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Original Article

Plaque characteristics of culprit lesions in patients with unstable angina with and without diabetes and their relationship with outcomes of PCI: IVUS analysis

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Abstract: Background: This study aimed to analyze plaque composition and morphology using intravascular ultrasound (IVUS), examining the interaction between plaque morphology and outcomes of percutaneous coronary intervention (PCI) in patients with type 2 diabetes mellitus (T2DM), compared with those without DM. Methods: A total of 92 patients with UA and T2DM and 87 patients without DM, that underwent angiographies, were enrolled in the study, between June 2015 and September 2017. *In vivo* plaques of culprit lesions were measured by IVUS. Results: Compared with patients without DM, hypoechoic and dense calcified plaque was higher in patients with T2DM (6% vs 24%, P = 0.001), while the percentage of hyperechoic plaque was lower (82% vs 50%, P<0.001). In addition, ruptured plaque was higher in DM patients, compared with patients without diabetes (22% vs 8%, *P* = 0.011). Patients with T2DM had larger minimal lumen areas (3.43 ± 0.50 mm^2 vs 3.07 ± 0.34 mm^2, *P* = 0.002) and lower plaque burden (69% ± 8% vs 71% ± 6%, *P* = 0.035). During PCI, slow reflow occurred more often in patients with DM than without DM (27.2% vs 14.9%, P = 0.045). More slow flow occurred in hypoechoic plaque and dense calcified plaque than hyperechoic plaque (70.4% vs 25.8% vs 8.5%, P<0.001). The same phenomenon occurred in high-sensitivity troponin T (hs-TnT) elevation (63.0% vs 22.9% vs 6.0%, P<0.001). Conclusion: The plaque phenotype is probably more important in predicting cardiovascular events and may be related to the short-term prognosis of PCI. Hypoechoic plaque may be an index of slow reflow during PCI in patients with T2DM.

Keywords: Coronary plaque, diabetes, prognosis

Introduction

Coronary artery disease is the major cause of premature death, accounting for approximately one in every six deaths in the United States in 2009 [1]. Diabetes mellitus (DM) is an independent risk factor for development of coronary heart disease (CHD) [2, 3] . The risk of myocardial infarction or death in patients with DM, without known CHD, is as high as that in those without DM, with known CHD [4]. Although significant improvements in adverse events have been detected in patients with DM over time [5], they still have more diffuse and severe coronary artery disease than those without DM, resulting in worse outcomes after percutaneous coronary intervention (PCI) [6-8]. The underlying reason for this difference has not been fully elucidated, but it is presumed that DM predisposes to atherosclerotic plaque disruption and thrombus formation [9]. Plaque composition may play a role in plaque disruption and thrombosis, leading to acute coronary events [8, 10]. Many researchers are involved in identifying the composition and morphology of these plaques in patients with DM. Grayscale intravascular ultrasound (IVUS) has been widely used to investigate plaque morphology and composition in patients with coronary artery disease. This study aimed to investigate plaque characteristics in patients with DM.

PCI may be complicated by slow flow, no reflow, and distal embolization during the procedure [11, 12]. Post-procedural myocardial injury/infarction is manifested by elevated cardiac biomarkers, such as creatine kinase-myocardial band or troponin-T [13, 14]. These phenome-

na have been shown to be associated with poor functional recovery and adverse outcomes [15, 16]. Various mechanisms are responsible for slow flow and no reflow. Also, several studies have evaluated predictors and treatments [17, 18]. However, the types of plaques associated with these phenomena during PCI are unclear. A few studies have shown a relationship between plaque composition and morphology and post-PCI biomarker levels. Therefore, another purpose of the present study was to investigate the impact of pre-PCI coronary plaque composition and morphology, determined by grayscale IVUS, on slow flow, no reflow, and post-PCI hs-TnT elevation.

Methods

Patient population

This study assessed the impact of DM on IVUS findings in patients with primary unstable angina pectoris. This study included 92 patients with T2DM and 87 without -DM, having de novo and single culprit coronary lesions and undergoing IVUS, between June 2015 and September 2017, in Shanghai Tongji Hospital. The study excluded patients with multivessel lesions, subacute or late stent thrombosis, totally occluded lesions, restenosis after stenting, coronary artery bypass graft failure, factors associated with increased risk of bleeding, severe heart failure or cardiogenic shock, systemic diseases, or serum creatinine ≥2.5 mg/dL.

Clinical demographics

Patient demographics were confirmed by hospital chart reviews. Unstable angina was defined as new-onset severe angina, accelerated angina, or rest angina with or without ST-T wave changes or positive cardiac biochemical markers (creatine kinase-myocardial band or cardiac-specific troponin-T). DM was defined as receiving oral hypoglycemic agents or insulin to lower blood glucose levels or known fasting blood glucose values of ≥6.0 mmol/L or postprandial 2-hour blood glucose values of ≥11.1 mmol/L. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive drugs. Hypercholesterolemia was defined as a history of low-density lipoprotein cholesterol levels of ≥3.6 mmol/L or use of statins. Definition of elevation of hs-troponin T was troponin T values >5 × the upper reference limit (URL) in patients with normal baseline values or manifesting a change from baseline values >20% if the baseline values are elevated.

Angiographic analysis

Angiograms were available for comparisons with 179 IVUS images in 179 arteries of 179 patients. All angiograms were analyzed by an independent angiographic core laboratory using standard methodology, blinded to clinical and IVUS findings. Quantitative coronary angiography analysis was performed using the Cardiovascular Measurement System (CMS, Medis Medical Imaging System, Leiden, The Netherlands). Angiographic lesion morphology was classified according to American College of Cardiology/American Heart Association classifications (ACC/AHA) [19]. The percentage of diameter stenosis was measured in the view that was the most severe and not foreshortened.

Frame counts were determined using a method described previously by Gibson et al. [20]. According to corrected thrombolysis in myocardial infarction (TIMI) frame counts, no reflow was defined as post-PCI TIMI grade 0 or 1 flow, in the absence of mechanical obstruction. Slow flow was defined as more than 2 standard deviations of frame counts (TIMI 2) from the normal published range for that particular vessel. Normal reflow was defined as TIMI grade 3 flow.

IVUS imaging and analysis

All IVUS studies were performed before any intervention and after intracoronary administration of 200 μg nitroglycerin, using a commercially available system (Boston Scientific Corporation/SCIMED, Minneapolis, MN, USA). The IVUS catheter was advanced distal to the lesion. Imaging was performed retrograde back to the aorto-ostial junction (motorized pullback speed = 0.5 mm/s). Qualitative and quantitative analyses were performed according to criteria of the ACC Clinical Expert Consensus document on IVUS [21].

Qualitative analysis

Hypoechoic plaque was less bright than the reference adventitia. Hyperechoic noncalcified plaque was as bright as or brighter than the reference adventitia, without acoustic shadowing. Hyperechoic calcified plaque was hyperechoic, with acoustic shadowing. A calcified lesion con-

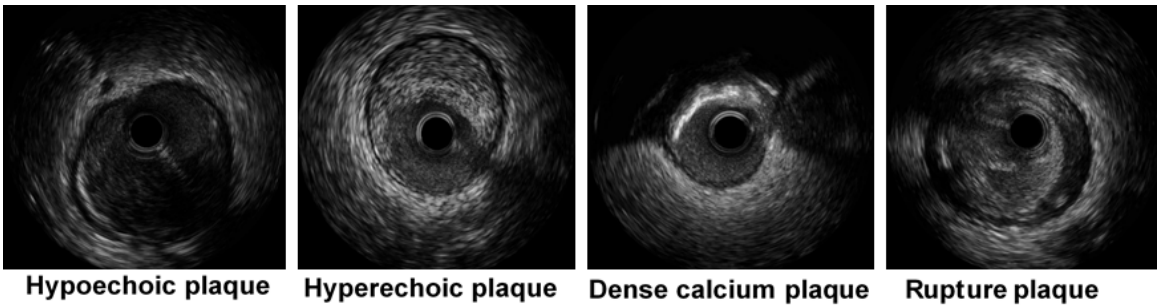

Figure 1. The types of Diabetic coronary plaque characteristics in IVUS.

Table 1. Baseline characteristics

	DM (*n* = 92)	Non-DM (*n* = 87)	*P* value
Age, year	63.4 ± 9.5	63.2 ± 10.0	0.913
Male (%)	55 (59.8%)	44 (50.6%)	0.216
Hypertension (%)	21 (22.8%)	19 (21.8%)	0.874
Current smoker (%)	23 (25%)	28 (32.2%)	0.287
Family history of coronary artery disease	28 (30.4%)	27 (30.1%)	0.931
Drinking	28 (30.4%)	34 (39.1%)	0.224
Pre-PCI aspirin use, *n* (%)	89 (96.7%)	82 (94.2%)	0.421
Pre-PCI clopidogrel use, *n* (%)	92 (100%)	87 (100%)	1.0
Aspirin loading (300 mg), n (%)	90 (97.8%)	85 (97.7%)	0.955
Clopidogrel loading (300 mg), *n* (%)	92 (100%)	87 (100%)	1.0
Pre-PCI statin use (%)	89 (96.7%)	83 (95.4%)	0.645
Fasting glucose (mmol/L)	5.96 ± 0.69	5.13 ± 0.47	<0.001
HbA1c (%)	6.54 ± 0.47	5.67 ± 0.75	<0.001
LDL-C (mmol/L)	3.04 ± 1.15	2.77 ± 0.82	0.072
HDL-C (mmol/L)	1.17 ± 0.35	1.09 ± 0.25	0.106
Total cholesterol (mmol/L)	4.33 ± 0.99	4.08 ± 0.83	0.075
Triglyceride (mmol/L)	1.42 ± 0.94	1.72 ± 1.47	0.100

HDL, high-density lipoprotein; hs-CRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein. Data are presented as *n* (%) of patients or mean ± SD.

tained >90° of circumferential lesion calcium. In the case of no dominant plaque composition, the plaque was classified as mixed. A thrombus was an intraluminal mass, having a layered or lobulated appearance, evidence of blood flow (microchannels) within the mass, and speckling or scintillation. A ruptured plaque contained a cavity that communicated with the lumen with an overlying residual fibrous cap fragment (**Figure 1**).

Quantitative analysis

Image slices with the largest intraplaque cavity and minimum lumen area (MLA), as well as the proximal and distal reference sites, were identified and measured using planimetry software (TapeMeasure, INDEC Systems Inc., CA, USA). Quantitative IVUS measurements included external elastic membrane (EEM), minimal lumen area (MLA), and plaque burden [defined as (EEM-MLA) divided by EEM]. If the EEM circumference could not be identified because of attenuation, the EEM area was interpolated. The lesion site was defined as the slice with the minimum lumen area. Proximal and distal reference sites were defined as the slices with the most normal-looking segments (largest lumen with least plaque) >5 mm proximal and distal to the lesion, but before a major side branch. The remodeling index was calculated as the lesion EEM divided by the mean reference EEM. Positive remodeling was defined as a remodeling index >1.0.

Statistical analysis

Data were analyzed using SPSS (version 21 SPSS Inc., IL, USA). Mean values ± standard deviations (or percentages) were calculated for all numerical variables. Categorical data are presented as numbers (percentage). Differences in the two numerical datasets were examined using Student's t-test. Mann-Whitney U-test was used if the sample could not be

Table 2. Angiographic and procedural results

	DM (*n* = 92)	Non-DM (*n* = 87)	*P* value
Target vessel, *n* (%)			0.452
LAD	41 (44.6)	33 (37.9)	
LCX	23 (25)	29 (33.3)	
RCA	28 (31.4)	25 (28.8)	
Pre-PCI TIMI flow grade 3	92 (100)	87 (100)	
Bifurcation lesions, n (%)	17 (18.5)	11 (12.6)	0.283

LAD, Left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.

Table 3. IVUS based quantitative analysis

	DM	No-DM	*P* value
EEM CSA (mm^2)	11.41 ± 2.45	10.23 ± 2.08	0.001
Minimal lumen area (mm^2)	3.43 ± 0.50	3.07 ± 0.34	0.002
Plaque burden (%)	69 ± 8	71 ± 6	0.035
Lesion length (mm)	29.3 ± 10.1	27.0 ± 10.9	0.152

CSA, Cross-sectional area; EEM, external elastic membrane.

Table 4. IVUS findings of culprit lesion

	Patients with DM	Patients without DM	*P* value
Hypoechoic plaque	22 (24%)	5 (6%)	0.001
Hyperechoic plaque	46 (50%)	71 (82%)	<0.001
Dense calcified plaque	24 (26%)	11 (12%)	0.023
Rupture plaque	20 (22%)	7 (8%)	0.011

DM, Diabetes mellitus. Data are presented as number and %.

Table 5. Rupture plaque and plaque characteristics

	Hypoechoic plaque	Hyperechoic plaque	Dense calcified plaque	*P* value
Rupture plaque	13 (48.1%)	5 (4.2%)	9 (25.7%)	<0.001

Data are presented as number and %.

Table 6. Slow flow phenomenon

	DM	Non DM	*P* value
Slow flow	25 (27.2%)	13 (14.9%)	0.045

Data are presented as number and %.

assumed to be normally distributed. *P*-values less than 0.05 indicate statistical significance.

Results

Patient characteristics

A total of 179 patients were enrolled, 92 with DM (28 with insulin therapy; 64 with oral hypoglycemic medication) and 87 with non-DM. Baseline characteristics are summarized in **Table 1**. Fasting blood glucose levels and hemoglobin A1c (HbA1c) were slightly higher in patients with DM than in those without DM. Baseline characteristics, such as coronary risk factors and medications, were similar between patients with and those without DM. However, patients with DM were more associated with hypertension and a family history of coronary artery disease than those without DM.

Angiographic and procedural results

Angiographic findings are summarized in **Table 2**. No significant differences were observed in culprit lesion distribution, pre-PCI TIMI flow grade, and bifurcation lesions.

Results of IVUS

Grayscale IVUS findings are summarized in **Tables 3** and **4**. At the minimum-lumen sites, patients with T2DM had a larger minimal lumen area (3.43 ± 0.50 mm^2 vs 3.07 ± 0.34 mm^2, P = 0.002) and lower plaque burden (69% ± 8% vs 71% ± 6%, P = 0.035), compared with those without DM. Regarding qualitative analysis, the percentage of plaques comprising hypoechoic plaque (24% vs 6%, P = 0.001) and dense calcified plaque (26% vs 12%, P = 0.023) was higher, while the percentage of hyperechoic plaque (50% vs 82%, P<0.001) was lower in patients with T2DM than those without DM. In addition, the number of ruptured plaques was higher in patients with T2DM than those without DM (22% vs 8%, P = 0.011). Ruptured plaque was more common in hypoechoic and dense calcified plaques than in hyperechoic plaques (48.1% vs 25.7% vs 4.2%, P<0.001) (**Table 5**).

IVUS findings and prognosis of PCI

During PCI, slow reflow occurred in 25 patients with T2DM, compared to 13 patients without diabetes. P value = 0.045 (**Table 6**). This was

Table 7. Slow flow phenomenon and plaque characteristic

	Hypoechoic plaque	Hyperechoic plaque	Dense calcified plaque	*P* value
Slow flow	19 (70.4%)	10 (8.5%)	9 (25.8%)	<0.001

Data are presented as number and %.

Table 8. Hs-TNT elevation and plaque characteristic

	Hypoechoic plaque	Hyperechoic plaque	Dense calcified plaque	*P* value
Hs-TNT elevation	17 (63.0%)	7 (6.0%)	8 (22.9%)	<0.001

Data are presented as number and %.

especially prevalent in patients with hypoechoic plaque, compared to those with hyperechoic and dense calcified plaques (70.4% vs 8.5% vs 28.5%, P<0.001) (**Table 7**).

Moreover, hs-TNT elevation was more often seen in patients with hypoechoic plaque than in those hyperechoic and calcified plaques (63.0% vs 6.0% vs 22.9%, P<0.001) (**Table 8**).

Discussion

The current study showed that patients with DM had more plaque, with plaque vulnerability and a different composition of plaques, compared with non-DM patients presenting with acute coronary syndrome (ACS) [22, 23]. The study also confirmed previous IVUS reports, indicating higher numbers of hypoechoic and dense calcified plaques in ACS [24]. However, this study demonstrated a larger minimal lumen area in patients with DM patients, contrary to the results of previous studies [8]. This might be because the present study involved only single culprit vessel lesions, while other studies included multivessel lesions. This indicates that the damage caused by hyperglycemia to the vessel was less in patients with DM in this study. Yang et al. found that coronary plaque composition and plaque volumes in patients with well-controlled DM were comparable with those in non-DM patients. Also, both groups had less dense calcium and necrotic core volumes, compared with patients with poorly controlled DM [25]. The present study, along with Yang's study, suggests that hyperglycemia control is important in patients with DM and angina. Early diagnosis of DM and hyperglycemia control may help in decreasing plaque progression and reducing cardiovascular events.

Although the present study suggests that plaque burden is an independent predictor of ACS, it seems that plaque composition and morphology, rather than degree of luminal narrowing, might be predictive of future coronary events in high-risk patients [26]. Virmani et al. found that, in ACS, plaque ruptures accounted for 75% of the deaths, while plaque erosion led to the residual 25%. They also demonstrated that, in humans, lesions with most rupture-prone plaques were unstable but not per se stenotic [26]. The present study also confirmed this conclusion. Results showed that the minimal lumen areas were larger, while the numbers of ruptured plaques, hypoechoic plaques, and dense calcified plaques were higher in patients with DM than in those without DM (**Figure 2**). This suggests that plaque complications were not just the result of increasing plaque size. In this respect, plaque phenotype is probably more important. Also, plaque stability is an important target in decreasing occurrence of major cardiovascular events. Although the mechanisms are not clear, ruptured or damaged lipid-rich coronary plaques may trigger subsequent thrombosis (i.e., atherothrombotic events), leading to the onset of ACS [27].

Calcification is another characteristic in patients with DM. A postmortem study showed that calcified plaque was significantly greater in patients with DM than in those without DM [28]. It also demonstrated that the extent of coronary artery calcification, as detected by electron beam CT, strongly correlated with severity of coronary stenosis [29], leading to subsequent coronary events [30]. In addition, previous virtual histology (VH)-IVUS and optical coherence tomography (OCT) studies have indicated that patients with DM had a higher incidence of calcification, compared with those without DM, in both culprit and non-culprit lesions [31, 32]. Moreover, the presence of coronary artery calcium indicates a higher risk of all-cause mortality in patients with DM than in those without DM [33]. The present study found more calcified plaque in patients with DM, in accord with previous findings. Severe stenosis resulting from calcified plaque has been associated with a high risk of stent mal-apposition

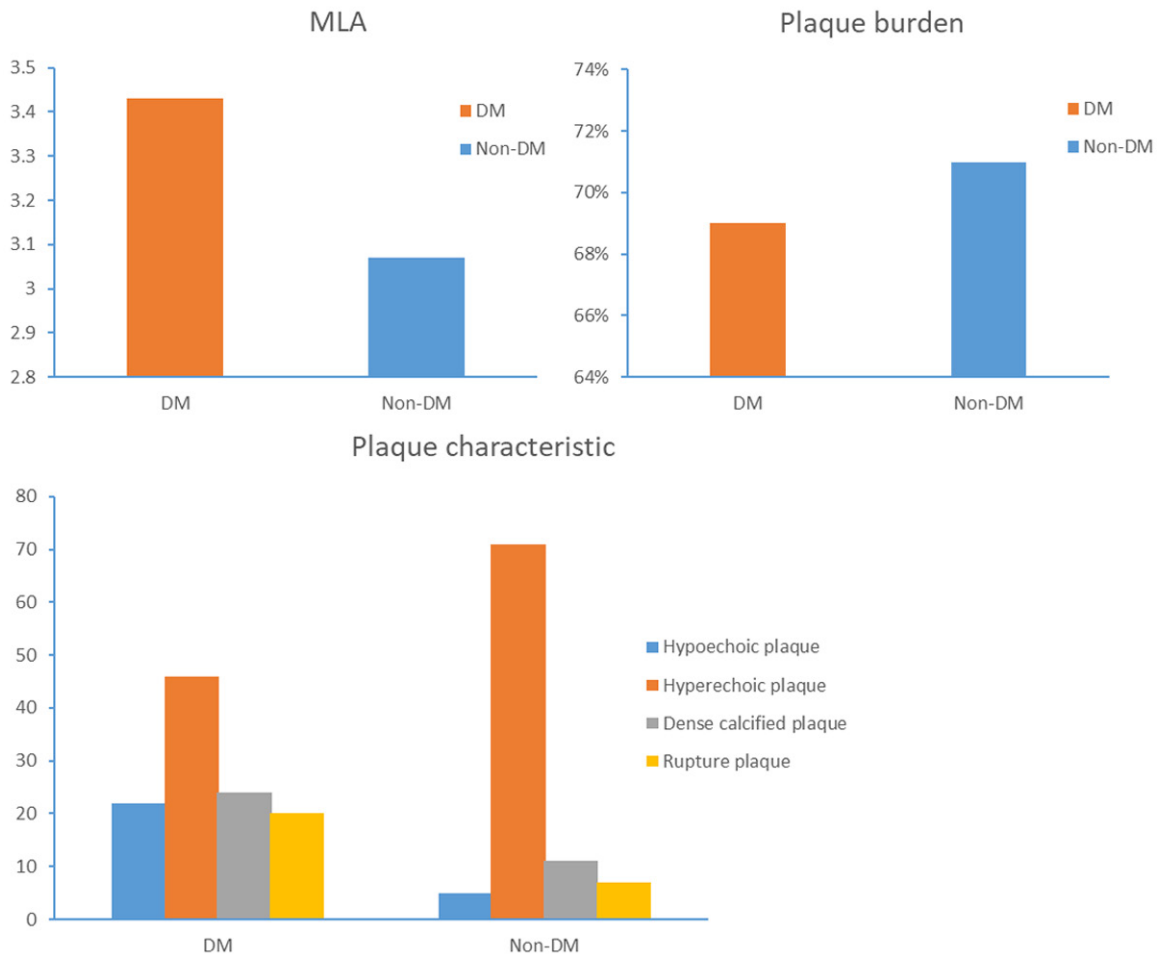

Figure 2. Comparisons of minimal lumen area (MLA), plaque burden (PB) and plaque characteristics in DM vs. non-DM patients. Patients with DM had larger MLA (mm^2) and lower PB (%) compared with those without DM. The percentage of plaques comprising hypoechoic plaques and dense calcium was higher, while the percentage of hyperechoic plaques was lower in DM patients than in those without DM. In addition, the number of ruptured plaques was higher in Diabetic patients.

and under-expansion and dissection after PCI. These are risk factors for in-stent thrombosis.

A recent meta-analysis demonstrated that plaque burden, positive remodeling, plaque ruptures, and attenuated plaques were associated with the distal embolization phenomenon related to PCI, leading to slow-flow or no-reflow phenomenon and myocardial biomarker elevation [12]. The present study found that hypoechoic plaque was related to the slow-flow phenomenon and elevation of post-PCI myocardial biomarkers indicated a direct relationship between pre-PCI plaque composition and slow flow during PCI procedures and post-PCI myonecrosis. Previous studies have suggested that slow-reflow and no-reflow phenomena are attributable to the embolization of thrombus and plaque debris that results from the mechanical fragmentation of vulnerable plaques by PCI [34]. The debris were washed out from the atheromatous core and embolized into the distal microvascular bed, leading to microinfarcts with regional myocardial dysfunction (even in the absence of a significant epicardial coronary stenosis) [35]. Results suggest that lesions, such as hypoechoic or ruptured plaques, are predisposed to iatrogenic distal embolization. The use of pre-intervention statins, vasodilators, or embolic protection devices might be particularly suited for these high-embolic-risk patients.

Study limitations

The current study had certain limitations. First, the study population was relatively small, increasing the possibility of selection bias.

Second, tissue characterization by grayscale IVUS might not be enough. IVUS shows the extent of plaque formation and remodeling. However, VH constructs tissue maps that classify plaque into four major components. Also, OCT helps in measuring cap thickness and visualizing microstructures near the lumen, such as calcified nodules, erosions, and small thrombi. No *ex vivo* comparisons were performed between the IVUS and histopathological findings of plaque ruptures. Finally, this study only investigated single culprit lesions in patients. Further investigation is required.

Conclusion

Patients with DM and UA have more plaque vulnerability and a different composition of plaque, compared with those without DM. Plaque phenotype is probably more important in predicting cardiovascular events and may be related to short-term prognosis of PCI.

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Disclosure of conflict of interest

None

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