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ORIGINAL PAPER

Impact of statins based on high-risk plaque features on coronary plaque progression in mild stenosis lesions: results from the PARADIGM study

Hyung-Bok Park[1,2], Reza Arsanjani[3], Ji Min Sung[2], Ran Heo[2,4], Byoung Kwon Lee[5], Fay Y. Lin[6], Martin Hadamitzky[7], Yong-Jin Kim[8], Edoardo Conte[9], Daniele Andreini[9], Gianluca Pontone[9], Matthew J. Budoff[10], Ilan Gottlieb[11], Eun Ju Chun[12], Filippo Cademartiri[13], Erica Maffei[13], Hugo Marques[14], Pedro de Araújo Gonçalves[14,15], Jonathon A. Leipsic[16], Sang-Eun Lee[2,17], Sanghoon Shin[2,17], Jung Hyun Choi[18], Renu Virmani[19], Habib Samady[20], Kavitha Chinnaiyan[21], Peter H. Stone[22], Daniel S. Berman[23], Jagat Narula[24], Leslee J. Shaw[6], Jeroen J. Bax[25], James K. Min[6], and Hyuk-Jae Chang[2,26]*

[1]Department of Cardiology, Catholic Kwandong University International St. Mary's Hospital, Incheon, South Korea; [2]CONNECT-AI Research Center, Yonsei University College of Medicine, Yonsei University Health System, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, South Korea; [3]Department of Cardiovascular Diseases, Mayo Clinic Arizona, Phoenix, AZ 85054, USA; [4]Department of Cardiology, Hanyang University Seoul Hospital, Hanyang University College of Medicine, Seoul, South Korea; [5]Department of Cardiology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea; [6]Department of Radiology, New York-Presbyterian Hospital and Weill Cornell Medicine, New York, NY 10021, USA; [7]Department of Radiology and Nuclear Medicine, German Heart Center Munich, Munich, Germany; [8]Division of Cardiology, Seoul National University College of Medicine, Cardiovascular Center, Seoul National University Hospital, Seoul, South Korea; [9]Centro Cardiologico Monzino, IRCCS, Milan, Italy; [10]Department of Medicine, Lundquist Institute at Harbor UCLA Medical Center, Torrance, CA 90502, USA; [11]Department of Radiology, Casa de Saude São Jose, Rio de Janeiro, Brazil; [12]Department of Radiology, Seoul National University Bundang Hospital, Sungnam, South Korea; [13]Department of Radiology, Fondazione Monasterio/CNR, Pisa, Italy; [14]Unit of Cardiovascular Imaging, Hospital da Luz, Catolica Medical School, Lisbon, Portugal; [15]Nova Medical School, Lisbon, Portugal; [16]Department of Medicine and Radiology, University of British Columbia, Vancouver, BC, Canada; [17]Department of Cardiology, Ewha Womans University Seoul Hospital, Seoul, South Korea; [18]Department of Cardiology, Pusan University Hospital, Busan, South Korea; [19]Department of Pathology, CVPath Institute, Gaithersburg, MD 20878, USA; [20]Department of Cardiology, Georgia Heart Institute, Northeast Georgia Health System, Gainesville, GA 30501, USA; [21]Department of Cardiology, William Beaumont Hospital, Royal Oak, MI 48073, USA; [22]Department of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA; [23]Department of Imaging and Medicine, Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA; [24]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, NY 10029, USA; [25]Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands; and [26]Department of Cardiology, Severance Cardiovascular Hospital, Yonsei University College of Medicine, Yonsei University Health System, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, South Korea

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Aims

To investigate the impact of statins on plaque progression according to high-risk coronary atherosclerotic plaque (HRP) features and to identify predictive factors for rapid plaque progression in mild coronary artery disease (CAD) using serial coronary computed tomography angiography (CCTA).

Methods and results

We analyzed mild stenosis (25–49%) CAD, totaling 1432 lesions from 613 patients (mean age, 62.2 years, 63.9% male) and who underwent serial CCTA at a ≥2 year inter-scan interval using the Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography Imaging (NCT02803411) registry. The median inter-scan period was 3.5 ± 1.4 years; plaques were quantitatively assessed for annualized percent atheroma volume (PAV) and compositional plaque volume changes according to HRP features, and the rapid plaque progression was defined by the ≥90th percentile annual PAV. In mild stenotic lesions with ≥2 HRPs, statin therapy showed a 37% reduction in annual PAV (0.97 ± 2.02 vs. 1.55 ± 2.22, $P = 0.038$) with decreased necrotic core volume and increased dense calcium volume compared to non-statin recipient mild lesions. The key factors

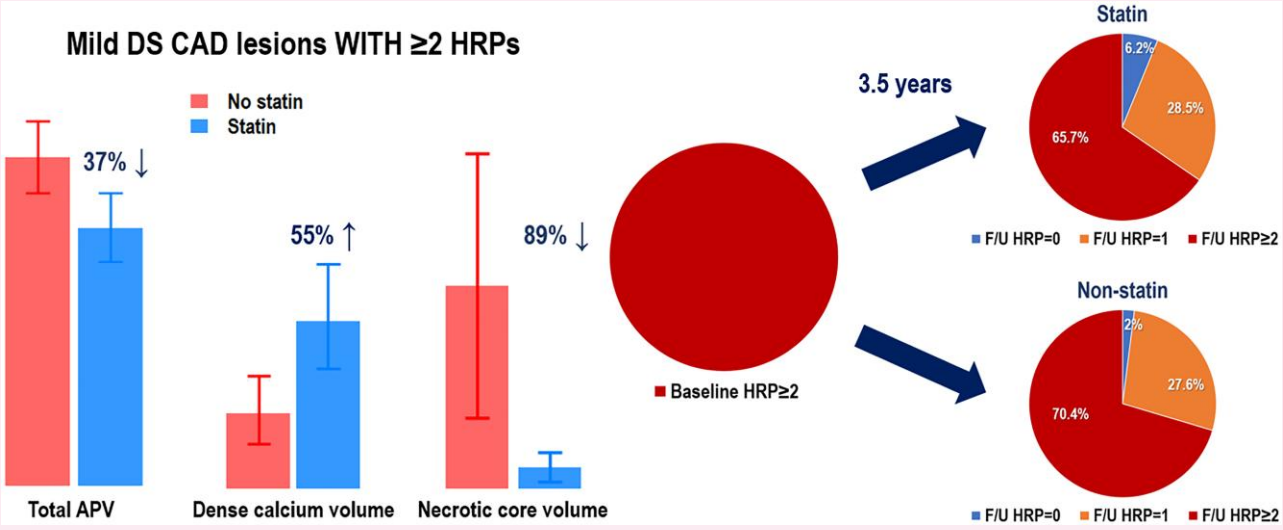
* Corresponding author. Tel: +82 (0)2 22288460; Fax: +82 (0)2 3932041; E-mail: hjchang@yuhs.ac

for rapid plaque progression were ≥2 HRPs [hazard ratio (HR), 1.89; 95% confidence interval (CI), 1.02–3.49; $P = 0.042$], current smoking (HR, 1.69; 95% CI 1.09–2.57; $P = 0.017$), and diabetes (HR, 1.55; 95% CI, 1.07–2.22; $P = 0.020$).

Conclusion In mild CAD, statin treatment reduced plaque progression, particularly in lesions with a higher number of HRP features, which was also a strong predictor of rapid plaque progression. Therefore, aggressive statin therapy might be needed even in mild CAD with higher HRPs.

Clinical trial registration ClinicalTrials.gov NCT02803411

Graphical Abstract



Keywords statin • high-risk plaque • coronary atherosclerosis • mild coronary stenosis • coronary computed tomography angiography

Introduction

Invasive and noninvasive studies have demonstrated that high-risk coronary atherosclerotic plaque (HRP) features provide incremental prognostic value in addition to the degree of luminal stenosis and baseline plaque burden.[1,2] In addition, these HRP features have been shown to be a marker of rapid plaque progression.[3] Moreover, plaque progression has been shown to be a strong independent predictor of future cardiovascular events regardless of baseline plaque characteristics.[4] Meanwhile, statin therapy has been demonstrated to be beneficial in mitigating future cardiovascular events by stabilizing HRP features and/or inhibiting progression of coronary artery disease (CAD).[5] An aggressive low-density lipoprotein (LDL) cholesterol-lowering strategy by intensive statin therapy may not only halt plaque progression, but also lead to plaque regression.[5]

The recently developed semi-automated quantitative plaque analysis by coronary computed tomography angiography (CCTA) is an accurate and noninvasive method for tracking plaque progression by quantifying three-dimensional (3D) plaque characteristics, including plaque volume and burden.[6,7] Serial quantitative plaque assessment by CCTA may serve as a strong clinical tool for re-stratifying cardiac event risks in patients with intermediate coronary lesions and assess the potential clinical benefits of lipid-lowering therapies, such as statin therapy, in regard to plaque stabilization. This is particularly important in patients with nonobstructive lesions who have no clear indication for invasive assessment; however, the risk for future events is nonnegligible.[8]

Although prior studies have revealed the protective role of statins in atherosclerotic plaque progression,[9,10] limited data exist on the potential differential impact of statins on HRP features, primarily focusing on mild stenotic CAD. Therefore, we aimed to investigate the impact of statin therapy on plaque progression according to HRP features based on serial CCTA quantitative analysis in coronary lesions with 25–49% diameter stenosis.

Methods

Study design and population

The Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography Imaging (PARADIGM; NCT02803411) study is a prospective, open-label, international, multicenter observational registry designed to track coronary atherosclerosis in serially acquired CCTA.[11]

A total of 2252 patients who underwent clinically indicated serial CCTA at an interscan interval of more than 2 years were enrolled from 13 hospitals in seven countries (Brazil, Canada, Germany, Italy, Portugal, South Korea, and the USA) between 2003 and 2015. The detailed study designs have been described previously.[11] We included 613 patients in the final analysis by using the following exclusion criteria: CCTAs of inadequate image quality for quantitative plaque analysis ($n = 492$), history of prior CAD (defined as myocardial infarction or revascularization before index CCTA) ($n = 227$), those for whom information regarding statin use was missing at the time of both CCTAs ($n = 192$), those who discontinued statin use

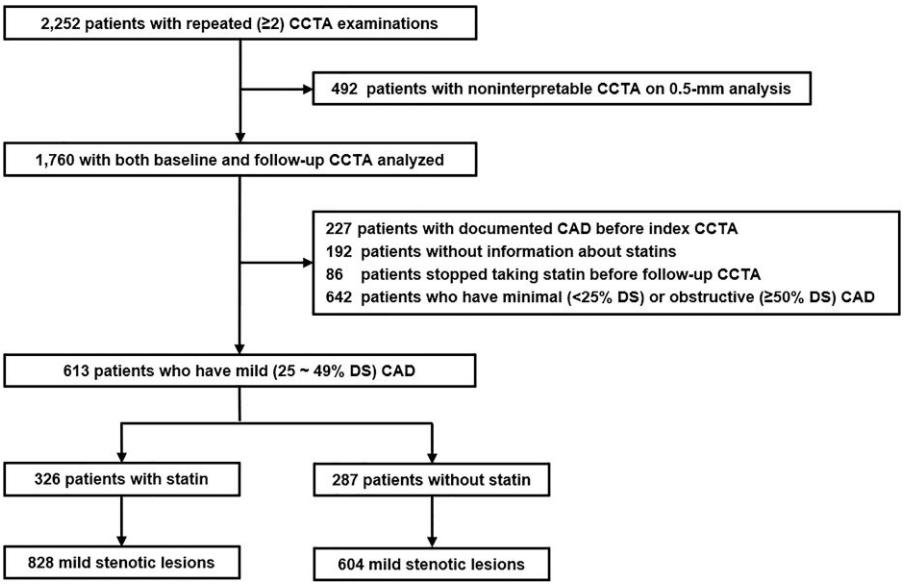


Figure 1 A flow diagram of the study population. CCTA = coronary computed tomography angiography; CAD = coronary artery disease; DS = diameter stenosis.

before follow-up CCTA ($n = 86$), and lastly, those who had less than minimal stenosis (<25% diameter stenosis by visual estimation) or obstructive CAD (≥50% diameter stenosis by visual estimation) ($n = 642$) (*Figure 1*). Among the 613 patients, 1432 mild stenotic coronary artery lesions were analyzed, including 828 mild stenotic lesions in 326 statin recipients and 604 mild stenotic lesions in 287 non-statin recipients (*Figure 1*). This study was approved by the Institutional Review Boards of all participating institutions, and was conducted in accordance with the Declaration of Helsinki.

Quantitative serial CCTA analysis

Anonymized CCTA images acquired from each participating institution in accordance with the Society of Cardiovascular Computed Tomography guidelines were transferred to the core laboratory (Severance Hospital, Seoul, South Korea) for blind analysis of coronary atherosclerosis. Quantitative plaque analysis was performed by nine independent level III-experienced computed tomography (CT) readers blinded to the clinical results using a semi-automated plaque analysis software (QAngioCT Research Edition v2.1.9.1, Medis Medical Imaging Systems, Leiden, the Netherlands), which has shown excellent intra-observer, inter-observer, and interscan reproducibility in previous studies.[6,7]

Quantitative two-dimensional (2D) parameters were measured, including lesion length, minimal lumen cross-sectional area (MLA), mean diameter stenosis (the average of maximum and minimum percentage of luminal diameter stenosis at MLA), lumen area stenosis (the percentage of lumen area divided by vessel area at MLA), plaque burden (the percentage of plaque area divided by vessel area at MLA), and the remodeling index (the ratio of maximal lesion vessel diameter divided by proximal reference vessel diameter at MLA). The 3D quantitative parameters were assessed as follows: plaque volume (subtracting lumen volume from vessel volume at each lesion), percent atheroma volume (PAV: the percentage of plaque volume divided by vessel volume at each lesion), and compositional plaque volume, such as necrotic core volume [intraplaque volume using the cutoff of Hounsfield unit (HU) -30 to 30], fibro-fatty volume (intraplaque volume of HU 30 to 130), fibrous volume (intraplaque volume of HU 131 to 350), and dense calcium volume (intraplaque volume of HU ≥351).[12]

Qualitative parameters were also evaluated, including plaque composition types (noncalcified/partially calcified/calcified), HRP features such as positive remodeling (a remodeling index of >1.1), low attenuation plaque (any voxel <30 HU within a coronary plaque), spotty calcification (an intralesional calcific plaque <3 mm in length that comprised <90° of the lesion circumference), and the napkin ring sign [a plaque cross-section with a central low CT attenuation area (HU ≤70) with circumferential high attenuation open ring area in a cross-sectional image].[4]

Longitudinal analysis of plaque progression

For the longitudinal analysis of plaque progression between the baseline and follow-up CCTAs, coronary lesions were co-registered using landmarks, including the distance from the ostium to the branch vessels. To determine plaque progression, annual PAV changes were defined as the PAV differences between follow-up and baseline, divided by follow-up years, and annual compositional plaque volume changes were defined as the compositional plaque volume differences between follow-up and baseline, divided by follow-up years. In addition, to identify the key factors associated with rapid plaque progression, we defined rapid plaque progression as the 90th percentile of annual PAV changes in a lesion-level analysis.

Statistical analysis

Continuous variables are presented as mean ± standard deviation or median and interquartile range, and differences were compared using Student's unpaired *t*-test or one-way analysis of variance for normally distributed variables and the Mann–Whitney *U* test for nonnormally distributed variables. Differences between categorical variables were examined using Pearson's Chi-square or Fisher's exact test, as appropriate. The relationship between statin treatment and annual PAV progression was analyzed using marginal Cox models by applying multivariate failure times to clarify the effect of common factors in clustered lesions within a person, with analyses presented as hazard ratios (HRs) at 95% confidence intervals (CIs). All statistical analyses were performed with SAS version 9.4 software (SAS Institute Inc., Cary, North Carolina) and MedCalc software (version 18.9; MedCalc Software, Mariakerke, Belgium) with a two-tailed $P < 0.05$ considered statistically significant.

Table 1 Baseline patient characteristics

	All Patients ($n = 613$)	Statin recipients ($n = 326$)	Non-statin recipients ($n = 287$)	*P* Value
Age, yrs	62.2 ± 8.4	63.2 ± 8.0	61.0 ± 8.6	0.001
Male (%)	392 (63.9)	214 (65.6)	178 (62.0)	0.351
CCTA interscan interval, yrs	3.5 ± 1.4	3.4 ± 1.2	3.7 ± 1.5	0.032
Body mass index, kg/m^2	25.2 ± 3.1	25.3 ± 2.9	25.1 ± 3.2	0.489
Hypertension	378 (61.8)	218 (66.9)	160 (55.9)	0.006
Diabetes mellitus	154 (25.1)	89 (27.3)	65 (22.6)	0.185
Stroke	32 (6.0)	20 (6.9)	12 (5.0)	0.464
Current smoker	127 (20.8)	70 (21.5)	57 (19.9)	0.639
Family history of CAD	163 (26.6)	92 (28.2)	71 (24.7)	0.331
Antiplatelets	295 (48.1)	195 (59.8)	100 (34.8)	<0.001
Beta-blockers	181 (29.6)	121 (37.1)	60 (21.0)	<0.001
Framingham risk score				
Low <10%	111 (18.1)	67 (20.5)	44 (15.4)	0.073
Intermediate (10% to 20%)	470 (76.9)	241 (73.9)	229 (80.4)	
High (>20%)	30 (4.9)	18 (5.5)	12 (4.2)	
Laboratory test before index CCTA				
Total cholesterol, mg/dL	186 (159 to 211)	178 (153 to 211)	191 (167 to 212)	0.005
LDL cholesterol, mg/dL	113 (88 to 137)	104 (79 to 135)	118 (96 to 137)	<0.001
HDL cholesterol, mg/dL	48 (41 to 57)	48 (41 to 58)	48 (41 to 57)	0.973
Triglyceride, mg/dL	122 (91 to 176)	120 (92 to 174)	123 (90 to 180)	0.987
Laboratory test at follow up CCTA				
Total cholesterol, mg/dL	162 (138 to 189)	155 (135 to 180)	170 (164 to 176)	<0.001
LDL cholesterol, mg/dL	92 (71 to 117)	86 (67 to 105)	101 (80 to 124)	<0.001
HDL cholesterol, mg/dL	47 (41 to 57)	47 (40 to 56)	48 (41 to 57)	0.282
Triglyceride, mg/dL	111 (80 to 152)	111 (81 to 154)	110 (77 to 151)	0.662

Values are mean ± SD, *n* (%), or median (interquartile range).
CAD = coronary artery disease; CCTA = coronary computed tomography angiography; LDL = low-density lipoprotein; HDL = high-density lipoprotein.

Results

Study population and baseline lesion characteristics

The baseline characteristics of the study population are shown in *Table 1*. Patients receiving statin therapy were slightly older, had a higher frequency of hypertension (HTN), a higher rate of use of other medications, such as antiplatelet and beta-blockers, apparently lower baseline and follow-up total/LDL cholesterol levels than those without statin therapy. However, there were no significant differences in cardiovascular risk according to Framingham risk scores between the two groups.

Baseline lesion characteristics are shown in Supplementary data online, *Table S1*. The lesion length was similar in both groups; however, there were more lesions in the right coronary artery and left circumflex artery in the statin recipient group than in the nonrecipient group. Among baseline 2D quantitative parameters, in lesions treated with statins, the MLA was smaller, and plaque burden and the remodeling index were higher than those in lesions without statin treatment, whereas the mean diameter stenosis and area stenosis were similar in both groups. In the volumetric 3D quantitative assessment, there were no baseline differences in PAV, plaque volume, fibrous volume, or dense calcium volume between statin and non-statin-treated lesions; however, fibrous-fatty and necrotic core volumes were higher in non-statin-treated lesions. In the qualitative lesion assessment, there were differences in plaque types, with more noncalcified plaques in the non-statin group and slightly more positive remodeling in the statin group.

Dynamic changes in plaque characteristics

Dynamic changes were observed in the longitudinal assessment of the HRP features (*Figure 2* and Supplementary data online, *Table S2*). Although half of the lesions with no HRP at baseline remained in the same state at follow-up, regardless of statin use (statin vs. non-statin: 49.8% vs. 48.9%, $P = 0.166$), the other half evolved to have more than one HRP feature. Similarly, the majority of baseline ≥2 HRPs with lesions continued to retain ≥2 HRPs at follow-up in both groups (statin vs. non-statin: 65.7% vs. 70.4%, $P = 0.096$). However, when all clinical variables were adjusted, such as age, sex, interval time of CT scans, body mass index (BMI), HTN, diabetes mellitus (DM), family history, smoking, aspirin/beta-blocker use, and baseline LDL cholesterol, the likelihood of maintaining ≥2 HRPs at follow-up was significantly higher in the non-statin group than in the statin group (HR, 1.80; 95% CI, 0.11–3.49; $P = 0.037$). Moreover, among those with baseline ≥2 HRPs, the statin group showed higher rates of HRP disappearance (no HRP) than the non-statin group (6.2% vs. 2.0%, $P = 0.048$).

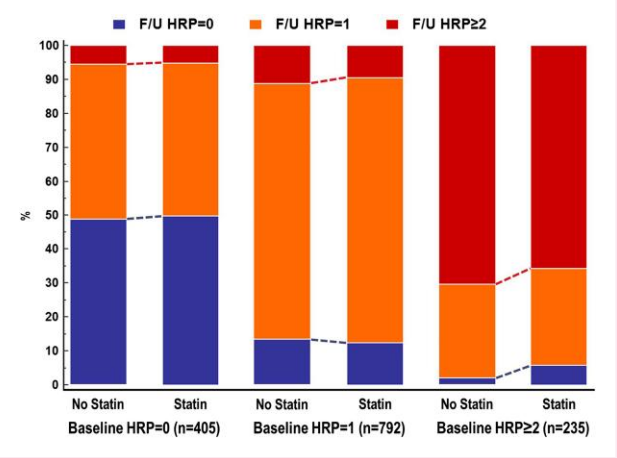


Figure 2 Dynamic changes between baseline and follow-up HRPs according to statin treatment. In baseline no HRP lesions, there showed similar frequency of development of HRPs at the time of follow up regardless of statin treatment. In baseline 1 HRP lesions, a similar pattern of dynamic changes of HRP over time was observed regardless of statin treatment. However, in lesions having 2 or more HRPs at baseline, according to statin treatment, a decreasing trend toward plaque stabilization during follow-up scan was noted. F/U = follow-up; HRP = high-risk plaque.

Differential impact of statin therapy on plaque progression according to baseline HRPs, area stenosis, and PAV

The annual PAV change in overall lesions was 1.30 ± 1.95%, with no significant differences in annual plaque progression according to statin use (statin vs. non-statin: 1.23 ± 1.99 vs. 1.39 ± 1.91, $P = 0.108$). Moreover, there were no significant differences in annual PAV changes based on the baseline HRP features (no HRP vs. 1 HRP vs. ≥ 2 HRPs: 1.28 ± 1.75 vs. 1.34 ± 2.01 vs. 1.21 ± 2.12, $P = 0.669$) or baseline area stenosis (<50% vs. ≥ 50%: 1.31 ± 1.87 vs. 1.29 ± 2.18, $P = 0.852$) (*Table 2*). However, in those lesions with baseline ≥2 HRPs, the statin group showed a 37% reduction in annual PAV changes when compared to the non-statin group (0.97 ± 2.02 vs. 1.55 ± 2.22, $P = 0.038$). Likewise, in lesions with baseline ≥50% area stenosis, the statin group also showed a significant reduction in annual PAV changes when compared to the non-statin group (1.11 ± 2.14 vs. 1.57 ± 2.22, $P = 0.044$) (*Figure 3*). However, after adjusting for all possible contributing factors for plaque progression (age, sex, interval CT scan time, BMI, HTN, DM, family history, smoking, aspirin, beta-blocker use, and baseline LDL cholesterol), statin use only slowed plaque progression in lesions with ≥2 HRPs ($P = 0.048$) at baseline and not in those with ≥50% area stenosis at baseline ($P = 0.089$) (*Table 2*). In contrast, there were no significant differences in annual PAV changes among the groups according to baseline PAV quartiles and statin use (*Table 2*).

In plaque composition analysis, the statin group showed a significant reduction in annualized change in necrotic core volume compared to the non-statin group in overall lesions (0.34 ± 1.77 vs. 1.50 ± 7.30, $P = 0.011$). In regard to baseline ≥2 HRPs lesions, the statin group showed more prominent decrements in annualized change of necrotic core volume (0.19 ± 1.23 vs. 1.69 ± 6.62, $P < 0.001$) at the same time increments in annualized dense calcium volume change (2.98 ± 4.52 vs. 1.35 ± 2.77, $P = 0.038$) compared to the non-statin group (see Supplementary data online, *Table S3*).

The prediction of rapid plaque progression

In mild stenotic CAD (25–49%), the presence of baseline ≥2 HRPs was the best predictor of rapid plaque progression on a per-lesion basis (HR, 1.89; 95% CI, 1.02–3.49; $P = 0.042$), defined as greater than the 90th percentile annual PAV change (≥3.1%/year, 95% CI, 2.85–3.29), followed by current smoking status (HR, 1.69; 95% CI, 1.09–2.57; $P = 0.017$) and DM (HR, 1.55; 95% CI, 1.07–2.22; $P = 0.020$) (*Table 3*).

Discussion

In the present study, we showed that statin therapy was most effective in retarding plaque progression in mild stenosis CAD lesions with more baseline HRP features (≥2 HRPs) and in those with a higher baseline degree of quantitative area stenosis (≥50%). In mildly stenotic lesions with baseline ≥2 HRPs, statin therapy was associated with higher disappearance rates of HRP and reduction of necrotic core volume with concurrent elevation of dense calcium volume, while non-statin therapy was associated with higher maintenance rates of ≥2 HRPs. Furthermore, baseline ≥2 HRPs was the most potent predictor for rapid plaque progression, defined by the ≥90th percentile of annual PAV changes per lesion level (greater than three times the average annual PAV changes), and other factors were active smoking and DM. Therefore, we were able to demonstrate that higher numbers of HRP features were the major driving force for rapid plaque progression in nonobstructive mild CAD and that statin therapy could effectively reduce plaque progression in nonobstructive HRP-containing lesions by stabilizing HRP features.

In a previous major study of 3575 lesions from the PARADIGM registry, the annual PAV changes for all, non-statin-treated, and statin-treated lesions were 1.85%, 2.04%, and 1.76%, respectively, demonstrating a significant reduction in annual PAV progression in the statin-treated group.[9] Our data, however, showed relatively lower annual PAV changes of 1.30%, potentially due to the selection of mild stenotic lesions that have a slower progressive nature than overall lesions. This possibly could have led to insufficient statistical differences in PAV changes according to statin usage during the 3.5-year follow-up period, although there was a numerical difference between the statin and non-statin groups (1.23% vs. 1.39%). However, in our study, in mild lesions with ≥2 HRP features, statin therapy exhibited a substantial reduction (more than 37%) in annual PAV progression compared to previously published studies, which showed a 13.7% reduction in the entire stenosis lesions.[9] Moreover, in those mild lesions with ≥2 HRP features, statin therapy also showed a substantial impact on lowering necrotic core volume and elevating dense calcium volume, which was also in line with previous results.[9]

The dynamicity of coronary atherosclerotic plaque characteristics was first presented by invasive intracoronary plaque imaging, mostly in high-risk patients with moderate to severe stenosis lesions.[5,13] In those studies, statins were demonstrated to remarkably inhibit coronary plaque progression, or even induce its regression; particularly, higher-intensity statins showed a higher regression effect with lowering LDL-C levels below 70 mg/dL, while simultaneously increasing calcium components, called the calcium paradox.[5,13]

These findings were also observed in noninvasive CCTA studies in low-to-moderate risk populations generally with mild-to-moderate stenosis lesions. A follow-up LDL cholesterol level of less than 70 mg/dL was independently associated with the retardation of plaque progression[14] and the 1 K plaque (very dense calcium, >1000 HU) volume had an inverse association with acute coronary syndrome (ACS).[15] While necrotic core volume along with HRP features had a strong association with ACS.[16] Moreover, HRP features with baseline plaque burden were strong predictors for rapid plaque progression,[17] which was further a strong predictor for adverse cardiovascular events.[3,4] In line with prior studies, we demonstrated dynamic changes in HRP features and plaque compositional volume changes according to statin use

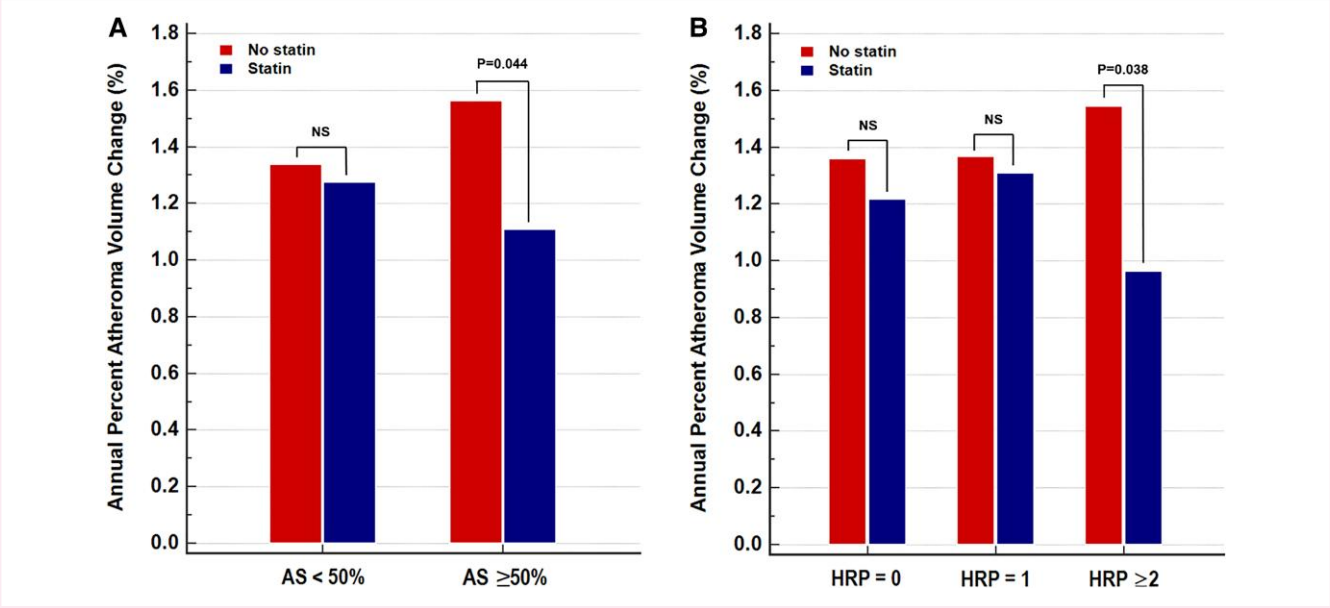


Figure 3 Annual PAV changes according to statin treatment by AS and HRPs. (*A*) In lesions with ≥50% baseline area stenosis, there was significantly lower annual PAV change progression as a result of statin treatment. (*B*) In lesions with 2 or more HRPs, significant reductions of annual PAV changes were observed by statin therapy. AS = area stenosis; PAV = percent atheroma volume; HRP = high-risk plaque.

Table 2 Annual PAV changes on a per-lesion basis in 25–49% DS lesions

	Annual PAV, % per year			
	Total (*n* = 1432)	**Statin (*n* = 828)**	**Non-statin (*n* = 604)**	***P* Value**
All lesions	1.30 ± 1.95	1.23 ± 1.99	1.39 ± 1.91	0.108
Baseline HRP features				
HRP = 0 (*n* = 405)	1.28 ± 1.75	1.22 ± 1.72	1.36 ± 1.80	0.414
HRP = 1 (*n* = 792)	1.34 ± 2.01	1.31 ± 2.10	1.37 ± 1.87	0.674
HRP ≥ 2 (*n* = 235)	1.21 ± 2.12	0.97 ± 2.02	1.55 ± 2.22	0.038
Baseline area stenosis				
<50% (*n* = 1037)	1.31 ± 1.87	1.28 ± 1.92	1.34 ± 1.79	0.590
≥50% (*n* = 395)	1.29 ± 2.18	1.11 ± 2.14	1.57 ± 2.22	0.044
Baseline PAV (%)				
Quartile 1 (6.9 ± 2.0, *n* = 358)	1.33 ± 1.59	1.33 ± 1.74	1.35 ± 1.39	0.898
Quartile 2 (12.6 ± 1.6, *n* = 358)	1.40 ± 1.85	1.36 ± 1.77	1.44 ± 1.97	0.713
Quartile 3 (18.7 ± 2.1, *n* = 358)	1.36 ± 2.04	1.27 ± 1.99	1.5 ± 2.09	0.293
Quartile 4 (30.5 ± 6.1, *n* = 358)	1.11 ± 2.29	0.97 ± 2.38	1.32 ± 2.15	0.148

Values are mean ± SD.
PAV = percent atheroma volume; HRP = high-risk plaque; DS = diameter stenosis.

exclusively in mild stenosis lesions, and we revealed that having ≥2 HRPs was a key predictor for rapid plaque progression.

Nevertheless, according to our data, statin therapy showed no protective effect against rapid plaque progression. This could potentially be explained by the fact that the follow-up LDL cholesterol level of 86 mg/dL in our statin recipients' data might not be low enough to prevent rapid plaque progression.[5,14] This result was consistent with previous results showing that statin therapy could lower the annualized incidence of HRPs but could not prevent the new development of obstructive (≥50%) diameter stenosis lesions from nonobstructive lesions.[9] Moreover, baseline PAV, which represents measures of plaque burden, was not associated with annual PAV increment or rapid plaque progression in our data. This could also be explained by our analysis focusing specifically on the mildly stenotic lesions (25–49%), while

Table 3 Rapid plaque progression prediction on a per-lesion basis in 25–49% DS lesions (90th percentile annual PAV progression)

	Hazard Ratio	95% CI	*P* Value
Age	0.99	0.98 to 1.02	0.996
Male	0.91	0.62 to 1.35	0.631
Diabetes mellitus	1.55	1.07 to 2.22	0.020
Hypertension	0.97	0.66 to 1.43	0.868
Current smoker	1.69	1.09 to 2.57	0.017
Antiplatelets	0.96	0.66 to 1.41	0.829
Statins	1.36	0.94 to 1.99	0.106
Baseline LDL-cholesterol	0.99	0.99 to 1.01	0.786
Baseline area stenosis	1.01	0.99 to 1.03	0.111
Baseline PAV (%)	0.99	0.97 to 1.02	0.688
Baseline high risk plaque features			
HRP = 0 (reference)	—	—	—
HRP = 1	1.59	0.99 to 2.62	0.061
HRP ≥ 2	1.89	1.02 to 3.49	0.042

LDL = low-density lipoprotein; PAV = percent atheroma volume; HRP = high-risk plaque; DS = diameter stenosis.

excluding minimal stenosis (<25%) based on insignificant prognostic implication in this subgroup,[18] which caused selection of mostly low and small variances of baseline PAV (majority were 10–30%), and thus might not be sufficient to generate statistical discrimination. In spite of these restrictions, the results are of interest and novel; the present study was the first to investigate, focusing on mild nonobstructive lesions, the differential dynamic interchange between HRP features depending on statin use and the divergent influence of statins on plaque progression according to baseline plaque characteristics.

Previously, the majority of acute coronary events were believed to be caused by the rupture of plaques with mild stenotic lesions embracing vulnerable plaque features such as positive remodeling, necrotic core with thin fibrous cap, macrophage infiltration, spotty calcification, and intraplaque hemorrhage.[1,16] Recent postmortem data, as well as invasive and noninvasive studies, suggest that myocardial infarction is preceded by sudden rapid plaque progression.[2–4] These findings highlight the importance of not only identifying the presence of vulnerable plaque features, even in nonobstructive stenotic atherosclerotic lesions, but also tracking the dynamic change in plaque features such as plaque progression rate in response to therapeutic intervention. Although invasive coronary imaging approaches such as intravascular ultrasound (IVUS) and optical coherence tomography have been regarded as the gold standard method for qualitative and quantitative plaque analysis using high resolution, given their inherently invasive nature, they are not an ideal option for serial tracing of atherosclerotic plaque, particularly in the low-risk patient population with nonobstructive stenotic lesions, even when HRP features may be present.[19] On the other hand, CCTA can be easily performed and serially followed up within this patient population with equivalent reliability when compared to invasive modalities.[4,8] Moreover, recent developments in semi-automated plaque quantification tools provide accurate and reproducible plaque quantification as well as monitor the plaque progression rate response to anti-atherosclerotic treatments, thus satisfying a great unmet need in clinical practice.[6,19] However, current expert consensus does not recommend further cardiac evaluation for populations with mild nonobstructive CAD, yet the risk for future events is nonnegligible. Therefore, our study suggests that serial CCTA evaluation may be beneficial for patients with mild CAD lesions showing ≥2 HRPs and ≥50% area stenosis.

In prior studies, DM status was more closely related to plaque progression as well as a higher frequency of HRPs than non-DM status, while strict glycemic control demonstrated an inverse relationship with plaque progression.[10] Our data also revealed that the presence of DM was a potent predictor of rapid plaque progression in mild CAD.

Smoking generally has been known as a primary risk factor for CAD, however, there have been confounding data called the 'Smoker's paradox' showing beneficial impact on those who have ACS in short-term favorable outcomes or those who have stable angina with percutaneous coronary intervention in long-term favorable outcomes.[20] Some IVUS studies have shown that current smokers had higher plaque burden, fibrofatty and necrotic core plaque volume, and lower fibrous plaque volume compared to nonsmokers,[21] although, another IVUS study could not demonstrate the association between smoking and the culprit lesion plaque burden and plaque vulnerability in patients with ACS.[22] However, we firstly exhibited the effect of smoking on rapid plaque progression even in mild CAD.

The present study has certain limitations. First, our analysis did not discern the differences in intensity and duration of statin therapy or achievement of the target LDL cholesterol level. The median follow-up LDL cholesterol was significantly lower in statin recipients than in non-statin recipients (86 mg/dL vs. 101 mg/dL, $P < 0.001$), although it was not low enough. Second, patients enrolled in the PARADIGM registry underwent serial CCTA; therefore, individuals who had significant CAD at baseline CCTA or those experiencing rapid deterioration of CAD before follow-up CCTA were excluded. Thus, most of the study population (97.8%) had nonobstructive CAD, which we further narrowed to only mild stenotic lesions. Hence, selection bias was inevitable, and generalization of our results to all mild stenotic atherosclerosis cases needs to be done cautiously. However, the PARADIGM registry sought to reveal the natural course of CAD in a low-risk population, which is frequently encountered on a daily basis. Most importantly, our data targeted mild stenotic lesions, being sure to exclude relatively unimportant minimal stenotic lesions, giving us considerable insight. Lastly, our relatively short follow-up period may not be sufficient to compare the differences in the natural course of subclinical atherosclerosis by statin treatment. However, nonobstructive stenosis CAD has a nonnegligible risk and is frequently encountered in clinical practice, there is very little data regarding the natural course and changes in plaque characteristics related to statin therapy. Our noninvasive quantitative and qualitative plaque analysis using CCTA was capable of investigating this unexplored area of interest.

In conclusion, we found that the plaque progression rate was lowered by statin treatment, particularly in lesions with a higher number of HRP features, which was also a strong predictor of rapid plaque progression. Therefore, our study suggests that aggressive statin therapy might be needed even in mild CAD with higher HRPs.

Supplementary data

Supplementary data is available at *European Heart Journal - Cardiovascular Imaging* online.

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Data availability

Due to privacy and ethical concerns, neither the data nor the source of the data can be made available.

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