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Perspective

The vulnerable or high-risk plaque and coronary thrombotic events

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Abstract: Atherosclerosis is a chronic systemic vascular disease known to start early in life. It progresses with age and other risk factors. When involving the coronary vessels, it may present gradually or acutely as anginal pain or as acute coronary syndrome. For decades this acute presentation has been studied. Certain plaque characteristics were identified to be the culprit for those acute coronary syndromes. Relentless efforts to increase the sensitivity of screening for these vulnerable plaques have been developed. The goal is to create a preemptive intervention strategy with effective medical or percutaneous therapies. In this article, we explore the different modalities for early identification and management of those vulnerable or high-risk plaques.

Keywords: acute coronary syndrome; vulnerable plaques; high-risk plaque; thin-capped fibroatheroma; atherosclerosis

1. Introduction

It was only within the last half-century that both pathological analysis at autopsy and invasive coronary angiography in living patients conclusively demonstrated that acute transmural myocardial infarction (MI), now recognized as ST-elevation myocardial infarction (STEMI), results from thrombosis of an epicardial coronary artery [1,2]. Since then, therapeutic advancements have substantially reduced the acute mortality associated with STEMI, with primary percutaneous coronary intervention (PCI) now regarded as a lifesaving procedure. While we have made significant strides in effectively treating acute MI, including both STEMI and Type 1 non-ST-elevation myocardial infarction (NSTEMI), the question remains: Can we prevent its occurrence? It is well-established that primary and secondary prevention strategies, focused on the identification and management of known cardiovascular risk factors, can mitigate the incidence and risk of recurrent MI and reduce long-term cardiac mortality. Despite these efforts, adverse events still occur, even with the best available therapeutic interventions. This raises the question: How can one improve outcomes further? Over the past 25 years, novel approaches have emerged for identifying and treating high-risk plaques (HRPs) or vulnerable plaques (VPs) that are responsible for acute myocardial infarction due to coronary thrombosis. These developments offer potential treatment options aimed at reducing these adverse events [3]. This review will explore the identification and potential treatment strategies for vulnerable or high-risk atherosclerotic plaques.

2. Identification of vulnerable plaques

Thrombus formation on a tear in the fibrous cap covering a lipid-rich atherosclerotic plaque, which leads to fatal MI and the majority of sudden cardiac

death, was first demonstrated by the pathologist Chapman in 1965 [4]. Subsequent pathological analyses identified two types of plaques responsible for nearly all fatal thrombotic episodes [5]. The most common plaque type, observed in approximately two-thirds of patients, is the thin-capped fibroatheroma (TCFA). In this condition, thrombus formation occurs following the rupture of a thin fibrous cap overlying a substantial lipid-rich core infiltrated by macrophages and T-lymphocytes. In about one-quarter to one-third of cases, the responsible plaque, which is proteoglycan-rich, lacks a thin cap, and thrombus formation occurs due to a defect in the endothelial layer covering the plaque, a phenomenon referred to as plaque erosion. Both STEMI and Type 1 NSTEMI are caused by coronary thrombosis; however, in NSTEMI, the thrombus is more likely to be non-occlusive. In addition to plaque rupture and erosion, calcified nodules with subsequent thrombosis can occasionally serve as a causative mechanism, particularly in elderly patients or those with renal failure. Efforts to identify vulnerable plaques in vivo have primarily focused on the TCFA, using non-invasive imaging modalities such as CT angiography or invasive intracoronary imaging during coronary angiography. Conversely, plaque erosions are more challenging to detect before clinical events occur.

3. Identification of VPs

3.1. Non-invasive identification of VPs

Coronary computed tomography angiography (CCTA) has emerged as a pivotal tool in preventive cardiology, facilitating the early detection of coronary artery disease (CAD) in asymptomatic patients due to its ability to accurately evaluate coronary vessel anatomy and contents [6]. Furthermore, CCTA has demonstrated the capability to identify HRP features—characteristics of vulnerable plaques—prior to an acute event. These features include low-attenuation plaque (LAP), positive remodeling (PR), the “napkin-ring” sign, and the presence of spotty calcifications [7,8].

Among these HRP features, LAP and PR are particularly significant, with their presence strongly associated with ACS [9]. Motoyama et al. conducted a study involving 1059 patients suspected of having CAD, followed for 12 to 50 months. The simultaneous presence of LAP and PR in a single patient was identified as a robust predictor of ACS development (hazard ratio: 22.8; 95% CI: 6.9–75.2; $p < 0.001$) [9]. Notably, the absence of HRP features was associated with a 0% ACS rate over 4.1 years. Furthermore, Nakanishi et al. confirmed LAP as an independent predictor of ACS over a 3-year follow-up period [10]. In patients with stable ischemic heart disease, HRP features have proven valuable for risk stratification. This was exemplified in the PROMISE study, which followed 4415 stable symptomatic CAD patients over 25 months [11]. Patients with HRP features (15% of the cohort, $n = 676$) exhibited a significantly higher rate of major adverse cardiovascular events (MACE) (6.4% vs. 2.4%; HR: 2.73; 95% CI: 1.89–3.93), even after adjustments for the ASCVD risk score and the presence of significant stenosis (adjusted HR: 1.72; 95% CI: 1.13–2.62). Similarly, in a post hoc analysis of the SCOT-HEART trial, the presence of LAP was a significant predictor of myocardial infarction (MI), with a 3-fold increase in the risk of CAD-related mortality or nonfatal MI (HR: 1.99; 95% CI: 1.05–3.79).

This risk was even more pronounced when LAP coexisted with obstructive disease (HR: 11.50; 95% CI: 3.39–39.04) [12].

Although CCTA aids in the early identification of patients at risk for future MACE events, its ability to detect the specific plaque responsible for these events remains uncertain. The nested case-control ICONIC study by Chang et al. investigated 25,416 patients with baseline CCTA, identifying ACS in 234 patients matched to non-event controls [13]. Notably, 69% of ACS lesions identified via invasive angiography on follow-up lacked HRP features at baseline CCTA, and 75% were non-obstructive. This raises concerns about the reliability of pinpointing the specific vulnerable or HRP lesion likely to trigger a thrombotic event, particularly if a localized interventional strategy is to be considered for prevention.

Recent findings have also implicated pericoronary adipose tissue (PCAT) in the progression of coronary atherosclerosis and the risk of MI. A post hoc analysis of the SCOT-HEART trial demonstrated that incorporating PCAT attenuation in the right coronary artery (RCA) with a LAP burden > 4% significantly improved the prediction of MI at 5 years (HR: 11.7; $p < 0.0001$) [14]. This association was independent of total body fat, suggesting that the PCAT-CT attenuation index serves as a surrogate marker of plaque development and a predictor of future cardiovascular events.

3.2. Invasive identification of VPs

The gold standard for coronary artery anatomical and functional assessment has traditionally been invasive angiography [15]. However, this method does not provide information about the coronary vessel wall, where VPs develop and progress. Over the past three decades, intravascular imaging has emerged as a valuable tool to address this limitation of invasive angiography [16]. Several imaging modalities have been extensively evaluated in vivo, including direct angioscopy, intravascular ultrasound (IVUS), virtual histology IVUS (VH-IVUS), optical coherence tomography (OCT), near-infrared spectroscopy (NIRS), and hybrid catheter systems. These tools have significantly advanced our understanding of plaque morphology, the distinction between stable and unstable plaques, and the role of calcium in plaque pathophysiology and have facilitated the management of complex lesions during interventions.

In a study aimed at identifying vulnerable plaques likely to cause ACS, Uchida et al. used direct angioscopy to describe the TCFA as a yellow, glistening plaque indicative of a large lipid core [17]. In contrast, IVUS enabled cross-sectional evaluation of the vessel wall, providing critical information about vessel size, plaque burden, and calcification. However, the resolution of IVUS (limited to 100–150 μm) was insufficient to measure fibrous cap thickness—a key determinant of plaque stability or vulnerability. To overcome this limitation, VH-IVUS was introduced, combining IVUS with virtual histology to improve the characterization of plaque composition and facilitate TCFA identification. This approach was utilized in the Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) study [18]. However, VH-IVUS was later found to lack accuracy in TCFA identification compared with OCT [19]. OCT, with its superior axial resolution of 10–15 μm, allowed precise measurement of fibrous cap thickness, lipid content, and

thrombus. It also enabled differentiation between plaque rupture and plaque erosion in most cases. Additionally, OCT's high resolution facilitated the detection of active inflammatory processes by identifying macrophages in vulnerable plaques [16]. NIRS represents another modality for detecting plaque lipid content by identifying the chemical signatures of cholesterol and its esters. Hybrid systems combining NIRS with IVUS (NIRS-IVUS) or OCT (NIRS-OCT) have been developed to further enhance the characterization of VP features. Among these, NIRS-IVUS is the only system that has gained Food and Drug Administration (FDA) approval for the detection of VPs [16].

4. Natural history studies

Many studies identified the TCFAs as potential VPs with intravascular imaging during coronary angiography to detect whether, on follow-up, it might lead to adverse cardiovascular events; Of note, most of those trials identified TCFAs in non-culprit arteries following PCI on the culprit plaque during the index procedure (**Table 1**)—summarizes these different natural history trials.

Table 1. Summary of the natural history studies.

Uchida et al. [17]	Studied 157 patients with stable angina for 12 months. It was found that patients with yellow plaques on angioscopy are more likely to develop ACS than white plaques. Moreover, glistening yellow plaques predicted ACS in the short-term follow-up period (9 of 13 vs. 2 of 26; $p = 0.00026$).
PROSPECT I [18]	In 697 patients undergoing PCI for ACS, 2383 lesions were identified in the non-culprit vessel using VH-IVUS. Multiple predictors for plaque rupture were detected. Large vessel area, plaque burden, proximal location, right coronary artery location, and lack of calcium were associated with TCFA-related adverse events. Very few of those events were myocardial infarctions. Vessel area per mm^2 is the strongest predictor of rupture among non-left main coronary arteries (OR: 1.14; 95% CI: 1.11–1.17; $p < 0.0001$).
PROSPECT II [20]	In 898 patients who had MI within a month, 3629 non-culprit lesions were identified using NIRS-IVUS. High lipid content and large plaque burden were associated with increased risk of future cardiac events on 4-year follow-up. The presence of one or more high-risk plaque features with NIRS-IVUS had a 4-year non-culprit lesion-related MACE rate of 13.2% (95% CI 9.4–17.6).
Lipid Rich Study [21]	In 1563 patients with suspected or known CAD, NIRS-IVUS used the maximum 4 mm Lipid Core Burden Index (maxLCBI4mm) as a marker for lipid burden. About 13% of patients with a high lipid index had an event in 2 years, vs. 6% with a lower lipid index. Moreover, 3% of 664 lesions with a high lipid index had an event in 2 years. For each 100-unit increase in maxLCBI4mm at the patient level and plaque level, there was an increase in non-culprit MACE on 2 years follow-up ($p < 0.0001$).
CLIMA [22]	In 1003 patients, 1776 lipid plaques were identified using OCT. The simultaneous presence of four high-risk OCT plaque features [minimal lumen area (MLA) < 3.5 mm^2, fibrous-cap thickness (FCT) < 75 μm, lipid-arc circumferential extension > 180°, and OCT-defined macrophages] was associated with high risk for major coronary events (HR 7.54, 95% CI 3.1–18.6) on 12 months follow-up. However, those 4 features were only seen in 3.6% of the total population.
Kubo et al. [23]	Of 1378 patients, 3533 non-culprit plaques were analyzed by OCT. The presence of both LRP and TCFA carried the highest risk for developing ACS events on follow-up for 6 years (HR 19.14; 95% CI 11.74–31.20, $p < 0.001$). However, this was a single-center, non-randomized study, and medical therapy on follow-up was not clarified.
COMBINE OCT-FFR [24]	Of the 390 FFR-negative lesions, 98 (25%) had OCT evidence of TCFA. Those 98 patients carried a 13.3% risk of composite cardiac death, target vessel MI, clinically driven target lesion revascularization, or unstable angina requiring hospitalization at 18 months follow-up compared to those without OCT evidence of TCFAs in TCFA-negative groups (3.1%). Hazard ratio 4.65; 95% CI 1.99–10.89; $p < 0.001$).

Summary of findings and limitations

1) Patients were not consistently managed to achieve an LDL cholesterol level of < 70 mg/dL during follow-up, indicating suboptimal adherence to recommended treatment guidelines.

2) Thrombotic events, such as MI or cardiac death, were rare, with most endpoints classified as "soft" (e.g., progressive angina or urgent revascularization). When MIs occurred, details about the type (STEMI vs. NSTEMI) were often unspecified. Some studies included Type 2 MIs, which are not thrombotic events, further complicating the interpretation of those trials' outcomes.
3) Similar to findings from CT studies, the presence of a VP anywhere in the vasculature correlated with an increase in patient-related endpoints, emphasizing its clinical significance.

5. Interventional treatment trials for vulnerable plaques

There are several trials, most are still ongoing, that are randomizing patients with VPs to guideline-directed medical therapy (GDMT) vs. stenting + GDMT and following up for the presence of adverse events. These events are a composite of MI, cardiovascular (CV) death, and other softer endpoints as outlined above. The following table summarizes these trials (**Table 2**).

Table 2. Summary of the interventional treatment trials for vulnerable plaques.

PREVENT [25]	An RCT of 1606 patients who have >50% stenosis but non-flow limiting (FFR > 0.80) lesions and intravascular imaging evidence of vulnerable plaque. Randomized to PCI + GDMT vs GDMT alone and followed up for 2 years. The intervention arm showed a statistically significant reduction (0.4 vs. 3.4%; 95% CI: −4.4 to −1.8; $p = 0.0003$) in the primary outcome of composite cardiac death, target-vessel MI, ischemia-driven target-vessel revascularization, or hospitalization for unstable or progressive angina in patients treated with PCI+GDMT compared to OMT alone without an increase in adverse events related to the stent procedure.
INTERCLIM (ongoing) [26]	An RCT to assess the effect of OCT-guided PCI + GDMT vs. physiology-guided PCI + GDMT on the non-culprit intermediate coronary lesions in ACS patients. The primary endpoints will be a composite of cardiac death and target-vessel MI at 2- and 5-year follow-ups.
COMBINE-INTERVENE (ongoing) [27]	This study will try to answer the question of whether using OCT evidence of high-risk plaque plus fractional flow reserve (FFR) to guide revascularization with focal PCI is superior to FFR alone in patients with multivessel CAD of intermediate lesions who show vulnerable plaque features.
PROSPECT ABSORB Trial [28]	This safety study investigated a total of 182 patients with intermediate non-flow limiting lesions who had NIRS-IVUS evidence of vulnerable plaque lesions. Those lesions were randomized to PCI with bioresorbable scaffold (BVS) vs optimal medical therapy (OMT) and followed for a median of 4.1 years. Although there was a decrease in major adverse cardiac events at the lesion level among the BVS arm vs. the OMT arm, this was not significant (odds ratio: 0.38; 95% CI: 0.11 to 1.28; $p = 0.12$). Of note, BVS achieved a higher luminal area. But later, BVS was found to have a high in-stent thrombosis risk.
DEBuT-LRP study [29]	Investigated the effect of Paclitaxel-coated balloon (PCB) on the LRP (MaxLCBI4mm > 325) in non-culprit non-flow limiting lesions in 20 NSTE-ACS patients using NIRS-IVUS. After 9 months of follow-up, there was 42% reduction of maxLCBI4mm in the PCB arm (95%CI −71 to −14; $p < 0.001$) compared to the OMT alone (−18%; 95% CI −42 to 27; $p = 0.11$). Interestingly, none of the clinical events (death, MI, bleeding, repeat revascularization) occurred in the PCB arm (0%), vs. 5 (25%) events in the 20 patients in the OMT arm.

Limitations to the interventional approach for VPs

While the interventional approach to an asymptomatic vulnerable plaque to reduce subsequent adverse cardiac events is intriguing, there are several potential limitations to its routine use [3]:

1) What about 1st adverse events? These are often STEMI or sudden cardiac death, and these critical initial events are excluded from any of the above trials.
2) Plaque erosions, which account for at least 25% of STEMI cases and

potentially an even greater proportion of NSTEMI cases, are excluded from these trials. This is because plaque erosions cannot currently be identified before the occurrence of the event, limiting the scope of these studies in addressing this significant pathology.

3) In the referenced trials, the majority of endpoints in natural history studies are not myocardial infarctions but rather recurrent angina or the need for intervention. It is plausible that, in therapeutic trials, preemptive stenting would primarily reduce non-MI events rather than acute thrombotic events, provided patients are appropriately managed with guideline-directed medical therapy (GDMT) during follow-up.
4) The VP is not static, and optimal medical therapy can stabilize plaques in many instances (see discussion below).
5) While intravascular imaging continues to improve the identification of VPs, so does non-invasive imaging (and medical therapy), allowing for earlier and more effective medical management.

6. Non-invasive stabilization for vulnerable plaques

Preventive therapies targeting HRP/VP could theoretically lower MACE and overall mortality through plaque stabilization and regression. This is achieved by lowering cholesterol levels, reducing the inflammatory state, lowering thrombotic potential, altering atheroma structure from soft calcification to dense calcification, thickening the atheromatous fibrous cap, and overall plaque volume shrinkage. Recent studies have shown that statins are associated with a linear relationship between LDL-C reduction and increased fibrous cap thickness (FCT) [30]. Furthermore, statins, the primary medication utilized to lower LDL levels, promote plaque stabilization by other mechanisms as seen by other markers such as plaque atheroma volume (PAV) and total atheroma volume (TAV). In the ASTEROID trial, rosuvastatin, compared to placebo, reduced LDL-C levels and PAV [31]. Moreover, in the PARADIGM trial, high-dose statin was associated with a ~21% reduction in plaque progression, an increase in plaque calcium density, and a decrease in HRP by ~35% [32]. This linear effect of reduction is still seen even when high-dose is compared to medium-dose statins, with a reduction of PAV, TAV, and CRP levels [33]. Aggressive reduction in plaque volume was further achieved by taking LDL-C levels to substantially very low levels using PCSK-9 inhibitors [34]. It should be noted that most of these regression studies with high-dose statins are dealing with early stages of atherosclerosis and not advanced stages of atherosclerosis.

Although all of the above studies showed a reduction in plaque burden by IVUS and VH-IVUS, the modification of plaque phenotype remained lacking and was statistically insignificant. To effectively target vulnerable plaques, it is essential to study the impact of therapies on plaque composition, including changes in calcium, fibrous tissue, fibro-fatty components, and necrotic core volume. Such alterations are key to modifying plaque vulnerability and reducing the risk of adverse cardiovascular events.

In EAST-FIT, the effect of atorvastatin 5 mg vs. 20 mg dose on fibrous cap thickness was assessed using OCT in unstable angina patients [30]. The use of 20

mg/day was associated with an increase in FCT and a reduction in LDL-C and high-sensitivity CRP.

Additionally, in HUYGEN, the effect of PCSK-9 inhibitors on OCT-detected vulnerable plaques using evolocumab 420 mg/d vs placebo in ACS patients was assessed [35]. Of note, patients with FCT > 120 μm and lipid arc ≤ 90° were excluded. The primary endpoint was achieved by a minimum fibrous cap thickness of +39.0 (95% CI: 20.5–71.0 μm) with the PCSK-9 inhibitor vs. +22.0 (95% CI: 8.0–36.0 μm) in the usual treatment group; $p = 0.015$.

Another aspect of plaque stability is the calcium composition; cardiac CT and calcium score (CAC) may be the best modalities present for screening coronary artery disease and risk stratification [36]. Budoff et al. showed that asymptomatic patients with CAC > 300 had similar MACE rates as patients with established CAD [37]. However, the use of statins showed a paradoxical effect of increased coronary calcium detected by CT [38]. Non-invasive technologies like CT and FDG-PET would be essential in detecting the change in plaque composition not only in coronaries but also at the carotid and aortic levels for overall atherosclerosis response to therapy. Other markers of early atherosclerosis exist that do not involve any radiation and could also be used for screening. Atherosclerosis in the iliofemoral arteries may be the earliest sign of atherosclerosis in the body and can be readily assessed with ultrasound techniques, as seen in the PESA study [39] and in young patients < 40 years old, as seen in the PRECAD study [40].

7. Conclusion

The concept of the vulnerable or high-risk plaque as the precursor of acute thrombotic coronary events such as Type-1 NSTEMI, most STEMIs, and a proportion of sudden cardiac events has been a major contribution to CAD pathophysiology and management. It can be identified, but what is the best treatment to prevent the subsequent event? We believe that with the present technology, it is unlikely that the invasive approach will be very advantageous in reducing thrombotic events. However, a niche indication cannot be excluded. Furthermore, it remains to be seen whether other technologies, such as drug-coated balloons, might change this paradigm.

It is established that non-invasive therapies such as statins can stabilize some plaques by increasing fibrous cap thickness and by removing lipid content. However, wouldn't preventing VP development be another and possibly wiser approach? Earlier detection and treatment of atherosclerosis identified from a patient's risk factor profile and/or atherosclerosis screening (perhaps coronary artery Ca^{+2} scoring or even the demonstration of iliofemoral atherosclerosis from ultrasound) may provide enough information to proceed with statin and/or lifestyle change to prevent VP formation. These new developments in plaque formation and stabilization represent an evolving field of study that, one hopes, will lead to further reductions in cardiac mortality and morbidity.

Conflict of interest: The authors declare no conflict of interest.

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