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Preventive Percutaneous Intervention of Vulnerable Coronary Plaques

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ABSTRACT

Acute coronary syndromes and sudden cardiac death are frequently precipitated by the disruption and subsequent thrombotic occlusion of structurally vulnerable coronary plaques, most notably thin-cap fibroatheromas characterized by a large necrotic lipid core and a thin fibrous cap. A substantial proportion of these events arise from non-flow-limiting, hemodynamically insignificant lesions that are clinically silent prior to rapid destabilization. In addition to plaque rupture, thrombotic events may also result from superficial erosion or protruding calcified nodules. Conventional coronary angiography lacks the resolution and tissue characterization capability required to identify such high-risk morphological features, whereas advanced intravascular imaging modalities enable detailed plaque assessment. The detection of plaques with high-risk features has prompted investigation into prophylactic interventional strategies aimed at plaque stabilization. Emerging clinical data suggest that targeted treatment of vulnerable plaques may attenuate progression to acute coronary events. In conclusion, this review explores the evolving role of advanced imaging in identifying and potentially managing high-risk atherosclerotic lesions, with important implications for improving long-term cardiovascular outcomes.

Key words: *Coronary artery disease; Percutaneous coronary intervention; Vulnerable plaques; Drug-eluting stents.*

Introduction

Cardiovascular disease is the leading cause of mortality worldwide, with coronary artery disease being a significant contributor [1]. Vulnerable plaques in coronary arteries often lead to acute coronary syndromes (ACS), myocardial infarction (MI), or sudden cardiac death [2]. These plaques, characterized by large plaque burdens but often appearing non-obstructive on angiography due to positive remodelling [3], pose challenges for identification and management. Current guidelines focus on revascularizing flow-limiting lesions [4–6], leaving non-flow-limiting vulnerable plaques untreated, despite their considerable contribution to ACS. Standard treatments for obstructive lesions have uncertain roles for non-flow-limiting yet high-risk plaques. Potential benefits of percutaneous coronary intervention (PCI) may include thickening the fibrous cap and delipidating the lesion to reduce rupture and thrombus formation [7]. Emerging evidence suggests that preventive PCI could stabilize vulnerable plaques and lower the risk of adverse events[8,9]. However, concerns remain about the risks, magnitude of benefit and costs associated with these procedures. This review aims to: (i) define the pathophysiology of ACS and the role of vulnerable plaques; (ii) describe current imaging modalities for diagnosis; (iii) highlight management approaches and guidelines; and (iv) understand the potential for interventional techniques, including preventive PCI, in reducing future cardiac events.

Pathophysiology of ACS

Acute coronary events are primarily caused by thrombus formation triggered by rupture or erosion of atherosclerotic plaques[10]. Vulnerable plaques, particularly thin-cap fibroatheromas (TCFAs), are characterized by a lipid-rich core and thin fibrous cap, with their stability influenced by local inflammation, fibrous cap thickness, and lipid burden[11] . These high-risk plaques are commonly located in the proximal and mid segments of the left anterior descending and circumflex arteries, while plaques in the right coronary artery are more diffusely distributed[11,12]. Intravascular imaging techniques can identify such morphologic features prior to plaque disruption.

Plaque erosion, another major contributor to ACS, occurs when endothelial cells are lost over an intact cap, promoting thrombus formation without rupture[13]. Erosion is more prevalent in younger patients and women, and is associated with fibrotic, less lipid-laden plaques. Although risk factors such as smoking and hypertension contribute to endothelial damage, the precise triggers for erosion remain uncertain[14]. Currently, no imaging modality reliably predicts erosion-prone plaques before events occur.

Eruptive calcified nodules (ECNs) represent a less common but significant mechanism of ACS, involving protruding calcified fragments that disrupt endothelial integrity and trigger thrombosis[15]. These lesions, detectable via intravascular ultrasound (IVUS) and optical coherence tomography (OCT), are more resistant to conventional medical therapy and stenting due to their rigidity[13,15].

Rupture-induced thrombus formation involves platelet activation and aggregation, followed by activation of the coagulation cascade and fibrin clot development [14]. This can lead to partial or complete coronary occlusion, with varying clinical presentations from unstable angina to ST-elevation MI, as shown in Figure 1. Understanding these distinct mechanisms is critical for developing predictive strategies and improving ACS management and prevention[16].

Definition and Clinical Implications of Vulnerable Plaques

The concept of vulnerable plaques has evolved from autopsy-based identification of lesions causing acute MI and sudden cardiac death, to recognizing plaques that predispose patients to future cardiovascular events[17], as summarized in Table 1. TCFAs are the most studied vulnerable plaques, prone to rupture and thrombosis, often leading to sudden cardiac events[17,18]. Autopsy studies shifted the clinical focus from luminal stenosis to plaque composition and stability, demonstrating that even angiographically mild lesions may cause fatal events if they rupture[19,20].

TCFAs are defined by a fibrous cap less than sixty-five micrometers thick, separating a large lipid core from the arterial lumen. This cap is weakened by infiltration of inflammatory cells - macrophages, T-cells, and mast cells - which release matrix metalloproteinases that degrade structural proteins, increasing rupture risk[16,21] . The necrotic lipid core, composed of free cholesterol, foam cells, and cellular debris, further contributes to plaque instability. Neovascularization increases the likelihood of intraplaque hemorrhage, while local hemodynamic forces, such as low shear stress, promote formation, and high shear stress may trigger rupture[22,23], as illustrated in Figure 2.

Plaque rupture and ensuing thrombosis remain the leading cause of ACS presentations[24] . Histopathological studies of sudden cardiac death consistently reveal thin-capped, inflamed ruptured plaques, present in over 75% of fatal MI cases[25–28] . Beyond ACS, non-obstructive plaque rupture with healing contributes to chronic ischemia, stable angina, and heart failure [29,30]. Vulnerable plaques are also implicated in microvascular dysfunction and microvascular angina, with imaging studies showing a high burden of inflamed, lipid-rich plaques in these patients [31,32]. Importantly, while rupture causes acute events, gradual plaque progression - reflected in plaque burden and minimal lumen area (MLA) - remains a major driver of symptoms and need for revascularization[25,33].

Non-invasive Assessment of Vulnerable Plaques

Identifying vulnerable plaques before they cause significant clinical events is a key goal in cardiovascular medicine. Several non-invasive methods are now increasingly used to assess plaque vulnerability in clinical practice. These techniques aim to detect high-risk plaques that may not yet cause significant symptoms but are prone to rupture or erosion, triggering thrombosis. Imaging modalities such computed tomography angiography (CTA) and positron emission tomography (PET), as well biomarker-based approaches have shown promise in evaluating vulnerable plaques.

CTA provides detailed, non-invasive imaging of coronary arteries and can detect high-risk plaque features, such as low attenuation, positive remodeling, spotty calcification, and the napkin-ring sign [34]. In the SCOT-HEART trial substudy, patients with obstructive disease and adverse plaque features had a 10-fold higher risk of coronary death or nonfatal MI compared to those with normal arteries (HR: 11.50; 95% CI: 3.39–39.04; $p < 0.01$) [35]. While CTA lacks the resolution to detect inflammation or small plaques, it remains valuable for identifying rupture-prone plaques when integrated with clinical risk assessment. PET imaging, in combination with radiolabelled tracers (such as 18F-fluorodeoxyglucose, or FDG**)**, can assess plaque inflammation, a key feature of vulnerable plaques. Increased FDG uptake in plaques reflects active inflammation, that may indicate a higher likelihood of plaque rupture [36]. PET can also be used in conjunction with CT or MRI to provide a comprehensive picture of plaque burden and activity.

Inflammation plays a central role in plaque vulnerability. Non-invasive blood tests for markers like C-reactive protein (CRP)**,** interleukins (IL-6, IL-1β)**,** tumour necrosis factoralpha (TNF-α), and myeloperoxidase (MPO) can help assess systemic inflammation and predict vulnerable plaque rupture[37] . Emerging evidence suggests that circulating microRNAs, particularly those involved in endothelial function and plaque stability, may serve as non-invasive markers for lesion vulnerability[38]. Elevated levels of these biomarkers and small molecules may be associated with plaque instability and an increased risk of cardiovascular events, though more investigation into this space is required.

Functional Assessment of Vulnerable Plaques

Fractional flow reserve (FFR) and other non-hyperemic measures of vessel physiology such as the instantaneous wave-free ratio (iFR) are valuable tools for evaluating equivalents to ischemia in coronary arteries[39]. These have been correlated to adverse events, enabling clinicians to focus interventions on plaques that are truly hemodynamically significant [40]. Although FFR and other resting indices do not significantly impact hard clinical outcomes like death or MI and cannot identify non-flow-limiting vulnerable plaques, it is worth noting that these tools still provide a benefit by reducing unnecessary procedures [41], since the probability of a vulnerable plaque is higher in an obstructive plaque when compared to non-obstructive plaques[42]. However, further and larger studies, using both invasive and non-invasive hyperemic indices are required.

Intravascular Imaging of Vulnerable Plaques

The detection and characterization of vulnerable plaques is critical for prognostication and for potentially preventing ACS[43]. Several advanced imaging modalities have been developed to identify vulnerable plaque features. Among them, gray-scale and radiofrequency IVUS, near-infrared spectroscopy-IVUS (NIRS-IVUS), and OCT each provide unique insights into plaque composition and structure[44–50]. The main characteristics of these imaging modalities for the detection of vulnerable plaques are summarized in Table 2.

The integration of intravascular imaging into clinical practice has major implications for assessing and managing coronary atherosclerosis. Prior multicentre trials have demonstrated that identifying vulnerable plaques may enable targeted therapies to prevent rupture and thrombosis[51,52] . In PROSPECT, involving 697 ACS patients across 37 centers, multimodal imaging revealed that both culprit and nonculprit lesions contributed equally to major adverse cardiac events (MACE), with a 3-year MACE rate of 20.4%. Many nonculprit plaques appeared mild on angiography but had a plaque burden ≥70%, MLA ≤4.0 mm², or were TCFAs [51]. PROSPECT II assessed 3,629 lesions in 898 patients using IVUS and NIRS-IVUS and found that 13.2% experienced MACE, with 8.0% linked to untreated nonculprit lesions. Predictors included lipid core burden index ≥324.7, large plaque burden (OR 3.49), and MLA ≤4.0 mm² (OR 6.00)[52].

Nonetheless, all imaging techniques have limitations. IVUS struggles to penetrate calcified lesions, reducing accuracy in assessing calcium burden[15,22,53]. The CLIMA study, evaluating OCT criteria in nonculprit LAD lesions, found a composite endpoint rate of just 3.7%, with positive predictive values (PPVs) ranging from 5.3% to 19.4%[54] . Similarly, in the COMBINE FFR-OCT trial, the 18-month MACE rate was 13% among TCFA-positive, FFR-negative patients, with a PPV of 26.4%[17] . These low PPVs, possibly due to small sample sizes, highlight the need for larger studies.

Procedural risks such as vasospasm, dissection, or thrombosis, though rare, are concerns with intracoronary imaging [55]. Cost and resource requirements further limit widespread access [56,57]. Notably, only NIRS-IVUS currently holds United States Food and Drug Administration (FDA) approval for identifying vulnerable plaques, underscoring its clinical value. As technology advances and more evidence emerges, broader access and safer applications may expand the benefits of intracoronary imaging in routine practice [58].

Management of Vulnerable Plaques

While plaque morphology plays a central role in the pathogenesis of ACS, the clinical significance of a vulnerable plaque is often compounded by the patient's overall cardiovascular risk profile. Importantly, a plaque's vulnerability is not solely determined by its compositiotsn but also by the patient's systemic factors, such as hyperlipidemia, hypertension, diabetes, and smoking, that contribute to plaque instability, giving rise to the concept of a “vulnerable patient” [59] . Once identified, the current management of these patients requires a multifaceted approach. These involve the use of medical therapy, lifestyle changes and interventional strategies, and early detection and characterization of high-risk plaques using functional assessments and imaging can guide treatment decisions, allowing for more personalized and effective management.

Medical therapy

Medical management typically includes the use of systemic pharmacologic treatments that lower cholesterol levels, prevent clot formation, improve endothelial function and reduce local inflammation.

Statins are the cornerstone of managing vulnerable plaques. By lowering low-density lipoprotein (LDL) cholesterol levels, statins not only reduce plaque formation but also stabilize existing plaques by decreasing inflammation and promoting plaque regression [60]. High-dose statin therapy has been shown to reduce the risk of major cardiovascular events and improve plaque stability[61,62], particularly in patients with high cholesterol and atherosclerotic disease. In addition to statins, other lipid-lowering agents such as ezetimibe or

PCSK9 inhibitors may be considered in high-risk patients to further lower LDL cholesterol and stabilize plaques [63]. Some recent studies have shown that statins and PCSK9 inhibitors can thicken the fibrous cap of TCFA and reduce vulnerable plaque lipid content[64] , that presumably would passivate these high-risk lesions.

Antiplatelet therapies like aspirin and P2Y12 inhibitors help prevent platelet aggregation, a crucial step in thrombus formation following plaque rupture [65]. Dual antiplatelet therapy (DAPT) is particularly important after PCI but there is also data for long-term use in high-risk patients to prevent recurrent cardiovascular events, including MI and unstable angina.

ACE inhibitors have been shown to reduce the risk of plaque rupture and prevent future cardiovascular events by lowering blood pressure and reducing vascular inflammation [66]. Beta-blockers, on the other hand, are critical in managing vulnerable plaques, especially after an ACS by reducing myocardial oxygen demand. This limits the stress on vulnerable plaques and help prevent arrhythmias. These medications are particularly important in the post-acute phase to improve outcomes in patients with unstable coronary artery disease.

The CANTOS trial demonstrated that canakinumab significantly reduced the risk of cardiovascular events in patients with elevated C-reactive protein (CRP) levels, a marker of systemic inflammation[67]. In the COLCOT trial, the effect of low-dose colchicine on cardiovascular events in patients with recent MI was studied. The trial found that colchicine significantly reduced the risk of MACE by 23%, demonstrating its potential as an effective anti-inflammatory therapy in post-MI patients [68]. Inflammatory processes are key drivers of plaque instability, and targeting these pathways may further reduce the risk of plaque rupture and cardiovascular events.

Lifestyle Modifications

Lifestyle interventions, a heart-healthy diet, regular physical activity, diabetes control and smoking cessation, are crucial for reducing overall cardiovascular risk by reducing inflammation, and enhancing endothelial function. Medical treatments, when combined with proper lifestyle changes, form the basis of an effective strategy to prevent plaque rupture and reduce adverse cardiovascular events. However, no randomized trials with clinical endpoints evaluating the effect of lifestyle changes have been performed specifically in patients with non-ruptured vulnerable plaques.

Interventional Management

While systemic treatment can help stabilize lipid-rich plaques, it may not be sufficient to reduce the risk of further cardiovascular events, that remains significant in a proportion of patients. One potential approach to reducing the risk of recurrent cardiovascular events in patients with ACS or high-risk patients with stable coronary disease (e.g. diabetics) is through preventive revascularization of untreated vulnerable plaques that are often present and appear angiographically mild, but by intravascular imaging are typically severe, positively remodelled lesions[69].

Current American and European guidelines do not recommend revascularization for vulnerable plaques that do not cause ischemia[6,70]. The concept of preventive PCI is supported by prior small imaging studies that have shown that using metallic stents or bioresorbable vascular scaffold (BVS) on vulnerable plaques can thicken the fibrous cap and normalize wall shear stress simply while enlarging the coronary lumen[71,72]. The Preventive Angioplasty in Myocardial Infarction (PRAMI) trial randomized 465 STEMI patients with multivessel disease to preventive PCI of non-culprit lesions or culprit-only PCI. Preventive PCI significantly reduced the primary composite outcome of cardiac death, nonfatal MI, or refractory angina (9% vs. 23%; HR 0.35, 95% CI 0.21–0.58; $p < 0.001$)[73]. Nonfatal MI and refractory angina were also significantly lower. Despite early termination, PRAMI was the first trial to show that immediate preventive PCI may reduce future ischemic events in STEMI patients. Two recent randomized trials, PROSPECT ABSORB and PREVENT, have since evaluated the potential role of invasive treatment for high-risk, non-flow-limiting lesions. These are summarized in Table 3.

PROSPECT ABSORB was a pilot, lesion-level randomized trial assessing the safety and efficacy of percutaneous coronary intervention (PCI) using Absorb BVS in patients with angiographically mild, non-ischemic but vulnerable plaques [9]. A total of 182 patients with high plaque burden lesions (≥65%) and negative FFR or iFR were randomized to receive BVS plus guideline-directed medical therapy (GDMT) or GDMT alone. The median diameter stenosis was 41.6%, plaque burden 73.7%, and $maxLCBImm^4$ 334.2. At follow-up, lesions treated with BVS had significantly larger mean MLA (6.9 ± 2.6 mm² vs. 3.0 ± 1.0 mm²; $p < 0.01$) and lower lipid content (median $maxLCBImm^4$: 62.0 vs. 268.8; $p < 0.01$). A neocap of intimal hyperplasia (median thickness 210 μm) formed over BVS, consistent with plaque stabilization. While not powered for clinical events, lesion-related MACE was numerically reduced from 10.7% (GDMT) to 4.3% (BVS) over 4 years (OR 0.38, 95% CI: 0.11–1.30; $p = 0.12$).

PREVENT, a multicenter, open-label randomized controlled trial presented last year, enrolled 1,606 patients with 1,672 vulnerable plaque lesions identified using OCT, IVUS, and NIRS-IVUS [74]. Inclusion criteria included MLA <4.0 mm², plaque burden >70%, TCFA, or $maxLCBImm^4$ >315. Preventive PCI was performed in 91% of patients - 33% with BVS and 67% with everolimus-eluting stents. At 2 years, the primary endpoint (composite of cardiac death, target-vessel MI, ischemia-driven revascularization, or hospitalization) occurred in

0.4% of PCI patients vs. 3.4% with GDMT (difference: –3.0%, 95% CI: –4.4 to –1.8; p = 0.0003). In post-hoc analysis, all-cause death or target-vessel MI occurred in 0.6% vs. 1.9% (difference: –1.3%, 95% CI: –2.4 to –0.2), supporting preventive PCI for plaque passivation (Figure 3).

The PREVENT trial also showed a sustained reduction in target vessel failure (TVF) over 7 years with preventive PCI for FFR-negative, >50% stenosis lesions[74]. Outcomes were significantly better with everolimus-eluting stents (EES) than bioresorbable scaffolds (BVS), which are no longer available. Broader use of NIRS-IVUS and OCT might have improved lesion selection. While not all vulnerable plaques were treated, this is the first large trial suggesting a role for PCI in non-flow-limiting, high-risk plaques, highlighting the potential of focal intervention for secondary prevention.

There are still many questions left unanswered about the role of preventative PCI for patients with non-obstructive disease. In the PREVENT trial, the observed primary outcome rates were notably lower than expected in both groups, and the positive predictive value of most of these “high risk” features is relatively low. This may indicate that the study was underpowered, although the point estimates were accurate. Another limitation is that most participants had chronic coronary syndromes. It is important to consider that vulnerable plaques may be more common and biologically active in patients with troponin-positive disease.

To fully understand the effectiveness and safety of preventive PCI, further research and clinical trials are needed. In fact, the use of stents or scaffolds in treating vulnerable plaque lesions may lead to potential risks and complications. These include fibrous cap rupture, that could lead to acute MI by the release and embolization of the lipid-rich core, and impaired reendothelialization that may increase the risk of device thrombosis, particularly in the presence of prothrombotic conditions associated with ACS or in the longer term[50,75].

Bleeding risks from prolonged DAPT, and the potential economic burden of PCI also needs to be considered. The safety and effectiveness of preventive PCI must be proven in additional large-scale, randomized trials before this therapy is to be widely recommended.

Research Gaps and Possible Future Directions

Although invasive plaque characterization has been used in interventional cardiology for years, its clinical importance has only recently been appreciated with the now clear understanding of the relationship between atherosclerotic plaque morphology and patient prognosis[76]. At present, the optimal screening modality for high-risk plaques is also yet to be determined. Several randomized trials are underway as summarised in Table 4, with aims to demonstrate that preventive PCI is safe and improves long-term outcomes.

The DEBuT-LRP study evaluated the safety and efficacy of prophylactic PCI using drug-coated balloons (DCB) on lipid-rich, non-obstructive plaques in NSTEMI patients[77]. After PCI of all culprit lesions, three-vessel NIRS-IVUS was performed to identify lipid-rich plaques (LRP), defined by a $maxLCBImm^4$ ≥325. Patients with ≥1 LRP received DCB treatment under nominal inflation across the entire LRP plus 5 mm margins. At 9 months, treated LRPs showed a significant reduction in $maxLCBImm^4$ (from 397 [IQR: 299–527] to 211 [106–349], $p < 0.001$), while untreated plaques did not. No LRP-related events occurred in treated lesions within 12 months, suggesting safety and potential efficacy, though further trials are needed.

The COMBINE INTERVENE trial (NCT05333068) is the first to randomize patients to PCI based on combined FFR and OCT criteria versus FFR alone. Enrolling 1,222 patients with multivessel coronary artery disease, it includes patients with vulnerable plaques defined by OCT as thin-cap fibroatheroma (TCFA ≤75 μm), plaque rupture, erosion with ≥70% area stenosis, or MLA <2.5 mm^2. All ischemic and vulnerable lesions are treated with PCI. The primary outcome is a composite of cardiac death, MI, and clinically-driven revascularization at 24 months.

FAVOR V AMI (NCT05669222) is a 5,000-patient, multicenter randomized, sham-controlled trial comparing a novel FAST (Functional and Angiography-derived Strain Integration Technique) approach to standard care post-STEMI. In the experimental arm, lesions with μQFR ≤0.80 or radial wall strain ≥13% are treated with PCI. The primary endpoint is major adverse cardiovascular events (MACE) at up to five years.

The VULNERABLE trial is a prospective, multicenter RCT assessing whether preventive PCI plus optimal medical therapy (OMT) improves outcomes versus OMT alone in STEMI patients with multivessel disease[78] . Patients undergo FFR and OCT post-primary PCI. If OCT detects vulnerable plaque (e.g., TCFA) in a non-ischemic intermediate lesion (FFR >0.80), patients are randomized. The primary endpoint is TVF at four years in 600 patients.

Lastly, the INTERCLIMA trial (NCT05027984) compares OCT-guided versus physiology-guided PCI strategies in ACS patients with intermediate (40–70% stenosis) non-culprit lesions. It aims to enroll 1,420 participants across ~40 global sites. In the OCT arm, lesions with plaque vulnerability (MLA <3.5 mm², lipid arc >180°, macrophage clusters) undergo PCI; in the physiology arm, treatment is based on FFR/iFR. The primary endpoint is cardiac death or spontaneous target vessel MI at two and five years.

These trials will clarify whether treating non-obstructive but high-risk plaques reduces future cardiac events. They will also assess the long-term safety of PCI in this setting. As stent technology and alternative modalities like DCBs, bioadaptors, and thin-strut bioresorbable scaffolds evolve, these studies may help define the next frontier in preventive coronary intervention.

Conclusions

Vulnerable atherosclerotic coronary plaques are associated with a worsened prognosis during 3-5-year follow-up. These can be identified with modern high-resolution imaging techniques to provide prognostic guidance and potentially tailor therapy, at a minimum with intensive pharmacologic treatment and lifestyle modifications. At present, routine percutaneous intervention of vulnerable plaques is not recommended or indicated. However, ongoing and future studies will determine whether preventive PCI treatment of these non-flow-limiting but high-risk lesions can safely improve patient outcomes and is cost-effective.

REFERENCES

1. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Delling FN, Djousse L, Elkind MSV, Ferguson JF, Fornage M, Khan SS, Kissela BM, Knutson KL, Kwan TW, Lackland DT, Lewis TT, Lichtman JH, Longenecker CT, Loop MS, Lutsey PL, Martin SS, Matsushita K, Moran AE, Mussolino ME, Perak AM, Rosamond WD, Roth GA, Sampson UKA, Satou GM, Schroeder EB, Shah SH, Shay CM, Spartano NL, Stokes A, Tirschwell DL, VanWagner LB, Tsao CW, American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. *Circulation* 2020;141:e139–e596.

2. Gaba P, Gersh BJ, Muller J, Narula J, Stone GW. Evolving concepts of the vulnerable atherosclerotic plaque and the vulnerable patient: implications for patient care and future research. *Nat Rev Cardiol* 2023;20:181–196.

3. Mol J-Q, Volleberg RHJA, Belkacemi A, Hermanides RS, Meuwissen M, Protopopov AV, Laanmets P, Krestyaninov OV, Dennert R, Oemrawsingh RM, Kuijk J-P van, Arkenbout K, Heijden DJ van der, Rasoul S, Lipsic E, Rodwell L, Camaro C, Damman P, Roleder T, Kedhi E, Leeuwen MAH van, Geuns R-JM van, Royen N van. Fractional Flow Reserve-Negative High-Risk Plaques and Clinical Outcomes After Myocardial Infarction. *JAMA Cardiol* 2023;8:1013–1021.

4. Neumann F-J, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet J-P, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO, ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J* 2019;40:87–165.

5. Lawton JS, Tamis-Holland JE, Bangalore S, Bates ER, Beckie TM, Bischoff JM, Bittl JA, Cohen MG, DiMaio JM, Don CW, Fremes SE, Gaudino MF, Goldberger ZD, Grant MC, Jaswal JB, Kurlansky PA, Mehran R, Metkus TS, Nnacheta LC, Rao SV, Sellke FW, Sharma G, Yong CM, Zwischenberger BA. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart

Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2022;145:e18–e114.

6. Virani SS, Newby LK, Arnold SV, Bittner V, Brewer LC, Demeter SH, Dixon DL, Fearon WF, Hess B, Johnson HM, Kazi DS, Kolte D, Kumbhani DJ, LoFaso J, Mahtta D, Mark DB, Minissian M, Navar AM, Patel AR, Piano MR, Rodriguez F, Talbot AW, Taqueti VR, Thomas RJ, Diepen S van, Wiggins B, Williams MS, Peer Review Committee Members. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *Circulation* 2023;148:e9–e119.

7. Rodés-Cabau J, Bertrand OF, Larose E, Déry J-P, Rinfret S, Bagur R, Proulx G, Nguyen CM, Côté M, Landcop M-C, Boudreault J-R, Rouleau J, Roy L, Gleeton O, Barbeau G, Noël B, Courtis J, Dagenais GR, Després J-P, DeLarochellière R. Comparison of Plaque Sealing With Paclitaxel-Eluting Stents Versus Medical Therapy for the Treatment of Moderate Nonsignificant Saphenous Vein Graft Lesions. *Circulation* 2009;120:1978–1986. Available at: https://www.ahajournals.org/doi/full/10.1161/circulationaha.109.874057. Accessed May 27, 2024.

8. Mol J-Q, Bom MJ, Damman P, Knaapen P, Royen N van. Pre-Emptive OCT-Guided Angioplasty of Vulnerable Intermediate Coronary Lesions: Results from the Prematurely Halted PECTUS-Trial. *J Intervent Cardiol* 2020;2020:8821525. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7737444/. Accessed May 27, 2024.

9. Stone GW, Maehara A, Ali ZA, Held C, Matsumura M, Kjøller-Hansen L, Bøtker HE, Maeng M, Engstrøm T, Wiseth R, Persson J, Trovik T, Jensen U, James SK, Mintz GS, Dressler O, Crowley A, Ben-Yehuda O, Erlinge D, PROSPECT ABSORB Investigators. Percutaneous Coronary Intervention for Vulnerable Coronary Atherosclerotic Plaque. *J Am Coll Cardiol* 2020;76:2289–2301.

10. Mintz GS, Popma JJ, Pichard AD, Kent KM, Satler LF, Chien Chuang Y, DeFalco RA, Leon MB. Limitations of Angiography in the Assessment of Plaque Distribution in Coronary Artery Disease. *Circulation* 1996;93:924–931. Available at: https://www.ahajournals.org/doi/full/10.1161/01.cir.93.5.924. Accessed May 27, 2024.

11. Hau WKT, Yan BPY. Fig. 14.3, [Thin-cap fibroatheroma (TCFA) is the...]. 2018. Available at: https://www.ncbi.nlm.nih.gov/books/NBK543577/figure/ch14.Fig3/. Accessed May 27, 2024.

12. Niccoli G, Montone RA, Di Vito L, Gramegna M, Refaat H, Scalone G, Leone AM, Trani C, Burzotta F, Porto I, Aurigemma C, Prati F, Crea F. Plaque rupture and intact fibrous cap assessed by optical coherence tomography portend different outcomes in patients with acute coronary syndrome. *Eur Heart J* 2015;36:1377–1384.

13. Jia H, Abtahian F, Aguirre AD, Lee S, Chia S, Lowe H, Kato K, Yonetsu T, Vergallo R, Hu S, Tian J, Lee H, Park S-J, Jang Y-S, Raffel OC, Mizuno K, Uemura S, Itoh T, Kakuta T, Choi S-Y, Dauerman HL, Prasad A, Toma C, McNulty I, Zhang S, Yu B, Fuster V, Narula J, Virmani R, Jang I-K. In vivo diagnosis of plaque erosion and calcified nodule in patients with acute coronary syndrome by intravascular optical coherence tomography. *J Am Coll Cardiol* 2013;62:1748–1758.

14. Shah PK. Mechanisms of plaque vulnerability and rupture. *J Am Coll Cardiol* 2003;41:S15–S22. Available at: https://www.sciencedirect.com/science/article/pii/S0735109702028346. Accessed May 27, 2024.

15. Alfonso F, Joner M. Untangling the Diagnosis and Clinical Implications of Calcified Coronary Nodules. *JACC Cardiovasc Imaging* 2017;10:892–896.

16. Finn AV, Nakano M, Narula J, Kolodgie FD, Virmani R. Concept of vulnerable/unstable plaque. *Arterioscler Thromb Vasc Biol* 2010;30:1282–1292.

17. Kedhi E, Berta B, Roleder T, Hermanides RS, Fabris E, IJsselmuiden AJJ, Kauer F, Alfonso F, Birgelen C von, Escaned J, Camaro C, Kennedy MW, Pereira B, Magro M, Nef H, Reith S, Al Nooryani A, Rivero F, Malinowski K, De Luca G, Garcia Garcia H, Granada JF, Wojakowski W. Thin-cap fibroatheroma predicts clinical events in diabetic patients with normal fractional flow reserve: the COMBINE OCT-FFR trial. *Eur Heart J* 2021;42:4671–4679.

18. Sakamoto A, Cornelissen A, Sato Y, Mori M, Kawakami R, Kawai K, Ghosh SKB, Xu W, Abebe BG, Dikongue A, Kolodgie FD, Virmani R, Finn AV. Vulnerable Plaque in Patients with Acute Coronary Syndrome: Identification, Importance, and Management. 2021. Available at: https://www.uscjournal.com/articles/vulnerable-plaque-patients-acute-coronary-syndrome-identification-importance-and. Accessed May 27, 2024.

19. Holmström L, Juntunen S, Vähätalo J, Pakanen L, Kaikkonen K, Haukilahti A, Kenttä T, Tikkanen J, Viitasalo V, Perkiömäki J, Huikuri H, Myerburg RJ, Junttila J. Plaque histology and myocardial disease in sudden coronary death: the Fingesture study. *Eur Heart J* 2022;43:4923–4930.

20. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. *Arterioscler Thromb Vasc Biol* 2000;20:1262–1275.

21. Song B, Bie Y, Feng H, Xie B, Liu M, Zhao F. Inflammatory Factors Driving Atherosclerotic Plaque Progression New Insights. *J Transl Intern Med* 2022;10:36–47.

22. Sakamoto A, Suwa K, Kawakami R, Finn AV, Maekawa Y, Virmani R, Finn AV. Significance of Intra-plaque Hemorrhage for the Development of High-Risk Vulnerable Plaque: Current Understanding from Basic to Clinical Points of View. *Int J Mol Sci* 2023;24:13298.

23. Dhawan SS, Avati Nanjundappa RP, Branch JR, Taylor WR, Quyyumi AA, Jo H, McDaniel MC, Suo J, Giddens D, Samady H. Shear stress and plaque development. *Expert Rev Cardiovasc Ther* 2010;8:545–556.

24. Braunwald E. Unstable Angina and Non–ST Elevation Myocardial Infarction. *Am J Respir Crit Care Med* 2012;185:924–932. Available at: https://www.atsjournals.org/doi/10.1164/rccm.201109-1745CI. Accessed May 27, 2024.

25. Narula J, Nakano M, Virmani R, Kolodgie FD, Petersen R, Newcomb R, Malik S, Fuster V, Finn AV. Histopathologic characteristics of atherosclerotic coronary disease and

implications of the findings for the invasive and noninvasive detection of vulnerable plaques. *J Am Coll Cardiol* 2013;61:1041–1051.

26. Luo X, Lv Y, Bai X, Qi J, Weng X, Liu S, Bao X, Jia H, Yu B. Plaque Erosion: A Distinctive Pathological Mechanism of Acute Coronary Syndrome. *Front Cardiovasc Med* 2021;8:711453.

27. Liu X, He W, Hong X, Li D, Chen Z, Wang Y, Chen Z, Luan Y, Zhang W. New insights into fibrous cap thickness of vulnerable plaques assessed by optical coherence tomography. *BMC Cardiovasc Disord* 2022;22:484.

28. Bentzon JF, Otsuka F, Virmani R, Falk E. Mechanisms of Plaque Formation and Rupture. *Circ Res* 2014;114:1852–1866. Available at: https://www.ahajournals.org/doi/10.1161/CIRCRESAHA.114.302721. Accessed May 27, 2024.

29. Srikanth S, Ambrose JA. Pathophysiology of coronary thrombus formation and adverse consequences of thrombus during PCI. *Curr Cardiol Rev* 2012;8:168–176.

30. Badimon L, Padró T, Vilahur G. Atherosclerosis, platelets and thrombosis in acute ischaemic heart disease. *Eur Heart J Acute Cardiovasc Care* 2012;1:60–74.

31. Aldiwani H, Mahdai S, Alhatemi G, Bairey Merz CN. Microvascular Angina: Diagnosis and Management. *Eur Cardiol Rev* 2021;16:e46. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8674627/. Accessed May 27, 2024.

32. Pellegrini D, Konst R, Oord S van den, Dimitriu-Leen A, Mol J-Q, Jansen T, Maas A, Gehlmann H, Geuns R-J van, Elias-Smale S, Royen N van, Damman P. Features of atherosclerosis in patients with angina and no obstructive coronary artery disease. Available at: https://eurointervention.pcronline.com/article/features-of-atherosclerosis-in-patients-with-angina-and-no-obstructive-coronary-artery-disease. Accessed May 27, 2024.

33. Honda S, Kataoka Y, Kanaya T, Noguchi T, Ogawa H, Yasuda S. Characterization of coronary atherosclerosis by intravascular imaging modalities. *Cardiovasc Diagn Ther* 2016;6:368–381.

34. Kolossváry M, Szilveszter B, Merkely B, Maurovich-Horvat P. Plaque imaging with CT-a comprehensive review on coronary CT angiography based risk assessment. *Cardiovasc Diagn Ther* 2017;7:489–506.

35. Amin SB, Stillman AE. SCOT-HEART trial: reshuffling our approach to stable ischemic heart disease. *Br J Radiol* 2020;93:20190763.

36. Lee R, Seok JW. An Update on [18F]Fluoride PET Imaging for Atherosclerotic Disease. *J Lipid Atheroscler* 2020;9:349–361. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7521973/. Accessed June 29, 2025.

37. Fernández-Alvarez V, Linares-Sánchez M, Suárez C, López F, Guntinas-Lichius O, Mäkitie AA, Bradley PJ, Ferlito A. Novel Imaging-Based Biomarkers for Identifying Carotid Plaque Vulnerability. *Biomolecules* 2023;13:1236. Available at: https://www.mdpi.com/2218-273X/13/8/1236. Accessed May 27, 2024.

38. Teixeira AR, Ferreira VV, Pereira-da-Silva T, Ferreira RC. The role of miRNAs in the diagnosis of stable atherosclerosis of different arterial territories: A critical review. *Front Cardiovasc Med* 2022;9:1040971.

39. Balanescu S. Fractional Flow Reserve Assessment of Coronary Artery Stenosis. *Eur Cardiol Rev* 2016;11:77–82. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6159406/. Accessed July 24, 2024.

40. Asano T, Tanigaki T, Ikeda K, Ono M, Yokoi H, Kobayashi Y, Kozuma K, Tanaka N, Kawase Y, Matsuo H. Consensus document on the clinical application of invasive functional coronary angiography from the Japanese Association of Cardiovascular Intervention and Therapeutics. *Cardiovasc Interv Ther* 2024;39:109–125. Available at: https://doi.org/10.1007/s12928-024-00988-5. Accessed July 24, 2024.

41. Hong D, Kim H, Lee H, Lee J, Cho J, Shin D, Lee SH, Kim HK, Choi KH, Park TK, Yang JH, Song YB, Hahn J-Y, Choi S-H, Gwon H-C, Kang D, Lee JM. Long-Term Cost-Effectiveness of Fractional Flow Reserve-Based Percutaneous Coronary Intervention in Stable and Unstable Angina. *JACC Adv* 2022;1:100145.

42. Ferraro RA, Rosendael AR van, Lu Y, Andreini D, Al-Mallah MH, Cademartiri F, Chinnaiyan K, Chow BJW, Conte E, Cury RC, Feuchtner G, Araújo Gonçalves P de, Hadamitzky M, Kim Y-J, Leipsic J, Maffei E, Marques H, Plank F, Pontone G, Raff GL, Villines TC, Lee S-E, Al'Aref SJ, Baskaran L, Cho I, Danad I, Gransar H, Budoff MJ, Samady H, Stone PH, Virmani R, Narula J, Berman DS, Chang H-J, Bax JJ, Min JK, Shaw LJ, Lin FY. Non-obstructive high-risk plaques increase the risk of future culprit lesions comparable to obstructive plaques without high-risk features: the ICONIC study. *Eur Heart J Cardiovasc Imaging* 2020;21:973–980.

43. Prati F, Arbustini E, Alfonso F. Potential of an Approach Based on the Identification and Treatment of Vulnerable Coronary Plaques. *JACC Cardiovasc Interv* 2021;14:468–473.

44. Baruś P, Modrzewski J, Gumiężna K, Dunaj P, Głód M, Bednarek A, Wańha W, Roleder T, Kochman J, Tomaniak M. Comparative Appraisal of Intravascular Ultrasound and Optical Coherence Tomography in Invasive Coronary Imaging: 2022 Update. *J Clin Med* 2022;11:4055.

45. Roleder T, Kovacic JC, Ali ZA, Sharma RP, Cristea E, Moreno P, Sharma S, Narula J, Kini A. Combined NIRS and IVUS imaging detects vulnerable plaque using a single catheter system: a head-to-head comparison with OCT. Available at: https://eurointervention.pcronline.com/article/combined-nirs-and-ivus-imaging-detects-vulnerable-plaque-using-a-single-catheter-system-a-head-to-head-comparison-with-oct. Accessed May 27, 2024.

46. Kuku KO, Singh M, Ozaki Y, Dan K, Chezar-Azerrad C, Waksman R, Garcia-Garcia HM. Near-Infrared Spectroscopy Intravascular Ultrasound Imaging: State of the Art. *Front Cardiovasc Med* 2020;7:107.

47. Araki M, Park S-J, Dauerman HL, Uemura S, Kim J-S, Di Mario C, Johnson TW, Guagliumi G, Kastrati A, Joner M, Holm NR, Alfonso F, Wijns W, Adriaenssens T, Nef H, Rioufol G, Amabile N, Souteyrand G, Meneveau N, Gerbaud E, Opolski MP, Gonzalo N, Tearney GJ, Bouma B, Aguirre AD, Mintz GS, Stone GW, Bourantas CV, Räber L, Gili S,

Mizuno K, Kimura S, Shinke T, Hong M-K, Jang Y, Cho JM, Yan BP, Porto I, Niccoli G, Montone RA, Thondapu V, Papafaklis MI, Michalis LK, Reynolds H, Saw J, Libby P, Weisz G, Iannaccone M, Gori T, Toutouzas K, et al. Optical coherence tomography in coronary atherosclerosis assessment and intervention. *Nat Rev Cardiol* 2022;19:684–703.

48. Bouma BE, Boer JF de, Huang D, Jang IK, Yonetsu T, Leggett CL, Leitgeb R, Sampson DD, Suter M, Vakoc B, Villiger M, Wojtkowski M. Optical coherence tomography. *Nat Rev Methods Primer* 2022;2:79.

49. Gupta A, Shrivastava A, Vijayvergiya R, Chhikara S, Datta R, Aziz A, Singh Meena D, Nath RK, Kumar JR. Optical Coherence Tomography: An Eye Into the Coronary Artery. *Front Cardiovasc Med* 2022;9:854554.

50. Stone GW, Maehara A, Muller JE, Rizik DG, Shunk KA, Ben -Yehuda Ori, Genereux P, Dressler O, Parvataneni R, Madden S, Shah P, Brilakis ES, Kini AS, null null. Plaque Characterization to Inform the Prediction and Prevention of Periprocedural Myocardial Infarction During Percutaneous Coronary Intervention. *JACC Cardiovasc Interv* 2015;8:927–936. Available at: https://www.jacc.org/doi/10.1016/j.jcin.2015.01.032. Accessed May 23, 2024.

51. Xie Y, Mintz GS, Yang J, Doi H, Iñiguez A, Dangas GD, Serruys PW, McPherson JA, Wennerblom B, Xu K, Weisz G, Stone GW, Maehara A. Clinical outcome of nonculprit plaque ruptures in patients with acute coronary syndrome in the PROSPECT study. *JACC Cardiovasc Imaging* 2014;7:397–405.

52. Erlinge D, Maehara A, Ben-Yehuda O, Bøtker HE, Maeng M, Kjøller-Hansen L, Engstrøm T, Matsumura M, Crowley A, Dressler O, Mintz GS, Fröbert O, Persson J, Wiseth R, Larsen AI, Okkels Jensen L, Nordrehaug JE, Bleie Ø, Omerovic E, Held C, James SK, Ali ZA, Muller JE, Stone GW, PROSPECT II Investigators. Identification of vulnerable plaques and patients by intracoronary near-infrared spectroscopy and ultrasound (PROSPECT II): a prospective natural history study. *Lancet Lond Engl* 2021;397:985–995.

53. Mintz GS. Intravascular imaging of coronary calcification and its clinical implications. *JACC Cardiovasc Imaging* 2015;8:461–471.

54. Prati F, Romagnoli E, Gatto L, La Manna A, Burzotta F, Ozaki Y, Marco V, Boi A, Fineschi M, Fabbiocchi F, Taglieri N, Niccoli G, Trani C, Versaci F, Calligaris G, Ruscica G, Di Giorgio A, Vergallo R, Albertucci M, Biondi-Zoccai G, Tamburino C, Crea F, Alfonso F, Arbustini E. Relationship between coronary plaque morphology of the left anterior descending artery and 12 months clinical outcome: the CLIMA study. *Eur Heart J* 2020;41:383–391.

55. Barlis P, Gonzalo N, Di Mario C, Prati F, Buellesfeld L, Rieber J, Dalby MC, Ferrante G, Cera M, Grube E, Serruys PW, Regar E. A multicentre evaluation of the safety of intracoronary optical coherence tomography. *EuroIntervention J Eur Collab Work Group Interv Cardiol Eur Soc Cardiol* 2009;5:90–95.

56. Mueller C, Hodgson JMB, Schindler C, Perruchoud AP, Roskamm H, Buettner HJ. Cost-effectiveness of intracoronary ultrasound for percutaneous coronary interventions. *Am J Cardiol* 2003;91:143–147.

57. Dawson LP, Layland J. High-Risk Coronary Plaque Features: A Narrative Review. *Cardiol Ther* 2022;11:319–335.

58. Osborn EA, Johnson M, Maksoud A, Spoon D, Zidar FJ, Korngold EC, Buccola J, Garcia Cabrera H, Rapoza RJ, West NEJ, Rauch J. Safety and efficiency of percutaneous coronary intervention using a standardised optical coherence tomography workflow. *EuroIntervention J Eur Collab Work Group Interv Cardiol Eur Soc Cardiol* 2023;18:1178–1187.

59. Stone GW, Mintz GS, Virmani R. Vulnerable Plaques, Vulnerable Patients, and Intravascular Imaging. *J Am Coll Cardiol* 2018;72:2022–2026.

60. Rouleau J. Improved outcome after acute coronary syndromes with an intensive versus standard lipid-lowering regimen: results from the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial. *Am J Med* 2005;118 Suppl 12A:28–35.

61. Kini AS, Baber U, Kovacic JC, Limaye A, Ali ZA, Sweeny J, Maehara A, Mehran R, Dangas G, Mintz GS, Fuster V, Narula J, Sharma SK, Moreno PR. Changes in plaque lipid content after short-term intensive versus standard statin therapy: the YELLOW trial (reduction in yellow plaque by aggressive lipid-lowering therapy). *J Am Coll Cardiol* 2013;62:21–29.

62. Komukai K, Kubo T, Kitabata H, Matsuo Y, Ozaki Y, Takarada S, Okumoto Y, Shiono Y, Orii M, Shimamura K, Ueno S, Yamano T, Tanimoto T, Ino Y, Yamaguchi T, Kumiko H, Tanaka A, Imanishi T, Akagi H, Akasaka T. Effect of Atorvastatin Therapy on Fibrous Cap Thickness in Coronary Atherosclerotic Plaque as Assessed by Optical Coherence Tomography: The EASY-FIT Study. *J Am Coll Cardiol* 2014;64:2207–2217. Available at: https://www.sciencedirect.com/science/article/pii/S0735109714064754. Accessed June 11, 2024.

63. De Luca L, Halasz G. The PACMAN-AMI trial: a revolution in the treatment of acute coronary syndromes. *Eur Heart J Suppl J Eur Soc Cardiol* 2023;25:C90–C95. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10132619/. Accessed August 1, 2024.

64. Nicholls SJ, Nissen SE, Prati F, Windecker S, Kataoka Y, Puri R, Hucko T, Kassahun H, Liao J, Somaratne R, Butters J, Di Giovanni G, Jones S, Psaltis PJ. Assessing the impact of PCSK9 inhibition on coronary plaque phenotype with optical coherence tomography: rationale and design of the randomized, placebo-controlled HUYGENS study. *Cardiovasc Diagn Ther* 2021;11:120–129. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7944215/. Accessed August 1, 2024.

65. Ferreiro JL, Angiolillo DJ. New directions in antiplatelet therapy. *Circ Cardiovasc Interv* 2012;5:433–445.

66. Mayor S. ACE inhibitor reduces cardiovascular events by 22%. *BMJ* 1999;319:661.

67. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, Kastelein JJP, Cornel JH, Pais P, Pella D, Genest J, Cifkova R, Lorenzatti A, Forster T, Kobalava Z, Vida-Simiti L, Flather M, Shimokawa H, Ogawa H, Dellborg M, Rossi PRF, Troquay RPT, Libby P, Glynn RJ, CANTOS Trial Group.

Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. *N Engl J Med* 2017;377:1119–1131.

68. Tardif J-C, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, Pinto FJ, Ibrahim R, Gamra H, Kiwan GS, Berry C, López-Sendón J, Ostadal P, Koenig W, Angoulvant D, Grégoire JC, Lavoie M-A, Dubé M-P, Rhainds D, Provencher M, Blondeau L, Orfanos A, L'Allier PL, Guertin M-C, Roubille F. Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction. *N Engl J Med* 2019;381:2497–2505.

69. Pinilla-Echeverri N, Mehta SR, Wang J, Lavi S, Schampaert E, Cantor WJ, Bainey KR, Welsh RC, Kassam S, Mehran R, Storey RF, Nguyen H, Meeks B, Wood DA, Cairns JA, Sheth T. Nonculprit Lesion Plaque Morphology in Patients With ST-Segment-Elevation Myocardial Infarction: Results From the COMPLETE Trial Optical Coherence Tomography Substudys. *Circ Cardiovasc Interv* 2020;13:e008768.

70. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, Agewall S, Dickstein K, Edvardsen T, Escaned J, Gersh BJ, Svitil P, Gilard M, Hasdai D, Hatala R, Mahfoud F, Masip J, Muneretto C, Valgimigli M, Achenbach S, Bax JJ, ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020;41:407–477.

71. Brugaletta S, Cequier A, Alfonso F, Iñiguez A, Romaní S, Serra A, Salinas P, Goicolea J, Bordes P, Del Blanco BG, Hernández-Antolín R, Pernigotti A, Gómez-Lara J, Sabaté M. MAGnesium-based bioresorbable scaffold and vasomotor function in patients with acute ST segment elevation myocardial infarction: The MAGSTEMI trial: Rationale and design. *Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv* 2019;93:64–70.

72. Bourantas CV, Papafaklis MI, Kotsia A, Farooq V, Muramatsu T, Gomez -Lara Josep, Zhang Y-J, Iqbal J, Kalatzis FG, Naka KK, Fotiadis DI, Dorange C, Wang J, Rapoza R, Garcia -Garcia Hector M., Onuma Y, Michalis LK, Serruys PW. Effect of the Endothelial Shear Stress Patterns on Neointimal Proliferation Following Drug-Eluting Bioresorbable Vascular Scaffold Implantation. *JACC Cardiovasc Interv* 2014;7:315–324. Available at: https://www.jacc.org/doi/10.1016/j.jcin.2013.05.034. Accessed May 23, 2024.

73. Wald DS, Morris JK, Wald NJ, Chase AJ, Edwards RJ, Hughes LO, Berry C, Oldroyd KG, PRAMI Investigators. Randomized trial of preventive angioplasty in myocardial infarction. *N Engl J Med* 2013;369:1115–1123.

74. Park S-J, Ahn J-M, Kang D-Y, Yun S-C, Ahn Y-K, Kim W-J, Nam C-W, Jeong J-O, Chae I-H, Shiomi H, Kao H-L, Hahn J-Y, Her S-H, Lee B-K, Ahn TH, Chang K-Y, Chae JK, Smyth D, Mintz GS, Stone GW, Park D-W, Park S-J, Ahn J-M, Kang D-Y, Yun S-C, Ahn Y-K, Kim W-J, Nam C-WN, Jeong J-O, Chae I-H, Shiomi HS, Kao H-L, Hahn J-Y, Her S-H, Lee B-K, Ahn TH, Chang K-Y, Chae J-K, Smyth D, Mintz G, Stone G, Park D-W. Preventive percutaneous coronary intervention versus optimal medical therapy alone for the treatment of vulnerable atherosclerotic coronary plaques (PREVENT): a multicentre, open-label, randomised controlled trial. *The Lancet* 2024;403:1753–1765. Available at: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(24)00413-6/abstract. Accessed May 23, 2024.

75. Stone GW, Généreux P, Harrington RA, White HD, Gibson CM, Steg PG, Hamm CW, Mahaffey KW, Price MJ, Prats J, Deliargyris EN, Bhatt DL. Impact of lesion complexity on

peri-procedural adverse events and the benefit of potent intravenous platelet adenosine diphosphate receptor inhibition after percutaneous coronary intervention: core laboratory analysis from 10 854 patients from the CHAMPION PHOENIX trial. *Eur Heart J* 2018;39:4112–4121. Available at: https://doi.org/10.1093/eurheartj/ehy562. Accessed May 23, 2024.

76. Stone GW, Maehara A, Lansky AJ, Bruyne B de, Cristea E, Mintz GS, Mehran R, McPherson J, Farhat N, Marso SP, Parise H, Templin B, White R, Zhang Z, Serruys PW, PROSPECT Investigators. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med* 2011;364:226–235.

77. Veelen A van, Küçük IT, Fuentes FH, Kahsay Y, Garcia-Garcia HM, Delewi R, Beijk MAM, Hartog AW den, Grundeken MJ, Vis MM, Henriques JPS, Claessen BEPM. First-in-Human Drug-Eluting Balloon Treatment of Vulnerable Lipid-Rich Plaques: Rationale and Design of the DEBuT-LRP Study. *J Clin Med* 2023;12:5807. Available at: https://www.mdpi.com/2077-0383/12/18/5807. Accessed May 27, 2024.

78. Anon. Treatment of Functionally Non-significant Vulnerable Plaques in Patients With Multivessel ST-elevation Myocardial Infarction The VULNERABLE Randomized Trial. *MediFind*. Available at: https://www.medifind.com/articles/clinical-trial/351981308. Accessed July 27, 2024.

FIGURE AND TABLE LEGENDS

Figure 1. Pathophysiology of ACS. ACS – acute coronary syndrome; TLR2 – Toll-like receptor 2.

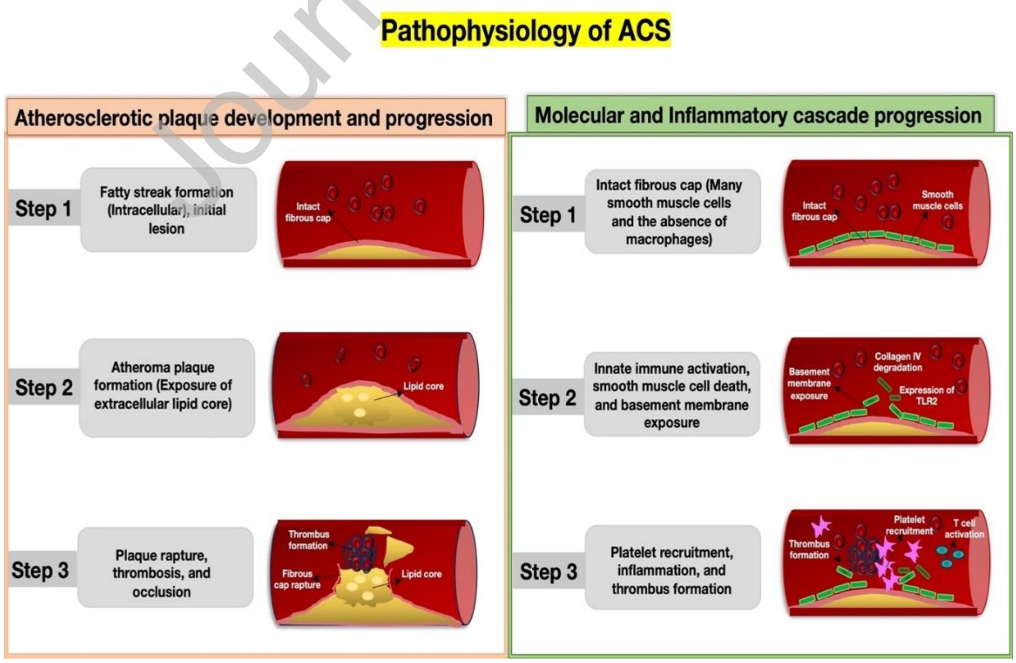


Figure 2. Concept of Vulnerable Plaque. IVUS – intravascular ultrasound; NIRS-IVUS – Near infrared spectroscopy-IVUS; OCT – optical coherence tomography.

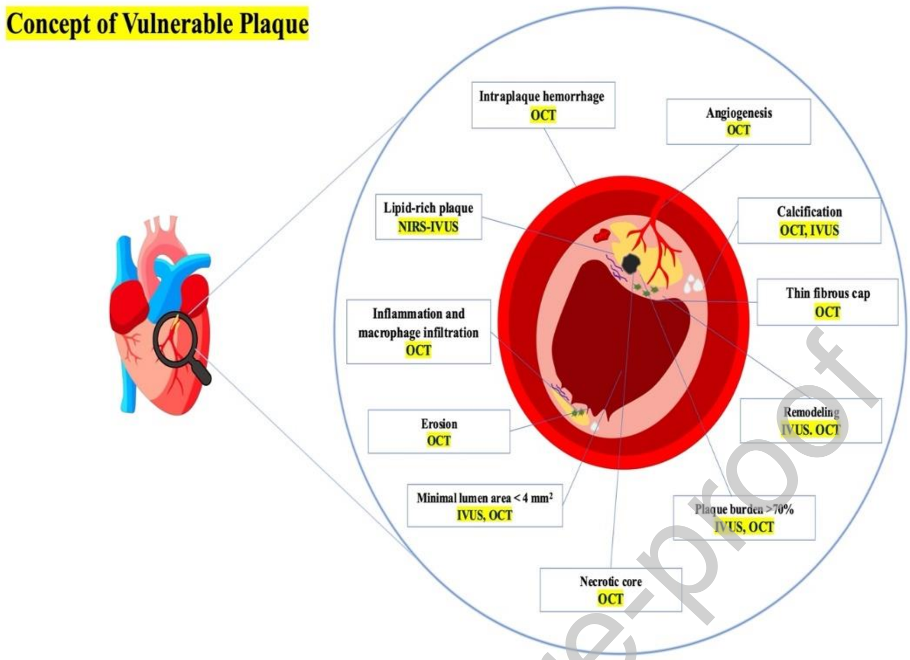
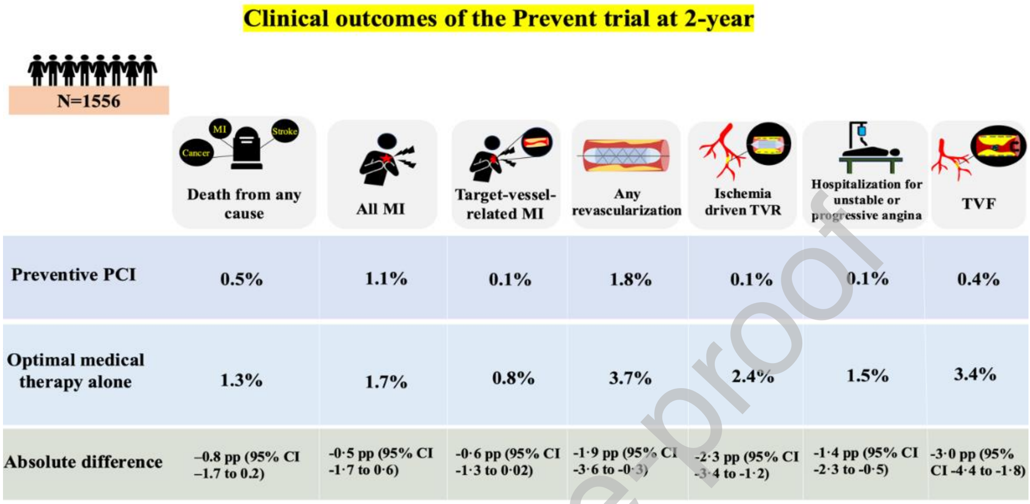


Figure 3. Outcomes of preventive PCI in treating patients with vulnerable plaques at 2-year follow-up in the PREVENT trial. MI – myocardial infarction; PCI – percutaneous coronary intervention; TVR – Target vessel revascularization.



	Death from any cause	All MI	Target-vessel-related MI	Any revascularization	Ischemia driven TVR	Hospitalization for unstable or progressive angina	TVF
Preventive PCI	0.5%	1.1%	0.1%	1.8%	0.1%	0.1%	0.4%
Optimal medical therapy alone	1.3%	1.7%	0.8%	3.7%	2.4%	1.5%	3.4%
Absolute difference	–0.8 pp (95% CI –1.7 to 0.2)	-0·5 pp (95% CI -1·7 to 0·6)	-0·6 pp (95% CI -1·3 to 0·02)	-1·9 pp (95% CI -3·6 to -0·3)	-2·3 pp (95% CI -3·4 to -1·2)	-1·4 pp (95% CI -2·3 to -0·5)	-3·0 pp (95% CI -4·4 to -1·8)

Central Illustration: Role of preventive percutaneous coronary intervention (PCI) in vulnerable plaque. IVUS – intravascular ultrasound; MACE – major adverse cardiovascular event; NIRS-IVUS – near-infrared spectroscopy-IVUS; OCT – optical coherence tomography; RF – radiofrequency.

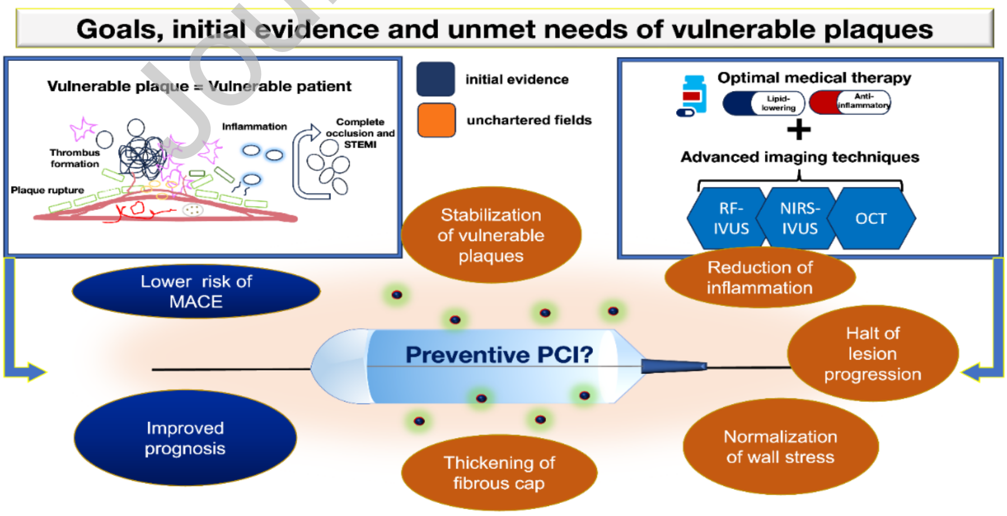


Table 1. Milieus of vulnerable plaques. IVUS – intravascular ultrasound; NIRS-IVUS – near infrared spectroscopy-IVUS; OCT – optical coherence tomography.

Characteristic Features	Best Imaging Modality to Identify
Thin fibrous cap (<65 micrometers)	OCT
Large plaque burden (≥70%) with positive remodelling	IVUS, OCT
Large necrotic lipid-rich core	NIRS-IVUS, OCT
Increased microvasculature with intraplaque haemorrhage	OCT
Inflammatory cells infiltration (macrophage and foam cells)	OCT
Minimal lumen area (MLA) < 4mm^2	IVUS, OCT
Spotty calcification (with low overall calcification grade)	IVUS, OCT

Table 2. Characteristics of Coronary Imaging Modalities for Detecting Vulnerable Plaques. IVUS – intravascular ultrasound; NIRS-IVUS – near-infrared spectroscopy-IVUS; OCT – optical coherence tomography; RF – radiofrequency; US – ultrasound.

Imaging Modality	Energy source	Resolution	Penetration Depth	Strengths	Clinical Utility	Key Features for Vulnerable Plaque Detection	Cost and Availability	Limitations
IVUS (gray-scale, radiofrequency)	US (20–60 MHz)	150–200 µm	8–10 mm (can't image through calcium)	Provides detailed images of plaque burden and artery structure Allows assessment of plaque size and composition	Used to assess overall plaque burden and vessel remodelling Guides interventional procedures Monitors stent deployment and apposition	Differentiates between fibrous and calcified plaques Limited in detecting thin fibrous caps and lipid cores	Moderate cost Widely available in catheterization labs	Lower resolution than OCT Cannot reliably differentiate between lipid and fibrous tissue Artifacts may obscure images
NIRS-IVUS	Near-infrared spectroscopy	NA	3-4 mm	Identifies lipid-rich tissue more accurately than any other technique Provides a chemogram (color-coded map) of lipid content	Combined with IVUS, provides structural and compositional information Useful in high-risk patients to guide therapeutic decisions	Detects lipid core plaques that may not be obstructive Assesses lipid content and distribution Useful for identifying high-	High cost when combined with an IVUS imaging core (NIRS-IVUS) Limited	No structural detail with NIRS alone (relies on co-registered imaging with IVUS)

						risk plaques prone to rupture	availability, mainly only in specialized centers	
OCT	Near-infrared light	10–15 µm	3-4 mm (less through lipid)	Provides the highest resolution among the modalities Can detect thin fibrous caps, ruptures, and small intraplaque features Visualizes stent placement and apposition	Ideal for detailed plaque characterization and assessing stent deployment Guides interventional procedures, especially in complex cases	Excellent for detecting thin fibrous caps Visualizes microstructures within plaques (e.g., macrophages, microvessels, spotty calcification) Best for assessing fibrous cap thickness and stent apposition	High cost Availability increasing but still limited	Limited penetration depth (3-4 mm), less through lipid Requires blood displacement for clear imaging, usually with contrast media Limited use in patients with renal insufficiency

Table 3. Clinical trials evaluating the role of invasive treatments for high-risk, vulnerable plaques. ACS – acute coronary syndrome; BRS - bioresorbable scaffold; DES – drug eluting stent; DoCE – device-oriented composite endpoints; ESS – endothelial shear stress; GDMT – goal-directed medical therapy ; ID-TVR – ischemia-driven target vessel revascularisation; MLA – minimal lumen area; MACE – major adverse cardiovascular event; PCI – percutaneous coronary intervention; OCT – optical coherence tomography; POCE – patient-oriented composite endpoints; RCT – randomized controlled trial; STEMI – ST-elevation myocardial infarction; TLF – target lesion failure.

Trial Name	Design & Population	Primary Endpoint(s)	Key Results (HR / OR / p-values)
MAGSTEMI	Prospective, randomized in STEMI patients (~150); Mg-based BRS vs. metallic DES	DoCE: cardiac death, target-vessel MI, TLR) at 3 years	DoCE: 17.6% vs. 6.6%; Δ 11.0% (95% CI –21.3 to –0.7); p=0.038. TLR: 16.2% vs. 5.3%; Δ 10.9% (95% CI –20.7 to –1.2); p=0.030.
ESS Pattern Study	Prospective intravascular imaging mechanistic study in BRS recipients	Correlation between ESS and neointimal proliferation	Low ESS regions exhibited significantly greater neointimal thickness. No HRs or p-values reported—purely mechanistic.
PRAMI	Randomized, multicenter, patient-blinded trial; 465 STEMI patients with multivessel coronary artery disease	Composite of cardiac death, nonfatal MI, or refractory angina	Primary outcome: 9% vs. 23% (HR 0.35, 95% CI 0.21–0.58; p < 0.001) ↓ Nonfatal MI (3% vs. 8.7%, p = 0.009) ↓ Refractory angina (5.1% vs. 13.0%, p = 0.002) ↓ Repeat revascularization (6.8% vs. 19.9%, p < 0.001) Trial stopped early due to clear benefits.
PROSPECT ABSORB	Randomized lesion-level RCT nested in PROSPECT II; ACS patients post-PCI (n=182); NIRS-IVUS-imaged	Primary effectiveness: follow-up MLA at 25 months; safety: TLF at 24 months; controlled endpoint: lesion-related MACE through follow-up	MLA: 6.9±2.6 mm² vs. 3.0±1.0; Δ 3.9 mm² (95% CI 3.3–4.5); p<0.0001. TLF: 4.3% vs. 4.5%, p=0.96. Lesion-related MACE: 4.3% vs. 10.7%; OR 0.38 (95% CI 0.11–1.28); p=0.12.

	non-culprit plaques with plaque burden ≥65% randomized to BRS + GDMT (n=93) vs. GDMT alone (n=89)		
PREVENT	Multicenter, open-label RCT (n=1,606) in patients with angiographically mild but OCT-imaged vulnerable plaques	Composite: cardiac death, target-vessel MI, ID-TVR, or unstable angina hospitalization at 2 and ~4.4 years	At 2 years: event rate 0.4% vs. 3.4%; HR 0.11 (95% CI 0.03–0.36); p=0.0003. At 4.4 years: 6.5% vs. 9.4%; HR 0.54 (95% CI 0.33–0.87); p=0.0097. POCE (all-cause death/MI/revasc): HR 0.69(95% CI 0.50–0.95); p=0.022.

Table 4. Ongoing trials of preventive PCI in vulnerable plaque treatment. FFR – fractional flow reserve; LCBI – lipid core burden index; LRPs – lipid rich plaques; PE-DCB – paclitaxel eluting-drug coated balloon; iFR – instantaneous wave-free ratio; MI – myocardial infarction; MACE – major adverse cardiac events; OMT – optimal medical treatment; OCT – optical coherence tomography; PCI – percutaneous coronary intervention; µQFR – next-generation quantitative flow ratio; RWS – radial wall strain; RFR – resting full-cycle ratio; TLR – target lesion revascularization; TVF – target vessel failure.

Trial	NCT Number	Status/ Population	Assessment/treatment	Primary Endpoint	Follow up (years)
DEBuT-LRP		Recruited/ 20 patients	PE-DCB	Change in maxLCBImm^4 between baseline and 9 months follow up in PE-DCB treated LRPs	0.75
COMBINE-INTERVENE	NCT05333068	Recruiting/ 1222 patients	FFR + OCT vs. FFR	Cardiac death, MI, clinically-driven TLR	2
FAVOR V AMI	NCT05669222	Not yet recruiting/ 5000 patients	µQFR+RWS vs. Standard treatment strategy	MACE	5
INTERCLIMA	NCT05027984	Recruiting/ 1420 patients	OCT vs. iFR/FFR/RFR	Cardiac death, non-fatal target-vessel MI	2
VULNERABLE	NCT05599061	Recruiting/ 600 patients	OMT + PCI vs. OMT	TVF	4

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: