Intravascular imaging beyond ischaemia assessment: a possible way for improving risk stratification

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The identification of coronary 'vulnerable' plaques has remained elusive and controversial for decades. Recently the use of intracoronary imaging has played a crucial role to elucidate this controversy. Novel findings support the hypothesis that ischaemia and future adverse events may represent two separate concepts due to the disconnection between the current functional impact of a coronary lesion and the lesion's later propensity for causing clinical events. Indeed, the traditional dichotomous definition of coronary artery disease as 'obstructive or flow-limiting' and 'non-obstructive' appears inaccurate for identifying truly high-risk patients. As shown from histopathology studies, acute coronary syndromes (ACSs) arise from rupture and thrombosis of plaques which may be only mild or moderate on angiography but characterized by a large lipidic core and a thin-cap fibroatheroma (TCFA).

The PROSPECT study[1] was the first 'proof of concept' study able to show that coronary plaques with a large plaque burden and a TCFA, were associated with future adverse events. However, the capability of intravascular ultrasound (IVUS) in detecting vulnerable plaques is limited by its low resolution. Further technological progress with near-infrared spectroscopy imaging/IVUS (NIRS–IVUS), capable of accurately detecting and quantifying the lipid core within the atherosclerotic plaque opened new opportunities in understanding the impact of plaque vulnerability. The Lipid-Rich Plaque study[2] has established the ability of IVUS–NIRS to detect lesions at high risk for future adverse events as well as a prespecified cut-off of the Lipid Core Burden Index >400. In the same line, the PROSPECT II study[3] showed that the presence of NIRS–IVUS detected lipid-rich plaque in non-culprit lesions of myocardial infarction patients was associated with future major cardiovascular events (MACE) in 13% of patients within 4 years, of which 8% arising from untreated angiographically benign-appearing and non-flow-limiting at baseline.

While NIRS–IVUS sets a step ahead in detecting vulnerable plaque with large lipid cores, this technology is still limited by the IVUS low resolution, and therefore is not able to detect another important predictor of future adverse events: the atheroma plaque cap thickness.

The high resolution of optical coherence tomography (OCT), on the other hand, provide a very accurate evaluation of plaque composition and can also accurately measure plaque cap thickness.

The recent CLIMA study[4] evaluated with OCT untreated proximal left anterior descending coronary artery and identified a fibrous cap thickness <75 mm as the strongest predictor of adverse cardiovascular events.

Another recent prospective natural history study, the COMBINE trial,[5] showed that TCFA lesions in diabetic patients were responsible for future MACE despite the absence of ischaemia. Although the study was smaller compared to previous cited studies, this is the first trial to point out that future events occur despite the absence of ischaemia and are related to certain plaque morphology. TCFA represented 25% of the total fractional flow reserve (FFR)-negative lesions and were associated with a 4.7-fold higher incidence of MACE as compared to patients with TCFA-negative FFR-negative lesions.

These studies, enrolling both patients with ACS and chronic stable ischaemia, established the need for intravascular imaging to detect vulnerable plaques (*Table 1*) and emphasized the importance of a combined haemodynamic and morphologic evaluation for identifying truly high-risk patients. The identification of plaque characteristics heralding vulnerability is needed especially in high-risk patients with intermediate residual coronary disease.

These novel findings pave the way for further research to establish novel systemic and focal treatments, including aggressive pharmacological treatment and to derive more stringent criteria to guide preventive, individualized treatment.

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Table 1 **Main trials establishing vulnerable plaque characteristics**

Study	Year	Setting	Intravascular imaging tool	Lesions	Lesion characteristics predictive of MACE
PROSPECT[1]	2011	697 ACS patients	Gray scale and radiofrequency IVUS imaging	Non-culprit lesions	Plaque burden ≥ 70% (HR 5.03, 95% CI 2.51–10.11) MLA ≤ 4.0 mm^2 (HR 3.21, 95% CI 1.61–6.42) Presence of TCFA (HR 3.35, 95% CI 1.77–6.36)
LIPID-RICH PLAQUE[2]	2019	1552 patients with known or suspected coronary artery disease	NIRS–IVUS imaging	Non-culprit lesions	Segments with max LCBI4 mm > 400 (plaque level adjusted HR 3.39, 95% CI 1.85–6.20)
CLIMA[4]	2020	ACS ($n = 536$) and stable angina ($n = 467$) patients	Optical coherence tomography	Untreated left anterior descending lesion	MLA <3.5 mm^2 (HR 2.1, 95% CI 1.1–4.0) FCT < 75 µm (HR 4.7, 95% CI 2.4–9.0) Lipid arc > 180° (HR 2.4, 95% CI 1.2–4.8) Macrophages (HR 2.7, 95% CI 1.2–6.1)
PROSPECT II[3]	2021	898 patients with previous MI (within past 4 weeks)	NIRS–IVUS imaging	Non-flow-limiting non-culprit lesions	Max LCBI4 mm ≥ 324.7 (Lesion-level OR 7.83, 95% CI 4.12–14.89) Plaque burden ≥ 70% (Lesion-level OR 12.94, 95% CI 6.36–26.32) MLA ≤ 4.0 mm^2 (Lesion-level OR 4.97, 95% CI 2.59–9.53)
COMBINE[5]	2021	550 diabetic mellitus patients with ACS or stable coronary disease	Optical coherence tomography	FFR-negative non-culprit lesions	Presence of TCFA (HR 4.65; 95% CI 1.99–10.89)

ACS, acute coronary syndrome; CI, confidence interval; HR, hazard ratio; FCT, fibrous cap thickness; FFR, fractional flow reserve; IVUS, intravascular ultrasound; MACE, major cardiovascular events; Max LCBI4 mm, maximum 4 mm Lipid Core Burden Index; MI, myocardial infarction; MLA, minimal luminal area; NIRS, near-infrared spectroscopy; TCFA, thin-cap fibroatheroma.

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