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VIEWPOINT

High-risk plaques: intervene early or hold the line?

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Plaque rupture with thrombosis is the predominant mechanism of acute coronary syndrome and sudden cardiac death, and a thin-capped fibroatheroma is the prototype of the rupture-prone plaque. A recent meta-analysis summarised the imaging features that characterise high-risk, rupture-prone plaques[1]. Findings were consistent across imaging modalities and clinical presentations, in studies with outcomes on both a patient and a lesion level, and including both invasive and non-invasive imaging: large plaque burden, small minimum lumen area (MLA), thin-cap fibroatheroma (TCFA), large lipid core burden index (LCBI) by near infrared spectroscopy (NIRS), low-attenuation plaque, positive remodelling, napkin ring sign, and spotty calcification. Plaques with more than one of these findings, especially using intravascular imaging, were most predictive of lesion-level events. However, the absolute event rate was low (median patient-level event rate of 4.2%), and most of the events associated were revascularisation and/or rehospitalisation with death or myocardial infarction (MI) representing the minority of events (approximately a 1% annual event rate). This is consistent with pathology studies indicating that the vast majority of plaque ruptures are silent and contribute to lesion progression rather than to death or myocardial infarction[2].

If we can identify high-risk plaques, should we treat them prophylactically with percutaneous coronary intervention (PCI)? While there are a number of ongoing trials – DEBuT-LRP (ClinicalTrials.gov: NCT04765956), COMBINE-INTERVENE (NCT05333068), FAVOR V AMI (NCT05669222), INTERCLIMA (NCT05027984), and VULNERABLE (NCT05599061) – that may help to answer this question, at the present time we must rely on the two largest trials that have been completed and published: PROSPECT ABSORB[3] and PREVENT[4].

PROSPECT ABSORB was a randomised trial in 182 patients assessing the safety and efficacy of PCI using Absorb bioresorbable vascular scaffolds (BVS; Abbott) in patients with angiographically mild and non-ischaemic (by fractional flow reserve [FFR] or instant wave-free ratio [iFR]) high-risk plaques, defined as a plaque burden ≥65% by intravascular ultrasound (IVUS)[3]. At follow-up, lesions treated with BVS had significantly larger MLA (primary endpoint) than those without BVS (6.92 mm^2 vs 3.00 mm^2, respectively; p<0.001). A neocap of intimal hyperplasia formed over BVS, consistent with plaque stabilisation. While there was no late lumen loss in the guideline-directed medical therapy-alone group, the primary endpoint was positive because of the acute lumen gain at the time of the BVS implantation.

PREVENT was a randomised trial that enrolled patients with high-risk, non-flow-limiting (by FFR) plaques identified using IVUS, radiofrequency (RF)-IVUS, NIRS-IVUS, and/or optical coherence tomography (OCT)[4]. Inclusion criteria mandated two of the following: MLA <4.0 mm^2, plaque burden >70%, RF-IVUS or OCT-derived TCFA, or NIRS-IVUS maximum lipid core burden index in a 4 mm segment (maxLCBI$_{4mm}$) >315. Patients were randomised to optimal medical therapy (OMT) or optimal medical therapy plus preventive, IVUS-guided PCI. Almost all of the lesions had both a plaque burden >70% and an MLA <4 mm^2, and of the morphological assessments, only a maxLCBI$_{4mm}$ >315 was predictive of events. The mean stent

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diameter was 3.5 mm, and the mean stent length was 23 mm; thus, these were short lesions in large vessels. At baseline, low-density lipoprotein (LDL) cholesterol was 88±34 mg/dl in the preventive PCI group and 93±34 mg/dl in the OMT group. High-dose statins or moderate-dose statins and ezetimibe were prescribed in 69% at discharge, 57% at 2 years, and 60% at maximum follow-up; the mean LDL cholesterol was 64±21 mg/dL in both groups at last follow-up. Few, if any, patients in the OMT group were treated with proprotein convertase subtilisin/kexin type 9 inhibitors. At 7 years, there were 7 cardiac deaths in the PCI group and 8 in the OMT group – in other words, less than 0.1% per year – with similar rates of target vessel myocardial infarction. At 2 years, the primary endpoint (composite of cardiac death, target vessel MI, ischaemia-driven revascularisation, or rehospitalisation) occurred in 0.4% of PCI patients versus 3.4% of patients treated with just OMT (difference: –3.0%, 95% confidence interval [CI]: –4.4 to –1.8; p=0.0003). However, the primary endpoint was no longer positive at 4 or 7 years, and the hard component endpoints of cardiac death and target vessel myocardial infarction were not different at 2, 4, or 7 years in the intention-to-treat, per-protocol, or as-treated analyses. Conversely, what was clear and consistent was that early PCI prevented late PCI. Performing 739 PCIs (according to the as-treated analysis) merely prevented 20 PCIs at 2 years and 36 PCIs at 4 years **(Table 1)**.

When planning PREVENT, the primary event rate at 2 years was estimated to be 8.4% in the preventive PCI group and 12.0% in the OMT-alone group. Yet, the actual event rates were 0.4% and 3.4%, respectively, illustrating the low risk of these "high-risk" plaques when treated with optimal guideline-directed medical therapy even though many of the patients in the medical therapy group would not meet current optimal guidelines.

The results of PREVENT were supported by a meta-analysis of 4 randomised clinical trials performed[5]. Patients in the PCI group had a similar incidence of major adverse cardiac events compared with the OMT group (risk ratio [RR] 0.38, 95% CI: 0.10-1.45; p=0.16). PCI plus OMT showed similar incidences of all-cause death (RR 0.55, 95% CI: 0.05-6.51; p=0.64) and myocardial infarction (RR 0.81, 95% CI: 0.12-5.19; p=0.82) compared with OMT. The favourable clinical outcome of preventive PCI was mainly driven by a reduction of clinically driven revascularisation (RR 0.11, 95% CI: 0.03-0.40; p<0.001) and rehospitalisation for unstable or progressive angina (RR 0.16, 95% CI: 0.05-0.56; p=0.004).

What would happen if a high-risk plaque was not treated with PCI, but the patient was treated medically and PCI performed only when the patient became symptomatic? In PROSPECT II (NCT02171065), there were 374 high-risk plaques (plaque burden >70% and max$LCBI_{4mm}$ >325, representing 11% of the total number of non-culprit plaques) that were treated medically. Late revascularisation and/or rehospitalisation occurred in 1% at one year, 2-3% at two years, 4-5% at three years, and 7% at four years. In PREVENT, there were 867 patients who were treated medically, representing 15% of those screened. Late revascularisation was necessary in 20 patients at two years, 33 patients at four years, and

Table 1. As-treated analysis in PREVENT (patients analysed by the treatment they actually received).

Endpoints	Preventive PCI (n=739)	OMT (n=867)	Δ (95% CI)	HR (95% CI)
Primary endpoint				
2 yrs	1 (0.1)	29 (3.4)	–3.3 (–4.5 to –2.0)	0.37 (0.22 to 0.64)
4 yrs	9 (1.6)	45 (6.2)	–4.6 (–6.6 to –2.5)	
7 yrs	18 (5.7)	55 (9.8)	–4.1 (–8.5 to 0.3)	
Cardiac death				
2 yrs	1 (0.1)	6 (0.7)	–0.6 (–1.2 to 0.1)	0.43 (0.14 to 1.34)
4 yrs	2 (0.3)	10 (1.4)	–1.1 (–2.0 to –0.1)	
7 yrs	4 (0.9)	11 (1.7)	–0.8 (–2.2 to 0.7)	
Target vessel myocardial infarction				
2 yrs	0 (0)	7 (0.8)	–0.8 (–1.4 to –0.2)	0.52 (0.16 to 1.68)
4 yrs	3 (0.6)	8 (1.0)	–0.5 (–1.4 to 0.5)	
7 yrs	4 (1.0)	9 (1.4)	–0.4 (–1.8 to 1.1)	
Target vessel revascularisation				
2 yrs	0 (0)	20 (2.4)	–2.4 (–3.4 to –1.3)	0.35 (0.19 to 0.66)
4 yrs	6 (1.1)	33 (4.7)	–3.6 (–5.4 to –1.8)	
7 yrs	13 (4.6)	42 (8.0)	–3.4 (–7.6 to 0.8)	
Hospitalisation for unstable angina				
2 yrs	0 (0)	13 (1.5)	–1.5 (–2.4 to –0.7)	0.16 (0.05 to 0.52)
4 yrs	3 (0.6)	17 (2.3)	–1.7 (–3.0 to –0.4)	
7 yrs	3 (0.6)	22 (4.6)	–4.0 (–6.6 to –1.5)	

Data shown as n (%). Event rates (%) are Kaplan-Meier estimates and not the ratio of the numerator and denominator. CI: confidence interval; HR: hazard ratio; OMT: optimal medical therapy; PCI: percutaneous coronary intervention

42 patients at maximum follow-up. Thus, and according to the PREVENT results, almost all PCIs would be avoided by a wait-and-see approach compared to stenting all of these 867 lesions upfront, and the PCIs actually performed would be delayed without consequences. Furthermore, non-culprit event rates have gone down from PROSPECT I (NCT00180466) to PROSPECT II to PREVENT and continue to decline, supporting a wait-and-see approach.

A more comprehensive strategy for plaque risk stratification may emerge from integrating imaging, physiology, and inflammation. Beyond morphology alone, combining intravascular imaging (IVUS, OCT, NIRS) with physiological indices (FFR or flow dynamics derived from imaging) and biomarkers of systemic or localised inflammation could refine our understanding of which plaques are biologically active. Such stratification could ultimately increase the specificity in identifying those few plaques whose disruption is both imminent and clinically meaningful.

Importantly, the detection of a high-risk plaque should not automatically prompt invasive treatment. Instead, it should trigger the institution or intensification of optimal medical therapy and, at most, structured surveillance. This follow-up can be performed through coronary computed tomography angiography and quantitative plaque characterisation, offering a non-invasive approach to monitoring plaque progression and response to medical therapy.

What would shift this argument in favour of preventive PCI? The first condition would be the results of ongoing clinical trials being less equivocal. The second would be the ability to identify not only generic high-risk plaques, but specifically those whose rupture would cause death or myocardial infarction, and not just disease progression. The third would be PCI treatment (or great adoption of intravascular imaging guidance) that would reduce the rate of procedural complications or stent thrombosis, restenosis, or neovascularisation leading to the need for repeat revascularisation – currently estimated at 4-5% in the first year and 2-3% per year thereafter. Until then, the data clearly favour a "hold-the-line" approach.

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Conflict of interest statement

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