity were missing for four participants.

[c] HRs compare the effects of estrogen + progestin versus placebo on coronary heart disease event risk.