JACC: CARDIOVASCULAR IMAGING VOL. 14, NO. 1, 2021

PUBLISHED BY ELSEVIER

ORIGINAL RESEARCH

Oral Calcium Supplements Associate With Serial Coronary Calcification

Insights From Intravascular Ultrasound

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ABSTRACT

OBJECTIVES This study sought to evaluate and assess the extent of serial coronary artery calcification in response to oral calcium supplementation.

BACKGROUND Oral calcium supplements are frequently used despite their cardiovascular safety remaining controversial. Their effects on serial coronary calcification are not well established.

METHODS In a post hoc patient-level analysis of 9 prospective randomized trials using serial coronary intravascular ultrasound, changes in serial percentage of atheroma volume (PAV) and calcium indices (CaI) were compared in matched segments of patients coronary artery disease who were receiving concomitant calcium supplements (n = 447) and in those who did not receive supplements (n = 4,700) during an 18- to 24-month trial period.

RESULTS Patients (mean age 58 ± 9 years; 73% were men; 43% received concomitant high-intensity statins) demonstrated overall annualized changes in PAV and CaI with a mean of −0.02 ± 1.9% (p = 0.44) and a median of 0.02 (interquartile range: 0.00 to 0.06) (p < 0.001) from baseline, respectively. Following propensity-weighted mixed modeling adjusting for treatment and a range of demographic, clinical, ultrasonic, and laboratory parameters (including but not limited to sex, race, baseline, and annualized change in PAV, baseline CaI, concomitant high-intensity statins, diabetes mellitus, renal function), there were no significant between-group differences in annualized changes in PAV (least-squares mean: 0.09; 95% confidence interval [CI]: −0.20 to 0.37 vs. 0.01; 95% CI: −0.27 to 0.29; p = 0.092) according to calcium supplement intake. Per a multivariable logistic regression model accounting for the range of covariates described, calcium supplementation independently associated with an increase in annualized CaI (odds ratio: 1.15; 95% CI: 1.05 to 1.26; p = 0.004).

CONCLUSIONS Oral calcium supplementation may increase calcium deposition in the coronary vasculature independent of changes in atheroma volume. The impact of these changes on plaque stability and cardiovascular outcomes requires further investigation. (J Am Coll Cardiol Img 2021;14:259–68) © 2021 by the American College of Cardiology Foundation.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received December 31, 2019; revised manuscript received June 4, 2020, accepted June 26, 2020.

ISSN 1936-878X/$36.00 https://doi.org/10.1016/j.jcmg.2020.06.030

JACC: CARDIOVASCULAR IMAGING, VOL. 14, NO. 1, 2021
JANUARY 2021:259–68

ABBREVIATIONS AND ACRONYMS

CAI = calcium index

CI = confidence interval

IPTW = inverse probability of treatment weight

IQR = interquartile range

IVUS = intravascular ultrasound

PAV = percentage of atheroma volume

Calcium supplements are frequently prescribed to prevent or treat bone-related disorders. Whereas the bone benefits of calcium supplementation appear notionally valid (1–3), their effects on coronary arteries and overall cardiovascular risk remains controversial. Coronary atheromas appear susceptible to calcification via various pathophysiological mechanisms, rendering certain plaques unstable or vulnerable, and possibly promoting their progression (4). Although a precise mechanistic understanding of the effects of oral calcium supplementation on the coronary arterial vasculature remains unknown, it has been hypothesized that increased circulating calcium levels induced by exogenous supplementation could directly calcify the vascular endothelium (5). Furthermore, a prospective longitudinal cohort study demonstrated an increased risk of cardiovascular disease when calcium supplement intake exceeded 1,400 mg/day as compared with daily intakes of 600 to 1,000 mg (6).

Serial coronary intravascular ultrasound (IVUS) has been pivotal in elucidating factors promoting coronary atheroma progression and regression (7) and its relationship with clinical events (8,9). Measuring plaque calcification and atheroma volume with the high imaging resolution of coronary IVUS is well described and validated (10). In patients with coronary artery disease, we assessed serial changes in coronary arterial calcium in patients receiving calcium supplements compared with those not receiving calcium supplements.

METHODS

STUDY POPULATION. The current analysis combined 9 prospective clinical trials that used IVUS to evaluate the impact of a range of therapies on serial changes in coronary atheroma burden (Supplemental Table 1). For every participating center across each trial, institutional review board approval was obtained for participant enrolment. In this study, we combined and analyzed trials evaluating the following: high-intensity lipid-lowering statins (REVERSAL [Reversal of Atherosclerosis with Aggressive Lipid Lowering], ASTERIOD [A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Atheroma Burden], and SATURN [The Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin]) (11–13); PCSK9 inhibitor effects on serial coronary atheroma volume (GLAGOV [global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound]) (14); antihypertensive therapies (NORMALISE [Norvasc for Regression of Manifest Atherosclerotic Lesions by Invasive Sonographic Evaluation] and AQUARIUS [Aliskiren Quantitative Atherosclerosis Regression Intravascular Ultrasound Study]) (15,16); the anti-atherosclerotic efficacy of acyl-coenzyme A:cholestryl ester transfer protein inhibition (ACTIVATE [ACAT Intravascular Atherosclerosis Treatment Evaluation]) (17); cholesteryl ester transfer protein inhibition (ILLUSTRATE [Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation]) (18); and the effects of peroxisome proliferator-activated receptor-gamma agonism (PERISCOPE [Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation]) (19). From these trials, included in the present analysis were 447 patients who received calcium supplements and 4,700 patients who did not receive calcium. Patients were identified based on their listed medications in the case report form from each trial.

ACQUISITION AND ANALYSIS OF SERIAL IVUS IMAGES. The acquisition and serial analysis of IVUS images in each of these trials have been previously described in detail (12,13,15,17–21). Briefly, target vessels for imaging were selected if they contained no luminal stenosis of >50% angiographic severity within a coronary segment at least 30 mm in length. Imaging was performed within the same coronary artery at baseline and at study completion, which ranged from 18 to 24 months. Imaging in all trials was screened by the Atherosclerosis Imaging Core Laboratory of the Cleveland Clinic Coordinating Center for Clinical Research. Patients meeting pre-specified requirements for image quality were eligible for randomization. An anatomically matched segment was defined at the 2-time points on the basis of proximal and distal side branches (fiduciary points). Cross-sectional images spaced precisely 1 mm apart were selected for measurement. Leading edges of the lumen and external elastic membrane were traced by manual planimetry. Plaque area was defined as the area occupied between these leading edges. The accuracy and reproducibility of this method have been reported previously (22). The percentage of atheroma volume (PAV) was determined by calculating the proportion of the entire vessel wall occupied by

atherosclerotic plaque throughout the segment of interest as follows:

$$PAV = \frac{\sum(EEM_{area} - Lumen_{area})}{\sum EEM_{area}} \times 100$$

Calcium was identified by an echogenic signal brighter than the adventitia with corresponding acoustic shadowing. A calcium grade was assigned for each analyzed image, reflecting the degree of acoustic shadowing (0 = no calcium; 1 = calcium with acoustic shadowing <90°; 2 = calcium with shadowing ≥90° but <180°; 3 = calcium with shadowing ≥180° but <270°; 4 = calcium ≥270°) (10,23,24). For images containing multiple calcium deposits, the grade represented the summation of all angles of acoustic shadowing. For each pull back, a calcium index (CaI) was thus calculated as follows (24-26):

$$CI = \frac{Total\ no.\ of\ analyzed\ frames\ with\ any\ calcium}{Total\ no.\ of\ analyzed\ frames} \times \frac{Maximal\ arc\ of\ calcium}{4}$$

Change in CaI was defined as follow-up CaI minus baseline CaI (24).

STATISTICAL ANALYSIS. In these trials employing serial coronary IVUS, we identified 447 patients who took concomitant calcium supplements and 4,700 patients who did not take any calcium supplements. Continuous variables were compared between groups using the Student's *t*-test or Wilcoxon rank sum test, as appropriate, and within groups using the paired Student's *t*-test or Wilcoxon signed rank test, as appropriate. Mean ± SD is reported when normally distributed and median (interquartile range [IQR]) when non-normally distributed. Categorical variables were compared between groups using the chi-square or Fisher exact test. Frequency (percentage) is reported. Due to the fact that CaI (both baseline and change) contained many zero values, rank transformation was implemented.

As a consequence of differences in many baseline characteristics among calcium supplement use and noncalcium supplement use, a propensity score-weighting approach was applied. Two sets of propensity scores and a corresponding inverse probability of treatment weight (IPTW) (the reciprocal of propensity scores) were valued by a generalized linear model, utilizing as covariates all the potential confounders observed for calcium supplement use versus change in CaI. The equilibrium of the pretreatment covariates was evaluated by examining absolute standardized differences in baseline confounders between concomitant calcium supplement use and noncalcium supplement use prior to and following IPTW adjustment, and significant improvement in baseline balance was achieved following weighting, as judged by a 10% threshold. IPTW on PAV shared the same covariate set and hence had the same significance of weighting.

All consecutive analyses of the calcium supplement effect were weighted by IPTW. Serial changes in IVUS measurements were analyzed by analysis of covariance, adjusting for their baseline correlate, and treating clinical trial as a random factor to account for heterogeneity across trials. Least-squares mean with 95% confidence interval (CI) is reported. A similar multivariable analysis was performed for rank-transformed CaI change for which PAV was additionally adjusted because calcium is a component of plaque. With each trial's duration varying between 18 and 24 months, changes in CaI and PAV were interpolated at 1 year and therefore reported as annualized changes. To further determine clinical risk factors for coronary calcification, a multivariable logistic regression model was created for CaI increase versus no increase.

Examination of multicollinearity was performed in the full models. Whereas propensity scores tend to yield extreme values or degrees of overlap, a sensitivity analysis with trimmed outliers was performed to reduce extreme values or degrees generated by possible propensity score weighting by removing the

TABLE 1 Demographics, Clinical and Angiographic Characteristics, and Medications by Calcium Supplement Intake

		Any Calcium Supplements Taken		
	Total	No	Yes	p Value
Subjects	5,147	4,700	447	
Age, yrs	58.2 ± 9.17	57.9 ± 9.19	60.8 ± 8.64	<0.001
Female	1,404 (27.3)	1,148 (24.4)	256 (57.3)	<0.001
Caucasian	4,771 (92.7)	4,349 (92.5)	422 (94.4)	0.145
BMI, kg/m^2	29.9 ± 5.39	29.9 ± 5.32	30.7 ± 5.99	0.002
Diabetes mellitus	1,368 (26.6)	1,245 (26.5)	123 (27.5)	0.638
Hypertension	3,961 (77.0)	3,611 (76.8)	350 (78.3)	0.481
Prior myocardial infarction	1,537 (29.9)	1,438 (30.6)	99 (22.1)	<0.001
Peripheral arterial disease	210 (4.1)	183 (3.9)	27 (6.0)	0.028
Prior stroke	147 (2.9)	132 (2.8)	15 (3.4)	0.507
Aspirin	4,753 (92.3)	4,331 (92.1)	422 (94.4)	0.086
Beta blockers	3,957 (76.9)	3,623 (77.1)	334 (74.7)	0.257
ACE inhibitor or ARB	3,514 (68.3)	3,215 (68.4)	299 (66.9)	0.511
Warfarin	203 (3.9)	177 (3.8)	26 (5.8)	0.033
High intensity statin	2,047 of 4,721 (43.4)	1,900 of 4,335 (43.8)	147 of 386 (38.1)	0.029
Baseline diameter stenosis, %	41.0 ± 17.44	41.2 ± 17.40	39.6 ± 17.75	0.246
Maximum diameter stenosis >50%	480 of 1,877 (25.6)	431 of 1,685 (25.6)	49 of 192 (25.5)	0.986

Values are n, mean ± SD, or n (%), unless otherwise indicated. Medications listed are concomitant.
ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index.

TABLE 2 Baseline and Follow-Up Laboratory Values According to Calcium Supplement Intake

	Any Calcium Supplements Taken			
	Total (N = 5,147)	No (n = 4,700)	Yes (n = 447)	p Value
Baseline				
LDL-C, mg/dl	105.1 ± 34.79	105.5 ± 34.83	101.0 ± 34.12	0.009
HDL-C, mg/dl	44.4 ± 11.91	44.1 ± 11.65	47.7 ± 13.94	<0.001
Non-HDL-C, mg/dl	135.1 ± 40.33	135.4 ± 40.36	131.2 ± 39.80	0.036
Triglycerides, mg/dl	133 (97-188)	133 (97-188)	133 (91-190)	0.828
CRP, mg/l	2.0 (1.0-4.4)	2.0 (0.9-4.3)	2.2 (1.1-5.1)	0.005
Creatinine, mg/dl	0.9 (0.8-1.1)	1.0 (0.8-1.1)	0.9 (0.8-1.0)	<0.001
Calcium, mg/dl	9.3 (8.9-9.6)	9.3 (8.9-9.6)	9.2 (8.9-9.6)	0.133
Phosphate, mg/dl	3.4 (3.0-3.7)	3.4 (3.0-3.7)	3.5 (3.1-3.9)	0.007
Follow-up				
LDL-C, mg/dl	78.9 ± 30.04	78.8 ± 30.34	79.5 ± 26.68	0.651
HDL-C, mg/dl	49.1 ± 14.59	48.6 ± 14.13	54.1 ± 18.06	<0.001
Non-HDL-C, mg/dl	106.1 ± 35.48	106.1 ± 35.80	106.9 ± 31.90	0.623
Triglycerides, mg/dl	125 (93-169)	125 (93-169)	128 (92-172)	0.720
CRP, mg/l	1.6 (0.8-3.8)	1.6 (0.8-3.7)	1.8 (0.9-4.0)	0.051
Last CRP, mg/l	1.5 (0.7-3.5)	1.5 (0.7-3.5)	1.7 (0.8-4.1)	0.022
Last creatinine, mg/dl	0.9 (0.8-1.1)	0.9 (0.8-1.1)	0.9 (0.8-1.0)	0.008
Calcium,* mg/dl	9.3 (9.0-9.6)	9.3 (9.0-9.6)	9.3 (9.0-9.5)	0.199
Phosphate,* mg/dl	3.4 (3.1-3.7)	3.3 (3.0-3.6)	3.5 (3.2-3.8)	<0.001

Values are mean ± SD or median (interquartile range). *Laboratory values obtained during treatment are the time-weighted averages of all post-baseline values.

CRP = C-reactive protein; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

top and bottom 1% of propensity scores within each calcium supplement group.

A 2-sided p value of 0.05 was considered statistically significant. All analyses were executed using SAS software version 9.4 (SAS Institute, Cary, North Carolina). Figures were created using R version 3.6.1 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Table 1 describes the clinical characteristics, concomitant medications during the study period, and angiographic characteristics of the imaged vessel at baseline corresponding to calcium supplement intake or not. The mean age of the overall population was 58.2 ± 9.2 years, the majority of subjects (73%) were male, and 43.4% of the study population received concomitant high-intensity statins. Compared with those not receiving calcium supplements, those receiving calcium supplements were older (60.8 ± 8.6 vs. 57.9 ± 9.2 years; p < 0.001), more likely to be women (57.3% vs. 24.4%; p < 0.001), have a lower incidence of prior myocardial infarction (22.1% vs. 30.6%; p < 0.001), more likely to be receiving concomitant aspirin (95.1% vs. 91.2%; p = 0.005) and warfarin (5.8% vs. 3.8%; p = 0.03), but less likely to receive concomitant high-intensity statins (38.1% vs. 43.8%; p = 0.029). There were no between-group differences in the angiographic characteristics of the imaged coronary artery.

Table 2 summarizes laboratory biochemical measures at baseline and follow-up. Compared with those not receiving calcium supplements, those receiving calcium supplements had significantly greater baseline levels of high-density lipoprotein cholesterol (47.7 ± 13.9 vs. 44.1 ± 11.7 mg/dl; p < 0.001), C-reactive protein (median: 2.2; IQR: 1.1 to 5.1 vs. 2.0; IQR: 0.9 to 4.3 mg/l; p = 0.005) and phosphate levels (median: 3.5; IQR: 3.1 to 3.9 vs. 3.4; IQR: 3.0 to 3.7 mg/dl; p = 0.007), but significantly lower baseline levels of low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol. At follow-up, compared with the noncalcium supplements group, those receiving calcium supplements demonstrated significantly greater high-density lipoprotein cholesterol (54.1 ± 18.1 vs. 48.6 ± 14.1 mg/d; p < 0.001).

Table 3 summarizes baseline, follow-up, and changes in PAV over time according to treatment disposition, in addition to comparisons of differences in PAV following propensity matching. Compared with the noncalcium supplements group, those

TABLE 3 Baseline and Changes in IVUS-Derived PAV According to Calcium Supplement Intake

	Any Calcium Supplements Taken			
	Total (N = 5,147)	No (n = 4,700)	Yes (n = 447)	p Value
Baseline PAV	37.9 ± 9.04	38.0 ± 9.04	36.6 ± 8.89	0.001*
	38.5 (37.3-39.7)	38.7 (37.5-39.9)	36.9 (35.5-38.3)	<0.001†
Follow-up PAV	37.8 ± 9.09	37.9 ± 9.11	36.7 ± 8.85	0.012*
Annualized change in PAV	−0.02 ± 1.915	−0.03 ± 1.923	0.12 ± 1.832	0.092*
Within group p value‡	0.435*	0.216*	0.150*	
LS mean (95% CI)	0.04 (−0.24 to 0.32)	0.01 (−0.27 to 0.29)	0.09 (−0.20 to 0.37)	0.092§

Values are mean ± SD or median (interquartile range), unless otherwise indicated. *Unadjusted results with mean ± SD reported. †Linear mixed model adjusting for trial. ‡Paired Student's *t*-test. §Inverse probability of treatment-weighted linear mixed model for annualized change in PAV adjusting for age, sex, race, BMI, diabetes mellitus, history of myocardial infarction, baseline ACE or ARB, concomitant high-intensity statins, baseline PAV, and trial. Due to missing values of covariates, 4,639 records were used here.

CI = confidence interval; IPTW = inverse probability of treatment weight; IVUS = intravascular ultrasound; LS = least squares; PAV = percentage of atheroma volume; other abbreviations as in Table 1.

TABLE 4 Baseline, Follow-Up, and Continuous Change in CaI According to Calcium Supplement Intake

	Any Calcium Supplements Taken			
	Total (N = 5,147)	No (n = 4,700)	Yes (n = 447)	p Value
Baseline CaI	0.29 (0.09–0.55)	0.29 (0.09–0.55)	0.26 (0.07–0.56)	0.30*
Follow-up CaI	0.35 (0.12–0.63)	0.35 (0.12–0.63)	0.33 (0.10–0.61)	0.438*
Annualized change in CaI	0.02 (0.00–0.06)	0.02 (0.00–0.06)	0.02 (0.00–0.06)	0.95*
Within group p†	<0.001*	<0.001*	<0.001*	
Quantiles of ranks, multivariable	50.2 (47.4–52.9)	49.5 (46.7–52.3)	50.9 (48.1–53.8)	0.067‡

Values are median (interquartile range), unless otherwise indicated. *Unadjusted univariate results with median (interquartile range) reported. †Wilcoxon signed-rank test. ‡IPTW-weighted linear mixed model for change in CaI (quantiles of ranks because there are many zero values) adjusting for sex, race, BMI, hypertension, prior myocardial infarction, diabetes mellitus, concomitant high-intensity statins, concomitant warfarin, renal function (last creatinine), baseline and annualized change in PAV, baseline CaI (quantiles of ranks), and trial. Least-squares mean with 95% CI reported. Due to missing values of covariates, 4,634 records were used here.

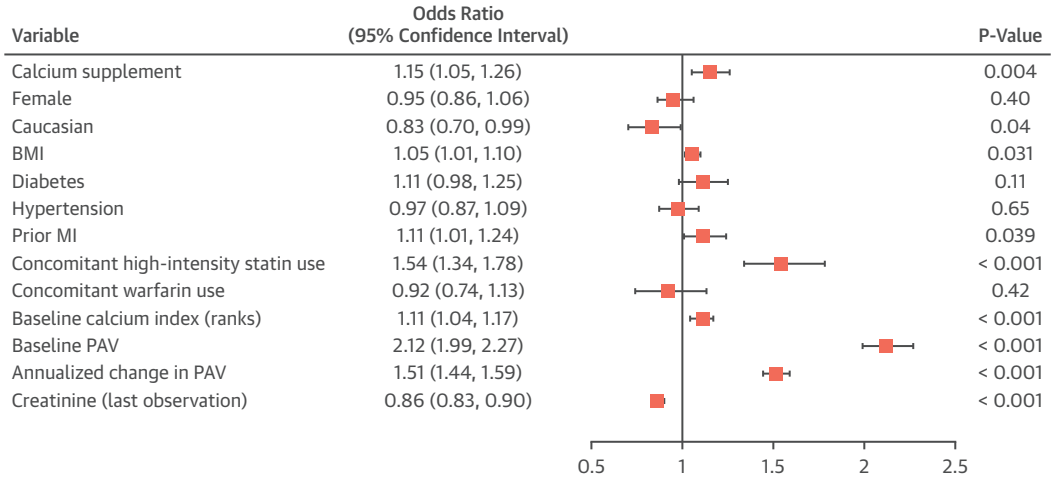
CaI = calcium index; other abbreviations as in Tables 1 and 3.

receiving calcium supplements had significantly less atheroma volume at baseline (36.6 ± 8.9% vs. 38.0 ± 9.0%; p = 0.001) and follow-up (36.7 ± 8.85% vs. 37.9 ± 9.1%; p = 0.012). However, whether adjusted or unadjusted, there were no significant within-group nor between-group differences in annualized changes in PAV.

Table 4 summarizes baseline, follow-up, and continuous change in CaI for each treatment group along with analysis of continuous changes in CaI following propensity score weighting and adjustment for the baseline measure of plaque burden and CaI, treatment, and other covariates. When unadjusted, there was no significant difference in the change in CaI between treatment groups. Following additional adjustment for baseline PAV within a full multivariable model, the (quantiles of the ranks for) annualized change in CaI were similar between the 2 groups (least-squares mean: 49.5; 95% CI: 46.7 to 52.3 vs. 50.9; 95% CI: 48.1 to 53.8; p = 0.067), with a trend toward being greater in those receiving calcium supplements.

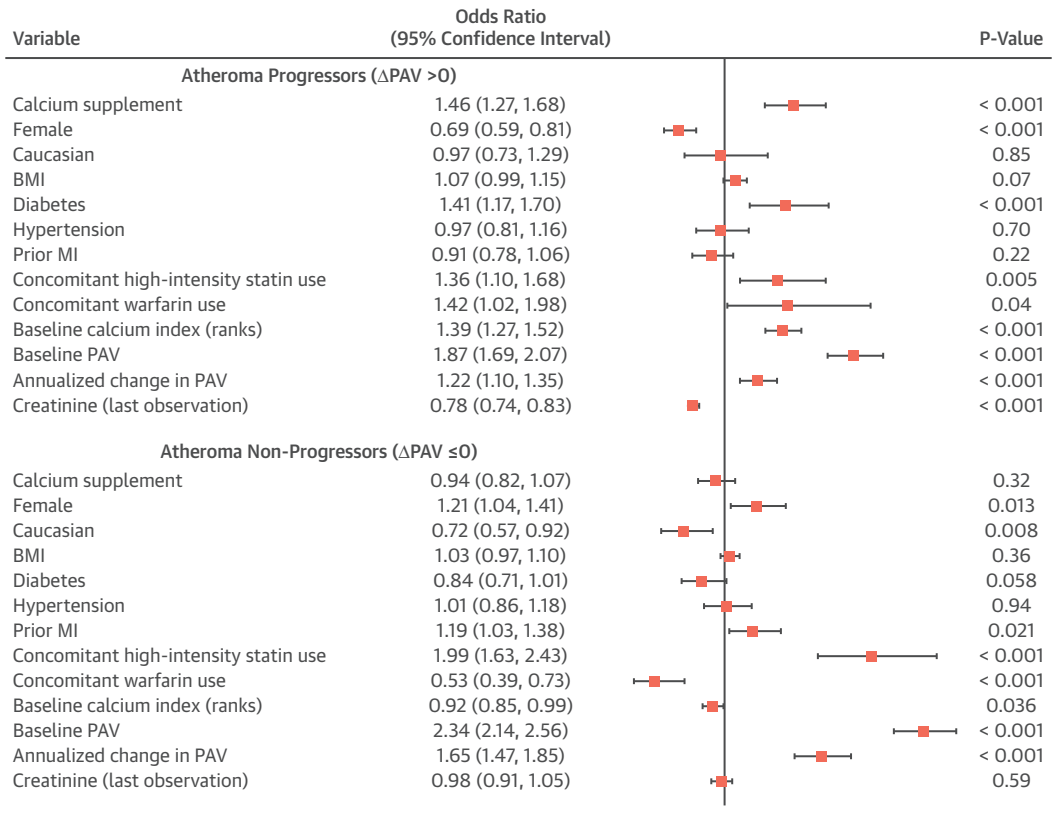
Figure 1 describes a multivariable logistic regression model describing factors independently associated with an increase in CaI following IPTW weighting. The use of calcium supplements was independently associated with progressive coronary artery calcification (odds ratio: 1.15; 95% CI: 1.05 to 1.26; p = 0.004). Other significant variables associated with a rising CaI included a non-Caucasian race,

FIGURE 1 Full Multivariable Model for Annualized CI Increase



Odds ratios for body mass index (BMI), rank-transformed baseline calcium index (CaI), baseline percentage of atheroma volume (PAV), annualized change in PAV, and last observation creatinine are reported per SD. The model was also adjusted for trial and was weighted by the inverse probability of treatment. Due to missing values of covariates, 4,634 records were used here. MI = myocardial infarction.

FIGURE 2 Full Multivariable Model for Annualized CaI Increase in Atheroma Progressors and Nonprogressors



ORs for BMI, rank-transformed baseline CaI, baseline PAV, annualized change in PAV, and last observation creatinine are reported per SD. The model was also adjusted for trial and was weighted by the inverse probability of treatment. Due to missing values of covariates, 2,149 of the progressors' records and 2,485 of the 2,706 nonprogressors' records were used here. The interaction p value between calcium supplement use and PAV progressor status was <0.001. Abbreviations as in Figure 1.

greater body-mass index, concomitant high-intensity statin use, greater baseline PAV and CaI, and higher annualized change in PAV.

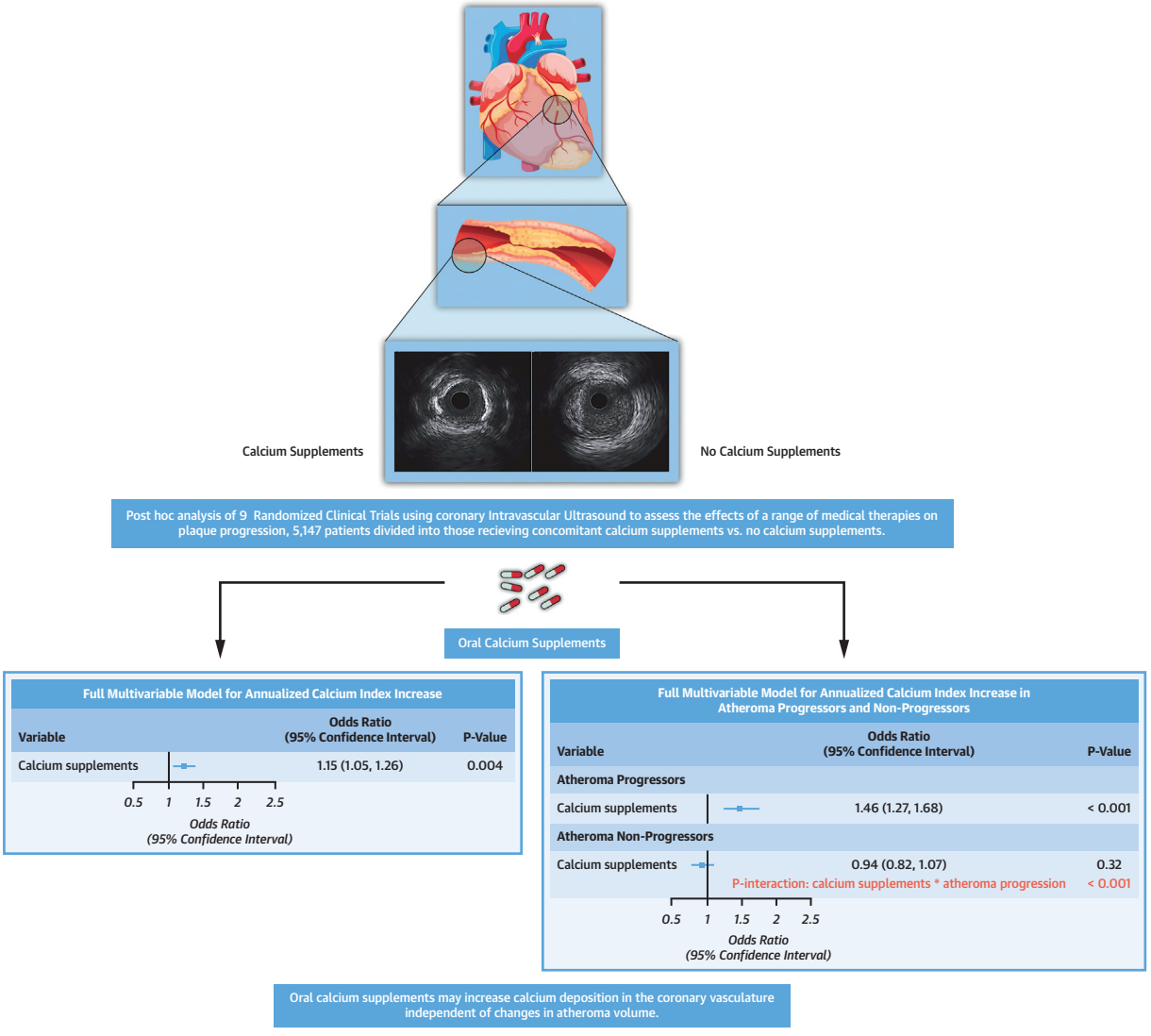
A sensitivity analysis examining for potential interactions among atheroma progressors (ΔPAV >0), nonprogressors (ΔPAV ≤0), and calcium supplement use on an increase in CaI is described in Figure 2. In those demonstrating coronary atheroma progression, calcium supplements significantly associated with an increasing CaI, whereas in those not demonstrating coronary atheroma progression, there was no significant association between calcium supplement use and an increase in CaI (p-interaction < 0.001).

A further sensitivity (trimmed) analysis was performed, trimming the top and bottom 1% of propensity scores within each calcium supplement group. When treating change in annualized CaI as a continuous variable (Table 4), the p value for calcium supplement use versus nonuse went from 0.067 to 0.011 following trimming.

DISCUSSION

In this post hoc propensity-weighted analysis of patients with coronary artery disease undergoing serial coronary IVUS evaluation in the context of 9 randomized clinical trials, we demonstrate for the first time a statistically significant independent association between oral calcium supplementation and progressive coronary arterial calcification (Central Illustration). These findings were irrespective of the concomitant changes in coronary atheroma volume, patient age, concomitant statin or warfarin therapy, as well as renal function and the calcium-phosphate product: factors all known to associate with arterial calcification. The longer-term clinical implications of the demonstrated isolated pro-calcific effects of exogenous oral calcium supplements were beyond the scope of the present analysis. However, these effects on plaque stability and clinical outcomes require further investigation.

CENTRAL ILLUSTRATION **Use of Oral Calcium Supplements and Effects on Coronary Calcification**



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A broad study outline is depicted, and results of the multivariable analysis are provided, highlighting oral calcium supplement use to independently associate with progressive coronary atheroma calcification. IVUS = intravascular ultrasound; RCT = randomized clinical trial.

Historically, oral calcium supplements had been thought to not significantly affect coronary arterial calcification (27,28). Data gleaned from a mini-swine model of exogenous calcium supplementation supported this notion, whereby swine afflicted with metabolic syndrome fed a high-calcium diet were found to have low levels of calcium carbonate in their coronary arteries (29). However, meta-analyses and prospective cohorts evaluating calcium supplements suggested an association between calcium supplementation and myocardial infarction risk in healthy post-menopausal women (30). Furthermore, data from the EPIC-Heidelberg (European Prospective Investigation into Cancer and Nutrition) study demonstrated a statistically significant increased risk of myocardial infarction in patients using calcium supplements (31). Additionally, the WHI CaD (Woman's Health Initiative Calcium/Vitamin D Supplementation Study) examined the association between calcium supplements with and without vitamin D and

cardiovascular outcomes, and a modest increase in cardiovascular risk was observed, most notably myocardial infarction (32). Whether these observations related to an underlying propensity for enhanced intimal calcification as the nidus for myocardial infarction versus an alternative pathophysiological explanation remains to be explored. Consequently, the present observations could have potential implications in patients prescribed long-term calcium supplements, most notably in those with concomitant atherosclerotic risk factors. Further studies are required to elucidate the clinical implications of the present findings.

The present analysis is unique in that it enabled the assessment of the impact of exogenous calcium supplements on the serial behavior of coronary atheroma using IVUS as a sensitive imaging modality for tracking volumetric plaque changes. Other studies evaluating the effects of oral calcium supplementation on the vessel wall involved static assessments of the arterial vasculature in relation to the history of calcium intake. The MESA (Multi-Ethnic Study of Atherosclerosis) evaluated the impact of calcium supplements intake on the increase of coronary artery calcium on cardiac computed tomography and found a 22% increase in incidence of coronary artery calcium. However, it is worth noting that there was no significant coronary artery calcium progression over an average 10-year follow-up (33).

The present data demonstrate that calcium supplementation associates with progressive arterial calcium regardless of the baseline extent of calcium and plaque volume, concomitant statin use, age, renal function, and sex. A further notable finding from the present analysis was the significant interaction between calcium supplement use, atheroma progression-regression, and change in CaI. Increases in CaI corresponded with those demonstrating coronary atheroma progression who received calcium supplements. However, in those without plaque progression, calcium supplement use imparted no significant effect on the change in CaI. These mechanistic observations will ultimately need to be prospectively investigated in appropriately designed clinical trials to better understand the cardiovascular safety of oral calcium supplementation. Furthermore, the present analysis could have implications in those undergoing cardiac computed tomography scanning for coronary calcium scoring as a means of cardiovascular risk stratification. Whether a history of prior and/or active calcium supplementation significantly affects the Agatston score and thus cardiovascular prognostication requires further investigation. The density of coronary calcium rather than simply its aggregate may associate more strongly with incident cardiovascular events (34), and how calcium supplements influence these differential parameters is presently unknown.

STUDY LIMITATIONS. Several caveats of the present analysis warrant further consideration. We were unable to assess for a dose-response association between oral calcium supplementation and subsequent pro-calcific plaque effects. Also, trial participants were asked to list their concomitant medication, rather than "supplement" use, which could have resulted in inadvertent under-reporting of calcium supplement use. We demonstrated significant differences in plaque calcification despite a follow-up period of 18 to 24 months, a relatively modest time period compared with the duration of calcium supplement therapy typically prescribed for individuals with appropriate clinical indications. Given the significant procalcific effects in calcium supplement-treated individuals demonstrated within this relatively short 18- to 24-month time frame, one could, therefore, speculate on the extent of coronary atheroma calcification following a much more extended period of calcium supplement therapy. The current analysis was not a placebo-controlled trial and a degree of heterogeneity should be considered when interpreting the results of our current study. Nevertheless, to the best of our knowledge, this analysis currently serves as the best available evidence to date of the serial, procalcific effects of calcium supplements in human coronary atheroma in vivo. There is the possibility of unmeasured confounders influencing our analysis. However, a range of clinical, ultrasonic, and metabolic parameters, as well as clinical trials, have been extensively controlled for in the present analysis, thus minimizing the effects of potential biases. Moreover, the inclusion and exclusion criteria for all the included serial IVUS trials were relatively uniform, and the analysis was performed within a single core laboratory using standardized analytic techniques. Furthermore, concordant results in a differing propensity model (sensitivity analysis) highlight the consistency and biological plausibility of these findings. Depth analysis of calcium is not a standard component of our core laboratory's IVUS imaging protocol. Consequently, the relative location of the calcium (intimal vs. adventitial) was not ascertained. Whereas calcium deposits may be assessed

quantitively utilizing IVUS by measuring the arc and length, a fraction of the ultrasound beam penetrates the calcium deposits showing only the leading edge of the calcification and therefore does not represent its anatomic thickness, precluding true volumetric calcium assessment.

CONCLUSIONS

Oral calcium supplement use is independently associated with serial procalcific effects within the coronary vasculature in vivo, irrespective of concomitant changes in atheroma volume, concomitant warfarin and statin therapy, and renal function. These findings are consistent with prior preclinical cross-sectional human vascular imaging data. The longer-term clinical implications on atherosclerotic cardiovascular risk of these data remain unknown, thus necessitating further investigations.

AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Patients receiving calcium supplements with angiographically apparent coronary artery disease demonstrate progressive coronary arterial calcification in vivo, independent of its baseline extent, the degree of baseline plaque burden, baseline or concomitant statin use, or renal function.

TRANSLATIONAL OUTLOOK: Further studies are needed to determine whether these observations relate to intensity and duration of calcium supplement exposure and whether calcium supplement–induced atheroma calcification renders a plaque to be more vulnerable.

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KEY WORDS calcium supplements, coronary artery calcification, IVUS

APPENDIX For a supplemental figure, please see the online version of this paper.