The relationship among extent of lipid-rich plaque, lesion characteristics, and plaque progression/regression in patients with coronary artery disease: a serial near-infrared spectroscopy and intravascular ultrasound study

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Aims
To evaluate the relationship between lipid content and plaque morphometry as well as the process of lesion progression and regression in patients with significant coronary artery disease.

Methods and results
The present study, using data from the YELLOW trial, was conducted in patients having significant coronary lesions (fractional flow reserve < 0.8) who underwent serial intravascular ultrasound (IVUS) and near-infrared spectroscopy (NIRS) at baseline and after 7 weeks. For each coronary plaque (≥50% plaque burden that was ≥5 mm in length), we evaluated plaque characteristics and the extent of lipid-rich plaque (LRP, defined as the 4 mm long segment with the maximum lipid-core burden index (maxLCBI4mm)) on NIRS. Among 66 patients (age 63.0 ± 10.1 years; 82% statin use at baseline), 94 plaques were identified. The extent of LRP at baseline was positively correlated with IVUS plaque burden (r = 0.317, P = 0.002). A large LRP (maxLCBI4mm ≥ 500) was present only in plaques with a large plaque burden (≥70%). Multivariate analysis demonstrated that plaque burden was the best predictor of the extent of LRP (P < 0.001). In lesions with a large plaque burden and a large amount of LRP at baseline, a reduction in LRP was seen in all lesions in patients receiving intensive statin therapy (P = 0.004) without a significant change in plaque burden.

Conclusions
Coronary lesions containing a large amount of LRP also had a large plaque burden. Short-term regression of LRP (without a change in plaque burden) was observed mainly in plaques with a large plaque burden and a large amount of LRP at baseline.

Clinical Trial Registration

Keywords
Lipid-rich plaque • Near-infrared spectroscopy • Intravascular ultrasound • Plaque regression

Introduction
Despite recent advances in medical and interventional therapies, coronary artery disease (CAD) continues to be a major cause of morbidity and mortality.1 As coronary lesions progress, they evolve into lipid-rich core containing fibroatheromas that are responsible for most acute coronary events.2,3 At necropsy, high-risk lesions have a thin fibrous cap overlying a large lipid-rich necrotic core in the setting of an active inflammatory infiltrate.4,5 A better understanding of the pathophysiology of the atherosclerotic process as well as the

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availability of powerful pharmacological agents have permitted con-
sideration of plaque regression and stabilization as a therapeutic goal. 
Greyscale intravascular ultrasound (IVUS) can determine plaque 
burden, plaque distribution, and vascular remodelling, but is limited 
in its ability to estimate plaque composition, including the extent of 
lipidic plaque.6 However, intracoronary near-infrared spectroscopy 
(NIRS) detects lipid-rich plaque (LRP) with high sensitivity and spe-
cificity.7–12 Recently, the YELLOW (reduction in yellow plaque by 
aggressive lipid-lowering therapy) trial showed that short-term 
intensive statin therapy significantly reduced the lipid content of 
obstructive coronary lesions.13 The current analysis used the data 
from the YELLOW trial to explore the relationship among coronary 
lesion characteristics, the extent of LRP detected by NIRS at baseline, 
and the short-term impact of statin therapy on LRP.

Methods

Study purpose and subjects

The details of the YELLOW trial have been described previously.13 In 
brief, the YELLOW trial was a prospective, randomized, single-centre, 
and single-blinded trial in which patients with stable CAD and multivessel 
disease undergoing staged drug-eluting stent implantation for a significant 
secondary lesion (fractional flow reserve <0.8) were randomized to 
intensive statin therapy (rosuvastatin 40 mg/day (AstraZeneca, Cheshire, 
UK)) vs. standard statin therapy after the primary lesion was treated. We 
excluded patients with acute coronary syndromes, left main disease, liver 
disease, serum creatinine >2.0 mg/dL, known hypersensitivity to statins, 
single-vessel or non-obstructive CAD, and lesions not amenable to per-
cutaneous coronary intervention (PCI). The primary end point of the 
YELLOW trial was the change in the extent of LRP defined as the 
4 mm long segment with the maximum lipid-core burden index 
(maxLCBI4mm) of the secondary lesion between baseline and 6–8 
weeks as assessed by NIRS. All patients provided written informed 
consent.

Serial IVUS and NIRS of the secondary lesions were performed after 
administration of intracoronary nitrates both at baseline (after the first 
percutaneous intervention) and after 6–8 weeks (at the time of the 
staged percutaneous intervention, but before the start of the interven-
tional procedure). The IVUS and NIRS imaging catheters were positioned 
at least 10 mm distal to the lesion, and automatic pullback was performed 
at 0.5 mm/s to the aorta. The distal starting points of both IVUS and NIRS 
imaging were recorded angiographically along with the proximal and 
distal fiduciary points to assist in registration of the corresponding 
IVUS and NIRS segments at baseline and follow-up (Figure 1). All image 
data were archived onto DVD and sent to the blinded intravascular 
imaging core laboratory of the Cardiovascular Research Foundation 
(New York, NY, USA) for off-line analysis.

IVUS imaging acquisition and analysis

IVUS was performed using the Eagle Eye 20 MHz, 3.2 Fr, synthetic aper-
ture array catheter (Volcano Corporation, Rancho Cordova, CA, USA)14 
and analysed using the validated planimetry software (echoPlaque, 
INDEC Medical Systems, Inc., Mountain View, CA, USA). Planar and volu-
metric quantitative and qualitative analyses were performed according to

Figure 1: Representative NIRS and corresponding IVUS images. A region of interest was chosen from the baseline IVUS as a segment with a ≥ 50% plaque burden that was ≥ 5 mm in length (left). On the right is the corresponding NIRS segment identified at baseline and follow-up. MLA, minimum lumen area.
criteria from the American College of Cardiology consensus statement on IVUS. Baseline and follow-up IVUS images were reviewed side-by-side on a display. Each coronary plaque contained a plaque burden ≥ 50% that was ≥ 5 mm in length. Coronary plaques were considered separate if there was a ≥ 5 mm long-intervening segment with <50% plaque burden. The minimum lumen area (MLA) within the plaque was identified; and plaque burden [plaque area divided by the external elastic membrane (EEM) area] was calculated at the MLA site. A large plaque burden was defined as a plaque burden of ≥ 70%. Remodeling index was calculated as the EEM area at the MLA site divided by the mean reference EEM area.

**NIRS imaging and analysis**

NIRS was performed using a 3.2 Fr NIRS catheter (InfraReDx, Burlington, MA, USA). Raw spectroscopic information was transformed into a probability of LRP that was mapped to a red-to-yellow colour scale, with a low probability of lipid shown as red and a high probability of lipid shown as yellow. Yellow pixels (probability ≥ 0.6) within the plaque were divided by all viable pixels within the plaque to generate the LCBI, as previously described. The software counted the number of yellow pixels every 0.1 mm, summed the total number of yellow pixels for each possible 4 mm long axial segment, and identified the 4 mm long segment with the maximum LCBI (maxLCBI<sub>4mm</sub>)

**Statistical analysis**

All data were analysed using SAS version 9.2 (SAS Institute, Inc., Cary, NC, USA) and JMP version 9.0 (SAS Institute, Inc.). Continuous variables are expressed as mean ± SD or median and interquartile range if not normally distributed. Categorical data are presented as numbers and ratios (%). Paired data have been compared using the Student’s t-test or the Wilcoxon rank sum test, and intergroup data have been analysed by the one-way analysis of variance (ANOVA) or the Kruskal–Wallis test. Tukey’s HSD and Steel–Dwass tests were used for post hoc analysis. Correlations have been evaluated by Spearman rank correlation. Receiver operating characteristic curves have been used to determine the cut-off values of maxLCBI<sub>4mm</sub> to discriminate between the small and large LRP groups. For plaque-level data, a model with a generalized estimating equation approach has been used to compensate for any potential cluster effect of multiple plaques in the same individual. Multivariate linear regression analysis has characterized the independent effect of the extent of LRP. A P-value of <0.05 has been considered statistically significant.

**Results**

**Patient characteristics and lesion analysis**

Among 87 patients with stable CAD who were enrolled into the Yellow trial, we included 66 patients in this lesion-level substudy. Twenty-one patients were excluded because of no available paired (baseline and follow-up) NIRS and IVUS data. Patient baseline characteristics are summarized in Table 1. Mean age was 63.0 ± 10.1 years, and 50 were men (76%). The left anterior descending artery was imaged in 46% of patients. Baseline value for low-density lipoprotein cholesterol (LDL-C) was 81.8 ± 27.0 mg/dL. Overall, 54 patients (82%) were taking statins at the time of the first procedure. Thirty-one patients were randomized to receive intensive statin therapy (rosuvastatin 40 mg/day), and 35 were randomized to standard lipid-lowering therapy. The LDL-C values in the intensive statin therapy and standard lipid-lowering therapy groups at follow-up were 57.0 ± 27.5 mg/dL (P < 0.001 vs. baseline) and 82.9 ± 23.5 mg/dL (P = 0.654 vs. baseline), respectively; and the percent changes from baseline were -23.2 ± 33.6 and 4.9 ± 41.9%, respectively (P = 0.005).

Overall, 94 plaques (≥50% plaque burden that was ≥5 mm in length) at baseline were identified. In eight patients, IVUS pullback data were not reliable, and only the MLA and reference site cross-sections were analysed. The plaque length and plaque burden assessed by IVUS at baseline were 11.5 ± 5.0 mm and 72.1 ± 7.2%, respectively. Median maxLCBI<sub>4mm</sub> at baseline was 324 (119, 513). The extent of LRP within the maxLCBI<sub>4mm</sub> at baseline was positively, albeit weakly, correlated with the IVUS plaque burden at baseline (r = 0.317, P = 0.002). In contrast, the extent of LRP within the maxLCBI<sub>4mm</sub> was negatively, albeit weakly, correlated with the IVUS MLA at baseline (r = -0.211, P = 0.040).

**Relationship between LRP and plaque morphology**

The NIRS maxLCBI<sub>4mm</sub>, that best identified a large IVUS plaque burden (≥70%) at baseline was 482 (positive predictive value, 100%; negative predictive value, 46%; sensitivity, 39%; specificity, 100%; and area under the curve = 0.696). Furthermore, there was no plaque with a plaque burden of <70% in combination with a maxLCBI<sub>4mm</sub> of >500 (large LRP) at baseline (Figure 2). The maximum arc of calcium trended towards being greater in plaques with a large plaque burden compared with those with a small plaque burden. The remodelling index was less in plaques with a large plaque burden and a small LCBI compared with either plaques with a small plaque burden and a small LCBI or plaques with a large plaque burden and a large LCBI (Table 2).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline clinical characteristics of the study patients (n = 66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
<td>Value</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63.0 ± 10.1</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>50 (76)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>29.1 ± 5.4</td>
</tr>
<tr>
<td>Medical history, n (%)</td>
<td>27 (41)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>63 (95)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>39 (59)</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>61 (92)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>11 (17)</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>12 (18)</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>31 (47)</td>
</tr>
<tr>
<td>Statin use at enrolment</td>
<td>54 (82)</td>
</tr>
<tr>
<td>Other lipid-lowering agent at enrolment</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Beta-blocker use at enrolment</td>
<td>49 (74)</td>
</tr>
<tr>
<td>ACE-I/ARB use at enrolment</td>
<td>28 (42)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>144.8 ± 28.6</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol (mg/dL)</td>
<td>81.8 ± 27.0</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol (mg/dL)</td>
<td>38.7 ± 10.8</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>120.4 ± 69.2</td>
</tr>
<tr>
<td>High-sensitivity C-reactive protein (mg/L)</td>
<td>1.9 (0.9, 5.9)</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or median and interquartile range.

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.
best cut-off value of the maxLCBI4mm at baseline for predicting significantly associated with the maxLCBI 4mm at baseline. Multivariate plaque burden, diabetes, and prior myocardial infarction were significantly LRP regression was 262 (sensitivity, 100%; specificity, 57%; and area under the curve 0.832; $P = 0.004$) and the median change in maxLCBI4mm was −202. However, this was true only in patients treated with intensive statin therapy and not in patients treated with standard statin therapy (Figure 3). When significant regression in maxLCBI4mm was defined as a decrease of $>200$, the best cut-off value of the maxLCBI4mm at baseline for predicting significant LRP regression was 262 (sensitivity, 100%; specificity, 57%; and area under the curve $= 0.832$); and the best cut-off in plaque burden at baseline for predicting significant LRP regression was 70% (sensitivity, 86%; specificity, 38%; and area under the curve $= 0.541$).

Serial NIRS analysis
During the follow-up period (mean 7 weeks), plaque burden at the MLA site did not change from baseline to follow-up (from 72.1 ± 7.2 to 71.8 ± 8.3%; $P = 0.734$). On the other hand, the maxLCBI4mm significantly decreased from 302 (117, 482) to 220 (43, 400) ($P = 0.022$). Among the 20 plaques with a large plaque burden and a large amount of LRP at baseline, a decrease in LRP was identified in all of the plaques receiving intensive statin therapy without a change in plaque burden. The maxLCBI4mm in these 11 plaques significantly decreased from 703 (525, 749) to 399 (336, 532), $P = 0.004$; and the median change in maxLCBI4mm was −202. However, this was true only in patients treated with intensive statin therapy and not in patients treated with standard statin therapy (Figure 3). When significant regression in maxLCBI4mm was defined as a decrease of $>200$, the best cut-off value of the maxLCBI4mm at baseline for predicting significant LRP regression was 262 (sensitivity, 100%; specificity, 57%; and area under the curve $= 0.832$); and the best cut-off in plaque burden at baseline for predicting significant LRP regression was 70% (sensitivity, 86%; specificity, 38%; and area under the curve $= 0.541$).

Discussion
In the present study, we found that coronary plaques containing a large lipidic core had a large plaque burden ($\geq 70\%$) compared with those containing a small amount of LRP. In contrast, there was no plaque having a plaque burden of $<70\%$, but a large amount of LRP. Consequently, plaque burden was the best indicator of the extent of LRP in significant coronary lesions. Furthermore, our serial plaque-level analysis demonstrated that intensive statin therapy reduced lipid content without changing plaque burden in lesions with a large plaque burden and a large amount of LRP at baseline.

**LRP and lesion morphology and the process of plaque progression**

The size of the lipid-rich necrotic core, positive remodelling, and fibrous cap thickness are critical morphological features that distinguish unstable high-risk plaques and plaque ruptures from earlier progressive lesions. As a plaque progresses from early atherosclerosis to a fibroatheroma, the free cholesterol content of the lesion increases. Vascular remodelling is a fundamental component of this process. Burke et al. reported that positive remodelling was associated with an increase in the size of the lipid-rich core, development of a thin-cap fibroatheroma, and intraplaque haemorrhage. These pathologic observations were supported by in vivo studies using radiofrequency IVUS, optical coherence tomography, and NIRS. In the current study, coronary plaques containing a large lipidic core had a higher remodelling index compared with those containing a small amount of LRP.

**Lipid-lowering therapy and intravascular imaging trials for plaque progression and regression**
Lipid-lowering strategies, particularly statins, have become the cornerstone of the prevention and treatment of cardiovascular disease. Cardiovascular outcomes and the occurrence of acute coronary events depend not only on the severity of luminal narrowing, but also on plaque burden and plaque characteristics. So far IVUS has evolved as the imaging modality that generates precise volumetric quantification of coronary atherosclerosis. By measuring the change in plaque burden over time, IVUS can evaluate the potential anti-atherosclerotic efficacy of pharmacological interventions. Serial IVUS trials have shown that intensive statin therapy slows the progression of coronary atherosclerosis and may even result in disease regression. In the present study, three quarters of patients were already taking statins at baseline, the mean baseline LDL-cholesterol levels were $<100$ mg/dL, and the mean follow-up
Table 2  IVUS and NIRS data among three groups of plaques based on plaque burden and extent of LRP

<table>
<thead>
<tr>
<th>Plaque burden and maxLCBI_{4mm}</th>
<th>Plaque burden ≥70% and maxLCBI_{4mm} &lt;500 (Group 1, n = 38)</th>
<th>Group 1 vs. Group 2 P-value</th>
<th>Group 2 vs. Group 3 P-value</th>
<th>Group 1 vs. Group 3 P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plaque burden (%)</td>
<td>65.4 ± 5.7</td>
<td>76.9 ± 4.1</td>
<td>76.3 ± 3.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Percent plaque volume (%)</td>
<td>58.6 ± 6.4</td>
<td>65.4 ± 4.8</td>
<td>65.0 ± 4.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Minimum lumen CSA (mm²)</td>
<td>32 ± 1.1</td>
<td>2.8 ± 1.0</td>
<td>2.7 ± 1.0</td>
<td>0.113</td>
</tr>
<tr>
<td>Maximum calcium arc (%)</td>
<td>45 (0.71)</td>
<td>60 (24.111)</td>
<td>89 (49.110)</td>
<td>0.057</td>
</tr>
<tr>
<td>Remodelling index</td>
<td>1.07 (0.98, 1.27)</td>
<td>0.95 (0.83, 1.10)</td>
<td>1.06 (0.94, 1.14)</td>
<td>0.037</td>
</tr>
<tr>
<td>MaxLCBI_{4mm}</td>
<td>151 (8, 302)</td>
<td>299 (23, 369)</td>
<td>664 (335, 743)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Follow-up data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plaque burden (%)</td>
<td>67.1 ± 7.5</td>
<td>75.0 ± 6.4</td>
<td>75.1 ± 6.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MaxLCBI_{4mm}</td>
<td>86 (8, 254)</td>
<td>232 (37, 400)</td>
<td>500 (342, 632)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change from baseline to follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in plaque burden (%)</td>
<td>1.8 ± 6.2</td>
<td>−1.8 ± 5.9</td>
<td>−0.6 ± 5.8</td>
<td>0.087</td>
</tr>
<tr>
<td>Intensive statin therapy</td>
<td>0.5 ± 5.4</td>
<td>−1.8 ± 5.3</td>
<td>−1.3 ± 6.4</td>
<td>0.554</td>
</tr>
<tr>
<td>Standard lipid-lowering therapy</td>
<td>2.6 ± 8.1</td>
<td>−1.7 ± 6.5</td>
<td>0.7 ± 4.5</td>
<td>0.210</td>
</tr>
<tr>
<td>Change in maxLCBI_{4mm}</td>
<td>0 (−120, 35)</td>
<td>−9 (−87, 64)</td>
<td>−187 (−423, −37)*</td>
<td>0.003</td>
</tr>
<tr>
<td>Intensive statin therapy</td>
<td>2 (−49, 91)</td>
<td>−7 (−158, 127)</td>
<td>−202 (−322, −107)†</td>
<td>0.005</td>
</tr>
<tr>
<td>Standard lipid-lowering therapy</td>
<td>0 (−123, 15)</td>
<td>−13 (−92, 86)</td>
<td>−70 (−266, 212)</td>
<td>0.660</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or median and interquartile range.

CSA, cross-sectional area; IVUS, intravascular ultrasound; LCBI, lipid-core burden index; LRP, lipid-rich plaque; NIRS, near-infrared spectroscopy.

*P = 0.010.
†P = 0.005 for baseline vs. follow-up by the Wilcoxon rank sum test.
LDL-cholesterol levels were 70 mg/dL (rate of statin use, 91%). Previous statin treatment might have affected lesions resistant to plaque volume regression. In addition, follow-up period may have affected the findings in the current study since the period of our study was only 7 weeks while treatment periods in most of the IVUS progression-regression trials have been at least 6–12 months. Nevertheless, the efficacy of intensive statin therapy (a decrease in LRP, especially in the setting of a large amount of lipidic plaque at baseline) was observed by NIRS, but without a change in plaque burden as observed by IVUS. Williams et al. suggested that regression is not merely a reversal of progression, but instead involves emigration of the maladaptive macrophage infiltrate, followed by initiation of a stream of healthy, normally functioning phagocytes that mobilize necrotic debris and all other components of advanced plaques. A previous animal study reported that the early phase of regression showed loss of foam cells from the lesions and an increase in non-foam cell macrophages around areas of necrosis. Long term, the necrotic areas virtually disappeared, indicating removal of the material by an influx of functioning, healthy phagocytes. Serial angioscopic patient studies have also indicated that plaque stabilization was observed without a reduction of IVUS plaque burden following statin treatment.

In addition, the YELLOW trial showed that short-term intensive statin treatment appeared to reduce lipid content as assessed by NIRS without any change in lesion severity as assessed by fractional flow reserve (FFR). Thus, evaluation by NIRS might be a clinically useful index of plaque compositional change in the assessment of residual high-risk LRPCs in statin-treated patients compared with conventional plaque estimation by IVUS and physiological measurements by fractional flow reserve, especially when co-registered to IVUS assessment of plaque burden that is now possible in a single catheter.

**Limitations**

The present study had several limitations. First, the present study included a small number of patients and a short duration of follow-up. Secondly, the NIRS lipid composition data and the IVUS plaque burden data were obtained by separate catheters that were co-registered according to angiographic geographic markers. We relied on coronary angiography to facilitate co-registration of IVUS and NIRS images; a new NIRS catheter has been developed to simultaneously acquire NIRS and IVUS data. Thirdly, we only focused on

**Table 3** Predictors of the extent of LRP (maxLCBI<sub>4mm</sub>) in the multiple linear regression model

<table>
<thead>
<tr>
<th>Independent parameter</th>
<th>Unstandardized coefficient (95% CI)</th>
<th>GEE adjusted P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaque burden, per 10%</td>
<td>106 (42 to 171)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>93 (−1 to 186)</td>
<td>0.057</td>
</tr>
</tbody>
</table>

CI, confidence interval; GEE, generalized estimating equation.

**Figure 3**: Change in the extent of lipid contents within coronary plaques from baseline to follow-up (mean, 7 weeks) evaluated by serial NIRS analysis. Lipid-rich plaque regression was identified in plaques having large lipid contents at baseline (maxLCBI<sub>4mm</sub> ≥ 500) receiving intensive statin therapy. *P = 0.004.
lesions having haemodynamic significance (FFR < 0.8) with angiographic diameter stenosis > 70% and only studied a single lesion at baseline and at follow-up. Ideally, multiple lesions should be studied. Finally, the majority of patients were taking statins at baseline and at follow-up. Ideally, multiple lesions should be studied.

Conclusion

The present study demonstrated an important relationship between NIRS determined LRPs and plaque morphology in patients who had clinically significant atherosclerotic plaques. Coronary lesions containing a large amount of LRP also had a large plaque burden (≥70%). In our serial NIRS findings, short-term regression of LRP (without a change in plaque burden) was observed mainly in plaques with a large plaque burden and a large amount of LRP at baseline.

Conflict of interest: T.D. has received grant support from the Banyu Life Science Foundation International. A.M. has received grant support and is a consultant for Boston Scientific. P.R.M. is a founder and stockholder of InfraReDx, Inc. J.C.K. has received research support from the National Institutes of Health (K08HL111330), the Leducq Foundation (Translaticnt Network of Excellence Award), and AstraZeneca. R.M. and G.D.D. have received research grant support (institutional) from The Medicines Company, Bristol-Myers Squibb/Sanofi and Eli Lilly, and Company/Daiichi-Sankyo, and are consultants for Abbott Vascular, AstraZeneca, Boston Scientific, Coviden, Janssen Pharmaceuticals, Regado Biosciences, Maya Medical, Merck & Co., and The Medicines Company. G.S.M. has received grant support from and is a consultant to Volcano Corporation, Boston Scientific Corporation, and InfraReDx. The rest of the authors have nothing to disclose.

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Although there was no direct external funding provided for the YELLOW trial, all YELLOW trial participants were also enrolled in the COLOR registry, which was partially supported by InfraReDx, Inc. (Burlington, MA, USA).

References