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Decrease in LDL-C is associated with decrease in all components of noncalcified plaque on coronary CTA

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HIGHLIGHTS

- All components of noncalcified plaque decrease with LDL reduction.
- Calcified plaque volume increases in patients with LDL decrease and no decrease.
- Noncalcified plaque volume change may be optimal to assess efficacy of statin.

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ABSTRACT

Background and aims: LDL-C reduction has been associated with a decrease in noncalcified plaque (NCP) by serial quantitative coronary CT angiography (CTA). We evaluated the effect of LDL-C reduction on specific components of noncalcified plaque (NCP).

Methods: We analyzed 154 patients undergoing serial CTAs (118 men, 60 ± 10 years, interval 4 ± 2 years) with baseline LDL-C ≥ 70 mg/dl. Semi-automated software was used for quantifying plaque components based on CT attenuation in Hounsfield units (HU): 30-75, low attenuation plaque (LAP); 76–130, medium-low attenuation plaque (MLAP); 131–350, medium attenuation plaque (MAP); > 350, calcified plaque (CP). Decrease in LDL-C was defined as a reduction > 10% of baseline LDL-C. Plaque volume changes were compared between patients with (n = 85) and without (n = 69) LDL-C decrease.

Results: There was interval reduction in total plaque, LAP, MLAP, and MAP volumes in patients with LDL-C decrease *vs*. patients without LDL-C decrease before and after adjusting for differences between the two groups (all $p \leq 0.001$). An increase in CP volume occurred in both groups ($p = 0.42$).

Conclusions: Decrease in LDL-C was associated with reduction in all components of NCP measured by quantitative CTA. Change in total NCP volume may be the optimal measurement for assessing changes over time of coronary plaque on CTA.

1. Introduction

Low-density lipoprotein cholesterol (LDL-C) lowering with statins is associated with a reduction in major adverse cardiovascular events [1–3]. Studies employing gray scale intravascular ultrasound (IVUS) and virtual histology IVUS (VH-IVUS) have shown that LDL-C lowering is associated with a reduction in necrotic core and a concomitant increase in fibrofatty plaque [4–7]. As IVUS is invasive, it is not used for routine clinical monitoring of response to treatment. Coronary computed tomographic angiography (CTA) allows noninvasive

Abbreviations: CDD, contrast density difference; CP, calcified plaque; CTA, coronary CT angiography; DS, diameter stenosis; HDL-C, high-density lipoprotein cholesterol; HU, Hounsfield unit; IVUS, intravascular ultrasound; LAP, low attenuation plaque; LDL-C, low-density lipoprotein cholesterol; MAP, medium attenuation plaque; MLAP, medium-low attenuation plaque; NCP, noncalcified plaque; VH-IVUS, virtual histology IVUS

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quantification of plaque burden and plaque composition. We and others have shown with quantitative sequential CTA studies that a decrease in LDL-C is associated with a reduction or a slowing of increase of non-calcified plaque (NCP) [8,9]. Various components of NCP on CTA have been classified based on CT attenuation as a lipid rich component [low attenuation plaque (LAP)] and a non-LAP component comprised of a fibrofatty portion [medium low-attenuation plaque (MLAP)] and a fibrous portion [medium attenuation plaque)]. In our previous study, we observed that LDL-C lowering was associated with an overall reduction in NCP [9]; however, it is not known if change in NCP volume associated with a decrease in LDL-C is due to a reduction of specific components of NCP. By using semi-automated quantitation of these various plaque components, we sought to determine which components of NCP are associated with LDL-C decrease in patients who underwent sequential CTA studies.

2. Patients and methods

2.1. Study design

The study was based on 531 consecutive patients who underwent sequential CTA studies for clinical purposes at Cedars-Sinai Medical Center from 2007 to 2017 with at least 1 year between scans, and without percutaneous coronary intervention or coronary bypass grafting between scans (Fig. 1). After excluding patients with inadequate imaging quality (n = 47), absence of coronary artery plaque (n = 110), different CT imaging parameters between initial and follow-up scan (n = 32) and without lipid measurements within 30 days of CTA on both scans (n = 151), 191 patients were identified. After further exclusion of 37 patients with baseline LDL-C < 70 mg/dl, 154 patients were included in the study. The study was approved by the institutional review board and written informed consent was obtained.

2.2. Coronary computed tomographic angiography acquisition

CTA was performed on a dual-source CT scanner (Somatom, Siemens Medical Solutions, Forchheim, Germany) as previously described [10,11]. When needed, oral and/or intravenous beta blockers (metoprolol) were administered to achieve a target heart rate of 60 beats/min (bpm). Immediately before CTA scanning, 0.4 mg of sublingual nitroglycerin (ScielePharma, Alpharetta, Georgia) was administered. During a single breath-hold, images were acquired from the carina to the diaphragm. Images were acquired after a bolus injection of 80–100 ml contrast (Omnipaque or Visipaque, GE Healthcare, Princeton, New Jersey) at a rate of 5–6 ml/s, using either electrocardiography-gated prospective or helical scanning with dose modulation. The scan parameters were as follows: section collimation of 0.6 mm with z-flying focal spot, 330 ms gantry rotation time, reference tube current of 400 mAs per rotation, and a tube voltage of 120 kVp. Transverse images were reconstructed using filtered back projection with 0.75-mm slice thickness, 0.4 mm increment, and a medium-soft convolution kernel (B26f) [11]. Images with the least coronary artery motion, typically in mid-diastole, were collected for analysis and transferred to an off-line standard Windows workstation. The same scanner was used for all sequential CTA image acquisition and the same protocols were employed for image acquisition and reconstruction during baseline and follow-up scans in any individual patient. Patients with differences in acquisition and reconstruction protocols between the baseline and follow-up CTA were excluded from quantitative analysis. Quality assurance was tested daily with a CT water phantom to calibrate Hounsfield units.

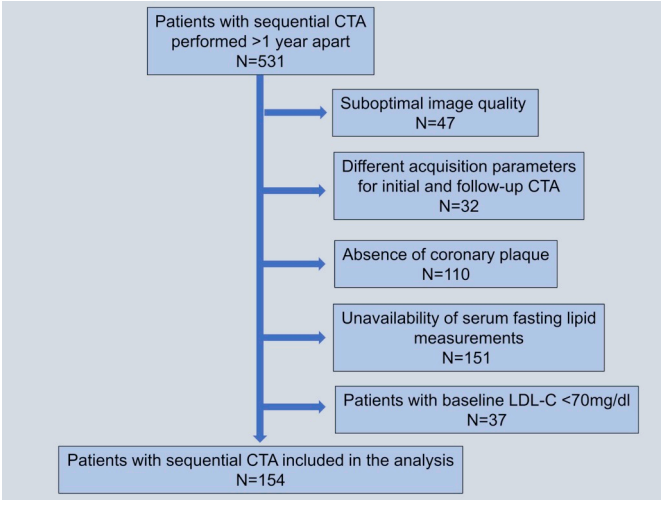

Fig. 1. Selection of patients for coronary CTA analysis.
Among 531 consecutive patients who underwent sequential CTA studies with at least 1 year between scans, we excluded patients with inadequate image quality, absence of coronary artery plaque, different CT imaging parameters between initial and follow-up scan, unavailability of fasting serum lipid measurements on both scans and baseline LDL-C < 70 mg/dl. The remaining 154 patients were included in the study. CTA = computed tomography angiography.

2.3. Coronary plaque analysis

All coronary segments with plaque ≥2 mm were analyzed using semi-automated software (Autoplaque version 2.0, Cedars-Sinai Medical Center, Los Angeles, CA, USA). Four experienced readers (B.T., Y·O., Y.A. and M.D.) who were blinded to the laboratory test data, performed the analyses of vessels with visible plaque in CTA images. The same reader analyzed the baseline and follow-up CTA scans side by side, using axial and multiplanar reformatted views, without knowledge of whether scans were at baseline or follow-up. The centerline for each coronary artery was extracted. Plaque and lumen characterization was performed semi-automatically on a per-segment basis between proximal and distal reference points, with manual adjustments by the expert reader as necessary. The minimum diameter stenosis (DS) was calculated as the ratio between the narrowest lumen diameter and the mean of the reference cross-sections. Remodeling index was determined as the ratio of maximum vessel area to that at the proximal normal reference point [12]. Luminal contrast density, defined as attenuation per unit area, was computed over 1-mm cross sections of the involved and adjacent arterial segments [13]. Contrast density difference (CDD) was defined as the maximum percent difference in luminal contrast densities relative to the proximal reference cross section without disease.

Four HU cut-off values were used for quantifying the following plaque components previously validated with VH-IVUS [14,15]; low attenuation plaque (LAP) (−30 to 75 HU), medium-low attenuation plaque (MLAP) (76–130 HU), medium attenuation plaque (MAP) (131–350 HU) and calcified plaque (CP) (> 350 HU). The corresponding plaque component volumes were computed. Plaque and stenosis measures were exported for analysis.

2.4. Measurement of clinical variables and definition of LDL-C groups

The assessment of clinical risk factors was performed from patient questionnaires at the time of CTA and by review of electronic medical records. Total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and LDL-C levels were measured on whole blood using a point of care device at the time of scanning (CholesTech LDX Cholesterol Analyzer [Abbott Laboratories, Princeton, NJ]) [16] or from plasma lipid panels obtained at the time of baseline and follow-up CTA. 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. Smoking was defined as either current use of cigarettes or their use within the past year [17]. Dyslipidemia was defined as TC ≥ 240 mg/dl, LDL-C ≥ 130 mg/dl, HDL-C ≤ 40 mg/dl, TG ≥ 150 mg/dl, or treatment with lipid-lowering agents. The decision to use statin therapy was determined by the referring clinician. Changes in volumes of individual plaque components, DS, CDD, remodeling index, and lesion length between the second and baseline study were compared between patients who experienced a decrease in LDL-C (decreased LDL-C group) with those who had no decrease in LDL-C (no decrease in LDL-C group). Changes in the volume of plaque components per year were given by dividing change in plaque volume by the time-in years-between serial CTA.

2.5. Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD), median and interquartile range, or mean and 95% confidence interval. Categorical variables are presented as numbers and proportions. Continuous variables were compared using the Wilcoxon rank-sum (Mann-Whitney) test. Wilcoxon signed-rank test was used to compare plaque parameters between baseline and follow-up scans. Chi-square test was used for the comparison of proportions. The relationship between decrease in LDL-C and changes in plaque volume per year was evaluated after adjusting for the effects of confounding variables including age, male gender, baseline LDL-C, uses of statin or angiotensin-converting-enzyme inhibitor at baseline, and total plaque volume at baseline. A p-value < 0.05 defined significant difference. Statistical analyses were performed with Stata software version 13 (StataCorp, College Station, TX, USA).

3. Results

3.1. Study population

Clinical characteristics of the study population are shown in Table 1. There was no significant difference in age, sex, body mass index (BMI) and prevalence of risk factors and symptom between decreased LDL-C group and no decrease in LDL-C group. The use of medications was similar between two groups except that ACE inhibitor was more commonly used in decreased LDL-C group. Indications for initial CTA at baseline were chest pain (46%), dyspnea (32%), risk factors for coronary artery disease (22%), abnormal stress test (6%), abnormal calcium score (6%), abnormal ECG (5%), and heart failure (1%). The mean interval between the CTA scans was 3.9 ± 1.9 years. There was no difference in the interval of serial CTA scans between patients with LDL-C decrease and no decrease (p = 0.60).

3.2. Statin use and lipid values

Changes in statin use and lipid values between baseline and follow-up scans are shown in Table 2. There were 85 patients with a decrease in LDL-C and 69 patients with no decrease. Baseline values of TC and LDL-C were significantly higher in the decreased LDL-C group compared to the no decrease group (p = 0.0005). At follow-up, TC, LDL-C, and TG were also significantly lower in the decreased LDL-C group compared to the no decrease group (p for all < 0.01). There was no significant difference in reported statin use at baseline and at follow-up between the two groups (33% vs 43% at baseline, p = 0.18; 60% vs 45% at follow-up, p = 0.06). However, there was an increase in statin use at follow-up in the LDL-C decrease group to 60% (p < 0.0001), whereas the proportion of statin treated patients in the no LDL-C decrease group remained relatively unchanged at 45% (p = 0.74).

3.3. Coronary plaque characteristics and composition at baseline

Baseline CT findings in the patients with and without decrease in LDL-C are shown in Table 3. There was no significant difference in the baseline coronary artery calcium score (available in 110 patients) or coronary plaque characteristics quantified by automated assessment including TP, total NCP, LAP, MLAP, MAP, and CP volumes, % DS, CDD and remodeling index and a borderline difference in lesion length.

3.4. Baseline, follow-up and changes in quantitative plaque parameters in LDL-C decrease and no decrease groups

Changes in coronary plaque parameters between baseline and follow-up in patients with LDL-C decrease and no decrease are shown in Table 4. The decreased LDL-C group had a reduction in TP, total NCP, LAP, MLAP, and MAP volumes at follow-up compared to baseline (p < 0.05 for all). In contrast, among patients who did not experience a decrease in LDL-C, there was an increase in TP, total NCP, and MAP volumes (p < 0.01 for all) and a statistically insignificant increase in

Table 1
Baseline clinical characteristics.

	All patients	LDL-C decrease	No LDL-C decrease	p value
Number of patients	154	85	69	
Age, years,	60 ± 10	61 ± 10	59 ± 10	0.28
Male, n, %	118, 77%	67, 79%	51, 74%	0.51
BMI, kg/m^2	26 ± 4	26 ± 4	27 ± 4	0.45
Risk factors, n, %				
Hypertension	67, 44%	40, 47%	27, 39%	0.32
Diabetes mellitus	14, 9%	8, 9%	6, 9%	0.88
Active smoking	7, 5%	2, 2%	5, 7%	0.15
Dyslipidemia	102, 66%	59, 69%	43, 62%	0.36
Symptom, n, %				
Chest pain	66, 43%	38, 45%	28, 41%	0.61
Dyspnea	50, 32%	25, 29%	25, 36%	0.37
Asymptomatic	77, 50%	42, 49%	35, 51%	0.87
Medications, n, %				
Statin	58, 43%	28, 37%	30, 50%	0.12
Beta blocker	32, 21%	22, 26%	10, 14%	0.08
ACE inhibitor	16, 10%	13, 15%	3, 4%	0.03
ARB	29, 19%	15, 18%	14, 20%	0.68
Ezetimibe	12, 8%	4, 5%	8, 12%	0.11
Time interval between studies (years), mean ± SD, median (IQR)	3.9 ± 0.2 3.7 (2.5–4.9)	3.9 ± 1.8 3.4 (2.3–4.7)	4.0 ± 2.0 3.8 (2.6–5.0)	0.60

ACE = angiotensin-converting-enzyme, ARB = Angiotensin II receptor blocker, BMI = body mass index, LDL-C = low density lipoprotein cholesterol.

Table 2
Circulating lipid levels and statin use at baseline and follow-up.

		All patients	LDL-C decrease	No LDL-C decrease	*p* value
Number of patients		154	85	69	
Statin use, n (%)	baseline	58, 38%	28, 33%	30, 43%	0.18
	follow-up	82, 53%	51, 60%	31, 45%	0.06
Baseline lipid values [median, IQR]					
TC, mg/dL		174, 149 - 200	186, 163 - 205	157, 144 - 184	0.0005
HDL-C, mg/dL		48, 37 - 61	45, 37 - 60	49, 40 - 62	0.66
LDL-C, mg/dL		101, 83 - 121	107, 90 - 130	89, 80 - 114	0.0005
TG, mg/dL		91, 62 - 130	98, 68 - 132	78, 58 - 121	0.07
Follow-up lipid values [median, IQR]					
TC, mg/dL		151, 132 - 187	134, 121 - 156	186, 152 - 217	< 0.0001
HDL-C, mg/dL		48, 38 - 61	48, 38 - 58	50, 40 - 63	0.36
LDL-C, mg/dL		84, 65 - 109	67, 57 - 83	107, 87 - 131	< 0.0001
TG, mg/dL		80, 52 - 121	76, 48 - 108	95, 62 - 144	0.0097

HDL-C = high-density lipoprotein cholesterol, IQR = interquartile range, LDL-C = low density lipoprotein cholesterol, TC = total cholesterol, TG = triglyceride.

Table 3
Baseline CTA findings.

	All	LDL-C decrease	No LDL-C decrease	*p* value
CAC	279 ± 426	306 ± 431	241 ± 419	0.26
Quantitative assessment				
TP volume, mm^3	644 ± 566	694 ± 569	581 ± 559	0.10
NCP volume, mm^3	579 ± 489	621 ± 484	527 ± 494	0.11
LAP volume, mm^3	172 ± 151	187 ± 160	154 ± 138	0.21
MLAP volume, mm^3	148 ± 121	159 ± 124	135 ± 117	0.17
MAP volume, mm^3	235 ± 224	252 ± 215	215 ± 235	0.07
CP volume, mm^3	86 ± 124	94 ± 134	76 ± 111	0.21
DS, %	42 ± 27	46 ± 29	37 ± 24	0.12
CDD, %	24 ± 23	27 ± 27	20 ± 17	0.12
Remodeling index	1.7 ± 0.4	1.7 ± 0.4	1.6 ± 0.4	0.36
Lesion length, mm	66 ± 49	73 ± 51	57 ± 45	0.05

Values are shown as mean ± standard deviation.
CAC = coronary calcium score, CDD = contrast density difference, CP = calcified plaque, DS = diameter stenosis, LAP = low attenuation plaque, LDL-C = low density lipoprotein cholesterol, MAP = medium attenuation plaque, MLAP = medium-low attenuation plaque, NCP = noncalcified plaque, TP = total plaque.

LAP and MLAP volumes. There was an increase in CP volume between baseline and follow-up in both groups ($p < 0.0001$ for both). The percent DS, CDD and remodeling index remained similar between baseline and follow-up in both groups. Lesion length significantly increased in patients who did not experience a decrease in LDL-C ($p = 0.0003$). TP, total NCP, LAP, MLAP and MAP volumes adjusted for time interval between CTA in patients were reduced in the LDL-C decrease group compared to the no decrease group, $p \leq 0.001$ (Fig. 2 and Table 5). The greatest difference between the groups was in NCP volume which increased by 27 mm^3/y in the group with no decrease in LDL-C vs. a decrease of 46 mm^3/y in the decreased LDL-C group, $p < 0.0001$. Small but non-significant decreases in %DS and %CDD were observed in the decreased LDL-C group. In contrast, small non-significant increases in %DS and %CDD along with a significant increase in lesion length was observed in the group with no decrease in LDL-C by the analysis adjusted for time interval. There was no change in annual remodeling index in either group (Table 5).

3.5. Changes in quantitative plaque parameters in the LDL-C decrease and no decrease groups after adjustment for confounding variables

After adjusting for age, sex, baseline LDL-C, use of statin or angiotensin-converting-enzyme inhibitor at baseline and TPV at baseline,

Table 4
Quantitative coronary plaque assessment at baseline and follow-up.

		Baseline	Follow-up	*p* value
TP volume, mm [3]	LDL-C decrease	694 ± 569	610 ± 461	0.006
	No LDL-C decrease	581 ± 559	710 ± 614	0.003
NCP volume, mm [3]	LDL-C decrease	621 ± 484	515 ± 379	0.0001
	No LDL-C decrease	527 ± 494	629 ± 534	0.03
LAP volume, mm [3]	LDL-C decrease	187 ± 160	136 ± 112	< 0.0001
	No LDL-C decrease	154 ± 138	177 ± 148	0.20
MLAP volume, mm [3]	LDL-C decrease	159 ± 124	126 ± 94	< 0.0001
	No LDL-C decrease	135 ± 117	153 ± 121	0.41
MAP volume, mm [3]	LDL-C decrease	252 ± 215	225 ± 169	0.04
	No LDL-C decrease	215 ± 235	262 ± 235	0.003
CP volume, mm [3]	LDL-C decrease	94 ± 134	122 ± 136	< 0.0001
	No LDL-C decrease	76 ± 111	113 ± 151	< 0.0001
DS, %	LDL-C decrease	46 ± 29	39 ± 21	0.09
	No LDL-C decrease	37 ± 24	40 ± 26	0.41
CDD, %	LDL-C decrease	27 ± 27	20 ± 13	0.34
	No LDL-C decrease	20 ± 17	23 ± 23	0.73
Remodeling index	LDL-C decrease	1.7 ± 0.4	1.7 ± 0.4	0.29
	No LDL-C decrease	1.6 ± 0.4	1.6 ± 0.3	0.76
Lesion length, mm	LDL-C decrease	73 ± 51	69 ± 48	0.14
	No LDL-C decrease	57 ± 45	70 ± 50	0.0003

Values are shown as mean ± standard deviation.
CDD = contrast density difference, CP = calcified plaque, DS = diameter stenosis, LAP = low attenuation plaque, LDL-C = low density lipoprotein cholesterol, MAP = medium attenuation plaque, MLAP = medium-low attenuation plaque, NCP = noncalcified plaque, TP = total plaque.

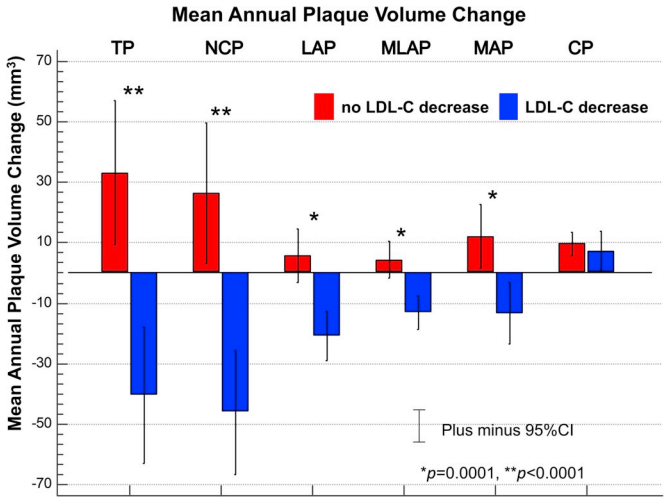

Fig. 2. Annual change in plaque volume and its components stratified by interval change in LDL-C from baseline after adjusting for confounding variables. Annual change in volume between baseline and follow-up studies (y-axis) of specific plaque components, expressed as mean and 95%CI. Blue bars represent patients with decrease in LDL-C; Red boxes represent patients with no decrease in LDL-C. Comparisons between the groups were adjusted for age, sex, LDL-C at baseline, use of statin or angiotensin-converting-enzyme inhibitor and plaque volume at baseline. CP = calcified plaque, CI = confidence interval, LAP = low attenuation plaque, LDL-C = low-density lipoprotein cholesterol, MAP = medium attenuation plaque, MLAP = medium-low attenuation plaque, NCP = noncalcified plaque, TP = total plaque.

patients with LDL-C decrease had a reduction in TP, total NCP, LAP, MLAP and MAP volumes expressed as change/year; whereas, in patients with no LDL-C decrease there was progression of atheroma with an increase in TP, total NCP, LAP, MLAP and MAP volumes ($p < 0.001$ for all, Table 5). As with the unadjusted data, the greatest difference in plaque volumes over time was in total NCP. The magnitude of increase in CP volume was similar between the two groups after adjustment for confounders ($p = 0.42$, Table 5).

4. Discussion

Reduction in LDL-C with statins has been consistently associated with improved clinical outcomes in multiple large randomized clinical trials. Trials using IVUS to assess plaque burden have demonstrated the association between a decrease in LDL-C and reduction in atherosclerotic plaque burden [18–20]. VH-IVUS studies have demonstrated a reduction in the necrotic core volume in response to statin therapy [21]. However, there are no prior studies with noninvasive imaging techniques that have quantitatively evaluated changes in the various components of noncalcified plaque (NCP) in response to LDL-C reduction. In this study, using an automated assessment of plaque on coronary CTA, we found that a modest reduction in LDL-C was associated with a reduction in the LAP, MLAP and MAP components of NCP while these volumes either increased or did not change in the LDL-C no decrease group. Since all changes in individual components of NCP were in the same direction, the greatest difference between the plaque measurements in the decrease in LDL-C and no decrease groups was in total NCP.

Prior studies have also evaluated serial change in coronary plaque on CTA. In a study of 116 patients, we have recently shown that LDL-C lowering is associated with a reduction in overall NCP volume using CTA [9]. A recent study by Shin et al. of 467 patients who underwent serial CTA demonstrated greater regression of NCP in statin treated patients with LDL-C < 70 mg/dl at follow-up compared to patients with LDL-C ≥ 70 mg/dl [22]. Zeb et al. reported changes in plaque components on serial CTA studies from 100 patients among whom 60 patients were treated with statins [23]. As with the current study, Zeb et al. documented a decrease in NCP volume among statin treated patients. They also reported a greater reduction in LAP, defined as plaque with < 30HU on CTA, in statin treated patients compared to non-treated controls. Similarly, in a prospective nonrandomized study of 32 patients, statin treatment in 24 patients was associated with a greater reduction in the volume of LAP (< 30HU) on serial CTA compared to non-treated controls [24]. In our study, there was an increase in statin use in the population witl LDL-C decrease, most likely driving the decrease observed in NCP volumes.

Findings regarding serial plaque changes on CTA were also studied in the recently reported PARADIGM study [8], which compared changes in fibrous, fibro-fatty and LAP volumes in 1255 statin-naïve and statin-treated patients who underwent serial coronary CTA studies at a mean interval of 3.8 years. Baseline LDL-C values and changes in LDL-C in the statin treated and non-treated groups in PARADIGM were similar to our study. In multivariable analysis, adjusting for baseline plaque volume, LDL-C, lesion location, use of antiplatelets and beta-blockers, and clinical risk factors for CAD, there was a reduction of the rate of increase in LAP and MLAP volumes in the statin-treated compared to the statin-naïve patients, but no difference in the rate of increase in calcified plaque volume.

The results of the current study are similar to PARADIGM in showing an association between both LDL-C reduction and statin use with beneficial changes in NCP volumes. Different software and different HU thresholds for LAP and MLAP (fibro-fatty) and MAP (fibrous) were used to define three different types of NCP. The current study used

Table 5
Annual change in quantitative plaque characteristics stratified by changes in LDL-C.

	Mean [95%CI]		p^a unadjusted	p^b adjusted for confounding variables
	LDL-C reduction	No LDL-C reduction		
TP volume, mm [3]/year	−40 [-63, −18]	33 [9, 57]	< 0.0001	< 0.001
NCP volume, mm [3]/year	−46 [-67, −26]	27 [3, 50]	< 0.0001	< 0.001
LAP volume, mm [3]/year	−21 [-29, −13]	6 [-3, 15]	0.0001	< 0.001
MLAP volume, mm [3]/year	−13 [-19, −8]	4 [-2, 10]	0.0001	< 0.001
MAP volume, mm [3]/year	−13 [-23, −3]	12 [2, 23]	0.0001	< 0.001
CP volume, mm [3]/year	7 [1, 14]	10 [6, 14]	0.85	0.42
DS, %/year	−3 [-5, −1]	0 [-2, 2]	0.08	
CDD, %/year	−4 [-6, −1	1 [0, 2	0.26	
Remodeling index/year	0]	0]	0.33	
Lesion length, mm/year	−3 [-5, 0]	4 [1, 6]	0.0001	

CDD = contrast density difference, CI = confidence interval, CP = calcified plaque, DS = diameter stenosis, LAP = low attenuation plaque, LDL-C = low density lipoprotein cholesterol, TP = total plaque, MAP = medium attenuation plaque, MLAP = medium low attenuation plaque, NCP = noncalcified plaque.

[a] Unadjusted comparisons.

[b] comparisons adjusted for age, sex, LDL-C at baseline, use of statin or angiotensin-converting-enzyme inhibitor and plaque volume at baseline.

a broader HU window for LAP (−45HU to 30 HU) compared to the PARADIGM study (−30HU to 30HU), potentially explaining the non-significant difference in LAP among statin treated and statin naïve groups in PARADIGM. Of interest, PARADIGM showed that statin use was associated with slower progression of all components of NCP including LAP, whereas in our study, the LDL-C decrease group showed a reduction in NCP and all components. The reason for this difference is not clear, but may be due to the differences in software employed. Our findings of a reduction in LAP, MLAP, and MAP components of NCP in response to a reduction in LDL-C using quantitative CTA are consistent with a previous report of reductions in necrotic core, fibrofatty and fibrous components of plaque in patients with acute coronary syndrome who were treated with statins and underwent sequential imaging with VH-IVUS [7].

We found that there was a non-significant decrease in %DS in both the LDL-C decrease and the no decrease groups. There was also a non-significant decrease in CDD, a parameter related to hemodynamically significant stenosis [25]. The minor changes observed in these parameters indicate that they are less likely to be useful than changes in coronary plaque components for assessing the effects of therapy.

Regarding the increase in CP volume among both the LDL-C decrease and no LDL-C decrease groups, multiple randomized trials have shown either no effect or, in more recent studies, an increase in coronary calcium score in patients treated with statins compared to controls [26–29]. Based on our results and those of PARADIGM, serial measurement of NCP volume and components of NCP would be superior for the assessment of coronary calcium in response to therapy aimed at LDL-C reduction.

4.1. Limitations

This was a retrospective study with small sample size from a single center and the results may not be generalizable to large populations with different demographic characteristics. The study was not designed to test the effect of statins on plaque composition since patients were not randomized to different treatment arms, and changes in LDL-C could have occurred due to other factors such as diet and exercise. Since the information regarding the use of all other lipid-lowering therapies (i.e., niacin, fibrates) was not available, adjustment for potential confounding effects from other lipid lowering medications was not performed.

4.2. Conclusions

LDL-C reduction is associated with reduction in volumes of all components of NCP measured by semi-automated quantitative software from CTA. Change in total NCP may be the optimal measurement for assessing changes over time of coronary artery plaque on CTA for clinical or research purposes.

Conflict of interest

Drs. Berman, Dey, and Slomka participate in software royalties at Cedars–Sinai Medical Center. No other potential conflict of interest relevant to this article was reported.

Author contributions

Drs. Otaki, Tamarappoo and Berman conceived planned the study design. Drs. Otaki, Tamarappoo, Doris, and Arnson performed quantitative plaque analysis. Dr. Otaki performed the statistical analysis and took the lead in writing the manuscript with input from Drs. Tamarappoo and Berman. Drs. Tamarappoo and Berman encouraged Dr. Otaki to investigate and supervised the findings of this work. All authors discussed the results and contributed to the final manuscript.

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