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Coronary plaque burden regression and high-risk plaque reversal: Potential biomarkers for secondary prevention?

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Approximately 300,000 Americans have a recurrent coronary attack each year [1]. Effective medical therapies reduce event frequency, and newer, potentially more effective anti-atherosclerotic therapies are being studied [2–4] and becoming available [5,6]. The therapeutic implications of these novel agents are likely to have significant expense and some significant risk such that their appropriate selection for the individual patient will become increasingly important. A question that arises is whether in-vivo coronary plaque assessment can appropriately select high-risk patients for this therapy and monitor treatment response.

In the article “Regression of Coronary Atherosclerosis: Current Evidence and Future Perspectives”, Koskinas et al. [7] reviewed intracoronary imaging modalities for the evaluation of plaque burden and morphology. The authors conclude that while there is currently insufficient data to demonstrate the impact of plaque regression or stabilization on reducing coronary events, in-vivo plaque evaluation may ultimately help identify high-risk patients who will benefit from novel aggressive anti-atherosclerotic therapy. They summarize current evidence of coronary plaque regression and stabilization with intensive anti-atherosclerotic therapy using intravascular ultrasound (IVUS), optical coherence tomography, and near infrared spectroscopy. These intracoronary imaging modalities have allowed investigators to quantify plaque burden, characterize high-risk plaque, and assess plaque responses to therapy. The authors note atheroma volume, fibrous cap thickness, arterial remodeling, lipid pool/necrotic core, and macrophage accumulation to be important characteristics. However, catheter-based intracoronary imaging has demonstrated only modest changes with anti-atherosclerotic therapy, as detailed by the authors. Hybrid noninvasive coronary plaque imaging may be needed to help us understand the discordance between the substantial clinical impact of statins vs their modest plaque regression and minor changes in plaque morphology. Advances in noninvasive coronary plaque imaging may bridge this knowledge gap, as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) can also evaluate plaque burden and/or high-risk plaque morphology, although each has its limitations (Table).

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CT

Coronary CT angiography (CCTA) can quantify calcified and non-calcified plaque and characterize high-risk plaque features, with high correlation and accuracy compared to IVUS [8]. Automated plaque quantification software have high test-retest reproducibility [9], making standardization feasible. Positive remodeling, low-attenuation plaque (Hounsfield units<30) representative of lipid-rich necrotic core [10], napkin-ring sign, and spotty calcification are high-risk plaque features that predict coronary events independently of obstructive stenosis and clinical risk factors [11]. Recently demonstrated in patients with serial CCTA, plaque progression and evolution to high-risk plaque were associated with increased coronary events [12]. In addition, statin therapy reduced both non-calcified plaque volume and high-risk plaque features in a small trial of HIV patients [13]. Further work is needed to evaluate the clinical impact of CCTA for monitoring treatment response. CCTA limitations include insufficient resolution to identify fibrous cap thickness and inability to evaluate inflammation.

MRI

Advances in coronary vessel wall MRI have allowed investigators to evaluate high-risk plaque features, including intraplaque hemorrhage represented by T1-weighted high-intensity plaque [14,15] and inflammation represented by coronary wall contrast enhancement [16]. Intraplaque hemorrhage is a marker for plaque progression and vulnerability [14,17] while coronary wall contrast enhancement corresponds to inflammation and increased plaque burden [18]. Validation with coronary histology is lacking, but inference from carotid MRI and histology correlations supports that these two MRI features represent high-risk plaque. Although these biomarkers have potential for identifying high-risk patients for advanced therapy, therapies for the prevention of intraplaque hemorrhage or coronary inflammation are currently absent. Limitations to coronary MRI include motion artifacts and low spatial resolution for the detection of lipid-rich necrotic core, fibrous cap thickness, or accurate plaque burden quantification. Technical developments are ongoing.

PET

Coronary PET can provide a novel approach for secondary prevention of coronary events, specifically (19)F-sodium fluoride(NaF) uptake. PET-CT (18)F-NaF uptake has been demonstrated to localize ruptured and high-risk coronary plaque and to correlate with active microcalcification, macrophage infiltration, and necrosis in ruptured carotid plaque specimens [19]. Prospective clinical trials are needed to determine whether (19)F-NaF uptake changes with anti-atherosclerotic therapy and whether this corresponds in coronary event reduction. (19)F-FDG PET-CT imaging of coronary artery inflammation is also promising but challenging due to unreliable myocardial uptake suppression [20]. Other PET limitations include low resolution, motion artifact, and radiation. Further technological advances involving simultaneous PET-MRI may provide improvements in this technique.

As noted by Koskinas et al., plaque progression and high-risk plaque development involve complex mechanisms. Along with invasive intracoronary methods, CT, MRI, and PET to evaluate plaque burden regression and high-risk plaque reversal have potential to help identify high-risk patients for novel secondary prevention strategies.

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Table

Comparison of CT, MRI, and PET for assessment of coronary plaque morphology and composition.

	CT	MRI	PET
Spatial resolution (μm)	0.4	0.8 ^a	1.0
Atheroma volume	++	–	–
Cap thickness	–	–	–
Arterial remodeling	++	+	–
Macrocalcification	+++	+	–
Lipid pool/necrotic core	+	–	–
Inflammation	–	+	+
Microcalcification	–	–	+++
Neovessels/intraplaque hemorrhage	–	+	–
Luminal integrity	–	–	–
In-stent neoatherosclerosis	+	–	–

^aDouble inversion recovery, ECG-triggered navigator-gated, fat-suppressed, turbo spin-echo sequence.