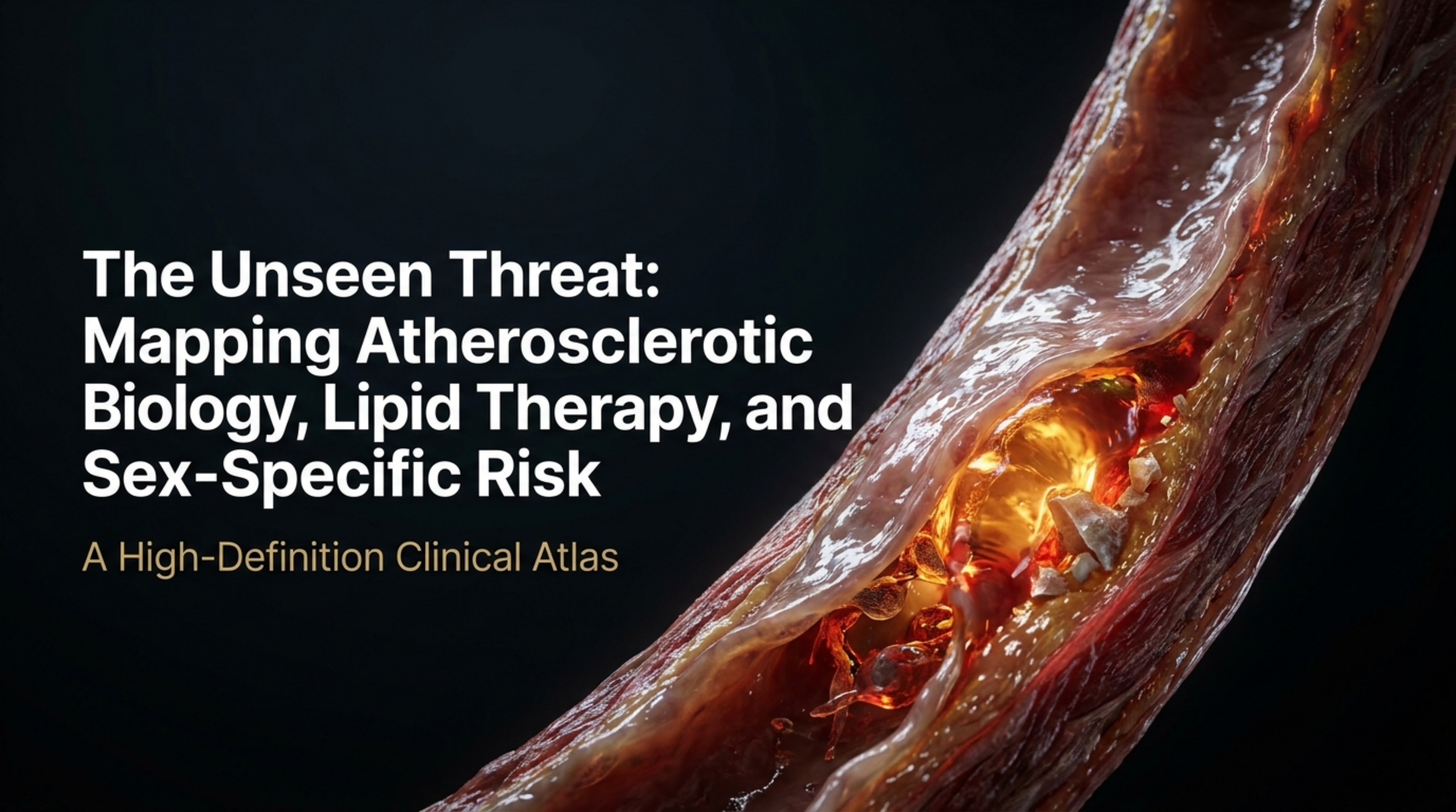
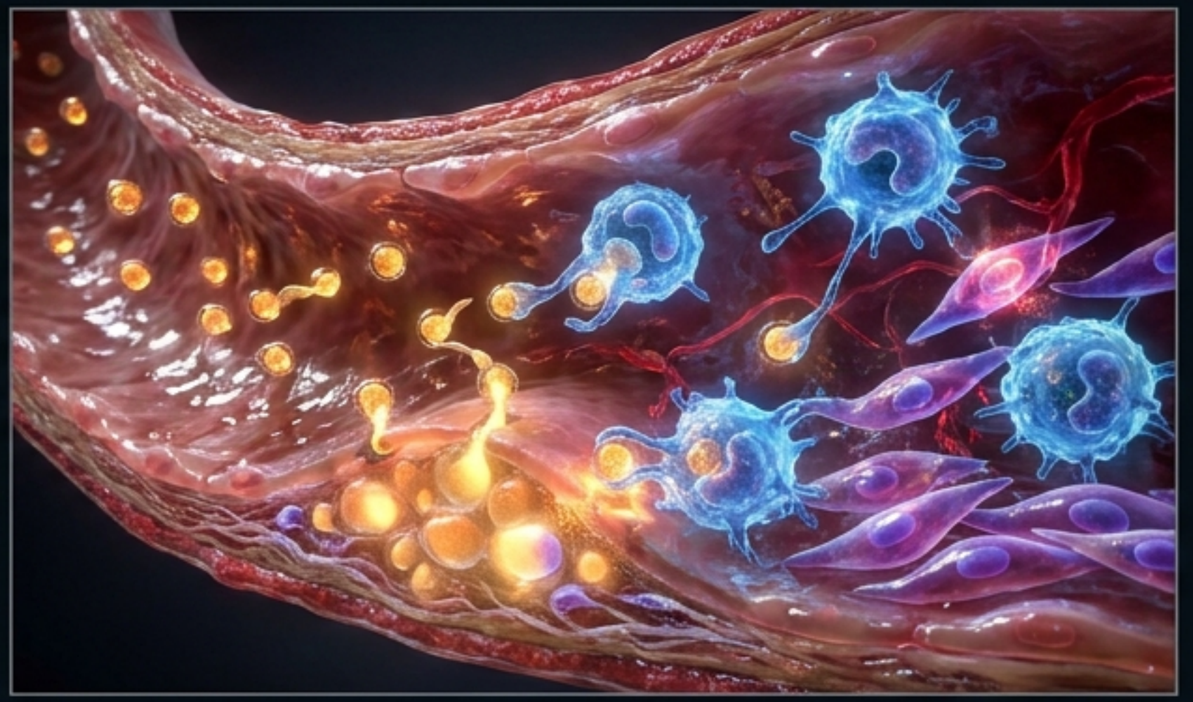
The Unseen Threat: Mapping Atherosclerotic Biology, Lipid Therapy, and Sex-Specific Risk

A High-Definition Clinical Atlas



The Atherosclerotic Paradigm Shift

Historical View: Linear mechanical obstruction of blood flow.

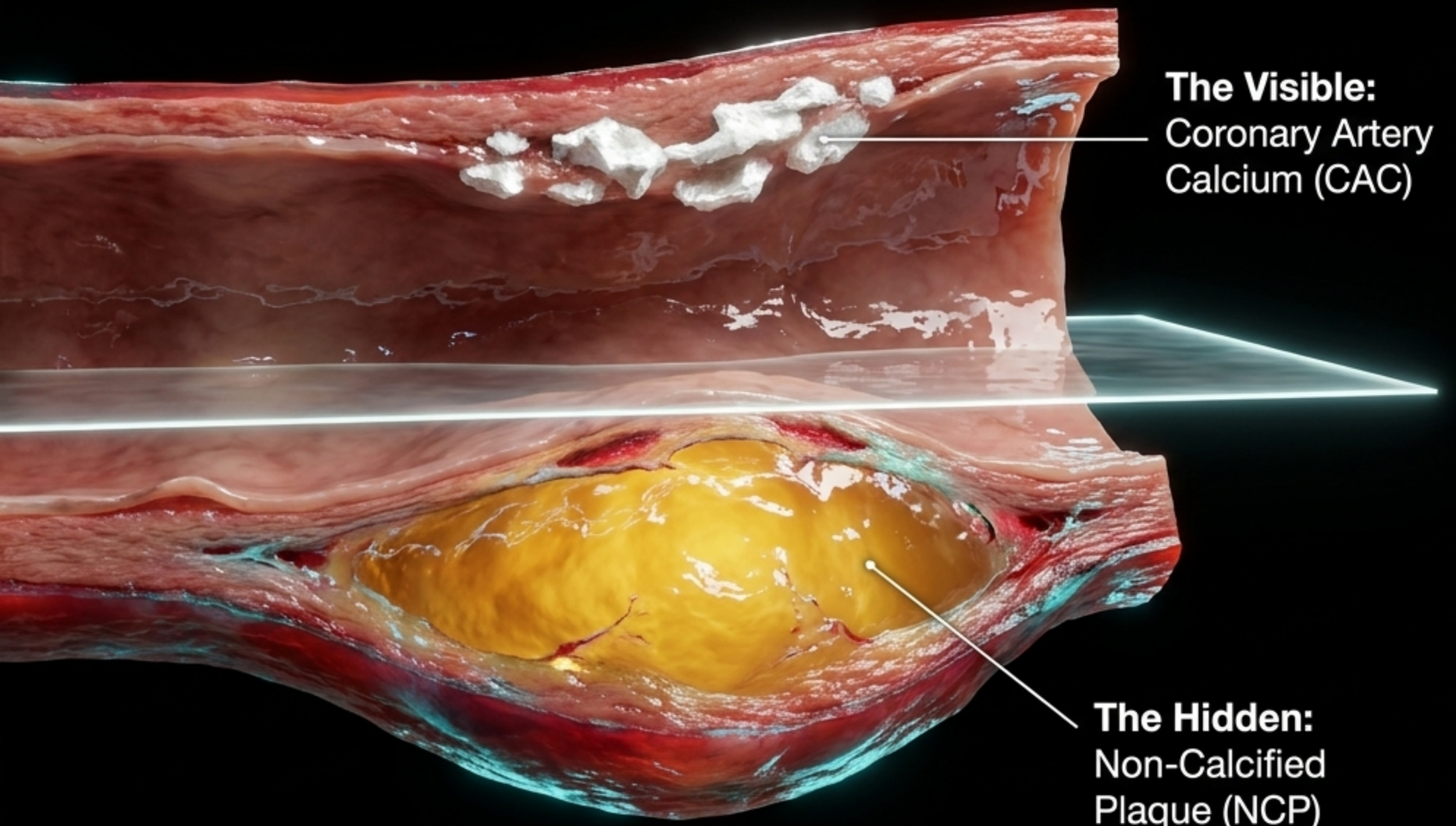


Contemporary View: A chronic immunoinflammatory disease driven by subendothelial apoB-lipoprotein deposition and immune activation.

Disease progression is dictated by plaque composition and stability, not merely plaque volume.

High-Definition Physiological Atlas

The Limits of CAC = 0: The Underdetected Component



Main Point

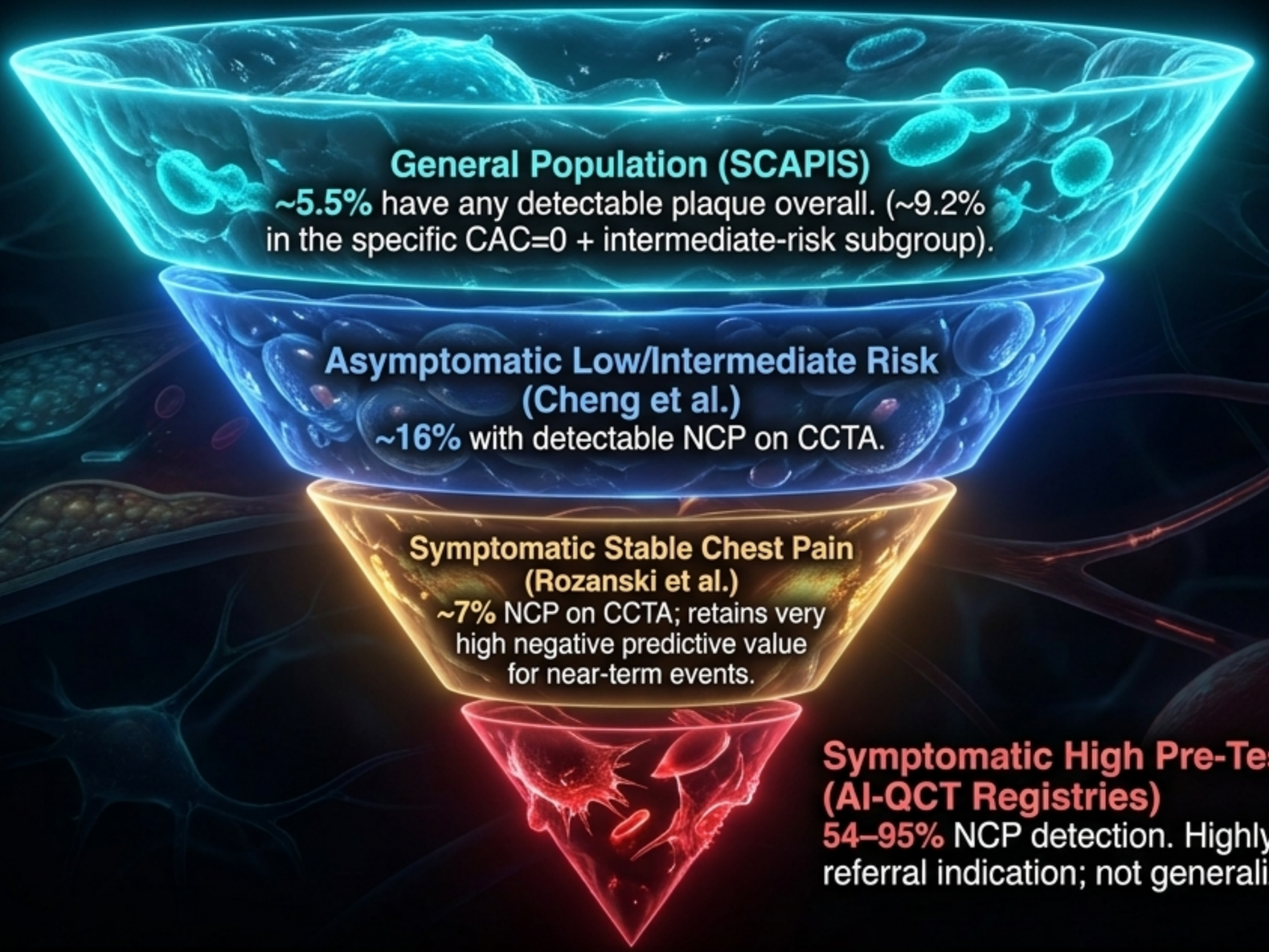
A Coronary Artery Calcium (CAC) score of 0 is a powerful short-term negative risk marker, but it entirely misses lipid-rich, rupture-prone Non-Calcified Plaque (NCP).

Data Highlights

NCP is invisible on non-contrast CT.

Approximately 15–17% of low-to-intermediate-risk individuals with CAC = 0 harbor detectable atherosclerosis.

Context-Dependent Plaque Prevalence in CAC = 0

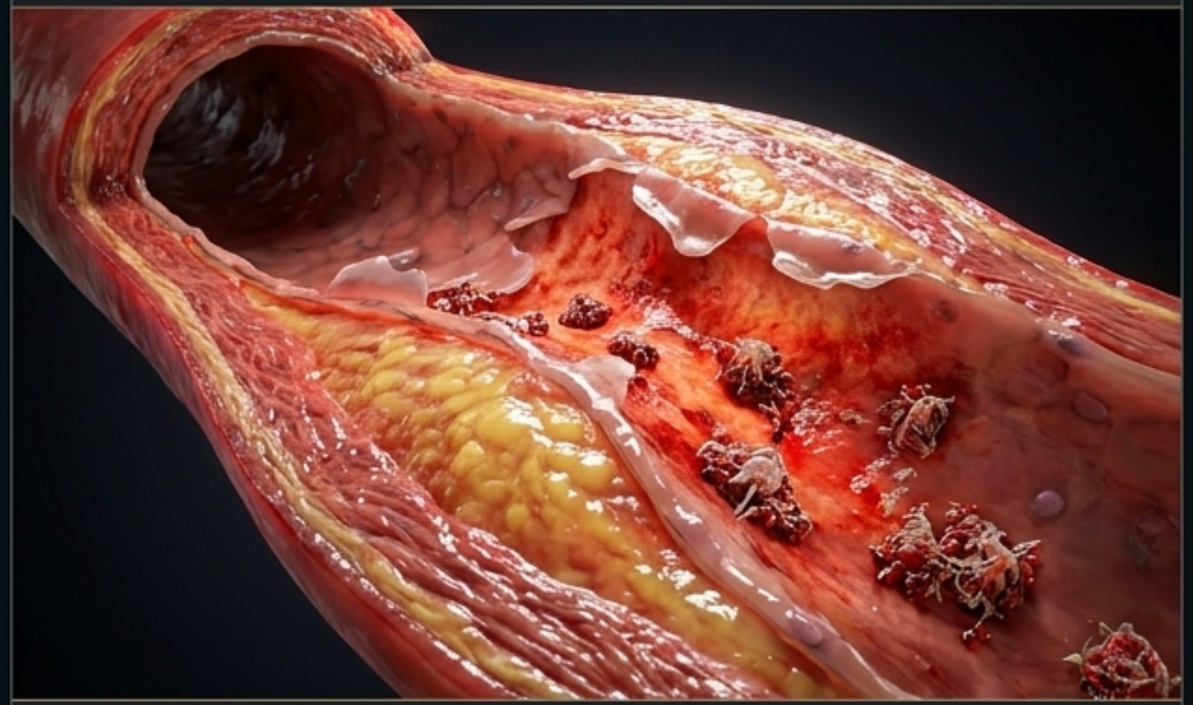


Anatomy of an Event: Rupture vs. Erosion

Plaque Rupture

Disruption of a thin, inflamed fibrous cap over a large necrotic core.

Plaque Erosion

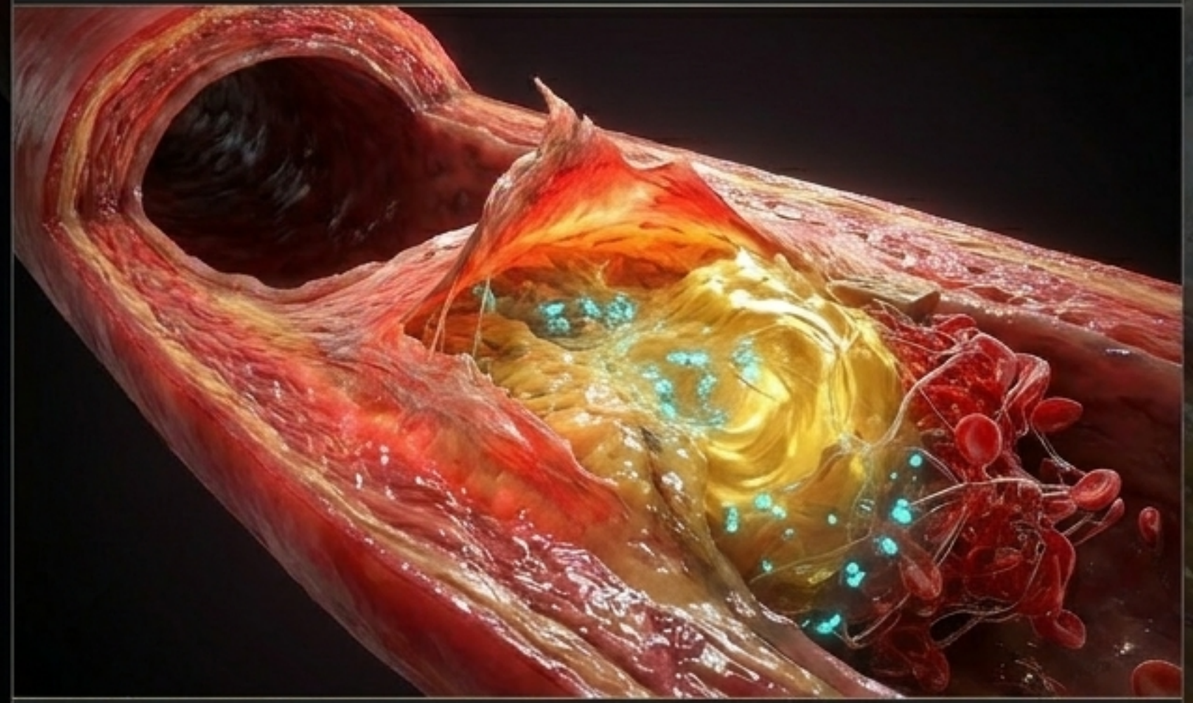


Disruption of the endothelial surface over a lipid-rich non-calcified plaque.

Erosion is significantly more common in women and younger individuals, presenting a distinct diagnostic challenge for calcium-only screening.

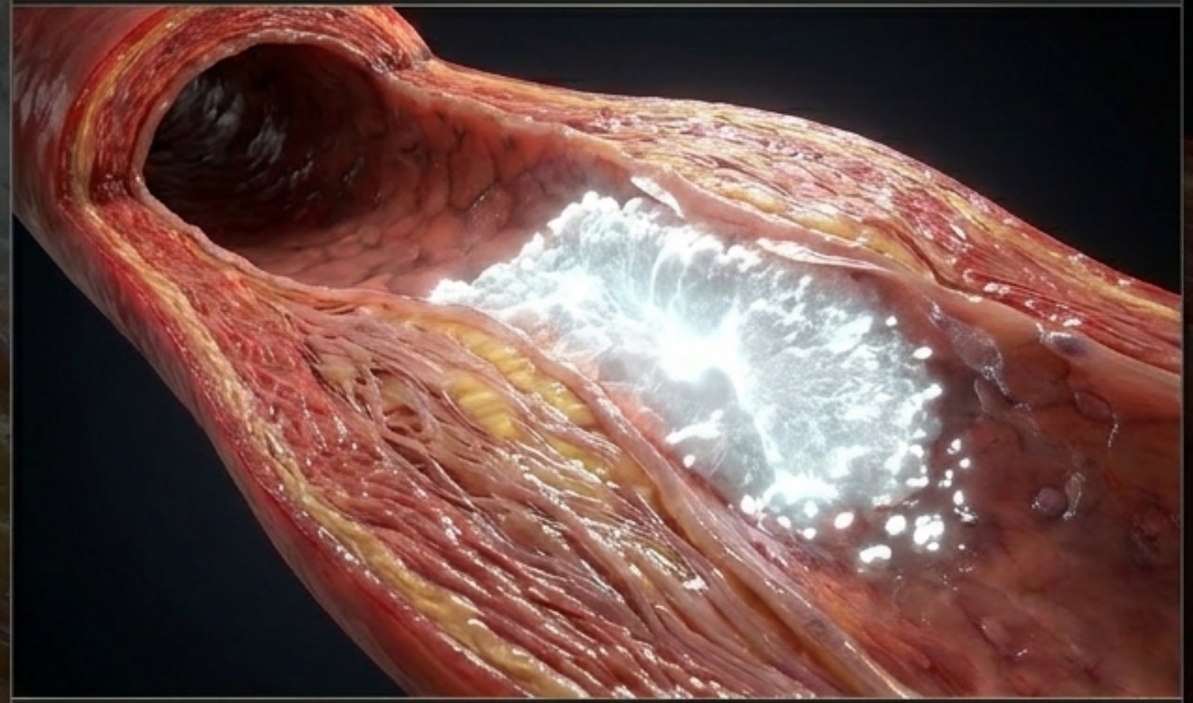
The Statin–CAC Paradox: Disease Progression vs. Plaque Remodeling

Untreated Disease Progression



- **Composition:** High lipid/large necrotic core
- **Calcium Phenotype:** Spotty, low-density microcalcification
- **Fibrous Cap:** Thin, inflamed, rupture-prone
- **Agatston Score Trend:** Rising (new lesions)
- **Clinical Risk:** Highly elevated

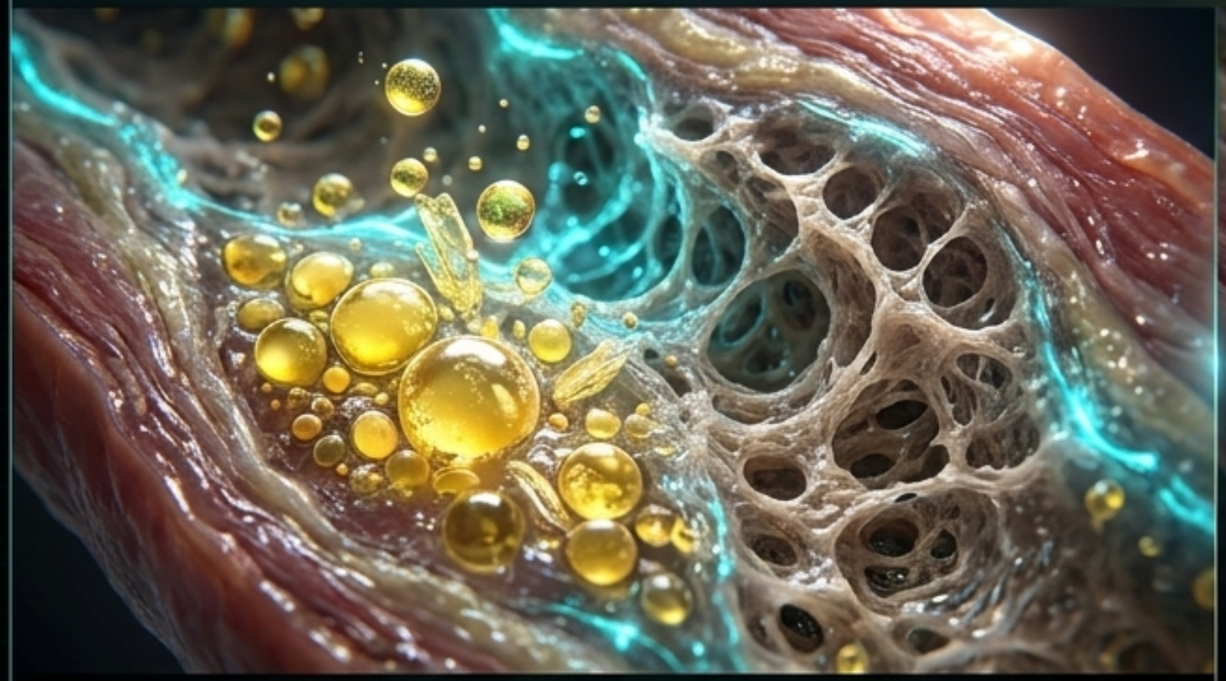
Statin-Associated Remodeling



- **Composition:** Fibrotic/reduced lipid
- **Calcium Phenotype:** Shift toward denser, coalescent calcium strata
- **Fibrous Cap:** Thickened, mechanically stable
- **Agatston Score Trend:** Rising (calcium densification)
- **Clinical Risk:** Significantly reduced

Mechanistic Basis of Plaque Stabilization

4K calcium densification



Step 1: Lipid Resolution & Scaffolding Clearance

Step 2: Calcium Densification & Reinforcement

Core Concept: The “Healing Hypothesis”

As lipid components are resolved, dense calcium serves as structural reinforcement around the necrotic core, reducing mechanical stress on the fibrous cap.

Evidence Base

Serial CCTA (PARADIGM) and 2025 noncontrast CT data show statins decrease low-attenuation plaque while increasing high-density calcified plaque.

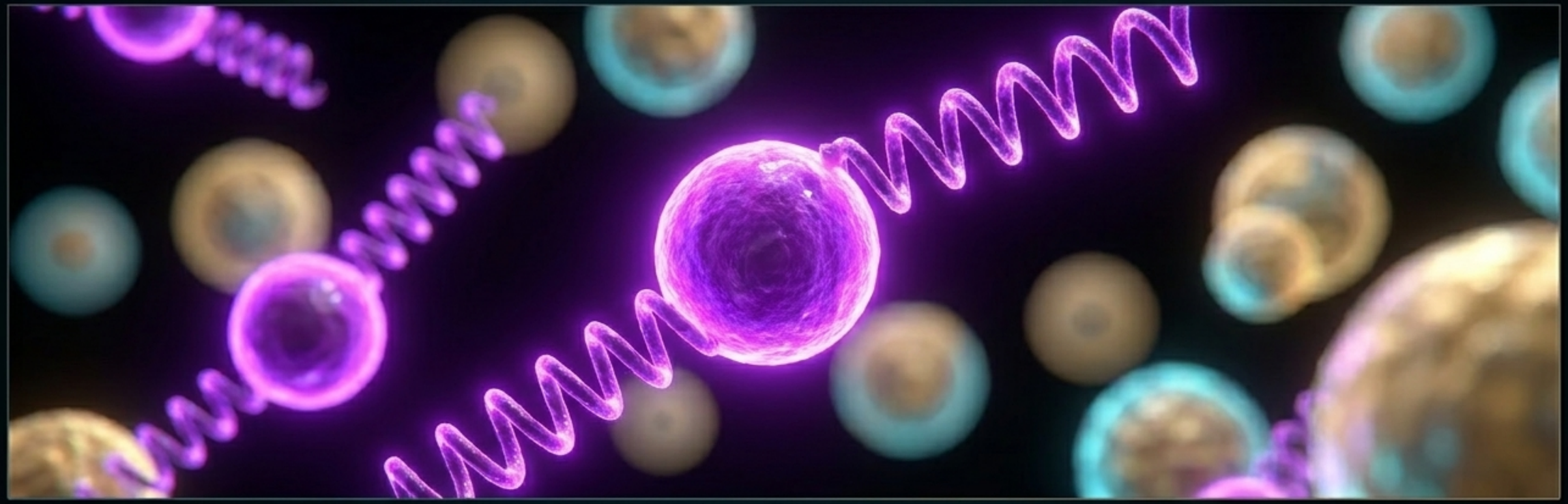
Proposed Pathways

Theorized to involve inhibition of Vitamin K2 synthesis (reducing Matrix Gla-protein) and macrophage-mediated pathways, though human randomized validations remain pending.

PCSK9 Inhibitors: Regression and Structural Restoration

Mechanism	Imaging Trial Evidence (Add-on to Statins)
Profound LDL-C reduction via prevention of hepatic LDLR degradation. Clinical benefit is driven by lipid lowering, with minimal systemic hsCRP change.	• **GLAGOV:** Significant regression of atheroma volume (-0.95% vs +0.05% placebo). • **HUYGENS:** Greater minimum fibrous cap thickness increase (+42.7 μm vs +21.5 μm). • **PACMAN-AMI:** Greater regression in percent atheroma volume (-2.13% vs -0.92%) post-MI.

Lipoprotein(a): The Independent Risk Vector



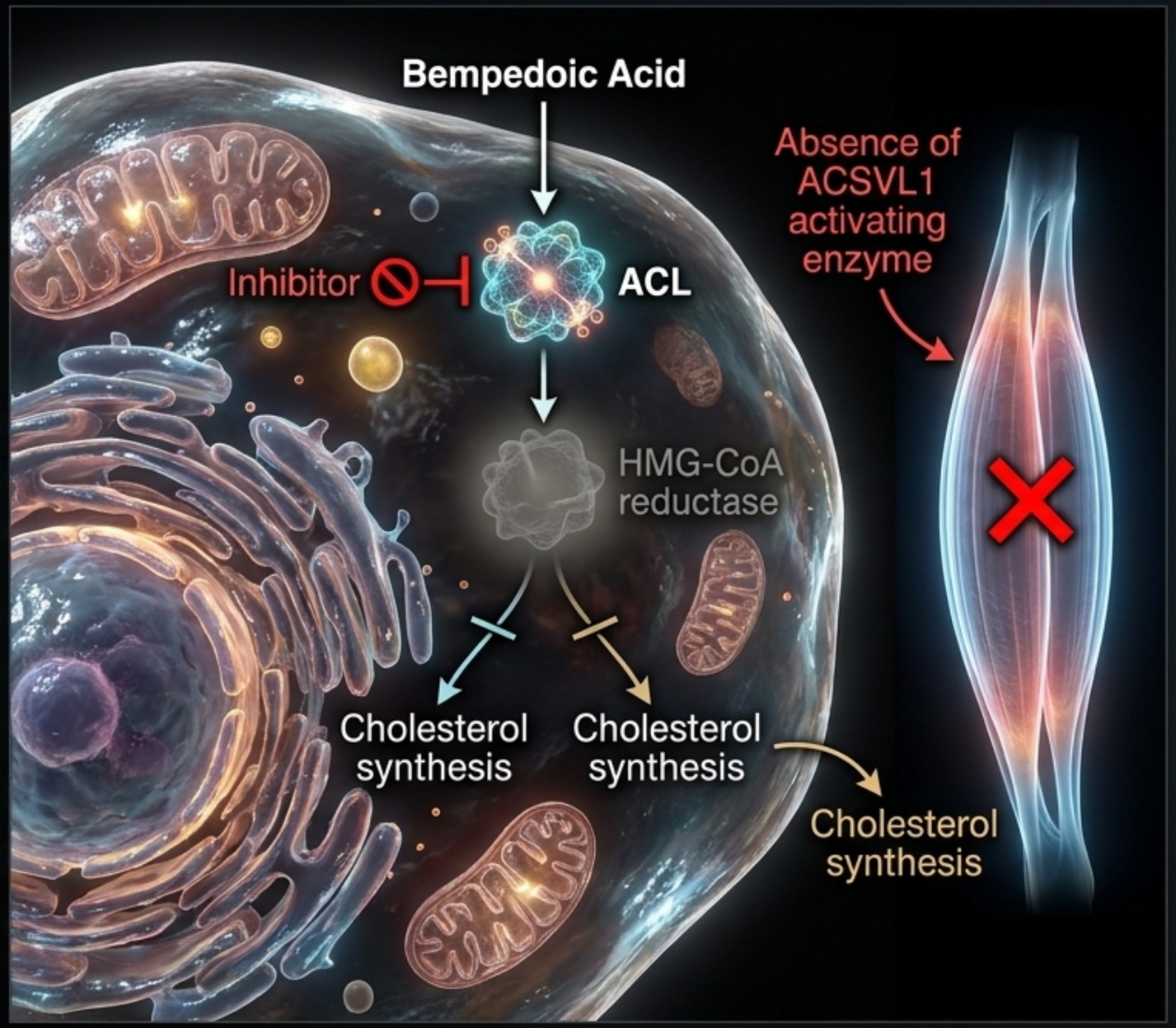
The Challenge

Lp(a) is a genetically determined ASCVD risk factor largely unaffected by standard statin therapy. Its relationship with CAC burden is inconsistent, acting as an independent marker rather than a direct predictor of calcification.

The PCSK9i Advantage

PCSK9 inhibitors reduce Lp(a) by approximately 25–27% (median 26.9% in the FOURIER cohort), offering a specific therapeutic lever for this distinct physiological threat.

Bempedoic Acid: Upstream Action and Inflammation Control



Mechanism

Oral ATP citrate lyase (ACL) inhibitor. Prodrug activated only in the liver, bypassing skeletal muscle to minimize statin-intolerant adverse effects.

CLEAR Outcomes Trial Data

- **Primary MACE-4:** 13% relative risk reduction (HR 0.87, P=0.004).
- **Total MACE-4 Events:** 20% reduction (HR 0.80, P<0.001).

Inflammatory Profile

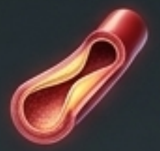
Achieved a 22% placebo-corrected median reduction in hsCRP at 6 months. Plaque-imaging evidence remains limited pending phase 3 trials.

Comparative Therapeutic Profile

The Therapeutic Arsenal Matrix

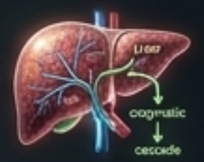
Statins

- **Primary Effect:** Plaque stabilization & lipid reduction.
- **Morphology:** Promotes dense, stable calcium phenotype.
- **Imaging Evidence:** Robust serial CCTA data.



PCSK9 Inhibitors

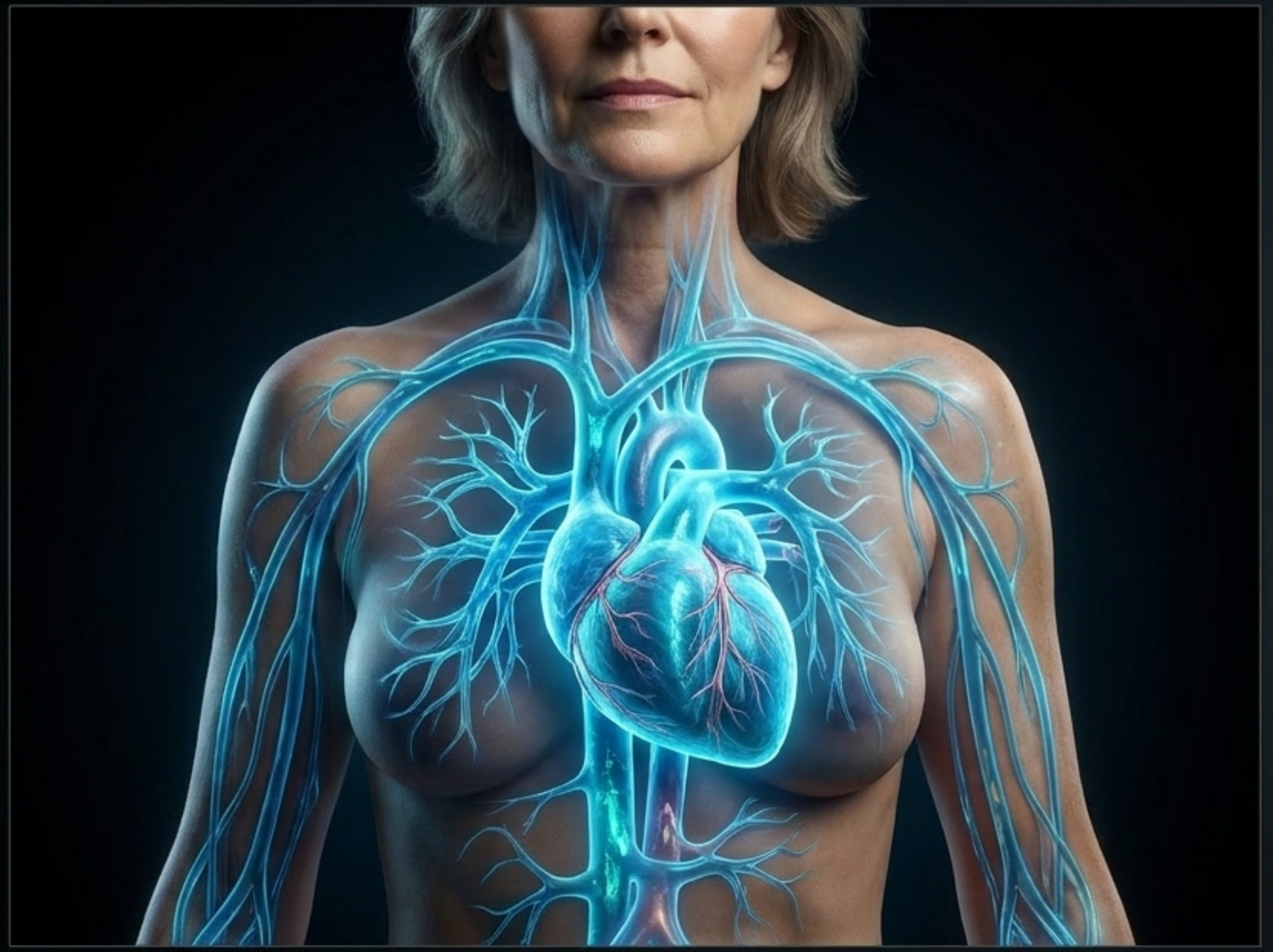
- **Primary Effect:** Plaque regression & cap restoration (added to statins).
- **Morphology:** Shrinks necrotic core, thickens fibrous cap.
- **Imaging Evidence:** Strong IVUS/OCT trial data (GLAGOV, HUYGENS).



Bempedoic Acid

- **Primary Effect:** Upstream LDL lowering & systemic hsCRP reduction.
- **Morphology:** Plausible modification; unproven class effect.
- **Imaging Evidence:** Limited (single case reports; awaiting Phase 3).

The Female Cardiovascular Baseline: Estrogen's Protective Shield



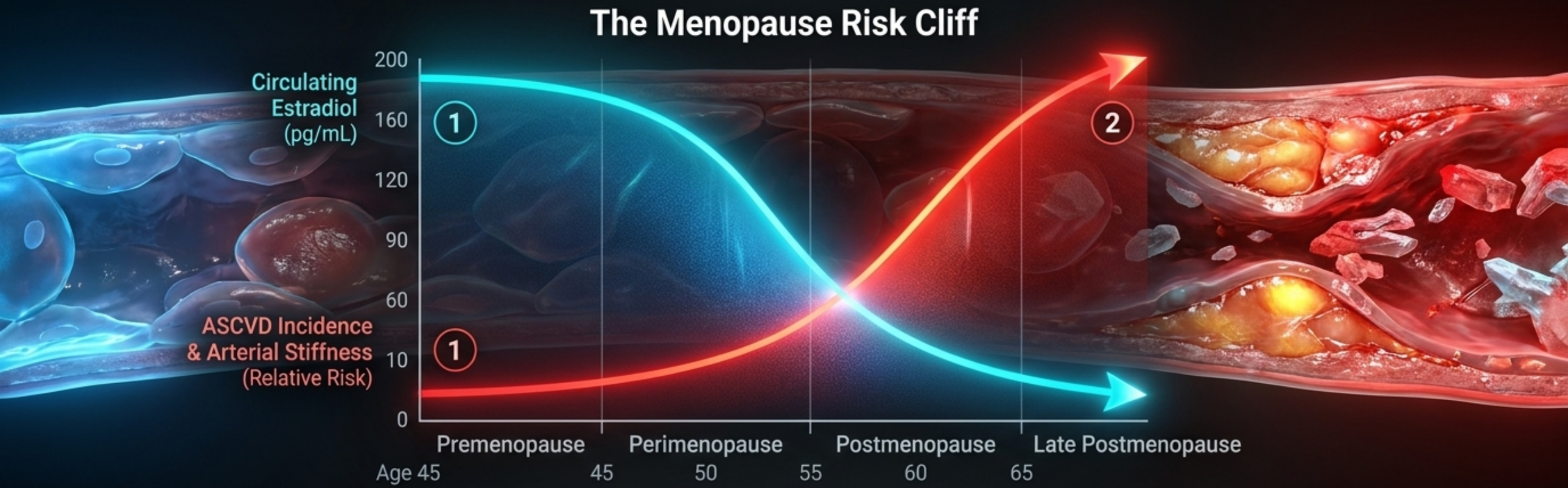
The Decade Delay

Women generally develop clinically manifest coronary artery disease approximately a **decade later** than men.

Vascular Maintenance

Endogenous estrogen promotes endothelium-dependent vasodilation (stimulating nitric oxide and prostacyclin), inhibits vascular smooth muscle cell proliferation, and exerts deep anti-inflammatory effects on the vessel wall.

The Menopause Transition: Accelerated Vascular Aging



The Shift:

The precipitous decline in estradiol triggers measurable reductions in endothelial function.

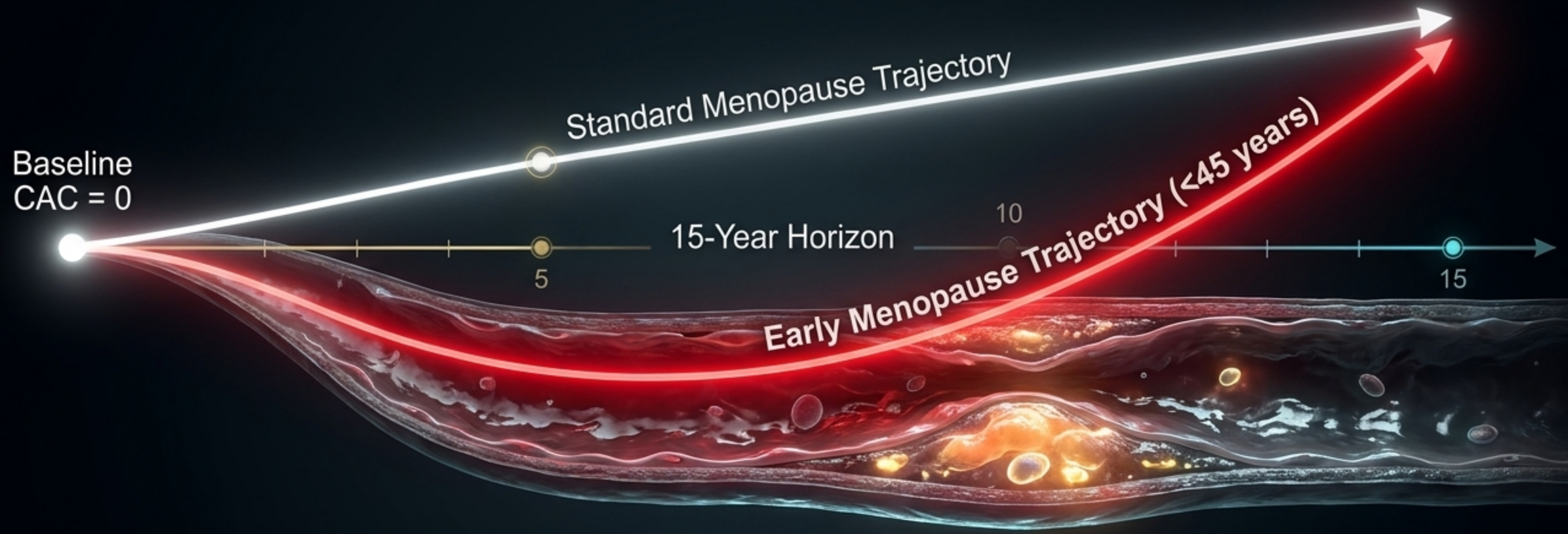
Flow-Mediated Dilation (FMD):

FMD in late postmenopausal women is ~50% lower than in premenopausal women, with the sharpest drop during perimenopause.

Risk Convergence:

By their 60s, women's cardiovascular risk accelerates dramatically, approaching that of age-matched men.

Early Menopause: The Diagnostic Illusion of CAC = 0



MESA Data Context

More than half of postmenopausal women with early menopause (<45 years) have a baseline CAC score of 0.

The Risk Trap

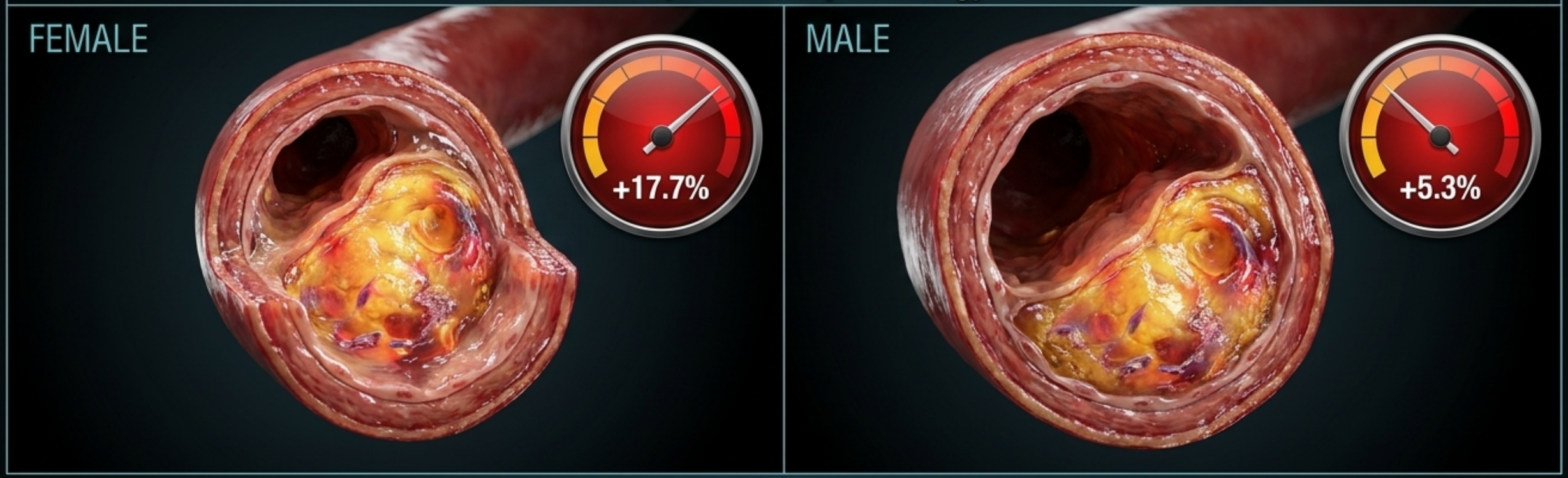
While 10-year risk remains low, 15-year risk is significantly higher (adjusted HR 1.96) compared to standard menopause.

Systematic Impact

Early menopause is independently associated with a 50–60% increase in lifetime coronary heart disease risk. The absence of calcium masks the active accumulation of lipid-rich inflammatory plaque.

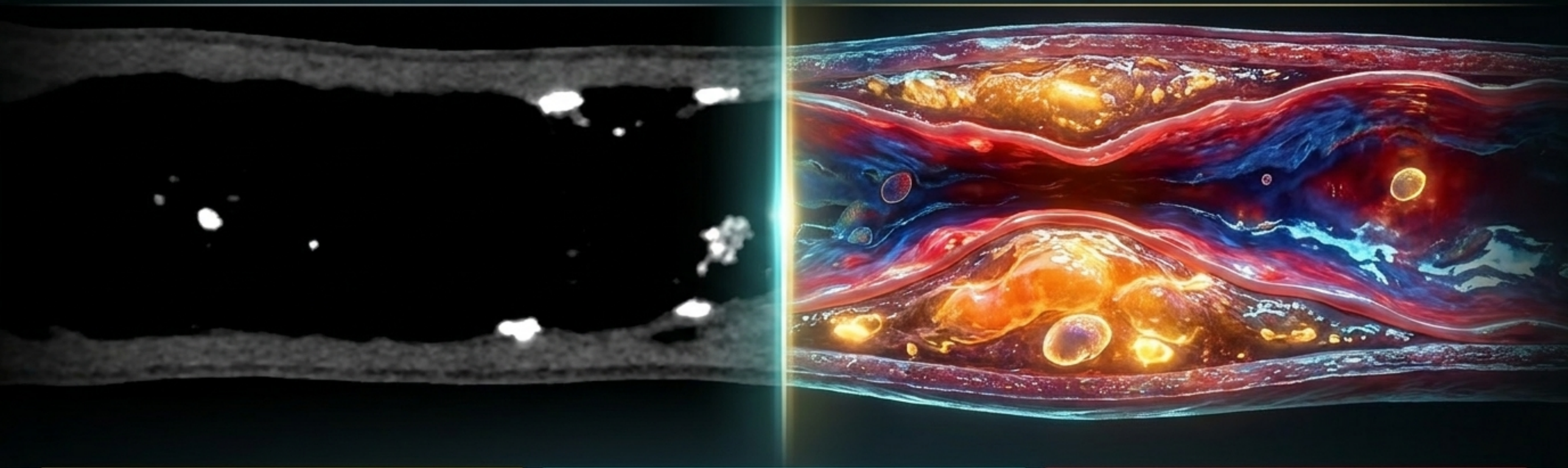
The CONFIRM2 Reality: Higher Relative Risk per Unit of Plaque

Sex-Specific Plaque Biology



Plaque Composition Tendency:	Relative Risk Increment:	Clinical Bottom Line:
Women carry a greater proportion of total plaque burden in non-calcified, erosion-prone forms.	Per 50 mm^3 of total plaque volume, women experience a +17.7% relative risk increase, compared to just +5.3% in men.	Because women's vessels are typically smaller, each unit of high-risk plaque is more hemodynamically consequential. CAC scoring—which only sees calcium—disproportionately underestimates true risk in mid-life women.

Advanced Imaging: The AI-QCT Lens



Comprehensive Characterization

AI-based quantitative CT automates the measurement of total plaque burden, capturing calcified, non-calcified, and low-attenuation components.

Symptomatic Reclassification

AI-QCT frequently identifies significant NCP in symptomatic patients with zero Agatston scores—particularly meaningful for women with additional risk features.

Current Status

A promising emerging modality requiring further broad standardization, external validation, and sex-specific risk thresholds before fully replacing current frameworks.

Beyond the Lumen: Epicardial Adipose Tissue (EAT)

Metabolic Engine

Automated analysis from routine calcium-scoring CT scans can quantify EAT volume and attenuation.

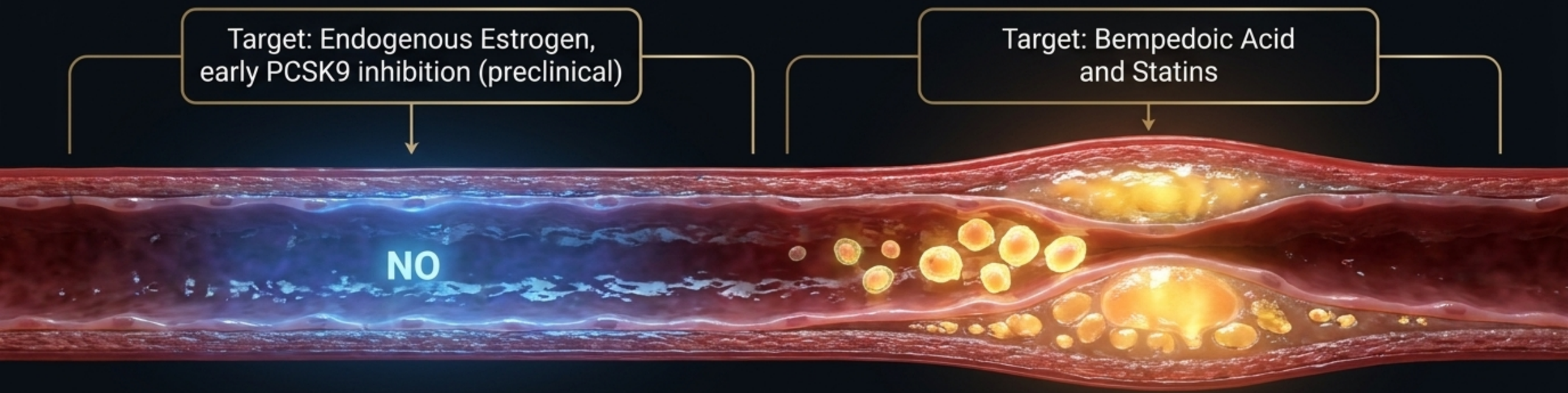
Paracrine Threat

EAT is metabolically active, exerting pro-inflammatory and pro-atherogenic effects on adjacent arteries via cytokines and adipokines.

Sex-Specific Value

Integrating quantitative EAT features with conventional risk factors significantly enhances MACE prediction, with particularly strong incremental diagnostic value in women.

Integrated Framework for Therapeutic Mapping: Stages 1 & 2



Stage 1 — Endothelial Activation

Subendothelial retention of apoB lipoproteins and reduced NO bioavailability.

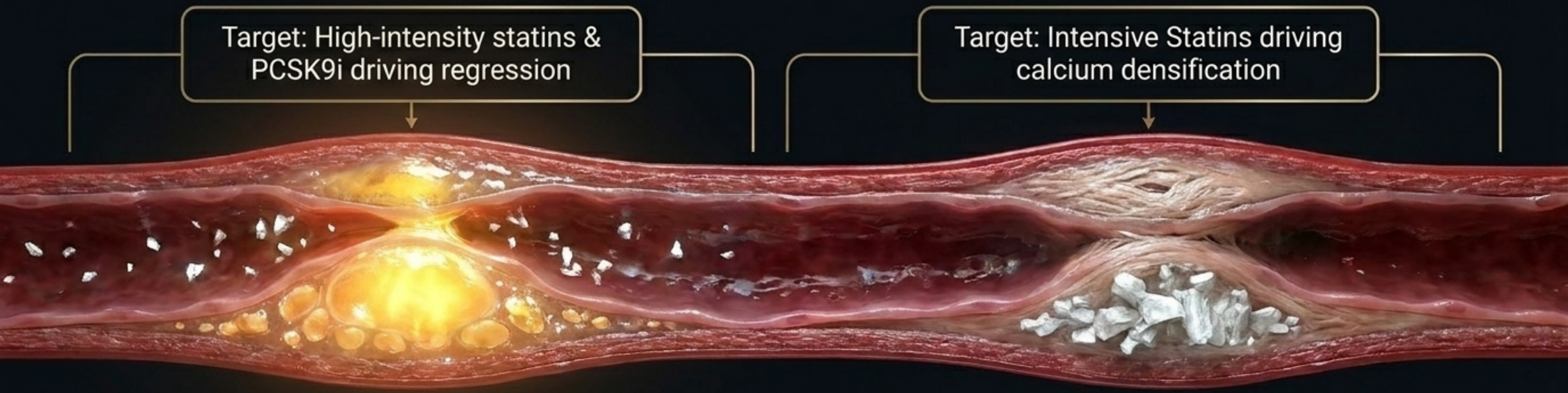
Primary Modulators: Endogenous Estrogen, early PCSK9 inhibition (preclinical).

Stage 2 — Early Non-Calcified Plaque

Macrophage foam cell formation establishes the atheromatous lesion.

Primary Modulators: Statins and Bempedoic Acid dampen systemic inflammation and reduce the circulating lipid pool.

Integrated Framework for Therapeutic Mapping: Stages 3 & 4



Stage 3 — Intermediate / Mixed Plaque

Extracellular lipid accumulation and microcalcifications emerge.

Primary Modulators: High-intensity statins and PCSK9i drive massive plaque regression and fibrous cap maturation.

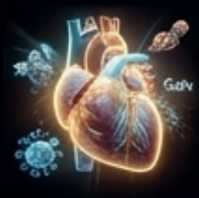
Stage 4 — Fibrocalcific / Stable Plaque

Dense, coalescent calcification with a thick collagen-rich cap.

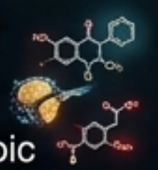
Primary Modulators: The histopathological end-state of healed plaque, associated primarily with statin-induced calcium densification.

A Biologically Informed Clinical Synthesis

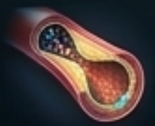
Therapeutic Precision

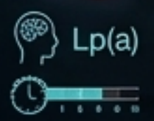


Drug classes possess distinct imaging footprints. Statins stabilize and densify; PCSK9i regress and restore; Bempedoic acid reduces upstream inflammation.



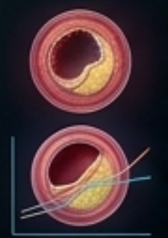
Reassessing the Gatekeeper





CAC = 0 provides powerful short-term reassurance, but it should prompt rather than conclude risk stratification in the presence of symptomatic presentation, elevated Lp(a), or early menopause.

The Individualized Standard



Because plaque biology in women is uniquely characterized by early non-calcified lesions and steep post-menopausal risk acceleration, equitable prevention demands multi-modal imaging and sex-specific clinical context.