Management and Outcome of Patients With Acute Coronary Syndrome Caused by Plaque Rupture Versus Plaque Erosion: An Intravascular Optical Coherence Tomography Study

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Background—Plaque rupture and erosion are the 2 most common mechanisms for acute coronary syndromes. However, the outcome of these 2 distinct pathologies in patients with acute coronary syndromes has never been studied.

Methods and Results—We retrospectively studied 141 patients with acute coronary syndromes who underwent optical coherence tomography (OCT) imaging of the culprit lesion prior to stenting from the Massachusetts General Hospital OCT Registry. Management (stent versus no stent), poststenotic OCT findings, and outcomes were compared. Among the 141 culprit lesions, rupture was found in 79 (56%) patients and erosion in 62 (44%). Stent implantation was performed in 77 (97.5%) patients with rupture versus 49 (79.0%) in those with erosion (P<0.001). Immediately after percutaneous coronary intervention, OCT showed a higher incidence of malapposition (37.5% versus 7.3%, P<0.001), thrombus (59.4% versus 14.6%, P=0.001), and protrusion (93.8% versus 73.2%, P=0.008) in the rupture group compared with the erosion group. Plaque rupture was associated with a higher incidence of no reflow or slow flow and distal embolization. Although cardiac event rates were comparable between the two groups at the 1-year follow-up, none of the erosion patients who were treated conservatively without stenting had adverse cardiac events.

Conclusions—Unfavorable poststenotic OCT findings were more frequent in rupture patients compared with erosion patients. A subset of erosion patients who were treated conservatively without stenting remained free of adverse cardiac events for up to 1 year. (J Am Heart Assoc. 2017;6:e004730. DOI: 10.1161/JAHA.116.004730.)

Key Words: acute coronary syndrome • optical coherence tomography • plaque erosion • plaque rupture
smokers. Limited data from the pathology and in vivo studies suggest that underlying plaque morphology other than clinical characteristics may play a critical role in determining early and long-term outcomes in response to stent implantation. In light of the relatively well-preserved vascular structure and less severe luminal narrowing, it is conceivable that ACS caused by PE without significant luminal narrowing may be stabilized by effective antithrombotic treatment without stent implantation. This conservative strategy would avoid both early (vessel dissection, distal embolism, and acute stent thrombosis) and late (restenosis, neatherosclerosis, and late and very late stent thrombosis) complications of stent implantation. Indeed, few reports with a small number of cases have suggested that a subset of patients with ST-segment elevation myocardial infarction caused by PE might be treated by antithrombotic therapy with favorable outcome. However, data on the outcomes of patients with ACS caused by rupture or erosion are limited.

Optical coherence tomography (OCT) has recently been introduced as a high-resolution intravascular imaging modality that enables in vivo diagnosis of PE as well as evaluation of vascular response to stent implantation. In the present study, we investigated the acute stent complications (dissection, malapposition, and intrastent tissue prolapsed) and 1-year outcomes in patients with ACS caused by PR versus PE.

**Methods**

**Study Populations**

From August 2010 to September 2013, a total of 710 patients with ACS who underwent OCT imaging were enrolled in the Massachusetts General Hospital OCT Registry (http://www.clinicaltrials.gov: NCT01110538). A total of 421 patients were excluded for the following reasons: (1) no preprocedure OCT imaging (n=69); (2) no poststenting imaging (n=304); (3) in-stent thrombosis or restenosis (n=33); (4) coronary artery bypass grafting (n=3); or (5) unidentifiable culprit lesions (n=12). Of 289 patients with de novo lesions, 109 patients were additionally excluded for the following reasons: (1) poor image quality (n=22); (2) covered stent (n=6); (3) predilatation before OCT imaging (n=50); (4) massive thrombus (n=6); or (5) missing clinical data (n=25). Finally, 141 patients with 141 identifiable culprit lesions were included in the analysis, including 79 patients with PR and 62 with PE (Figure 1). The culprit lesion was identified on the basis of coronary angiogram, stress test, ECG, left ventriculogram, or echocardiogram. After OCT imaging, percutaneous coronary intervention (PCI) was performed according to the local practice. The decision to perform aspiration thrombectomy, balloon angioplasty, or stent implantation was left at the operator’s discretion.

ST-segment elevation myocardial infarction was defined as continuous chest pain that lasted >30 minutes, arrival at the hospital within 12 hours from the onset of symptoms, ST-segment elevation >0.1 mV in >2 contiguous leads or new left bundle branch block on the 12-lead ECG, and elevated cardiac markers. Non–ST-segment elevation myocardial infarction was defined as ischemic symptoms in the absence of ST elevation on the ECG with elevated cardiac markers. Unstable angina pectoris was defined as having newly developed/accelerating chest symptoms on exertion or rest angina within 2 weeks.

Demographic and clinical data were prospectively collected. All of the images were digitally stored and submitted to the core laboratory at Massachusetts General Hospital. The protocol for the registry was approved by each site’s institutional review board, and all patients provided informed consent.

**PCI Procedure and OCT Image Acquisition**

After intracoronary nitroglycerine administration, the OCT catheter was advanced distal to the culprit lesion. Imaging of
the culprit lesion was then acquired using either the commercially available time-domain (M2/M3 Cardiology Imaging System, Lightlab Imaging/St. Jude Medical, Westford, MA) or frequency-domain OCT C7XR system and the Dragonfly catheter (Lightlab Imaging/St. Jude Medical, Westford, MA) as previously reported.2,18 Aspiration thrombectomy prior to OCT imaging was allowed in patients with large occlusive thrombus or a thrombolysis in myocardial infarction (TIMI) flow grade <2. Predilatation, however, was not allowed. All treatment strategies were decided on by the operators at each institution according to local practice. At the end of the procedure, final OCT imaging was acquired in patients treated with stent implantations. The images were digitally stored and deidentified for offline analysis.

OCT Image Analysis

After the culprit lesion was identified, underlying plaque morphology was analyzed by 2 experienced reviewers using the previously reported criteria.2,17–19 Plaques were classified as: (1) fibrous (homogeneous, high backscattering region) or (2) lipid (low-signal region with diffuse border).17,20 In lipid plaques, fibrous cap thickness was measured 3 times at the thinnest part, and the average value was calculated. Lipid arc was measured at 1-mm intervals and lipid length was measured on the longitudinal view. Thin-cap fibroatheroma was defined as a plaque with lipid content in at least 2 quadrants, with the thinnest part of the fibrous cap measuring <65 μm.21 PR was identified by the presence of fibrous cap discontinuity with a clear cavity formed inside the plaque.2,22,23 PE was defined as a plaque with no detectable signs of fibrous cap rupture with or without thrombus attached, including both definite and probable erosion.2,23 Thrombus was defined as a mass floating in or protruding into the lumen with a dimension of at least 250 μm. Thrombus score was calculated as the sum of the number of quadrants with visible thrombus. The poststent OCT findings including edge dissection, in-stent dissection, incomplete stent apposition, and tissue protrusion were assessed using the previously reported definitions.24 Tissue protrusion was defined as a bowing of the plaque into the lumen between stent struts. Edge dissection was defined as the disruption of the vessel luminal surface with a visible flap at the proximal or distal stent edge. In-stent dissection was defined as the disruption of the vessel luminal surface with a visible flap within the stented area. Incomplete stent apposition was defined as any strut with a distance of more than the sum of strut thickness plus polymer thickness from the surface reflection of the strut to the adjacent visible surface of the vessel. Malapposition area was calculated as (lumen area–stent area) in a cross-sectional image containing malapposed struts.

Quantitative Coronary Angiography Analysis

Angiographic images were analyzed using a quantitative coronary angiogram analysis program (CAAS 5.10.1, Pie Medical Imaging BV, Maastricht, the Netherlands). Reference diameter, minimum lumen diameter, lesion length, and percent diameter stenosis were measured.

Clinical Outcomes

Patients were followed up by telephone call or hospital visit at 6 and 12 months. The occurrence of major adverse cardiac events was recorded, which included death from any cause, nonfatal myocardial infarction, and revascularization.

Statistical Analysis

All statistical analyses were performed by an independent statistician at the core laboratory. Categorical data were compared using either chi-square test or Fisher exact test, and are presented as counts (proportions). Continuous variables are expressed as mean±SD and compared using the independent sample t test. All statistical analyses were performed using SPSS version 18.0 (SPSS Inc, Chicago, IL). P<0.05 was considered statistically significant.

Results

Baseline Characteristics

The baseline characteristics of patients with PR and those with OCT-erosion are summarized in Table 1. Among the 141 patients enrolled, 79 (56%) patients had PR at a culprit lesion and 62 (44%) had OCT-erosion. The plaque characteristics of 94 patients were reported in our previous study.2 No significant difference was observed in sex, coronary risk factors, laboratory findings, and medications between the 2 groups, except younger age, higher frequency of NSTE-ACS, and higher level of high-density lipoprotein in the OCT-erosion group.

Angiographic Findings

The culprit lesion distribution and quantitative coronary angiogram analysis data are listed in Table 2. OCT-erosion was most frequently detected in the left anterior descending artery. PR was equally distributed in the LAD and right coronary artery. There was no significant difference in the culprit lesion distribution between the proximal, mid, and distal segments of coronary arteries. The minimum lumen diameter was larger (P<0.001) and the diameter stenosis was less severe (P=0.001) in the OCT-erosion group compared
with the PR group. Patients with PR had a higher incidence of multivessel disease ($P<0.001$) and more complicated lesion type (type B2/C) ($P<0.001$) compared with those with OCT-erosion.

### Procedural Characteristics

Procedural data are summarized in Table 3. Of the 79 patients with PR, 77 (97.5%) were treated with stent implantation (drug-eluting stent=86, bare metal stent=12). Among the 62 patients with OCT-erosion, 49 (79.0%) were treated with stent implantation (drug-eluting stent=57, bare metal stent=4). The mean stent length and mean stent diameter were similar between the two groups. Compared with patients with PR, those with OCT-erosion had higher baseline thrombolysis in myocardial infarction flow grade, lower incidence of thrombolysis in myocardial infarction flow grade ≤2 after stenting, and lower incidence of distal embolization.

### OCT Findings After PCI

Post-PCI OCT findings in patients with PR and OCT-erosion are listed in Table 4. Post-PCI OCT imaging was acquired in 61 patients with PR and in 46 with OCT-erosion. Patients with PR had a higher incidence of in-stent dissection or thrombus, compared with those with OCT-erosion after stent implantation. The incidence of malapposition was significantly higher and the malapposed area was significantly larger in patients...
Clinical Outcomes at 1-Year Follow-Up

Table 5 shows the clinical outcomes at the 1-year follow up. Of the 141 enrolled patients, 134 (95.0%) were followed up to 1 year. Mean follow-up time was 367.3±22.3 days. Statistically, no significant differences were observed between the 2 groups in rates of death, myocardial infarction, target lesion revascularization, or nontarget lesion revascularization. However, the rate of revascularization in patients with PR was numerically higher than those with OCT-erosion (12.5% versus 6.5%, P=0.238). Two of 79 (2.5%) patients in the rupture group and 13 of 62 (21.0%) in the erosion group were treated conservatively without stent implantation. Clinical outcomes of patients with PR and OCT-erosion stratified by treatment strategy are summarized in Table S1. At 1-year follow-up, 1 of 2 patients in the rupture group who was treated medically died. All 13 patients in the erosion group who were treated medically remained free of adverse events for up to 1 year.

Discussion

This study shows that, in the real world, patients with ACS caused by PE were more likely to be treated conservatively compared with those caused by PR (21.0% versus 2.5%). Among the patients who were treated with stent implantation, patients with PR had a higher incidence of malapposition, with PR than in those with OCT-erosion. The representative cases of PE and PR are shown in Figures 2 and 3.
tissue protrusion, and thrombus compared with those with PE. At the 12-month follow-up, the rate of revascularization in patients with PR was numerically higher than those with OCT-erosion although no statistical difference was observed. Importantly, patients with erosion who were treated conservatively were free of cardiovascular events up to the 1-year follow-up.

Impact of Underlying Plaque Morphology on Management of ACS

PEs are responsible for 25% to 44% of ACS cases. PE is characterized by a less occlusive plaque with relatively preserved vascular integrity. The autopsy study showed that ruptured plaque is often significantly obstructive and has a large plaque burden and a large necrotic core with an overlying disrupted fibrous cap, which is attenuated and inflamed. Disruption of the fibrous cap exposes a great amount of highly thrombogenic necrotic core to circulating platelets, leading to occlusive thrombus and acute ischemic events. In contrast, PE often has a less severe obstruction, a less superficial necrotic core, and a smaller plaque burden. Furthermore, luminal thrombus in PE has been attributed to apoptosis or denudation of superficial endothelial cells and is rich in platelets. These distinct characteristics associated with PE provide rationale for conservative treatment with potent antithrombotic therapy without stenting. Indeed, patients with PE have a more favorable response to thrombolytic therapy compared with those with PR.

Current treatment of ACS is routine PCI with stenting, regardless of underlying pathologies. The culprit plaque morphology is not routinely evaluated. Therefore, the impact of underlying lesion characteristics on treatment strategy selection has never been investigated in the setting of ACS. Although our investigation was a retrospective study without predefined criteria for the selection of treatment strategy and all of the patients were treated according to local practice without knowledge of underlying pathology, patients with PE were more frequently treated “conservatively” without stent implantation compared with patients with PR (21.0% versus 2.5%, \( P < 0.001 \)). Of the 62 patients with PE, 13 who had moderate stenosis were treated with antithrombotic therapy without stent implantation. Remarkably, those who were treated conservatively had no adverse cardiac events during the 1-year follow-up. In contrast, 7 events were observed among the 49 patients who were treated with stenting. Consistent with this finding, Prati et al retrospectively investigated 31 patients with ST-segment elevation myocardial infarction. After thrombus was removed by thrombectomy, OCT showed the intact fibrous cap without evidence of PR and no significant residual obstruction. Among these 31 patients, 19 were treated with stents and 12 were treated with only...
antithrombotic therapy without angioplasty or stenting. None of these 12 patients required an additional revascularization during the 12-month follow-up.30

Underlying Plaque Morphology and Clinical Outcomes After PCI

In our previous study of the mechanism responsible for ACS, lipid plaques were less frequently detected in patients with OCT-erosion than in those with PR. When lipids were present, the overlying fibrous cap was thicker, the lipid arc was smaller, and the lipid length was shorter in patients with OCT-erosion compared with those with PR.2 Ruptured plaque releases highly thrombogenic substrates, which may induce recurrent local thrombosis and distal embolization, perturbing the coronary microcirculation. These findings suggest that PR may be associated with worse outcomes after stenting. Higuma et al27 reported that PR was associated with worse myocardial perfusion after PCI compared with PE. In the present study, we also found that PR had a higher incidence of acute stent complications (in-stent dissection, tissue protrusion, malapposition, and thrombus) and higher frequency of distal embolization. Recently, Niccoli et al31 demonstrated that patients with PR have a worse prognosis after 3-year follow-up when compared with those with PE, which is mainly driven by a higher risk of revascularization and unstable angina. In our study, we did not observe different clinical outcomes between the 2 groups, which may be attributed to the small sample size and short follow-up period. However, the favorable clinical outcomes in patients with erosion treated conservatively highlights the new concept that in a subset of patients with ACS caused by PEs, conservative therapy without stent implantation might be feasible and safe.

Table 5. Clinical Outcomes at 1 Year

<table>
<thead>
<tr>
<th>Events</th>
<th>Overall (N=134)</th>
<th>PR (n=72)</th>
<th>OCT-Erosion (n=62)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>2 (1.5)</td>
<td>1 (1.4)</td>
<td>1 (1.6)</td>
<td>1.000</td>
</tr>
<tr>
<td>Acute MI or ACS</td>
<td>3 (2.2)</td>
<td>1 (1.4)</td>
<td>2 (3.2)</td>
<td>0.596</td>
</tr>
<tr>
<td>Revascularization</td>
<td>13 (9.7)</td>
<td>9 (12.5)</td>
<td>4 (6.5)</td>
<td>0.238</td>
</tr>
<tr>
<td>TLR</td>
<td>6 (4.6)</td>
<td>5 (6.9)</td>
<td>1 (1.6)</td>
<td>0.216</td>
</tr>
<tr>
<td>Non-TLR</td>
<td>7 (5.2)</td>
<td>4 (5.6)</td>
<td>3 (4.8)</td>
<td>1.000</td>
</tr>
<tr>
<td>Overall MACE</td>
<td>17 (12.7)</td>
<td>10 (13.9)</td>
<td>7 (11.3)</td>
<td>0.652</td>
</tr>
</tbody>
</table>

Data are presented as number (percentage). Comparisons of the events between the two groups were performed using Fisher exact test. ACS indicates acute coronary syndrome; MACE, major adverse cardiovascular events; MI, myocardial infarction; OCT, optical coherence tomography; PR, plaque rupture; TLR, target lesions revascularization.

Figure 3. Representative optical coherence tomography (OCT) images of plaque rupture. A 60-year-old woman with ST-segment elevation myocardial infarction was admitted after 11 hours of chest pain. Results from diagnostic angiogram showed total occlusion in the proximal left anterior descending artery (LAD). Angiogram results after thrombectomy demonstrates dissection lesion in the proximal LAD (white arrow, left upper panel). Cross-sectional OCT images of the culprit lesion show disrupted fibrous cap (white arrows) and cavity (asterisk) formation (A through C). The patient was treated with a drug-eluting stent (3.0 x 18 mm). Poststenting OCT revealed in-stent thrombus (red arrows, D), malapposed struts (white arrows, E), and stent protrusion (yellow arrows, F).
This concept was prospectively tested in a recent clinical trial that was performed by our group. If this conservative approach without a metallic stent or polymer scaffold proves to be effective and safe, it may become a new treatment paradigm for one fourth of patients with ACS. Randomized trials will be needed to reproduce this pilot data and to evaluate the long-term outcomes of this new strategy.

Limitations
Several limitations need to be mentioned in this study. First, this is a retrospective analysis of a small number of patients. Because of the retrospective nature of the analysis, there was no systematic decision process for how to treat patients. However, although this was a retrospective study, it may provide important evidence for better individualized management of patients with ACS based on underlying lesion characteristics. In addition, the registry included only patients who underwent OCT according to the operator’s discretion. Therefore, the issue of selection bias cannot be avoided. Second, the underlying plaque characteristics might be obscured by residual thrombus (specifically, red thrombus) in some cases. Although we excluded cases with massive residual thrombus after thrombus aspiration to avoid misclassification of culprit plaques, we have to acknowledge that some ruptured cases might be misdiagnosed as erosion due to invisibility of the ruptured site, which was hidden underneath the thrombus. Third, thrombus aspiration was performed to facilitate reperfusion prior to OCT imaging. Although care was taken to avoid excessive mechanical injury during thrombectomy, it is possible that this procedure may have altered the morphologic features of the underlying plaque. Therefore, we cannot exclude that in some patients, PR was iatrogenic, being caused by thrombus aspiration. Fourth, due to safety concerns, 16 (20.8%) patients in the rupture group did not undergo poststenting OCT imaging, whereas only 3 (6.1%) in the erosion group did not undergo poststenting OCT imaging (P<0.05). This difference might result in selection bias in our study. However, the main findings of the present study are unlikely changed even though poststenting OCT imaging was performed in patients with worse conditions.

Conclusions
Patients with PE are more likely to be treated with medical therapy without stent implantation compared with patients with PR. Patients with PE treated conservatively remained free of major adverse cardiac events for up to 1 year. Patients with PR had worse vascular response to stent implantation with a higher incidence of malapposition, tissue protrusion, and thrombus, compared with patients with PE.

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References
SUPPLEMENTAL MATERIAL
Table S1. Clinical outcomes of patients with stent implantation and without stent implantation stratified by treatment strategy

<table>
<thead>
<tr>
<th></th>
<th>PR</th>
<th>OCT-erosion</th>
<th>p</th>
<th>Non-stent</th>
<th>Stent</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1(50)</td>
<td>0(0)</td>
<td>1.0</td>
<td>0(0)</td>
<td>1(2.0)</td>
<td>0.76</td>
</tr>
<tr>
<td>Acute MI or ACS</td>
<td>0(0)</td>
<td>1(1.4)</td>
<td>0.94</td>
<td>0(0)</td>
<td>2(4.0)</td>
<td>0.66</td>
</tr>
<tr>
<td>Revascularization</td>
<td>0(0)</td>
<td>9(12.9)</td>
<td>0.72</td>
<td>0(0)</td>
<td>4(8.0)</td>
<td>0.54</td>
</tr>
<tr>
<td>TLR</td>
<td>0(0)</td>
<td>5(7.1)</td>
<td>0.79</td>
<td>0(0)</td>
<td>1(2.0)</td>
<td>0.76</td>
</tr>
<tr>
<td>Non-TLR</td>
<td>0(0)</td>
<td>4(5.7)</td>
<td>0.82</td>
<td>0(0)</td>
<td>3(6.0)</td>
<td>0.59</td>
</tr>
<tr>
<td>Any events</td>
<td>1(50)</td>
<td>9(12.9)</td>
<td>0.21</td>
<td>0(0)</td>
<td>7(14.0)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Data are presented as n (%). MI = myocardial infarction; ACS = acute coronary syndrome; TVR = target vessel revascularization; TLR = target lesions revascularization.