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Calcium/Vitamin D Supplementation and Coronary Artery Calcification

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Abstract

Objectives—Coronary artery calcified plaque is a marker for atheromatous plaque burden and predicts future risk of cardiovascular events. The relationship between calcium plus vitamin D supplementation and coronary artery calcium (CAC) has not been previously assessed in a randomized trial setting. We compared coronary artery calcium scores among women randomized to calcium/vitamin D supplementation versus placebo following trial completion.

Methods—In an ancillary substudy of women randomized to calcium carbonate (1000 mg of elemental calcium daily) plus vitamin D₃ (400 IU daily) versus placebo, nested within the Women's Health Initiative trial of estrogen among women with hysterectomy, we measured CAC with cardiac computed tomography in 754 women aged 50–59 years at randomization. Imaging for CAC was

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performed at 28 of 40 centers following a mean of 7 years of treatment and scans were read centrally. Coronary artery calcium scores were measured by a central reading center with masking to randomization assignments.

Results—Post-trial CAC measurements were similar in women randomized to calcium/vitamin D supplementation (calcium/D) and those receiving placebo. The mean CAC score was 91.6 for calcium/D and 100.5 for placebo (rank test p -value=0.74). After adjustment for coronary risk factors, multivariate odds ratios for increasing CAC score cutpoints (CAC >0, ≥ 10 , and ≥ 100) for calcium/D vs placebo were 0.92 (95% confidence interval, 0.64–1.34), 1.29 (0.88–1.87), and 0.90 (0.56–1.44), respectively. Corresponding odds ratios among women with >50% adherence to study pills and for higher levels of CAC (>300), were similar.

Conclusions—Treatment with moderate doses of calcium plus vitamin D₃ did not appear to alter coronary artery calcified plaque burden among postmenopausal women.

Keywords

calcium; vitamin D; supplementation; coronary artery calcification; coronary heart disease; women's health

INTRODUCTION

The relationship between calcium and/or vitamin D supplementation and cardiovascular disease (CVD) remains controversial and recent studies have produced conflicting results.^{1–4} A recent randomized clinical trial suggested that calcium supplementation may increase the risk of cardiovascular events in postmenopausal women.¹ Among 1471 women (mean age 74 years) in New Zealand, those randomized to 1000 mg of elemental calcium daily had twice the risk of myocardial infarction (relative risk [RR] = 2.12; 95% confidence interval [CI], 1.01–4.47) and a borderline elevation in risk of a composite endpoint of MI, stroke, or sudden death (RR=1.47; 95% CI 0.97–2.23), compared to women randomized to placebo. However, the Women's Health Initiative² and other clinical trials^{3,4} that have assessed clinical vascular events with calcium supplementation have observed no significant relationship between supplementation and CVD outcomes. Moreover, emerging evidence suggests that calcium and/or vitamin D supplementation may have favorable effects on blood pressure,^{5,6} glucose tolerance,^{7,8} and lipids,^{9,10} and several observational studies have suggested inverse associations between one or both of these micronutrients and the risk of CVD.^{11–13}

Coronary artery calcification is a marker of total atheromatous plaque burden and is a strong predictor of future risk of CVD events.^{14–16} Calcium phosphate is the principal salt in calcified arterial plaque and vascular calcification is a regulated process with morphologic similarities to bone formation and remodeling.^{17–19} Calcified atheroma can be detected and quantified noninvasively by cardiac computed tomography (CT) imaging in a standardized and reproducible manner.^{20–22} Physicians are commonly asked by their patients whether calcium supplementation is a risk factor for coronary artery calcification.²⁴ In view of the high prevalence of both calcium supplementation and vascular disease in postmenopausal women, and previous conflicting data on the relationship between the two, we assessed the association between calcium/vitamin D supplementation and coronary artery calcium (CAC) in the Women's Health Initiative Coronary Artery Calcium Study (WHI-CACS). To our knowledge, this relationship had not been previously assessed in the setting of a randomized clinical trial.

METHODS

Detailed descriptions of the WHI Coronary Artery Calcium Study and the calcium/vitamin D supplementation trial have been previously published.^{25–27} WHI-CACS was conducted

among 1064 women who were aged 50–59 years at WHI enrollment and had participated in the conjugated equine estrogens (CEE)-alone trial, conducted among women with hysterectomy. Eligible participants in the CEE trial had been invited to join the double-blinded, placebo-controlled calcium plus vitamin D trial at their first annual visit. The primary goal of WHI-CACS was to determine whether CAC burden differed by CEE treatment group following completion of the CEE trial (average 7.4 year randomized treatment period among women aged 50–59 at baseline),²⁵ but it also provided an opportunity to assess the association between calcium/vitamin D supplementation and CAC. Approximately 70 percent of the participants in the CEE trial were further randomized, in a factorial design, to receive calcium carbonate (1000 mg of elemental calcium daily) with vitamin D₃ (400 IU daily) in two divided doses or a matching placebo (GlaxoSmithKline, Research Triangle Park, NC). Eligible women were randomly assigned in a double-blind fashion to receive supplements or placebo in equal proportions with use of a permuted-block algorithm stratified according to clinical center and age. The active supplements and placebo tablets were identical in appearance. Women were not restricted from taking concurrent personal calcium supplements (up to 1000 mg per day) or vitamin D (up to 600 IU/day). Methods for data collection, management, and quality assurance have been previously published.²⁸

A total of 28 of the 40 WHI clinical centers had cardiac imaging facilities in close proximity and participated in WHI-CACS. A central reading center at Wake Forest University School of Medicine (J. Jeffrey Carr, MD, Director) was selected after a competitive bidding process. Following study approval by central and local institutional review boards, eligible women in the CEE trial who were aged 50–59 at time of randomization to CEE or placebo at these 28 centers (N=1742, out of 2,271 originally randomized in this age group) were invited to participate. Exclusion criteria were participant request for no further clinic visits, a weight of 300 lbs or higher (due to technical restrictions), or participant lost to follow-up or deceased since randomization (23.3% of participants, were excluded for one or more of these reasons). A total of 1079 women (61.9% of those eligible at the 28 clinical centers) provided written informed consent and received cardiac CT exams between May and September 2005. Of these, 754 women (approximately 70 percent) were also enrolled in the calcium/vitamin D randomized trial. Women in the calcium/vitamin D trial had undergone intervention close-out visits between October 2004 and March 2005, at which time they were instructed to discontinue study pills and were unblinded to their treatment assignment. Due to the seven-year average treatment period and several months' interval between discontinuation of study intervention and CAC scanning in May to September 2005, participants had a mean age of 64.8 years at the time of the imaging studies.

Coronary Artery Calcified Plaque Measurements

Noninvasive imaging of the coronary arteries was performed by electron beam or multidetector-row computed tomography at the 28 participating centers.²⁵ A standardized protocol was developed based on prior multi-center experience with cardiac CT20-21 and phantom and test images were obtained from each CT system to verify technical parameters and performance. CAC measurements were performed by the central reading center at Wake Forest University and readers were masked to participants' treatment assignment.²⁰ The Agatston score²⁹ was calculated on a computer workstation (TeraRecon Inc, San Mateo, CA) by experienced image analysts using established parameters.^{15,20-29}

Women with a history of coronary revascularization procedures prior to randomization, missing data on this variable, or incomplete scans were excluded from this analysis. The reading center protocol also specified exclusion of coronary stents, pacemakers, metallic clips, and other surgical remnants from the analysis process. The final dataset included 754 participants.

Statistical Analyses

Baseline distributions of cardiovascular risk factors and other characteristics of participants in WHI-CACS were tested for differences between treatment groups using t-tests for continuous variables and chi-square tests for categorical variables. CAC scores in the calcium/vitamin D and placebo groups were compared using the Kruskal-Wallis rank test. Because the distribution of CAC scores was skewed with approximately 50% of participants having calcium scores of zero, tobit regression analyses for left-censored data, utilizing a cube root transformation (to the CAC score plus one), were also performed.³⁰ CAC was also categorized as 0 (none), 1–100 (mild), 101–300 (moderate), and >300 (extensive).^{29–32} The association between calcium/vitamin D supplementation and CAC was assessed by dichotomous logistic regression for CAC >0, ≥ 10 , and ≥ 100 , and by polychotomous logistic regression to assess higher levels of CAC. Primary analyses used the intention-to-treat design, with and without further adjustment for coronary risk factors, as well as for randomization assignment in the CEE trial, race/ethnicity, body mass index, and baseline intake of calcium and vitamin D. Secondary analyses, restricted to adherent women (those who took at least 50% of their study pills [calcium/vitamin D or placebo] for at least five years), were performed with and without multivariate adjustments. All of the p-values were two-sided. The statistical analyses were performed with SAS statistical software version 9 (SAS Institute, Cary, NC).

RESULTS

Baseline cardiovascular risk factors and other health-related characteristics were similar among WHI-CACS participants in the two randomized treatment groups (Table 1). Although women in the placebo group were slightly more likely to be current or past smokers than women in the calcium/vitamin D group, total pack-years of smoking did not differ significantly between the two groups. Moreover, there were no significant differences between the calcium/vitamin D and placebo groups in the WHI-CACS sample by age, ethnicity, other traditional coronary risk factors, key lifestyle and reproductive variables, or baseline dietary intake of calcium or vitamin D. Additionally, the coronary risk factor status of WHI-CACS participants was similar to that of all age-eligible women in the trial.

Among the 754 participants with non-missing CAC scores, the mean score was 91.6 among women randomized to calcium/vitamin D and 100.5 among women randomized to placebo (Kruskal-Wallis p-value=0.74) (Table 2). The 50th, 60th, 75th, and 95th percentile cutpoints were 0, 12, 62, and 490 for calcium/vitamin D and 0, 5, 54, and 549 for placebo, respectively.

In the tobit regression analyses to assess the overall distribution of CAC scores,³⁰ levels were similar in the calcium/vitamin D and placebo groups (Table 2). After adjustment for age, ethnicity, coronary risk factor status, randomization status in the CEE trial, and baseline intake of calcium and vitamin D, the CAC score distributions were similar in the two treatment groups in the intention-to-treat analyses (multivariate p-value = 0.98). The results were similar when the analyses were restricted to adherent participants (those taking $\geq 50\%$ of their study pills for at least five years) (Table 2).

In analyses of prevalence of CAC comparing women randomized to calcium/vitamin D versus placebo, the multivariate odds ratios (OR) for progressively higher CAC cutpoints (>0, ≥ 10 , ≥ 100) were 0.92, 1.29, 0.90, respectively (Table 3). In secondary analyses restricted to adherent women, the corresponding ORs were 0.86, 1.17, 0.83 (all p-values nonsignificant) (Table 3).

To assess higher levels of CAC, we conducted polychotomous logistic regression, using CAC=0 as the referent category (Table 4). In intention-to-treat analyses, women in the calcium/vitamin D treatment group had multivariate ORs of 0.96 for CAC scores 1–100, 0.72 for scores 101–300, and 1.09 for scores >300 (all p-values ≥ 0.30); in secondary analyses restricted to

adherent women, ORs were similar and did not differ significantly from unity (Table 4). When using <10 as the referent in the intention-to-treat analyses, calcium/vitamin D supplementation was associated with a borderline elevation in mild CAC (multivariate OR =1.59; 95% CI 1.00–2.53 for CAC scores 10–100) but no elevation in the odds for higher levels of CAC (ORs were 0.84 [95% CI, 0.45–1.55] and 1.27 [95% CI, 0.66–2.46] for CAC scores 100–300 and >300, respectively). In secondary analyses restricted to adherent women, calcium/vitamin D supplementation was not associated with a significant increase or decrease in any category of CAC.

We next examined whether the relationship between calcium/vitamin D supplementation and CAC was modified by intake of calcium or vitamin D at baseline, as assessed by a medication/supplement inventory and semiquantitative food frequency questionnaire.³³ The odds ratios for CAC (scores greater than zero) were not significantly increased or decreased in any intake subgroup, and baseline consumption of these micronutrients did not appear to influence the findings (Figure 1). Additionally, the association between calcium/vitamin D supplementation and CAC was not significantly modified by randomization to estrogen (CEE) vs placebo in the hormone therapy trial (p-value for interaction = 0.33) or by coronary risk factor status (all p-values for interaction >0.20).

DISCUSSION

Women in the WHI Coronary Artery Calcium Study who were randomized to calcium/vitamin D supplementation had a similar prevalence and quantity of coronary artery calcified plaque following trial completion as those assigned to placebo. We did not observe evidence for an increased or decreased risk of developing CAC among women receiving supplementation, even among women with relatively high dietary intake of these micronutrients at baseline.

The relationship between calcium/vitamin D supplementation and cardiovascular disease remains controversial, and both favorable and adverse effects on atherosclerotic progression would be biologically plausible. Both calcium and/or vitamin D supplementation may have beneficial effects on blood pressure,^{5,6} glucose tolerance,^{7,8} and lipids.^{9,10} Moreover, in vitro and in vivo studies suggest that 1,25 (OH)₂D may induce relaxation of vascular smooth muscle cells and downregulate renin production by the kidneys,³⁴ suggesting mechanisms by which vitamin D may lower blood pressure. Additionally, vitamin D may reduce inflammation,^{35,36,37} cytokine levels,³⁷ and vascular smooth muscle cell proliferation,¹² and improve left ventricular function,³⁸ but higher doses may be required to produce these benefits. Observational studies have suggested inverse associations between these micronutrients and the risk of CVD events.^{11–13} However, observational studies may be susceptible to bias, particularly confounding by health-promoting behaviors associated with the choice to take micronutrient supplementation, emphasizing the need to examine these relationships in randomized clinical trial settings.

Previous clinical trials of calcium and/or vitamin D supplementation and risk of cardiovascular events have produced conflicting results.^{1–4,39} In the Women's Health Initiative's calcium/vitamin D supplementation trial, in which 36,282 postmenopausal women were followed for a mean of seven years, no association between the intervention and CVD events was observed; the hazard ratio was 1.04 (95% CI, 0.92–1.18) for CHD and 0.95 (95% CI, 0.92–1.18) for stroke.² In contrast, a British trial in which 2686 men and women aged 65–85 were randomized to a much higher dose of vitamin D (100,000 IU of oral vitamin D₃ [cholecalciferol] every four months) or placebo and followed for up to five years, suggested a borderline reduction in CVD risk; treatment-associated RRs for CVD incidence and CVD mortality were 0.90 (95% CI 0.77–1.06) and 0.84 (95% CI: 0.65–1.10), respectively.³⁹ However, a recent randomized clinical trial of calcium supplementation (without vitamin D) in New Zealand reported an increased

risk of cardiovascular events in postmenopausal women.¹ Among 1471 women (mean age 74 years), those randomized to 1000 mg of elemental calcium daily had twice the risk of myocardial infarction (relative risk [RR] = 2.12; 95% confidence interval [CI], 1.01–4.47) and a borderline elevation in risk of a composite endpoint of MI, stroke, or sudden death (RR=1.47; 95% CI 0.97–2.23), compared to women randomized to placebo. Thus, results have been conflicting and emerging evidence suggests that calcium plus vitamin D supplementation may have a more favorable effect on CVD risk than calcium supplementation alone.^{1–4, 35–39}

Coronary artery calcification represents calcified atheroma and is a marker for total plaque burden.^{20–22} The presence of calcium in atherosclerotic lesions reflects the progression from simple fatty streaks to complex plaques, and coronary calcium measurements correlate with histologic measures of atheromatous plaques.^{14,18} Vascular calcification is an organized process with morphologic similarities to bone formation and remodeling.^{17–19} An inverse relationship between bone mineral density and vascular calcification and atherosclerosis has been reported.^{40,41} However, the events that contribute to hydroxyapatite formation in the artery, as well as the role of bone resorption or availability of substrate including mineral ions and/or complexes, remain uncertain. In a large cross-sectional study, the odds of prevalent CHD increased markedly across increasing quartiles of CAC scores.³² Traditional coronary risk factors were shown to be strongly associated with higher quantities of CAC in WHI-CACS,²⁵ supporting the role of this measurement as a marker of atherosclerosis. Additionally, CAC measurements have been shown to be strongly predictive of future cardiovascular events in several studies, independent of traditional risk factors.^{14–16}

Our findings indicate that calcium/vitamin D supplementation, at least at moderate doses of 1000 mg of elemental calcium and 400 IU of vitamin D₃ daily, does not alter the prevalence or quantity of coronary artery calcified plaque. Even among women with relatively high baseline intake of calcium (above 1200 mg daily) and/or vitamin D (above 600 IU daily) at baseline, moderate levels of supplementation did not confer favorable or deleterious effects on the development of CAC. It remains uncertain whether higher or lower doses, or different ratios of calcium and vitamin D supplementation, would modify the level of CAC. These findings are in contrast to our previously reported findings for estrogen (CEE) and prevalence of CAC.²⁵ Women who had been randomized to CEE had a substantially lower prevalence of CAC following trial completion than those assigned to placebo, with odds ratios for high levels of CAC generally 30–40% lower in intention-to-treat analyses and 60% lower in analyses among women adherent to study pills.²⁵ CEE randomization status did not modulate the association between calcium/vitamin D and CAC.

Strengths of the present study include the randomized trial design of the parent study, the relatively long duration of supplementation with calcium/vitamin D (7 years), the standardized assessment of CAC utilizing a central reading center, and the large number of women receiving CT scans, providing good statistical power to detect moderate associations. However, limitations of the present study also deserve consideration. In the WHI calcium/vitamin D trial, a moderate percentage of women had stopped study medication before the trial was terminated and several months had elapsed between trial completion and CAC scanning. Both of these limitations could have led to an attenuation of the association between calcium/vitamin D and CAC measurements. However, results were similar when analyses were restricted to women compliant with study pills, suggesting this was unlikely to explain our findings. Although WHI-CACS did not include all participants randomized in the trial and prerandomization CAC measurements were not available, the distribution of coronary risk factors and behavioral characteristics were similar in the treatment groups at baseline and adjustment for a large number of variables potentially related to participation or adherence did not influence the findings. Finally, although we were able to stratify our study results by baseline intake of calcium and vitamin D, we did not have 25(OH)vitamin D measurements on the cohort.

CONCLUSION

The WHI Coronary Artery Calcium Study indicates that women aged 50–59 who had been randomly assigned to treatment with calcium/vitamin D supplementation for seven years had a similar prevalence and quantity of coronary artery calcified plaque following trial completion as women assigned to placebo. These findings indicate that moderate supplementation with calcium and vitamin D does not affect CAC levels in menopausal women. These findings may be reassuring to women who are concerned about a potentially adverse effect of these supplements on coronary artery calcification. The possibility of a favorable or deleterious effect of higher doses of calcium/vitamin D supplementation cannot be excluded by this study and warrants further research.

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APPENDIX

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* Odds ratios (for CAC >0, referent 0) for active calcium/vitamin D versus placebo group, adjusted for age and ethnicity.

[†] Intake based on medication/supplementation inventory and semiquantitative food frequency questionnaire completed at baseline.

Figure 1.

Odds ratios for coronary artery calcium (Agatston scores >0) according to calcium/vitamin D randomization status, stratified by baseline intake of calcium and vitamin D.

Table 1

Baseline Characteristics and Cardiovascular Risk Factor Status of Participants in the Women's Health Initiative Coronary Artery Calcium Study, According to Randomized Assignment to Calcium/Vitamin D or Placebo

	Calcium/D	Placebo	P-Value*
	Mean (SD) or %	Mean (SD) or %	
Number of Women	374	380	
Age at screening, mean (SD), years	55.1 (2.9)	55.1 (2.9)	0.88
50–54	41.8	38.6	
55–59	58.2	61.4	
Race/Ethnicity			0.16
White	76.9	74.5	
Black	13.9	17.6	
Hispanic	7.3	4.3	
American Indian	0.5	1.9	
Asian/Pacific Islander	0.3	0.5	
Unknown	1.1	1.3	
Smoking			0.03
Never	53.3	44.9	
Past	37.7	41.4	
Current	9.0	13.6	
Pack years of smoking; [†] mean (SD)	10.6 (18.8)	10.5 (17.3)	0.16
Total expenditure from physical activity, mean MET hrs/wk (SD)	9.7 (13.0)	10.1 (13.8)	0.69
Body mass index (BMI), [‡] mean (SD), kg/m ²	30.8 (6.0)	30.4 (6.1)	0.39
Waist circumference, mean (SD), cm	92.7 (13.9)	91.3 (13.5)	0.18
Systolic blood pressure, [‡] mean (SD), mmHg	123.9 (15.3)	124.9 (15.7)	0.36
Diastolic blood pressure, mean (SD), mmHg	78.2 (8.8)	77.3 (8.7)	0.16
History of treated hypertension, BP $\geq$ 140/90, or taking antihypertensive medication	30.4	26.1	0.22
History of high cholesterol or taking lipid- lowering meds	11.8	11.5	0.91
History of diabetes	4.9	7.2	0.19
History of treated diabetes (pills or shots)	4.4	5.3	0.54
MI in first degree relative	44.8	50.6	0.13
History of MI, stroke or TIA	0.5	2.1	0.06

	Calcium/D	Placebo	P-Value*
	Mean (SD) or %	Mean (SD) or %	
Randomized to Diet Modification Trial	38.3	42.3	0.27
CEE Trial randomization assignment			0.83
CEE Placebo	48.6	47.9	
CEE	51.4	52.1	
Moderate to severe vasomotor symptoms	26.0	23.1	0.36
Age at hysterectomy, years			0.23
<35	24.9	27.7	
35–39	25.5	26.1	
40–44	20.8	23.9	
≥45	28.8	22.3	
Age at menopause, mean (SD), years	44.1 (7.1)	43.2 (7.4)	0.13
Hormone use status			0.19
Never	44.0	49.2	
Past	32.6	32.4	
Current [‡]	23.4	18.4	
Total calcium intake at baseline, mean (SD), mg/d (supplements, diet, medications) [†]	1112.7 (606.4)	1056.2 (622.4)	0.09
<800	33.7	40.9	
800 – <1200	29.2	25.0	
≥1200	37.0	34.1	
Total vitamin D intake at baseline, mean (SD), IU/d (supplements, diet) [†]	347.2 (278.5)	328.9 (268.5)	0.25
<200	42.9	48.1	
200 – <400	19.5	17.0	
400 – <600	20.1	18.4	
≥600	17.5	16.5	

* P-values are from Chi-Square tests for categorical variables and from two-sample t-tests for continuous variables.

[†] Tested on the log scale.

[‡] Current users were required to undergo a 3 month “washout” period prior to randomization.

Table 2

Distribution of Agatston Coronary Artery Calcium Scores After Trial Completion, According to Randomized Treatment Assignment in the Calcium/D Trial

	Calcium/D (N = 374)	Placebo (N = 380)	P-value*
Mean CAC score (SD)	91.6 (245.3)	100.5 (286.9)	0.74
CAC Score Percentile Distribution (50 th , 60 th , 75 th , 95 th cutpoints)	0, 12, 62, 490	0, 5, 54, 549	
Tobit Model with Transformation			
<u>Intention-to-Treat Analyses</u>	<u>Wald Chi-square (1 df)</u>	<u>P-value</u>	
Unadjusted [†]	0.07	0.79	
Multivariate, ^{§,‡}	0.001	0.98	
<u>Analyses Restricted to Participants with ≥50% Adherence to Study Medication**</u>			
Unadjusted ^{††}	0.12	0.73	
Multivariate ^{§,‡,‡‡}	0.14	0.71	

* P-value is from a Kruskal-Wallis rank test. Transformation was performed according to the method of Han and Kronmal.³⁰

[†] In the intention-to-treat group, data in unadjusted analyses were from 754 women.

[§] Multivariate analyses and p-values are adjusted in logistic regression models for age, race/ethnicity, education, smoking, history of hypertension, high cholesterol, diabetes, family history of myocardial infarction, body mass index, history of HT use, oophorectomy status, CEE trial randomization arm, and baseline intake of calcium and vitamin D.

[‡] Data in the multivariate analyses were from the 556 women with full covariate data.

** Analyses include participants adherent to >50% of study medication (calcium/vitamin D or placebo) for at least five years.

^{††} In adherence-based analyses, data in unadjusted analyses were from 518 women with at least 80% adherence to study medication for at least 5 years.

^{‡‡} Data in the multivariate analyses were from the 386 women who were adherent to study medication and had full covariate data.

Table 3

Prevalence of Positive Coronary Artery Calcium After Trial Completion in Women Randomized to Calcium/D vs Placebo, According to Increasing Agatston Score Cutpoints

Coronary Artery Calcium Score	Calcium/D N (%)	Placebo N (%)	Odds Ratio (95% CI)		Multivariate P-value
			Unadjusted (N = 754)	Multivariate* (N = 548)	
Intention-to-Treat Analyses					
0 (referent)	197 (52.7)	201 (52.9)	1.00	1.00	
>0	177 (47.3)	179 (47.1)	1.00 (0.75–1.33)	0.92 (0.64–1.34)	0.67
<10 (referent)	218 (58.3)	242 (63.7)	1.00	1.00	
≥10	156 (41.7)	138 (36.3)	1.24 (0.92–1.67)	1.29 (0.88–1.87)	0.19
<100 (referent)	301 (80.5)	309 (81.3)	1.00	1.00	
≥100	73 (19.5)	71 (18.7)	1.03 (0.71–1.48)	0.90 (0.56–1.44)	0.66
Analyses Restricted to Participants with ≥ 50% Adherence to Study Medication [†]					
0 (referent)	138 (53.3)	139 (53.7)	1.00	1.00	
>0	121 (46.7)	120 (46.3)	1.01 (0.72–1.44)	0.86 (0.55–1.34)	0.51
<10 (referent)	150 (57.9)	165 (63.7)	1.00	1.00	
≥10	109 (42.1)	94 (36.3)	1.27 (0.89–1.82)	1.17 (0.74–1.83)	0.50
<100 (referent)	214 (82.6)	212 (81.9)	1.00	1.00	
≥100	45 (17.4)	47 (18.1)	0.93 (0.59–1.47)	0.83 (0.47–1.46)	0.52

CI = confidence interval

* Multivariate odds ratios, 95% confidence intervals and p-values are adjusted in logistic regression models for age, race/ethnicity, education, smoking, history of hypertension, high cholesterol, diabetes, family history of myocardial infarction, body mass index, CEE randomization, and baseline intake of calcium and vitamin D.

[†] Analyses include participants adherent to ≥50% of study medication (calcium/vitamin D or placebo) for at least five years. The unadjusted model includes 518 observations and the multivariate model includes 383 observations.

Table 4

Odds Ratios for Categories of Elevation in the Coronary Artery Calcium Score in Women Randomized to Calcium/D versus Placebo

Odds Ratio (95% CI)					Multivariate P-value
Coronary Artery Calcium Score	Calcium/D N (%)	Placebo N (%)	Unadjusted (N = 754)	Multivariate* (N = 548)	
Intention-to-Treat Analyses					
0 (referent)	197 (52.7)	201 (52.9)	1.00	1.00	
>0-100	104 (27.8)	108 (28.4)	0.98 (0.70-1.37)	0.96 (0.63-1.45)	0.84
100-300	36 (9.6)	39 (10.3)	0.92 (0.56-1.51)	0.72 (0.38-1.34)	0.30
>300	37 (9.9)	32 (8.4)	1.15 (0.68-1.94)	1.09 (0.56-2.13)	0.79
Analyses Restricted to Participants with $\geq 50\%$ Adherence to Study Medication [†]					
0 (referent)	138 (53.3)	139 (53.7)	1.00	1.00	
>0-100	76 (29.3)	73 (28.2)	1.06 (0.71-1.58)	0.92 (0.55-1.52)	0.74
100-300	21 (8.1)	30 (11.6)	0.71 (0.39-1.30)	0.53 (0.25-1.13)	0.10
>300	24 (9.3)	17 (6.6)	1.37 (0.70-2.68)	1.25 (0.53-2.92)	0.61

CI – confidence interval

* Multivariate odds ratios, 95% confidence intervals and p-values are adjusted in logistic regression models for age, race/ethnicity, education, smoking, history of hypertension, high cholesterol, diabetes, family history of myocardial infarction, body mass index, CEE randomization, and baseline intake of calcium and vitamin D.

[†] Analyses include participants adherent to >50% of study medication (calcium/vitamin D or placebo) for at least five years. The unadjusted model includes 518 observations and the multivariate model includes 383 observations.