

# Effect of atorvastatin therapy on borderline vulnerable lesions in patients with acute coronary syndrome

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## Abstract

**Introduction:** It is still controversial whether borderline lesions with a vulnerable plaque should be stented early or simply treated pharmacologically. No data exist concerning the potential effects of statin therapy on borderline vulnerable lesions in patients with acute coronary syndrome (ACS).

**Material and methods:** Fifty patients with ACS whose culprit lesions were classified as "borderline lesions" were enrolled. All patients were treated with atorvastatin (20 mg) for 12 months. Intravascular ultrasound (IVUS) was performed and matrix metalloproteinase-9 (MMP-9), tissue inhibitor of metalloproteinase-1 (TIMP-1), and high-sensitive C-reactive protein (hsCRP) levels were measured at baseline and 12-month follow-up.

**Results:** At 12-month follow-up, we found: 1) IVUS revealed that minimal lumen cross-sectional area (CSA) increased but plaque/media (P&M) area and plaque burden decreased. A total of 25 soft plaques (50%) were transformed into fibrous plaques. 2) ApoB, MMP-9 and hsCRP levels decreased, but TIMP-1 level increased. 3) Stepwise multivariate linear regression analysis showed that the independent predictors for changes in P&M area/year were the decrease in MMP-9 and hsCRP levels.

**Conclusions:** Atorvastatin therapy stabilized borderline vulnerable plaques and reversed atherosclerosis progression in patients with ACS. Reversal of this progression was accompanied by a decrease in the levels of plasma MMP-9 and hsCRP. Changes in MMP-9 and hsCRP could predict vulnerable plaque stabilization.

**Key words:** intravascular ultrasound, atorvastatin, acute coronary syndrome, vulnerable plaque.

## Introduction

The pathological mechanisms of acute coronary syndrome (ACS) are based on thrombosis secondary to unstable plaque rupture [1]. In many cases, less than 70% of local stenosis of the culprit lesions (lesions directly responsible for the ischaemia episode) is detected by coronary angiography (CAG) [2, 3]. At present, the threshold for clinical revascularization therapy is 70% narrowing [4]. Interventional guidelines of CAD (ACC/AHA 2005) [5] assign those with less than 50% narrowing as Class III, indicating whether angina does or does not exist. It is still controversial whether borderline lesions with a vulnerable plaque should be stented early or only treated pharmacologically. Statins improve the long-term prognosis of

patients with coronary artery disease due to plaque stabilization [6]. There are no reports on the frequency of new events caused by progression of borderline lesions in patients with ACS. Evidence suggests that there are no differences between mechanical and pharmacological stabilization of borderline coronary lesions in patients with ACS [7]. The present study prospectively investigates the effect of atorvastatin therapy on borderline vulnerable lesion progression with serial intravascular ultrasound (IVUS) in patients with ACS.

## Material and methods

### Study population

From May 2007 to December 2008, we enrolled 50 patients with ACS (based on typical symptoms, ECG changes and elevated cardiac troponin T level > 0.1 ng/dl) admitted to the Cardiac Unit in Guangdong Cardiovascular Institute. According to the AHA/ACC guidelines for ACS [5], all patients were treated after admission with antiplatelet and other therapies including angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers,  $\beta$ -blockers and statins. Twenty-two of these patients had received statin therapy prior to admission. Atorvastatin (20 mg) was prescribed to all patients as statin therapy for 12 months. Inclusion criteria for these lesions were an angiographic lumen diameter stenosis 50~70% termed borderline lesions, a minimal lumen cross-sectional area  $\geq 4.0$  mm<sup>2</sup> by IVUS, and lesions located in 1 of 3 major epicardial arteries where stent implantation was not performed. When > 1 lesion/patient was studied, the lesion with the larger plaque burden was selected for this study. Culprit lesions were identified by a combination of ECG and CAng. Exclusion criteria included severe calcified lesions and patients with acute ST-elevated acute myocardial infarction (STEMI) where reperfusion strategy is the treatment of choice. Measurements of chemical indicators were altered by acute inflammation or infection, pregnancy or contraindications to therapy with atorvastatin. During the 12-month follow-up, occurrence of major adverse cardiac events, such as acute myocardial infarction (creatinine kinase-MB fraction increased to 3 times the upper limit of normal), target lesion revascularization (percutaneous or surgical intervention of lesions), or death from any cause was evaluated. This study was performed with the patients' written informed consent and approval of the institutional review board. Changes in lipid profiles were calculated at baseline and at 12-month follow-up.

### Selective coronary angiography

Selective CAG was performed according to the standard Judkins technique [8]. Before CAG,

nitroglycerine (200  $\mu$ g) was injected into the coronary artery to prevent vessel spasm. Vessel diameters were determined with a 6 F angiographic catheter used as a scaling device. Quantitative coronary analysis was performed using the Digital Cardiac Imaging (DCI) system.

### Intravascular ultrasound imaging and analysis

Baseline and 12-month follow-up IVUS examination of culprit lesions were performed in the same manner after intracoronary administration of nitroglycerine (200  $\mu$ g) with a motorized transducer pull-back system (0.5 mm/s) and a commercial scanner (Boston Scientific Corp./SCIMED, Natick, Massachusetts), consisting of a rotating 40-MHz transducer with a 2.9 Fr imaging sheath. Intravascular ultrasound images were recorded using the iLab ultrasound imaging system. Quantitative and qualitative analyses were performed according to the criteria of the clinical expert consensus document on IVUS [9] while quantitative IVUS analysis was performed using computerized planimetry (Boston Scientific iReview 1.0 Software). All of these analyses were independently performed by an experienced analyst who was blinded to the lesion and patient background. On playback of the baseline and 12-month follow-up IVUS studies, matching image slices were acquired at 3 different sites of the culprit lesions: the segment with the narrowest lumen cross-sectional area (CSA) and sites 2 mm proximal and distal to the narrowest segment. Quantitative measurements included the external elastic membrane (EEM) CSA, lumen CSA and plaque and media (P&M = external elastic membrane – lumen) CSA. Plaque burden was calculated as the P&M area divided by the EEM CSA. Changes in IVUS measurements between baseline and 12-month follow-up were determined.

### Sample measurements

Blood samples were acquired on admission and at the end of follow-up. Commercially available ELISA kits were used for measurement of matrix metalloproteinase-9 (MMP-9; human MMP-9 ELISA, Bender MedSystems Inc), tissue inhibitor of metalloproteinase-1 (TIMP-1) (human TIMP-1 ELISA, Bender MedSystems Inc) and high-sensitive C-reactive protein (hsCRP, hsCRP ELISA, Bender MedSystems Inc).

### Statistical analysis

Statistical analyses were performed using SPSS 13.0 software. Data are presented as frequencies or mean  $\pm$  SD. Comparison was performed with a  $\chi^2$  test or paired Student's *t* test. Multivariate stepwise

regression analyses were performed to determine the independent predictors of change in annual changes of P&M cross-sectional area. A  $p < 0.05$  (two-tailed) was considered significant.

## Results

### Demographic and baseline characteristics

This study involved 50 patients (39 male, 11 female) aged 44-76 years (mean  $63.8 \pm 10.9$  years) with ~50 culprit lesions. Hypertension was found in 32 patients (64%) and type 2 diabetes mellitus in 8 patients (16%). Twenty-nine patients (58%) were smokers. Two patients had previous myocardial infarction and 1 patient had a family history of coronary heart disease. Thirty-eight lesions (73.1%) were located at the anterior descending artery, 8 lesions (15.4%) at the circumflex and 6 (11.5%) at the right coronary artery. Two-vessel disease was found in 2 patients.

### Lipid profile

Apolipoprotein B (ApoB) levels decreased significantly at follow-up compared with baseline. Levels of other lipoproteins showed minimal change (Table I).

### Coronary angiography and intravascular ultrasound data

At 12-month follow-up, CAG showed little change in diameter stenosis ( $62.50 \pm 10.21\%$  vs.  $54.79 \pm 12.35\%$ ,  $p = 0.48$ ) and area stenosis ( $58.61 \pm 8.36\%$  vs.  $48.18 \pm 10.56\%$ ,  $p = 0.78$ ). Minimal lumen CSA increased ( $p < 0.01$ ), P&M area decreased, and plaque burden decreased ( $p < 0.01$ ) at 12-month follow-up. Soft plaques transformed into fibrous

plaques in 25 cases, indicating stabilization of the plaques (Table II, Figures 1, 2).

### Changes in plasma matrix metalloproteinase-9, tissue inhibitor of metalloproteinase-1 and high-sensitive C-reactive protein

Plasma MMP-9 and hsCRP decreased significantly, while plasma TIMP-1 levels increased significantly (Table III).

### Clinical follow-up

There were no adverse events reported during the following-up period.

### Relationship between plaque changes and plasma matrix metalloproteinase-9, tissue inhibitor of metalloproteinase-1 and high-sensitive C-reactive protein levels

The mean annual change in P&M area was  $1.34 \pm 0.97$  mm<sup>2</sup>/year. Using a stepwise regression model, annual change in MMP-9, annual change in TIMP-1 and annual change in hsCRP were the independent variables, while annual change in P&M area was the dependent variable. The regression equation was: annual change in P&M area =  $-1.327 \pm 0.003$ , annual change in MMP-9  $\pm 0.344$ , annual change in hsCRP,  $R^2 = 0.830$ , adjusted  $R^2 = 0.819$ ,  $F = 78.152$ ,  $p = 0.000$  (Figure 3).

## Discussion

Although patients with ACS can benefit from revascularization, medical therapy is the basis for their treatment. Atherosclerosis affects not only the culprit lesion but the whole coronary artery tree [10, 11]. As the most important agents in the

Table I. Lipid profile at baseline and at follow-up

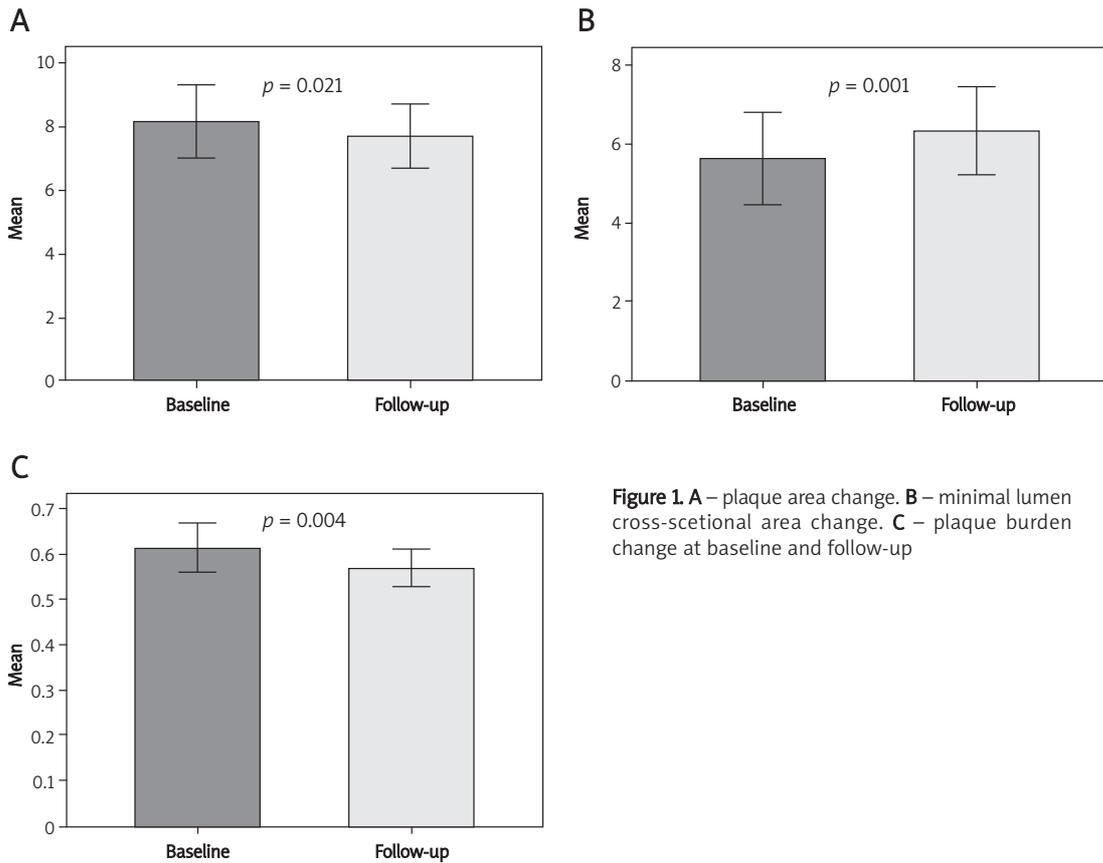
	TC [mmol/l]	LDL-C [mmol/l]	HDL-C [mmol/l]	TG [mmol/l]	ApoA1 [g/l]	ApoB [g/l]
Baseline	4.10 $\pm$ 0.89	1.83 $\pm$ 0.59	1.12 $\pm$ 0.25	1.83 $\pm$ 1.50	1.21 $\pm$ 0.26	0.68 $\pm$ 0.13
Follow-up	3.85 $\pm$ 0.96	1.91 $\pm$ 0.61	1.12 $\pm$ 0.19	1.55 $\pm$ 1.27	1.10 $\pm$ 0.16	0.59 $\pm$ 0.14
Value of <i>p</i>	NS	NS	NS	NS	NS	< 0.05

TC – total cholesterol, LDL-C – low-density lipoprotein cholesterol, HDL-C – high-density lipoprotein cholesterol, TG – triglyceride, ApoA1 – apolipoprotein A-I, ApoB – apolipoprotein B

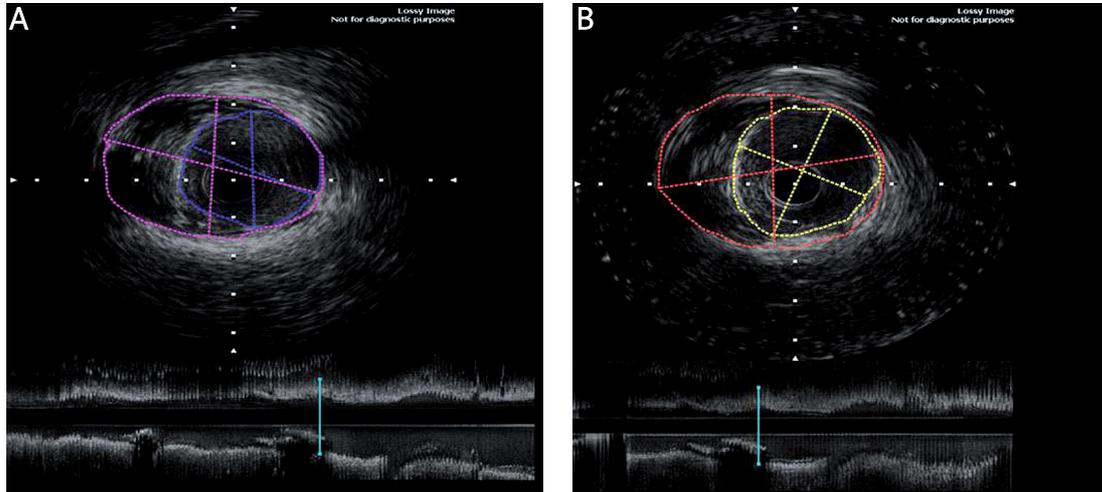
Table II. Intravascular ultrasound imaging at baseline and follow-up

	EEM CSA [mm <sup>2</sup> ]	Minimal lumen CSA [mm <sup>2</sup> ]	P&M area [mm <sup>2</sup> ]	Plaque Burden [%]	Soft plaque n (%)	Fibrous plaque n (%)	Coronary thrombus n (%)	Plaque rupture n (%)
Baseline	13.79 $\pm$ 3.19	5.63 $\pm$ 2.51	8.17 $\pm$ 2.55	61.41 $\pm$ 10.34	43 (86.0%)	5 (10.0%)	7 (20%)	5 (14%)
Follow-up	14.07 $\pm$ 2.10	6.32 $\pm$ 2.42	7.70 $\pm$ 2.19	56.94 $\pm$ 8.47	18 (36.0%)	30 (60.0%)	0 (0%)	0 (0%)
Value of <i>p</i>	NS	< 0.01	< 0.05	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01

CSA – cross-sectional area, EEM – external elastic membrane, P&M area – plaque and media cross-sectional area



**Figure 1.** A – plaque area change. B – minimal lumen cross-sectional area change. C – plaque burden change at baseline and follow-up



**Figure 2.** Representative 3-dimensional intravascular ultrasound analysis at both baseline and follow-up. A – IVUS imaging at baseline. B – IVUS imaging at follow-up

secondary prevention of coronary artery disease, statins have many pleiotropic effects on the cardiovascular system, including effects on endothelial cells, smooth muscle cells, leukocytes, and platelets [12]. Due to the “pleiotropic” effects of a reduction in inflammation, intensive statin therapy beginning soon after ACS provides a rapid early reduction in clinical events [13]. Many studies have shown that intensive statin therapy could contribute to reversing atherosclerosis progression

[14, 15]. By reducing inflammation and improving endothelial function, statins promote plaque stability and prevent ACS [16]. We propose that statins could also stabilize vulnerable lesions in ACS and reverse their progression. This may influence the strategy used in treatment of borderline vulnerable lesions.

In the ESTABLISH [17] trial, a randomized open clinical trial in Japan, 70 patients with ACS received atorvastatin 20 mg daily for 6 months, resulting in

a reduction of 13.1% in plaque volume. In contrast, an increase of 8.7% was observed in the control group. The present study also demonstrated that treatment with 20 mg of atorvastatin daily resulted in an increase in minimal lumen CSA as well as a decrease in P&M area. These data support daily administration of 20 mg atorvastatin for inhibition of plaque progression in Asian populations.

The primary goal of lipid-lowering treatment and the importance of low-density lipoprotein cholesterol (LDL-C) as the predictor for coronary events has been emphasized in various guidelines [18, 19]. In the present study, we administered atorvastatin 20 mg daily to patients whose LDL-C levels were at a lower level (LDL-C =  $1.83 \pm 0.59$  mmol/l) prior to enrolment. After 12 months on atorvastatin, there was no significant change in the LDL-C level. However, for borderline vulnerable lesions, minimal lumen CSA increased, P&M area decreased, and plaque burden decreased. Furthermore, soft plaques in 25 cases changed to fibrous plaques, indicating stabilization of the plaque. These findings demonstrated that the benefits of atorvastatin therapy for atherosclerosis progression may not be related to LDL-C lowering.

Several studies have focused on lipoproteins other than LDL-C. Long-term prospective studies showed that apolipoprotein A-I (ApoA1), ApoB and the ApoB/ApoA1 ratio correlated with the risk of atherosclerotic cardiovascular disease better than the levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG) [20, 21]. Compared with TC/HDL-C and HDL-C/LDL-C, the ApoB/ApoA1 ratio is a more powerful predictor of risk of a coronary event among untreated patients [22, 23]. For patients who have been previously treated with a statin, LDL-C levels lose their predictive strength but the levels of ApoB

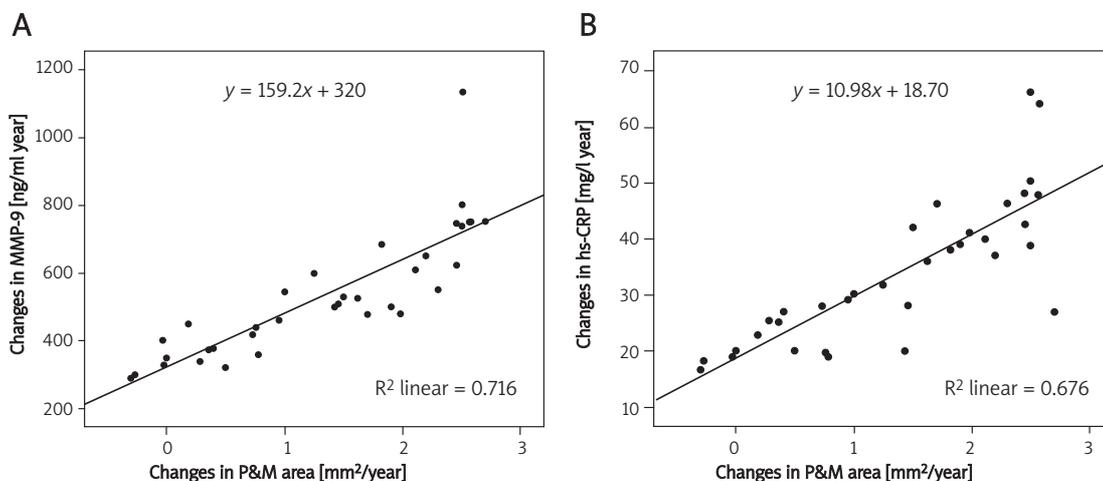
**Table III.** Levels of MMP-9, TIMP-1, and hsCRP at baseline and follow-up

	MMP-9 [ng/ml]	TIMP-1 [ng/ml]	hsCRP [mg/l]
Baseline	2192 $\pm$ 881	657 $\pm$ 247	3.48 $\pm$ 1.50
Follow-up	1773 $\pm$ 1085	709 $\pm$ 227	0.39 $\pm$ 0.19
Value of <i>p</i>	< 0.01	< 0.01	< 0.01

MMP-9 – matrix metalloproteinase-9, TIMP-1 – tissue inhibitor of metalloproteinase-1, hsCRP – high-sensitive C-reactive protein

and ApoB/A1 work the same way as in untreated patients [23-25].

In the present study, after 12 months on atorvastatin, there were no significant changes in LDL-C. We believe this finding to be attributable to the following factors: 1) 22 patients received statin therapy prior to admission, which was a very high ratio (44%). Since most of these patients' lipid levels did not change between baseline and follow-up, this high ratio will affect the statistical results even after atorvastatin therapy. 2) The lipid levels of our patients were lower relative to baseline. Therefore, the lipid levels may not change significantly even after atorvastatin therapy at follow-up. 3) The lipid levels of most Chinese patients were low to moderate. However, there was a sharp reduction in ApoB after 12 months. ApoB is found in lipoproteins originating from the liver [very low-density lipoprotein (VLDL), intermediate density lipoprotein (IDL), LDL] and is the primary apolipoprotein component for lipoproteins with the exception of HDL [26]. ApoB acts as a ligand for lipoprotein receptors in various cells throughout the body, thus playing an important role in atherosclerosis. The significance of the sharp reduction in ApoB in the present study remains unclear. It may suggest a possible reduction in very-low density lipoprotein cholesterol (VLDL-C). Decreases in the level of ApoB



**Figure 3.** **A** – relationship between plaque changes and changes in the levels of plasma MMP-9. **B** – relationship between plaque changes and changes in the levels of plasma hs-CRP

may have direct or indirect effects on plaque stability.

Inflammation also plays an important role in ACS progression. Imbalance in the MMPs contributes to plaque instability. Yip *et al.* [27] and Nomoto *et al.* [28] demonstrated that an increase in hsCRP is positively related to unstable plaque rupture in local arteries. The present study also showed that the levels of plasma MMP-9 and hsCRP were higher and TIMP-1 was lower following ACS compared with those after 12 months of treatment. Multivariate stepwise regression analyses revealed that decreases in the levels of MMP-9 and hsCRP were positively correlated with the reversion of atherosclerosis progression. The effect of atorvastatin on reversal of atherosclerotic progression was accompanied by changes in the level of inflammatory markers. Therefore, detection of changes in the levels of MMP-9 and hsCRP may provide guidance in monitoring plaque progression and making treatment decisions.

Coronary angiography has long been considered the “gold standard” in diagnosing coronary artery disease [29]. Unlike CAG, which displays the coronary artery as a silhouette of the contrast-filled lumen, IVUS is a new diagnostic technique that provides unique information concerning arterial wall structure and luminal dimensions. Intravascular ultrasound reveals the severity and eccentric nature of the plaque lesions, which may be underestimated in angiographic measurements. Intravascular ultrasound also provides insights into the extent of the lipid-rich plaques, calcification and thickness of the fibrous cap, providing valuable information. De Scheerder *et al.* [30] found that for borderline lesions detected by CAG, the correlation between IVUS and quantitative CAG data was very weak. Studies by Nishioka *et al.* [31] and Abizaid *et al.* [32] supported an IVUS minimum luminal CSA < 4.0 mm<sup>2</sup> as a criterion for defining significant stenoses in proximal vessels. Therefore, the present study provided medical therapy for borderline vulnerable lesions without coronary intervention. The ability of atorvastatin to stabilize such lesions defined by CAG and IVUS simultaneously in patients with ACS was confirmed.

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We declare that we have no financial or personal relationships with other people or organizations that can inappropriately influence our work. There is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript.

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