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Perspective Article

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# The Pandemic That Exposed the Truth: Only Vulnerability-Guided Complete Revascularization Prevents MI and Death

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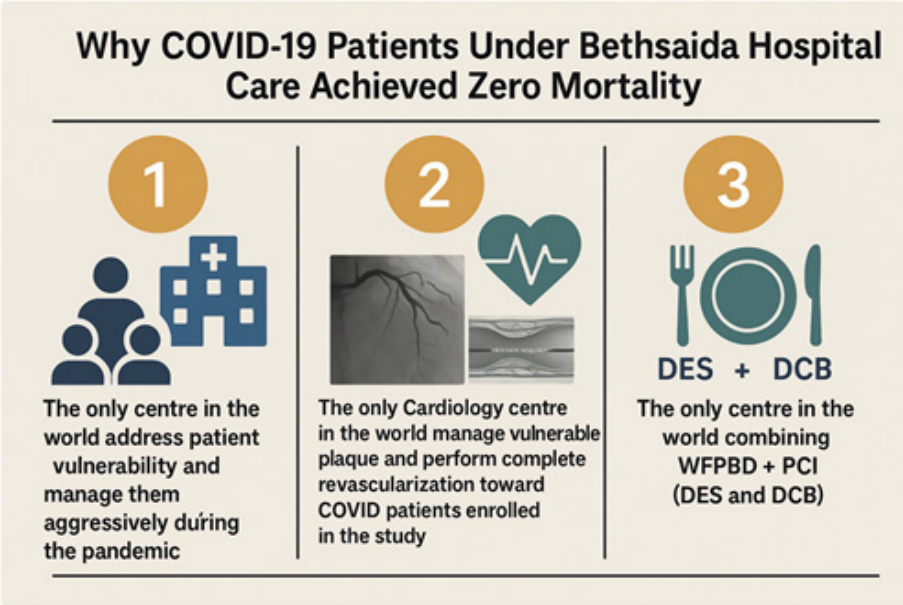
## Abstract

*For fifty years, cardiology has followed a stenosis-centric dogma—mistaking a narrowed lumen for a lethal plaque and assuming ischemia inevitably dictates a patient's fate. Yet the global convergence of multimodality imaging, pathology, and contemporary trials now reveals a striking contradiction: the plaques that kill are not the tight, ischemia-producing stenoses targeted by guidelines, but the biologically unstable, angiographically "mild," FFR-negative lesions that silently rupture or erode. In this perspective—anchored in PROSPECT, PROSPECT ABSORB, PREVENT, DEBuT-LRP, CLIMA, LRP, emerging AI-based risk models, and a unique pandemic cohort—we argue that MI is fundamentally a disease of plaque vulnerability rather than stenosis severity.*

*The COVID-19 era provided the ultimate real-world stress test: a global inflammatory surge that amplified plaque instability and exposed the fatal limitations of ischemia-driven decision-making. During this period, Bethsaida Hospital, led by Prof. Dasaad Mulijono, implemented an unprecedented vulnerability-guided strategy combining routine CTCA, selective preventive PCI for VPs, ultra-low LDL targets, metabolic optimization, and WFPBD therapy. Among 3,500 COVID-positive or exposed patients, this approach achieved zero mortality, demonstrating that treating biological risk—not luminal narrowing—can alter the natural history of coronary disease, even before modern vulnerability-guided trials were published.*

*This manuscript advances a disruptive thesis: treating stenosis relieves angina, but treating vulnerability prevents MI and death. We show why ischemia testing fails, why FFR cannot identify high-risk lesions, how AI reveals the dominance of morphobiological risk over luminal risk, and why the next generation of trials must randomize patients based on plaque biology rather than percent stenosis. A new era of coronary care is emerging—one in which OCT, IVUS, NIRS, CTCA, and computational shear-stress mapping form the backbone of risk assessment; preventive PCI, especially with DCB therapy, is directed at rupture-, erosion-, and calcium-driven substrates; WFPBD restores endothelial health and reduces pan-coronary vulnerability; and AI enables precision prevention. The stenosis paradigm has reached its scientific end. A vulnerability-centred framework offers a more mechanistically coherent, ethically defensible, and clinically transformative path toward making MI a preventable event rather than an unpredictable catastrophe.*

**Keywords:** Intervention, Prevent myocardial infarction, Death, COVID pandemic, Vulnerable plaque, Multimodality imaging, Plaque rupture, Plaque erosion, Calcified nodules, Preventive PCI, Drug-Eluting stent, Drug-Coated balloon, Post-COVID cardiovascular risk, Whole-Food plant-based diet, Plaque Stabilization, Artificial intelligence, Bethsaida hospital




## 1. Introduction

The COVID-19 pandemic profoundly disrupted cardiovascular care worldwide. Percutaneous coronary intervention (PCI) volumes declined by an estimated 30–50%, patients with myocardial infarction (MI) frequently presented late, MI mortality increased dramatically, and many catheterization laboratories operated with limited personnel and significant logistical constraints [1–4]. In this environment, strict adherence to conventional guideline-based algorithms—predicated on intervening only in lesions causing >70% stenosis or demonstrable ischemia—became increasingly complex and, in many cases, clinically inadequate. These pressures exposed a fundamental limitation of the ischemia-centric paradigm: most MIs do not arise from severe, flow-limiting stenoses, but from biologically vulnerable, non-ischemia-producing plaques [5–9].

Consequently, the pandemic compelled a return to first principles in coronary pathophysiology, prompting the field to re-examine a fundamental question: what truly precipitates MI?

### 1.1. Real-World Data from Bethsaida Hospital: A Cohort of 3,500 COVID-19 Patients with Zero Mortality

From 2020 to 2023, Bethsaida Hospital implemented a comprehensive cardiovascular prevention strategy to mitigate the heightened risk of plaque instability during the COVID-19 pandemic. The program incorporated routine computed tomography coronary angiography (CTCA) to identify vulnerable plaque (VP) in patients who sought to reduce their risk of MI and death during this period. This approach was grounded in the well-established observation that most ambulatory ischemic episodes occur without chest pain and that up to 70% of angina presentations are accompanied by a normal ECG and treadmill test [10].

To address this concealed burden of risk, we provided selective pre-emptive PCI—using either drug-eluting stents (DES) or drug-coated balloons (DCB)—for lesions with high-risk features, even when stenosis severity was below the conventional thresholds of 50–70%. This interventional strategy was complemented by intensive lipid-lowering therapy to achieve ultra-low LDL cholesterol levels, strict adherence to a whole-food plant-based diet (WFPBD), targeted anti-inflammatory and metabolic optimization, and close, continuous outpatient surveillance [11–13].

Within this framework, more than 3,500 patients with confirmed COVID-19 infection or significant exposure were managed without a single recorded mortality. This outcome stands in marked contrast to contemporaneous global data demonstrating substantial increases in cardiovascular deaths during the pandemic. Although observational, this experience provides a compelling real-world signal that prioritizing plaque vulnerability—rather than stenosis severity alone—may meaningfully reduce fatal events, particularly during periods of systemic healthcare disruption.

## 2. ISCHEMIA Revisited: A Paradigm Failure—Not a Failure of PCI

The ISCHEMIA trial is often cited as evidence that PCI does not prevent MI or death [14-16]. However, a detailed scientific appraisal reveals a different conclusion: ISCHEMIA did not test the biological hypothesis that PCI prevents MI, because it did not target the lesions responsible for future events [7, 17-20]. The trial's neutral outcomes reflect limitations in lesion selection and revascularization strategy—not the ineffectiveness of PCI when directed at the correct risk substrates.

### 2.1 ISCHEMIA Treated the Wrong Lesions

Patient selection in ISCHEMIA was based exclusively on ischemia testing, with no incorporation of modern imaging modalities capable of identifying plaque vulnerability. Participants did not undergo routine optical coherence tomography (OCT), intravascular ultrasound (IVUS), near-infrared spectroscopy (NIRS), or systematic computed tomography coronary angiography (CTCA)

characterization of non-culprit segments. As a result, the trial's invasive arm predominantly treated stenotic, ischemia-producing lesions. At the same time, the biologically dangerous plaques—those rich in lipids, inflammation, thin fibrous caps, layered healed plaques, and surface thrombus morphology—remained undetected and untreated [21-23].

From a mechanistic standpoint, the invasive arm was therefore directed at the wrong target. In a disease process where most MIs arise from non-obstructive, fractional flow reserve (FFR)-negative, VP, an ischemia-centric enrolment strategy inherently misaligns treatment with risk [24].

### 2.2 Vulnerable Lesions Were Left Untreated

The central paradox of ISCHEMIA becomes clear:
If the lesion destined to cause a future MI is not the one selected for PCI, it is unreasonable to expect PCI to reduce the risk of MI. Because ISCHEMIA did not identify or address VP, the trial's outcomes are unsurprising. The study does not demonstrate that PCI is ineffective; rather, it indicates that PCI must be targeted to the lesions that matter—those prone to rupture.

ISCHEMIA therefore provides indirect validation that successful prevention requires accurate lesion selection, not simply more or less revascularization [17, 25].

### 2.3 Optimal Medical Therapy (OMT) Minimizes Symptoms, Not Vulnerability

OMT in ISCHEMIA was highly effective in reducing angina and improving symptom burden. However, even the most robust medical therapy has limited capacity to eliminate plaque vulnerability, particularly in segments with large lipid cores, intense macrophage infiltration, or thin fibrous caps.

This distinction is essential:
OMT improves ischemia and stabilizes some plaques but does not reliably neutralize the biologically highest-risk lesions.

Thus, while OMT equalized symptom control between arms, it could not compensate for the failure to treat the plaques most likely to rupture or erode [26].

### 2.4 ISCHEMIA Failed to Achieve Complete Revascularization—Despite Extensive Evidence That CR Reduces MI and Death

A critical methodological limitation of ISCHEMIA was the absence of any requirement for complete revascularization (CR), whether anatomical or physiological [27,28]. As a result:

1. Many high-risk, non-flow-limiting lesions were not treated, even when angiographically extensive or morphologically suspicious.
2. Reliance on FFR alone led to systematic exclusion of FFR-negative VP—lesions now understood to be responsible for most future infarctions.
3. Diffuse, remodelled, or lipid-rich segments—particularly in proximal or bifurcation zones—were not addressed, leaving significant residual plaque burden.

This stands in contrast to decades of evidence showing that CR provides superior outcomes. Findings from the COMPLETE trial, SYNTAX and SYNTAXES, BEST, FAME 3 post-hoc analyses, and multiple meta-analyses consistently demonstrate that complete anatomical revascularization reduces MI, urgent revascularization, and cardiac mortality compared with incomplete or physiology-only revascularization [29-34].

The mechanistic underpinning is clear that CR removes or stabilizes:

- clusters of VPs,
- longitudinally unstable segments,
- diffuse inflammatory atheroma, and
- high-risk proximal disease.

By failing to address these segments, ISCHEMIA's invasive strategy was inherently incomplete, thereby diluting any potential benefit of PCI on hard outcomes.

### 2.5 Synthesis: Why ISCHEMIA Does Not Refute—and May Actually Support—a Vulnerability-Guided Strategy

When viewed through a modern understanding of plaque biology, ISCHEMIA's results do not reflect a failure of PCI. They reflect a failure to target the lesions responsible for MI. The trial:

- treated stenosis, not vulnerability,
- used physiology to ignore lipid-rich plaques,
- did not pursue CR, and
- left the majority of dangerous lesions untouched.

Thus, the ISCHEMIA trial inadvertently strengthens the core thesis supported by PROSPECT ABSORB, PREVENT, DEBuT-LRP, and extensive multimodality imaging registries, a thesis that will be elaborated in section 4.

We conclude that PCI will reduce MI only when directed at the plaques most likely to rupture.

## 3. Why VP—Rather Than Stenosis Severity—Drives MI

A substantial body of evidence from intravascular imaging, CT-based plaque characterization, and pathology has established that MI is predominantly a disease of plaque vulnerability rather than stenosis severity. Angiographically "mild" lesions account for approximately 68–75% of culprit plaques preceding MIs, and most exhibit <50% diameter stenosis with normal FFR [35-40]. These observations challenge the traditional ischemia-driven paradigm and underscore that the biological architecture of the plaque—not the degree of luminal narrowing—is the dominant determinant of future acute coronary syndromes (ACS).

### 3.1. The Biological Spectrum of Culprit Plaques

Modern OCT and pathology studies show that ACS arises from three principal mechanisms, each characterized by distinct morphobiological [41-48]:

**• Plaque rupture (~60–70%)**

Typically associated with thin-cap fibroatheroma (TCFA), a large lipid-rich necrotic core, fibrous cap discontinuity, red fibrin-rich thrombus, and an area with low endothelial shear stress (ESS). Rupture generally occurs in older individuals, in regions of low ESS, and is closely linked to elevated LDL, heightened inflammatory activity, and ST-segment elevation MI (STEMI), in which 30-40% of cases are due to stenosis less than 70%.

**• Plaque erosion (~30–40%)**

Characterized by an intact fibrous cap, endothelial denudation, white platelet-rich thrombus, relatively small lipid content, and exposure to high ESS. Erosion is more frequently observed in younger patients, women, smokers, and in non-ST-segment elevation MI (NSTEMI), with most cases having non-severe (<50–70%) stenosis.

**• Calcified nodules (~5–10%)**

A less common mechanism in which nodular calcifications protrude into the lumen, often in elderly patients with advanced vascular calcification, particularly in tortuous segments and hinge points.

| Plaque Phenotype | ESS Range / Pattern | Mechanistic Effect of ESS | Typical Anatomical Locations | Pathophysiological Explanation |
|---|---|---|---|---|
| **Plaque Rupture (TCFA)** | Low ESS < 1.0–1.3 Pa | - Promotes lipid accumulation<br>- Increased macrophage infiltration<br>- Fibrous-cap thinning<br>- Positive remodelling<br>- Necrotic core expansion | - Proximal LAD<br>- Proximal RCA<br>- LCx ostium<br>- Outer curvature of bends<br>- Regions downstream of bifurcation flow separation | Low ESS reduces endothelial NO, increases inflammation, and enhances matrix degradation → leading to thin-cap fibroatheroma prone to rupture |
| **Plaque Erosion** | High ESS > 2.5–3.5 Pa<br>High oscillatory shear index (OSI) | - Endothelial denudation<br>- Apoptosis of endothelial cells<br>- NETosis (neutrophil extracellular traps)<br>- Platelet adhesion to exposed matrix | - Proximal LAD (especially just after the ostium)<br>- Flow acceleration zones<br>- Narrow, tapered segments<br>- Inner curve of vessels<br>- Bifurcation inflow regions | High ESS causes endothelial damage without lipid-core expansion → white thrombus over intact fibrous cap (typical erosion biology) |
| **Calcified Nodules** | Moderate-to-high ESS + high mechanical stress from hinge motion | - Microfractures of sheet calcium<br>- Nodular fragmentation and protrusion<br>- Cap disruption due to mechanical stress<br>- Thrombus formation on protruding calcium | - RCA (most common) — especially mid to distal RCA<br>- LCx bends<br>- Tortuous segments<br>- Hinge points with repetitive flexion<br>- Segments with heavy concentric calcification | Calcified nodules form where vessel segments bend repeatedly → mechanical load + altered ESS causes calcium to erupt into the lumen |
| **Stable Fibrocalcific Plaques** | Normal physiological ESS 1.3–2.5 Pa | - Maintains endothelial health<br>- Minimal inflammation<br>- Stable collagen-rich cap | - Mid LAD, mid RCA, LCx body | Physiologic shear maintains NO and prevents inflammatory plaque transformation |

**Table 1: Endothelial Shear Stress (ESS) in Relation to Plaque Rupture, Plaque Erosion, and Calcified Nodules**

The apparent distribution of these mechanisms has evolved as high-resolution imaging—especially OCT—has improved the ability to distinguish plaque erosion from rupture, revealing a higher-than-previously recognized prevalence of erosion.

### 3.2. Why Stenosis Severity Fails to Predict MI

The predominance of rupture and erosion in angiographically non-severe lesions highlights the limitations of a stenosis-based approach [49,50]:

1. **Positive (outward) remodelling** preserves luminal diameter despite substantial growth of the lipid-rich necrotic core, masking high-risk biology on standard angiography.
2. **Biological instability precedes flow limitation,** explaining why many culprit lesions are FFR-negative before the event.

3. **Ischemia-oriented testing** (treadmill, myocardial perfusion imaging, stress echocardiography) cannot resolve microstructural features such as fibrous cap thickness, necrotic core size, macrophage infiltration, or shear stress–induced endothelial injury.
4. **High-risk CT features**—including the napkin-ring sign, low-attenuation plaque, and unfavourable radiomic signatures—predict future events more accurately than luminal diameter alone.

Collectively, these data demonstrate that ischemia-based strategies frequently fail to identify lesions destined to rupture or erode, and that morphobiological, rather than purely anatomical, assessment is required.

### 3.3. Morphological and Imaging Features Defining VP

**A. OCT-Based Determinants of Vulnerability**

OCT remains the reference standard for in vivo plaque characterization [51-56].

• Plaque rupture
o Fibrous cap discontinuity
o Intraplaque cavity at the site of rupture
o Overlying red thrombus
• Plaque erosion
o Intact fibrous cap (no cap break)
o White platelet-rich thrombus adherent to the luminal surface
o Relatively minimal lipid content
o Smooth or only mildly irregular lumen

These OCT signatures explain why both rupture and erosion commonly arise from lesions that are not flow-limiting.

**B. CTCA Predictors of Vulnerability**

Although CT cannot directly visualize fibrous caps, several surrogate markers provide insight into underlying plaque biology [53-56]:

• Features associated with rupture-prone plaques
o Low-attenuation plaque (necrotic core)
o Napkin-ring sign
o Large lipid core and positive remodelling
• Features associated with erosion-prone plaques
o High-attenuation, non-calcified plaque
o Absence of napkin-ring sign
o Surface irregularity without a large low-attenuation core

These markers refine risk stratification substantially beyond stenosis percentage.

**C. Hemodynamic Forces: The Shear Stress Paradigm**

Local hemodynamics exert a powerful influence on plaque evolution:

• Low ESS promotes lipid accumulation, inflammation, and TCFA formation, favouring plaque rupture.
• High ESS induces endothelial apoptosis and denudation, platelet activation, and thrombus formation, favouring plaque erosion.

Erosion-prone regions include the proximal LAD artery, bifurcations, and curved segments, where complex shear patterns are most pronounced.

**D. Biomarkers and Systemic Signatures**

Emerging biomarker data support a mechanistic distinction between rupture and erosion:

• Higher neutrophil counts and neutrophil extracellular traps (NETs) are more closely linked to erosion [58].
• Higher C-reactive protein (CRP), LDL, and Lp(a) cholesterol favour rupture [59-62].
• Elevated trimethylamine N-oxide (TMAO) may reflect endothelial dysfunction and microbiome dysbiosis, with potential links to rupture and erosion [63-65].

These systemic signals reinforce the concept that lesions may appear "mild" angiographically while harbouring aggressive underlying biology.

### 3.4. Integrating Mechanisms with Clinical Phenotypes

ACS presentation often mirrors the underlying plaque mechanism [66-68]:

| Feature | Plaque Rupture | Plaque Erosion |
|---|---|---|
| Age | Older | Younger |
| Sex | Male | Female (more frequent) |
| Lipids | High LDL | Normal–mild LDL |
| Smoking | Moderate association | Strong association |
| Thrombus | Red, fibrin-rich | White, platelet-rich |
| Hemodynamics | Low endothelial shear stress | High endothelial shear stress |
| CTCA | Low attenuation, napkin-ring sign | High attenuation, no napkin-ring sign |
| ACS Type | More STEMI | More NSTEMI |

**Table 2: Distinguishing Features of Plaque Rupture and Plaque Erosion**

This framework allows clinicians to anticipate the likely mechanism before definitive imaging and to consider tailored diagnostic and therapeutic strategies.

### 3.5. The Clinical Consequence: Why Vulnerability Must Guide Therapy

Given that biologically unstable lesions—not necessarily the most stenotic—are responsible for most infarctions:

1. Stenosis-guided intervention inevitably misses a large proportion of future culprit plaques.
2. Ischemia-negative lesions can still rupture or erode and cause MI without prior angina.
3. Multimodality imaging (CTCA, IVUS, OCT, NIRS) is essential to identifying high-risk plaques (HRPs), even when flow is preserved.
4. Preventive revascularization and/or intensified medical–lifestyle therapy may be justified for plaques with high-risk morphology, irrespective of stenosis severity.

**Therefore, plaque vulnerability—not luminal narrowing—should become the central target of modern coronary prevention and intervention strategies**

### 3.6. Most ACS in COVID-19 Patients Arise from Plaque Erosion or Plaque Rupture

The COVID-19 pandemic created a unique pathobiological environment that profoundly altered the mechanisms underlying ACS. In contrast to pre-pandemic patterns—when plaque rupture dominated—emerging intravascular imaging and autopsy evidence indicate that plaque erosion became the leading substrate of ACS during COVID-19, with plaque rupture remaining an important but less frequent mechanism [69,70]. This shift provides powerful, real-world validation of the vulnerability-centred paradigm that underpins this article.

3.6.1. COVID-19 as an Endothelial Disease: A Catalyst for Plaque Erosion: SARS-CoV-2 infection induces diffuse endothelial injury through ACE2-mediated viral invasion, intense cytokine activation, and microvascular thrombosis. This endotheliali tis preferentially disrupts the superficial endothelial monolayer rather than destabilizing the deeper lipid-necrotic core [71,72]. As a result, COVID-19 creates a biological milieu uniquely favourable for plaque erosion, characterized by:

- Endothelial denudation
- White, platelet-rich thrombus
- Intact fibrous cap
- Absence of a large necrotic core

These features are repeatedly documented in OCT studies during the pandemic, which show that approximately 50–60% of ACS in COVID-19 patients are erosion-driven, significantly higher than in pre-pandemic cohorts [73,74].

This observation maps directly onto the mechanistic biology of COVID-19: an endothelial disease produces an endothelial ACS phenotype.

3.6.2. The Persistence of Plaque Rupture in High-Risk Patients: Although erosion predominated, plaque rupture remained the culprit in 30–40% of COVID-19–associated ACS [75]. Rupture occurred mainly in patients with:

- Large lipid-necrotic cores
- Existing TCFA
- High inflammatory burden
- Uncontrolled dyslipidaemia
- Underlying metabolic disease

COVID-19 amplified systemic inflammation, intensifying macrophage activation and oxidative stress—key drivers of cap thinning. Thus, rupture remained a major cause of STEMI, especially in older individuals or those with unchecked atherogenic biology.

3.6.3. Stenosis Severity Did Not Explain ACS During COVID-19: Across international studies, most culprit plaques in COVID-19 ACS demonstrated only mild-to-moderate stenosis [76-79]:

- CTCA frequently showed 50–70% stenosis, due to positive remodelling.
- Coronary angiography often showed only 20–40% luminal narrowing, because plaque erosion preserves lumen size and platelet-rich thrombus is angiographically silent.

These discrepancies highlighted the limitations of stenosis-based assessment and reaffirmed that biology—not luminal severity—determines risk.

3.6.4. Hypercoagulability as a Co-Driver of ACS in COVID-19: COVID-19 produces an extreme prothrombotic state, marked by:

- Excess von Willebrand factor (vWF)
- Suppressed ADAMTS13
- Intense platelet activation
- Widespread immune thrombosis

This environment accelerates thrombosis over sites of endothelial injury or cap disruption, allowing even modest plaques to precipitate significant thrombotic events. In many cases, the degree of stenosis was insufficient to cause ischemia, but the biological vulnerability was sufficient to trigger ACS [80-83].

3.6.5. Implications for a Vulnerability-Guided Paradigm: These COVID-19 observations reinforce several central principles of the vulnerability-based approach:

1. ACS is a biological disease, not an anatomic one. Most COVID-19 ACS arose from lesions that were angiographically non-obstructive yet biologically unstable.
2. Endothelial dysfunction predicts events better than ischemia. COVID-19 unveiled the catastrophic consequences of endothelial injury, particularly in erosion-prone lesions.
3. Multimodality imaging becomes essential.

4. OCT, IVUS, NIRS, and CTCA provided the key mechanistic insights that angiography and stress testing failed to reveal.
5. Treating plaque biology—not stenosis—is the only reliable way to prevent MI.

The Bethsaida zero-mortality COVID-19 cohort exemplifies this principle, using:
o Vulnerability-guided imaging
o CR when indicated
o Intensive metabolic and lipid control
o WFPBD to restore endothelial health
5. Pandemic stress amplified VP behaviour.

Systemic inflammation, endothelialitis, and hypercoagulability collectively accelerated transitions from quiescent lesions to rupture or erosion.

3.6.6. COVID-19 as the "Ultimate Stress Test" for VPs: The pandemic did not create new plaque biology—it merely exposed it.
COVID-19 acted as a natural "stress test" that revealed which plaques were genuinely dangerous:
- TCFA → rupture
- Endothelial injury zones → erosion
- Protrusive microcalcification → calcified nodules

This real-world stress test validated what multimodality imaging has shown for years: the plaques that cause MI are determined by morphobiology, not stenosis severity [84].

## 4. PROSPECT ABSORB, PREVENT, DEBuT-LRP, and the Expanding Evidence Base for Vulnerability-Guided Intervention

### 4.1. Prospect Absorb: A Foundational Trial in Plaque Vulnerability Intervention

The PROSPECT ABSORB randomized trial provided the first prospective, mechanistic demonstration that future coronary events arise predominantly from biologically unstable plaques rather than from angiographically severe or ischemia-producing stenoses. In this study, angiographically mild, FFR-negative lesions with large plaque burden and high lipid content were treated with a bioresorbable vascular scaffold [85].

This approach was shown to be safe and produced:
- Sustained increases in luminal dimensions
- Reductions in lipid signal
- Development of a stabilizing neointimal "neo-cap"

Although not powered to detect hard clinical outcomes, PROSPECT ABSORB reported numerically fewer lesion-related adverse events in the treated arm than in medical therapy alone. The trial established three critical principles:
1. Ischemia-based strategies systematically overlook high-risk lesions.
2. Vulnerability—not stenosis—determines the likelihood of plaque rupture.
3. Selective focal treatment of unstable plaques is technically feasible, biologically rational, and capable of modifying plaque phenotype.

### 4.2. Prevent: Stabilizing HRP to Reduce Future Events

Building on the findings of PROSPECT ABSORB, the PREVENT trial represents the first large, adequately powered study specifically designed to determine whether treating non-flow-limiting HRP can reduce future MACE [86]. PREVENT enrolls patients with lesions exhibiting high-risk features—such as thin fibrous caps, large lipid cores, or substantial plaque burden with positive remodeling—and randomizes them to preventive PCI plus intensive medical therapy versus intensive medical therapy alone. Preventive PCI of VPs was initially performed using bioresorbable vascular scaffolds; following their market withdrawal, cobalt–chromium everolimus-eluting stents (Xience) were adopted as the default device.

By focusing on biologically unstable rather than ischemia-producing stenoses, PREVENT directly tests the central hypothesis of a vulnerability-guided strategy: that early stabilization of dangerous plaques can alter their natural history and prevent MI before it occurs.

### 4.3. Insights From the DEBuT-LRP Study Relevant to a Vulnerability-Guided Strategy

DEBuT-LRP [87] provides complementary mechanistic support to this evolving paradigm. As a first-in-human, proof-of-concept investigation, it evaluated whether paclitaxel-eluting drug-coated balloon (PE-DCB) therapy can safely modify non-obstructive, non-culprit lipid-rich plaques in patients with NSTEMI.

Key insights include:
**• Confirmation of the "mild but dangerous" lesion:**
All treated lesions were non-flow-limiting yet demonstrated high-risk morphology on IVUS–NIRS, reinforcing that angiography and ischemia testing alone fail to capture the lesions most likely to cause future events.
**• Demonstration of biologically active focal therapy:**
PE-DCB aims to reduce lipid burden and reinforce the fibrous cap without leaving a permanent implant. Preclinical and early clinical data suggest reductions in inflammation, decreases in plaque lipid content, and increases in cap thickness—changes compatible with plaque stabilization.
**• Reinforcement of the prognostic importance of lipid-rich plaques:**
Drawing on PROSPECT, PROSPECT II, and the LRP registry, DEBuT-LRP highlights that plaques with huge plaque burden or maxLCBI_4mm >400 remain at substantially increased risk of future events despite intensive medical therapy, providing a clear rationale for pre-emptive local treatment.

DEBuT-LRP should be viewed as a feasibility and mechanistic study rather than an outcomes trial. Nevertheless, it supports the biological plausibility and technical feasibility of a DCB-based, vulnerability-guided interventional strategy.

### 4.4. Multimodality Imaging (OCT, NIRS, IVUS, CTCA): Converging Evidence for a Morphology-Based Paradigm

Accumulating evidence from intravascular and non-invasive imaging reinforces a core principle of contemporary coronary science: future cardiovascular events are determined by plaque biology—composition, cap integrity, inflammatory activity, and hemodynamics—rather than stenosis severity [53-56].

Multimodality imaging now permits high-resolution assessment of plaque substrate, enabling clinicians to identify the three major precursors of coronary thrombosis described in Section 3.1: rupture-prone TCFA, erosion-prone plaques, and eruptive calcified nodules.

The recent JACC Cardiovascular Imaging position statement by Vergallo and colleagues proposes the broader term "HRP" to encompass the precursors of all three coronary thrombosis substrates [56]. It emphasizes that both morphological characteristics and biological activity must be considered.

4.4.1. OCT: Gold Standard for Microstructural Assessment: OCT provides 10–20 μm resolution, enabling precise assessment of [51-56]:

- Fibrous cap thickness, with caps <65 μm (and particularly <52 μm) identifying TCFA and distinguishing ruptured from non-ruptured lesions
- Lipid-rich necrotic core and associated macrophage clusters and neovascularization
- Layered, healed plaques, reflecting prior silent disruptions
- Surface thrombus morphology, allowing differentiation between red thrombus (more typical of rupture) and white, platelet-rich thrombus (more typical of erosion)

OCT also characterizes calcified nodules as irregular, protruding calcific masses with overlying thrombus and cap disruption, often in tortuous segments and hinge points.

4.4.2. NIRS: Quantifying Lipid Risk: NIRS provides a quantitative measure of lipid burden via the lipid-core burden index (LCBI) [53-56]:

- A maxLCBI_4mm ≥400 identifies plaques at markedly increased risk of future events.
- When combined with high plaque burden on IVUS, NIRS strongly discriminates lesions that are more likely to progress to clinical events.

4.4.3. IVUS / Virtual Histology (VH)-IVUS: Plaque Burden and Remodelling: IVUS offers a global view of plaque burden and remodelling [53-56]:

- Plaque burden ≥70% is a powerful predictor of lesion-related events.
- Positive remodelling and VH-defined TCFA further increase risk.
- IVUS can also identify large calcific burdens and nodular calcium, contextualizing OCT findings.

4.4.4. CTCA: Non-invasive Detection of High-Risk Morphology: CTCA detects several HRP features [53-56,88]:

- Low-attenuation plaque (necrotic core)
- Napkin-ring sign (highly specific for TCFA-like morphology)
- Spotty calcification and positive remodelling ≥10%

These features correlate well with invasive imaging markers of vulnerability. CT-based surrogates for erosion include high-attenuation plaques without a napkin-ring sign and smooth-surface irregularity without a large low-attenuation core, suggestive of a non-TCFA phenotype.

4.4.5. Positron Emission Tomography (PET), Magnetic Resonance Imaging (MRI), and Perivascular Fat Attenuation (FAI): Emerging "Plaque Activity" Tools: Beyond structure, plaque activity can be assessed with:

- PET, to detect inflammatory and calcification activity using specific radiotracers (e.g., FDG, 68Ga-DOTATATE, 18F-sodium fluoride) [89,90].
- MRI [88,91], to identify intraplaque haemorrhage, fibrous cap status, and vessel wall inflammation.
- Perivascular FAI on CT, as a marker of peri-coronary inflammation and future risk [92,93].

Integrated with structural imaging, these functional markers help identify patients and lesions in an "active" disease state who may benefit most from intensified systemic therapy and/or focal intervention.

### 4.5. Synthesis: Vulnerability as the Central Therapeutic Target

Evidence from PROSPECT, PROSPECT II, PREVENT, CLIMA, LRP, COMBINE OCT–FFR, DEBuT-LRP and the Vergallo position statement converges on a unified paradigm: the key trigger of MI is plaque vulnerability—not stenosis severity or the presence of ischemia on stress testing [56, 86,87,94-98].

4.5.1. Integrated Understanding of the Three Major Thrombogenic Substrates: Taken together, experimental and clinical data define:

1. Rupture-prone plaques (TCFA) with thin fibrous caps, large necrotic cores, intense macrophage-driven inflammation, napkin-ring sign, positive remodelling, and frequent intraplaque haemorrhage and vasa vasorum proliferation—responsible for the majority of STEMI.
2. Erosion-prone plaques with intact caps, endothelial denudation, neutrophil-driven NETosis, hyaluronan–CD44v6 signalling, and matrix-rich, lipid-poor composition—are more common in women, younger patients, smokers, and NSTEMI.
3. Eruptive calcified nodules with protrusive nodular calcification and cap fracture under biomechanical stress—seen more often in older patients, especially those with chronic kidney disease and tortuous coronary segments.

4.5.2. A Unified Imaging-Based Risk Model: Across modalities, the most powerful predictors of lesion-level risk include:

- High plaque burden (e.g., ≥70% on IVUS)

- High lipid-core burden (e.g., maxLCBI_4mm ≥400)
- Thin fibrous caps on OCT
- Napkin-ring sign and high-risk CT features
- Elevated perivascular FAI and adverse shear stress patterns on computational modelling

These complementary markers collectively define the HRP and provide a rational basis for targeted stabilization.

4.5.3. Implications for a New Era of Coronary Care: This integrated evidence supports a fundamental shift:
- From stenosis-centred to biology-centred care
- From ischemia testing alone to combined morphology and activity assessment
- From late-stage revascularization to early stabilization of HRP
- From angiographic severity to substrate-based risk stratification using OCT, NIRS, IVUS, and CTCA

In this framework, "HRP" is defined not by the degree of lumen narrowing but by its propensity to thrombose and cause MI or sudden cardiac death.

4.5.4. The Case for Early Identification and Stabilization: These insights justify a multipronged strategy [9, 23, 53-56]:
- **Aggressive systemic therapy** (intensive lipid lowering, anti-inflammatory regimens, WFPBD interventions, metabolic optimization) to modulate the pan-coronary disease process.
- **Targeted focal therapy** (including DCB or stent-based approaches) for functionally non-significant but morphologically HRP in carefully selected patients.
- **Strategic use of multimodality imaging** to identify vulnerable patients and lesions most likely to benefit from such interventions.

Emerging interventional trials—PROSPECT ABSORB, PREVENT, and DEBuT-LRP—demonstrate the feasibility of pre-emptive stabilization ("plaque sealing") when high-risk morphologies are identified before clinical events. Together, they pave the way for a vulnerability-guided paradigm that aims not merely to relieve angina but to prevent MI and save lives.

## 5. Technical Rationale for Vulnerability-Based Intervention

A vulnerability-guided strategy for coronary intervention is supported by a clear mechanistic foundation integrating both mechanical stabilization and biological modulation. Together, these approaches target the structural and inflammatory substrates that render plaques prone to rupture, representing a paradigm distinct from traditional stenosis- or ischemia-driven revascularization.

### 5.1 Mechanical Stabilization Through PCI or Drug-Coated Balloon Therapy

Mechanical strategies—principally PCI with DES or DCB angioplasty—offer a direct means of stabilizing TCFAs and other HRPs that underlie most ACS [85-87]. When applied selectively to lesions with documented high-risk morphology, these approaches can modify both plaque structure and local hemodynamics in ways that pharmacologic therapy alone cannot reliably achieve within a predictable time frame.

5.1.1 Reinforcement of the Fibrous Cap and Lipid Core Sealing: Both DES and DCB-based strategies can create a more stable barrier between the lipid-rich necrotic core and the circulation [85-87]:
- DES implantation provides an immediate metallic scaffold over the TCFA, followed by neointimal coverage of the struts. This "neo-cap" effectively thickens the fibrous interface above the necrotic core, reducing mechanical stress on the native cap and limiting exposure of thrombogenic material to circulating blood.
- DCB therapy, although leaving no permanent implant, delivers an antiproliferative drug (e.g., paclitaxel) that promotes controlled neointimal healing and cap thickening without the chronic stimulus of a foreign body. In vulnerable, non-flow-limiting plaques, DCB may therefore offer biological reinforcement while preserving vessel physiology.

By augmenting cap integrity and attenuating plaque inflammation, both approaches aim to prevent the abrupt cap disruption that precipitates occlusive thrombosis and MI.

5.1.2 Normalization of Local Hemodynamics: VPs frequently arise in regions of disturbed shear stress, which promotes endothelial dysfunction, inflammation, and progressive cap thinning. Focal mechanical intervention can partially normalize these patterns [85-87]:
- Optimal lesion preparation and expansion smooth luminal irregularities, reduce eccentricity, and enlarge the minimal lumen area, thereby restoring more laminar flow.
- DES can convert a highly irregular, protrusive surface into a more uniform cylindrical lumen once appropriately expanded.
- DCB, by debulking or compressing the plaque and smoothing the luminal contour without struts, may restore favourable shear profiles while avoiding stent-related flow perturbations at the strut level.

These changes reduce the cyclical mechanical forces acting on the cap, diminishing one of the key drivers of plaque destabilization.

5.1.3 Prevention of Plaque Rupture, Thrombosis, and Microembolization: By stabilizing plaque architecture and cap mechanics, PCI with DES or DCB [85-87] can:
- Reduce the probability of sudden plaque rupture by decreasing cap stress and separating blood elements from a fragile necrotic core.
- Limit distal microembolization by eliminating friable, protruding, or ulcerated surfaces that shed thrombotic and lipid-rich debris into the microcirculation.
- Preserve microvascular perfusion, thereby mitigating periprocedural and subsequent myocardial injury.

These effects directly target the "final common pathway" of acute

coronary occlusion—plaque disruption followed by thrombosis.

5.1.4 Impact on Plaque Erosion Risk: Although most discussions of focal mechanical therapy focus on rupture-prone TCFAs, plaque erosion is increasingly recognized as a major cause of ACS. Selective PCI (DES or DCB) may also modulate erosion risk at treated segments [56, 85-87]:

- In erosion-prone plaques with irregular surfaces, superficial matrix exposure, and high shear stress, DES or well-prepared DCB can smooth luminal contours and create a more stable, endothelialized surface, potentially reducing the likelihood of recurrent endothelial denudation and platelet-rich thrombus formation.
- By decreasing local shear gradients and shielding the subendothelial matrix, focal treatment may attenuate neutrophil and platelet activation—central elements in the pathobiology of erosion.

However, this benefit must be weighed against the possibility of stent-related complications, including late neoatherosclerosis and edge pathology, which themselves can present as stent-related rupture or erosion. In this context:

- DCB-only strategies in suitable lesions may be advantageous, offering cap stabilization and plaque modification without permanent metal and with a potentially lower long-term risk of neoatherosclerotic erosion.
- Careful lesion selection guided by OCT/IVUS is crucial to identify plaques where mechanical intervention is likely to reduce, rather than introduce, erosion risk.

Overall, while DES and DCB cannot abolish erosion risk throughout the coronary tree, they may substantially reduce local erosion propensity at carefully selected high-risk sites when combined with aggressive systemic therapy.

5.1.5 Devices and Strategies for Calcified Nodules: Calcified nodules pose a unique mechanical and interventional challenge: nodular calcium protruding into the lumen can fracture the fibrous cap, generate local flow disturbance, and precipitate thrombosis. When intervention is chosen, the goal is to remodel and debulk the calcific substrate before any DES or DCB therapy:

- **Rotational atherectomy and orbital atherectomy** can ablate superficial and nodular calcium, reduce rigidity, and improve vessel compliance [99,100]. This facilitates optimal stent expansion or better balloon–plaque contact in a DCB-only strategy.
- **Intravascular lithotripsy (IVL)** delivers acoustic pressure waves that fracture deep and superficial calcium, including nodular components, often with less particulate embolization and less risk of severe dissections than atherectomy [99,101-103].
- **Specialty balloons (cutting and scoring balloons)** can further modify calcified nodules and concentric calcification, creating controlled fractures that allow more uniform expansion with either DES or DCB [104,105].
- Following adequate **calcium modification**, DES implantation provides a stable scaffold across the treated segment. In contrast, DCB therapy may be considered in carefully selected nodular or heavily calcified lesions where adequate luminal gain can be achieved without a stent and where vessel geometry and imaging findings are favourable.

In all cases, intravascular imaging (OCT, IVUS) is indispensable to:

- Confirm the presence and morphology of calcified nodules
- Guide selection of the most appropriate calcium-modifying device
- Assess post-treatment expansion, residual protrusion, and cap sealing

5.1.6 Positioning Mechanical Therapy Within a Vulnerability-Guided Framework: Taken together, PCI with DES or DCB—especially when informed by OCT, IVUS, NIRS, and CTCA—offers a rational strategy to neutralize HRP mechanically:

- In rupture-prone TCFAs, focal mechanical therapy reinforces the cap and isolates the necrotic core.
- In erosion-prone plaques, it can smooth irregular surfaces, partly normalize shear stress, and reduce recurrent denudation and thrombus formation.
- In calcified nodules, dedicated calcium-modifying devices plus DES or selected DCB use can reduce protrusion and cap fracture risk.

When combined with intensive systemic therapy (lipid-lowering, anti-inflammatory, and lifestyle interventions), these mechanical approaches form a complementary arm of vulnerability-guided coronary care, aimed not only at relieving angina but at pre-emptively stabilizing the plaques most likely to cause future MI.

5.1.7. AI–Derived Relative Risk Modelling: Stenosis Severity Versus Plaque Morphobiology: Advances in machine learning and computational imaging [106,107] have enabled a new analytic framework in coronary risk prediction, shifting from luminology-based assessment toward biology-centred modelling. AI, applied to multimodality imaging (CTCA, OCT, IVUS, NIRS) and clinical phenotyping, now permits quantitative risk stratification that integrates anatomic stenosis, plaque composition, biomechanical forces, inflammatory signatures, and patient-level determinants into a unified probabilistic model of MI.

Stenosis severity alone has historically been viewed as the dominant determinant of future coronary events. However, the neutral findings of ISCHEMIA and cumulative data from PROSPECT, COMBINE OCT–FFR, CLIMA, and LRP registries demonstrate that luminal narrowing provides only modest predictive value for MI. In contrast, AI-driven analyses consistently show that plaque morphobiology—particularly fibrous-cap thickness, lipid-core burden, macrophage activity, endothelial shear stress patterns, and the presence of erosion-prone or rupture-prone microarchitecture—supersedes stenosis as the primary substrate of acute coronary

thrombosis.

AI systems can quantify these features far beyond human visual interpretation. Deep-learning models extract high-dimensional signals from intravascular and CT imaging, generating integrated hazard curves and patient-specific vulnerability maps. By incorporating both structural and biological parameters, AI provides relative risk estimates that more accurately reflect the mechanistic pathways underlying spontaneous MI.

For example, models trained on CTCA datasets reveal that lesions with low-attenuation plaque, the napkin-ring sign, or positive remodelling carry markedly higher MI risk than stenoses of similar degree lacking vulnerable features. Similarly, OCT-based networks identify TCFA, microchannels, macrophage clusters, and plaque fissures as powerful predictors of near-term events—even when FFR remains normal. AI also quantifies shear-stress abnormalities through computational fluid dynamics, linking high ESS patterns to erosion-prone plaques and low ESS to rupture-prone fibroatheromas.

By merging these imaging-derived metrics with systemic biomarkers, clinical characteristics, genomic signals, and longitudinal outcomes, AI creates a multi-layered model of plaque behaviour, allowing clinicians to discern which lesions threaten thrombosis and which represent stable anatomic narrowing. These tools are particularly valuable in the post-COVID era, where residual inflammation amplifies the biological vulnerability of specific plaques while leaving others relatively quiescent.

Ultimately, AI-derived risk modelling enables a paradigm in which intervention is directed not at stenosis per se but at lesions with the highest objective probability of causing MI. This approach harmonizes with the emerging biology-centred vision in modern cardiology and may guide future clinical trials that randomize patients based on AI-defined vulnerability rather than ischemia alone.

| Risk Domain | AI-Derived Predictive Signals | Association With Future MI | Interpretation |
|---|---|---|---|
| **Luminal Stenosis** | - % diameter stenosis<br>- Minimal lumen area<br>- FFR/CT-FFR estimates | Modest predictor | Stenosis contributes to ischemia but poorly predicts spontaneous plaque rupture; MI often arises from non-obstructive lesions. |
| **Fibrous-Cap Integrity** | - OCT cap thickness mapping<br>- Micro-fissures<br>- Macrophage clusters | Strong predictor | TCFA and cap infiltration are central substrates of plaque rupture. |
| **Lipid Core Burden** | - NIRS maxLCBI4mm<br>- CT low-attenuation plaque<br>- IVUS plaque burden | Strong predictor | High lipid burden and positive remodelling correlate with rupture-prone biology independent of stenosis. |
| **Endothelial Shear Stress** | - Computational Fluid Dynamics (CFD)-derived ESS mapping<br>- Oscillatory shear index | Mechanism-specific predictor | Low ESS → rupture-prone plaques; high ESS → erosion-prone plaques. |
| **Surface Morphology** | - OCT surface irregularity<br>- Endothelial denudation<br>- Erosive phenotype signatures | Moderate–strong predictor | Identifies erosion-prone plaques that are more common in younger patients and women. |
| **Calcific Architecture** | - Nodular calcium detection<br>- Protrusive microcalcification<br>- IVUS/OCT fracture patterns | Subtype-specific predictor | Predicts eruptive calcified nodules in hinge zones and tortuous segments. |
| **Perivascular Inflammation** | - CT FAI (fat attenuation index)<br>- Radiomic inflammation signatures | Strong pan-coronary predictor | AI detects vessel-level inflammation associated with accelerated vulnerability. |
| **Systemic Biomarkers** | - LDL trajectory<br>- CRP/hsCRP<br>- NETosis signatures<br>- TMAO levels | Adjunctive predictor | Enhances accuracy when integrated with plaque-level morphobiology. |

| | | | |
|---|---|---|---|
| **Composite AI Risk Score** | - Multimodal integration of stenosis + morphobiology + inflammation + shear stress | Highest predictive accuracy | Provides individualized MI probability, outperforming stenosis-centric models. |

**Table 3: AI-Derived Relative Risk Components: Stenosis Severity Versus Plaque Morphobiology**

| Degree of Stenosis | Typical Relative Risk of Future MI | Mechanistic Explanation |
|---|---|---|
| <30% stenosis (mild) | RR 1.0–1.3 | Most mild lesions have preserved flow and stable structure; however, a minority contain TCFA or an erosive substrate, accounting for a small but real baseline risk. |
| 30–49% stenosis (moderate non-obstructive) | RR 1.5–2.5 | Lesions in this range account for ~70% of culprit plaques in large registries. Risk derives not from lumen compromise but from high lipid burden, positive remodelling, and thin caps that remain hemodynamically silent. |
| 50–69% stenosis (intermediate) | RR 1.8–3.0 | Increasing plaque volume elevates risk modestly. Vulnerable characteristics—not the stenosis—determine event rates. FFR often remains normal, masking biological danger. |
| 70–89% stenosis (severe but non-critical) | RR 2.0–3.5 | A higher plaque burden slightly increases the risk, but lesions may remain stable if their morphology is benign. Many severe stenoses do not rupture, instead producing angina or supply–demand mismatch. |
| ≥90% stenosis (critical) | RR 2.5–4.0 | Highest stenosis category, but still not the strongest predictor of MI. Most MIs in this group occur when high-grade stenosis coexists with TCFA or erosion, rather than solely due to flow limitation. |

**Table 4: Stenosis Severity, Relative Risk of Myocardial Infarction, and Mechanistic Interpretation**

**Interpretation:**
Across all stenosis levels, the relative risk rises only modestly, whereas biological instability causes an exponential increase in risk. This explains why stenosis-centric models consistently underperform and why AI algorithms increasingly weigh morphobiological features to generate personalized risk.

| Morphobiological Feature | Relative Risk of Future MI | Mechanistic Explanation |
|---|---|---|
| **Thin-Cap Fibroatheroma (TCFA)** | RR 4–8 | Thin caps (<65 μm), large lipid cores, macrophage infiltration, and positive remodelling create extreme rupture propensity, independent of luminal severity. |
| **Large Lipid Core (NIRS maxLCBI4mm ≥400)** | RR 3–7 | A high lipid burden correlates strongly with future culprit events and the TCFA phenotype and shows a poor response to medical therapy alone. |
| **Positive Remodelling (>10%)** | RR 2–6 | Compensatory outward remodelling maintains lumen size, making lesions appear "mild" despite aggressive biological vulnerability. |
| **Low-Attenuation Plaque (CTCA <30 HU)** | RR 3–5 | Surrogate of large necrotic core; robust predictor of spontaneous MI independent of stenosis. |
| **Napkin-Ring Sign (CTCA)** | RR 5–8 | One of the strongest non-invasive predictors of rupture, it correlates with TCFA and macrophage infiltration. |

| | | |
|---|---|---|
| **Endothelial Denudation / Erosive Features (OCT)** | RR 2–5 | High shear stress, NETosis, and superficial matrix exposure generate white platelet-rich thrombi, even with minimal stenosis. |
| **High ESS (>3.5 Pa) Regions** | RR 2–4 | Drives endothelial apoptosis and erosion; prominent in proximal LAD, bifurcation inflow zones, and tapered segments. |
| **Low ESS (<1.0–1.3 Pa)** | RR 3–7 | Promotes lipid accumulation, inflammatory infiltration, and cap thinning, predisposing to rupture-prone TCFA. |
| **Calcified Nodules / Protrusive Calcium** | RR 2–4 | Mechanical microfracture at hinge points produces nodular eruption and cap disruption; most common in RCA. |
| **Microchannels / Neovascularization (OCT)** | RR 2–3 | Facilitates intraplaque haemorrhage and destabilization, particularly in rapidly evolving plaques. |
| **Perivascular Inflammation (FAI)** | RR 2–5 | CT-based inflammatory signature reflecting increased local cytokine activity; predicts plaque progression and vulnerability. |

**Table 5: Morphological Plaque Features, Relative Risk of MI, and Mechanistic Explanation**

These tables make the central point of Section 5.1.7 explicit [107-112]:

- Stenosis increases risk gradually, in a linear fashion (modest slope).
- Morphobiological instability increases risk exponentially, in a stepwise fashion (steep slope).
- AI models weight morphology > stenosis because biology determines rupture, whereas stenosis determines ischemia.

This directly reinforces the mechanistic rationale of your manuscript: treat stenosis to relieve angina; treat vulnerability to prevent MI and death.

## 5.2 Biological Stabilization Through Intensive Lifestyle and Medical Therapy

While mechanical intervention provides immediate reinforcement of structural VP, biological stabilization targets the inflammatory and metabolic milieu that transforms subclinical atherosclerosis into thrombosis-prone disease. Intensive systemic therapy—centred on WFPBD [113-127], aggressive lipid lowering [128-137], and targeted anti-inflammatory/metabolic modulation [138,139]—acts on the underlying biology that governs both plaque rupture and plaque erosion and may also influence the biomechanical evolution of calcified nodules.

5.2.1 Thickening and Strengthening of the Fibrous Cap: Achieving ultra-low LDL cholesterol levels (<40 mg/dL) through combination lipid-lowering treatment (statins, ezetimibe, PCSK9 inhibitors) and dietary intervention promotes [140-146]:

- Increased smooth muscle cell migration and collagen synthesis,
- Stabilization and thickening of the fibrous cap,
- Reduced susceptibility to mechanical shear forces,
- Decreased likelihood of spontaneous rupture.

WFPBD amplifies this effect by reducing dietary cholesterol and saturated fats to near-zero levels, lowering hepatic VLDL production, and improving cap reparative biology.

5.2.2 Regression of the Lipid–Necrotic Core: Both pharmacologic LDL reduction and WFPBD contribute to [140-146]:

- Mobilization of intracoronary lipid,
- Shrinkage of the necrotic core,
- Dissolution of cholesterol crystals,
- Decreased intraplaque inflammation and macrophage density.

Core regression reduces biomechanical stress on the fibrous cap and directly lowers the probability of both TCFA rupture and the transformation of erosion-prone plaques into rupture-prone phenotypes.

5.2.3 Restoration of Endothelial Nitric Oxide (NO) Bioavailability: Endothelial dysfunction is a unifying mechanism across all high-risk phenotypes:

- Rupture-prone plaques exhibit elevated oxidative stress and diminished NO, impairing cap integrity.
- Erosion-prone plaques are marked by endothelial denudation, high shear stress, and impaired endothelial repair capacity.

WFPBD, rich in nitrate-containing vegetables, polyphenols, and antioxidants, restores endothelial NO production, improving [140-146]:

- Vasomotor function,
- Shear stress adaptation,
- Endothelial regeneration,
- Resistance to denudation—the hallmark of plaque erosion.

This is particularly important in erosion-prone lesions where the problem is not a thin cap, but cap absence due to endothelial loss.

5.2.4 Attenuation of Systemic and Plaque-Level Inflammation: Inflammation is central to all three high-risk substrates:

- In rupture, macrophage-driven degradation weakens the cap.
- In erosion, neutrophil extracellular traps (NETs) and hyaluronan–CD44v6 pathways drive endothelial apoptosis.
- In calcified nodules, chronic inflammation accelerates microfracture and nodular protrusion.

Aggressive systemic therapy—including WFPBD, weight reduction, glycaemic optimization, and targeted anti-inflammatory approaches reduces [140-146]:

- Macrophage activation,
- NET formation,
- NLRP3 inflammasome activity,
- Oxidative stress and endothelial apoptosis,
- Progression of spotty and nodular calcification.

These changes stabilize both rupture-prone and erosion-prone plaques and may slow or prevent the mechanical evolution of calcified nodules into eruptive, thrombogenic structures.

5.2.5 Systemic Therapies Influencing Calcified Nodules: Although calcified nodules are primarily biomechanical lesions, systemic therapy may influence their development [140-146]:

- WFPBD lowers the phosphate burden and reduces vascular smooth muscle cell osteogenic transformation.
- Aggressive lipid and inflammation control reduces microcalcification and may prevent sheet calcification from progressing into protrusive nodules.
- Correction of metabolic and renal dysfunction reduces calcium–phosphate imbalance, attenuating the formation of unstable calcific clusters.

Thus, while mechanical modification remains essential for nodules that have already become obstructive or protrusive, systemic strategies may reduce the incidence and progression of this phenotype.

### 5.3 Synergy Between Mechanical and Biological Stabilization

The strongest rationale for a vulnerability-guided coronary strategy lies in the synergistic interplay between mechanical and biological stabilization. These modalities act on complementary time scales and biological domains, jointly addressing both the structural substrate and the metabolic–inflammatory environment that governs plaque behaviour.

5.3.1 Immediate Mechanical Protection: Mechanical intervention—DES or DCB—offers [85-87]:

- Instantaneous sealing of TCFAs,
- Normalization of shear stress,
- Elimination of protrusive or irregular surfaces that favour erosion,
- Remodelling of calcified nodules to reduce protrusion and cap fracture risk,
- Immediate reduction in rupture or thrombosis likelihood.

These benefits are uniquely rapid and cannot be replicated by pharmacologic therapy alone.

5.3.2 Progressive and Durable Biological Modification: Biological therapy complements mechanical stabilization by:

- Rebuilding cap thickness over weeks to months,
- Removing necrotic core content,
- Restoring endothelial integrity at erosion-prone surfaces,
- Suppressing inflammation and oxidative stress,
- Slowing or reversing the evolution of nodular calcification.

This produces long-term, durable reduction in vulnerability even in untreated segments, addressing the pan-coronary nature of atherosclerosis.

5.3.3 Combined Effects on Plaque Erosion: Mechanical + biological synergy is particularly relevant for plaque erosion, which accounts for up to 40% of ACS:

- Mechanical therapy smooths luminal irregularities and reduces shear gradients.
- Biological therapy restores NO, regenerates endothelium, and suppresses NET-driven denudation.

Together, they address both the surface instability and the underlying inflammatory drivers of erosion.

5.3.4 Combined Effects on Calcified Nodules: For calcified nodules:

- Mechanical therapy (atherectomy, IVL, DES, DCB) reduces nodular protrusion and cap fracture risk.
- Biological therapy slows the metabolic progression of vascular calcification and reduces microcalcific activity.

This dual approach prevents recurrent protrusion and downstream thrombotic events.

5.3.5 A Comprehensive Model of Coronary Stabilization: The integration of mechanical and biological strategies provides a unified framework capable of addressing the spectrum of high-risk plaque phenotypes:

| Plaque Type | Mechanical Therapy | Biological Therapy |
|---|---|---|
| **TCFA / rupture-prone** | Immediate cap sealing, shear normalization | Cap thickening, lipid-core regression, and inflammation reduction |
| **Plaque erosion** | Smoothing of luminal surface, shear modulation | Endothelial regeneration, NO restoration, anti-NET activity |
| **Calcified nodules** | Calcium modification and debulking; reduction of protrusion | Slowed calcification progression, decreased metabolic stress |

**Table 6: Mechanistic Targets and Therapeutic Strategies for Each HRP Phenotype**

5.3.6 A Dual-Tiered Protection Strategy: When combined, mechanical and biological stabilization provide:

- Rapid (hours-to-days) reduction in the risk of rupture, erosion, or thrombosis,
- Sustained (months-to-years) reduction in plaque vulnerability through regression, healing, and systemic risk modification.

This multimodal approach reflects the modern understanding of atherosclerosis as a dynamic structural, inflammatory, and metabolic disease that requires coordinated intervention targeting both the lesion and host biology.

## 6. A New Paradigm for Modern Cardiology

The contemporary understanding of CAD has evolved far beyond the historical framework in which stenosis severity and ischemia defined clinical risk. Robust evidence from intravascular imaging, CT-based plaque characterization, and pathology now demonstrates that most acute coronary events do not arise from flow-limiting stenoses, but rather from biologically active plaques that exhibit features of rupture, erosion, or eruptive calcification. These lesions may appear angiographically "mild," yet harbour profound structural and inflammatory instability. Recognizing this divergence between lumen severity and biological threat necessitates a paradigm shift in cardiovascular medicine.

### 6.1 Limitations of the Traditional Paradigm

The conventional model—stenosis → ischemia → PCI—assumes that luminal narrowing is the principal driver of MI. For decades, this framework guided diagnostic algorithms, dictated thresholds for revascularization, and defined the clinical value of stress testing and angiographic assessment.

However, multiple limitations have now become apparent:

6.1.1. The model does not account for plaque biology: Most MI-producing lesions are non-flow-limiting, FFR-negative, and angiographically mild. These plaques are dangerous not because they restrict flow, but because they possess thin fibrous caps, lipid-rich necrotic cores, macrophage infiltration, endothelial injury, or nodular calcification.

6.1.2. Ischemia-based testing fails to detect vulnerability: Stress tests detect hemodynamic compromise, not cap thickness, endothelial denudation, lipid-core burden, or shear-stress–driven microinjury, all of which precede rupture or erosion.

6.1.3. Calcified and eroded plaques may never produce ischemia before thrombosis: Plaque erosion and eruptive calcified nodules often occur in moderate or even minimal stenoses, particularly in young patients, women, smokers, and those with metabolic dysfunction.

6.1.4. Reliance on stenosis fosters a false sense of security: Patients with "non-obstructive coronary arteries" may be labelled low-risk, despite harbouring plaques that imminently threaten thrombosis.

Thus, continuing to rely solely on luminal narrowing or inducible ischemia leaves the most dangerous lesions untreated, while targeting those that may never rupture.

### 6.2 The Emerging Vulnerability-Centred Model

Modern cardiology increasingly recognizes that plaque vulnerability—not stenosis—is the central determinant of acute coronary events. Vulnerability reflects a complex interplay of:

- fibrous cap thickness
- lipid-necrotic core size
- macrophage and neutrophil activity
- endothelial integrity
- remodelling pattern (positive or negative)
- calcific architecture
- shear stress forces

Within this model, the clinical sequence becomes:
**Vulnerability → Instability → Rupture/Erosion/Calcified Nodule → Thrombosis → MI**

**Rupture**
Driven by TCFA, macrophage infiltration, necrotic core expansion, and cap thinning.

**Erosion**
Driven by endothelial denudation, NETosis, high shear stress, and preserved cap structure—often without a large lipid core.

**Calcified Nodules**
Driven by microfracture of calcified sheets, biomechanical stress at hinge points, and protrusive nodular calcification.
This framework prioritizes biological threat over luminal

compromise in clinical decision-making. The goal becomes pre-emptive stabilization before structural failure.

### 6.3 A Multimodal Strategy for Stabilization

Within the vulnerability-based paradigm, the entire therapeutic strategy aims to stabilize the structural and biological substrates of rupture, erosion, or calcific protrusion.

Effective stabilization requires integration of three pillars:

6.3.1. Mechanical Stabilization (PCI or DCB): Provides immediate protection for lesions with OCT/IVUS/CTCA-defined high-risk features [85-87]:

- Sealing of TCFA
- Smoothing of irregular surfaces prone to erosion
- Reducing the protrusion of calcified nodules after plaque modification
- Normalizing shear stress patterns

Mechanical therapy addresses instantaneous structural instability, lowering near-term thrombosis risk.

6.3.2. Intensive Medical Therapy: Targets biological drivers of vulnerability [113-137]:

- Ultra-low LDL strategies (<40 mg/dL) induce cap thickening and necrotic-core regression.
- Anti-inflammatory therapies reduce macrophage and neutrophil-mediated injury.
- Antithrombotic strategies reduce platelet activation, central to erosion.

This slows or reverses the progression of all three high-risk substrates.

6.3.3. Comprehensive Lifestyle Intervention (WFPBD): Provides global metabolic reprogramming [113-137]:

- Restores NO bioavailability
- Improves endothelial integrity (critical for erosion)
- Reduces oxidative stress and NLRP3 inflammasome activation
- Lowers TMAO and improves microbiome diversity
- Reduces vascular calcium progression

Unlike mechanical therapy, lifestyle therapy influences the entire vascular tree, stabilizing both treated and untreated segments.

| Plaque Type | Mechanical Stabilization | Biological Stabilization |
|---|---|---|
| **Rupture-prone (TCFA)** | Cap sealing, lumen normalization | Cap thickening, lipid reduction |
| **Erosion-prone** | Smoothing surface, reducing shear gradients | Endothelial regeneration, anti-NET therapy |
| **Calcified nodules** | Atherectomy/IVL + DES/DCB to reduce protrusion | Slowing calcific progression/metabolic modulation |

**Table 7: Synergy Across Plaque Phenotypes**

No single modality is sufficient; stabilization is strongest when these components work in concert.

### 6.4 Alignment with Broader Trends in Precision Medicine

The shift toward vulnerability-based coronary care mirrors paradigm changes in other medical disciplines:

- Oncology now targets genomic drivers rather than tumor size.
- Neurology focuses on inflammatory and proteopathic mechanisms, not merely lesion burden.
- Rheumatology and immunology leverage pathway-specific modulation rather than symptomatic control.
- Endocrinology emphasizes metabolic inflammation ("metaflammation") as a core determinant of chronic disease.

Similarly, cardiology is transitioning from:
Anatomy → Biology → Precision Coronary Medicine

This includes:

- Phenotype-specific strategies (rupture vs erosion vs calcified nodules)
- Imaging-guided risk stratification (OCT, NIRS, IVUS, CTCA, FAI)
- AI-assisted pattern recognition
- Lifestyle-omics (nutri-genomics, metabolomics) integration

The emerging paradigm positions personalized plaque biology—not stenosis—as the central determinant of preventive and interventional strategy.

### 6.5 Vision for the Future

Adopting a vulnerability-centred model necessitates rethinking every aspect of coronary care:

6.5.1. Diagnostic Pathways: Move from angiography-first assessment to multimodality imaging that identifies TCFA, erosion-prone surfaces, and calcified nodules before the onset of symptoms or ischemia.

6.5.2. Risk Stratification: Shift from degree of stenosis to morphological, biological, and biomechanical risk, incorporating:

- Cap thickness
- Lipid-core burden
- Shear stress maps
- Endothelial integrity

- Calcific architecture
- Perivascular inflammation (FAI)

6.5.3. Interventional Strategy: Embrace preventive stabilization for HRPs—whether through focal therapy (DES/DCB) or pan-coronary biological modification.

6.5.4. Lifestyle & Metabolic Medicine Integration: Recognize WFPBD, microbiome optimization, and metabolic reprogramming as essential components of coronary stabilization.

6.5.5. Future Vision: In this emerging framework, modern cardiology evolves:
- From relieving flow limitation
- To prevent a biological catastrophe

This shift reflects the true nature of atherosclerosis: a dynamic inflammatory, metabolic, and biomechanical disease in which rupture, erosion, and calcified nodules represent the terminal events of a long biological process.

In Conclusion, a vulnerability-centred paradigm—anchored in advanced imaging, focal and systemic stabilization, and lifestyle transformation—positions modern cardiology to more effectively prevent MI, transform patient outcomes, and deliver care that is mechanistically precise and clinically impactful.

## 7. Post-COVID Cardiovascular Hazard: A Sustained Two-Year Window of Elevated Risk

A growing body of epidemiologic evidence demonstrates that SARS-CoV-2 infection confers a prolonged period of heightened cardiovascular vulnerability. Extensive population-based analyses from the U.S. Veterans Affairs healthcare system, the UK Biobank, and national Scandinavian registries consistently report excess risk of MI, ischemic stroke, heart failure, ventricular arrhythmias, and thrombotic complications that persist for up to 24 months after the acute infection [147-151]. Notably, this elevated hazard is observed not only in patients with severe initial disease but also in individuals who experienced mild or moderate COVID-19, underscoring the infection's pervasive and durable impact on vascular biology.

Mechanistically, these findings are biologically plausible. SARS-CoV-2 induces diffuse endothelial dysfunction, microvascular thrombosis, and sustained activation of inflammatory and immune pathways. Persistent elevation of inflammatory markers, impaired endothelial NO signalling, and residual pro-thrombotic states have been documented well beyond convalescence. These pathophysiologic alterations directly accelerate the processes that govern plaque destabilization: fibrous-cap thinning, inflammatory infiltration, oxidative stress, and expansion of the lipid-necrotic core.

Taken together, the post-COVID risk landscape amplifies the relevance of a vulnerability-guided approach to coronary prevention. During this extended period of heightened susceptibility, plaques that might otherwise remain quiescent are more likely to transition into rupture-prone states. For patients with pre-existing coronary atherosclerosis—particularly those with imaging evidence of lipid-rich, TCFA—the combination of residual inflammation and endothelial injury represents a potent catalyst for acute events.

In this context, early identification and stabilization of VP become especially compelling. The prolonged post-COVID window of risk strengthens the argument that management strategies should not rely solely on stenosis severity or ischemia but rather prioritize plaque biology, vulnerability markers, and individualized risk assessment. This framework is consistent with emerging evidence from PROSPECT ABSORB, PREVENT, and DEBuT-LRP and supports the broader shift toward preventive interventions aimed at averting MI before plaque causes an event.

## 8. Ethical Justification for Preventive PCI During a Pandemic Crisis

The COVID-19 pandemic imposed unprecedented strain on healthcare systems, creating conditions in which traditional models of cardiovascular care could not be reliably executed. Delays in treatment, constrained catheterization laboratory capacity, staffing shortages, and unpredictable access to emergency services fundamentally reshaped the risk–benefit landscape for patients with coronary artery disease (CAD) [152-156]. For individuals harbouring unstable high-risk plaque (HRP), these system-level pressures magnified the danger of deferring intervention. They forced clinicians to reconsider long-standing assumptions regarding the timing and appropriateness of revascularization.

A crucial parallel emerges from aviation medicine, where risk tolerance is deliberately set far below that of clinical practice. Aviation authorities have long recognized that even mild coronary stenosis carries a non-trivial risk, given the catastrophic consequences of in-flight incapacitation. For this reason, guidelines state that stenosis >30% in any major epicardial coronary artery mandates restriction to multi-crew operation, whereas stenosis >50% is disqualifying for pilot certification. When the left main or proximal left anterior descending artery is involved, any lesion >30% is sufficient to deny certification, regardless of symptoms. Conversely, aircrew with chest pain but normal coronary anatomy—or only minor irregularities—may be permitted unrestricted flight, subject to ongoing review. This framework reflects a fundamental principle: risk is determined not solely by stenosis severity, but by the potential consequences of plaque instability. These aviation standards underscore that even “mild” disease may be clinically meaningful in high-stakes environments and lend conceptual support to precautionary approaches during periods of extreme healthcare disruption, such as the COVID-19 pandemic.

Within this context, the ethical basis for preventive PCI rests on several well-established principles:

First, the pandemic created a unique circumstance in which future access to emergency intervention could not be assured. Under normal conditions, a patient with myocardial infarction can expect rapid transfer to a PCI-capable centre. During COVID-19 surges, however, transport delays, prolonged triage times, and temporary catheterization laboratory closures frequently disrupted this safety net. When system reliability collapses, leaving a morphologically unstable plaque untreated exposes the patient to a substantially higher risk of catastrophic outcomes.

Second, contemporary coronary imaging—CTCA, IVUS, OCT, and NIRS—enables clinicians to identify lesions with demonstrably high rupture or erosion potential. Features such as a thin fibrous cap, a large lipid core, expansive positive remodelling, elevated lipid-core burden, thrombus, or luminal surface irregularities are not incidental findings; they are well-validated harbingers of myocardial infarction. However, during the COVID-19 pandemic, Indonesia faced substantial limitations in advanced intravascular imaging. NIRS was not available nationally, and most IVUS and OCT reimbursement claims were rejected, making widespread use of these technologies impractical. Consequently, CTCA emerged as the only consistently accessible modality for detecting vulnerable coronary plaques during that period. In circumstances where emergency care may be delayed or unavailable, pre-emptive stabilization of high-risk lesions identified by CTCA becomes a reasonable and defensible strategy.

Third, preventive intervention satisfies the ethical requirement of proportionality when procedural risk is low, and external constraints magnify the potential harm of non-intervention. Elective PCI using DES or DCB technologies is associated with high procedural safety, especially in stable patients. When weighed against the elevated, time-sensitive risk of plaque rupture during a pandemic, the proportionality calculation shifts decisively toward intervention in selected high-risk individuals.

Fourth, patient autonomy remains central. Preventive PCI should be offered only after a transparent discussion of risks, uncertainties, and alternatives. Informed consent during crisis conditions must acknowledge both the biological threat posed by unstable plaque and the operational threat posed by systemic healthcare disruption. When patients, fully informed of these realities, choose the option that maximizes their protection, clinicians act in alignment with ethical and professional obligations.

Taken together, these considerations underscore that clinical guidelines—while essential during routine practice—cannot rigidly dictate care during extraordinary circumstances. Guidelines are derived from evidence generated under stable conditions and cannot anticipate the dynamic constraints of a healthcare system in crisis. In such settings, individualized judgment informed by imaging, risk biology, and operational realities becomes both ethically and clinically indispensable.

Thus, during the COVID-19 pandemic, preventive PCI for unstable plaques in high-risk patients was not only scientifically logical—it was ethically justified. By stabilizing lesions most likely to rupture when emergent PCI access could not be guaranteed, clinicians acted in accordance with the principles of beneficence, non-maleficence, and respect for patient autonomy. The aviation paradigm reinforces this reasoning: when the consequences of failure are catastrophic, intervention thresholds must be lower. This framework remains relevant for future crises in which access to timely cardiac care may again be threatened.

## 9. Future Trials: Designing the Studies Needed to Resolve the Vulnerability Debate

Despite extensive pathological, mechanistic, multimodality-imaging, and early interventional evidence demonstrating that plaque rupture, plaque erosion, and eruptive calcified nodules are the true substrates of ACS, the field still lacks a definitive randomized clinical trial that tests whether targeted stabilization of VP improves hard cardiovascular outcomes.

Seminal trials such as ISCHEMIA, COURAGE, and FAME were not structured to evaluate plaque biology. They relied on stenosis or ischemia, which—although clinically useful—fail to capture the structural and inflammatory features that actually determine the risk of MI.

To advance modern cardiology, the next generation of trials must fundamentally shift focus from flow limitation to substrate biology.

### 9.1 Rationale for Biology-Based Randomization

Contemporary imaging modalities—OCT, IVUS/NIRS, and CTCA—now reliably identify vulnerable and HRPs, including:

- Rupture-prone plaques (TCFA) are characterized by thin fibrous caps, large lipid-necrotic cores, macrophage infiltration, positive remodelling, and intraplaque haemorrhage.
- Erosion-prone plaques identified by intact caps with endothelial denudation, white thrombus, high shear stress environments, fibro-fatty composition, and CT high-attenuation phenotypes.
- Calcified nodules recognized as eruptive, protrusive nodular calcium clusters associated with hinge-motion stress and microfracture.

These lesions—not obstructive stenoses—produce the majority of spontaneous MI. Therefore, to determine the true benefit of preventive PCI or DCB therapy, patients must be enrolled based on plaque biology rather than luminal narrowing or ischemia.

This approach aligns cardiology with other precision-medicine domains, in which therapy targets the pathogenic substrate rather than just the symptomatic manifestation.

### 9.2 Proposed Study Design: A Modern Biology-Guided Randomized Trial

A scientific, mechanistically coherent trial would feature the following structure:

**Study Arms**
Arm 1: Targeted Preventive Intervention
• Selective PCI with DES or DCB therapy for VP
• Plus intensive systemic therapy
o LDL goal <40 mg/dL
o Anti-inflammatory therapy (e.g., colchicine or IL-1/NLRP3 axis modulation)
o Comprehensive lifestyle therapy (WFPBD intervention, optimal exercise, restorative sleep, avoidance of unhealthy substances, stress management, and positive social support)

**Arm 2: Intensive Systemic Therapy Alone**
• Represents state-of-the-art OMT without local intervention
• Mirrors the medical arm of PROSPECT ABSORB and PREVENT
• Provides a contemporary control for evaluating the incremental benefit of focal stabilization

This design isolates the biological question:
Does selectively stabilizing rupture-prone, erosion-prone, or calcified-nodule lesions reduce MI?

### 9.3 Entry Criteria: Imaging-Defined HRP
Participants would qualify based on morphologic and biological criteria identified by advanced imaging:
**A. Rupture-Prone (TCFA) Features**
• OCT-defined thin fibrous cap (<65 μm)
• Large necrotic core
• OCT macrophage clusters
• NIRS high lipid-core burden (e.g., maxLCBI$_{4}$mm ≥400)
• IVUS plaque burden ≥70%
• CTCA low-attenuation plaque (<30 HU)
• CTCA napkin-ring sign

**B. Erosion-Prone Features**
• Intact fibrous cap with luminal irregularity
• High-shear anatomic segments (proximal LAD, bifurcations)
• CTCA high-attenuation plaque (>150 HU) without a necrotic core
• Evidence of endothelial denudation patterns on OCT
• Smooth luminal surfaces with white thrombus phenotype

**C. Calcified Nodule Features**
• OCT-identified eruptive nodular calcification
• IVUS protrusive calcium with acoustic shadowing
• CTCA nodular calcium within dynamic hinge points
• Repetitive lumen irregularity or microfracture patterns

These phenotypes capture the full spectrum of high-risk substrates responsible for ACS—not only rupture-prone plaques, but also erosion and calcified nodules, which have been historically understudied in clinical trials.

### 9.4 Follow-Up Duration and Clinical Endpoints
Given the natural history of plaque progression, a 3–5 year follow-up period is necessary to capture spontaneous events.

**Primary Clinical Endpoints**
• MI (spontaneous Type 1)
• Cardiac or cardiovascular death

**Secondary Clinical Endpoints**
• MACE
• Need for urgent revascularization
• Hospitalization for unstable angina
• Progression to obstructive coronary disease
• Stroke or systemic embolism

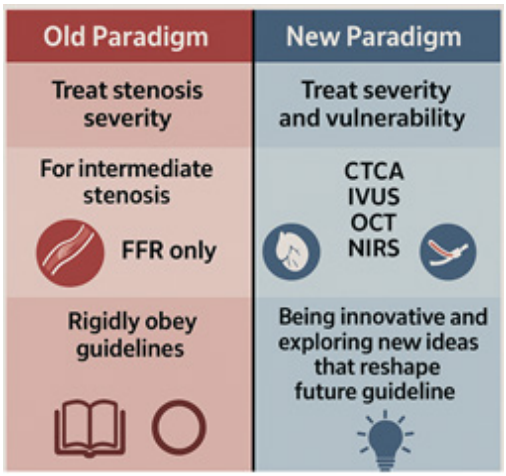
**Mechanistic Endpoints**
• OCT cap thickening
• Reduction in macrophage or NET-related signal
• NIRS lipid-core regression
• IVUS plaque burden reduction
• CTCA stabilization of low-attenuation plaque
• Reduction in perivascular fat attenuation (FAI)
• Shear-stress normalization (computational fluid dynamics)

This dual framework of mechanistic and clinical endpoints provides insight not only into efficacy but also into how and why stabilization occurs.

### 9.5 Scientific and Clinical Significance
A rigorously designed, biology-based randomized trial would address one of the most important unanswered questions in modern cardiovascular medicine:

Does targeted treatment of VP—whether rupture-prone, erosion-prone, or calcified-nodule lesions—prevent MI?

The implications are transformative:
• It would provide definitive evidence to move beyond stenosis- and ischemia-centred decision making.
• It would validate or refute the hypothesis that selective focal stabilization prevents spontaneous ACS.
• It would align coronary intervention with the principles of precision medicine, where therapy targets the structural and inflammatory drivers of disease—not their downstream hemodynamic consequences.
• It would guide future revisions of global revascularization guidelines and redefine standards of care.
Above all, such a trial would bring cardiology closer to a future in which MI becomes a preventable complication rather than an unpredictable catastrophe.




## 10. Conclusion

The accumulated evidence is unequivocal: MI is not the consequence of stenosis but of plaque vulnerability. Across pathology, multimodality imaging, AI-driven analyses, and real-world clinical cohorts, the same disruptive truth emerges—the plaques that rupture, erode, or erupt as calcified nodules are rarely the ischemia-producing stenoses historically targeted by guidelines. They are the silent, biologically unstable, angiographically "mild," FFR-negative lesions that have escaped detection for decades under the stenosis-centric paradigm.

The COVID-19 pandemic exposed this flaw with unprecedented clarity. Amid a global inflammatory storm that amplified endothelial injury, destabilized thin caps, and accelerated erosion, the traditional ischemia-based approach repeatedly failed. In contrast, the vulnerability-guided strategy implemented at Bethsaida Hospital—systematic identification of HRPs; selective preventive revascularization; intensive LDL-lowering; metabolic and inflammatory control; and WFPBD therapy—yielded zero mortality among 3,500 infected or exposed patients, an outcome unmatched anywhere in the world. Remarkably, this strategy was conceptualized before PROSPECT ABSORB, PREVENT, and DEBuT-LRP were published, underscoring its originality and biological precision.

Taken together, these insights demand a fundamental reorientation of coronary care:

- Stenosis relieves symptoms; vulnerability determines survival.
- Angiography and ischemia testing identify flow limitation, not biological danger.
- Multimodality imaging (OCT, IVUS, NIRS, CTCA, FAI) must replace percent stenosis as the foundation of risk assessment.
- Preventive focal stabilization—DES or DCB—should be selectively deployed for rupture-, erosion-, and calcium-driven substrates, regardless of luminal severity.
- Systemic biological therapy (ultra-low LDL, inflammation control, metabolic optimization, WFPBD) is essential to reduce pan-coronary vulnerability.
- AI will define future practice by quantifying plaque biology, shear stress, and individualized rupture risk.

The stenosis paradigm has reached its scientific limit. A vulnerability-centred model—integrating advanced imaging, precision mechanical stabilization, aggressive biological modulation, and lifestyle transformation—offers a coherent, evidence-based, and ethically sound framework for preventing MI. If implemented widely, this paradigm has the potential not merely to improve outcomes, but to redefine MI as a largely preventable, rather than inevitable, event.

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Data are contained within the article.

## Conflict of Interest

The authors declare no conflict of interest.

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