Circulation Research Compendium on Acute Coronary Syndromes

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Guest Editors: Valentin Fuster and Jason Kovacic

Imaging Plaques to Predict and Better Manage Patients With Acute Coronary Events
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Abstract: Culprit lesions of patients, who have had an acute coronary syndrome commonly, are ruptured coronary plaques with superimposed thrombus. The precursor of such lesions is an inflamed thin-capped fibroatheroma. These plaques can be imaged by means of invasive techniques, such as intravascular ultrasound (and derived techniques), optical coherence tomography, and near-infrared spectroscopy. Often these patients exhibit similar (multiple) plaques beyond the culprit lesion. These remote plaques can be assessed noninvasively by computed tomographic angiography and MRI and also using invasive imaging. The detection of these remote plaques is not only feasible but also in natural history studies have been associated with clinical coronary events. Different systemic pharmacological treatments have been studied (mostly statins) with modest success and, therefore, newer approaches are being tested. Local treatment for such lesions is in its infancy and larger, prospective, and randomized trials are needed. This review will describe the pathological and imaging findings in culprit lesions of patients with acute coronary syndrome and the assessment of remote plaques. In addition, the pharmacological and local treatment options will be reviewed. (Circ Res. 2014;114:1904-1917.)

Key Words: atherosclerosis ■ cardiac imaging techniques ■ coronary artery disease ■ interventional ultrasonography ■ therapeutics

Acute coronary events often comprise the first manifestation of coronary artery disease in an asymptomatic subject. The main challenge that we face today is to identify patients at risk before those events occur. In this regard, clinical evaluation alone might be insufficient because only a minority of patients experiencing an acute myocardial infarction (AMI) would have been identified as high risk by the available risk factor–based scores before the event. Therefore, screening for subclinical atherosclerosis by means of noninvasive methods has been advocated to be used for identifying subjects at risk of thrombotic and arrhythmogenic events (vulnerable patients). However, in this review, we will focus on

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The literature increasingly demonstrates that plaque morphology, not the extent of luminal stenosis, determines the susceptibility of an individual to develop an acute coronary event. In addition, in the Courage study, patients treated with optimal medical treatment, the total number of segments with significant disease was a consistent predictor of death, myocardial infarction, and non–ST-segment–elevation ACS, whereas ischemic burden was not. This indicates that the occurrence of major adverse clinical outcomes may be because of their disruption rather than by the ischemia-producing nature of obstructive plaques.

Plaque rupture (PR) is the underlying substrate in victims of ACSs more than two thirds of the time; plaque erosion is the substrate in the remaining one third (Figure 1). The culprit lesions in the acute events caused by ruptured plaques demonstrate a disrupted fibrous cap that is inflamed and overlying large, partially sloughed off necrotic cores. Even with the large plaque and necrotic core volumes, these lesions may not necessarily be luminally occlusive at the start because of expansive or outward vascular remodeling. Such lesions are abundantly neovascularized and often reveal copious presence of cytokines, proteases, and inflammatory mediators. Lesions with these histomorphologic characteristics but intact fibrous caps are considered high risk and vulnerable to rupture; they have been pathologically ascribed as thin-capped fibroatheromas (TCFA). Local conditions, such as low endothelial shear stress, may lead to plaque development and progression further until they produce lumen narrowing.

In a recent postmortem analysis of 213 hearts from the victims of sudden cardiac death, a hierarchical importance of these pathological characteristics was established so as to develop a strategy to differentiate stable plaques or fibroatheromas from TCFA and PR by invasive and noninvasive imaging of atherosclerotic plaques.

Figure 1. Photomicrographic cross section of human coronary plaque rupture (PR), thin-capped fibroatheromas (TCFA), and fibroatheromas (FA) with varying degree of luminal stenosis (A–C). PR with mild, moderate, and severe luminal stenosis, respectively. Nonocclusive thrombus (Thr) is observed in the microphotograph A, whereas occlusive Thr is occupying the lumen in B and C. D, E, and F, TCFA with mild, moderate, and severe luminal stenosis, respectively. Necrotic core (NC) is covered by a thin fibrous cap, and Thr is not present in the lumen. G, H, and I, Stable plaque or FA with mild, moderate, and severe luminal stenosis, respectively. The size of necrotic core is relatively small when present, and calcification (Ca++) is frequently seen. Reprinted from Narula et al12 with permission of the publisher.

The hierarchical analysis included fibrous cap thickness, luminal stenosis, plaque area, necrotic core area, macrophage area, and calcification for developing diagnostic algorithms (Figure 2). The partitioning analysis of 105 fibroatheroma, 88 TCFA, and 102 ruptured plaques identified fibrous cap thickness as the most important plaque characteristic to discriminate among fibroatheroma (almost always >85 μm), ruptured plaques (<55 μm), and the TCFA (between 55 and 85 μm) plaque types. Because clinically the fibrous cap thickness currently can only be measured using optical coherence tomography (OCT), we excluded the cap thickness from the repeat analysis, so as to identify morphological characteristics that might be amenable to noninvasive interrogation. In the repeat modeling, the magnitude of macrophage inflammation and the size of necrotic core emerged as the discriminatory features of plaque instability. The necrotic cores are visible by OCT, virtual histology (VH), near-infrared spectroscopy (NIRS), or coronary computed tomography angiography (CCTA). The assessment of inflammation is based on the systemic biomarkers, but radiolabeled sugars are currently being exploited for the assessment of the extent of macrophage infiltration in the individual plaques.

It has been traditionally taught that the acute event almost always results from the rupture of a plaque that is not associated with significant luminal narrowing. Even though they are voluminous, these plaques are not stenotic because of expansive remodeling. However, this large study refutes the myth of mild vulnerable plaque because 70% of disrupted plaques...
occupied >75% cross-sectional vascular area, and only 5% were <50% occlusive. However, >75% cross-sectional area stenosis was observed in 40% of the TCFA, and only 10% of the TCFA were <50% occlusive. Therefore, 1 of 4 of the ruptured plaques and half of TCFA revealed intermediate degree or 50% to 75% cross-sectional area stenosis, and the difference in distribution of the extent of stenosis in TCFA and ruptured plaques suggests that TCFAs expand and evolve to be significantly larger before they become candidates for ruptured plaques.

The results support the proposal that either only severely stenotic TCFA rupture or TCFA evolve before they rupture. In the prospectively performed large Providing Regional Observations to Study Predictors of Events in the Coronary

Tree (PROSPECT) study, the paired angiography and intravascular imaging data were available. This study demonstrated a progressive expansion of plaques before they ruptured. The PROSPECT study documented the increase in luminal diameter occlusion from 32±21% at baseline to 65±16% at 3.4-year follow-up.

Histological studies, such as this by Narula et al., have advanced our understanding of coronary atherosclerosis, but they have inherent limitations, such as (1) there was no information to associate the clinical presentation (ie, infarct location) to the studied vessel; (2) vessel wall remodeling was not studied; (3) there was no serial analysis, it can only be a cross-sectional analysis; (4) because only 1 histological section was analyzed (the one with the smallest lumen diameter),

![Figure 2. Left, multivariate recursive partitioning analysis (RPA) model, including all cases and all candidate variables. Cap thickness was the key plaque characteristic in its ability to discriminate among the 3 plaque types, with all stable fibroatheroma (FA; green) separated into a subgroup of >84 μm. Fibrous cap thickness in plaque erosion (PR) measured <54 μm (red). Blue represents thinned fibroatheromas (TCFA). The receiver-operating characteristic curve generated from the analysis suggested the following area under the curve: FA, 0.82; TCFA, 0.58; and PR, 0.72. G^2 statistic is a likelihood-ratio χ^2 test on which the candidate variables are evaluated for inclusion in the partitioning process. Similar to the Pearson χ^2 test (and asymptotically equal), G^2 is a goodness-of-fit test and considered more appropriate for smaller samples and for nested models. Right, Multivariate RPA model, including all cases but excluding cap thickness as the candidate variable. Predominance of macrophage infiltration identified a majority of PR (red) and TCFA (blue). TCFA and PR in the less-inflamed group (contaminating the FA group) showed larger NC. The few remaining less inflamed and small core PR and TCFA could be isolated from FA (green) once again by the degree of inflammation. The receiver-operating characteristic curve generated from the analysis suggested the following area under the curve: FA, 0.82; TCFA, 0.58; and PR, 0.72. Essentially, similar results were observed in reanalysis, including only the lesions showing 50% to 75% luminal diameter stenosis; area under the curve: FA, 0.81; TCFA, 0.70; and PR, 0.85. The results were similar for those with >75% diameter stenosis; area under the curve: FA, 0.86; TCFA, 0.59; and PR, 0.82. Reprinted from Narula et al with permission of the publisher.]
no volumetric analysis is possible and; (4) the histological findings of these autopsy hearts may or not represent the ones in patients who survive.

**Can We Predict Plaque Vulnerability by Noninvasive and Invasive Imaging?**

Imaging of coronary plaques can be achieved by assessing their appearance angiographically either by noninvasive or by invasive methods. Luminography, namely assessing the changes in lumen delineation, is limited because it only informs about the bidimensional aspect of the lesions where we know much more information is available in a 3-dimensional (3D) and tomographic-based evaluation. Nevertheless, Goldstein et al\(^1\) reported that patients treated for an AMI who have also complex lesions in other territories (those with % diameter stenosis >50 and ≥2 of the following characteristics: thrombus, ulceration, lumen irregularity, or impaired flow) had an increased risk of subsequent ACSs in the following year. This is important because coronary angiography may provide valuable information about coronary plaques without the need for using additional resources, such as intravascular imaging modalities. However, contemporary studies showed that clinical and angiographic characteristics had poor predictive accuracy in identifying patients who have coronary plaques with high-risk characteristics.\(^1\) Thus, the combined use of coronary angiography and invasive imaging provides the most comprehensive study of coronary plaques.

**Assessment of Plaque Burden**

Plaque burden is defined as the cross-sectional vascular area narrowing. Intravascular imaging, such as intravascular ultrasound (IVUS), has been traditionally taken as the benchmark for measuring plaque burden.

One of the most important noninvasive techniques for the evaluation of the coronary tree (because of its wide availability and adoption) is CCTA. Several studies have reported on the correlation between CCTA plaque features with invasive coronary imaging modalities, such as IVUS, IVUS-VH, and OCT. In a recent meta-analysis, CCTA had a good diagnostic accuracy to detect coronary plaques when compared with the gold standard IVUS, with an area under the curve for the receiver-operating characteristics analysis of 0.94, a sensitivity of 90%, and a specificity of 92%, with small differences in the assessment of plaque area and volume, percentage area stenosis, and a slight overestimation of lumen area.\(^1\)

Visualization of the coronary vessel wall using noncontrast-enhanced cardiovascular magnetic resonance (CMR) imaging with acquired in-plane spatial-resolution of 0.78x0.78 mm at 1.5T has proven to be feasible. In a small study, 22 patients underwent CMR of the right coronary artery. In 21/22 patients, stenoses detected by CMR corresponded to stenoses detected with conventional angiography.\(^1\) Later on, the same group compared CMR with IVUS for the assessment of plaque detection and wall thickness measurements of the right coronary artery. Although CMR showed a sensitivity of 94% and specificity of 76% for qualitative assessment of the presence of disease, the mean wall thickness on IVUS and MR was different (0.48 versus 1.24 mm; \(P<0.001\), respectively).\(^1\) This latter is not aligned with the findings of He et al, in which matched MRI and IVUS frames showed good correlation for vessel cross-sectional area (16.77±10.67 versus 16.97±8.36; \(r=0.79\); \(P<0.01\)), luminal cross-sectional vascular area (5.18±5.01 versus 7.13±5.14; \(r=0.88\); \(P<0.01\)), and plaque burden (0.71±0.63 versus 0.59±0.15; \(r=0.67\); \(P<0.01\)) in segments containing plaques.\(^1\)

In another small study, 25 lesions were evaluated with noncontrast T1-weighted imaging in CMR, multislice computed tomography, and IVUS. Hyperintense plaques were associated with ultrasound attenuation, positive remodeling, and low values of Hounsfield units by computed tomography.\(^1\)

In the Multi-Ethnic Study of Atherosclerosis (MESA) study, the maximum coronary wall thickness by CMR was related to the presence of cardiovascular risk factors (2.59±0.33 mm when ≥2 risk factors were present versus 2.36±0.30 mm when none or 1 risk factor was present; \(P<0.05\)).\(^1\)

Recently, coronary plaque imaging with contrast-enhanced T1-weighted CMR has been used to evaluate coronary wall thickness and remodeling. Patients with CAD who underwent noncontrast T1-weighted imaging and had high-intensity plaques, which have a plaque:myocardium signal intensity ratio of ≥1.4, had an increased risk of coronary events at a median time follow-up of 55 months.\(^1\)

Invasive coronary studies using IVUS have confirmed that PRs occur at sites of significant plaque accumulation associated with positive remodeling.\(^2\) In an analysis of 51 ruptures plaques, the size of the emptied cavity was on average larger in lesions with positive remodeling and showed a linear relationship with lesion plaque and vessel size but not with the degree of narrowing.\(^2\) Also, it has been reported that ruptured plaques have more varied distribution, and the presence of thrombus is more common in culprit lesions in patients with unstable angina or AMI and in multiple ruptures.\(^2\) Ruptured plaques in culprit lesions in ACSs also have smaller lumen, greater plaque burden, area stenosis, and positive remodeling.\(^2\)

In summary, despite the fact that IVUS is the preferred method for assessing the plaque burden, the following limitations should be acknowledged: (1) the increased noise and artifacts seen in the obtained images often make their interpretation difficult; (2) its poor spatial-resolution does not permit accurate assessment of the thickness of the fibrous cap over necrotic cores, and imaging of microfeatures (ie, microcalcifications and macrophages) is related with increased vulnerability; (3) IVUS gives no information about vessel 3D geometry and gives only indirect information about the distribution of the plaque onto the vessel, and (4) these limitations can be extended to all other IVUS-based imaging modalities, such as VH and integrated backscattered radiofrequency.

**Assessment of Fibrous Cap**

Although noninvasive imaging modalities and conventional intracoronary imaging techniques do not have enough spatial-resolution to evaluate the fibrous cap in detail; OCT has demonstrated in correlation with histological examinations that it is able to provide accurate measurements of the thickness of the fibrous cap.\(^2\) Therefore, it could be useful for the in vivo detection of TCFA (Figure 3). In the study by Kubo et al\(^2\) with IVUS, OCT, and angioscopy in patients with AMI, the incidence of TCFA was 83% and only OCT was able to
estimate the fibrous cap thickness (mean, 49±21 μm). Two studies have reported that the plaque color by angioscopy is related to the thickness of the fibrous cap as measured by OCT with yellow plaques often presenting thin caps.23,24 It has been suggested that the capability of OCT to measure changes in the fibrous cap thickness could be useful to assess the effect of statins in plaque stabilization.24,25 Furthermore, recent data suggest that new OCT technology (such as polarization-sensitive OCT) can assess the collagen content and smooth muscle cell density in the fibrous cap.26 This could provide valuable information about the mechanical stability of the fibrous cap, enabling the identification of lesions at high risk of rupture.

Necrotic Core Characterization

In pathological studies, the size of necrotic core in TCFAs ranges from 1.6 to 1.7 mm² with a length of 8 mm (range, 2–17 mm), and in ruptured plaques ranges from 2.2 to 3.8 mm² with a length of 9 mm (range, 2.5–22 mm).27,28 Identification of subclinical high-risk plaques (eg, necrotic core-rich plaques) is potentially important because they may have greater likelihood of rupture and subsequent thrombosis. There are 2 imaging modalities that are able to characterize in vivo necrotic core, IVUS-VH, and NIRS. The VH tissue maps have been validated ex vivo by comparison with histology. The overall predictive accuracies were 93.5% for fibrous, 94.1% for fibro-fatty, 95.8% for necrotic core, and 96.7% for dense calcium, with sensitivities and specificities ranging from 72% to 99%.29

NIRS takes advantage of the fact that different organic molecules absorb and scatter the NIR light at different degrees and at various wavelengths. The processing of the reflected signal provides information about the chemical composition of different tissues and seems to permit reliable detection of the lipid component. The reliability of this technique has been evaluated in histology-based studies, whereas the SPECTroscopic Assessment of Coronary Lipid (SPECTACL) study was the first report to demonstrate the feasibility of a NIRS catheter in a clinical setting.30,31

In 55 patients, the mean necrotic core percentage—in non-culprit vessels—was significantly larger in patients with ACS when compared with stable patients (12.2±7.0% versus 7.4±5.5%; P=0.006). In addition, stable patients showed more fibrotic vessels (70.9±9.3% versus 63.9±9.1%; P=0.007).32

VH can potentially identify different plaque types, including TCFAs. VH plaque and lesion types that are proposed based on the pathological data are shown in Figure 4.
The current definition of an IVUS-derived TCFA is a lesion fulfilling the following criteria in ≥3 frames: (1) plaque burden ≥40% and (2) confluent necrotic core ≥10% in direct contact with the lumen (ie, no visible overlying tissue). Using this definition of IVUS-derived TCFA, in patients with ACS who underwent an IVUS of all 3 epicardial coronaries, on average, there were 2 IVUS-derived TCFAs per patient, with half of them showing outward remodeling.

Three trials—Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT),13 VH-IVUS in Vulnerable Atherosclerosis (VIVA),14 and the European Collaborative Project on Inflammation and Vascular Wall Remodeling in Atherosclerosis (ATHEROREMO-IVUS)15—studied the value of VH in detecting plaque characteristics associated with future events and identifying high-risk prone-to-rupture plaques. The highest risk PROSPECT plaque type being VH TCFA with a minimum lumen area of ≤4 mm² and a large plaque burden (≥70%) had a 17.2% likelihood of causing an event within 3 years (hazard ratio, 10.8; 95% confidence interval [CI], 4.3 to 27.2; P<0.001). Although in the VIVA study, the presence of a noncalcified TCFA lesion was the only factor that was associated with major adverse cardiac events (MACE), which was mainly driven by coronary revascularizations (unadjusted hazard ratio, 1.79; 95% CI, 1.20 to 2.66; P=0.004). Finally, in ATHEROREMO-IVUS study, the presence of TCFA was an independent predictor of MACE (adjusted hazard ratio, 1.98; 95% CI, 1.09 to 3.60; P=0.026). Furthermore, the predictive value of TCFA lesions for the occurrence of acute cardiac events (composite of death or ACS only) was even stronger (adjusted hazard ratio, 2.51; 95% CI, 1.15 to 5.49; P=0.021). These findings emphasize the biological importance of TCFA for PR.

Although the 3 trials point to the same association, namely the presence of high-risk plaque characteristics with clinical outcomes, the following should be acknowledged: (1) in the PROSPECT trial, the total number of events was low, particularly the incidence of myocardial infarction (≥1%). Most of MACE were either unstable angina or revascularization; (2) The VIVA study has a limited sample size; ATHEROREMO study has performed only 1 vessel imaging (versus 3-vessel imaging in the PROSPECT and VIVA studies) and associations were performed in a patient-level basis (versus lesion level in the PROSPECT and VIVA studies).

Recently, NIRS has been used to assess changes in the composition of the plaque and the prognostic implications of plaque morphology. In the Reduction in Yellow Plaque by Aggressive Lipid-Lowering Therapy (YELLOW) trial,36 NIRS was implemented to assess the short-term effect of intensive medical treatment with rosuvastatin on the burden and composition of the plaque in obstructive lesions. Although in the ATHEROREMO–NIRS substudy, NIRS was used to examine the prognostic implications of the presence of lipid-rich atherosclerotic plaques. Patients with coronary artery disease and a lipid core burden index equal or above the median of 43.0, as assessed by NIRS in a nonculprit coronary artery, had a 4-fold risk of adverse cardiovascular events during 1-year follow-up.

PROSPECT II is natural history, multicenter study, which will assess the ability of intracoronary NIRS to identify nonflow obstructing vulnerable plaques that subsequently lead to coronary events. Similarly, The Lipid-Rich Plaque (LRP) study (NCT02033694) has been started. This study will enroll 9000 patients, and the main objective is to assess whether cholesterol-containing plaques are associated with clinical events.

### Assessment of Positive Remodeling

Vessel remodeling can readily be evaluated with either noninvasive (CCTA) or invasive imaging modalities (IVUS). Positive or outward vascular remodeling is defined as a compensatory enlargement of the vessel wall coronary arteries in response to an increase in plaque area.15 Pathological studies have established a relationship between positive vessel remodeling and plaque vulnerability, showing an increase in inflammatory marker concentrations, larger lipid cores, paucity of smooth muscle cells, and medial thinning in positively remodeled vessels.16

In a study conducted by Hoffmann et al,36a a significantly larger plaque area and positive remodeling, as assessed by CCTA, were found in culprit lesions of patients with ACS when compared with patients with stable coronary artery disease.

In another small study, Motoyama et al38b found that culprit lesions of patients with ACS had more frequent positive remodeling, low-density plaque (<30 HU), and spotty calcifications. Extending on these results, the same authors conducted a large prospective trial, including 1059 patients who underwent CCTA, and demonstrated that positive remodeling and low-attenuation plaques were associated with the subsequent development of ACS.38b In this study, the percentage of patients with these 2 features that subsequently developed and ACS was 22.2% when compared with only 3.7% for patients with only 1 feature and 0.5% for patients with neither positive remodeling nor low-attenuation plaques. In a study by Kashiwagi et al,38c evaluating 105 patients with CAD, CCTA findings have been also validated against OCT. In this study, TCFAs had higher remodeling indexes, lower CT attenuation values, and more often ring-like enhancement by CCTA (44% in the TCFA group versus 4% for the non-TCFA group).

In several IVUS studies, positive vessel remodeling has been identified as one of the features associated with culprit coronary lesions36d and is also frequently observed in ruptured plaques. It occurs significantly more often in patients with ACS than in those with stable CAD.36c,e,f In patients with unstable angina, outward remodeling has been defined as a significant independent predictor of major adverse cardiac events,36g and a prospective IVUS study in these patients revealed that plaques exhibiting positive remodeling had more often thrombus or signs of rupture. The remodeling pattern also has been correlated with the plaque composition. Tauth et al39 showed that soft plaques were associated with positive remodeling, whereas fibrocalcific plaques showed more often constrictive remodeling. Rodriguez-Granillo et al40 found a positive correlation between outward remodeling and necrotic core and a negative correlation between outward remodeling and fibrous tissue.

### Inflammation

Recently, a feasibility study by Rogers et al41 demonstrated that fusion of the fluorodeoxyglucose positron emission tomography (FDG-PET) and CCTA allows detection of

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coronary inflammation. This innovative approach has been used to examine the effect of treatment on vascular inflammation, but it has poor spatial-resolution and does not allow identification of the exact location of the culprit lesion. The use of combined MR/PET or advances in molecular imaging using targeted MR or PET tracers, such as sodium fluoride or mannose receptors, holds promise in improving the noninvasive coronary plaque imaging and characterization.

Maintz et al performed MRI immediately before and 3 hours after an intravenous injection of contrast medium (gadolinium-chelate) application, which allows the assessment of the late enhancement. The authors hypothesized that the observed contrast uptake may be associated with inflammatory or fibrous coronary plaques and thus may reflect acute and chronic vascular inflammation. Ibrahim et al performed serial contrast-enhanced CMR and C-reactive protein in patients with AMI. They found a drop in contrast:noise ratio on CMR between the immediate and 3-month period, which paralleled the decline in blood C-reactive protein. The authors concluded that the significantly increased coronary wall enhancement may represent edema and exacerbated inflammatory activity in coronary atherosclerosis with ACS.

Multimodality imaging catheters that provide accurate visualization of plaque morphology, composition, and simultaneous detection of plaque inflammation are currently available (eg, catheters that permit concurrent IVUS and intravascular photoacoustic data acquisition or combined OCT and near-infrared fluorescence imaging). These catheters show promise in allowing us to recognize mechanisms of vascular inflammation, understand its role on plaque destabilization, investigate the effect of new pharmaceutical and invasive treatments, and probably predict future culprit lesions.

Endothelial Function
A nonatherosclerotic coronary endothelial layer is able to release and respond to nitric oxide, which under normal conditions induces coronary vasodilation. An abnormal vasomotor response is related to endothelial dysfunction, which has been associated with cardiovascular end points. Noncontrast-enhanced CMR has the capability of evaluating the vasomotor response of the coronary vessel to the pharmacological stimuli.

Pharmacological Plaque Modulation With Imaging-Based Assessment
Invasive Techniques
Optimal management of conventional coronary risk factors, such as hyperlipidemia, hypertension, and diabetes mellitus, has been shown to improve clinical outcomes. Although the improved outcomes are attributed to stabilization of vulnerable coronary plaques, the exact changes in plaque phenotype have never been prospectively studied. Noninvasive modalities are ideal to study serial morphological changes over time. However, the spatial-resolution of the currently available noninvasive imaging modalities, such as MR or CCTA, does not allow for the detection of subtle structural changes. Therefore, at the present time, invasive imaging modalities are the only feasible tools to study subtle changes of plaque phenotypes. There is only one exception that is the assessment of inflammation, achieved by FDG-PET is discussed below.

Although IVUS and OCT are more widely used, it is difficult to perform serial studies in asymptomatic patients because of the invasive nature of these tests. Despite this limitation, several studies have been reported using these modalities. In this section, we summarize the results of clinical studies, testing the effect of pharmacological intervention of plaque phenotype.

Intravascular Ultrasound
Because of its limited spatial-resolution, most IVUS studies use plaque volume as a primary target. The change in plaque volume was expressed by percentage change in total atheroma volume (TAV), where TAV was calculated as the sum of plaque areas for each slice. The most widely used pharmacological intervention for plaque stabilization is lipid-lowering therapy. The first prospective randomized IVUS trial was the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) study, which demonstrated that atorvastatin 80 mg daily could halt the progression of atherosclerosis. Percentage change in TAV was −0.4% in 1.5 years, with significant reduction in low-density lipoprotein and high-sensitivity C-reactive protein by 47% and 36.4%, respectively. These initial findings were confirmed in the subsequent trials: the A Study To Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID) and The Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin (SATURN). In the ASTEROID trial, the mean change in percentage atheroma volume (PAV) was −0.98% with rosvastatin 40 mg per day. In the SATURN trial, the mean change in PAV was −1.22% with rosvastatin 40 mg daily and −0.99% with atorvastatin 80 mg daily.

Although several large, prospective trials consistently showed significant reduction of clinical events with lipid-lowering therapy, the reduction of plaque volume was relatively minimal (0.4%–1.2%), even with aggressive lipid-lowering therapy. This discrepancy suggests that other statin systemic effects (ie, reduction in thrombogenicity) and plaque characteristics are more important than plaque volume reduction for prevention of future adverse events (Figure 5). One small study, using integrated back scatter IVUS, showed that, after a 6-month treatment with lipid-lowering therapy, there was a significant increase in fibrous volume and a significant reduction in lipid volume. A serial IVUS and OCT study showed no correlation between the changes in TAV and fibrous cap thickness after 9 months in patients with ACS.

IVUS studies have also demonstrated coronary plaque modification in high-density lipoprotein (HDL)–treated patients. The infusion of synthetic HDL-cholesterol particles containing the variant apolipoprotein, apoA-I Milano, complexed with phospholipids (ETC-216) reduced the PAV by −1.06% (3.17% P=0.02 compared with baseline) in the combined ETC-216 group at 5 weeks. In the ERASE (Effect of rHDL on Atherosclerosis-Safety and Efficacy) study, patients were randomly assigned to receive 4 weekly infusions of placebo (saline), 111 to receive 40 mg/kg of reconstituted HDL (CSL-111), and 12 to receive 80 mg/kg of CSL-111. The
Figure 5. Serial coronary plaque size and compositional changes assessed by intravascular ultrasound virtual histology. A. The line graph shows in green the plaque burden at baseline (○) and at 12 months (●) of the same coronary segment. The plaque burden at follow-up is smaller than at the baseline. In the line graph in red, the necrotic core area of the same coronary segment is depicted at baseline (○) and at 12 months (●). It can be seen an important increase in necrotic core area along the whole length of the coronary segment. B. A frame-to-frame comparison is shown. At baseline, the grayscale frame shows a normoechogenic and eccentric plaque, which corresponds to a virtual histology plaque containing mostly fibrotic (dark green) and fibrofatty (light green) with small amount of necrotic core (red) and dense calcium (white). This plaque is a pathological intimal thickening as assessed by virtual histology. At follow-up, the grayscale frame shows a change in the echogenicity of the plaque (it became hyperechogenic at 6 o’clock), which corresponds to a plaque containing a confluent area of necrotic core (red) and spotty dense calcium (white). This plaque is a thick fibroatheroma (FA) as assessed by virtual histology. This figure highlights that despite small reduction in plaque size ≥12 months, there was an important change in the composition of the plaque, transforming a pathological intimal thickening into a thick FA.
latter was discontinued because of liver function test abnormalities. Within the treated group, the percentage change in atheroma volume was $-3.4\%$ with CSL-111 ($P<0.001$ versus baseline), whereas for the placebo group was $-1.6\%$ ($P=0.48$ between groups). There has been no clinical studies using these compounds and is still unclear what the future holds for these therapeutic agents.

Patients with human deficiency of cholesteryl ester transfer protein have elevated circulating levels of HDL-cholesterol. This has led to investigation on cholesteryl ester transfer protein inhibition as a novel and potentially effective approach to elevate HDL-cholesterol. In the ILLUSTRATE (Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation) trial, the PAV increased similarly in patients receiving atorvastatin monotherapy versus in those receiving the combined torcetrapib–atorvastatin therapy after 24 months ($0.19\%$ versus $0.12\%$, respectively). In line with these results, the ILLUMINATE (Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events) study showed an increased mortality rate in patients treated with torcetrapib.40

The enzyme acyl-coenzyme A: cholesterol acyltransferase esterifies cholesterol in a variety of cells and tissues. Inhibition of acyl-coenzyme A: cholesterol acyltransferase 1, by blocking the esterification of cholesterol, could prevent the transformation of macrophages into foam cells and could slow the progression of atherosclerosis, whereas the inhibition of acyl-coenzyme A: cholesterol acyltransferase 2 would be expected to decrease serum lipid levels. In the ACTIVATE (ACAT Intravascular Atherosclerosis Treatment Evaluation) study, the change in PAV was similar in the pactimibe (100 mg daily) and placebo groups ($0.69\%$ and $0.59\%$, respectively; $P=0.77$). Systolic blood pressure has been shown to be an independent predictor of plaque progression by IVUS. A randomized study of patients with CAD and a diastolic blood pressure $<100$ mm Hg treated with placebo or antihypertensive therapy using either amloidipine 10 mg daily or enalapril 20 mg daily showed that patients treated with amloidipine had a reduction in plaque size and also a reduction in cardiovascular events when compared with placebo at 24 months. The PERSPECTIVE (PERKindopril’S Prospective Effect on Coronary aTherosclerosis by Angiography and IntraVascular Ultrasound Evaluation) study, a substudy of the EUROPA (EUROpean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease) trial, evaluated the effect of perindopril on coronary plaque progression in 244 patients. There were no differences in changes in IVUS plaque measurements detected between the perindopril and placebo groups. Another study, the administration of a renin inhibitor (aliskiren), the PAV did not differ between groups.41

Thiazolidinediones increase insulin sensitivity in peripheral tissues thereby lowering glucose and also lower blood pressure, inflammatory markers, and improve lipid profile, endothelial function, and carotid intima-media thickness. Thiazolidinediones (ie, rosiglitazone and pioglitazone) may, therefore, reduce progression of coronary atherosclerosis when compared with other anti-diabetic drugs. Two studies have addressed this question. The APPROACH (The Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in Diabetes Patients With Cardiovascular History; rosiglitazone study) and the PERISCOPE (Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation; pioglitazone study) trials. The change in PAV in the APPROACH study was not different in patients allocated to glipizide or rosiglitazone ($-0.64\%$; $95\%$ CI, $-1.46$ to $0.17$; $P=0.12$), whereas in the PERISCOPE study pioglitazone versus glimepiride was associated with favorable effects on change of PAV ($-0.16\pm0.21$ versus $0.73\pm0.20\%$, $P=0.002$). Rosiglitazone significantly reduced normalized TAV by $5.1$ mm$^3$ ($95\%$ CI $-10.0$ to $-0.3$; $P=0.04$) when compared with glipizide, whereas pioglitazone just failed to achieve statistically significant in change in TAV ($-5.5\pm1.6$ versus $-1.5\pm1.5$ mm$^3$; $P=0.06$) when compared with glimepiride. Pioglitazone resulted in comparable plaque size reduction (ie, TAV) as rosiglitazone, but this reduction was associated with an almost double reduction in vessel size. The change in PAV with as numerator change in atheroma volume and as denominator change in vessel volume may mask the specific directional changes in its numerator and denominator when used as primary end point to compare 2 pharmacological agents.

In the Integrated Biomarker and Imaging Study (IBIS) 2, the effects of a lipoprotein-associated phospholipase A(2) inhibitor (darapladib, 160 mg daily) versus standard of care were compared in 330 patients. After 12 months, there were no significant differences between groups in plaque deformability ($P=0.22$) or plasma high-sensitivity C-reactive protein ($P=0.35$). However, in the placebo-treated group, necrotic core volume increased significantly ($4.5\pm17.9$ mm$^3$; $P=0.009$), whereas darapladib halted this increase ($-0.5\pm13.9$ mm$^3$; $P=0.71$), resulting in a significant treatment difference of $-5.2$ mm$^3$ ($P=0.012$). These intraplaque compositional changes occurred without a significant treatment difference in TAV ($P=0.95$). These results contributed to the planning of 2 large randomized clinical trials: the Stabilization Of Plaques using Darapladib-Thrombolysis In Myocardial Infarction 52 Trial (SOLID-TIMI 52; NCT01000727), which showed that darapladib did not reduce the primary endpoint in patients suffering from an acute coronary syndrome, and the Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy Trial (STABILITY) trial. This latter study showed that patients with stable coronary heart disease treated with darapladib did not reduce the risk of the primary composite end point of cardiovascular death, myocardial infarction, or stroke. However, darapladib did show a reduction in coronary events. Inhibition of secretory phospholipase A2, by means of varespladib, blocks generation of phospholipid products implicated in atherosclerosis. This hypothesis has been tested in the VISTA-16 (Varespladib and cardiovascular events in patients with an acute coronary syndrome) randomized clinical trial, which showed that varespladib did not reduce the incidence of the composite of cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke, or unstable angina with...
evidence of ischemia requiring hospitalization at 16 weeks. On the contrary, an increase in the rate of MI was observed.68

Optical Coherence Tomography
Among several characteristics of vulnerable plaque, which include fibrous cap thickness, necrotic core, macrophages, positive remodeling, and increased vasa vasorum, fibrous cap thickness is probably the most important determinant in the development of clinical events. The only currently available imaging modality with a sufficient spatial-resolution to measure thin fibrous cap thickness accurately (65 μm) is OCT. Because OCT is a relatively new imaging technology, data from a prospective study are not available. In 1 small retrospective study, OCT was performed in 40 patients with AMI at baseline and 9 months.25 The study compared patients treated with a stent with those in the control group for changes in fibrous cap thickness. Both groups showed increase in fibrous cap thickness. However, the degree of increase was significantly greater in the statin treatment group than in the control group (Figure 3). Because OCT was the only modality, no data on plaque burden or remodeling were reported.

In summary, intravascular imaging techniques help us not only to evaluate vascular responses to pharmacological interventions but also to understand the natural history of these vascular changes over time. However, other factors, such as systemic coagulability, local thrombogenecity, and vascular tone also contribute to the outcome of plaque disruption.

Noninvasive Techniques
Necrotic core–rich plaques contain M1 polarized macrophages, which exhibit intense glycolysis, and are thereby associated with higher FDG uptake. Positive correlations between FDG uptake and metabolically active macrophages and macrophage infiltration into the vessel wall have been previously demonstrated.69 Therefore, FDG-PET has been used to assess in vivo plaque inflammation mostly in areas outside of the coronary tree. Although this review focuses on the coronary tree, it is important to touch on this topic briefly.

There have been numerous small FDG-PET studies, showing the effects of novel compounds targeting intraplaque inflammation, but they mostly imaged carotid vessels. High dose of atorvastatin and simvastatin attenuate plaque inflammation, a low-density lipoprotein-cholesterol–independent effect, using 18F-FDG-PET coregistered with computed tomography.70,71 Losmapimod, a p38 mitogen-activated protein kinase inhibitor, reduced vascular inflammation in the most inflamed regions of the carotid vessels.72 Conversely, dalceplapib (Hoffman-La Roche, Basel, Switzerland) and rilapladib (GlaxoSmithKline), which modulate cholesteryl ester transfer protein activity to raise HDL-cholesterol and inhibit lipoprotein-associated phospholipase A(2) respectively, did not show a pathological effect on the vessel wall.73,74

There have been a handful of small studies, showing that CMR is able to characterize and follow-up changes in the vessel wall of the coronary vessels. Specifically, patients (n=22) presenting with non–ST-segment–elevation ACS were imaged at baseline and at 6 months after stabilization and optimization of medical therapy. A significant regression of the remodeling and plaque area was observed.75

Should Imaging-Verified High-Risk Plaques Be Treated Mechanically Regardless of Luminal Stenosis?
Pharmacological and mechanical treatments aimed at stabilizing TCFA are currently a popular topic of research. Takarada et al25 showed that pharmacological treatment, such as statins, enables to increase the fibrous cap thickness of coronary plaques significantly. Although the pilot vShield Evaluated at Cardiac hospital in Rotterdam for Investigation and Treatment of TCFA (SECRITT) trial assessed for the first time whether a mechanical preventive treatment of such kind of plaques by means of self-expandable metallic stent (vShield) may be feasible and safe.76 The percutaneous treatment of a TCFA by a bare-metal stent triggered the formation of a fibrotic layer (more or less thick) on the top of the thin cap covering the lipid pool, potentially reducing the probability of PR/plaque erosion. However, the persistence of metal and nondegradable polymers into the vessel wall can have some detrimental effects (eg, permanent presence of foreign body). With regard to the absorb bioresorbable vascular scaffold (Abbott Vascular, Santa Clara, CA), it has been established that at ≥2 years the polymeric material has been fully degraded and replaced by proteoglycans. At 4 years, the initial location of the struts in the vessel wall is no longer identifiable by histology or OCT, and the neointimal layer built up on the scaffolding structure becomes a de novo cap, which cannot be distinguished from a fibrotic cap, normally seen in fibroatheroma. The formation of a symmetrical neotissue with a mean thickness of 220 μm without remnants of polymeric struts, when the device is completely bioresorbed, may, therefore, favor the use of a bioresorbable device for the treatment of TCFAs. On the basis of these findings of our previous preclinical studies, we have established that the main component of the neointima after absorb bioresorbable vascular scaffold implantation is fibrous tissue, whereas fibrin and granulomatous cells are scarce at long-term follow-up.77

Nevertheless, this mechanical sealing should not be considered as the first-line treatment choice of vulnerable plaque until more evidence is available. Upcoming studies may further shed light onto this approach. For example, PROSPECT ABSORB will evaluate the ability of a bioresorbable scaffold to increase luminal dimensions of vulnerable plaque safely. To this aim, 300 patients with a plaque at high risk of causing future coronary events, as shown in the original PROSPECT study (plaque burden ≥70%), will be randomized to treatment with absorb bioresorbable vascular scaffold plus guideline-directed medical therapy or medical therapy alone, with each patient undergoing angiography and IVUS/NIRS after 2 years.

Is It Feasible to Define Plaque Erosion Clinically?
The current knowledge of plaques associated with acute coronary events is based on the pathological reports obtained from the autopsy of the victims of sudden cardiac death. The clinical definition of such plaques is not feasible or was an attempt made to evaluate the potential implications
for management strategies. Acute coronary events could be classified based on the clinical imaging, as ACS with ruptured fibrous caps or intact fibrous caps, respectively. A recent OCT registry has reported similar proportion of PRs and erosions in patients presenting with acute coronary events. It has also been proposed that a priori knowledge of the mechanism of ACS would allow a tailored management of these 2 (pathologically) distinct entities (Figure 6). Currently, infarct-related vessels are usually recommended to be treated with primary intervention with stent placement regardless of the underlying plaque morphology. However, it may be logical to forego the stent placement and treat with dual antiplatelet agents if the culprit lesion has intact fibrous caps and the luminal stenosis is not critical. Although challenging to assess, OCT imaging after thrombus aspiration is able to differentiate the plaque morphology associated with ruptured fibrous caps or intact fibrous caps, it should become possible to develop a more conservative therapy for the management of acute events resulting from plaque erosion. However, a prospective randomized study is required to identify the noninferiority of the conservative approach. It will also be necessary to evaluate the ideal pharmacological regimen, including the optimal combination of antiplatelet agents, newer anticoagulants such as factor Xa inhibitor, and direct clot-busters such as plasminogen activators locally.

Conclusions
An acute coronary event often comprises the first presentation of coronary disease in asymptomatic patients. Recent research has shown that certain plaque characteristics, especially the fibrous cap, inflammation, and the necrotic core size best determine the likelihood of future adverse events. Because of the limitations of currently available noninvasive imaging techniques, invasive imaging modalities present the best hope in assessing the high-risk plaque phenotype. Although pharmacological therapy remains the cornerstone for prevention, using these invasive modalities to pinpoint the exact time for mechanical intervention remains elusive. The ongoing studies will continue to shed light on this important, clinical issue.
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References


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