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**Review Article**

# Coronary Vulnerable and High-Risk Plaque: Current Concepts, Selective Preventive PCI, and an ISIC Position Statement

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**Abstract**

The concept of coronary vulnerable plaque has evolved from a histopathological concept into a potential therapeutic target for precision cardiovascular prevention. Recent evidence has expanded this paradigm beyond the traditional vulnerable-plaque construct towards the broader concept of high-risk plaque, encompassing rupture-prone plaques, erosion-prone plaques, calcified nodules, plaque burden, inflammatory activity, healing capacity, and patient-level susceptibility to thrombosis. Advances in Coronary Computed Tomography Angiography (CCTA), Intravascular Ultrasound (IVUS), Optical Coherence Tomography (OCT), Near-Infrared Spectroscopy (NIRS), molecular imaging, and Artificial Intelligence (AI) have substantially improved the detection and characterization of high-risk plaque. Circulating lipid, inflammatory, metabolic, and renal biomarkers provide complementary information regarding patient vulnerability. Concurrently, contemporary pharmacological therapy has substantially improved the natural history of coronary atherosclerosis by promoting plaque stabilization, fibrous cap thickening, lipid core regression, and attenuation of vascular inflammation.

The emergence of preventive Percutaneous Coronary Intervention (PCI) for non-flow-limiting vulnerable plaques, particularly following the PREVENT trial, has reignited interest in focal treatment before clinical destabilization. Nevertheless, important uncertainties remain regarding patient selection, diagnostic thresholds, imaging strategies, device selection, long-term durability, cost-effectiveness, and applicability in resource-limited healthcare systems. Drug-Eluting Stents (DES) remain the most established device platform, whereas next-generation bioresorbable scaffolds and Drug-Coated Balloons (DCB) may offer future approaches to local plaque treatment without permanent metallic implantation. Although Coronary Artery Bypass Grafting (CABG) does not directly treat vulnerable plaques, it may indirectly protect selected patients with diffuse multivessel disease by bypassing plaque-bearing coronary segments.

For Indonesia and other resource-constrained healthcare systems, future implementation should emphasize pragmatic implementation rather than widespread adoption of advanced technologies. Emphasis should remain on aggressive Optimal Medical Therapy (OMT), selective use of advanced imaging, careful identification of patients at the highest absolute cardiovascular risk, structured operator training, national registries, and rigorous evaluation of cost-effectiveness. The ultimate objective is not simply to detect more vulnerable plaques but to prevent more myocardial infarctions and cardiovascular deaths through efficient use of healthcare resources.

The Indonesian Society of Interventional Cardiology (ISIC) recommends that aggressive systemic prevention, centered on OMT, should remain the foundation of care. Advanced plaque imaging and preventive PCI should be reserved for carefully selected patients with converging high-risk plaque characteristics, high patient-level risk, and a favorable benefit–risk profile.

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**Keywords:** High-risk plaque; vulnerable plaque; preventive PCI; precision prevention; coronary computed tomography angiography; intravascular ultrasound; optical coherence tomography; biomarkers; bioresorbable scaffold; drug-coated balloon

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## Introduction

Despite remarkable advances in cardiovascular prevention, lipid-lowering therapy, antithrombotic treatment, and coronary revascularisation, Coronary Artery Disease (CAD) remains one of the leading causes of morbidity and mortality worldwide. Acute Coronary Syndromes (ACS) continue to impose a substantial clinical and socioeconomic burden because many events arise unexpectedly from angiographically non-obstructive lesions rather than from severely flow-limiting stenoses. This long-standing paradox has driven the development of the vulnerable-plaque concept, traditionally defined as an atherosclerotic lesion with a high propensity for rupture, erosion, thrombosis, and the subsequent occurrence of myocardial infarction or sudden cardiac death.[1–3]

The traditional concept of vulnerable plaque has been largely based on plaque morphology. Plaque rupture has traditionally been regarded as arising from Thin-Cap Fibroatheroma (TCFA), which contains a large lipid-rich necrotic core covered by a thin fibrous cap infiltrated by macrophages. Other features such as positive remodeling, large plaque burden, spotty calcification, intraplaque hemorrhage, inflammation, and adverse endothelial shear stress have also been associated with plaque destabilization.[4–7] However, later clinical studies have shown that plaque morphology alone is not enough to predict future events with high positive predictive value. Many plaques with high-risk features remain clinically silent. Plaque vulnerability itself is dynamic and may evolve under the influence of systemic inflammation, lipid metabolism, thrombogenicity, hemodynamic forces, and pharmacological therapy.[8-9]

More recently, accumulating evidence has substantially refined this traditional paradigm. The 2025 JACC Cardiovascular Imaging Position Statement proposed the broader concept of the high-risk plaque, acknowledging that coronary thrombosis may arise not only from rupture-prone TCFA but also from erosion-prone plaques and eruptive calcified nodules. In addition, plaque-related risk is determined by plaque burden, inflammatory activity, endothelial injury, local hemodynamic conditions, healing capacity, and the amount of myocardium subtended by the lesion.[10] This contemporary framework shifts the focus from a single vulnerable lesion toward a more integrated assessment of high-risk plaque, high-risk patient, and high-risk coronary phenotype. Because plaque morphology alone has limited positive predictive value, this evidence has prompted a major conceptual shift. Today's thinking has come to recognize that plaques do not act alone. Future prevention should focus not only on vulnerable plaque but also on high-risk plaque, vulnerable patients, and high-risk coronary phenotypes. This phenotype encompasses plaque morphology, plaque biology, systemic inflammatory milieu, metabolic risk, hemodynamic stress, genetic susceptibility, and treatment responsiveness.[8,10] In this context, imaging is not only a tool to label a plaque as "vulnerable", but part of a wider risk-stratification ecosystem intended to guide precision prevention. This framework proposed by Vergallo and colleagues represents one of the most comprehensive contemporary models of coronary vulnerability and serves as an important conceptual foundation for the present Indonesian Society of Interventional Cardiology (ISIC) position statement. The conceptual evolution from the traditional vulnerable-plaque paradigm towards the integrated high-risk coronary phenotype proposed in this Position Statement is summarised in Figure 1.

The advent of preventive Percutaneous Coronary Intervention (PCI) has further fuelled this debate. The PREVENT trial showed that in selected patients with non-flow-limiting vulnerable plaques, preventive PCI plus Optimal Medical Therapy (OMT) reduced the risk of target vessel failure compared with OMT alone.[11] This trial is an important milestone because it provides randomized evidence in support of focal treatment of selected high-risk plaques. Nonetheless, PREVENT should be viewed as the start of a new clinical hypothesis rather than the final justification for widespread plaque stenting. The trial leaves some questions unanswered. Who should we screen? Which imaging modality to use? What plaque features should prompt intervention? What device platform fits best? Is the benefit driven by hard endpoint prevention or by reduction in softer events like unstable angina and revascularisation? Is the approach cost-effective across various healthcare systems?

These are particularly relevant questions for Indonesia. Indonesia has a substantial and increasing burden of cardiovascular disease, marked geographic variation in access to catheterization laboratories, limited availability of advanced intracoronary imaging in many regions, and constrained healthcare resources and budgetary capacity.[12–14] Future adoption of high-risk plaque assessment and preventive PCI must be clinically meaningful, economically defensible, and operationally feasible. A strategy developed in high-income healthcare

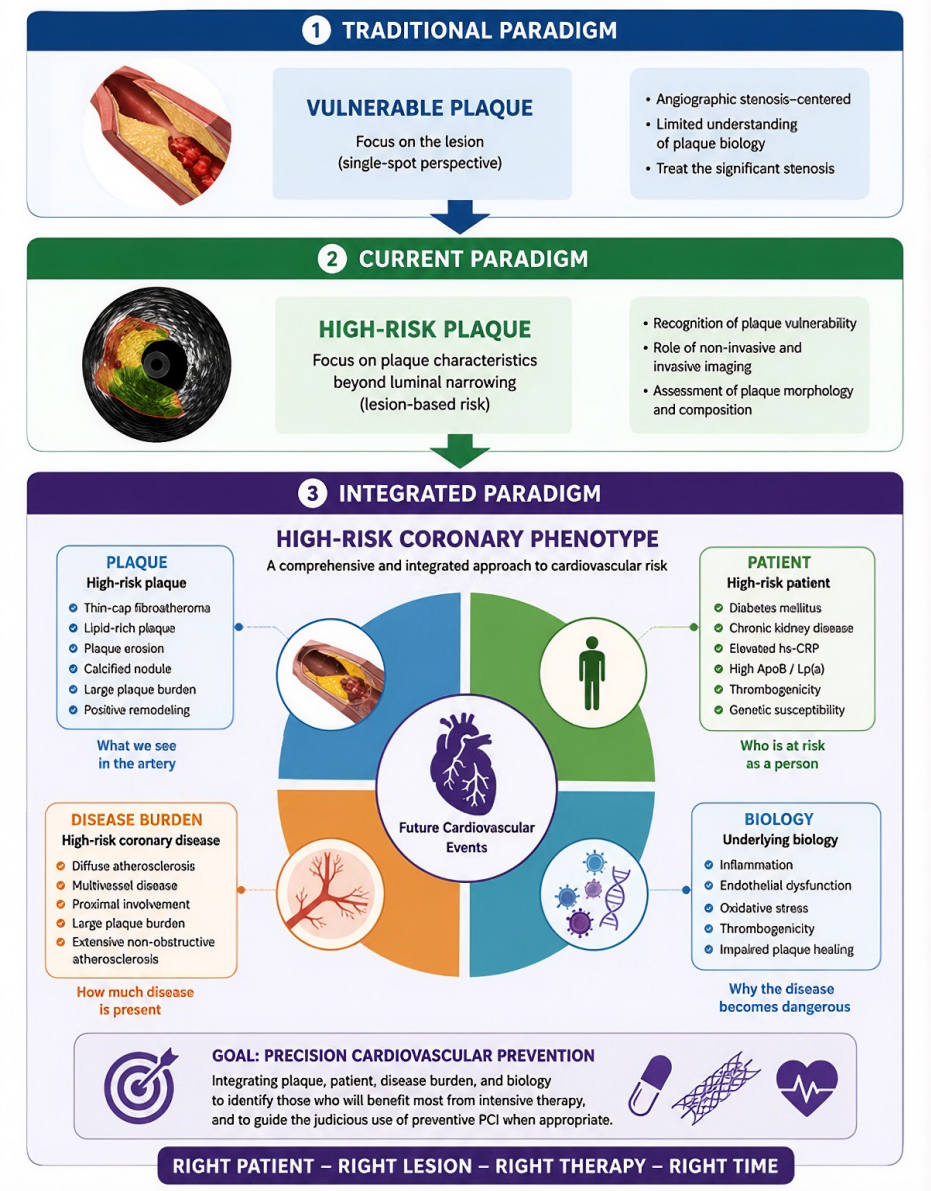


**Figure 1.** Evolution of the Coronary Risk Paradigm.
This figure illustrates the evolution from the traditional vulnerable-plaque paradigm to the contemporary high-risk plaque concept and, ultimately, to an integrated high-risk coronary phenotype. The traditional paradigm focused primarily on angiographic stenosis and individual rupture-prone lesions, whereas the current paradigm incorporates plaque characteristics beyond luminal narrowing. The integrated paradigm combines plaque morphology, patient-level vulnerability, overall disease burden, and biological activity to support precision cardiovascular prevention. The overarching goal is to identify the right patient, the right lesion, and the right therapy at the right time.

systems cannot be directly implemented in Indonesia without contextual adaptation. The aim should be to achieve the largest reduction in cardiovascular events for every unit of healthcare resources invested. Accordingly, the primary objective is not to detect a greater number of high-risk plaques, but to identify those patients in whom additional diagnostic or therapeutic intervention is most likely to improve clinical outcomes.

This position statement reviews future directions in the management of coronary vulnerable plaque, including invasive and non-invasive diagnosis; pharmacological stabilization; preventive PCI; Coronary Artery Bypass Grafting (CABG); emerging device platforms, such as Drug-Eluting Stents (DES), bioresorbable scaffolds, and Drug-Coated Balloons (DCB); and implementation challenges relevant to Indonesia and other resource-

limited settings. In addition, this position statement reflects the perspective of the ISIC, which recognizes the growing importance of imaging-defined plaque vulnerability and the emerging role of preventive PCI, while emphasizing that OMT remains the cornerstone of management. ISIC supports a cautious, evidence-based, imaging-guided, and highly selective approach to preventive plaque intervention, recognizing that patient-level risk, healthcare resource considerations, procedural safety, and cost-effectiveness must remain central to clinical decision-making, particularly in Indonesia and similar resource-constrained healthcare systems.

Against this background, ISIC believes that the contemporary management of coronary vulnerability should move beyond a purely lesion-centered paradigm. Although advances in coronary imaging have improved the identification of high-risk plaque features and recent evidence has reinvigorated the debate on preventive PCI, current evidence does not support indiscriminate intervention on all imaging-defined vulnerable plaques. Rather, OMT should remain the foundation of care, while advanced imaging and preventive PCI should be reserved for carefully selected patients in whom the anticipated clinical benefit outweighs procedural risks, costs, and resource implications.

## From Vulnerable Plaque to High-Risk Plaque and High-Risk Coronary Phenotype

The historical concept of the vulnerable plaque originated from pathological studies of culprit lesions responsible for fatal coronary thrombosis. These landmark investigations established plaque rupture, plaque erosion, and calcified nodules as the principal pathological substrates underlying ACS. Plaque rupture is typically associated with TCFA, characterized by a large lipid-rich necrotic core covered by a thin fibrous cap infiltrated with inflammatory cells, particularly macrophages. Plaque erosion, in contrast, is characterized by endothelial denudation, a proteoglycan-rich extracellular matrix, and a predominance of smooth muscle cells with relatively less lipid accumulation. Calcified nodules, although less common, may also precipitate coronary thrombosis through disruption of the luminal surface.[4-5]

For more than two decades, TCFA has been regarded as the archetypal vulnerable plaque. Nevertheless, advances in pathology, intracoronary imaging, and clinical investigation have demonstrated that coronary thrombosis cannot be explained by a single morphological substrate alone. Coronary events arise from multiple biological pathways, including plaque composition, vascular inflammation, endothelial integrity, thrombogenicity, hemodynamic forces, vascular healing, and systemic patient-related factors. Consequently, the traditional lesion-centered paradigm has gradually evolved into a broader, more biologically comprehensive framework.

Contemporary evidence therefore favors the concept of the high-risk plaque, which extends beyond rupture-prone TCFA to encompass erosion-prone plaques, eruptive calcified nodules, extensive plaque burden, inflammatory activity, endothelial dysfunction, impaired healing capacity, and adverse local hemodynamics. Importantly, the probability that an individual plaque will result in an acute coronary event is determined not only by its intrinsic morphology but also by the biological vulnerability of the patient in whom it resides. This conceptual evolution recognizes that plaque-related risk is dynamic rather than static and reflects the complex interaction between local plaque characteristics and systemic disease processes.[10]

The 2025 JACC: Cardiovascular Imaging Position Statement by Vergallo and colleagues represents the most comprehensive contemporary synthesis of this evolving concept. Rather than defining vulnerability solely according to plaque morphology, the document proposes an integrated framework that incorporates lesion characteristics, plaque biology, inflammatory activity, endothelial injury, vascular healing, hemodynamic stress, the amount of subtended myocardium, and patient-level susceptibility to thrombosis.[10] This framework acknowledges that clinically relevant coronary events occur when multiple determinants of vulnerability converge, rather than as the consequence of a single morphological abnormality.

Accordingly, contemporary coronary risk assessment has shifted from identifying isolated vulnerable plaques towards recognizing the broader high-risk coronary phenotype. This phenotype integrates three complementary domains: high-risk plaque, high-risk patient, and high-risk coronary disease. High-risk plaque describes adverse morphological and biological plaque characteristics; high-risk patient reflects systemic factors such as persistent dyslipidemia, residual inflammatory risk, diabetes mellitus, Chronic Kidney Disease (CKD), thrombogenicity, and genetic susceptibility;

whereas high-risk coronary disease encompasses diffuse atherosclerotic burden, extensive plaque distribution, proximal lesion location, and the volume of myocardium at risk. Considered together, these domains provide a more accurate representation of future cardiovascular risk than plaque morphology alone.

This paradigm shift also explains why the predictive value of imaging-defined vulnerable plaque has historically been modest. Several prospective studies, including PROSPECT, have consistently demonstrated that lesions exhibiting large plaque burden, positive remodeling, TCFA, or small minimal lumen area are associated with a significantly higher probability of subsequent cardiovascular events.[15] However, the absolute event rate attributable to any individual lesion remains relatively low. Similar observations have subsequently been confirmed using Optical Coherence Tomography (OCT), Near-Infrared Spectroscopy (NIRS), and Coronary Computed Tomography Angiography (CCTA), each demonstrating that although high-risk plaque features are prognostically important, the majority of imaging-defined high-risk plaques never progress to clinically manifest ACS.[16–19]

Several biological mechanisms explain this apparent paradox. First, plaque vulnerability is inherently dynamic. Lesions that appear biologically active at one time point may subsequently stabilize or regress under intensive lipid-lowering and anti-inflammatory therapy. Second, plaque disruption frequently occurs without clinical manifestation because thrombosis remains limited or is effectively counterbalanced by endogenous fibrinolytic mechanisms. Third, systemic determinants—including inflammation, diabetes mellitus, renal dysfunction, smoking, coagulation status, and residual lipid burden—substantially influence whether plaque disruption ultimately culminates in myocardial infarction. Finally, patients rarely harbor a single vulnerable lesion; rather, they often exhibit diffuse coronary atherosclerosis containing multiple plaques at different stages of biological evolution. Consequently, focal treatment of one lesion cannot eliminate the systemic processes responsible for continued disease progression.

The recognition of these limitations has profound implications for future preventive strategies. The central clinical question is no longer whether an individual plaque fulfills the criteria for vulnerability, but whether the overall coronary phenotype places the patient at sufficiently high absolute risk to justify escalation beyond OMT. This broader perspective aligns with the principles of precision cardiovascular prevention, whereby diagnostic imaging, circulating biomarkers, clinical characteristics, and therapeutic responsiveness are integrated to guide personalized management.

An additional dimension of this evolving paradigm is the concept of plaque healing. Increasing pathological and intracoronary imaging evidence suggests that repeated episodes of clinically silent plaque disruption may be followed by reparative healing, characterized by increased fibrous tissue deposition and progressive plaque stabilization. Conversely, the absence of healed plaque may identify lesions with persistent biological activity despite similar anatomical appearance.[10] Recognition of plaque healing further emphasizes that plaque morphology represents only a single component of vulnerability and reinforces the importance of considering biological activity alongside structural characteristics.

Taken together, these observations establish an important conceptual transition. Accordingly, the central challenge is no longer plaque detection itself, but appropriate patient selection. The value of advanced plaque imaging ultimately lies in identifying patients whose overall coronary phenotype justifies intensification of therapy beyond optimal medical treatment. This integrated framework provides the scientific foundation for precision prevention and underpins the recommendations presented throughout this ISIC Position Statement.

## Future Directions in Non-invasive Diagnostics

### Coronary CT Angiography: A Scalable Platform

Coronary CT angiography is expected to play an increasingly important role as a scalable non-invasive platform for future assessment of high-risk coronary plaque. Compared with invasive imaging, CCTA is non-invasive and more scalable for broader risk stratification. Several high-risk plaque features can be identified by modern CCTA, including low-attenuation plaque, positive remodeling, spotty calcification, and napkin-ring sign. These features have been associated with increased risk of myocardial infarction and coronary death in observational studies.[20–22]

The future role of CCTA may extend beyond the assessment of anatomical stenosis. Quantitative plaque analysis provides measures of total plaque volume, non-calcified plaque volume, low-

attenuation plaque burden, calcified plaque burden, and progression over time. Serial CCTA may be useful for assessing the response to intensive lipid-lowering therapy or anti-inflammatory treatment. This is particularly relevant because plaque stabilization, not just luminal improvement, may represent the desired therapeutic endpoint in vulnerable plaque management.

In resource-limited settings, CCTA may provide a practical gatekeeper role. Instead of routine intracoronary imaging in all patients undergoing angiography, CCTA may help identify patients with extensive non-obstructive plaque burden or high-risk plaque features who might benefit from intensification of medical therapy and, in selected cases, invasive plaque assessment. The strengths, limitations, and potential future roles of currently available and emerging diagnostic modalities are summarised in Table 1.

## Imaging of Perivascular Fat and Radiomics, Artificial Intelligence

Artificial Intelligence (AI) and radiomics may further enhance the value of CCTA. Traditional visual interpretation can only extract a small fraction of the information present in CT datasets. Radiomics can extract high-dimensional quantitative features related to plaque texture, attenuation heterogeneity, vessel geometry, and perivascular tissue characteristics. These features may be combined with clinical variables, laboratory markers, and longitudinal data by machine-learning algorithms to create individualized risk prediction.

Another promising marker is the perivascular fat attenuation index. Perivascular adipose tissue is a surrogate for local vascular inflammation because inflammatory signals from the coronary wall affect adipocyte lipid content and CT attenuation. Perivascular fat assessment could thus offer indirect information on coronary inflammation, complementing anatomical plaque assessment.[23] In the future, CCTA may serve as a comprehensive non-invasive coronary vulnerability platform integrating plaque morphology, perivascular inflammation, coronary flow modeling, and clinical risk.

By enabling automated plaque characterization, quantitative assessment of plaque burden, and individualized risk prediction, AI-enhanced CCTA may help narrow the traditional gap between non-invasive and invasive plaque assessment, although prospective outcome validation remains essential.

However, AI-CCTA for Indonesia should be treated pragmatically. Its promise is contingent on scanner quality, standardized acquisition protocols, computational infrastructure, validation in local populations, and reimbursement policy. As an expert position, ISIC considers that broad adoption of proprietary AI-CCTA platforms should be preceded by local validation, demonstration of incremental clinical value, and evaluation of cost-effectiveness.[13-14] Local validation studies and registries should therefore be prioritized.

**Table 1.** Complementary roles of contemporary imaging modalities in high-risk coronary plaque assessment.

| Imaging modality | Principal information provided | Major strengths | Main limitations | Clinical implication |
|---|---|---|---|---|
| CCTA | Plaque burden, phenotype, low-attenuation plaque, positive remodeling | Non-invasive, scalable, AI-assisted quantitative analysis | Limited fibrous-cap resolution; affected by calcification/ motion | First-line risk stratification and selection for further evaluation |
| IVUS | Plaque burden, remodeling, lumen dimensions | Excellent penetration; PCI optimization | Limited fibrous-cap resolution | Structural plaque assessment and PCI optimization |
| OCT | Fibrous cap, rupture, erosion, macrophages, thrombus | Highest spatial resolution | Limited penetration; contrast required | Assessment of plaque vulnerability and procedural guidance |
| NIRS-IVUS | Lipid-core burden (maxLCBI4mm) | Direct lipid assessment | Limited availability | Refines lesion-level risk in specialized centers |

Notes: No single imaging modality captures all dimensions of coronary plaque vulnerability. CCTA provides a scalable non-invasive assessment of plaque burden and phenotype, whereas IVUS, OCT, and NIRS offer complementary information on plaque structure, microarchitecture, and composition. Integrated interpretation of these modalities,

together with clinical characteristics, circulating biomarkers, and OMT, may improve patient selection for advanced imaging or selective preventive PCI. Routine use of invasive imaging should remain individualized and guided by clinical context, expected impact on management, and resource availability.

### Molecular Imaging

Molecular imaging offers a biologically attractive approach, as plaque destabilization is driven not only by morphology but also by inflammation, microcalcification, apoptosis, protease activity, and thrombosis. Positron Emission Tomography (PET) using tracers such as 18F-fluorodeoxyglucose and 18F-sodium fluoride has been investigated for the detection of vascular inflammation and active microcalcification.[24-25] Experimental tracers that target macrophages, integrins, somatostatin receptors, fibrin, and matrix metalloproteinases may further refine biological characterization.

Although it has scientific interest, molecular imaging may not be a routine tool for vulnerable plaque screening in Indonesia in the near future. Its scalability is limited by cost, limited availability, radiation exposure, tracer logistics, and uncertain treatment implications. Its most appropriate role may be in research, drug development, and selected tertiary center evaluation of inflammatory plaque biology. Molecular imaging may identify which systemic therapies alter plaque inflammation and which biological phenotypes remain high-risk despite optimal conventional therapy.

## Future Directions in Invasive Diagnosis

### Intravascular Ultrasound (IVUS)

IVUS remains one of the cornerstones of intracoronary imaging modalities. It allows deep tissue penetration and quantification of vessel size, plaque burden, remodeling, and minimum lumen area. IVUS-derived plaque burden has been consistently associated with future events, and plaque burden ≥70% has been one of the most reproducible high-risk features in prospective studies.[15]

Future IVUS platforms may increasingly be combined with radiofrequency analysis, automated plaque quantification, co-registration with angiography, and AI-assisted interpretation. IVUS may be especially useful in large vessels, left main disease, diffuse atherosclerosis, and situations where contrast load must be minimized. In many centers in Indonesia, IVUS is more available than OCT and may therefore represent the most practical invasive platform for early adoption of plaque-guided strategies.

IVUS does have limitations, however. Its axial resolution is insufficient to directly measure thin fibrous caps or to identify microstructural features of plaque erosion. Virtual histology and other tissue characterization algorithms have improved plaque classification, but are not equivalent to histology. Thus, IVUS should be used to detect plaque burden and remodeling rather than as an independent tool for all dimensions of vulnerability.

### Optical Coherence Tomography

Among the intracoronary imaging modalities available for clinical use, OCT offers the highest resolution. It can directly assess fibrous cap thickness, lipid arc, macrophage accumulation, microchannels, calcification, plaque rupture, plaque erosion, and thrombus. OCT is thus uniquely suited to characterize TCFA and mechanisms of ACS.[16-17]

Within the high-risk plaque framework, OCT occupies a particularly important position because it is the only clinically available intracoronary imaging modality that can directly measure fibrous cap thickness in vivo. In addition to identifying TCFA, OCT may help characterize plaque rupture, plaque erosion, thrombus, macrophage accumulation, microchannels, calcific nodules, and healed plaque. Therefore, OCT may be especially useful when preventive PCI is being considered, provided that the result will meaningfully alter management.

OCT could play two major roles in the future management of vulnerable plaque. First, it can improve risk stratification in non-flow-limiting lesions when preventive PCI is considered. Second, it can optimize PCI by providing adequate lesion preparation, stent expansion, apposition, and edge assessment.[26] Preventive PCI is performed in lesions that may not yet be ischemia-producing, raising ethical and clinical issues regarding procedural safety and optimization.

Cost, the need for contrast injection, limited penetration depth, and the requirement for expertise are the main barriers to OCT. OCT should not be used as a general screening tool indiscriminately in Indonesia. Instead, it should be concentrated in centers with proper training and applied to carefully selected cases, including ambiguous culprit lesions, high-risk non-culprit lesions in patients with recurrent events, and research registries. In research settings, serial OCT or IVUS may also provide valuable surrogate markers of plaque stabilization

or regression during intensive lipid-lowering or anti-inflammatory therapy, although their routine use for treatment monitoring cannot currently be recommended.

### Near-Infrared Spectroscopy and Multimodal Imaging

NIRS detects lipid-rich plaques by their chemical signature and quantifies lipid burden using parameters such as the maximum lipid-core burden index within any 4-mm segment (maxLCBI4mm). NIRS is often combined with IVUS, allowing simultaneous evaluation of lipid content and plaque structure. Studies have demonstrated that lipid-rich plaques detected by NIRS-IVUS are associated with future coronary events.[18-19]

Multimodality imaging is an important future direction, because no single modality captures all dimensions of vulnerability. OCT provides microstructural detail, IVUS provides plaque burden and vessel remodeling, NIRS provides lipid content, and angiography provides procedural orientation. Future hybrid catheters or integrated software platforms might combine structural, compositional, biological, and hemodynamic information into a single vulnerability score. A next step in hybrid intravascular imaging is the integration of Optical Coherence Tomography with Near-Infrared Spectroscopy (OCT–NIRS) in a single catheter. By combining the very high axial resolution of OCT for assessment of fibrous cap thickness and microstructure with the compositional information of NIRS on lipid burden, OCT–NIRS has the theoretical potential to identify TCFA with large lipid cores and macrophage-related optical signals within one pullback, thereby improving selection of lesions for preventive PCI compared with single-modality imaging. First-in-human experience with a next-generation combined DeepOCT–NIRS system suggests that such multimodality catheters can provide enhanced plaque characterization and procedural guidance, although their clinical impact on outcomes and cost-effectiveness still needs to be established in larger studies.[27]

However, hybrid imaging may remain expensive and restricted to specialized centers. Its future role in Indonesia should be assessed through specific clinical research, not by immediate routine implementation.

Future patient selection will likely evolve beyond plaque morphology alone by integrating complementary physiological and biological information, although the precise role of coronary physiology, endothelial function, and microvascular assessment in selecting candidates for preventive PCI remains to be established.

## Pharmacological Treatment: The Mainstay of Plaque Stabilization

Any discussion of vulnerable plaque management must start with pharmacological therapy. Systemic therapy is directed at the entire coronary tree, not just a single imaged lesion. The advantage of this is crucial, as vulnerable plaques are often multiple, dynamic, and located within diffuse atherosclerosis.

### Biomarkers, Residual Risk, and the High-Risk Patient

Plaque imaging describes local lesion-level vulnerability, whereas circulating biomarkers reflect the systemic milieu that determines whether plaque disruption becomes clinically manifest. Lipid-related markers such as LDL cholesterol, non-HDL cholesterol, apolipoprotein B (Apo B), triglyceride-rich lipoproteins or remnant cholesterol, and Lipoprotein(a) [Lp(a)] may identify residual atherogenic risk not fully captured by angiographic stenosis or a single plaque phenotype. ApoB is particularly useful when LDL cholesterol and atherogenic particle number are discordant, whereas Lp(a) represents a largely genetically determined risk modifier that remains relevant even when LDL cholesterol is well controlled.[28-29]

Inflammatory biomarkers provide complementary information on patient-level vulnerability. High-sensitivity C-reactive protein (hs-CRP) is the most practical marker of residual inflammatory risk, while the interleukin-1β, interleukin-6, and NLRP3 inflammasome pathways provide mechanistic links between systemic inflammation, endothelial injury, plaque destabilization, and thrombosis.[30–32] The clinical implications remain context-dependent because benefits from anti-inflammatory treatment have varied across patient populations.[33]

Metabolic and renal factors, including diabetes, glycaemic control, CKD, smoking, obesity, thrombogenicity, and bleeding risk, further modify the probability that an imaging-defined high-risk plaque will produce a clinical event. In Indonesia, readily available measurements—including a standard lipid profile, glycated hemoglobin (HbA1c), and renal function, with hs-CRP, ApoB, and at least one lifetime Lp(a) measurement in selected patients where feasible—may help prioritize intensive systemic prevention before costly invasive plaque

assessment. Biomarkers should complement, not replace, plaque imaging.

The concept of plaque healing further reinforces the central role of systemic therapy. Plaque stabilization is not limited to lipid-core regression or fibrous cap thickening; it also includes favorable biological healing following subclinical plaque disruption. In this context, OMT may reduce risk not only by modifying plaque morphology but also by improving the systemic milieu that determines whether plaque disruption becomes clinically manifest as thrombosis.

## Aggressive Lipid-Lowering Therapy

Statins remain the mainstay of plaque stabilization. High-intensity statin therapy reduces cardiovascular events, induces plaque regression, increases fibrous cap thickness, reduces lipid content, and exerts anti-inflammatory effects.[34-35] Ezetimibe adds benefit for LDL cholesterol lowering and outcomes when added to statins, especially after ACS.[36] PCSK9 inhibitors further lower LDL cholesterol and reduce cardiovascular events in high-risk patients.[37-38] Multimodality imaging in PACMAN-AMI showed favorable changes in plaque burden, lipid content, and fibrous cap thickness when alirocumab was added to high-intensity statin therapy.[39]

Future lipid management may increasingly focus on earlier, deeper, and more durable reductions in LDL cholesterol. Inclisiran, a small interfering RNA therapy targeting PCSK9 synthesis, is administered twice yearly and may enhance adherence, although outcome data remain an important consideration.40 Inhibition of ANGPTL3 and other emerging lipid pathways may become relevant for select patients with refractory dyslipidemia.

Another major future target is Lp(a). High Lp(a) levels are genetically determined and associated with atherosclerotic cardiovascular disease. Antisense oligonucleotides and small interfering RNA therapies targeting Lp(a) are being investigated, including pelacarsen and olpasiran. If outcome trials are positive, Lp(a)-lowering therapy might become an important component of precision prevention in patients with residual risk despite optimal LDL cholesterol control.[29]

For Indonesia, the biggest near-term opportunity remains improving access and adherence to proven, affordable lipid-lowering therapy. From a public-health perspective, improving access and adherence to proven, affordable therapies such as high-intensity statins and ezetimibe may provide broader population-level benefit before widespread deployment of costly advanced imaging or intervention.[12,14] PCSK9 inhibitors, inclisiran and future Lp(a) therapies should be initially reserved for very-high-risk patients within evidence-based and economically sustainable frameworks.

## Anti-inflammatory treatment

Inflammation is central to plaque initiation, progression, destabilization, and thrombosis. The CANTOS trial showed that targeting interleukin-1β reduced recurrent cardiovascular events regardless of lipid lowering, providing proof of concept for inflammatory risk reduction.[30] Colchicine has since become a more practical anti-inflammatory therapy. Low-dose colchicine has been shown to reduce cardiovascular events in trials in post-myocardial infarction and chronic coronary disease populations.[31-32] Plaque-specific imaging data from COLOCT suggested favorable OCT changes in fibrous cap thickness and lipid or inflammatory features, whereas CLEAR SYNERGY did not reduce major cardiovascular events in a broad acute myocardial infarction population, highlighting the importance of clinical context and patient selection.[33,41]

Future anti-inflammatory strategies could focus on the NLRP3 inflammasome, the interleukin-6 pathway, residual inflammatory risk measured by hs-CRP, or imaging-defined coronary inflammation. However, anti-inflammatory therapy has to be balanced against cardiovascular benefit, infection risk, tolerability, drug interactions, and cost.

In Indonesia, a cheap and widely available drug such as colchicine is attractive. However, implementation should be guided by guideline-based indications, careful patient selection, assessment of renal function, and attention to gastrointestinal intolerance and drug interactions. In the absence of compelling cost-effectiveness data, broader implementation of expensive biologic anti-inflammatory agents may be difficult in Indonesia.

## Antiplatelet therapy

Plaque disruption causes clinical events through thrombosis. Antiplatelet therapy is still crucial after ACS and PCI, whereas some high-risk patients with chronic coronary disease could benefit from intensified antithrombotic strategies. However, antithrombotic intensification increases bleeding risk and does not directly stabilize plaque architecture. Future precision prevention will combine plaque burden, thrombotic risk, inflammatory markers, and bleeding risk to personalize antithrombotic therapy. A summary of current and emerging pharmacological strategies for plaque stabilization is presented in Table 2.

**Table 2.** Future pharmacological strategies for high-risk plaque stabilization.

| Therapeutic strategy | Primary mechanism | Current evidence | Main limitations | Clinical implication |
|---|---|---|---|---|
| High-intensity statins | LDL-C reduction | Established | Residual risk persists | Foundation therapy |
| Ezetimibe | Additional LDL-C reduction | Established | Moderate incremental efficacy | Early combination |
| PCSK9 inhibitors | Profound LDL-C lowering | Established in very-high-risk patients | Cost/access | Residual lipid risk |
| Inclisiran | PCSK9 synthesis inhibition | Outcome evidence evolving | Long-term data evolving | Adherence-enhancing option |
| Lp(a)-lowering therapy | Lp(a) reduction | Investigational | Outcome trials ongoing | Future precision therapy |
| Colchicine | Anti-inflammatory | Selected CAD evidence | Variable tolerability | Residual inflammatory risk |
| IL-1β/IL-6/NLRP3 | Targeted inflammation | Emerging | Cost/availability | Future therapy |
| Antithrombotic intensification | Reduce thrombosis | Established in selected patients | Bleeding risk | Individualised therapy |

This table summarises current and emerging pharmacological strategies aimed at reducing plaque vulnerability through modification of lipid burden, vascular inflammation, thrombosis, and other residual cardiovascular risk pathways. Contemporary management should prioritize aggressive systemic prevention, with intensive lipid-lowering therapy remaining the foundation of treatment. Novel therapies targeting Lp(a), inflammatory pathways, and thrombosis may further individualize treatment in selected patients, although several approaches remain investigational and should be implemented according to evolving clinical evidence, cost-effectiveness, and local healthcare resources.

Antiplatelet requirements are particularly important for preventive PCI. Treating non-flow-limiting plaques with a device exposes patients to Dual Antiplatelet Therapy (DAPT) and potential bleeding. Thus, device platforms that enable shorter DAPT without compromising safety may become attractive, particularly in patients at high bleeding risk.

## Preventive PCI: Promise, Limitations and Future Indications

Preventive PCI aims to seal or passivate vulnerable plaques before they rupture or erode, leading to ACS. The biological rationale is plausible. Stenting or scaffolding of a high-risk plaque may lead to the formation of a neointimal layer, sequestration of thrombogenic lipid core material from contact with the bloodstream, normalization of local wall stress, and enlargement of the lumen. The clinical question is whether this focal approach adds any meaningful benefit beyond OMT. Importantly, preventive PCI should be viewed as a focal mechanical strategy directed at carefully selected lesions, whereas high-risk coronary disease is often diffuse, dynamic, and biologically heterogeneous. Therefore, preventive PCI cannot substitute for systemic prevention and should be considered only when local plaque risk, patient-level vulnerability, and procedural feasibility converge. Moreover, because coronary atherosclerosis is fundamentally a diffuse systemic disease, coronary events frequently arise from multiple biologically active plaques distributed throughout the coronary tree. Consequently, successful treatment of a single high-risk plaque does not eliminate the patient's ongoing residual cardiovascular risk, underscoring why aggressive OMT and comprehensive risk-factor control must remain the cornerstone of management.

Early randomized evidence came from the PROSPECT ABSORB trial, which demonstrated that PCI of angiographically mild lesions with large plaque burden was feasible and could increase minimum lumen area, but was not powered to assess clinical events.[42] The PREVENT trial subsequently randomized patients with non-flow-limiting vulnerable plaques to preventive PCI plus OMT versus OMT alone. The trial showed a significant reduction in target vessel failure at 2 years and sustained benefit at longer follow-up.[11]

These results are important, but there are several issues which demand careful interpretation. PREVENT included selected patients, used intravascular imaging-defined criteria and was performed in experienced centers. The primary

composite endpoint included ischemia-driven revascularisation and hospitalization for unstable or progressive angina. The absolute rate of events was rather low, and the size of benefit for hard endpoints such as cardiovascular death or myocardial infarction needs further confirmation.

Importantly, the relative benefit demonstrated in PREVENT should not obscure the fact that the absolute risk of future events arising from any individual imaging-defined high-risk plaque remains relatively low. Consequently, the clinical value of preventive PCI depends less on plaque detection itself than on identifying patients with a sufficiently high absolute cardiovascular risk in whom the expected reduction in myocardial infarction or other clinically meaningful events outweighs procedural risk, prolonged DAPT, and healthcare resource utilization. This distinction reinforces the concept that preventive PCI should be regarded as a strategy for carefully selected high-risk patients rather than for imaging-positive plaques in general.

The future role of preventive PCI, therefore, should be selective rather than universal. Potential candidates may include patients with documented CAD and focal non-flow-limiting lesions with multiple high-risk imaging features, large plaque burden, recurrent events despite optimal therapy, diabetes, multivessel disease, or high-risk proximal coronary segments. Preventive PCI should not be performed solely because plaque appears lipid-rich or because advanced imaging is available.

In Indonesia, preventive PCI should initially be restricted to centers with expertise in intracoronary imaging, high procedural volume, established PCI quality metrics, and the capacity to participate in national registries. This cautious approach would protect patients, preserve resources, and generate local evidence.

## Choice of Device for Preventive PCI

### Drug-Eluting Stents

Current DES represent the most established device platform for PCI. They deliver well, have low restenosis rates, better polymer biocompatibility, thin struts, and a wealth of outcome data. If preventive PCI is performed today, the new-generation DES will likely remain the default device.

Conceptually, preventive PCI differs fundamentally from conventional PCI. In obstructive coronary lesions, permanent metallic stenting is justified because it relieves myocardial ischemia and prevents acute vessel closure. In contrast, in non-flow-limiting high-risk plaques, the anticipated benefit is preventive and probabilistic rather than immediate. Consequently, concerns have been raised regarding overtreatment, late stent failure, neoatherosclerosis, prolonged DAPT, and cumulative device burden, particularly in patients with diffuse CAD, where a permanent metallic implant may be placed in a lesion that might never have progressed to a clinical event. Therefore, despite stronger evidence for DES at present, it might not be the ideal long-term platform for preventive plaque sealing.

### Bioresorbable vascular scaffold

Bioresorbable Vascular Scaffolds (BVS) are conceptually attractive for the treatment of vulnerable plaque, as they can potentially provide temporary plaque sealing and mechanical support without the implantation of a permanent metallic device. However, the first-generation Absorb scaffold was limited by thick struts, a challenging implantation technique, increased scaffold thrombosis, and unfavorable safety signals compared with contemporary DES.[43] This experience appropriately tempered enthusiasm.

But the failure of first-generation devices does not invalidate the larger idea. Development of new-generation bioresorbable scaffolds should focus on thinner struts, improved radial strength, enhanced deliverability, optimized degradation kinetics, and alternative materials such as magnesium alloys or improved polymer platforms. Magnesium-based scaffolds and newer polymeric scaffolds with reduced risk of thrombosis and preservation of temporary plaque passivation are potential future candidates.

From an expert-consensus perspective, an optimal scaffold for preventive PCI would ideally seal the plaque, promote neocap formation, minimize inflammation, preserve vessel physiology, resorb predictably, and preserve future surgical or percutaneous options. Whether new-generation BVS can achieve this balance remains an open question. Their role should be investigational until large randomized data show safety and clinical benefit in vulnerable plaque populations.

### Drug-Coated Balloons

Another interesting future direction is DCB. The theoretical appeal is significant: deliver antiproliferative therapy without permanent implantation. In the management of vulnerable plaque, DCB could potentially modify the plaque surface, reduce neointimal proliferation after lesion

preparation, and avoid the need for a permanent metal or scaffold. Shorter DAPT requirements may also be appealing.

However, the present evidence base for DCB in de novo vulnerable plaques is minimal. Adequate lesion preparation is generally required for DCB therapy and is best established in in-stent restenosis and selected small-vessel de novo disease. Without a scaffold, treatment of lipid-rich vulnerable plaques may not reliably seal the fibrous cap or the lipid core. Aggressive lesion preparation can also theoretically injure a non-flow-limiting plaque and increase procedural risk.

Thus, DCB should be regarded as a hypothesis-generating future technology, rather than a current strategy for preventive plaque treatment. Research should elucidate whether DCB alone, DCB after mild plaque modification, or hybrid DCB-bioresorbable strategies can safely stabilize vulnerable plaques.

## Is there a role for CABG?

CABG does not directly treat vulnerable plaques. It does not seal thin fibrous caps, reduce local inflammation, or modify plaque composition. Thus, CABG should not be considered a vulnerable plaque therapy at the lesion level.

However, CABG may have an indirect protective role in certain patients with diffuse multivessel disease. CABG may protect the myocardium from future events in proximal segments by bypassing long segments of plaque-bearing coronary arteries, especially when durable arterial grafts, such as the left internal mammary artery to the left anterior descending artery, are used. This may, in part, explain the prognostic advantage of CABG in selected patients with diabetes, complex multivessel disease, or left main CAD.

**Table 3.** Future revascularisation and device strategies for high-risk plaque management.

| Strategy | Principal concept | Current evidence | Main limitations | Clinical implication |
|---|---|---|---|---|
| DES preventive PCI | Permanent plaque sealing | Supported by PREVENT | Permanent implant; overtreatment | Current default |
| 1st-generation BVS | Temporary scaffold | Unfavourable vs DES | Thrombosis risk | Historical lesson |
| New-generation BVS | Temporary plaque passivation | Emerging | Need RCTs | Potential future platform |
| Drug-coated balloon | Drug delivery without implant | Limited for plaque | No mechanical sealing | Investigational |
| CABG | Bypass plaque-bearing segments | Established | Not lesion-specific | Diffuse disease strategy |

This table summarises the current evidence and future perspectives regarding revascularisation strategies and device platforms for imaging-defined high-risk coronary plaque. Contemporary DES represent the most established platform when preventive PCI is considered, whereas new-generation BVS and DCB remain investigational approaches requiring further clinical validation. CABG should be regarded as a patient-level revascularisation strategy for diffuse or complex CAD rather than as a lesion-level therapy for vulnerable plaque.

Within the vulnerable plaque framework, CABG should be considered at the patient-phenotype level, not the plaque level, in the future. Patients with diffuse high-risk atherosclerosis, diabetes, complex anatomy, impaired ventricular function, or high SYNTAX score may benefit more from surgical revascularisation than from repeated focal PCI of multiple non-flow-limiting plaques. This underscores the importance of multidisciplinary Heart Team decision-making. The potential roles, advantages, limitations, and future directions of preventive revascularisation strategies are summarised in Table 3.

## Resource-Aware Implementation in Indonesia

A different strategy is required for the Indonesian context. Advanced plaque imaging and preventive PCI may benefit selected patients, but indiscriminate use may increase costs without commensurate population-level benefit. A national approach should rest on five principles: optimization of systemic prevention, clinical selectivity, economic responsibility, local data generation, and workforce readiness. In Indonesia, adoption of the high-risk plaque concept should not imply indiscriminate expansion of advanced imaging or preventive PCI.

Rather, the Vergallo framework should be adapted as a risk-stratification concept to identify which patients may benefit most from intensified medical therapy, selective imaging, registry enrolment, or highly selected focal intervention.

First, OMT needs improvement. Indonesia should focus on improving access to high-intensity statins, adherence programs, smoking cessation, hypertension control, management of diabetes, cardiac rehabilitation, and secondary prevention post-ACS. These are scalable interventions and are likely to have the greatest benefit to society.

Second, advanced imaging should be used judiciously. CCTA may be the most scalable non-invasive platform for risk stratification, whereas IVUS and OCT should be concentrated in tertiary centers and reserved for patients in whom imaging results will alter management. Given current infrastructure and resource constraints, routine intracoronary imaging of all angiographic lesions may be difficult to justify outside selected clinical scenarios, registries, or research programs.[13-14]

Third, preventive PCI should be introduced as part of structured programs rather than through unregulated expansion. Candidate lesions should ideally meet the rigorous criteria used in randomized trials: non-flow-limiting physiology, significant plaque burden, multiple imaging-defined high-risk features, and a patient-level high-risk phenotype. Procedures should be performed by trained operators using optimized, imaging-guided PCI techniques.

Fourth, Indonesia needs country data. A national high-risk plaque registry should capture patient characteristics, imaging findings, treatments, devices, procedural details, medications, costs, and long-term clinical outcomes. Without local data, policy decisions will be based entirely on extrapolation from elsewhere.

Finally, human-resource development is essential. Technology without adequate expertise may expose patients to avoidable harm. Standardized training in OCT, IVUS, CCTA plaque interpretation, physiological assessment, and preventive PCI decision-making should be implemented. Imaging core laboratories and competency-based certification may help to reduce variability and improve quality. From a health-system perspective, indiscriminate plaque detection may increase procedural volume without proportionate clinical benefit. Therefore, the principal objective of advanced imaging should be to improve patient selection rather than to maximize plaque detection.

## Proposed Algorithm for the Future

An Indonesian algorithm may pragmatically start with patient-level risk assessment, not plaque hunting. All patients with established CAD should be treated with optimized medical therapy. Further risk stratification may be considered in patients with recurrent events, diabetes, multivessel disease, premature coronary disease, or extensive plaque burden on non-invasive imaging. CCTA can detect the diffuse high-risk plaque phenotype. Invasive imaging may then be considered if the result will influence the choice of treatment. Preventive PCI may be considered for focal lesions with non-flow-limiting physiology but multiple high-risk features in patients at high absolute risk. Diffuse multivessel high-risk anatomy may warrant consideration of CABG, as surgical revascularisation may provide wider myocardial protection.

This stepwise approach is intended to align technological innovation with healthcare sustainability. The proposed diagnostic pathway for high-risk coronary plaque assessment in Indonesia is illustrated in Figure 2. The proposed algorithm deliberately begins with patient-level risk assessment rather than plaque identification, reflecting the principle that patient selection is more important than plaque detection alone.

## ISIC Position Statement

The ISIC recognizes and adopts the contemporary transition from the traditional vulnerable plaque paradigm to the broader concept of high-risk plaque, as emphasized in the 2025 JACC Cardiovascular Imaging Position Statement by Vergallo and colleagues. Coronary thrombosis may arise from rupture-prone plaques, erosion-prone plaques, or eruptive calcified nodules. Therefore, risk assessment should integrate plaque morphology, plaque burden, inflammatory activity, endothelial injury, healing capacity, local hemodynamic conditions, myocardial territory at risk, and patient-level vulnerability. The proposed ISIC adaptation of major and minor high-risk plaque features is presented in Table 4. The ISIC also recognizes that advances in intracoronary imaging have substantially improved contemporary understanding of coronary plaque biology and vulnerability. Imaging-defined high-risk plaque characteristics are associated with increased future cardiovascular risk and provide prognostic information beyond angiographic stenosis severity alone.

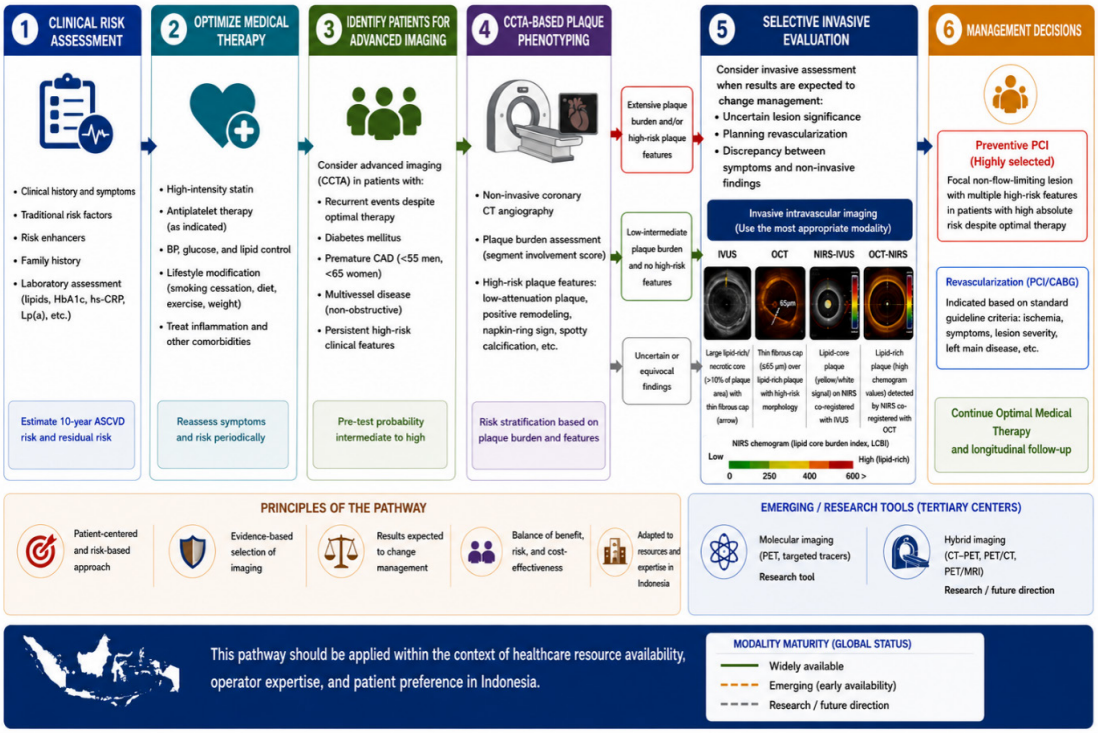


**Figure 2.** Proposed diagnostic pathway for high-risk coronary plaque assessment in Indonesia. This figure presents a stepwise diagnostic pathway beginning with clinical risk assessment and optimization of medical therapy. Patients with recurrent events, diabetes, premature CAD, multivessel disease, or persistent high-risk clinical features may undergo CCTA-based plaque phenotyping, followed by selective invasive evaluation with IVUS, OCT, or NIRS-IVUS when the findings are expected to change management. Preventive PCI is considered only for focal non-flow-limiting lesions with multiple high-risk plaque features in patients with high absolute clinical risk. The pathway should be interpreted as a resource-aware clinical framework rather than a mandate for routine plaque screening.

**Table 4.** Proposed ISIC adaptation of high-risk plaque features.

| Domain | Representative features | Clinical implication | Role in patient selection |
|---|---|---|---|
| Plaque morphology | Thin cap, lipid core, plaque burden | Higher lesion vulnerability | Lesion-level risk |
| Plaque biology | Inflammation, endothelial injury | Active disease | Biological risk |
| Biomarkers | LDL-C, ApoB, Lp(a), hsCRP | Residual risk | Patient-level risk |
| Clinical modifiers | Diabetes, CKD, recurrent ACS | Higher absolute risk | Patient selection |
| ISIC interpretation | Integrated assessment | No single feature sufficient | Individualised decisions |

This table presents the proposed ISIC framework for integrating plaque morphology, biological activity, systemic biomarkers, and clinical characteristics of assessing high-risk coronary plaque. The proposed classification is intended to facilitate comprehensive risk stratification rather than provide automatic indications for preventive PCI. Decisions regarding treatment escalation should integrate plaque characteristics with patient-level vulnerability, expected absolute cardiovascular risk, procedural feasibility, anticipated clinical benefit, and healthcare resource considerations.

The ISIC supports the use of major and minor high-risk plaque features as a conceptual framework for risk stratification. However, in the Indonesian context, these features should not be interpreted as automatic indications for preventive PCI. Instead, they should be used to guide the intensification of OMT, the selective use of advanced imaging, structured follow-up, and carefully selected interventions in experienced centers.

However, current evidence remains insufficient to support routine preventive PCI for all non-flow-limiting imaging-defined vulnerable plaques. Most vulnerable plaques do not subsequently rupture or produce clinical events, and coronary atherosclerosis fundamentally represents a diffuse systemic disease process requiring comprehensive systemic preventive therapy.

Aggressive OMT, therefore, remains the foundation of management for patients with high-risk coronary plaque. Intensive lipid lowering, anti-inflammatory therapy, smoking cessation, glycaemic control, blood pressure optimization, and lifestyle modification should remain central therapeutic priorities. Assessment of residual lipid, inflammatory, metabolic, and renal risk should complement plaque imaging and guide the intensity of systemic prevention.

Advanced intracoronary imaging using OCT, IVUS, NIRS, or hybrid imaging approaches may be considered in selected patients to further characterize plaque morphology, plaque burden, and biological plaque activity, particularly in complex coronary disease or in patients with high residual cardiovascular risk.

Preventive PCI may be considered selectively in carefully selected patients with multiple converging high-risk plaque features, particularly when supported by advanced intracoronary imaging and performed at experienced centers with expertise in imaging-guided PCI. Key ISIC considerations regarding the use of preventive PCI are summarised in Table 5.

Routine preventive PCI for all imaging-positive plaques is not currently recommended. Decisions regarding preventive PCI should integrate plaque morphology, patient-level vulnerability, ischaemic burden, procedural feasibility, bleeding risk, anticipated exposure to DAPT, and healthcare resource considerations.

The ISIC additionally recognizes the importance of ongoing clinical trials and future technological advances, including OCT-NIRS integration, AI-assisted plaque analysis, computational hemodynamic modeling, and biological imaging approaches, which may further refine future preventive strategies.

Accordingly, the ISIC supports a cautious, evidence-based, imaging-guided, and highly selective approach to preventive PCI, pending further evidence on hard clinical outcomes, long-term safety, cost-effectiveness, and optimal patient selection. For clarity, the key ISIC position statements are summarised in Table 6.

**Table 5.** Proposed ISIC considerations for preventive PCI.

| Clinical scenario | Recommendation | Principal rationale | Clinical implication |
|---|---|---|---|
| Optimal medical therapy | Mandatory | Foundation of care | All patients |
| TCFA alone | Not sufficient | Low absolute event rate | Do not PCI on morphology alone |
| Multiple high-risk features | Consider | Higher event probability | Individualised selection |
| Diabetes/residual risk | Consider | Higher absolute risk | Integrate imaging |
| Diffuse disease | Prioritise systemic therapy | Competing plaques | Avoid focal-only strategy |
| Routine PCI for all imaging-positive plaques | Not recommended | Insufficient evidence | Avoid overtreatment |

This table summarises the practical considerations proposed by the Indonesian Society of Interventional Cardiology (ISIC) regarding preventive PCI. The recommendations emphasize that aggressive OMT remains mandatory first-line treatment and that preventive PCI should be reserved for carefully selected patients in whom multiple plaque-related and patient-level risk factors converge. These considerations are intended to support clinical judgment rather than replace individualized multidisciplinary decision-making.

**Table 6.** Key ISIC position statements on high-risk coronary plaque and selective preventive PCI.

| Key recommendation | Supporting concept | Strength | Clinical implication |
|---|---|---|---|
| Integrated high-risk coronary phenotype | Beyond vulnerable plaque | Core | Precision prevention |
| Integrate plaque + patient biology | Multidimensional risk | Core | Comprehensive assessment |
| OMT cornerstone | Systemic disease | Strong | Mandatory first-line |
| Selective CCTA | Gatekeeper | Conditional | Patient selection |
| Selective IVUS/OCT/NIRS | Change management | Conditional | Complementary imaging |
| Selective preventive PCI | High absolute risk | Conditional | Carefully selected patients |
| No routine PCI for all imaging-positive plaques | Avoid overtreatment | Not recommended | Evidence insufficient |
| DES current standard | Technology evolving | Current evidence | Individualised device |
| Resource-aware implementation | Indonesian context | Priority | Sustainable adoption |

This table summarises the principal recommendations of the Indonesian Society of Interventional Cardiology (ISIC) regarding the contemporary management of high-risk coronary plaque. These position statements reflect the current balance of available evidence and emphasize that OMT remains the cornerstone of management, whereas advanced coronary imaging and preventive PCI should be applied selectively in carefully chosen patients. The recommendations are expected to evolve as further evidence emerges from ongoing clinical trials, technological innovation, and future studies evaluating long-term clinical outcomes and cost-effectiveness.

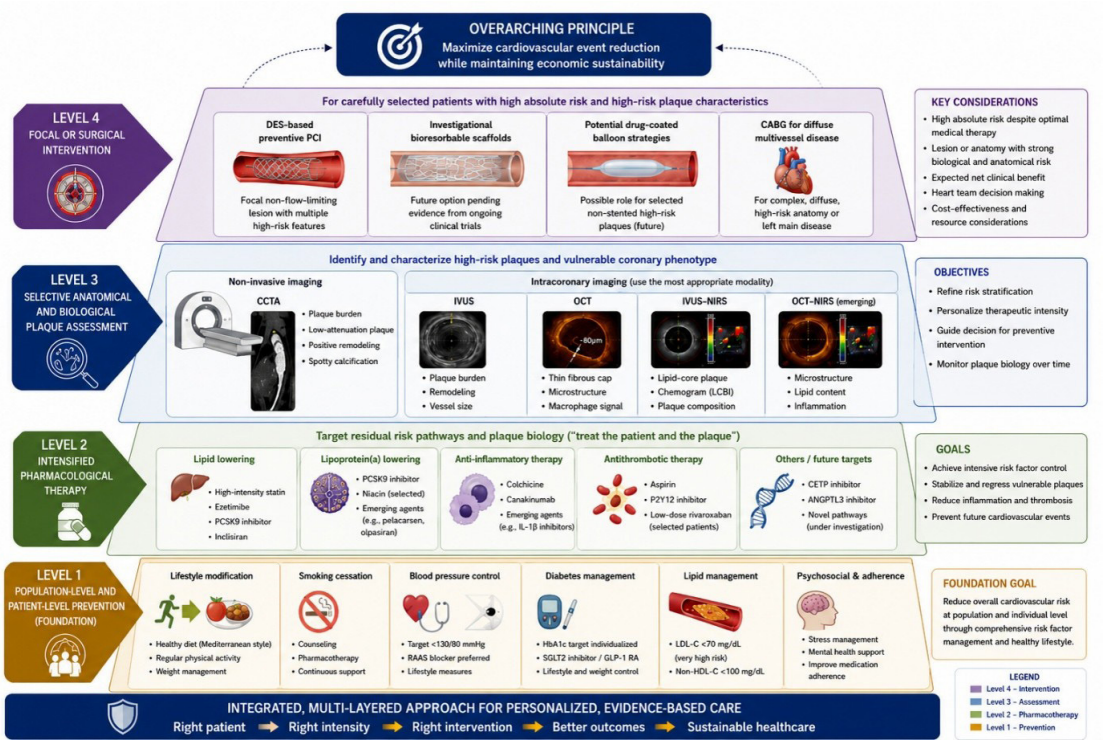


**Figure 3.** Future therapeutic framework for high-risk coronary plaque management.
This figure illustrates a layered therapeutic framework for high-risk coronary plaque management. The foundation is population-level and patient-level prevention, including lifestyle intervention, smoking cessation, blood pressure control, diabetes management, lipid lowering, and psychosocial risk reduction. Subsequent layers include intensified pharmacological therapy, selective anatomical and biological plaque assessment, and focal or surgical intervention in carefully selected patients. The framework emphasises that OMT remains the foundation of care, while preventive PCI and other revascularisation strategies should complement, not replace, systemic prevention.

## Conclusion

The future of coronary vulnerable and high-risk plaque management should focus not merely on detecting vulnerable lesions, but on identifying high-risk plaques, high-risk patients, and high-risk coronary phenotypes in whom additional diagnostic or therapeutic escalation is likely to improve clinical outcomes.

Consistent with the ISIC position statement, OMT remains the foundation of management for patients with high-risk coronary plaque. Advanced imaging modalities, including CCTA, IVUS, OCT, NIRS, and emerging hybrid technologies, may improve risk stratification and guide individualized treatment in selected patients. Preventive PCI remains a promising but highly selective strategy and should not be routinely applied to all imaging-defined vulnerable plaques pending further evidence. The overall future therapeutic framework integrating prevention, imaging, pharmacological therapy, and selective intervention is illustrated in Figure 3.

The ISIC recognizes that the framework proposed by Vergallo and colleagues provides an important conceptual advance. Nevertheless, in Indonesia and other resource-limited healthcare systems, this framework must be implemented pragmatically. The priority should remain aggressive, affordable, and scalable systemic prevention, while advanced imaging and preventive PCI should be reserved for patients in whom the expected absolute benefit justifies procedural risk and resource use.

For Indonesia, future implementation should be pragmatic, evidence-based, and resource-conscious, balancing technological innovation with healthcare sustainability while maximizing cardiovascular risk reduction at both the patient and population levels.

In the view of ISIC, the future value of precision prevention will depend less on detecting an increasing number of high-risk plaques and more on identifying patients in whom additional intervention meaningfully reduces myocardial infarction and cardiovascular death. Patient selection therefore remains more important than plaque detection alone.

## List of Abbreviations

| | |
|---|---|
| ACS | Acute Coronary Syndrome |
| AI | Artificial Intelligence |
| Apo B | Apolipoprotein B |
| BVS | Bioresorbable Vascular Scaffold |
| CABG | Coronary Artery Bypass Grafting |
| CAD | Coronary Artery Disease |
| CCTA | Coronary Computed Tomography Angiography |
| CKD | Chronic Kidney Disease |
| DAPT | Dual Antiplatelet Therapy |
| DCB | Drug-Coated Balloon |
| DES | Drug-Eluting Stent |
| HbA1c | glycated hemoglobin |
| hs-CRP | high-sensitivity C-Reactive Protein |
| ISIC | Indonesian Society of Interventional Cardiology |
| IVUS | Intravascular Ultrasound |
| LDL-C, | Low-Density Lipoprotein Cholesterol |
| Lp(a) | Lipoprotein(a) |
| maxLCBI4mm, | maximum lipid-core burden index within any 4-mm segment |
| NIRS | Near-Infrared Spectroscopy |
| OCT | Optical Coherence Tomography |
| OMT | Optimal Medical Therapy |
| PCI | Percutaneous Coronary Intervention |
| PET | Positron Emission Tomography |
| RCT | Randomized Controlled Trials |
| TCFA | Thin-Cap Fibroatheroma. |

## Ethical Clearance

Not applicable.

## Publication Approval

All authors consent to the publication of this manuscript.

## Authors Contributions

All authors contributed to the conception, drafting, and revision of the article, provided final approval for publication, agreed on the journal, and took accountability for all aspects of work.


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None.

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