Glycemic Variability on Continuous Glucose Monitoring System Correlates With Non-Culprit Vessel Coronary Plaque Vulnerability in Patients With First-Episode Acute Coronary Syndrome – Optical Coherence Tomography Study –

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**Background:** Glycemic variability (GV) is associated with coronary plaque rupture at the culprit lesion in acute myocardial infarction (AMI). The present study determined the relationship between GV and coronary plaque vulnerability in the non-culprit vessel.

**Methods and Results:** The present prospective study involved 46 patients with first-episode acute coronary syndrome (ACS) who underwent optical coherence tomography in the non-culprit vessel. The relationship between GV, assessed with continuous glucose monitoring system, and the presence of thin-cap fibroatheroma (TCFA) at the non-culprit plaque with mild-to-moderate stenosis in the non-culprit vessel, was assessed. GV was quantified using mean amplitude of glycemic excursion (MAGE). Patients were divided into tertiles according to MAGE. TCFA was observed in 13 (28%) of the 46 patients. Fibrous cap thickness was thinner (MAGE tertiles: high, 80±40µm; intermediate, 152±122µm; low, 155±102µm; P=0.01), and TCFA was more common (MAGE tertiles: high, 50%; intermediate, 27%; low, 7%; P=0.03) in patients with high MAGE. On multivariate logistic analysis high MAGE was the only significant determinant of TCFA, independent of coronary risk factors (OR, 5.000; P=0.021), homeostasis model assessment of insulin resistance, and hemoglobin A1c (OR, 5.674; P=0.018).

**Conclusions:** High MAGE measured early after the onset of first-episode ACS correlated with thinner fibrous cap thickness and higher prevalence of TCFA at the non-culprit plaque in the non-culprit vessel. (Circ J 2016; 80: 202–210)

**Key Words:** Acute coronary syndrome; Continuous glucose monitoring system; Glucose; Glycemic variability; Optical coherence tomography
evaluation of GV. Mean amplitude of glycemic excursion (MAGE) calculated using CGMS is a representative marker of GV and, recently, Su et al showed that high MAGE is a poor prognostic factor in patients with acute myocardial infarction (AMI). In addition, Teraguchi et al found that patients with high MAGE were more likely to have coronary plaque rupture at the culprit lesions, compared with those with low MAGE in the setting of AMI, indicating that high MAGE is associated with increased coronary plaque vulnerability at the culprit lesion. According to guidelines for secondary prevention of MI, however, the only target value for glycemic control is HbA1c <7.0%. Intracoronary optical coherence tomography (OCT) is a novel technique for the measurement of fibrous cap thickness (FCT) with a high resolution of 10-20 µm. Thus, OCT can detect thin-cap fibroatheroma (TCFA) and plaque rupture, which are representative features of coronary plaque vulnerability.

To investigate whether patients with high MAGE are at high risk of coronary plaque vulnerability in the non-culprit vessel, we investigated the association between MAGE and TCFA at the non-culprit plaque with mild-to-moderate stenosis of the non-culprit vessel in patients with first-episode ACS.

Methods

Patients

This study was a prospective observational study of non-culprit coronary plaques in patients with first-episode ACS at Yokohama City University Medical Center between April 2012 and September 2014. Consecutive patients with first-episode ACS who underwent percutaneous coronary intervention (PCI) with OCT guidance and CGMS in a stable phase during hospitalization were screened for eligibility.

ACS was defined as ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), or unstable angina (UA). STEMI was defined as chest pain lasting ≥30 min accompanied by new ST-segment elevation and a rise in cardiac-specific troponin I >99th percentile of a normal reference population. The following criteria were used to define ST-segment elevation: new ST elevation at the J point in at least 2 contiguous leads of 0.2 mV in men or 0.15 mV in women in leads V2–V3, or of 0.1 mV in other leads. New left bundle-branch block was considered equivalent to STEMI. NSTEMI was defined as chest pain and a rise in cardiac-specific troponin I without new ST-segment elevation. UA was defined as new-onset severe angina, accelerated angina, or angina at rest without a significant rise in cardiac-specific troponin I. New-onset angina was defined as <2 months from the date of initial symptoms. Accelerated angina was defined as angina in which symptoms were more frequent, more severe, longer, or precipitated by distinctly less exertion than previously, while the patient was in a stable condition.

We excluded patients with any of the following characteristics: (1) history of ACS; (2) history of coronary artery bypass surgery; (3) lack of significant stenosis as confirmed on coronary angiography (CAG); (4) treatment for DM or hyperglycemia (including insulin); (5) estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m²; (6) cardiogenic shock; and (7) refusal to sign informed consent to participate in the study. A total of 46 patients with first-episode ACS met the eligibility criteria and were enrolled in the study. The study protocol was approved by the Yokohama City University Medical Center Institutional Review Board, and all patients gave written informed consent (UMIN-CTR ID: UMIN000010620).

Blood Sampling

Blood samples were obtained on admission for measurement of blood glucose, HbA1c, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, eGFR, and high-sensitivity C-reactive protein (hs-CRP). Fasting glucose and fasting immunoreactive insulin (IRI) were measured between day 4 after admission and day of discharge after stabilization of the clinical condition.

Oral Glucose Tolerance Test (OGTT)

All patients who had not been diagnosed with DM underwent a standard 75-g OGTT between day 4 after admission and the day of discharge. After an overnight fast, venous blood samples were taken for measurement of blood glucose at 0, 30, 60, and 120 min after the glucose load. Based on the results of 75-g OGTT the patients were classified as having either DM, IGT, or normal glucose tolerance, based on the criteria of the American Diabetes Association. Glucose metabolism was also classified according to 75-g OGTT into a DM pattern (fasting blood glucose ≥126 mg/dl or 120-min post-load blood glucose ≥200 mg/dl) or IGT (fasting blood glucose <126 mg/dl and 120-min post-load blood glucose ≥140 mg/dl, but <200 mg/dl). Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the fasting blood glucose and fasting IRI.

Figure 1. Glycemic variability recorded by the continuous glucose monitoring system. Mean amplitude of glycemic excursions is calculated by measuring the arithmetic mean of the differences between consecutive peaks and nadirs (arrows) that are >1 SD of the mean glucose.

GV and Coronary Plaque Vulnerability
Figure 2. Representative cases of thin-cap fibroatheroma (TCFA) in patients with (A) low-tertile and (B) high-tertile mean amplitude of glycemic excursion (MAGE). (A) The thinnest fibrous cap thickness (FCT) of 300 \( \mu m \) was located at the mid-portion of the left anterior descending artery with mild stenosis on angiography (white arrow). (B) The thinnest FCT of 60 \( \mu m \) was located at the proximal portion of the left anterior descending artery with mild stenosis on angiography (white arrow). This plaque was considered as TCFA (white arrowheads).
resistance (HOMA-IR) score was calculated using the formula HOMA-IR=(fasting blood glucose×fasting IRI)/405.

**CGMS Protocol**

For patients with STEMI, fasting period after admission was 0.8±0.4 days. Each participant was equipped with a CGMS (iPro2, Medtronic, Minneapolis, MN, USA) in the stable phase after admission and monitored consecutively for at least 24 h. The CGMS sensor was inserted into the subcutaneous abdominal fat tissue. During CGMS monitoring, blood glucose was checked for calibration at least 4 times each day with the self-monitoring of blood glucose device (Medisafe Mini, Terumo, Tokyo, Japan) to calibrate the CGMS data. We excluded patients on medication for DM or hyperglycemia, in order to eliminate the effect of medication on GV. Thus, none used glucose-lowering agents (including insulin) before admission and during hospitalization. The CGMS data were recorded and analyzed offline (Figure 1). The 24-h period of monitoring included 3 energy-controlled meals per day in the most stable phase with regard to patient condition, and the data were interpreted by 2 experienced observers (a 24-h period during the 8±4 days after admission was used for analysis).

MAGE was calculated as the arithmetic mean of the differences between consecutive peaks and nadirs that are >1 SD of the mean glucose level.17 Patients were classified according to MAGE tertile: tertile 1 (low tertile), 15 patients with MAGE <31.9 mg/dl; tertile 2 (intermediate tertile), 15 patients with MAGE 31.9–47.2 mg/dl; and tertile 3 (high tertile), 16 patients >47.2 mg/dl.

**Quantitative CAG (QCA)**

QCA of the target plaque was analyzed using QCA-CMS, QAngio XA 7.1 (MEDIS Medical Imaging Systems, Leiden, the Netherlands). The minimal luminal diameter (MLD) was defined as the smallest lumen diameter in the segment of a target plaque. The location of the target plaque was identified with anatomical landmarks. OCT was analyzed according to the Consensus Standards for Acquisition, Measurement, and Reporting of Intravascular Optical Coherence Tomography Studies.18 FCT was measured at the thinnest part 3 times, and the average of each plaque was used for analysis. TCFA was defined as plaque with fibrous cap thickness <65 µm overlying a lipid-rich plaque (maximum lipid arc >90°; Figure 2).

Plaque rupture was defined as the presence of fibrous cap discontinuity and cavity formation in the plaque. Macrophage image was defined as linear strong OCT image on plaque surface accompanied by high attenuation.19 OCT was analyzed by an investigator blinded to patient characteristics. Previously, we demonstrated that intra-observer and inter-observer difference for the measurement of FCT at Yokohama City University Medical Center were low (±20 and 11±22 mm, respectively), and the correlation coefficients were high for repeated measurements by the same observer (r=0.97) as well as for the measurements by 2 different observers (r=0.90).20

**Statistical Analysis**

Continuous variables are expressed as mean±SD for parameters with normal distribution and as median (25th–75th percentile) for parameters with skewed distribution. Differences between 2 groups were tested using Student’s t-test for variables with normal distribution; Mann-Whitney test for variables with skewed distribution (triglycerides and hs-CRP); and chi-squared test or Fisher’s exact test as appropriate for categorical variables. The correlation between MAGE and FCT was determined using power-law cross-correlation coefficient. Differences in continuous variables between 3 or more groups were tested using 1-way analysis of variance (ANOVA), followed by post-hoc comparisons (Tukey HSD test when equal variance was assumed and Games-Howell test when equal variance was not assumed). Receiver operating characteristics (ROC) curves were constructed for the prediction of TCFA with 95% CI. The area under the curve (AUC) was calculated to predict TCFA, with AUC=0.50 representing no accuracy and AUC=1.00 indicating maximum accuracy. In addition to HbA1c and high MAGE (tertile 3), coronary risk factors (age, male sex, body mass index, hypertension, dyslipidemia, current smoking) and variables that were considered in previous studies as predictors of TCFA (HOMA-IR >2.5 and hs-CRP11,22) were included in univariate analysis for the prediction of TCFA. Univariate predictors of TCFA with P<0.2 were entered into a multivariate logistic analysis with a forward stepwise algorithm (model 1). To investigate the significance of MAGE among various markers of glycemic metabolism, we also carried out multivariate logistic analysis with a forced inclusion model (model 2: HOMA-IR >2.5, HbA1c, and MAGE). All statistical tests were 2-tailed, and P<0.05 was considered to indicate statistical significance. All statistical analysis was carried out using SPSS version 18.0 (SPSS, Japan, Tokyo, Japan).

**Results**

**Baseline Characteristics**

Table 1 summarizes baseline patient characteristics according to MAGE tertile. Most of the patients with high MAGE (tertile 3) were male (compared with tertiles 1 and 2, P<0.01) and young (compared with low MAGE, tertile 1, P=0.03, ANOVA). Blood glucose at admission, fasting glucose, fasting IRI, HOMA-IR, and HbA1c, however, were not significantly different among the 3 groups (Table 1).

**Angiography and OCT**

There were no significant differences between the 3 groups with regard to the angiographic parameters, including target plaque location, MLA, reference vessel diameter, diameter stenosis, and lesion length (Table 2). Moreover, OCT-derived MLA at the target plaques was not different between the 3 groups (Table 2). TCFA was identified in 13 out of the 46 patients (28%) and was more frequently found in patients with high MAGE (high tertile vs. intermediate tertile vs. low tertile; 50% vs. 27% vs. 7%, P=0.03; Table 2). FCT was thinner in
while maximum glucose level measured on CGMS was not (AUC, 0.676; 95% CI: 0.505–0.847, P=0.065, Figure 4B).

**Univariate and Multivariate Logistic Analysis**

We hypothesized that high MAGE was a predictor of TCFA. To test this hypothesis, we conducted univariate logistic
The present study has shown that FCT of non-culprit plaques with mild-moderate stenosis was thinner and TCFA was more frequently observed in patients with high MAGE, compared to those with low MAGE. To identify predictors of TCFA, we performed univariate logistic analysis, multivariate logistic analysis with forward stepwise algorithm (model 1: male, hypertension, and high MAGE), and multivariate logistic analysis with a forced inclusion model (model 2: HOMA-IR>2.5, HbA1c, and high MAGE) on the 10 parameters tested. On univariate logistic analysis, high MAGE correlated with TCFA. Multivariate logistic analysis with forward stepwise algorithm (model 1) also identified high MAGE as an independent and significant predictor of TCFA (OR, 5.000; 95% CI: 1.268–19.72; P=0.021). Similarly, multivariate logistic analysis with the forced inclusion model (model 2) showed that high MAGE was a significant predictor of TCFA, independent of HOMA-IR and HbA1c (OR, 5.674; 95% CI: 1.339–24.05; P=0.018).

Subgroup Analysis of Non-DM Patients

TCFA was identified in 9 out of the 35 non-DM patients (26%). We conducted univariate logistic analysis, multivariate logistic analysis with forward stepwise algorithm (model 1: hypertension, and high MAGE), and multivariate logistic analysis with a forced inclusion model (model 2: HOMA-IR>2.5, HbA1c, and high MAGE) to identify predictors of TCFA (Table 3). On univariate logistic analysis, of the 10 parameters tested, only high MAGE correlated with TCFA. Multivariate logistic analysis with forward stepwise algorithm (model 1) also identified high MAGE as an independent and significant predictor of TCFA (OR, 5.000; 95% CI: 1.268–19.72; P=0.021). Similarly, multivariate logistic analysis with the forced inclusion model (model 2) showed that high MAGE was a significant predictor of TCFA, independent of HOMA-IR and HbA1c (OR, 5.674; 95% CI: 1.339–24.05; P=0.018).

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Figure 4. Receiver operating characteristic curves for (A) mean amplitude of glycemic excursion (MAGE) and (B) maximum continuous glucose monitoring system (CGMS) glucose level as predictors of thin-cap fibroatheroma (TCFA). MAGE was a significant predictor of TCFA (area under the curve [AUC], 0.721; 95% CI: 0.573–0.869, P=0.020), but maximum CGMS glucose level was not (AUC, 0.676; 95% CI: 0.505–0.847, P=0.065).

Table 3. Significant Indicators of TCFA

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate</th>
<th>Multivariate (model 1)</th>
<th>Multivariate (model 2)</th>
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<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>P-value</td>
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<tr>
<td>Age per 1 year</td>
<td>1.027</td>
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<td>Male</td>
<td>6.857</td>
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<td>Hypertension</td>
<td>3.575</td>
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<tr>
<td>Dyslipidemia</td>
<td>0.500</td>
<td>0.115–2.181</td>
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<td>Current smoker</td>
<td>0.462</td>
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<td>hs-CRP at admission per 1 mg/dl</td>
<td>0.867</td>
<td>0.498–1.510</td>
<td>0.614</td>
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<td>HOMA-IR &gt;2.5</td>
<td>0.684</td>
<td>0.174–2.689</td>
<td>0.586</td>
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<tr>
<td>HbA1c per 1%</td>
<td>0.829</td>
<td>0.344–1.999</td>
<td>0.677</td>
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<tr>
<td>High MAGE (tertile 3)</td>
<td>5.000</td>
<td>1.268–19.72</td>
<td>0.021</td>
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</table>

Model 1, male, hypertension, and high MAGE; model 2, HOMA-IR >2.5, HbA1c, and high MAGE. Abbreviations as in Table 1.

Table 4. Significant Indicators of TCFA in Non-DM Patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate</th>
<th>Multivariate (model 1)</th>
<th>Multivariate (model 2)</th>
</tr>
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<tr>
<td></td>
<td>OR</td>
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<td>P-value</td>
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<td>Age per 1 year</td>
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<td>Male</td>
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<td>BMI per 1 kg/m²</td>
<td>0.989</td>
<td>0.824–1.187</td>
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<td>Hypertension</td>
<td>5.867</td>
<td>0.637–53.99</td>
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<td>Dyslipidemia</td>
<td>1.050</td>
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<td>Current smoker</td>
<td>0.540</td>
<td>0.092–3.159</td>
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<td>hs-CRP at admission per 1 mg/dl</td>
<td>0.942</td>
<td>0.593–1.497</td>
<td>0.801</td>
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<tr>
<td>HOMA-IR &gt;2.5</td>
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<td>0.092–3.159</td>
<td>0.494</td>
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<td>HbA1c per 1%</td>
<td>0.872</td>
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<td>MAGE per 1 mg/dl</td>
<td>1.069</td>
<td>1.013–1.128</td>
<td>0.014</td>
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Model 1, hypertension and MAGE; model 2, HOMA-IR >2.5, HbA1c, and MAGE. Abbreviations as in Table 1.
with those with low and intermediate MAGE after the first occurrence of ACS. Furthermore, MAGE, but not maximum glucose as determined on CGMS, was independently associated with the presence of TCFA in the non-culprit vessel. MAGE was also independently associated with TCFA in the non-DM patient subgroup. To the best of our knowledge, this is the first study to demonstrate a correlation between high MAGE and TCFA in the non-culprit vessel.

Previous pathological and in vivo intravascular ultrasound (IVUS) studies indicated that TCFA causes plaque rupture, resulting in ACS. 22,24 TCFA is observed not only in the culprit lesion of ACS but also in plaques associated with mild-moderate stenosis. Tian et al reported that TCFA was observed 3-fold more frequently in plaques with mild-moderate stenosis than in that with severe stenosis. 25 In addition, the PROSPECT study, in which ACS patients underwent 3-vessel IVUS, reported a similar incidence of cardiovascular events during the 3-year period after PCI, in treated culprit lesions and in non-culprit lesions. 26 That study showed that although non-culprit lesions that were responsible for unanticipated events were frequently angiographically mild, most were TCFA or were characterized by large plaque burden and small luminal area as determined on grayscale IVUS. Their results suggested that it is important to identify TCFA at non-culprit plaque with mild-moderate stenosis to prevent future ACS. In the present study, we showed that MAGE was an independent predictor of TCFA at the non-culprit plaque in patients with first-episode ACS, indicating that high MAGE may identify patients with TCFA at the non-culprit plaque. Therefore, more aggressive treatment including lifestyle modification, 27 intensive lipid-lowering therapy, 28 and aggressive antiplatelet therapy 29 may be required in these patients to suppress coronary plaque vulnerability and to prevent thrombus formation.

Given that our group and other investigators reported that MAGE was an independent predictor of plaque rupture at the culprit plaque in patients with AMI, 30 of coronary rapid progression in patients with ACS, 31 and of LV remodeling in patients with AMI, 32 we believe that assessment of MAGE is clinically important in patients with ACS.

Hyperinsulinemia is caused by hyperglycemic status in patients with insulin resistance, and serves to reduce blood glucose. Hyperglycemia followed by hyperinsulinemia could sometimes lead to hypoglycemic status. Given that these dynamic changes in blood glucose level result in GV, it is possible that hyperinsulinemia is associated with GV. We have recently shown that hyperinsulinemia was associated with greater plaque volume and increased lipid content in non-culprit intermediate lesions in non-DM patients with ACS. 33 Amano et al also reported that coronary lesions in patients with impaired glucose metabolism are associated with greater lipid-rich plaque content. 33 The present finding of an association between high MAGE and TCFA at the non-culprit plaque in patients with mild-moderate stenosis, is consistent with the aforementioned studies. In addition, GV has a more specific triggering effect on oxidative stress than sustained hyperglycemia. 34 Oxidative stress has been reported to be associated with coronary plaque instability. 35 Moreover, GV can also trigger endothelial dysfunction 36 and inflammation. 37 Given that GV is associated with these multifactorial processes, it could have a more powerful impact on TCFA than coronary risk factors or previously reported predictors, as indicated in the present analyses.

Blunting of GV by dipeptidyl peptidase-IV inhibitor has been reported to reduce oxidative stress and inflammation. 37 In addition, Yamazaki et al showed that a switch from sulfonylurea to meglitinide reduced GV despite similar glucose control parameters (HbA1c, glycoalbumin, and mean blood glucose), and resulted in a significant decrease in both oxidative stress and inflammation. 38 These findings suggest that blunting of GV could be beneficial for coronary plaque stabilization. Further studies are needed to confirm that blunting of GV can prevent future coronary events.

**Study Limitations**

The present study had several limitations. First, the study group included a relatively small number of patients enrolled in a single center. Second, we did not measure markers of oxidative stress. It is widely recognized, however, that GV causes much higher oxidative stress than chronic sustained hyperglycemia. 39,40 Third, MAGE was calculated during hospitalization; and patient diet could differ from their ordinary diet, which could have influenced GV. We used a 24-h period during the 8±4 days after the patients’ condition had stabilized. Given that patients had energy-controlled meals during hospitalization, the present results might have underestimated the association between MAGE and TCFA. Under those conditions, however, a significant association was noted between MAGE and TCFA in the present study. Moreover, the optimal 24-h period for CGMS monitoring is unknown. Further studies are needed to clarify the most adequate 24-h period of CGMS monitoring. Fourth, we excluded some patients, as mentioned earlier, and it remains uncertain whether the present results can be applied to these patients. Fifth, HOMA-IR 2.5 and hs-CRP were not found to be predictors of TCFA. This could be due to the small sample size, but, given that same small sample size, MAGE was still found to be an independent predictor of TCFA.

**Conclusions**

MAGE measured soon after the onset of first-episode ACS identified patients with TCFA at the non-culprit plaque with mild-moderate stenosis in the non-culprit vessel. Evaluation of MAGE may identify a certain subset of patients for whom more aggressive treatment may be necessary to prevent recurrence of ACS.

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**References**
