ORIGINAL ARTICLE

Estrogen Therapy and Coronary-Artery Calcification

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ABSTRACT

BACKGROUND

Calcified plaque in the coronary arteries is a marker for atheromatous-plaque burden and is predictive of future risk of cardiovascular events. We examined the relationship between estrogen therapy and coronary-artery calcium in the context of a randomized clinical trial.

METHODS

In our ancillary substudy of the Women's Health Initiative trial of conjugated equine estrogens (0.625 mg per day) as compared with placebo in women who had undergone hysterectomy, we performed computed tomography of the heart in 1064 women aged 50 to 59 years at randomization. Imaging was conducted at 28 of 40 centers after a mean of 7.4 years of treatment and 1.3 years after the trial was completed (8.7 years after randomization). Coronary-artery calcium (or Agatston) scores were measured at a central reading center without knowledge of randomization status.

RESULTS

The mean coronary-artery calcium score after trial completion was lower among women receiving estrogen (83.1) than among those receiving placebo (123.1) (P=0.02 by rank test). After adjustment for coronary risk factors, the multivariate odds ratios for coronary-artery calcium scores of more than 0, 10 or more, and 100 or more in the group receiving estrogen as compared with placebo were 0.78 (95% confidence interval, 0.58 to 1.04), 0.74 (0.55 to 0.99), and 0.69 (0.48 to 0.98), respectively. The corresponding odds ratios among women with at least 80% adherence to the study estrogen or placebo were 0.64 (P=0.01), 0.55 (P<0.001), and 0.46 (P=0.001). For coronary-artery calcium scores of more than 300 (vs. <10), the multivariate odds ratio was 0.58 (P=0.03) in an intention-to-treat analysis and 0.39 (P=0.004) among women with at least 80% adherence.

CONCLUSIONS

Among women 50 to 59 years old at enrollment, the calcified-plaque burden in the coronary arteries after trial completion was lower in women assigned to estrogen than in those assigned to placebo. However, estrogen has complex biologic effects and may influence the risk of cardiovascular events and other outcomes through multiple pathways. (ClinicalTrials.gov number, NCT00000611.)

Although it has been hypothesized that postmenopausal estrogen therapy delays atherosclerosis,[1-3] recent findings from randomized clinical trials have cast doubt on a cardioprotective role of exogenous estrogen. The Women's Health Initiative (WHI) trial of conjugated equine estrogens, administered to postmenopausal women who had undergone hysterectomy, reported a hazard ratio of 0.95 (95% confidence interval [CI], 0.79 to 1.16) for nonfatal myocardial infarction plus fatal coronary heart disease (CHD) among women receiving conjugated equine estrogens as compared with those receiving placebo, but secondary analyses according to age group suggested that the results differed in younger women.[4,5] The corresponding hazard ratio was 0.63 (95% CI, 0.36 to 1.08) for women 50 to 59 years old, as compared with 0.94 (0.71 to 1.24) for women 60 to 69 years old and 1.11 (0.82 to 1.52) for women 70 to 79 years old. The findings for the younger women, although limited by a small number of events related to CHD, were consistent with the results of previous observational studies, which tended to include women who initiated estrogen therapy early in menopause.[1,6] Additional analyses in the WHI trial of conjugated equine estrogens indicated a reduced risk of a need for coronary revascularization among women 50 to 59 years old who were receiving estrogen (hazard ratio 0.55; 95% CI, 0.35 to 0.86) but not among older women.[5]

To explain the findings related to estrogen and CHD in younger women, we initiated an ancillary substudy of estrogen and coronary-artery calcium shortly after the WHI trial of conjugated equine estrogens ended. The goal of the WHI Coronary-Artery Calcium Study (WHI-CACS) was to determine whether the coronary-artery calcium burden differed according to randomized-group assignment among women aged 50 to 59 years after a mean of 7.4 years. Atherosclerotic calcification in the coronary arteries is a subcomponent of atherosclerotic plaque and a marker of the total plaque burden in the coronary arteries[7,8] and has been shown to be predictive of future cardiovascular events, independently of traditional risk factors.[8-11] Vascular deposits of calcium develop as part of the chronic inflammatory process of atherosclerosis[12]; the calcified atheroma can be detected and quantified noninvasively, in a standardized and reproducible manner, on computed tomography (CT) of the heart.[8,13-16] Previous studies of postmenopausal hormone therapy and coronary-artery calcium have been observational only and have generally suggested a reduced prevalence of coronary-artery calcium among hormone users.[17-19] To our knowledge, the relationship between hormone therapy and the prevalence and extent of calcified plaque in the coronary arteries has not been previously assessed in the context of a randomized trial.

METHODS

WHI TRIAL OF ESTROGEN ALONE

Detailed descriptions of the design of the WHI trial of conjugated equine estrogens and the baseline characteristics of the participants have been published previously.[4,20,21] Briefly, the participants were postmenopausal women who were 50 to 79 years of age at randomization and had undergone hysterectomy. We randomly assigned the participants to receive oral conjugated equine estrogens (0.625 mg per day) (Premarin, Wyeth Pharmaceuticals) or placebo. Methods regarding data collection, data management, and assurance of the quality of the data have been published previously.[22]

The WHI trial of conjugated equine estrogens was originally scheduled to continue until close-out visits between October 2004 and March 2005. However, the National Institutes of Health stopped the trial approximately 1 year early, owing to an increased risk of stroke in the absence of apparent benefit for the risk of CHD.[4] Study participants were informed of this decision on March 1, 2004, were instructed to discontinue the study medication, and were informed of their group assignment. Although the evidence suggested a reduced risk of CHD among the women aged 50 to 59 years who were receiving conjugated equine estrogens,[4,5] the statistical power of the study was inadequate to provide conclusive results. Therefore, an explanatory ancillary substudy (WHI-CACS) was proposed to provide mechanistic information that might elucidate this finding. WHI-CACS was restricted to women aged 50 to 59 years, both to clarify the results concerning conjugated equine estrogens in this age group and because this age group is the most clinically relevant with regard to initiation of hormone therapy for menopausal symptoms.

DESIGN OF THE ANCILLARY STUDY (WHI-CACS)

A total of 28 of the 40 WHI clinical centers were in close proximity to the requisite imaging facilities and had the ability to mobilize quickly to participate in WHI-CACS. A central reading center at

Wake Forest University School of Medicine was selected by means of a competitive bidding process. After the study was approved by central and local institutional review boards, we mailed invitational letters to the 1742 eligible women among the 2271 women who had participated in the trial of conjugated equine estrogens at these 28 centers and who were 50 to 59 years old at the time of randomization in the WHI trial. Exclusion criteria were a request by the participant for no further clinic visits, a weight of 300 lb (136 kg) or higher (owing to technical restrictions), or a loss to follow-up or death since randomization. A total of 529 of the original participants (23.3%) were excluded for one or more of these reasons. A total of 1079 women (61.9% of the 1742 eligible participants at the 28 clinical centers) provided written informed consent and underwent CT examinations of the heart between May 2005 and September 2005. Because the study period was a mean of 7.4 years and coronary-artery calcium was measured on average 1.3 years after the trial, the women had a mean age of 64.8 years at the time of the coronary-artery calcium measurements.

MEASUREMENT OF CALCIFIED PLAQUES

Noninvasive imaging of the coronary arteries was performed with the use of electron-beam or multidetector-row CT at the 28 participating centers, all of which used CT systems with the capability to acquire cardiac images in approximately 250 msec or less. A standardized protocol was developed on the basis of previous multicenter experience with CT of the heart.[13,14] Phantom and test images were obtained with the use of each CT system to verify technical settings and system performance. The measurements were analyzed at a central reading center at Wake Forest University without knowledge of randomization status.[13] The Agatston scores[23] were calculated at a computer workstation (TeraRecon) by experienced image analysts using established criteria.[8,13,23]

Twelve women were excluded owing to a history of coronary revascularization procedures before randomization or missing data on this variable, and three women were excluded because of incomplete scans. In addition, the reading protocol specified the exclusion of data from patients with coronary stents, pacemakers, metallic clips, and other surgical remnants. The final data set represented 1064 participants.

STATISTICAL ANALYSIS

Baseline cardiovascular risk factors and other characteristics of participants receiving conjugated equine estrogens and those receiving placebo were tested for differences with the use of t-tests for continuous variables and chi-square tests for categorical variables. Coronary-artery calcium scores in the group receiving estrogen and the placebo group were compared with the use of the Kruskal–Wallis rank test. Because the distribution of coronary-artery calcium scores was skewed, with 53% of participants having scores of 0, we also performed tobit regression analyses for left-censored data, using a cube root transformation (to the coronary-artery calcium score + 1).[24] Coronary-artery calcium scores were also grouped as follows: 0 (no calcification), 1 to less than 10 (minimal calcification), 10 to 100 (mild calcification), 101 to 300 (moderate calcification), and more than 300 (extensive calcification).[8,25,26] Associations between study group and coronary-artery calcium score were assessed with the use of dichotomous logistic-regression analysis for coronary-artery calcium scores of more than 0 (vs. 0), 10 or more (vs. <10), and 100 or more (vs. <100), as well as ordinal (polychotomous) logistic-regression analysis for higher scores.

Primary analyses were conducted according to the intention-to-treat design, with and without further adjustment for coronary risk factors. Additional models also involved adjustment for educational level, presence or absence of a history of oophorectomy, reproductive status, and presence or absence of randomization in the WHI diet-modification trial, the WHI calcium and vitamin D trial, or both trials. Inverse-probability-of-censoring weighted analyses[27] were also conducted to estimate the results for all eligible women in the WHI trial of conjugated equine estrogens. Secondary analyses, restricted to women with at least 80% adherence to the study medication for at least 5 years, were performed with and without multivariate adjustment. All P values are two-sided, and P values of less than 0.05 were considered to indicate statistical significance. Statistical analyses were performed with the use of SAS statistical software, version 9 (SAS Institute).

RESULTS

Cardiovascular risk factors and other characteristics at baseline were similar among WHI-CACS

Table 1. Baseline Characteristics and Cardiovascular-Risk-Factor Status, According to Randomized-Group Assignment.*

Characteristic	Conjugated Equine Estrogens	Placebo	P Value†
Age at screening — no./total no. (%)			0.85
50–54 yr	210/537 (39.1)	209/527 (39.7)	
55–59 yr	327/537 (60.9)	318/527 (60.3)	
Race or ethnic group — no./total no. (%)‡			0.16
White	414/537 (77.1)	385/527 (73.1)	
Black	80/537 (14.9)	97/527 (18.4)	
Hispanic	28/537 (5.2)	37/527 (7.0)	
American Indian	6/537 (1.1)	3/527 (0.6)	
Asian or Pacific islander	3/537 (0.6)	0	
Unknown	6/537 (1.1)	5/527 (0.9)	
Smoking — no./total no. (%)			0.74
None	256/534 (47.9)	259/524 (49.4)	
Previous	210/534 (39.3)	206/524 (39.3)	
Current	68/534 (12.7)	59/524 (11.3)	
Hypertension — no./total no. (%)§			0.80
No	307/473 (64.9)	302/471 (64.1)	
Yes	166/473 (35.1)	169/471 (35.9)	
High cholesterol level — no./total no. (%)¶			0.85
No	414/461 (89.8)	404/448 (90.2)	
Yes	47/461 (10.2)	44/448 (9.8)	
Diabetes — no./total no. (%)			0.87
No	503/537 (93.7)	494/526 (93.9)	
Yes	34/537 (6.3)	32/526 (6.1)	
Myocardial infarction in first-degree relative — no./total no. (%)			0.96
No	263/503 (52.3)	266/507 (52.5)	
Yes	240/503 (47.7)	241/507 (47.5)	
Previous myocardial infarction, stroke, or transient ischemic attack — no./total no. (%)			0.97
No	529/537 (98.5)	519/527 (98.5)	
Yes	8/537 (1.5)	8/527 (1.5)	
Random assignment to WHI diet-modification trial — no./total no. (%)			0.15
No	340/537 (63.3)	311/527 (59.0)	
Yes	197/537 (36.7)	216/527 (41.0)	
Random assignment to WHI calcium and vitamin D trial — no./total no. (%)			0.23
No	152/537 (28.3)	167/527 (31.7)	
Yes	385/537 (71.7)	360/527 (68.3)	
Moderate-to-severe vasomotor symptoms — no./total no. (%)			0.23
Yes	123/529 (23.3)	138/521 (26.5)	
No	406/529 (76.7)	383/521 (73.5)	

Table 1. (Continued.)*

Characteristic	Conjugated Equine Estrogens	Placebo	P Value†
Age at hysterectomy — no./total no. (%)‖			0.59
<35 yr	145/537 (27.0)	152/524 (29.0)	
35–39 yr	146/537 (27.2)	124/524 (23.7)	
40–44 yr	121/537 (22.5)	118/524 (22.5)	
≥45 yr	125/537 (23.3)	130/524 (24.8)	
Hormone therapy — no./total no. (%)			0.77
None	248/537 (46.2)	255/527 (48.4)	
Previous	172/537 (32.0)	162/527 (30.7)	
Current**	117/537 (21.8)	110/527 (20.9)	
Risk factor			
Age at screening — yr	55.2±2.8	55.1±3.0	0.85
Body-mass index††	30.6±6.0	30.5±6.2	0.76
Waist circumference — cm	92.0±14.5	91.4±14.1	0.49
Smoking — pack-yr	9.8±17.6	10.5±17.4	0.50
Blood pressure			
Systolic	124.1±14.9	125.3±16.4	0.20
Diastolic	77.6±8.9	78.1±8.8	0.34
Age at menopause — yr	43.8±7.1	43.4±7.8	0.34
Physical activity — total MET-hr/wk	9.4±11.7	10.6±14.3	0.14

* Plus–minus values are means ±SD. MET denotes metabolic equivalent.
† P values for percentages were calculated with the use of the chi-square test. P values for means were calculated with the use of F statistics from a linear regression model.
‡ Race or ethnic group was self-reported.
§ Patients with hypertension were those who had been treated with antihypertensive medication or those with a blood pressure of 140/90 mm Hg or higher at screening.
¶ Patients with a high cholesterol level were those who had a history of a high cholesterol level or who had been treated with cholesterol-lowering medication.
‖ Bilateral oophorectomy was reported by 35.5% of women.
** Participants who were receiving hormone therapy at enrollment were required to undergo a 3-month washout period before randomization.
†† The body-mass index is the weight in kilograms divided by the square of the height in meters.

participants receiving conjugated equine estrogens and those receiving placebo (Table 1). There were no significant differences between the two groups on the basis of age, race or ethnic group, traditional coronary risk factors, or key lifestyle or reproductive variables. In addition, the coronary-risk-factor status among the participants was similar to that among all women of eligible age in the WHI trial of conjugated equine estrogens.

Among the 1064 participants for whom coronary-artery calcium scores were available, the mean (±SD) score was 102.9±303.5, with a range of 0.0 to 4506.6. The mean score was 83.1 among women receiving conjugated equine estrogens and 123.1 among women receiving placebo (P=0.02 by the Kruskal–Wallis rank test) (Table 2). The 50th, 60th, 75th, and 95th percentile values of the coronary-artery calcium scores were 0, 3, 43, and 452 for conjugated equine estrogens and 0, 17, 84, and 689 for placebo, respectively.

The tobit regression analyses, which were performed to assess the overall distribution of coronary-artery calcium scores,[24] showed that the overall distribution of scores was significantly lower in the group receiving estrogen than in the placebo group (Table 2). After adjustment for age, race or ethnic group, and coronary-risk-factor status, the multivariate P value for this difference was 0.03 in intention-to-treat analyses. The multivariate P value was 0.002 when analyses were restricted to

Table 2. Distribution of Coronary-Artery Calcium Scores after Trial Completion, According to Randomized-Group Assignment.*

Score and Model	Conjugated Equine Estrogens (N=537)	Placebo (N=527)	Wald Chi-Square Statistic (1 df)	P Value
Mean score	83.1±250.2	123.1±348.6		0.02†
Score distribution				
50th percentile	0	0		
60th percentile	3	17		
75th percentile	43	84		
95th percentile	452	689		
Tobit model with transformation‡				
Intention-to-treat analyses§				
Unadjusted			5.89	0.02
Multivariate¶			4.83	0.03
Analyses restricted to participants with ≥80% adherence to study medication‖				
Unadjusted			10.0	0.002
Multivariate¶			9.4	0.002

* Plus–minus values are means ±SD. Higher calcium scores indicate greater calcification.
† The P value is from the Kruskal–Wallis rank test.
‡ Transformation was performed according to the method of Han and Kronmal.[24]
§ In the intention-to-treat group, data in unadjusted analyses were from 1064 women; data in multivariate analyses were from the 858 women with full covariate data.
¶ Multivariate logistic-regression analyses and P values were adjusted for age, race or ethnic group, smoking status, body-mass index, and presence or absence of a history of hypertension, a high cholesterol level, diabetes, and a family history of myocardial infarction.
‖ Data in unadjusted analyses were from all 739 women with at least 80% adherence to estrogen or placebo for at least 5 years; data in multivariate analyses were from the 601 women with full covariate data.

participants who had at least 80% adherence to the study treatment (estrogen or placebo) for at least 5 years (Table 2).

In analyses of the prevalence of coronary-artery calcium, multivariate odds ratios for coronary-artery calcium scores of more than 0 (vs. 0), 10 or more (vs. <10), and 100 or more (vs. <100) were 0.78, 0.74, and 0.69, respectively (Table 3). In secondary analyses restricted to data for women with at least 80% adherence for at least 5 years, the corresponding multivariate odds ratios were substantially reduced: 0.64 (P=0.01), 0.55 (P<0.001), and 0.46 (P=0.001), respectively (Table 3).

To examine higher levels of coronary-artery calcium, we conducted prespecified ordinal logistic-regression analyses, using a coronary calcium score of less than 10 as the reference category (Table 4).[10,25] In intention-to-treat analyses, women receiving estrogen had a multivariate odds ratio of 0.58 (P=0.03) for extensive coronary-artery

calcification (score >300); in secondary analyses restricted to women with at least 80% adherence, the multivariate odds ratio was 0.39 (P=0.004) (Table 4).

Further adjustment for additional variables — including educational level, presence or absence of a history of oophorectomy, reproductive status, and presence or absence of randomization in the WHI diet-modification trial, the WHI calcium and vitamin D trial, or both trials — did not materially alter the results. In ordinal logistic-regression analyses, with a coronary-artery calcium score of less than 10 as the reference category, the odds ratios for coronary-artery calcium scores of more than 100 and more than 300 in the estrogen group were 0.66 and 0.57, respectively (P=0.04 for both comparisons), and were 0.44 (P=0.002) and 0.41 (P=0.009), respectively, among women with at least 80% adherence. Inverse-probability-of-censoring weighted analyses,[27] conducted to estimate

Table 3. Coronary-Artery Calcium Scores after Trial Completion, According to Score Category.*

Coronary-Artery Calcium Score	Conjugated Equine Estrogens	Placebo	Odds Ratio (95% CI)		Multivariate P Value
			Unadjusted	Multivariate	
	no. (%)				
Intention-to-treat analyses†	N = 537	N = 527			
0 (referent)	299 (55.7)	266 (50.5)	1.00	1.00	
>0	238 (44.3)	261 (49.5)	0.81 (0.64–1.03)	0.78 (0.58–1.04)	0.09
<10 (referent)	348 (64.8)	302 (57.3)	1.00	1.00	
≥10	189 (35.2)	225 (42.7)	0.73 (0.57–0.93)	0.74 (0.55–0.99)	0.04
<100 (referent)	448 (83.4)	408 (77.4)	1.00	1.00	
≥100	89 (16.6)	119 (22.6)	0.68 (0.50–0.93)	0.69 (0.48–0.98)	0.04
Analyses restricted to participants with ≥80% adherence to study medication‡	N = 387	N = 352			
0 (referent)	227 (58.7)	172 (48.9)	1.00	1.00	
>0	160 (41.3)	180 (51.1)	0.67 (0.50–0.90)	0.64 (0.46–0.91)	0.01
<10 (referent)	262 (67.7)	191 (54.3)	1.00	1.00	
≥10	125 (32.3)	161 (45.7)	0.57 (0.42–0.76)	0.55 (0.39–0.79)	<0.001
<100 (referent)	333 (86.0)	269 (76.4)	1.00	1.00	
≥100	54 (14.0)	83 (23.6)	0.53 (0.36–0.77)	0.46 (0.29–0.73)	0.001

* Higher calcium scores indicate greater calcification. All odds ratios were calculated for the estrogen group as compared with the placebo group. Multivariate odds ratios and P values from logistic-regression models were adjusted for age, race or ethnic group, smoking status, body-mass index, and presence or absence of a history of hypertension, a high cholesterol level, diabetes, and a family history of myocardial infarction.
† In the intention-to-treat group, data in unadjusted analyses were from 1064 women; data in multivariate analyses were from the 858 women with full covariate data.
‡ Data in unadjusted analyses were from all 739 women with at least 80% adherence to estrogen or placebo for at least 5 years; data in multivariate analyses were from the 601 women with full covariate data.

the results for all eligible women in the WHI trial of conjugated equine estrogens, provided similar findings.

The odds ratios for a coronary-artery calcium score of more than 100, among participants receiving conjugated equine estrogens as compared with those receiving placebo, are shown in Figure 1, as are the associations between traditional risk factors for CHD and coronary-artery calcium scores. Past or current smoking and the presence of hypertension, a high cholesterol level, and diabetes were all strongly predictive of elevated coronary-

artery calcium scores. However, these risk factors did not significantly alter the relationship between treatment with conjugated equine estrogens and coronary-artery calcium scores (all P values for interaction >0.30).

DISCUSSION

The WHI-CACS assessed the post-trial burden of calcified atheroma in the coronary arteries in women 50 to 59 years old at the time of randomization in the WHI trial of conjugated equine estrogens.

Table 4. Odds Ratios for Various Categories of Elevation in the Coronary-Artery Calcium Score.*

Coronary-Artery Calcium Score	Conjugated Equine Estrogens	Placebo	Odds Ratio (95% CI)		Multivariate P Value
			Unadjusted	Multivariate	
	no. (%)				
Intention-to-treat analyses†	**N = 537**	**N = 527**			
<10 (referent)	348 (64.8)	302 (57.3)	1.00	1.00	
10–100	100 (18.6)	106 (20.1)	0.82 (0.60–1.12)	0.82 (0.57–1.18)	
>100–300	48 (8.9)	61 (11.6)	0.68 (0.45–1.03)	0.72 (0.44–1.17)	
>300	41 (7.6)	58 (11.0)	0.61 (0.40–0.94)	0.58 (0.35–0.95)	0.03
Analyses restricted to participants with ≥80% adherence to study medication‡	**N = 387**	**N = 352**			
<10 (referent)	262 (67.7)	191 (54.3)	1.00	1.00	
10–100	71 (18.3)	78 (22.2)	0.66 (0.46–0.96)	0.67 (0.44–1.02)	
>100–300	29 (7.5)	45 (12.8)	0.47 (0.28–0.78)	0.43 (0.23–0.80)	
>300	25 (6.5)	38 (10.8)	0.48 (0.28–0.82)	0.39 (0.21–0.73)	0.004

* Higher calcium scores indicate greater calcification. All odds ratios were calculated for the estrogen group as compared with the placebo group. Multivariate odds ratios for a calcium score of 10 or higher (as compared with a score of <10) and P values from logistic-regression models were adjusted for age, race or ethnic group, smoking status, body-mass index, and presence or absence of history of hypertension, high cholesterol level, diabetes, and family history of myocardial infarction.

† In the intention-to-treat group, data in unadjusted analyses were from 1064 women; data in multivariate analyses were from the 858 women with full covariate data.

‡ Data in unadjusted analyses were from all 739 women with at least 80% adherence to estrogen or placebo for at least 5 years; data in multivariate analyses were from the 601 women with full covariate data.

An average of 8.7 years after randomization, women receiving estrogen had a lower prevalence and quantity of coronary-artery calcium than those receiving placebo, with odds ratios for high levels of coronary-artery calcium generally 30 to 40% lower in intention-to-treat analyses and 60% lower in analyses among women with at least 80% adherence to the study medication for at least 5 years. The results remained robust and significant in analyses that involved diverse analytic approaches. These findings, in conjunction with the suggestion of a reduced risk of clinical coronary events among women treated with conjugated equine estrogens in this age group,[5] are consistent with previous evidence from laboratory, animal, and observational studies.[2,3,6]

Previous studies of postmenopausal hormone therapy and coronary-artery calcium have been observational only. Like observational studies of hormone therapy and clinical coronary events that have suggested cardiac benefits,[1,28] most previous coronary imaging studies indicate that users of hormone therapy have less coronary-artery calcium than nonusers.[17-19,29] However, observational studies may be susceptible to bias — in particular, confounding by health-promoting behaviors associated with the choice to use hormone therapy — underscoring the need to examine these relationships in the context of randomized clinical trials.[6,30]

Coronary-artery calcification serves as a marker of calcified atheroma and total plaque burden.[7,8,13,16] The presence of calcium in atherosclerotic lesions reflects the progression from simple fatty streaks to complex plaques, and coronary calcium measurements have been shown to be directly related to histologic measures of atheromatous plaques.[7,31] In a large cross-sectional study, the risk of CHD increased by a factor of 30 from the lowest to the highest quartile of coronary-artery calcium scores.[26] In our study, traditional coronary risk factors were strongly associated with increased quantities of coronary-artery calcium, providing support for the role of this measure as

Variable	No. of Participants	Coronary-Artery Calcium Score		P Value	Multivariate Odds Ratio for a Coronary-Artery Calcium Score >100
		≥10	>100		
		percent			
Study group					
Placebo (referent)	527	43	23		
Conjugated equine estrogens					
Intention-to-treat group	537	35	17	0.03	0.65
Group with adherence of ≥80% for ≥5 yr	387	32	14	<0.001	0.41
Coronary risk factor					
Smoking status					
Never (referent)	515	34	17		
Past	416	40	20	0.04	1.53
Current	127	53	29	<0.001	4.18
Hypertension					
No (referent)	609	34	16		
Yes	335	45	25	0.01	1.67
High cholesterol level					
No (referent)	818	36	17		
Yes	91	53	30	0.03	1.89
Diabetes					
No (referent)	997	38	19		
Yes	53	56	39	0.003	3.08
Family history of myocardial infarction					
No (referent)	529	37	16		
Yes					
At any age	481	42	24	0.10	1.38
At a premature age	130	41	24	0.04	1.60
Body-mass index					
<25.0 (referent)	184	29	13		
25.0–29.9	359	34	18	0.29	1.37
≥30.0	516	44	22	0.03	1.85
≥35.0	232	47	21	0.03	2.04

0.00 0.50 1.00 2.00 3.00 4.00 5.00

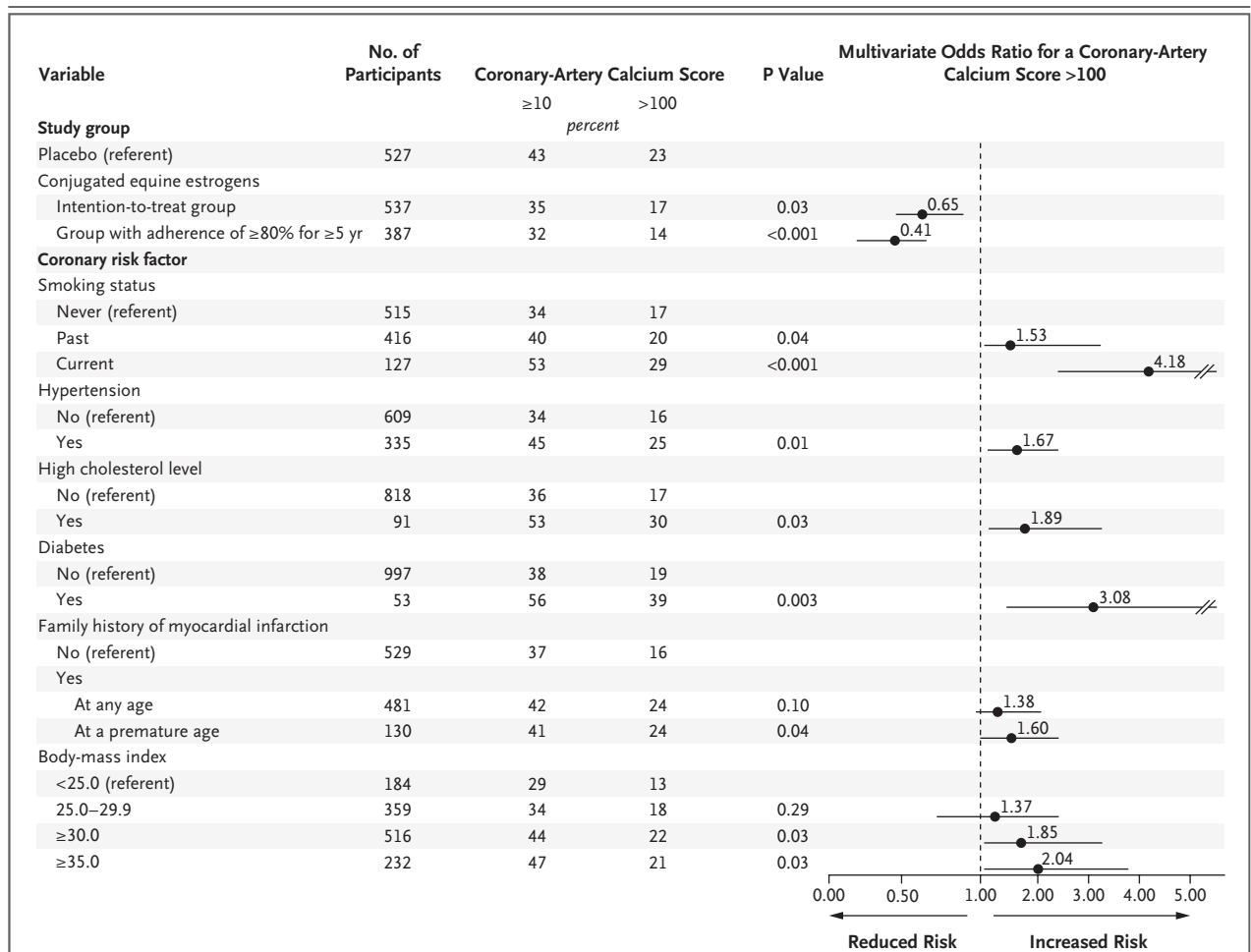Reduced Risk   Increased Risk

Figure 1. Multivariate Odds Ratios for a Coronary-Artery Calcium Score of More Than 100, According to Randomized-Group Assignment and Coronary-Risk-Factor Status.

Multivariate odds ratios were adjusted simultaneously for coronary risk factors. The reference category for the calcium score was a score of less than 10. Data for some risk factors were missing for some participants. For a family history of myocardial infarction, premature age was defined as younger than 55 years for a male first-degree relative and younger than 65 years for a female first-degree relative. The body-mass index is the weight in kilograms divided by the square of the height in meters.

a marker of atherosclerosis. Moreover, coronary-artery calcium measurements have been shown to be highly predictive of future cardiovascular events in several studies, independently of traditional risk factors.[8-11]

The new findings from WHI-CACS indicate that estrogen therapy initiated in women at 50 to 59 years of age is related to a reduced plaque burden in the coronary arteries and a reduced prevalence of subclinical coronary artery disease, providing support for the hypothesis that estrogen therapy may have cardioprotective effects in younger women. Although the WHI trial of conjugated equine estrogens suggested that younger women, but not older women, may have a reduced risk of

myocardial infarction and coronary revascularization when using estrogen, statistical tests for an interaction according to age were nonsignificant (range of P values, 0.07 to 0.09).[5] Estrogen has complex biologic effects that may vary according to the underlying state of the vasculature and other tissues.[30,32-34] Conclusive answers, however, can be derived only from large-scale trials involving sufficient numbers of clinical events among women in early menopause.

The strengths of our study include the randomized design of the main WHI trial of conjugated equine estrogens, the relatively long duration of treatment with estrogen, the standardized assessment of coronary-artery calcium at a central read-

ing center, and the large number of women studied, providing good statistical power to detect moderate associations. However, limitations of the study also warrant consideration. In the WHI trial of conjugated equine estrogens, a large percentage of women had stopped taking the study medication before the trial was terminated, and an average of 1.3 years had elapsed between completion of the trial and coronary-artery calcium measurement. Both of these limitations, however, would lead to an attenuation of the association between treatment with conjugated equine estrogens and coronary-artery calcium scores and would not explain our findings.

Although WHI-CACS did not include all participants who had undergone randomization in the estrogen trial and coronary-artery calcium measurements were not available before randomization, the distributions of coronary risk factors and behavioral characteristics at baseline were similar among the women receiving estrogen and those receiving placebo. In addition, adjustment for a large number of variables potentially related to participation or adherence did not result in a weakening of the associations. It would have been of interest to have coronary-artery calcium measurements for women in the older age groups, to allow a comparison of findings for younger and older women. Logistic and operational constraints precluded imaging of the full cohort without a substantial extension of the interval between the discontinuation of study medication and the measurement of coronary-artery calcium.

Moreover, coronary-artery calcium measurements in the older women would not have necessarily informed or elucidated our findings with respect to CHD among participants 50 to 59 years of age. It is possible that estrogen could reduce coronary-artery calcium scores but still increase the risk of clinical CHD events, owing to adverse effects on thrombosis and plaque rupture, which are more likely in older women with advanced stages of atherosclerosis. Such a duality of effects would not necessarily apply to younger women with lower burdens of atherosclerosis. Data from studies of nonhuman primates suggest that estrogen inhibits the progression of atherosclerosis during the early period after bilateral oophorectomy but not later,[3] and previous angiographic trials involving women with CHD have suggested that hormone therapy does not prevent atherosclerosis progression in high-risk women.[35,36]

The WHI-CACS focused on women 50 to 59 years old because women in this age group are most likely to be engaged in decision making about whether to use hormone therapy for menopausal symptoms.

In conclusion, the results of WHI-CACS indicate that women 50 to 59 years old when they were randomly assigned to receive conjugated equine estrogens had a lower coronary-plaque burden and a lower prevalence of subclinical coronary artery disease after completion of the WHI trial of estrogen than did women receiving placebo. These findings, in conjunction with the data on clinical CHD events among younger women in the WHI trial, provide some reassurance that estrogen is unlikely to have an adverse effect on the risk of coronary events among women who have recently undergone menopause and are considering hormone therapy for the treatment of menopausal symptoms. However, the possibility of a favorable effect of estrogen on atherosclerosis in younger women requires confirmation in future studies,[37,38] and other risks and benefits of treatment[4,39] must be considered. We could not address the question of whether any vascular benefits of treatment with estrogen initiated at a younger age will, with prolonged use, persist at older ages. Additional research on various formulations and regimens of hormone therapy will also be important. In the meantime, hormone therapy should not be initiated (or continued) for the express purpose of preventing cardiovascular disease in either younger or older postmenopausal women. The current recommendations from many organizations that hormone therapy be limited to the treatment of moderate-to-severe menopausal symptoms, with the lowest effective dose used for the shortest duration necessary, remain appropriate.

APPENDIX

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