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Effects of Statins on Coronary Atherosclerotic Plaques

The PARADIGM (Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography Imaging) Study

Sang-Eun Lee, MD, PhD,[a,b] Hyuk-Jae Chang, MD, PhD,[a,b] Ji Min Sung, PhD,[a,b] Hyung-Bok Park, MD,[b,c] Ran Heo, MD,[b,d] Asim Rizvi, MD,[e] Fay Y. Lin, MD,[e] Amit Kumar, MSc,[e] Martin Hadamitzky, MD,[f] Yong Jin Kim, MD, PhD,[g] Edoardo Conte, MD,[h] Daniele Andreini, MD, PhD,[h] Gianluca Pontone, MD, PhD,[h] Matthew J. Budoff, MD,[i] Ilan Gottlieb, MD, PhD,[j] Byoung Kwon Lee, MD, PhD,[k] Eun Ju Chun, MD, PhD,[l] Filippo Cademartiri, MD, PhD,[m] Erica Maffei, MD,[n] Hugo Marques, MD,[o] Jonathon A. Leipsic, MD,[p] Sanghoon Shin, MD,[q] Jung Hyun Choi, MD, PhD,[r] Kavitha Chinnaiyan, MD,[s] Gilbert Raff, MD,[s] Renu Virmani, MD,[t] Habib Samady, MD,[u] Peter H. Stone, MD,[v] Daniel S. Berman, MD,[w] Jagat Narula, MD, PhD,[x] Leslee J. Shaw, PhD,[u] Jeroen J. Bax, MD, PhD,[y] James K. Min, MD[e]

ABSTRACT

OBJECTIVES This study sought to describe the impact of statins on individual coronary atherosclerotic plaques.

BACKGROUND Although statins reduce the risk of major adverse cardiovascular events, their long-term effects on coronary atherosclerosis remain unclear.

METHODS We performed a prospective, multinational study consisting of a registry of consecutive patients without history of coronary artery disease who underwent serial coronary computed tomography angiography at an interscan interval of ≥2 years. Atherosclerotic plaques were quantitatively analyzed for percent diameter stenosis (%DS), percent atheroma volume (PAV), plaque composition, and presence of high-risk plaque (HRP), defined by the presence of ≥2 features of low-attenuation plaque, positive arterial remodeling, or spotty calcifications.

RESULTS Among 1,255 patients (60 ± 9 years of age; 57% men), 1,079 coronary artery lesions were evaluated in statin-naive patients (n = 474), and 2,496 coronary artery lesions were evaluated in statin-taking patients (n = 781). Compared with lesions in statin-naive patients, those in statin-taking patients displayed a slower rate of overall PAV progression (1.76 ± 2.40% per year vs. 2.04 ± 2.37% per year, respectively; $p = 0.002$) but more rapid progression of calcified PAV (1.27 ± 1.54% per year vs. 0.98 ± 1.27% per year, respectively; $p < 0.001$). Progression of noncalcified PAV and annual incidence of new HRP features were lower in lesions in statin-taking patients (0.49 ± 2.39% per year vs. 1.06 ± 2.42% per year and 0.9% per year vs. 1.6% per year, respectively; all $p < 0.001$). The rates of progression to >50%DS were not different (1.0% vs. 1.4%, respectively; $p > 0.05$). Statins were associated with a 21% reduction in annualized total PAV progression above the median and 35% reduction in HRP development.

CONCLUSIONS Statins were associated with slower progression of overall coronary atherosclerosis volume, with increased plaque calcification and reduction of high-risk plaque features. Statins did not affect the progression of percentage of stenosis severity of coronary artery lesions but induced phenotypic plaque transformation. (Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography Imaging [PARADIGM]; NCT02803411.) (J Am Coll Cardiol Img 2018;■:■–■) © 2018 by the American College of Cardiology Foundation.

From the [a]Division of Cardiology, Severance Cardiovascular Hospital, Yonsei University College of Medicine, Yonsei University Health System, Seoul, South Korea; [b]Yonsei-Cedars-Sinai Integrative Cardiovascular Imaging Research Center, Yonsei University College of Medicine, Yonsei University Health System, Seoul, South Korea; [c]Department of Internal Medicine, Division of Cardiology, Catholic Kwandong University International St. Mary's Hospital, Incheon, South Korea; [d]Division of Cardiology, Asan Medical Center, College of Medicine, University of Ulsan, Seoul, South Korea; [e]Dalio Institute of Cardiovascular Imaging, New York-Presbyterian Hospital and Weill Cornell Medical College, New York, New York; [f]Department of Radiology and Nuclear Medicine, German Heart Center Munich, Munich, Germany; [g]Seoul National

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ABBREVIATIONS AND ACRONYMS

%DS = percent diameter stenosis

CAD = coronary artery disease

CTA = computed tomography angiography

CTA-1 = baseline computed tomography angiography

CTA-2 = follow-up computed tomography angiography

HRP = high-risk plaque

PAV = percent atheroma volume

PV = plaque volume

In numerous randomized controlled trials in patients eligible for primary and secondary prevention therapies, statins have been effective in reducing the risk of major adverse cardiac events (1-3). A recent pooled analysis of patients from 8 randomized clinical trials undergoing serial intravascular ultrasonography examinations over 18 to 24 months demonstrated the insight that may be afforded by serial plaque evaluation, finding that statins exhibit pro-calcific effects independently of their effects on reducing plaque progression (4). These findings may unify the paradox of increased coronary artery calcium progression seen in statin trials, despite reduced events.

However, intravascular techniques are subject to calcium shadowing and thus must rely on semiquantitative indices (5). Additionally, the generalizability of intravascular ultrasonography data to a lower risk population beyond secondary prevention population or advanced coronary disease (CAD), or beyond 24-months, is unknown because the invasiveness of the method applied has limited the study population to those patients who are at relatively high risk or who already have advanced CAD (6-8). Prior serial coronary computed tomography angiography (CTA) studies are limited to their number and qualitative methods (4,9).

To address this knowledge gap, we prospectively enrolled a large multinational cohort of consecutive patients with suspected CAD who underwent serial coronary CTA at a minimum of 2-year interscan intervals to determine the long-term effects of statins on plaque progression and calcification in a low-risk patient population.

METHODS

STUDY DESIGN. The PARADIGM (Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography Imaging) study was a dynamic, multinational observational registry that prospectively collected clinical, procedural, and

University College of Medicine, Seoul National University Hospital, South Korea; [h]Centro Cardiologico Monzino, IRCCS, Milan, Italy; [i]Department of Medicine, Los Angeles Biomedical Research Institute, Torrance, California; [j]Department of Radiology, Casa de Saude São Jose, Rio de Janeiro, Brazil; [k]Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea; [l]Seoul National University Bundang Hospital, Seoul, South Korea; [m]Cardiovascular Imaging Center, SDN Foundation IRCCS, Naples, Italy; [n]Department of Radiology, Area Vasta 1/ASUR Marche, Urbino, Italy; [o]UNICA, Unit of Cardiovascular Imaging, Hospital da Luz, Lisbon, Portugal; [p]Department of Medicine and Radiology, University of British Columbia, Vancouver, British Columbia, Canada; [q]National Health Insurance Service Ilsan Hospital, Goyang, South Korea; [r]Busan University Hospital, Busan, South Korea; [s]Department of Cardiology, William Beaumont Hospital, Royal Oak, Michigan; [t]Department of Pathology, CVPath Institute, Gaithersburg, Maryland; [u]Division of Cardiology, Emory University School of Medicine, Atlanta, Georgia; [v]Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, Massachusetts; [w]Department of Imaging and Medicine, Cedars-Sinai Medical Center, Los Angeles, California; [x]Icahn School of Medicine at Mount Sinai, Mount Sinai Heart, Zena and Michael A. Wiener Cardiovascular Institute, and Marie-Josée and Henry R. Kravis Center for Cardiovascular Health, New York, New York; and the [y]Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands. Supported in part by the Leading Foreign Research Institute Recruitment Program through the National Research Foundation (NRF) of Korea, funded by Ministry of Science and ICT (MSIT) grant 2012027176 and by gifts from the Dalio Institute of Cardiovascular Imaging and the Michael Wolk Foundation. Funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Dr. Chang had full access to all data in the study and final responsibility for the decision to submit the manuscript for publication. Dr. Chang has received funding from Leading Foreign Research Institute Recruitment Program through NRF of Korea funded by MSIT grant 2012027176). Dr. Min has received funding from U.S. National Institutes of Health (NIH) grants R01 HL111141, R01 HL115150, R01 118019, and U01 HL 105907, Qatar National Priorities Research Program grant 09-370-3-089, and GE Healthcare. Dr. Min has consulted for HeartFlow; has served on the scientific advisory board of Arineta; and holds equity interest in MDDX. Dr. Bax has received unrestricted research grants from Biotronik, Medtronic, Boston Scientific, and Edwards Lifesciences. Dr. Chun has received funding from NRF grant NRF-2015R1D1A1A01059717, funded by the Korean Government (Ministry of Education, Science and Technology [MEST]). Dr. Leipsic has consulted for and holds stock in HeartFlow and Circle Cardiovascular Imaging; and has received speakers fees from GE Healthcare. Dr. Budoff has received grants from NIH and GE Healthcare. Dr. Samady has received grant support from Phillips/Volcano and St. Jude and Abbott, Medtronic, and Gilead. Dr. Andreini is a member of the speakers bureau for GE Healthcare; and has received grant support from GE Healthcare and Bracco. Dr. Pontone has received institutional research grants from GE Healthcare, HeartFlow, Medtronic, Bracco, and Bayer. Dr. Berman has received royalties from Cedars-Sinai. Dr. Virmani has received institutional research support from 480 Biomedical, Abbott Vascular, Arterial Remodeling Technologies (ART) BioSensors International, Biotronik, Boston Scientific, Celonova, Claret Medical, Cook Medical, Cordis, Edwards Lifesciences, Medtronic, MicroVention, OrbusNeich, ReCord, SINO Medical Technology, Spectranetics, Surmodics, Terumo Corporation, W.L. Gore, and Xeltis; and has received honoraria from 480 Biomedical, Abbott Vascular, Boston Scientific, Cook Medical, Lutonix, Medtronic, Terumo Corporation, and W.L. Gore; and has consulted for 480 Biomedical, Abbott Vascular, Medtronic, and W.L. Gore. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Todd Villines, MD, served as the Guest Editor for this paper.

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follow-up data for patients who underwent clinically indicated serial coronary CTA (10). The study protocol was approved by the institutional review boards of all participating centers.

STUDY POPULATION. The PARADIGM study consisted of 2,252 patients managed at 13 sites in 7 countries (Brazil, Canada, Germany, Italy, Portugal, South Korea, and the United States), who were enrolled between 2003 and 2015. The study included consecutive patients with suspected or known CAD undergoing serial coronary CTA at an interscan interval of ≥2 years and excluded patients with complete absence of clinical data at baseline (coronary CTA-1) or follow-up (coronary CTA-2) (10).

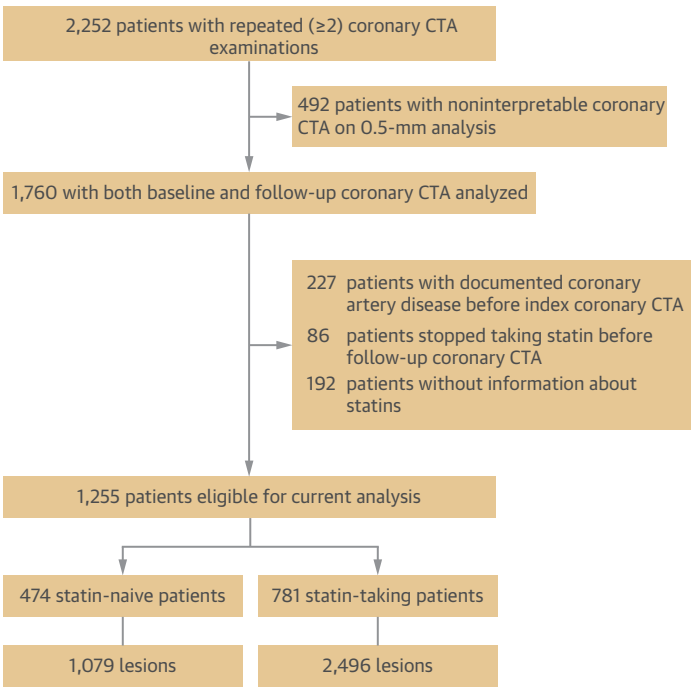
For this analysis, further exclusion criteria included documented prior CAD (defined as myocardial infarction or revascularization before coronary CTA-1 (n = 227), patients without information on statin use at the time of both coronary CTAs (n = 192), patients who discontinued statin use after coronary CTA-1 (n = 86), and patients with either coronary CTA results uninterpretable for quantitative coronary CTA measurement (n = 492); 1,255 patients were included in the final analysis. Patients were divided into a statin-naive group (n = 474), if they were not taking a statin at the time of coronary CTA-1 and follow-up coronary CTA (coronary CTA-2), and a statin-taking group (n = 781), if they were taking a statin at the time of coronary CTA-2 (**Figure 1**). In case of patients with ≥3 coronary CTA scans, the first and last coronary CTAs were analyzed. Patients who experienced a clinical event between the 2 coronary CTAs were not omitted.

CORONARY CTA ANALYSIS PROTOCOL. All coronary CTAs were performed in accordance with Society of Cardiovascular Computed Tomography guidelines (11,12). Datasets from each participating site were transferred to a core laboratory for blinded image analysis. Coronary atherosclerosis was evaluated on multiplanar and cross-sectional coronary CTA images. All evaluations were performed by level III experienced readers masked to clinical results, using semi-automated plaque analysis software (QAngioCT Research Edition v2.1.9.1, Medis Medical Imaging Systems, Leiden, the Netherlands) with manual correction (13).

Briefly, all coronary arteries with a diameter ≥2 mm were evaluated on every coronary artery and its branches (Online Methods Part VI, Online Figure 1). The presence of atherosclerosis was defined as any tissue ≥1 mm^2 within or adjacent to the lumen that could be discriminated from surrounding pericardial tissue, epicardial fat, or lumen, and identified in >2 planes (12,14). Plaque volume (PV) (mm^3) and vessel volume (mm^3) measurements were obtained for all coronary lesions (15). Percent atheroma volume (PAV) was defined as [(PV/vessel volume) × 100] (%) (15). To determine progression and/or regression of the lesion, annual change in PAV (△ PAV/year, %/year) was defined as follows: (△ PAV)/(interval between coronary CTA examinations). Atherosclerotic PAV was subclassified by composition, using pre-defined intensity cutoff values in Hounsfield units (HU) that have been validated relative to intravascular ultrasonography studies, into noncalcified plaque (−30 to 350 HU); encompassing low-attenuation plaque (−30 to 30 HU); fibro-fatty plaque (30 to 130 HU); fibrous PAV (131 to 350 HU); and calcified PAV (≥351 HU) (16,17). The interobserver and intraobserver intraclass correlation for total PV was 0.992 and 0.996 ($p < 0.001$), respectively, and ranged between 0.95 and 0.99 for PV by composition (Online Table 1, Online Figures 2 and 3).

Additionally, measurements for each lesion included length, volume, and plaque composition, as

FIGURE 1 CONSORT Diagram



Among 2,252 patients who had undergone coronary CTA examinations, those with noninterpretable coronary CTA scans on 0.5-mm analysis, those with a history of coronary artery disease, those who stopped taking statins before follow-up coronary CTA, and those without information about statin use were excluded. Finally, 1,255 patients were eligible for the current analysis. CAD = coronary artery disease; CTA = computed tomography angiography.

TABLE 1 Baseline Clinical Characteristics and Lipid Profiles

	Total (N = 1,255)	Statin-Naive Patients (n = 474)	Statin-Taking Patients (n = 781)	p Value Between Groups
Age, yrs	60.4 ± 9.2	59.2 ± 9.6	61.1 ± 8.8	<0.001
Men	712 (56.7)	260 (54.9)	452 (57.9)	0.295
Coronary CTA interscan interval, yrs	3.8 ± 1.6	3.7 ± 1.6	3.9 ± 1.6	0.016
Body mass index, kg/m^2	25.2 ± 3.2	25.3 ± 3.4	25.1 ± 3.2	0.334
Systolic blood pressure, mm Hg	130 ± 18	128 ± 17	131 ± 18	0.005
Diastolic blood pressure, mm Hg	78 ± 11	77 ± 11	79 ± 11	0.663
Hypertension	654 (52.2)	217 (45.8)	437 (56.2)	<0.001
Diabetes mellitus	261 (20.8)	70 (14.8)	191 (24.5)	<0.001
Family history of CAD	337 (26.9)	117 (24.7)	220 (28.2)	0.177
Smoking history	467 (37.3)	178 (37.7)	289 (37.1)	0.828
Antiplatelets	507 (40.4)	125 (26.4)	382 (48.9)	<0.001
Beta-blockers	349 (27.9)	102 (21.6)	247 (31.7)	<0.001
Framingham risk score				
Low (<10%)	682 (54.6)	287 (60.8)	395 (50.8)	0.002
Intermediate (10% to 20%)	419 (33.4)	145 (30.6)	274 (35.1)	
High (>20%)	149 (11.9)	40 (8.5)	109 (14.0)	
Baseline lipid profile				
Total cholesterol, mg/dl	188 (162 to 215)	186 (165 to 210)	190 (161 to 222)	0.040
Low density lipoprotein, mg/dl	115 (91 to 138)	114 (95 to 132)	116 (88 to 142)	0.321
High density lipoprotein, mg/dl	49 (41 to 58)	49 (41 to 60)	49 (41 to 58)	0.532
Triglycerides, mg/dl	124 (89 to 179)	114 (83 to 176)	130 (92 to 183)	0.008
Change in lipid profile between index and follow-up coronary CTA				
Total cholesterol, mg/dl	−12 (−45 to 12)	1 (−16 to 19)	−27 (−60 to 2)	<0.001
Low-density lipoprotein, mg/dl	−8 (−40 to 7)	0 (−15.4 to 13)	−21 (−55.8 to 1.4)	<0.001
High-density lipoprotein, mg/dl	0 (−6 to 4)	0 (−6 to 4)	0 (−5 to 4)	0.646
Triglycerides, mg/dl	−4 (−44 to 17)	0 (−35 to 22)	−9 (−50 to 13)	0.001

Values are mean ± SD, n (%), or median (interquartile range).
CAD = coronary artery disease; CTA = computed tomography angiography.

well as percent diameter stenosis (%DS). A cutpoint of ≥50%DS was used for obstructive CAD (18).

We evaluated atherosclerotic plaque features previously which have been reported as being associated with incident major adverse cardiac events and coronary ischemia and which have been termed high-risk plaque(s) (HRP) (14,19). HRP were defined as coronary lesions with ≥2 of the following features: positive arterial remodeling, low-attenuation plaque, or spotty calcification (19). Low-attenuation plaque, previously correlated with low attenuation, was defined as any plaque containing ≥1 voxels with HU ≤30 (14,20). Spotty calcification was defined as presence of calcification <3 mm in any direction within a plaque (19,21).

For longitudinal comparisons of coronary CTAs, coronary segments and lesions were co-registered between the coronary CTA-1 and coronary CTA-2 evaluations by using fiduciary landmarks including the distance from the ostium and the branch vessels (Online Figures 4 and 5).

STUDY ENDPOINTS. The primary study objective was to compare the annualized within-lesion change in PAV between coronary CTA-1 and coronary CTA-2 by statin exposure. Secondary endpoints included annualized changes in PAV by plaque composition and development of HRP and its constituent features, increased percent diameter of stenosis, and development of obstructive lesion.

STATISTICAL ANALYSIS. Continuous variables are expressed as mean ± SD, whereas categorical variables are presented as absolute counts and percentages. Differences between categorical variables were analyzed using the chi-square or Fisher exact test, as appropriate, and those between continuous variables using Student's *t*-test. Changes between coronary CTA-1 and coronary CTA-2 were assessed using paired *t*-tests.

To account for the effect of common factors in clustered lesions within a single patient, marginal Cox models for multivariate failure times were used to determine the association between statin use and progression of coronary atherosclerosis and reported in terms of hazard ratios (HRs) and 95% confidence intervals (CI) (22). Multivariate adjustment was performed for known CAD risk factors, for

TABLE 2 Coronary Computed Tomography Angiography Findings at Baseline and Follow-Up Stratified According to Statin Therapy Status

	Total (N = 3,575)		p Value Between Baseline vs. Follow-Up	Lesions in Statin-Naive Patients (n = 1,079)		p Value Between Baseline vs. Follow-Up	Lesions in Statin-Taking Patients (n = 2,496)		p Value Between Baseline vs. Follow-Up	p Value Between Groups	
	Baseline	Follow-Up		Baseline	Follow-Up		Baseline	Follow-Up		Baseline	Follow-Up
Lesion length, mm	22.0 ± 14.5	22.2 ± 14.2	<0.001	19.9 ± 11.7	20.7 ± 12.0	<0.001	22.8 ± 15.4	22.9 ± 15.0	<0.001	<0.001	<0.001
Stenosis severity											
Diameter stenosis ≥50%	52 (1.6)	99 (2.8)	<0.001	12 (1.1)	23 (2.1)	0.028	40 (1.6)	76 (3.0)	<0.001	0.261	0.127
Stenosis severity, %	13.6 ± 13.6	19.5 ± 13.0	<0.001	11.6 ± 12.7	18.2 ± 12.4	<0.001	14.4 ± 13.8	20.1 ± 13.2	<0.001	<0.001	<0.001
Annualized change in %DS, % per yr		1.6 ± 3.8			1.9 ± 3.8			1.5 ± 3.8		0.009	
High-risk plaque characteristics*											
High-risk plaque	450 (12.6)	598 (16.7)	<0.001	108 (10.0)	170 (15.8)	<0.001	342 (13.7)	428 (17.2)	<0.001	0.002	0.306
Positive arterial remodeling	1,912 (53.5)	2,700 (75.5)	<0.001	514 (47.6)	799 (74.1)	<0.001	1,398 (56.0)	1,901 (76.2)	<0.001	<0.001	0.178
Law-attenuation plaque	303 (8.5)	344 (9.6)	0.008	91 (8.4)	111 (10.3)	0.027	212 (8.5)	233 (9.3)	0.096	0.953	0.375
Spotty calcification	327 (9.2)	445 (12.5)	<0.001	73 (6.8)	113 (10.5)	<0.001	254 (10.2)	332 (13.3)	<0.0001	0.001	0.019
PAV at baseline, %											
Total PAV		13.3 ± 12.6			10.9 ± 11.2			14.4 ± 13.1		<0.001	
Calcified PAV		4.6 ± 7.0			3.2 ± 5.6			5.2 ± 7.4		<0.001	
Noncalcified PAV†		8.7 ± 9.9			7.6 ± 9.4			9.1 ± 10.0		<0.001	
Fibrous PAV		6.1 ± 6.2			5.2 ± 5.6			6.5 ± 6.4		<0.001	
Fibro-fatty PAV		2.3 ± 4.7			2.2 ± 4.5			2.4 ± 4.8		0.303	
Low-attenuation PAV		0.3 ± 1.1			0.3 ± 1.0			0.3 ± 1.2		0.458	
Annualized change in PAV, % per yr											
Total PAV		1.85 ± 2.39			2.04 ± 2.37			1.76 ± 2.40		0.002	
Calcified PAV		1.18 ± 1.47			0.98 ± 1.27			1.27 ± 1.54		<0.001	
Noncalcified PAV†		0.66 ± 2.42			1.06 ± 2.42			0.49 ± 2.39		<0.001	
Fibrous PAV		0.64 ± 1.81			0.89 ± 1.78			0.53 ± 1.81		<0.001	
Fibro-fatty PAV		0.03 ± 1.22			0.16 ± 1.28			−0.03 ± 1.18		<0.001	
Low-attenuation PAV		0.00 ± 0.34			0.01 ± 0.34			0.00 ± 0.34		0.202	

Values are mean ± SD or n (%), unless otherwise specified. *High-risk plaque is defined as a lesion with ≥2 features indicative of positive arterial remodeling, low-attenuation plaque, or spotty calcification. †Noncalcified PAV is the summation of fibrous, fibro-fatty, and low-attenuation PAV.

%DS = percentage of diameter stenosis; PAV = percent atheroma volume.

example, age, sex, hypertension, diabetes mellitus, family history of CAD, history of smoking, and blood pressure (23). The analysis also accounted for total PAV and low-density lipoprotein level at baseline, use of antiplatelet therapy and beta-blocker, and location of each lesion within the 3 major coronary vessels (left anterior descending, left circumflex, and right coronary artery).

To investigate whether the results of marginal Cox models would remain consistent if the differences in baseline characteristics between the statin-naive and statin-taking group was compensated, marginal Cox models were repeated after patients were matched in 1:1 manner using propensity score method (Online Methods Part V).

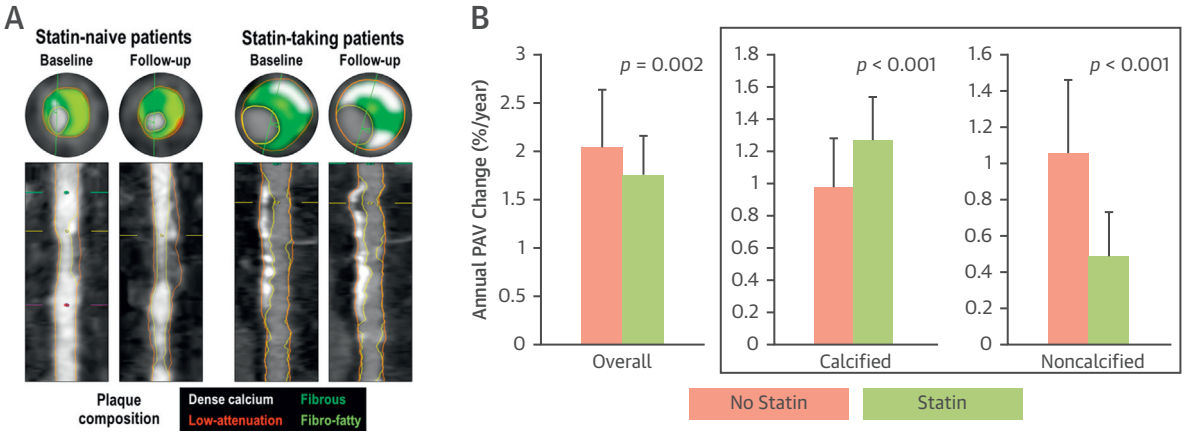
A two-tailed p value <0.05 was considered statistically significant. All analyses were performed using SAS version 9.4 software (SAS Institute Inc., Cary, North Carolina) and R version 3.3.0 software (R Development Core Team, Vienna, Austria).

RESULTS

STUDY POPULATION AND BASELINE CHARACTERISTICS. The study population consisted of 1,255 patients (60 ± 9 years of age; 56.7% men) (Table 1). At coronary CTA-1, patients presented mainly for 1 or more cardiac symptoms (97%), and the major reason for undergoing coronary CTA-2 was persistent or worsening cardiac symptoms (64%) (Online Table 2). The interscan interval between coronary CTAs was 3.8 ± 1.6 years (median 3.4 years; interquartile range: 2.6 to 4.8 years). Both the tube voltage and the tube current decreased at coronary CTA-2 compared with those at coronary CTA-1 (Online Table 2).

Between coronary CTA-1 and coronary CTA-2, 102 patients (8.1%) experienced revascularization (11 surgical and 92 percutaneous coronary interventions); 6 statin-naive patients and 96 statin-taking patients (p < 0.001).

FIGURE 2 Temporal Changes in Composition of Noncalcified Plaque Volumes According to Statin



(A) Representative coronary computed tomography angiography images of lesions at baseline and follow-up. **(B)** Annualized change in percent atheroma volume (PAV) and PAV by composition according to statin. Annualized change in PAV per lesion was lower in statin-taking patients **(green bars)** than in statin-naive patients **(pink bars)**, driven from slower progression of noncalcified PAV. Noncalcified PAV is the summation of fibrous, fibro-fatty, and low-attenuation PAV.

Most statin-taking patients (94%) were taking moderate to high-intensity statins, which consisted of atorvastatin or rosuvastatin (24). At coronary CTA-1, statin-taking patients were older and had higher prevalence of hypertension and diabetes mellitus than statin-naive patients ($p < 0.05$ for all), with higher total cholesterol and similar low-density and high-density lipoprotein levels. At coronary CTA-2, total cholesterol and low-density lipoprotein levels were lower in statin-taking patients with no differences in high-density lipoprotein levels.

TABLE 3 Effects of Statins on Atherosclerosis

	Hazard Ratio of Statin	95% Confidence Interval	p Value
Newly developed diameter stenosis ≥50%	0.660	0.345-1.335	0.225
Annualized progression of atherosclerosis (% per yr) to above median			
Total PAV	0.796	0.687-0.925	0.003
Calcified PAV	0.940	0.822-1.076	0.365
Noncalcified PAV*	0.703	0.605-0.82	<0.001
Fibrous PAV	0.701	0.603-0.817	<0.001
Fibro-fatty PAV	0.745	0.633-0.879	<0.001
Low-attenuation PAV	0.644	0.522-0.798	<0.001
Newly developed adverse atherosclerotic features			
High-risk plaque†	0.670	0.473-0.96	0.026
Positive arterial remodeling	0.764	0.596-0.983	0.034
Low-attenuation plaque	0.718	0.413-1.291	0.252
Spotty calcification	0.849	0.561-1.314	0.451

*Noncalcified PAV is the summation of fibrous, fibro-fatty, and low-attenuation PAV. †High-risk plaque is defined as a lesion with ≥2 features indicative of positive arterial remodeling, low-attenuation plaque, or spotty calcification.

PAV = percent atheroma volume.

CHANGES IN STENOSIS SEVERITY ACCORDING TO STATIN USE. Overall, 3,575 coronary lesions (2.9 lesions per patient) were analyzed, with 2,496 lesions in statin-taking patients (3.2 lesions per patient) and 1,079 lesions in statin-naive patients (2.3 lesions per patient) (**Table 2,** Online Table 3). The average stenosis severity per lesion was low (13.6 ± 13.6%), with only 52 lesions (1.6%) showing diameter stenosis ≥50% at baseline. Over time, statin therapy slowed the increase in %DS (1.5 ± 3.8% per year vs. 1.9 ± 3.8% per year, respectively; $p = 0.009$), although not enough to observe an impact in the binary progression of nonobstructive coronary lesion to ≥50% DS (1.0% vs. 1.4%, respectively; $p > 0.05$).

CHANGES IN PV AND PLAQUE COMPOSITION ACCORDING TO STATIN USE. Compared with statin-taking patients, statin-naive patients exhibited higher PAV per lesion at coronary CTA-1 (14.4 ± 13.1 mm^3 vs. 10.9 ± 11.2 mm^3, respectively; $p < 0.001$) and calcified and noncalcified PAV (5.2 ± 7.4 mm^3 vs. 3.2 ± 5.6 mm^3 and 9.1 ± 10.0 mm^3 vs. 7.6 ± 9.4 mm^3, respectively; both $p < 0.05$).

Over time, the atherosclerotic lesion composition changes in statin-taking patients differed from those in statin-naive patients. Annualized progression of coronary lesion PAV was slower in statin-taking patients than in statin-naive patients (1.76 ± 2.40 mm^3

per year vs. 2.04 ± 2.37 mm^3 per year, respectively; p = 0.002) (Figure 2). Furthermore, lesions in statin-taking patients experienced higher annualized progression of calcified PAV (1.27 ± 1.54 mm^3 per year vs. 0.98 ± 1.27 mm^3 per year, respectively; p < 0.001) but slower progression of noncalcified PAV than lesions in statin-naive patients (0.49 ± 2.39 mm^3 per year vs. 1.06 ± 2.42 mm^3 per year, respectively; p < 0.001).

Within noncalcified PAV, the progression rates of fibrous and fibro-fatty PAVs were slower in statin-taking patients than in statin-naive patients (0.53 ± 1.81 mm^3 per year vs. 0.89 ± 1.78 mm^3 per year and −0.03 ± 1.18 mm^3 per year vs. 0.16 ± 1.28 mm^3 per year, respectively; both p < 0.001), with no significant differences for low-attenuation PAV (p = 0.202) (Figure 2).

CHANGES IN HIGH-RISK PLAQUE FEATURES ACCORDING TO STATIN USE. At coronary CTA-1, statin-taking patients exhibited a higher prevalence of HRP, positive remodeling, and spotty calcification (13.7% vs. 10.0%; 56.0% vs. 47.6%; and 10.2% vs. 6.8%, respectively; all p < 0.05), with no differences in low-attenuation plaque (8.5% vs. 8.4%, respectively; p = 0.95). The annualized incidence of HRP, positive remodeling, spotty calcification, and low-attenuation plaques were lower in statin-taking patients (0.9% per year vs. 1.6% per year; 5.2% per year vs. 7.2% per year; 0.2% per year vs. 0.5% per year; and 0.8% per year vs. 1.0% per year, respectively; p < 0.001 for all).

IMPACT OF STATINS ON PROGRESSION OF CORONARY ATHEROSCLEROSIS. Multivariate Cox proportional hazards model adjusted for baseline PAV, low-density lipoprotein level at baseline, lesion location, use of antiplatelets and beta-blockers, and clinical risk factors for CAD indicated that statins exerted no effect on the rate of progression to ≥50%DS at the time of coronary CTA-2 (p = 0.225) (Table 3). Statins reduced the risk of annualized total PAV increase above the median of the study population (HR: 0.796; 95% CI: 0.687 to 0.925; p = 0.003).

Upon stratification by plaque composition, statins also reduced the risk of annualized increase in noncalcified PV above the median (HR: 0.703; 95% CI: 0.605 to 0.820; p < 0.001), which held true for each of the 3 noncalcified components (fibrous PAV HR: 0.701; 95% CI: 0.603 to 0.817; fibro-fatty PAV HR: 0.745; 95% CI: 0.633 to 0.879; and low-attenuation PV HR: 0.644; 95% CI: 0.522 to 0.798; all p < 0.001) but not for calcified PV (p = 0.365).

Statin therapy was associated with lower rates of formation of lesions possessing positive arterial remodeling at the time of coronary CTA-2 (HR: 0.764; 95% CI: 0.596 to 0.983; p = 0.034), which was associated with a reduced risk of new high-risk plaque lesions (HR: 0.670; 95% CI: 0.473 to 0.960; p = 0.026). No effect of statins was observed regarding the development of low-attenuation plaque or spotty calcification (all p > 0.05).

These findings remained consistent when the statin-naive and statin-taking patients were matched using propensity scores (Online Tables 4, 5, and 6). Statins continued to be associated with the reduced risk of annualized total and noncalcified PAV increase above the median and also reduced the risk of developing HRP and positive arterial remodeling.

DISCUSSION

In the analysis of this large, prospective observational cohort evaluating temporal changes in plaque characteristics by using quantitative assessment, statin therapy was associated with slower rates of progression of overall coronary atherosclerosis volumes with differential effects on different plaque types. Statins were also associated with the increase of calcified plaque components and reduced progression of noncalcified portions of atherosclerotic lesions. Moreover, although statins did not have a protective effect against the development of high-grade coronary stenoses, they successfully reduced the risk of positive remodeling and HRPs. Furthermore, we can generalize observations of the pro-calcific effects of statins, independent of their reduction in plaque progression, to a multiethnic, multinational, low-risk cohort outside of a clinical trial setting. Our study provides a context and data that have not been available previously for interpretation of serial coronary CTA and that provide insight into the natural history of both vulnerable and calcific plaque. Importantly, coronary CTA was able to effectively measure the impact of statin use on decreased progression of subclinical atherosclerosis.

Corresponding with early serial angiographic statin trials, we demonstrated slower coronary artery luminal narrowing, without affecting the binary development of obstructive CAD (25,26). In line with both prior landmark studies of serial invasive imaging (7,27) and more recent small coronary CTA studies (8,9), we demonstrated that statins slow the progression of coronary atherosclerosis in whole-heart evaluations by coronary CTA, beyond the proximal arterial segments interrogated by intravascular ultrasonography. These prior studies preferentially used either invasive modalities focusing on a single culprit plaque or noninvasive modalities assessing the change in atherosclerosis on a per-patient level (4,9).

However, neither approach can fully evaluate the impact of statin therapy on coronary atherosclerotic lesions, as evaluating only a single plaque will neglect the interactions between coexisting plaques, and per-patient analysis will aggregate the findings of individual plaques (28). Moreover, previous invasive studies have enrolled mainly patients undergoing clinically indicated invasive coronary angiography, meaning patients not indicated for invasive assessment, most of whom were at an earlier stage of CAD and possibly exhibited a different pattern of disease progression, and who accounted for much a greater portion of the population, were omitted. Therefore, the strengths of the current study include not only the large sample size and long follow-up duration but also the methodology of examining lesion-specific changes over time in a population with relatively lower risk, by quantitatively analyzing the entire coronary tree, using a noninvasive imaging modality.

Coronary artery calcium scoring is a robust tool for prognostication of future adverse cardiovascular events (29); and elevated coronary artery calcium score progression portends worse prognosis (5). However, a randomized controlled trial of statin therapy demonstrated no impact on slowing the progression of coronary artery calcium score (30-32). Given the present findings, it remains unknown whether an increasing calcium score in a patient who is being treated with statins represents a malignant or benign process, and uncertainty exists as to the utility of serial coronary calcium scoring for monitoring therapeutic efficacy in patients being treated with statins (5,28).

Taken together, our results suggest that interpretation of calcium progression should be stratified by statin treatment, as increasing coronary calcification in statin-taking patients may represent stabilization of atherosclerotic lesions. Even furthermore, inducing calcification of plaques may be one of the mechanisms by which statins exert a positive effect in reducing the risk of major adverse cardiovascular events. This hypothesis, although attractive, remains to be proven; and future large-scale trials evaluating atherosclerosis treatment by targeting specific atherosclerotic characteristics based upon plaque composition and other high-risk plaque features now seem warranted.

Our results complement those of the ICONIC (Incident COroNary Syndromes Identified by Computed Tomography) trial, a nested case control study of atherosclerotic plaque precursors to acute coronary syndrome. In the ICONIC study, we observed that lesion characteristics and plaque burden by composition had predictive value for acute coronary syndrome, independent of clinical risk factors and total plaque burden. There was a continuum of risk of acute coronary syndromes by plaque composition, with greater weight for lower attenuation plaque burden. In the PARADIGM study, we observed that plaque composition and characteristics can be decoupled from plaque burden due to treatment effects. Increased calcification with statins, coherent with its known impact on reducing clinical events, support the concept of increased HU attenuation as evidence of plaque stabilization. Together, the results of these 2 studies demonstrate the applicability and insight of noninvasive plaque evaluation in the ranges of high and low risk.

STUDY LIMITATIONS. First, our results did not attempt to distinguish between the impact of high- and low-intensity statins, and we cannot exclude confounding by indication or unmeasured and time-varying confounders. Among the statin-taking group, 303 patients began statin therapy during the interval (38.8%). However, the coherence of our study with findings in a large, pooled, high-risk intravascular ultrasonography cohort randomized to statins supports the validity of our finding. Second, although the HU thresholds for plaque composition were validated by using virtual histology-intravascular ultrasonography, the HU thresholds of low-attenuation and fibrous plaque demonstrate significant overlap relative to histopathology, and the spatial resolution of coronary CTA may result in partial volume effects within a pixel (17). Thus, the categories of plaque composition described should not be taken as discrete histopathological entities but rather as gradations of risk in plaques. Third, because of the observational design of the study, patients were not randomized, and there is a major difference in baseline characteristics between groups. However, the main findings of this study remained consistent even after propensity score matching. Additionally, because only patients who had 2 coronary CTA scans were eligible, patients had a relatively low prevalence of obstructive CAD and event rate. Patients who progress more rapidly and, hence, who more likely to experience clinical events may not attend for a second coronary CTA. Thus, selection bias is inevitable, and the generalizability of our results to high-risk populations is not known, and our study was not powered to estimate the coronary event risk of plaque progression. To overcome these limitations, prediction models will require large, ideally,

population-based prospective cohorts of serial coronary CTA or randomized study that may be economically feasible only with completely automated coronary CTA measurements. However, as there are no current professional society recommendations endorsing the routine use of serial coronary CTA for evaluation of CAD (18), an observational registry such as the present study provides a unique opportunity to assess the natural history of CAD.

CONCLUSIONS

Our findings suggest that, over a longer term and among lower-risk patients undergoing serial coronary CTA, statins are associated with slower progression of overall coronary atherosclerosis volume, with increased plaque calcification and reduction of high-risk plaque features.

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ADDRESS FOR CORRESPONDENCE: Dr. Hyuk-Jae Chang, Division of Cardiology, Severance Cardiovascular Hospital, Yonsei-Cedars-Sinai Integrative Cardiovascular Imaging Research Center, Yonsei University College of Medicine, Yonsei University Health System 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, South Korea. E-mail: hjchang@yuhs.ac.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Statins change the composition of intraplaque constituents by increasing calcification and reducing the noncalcified portion within plaques. Although statins do not have protective effect against the progression of coronary lesions to high-grade stenoses, statins reduce the risk of developing adverse plaque characteristics, including high-risk plaques and positive remodeling.

TRANSLATIONAL OUTLOOK: Prospective clinical trials targeting specific coronary atherosclerotic phenotypes based upon high-risk plaque features and plaque constituents are necessary to delineate the impact of statin-induced plaque calcification on clinical outcomes.

REFERENCES

1. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383–9.

2. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359:2195–207.

3. Sacks FM, Pfeffer MA, Moye LA, et al., Cholesterol and Recurrent Events Trial investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. N Engl J Med 1996;335:1001–9.

4. Puri R, Nicholls SJ, Shao M, et al. Impact of statins on serial coronary calcification during atheroma progression and regression. J Am Coll Cardiol 2015;65:1273–82.

5. Shaw LJ, Narula J, Chandrashekhar Y. The never-ending story on coronary calcium: is it predictive, punitive, or protective? J Am Coll Cardiol 2015;65:1283.

6. Hattori K, Ozaki Y, Ismail TF, et al. Impact of statin therapy on plaque characteristics as assessed by serial OCT, grayscale and integrated backscatter-IVUS. J Am Coll Cardiol Img 2012;5:169–77.

7. Nissen SE, Nicholls SJ, Sipahi I, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. JAMA 2006;295:1556–65.

8. Inoue K, Motoyama S, Sarai M, et al. Serial coronary CT angiography-verified changes in plaque characteristics as an end point: evaluation of effect of statin intervention. J Am Coll Cardiol Img 2010;3:691–8.

9. Zeb I, Li D, Nasir K, et al. Effect of statin treatment on coronary plaque progression—a serial coronary CT angiography study. Atherosclerosis 2013;231:198–204.

10. Lee SE, Chang HJ, Rizvi A, et al. Rationale and design of the Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography IMaging (PARADIGM) registry: a comprehensive exploration of plaque progression and its impact on clinical outcomes from a multicenter serial coronary computed tomographic angiography study. Am Heart J 2016;182:72–9.

11. Abbara S, Blanke P, Maroules CD, et al. SCCT guidelines for the performance and acquisition of coronary computed tomographic angiography: a report of the society of Cardiovascular Computed Tomography Guidelines Committee: endorsed by the North American Society for Cardiovascular Imaging (NASCI). J Cardiovasc Comput Tomogr 2016;10:435–49.

12. Leipsic J, Abbara S, Achenbach S, et al. SCCT guidelines for the interpretation and reporting of coronary CT angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. J Cardiovasc Comput Tomogr 2014;8:342–58.

13. Park HB, Lee BK, Shin S, et al. Clinical feasibility of 3D automated coronary atherosclerotic plaque quantification algorithm on coronary computed tomography angiography: comparison with intravascular ultrasound. Eur Radiol 2015;25:3073–83.

14. Motoyama S, Ito H, Sarai M, et al. Plaque characterization by coronary computed tomography angiography and the likelihood of acute coronary events in mid-term follow-up. J Am Coll Cardiol 2015;66:337–46.

15. Papadopoulou SL, Neefjes LA, Garcia-Garcia HM, et al. Natural history of coronary atherosclerosis by multislice computed tomography. J Am Coll Cardiol Img 2012;5:S28–37.

16. de Graaf MA, Broersen A, Kitslaar PH, et al. Automatic quantification and characterization of coronary atherosclerosis with computed tomography coronary angiography: cross-correlation with intravascular ultrasound virtual histology. Int J Cardiovasc Imaging 2013;29:1177–90.

17. Pundziute G, Schuijf JD, Jukema JW, et al. Evaluation of plaque characteristics in acute coronary syndromes: non-invasive assessment with multi-slice computed tomography and invasive evaluation with intravascular ultrasound radiofrequency data analysis. Eur Heart J 2008;29:2373–81.

18. Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable

coronary artery disease: the Task Force on the Management of Stable Coronary Artery Disease of the European Society of Cardiology. Eur Heart J 2013;34:2949-3003.

19. Puchner SB, Liu T, Mayrhofer T, et al. High-risk plaque detected on coronary CT angiography predicts acute coronary syndromes independent of significant stenosis in acute chest pain: results from the ROMICAT-II trial. J Am Coll Cardiol 2014; 64:684-92.

20. Achenbach S, Moselewski F, Ropers D, et al. Detection of calcified and noncalcified coronary atherosclerotic plaque by contrast-enhanced, submillimeter multidetector spiral computed tomography a segment-based comparison with intravascular ultrasound. Circulation 2004;109: 14-7.

21. Motoyama S, Kondo T, Sarai M, et al. Multislice computed tomographic characteristics of coronary lesions in acute coronary syndromes. J Am Coll Cardiol 2007;50:319-26.

22. Hernan MA, Brumback B, Robins JM. Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. Epidemiology 2000;11:561-70.

23. Min JK, Dunning A, Gransar H, et al. Medical history for prognostic risk assessment and diagnosis of stable patients with suspected coronary artery disease. Am J Med 2015;128: 871-8.

24. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129:S1-45.

25. MAAS Investigators. Effect of simvastatin on coronary atheroma: the Multicentre Anti-Atheroma Study (MAAS). Lancet 1994;344: 633-8.

26. Investigators PCABGT. The effect of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation on obstructive changes in saphenous-vein coronary-artery bypass grafts. N Engl J Med 1997;1997: 153-63.

27. Nicholls SJ, Ballantyne CM, Barter PJ, et al. Effect of two intensive statin regimens on progression of coronary disease. N Engl J Med 2011; 365:2078-87.

28. Maehara A, Stone GW. High-risk coronary atherosclerosis: is it the plaque burden, the calcium, the lipid, or something else? Circ Cardiovasc Imaging 2017;10:e007116.

29. Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med 2008;358:1336-45.

30. Callister TQ, Raggi P, Cooil B, Lippolis NJ, Russo DJ. Effect of HMG-CoA reductase inhibitors on coronary artery disease as assessed by electron-beam computed tomography. N Engl J Med 1998;339:1972-8.

31. Raggi P, Callister TQ, Shaw LJ. Progression of coronary artery calcium and risk of first myocardial infarction in patients receiving cholesterol-lowering therapy. Arterioscler Thromb Vasc Biol 2004;24:1272-7.

32. Raggi P, Davidson M, Callister TQ, et al. Aggressive versus moderate lipid-lowering therapy in hypercholesterolemic postmenopausal women: Beyond Endorsed Lipid Lowering with EBT Scanning (BELLES). Circulation 2005;112:563-71.

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APPENDIX For an expanded Methods section and supplemental figures and tables, please see the online version of this paper.