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Citation: Wang, Zhao; Cho, Young-Seok; Soeda, Tsunenari et al. "Three-Dimensional Morphological Response of Lipid-Rich Coronary Plaques to Statin Therapy." *Coronary Artery Disease* 27, 5 (August 2016): 350–356 © 2016 Wolters Kluwer Health, Inc

As Published: <http://dx.doi.org/10.1097/mca.0000000000000370>

Publisher: Lippincott Williams & Wilkins

Persistent URL: <http://hdl.handle.net/1721.1/110913>

Version: Author's final manuscript: final author's manuscript post peer review, without publisher's formatting or copy editing

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Published in final edited form as:

Coron Artery Dis. 2016 August ; 27(5): 350–356. doi:10.1097/MCA.0000000000000370.

Three Dimensional Morphological Response of Lipid-Rich Coronary Plaques to Statin Therapy: A Serial Optical Coherence Tomography Study

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Abstract

Objective—Previous studies have suggested that intensive statin therapy, compared with moderate statin therapy, provided greater reduction of low-density lipoprotein and better protection against major cardiovascular events. However, the exact dose-dependent mechanism of plaque stabilization remains unclear. The objective of this study is to investigate the 3-D response of fibrous caps overlying lipid plaques to statin therapy.

Methods—We applied a novel computer algorithm to investigate the fibrous cap 3-D morphological change over time in patients with coronary artery disease. Patients were treated with either atorvastatin 20 mg/day (moderate intensity) or atorvastatin 60 mg/day (high intensity). Optical coherence tomography was performed at baseline, 6 months and 12 months. A total of 31 lipid plaques from 21 patients were analyzed.

Results—Conventional metrics such as the minimum fibrous cap thickness change between the two treatment groups were not significantly different between baseline and 12-month follow-up. In contrast, the 3-D metric thin cap (<80µm) surface area change between baseline and 12-month follow-up showed dose-dependent, significant differences between the statin treatment groups ($p <$

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Conflicts of interest and source of funding

Other authors have no conflicts of interest.

0.001). 3-D reconstructions of fibrous caps further revealed that fibrous caps exhibited diverse (scattered vs. confluent) patterns and could evolve in a complex manner.

Conclusions—High intensity statin therapy more effectively stabilized fibrous caps at follow-up. The new 3-D algorithm provided more comprehensive and detailed information on changes in plaque phenotype in response to statin therapy.

Keywords

Statin therapy; fibrous cap; optical coherence tomography

Introduction

Previous studies have suggested that lipid-lowering therapy with statin reduces low-density lipoprotein (LDL) and the risk of cardiovascular events [1]. The improved outcome is thought to be due to stabilization of vulnerable plaques. Optical coherence tomography (OCT) allows accurate assessment of fibrous cap thickness (FCT) [2]. Recent studies showed that statin therapy induced thickening of FC [3–4]. Komukai et al [5] showed that 20 mg/day atorvastatin provided a greater increase in minimum FCT compared with 5 mg/day atorvastatin. However, the 3-D vascular response of FC to statin therapy is unknown. In this study, we investigated the 3-D morphological change of FC using a novel 3-D algorithm and compared the results with those generated by conventional methods in randomly selected subset of patients from a larger prospective study (registered in [ClinicalTrials.gov](https://clinicaltrials.gov) as NCT01023607) [6].

Methods

Study Design and Participants

Eligible participants were statin-naïve patients aged 18–75 years old with coronary artery disease. Study inclusion criteria were: 1) at least one de novo lesion with luminal diameter stenosis between 20% and 70% on coronary angiogram, 2) a lipid rich plaque on OCT, and 3) LDL<160 mg/dL. The exclusion criteria included: 1) Life expectancy <12 months, 2) Contraindication to atorvastatin or rosuvastatin, 3) Creatinine level more than 2.0 mg/dL or end stage renal disease, 4) Severe hepatic dysfunction (AST and/or ALT more than 3 times the upper limit of normal), 5) Congestive heart failure (left ventricular ejection fraction 35%). The patients who met the study criteria were randomly assigned (1:1:1) to receive atorvastatin 20 mg (AT20, moderate intensity), rosuvastatin 10 mg (RT10, moderate intensity), or atorvastatin 60 mg (AT60, high intensity) [7] for 12 months. OCT was performed at baseline, 6- and 12-month follow-ups. Patients, study personnel, and study staff were blinded to treatment assignment. This protocol was approved by the institutional review board of Harbin Medical University. All patients provided informed consent prior to participation. Because the purpose of this study is to compare the fibrous cap (FC) differences induced by high intensity vs. moderate intensity statin therapy, only patients treated with AT20 or AT60 for 1 year were randomly selected from the main study and included for this study.

OCT Imaging and Image Analysis

All OCT procedures were performed after an intracoronary administration of 100–200 µg of nitroglycerin, either using a time-domain OCT (TD-OCT) system (M3 Cardiology Imaging System, LightLab Imaging, Inc., Westford, MA) or frequency-domain OCT (FD-OCT) system (C7-XR™ OCT Intravascular Imaging System, St. Jude Medical, St. Paul, MN). The study was conducted at Harbin Medical University between September 2009 and March 2013. All images were analyzed independently at Massachusetts Institute of Technology and Massachusetts General Hospital. A person who analyzed the images was blinded to the clinical and treatment information.

Lipid plaques at baseline were identified based on previously validated criteria on the presence of signal poor regions with diffuse borders [8]. Lipid plaques at baseline and follow-ups were matched using side branches and/or calcifications. FCs were assessed by three different methods (Fig. 1). First, conventional thinnest (minimum) fibrous cap thickness (tFCT) was assessed at each time point. Second, matched segment FCT (mFCT) was assessed by measuring the matching site at 6 and 12 months corresponding to the tFCT region at baseline. The definitions and measurements of tFCT and mFCT are consistent with previous studies [2], [6], respectively, but are named differently here to avoid confusion between each other. Third, the 3-D morphology of FC was analyzed by segmenting the FC boundaries using a recently developed algorithm [9]. This algorithm allows determination of the thickness of the entire FC and generation of 3-D metrics such as FC surface area, and was validated against three experienced human analysts [9]. Specifically, the algorithm asks the analyst to select the arc of each lipid plaque on a cross sectional image (Fig. 2A). Based on the lipid arc selection, the algorithm automatically computes the optimal FC boundaries by maximizing the intensity differences across the boundaries in the selected regions using a global optimization method (Fig. 2B) [9]. The FC boundaries of all the frames where a lesion is present are segmented (Fig. 2C). The analysts may adjust the boundaries if there was a segmentation error typically in case of luminal blood. Based on the segmentation, the computer algorithm automatically calculates a variety of volumetric metrics including the absolute FC surface area (SA) in a thickness category (Fig. 2D). For this study, we focused on FC surface area where FCT was $<80\mu\text{m}$ ($\text{SA}_{<80\mu\text{m}}$). The cut-off value was determined based on previous *in vivo* studies [10]. However, the measurement itself was intrinsically continuous as the thickness of all the points on the FC boundaries was determined. The segmented FCs were further rendered in 3D using a continuous colormap based on their thickness for 3-D visualization and assessment (Fig. 2D). It should be noted that although the single point analysis (e.g. mFCT) may be subject to difficulties of precisely matching the corresponding sites of FCs between baseline and follow-ups, the 3-D measurement does not suffer from this limitation because FCs of the whole plaque were segmented and compared. For FD-OCT, if a plaque was blocked by the guidewire, only the blocking part was excluded from the analysis.

To assess inter-observer variability of the FC surface area measurement, 20 OCT pullbacks including data acquired by TD-OCT (M3, LightLab Imaging, $n = 10$), and FD-OCT (C7-XR™, St. Jude Medical Inc. $n = 10$) were analyzed by two independent analysts. The longitudinal location of the plaque was defined by the first analyst according to objective

morphology of the plaque, but all algorithm-related process including Z-offset adjustment, segmentation of FC boundaries were independently and blindly done. To assess intra-observer variability, the same data were re-analyzed by the first analyst two weeks later.

Statistical Analysis

Categorical data were compared using either a Chi-square test or Fisher's exact test. Generalized estimating equations (GEE) were employed for comparing measurements between groups to take into account the correlation among multiple plaques within a single subject. Intra- and inter-observer agreement of the area measurement was evaluated by intra-class correlation coefficient (ICC). All statistical analyses were performed using SPSS version 17.0 (SPSS, Chicago, Illinois, USA). A two-sided p-value < 0.05 was considered statistically significant.

Results

A total of 31 lipid plaques (AT20 = 16, and AT60 = 15) from 21 patients (AT20 = 9 and AT60 = 12) were analyzed. There were no significant differences in baseline characteristics between the two groups (Table 1).

The laboratory finds are summarized in Table 2. LDL was significantly reduced from baseline to 6-month follow-up in both treatment groups. There was no further significant reduction of LDL from 6 to 12-month follow-up. Similar results were also observed for total cholesterol changes. There was no significant change of high-density lipoprotein (HDL) from baseline to follow-ups.

3-D FC surface area where FCT was <80 μ m ($SA_{<80\mu m}$) was assessed and compared with the conventional measurements including thinnest (minimum) FCT (tFCT) and matched-segment FCT (mFCT) (Fig. 3). The intra- and inter-observer agreement for assessing $SA_{<80\mu m}$ was 0.932 and 0.965 for TD-OCT cases, and 0.956 and 0.929 for FD-OCT cases, respectively. There were significant increases in tFCT from baseline to 12 months for both groups ($p = 0.005$ for AT20, and $p < 0.001$ for AT60). However, the change was not significantly different between the two groups (43.2 μ m [95% CI: 13.2 μ m to 73.2 μ m] for AT20, and 57.7 μ m [95% CI: 30.1 μ m to 85.4 μ m] for AT60, $p = 0.485$, Fig. 3A). Significant increases of mFCT were observed in both groups, and the change from baseline to 12 months was greater in AT60 than in AT20 ($p = 0.022$) (Fig. 3B). Significant decreases of $SA_{<80\mu m}$ were observed in AT60 (-7.84 mm² [95% CI: -10.07 mm² to -5.60 mm²], $p < 0.001$), but not in AT20 (-2.58 mm² [95% CI: -4.10 mm² to -1.06 mm²], $p = 0.140$). AT60 induced significantly greater decrease in $SA_{<80\mu m}$ from baseline to 12-month follow-up ($p < 0.001$, Fig. 3C). A complete comparison of the three measurements at the three time points is listed in Table 3. Representative cases after 3-D reconstructions show that the thin cap regions (red) presented as diverse patterns (scattered or confluent) in different locations at baseline (Fig. 4). In AT20 group the overall $SA_{<80\mu m}$ became smaller, however, new spots with $SA_{<80\mu m}$ appeared at 12 months. In contrast, AT60 group showed dramatic improvement with near complete disappearance of $SA_{<80\mu m}$.

Discussion

This is the first study that investigated the 3-D morphological changes of FC in response to different intensity statin therapy over time. The findings of this study have important clinical implications. Although the conventional methods (tFCT and mFCT) are useful, they suffer from sampling errors, and are insufficient to explain the 3-D remodeling of FC in response to statin therapy. The 3-D measurements generated full-segmentation of the FC boundaries, which promise a complete characterization of the FC morphology without requiring precisely matching the cross-sections of the plaque over time as required by the measurement of mFCT. In comparison, previous studies only evaluated FCT from single point measurements. For example, Komukai et al [5] demonstrated that the increase of tFCT was significantly greater with 20mg/day compared with 5 mg/day of atorvastatin. Hou et al [6] showed greater increase of mFCT with 60mg/day compared with 20mg/day of atorvastatin. However, it is unclear how the 3-D morphology of FC responds to different intensities of statin therapy. Our results complemented the previous studies, and further demonstrated that intensive statin therapy led to greater reduction of thin cap surface areas ($SA_{<80\mu m}$). This explains the lesion level mechanisms behind previous clinical findings that intensive statin therapy lowers major adverse cardiovascular events. Although the intensities of statin therapy compared in this study may not be exactly the same as some of the previous studies, the conclusion is consistent. Fibrous cap thickness is the most important determinant for plaque vulnerability [11]. Larger areas of thin cap directly translate into more vulnerable spots on a plaque. Therefore, the significant decrease of $SA_{<80\mu m}$ by intensive statin therapy may directly contribute to the reduction of risks of plaque rupture. However, future clinical studies by correlating the clinical outcomes of patients with 3D morphology of FC is needed to confirm this. In addition, 3-D measurements are not only more sensitive to detect difference in treatment effects, but can also provide additional information on the patterns of FC, which is potentially an important factor for vulnerability. It is conceivable that a plaque with a larger area of localized thin cap would be more vulnerable than a plaque with smaller scattered thin cap areas. Therefore, 3-D measurements should be a preferred method to better assess treatment effects and plaque vulnerability in future clinical studies.

The major limitation of this study is the small number of patients ($n = 21$). However, it is partially the purpose of this study to use a small number of patients for testing the efficacy of various metrics. Despite the small number of patients, the representative 3-D measurements such as $SA_{<80\mu m}$ changes between baseline and 12-month follow-up were already significantly different between the treatment groups ($p < 0.001$), supporting the value of the proposed 3-D metrics. Second, two groups with the same kind of statin were selected out of three original study, as the third group was treated with a different kind of statin (rosuvastatin). Third, due to the limited follow-up time, we have not assessed the association between the 3-D fibrous cap morphology and clinical outcome.

Conclusions

High intensity statin therapy more effectively stabilized fibrous caps at follow-up. The new 3-D algorithm provided more comprehensive information on fibrous cap morphology and is more sensitive to detect the changes in plaque phenotype in response to statin therapy.

Acknowledgments

This study was funded by the National Science Foundation of China (H.J., L.X. and B.Y.). Ik-Kyung Jang was supported by Mr. and Mrs. Michael A. Park, and by Mrs. and Mr. Gill and Allan Gray. Ik-Kyung Jang received a research grant and consulting fee from St. Jude Medical Inc.

References

1. Trialists CT. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. *The Lancet*. 2005; 366:1267–1278.
2. Kume T, Akasaka T, Kawamoto T, Okura H, Watanabe N, Toyota E, et al. Measurement of the thickness of the fibrous cap by optical coherence tomography. *Am Heart J*. 2006; 152:755.e1–e4. [PubMed: 16996853]
3. Hattori K, Ozaki Y, Ismail TF, Okumura M, Naruse H, Kan S, et al. Impact of statin therapy on plaque characteristics as assessed by serial OCT grayscale and integrated backscatter–IVUS. *JACC Cardiovasc Imaging*. 2012; 5:169–177. [PubMed: 22340823]
4. Takarada S, Imanishi T, Ishibashi K, Tanimoto T, Komukai K, Ino Y, et al. Inflammatory Profiles on the Morphological Changes of Lipid-Rich Plaques in Patients With Non–ST-Segment Elevated Acute Coronary Syndrome: Follow-Up Study by Optical Coherence Tomography and Intravascular Ultrasound. *JACC Cardiovasc Interv*. 2010; 3:766–772. [PubMed: 20650439]
5. Komukai K, Kubo T, Kitabata H, Matsuo Y, Ozaki Y, Takarada S, et al. Effect of Atorvastatin Therapy on Fibrous Cap Thickness in Coronary Atherosclerotic Plaque as Assessed by Optical Coherence Tomography The EASY-FIT Study. *J Am Coll Cardiol*. 2014; 64:2207–2217. [PubMed: 25456755]
6. Hou J, Xing L, Jia H, Vergallo R, Soeda T, Minami Y, et al. Comparison of Intensive versus Moderate Lipid-lowering Therapy on Fibrous Cap and Atheroma Volume of Coronary Lipid-rich Plaque Using Serial Optical Coherence Tomography and Intravascular Ultrasound Imaging. *Am J Cardiol*. 2015; 117:800–806. [PubMed: 26778524]
7. Stone NJ, Robinson JG, Lichtenstein AH, Merz CNB, Blum CB, Eckel RH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014; 129:S1–45. [PubMed: 24222016]
8. Yabushita H, Bouma BE, Houser SL, Aretz HT, Jang IK, Schlendorf KH, et al. Characterization of human atherosclerosis by optical coherence tomography. *Circulation*. 2002; 106:1640–1645. [PubMed: 12270856]
9. Wang Z, Chamie D, Bezerra HG, Yamamoto H, Kanovsky J, Wilson DL, et al. Volumetric quantification of fibrous caps using intravascular optical coherence tomography. *Biomed Opt Express*. 2012; 3:1413–1426. [PubMed: 22741086]
10. Yonetsu T, Kakuta T, Lee T, Takahashi K, Kawaguchi N, Yamamoto G, et al. In vivo critical fibrous cap thickness for rupture-prone coronary plaques assessed by optical coherence tomography. *Eur Heart J*. 2011; 32:1251–1259. [PubMed: 21273202]
11. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons From Sudden Coronary Death : A Comprehensive Morphological Classification Scheme for Atherosclerotic Lesions. *Arterioscler Thromb Vasc Biol*. 2000; 20:1262–1275. [PubMed: 10807742]

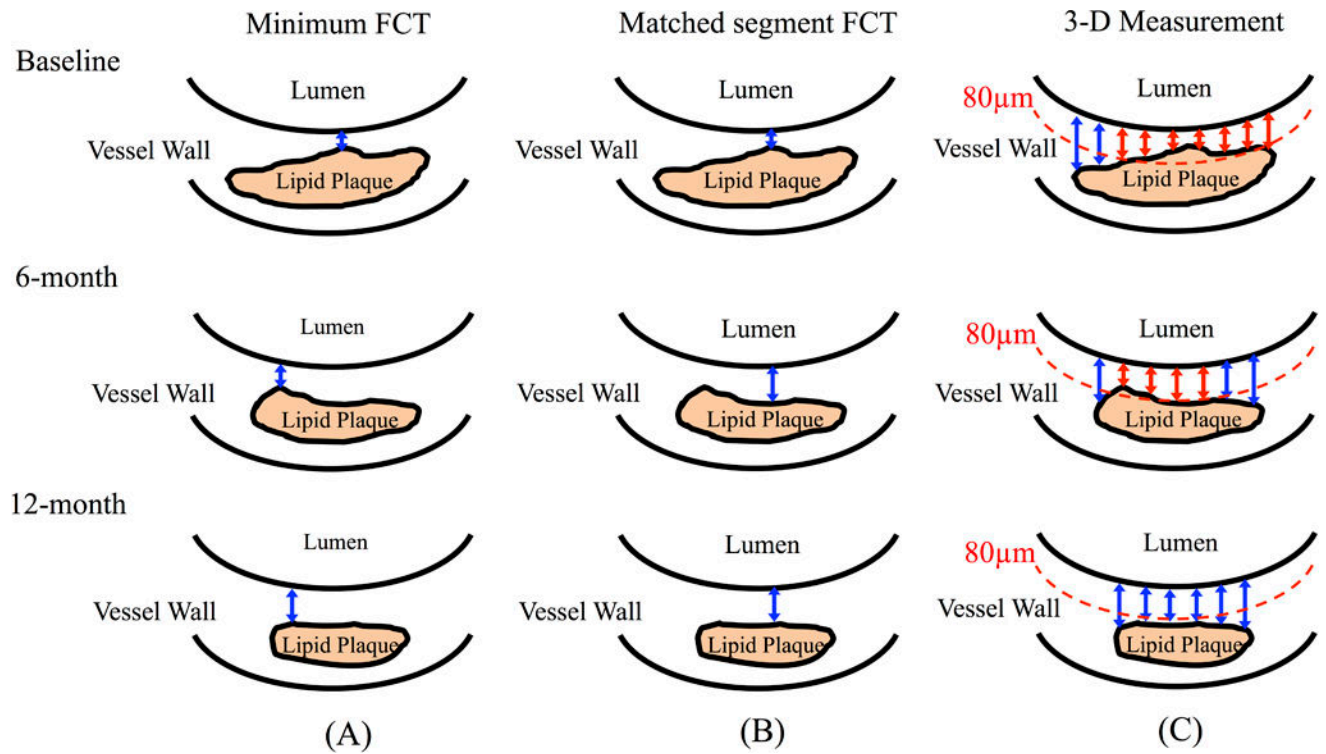


Figure 1.

Illustration of the three different ways to measure fibrous cap thickness (FCT). (A) Thinnest FCT was measured at the thinnest point of the fibrous cap at different time points. (B) Matched segment FCT was performed at the matching site of FCT at follow-ups corresponding to the thinnest FCT region at baseline. (C) 3-D measurement allowed the thickness of the entire fibrous cap boundaries to be determined. The fibrous cap area of each thickness category (e.g. $<80\mu\text{m}$) can further be computed.

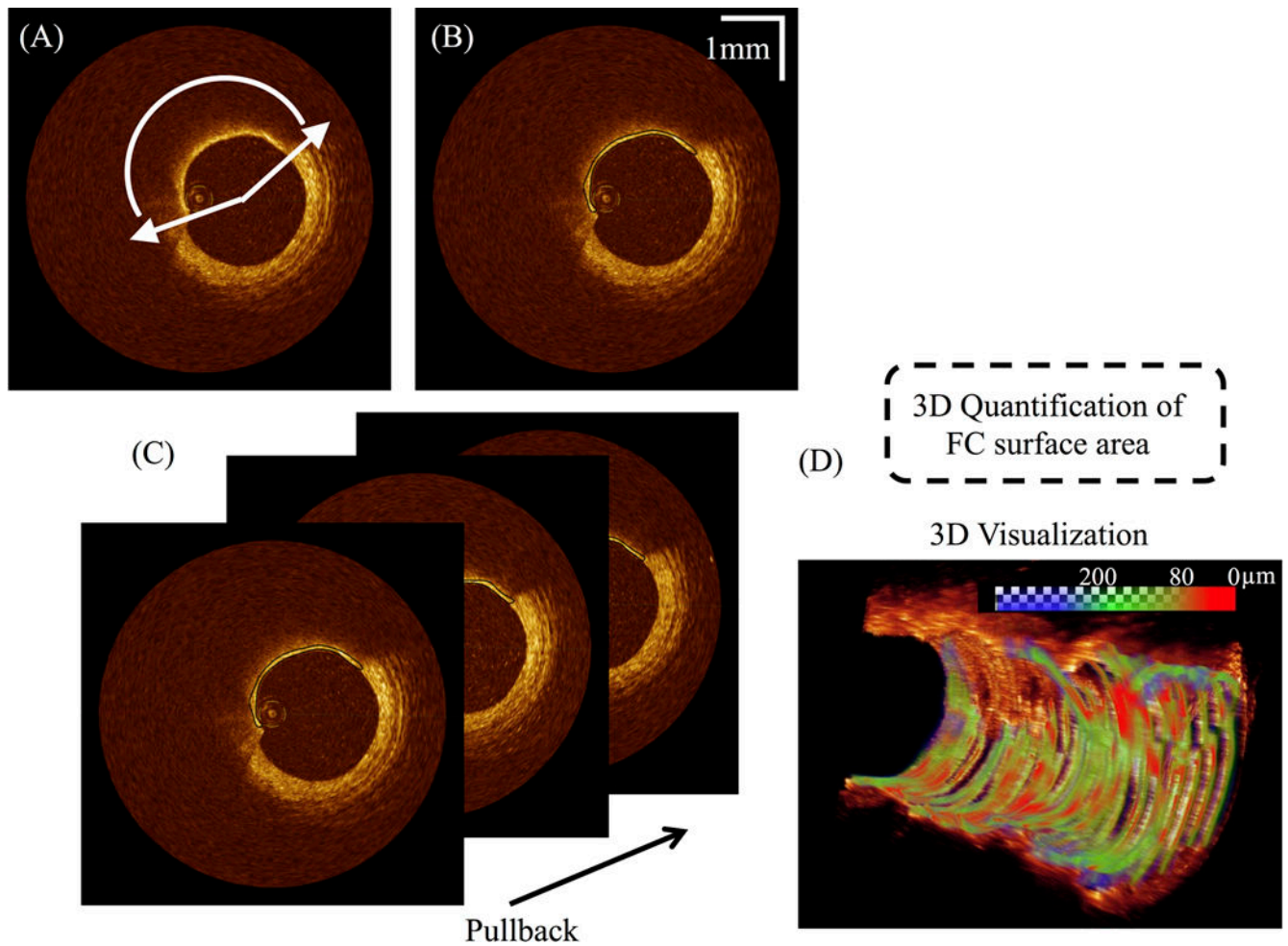


Figure 2.

Computer-aided image analysis algorithm for 3-D quantification of fibrous caps (FC). (A) A FC is shown at 8–1 o'clock. To perform 3-D analysis, one first selects the lipid arc as the input to the algorithm. (B) Based on the selected lipid arc, the algorithm automatically computes the optimal FC boundaries using a global optimization method. (C) The segmentation is performed in all frames where the FC is present. (D) 3-D metrics can be computed based on the segmentation. The FC can be reconstructed in 3D to assess plaque vulnerability.

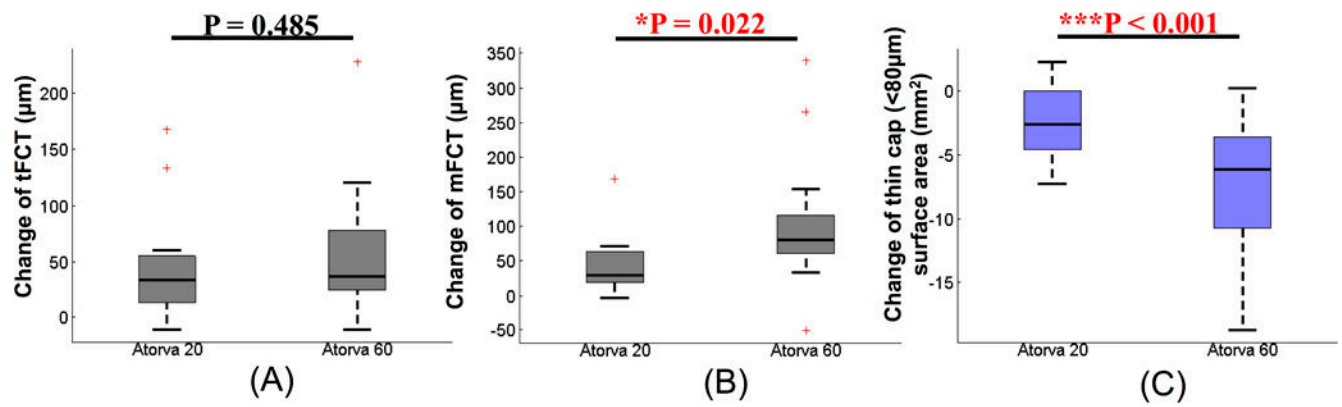


Figure 3.

Comparison between the changes of conventional fibrous cap (FC) measurements and 3-D measurements from baseline to 12 month follow-up. (A) Change of thinnest FCT. (B) Change of matched segment FCT. (C) Change of thin FC (<80µm) surface area.

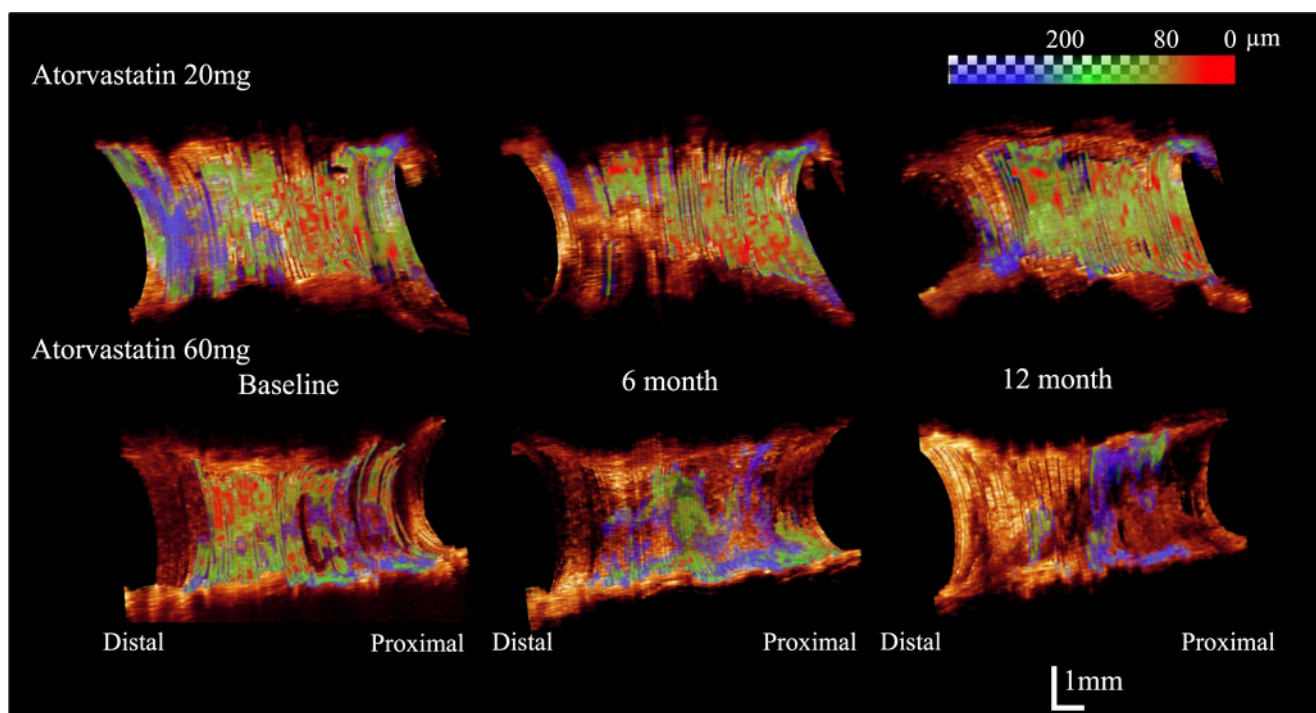


Figure 4. Examples of 3-D reconstructed fibrous caps between different treatment groups over time. FCs were rendered in a continuous colormap indicating the thickness. The vessel was rendered in orange and cut open to expose the FCs.

Table 1

Baseline characteristics

Patient level	AT20 (n=9)	AT60 (n=12)	P
Age, years	55.1±6.8	60.3±6.7	0.100
Male, n (%)	5 (55.6)	5 (41.7)	0.670
Risk factors			
Hypertension, n (%)	7 (77.8)	9 (75.0)	1.000
Diabetes, n (%)	5 (55.6)	3 (25.0)	0.203
Smoking, n (%)	4 (44.4)	5 (41.7)	1.000
Hyperlipidemia, n (%)	1 (11.1)	4 (33.3)	0.338
Previous MI, n (%)	3 (33.3)	2 (16.7)	0.611
Prior PCI, n (%)	1 (11.1)	2 (16.7)	1.000
Presentation			0.700
STEMI, n (%)	2 (22.2)	1 (11.1)	
UAP, n (%)	4 (44.4)	9 (75.0)	
SAP, n (%)	3 (33.3)	2 (16.7)	
Medication at discharge			
Beta-blocker, n (%)	6 (66.7)	9 (75.0)	1.000
ACEI/ARB, n (%)	6 (66.7)	5 (41.7)	0.387
Calcium blocker, n (%)	2 (22.2)	5 (41.7)	0.642
Nitrate, n (%)	5 (55.6)	6 (50.0)	1.000
Aspirin, n (%)	9 (100.0)	11 (88.9)	1.000
Clopidogrel, n (%)	9 (100.0)	11 (88.9)	1.000
Lesion level	AT20 (n=16)	AT60 (n=15)	P
Target vessel			0.374
LAD, n (%)	4 (25.0)	5 (33.3)	
LCX, n (%)	3 (18.8)	4 (26.7)	
RCA, n (%)	9 (56.3)	6 (40.0)	
Length, mm	9.3±2.4	12.0±4.8	0.053

Data are presented as mean ±SD, n (%).

AT20: atorvastatin 20mg; AT60: atorvastatin 60mg; MI: myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction; UAP: unstable angina pectoris; SAP: stable angina pectoris; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor antagonist; LAD: left anterior descending coronary artery; LCX: left circumflex coronary artery; RCA: right coronary artery.

Table 2

Laboratory findings

Patient level	Baseline	6 months	12 months	<i>P</i>				
				All	BL vs.		6M vs.	
					6M	12M	12M	12M
AT20 (n=9)								
TC, mg/dL	215.0±42.0	152.3±32.7	164.9±51.7	0.003	0.008	0.021	0.407	
LDL-C, mg/dL	121.2±26.9	84.0±27.8	93.0±35.3	0.032	0.015	0.086	0.441	
HDL-C, mg/dL	52.6±14.1	47.3±12.3	46.9±19.4	0.459	ND	ND	ND	
AT60 (n=12)								
TC, mg/dL	198.2±32.6	138.5±32.4	139.2±24.0	<0.001	0.005	0.002	0.754	
LDL-C, mg/dL	110.3±25.4	74.3±18.2	69.3±16.6	<0.001	0.005	0.002	0.388	
HDL-C, mg/dL	49.8±10.8	45.0±10.8	43.1±14.2	0.127	ND	ND	ND	

Data are presented as mean ±SD.

BL: baseline; 6M: 6-month follow-up; 12M: 12-month follow-up; TC: total cholesterol; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol.

ND: Test within individual period was not done because the entire period test result was not significant

Table 3

Thinnest FCT, matched segment FCT and 3D FCT measurements

Lesion level	AT20 (n=16)	P*	AT60 (n=15)	P*	P#
Thinnest FCT					
tFCT, BL, μm	59.1 \pm 21.8		47.3 \pm 8.5		0.059
tFCT, 6M, μm	71.1 \pm 36.4		87.1 \pm 43.8		0.316
tFCT, 12M, μm	102.3 \pm 56.0		105.1 \pm 59.1		0.906
Entire period		0.023		<0.001	
tFCT Change 0–6M, μm	11.9[–5.2, 29.1]	0.172	39.8[20.5, 59.1]	<0.001	0.034
tFCT Change 0–12M, μm	43.2[13.2, 73.2]	0.005	57.7[30.1, 85.4]	<0.001	0.485
tFCT Change 6–12M, μm	31.3[15.8, 46.7]	<0.001	17.9[0.9, 35.0]	0.071	0.257
Matched Segment FCT					
mFCT, BL, μm	61.0 \pm 20.3		53.1 \pm 18.0		0.221
mFCT, 6M, μm	86.3 \pm 42.4		141.2 \pm 117.8		0.062
mFCT, 12M, μm	103.8 \pm 48.1		156.7 \pm 89.4		0.049
Entire period		0.004		<0.001	
mFCT Change 0–6M, μm	25.3[4.8, 45.8]	0.015	88.1[38.7, 137.5]	<0.001	0.021
mFCT Change 0–12M, μm	42.8[21.8, 63.7]	<0.001	103.6[55.9, 151.4]	<0.001	0.022
mFCT Change 6–12M, μm	17.4[–0.3, 35.2]	0.054	15.5[–22.5, 53.4]	0.495	0.927
Fibrous Cap (<80 μm) Surface Area					
SA _{<80μm} BL, mm^2	6.58 \pm 4.72		10.37 \pm 6.08		0.062
SA _{<80μm} 6M, mm^2	4.47 \pm 4.14		4.02 \pm 3.79		0.722
SA _{<80μm} 12M, mm^2	4.00 \pm 3.87		2.53 \pm 4.01		0.319
Entire period		0.140		<0.001	
SA _{<80μm} Change 0–6M, mm^2	–2.12[–3.88, –0.36]	ND	–6.35[–8.91, –3.78]	<0.001	0.008
SA _{<80μm} Change 0–12M, mm^2	–2.58[–4.10, –1.06]	ND	–7.84[–10.07, –5.60]	<0.001	<0.001
SA _{<80μm} Change 6–12M, mm^2	–0.47[–2.40, 1.47]	ND	–1.49[–3.57, 0.59]	0.205	0.479

Data are presented as mean \pm SD or mean [95% confidence intervals].

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tFCT: thinnest fibrous cap thickness; mFCT: matched segment fibrous cap thickness; BL: baseline; 6M: 6-month follow-up; 12M: 12-month follow-up; SA<80µm: fibrous cap surface area with FCT<80µm

p* Test for significance of the within treatment group's longitudinal mean change

p# Test for between group difference in longitudinal mean changes

ND: Test within individual period was not done because the entire period test result was not significant