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ORIGINAL RESEARCH

Clinical and Coronary Plaque Predictors of Atherosclerotic Nonresponse to Statin Therapy

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ABSTRACT

BACKGROUND Statins reduce the incidence of major cardiovascular events, but residual risk remains. The study examined the determinants of atherosclerotic statin nonresponse.

OBJECTIVES This study aimed to investigate factors associated with statin nonresponse-defined atherosclerosis progression in patients treated with statins.

METHODS The multicenter PARADIGM (Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography Imaging) registry included patients who underwent serial coronary computed tomography angiography ≥2 years apart, with whole-heart coronary tree quantification of vessel, lumen, and plaque, and matching of baseline and follow-up coronary segments and lesions. Patients with statin use at baseline and follow-up coronary computed tomography angiography were included. Atherosclerotic statin nonresponse was defined as an absolute increase in percent atheroma volume (PAV) of 1.0% or more per year. Furthermore, a secondary endpoint was defined by the additional requirement of progression of low-attenuation plaque or fibro-fatty plaque.

RESULTS The authors included 649 patients (age 62.0 ± 9.0 years, 63.5% male) on statin therapy and 205 (31.5%) experienced atherosclerotic statin nonresponse. Age, diabetes, hypertension, and all atherosclerotic plaque features measured at baseline scan (high-risk plaque [HRP] features, calcified and noncalcified PAV, and lumen volume) were significantly different between patients with and without atherosclerotic statin nonresponse, whereas only diabetes, number of HRP features, and noncalcified and calcified PAV were independently associated with atherosclerotic statin nonresponse (odds ratio [OR]: 1.41 [95% CI: 0.95-2.11], OR: 1.15 [95% CI: 1.09-1.21], OR: 1.06 [95% CI: 1.02-1.10], OR: 1.07 [95% CI: 1.03-1.12], respectively). For the secondary endpoint (N = 125, 19.2%), only noncalcified PAV and number of HRP features were the independent determinants (OR: 1.08 [95% CI: 1.03-1.13] and OR: 1.21 [95% CI: 1.06-1.21], respectively).

CONCLUSIONS In patients treated with statins, baseline plaque characterization by plaque burden and HRP is associated with atherosclerotic statin nonresponse. Patients with the highest plaque burden including HRP were at highest risk for plaque progression, despite statin therapy. These patients may need additional therapies for further risk reduction. (J Am Coll Cardiol Img 2023;16:495-504) © 2023 the American College of Cardiology Foundation. Published by Elsevier. All rights reserved.

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ABBREVIATIONS AND ACRONYMS

CCTA = coronary computed tomography angiography

CRP = C-reactive protein

CT = computed tomography

HDL = high-density lipoprotein

HRP = high-risk plaque

LDL = low-density lipoprotein

MACE = major cardiovascular event(s)

PAV = percent atheroma volume

Statins have consistently been shown to reduce the incidence of future cardiovascular events, and higher intensity statins provoke more risk reduction than low-dose statins.[1] Favorable effects of statins include reduction in low-density lipoprotein (LDL) cholesterol, reduction in C-reactive protein (CRP), increase of high-density lipoprotein (HDL), and limitation of atherosclerosis progression.[2] However, residual cardiovascular risk remains despite statin therapy, especially in patients with a large burden of atherosclerosis, several risk factors, or persisting elevated CRP or LDL cholesterol.[3,4]

Atherosclerotic extent has been identified as a potent driver of major cardiovascular events (MACE), even in patients treated with statins.[5,6] Atherosclerosis represents a lifetime exposure to risk factors and is the direct substrate for the acute coronary syndrome. In 1,039 patients treated with high-intensity statins and undergoing baseline intravascular ultrasound imaging, baseline percent atheroma volume was the main predictor for MACE, despite the achievement of very low on-treatment LDL cholesterol levels.[5] In addition, progression of atherosclerosis has been associated with MACE and has been proposed as a surrogate marker for MACE in medication trials.[2]

Besides atherosclerotic extent, coronary computed tomography angiography (CCTA) allows quantification of the entire coronary tree to derive compositional plaque analysis, luminal measures, and high-risk markers, which have been associated with several clinical outcomes, independent from plaque burden.[7-9] The PARADIGM (Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography Imaging) registry aimed to understand the nature and rate of plaque progression and identify the factors determining it. The primary analysis demonstrated a slower total plaque progression associated with the use of statins during the study period. Subdividing according to compositional plaque type, progression of calcified plaque was larger with statins, whereas noncalcified plaque progression was slower.[10] Further subdividing into plaque composition showed an association of statins with a more rapid transformation of low-density noncalcified plaque toward high-density calcium.[11] Also, plaque progression associated with increases in calcium scores have been evaluated. This analysis shows that an increase in calcium score translates to an increase in calcified plaque, whereas calcium score progression in patients using statins equals increased progression of both calcified and noncalcified plaque.[12] Furthermore, the prognostic value of plaque progression has been demonstrated, independently from baseline plaque volume.[13,14] Specifically, the average absolute plaque progression of patients with events was 1.0% of percent atheroma volume (PAV). The current analysis differentiates by identifying patients that are likely to progress in plaque volume despite the use of statins. Given the association of plaque progression with events, these patients will represent a high-risk cohort.

We hypothesized that a comprehensive evaluation of atherosclerosis identifies patients whose atherosclerosis will progress despite the use of statin

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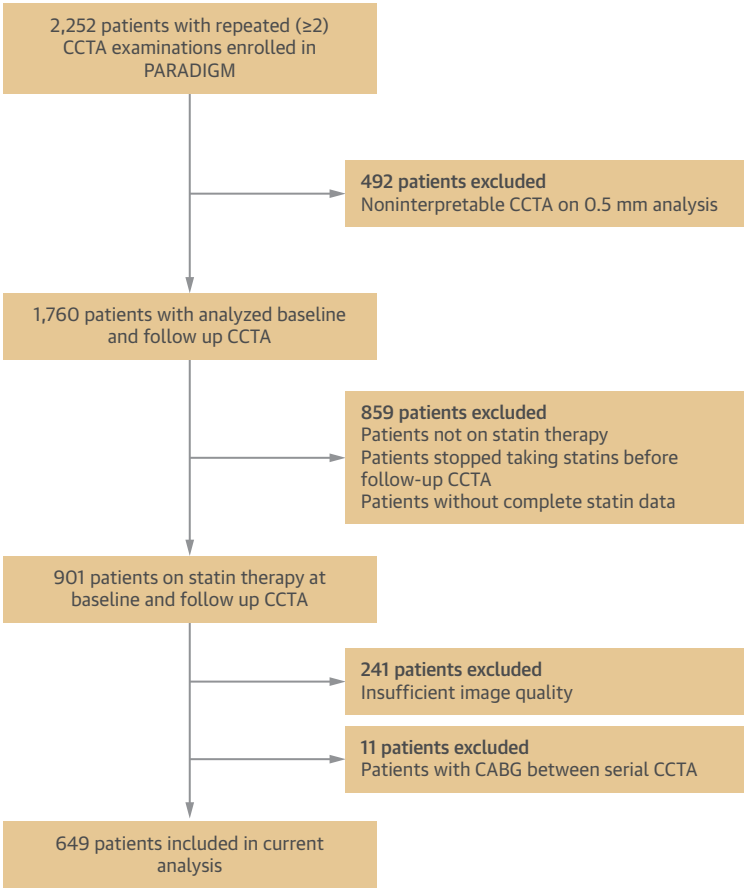
FIGURE 1 Flowchart of Study Population



CABG = coronary artery bypass graft; CCTA = coronary computed tomography angiography; PARADIGM = Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography Imaging.

therapy. The current study examined which factors, in patients treated with statins and undergoing serial CCTA, are associated with atherosclerotic statin nonresponse-defined atherosclerosis progression.

METHODS

PATIENTS. The PARADIGM registry study is a dynamic, multinational (13 sites, 7 countries) registry with prospective follow-up data for patients who underwent serial CCTA ≥2 years apart for clinical indications.[10,15] The institutional review board of all participating sites approved the study protocol. For the current analysis, patients who were on statin therapy at baseline and follow-up CCTA were selected (N = 901). Patients whose CCTA image quality was insufficient for slice-based quantitative plaque analysis (N = 241) and those who underwent coronary artery bypass graft between serial CCTA (N = 11) were

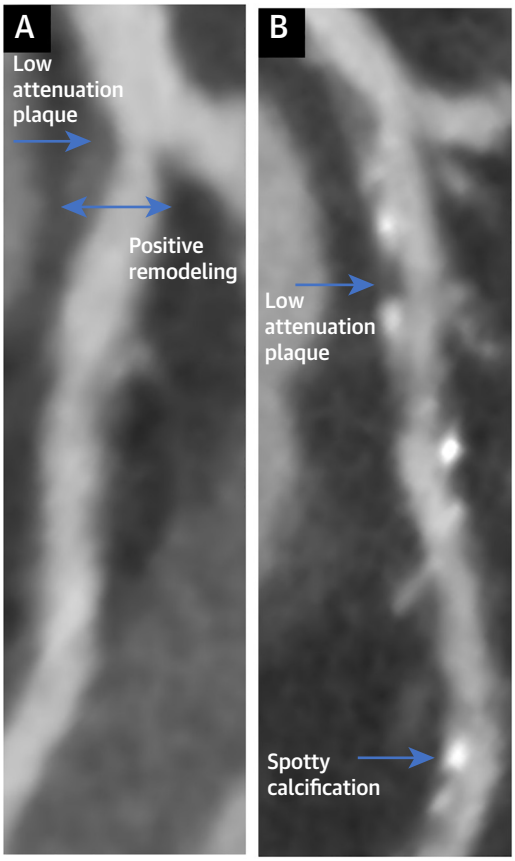
TABLE 1 Laboratory and CCTA Findings at Baseline and Follow-Up (N = 649)

	Baseline	Follow-Up	*P* Value
Laboratory results			
Total cholesterol, mg/dL	180.6 ± 44.6	160.8 ± 37.3	<0.001
LDL cholesterol, mg/dL	108.0 ± 40.5	88.7 ± 30.3	<0.001
HDL cholesterol, mg/dL	49.6 ± 13.0	49.1 ± 13.0	<0.001
Triglycerides, mg/dL	144 ± 78	125 ± 67	<0.001
HbA1c, %[a]	6.79 ± 1.39	6.70 ±1.15	0.835
CRP, mg/dL[b]	0.79 (0.28-2.14)	0.59 (0.18-1.20)	0.127
CCTA findings			
PAV, %	4.7 (1.3-10.8)	7.5 (2.7-15.2)	<0.001
Calcified, %	1.1 (0.1-3.7)	2.6 (0.58-7.2)	<0.001
Noncalcified, %	2.8 (0.71-6.3)	3.3 (1.0-7.4)	<0.001
No. of HRP, n	0.49 ± 0.82	0.55 ± 0.84	0.037
No. of HRP features, n	4.5 ± 3.8	5.0 ± 3.9	<0.001
Lumen volume, mm^3	1,750 ± 962	1,708 ± 952	<0.001

Values are mean ± SD or median (IQR). [a]N = 204. [b]N = 253.

CCTA = coronary computed tomography angiography; CRP = C-reactive protein; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; HRP = high-risk plaque; LDL = low-density lipoprotein; PAV = percent atheroma volume.

CENTRAL ILLUSTRATION Plaque on Baseline and Follow-Up



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Example of plaque on **(A)** baseline and **(B)** follow-up of the proximal left anterior descending artery in a patient with statin nonresponse. Example of plaque progression in a patient with coronary artery disease. **(A)** Curved multiplanar view of high-risk plaque features in the proximal left anterior descending artery. **(B)** Curved multiplanar view of the same left anterior descending artery with plaque progression.

excluded, leaving 649 patients in the current cohort (Figure 1). Patients were evaluated by their physician or nurse at time of baseline and follow-up CCTA and data regarding demographics, medication use, cardiovascular risk factors, and laboratory tests were collected. Standardized definitions for cardiovascular risk factors were used.

CCTA ANALYSIS. CCTA acquisition was performed in accordance with the Society of Cardiovascular Computed Tomography guidelines.[16] Baseline and follow-up DICOM files from each site were transferred to the core laboratory for blinded quantitative plaque analysis. Coronary atherosclerosis was evaluated on multiplanar and cross-sectional images and evaluations were performed by Level III readers, with systematic quality checks for intraobserver and interobserver concordance, as previously described.[10] Paired CCTA scans were analyzed by 2 independent readers blinded to clinical data. Semiautomated software (QAngioCT Research Edition v2.1.9.1, Medis Medical Imaging Systems) was used, with manual corrections where needed.

Segments from the entire coronary tree ≥2 mm in diameter were evaluated for coronary lumen, vessel wall, and plaque. Atherosclerosis was defined as tissue ≥1 mm^2 within the lumen that could be discriminated from the surrounding pericardial tissue, epicardial fat, or lumen, identified in >2 planes.[17] Baseline and follow-up coronary segments were matched based on fiduciary landmarks (eg, distance from ostium, branch vessels) to obtain a similar number of segments both computed tomography (CT) scans. Segmental data was summed to obtain per-patient level quantities. Similar to segments, coronary lesions were evaluated pairwise with the option to develop a new plaque at follow-up CCTA. Segments and lesions being revascularized between serial CCTA were censored for both scans. CCTA plaque was subdivided into calcified and noncalcified based on the threshold of 350 HU. Whole-heart atherosclerotic burden was defined as PAV, calculated as: plaque volume/vessel volume · 100%. Low-attenuation and fibro-fatty plaque together were defined by −30 to 130 HU. Coronary lesions were defined as high-risk plaque (HRP) in the presence of ≥2 of the following features: low-attenuation plaque, positive remodeling (remodeling index >1.1 compared with a proximal non-diseased coronary site), or spotty calcification.[18] Several coronary plaque features were calculated based on prior literature and representatives of coronary stenosis, extent, and composition.[7,10,19]

OUTCOMES. The primary outcome was the association of baseline clinical, laboratory, and CCTA findings with atherosclerotic statin nonresponse, defined as the absolute increase of 1.0 percentage points in PAV/y. Increase in PAV/y of 1.0% was selected based on its prognostic significance with MACE in prior CT and intravascular ultrasound literature.[20,21]

Statin use has been associated with low-attenuation and fibro-fatty plaque regression, and increased high-density calcium progression.[14] Therefore, a subanalysis was performed with an added requirement of increased low-attenuation and fibro-

fatty plaque at follow-up CT. Hence the secondary endpoint definition was defined as >1.0% increase in PAV/y in combination with progression of low-attenuation or fibro-fatty plaque (consisting of plaque with −30 to 130 HU).

STATISTICAL ANALYSIS. Continuous variables were presented as mean ± SD if normally distributed and median (25th-75th IQR) if non-normally distributed. Categorical data was presented as counts (%). Paired comparisons between baseline and follow-up data was performed with the paired Student's *t*-test or Wilcoxon signed-rank test. Unpaired data was compared with the independent Student's *t*-test or Mann-Whitney *U* test, or chi-square test as appropriate. Logistic regression was used to examine associations with atherosclerotic statin nonresponse and its independent determinants. Univariate analysis was performed including the following: baseline demographics, cardiovascular risk factors, baseline lipid profile, and baseline CCTA findings, such as PAV, number of HRP, number of HRP features, and lumen volume. Stepwise multivariate logistic regression was performed including the same variables as the univariate analysis. Notably, we chose to include calcified and noncalcified PAV in this multivariate analysis, rather than total PAV alone, because they provide independent value. Both univariate and multivariate analyses were reported in terms of odds ratios (ORs) with corresponding 95% CI. To measure correlation between baseline variables and increase in %PAV/y, scatter plots were made. All *P* values are 2-sided and significance was defined by <0.05.

RESULTS

PATIENTS. The study included 649 patients on statin therapy (age 62.0 ± 9.0 years, 63.5% male). During an interval of 3.6 ± 1.3 years, total and LDL cholesterol decreased, from 180 ± 45 mg/dL to 160 ± 37 mg/dL, $P < 0.001$, and from 108 ± 41 mg/dL to 89 ± 30 mg/dL, $P < 0.001$ (Table 1). Per-patient whole-heart PAV increased at follow-up (from 4.7%-7.5%, $P < 0.001$), similarly, all atherosclerotic features (number of HRPs and HRP features, calcified and noncalcified PAV) increased while the lumen volume decreased (Table 1).

DETERMINANTS OF ATHEROSCLEROTIC STATIN NONRESPONSE. In total, 205 (31.5%) patients were defined as atherosclerotic nonresponders (Central Illustration). Of the clinical variables, age, presence of diabetes, and hypertension were different in patients experiencing atherosclerotic nonresponse vs the remaining patients (Table 2). All baseline CCTA plaque variables were higher (except lumen volume) in the nonresponders. Follow-up laboratory results showed significantly lower values of total cholesterol, LDL, and HDL cholesterol in the atherosclerotic

TABLE 2 Baseline Characteristics and CCTA Findings at Baseline and Follow-Up Stratified According to Statin Response

	Atherosclerotic Statin Nonresponse+ (n = 205)	Atherosclerotic Statin Nonresponse− (n = 444)	*P* Value
Baseline demographics			
Age, y	63.8 ± 8.6	61.2 ± 9.1	0.001
Male	133 (64.9)	279 (62.8)	0.616
Body mass index, kg/m^2	25.6 ± 3.4	25.5 ± 3.2	0.626
Cardiovascular risk profile			
Diabetes	71 (34.6)	108 (24.4)	0.007
Hypertension	137 (66.8)	256 (57.9)	0.031
Current smoking	42 (20.5)	74 (16.7)	0.248
Family history for CAD	58 (28.3)	105 (23.6)	0.205
Prior revascularization	43 (21.0)	81 (18.2)	0.410
Interval revascularization	42 (20.5)	54 (12.2)	0.005
Medications			
Aspirin	146 (71.2)	270 (60.8)	0.010
Beta-blockers	83 (40.7)	192 (43.4)	0.511
ACE inhibitor and/or angiotensin II receptor blockers	105 (51.2)	156 (35.1)	0.001
Baseline laboratory results			
Total cholesterol, mg/dL	176.1 ± 43.4	182.8 ± 44.9	0.087
LDL cholesterol, mg/dL	106.4 ± 38.0	108.8 ± 41.8	0.508
HDL cholesterol, mg/dL	47.5 ± 11.9	50.7 ± 13.4	0.004
Triglycerides, mg/dL	140 ± 72	146 ± 81	0.403
HbA1c, %[a]	7.0 ± 1.3	6.6 ± 1.4	0.048
CRP, mg/dL[b]	0.80 (0.32-2.20)	0.75 (0.15-1.98)	0.145
Follow-up laboratory results			
Total cholesterol, mg/dL	153 ± 37	164 ± 37	0.002
LDL cholesterol, mg/dL	83 ± 29	91 ± 31	0.003
HDL cholesterol, mg/dL	47 ± 12	50 ± 13	0.025
Triglycerides, mg/dL	120 ± 57	128 ± 71	0.204
HbA1c, %[a]	6.9 ± 1.1	6.6 ± 1.1	0.155
CRP, mg/dL[b]	0.57 (0.3-1.0)	0.6 (0.07-1.3)	0.788
Baseline CCTA findings			
PAV, %	9.9 (5.2-16.7)	2.8 (0.61-7.4)	<0.001
Calcified	3.4 (1.1-7.6)	0.50 (0.00-2.3)	<0.001
Noncalcified	5.8 (2.9-9.7)	1.7 (0.31-4.8)	<0.001
No. of HRP	0.75 ± 1.0	0.36 ± 0.67	<0.001
No. of HRP features	6.4 ± 4.0	3.6 ± 3.3	<0.001
Lumen volume, mm^3	1,574 ± 813	1,831 ± 1013	<0.001
CT-interval, y	3.3 (2.5-4.3)	3.4 (2.7-4.9)	0.012
Follow-up CCTA findings			
PAV, %	17.6 (10.8-26.5)	4.2 (1.4-9.1)	<0.001
Calcified, %	6.9 (3.0-14.0)	1.7 (0.2-4.4)	<0.001
Noncalcified, %	8.7 (5.1-13.3)	2.0 (0.5-4.2)	<0.001
No. of HRP	0.89 ± 1.0	0.39 ± 0.69	<0.001
No. of HRP features	7.3 ± 3.9	3.9 ± 3.4	<0.001
Lumen volume, mm^3	1,464 ± 771	1,821 ± 1,006	<0.001

Values are mean ± SD or median (IQR). [a]N = 204. [b]N = 253.

ACE = angiotensin-converting enzyme; CAD = coronary artery disease; CT = computed tomography; other abbreviations as in Table 1.

TABLE 3 Univariable and Multivariable Predictors of Atherosclerotic Statin Nonresponse

	Univariate OR (95% CI)	*P* Value	Multivariate OR (95% CI)	*P* Value
Baseline demographics				
Age, y	1.03 (1.01-1.05)	0.001		
Male	0.92 (0.65-1.29)	0.616		
Body mass index, kg/m^2	1.01 (0.96-1.07)	0.626		
Cardiovascular risk profile				
Diabetes	1.64 (1.15-2.36)	0.007	1.41 (0.95-2.11)	0.009
Hypertension	1.46 (1.04-2.07)	0.031		
Current smoking	1.28 (0.84-1.95)	0.248		
Family history for CAD	1.27 (0.88-1.85)	0.205		
Prior revascularization	1.33 (0.92-1.92)	0.410		
Interval revascularization	1.86 (1.20-2.90)	0.005		
Baseline laboratory results				
Total cholesterol, mg/dL	1.00 (0.99-1.00)	0.087		
LDL cholesterol, mg/dL	1.00 (1.00-1.00)	0.508		
HDL cholesterol, mg/dL	0.98 (0.96-0.99)	0.004		
Triglycerides, mg/dL	1.00 (1.00-1.00)	0.403		
HbA1c, %[a]	1.23 (1.00-1.50)	0.048		
CRP, mg/dL[b]	1.02 (1.00-1.05)	0.145		
Baseline CCTA findings				
PAV, %	1.10 (1.07-1.12)	<0.001		
Calcified	1.15 (1.11-1.20)	<0.001	1.07 (1.03-1.12)	<0.001
Noncalcified	1.13 (1.09-1.17)	<0.001	1.06 (1.02-1.10)	<0.001
No. of HRP	1.72 (1.40-2.11)	<0.001		
No. of HRP features	1.23 (1.17-1.29)	<0.001	1.15 (1.09-1.21)	<0.001
Lumen volume, mm^3	1.00 (1.00-1.00)	<0.001		

[a]N = 204. [b]N = 253.
OR = odds ratio; other abbreviations as in Tables 1 and 2.

nonresponse group compared with the group with atherosclerotic response (Table 2).

The univariate associations of different variables and atherosclerotic statin nonresponse are presented in Table 3. Age, diabetes, hypertension, interval revascularization, HDL cholesterol, and HbA1c were all associated with statin nonresponse. In addition, all CCTA findings individually showed significant association with statin nonresponse as well. Stepwise multivariate logistic regression, including all univariate variables, identified diabetes, baseline noncalcified and calcified PAV, and HRP features as independent determinants of atherosclerotic statin nonresponse (Table 3). In patients with LDL <70 mg/dL (N = 157) at follow-up, HRP features and noncalcified PAV were the only significant variables (Table 4).

TABLE 4 Multivariable Predictors of Atherosclerotic Statin Nonresponse

	OR (95% CI)	*P* Value
Restricted to patients with LDL <70 mg/dL at follow-up		
No. of HRP features	1.15 (1.04-1.26)	0.005
Noncalcified PAV	1.11 (1.04-1.19)	0.002

Abbreviations as in Tables 1 and 3.

Results for the secondary endpoint—atherosclerotic nonresponse defined as >1.0% in PAV/y and an increase in low-attenuation or fibro-fatty plaque—are shown in Supplemental Table 1. Age, body mass index, and all atherosclerotic plaque features were higher in patients with atherosclerotic statin nonresponse. In the multivariable model, only the number of HRP features and the noncalcified PAV were independent associates (Supplemental Table 2).

The scatterplot of baseline PAV and increase in % PAV/y showed a positive correlation of $R^2 = 0.142$ (Figure 2). The correlation between baseline LDL cholesterol and increase in %PAV/y was nonsignificant ($R^2 < 0.001$).

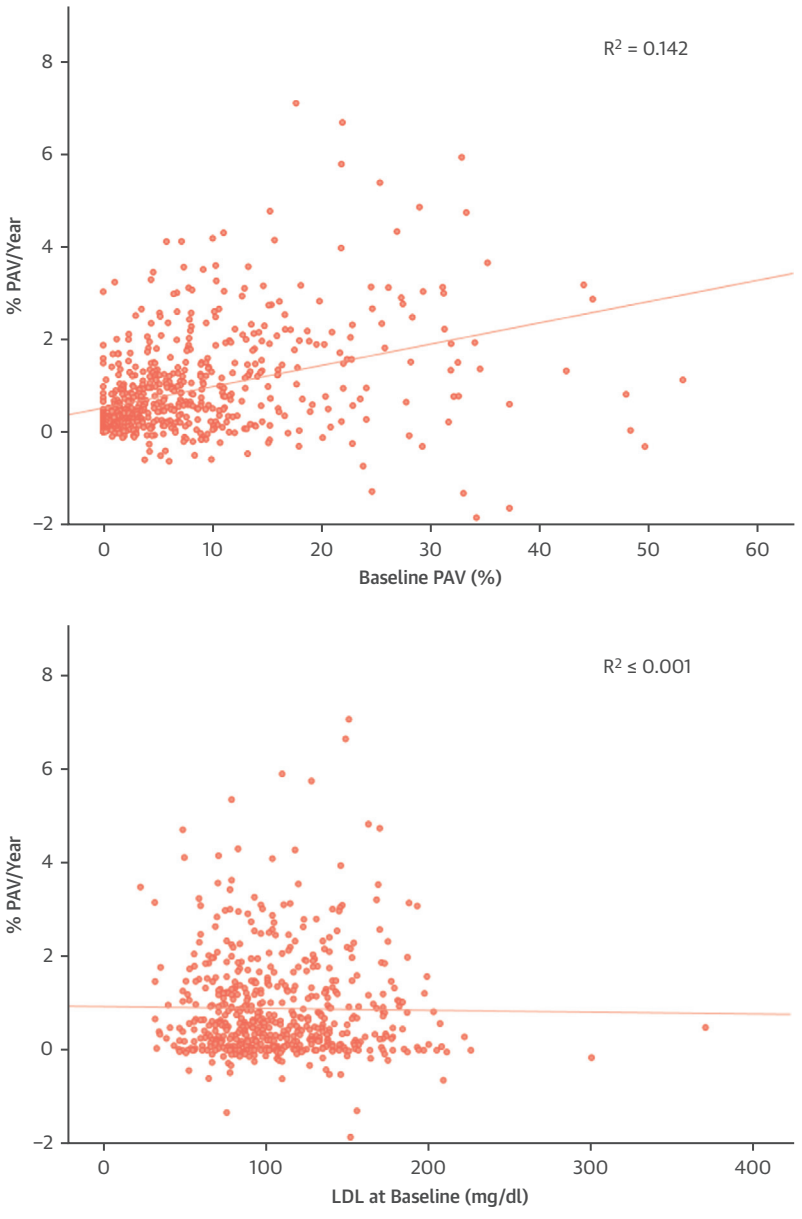
DISCUSSION

The main finding is that baseline plaque burden and HRP features were the strongest determinants of atherosclerotic statin nonresponse defined as significant plaque progression.

Atherosclerotic plaque burden represents the lifetime exposure to cardiovascular risk factors, lifestyle, and genetic predisposition and is the direct substrate for cardiovascular events. Either by CCTA or invasive coronary angiography, the extent of observed disease relates proportionally to future incidence of death, acute coronary syndrome, stroke, or revascularization procedures.[6,22] In addition to baseline atherosclerosis, the progression of plaque has emerged as a surrogate marker of risk for MACE.[23] Statins are the cornerstone of risk reduction therapies by reducing serum LDL cholesterol, CRP, and the associated decrease of lipid-rich plaque and increase in calcification burden that is observed in statin users.[2,5,10] A meta-analysis including 174,149 patients randomly assigned to statin therapy vs controls observed an approximately 20% reduction in major vascular events per 1 mmol/L reduction in LDL cholesterol.[1] Similarly, statins have been demonstrated to halt plaque progression; the ability of statins to slow plaque progression likely contributes to their protective effects on clinical events.[2,24]

However, residual MACE risk exists despite the achievement of very-low LDL cholesterol levels. In the randomized FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial, secondary prevention patients who received statins and the proprotein convertase subtilisin-kexin type 9 inhibitor evolocumab achieved LDL cholesterol levels of 30 mg/dL, but still experienced events in 9.8% compared with

FIGURE 2 Scatter Plots of Baseline Variables and % PAV/y



LDL = low-density lipoprotein; PAV = percent atheroma volume.

11.3% of patients treated with statins without evolocumab.[3]

CCTA PLAQUE CHARACTERIZATION AS DETERMINANT FOR ATHEROSCLEROTIC STATIN NONRESPONSE. A strong indicator of future major vascular events is the baseline amount of atherosclerotic plaque itself. In a post-hoc analysis from the SATURN (Study of Coronary Atheroma by Intravascular Ultrasound: effect of Rosuvastatin vs. Atorvastatin) trial, Puri et al[5] investigated predictors for MACE in a high-risk population of patients referred for invasive coronary angiography. During 2 years of follow-up, LDL cholesterol decreased to <70 mg/dL and 101 events (predominated by revascularization) were noted in the 1,039 patients in the study.[5] A strong independent association was observed for baseline PAV and MACE, whereas on-treatment LDL cholesterol did not predict

risk. Patients within the lowest PAV quartile experienced events in 5.1% compared with 12% for those in the highest PAV quartile. A pooled analysis of >4,000 patients undergoing intravascular ultrasound in 6 clinical trials demonstrated similar robust prognostic value for baseline plaque burden.[20]

CCTA allows detailed analysis of the whole coronary tree including arterial remodeling, compositional measures, and HRP features. Their value for MACE has not explicitly been examined in statin-taking patients. Similarly, associations between HRP markers and atherosclerosis progression have not been examined. More than 1.0% annual progression in PAV has been previously proposed as a clinically relevant threshold associated with MACE.[14,20] Reduction of LDL cholesterol with statin therapy has shown the potential of plaque regression on average, however, this does not apply to all patients. This study aimed to identify those that are at highest risk for further plaque progression despite the use of statins. We observed that baseline PAV (calcified and noncalcified), HRP features, and diabetes were independent determinants of atherosclerotic statin nonresponse. Because statins have been associated with reduced progression of low-attenuation and fibro-fatty plaque, and increased progression of high-density calcium,[11] we repeated the analyses with a secondary endpoint that also required progression of plaque between −30 and 130 HU to progress at follow-up CT. The results were fairly similar, with noncalcified PAV and HRP features being the only independent determinants.

The results suggest that patients with the largest baseline plaque burden and measures of plaque vulnerability represent the highest risk. Statin therapy will reduce risk, but prior data showed considerable residual risk when LDL cholesterol approaches zero.[25] Potentially these patients will be derive additional benefit from other therapies, such as icosapent ethyl,[26] colchicine,[27] antiplatelet, or anticoagulation therapy, but this will require further study.

Cholesterol levels were not associated with atherosclerotic nonresponse in the current study, which may relate to the fact that all patients received statin therapy and that those with large LDL reductions and reassuring clinical course may not have been referred for serial CCTA. Prognostic value of cholesterol has previously been established as a predictor for clinical events in unselected populations.[28] Absence of effect of CRP is likely related to the low average levels, indicating limited systemic inflammation in the current population. Average CRP at baseline and follow-up was <1 mg/dL, much lower than trials that demonstrated its value as determinant for residual cardiovascular risk in patients on cholesterol-lowering therapy.[29]

STUDY LIMITATIONS. The observational design of the study has all inherent limitations including selection bias and unmeasured confounding. The average on-treatment LDL at follow up was 88.7 mg/dL. Prior literature has shown that lower levels result in more plaque regression, which may have influenced the study findings.[23] Collinearity between the several quantitative plaque features is a limitation. Furthermore, duration between CT scans was slightly shorter in patients with statin nonresponse, possibly caused by recurrence of symptoms. Quantitative CCTA evaluation, as currently used, is time consuming and, therefore, not readily available for clinical practice. Fully automated software packages will need to be developed. In addition, the clinical value of our findings is unknown and needs further investigation.

CONCLUSIONS

In patients treated with statins, baseline plaque characterization by plaque burden and HRP is associated with atherosclerotic statin nonresponse defined as significant progression of coronary atherosclerosis. Patients with the highest plaque burden including HRP were at highest risk for plaque progression, despite statin therapy. These patients may be candidates for additional risk-reducing therapies.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Statins reduce MACE, but residual cardiovascular risk remains. The current study demonstrated that baseline plaque burden and the number of HRP features were the strongest determinants of significant plaque progression, which has been previously shown to correlate with events.

TRANSLATIONAL OUTLOOK: Besides statins, other therapies are available that reduce cardiovascular disease risk, and more are being developed. Future research should evaluate whether patients with high-baseline plaque burden and HRP may be candidates for these therapies.

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KEY WORDS atherosclerosis, coronary computed tomography angiography, plaque progression, statin nonresponse

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