Plaque Characterization to Inform the Prediction and Prevention of Periprocedural Myocardial Infarction During Percutaneous Coronary Intervention

The CANARY Trial (Coronary Assessment by Near-infrared of Atherosclerotic Rupture-prone Yellow)

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ABSTRACT

OBJECTIVES This study sought to determine whether pre-percutaneous coronary intervention (PCI) plaque characterization using near-infrared spectroscopy identifies lipid-rich plaques at risk of periprocedural myonecrosis and whether these events may be prevented by the use of a distal protection filter during PCI.

BACKGROUND Lipid-rich plaques may be prone to distal embolization and periprocedural myocardial infarction (MI) in patients undergoing PCI.

METHODS Patients undergoing stent implantation of a single native coronary lesion were enrolled in a multicenter, prospective trial. Near-infrared spectroscopy and intravascular ultrasound were performed at baseline, and lesions with a maximal lipid core burden index over any 4-mm length (maxLCBI4mm) ≥600 were randomized to PCI with versus without a distal protection filter. The primary endpoint was periprocedural MI, defined as troponin or a creatine kinase-myocardial band increase to 3 or more times the upper limit of normal.

RESULTS Eighty-five patients were enrolled at 9 U.S. sites. The median (interquartile range) maxLCBI4mm was 448.4 (274.8 to 654.4) pre-PCI and decreased to 156.0 (75.6 to 312.6) post-PCI (p < 0.0001). Periprocedural MI developed in 21 patients (24.7%). The maxLCBI4mm was higher in patients with versus without MI (481.5 [425.6 to 679.6] vs. 371.5 [228.9 to 611.6], p = 0.05). Among 31 randomized lesions with maxLCBI4mm ≥600, there was no difference in the rates of periprocedural MI with versus without the use of a distal protection filter (35.7% vs. 23.5%, respectively; relative risk: 1.52; 95% confidence interval: 0.50 to 4.60, p = 0.69).

CONCLUSIONS Plaque characterization by near-infrared spectroscopy identifies lipid-rich lesions with an increased likelihood of periprocedural MI after stent implantation, presumably due to distal embolization. However, in this pilot randomized trial, the use of a distal protection filter did not prevent myonecrosis after PCI of lipid-rich plaques.
Periprocedural myonecrosis is common after percutaneous coronary intervention (PCI), occurring in as many as 40% of patients (1,2). Although the threshold of post-PCI biomarker elevation that is prognostically relevant is controversial (3,4), there is general agreement that any level of periprocedural myonecrosis is undesirable. Previous studies have identified baseline clinical and angiographic lesion characteristics that are associated with intra-procedural thrombotic events and post-PCI myocardial infarction (MI) (5–8). Beyond these conventional features, certain plaque phenotypes may be particularly susceptible to distal embolization, microvascular obstruction, and myonecrosis after PCI. Specifically, lipid-rich fibroatheromas are friable and easily disrupted during PCI, predisposing to periprocedural MI (9). Over the past several years, case reports and uncontrolled or retrospective registries have suggested that plaque characterization by invasive imaging with gray-scale and radiofrequency intravascular ultrasound (IVUS), optical coherence tomography, and near-infrared spectroscopy (NIRS) may identify emboli-prone lesions (10–16). Moreover, distal protection devices have been shown to prevent embolization and reduce periprocedural myonecrosis after PCI of friable saphenous vein graft lesions (17,18). Brilakis et al. (19) reported that use of a filter-based catheter in the native coronary circulation before PCI of high-risk plaques may protect the distal microvasculature from embolization. Whether native coronary artery lesions prone to periprocedural myonecrosis can be identified before PCI and whether the use of a distal embolic protection device can reduce the incidence of periprocedural MI in high-risk lesions so identified have never been prospectively examined in a multicenter trial.

The TVC catheter (InfraReDx, Inc., Burlington, Massachusetts) is a U.S. Food and Drug Administration–approved dual-modality intravascular imaging device that coregisters a NIRS chemogram to a gray-scale IVUS image, allowing simultaneous assessment of plaque morphology and composition. NIRS has been validated to accurately identify fibroatheromas in humans (20) and provides an automated quantitative assessment of lipid burden in lipid-rich plaques (LRPs). We therefore sought to determine whether pre-PCI plaque characterization using NIRS is capable of identifying lesions at risk of periprocedural myonecrosis and whether these events may be prevented by the use of a distal protection filter during PCI in the native coronary circulation.

METHODS

PROTOCOL OVERVIEW. The CANARY (Coronary Assessment by Near-infrared of Atherosclerotic Rupture-prone Yellow) trial was a prospective, multicenter, randomized pilot trial designed to determine the relationship between NIRS lipid parameters and subsequent periprocedural myonecrosis after coronary stenting and whether the use of the FilterWire EZ (21) distal protection filter (Boston Scientific, Natick, Massachusetts) can reduce MI after PCI of LRPs. Patients with stable angina, silent ischemia, or stabilized acute coronary syndromes who had troponin I or T and creatine kinase-myocardial band levels all less than the local laboratory upper limit of normal within 12 h of the time of PCI were eligible for enrollment. Major clinical exclusion criteria included previous coronary artery bypass graft surgery, previous PCI within 24 h or future planned PCI within 30 days, left ventricular ejection fraction <25%, and the inability to take aspirin and a thienopyridine for at least 30 days. Angiographic inclusion criteria required planned PCI of a single de novo lesion in a native coronary artery with reference vessel diameter of 2.5 mm, diameter stenosis of ≥50% to <100%, and length of ≤60 mm. In addition, a nodulefree landing zone for the FilterWire EZ with a ≥2.5 mm reference diameter must be present ≥2.5 cm distal to the target lesion, and there could be no side branches greater than 2.0 mm in diameter within the target lesion or between the target lesion and the filter loop landing zone (21). Other angiographic exclusion criteria included a greater than 50% diameter stenosis in the left main coronary artery or left main equivalent disease or the presence of any of the following target lesion characteristics: ostial location; thrombus; or severe calcification. The study was approved by the investigational review board at Asahi, Abbott Vascular, Elsevier, Somahlution, and Boston Scientific; has received research support from Guerbet and InfraReDx; and that his spouse is an employee of Medtronic. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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each institution, and all patients provided written informed consent before enrollment.

All patients received $\geq 81$ mg aspirin orally at least 2 h before the procedure. A loading dose of an adenosine diphosphate receptor antagonist was strongly recommended pre-PCI, but in all cases was administered within 2 h post-procedure. Anticoagulation was achieved with either intravenous heparin or bivalirudin, with glycoprotein IIb/IIIa inhibitor use allowed per operator discretion.

After diagnostic angiography, NIRS-IVUS was performed with a 3.2-F TVC catheter from the distal target vessel to the guide catheter using a motorized pullback system at 0.5 mm/s. The locations of major side branches and the target lesion boundaries were marked and annotated during pullback using TVC system software. The total lesion lipid core burden index (LCBI) and maximal LCBI over any 4 mm segment ($\text{maxLCBI}_{4\text{mm}}$) were then automatically calculated as previously described (16). In summary, raw spectroscopic data are converted into a probability of LRP on a red-to-yellow color scale, with red representing low probability of lipid and yellow representing high probability. LCBI represents the proportion of yellow pixels (lipid probability $>0.6$) in the plaque, reported on a scale of 0 to 1,000 (signifying 0% to 100% lipid). The number of yellow pixels every 0.1 mm was determined by the automated software and summed over each possible 4-mm long axial segment to determine the $\text{maxLCBI}_{4\text{mm}}$ (Online Figure 1).

LRPs were pre-specified as those with $\text{maxLCBI}_{4\text{mm}} \geq 600$. LRPs were randomized 1:1 to PCI and stenting with versus without use of the FilterWire EZ distal protection device. For patients randomized to distal protection, the FilterWire EZ was required to be deployed for all interventions (balloon angioplasty and stenting). PCI with stenting was otherwise performed using standard techniques. Non-LRPs ($\text{maxLCBI}_{4\text{mm}} < 600$) underwent PCI without distal protection. After the final PCI, NIRS-IVUS imaging was repeated. A representative case is shown in Figure 1.

Creatine kinase-myocardial band and troponin I or T measurements were obtained at 8 and 16 h post-procedure in all patients and for any recurrent chest discomfort or other signs or symptoms of clinical instability. Patients were maintained on daily aspirin $\geq 81$ mg and an adenosine diphosphate receptor antagonist for at least 30 days.

**ENDPOINTS.** The primary endpoint was the incidence of periprocedural MI, defined as troponin or creatine kinase-myocardial band increase to 3 or more times the upper limit of normal within 72 h. Additional in-hospital endpoints included death (cardiac and noncardiac), any MI, target vessel revascularization, and stent thrombosis. All events were adjudicated by a clinical events committee blinded to NIRS measurement and randomization. Quantitative coronary angiography was performed at an independent core laboratory using standardized methodology. Gray-scale IVUS parameters were assessed by a blinded core laboratory as previously described (22). Quantitative IVUS measurements included external elastic membrane (EEM) cross-sectional area, plaque and media (EEM minus lumen) cross-sectional area, plaque burden (plaque and media divided by EEM cross-sectional area), and minimal lumen area (MLA). Measurements were taken both at the site of the MLA within the entire lesion and at the MLA site within the $\text{maxLCBI}_{4\text{mm}}$ segment. Attenuated plaque was defined as hypoechoic plaque with deep ultrasound attenuation without calcification or very dense fibrous plaque (12). The same core laboratory determined the LCBI, $\text{maxLCBI}_{4\text{mm}}$, and the lipid-rich plaque burden,
defined as the proportion of plaque-containing lipid (Online Figure 2).

**STATISTICAL METHODOLOGY.** Sample size was determined to show a reduction in periprocedural MI with FilterWire EZ use in LRPs. Given the restrictive enrollment criteria, a large effect size was assumed for this pilot study, the presence of which would be required to proceed to a pivotal trial. Anticipating a doubling of the periprocedural MI rate in LRPs compared with non-LRPs and the sensitive definition of MI being used, an event rate of 56% was assumed in the LRP control arm on the basis of historical control values (1-3). Randomizing 54 patients (27 in each group) would provide 80% power to show a reduction to 20% in the FilterWire EZ arm using a 2-sided alpha of 0.05. Thus, the study was planned to enroll up to 108 patients, including 54 randomized LRPs and 54 nonrandomized non-LRPs.

Categorical variables were compared using the chi-square or Fisher exact test. Continuous variables are displayed as median (interquartile range) and were compared using Student t test or the Wilcoxon rank sum test for non-normally distributed data. Receiver-operating characteristic curves were drawn and the cutoffs determined that best balanced sensitivity and specificity between NIRS parameters and periprocedural MI by identifying the point closest to (0,1) on the receiver-operating characteristic curve. All analyses are by intention-to-treat. All p values are 2-sided, and p < 0.05 was considered statistically significant.

**RESULTS**

**PATIENTS AND ENROLLMENT.** A total of 709 patients were prospectively screened at 8 U.S. sites, of whom 85 (12.0%) with qualifying lesions undergoing PCI were enrolled (Figure 2). A single site (Mount Sinai Hospital, New York, New York) enrolled 51 patients, whereas the other centers enrolled between 2 and 9 patients each. The maxLCBI₄mm was ≥600 in 31 lesions (36.5%), which were then randomized to PCI with (n = 14) and without (n = 17) distal protection with the FilterWire EZ. In the other 54 lesions, PCI was performed without distal protection. Because of difficult recruitment, the Data Safety and Monitoring Board reviewed the unblinded data after the 31 LRP lesions were randomized and recommended that the trial be terminated for futility (lack of evidence of any randomized treatment benefit).

Baseline clinical, angiographic, IVUS, and NIRS characteristics of the randomized and registry groups are shown in Tables 1 to 3. LCBI and maxLCBI₄mm were by definition substantially greater in the randomized (LRP) cohort compared with the registry (non-LRP) cohort (Table 3). In most other respects, the groups were not significantly different. Compared with the registry, randomized lesions were somewhat more severe by angiography but not by IVUS. The frequency of attenuated plaques was also similar in the 2 groups, although the length and angle of attenuation were greater in the randomized group, as were measures of LRP burden, again consistent with the stratification. Baseline features were well balanced among the LRP patients and lesions randomized to FilterWire EZ versus control group (Tables 1 to 3), although the FilterWire group had slightly more left anterior descending artery lesions but had shorter length of stents placed. NIRS and IVUS parameters were similar in the 2 randomized groups.

Stents were implanted in all patients. Considering all 85 lesions, the median (interquartile range) maxLCBI₄mm decreased from 448.4 (274.8 to 654.4) pre-PCI to 156.0 (75.6 to 312.6) post-PCI, and the total lesion LCBI decreased from 143.2 (74.3 to 236.4) to 17.9 (6.0 to 61.9) (p <.0001 for each comparison).

**PERIPROCEDURAL MI AND ADDITIONAL CLINICAL EVENTS.** Periprocedural MI developed in 21 of 85 patients (24.7%) (Figure 3). All were non-Q-wave MIs. Periprocedural MI according to the Third Universal MI definition (23) and the Society of Cardiac

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**FIGURE 2 Patient Flow Diagram**

Of 709 consented patients, 85 were enrolled (12.0%). Among excluded patients, more than 1 exclusion criteria were present in some patients, and infrequent exclusion criteria are not shown in this list. After near-infrared spectroscopy was performed in the 85 enrolled target lesions, patients were stratified to the randomized group (maxLCBI₄mm ≥600) or the registry group (maxLCBI₄mm < 600). maxLCBI₄mm = maximal lipid core burden index over any 4-mm length; PCI = percutaneous coronary intervention; RVD = reference vessel diameter.
### TABLE 1 Baseline Clinical Characteristics and Procedural Medications

<table>
<thead>
<tr>
<th>All Patients</th>
<th>Registry (n = 54)</th>
<th>Randomized (n = 31)</th>
<th>p Value</th>
<th>Randomized FilterWire EZ (n = 14)</th>
<th>Randomized No FilterWire EZ (n = 17)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>63.0 (56.0–69.0)</td>
<td>63.5 (56.0–69.0)</td>
<td>63.0 (56.0–69.0)</td>
<td>0.59</td>
<td>61.5 (52.0–69.0)</td>
<td>64.0 (57.0–66.0)</td>
</tr>
<tr>
<td>Female</td>
<td>15 (17.6)</td>
<td>8 (14.8)</td>
<td>7 (22.6)</td>
<td>0.37</td>
<td>5 (35.7)</td>
<td>2 (11.8)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>29.1 (26.3–32.6)</td>
<td>29.1 (26.3–32.6)</td>
<td>28.4 (24.8–34.6)</td>
<td>0.42</td>
<td>26.6 (24.4–30.4)</td>
<td>29.4 (27.2–34.6)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>28 (32.9)</td>
<td>19 (35.2)</td>
<td>9 (29.0)</td>
<td>0.56</td>
<td>5 (35.7)</td>
<td>4 (23.5)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>77 (90.6)</td>
<td>50 (92.6)</td>
<td>27 (87.1)</td>
<td>0.46</td>
<td>13 (92.9)</td>
<td>14 (82.4)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>78 (91.8)</td>
<td>51 (94.4)</td>
<td>27 (87.1)</td>
<td>0.25</td>
<td>12 (85.7)</td>
<td>15 (88.2)</td>
</tr>
<tr>
<td>Smoking, current</td>
<td>19 (13.3)</td>
<td>6 (11.1)</td>
<td>7 (22.6)</td>
<td>0.21</td>
<td>4 (28.6)</td>
<td>3 (17.6)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>19 (22.4)</td>
<td>12 (22.2)</td>
<td>7 (22.6)</td>
<td>0.97</td>
<td>3 (21.4)</td>
<td>4 (23.5)</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>44 (51.8)</td>
<td>30 (55.6)</td>
<td>14 (45.2)</td>
<td>0.36</td>
<td>7 (50.0)</td>
<td>7 (41.2)</td>
</tr>
</tbody>
</table>

**Presentation**

- STEMI: 1 (1.2) 0 (0) 1 (3.2) 0.36 0 (0) 1 (5.9) 1.0
- Non-STEMI: 5 (5.9) 4 (7.4) 1 (3.2) 0.65 0 (0) 1 (5.9) 1.0
- Unstable angina, troponin negative: 46 (54.1) 27 (50.0) 19 (61.3) 0.31 11 (78.6) 8 (47.1) 0.07
- Stable angina or silent ischemia: 33 (38.8) 23 (42.6) 10 (32.3) 0.35 3 (21.4) 7 (41.2) 0.28

**Procedural/discharge medications**

- Aspirin: 85 (100.0) 54 (100.0) 31 (100.0) – 14 (100) 17 (100) –
- ADP receptor antagonist: 85 (100.0) 54 (100.0) 31 (100.0) – 14 (100) 17 (100) –
- Clopidogrel: 69 (81.2) 43 (79.6) 26 (83.9) 0.63 12 (85.7) 14 (82.4) 1.0
- Prasugrel or ticagrelor: 16 (18.8) 11 (20.4) 5 (16.1) 0.63 2 (14.3) 3 (17.7) 1.0
- Statin: 73 (85.9) 49 (90.7) 24 (74.4) 0.11 12 (85.7) 12 (70.6) 0.41
- Heparin: 5/76 (6.6) 3/48 (5.9) 2/28 (7.1) 1.0 1/12 (8.3) 1/16 (6.3) 1.0
- Bivalirudin: 71/76 (93.4) 45/48 (94.1) 26/28 (92.9) 1.0 11/91 (11.3) 15/21 (10.9) 1.0
- Glycoprotein IIb/IIIa inhibitor*: 4/83 (4.8) 1/52 (1.9) 3 (9.7) 0.14 2 (14.3) 1 (5.9) 0.58

**Values are n (%), median (interquartile range), or n/N (%).** *All epftibatide.

**ADP = adenosine diphosphate; PCI = percutaneous coronary intervention; p_1 value = randomized vs. registry; p_2 value = FilterWire EZ vs. control.**

### TABLE 2 Baseline Angiographic and Procedural Characteristics

<table>
<thead>
<tr>
<th>All Patients</th>
<th>Registry (n = 54)</th>
<th>Randomized (n = 31)</th>
<th>p Value</th>
<th>Randomized FilterWire EZ (n = 14)</th>
<th>Randomized No FilterWire EZ (n = 17)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion location</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>44 (56.4)</td>
<td>27 (56.3)</td>
<td>17 (56.7)</td>
<td>0.97</td>
<td>11 (78.6)</td>
<td>6 (37.5)</td>
</tr>
<tr>
<td>Left circumflex</td>
<td>12 (15.4)</td>
<td>9 (18.8)</td>
<td>3 (10.0)</td>
<td>0.35</td>
<td>0 (0)</td>
<td>3 (18.8)</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>22 (28.2)</td>
<td>12 (25.0)</td>
<td>10 (33.3)</td>
<td>0.43</td>
<td>3 (21.4)</td>
<td>7 (43.8)</td>
</tr>
</tbody>
</table>

**Pre-PCI measurements**

- Reference vessel diameter, mm: 2.79 (2.59–3.23) 2.88 (2.59–3.24) 2.73 (2.59–3.22) 0.68 2.76 (2.70–3.26) 2.70 (2.49–3.18) 0.67
- Minimal luminal diameter, mm: 1.05 (0.66–1.36) 1.14 (0.72–1.41) 0.73 (0.54–1.10) 0.002 0.82 (0.70–0.97) 0.61 (0.51–1.17) 0.79
- Diameter stenosis, % | 63.0 (54.9–77.2) | 57.3 (53.6–72.1) | 73.8 (63.0–80.3) | 0.0006 | 73.8 (61.9–77.2) | 74.9 (64.1–81.2) | 0.82 |
- Lesion length, mm | 15.8 (12.1–22.3) | 15.5 (12.1–20.7) | 16.4 (11.9–24.0) | 0.63 | 15.1 (11.1–18.7) | 22.3 (12.2–27.0) | 0.10 |
- Bifurcation lesion | 22 (28.2)       | 10 (20.8)           | 12 (40.0) | 0.07 | 8 (57.1) | 4 (25.0) | 0.07 |
- Thrombus present | 3 (3.8)         | 1 (2.1)             | 2 (6.7) | 0.56 | 0 (0) | 2 (12.5) | 0.49 |
- Moderate or severe calcification*: 24 (30.8) 18 (37.5) 6 (20.0) 0.10 3 (21.4) 3 (18.8) 1.0

**Values are n (%) or median (interquartile range).** *Graded as moderate in all patients.

**Abbreviations as in Table 1.**
Angiography and Interventions clinically relevant MI definition (3) occurred in 14 of 85 (16.5%) and 2 of 85 (2.4%) patients, respectively. There were no other in-hospital major adverse cardiac events.

**TABLE 3 Baseline NIRS and IVUS Measurements**

<table>
<thead>
<tr>
<th>Measure</th>
<th>All Patients</th>
<th>Registry (n = 52)</th>
<th>Randomized (n = 31)</th>
<th>p1 Value</th>
<th>Randomized FilterWire EZ (n = 14)</th>
<th>Randomized No FilterWire EZ (n = 17)</th>
<th>p2 Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCBI</td>
<td>143.2 (74.3-236.4)</td>
<td>91.3 (49.1-133.6)</td>
<td>242.2 (205.3-356.4)</td>
<td>&lt;0.0001</td>
<td>242.2 (205.3-382.6)</td>
<td>245.4 (199.6-353.5)</td>
<td>0.90</td>
</tr>
<tr>
<td>MaxLCBI4mm</td>
<td>448.4 (274.8-654.4)</td>
<td>336.0 (183.8-422.2)</td>
<td>672.9 (615.6-789.2)</td>
<td>&lt;0.0001</td>
<td>665.9 (619.6-726.0)</td>
<td>683.6 (615.6-789.2)</td>
<td>0.58</td>
</tr>
</tbody>
</table>

**Baseline NIRS measures at the MLA site within the total lesion**
- Distance from the ostium, mm: 1 (1.3-29.5)
- EEM CSA, mm²: 12.3 (8.9-15.1)
- P&M CSA, mm²: 9.9 (6.8-12.5)
- Lumen area, mm²: 2.3 (1.9-3.1)
- Plaque burden, %: 79.6 (74.1-84.9)
- Attenuated plaque present (total lesion): 75 (90.4%)
- Length, mm: 14.2 (6.9-26.4)
- Maximal angle, degrees: 127 (97-210)

**Baseline IVUS measures at the MLA site within the maxLCBI4mm segment**
- Distance from the ostium, mm: 14.8 (9.9-28.1)
- EEM CSA, mm²: 12.9 (10.1-15.2)
- P&M CSA, mm²: 9.6 (7.0-12.2)
- Lumen area, mm²: 2.8 (2.2-3.7)
- Plaque burden, %: 76.1 (68.1-82.6)
- Lipid-rich P&M CSA, mm²: 4.8 (2.3-7.7)
- Lipid-rich plaque burden, %: 41.2 (19.1-62.4)

**Values are median (interquartile range).** *See Online Figure 2.

**IVUS** = intravascular ultrasound; **MLA** = minimal luminal area; **NIRS** = near-infrared spectroscopy; **EEM** = external elastic membrane; **CSA** = cross-sectional area; **LCBI** = lipid core burden index; **P&M** = plaque = media; **MaxLCBI4mm** = maximal lipid core burden index over any 4 mm segment; other abbreviations as in Table 1.

**CORRELATES OF PERIPROCEDURAL MI.** The univariable correlations between baseline clinical and lesion-related features and periprocedural MI were examined for all the variables listed in Tables 1 to 3, with the positive associations displayed in Table 4. No clinical or angiographic characteristics were predictive of periprocedural MI. A small baseline MLA was associated with periprocedural MI (C statistic of 0.64 and 0.63, respectively, with cutoffs of 144 and 388, respectively). **Figure 4** demonstrates the chemogram for each lesion in the study and its relationship to periprocedural MI. The predictive value for periprocedural MI was strengthened by considering the degree of plaque burden within the maxLCBI4mm segment (Table 4). In this regard, there was only a weak correlation between maxLCBI4mm and plaque burden at the maxLCBI4mm site (Figure 5).

**OUTCOMES ACCORDING TO RANDOMIZATION.** The FilterWire EZ was successfully deployed before PCI in 13 of 14 patients (92.9%) randomized to distal embolic protection. Periprocedural MI after stenting occurred in 5 of 14 patients (35.7%) assigned to...
PCI + FilterWire EZ compared with 4 of 17 patients (23.5%) assigned to PCI alone (relative risk: 1.52, 95% confidence interval: 0.50 to 4.60; p = .69). The single patient who did not have the FilterWire placed did not experience an MI. There were no significant differences in periprocedural myonecrosis between the 2 groups regardless of the threshold level of biomarker elevation (Figure 6). Of note, among the 14 patients assigned the FilterWire EZ, 8 (57.1%) of the target lesions were bifurcations, although by quantitative coronary angiography the median (interquartile range [IQR]) reference vessel diameter of the side branches was only 2.1 mm (1.8 to 2.5 mm). In addition, by quantitative coronary angiography, there was an additional median of 2 side branches (IQR: 1 to 3) between the lesion and the filter loop, with a reference vessel diameter of 2.2 mm (IQR: 2.1 to 2.5 mm). A representative case where small side branches were lost after stenting a LRP is shown in Online Figure 3.

**DISCUSSION**

The present report describes the outcomes of the first prospective, multicenter investigation seeking to determine whether lesions at risk of periprocedural myonecrosis could be prospectively identified by intravascular imaging and whether a distal embolic protection filter might reduce periprocedural MI after stenting of high-risk plaques. The major results of our study are the following. 1) Plaques responsible for periprocedural myonecrosis were lipid rich and had a large plaque burden and a small MLA. 2) Nonetheless, a substantial proportion of MIs arose from non-LRPs. 3) The use of a distal embolic protection filter did not reduce the rate of periprocedural MI after stenting of LRPs.

Intraprocedural complications of stenting, including distal embolization, side-branch closure, no-reflow, and other thromboembolic phenomena, are increased in patients with troponin-positive acute coronary syndromes; in larger vessels and in those with reduced Thrombolysis in Myocardial Infarction flow and myocardial blush; in lesions with thrombus and other complex features; and in more severe stenoses (5-7). Predicting (and preventing) periprocedural complications in patients in stable condition without these high-risk features has proven elusive. Previous case reports and uncontrolled series have suggested that plaques with high lipid content and/or a thin fibrous cap might be prone to embolization and periprocedural MI and that such fibroatheromas may be detected by several intravascular imaging modalities (10-16). These observations had heretofore not been prospectively validated.

**TABLE 4 Correlates of Periprocedural MI**

<table>
<thead>
<tr>
<th></th>
<th>MI (n = 21)</th>
<th>No MI (n = 64)</th>
<th>C Statistic</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline NIRS measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LCBI</td>
<td>194.0 (125.7-252.2)</td>
<td>124.7 (58.3-215.7)</td>
<td>0.64</td>
<td>0.05</td>
</tr>
<tr>
<td>MaxLCBlumen</td>
<td>481.5 (425.6-679.6)</td>
<td>371.5 (228.9-611.6)</td>
<td>0.63</td>
<td>0.05</td>
</tr>
<tr>
<td>Baseline IVUS measures at the MLA site within the total lesion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumen area, mm²</td>
<td>2.1 (1.7-2.4)</td>
<td>2.5 (2.0-3.1)</td>
<td>0.67</td>
<td>0.03</td>
</tr>
<tr>
<td>Baseline IVUS measures at the MLA site within the maxLCBlumen segment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumen area, mm²</td>
<td>2.3 (1.8-3.4)</td>
<td>3.0 (2.4-4.1)</td>
<td>0.67</td>
<td>0.02</td>
</tr>
<tr>
<td>Plaque burden, %</td>
<td>78.3 (72.3-87.0)</td>
<td>75.5 (66.2-81.3)</td>
<td>0.66</td>
<td>0.04</td>
</tr>
<tr>
<td>Lipid-rich P&amp;M CSA, mm²</td>
<td>6.2 (4.6, 11.2)</td>
<td>4.0 (1.4, 7.6)</td>
<td>0.71</td>
<td>0.006</td>
</tr>
<tr>
<td>Lipid-rich plaque burden, %</td>
<td>56.6 (42.7, 67.5)</td>
<td>32.9 (10.6, 59.4)</td>
<td>0.73</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Values are median (interquartile range). Univariable correlations of periprocedural MI were tested for all the variables in Tables 1 through 3. The p values for those variables not listed here were >0.05. These findings were consistent in the single high-enrolling site and the lower enrolling sites.

In the present study, we used NIRS to identify LRPs in a stable patient cohort, more than 90% of whom presented with troponin-negative coronary syndromes and had angiographically noncomplex lesions. Both the total lesion LCBI and MaxLCBlumen...
parameters were predictive of periprocedural MI after PCI. Our findings support the hypothesis that distal embolization with microvascular obstruction underlies many of these events as both lipid measures at the plaque site were markedly reduced after stent implantation. Compared with gray-scale IVUS, radiofrequency IVUS, and optical coherence tomography (all of which require substantial operator or technician involvement to draw contours, measure dimensions, and interpret morphology), LCBI and maxLCBI4 parameters are fully automated and quantitative and are generated in real time during catheter pullback, facilitating assimilation into the cath lab workflow without requiring complex image interpretation or introducing excessive delays. Nonetheless, in our study, gray-scale IVUS offered complementary predictive utility by identifying lesions with a high plaque burden and/or small MLA, which when combined with lipid parameters (as reflected in a high LRP burden) may identify lesions at particularly high risk. Future studies are required to determine whether optical coherence tomography would provide additional prognostic information to NIRS-IVUS.

Although the present study has now validated the previously conjectured correlation between greater plaque lipid content and peri-PCI MI (15,16), the relationship was modest, and more than half of MIs arose from lesions that were below the pre-specified maxLCBI4 cutoff of $>\$600$. Selecting a lower cutoff value would increase sensitivity although reducing specificity and positive predictive value. In this regard, different cutoff values may be desirable for different applications. However, not all periprocedural MIs are due to distal embolization. Loss of side branches arising from the lesion may also be caused by plaque or carina shift. Periprocedural MI may also be due to other angiographic complications such as severe dissection or vasospasm, perforation, or intraprocedural stent thrombosis.

**FIGURE 5** Correlation Between maxLCBI4 and Plaque Burden at the Minimal Luminal Area Site Within the maxLCBI4 Segment

The red dots represent cases with periprocedural myocardial infarction. The blue dots represent cases without periprocedural myocardial infarction. *Coefficient represents an increase of 10 units. The regression model met the criteria for linearity according to the Harvey-Collier test for linearity (p = 0.96). maxLCBI4 = maximal lipid core burden index over any 4-mm length.

**FIGURE 6** Periprocedural Myocardial Infarction After Randomization to PCI + FilterWire EZ Versus PCI Alone

There was no significant difference in the rate of periprocedural MI between the 2 groups according to the protocol definition (left) or by any other threshold definition of MI (right). CI = confidence interval; RR = relative risk; other abbreviations as in Figures 2 and 3.
Use of the FilterWire EZ did not prove effective in reducing periprocedural myonecrosis after stenting of LRPs. Although the reasons for this are uncertain, filter devices are unable to protect side branches arising from the target lesion or between the lesion and the filter landing zone. Although we excluded true bifurcation lesions and large side branches in the distal segment adjacent to the stenosis, small side branches were present in the majority of lesions that were unprotected. Additional study is warranted to determine whether there might be a role for GPIIb/IIIa inhibitors or other potent antiplatelet agents in preventing myonecrosis after PCI of LRPs.

STUDY LIMITATIONS. First, a sensitive definition was used to define periprocedural MI (post-PCI biomarker elevation to 3 or more times the upper limit of normal) for this proof of principle study. Not all of these MIs are of clinical consequence (3), although it is likely that the same predictive factors are related to larger clinically relevant post-procedure MIs as well, at least those due to distal embolization. Second, because the present study was designed principally to examine periprocedural events, patients were not routinely followed beyond the in-hospital phase. Third, filter contents were not routinely analyzed, and thus we cannot speak to the quantity and makeup of captured debris. Fourth, only 36.5% of lesions were protocol-defined LRPs, somewhat less than the 50% anticipated, which may have been due to enrollment of mostly biomarker-negative patients. Similarly, the 29.0% periprocedural MI rate after PCI of LRPs was lower than anticipated, possibly due to the characteristics of the patients and lesions studied, as well as the modest relationship between NIRS-defined lipid parameters and periprocedural myonecrosis. It is also possible that the distal protection filter might have been more successful in preventing distal embolization and myonecrosis had the lesions been even more lipid rich than in this study and with a thrombotic component, as was present in the report by Brilakis et al. (19). The fifth and most important limitation relates to the study size. Determining the lesion-specific characteristics responsible for periprocedural MI required enrolling patients undergoing PCI of single, noncomplex, native coronary artery stenoses in patients with normal baseline biomarkers. In addition, anatomic criteria had to be met for FilterWire use. A large number of patients had to be screened to identify such lesions, and the final sample size was modest. However, the trial was halted early for futility of the randomized therapy, and with 95% confidence, we were able to exclude a more than 50% treatment effect of the FilterWire in preventing periprocedural myonecrosis, the minimal effect size that might have warranted a pivotal randomized trial for this application. Moreover, the present study size was sufficient to confirm the hypothesized relationship between NIRS-identified LRPs and periprocedural myonecrosis. Nonetheless, a larger cohort would have provided greater precision, may have revealed additional correlates of periprocedural MI, and would have accommodated multivariable and subgroup analyses.

CONCLUSIONS

Pre-interventional intravascular imaging with a combined NIRS-IVUS catheter is able to identify lesions at increased risk of periprocedural myonecrosis. Such plaques are lipid rich and have high plaque burden and/or a small cross-sectional area. However, not all periprocedural MIs are caused by distal embolization, and the clinical utility of any single parameter to predict periprocedural MI is modest. Finally, a distal embolic protection filter is unlikely to be of use in reducing periprocedural myonecrosis after PCI of most LRPs in native coronary arteries. Further studies are warranted to determine whether potent antiplatelet agents such as cangrelor (24) and embolic protection stents (25) might have specific utility in patients with lesions at high risk of distal embolization and other periprocedural complications.

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PERSPECTIVES

WHAT IS KNOWN? Distal embolization and periprocedural myocardial infarction may occur after percutaneous coronary intervention of lipid-rich plaque.

WHAT IS NEW? Lipid-rich plaques that have increased risk to cause periprocedural myonecrosis can be identified by a combination intravascular ultrasound and near-infrared spectroscopy imaging catheter before stent implantation. However, use of a distal protection filter before stenting such high-risk lesions may not be protective.

WHAT IS NEXT? Further studies are warranted to determine whether potent antiplatelet agents or embolic protection stents might be protective in patients with lesions at high-risk of distal embolization and other periprocedural complications.
REFERENCES


KEY WORDS atherosclerosis, distal protection, embolization, myocardial infarction, near-infrared spectroscopy

APPENDIX For supplemental material and figures, please see the online version of this article.