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Association of statin therapy with reduced coronary plaque rupture: an optical coherence tomography study

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Abstract

Objective—Statin therapy induces plaque regression and may stabilize atheromatous plaques. Optical coherence tomography (OCT) is a high-resolution in-vivo imaging modality that allows characterization of atherosclerotic plaques. We aimed to demonstrate the potential utility of OCT in evaluating coronary plaques in patients with or without statin therapy.

Methods—Patients undergoing cardiac catheterization were enrolled. We identified culprit lesions and performed intracoronary OCT imaging. Plaque lipid pool, fibrous cap thickness, and frequency of thin-cap fibroatheroma were evaluated using previously validated criteria. Macrophage density was determined from optical signals within fibrous caps. Presence of calcification, thrombosis, and rupture was assessed.

Results—Forty-eight patients were included (26 on statins, 22 without statins). Baseline characteristics were similar apart from lipid profile. Patients on statin therapy had lower total and low-density lipoprotein cholesterol concentrations (4.45± 1.35 vs. 5.26 ± 0.83 mmol/l, $P = 0.02$; 2.23 ± 0.78 vs. 3.26 ±0.62 mmol/l, $P < 0.001$, respectively). Frequencies of lipid-rich plaque (69 vs. 82%), thin-cap fibroatheroma (31 vs. 50%), plaque calcification (15 vs. 5%) and thrombosis (15 vs. 32%), and fibrous cap macrophage density were comparable between statin and nonstatin groups (5.9 vs. 6.3%; all P =NS). Ruptured plaques were, however, significantly less frequent in patients on established statin therapy (8 vs. 36%; $P = 0.03$) with a trend toward increased minimum fibrous cap thickness (78 vs. 49 μm; $P = 0.07$).

Conclusion—We demonstrated the use of OCT in plaque characterization and found that patients on prior statin therapy have reduced incidence of ruptured plaques and a trend toward thicker fibrous caps. This suggests that statins may stabilize coronary plaques.

Keywords

optical coherence tomography; plaque rupture; plaque stabilization; statin

Introduction

Coronary thrombosis is responsible for the vast majority of acute coronary syndromes. Plaque rupture, the commonest underlying lesion, exposes the highly thrombogenic core to circulating

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platelets, activates the clotting cascade and results in luminal thrombosis [1]. The precursor lesion of acute plaque rupture has been postulated to be thin-cap fibroatheroma (TCFA), characterized by a necrotic core with overlying fibrous cap measuring less than 65 μm and infiltration by macrophages [2,3].

The effect of lipid-lowering therapy with statins in reducing ischemic coronary events is well recognized [4–6]. Recent trials have further demonstrated reduced progression of atherosclerotic plaques with intensive statin therapy [7,8]. However, the clinical benefits in avoiding adverse cardiac events are far greater than the relatively small change in stenosis severity or plaque volume [9]. Statins are known to have a wide range of biologic effects [10]. It is possible that statins may directly affect plaque stability by modifying plaque composition such as lipid content and fibrous cap thickness, leading to reduced risk of acute rupture [11–13].

In-vivo evaluation of plaque characteristics would be invaluable in understanding the effects of statins. Although intravascular ultrasound is the gold standard for coronary anatomy assessment in clinical practice, it has limited ability in quantifying plaque lipid content. Assessment of fibrous cap thickness is also not possible with current technology. Optical coherence tomography (OCT) is an optical analog of intravascular ultrasound that allows high-resolution (~10 μm) tomographic intraarterial imaging [14–16]. The resolution of OCT provides clear definition of coronary plaque features that has been validated in histology-controlled studies [17]. However, the effects of statins on coronary plaques composition have not been well demonstrated *in vivo*. We therefore aimed to demonstrate the potential utility of OCT in evaluating coronary plaques and to compare in-vivo coronary plaque characteristics in patients with or without prior statin therapy.

Methods

Study population

We enrolled patients undergoing coronary angiography for stable angina or acute coronary syndromes who had identifiable culprit lesions in native coronary arteries. Culprit lesion was identified on the basis of coronary angiography as area of tightest stenosis or where there is evidence of plaque rupture or thrombosis, and corroborated with information from the patient's electrocardiogram, nuclear or echocardiographic stress test. Exclusion criteria were significant left main coronary artery disease, congestive heart failure, renal insufficiency (serum creatinine > 160 μmol/l), emergency angioplasty, or extremely tortuous or heavily calcified arteries. Demographic and clinical data were collected prospectively and fasting lipid profile was obtained. Status of prior statin therapy was recorded. The institutional review board approved the study, and all patients provided written informed consent before participation.

Acquisition of optical coherence tomography images

We have previously described the technique of intravascular OCT imaging [14]. Briefly, following administration of intracoronary nitroglycerin, a 3.2-F OCT catheter was advanced through a 7-F guiding catheter over a 0.014-inch coronary guidewire to the area of tightest stenosis or ulcerated area on the angiogram. If coronary intervention was intended, OCT images were acquired before angioplasty. After imaging the center of the plaque, the catheter was moved to the proximal and distal shoulder regions. Images were obtained at four frames per second during intermittent saline flushing to transiently displace blood. Images were stored digitally for off-line analysis by two independent investigators using previously validated criteria for OCT plaque characterization [17]. The presence of plaque rupture, calcification, or thrombosis was noted. Lipid content of a plaque was semiquantified as the number of involved quadrants on cross-sectional OCT image. For each plaque, the image with the highest number

of lipid quadrants was used for analysis. If lipid was present in two or more quadrants, the plaque was considered lipid-rich. For all images of plaque with an OCT-determined lipid pool, the overlying fibrous cap was measured at its thinnest part. TCFA was defined as a lipid-rich plaque with fibrous cap thickness measuring less than 65 μm [2]. Fibrous cap macrophage density was evaluated in all plaques with a lipid pool using a previously validated method [18,19].

Statistical analysis

Quantitative data are presented as mean ± SD or median with interquartile ranges. Clinical and plaque characteristics were compared between the groups by the use of χ^2 and Fisher's exact tests for categorical data and Mann–Whitney or unpaired Student's *t*-tests for continuous variables as appropriate. All analyses were performed using SPSS version 14.0 (SPSS Institute Inc., Chicago, Illinois, USA). A *P* value of less than 0.05 was required for statistical significance.

Results

Baseline characteristics

A total of 48 patients were included. There were 26 patients on established statin therapy and 22 patients not on prior statin therapy. Baseline clinical characteristics are listed in Table 1. Coronary risk factors and clinical syndromes were similar between the two groups. Concomitant medications are similar except for fewer patients on angiotensin-converting enzyme inhibitor therapy in the nonstatin group ($P = 0.02$). Plasma total cholesterol concentrations (4.45 ± 1.35 vs. 5.26 ± 0.83 mmol/l, $P = 0.02$) and low-density lipoprotein cholesterol concentration (2.23 ± 0.78 vs. 3.26 ± 0.62 mmol/l, $P < 0.001$) were significantly lower in the statin group compared with the nonstatin group as expected.

Assessment of coronary plaques

The OCT findings are summarized in Table 2. The distribution of the plaques in the coronary arteries was comparable in both groups. Lipid-rich plaque was a common finding in this cohort but there was no significant difference in the frequency of lipid-rich plaque or TCFA between the two groups. Incidence of plaque thrombosis or calcification was not influenced by prior statin therapy. We, however, found that patients on established statin therapy had significantly fewer plaque ruptures (8 vs. 36%;$P = 0.03$) compared with those not on prior therapy. An example of a ruptured plaque is shown in Fig. 1. In parallel, there was a trend toward increased minimum fibrous cap thickness in patients on statins ($P = 0.07$; Fig. 2a). Post-hoc analysis also demonstrated a trend for reduced fibrous cap thickness in ruptured plaques (median: 44 vs. 71 μm; $P = 0.06$; Fig. 2b), although the presence of plaque rupture did not correlate with total or low-density lipoprotein cholesterol concentrations ($P = 0.39$ and 0.23, respectively). Fibrous cap macrophage density between patients with or without prior statin therapy was similar.

All imaging procedures were performed without complications or adverse events.

Discussion

Several large-scale randomized controlled trials have firmly established the benefits of statin therapy in both primary and secondary cardiovascular disease prevention, largely attributed to the substantial reduction in levels of atherogenic lipoproteins [4–6,20]. Whether statins have a direct role in stabilizing coronary plaques is less clear. In this report, we demonstrated the in vivo-use of OCT in assessing coronary plaque characteristics and found that patients with coronary artery disease on established statin therapy have lower frequency of culprit plaque rupture compared with those not on prior statin therapy. Furthermore, there was a trend toward

increased fibrous cap thickness, an indicator of plaque stability. The presence of plaque rupture was independent of total or low-density lipoprotein cholesterol concentrations, but demonstrated a trend toward decreased fibrous cap thickness. Our study therefore adds to the concept of plaque 'stabilization' and suggests that statin therapy may have a stabilizing effect on coronary plaques.

Mechanism of plaque rupture and vulnerability

Superimposition of arterial thrombus over disrupted atherosclerotic plaques is recognized to be the principal cause of acute ischemic coronary syndromes [2]. Plaque rupture is the most frequent underlying lesion of coronary thrombosis. Rupture of the fibrous cap leads to exposure of thrombogenic material with subsequent activation of the clotting cascade and platelet aggregation resulting in clot formation [1,12]. Thinning of the fibrous cap is considered to be a prelude to rupture and a marker of plaque instability. Macrophage infiltration of fibrous caps leads to expression of matrix-degrading metalloproteinases. Enhanced activity of these proteolytic enzymes depletes extracellular matrix that weaken the fibrous cap and may result in acute rupture.

The inflamed TCFA resembles ruptured coronary plaque in morphology and is proposed to be its precursor [3]. Characterized by a lipid-rich core with overlying thin fibrous cap infiltrated by macrophages, TCFA is frequently observed in patients dying suddenly of myocardial infarction with acute plaque rupture. Owing to its clinical significance, identification and monitoring of TCFA in living persons may represent a potential therapeutic concept and play a role toward reducing cardiovascular morbidity and mortality.

Effects of statin therapy

Studies with statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) have shown that their effect on cardiac events is much greater than the effect on angiographically determined progression or regression of atherosclerosis [8,9,21]. Hence, mechanisms other than plaque size are likely to be responsible for the onset of cardiac events. Statins have been recognized to have beneficial effects, independent of lipid lowering, on vascular inflammation, blood flow, lipid oxidation, and endothelial function, the so-called 'pleiotropic' properties, [10,12,13,22]. Recent evidence suggests that most of these effects are mediated by the inhibition of isoprenoid synthesis [22,23]. In particular, inhibition of Rho guanosine triphosphatases in vascular wall cells leads to increased expression of atheroprotective genes and inhibition of vascular smooth muscle cell proliferation. Statins may also stabilize TCFA by reducing the expression of adhesion molecules such as E-selectin and ICAM-1 on the surface of endothelial cells at the level of gene transcription [24], resulting in fewer inflammatory cells binding to an activated endothelium. Observations from animal studies strengthen this hypothesis to show that statins increase collagen content and decrease lipid deposition, macrophage accumulations, and matrix metalloproteinase activity in established atherosclerotic plaques [25,26]. A recent study with an apolipoprotein E-knockout mice model of spontaneous plaque rupture also found that pravastatin treatment directly inhibits plaque rupture [27].

Clinical studies have reported that irrespective of baseline lipid levels, statin therapy resulted in greater reduction in rates of recurrent myocardial infarction in patients who had higher C-reactive protein levels, a marker of systemic inflammation [28]. Two recent trials that adopted high dose intensive statin therapy in coronary artery disease patients also found improved survival and slower atherosclerotic progression among those with lower C-reactive protein levels [8,29]. These data collectively underscore the importance of both lipid-lowering as well as pleiotropic effects of statins in the treatment of atherosclerosis.

However, there is limited data on the effect of statins on the histologic composition of human coronary plaque. In human studies, short-term statin treatment modified carotid plaque composition to a more stable phenotype [30]. Using integrated backscatter intravascular ultrasound radio-frequency signal analysis, prospective studies have shown that in patients treated with statins, coronary plaque and lipid volumes were reduced, whereas the fibrous component was increased [31,32]. Direct visualization using coronary angioscopy further indicated that statin therapy changed superficial plaque color to a more stable grade [11]. Demonstration of detailed in-vivo coronary plaque characteristics is, however, hindered by the lack of sensitive imaging modalities.

Imaging with optical coherence tomography

In this study, we have used OCT in patients established on statin therapy to assess characteristics linked to plaque instability and TCFA – lipid pool, thin fibrous cap, and macrophage infiltration. We have previously validated the OCT features of various atheromatous plaque components [17] and also characterized plaque morphology in different clinical syndromes [15]. Thus this preliminary report shows that OCT technology has the potential to yield important information on the natural history of TCFA in future follow-up series.

The incidence of plaque rupture was significantly lower in patients on prior statin therapy in this study. The trend toward thicker fibrous caps in these patients also reflects greater collagen deposition and extracellular matrix. Although no significant difference in lipid content or frequency of TCFA was detected, the statin group had lower proportions of TCFA, lipid rich plaques, thrombosis, and increase calcification: all features consistent with plaque stability. Hence the lack of statistical significance could be due to small numbers in this trial. Taken together, these findings support the proposition that statin therapy stabilizes coronary plaque by modifying the determinants of plaque vulnerability.

Limitations

This study has several limitations. As indicated above, the small study size limits our interpretation and discussion. We did not assess the effects of statin therapy prospectively, hence the length of treatment duration or variation of plasma lipid concentrations over time was not known. The inherent limitations of OCT have been previously described [15,16]. Intracoronary saline flushing during OCT imaging may potentially embolize adherent thrombus, resulting in underestimation of plaque thrombosis. Finally, the incidence of ruptured plaques in our study cohort was lower than previous reports [2,33] and we may have failed to image an exact rupture site or thrombus within a culprit lesion. Enhancements to OCT technology [34,35] may eliminate many of the technical limitations of this study.

Conclusion

Patients on statin therapy have reduced the incidence of culprit plaque rupture with a trend toward increased fibrous cap thickness. This suggests that statin therapy may have a stabilizing effect on coronary plaques. Prospective randomized studies are needed to monitor the effects of statins on changes in plaque composition over time to validate these observations.

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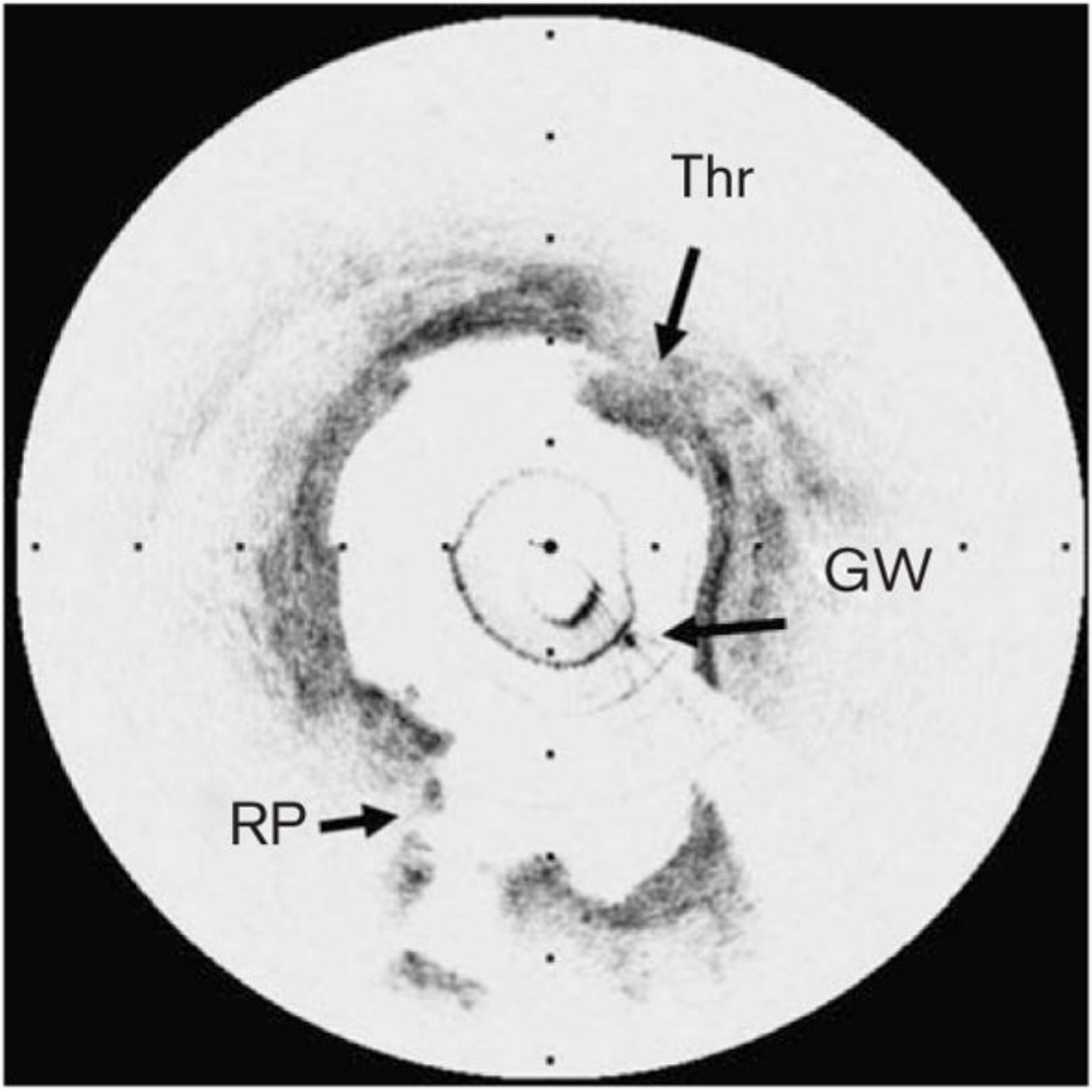

Fig. 1.
In-vivo optical coherence tomography image of a ruptured coronary plaque. Ruptured plaque (RP) is seen in this patient with severe disruption of plaque fibrous cap at the 6 o'clock position. Adherent thrombus (Thr) is also observed at 1 o'clock position. Guidewire artifact is represented by GW.

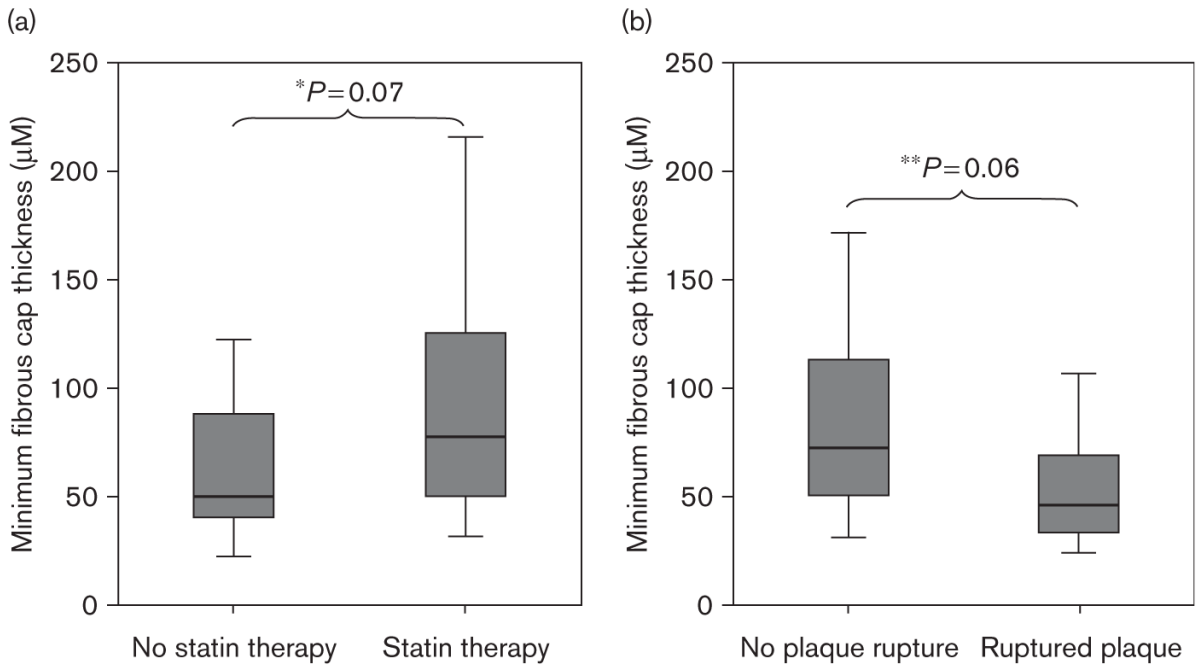

Fig. 2.

Minimum fibrous cap thickness in (a) patients with or without statin therapy; and (b) ruptured and nonruptured coronary plaques. A trend was observed toward increased fibrous cap thickness in patients with established statin therapy (*P = 0.07) that was also detected in nonruptured plaques (**P = 0.06). Fibrous cap thickness was measured at the thinnest part for all images with an optical coherence tomography-determined lipid pool. Median ± interquartile range.

Table 1

Baseline characteristics

	Statin therapy	No statin therapy	*P*
Number of patients (*n*)	26	22	
Age (years)	58 ± 9	58 ± 8	0.90
Sex (female/male)	5/21	4/18	1.00
Coronary risk factors, *n* (%)			
Hypertension	17 (65)	8 (36)	0.08
Diabetes mellitus	8 (31)	3 (14)	0.19
Smoking history	20 (77)	19 (86)	0.48
Family history of coronary artery disease	15 (58)	13 (59)	1.00
Prior myocardial infarction	5 (19)	2 (9)	0.43
Prior coronary revascularization	6 (23)	2 (9)	0.26
Clinical presentation, *n* (%)			0.60
Stable angina	5 (19)	7 (32)	0.34
Non-ST-elevation acute coronary syndrome	10 (38)	7 (32)	0.77
ST-elevation myocardial infarction	11 (42)	8 (36)	0.77
Other medications			
Antiplatelet therapy	26 (100)	22 (100)	
Other lipid lowering medication	0 (0)	0 (0)	
Angiotensin receptor antagonists	0 (0)	0 (0)	
Angiotensin-converting enzyme inhibitors	14 (54)	4 (18)	0.02
Beta-adrenoceptor antagonists	24 (92)	18 (82)	0.39
Calcium channel antagonists	4 (15)	1 (5)	0.36
Lipid profile			
Total cholesterol (mmol/l)	4.45 ± 1.35	5.26 ± 0.83	0.02
HDL cholesterol (mmol/l)	1.11 ± 0.52	1.01 ± 0.21	0.43
Total/HDL cholesterol ratio	4.6 ± 1.6	5.3 ± 1.1	0.08
Low-density lipoprotein cholesterol (mmol/l)	2.23 ± 0.78	3.26 ± 0.62	< 0.001
Triglycerides (mmol/l)	2.46 ± 2.67	2.43 ± 2.34	0.97

Values are mean ± SD or *n* (%).

HDL, high-density lipoprotein.

Table 2

Coronary plaque characteristics

	Statin therapy (*n* = 26)	No statin therapy (*n* = 22)	*P*
Culprit artery			0.97
Left anterior descending artery	4	4	
Left circumflex artery	6	5	
Right coronary artery	16	13	
Number of lipid quadrants (*n*)			0.12
0	4	1	
1	4	3	
2	9	7	
3	7	6	
4	2	5	
Lipid-rich plaque (≥2 quadrants)	18 (69)	18 (82)	0.51
Thin-cap fibroatheroma	8 (31)	11(50)	0.24
Minimum fibrous cap thickness (μm)[a]	78 (77)	49 (55)	0.07
Fibrous cap macrophage density (%)	5.9 ± 1.2	6.3 ± 1.8	0.49
Plaque rupture	2 (8)	8 (32)	0.03
Calcification	7 (15)	2 (5)	0.15
Thrombus	4 (31)	7 (50)	0.30

Values are expressed as mean ± SD, *n* (%) or

[a] median (interquartile range).