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Impact of Intensive LDL Cholesterol Lowering on Coronary Artery Atherosclerosis Progression

A Serial CT Angiography Study

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ABSTRACT

OBJECTIVES The aim of this study was to explore the relationship between temporal changes in coronary plaque volume and the intensity of lipid-lowering treatments, utilizing coronary computed tomography angiography (CTA).

BACKGROUND Coronary CTA has acceptable accuracy in terms of quantitative measurement of plaque volume. Although, coronary CTA is perhaps capable of identifying the differences in plaque volume progression according to the intensity of lipid lowering treatment, to date, few studies have examined this notion.

METHODS In this multicenter, observational study, the authors reviewed 467 patients who underwent serial coronary CTA with a scan period of more than 2 years (median 3.2 years [2.4 to 4.8]) apart, and whose laboratory data were available within 1 month of both the baseline and follow-up coronary CTA. Among them, 147 patients (comprising 336 vessels) with visible plaque were enrolled in this study. The authors performed quantitative assessment of coronary plaque in both. Patients who achieved a low-density lipoprotein cholesterol (LDL-C) with a cut off value below 70 mg/dl at follow-up were compared with those who did not.

RESULTS Patients with LDL-C below 70 mg/dl displayed a significant attenuation in plaque progression as compared with those with follow-up LDL-C levels ≥70 mg/dl (12.7 ± 38.2 mm^3 vs. 44.2 ± 73.6 mm^3, respectively; $p = 0.014$). In multivariate analysis, factors influencing plaque progression per year was follow-up LDL-C levels ≥70 mg/dl (beta 0.193; $p = 0.021$).

CONCLUSIONS Strict LDL-C control appeared to significantly attenuate plaque volume progression based on noninvasive quantitative assessment by coronary CTA. (J Am Coll Cardiol Img 2017;10:437–46)

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CAD = coronary artery disease

CTA = computed tomography angiography

ECG = electrocardiogram

HDL-C = high-density lipoprotein cholesterol

IVUS = intravascular ultrasound

LDL-C = low-density lipoprotein-cholesterol

Coronary atherosclerosis is a major cause of morbidity and mortality, carrying a global burden of 17 million deaths annually (1). Low-density lipoprotein cholesterol (LDL-C) has been demonstrated to play an essential role in the progression of atherosclerotic coronary artery disease (CAD). Prior clinical trials have demonstrated a salutary effect of lowering LDL-C with statins (2,3), whereby intensive LDL-C lowering was found to be associated with improved event-free survival (4). Early studies documented that lowering LDL-C levels reduces the progression of CAD observed via serial coronary angiography (5). Further still, the precise quantification of atheroma volume using intravascular ultrasound (IVUS) has shown that intensive lowering of LDL-C levels can halt the progression of CAD (6), or even promote atherosclerotic regression (7).

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Serial assessment of coronary plaques using coronary angiography or IVUS has contributed to the understanding of the natural history and pathophysiology of CAD, and is therefore considered a surrogate endpoint for evaluating novel cardiovascular therapeutics (8–10). Nevertheless, these methods are invasive, expensive, and can be associated with significant adverse complications, making them unsuitable for routine clinical use. In addition, most available studies relative to invasive imaging techniques have typically included fewer numbers of patients with a generally shorter-term follow-up. Recent improvements in coronary computed tomography angiography (coronary CTA) technology have allowed for the noninvasive assessment of CAD with high diagnostic performance compared with invasive measures (11,12). In light of this, coronary CTA has emerged as a potential alternative to invasive angiography in many circumstances, including (but not confined to) stenosis grading and plaque quantification (13–15). Although a small number of serial coronary CTA studies have been published (16–18), most prior analyses were limited to a small study sample or a specific subset of lesions. Thus, in the present study, our objective was to examine changes in coronary atherosclerosis along the full length of the coronary vascular tree using coronary CTA, as well as to assess the serial changes in coronary plaque volume occurring as a result of intensive lowering of LDL-C levels.

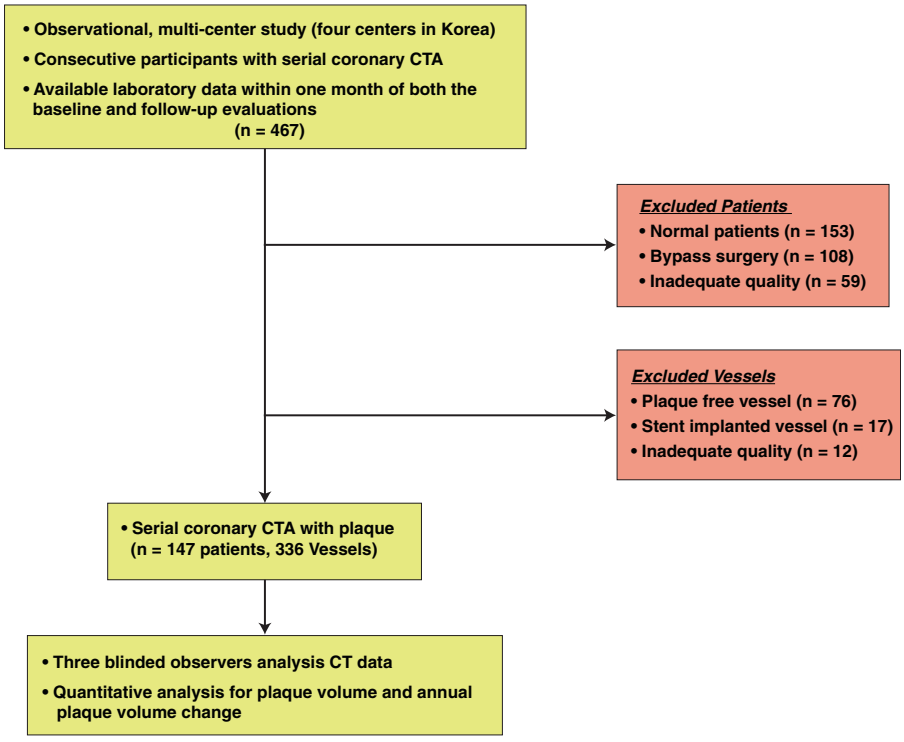
METHODS

PATIENT SELECTION. In this multicenter, observational study, we enrolled 467 consecutive participants who underwent serial coronary CTA using 64-slice multidetector computed tomography and whose laboratory data were available within 1 month of both the baseline and follow-up evaluations at 4 centers in Korea consisting of Severance Cardiovascular Hospital, Seoul National University Hospital, Gangnam Severance Hospital, and Busan Medical Center. Patients with plaque-free coronary arteries (n = 153), a history of coronary bypass surgery (n = 108), or inadequate imaging quality for analysis (n = 59) were excluded. Normal, plaque-free coronary arteries (n = 76), stent-implanted vessels (n = 17), or vessels with poor imaging quality due to artifacts (n = 12) were excluded from the per-vessel analysis. In total, 147 patients (comprising 336 vessels) with plaque visible using coronary CTA were enrolled in this study (**Figure 1**). The period between coronary CTA scans was at least 24 months. Patients were referred for coronary CTA for a variety of indications, including general health evaluation, evaluation of symptoms, and signs of cardiac disease (**Table 1**). The appropriate institutional review board committee approved this study.

CORONARY CTA PROTOCOL. Patients with pre-multidetector computed tomography heart rates >65 beats/min received a single oral dose (50 mg) of metoprolol tartrate (Betaloc, Yuhan, Seoul, Korea), 1 to 2 h before their CT examination unless β-adrenergic blocking agents were contraindicated (overt heart failure or atrioventricular conduction abnormalities). Patients were scanned using a 64-slice CT scanner in various centers. Coronary CTA was performed using prospective electrocardiogram (ECG) gating with the following scan parameters: rotation time 330 ms; slice collimation 64.0 × 0.6 mm; tube voltage 100 to 120 kV; tube current 600 to 800 mA, depending on patient size; table feed/scan 3.8 mm; and pitch factor 0.2. ECG-based tube current modulation was applied to 65% of the R-R interval. A real-time bolus-tracking technique was used to trigger scan initiation.

Contrast enhancement was achieved with 60 ml iopamidol (370 mg iodine/ml, Iopamiro, Bracco, Milan, Italy) injected at 5 ml/s, followed by an injection of 30 ml of diluted contrast (contrast agent/saline = 3:7), followed by 30 ml of saline (5 ml/s) using a power injector (Envision CT, Medrad, Indianola, Pennsylvania) via an antecubital vein. Axial images were reconstructed using retrospective ECG gating, with a slice thickness of 0.75 mm, a slice increment of 0.4 mm, and a medium-to-smooth convolution kernel. Optimal datasets with the best image quality were reconstructed, mainly during the mid-to-end

FIGURE 1 A Flowchart Demonstrating Selection of the Study Population



Among 467 consecutive participants, we excluded patients with plaque-free coronary arteries, a history of coronary bypass surgery, or inadequate imaging quality for analysis. Furthermore, normal, plaque-free coronary arteries, stent-implanted vessels, or vessels with poor imaging quality due to artifacts were excluded from the per-vessel analysis. CTA = computed tomography angiography.

diastolic phase. The follow-up scan was performed at least 2 years after the initial CT using the same protocol.

CORONARY CTA IMAGE ANALYSIS. Datasets (baseline and follow-up) were transferred to an offline workstation for analysis using semiautomated plaque analysis software (QAngioCT Research Edition v2.0.2, Medis Medical Imaging Systems, Leiden, the Netherlands) (19). Three experienced observers (more than 3 years coronary CTA experience) blinded to the groups analyzed all the scans and confirmed by Level III-equivalent cardiologists with experience interpreting several thousand coronary CTA scans. The major vessels (left anterior descending coronary artery, left circumflex coronary artery, and right coronary artery) were considered for analysis using the modified 17-segment American Heart Association model for coronary segment classification (20). Lesions were matched in baseline and follow-up images using branch points as landmarks. Definitions of the inner lumen and outer vessel areas were performed semiautomatically, following a stepwise approach. First, the observer placed an ostial proximal point and a distal point, and then a centerline originating from the ostium was automatically extracted. Straightened, multiplanar reformatted images were then generated, and the lumen and vessel borders were detected longitudinally by the software in 4 different cut planes and corrected by the observer. On the basis of these longitudinal contours, cross-sectional images at 0.5-mm intervals were calculated to create transversal lumen and vessel wall contours. These were

TABLE 1 Causes of Referral for Coronary CTA

	Initial	Follow-Up
Asymptomatic	83 (56.5)	93 (63.3)
Noncardiac chest pain	12 (8.2)	9 (6.1)
Atypical chest pain	42 (28.6)	33 (22.4)
Typical chest pain	5 (3.4)	8 (5.4)
Shortness of breath	5 (3.4)	4 (2.7)

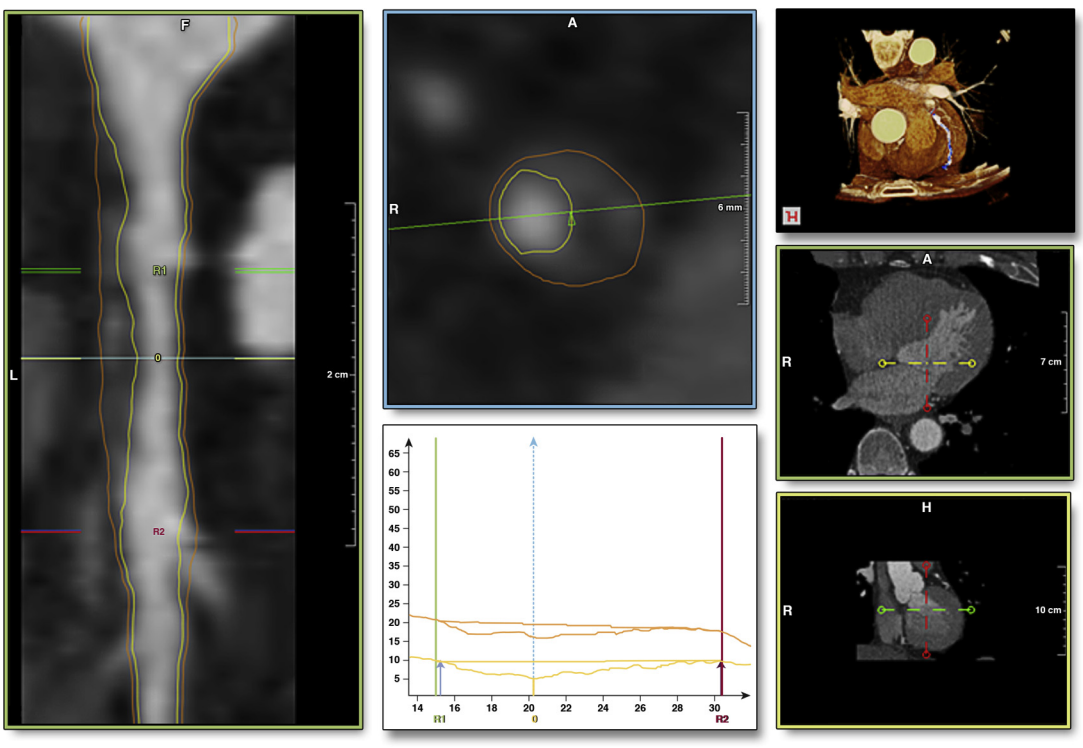
Values are n (%).
CTA = computed tomography angiography.

examined, and if necessary, adjusted by the observer. Gradient magnitude images derived from the coronary CTA images and displaying the degree of CT density change were used to verify the lumen and vessel wall borders (**Figure 2**, Online Figure 1).

MEASUREMENT OF CLINICAL VARIABLES AND CONFOUNDING VARIABLES. Clinical risk factors, including hypertension, diabetes mellitus, and smoking status, were systematically obtained. Height, body weight, and blood pressure were measured during the visits. Total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), LDL-C, fasting plasma glucose, glycated hemoglobin, blood urea nitrogen, and serum creatinine levels were measured within 1 month of the CT scan. Diabetes was defined as treatment with oral hypoglycemic agents or insulin, or fasting glucose ≥126 mg/dl. Hypertension was defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg, or treatment with antihypertensive agents. Patients were considered to be active smokers if they currently smoked or had smoked within the month before the initiation of the study. Dyslipidemia was defined as total cholesterol ≥240 mg/dl, LDL-C ≥130 mg/dl, HDL-C ≤40 mg/dl, triglycerides ≥150 mg/dl, and/or treatment with lipid-lowering agents. Laboratory values for the lipid parameters were obtained within 1 month before coronary CTA examination. The decisions to use statin therapy and the treatment target of LDL-C were determined by the individual clinician.

STATISTICAL METHODS. Continuous variables are expressed as median and interquartile range, whereas categorical variables are presented as absolute values and proportions. Differences between continuous variables were analyzed using an independent Student *t* test, whereas differences between categorical variables were analyzed by the use of a chi-square test. Changes in lesion characteristics were analyzed using a Wilcoxon signed rank test. Variables that

FIGURE 2 Representative Imaging for Lumen and Vessel Wall Contour Using Q-angio CT



Example of vessel analysis using semi-automated plaque analysis software (QAngioCT Research Edition v2.0.2, Medis Medical Imaging Systems, Leiden, the Netherlands). After the 3-dimensional centerline was generated from the computed tomography (CT) dataset, automated lumen and vessel wall contour detection was performed.

showed a significant relationship in previous studies and parameters with a p value <0.3 in the univariate analysis were defined as confounding variables related to the dependent and independent measures. The latter covariates included age, hypertension, active smoking, and follow-up LDL-C <70 mg/dl. All statistical analyses were performed using the Statistical Package for the Social Sciences version 19 (SPSS, Chicago, Illinois), and a p value <0.05 was considered significant for all analyses.

RESULTS

STUDY POPULATION. Clinical characteristics of the patients are reported in Table 2. The mean age was 62 ± 8 years, and 57% of the patients were male. Hypertension, diabetes mellitus, and dyslipidemia were present in 65%, 33%, and 47% of the patients, respectively. In addition, 20% of the patients were active smokers. Patients exhibiting a follow-up LDL-C <70 mg/dl had a higher prevalence of diabetes mellitus (p = 0.002). Although, there was no difference in National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (NCEP ATP III) score and Framingham risk scores between the 2 groups, the number of risk factors were greater in the follow-up LDL <70 mg/dl group (1.95 ± 1.08 vs. 1.54 ± 0.95; p = 0.029). During a mean interscan period of 3.2 ± 1.1 years, use of statins increased considerably after baseline coronary CTA imaging (38.8% vs. 72.8%; p < 0.001), with a higher rate of use in patients achieving follow-up LDL-C <70 mg/dl (Table 3, Figure 3).

COMPARISON BETWEEN BASELINE AND FOLLOW-UP CHANGES IN CORONARY ARTERIES AND ATHEROSCLEROSIS PROGRESSION. Changes in coronary artery severity and atherosclerotic progression between baseline and follow-up study are displayed in Table 4. During this time, the lumen volume decreased (p < 0.001), whereas the vessel volume (p = 0.029), plaque volume (p < 0.001), and the proportion of dense calcified plaque (p < 0.001) increased. Furthermore, significant elevation in mean plaque burden (p < 0.001) and plaque burden at the minimal lumen area (p < 0.001) were also observed. Total plaque volume change was 36.3 ± 67.7 mm^3, and the annual change in plaque volume was 13.0 ± 25.1 mm^3 based on a per-patient analysis. The mean annual plaque volume progression rate was 3.63 ± 5.83% (Figure 4).

CORONARY ARTERY AND ATHEROSCLEROSIS CHANGES AS A FUNCTION OF LDL-C CONTROL. Patients achieving a LDL-C <70 mg/dl demonstrated a lower progression in plaque volume compared with patients with follow-up LDL-C levels ≥70 mg/dl (p = 0.014). Likewise, the annual change in plaque volume was also attenuated for patients achieving low LDL-C <70 mg/dl levels (p = 0.018) (Figure 5). Factors associated with annual plaque progression in the univariate analysis were age, body mass index (BMI), hypertension, and follow-up LDL-C level ≥70 mg/dl.

TABLE 2 Baseline Patient Characteristics Split Up Based on Follow-Up LDL-C Level

	All Patients (N = 147)	F/U LDL-C <70 mg/dl (n = 37)	F/U LDL-C ≥70 mg/dl (n = 110)	p Value
Age, yrs	62 ± 8	62 ± 8	62 ± 8	0.982
Male	84 (57.1)	20 (54.1)	64 (58.2)	0.661
BMI, kg/m^2	25.1 ± 2.7	24.4 ± 2.4	25.4 ± 2.8	0.079
Hypertension	96 (65.3)	26 (70.3)	70 (63.6)	0.463
Diabetes mellitus	49 (33.3)	20 (54.1)	29 (26.4)	0.002
Active smoking	30 (20.4)	8 (21.6)	22 (21.2)	0.952
Dyslipidemia	42 (27.3)	12 (32.5)	28 (25.5)	0.409
History of PCI	7 (4.8)	3 (8.1)	4 (3.7)	0.269
History of CVA	7 (4.8)	3 (8.1)	4 (3.7)	0.269
NCEP ATP III risk	9.8 ± 7.5	8.5 ± 5.9	10.2 ± 7.9	0.232
Low (<10)	81 (55.1)	21 (56.8)	60 (54.5)	
Intermediate (10–20)	47 (32.0)	12 (32.4)	35 (31.8)	
High (>20)	19 (12.9)	4 (10.8)	15 (13.6)	
Framingham risk	10.3 ± 7.9	9.9 ± 5.8	10.5 ± 8.5	0.694
Low (<10)	92 (62.6)	22 (59.5)	70 (63.6)	
Intermediate (10–20)	42 (28.6)	13 (35.1)	29 (26.4)	
High (>20)	13 (8.8)	2 (5.4)	11 (10.0)	
Number of risk factors	1.64 ± 0.99	1.95 ± 1.08	1.54 ± 0.95	0.029

Values are mean ± SD or n (%). The mean interscan period was 3.2 ± 1.1 years.

BMI = body mass index; CVA = cerebrovascular accident; F/U = follow-up; LDL-C = low-density lipoprotein cholesterol; NCEP ATP III = the National Cholesterol Education Program Adult Treatment Panel III; PCI = percutaneous coronary intervention.

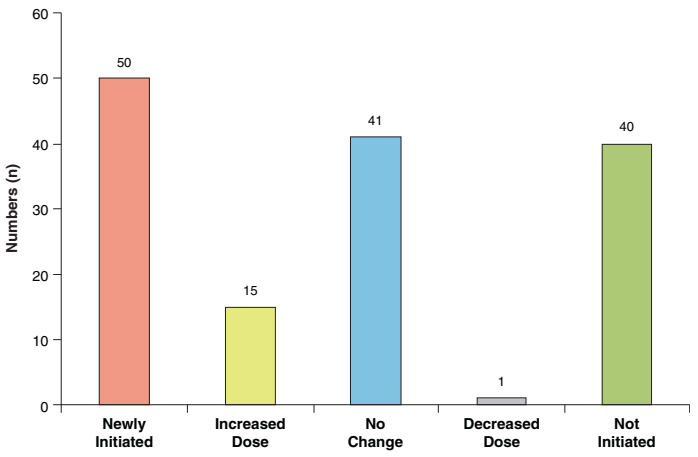
TABLE 3 The Change of Statin Use and Laboratory Test After Index Coronary CTA

	All Patients (N = 147)	F/U LDL-C <70 mg/dl (n = 37)	F/U LDL-C ≥70 mg/dl (n = 110)	p Value
Statin use before index coronary CTA	57 (38.8)	21 (56.8)	36 (32.7)	0.009
Statin use at follow up coronary CTA	107 (72.8)	37 (100)	70 (63.6)	<0.001
Laboratory test before index coronary CTA				
T-chol, mg/dl	183 ± 35	177 ± 38	185 ± 32	0.242
HDL-C, mg/dl	48 ± 10	48 ± 9	48 ± 11	0.959
LDL-C, mg/dl	114 ± 35	106 ± 37	116 ± 32	0.125
TG, mg/dl	154 ± 8.2	150 ± 69	157 ± 88	0.689
Statin use	57 (38.8)	21 (56.8)	36 (32.7)	0.009
Laboratory test at follow up coronary CTA				
T-chol, mg/dl	162 ± 37	126 ± 15	176 ± 34	<0.001
HDL-C, mg/dl	48 ± 11	48 ± 12	47 ± 10	0.832
LDL-C, mg/dl	92 ± 32	57 ± 12	104 ± 27	<0.001
TG, mg/dl	122 ± 72	104 ± 52	126 ± 76	0.105

Values are n (%) or mean ± SD.

HDL-C = high-density lipoprotein cholesterol; T-chol = total cholesterol; TG = triglyceride; other abbreviations as in Tables 1 and 2.

FIGURE 3 The Change of Statin Use After Index Coronary CTA



Use of statins increased considerably after baseline coronary computed tomography angiography (CTA) imaging. Fifty patients newly initiated using statin, and 15 patients increased the dose of statin.

In per-patient multivariate analysis, follow-up LDL-C levels ≥70 mg/dl (beta 0.193; p = 0.021) were strong determinants of annual plaque progression adjusted by age, BMI, hypertension, and active smoking (Table 5). However, when the baseline plaque volume was adjusted, the plaque volume was verified as a significant factor (beta 0.324; p < 0.001), and the follow-up LDL ≥70 mg/dl was found not to be significant, but rather only showed a trend (beta 0.158; p = 0.059). Additionally, according to the per-vessel analysis, age, BMI, active smoking, and follow-up LDL-C ≥70 mg/dl were determinant factors for annual plaque progression (Online Tables 1, 2).

TABLE 4 Change in Lesion Characteristics Between Initial and Follow-Up Coronary CTA

	Initial (N = 336)	Follow Up (N = 336)	p Value
Lesion length, mm	17.0 (10.1–25.8)	17.0 (10.1–25.8)	0.486
Vessel volume, mm^3	220.8 (124.0–377.5)	223.2 (130.7–379.4)	0.616
Lumen volume, mm^3	105.9 (63.4–197.5)	97.9 (58.1–170.1)	<0.001
Plaque volume, mm^3	114.3 (63.8–200.3)	118.7 (69.1–221.6)	<0.001
Dense calcium, mm^3	10.8 (3.1–33.7)	24.4 (9.8–60.6)	<0.001
Proportion of dense calcium, %	10.0 (3.3–22.6)	22.3 (11.9–33.9)	<0.001
Mean plaque burden, %	51.7 (44.2–57.7)	55.1 (48.9–60.9)	<0.001
Maximal plaque thickness, mm	1.73 (1.37–2.12)	1.85 (1.59–2.28)	<0.001
Minimal lumen area, mm^2	5.0 (3.7–6.9)	4.5 (3.2–6.1)	<0.001
Minimal lumen diameter, mm	2.3 (1.9–2.7)	2.1 (1.7–2.5)	<0.001
Plaque burden at minimal lumen area, %	61.4 (52.4–70.5)	66.6 (59.9–74.4)	<0.001

Values are median (interquartile range).

LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; RCA = right coronary artery.

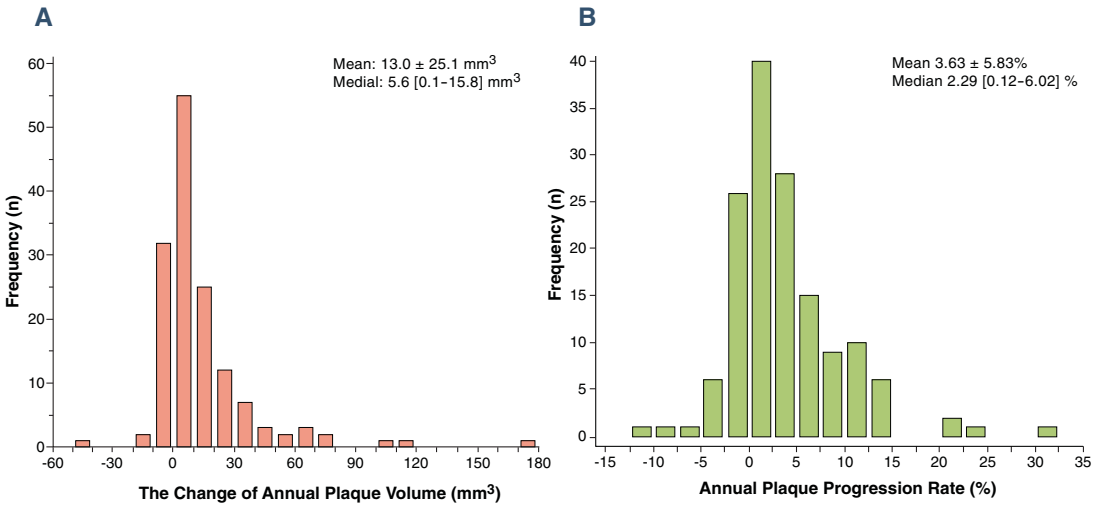
SUBGROUP ANALYSIS COMPARING STATIN USERS WHO ACHIEVED LDL-C <70 mg/dl VERSUS THOSE WHO DID NOT. A subgroup analysis on all statin users (n = 107), to see whether a more aggressive LDL-C approach could reduce plaque progression, was performed. All patients achieving a LDL-C <70 mg/dl took statin (n = 37), whereas 63% (n = 70) patients with follow-up LDL-C levels ≥70 mg/dl were on statin. Subgroup analysis of patients taking statins demonstrate that the annual plaque volume progression (4.6 ± 15.0 mm^3 vs. 14.5 ± 22.0 mm^3; p = 0.015) could be attenuated with aggressive LDL control (Table 6).

DISCUSSION

The present study demonstrated that achievement of LDL-C control to levels <70 mg/dl is associated with a reduced rate and volume of plaque progression, both on a per-patient as well as per-vessel basis. Further, we observed that per-patient annual plaque volume increased in this near-term period on the basis of presence of age and active smoking, but not by the presence of diabetes mellitus or hypertension.

Conventionally, quantitative coronary angiography or IVUS have been employed for diagnosis of coronary atherosclerosis or coronary artery stenosis. However, a potential pitfall of these procedures is their relatively expensive cost as well as their inherent invasive nature (21,22). Recent improvements in CT technology have permitted characterization of plaque morphology (23,24), quantification of plaque volume (25,26), and stenosis evaluation (12,27). There have been numerous attempts to utilize coronary CTA for measuring plaque volume and to reveal other clinical implications, such as use for estimating ischemia (28). However, these attempts have been performed manually, examining 1-mm cross-sectional slices of the coronary vascular bed, requiring considerable time and effort, and making large-scale investigations difficult. Hence, most research involving plaque volume assessments by coronary CTA have examined only a small number of patients. Recently developed semiautomated plaque quantification methods allow for the measurement of plaque volumes with only minor modifications, thereby increasing the speed of assessment and allowing more patients to be enrolled in these studies. Coronary CTA utilizing these semiautomated techniques is highly reproducible (29), with plaque volumes correlating well with plaque volumes measured by IVUS (19,30). Coronary CTA has several advantages over IVUS, given its noninvasive nature, as well as overall cost. Therefore, coronary CTA may prove useful for future quantitative research into plaque progression.

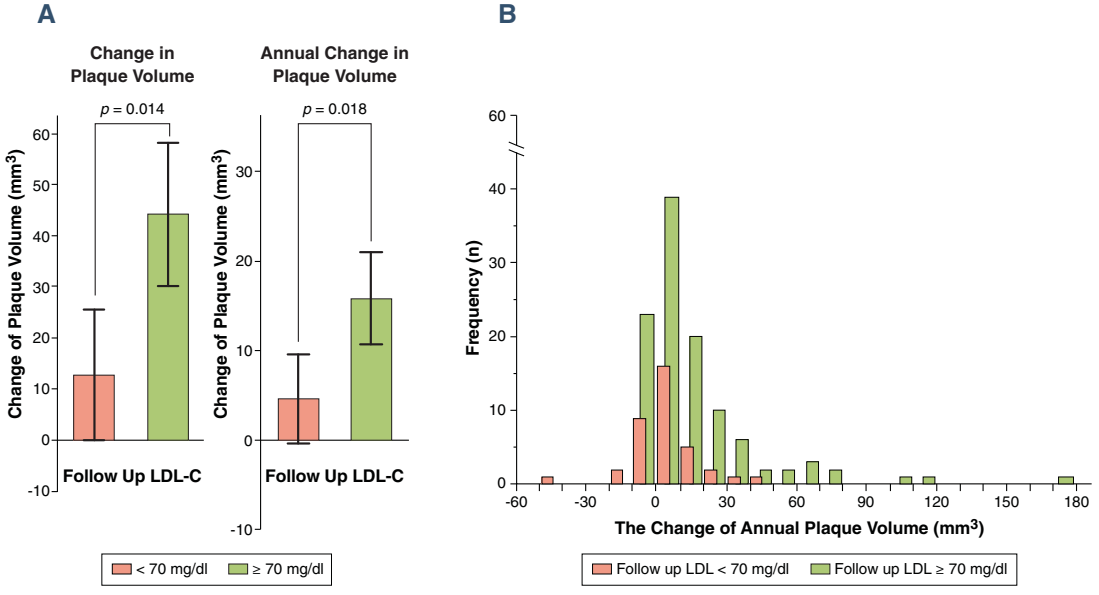
FIGURE 4 Changes in Coronary Artery and Atherosclerotic Progression Between Baseline and Follow-Up Periods



Total plaque volume change was 36.3 ± 67.7 mm^3 **(A)** and the mean annual plaque progression rate was 3.63 ± 5.83% **(B)**. LDL-C = low-density lipoprotein cholesterol.

LDL-C contributes to the progression of atherosclerotic CAD. Furthermore, numerous serial IVUS studies have demonstrated that strict LDL-C control can lead to plaque retardation or regression, as well as prior research studies incorporating CT. In the ASTEROID (A Study To Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden) trial (7), patients using very

FIGURE 5 Coronary Artery and Atherosclerosis Changes as a Function of LDL-C Control



Patients achieving a low-density lipoprotein cholesterol (LDL-C) <70 mg/dl demonstrated a lower progression in plaque volume compared with patients with follow-up LDL-C levels ≥70 mg/dl **(A)**. Likewise, the annual change in plaque volume was also attenuated for patients achieving low LDL-C <70 mg/dl level (the mean interscan period was 3.2 ± 1.1 years) **(A and B)**.

TABLE 5 Association Between Annual Plaque Volume Change and Clinical Variables

	Univariate Beta	p Value	Multivariate Beta	p Value
Age, yrs	0.130	0.118	0.149	0.077
Male	0.083	0.316		
BMI, kg/m^2	0.165	0.045	0.113	0.178
Hypertension	0.170	0.040	0.143	0.089
Diabetes mellitus	−0.039	0.639		
Active smoking	0.105	0.207	0.125	0.137
Follow-up LDL-C ≥70 mg/dl	0.195	0.018	0.193	0.021
Statin use	−0.123	0.137		

The mean interscan period was 3.2 ± 1.1 years.
Abbreviations as in Table 1.

high-intensity statin therapy achieved an average LDL-C of 60.8 mg/dl and demonstrated significant atherosclerosis regression. Similarly, Inoue et al. (18) enrolled 32 patients, with 24 individuals receiving fluvastatin treatment. These patients underwent serial coronary CTA imaging after a median treatment interval of 12 months. The study confirmed that plaque volume, especially low-attenuation plaque volume, was reduced. However, low-dose statin (10 mg) over this short period did not mediate changes in the total plaque volume. Moreover, the study omitted patients with severe calcification, thus introducing potential selection bias that may have influenced the general applicability of these findings. Recently, another serial coronary CTA study reported that statin therapy resulted in a reduced low-attenuation plaque progression compared to that observed in non-statin users (31). The present study's findings are in line with these prior studies and extend the overall literature that demonstrates the potential utility of coronary CTA, not only for clinical evaluation of atherosclerosis progression, but also for examining volumetric differences in atherosclerotic plaques over time. To our knowledge, these data represent the longest interscan period for a serial study to date, and provide information as to the longitudinal effects of therapy on atherosclerosis.

TABLE 6 Subgroup Analysis of Patients Taking Statins

	F/U LDL-C <70 mg/dl (n = 37)	F/U LDL-C ≥70 mg/dl (n = 70)	p Value
Initial plaque volume, mm^3	274 ± 193	359 ± 295	0.118
Change in plaque volume, mm^3	12.7 ± 38.2	41.8 ± 60.0	0.009
Annual change in plaque volume, mm^3	4.6 ± 15.0	14.5 ± 22.0	0.015

Values are mean ± SD.
Abbreviations as in Table 3.

The ACC/AHA guidelines (32), published in 2013, recommended basing the decision on scoring system and that patients whose overall 10-year risk score was determined to be 7.5% or greater should start statin therapy. In these guidelines, a "treat to target" goal for LDL-C is no longer recommended. However, our subgroup analysis showed that even though the patients used statin, reducing LDL-C lower than 70 mg/dl attenuated plaque progression, which means using statin is not always effective to reduce plaque progression.

Given the strong relationship between LDL-C lowering and reduction of atherosclerosis progression, the present findings indicate that noninvasive evaluation of plaque volumetric changes can be used as a surrogate marker of cardiovascular risk. Assessment of morbidity and mortality as primary endpoints in conventional large-scale clinical trials of established and novel agents is and will remain the "gold standard" assessment of therapeutic efficacy. Nevertheless, these studies are generally hindered by a considerable financial cost and lengthy follow-up duration. Invasive imaging has therefore been employed to evaluate atherosclerosis as a surrogate marker in clinical trials that are designed to investigate plaque progression. Given the safety concerns, patients enrolled in invasive imaging studies (primarily IVUS) have been selected as a function of the disease burden, with prior investigations requiring individuals to have one obstructed vessel and another diseased coronary vessel that has not undergone angioplasty. Therefore, only patients with advanced atherosclerotic, obstructive disease have traditionally been enrolled in IVUS studies. IVUS studies remain expensive and invasive, and are inappropriate for routine serial follow-up studies. By contrast, we were able to evaluate patients with mild and moderate plaque burden in our current study, based on the noninvasive nature of coronary CTA, which permits plaque quantification with accuracy similar to IVUS (19). However, a randomized prospective comparative trial between coronary CTA and IVUS will be needed.

STUDY LIMITATIONS. This was a retrospective study, which might have potentially led to selection bias. Furthermore, only baseline and final lipid data were available, and as a consequence, longitudinal LDL-C control between coronary CTAs could not be confirmed. The fact that the proportion of patients on statin during the follow-up period was higher in the LDL <70 mg/dl group was a predictable result, indicating the individual clinician felt the risk to be high enough in the LDL <70 mg/dl group to set up a low target for control. However, the lack of significant correlation between statin administration and plaque

progression (Table 5) could be secondary to the fact that statin usage at a given time point was denoted to represent the entire follow-up period, which is a limitation of this retrospective study. When the baseline plaque volume was adjusted, the plaque volume was verified as a significant factor, and this attenuates the impact of follow-up LDL ≥70 mg/dl level, but rather only showed a trend. Therefore, it is correct that larger plaque volume at baseline leads to larger increase in plaque volume. However, there was no significant difference in the baseline plaque volume between the 2 groups, and lower LDL level, which is a modifiable factor, can markedly influence plaque progression in addition to the baseline plaque volume. Although we employed strict, standardized criteria for coronary CTA assessment, atherosclerosis findings may be influenced by the Hounsfield unit density, which is affected by a myriad of factors. Hence, decisions regarding plaque, lumen, or vessel volumes in this study were based on consensus among at least 2 physicians viewing the same data. Despite these limitations, this study used coronary CTA to estimate plaque volume in multiple patients and confirmed that plaque progression was slowed in patients who strictly controlled their LDL-C levels.

CONCLUSIONS

The present study demonstrated that achievement of LDL-C control to levels <70 mg/dl are associated with a reduced rate and volume of plaque progression. Therefore, strict LDL-C control results in a decrease in the progression of annual plaque volumes as observed by serial coronary CTA.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: This study explores the relationship between temporal changes in coronary plaque volume and the intensity of lipid-lowering treatments by serial coronary CTA. Among the patients with CAD according to coronary CTA, achievement of LDL-C control to levels <70 mg/dl decreased the progression of annual plaque volumes as observed by serial coronary CTA. Furthermore, subgroup analysis of patients taking statins also demonstrated that the annual plaque volume progression could be attenuated with aggressive LDL control.

TRANSLATIONAL OUTLOOK: This study provides significant evidence that coronary plaque volume can be decreased by strict LDL-C control and also shows the possibility of quantitating plaque progression on the basis of serial coronary CTA. Additional studies are required to confirm that the noninvasive coronary CTA may be used as a useful tool for quantitative analysis of response to medications in the future.

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KEY WORDS atherosclerosis, coronary computed tomography angiography, coronary plaque quantification, low-density lipoprotein-cholesterol

APPENDIX For a supplemental figure and tables, please see the online version of this article.