JACC: CARDIOVASCULAR IMAGING VOL. 5, NO. 3, SUPPL 3, 2012

ISSN 1936-878X/$36.00

PUBLISHED BY ELSEVIER INC.

DOI:10.1016/j.jcmg.2012.01.009

Natural History of Coronary Atherosclerosis by Multislice Computed Tomography

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OBJECTIVES This study sought to analyze the natural history of coronary atherosclerosis by multislice computed tomography (MSCT) and assess the serial changes in coronary plaque burden, lumen dimensions, and arterial remodeling.

BACKGROUND MSCT can comprehensively assess coronary atherosclerosis by combining lumen and plaque size parameters.

METHODS Thirty-two patients with acute coronary syndromes underwent 64-slice computed tomography angiography after percutaneous coronary intervention at baseline and after a median of 39 months. All patients received contemporary medical treatment. All available coronary segments in every subject were analyzed. The progression of atherosclerosis per segment and per patient was assessed by means of change in percent atheroma volume (PAV), change in normalized total atheroma volume (TAVnorm), and percent change in TAV (% change in TAV). Serial coronary remodeling was also assessed. Measures of lumen stenosis included percent diameter stenosis (%DS), minimum lumen diameter (MLD), percent area stenosis (%AS), and minimum lumen area (MLA). For each patient, the mean of all matched segments was calculated at the 2 time points. Clinical events at follow-up were documented.

RESULTS The PAV did not change significantly ($-0.15 \pm 3.64\%$, $p = 0.72$). The mean change in TAVnorm was 47.36 ± 143.24 mm^3 ($p = 0.071$), and the % change in TAV was 6.7% ($p = 0.029$). The MLD and MLA increased by 0.15 mm (-0.09 to 0.24, $p = 0.039$) and 0.52 mm^2 (-0.38 to 1.04, $p = 0.034$) respectively, which was accompanied by vessel enlargement, with 53% of the patients showing expansive positive remodeling. Patients with clinical events had a larger TAVnorm at baseline (969.72 mm^3 vs. 810.77 mm^3, $p = 0.010$).

CONCLUSIONS MSCT can assess the progression of coronary atherosclerosis and may be used for noninvasive monitoring of pharmacological interventions in coronary artery disease. (PROSPECT: An Imaging Study in Patients With Unstable Atherosclerotic Lesions; NCT00180466) (J Am Coll Cardiol Img 2012;5:S28–37) © 2012 by the American College of Cardiology Foundation

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Manuscript received January 12, 2012; revised manuscript received January 30, 2012, accepted January 30, 2012.

Coronary atherosclerosis is a worldwide pandemic disease and accounts for almost 17 million deaths annually (1). Although quantitative coronary angiography (QCA) has been used in the past to study the extent of the disease (2), this technique can only depict the contrast-enhanced lumen, whereas atherosclerotic disease of the arterial wall does not necessarily result in narrowing of the vessel lumen. Currently, the preferred method to study atherosclerosis is by intracoronary, cross-sectional imaging methods, such as intravascular ultrasound (IVUS) (3). There are numerous serial studies on atherosclerosis progression/regression by QCA and IVUS, including randomized medical trials using imaged plaque modification as surrogate endpoints. However, QCA and IVUS are invasive and costly and are not free of complications and thus are not used for routine serial assessment of atherosclerosis.

On the other hand, multislice computed tomography (MSCT) can assess coronary plaque in a noninvasive manner. MSCT coronary angiography has emerged as a noninvasive technique for the detection of coronary artery disease and has demonstrated good accuracy for the detection of coronary artery stenosis (4,5). Furthermore, studies in patients undergoing both IVUS and MSCT support the feasibility of MSCT to assess atherosclerotic plaque burden, remodeling, eccentricity, and calcified and noncalcified plaque in both stable and unstable patients (6–8).

Although a few serial studies with MSCT have been published (9–15), most prior analyses were confined to a small segment of the coronary tree or a specific subset of lesions (i.e., noncalcified). In the present study, our objective was to study the natural history of coronary atherosclerosis along the full length of the coronary tree by MSCT and to assess the serial changes in coronary plaque size, lumen dimensions, and arterial remodeling.

METHODS

Study population. We prospectively included patients who were enrolled at the Erasmus Medical Center in the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study (16). PROSPECT was designed to identify nonobstructing lesions with an increased risk for future acute coronary events in patients presenting with acute coronary syndromes (ACS) using IVUS and serological markers of inflammation. ACS was defined as ST-segment elevation myocardial infarction, non–ST-segment elevation myocardial infarction (troponin positive), or unstable angina with ECG changes (troponin negative). As a substudy of the multicenter study, we additionally performed contrast-enhanced computed tomography (CT) coronary angiography to noninvasively evaluate the extent of coronary atherosclerosis at baseline and at 3 years' follow-up. Patients were considered for inclusion in the MSCT substudy only if they had a heart rate lower than 70 beats/min during the MSCT acquisition and had no prior coronary bypass surgery. Exclusion criteria included impaired renal function (serum creatinine >120 mmol/l), contrast allergy, and irregular heart rhythms. Levels of fasting lipids were measured at baseline and follow-up. Medication use (including statins) after discharge was according to standard of care. The institutional review board of our hospital approved the study, and all patients provided written informed consent before study participation.

MSCT acquisition. At baseline, all patients underwent CT coronary angiography with a 64-slice scanner (Sensation 64, Siemens Medical Solutions, Forchheim, Germany). Because patients in the acute phase of ACS were already treated with intravenous nitrates and beta-blockers, additional medication before CT scan was not necessary. Scan parameters were as follows: a gantry rotation time of 330 ms, 32 × 2 slices per rotation, 0.6-mm detector collimation, spiral scan mode with a table feed of 3.8 mm per rotation, a tube voltage of 120 kV, and tube current of 900 effective mAs. Prospective ECG-triggered x-ray tube modulation was not applied. A bolus of 100 ml of contrast material (400 mg/ml; Iomeron, Bracco, Milan, Italy) was injected intravenously at 5 ml/s flow rate followed by a saline chaser. The initiation of the scan was synchronized to the arrival of contrast in the coronary arteries by a bolus-tracking technique. The mean effective radiation dose was 14.0 ± 0.8 mSv, using the dose-length product and a conversion factor k (0.014 mSv/mGy/cm) (17). Axial CT images were reconstructed with a slice thickness of 0.75-mm and 0.4-mm increments using a retrospective ECG gating algorithm to obtain optimal, motion-free image quality. Optimal datasets with the best image quality were reconstructed mainly in the mid- to end-diastolic phase, using a medium-smooth convolution kernel.

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome
AS = area stenosis
CT = computed tomography
DS = diameter stenosis
ECG = electrocardiogram
IQR = interquartile range
IVUS = intravascular ultrasound
LDL = low-density lipoprotein
MLA = minimum lumen area
MLD = minimum lumen diameter
MSCT = multislice computed tomography
PAV = percent atheroma volume
QCA = quantitative coronary angiography
TAV = total atheroma volume

The follow-up scan was performed after 3 years, using a 64-slice dual-source CT scanner (Somatom Definition, Siemens Medical Solutions, Forchheim, Germany). Sublingual nitroglycerin was administered before the scan (0.4 mg/dose) provided that there were no contraindications, and pre-scan beta-blockers were given to patients with high heart rates >70 beats/min. The CT angiographic scan parameters were as follows: 32 × 2 × 0.6 mm collimation with z-flying focal spot for both detectors, gantry rotation time of 330 ms, tube voltage of 120 kV, and tube current of 320 to 412 mAs per rotation. A bolus of iodinated contrast material (370 mg/ml; Ultravist, Schering, Berlin, Germany), which varied between 60 and 100 ml, depending on the expected scan time, was injected intravenously (flow rate 5.5 ml/s) followed by a 40-ml saline chaser at the same injection rate. A bolus tracking technique was used to synchronize the arrival of contrast in the coronary arteries and the start of the acquisition. A spiral scan protocol with prospective ECG-triggered x-ray tube modulation and variable table feed depending on the heart rate was applied. The estimated mean effective radiation dose was 10.0 ± 3.2 mSv. Axial images were reconstructed using retrospective ECG gating, with a slice thickness of 0.75-mm, slice increment of 0.4-mm, and medium-to-smooth convolution kernel. Optimal datasets with the best image quality were reconstructed mainly in the mid- to end-diastolic phase.

MSCT analysis. All datasets were transferred to an offline workstation for analysis using a semiautomated plaque analysis software (QAngioCT Research Edition version 1.1.8, Medis Medical Imaging Systems, Leiden, the Netherlands) (18). An experienced observer blinded to the sequence of imaging evaluated the scans. Planimetry of the inner lumen and outer vessel areas was performed following a stepwise approach. First, a centerline originating from the ostium was automatically extracted; then straightened multiplanar reformatted images were generated, and the lumen and vessel borders were detected longitudinally on 4 different vessel views by the software. On the basis of these longitudinal contours, cross-sectional images at 0.5-mm intervals were calculated in order to create transversal lumen and vessel wall contours, which were examined and, if necessary, adjusted by an experienced observer (Fig. 1). The settings for window level and width were fixed at 740 HU and 220 HU, respectively. Gradient magnitude images, which are derived from the MSCT images and display the degree of CT density change, were used

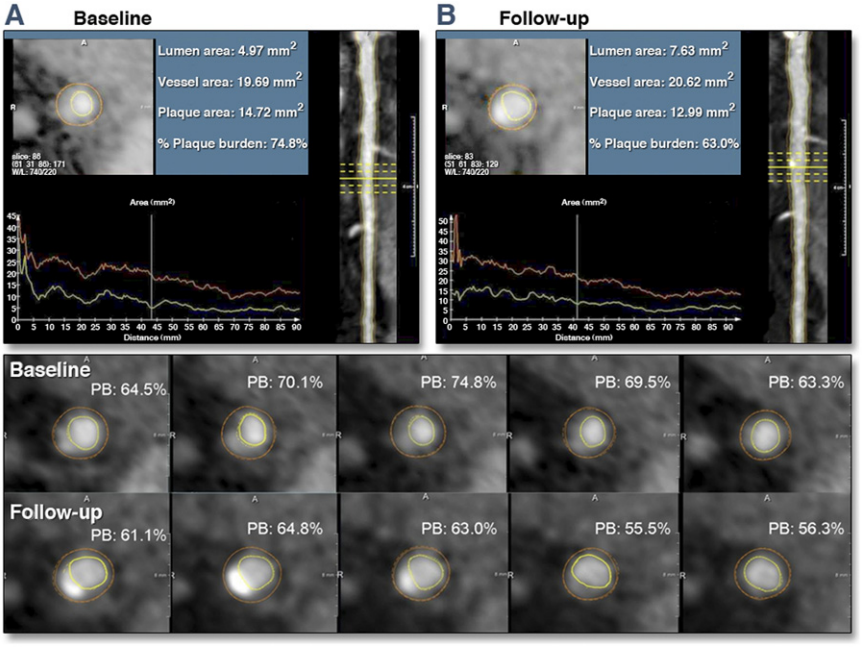

Figure 1. Multislice Computed Tomography Angiography Analysis

Example of vessel analyzed at baseline **(A)** and 3-year follow-up **(B)**. In both panels, 5 lines indicate the location in the vessel of the cross-sections shown at the bottom of the figure (from proximal to distal). In this lesion, the plaque burden (PB, %) decreases consistently from baseline to follow-up in the 5 cross-sections analyzed.

to facilitate detection of lumen and vessel wall borders.

All 3 vessels were assessed in every patient using the modified 17-segment American Heart Association model for coronary segment classification (19). Only the major epicardial vessels were considered for analysis (segments 1, 2, 3, 6, 7, 8, 11, 13, and 15). All anatomically available segments without implanted stents were examined; the segments of poor quality due to stack or movement artifacts or extreme calcification were excluded from analysis, as well as the segments distal to stents.

The following parameters were derived per segment: the mean lumen area, the mean vessel area, the mean percent plaque burden, the minimum and maximum lumen diameter, and the minimum and maximum lumen area. The mean areas were the averaged measurements of all cross-sections for each segment. The mean plaque area was calculated by subtracting mean lumen area from mean vessel area, and the plaque volume was calculated for every segment by using the mean segment length from the 2 time points (3). Furthermore, the composition of each coronary segment was semiquantitatively evaluated: Each individual cross-section was binary labeled for the presence of calcium (yes/no), and the degree of calcification was assessed as a percent of the segment length (number of frames containing calcium/total number of frames in the segment). To examine inter- and intra-observer variability, a second reader re-analyzed 7 randomly selected segments, and the first reader re-analyzed 11 randomly selected segments 3 months after his/her original analysis.

Study imaging endpoints. The following parameters were calculated per segment and per patient.

QCA-LIKE PARAMETERS

Minimum lumen diameter (MLD): the narrowest lumen diameter within each segment

Percent diameter stenosis (%DS): [(reference diameter − MLD)/reference diameter] × 100%. The reference diameter was the largest (maximal) lumen diameter within each segment.

For each patient, the average %DS of all segments at baseline and follow-up was calculated. From these values, the change from baseline was calculated for each patient. In addition, the per-patient average of MLD (mm) of all segments was calculated at baseline and at follow-up for the matching segments. The average change in MLD at baseline was calculated for each patient using these values. Clinically relevant regression or progression was defined as a nominal change (from baseline to 3 years) of 10% for %DS and 0.2 mm for MLD (20).

IVUS-LIKE PARAMETERS

Percent atheroma volume (PAV): [(total vessel volume − total lumen volume)/total vessel volume] × 100%

Total atheroma volume (TAV): total vessel volume − total lumen volume

Normalized TAV (TAVnorm): [(total vessel volume − total lumen volume)/segment length] × mean segment length in the population. Normalization for segment length provides equal weighting of each patient in the calculation of atheroma volume (3).

Percentage change in TAV (% change in TAV): [(TAV follow-up − TAV baseline)/TAV baseline] × 100%

Minimum lumen area (MLA): the narrowest lumen area in each segment

Percent area stenosis (%AS): [(reference lumen area − MLA)/reference lumen area] × 100. The reference lumen area used was the largest (maximal) lumen area within each segment.

For each patient, the average %AS of all segments at baseline and follow-up was calculated. From these values, the change from baseline was calculated for each patient. Also, the per-patient average of MLA (mm^2) of all segments was calculated at baseline and at follow-up for the corresponding segments. The average change in MLA from baseline was calculated for each patient using these values.

Clinically relevant regression or progression in PAV was defined as a change (from baseline to follow-up) of >1% for PAV, which was the threshold for significant regression previously detected under intensive lipid-lowering treatment (21).

Coronary remodeling. As recommended for serial studies (3), remodeling was assessed as vessel area at follow-up minus vessel area at baseline. An increase in vessel area was considered positive remodeling, no change in vessel area was considered absence of remodeling, and a decrease in vessel area was considered negative remodeling. Furthermore, segments with positive remodeling were subdivided as expansive (over-compensatory) when Δvessel area/Δatheroma >1 or incomplete when Δvessel area/Δatheroma was between 0 and 1.

Clinical endpoints. Clinical event data were collected throughout the duration of the study at regular follow-up intervals and registered in the hospital clinical database. Major adverse cardiovascular events were defined as the composite of cardiac

Table 1. Baseline Patient Characteristics (n = 32)

Age, yrs	53 ± 10
Male	26 (81)
Risk factors	
Hypertension	9 (28)
Hypercholesterolemia	11 (34)
Diabetes mellitus	3 (9)
Current smoking	18 (56)
Family history of coronary artery disease	19 (59)
Obesity	3 (9)
Clinical condition at enrollment	
Unstable angina	9 (28)
Acute myocardial infarction	23 (72)
Cholesterol	
Total, mg/dl	180 ± 41
Low-density lipoprotein, mg/dl	124 ± 42
High-density lipoprotein, mg/dl	43 ± 12
Triglycerides, mg/dl	139 ± 87

Values are mean ± SD or n (%).

death, cardiac arrest, myocardial infarction, and rehospitalization due to unstable or progressive angina (16).

Statistical analysis. Continuous variables are presented as mean ± SD and median (interquartile range [IQR]), as indicated. Categorical variables are presented as counts and percentages. Continuous variables between the 2 different time points were compared by the paired samples *t* test if the data were normally distributed or the Wilcoxon signed rank test for non-normal data (as tested by the Kolmogorov-Smirnov test). A p value <0.05 was considered significant. Statistical analyses were performed with use of SPSS version 17.0 software (SPSS, Chicago, Illinois).

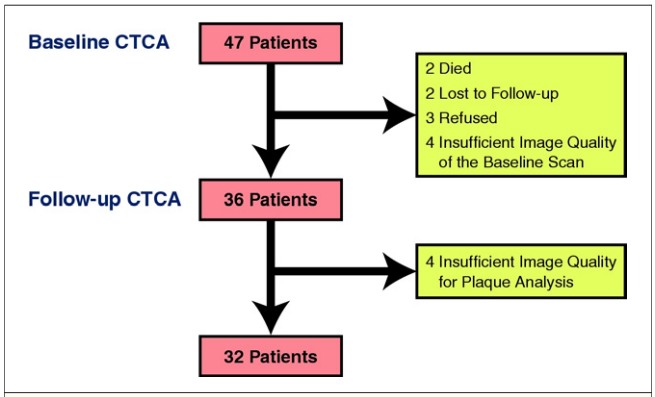

Figure 2. Flow of Study Patients

CTCA = computed tomography coronary angiography.

RESULTS

Baseline clinical and angiographic characteristics. From the original cohort of 47 patients undergoing baseline CTCA, 36 (77%) underwent a follow-up CTCA at 3 years. The follow-up scan was undertaken at a mean of 38 ± 3 months (median 39 months, IQR: 37 to 40 months) after the initial examination. The patients' baseline characteristics are shown in Table 1, and their disposition is shown in Figure 2. In total, 129 segments from 32 patients were analyzed. The mean length of analysis was 22.0 ± 9.5 mm per segment and 89.0 ± 40.5 mm per patient. The proportion of calcified frames per segment at baseline was 6 ± 12% versus 11 ± 17% at follow-up ($p < 0.001$).

All patients at discharge received standard-of-care medical therapy, including statins (29 patients received atorvastatin 40 mg/day, 2 patients received simvastatin 40 mg/day, and 1 patient received rosuvastatin 10 mg/day). One patient discontinued statin use due to an adverse effect. The mean total cholesterol was 180 ± 41 mg/dl at baseline and 150 ± 20 mg/dl at follow-up. The mean low-density lipoprotein (LDL) level was 124 ± 42 mg/dl at baseline and 85 ± 13 mg/dl at follow-up. The mean high-density lipoprotein level was 43 ± 12 mg/dl at baseline and 46 ±15 mg/dl at follow-up. The mean triglycerides value was 139 ± 87 mg/dl at baseline and 114 ± 76 mg/dl at follow-up.

MSCT QCA-like analysis. MEASURES OF STENOSIS PER SEGMENT. From baseline to 3-year follow-up, there was an increase in lumen dimensions, resulting in a decrease in the relative lumen stenosis (Table 2). In particular, there was a significant increase in MLD by 0.11 mm (IQR: −0.15 to 0.27 mm; p = 0.010), and this was accompanied by a decrease in %DS of −1.05% (IQR −7.15% to 5.08%; p = 0.257).

There were no clinically relevant changes in MLD (>0.2mm) in 45.7% of the segments, whereas 32.6% segments showed regression (≥0.2-mm increase in MLD) and 21.7% showed progression (≥0.2mm decrease in MLD) (Online Appendix). There was no statistically significant difference in the prevalence of progressors and regressors.

There were also no clinically relevant changes in %DS (>10%) in most of the segments (70.5%), whereas 17.8% of the segments showed regression (≥10% decrease in %DS) and 11.6% showed progression (≥10% increase in %DS). There was no statistically significant difference in the prevalence of progressors and regressors.

Table 2. MSCT QCA-Like Analysis

	Baseline	Follow-Up	Change	p Value	n (%) With Regression
Baseline and follow-up quantitative parameters analyzed per segment (n = 129)					
Minimum lumen diameter (mm)					82 (64)
Mean ± SD	2.49 ± 0.61	2.58 ± 0.72	0.09 ± 0.42		
Median (IQR)	2.36 (2.04–2.85)	2.41 (2.01–3.09)	0.11 (–0.15 to 0.27)	0.010*	
% Diameter stenosis					71 (55)
Mean ± SD	28.3 ± 10.0	27.6 ± 11.1	–0.68 ± 10.03		
Median (IQR)	27.6 (21.1–35.0)	26.0 (20.7–35.0)	–1.05 (–7.15 to 5.08)	0.257*	
Baseline and follow-up quantitative parameters analyzed per patient (n = 32)					
Minimum lumen diameter (mm)					23 (72)
Mean ± SD	2.51 ± 0.52	2.63 ± 0.62	0.11 ± 0.32		
Median (IQR)	2.42 (2.09–2.87)	2.47 (2.23–3.09)	0.15 (–0.09 to 0.24	0.039*	
% Diameter stenosis					17 (53)
Mean ± SD	28.1 ± 6.6	27.0 ± 7.5	–1.13 ± 6.39	0.326†	
Median (IQR)	28.6 (23.8–32.2)	26.4 (20.4–32.2)	–0.83 (–6.30 to 3.16)		

*Wilcoxon signed rank test; †paired *t* test.
IQR = interquartile range; MSCT = multislice computed tomography; QCA = quantitative coronary angiography.

MEASURES OF STENOSIS PER PATIENT. Similar findings were found on a per-patient level (i.e., an increase in lumen diameter and relative decrease in stenosis). The MLD increased by 0.15 mm (IQR: −0.09 to 0.24 mm; p = 0.039) and the %DS decreased by 0.83% (IQR: −6.3 to 3.16; p = 0.326).

There were no clinically relevant changes in MLD (>0.2 mm) in 46.9% of the patients, whereas 37.5% of patients showed regression (≥0.2 mm increase in MLD) and 15.6% showed progression (≥0.2 mm decrease in MLD). There was no statistically significant difference in the prevalence of progressors and regressors.

There were also no clinically relevant changes in %DS (>10%) in most of the patients (87.5%), whereas considerably fewer patients (9.4%) showed regression (≥10 decrease in %DS), and 3.1% showed progression (≥10% increase in %DS). There was no statistically significant difference in the prevalence of progressors and regressors.

MSCT IVUS-like analysis. PLAQUE VOLUMETRIC MEASURES PER SEGMENT. From baseline to 3-year follow-up, the PAV did not change significantly, whereas there was a significant relative percentage change in TAV by 5.8 ± 18.0% (p < 0.001) (Table 3). There were no clinically relevant changes in PAV (>1%) in 24.0% of the segments, whereas 38.8% segments showed regression (>1% decrease in PAV) and 37.2% showed progression (>1% increase in PAV) (Online Appendix). There was no statistically significant difference in the prevalence of progressors and regressors.

PLAQUE VOLUMETRIC MEASURES PER PATIENT. At 3-year follow-up, there was no significant change in PAV (mean difference −0.15 ± 3.64 mm^3; p = 0.819), whereas there was a trend toward increase in normalized TAV of 47.36 ± 143.24 mm^3 (p = 0.071). Similarly, there was a significant percentage change in TAV by 6.7 ± 16.6% (p = 0.029).

There were no clinically relevant changes in PAV (>1%) in 21.8% of the patients, whereas 34.4% patients showed regression (>1% decrease in PAV) and 43.8% showed progression (>1% increase in PAV). There was no statistically significant difference in the prevalence of progressors and regressors.

CORONARY REMODELING. Overall, the plaque increase occurred without compromising the lumen and was compensated for by an increase in vessel size (mostly expansive positive remodeling) (Table 4). Approximately one third of the patients/segments showed negative remodeling.

Clinical events. There were 8 clinical events in this cohort during the length of the study. Five events were related to the stented segment (3 patients with stent thrombosis, myocardial infarction, and repeat revascularization and 2 with repeat revascularization with angina), and the other 3 patients developed progressive angina. Of note, these patients presenting with clinical events had larger normalized TAV at baseline (969.72 vs. 810.77 mm^3; p = 0.010). We found no difference between patients with and without events regarding plaque progression (i.e., change from baseline in PAV or TAV).

Table 3. MSCT IVUS-Like Analysis

	Baseline	Follow-Up	Change	p Value	n (%) With Regression
Baseline and follow-up plaque quantitative parameters analyzed per segment (n = 129)					
Percent atheroma volume (%)					59 (46)
Mean ± SD	56.7 ± 7.3	56.7 ± 7.7	−0.07 ± 4.34		
Median (IQR)	58.0 (52.0–63.0)	58.0 (51.0–62.0)	0.0 (−3.0 to 3.0)	0.790*	
Total atheroma volume (mm^3)					49 (38)
Mean ± SD	217.2 ± 134.0	224.7 ± 136.9	7.52 ± 42.54		
Median (IQR)	183.4 (130.2–280.0)	194.2 (129.6–274.4)	7.08 (−14.38 to 29.01)	0.019*	
% Change in total atheroma volume					49 (38)
Mean ± SD			5.84 ± 17.98	<0.001‡	
Median (IQR)			4.55 (−4.27 to 20.96)		
Baseline and follow-up lumen quantitative parameters analyzed per segment (n = 129)					
Minimum lumen area (mm^2)					82 (64)
Mean ± SD	5.16 ± 2.68	5.65 ± 3.21	0.49 ± 1.84		
Median (IQR)	4.38 (3.27–6.34)	4.55 (3.17–7.49)	0.44 (−0.73 to 1.15)	0.009*	
% Area stenosis					70 (54)
Mean ± SD	47.6 ± 14.1	46.4 ± 15.2	−1.18 ± 13.86	0.336†	
Median (IQR)	47.8 (37.4–57.9)	44.8 (37.1–57.6)	−1.58 (−10.6 to 7.3)		
Baseline and follow-up plaque quantitative parameters analyzed per patient (n = 32)					
Percent atheroma volume (%)					15 (47)
Mean ± SD	56.0 ± 7.0	55.9 ± 7.3	−0.15 ± 3.64	0.819†	
Median (IQR)	56.6 (50.0–61.5)	57.9 (50.4–61.3)	0.72 (−2.75 to 2.41)		
Normalized total atheroma volume (mm^3)					11 (34)
Mean ± SD	850.5 ± 155.7	897.9 ± 175.4	7.36 ± 143.24	0.071†	
Median (IQR)	833.7 (753.4–930.1)	892.0 (736.0–993.1)	31.39 (−42.08 to 163.06)		
% Change in total atheroma volume					11 (34)
Mean ± SD			6.7 ± 16.55	0.029‡	
Median (IQR)			3.54 (−4.27 to 20.96)		
Baseline and follow-up lumen quantitative parameters analyzed per patient (n = 32)					
Minimum lumen area (mm^2)					22 (69)
Mean ± SD	5.26 ± 2.26	5.83 ± 2.78	0.57 ± 1.43		
Median (IQR)	4.66 (3.48–6.66)	4.84 (3.98–7.73)	0.52 (−0.38 to 1.04)	0.034*	
% Area stenosis					17 (53)
Mean ± SD	47.3 ± 9.4	45.5 ± 10.6	−1.72 ± 8.96	0.286†	
Median (IQR)	48.5 (41.8–43.5)	45.5 (36.5–52.8)	−0.68 (−9.31 to 3.92)		

*Wilcoxon signed rank test; †paired *t* test; ‡1-sample *t* test.
IVUS = intravascular ultrasound; other abbreviations as in Table 2.

Observer variability. For the 11 segments included in the intra-observer analysis, there were a total of 523 cross-sections analyzed. The mean differences were small for both lumen (−0.16 ± 0.93 mm^2) and vessel areas (−0.11 ± 1.17 mm^2). The correlations between the original and subsequent analysis were high (r = 0.98 for lumen areas, r = 0.98 for vessel areas). For the 7 segments included in the inter-observer analysis, there were a total of 335 cross-sections analyzed. The mean differences were also small for both lumen (0.01 ± 1.19 mm^2) and vessel areas (−0.08 ± 1.31 mm^2). Close correlations between the original analysis and re-analysis were found (r = 0.97 for lumen, r = 0.98 for vessel areas). The repeatability results are very much in line with previous IVUS reports.

DISCUSSION

The purpose of this exploratory substudy was to assess the natural history of coronary atherosclerosis by MSCT in patients with an ACS who were

Table 4. Coronary Remodeling Endpoints

Per segment (n = 129)	
Serial remodeling (mm^2)	0.82 ± 2.83*
Positive remodeling	
Expansive	61 (47)
Incomplete	23 (18)
Negative remodeling	45 (35)
Per patient (n = 32)	
Serial remodeling (mm^2)	1.10 ± 2.68†
Positive remodeling	
Expansive	17 (53)
Incomplete	6 (19)
Negative remodeling	9 (28)

Values are mean ± SD and n (%). *p = 0.001; †p = 0.027.

treated with percutaneous coronary intervention and contemporary medical therapy.

The main findings of this report are as follows: despite standard-of-care treatment, the atheroma size in untreated non-culprit lesions increased over 3 years, compensated for by an increase in the vessel size (positive expansive remodeling) and without compromising the lumen. Our MSCT findings on atherosclerosis progression fit closely to the regression line of the relationship between mean LDL under treatment and median change in PAV from previous IVUS studies (Fig. 3).

Plaque burden and coronary events. IVUS studies (28) have demonstrated that there is a direct association between the burden of coronary atherosclerosis, its progression, and the presence of clinical events at follow-up. Similarly, in the main PROSPECT study, lesions with plaque burden >70% were shown to be strongly associated with future clinical events (16). Our data are in accordance with these findings, because the patients presenting with clinical events had greater amount of plaque at baseline. This observation could contribute to the potential development of prediction models based on atherosclerotic plaque burden.

Coronary remodeling. Motoyama et al. (29) and Hoffmann et al. (6) described that the plaques in patients with ACS have positive remodeling and are associated with events. Consistent with the original description by Glagov et al. (30), our MSCT data showed that arteries enlarge as atherosclerosis progresses. Previous serial IVUS reports have demonstrated that atheroma burden does not limit com-

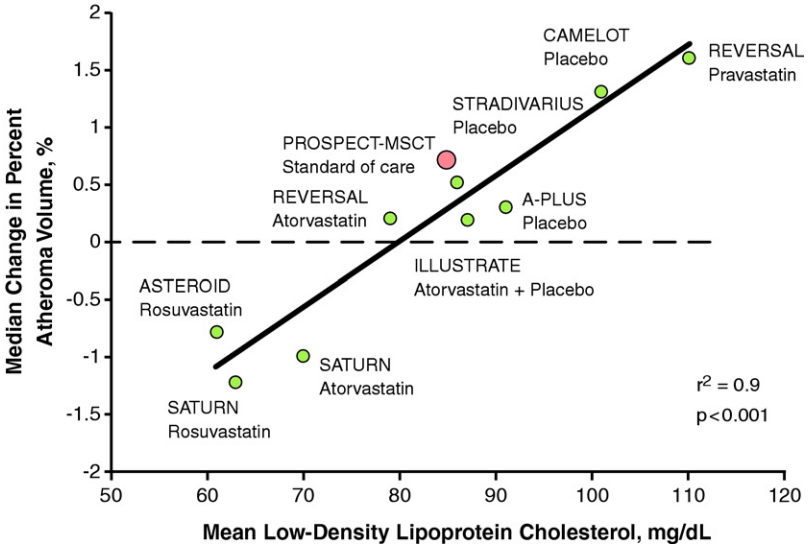

Figure 3. Association Between Mean Low-Density Lipoprotein Cholesterol Levels and Median Change in Percent Atheroma Volume for Several Intravascular Ultrasound Studies

A-Plus = Avasimibe and Progression of Lesions on Ultrasound (22); ASTEROID = A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (21); CAMELOT = Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis (23); ILLUSTRATE = Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation (24); REVERSAL = Reversal of Atherosclerosis With Aggressive Lipid-Lowering (25); SATURN = Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin (26); STRADIVARIUS = Strategy to Reduce Atherosclerosis Development Involving Administration of Rimonabant—The Intravascular Ultrasound Study (27); PROSPECT = Providing Regional Observations to Study Predictors of Events in the Coronary Tree (multislice computed tomography substudy). Modified from Nissen et al. (21).

pensatory remodeling (31), whereas there is a broad spectrum of serial remodeling responses in coronary atherosclerosis (32,33).

Importantly, arterial remodeling changes closely relate to changes in PAV, which is the most common primary IVUS endpoint. In the absence of actual change in plaque volume, positive remodeling could reduce PAV, whereas negative remodeling would increase PAV.

Progression/regression analysis using MSCT. MSCT can assess coronary atherosclerosis by combining the 2 "worlds" of QCA-like and IVUS-like parameters. To our knowledge, this comprehensive approach used in our study was not performed in previous MSCT studies. Furthermore, the follow-up time of our report (median 39 months) is the longest duration to date reported in progression/regression studies.

Previous papers have shown that MSCT is comparable to QCA angiography regarding lumen stenosis assessment (4,5); similarly, IVUS and MSCT comparative studies (6–8) have shown that the MSCT can reasonably evaluate atherosclerotic plaque size, remodeling, eccentricity, and composition, despite the acknowledged limitations of the technique. Voros et al. (8) suggested that quantitative MSCT angiography could be acceptably used in population-based approaches, given the small mean differences between MSCT and IVUS-virtual histology measurements.

Interestingly, our results closely fit the regression line in the classical graph depicting the relation between mean LDL levels and median change in PAV for several previous IVUS progression/regression studies.

Most prior IVUS studies have used PAV as the primary endpoint; however, the percentage change in TAV may be more suitable for MSCT studies, because not only 1 coronary segment can be imaged, but the full coronary tree can be assessed. Conversely, considering the resolution and reproducibility of MSCT, the minute changes in PAV observed in IVUS studies may be more difficult to detect.

Study limitations. This is a single-center feasibility study that comprised a selected small population of patients presenting with ACS, and the findings may be different in stable patients. Due to the small sample size, multivariate analysis was not performed. Furthermore, the baseline CT scans were obtained with an earlier generation 64-slice CT scanner, which may have produced inferior image quality compared with dual-source CT equipment used during follow-up. Nevertheless, we were able to detect changes of coronary atherosclerosis during the follow-up period. Because this was not a drug efficacy study, the patients received contemporary medical therapy at the discretion of the treating physician; however, the vast majority of patients (91%) received 40 mg of atorvastatin, which made the statin use relatively uniform. Finally, radiation exposure during MSCT coronary angiography still remains a matter of concern. Nonetheless, significant reductions of radiation dose are currently being achieved by implementation of dose-saving techniques (34), which result in effective dose less than the ~5 mSv of the invasive coronary angiography.

CONCLUSIONS

MSCT provides insightful information on the natural history of coronary atherosclerosis and may be used for noninvasive monitoring of pharmacological interventions for coronary artery disease.

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Key Words: atherosclerosis ■ computed tomography coronary angiography ■ coronary plaque ■ disease progression.

▶APPENDIX

For additional tables including supplemental data, please see the online version of this article.