The Athlete Plaque Paradox

Decoding mechanobiology, cumulative ApoB exposure, and subclinical coronary atherosclerosis in lifelong endurance athletes.

By Peter Megdal, PhD

The Traditional Paradigm: Regular aerobic training mitigates inflammation, improves lipid profiles, and significantly extends life expectancy.

The Imaging Paradox: Contemporary imaging reveals that high-volume endurance athletes often possess a higher prevalence and volume of subclinical coronary plaque than active, non-athletic controls with identical risk profiles.

The core clinical question: Does decades of extreme hemodynamic loading alter the local coronary microenvironment to accelerate plaque retention?

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The Particle-Centric Model

ApoB particle count is the causal driver of plaque initiation—outperforming LDL-C mass in predicting risk.

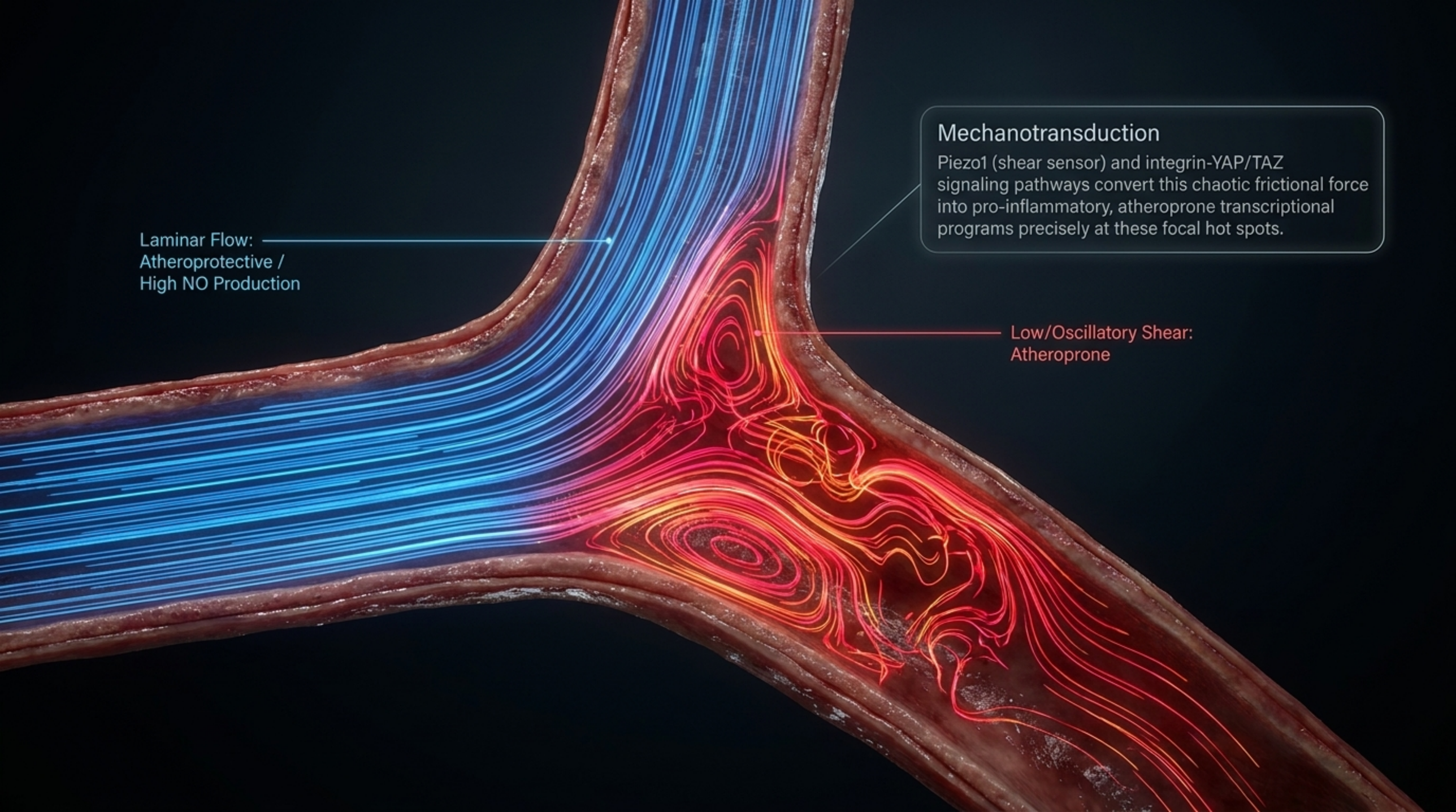
The ApoB-Years Burden

Risk = Magnitude × Duration. Early exposure drives subendothelial retention. Mendelian randomization shows lifelong genetically lower ApoB yields massive, unbiased protection.

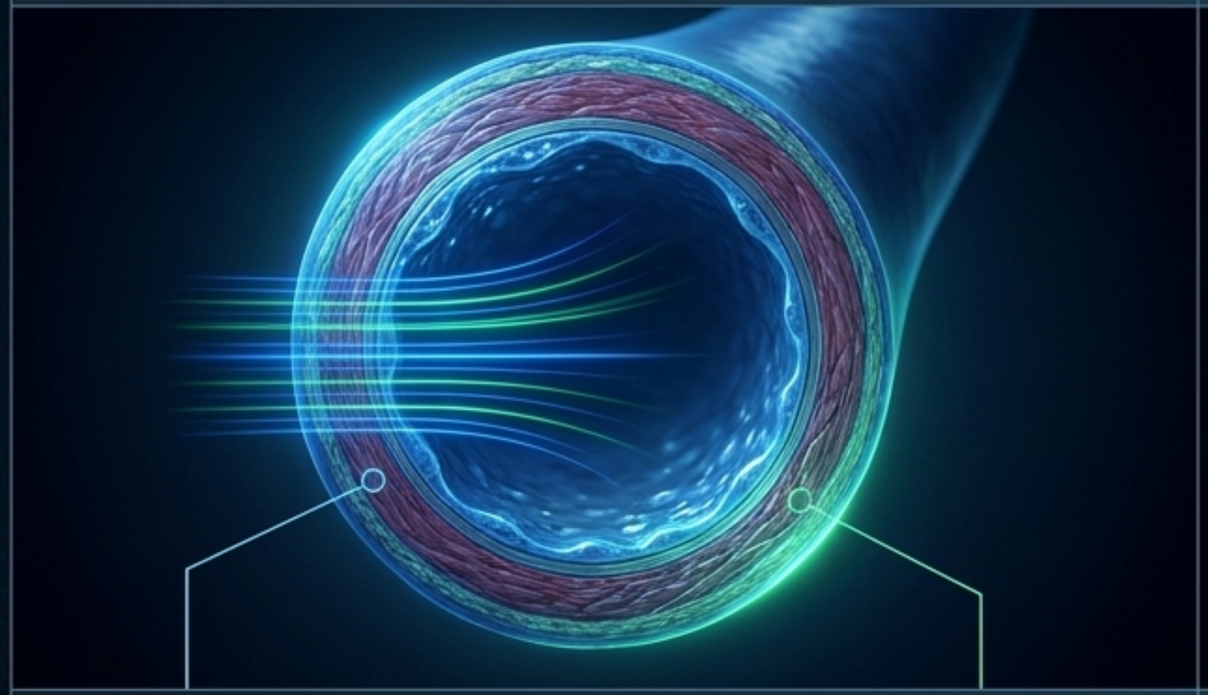
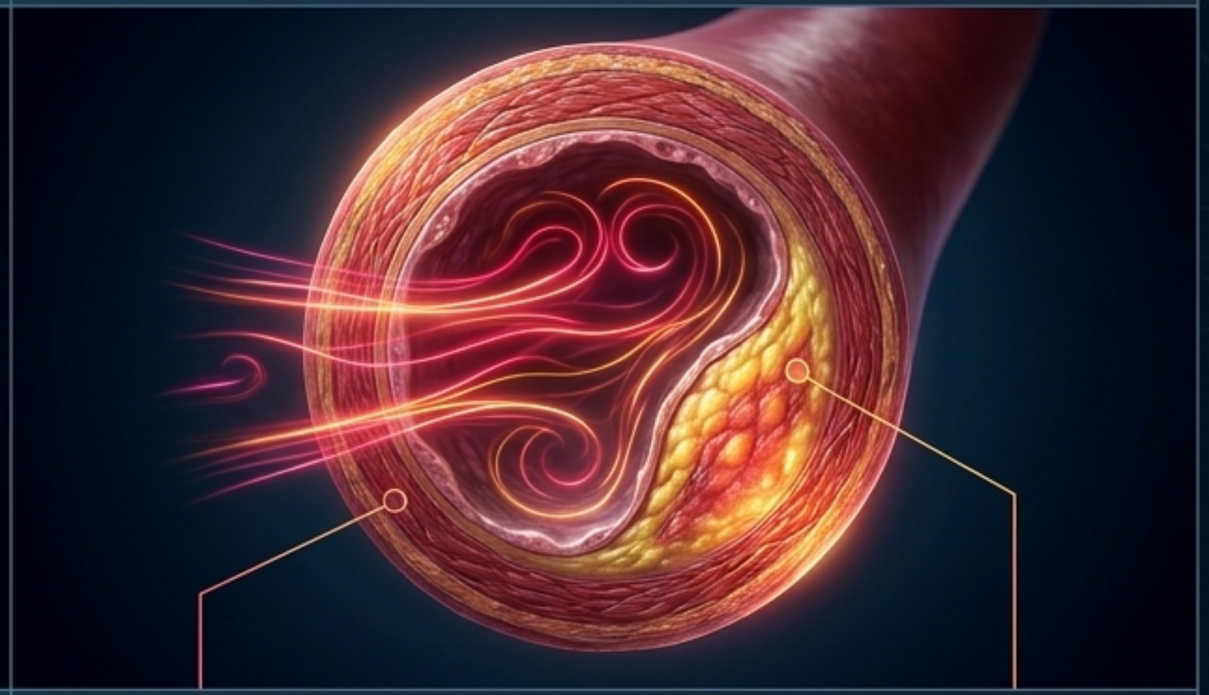
The Athletic Caveat

Athletes inherit no immunity to high ApoB. Roughly 32-36% of Olympians/Paralympians show lipid abnormalities.

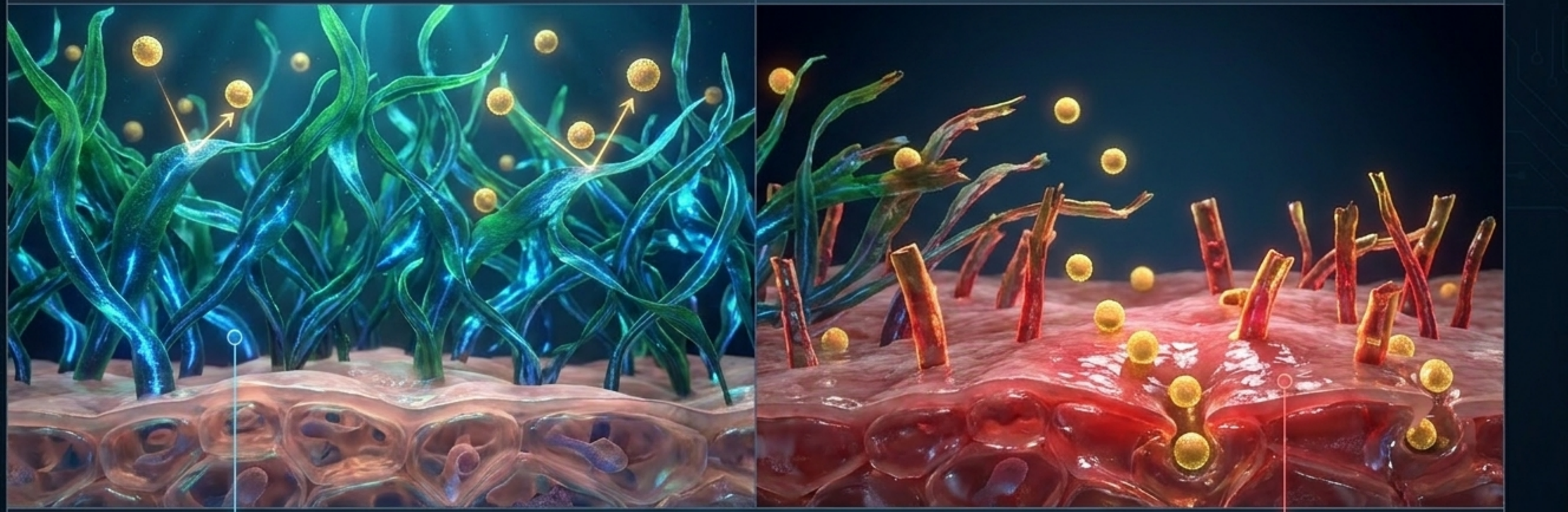

Circumferential Wall Stress
Systolic BP routinely reaches 180–220 mmHg (and up to 250 mmHg at peak effort) during exertion, massively increasing transmural pressure and stretching endothelial cells.
Tangential Shear Stress
Cardiac output rises 5–6x, driving high-velocity epicardial blood flow and frictional force.
Cyclic Deformation. Sustained HR of 150–180 bpm generates tens to hundreds of millions of additional high-pressure mechanical stretch cycles over a multi-decade athletic career.


Laminar Flow:
Atheroprotective /
High NO Production
Low/Oscillatory Shear:
Atheroprone
Mechanotransduction
Piezo1 (shear sensor) and integrin-YAP/TAZ signaling pathways convert this chaotic frictional force into pro-inflammatory, atheroprone transcriptional programs precisely at these focal hot spots.

The Double-Edged Sword of Remodeling

The Protective Buffer	The Clinical Delay
	
Mechanism: Exercise-induced outward remodeling and enhanced microvascular density.	**Mechanism:** Glagov-type positive remodeling accommodates plaque up to ~40% of the internal elastic lamina area before narrowing the lumen.
Result: Increased lumen diameter, high NO bioavailability, and preserved coronary flow reserve.	**Result:** Absence of classic stable angina despite advancing disease.
Clinical Reality: High ischemic-symptom threshold; sustains massive myocardial perfusion.	**Clinical Reality:** Subclinical plaque progresses unseen. The first manifestation may be a sudden acute event under extreme exertion.

THE SUBENDOTHELIAL SIEVE



Localized Glycocalyx Remodeling

High uniform shear (laminar flow) stimulates eGC synthesis globally. However, decades of exposure to disturbed flow, intermittent oxidative spikes, and high transmural pressure at bifurcations may trigger focal enzymatic cleavage (shedding of syndecan-1 and heparan sulfate), compromising the permeability barrier exactly where mechanical stress peaks.

THE APOB ENTRY ENGINE

Step 1: Caveolar Capture

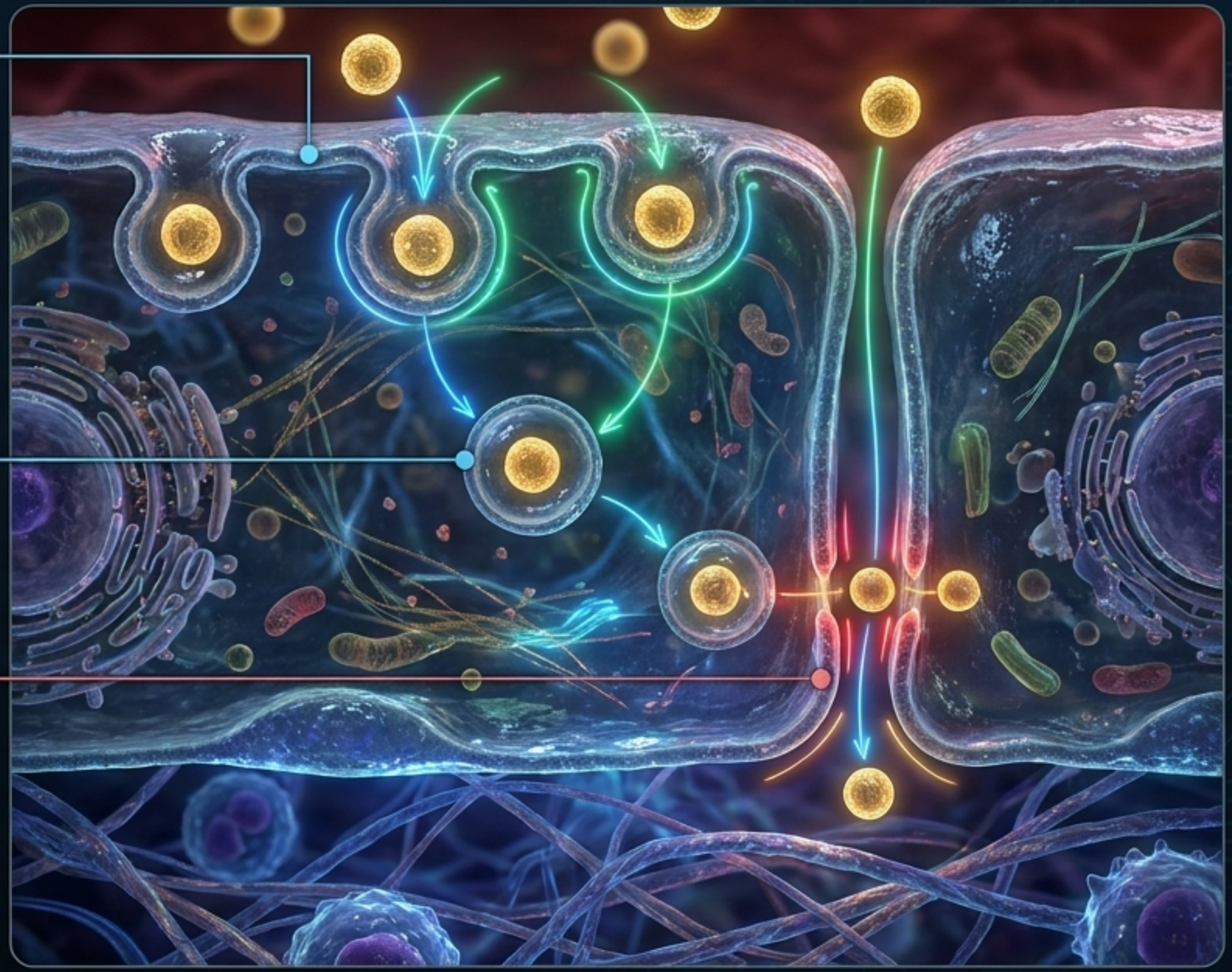
Intact ApoB particles (20–25 nm) are too large for normal intercellular junctions. They enter via caveolae—flask-shaped membrane invaginations.

Step 2: Active Transcytosis

SR-B1 and ALK1 act as cargo receptors, driving active vesicular transport across the cytoplasm. (Note: Mechanical strain can alter caveolar abundance).

Step 3: Paracellular Leaks

Concurrently, cyclic stretch and endothelial turnover open transient leaky junctions, allowing passive infiltration alongside active transport.



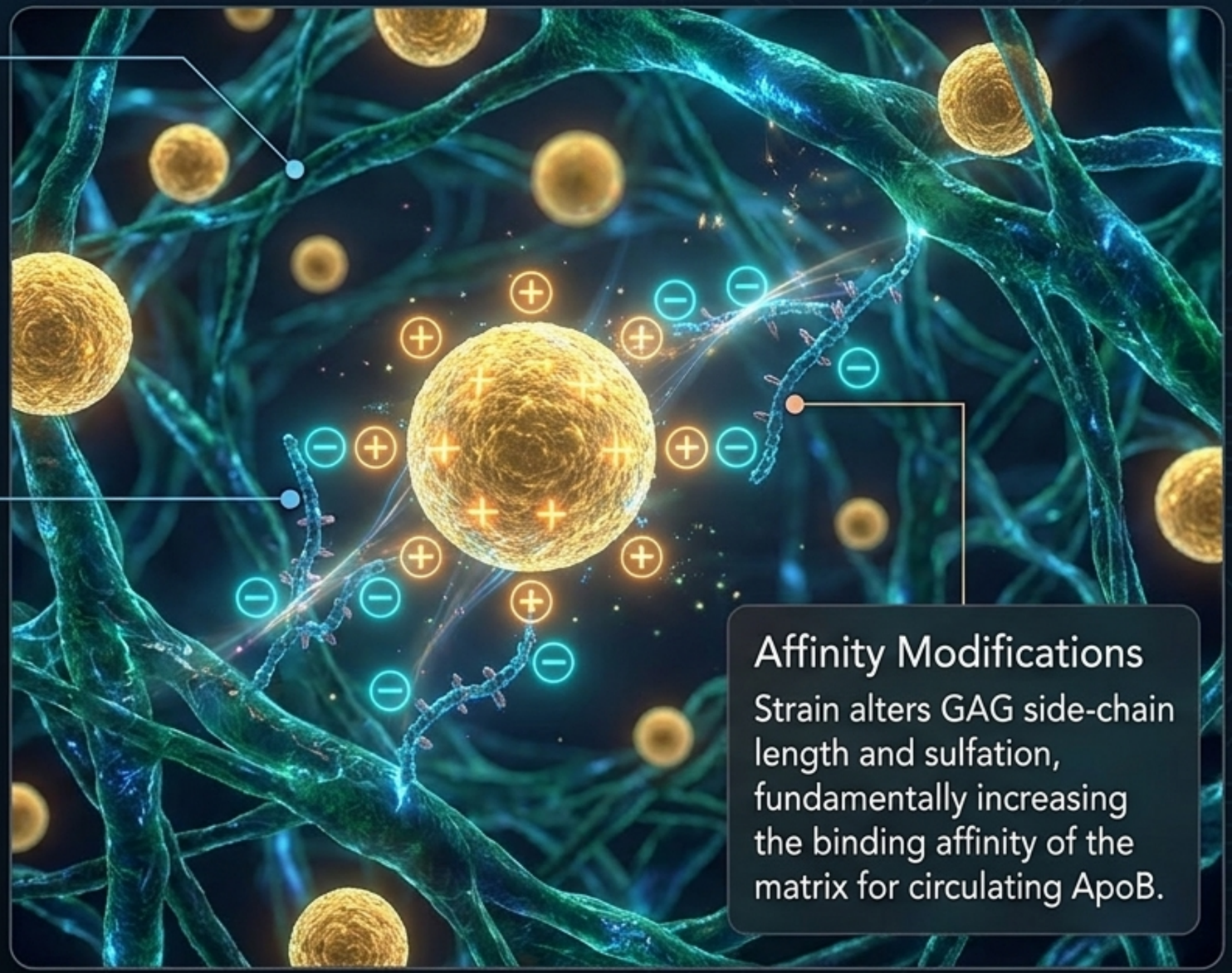
THE APOB RETENTION TRAP

The Matrix Trap

Lipoprotein retention requires physical entrapment by extracellular matrix proteoglycans synthesized by vascular smooth muscle cells (VSMCs).

Mechanically Driven Upregulation

In experimental models, repetitive mechanical stretch triggers TGF-β/Smad and FAK signaling, commanding VSMCs to synthesize highly charged proteoglycans like Biglycan.



Affinity Modifications

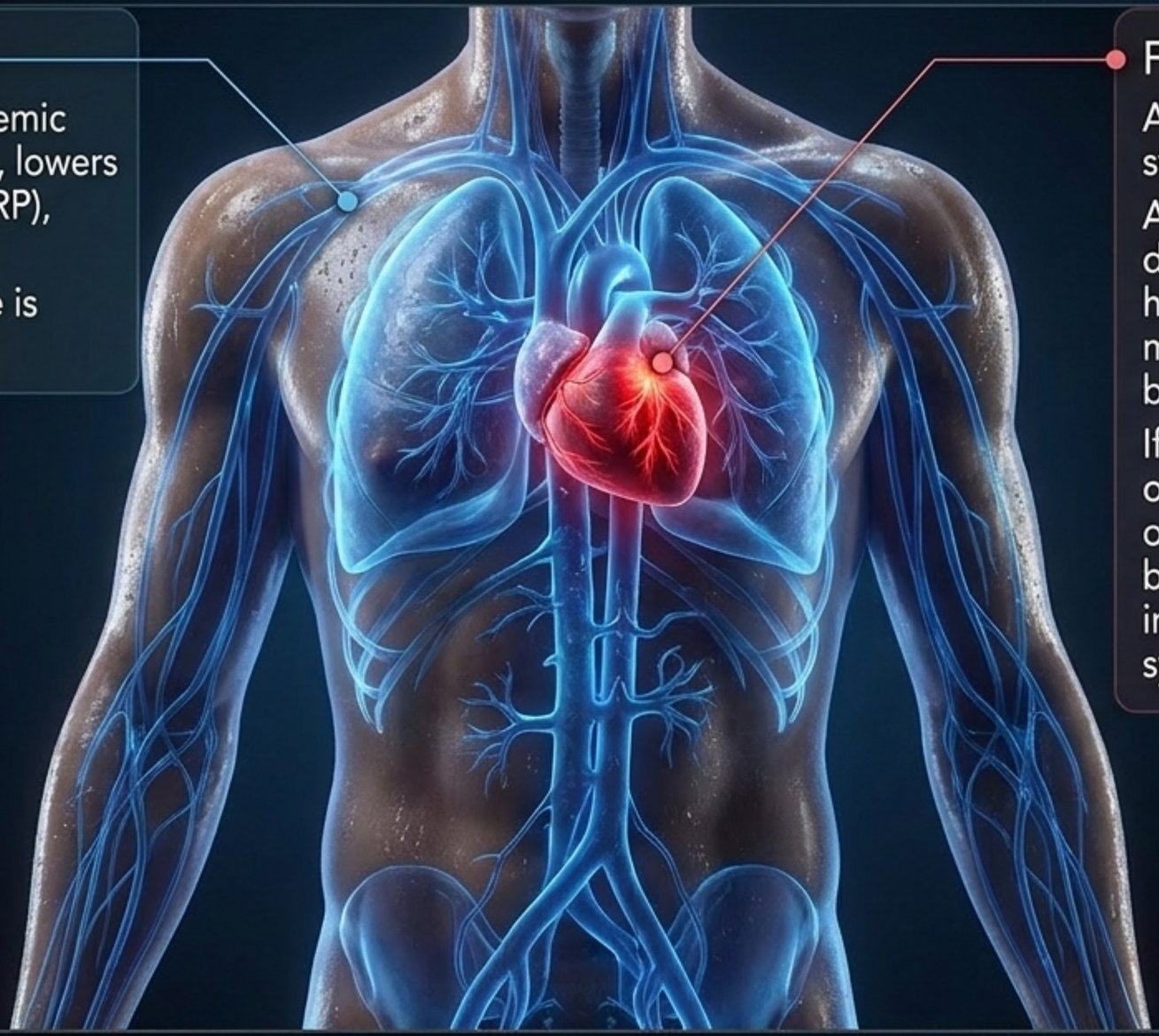
Strain alters GAG side-chain length and sulfation, fundamentally increasing the binding affinity of the matrix for circulating ApoB.

THE ASYMMETRY OF ADAPTATION

Global Protection

Habitual training raises systemic NO, upregulates autophagy, lowers systemic inflammation (hsCRP), and improves HDL efflux.

The endothelium as a whole is wildly healthy.



Focal Vulnerability

Atherosclerotic risk is structurally localized.

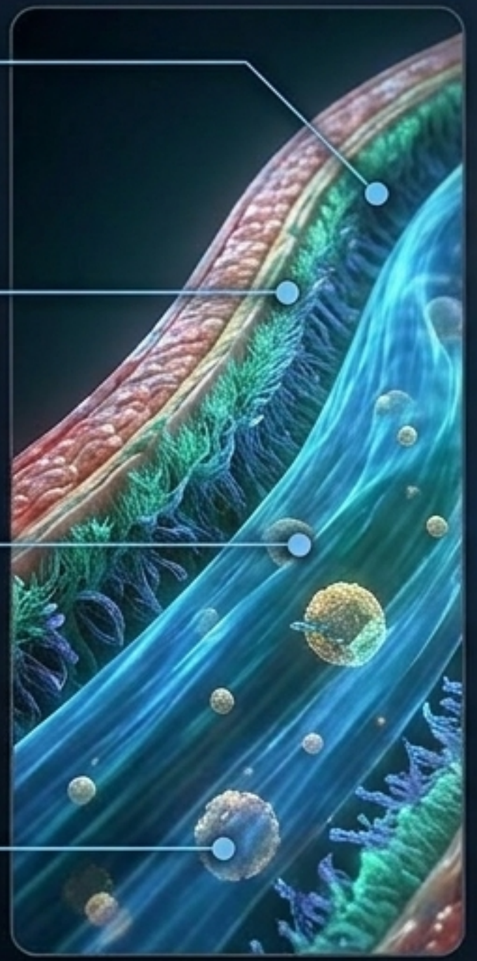
A globally optimized system does not override the fierce, highly concentrated fluid mechanics at geometric bends.

If retention pathways outpace clearance at just one highly stressed bifurcation, localized plaque initiates despite systemic systemic supremacy.

DIAGNOSTIC MATRIX: VASCULAR FACT vs. ATHLETIC HYPOTHESIS

Established Vascular Mechanisms

- The Response-to-Retention pathway initiates atherosclerosis.
- Glycocalyx shedding occurs under oxidative/inflammatory stress and disturbed shear.
- Caveolae-mediated active transport (SR-B1, ALK1) moves LDL.
- Mechanical strain upregulates biglycan via TGF-β in in-vitro/animal models.



Speculative Athletic Hypotheses

- Direct in-vivo visualization of exercise-induced local glycocalyx shedding in human coronaries.
- Exercise-specific proteoglycan affinity modifications occurring specifically in elite athletes.
- Proof that mechanically driven retention definitively outpaces metabolic clearance in structurally non-atherosclerotic walls.

MARC-2 (2023)

289 male athletes. Very vigorous exercise volume associated with **calcified plaque progression** (aOR 2.09).

No clinical hard endpoints.

Master@Heart (2023)

191 lifelong athletes vs 176 controls.

Lifelong athletes showed higher odds of **non-calcified proximal plaque** (OR 2.80).

Cyclist-dominant, exclusively white males.

Merghani et al. (UK Masters)

152 athletes vs 92 controls.

Severe CAC (≥300) in **11.3% of athletes** vs 0% of controls.

Athletes predominantly showed calcified morphology.

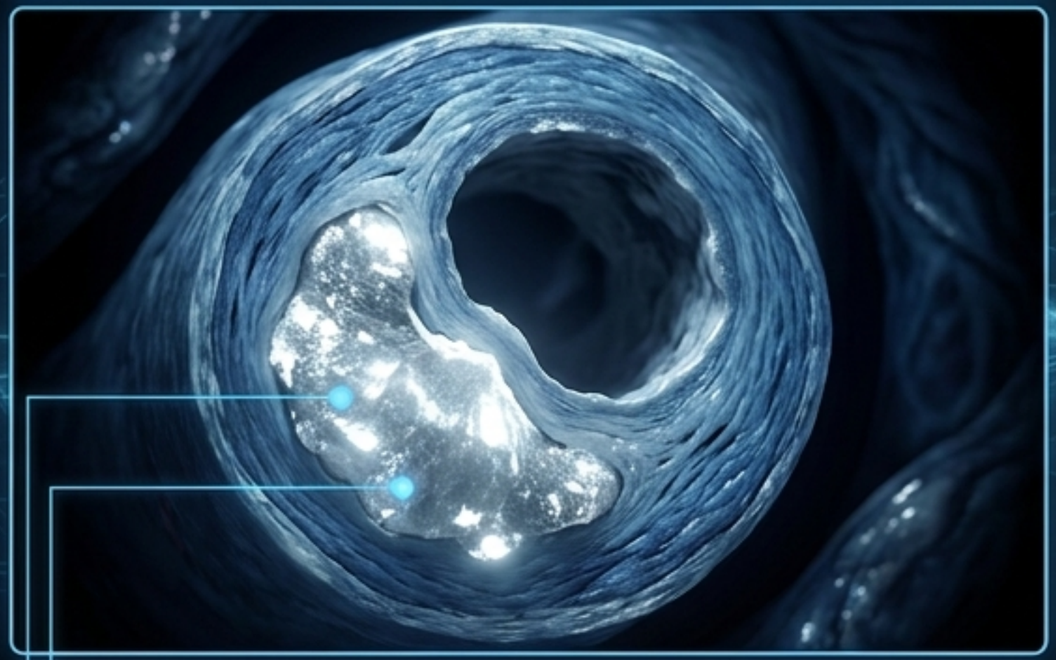
Möhlenkamp (Marathon Study)

108 marathoners.

Detectable CAC in **71%. 36% had CAC >100.**

THE PLAQUE SPECTRUM MATRIX

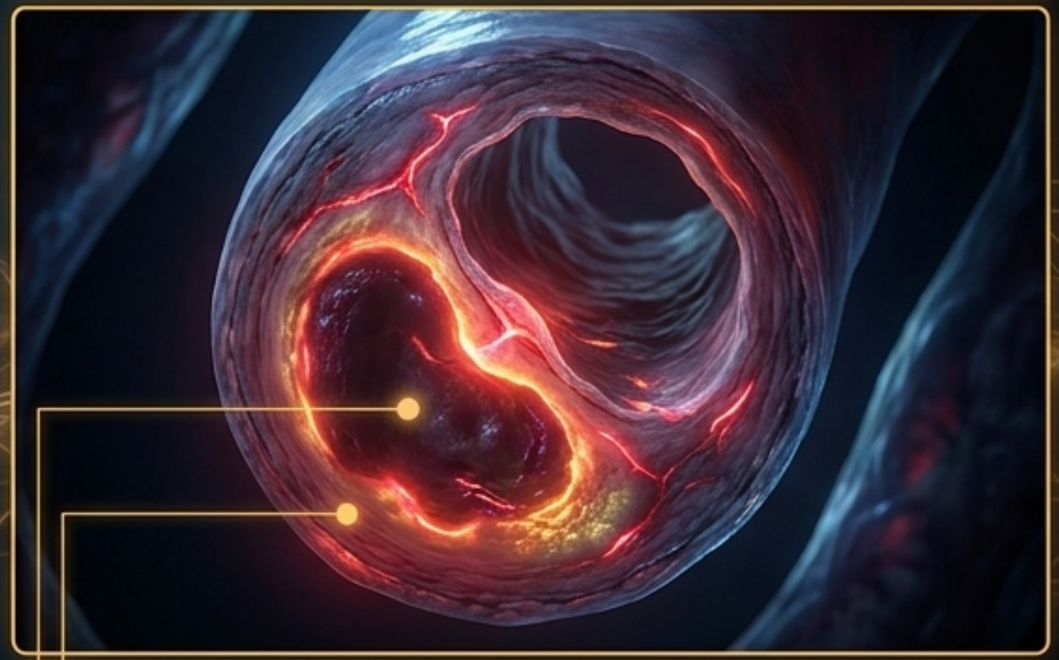
Densely Calcified Plaque



Densely Calcified Plaque

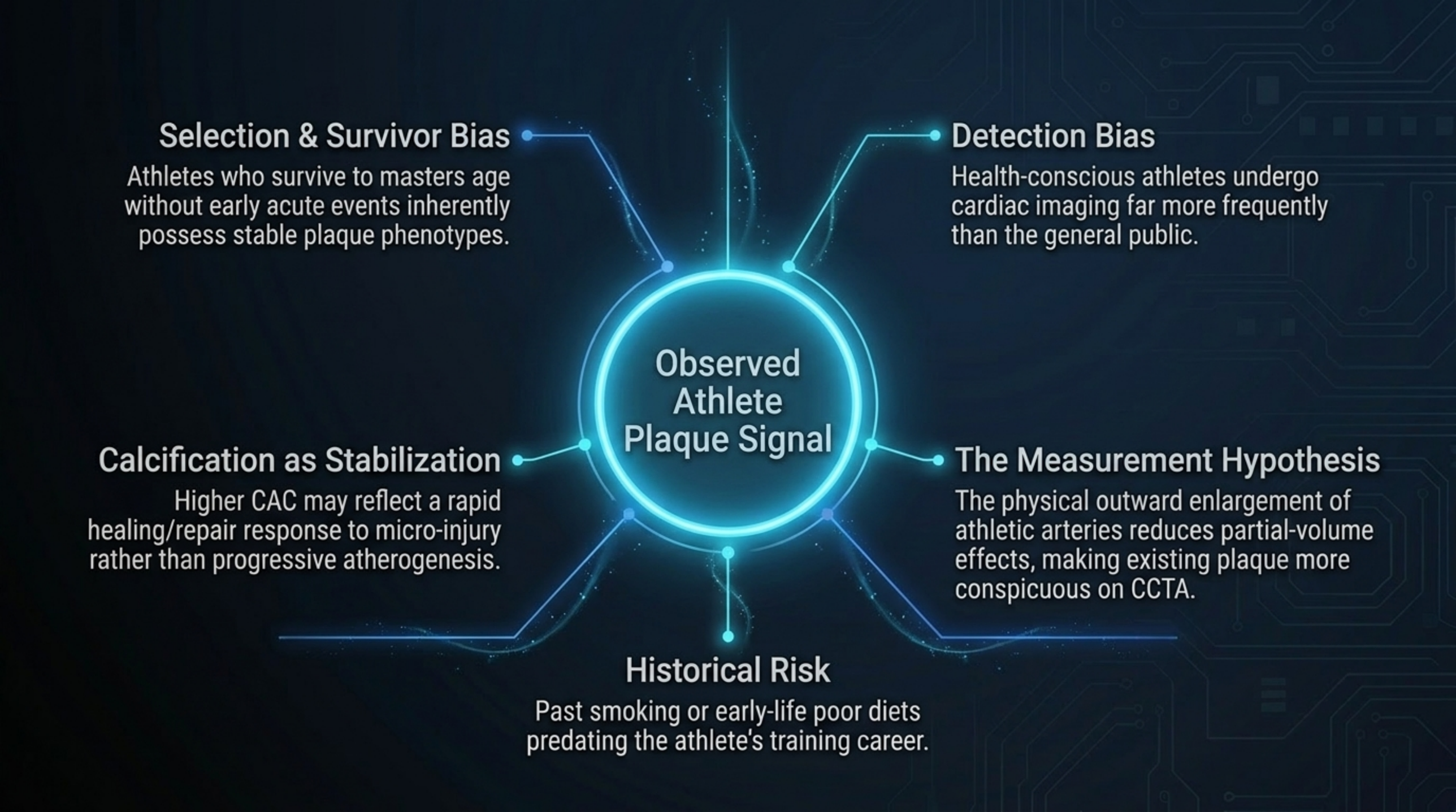
- **Imaging:** High attenuation (> 130 HU).
- **Features:** Compositionally stable, thick fibrous cap. Low risk of mechanical rupture. Promoted by very vigorous training. Often marks healed or biologically quiescent disease.

Vulnerable Soft Plaque



Vulnerable Soft Plaque

- **Imaging:** Low attenuation (< 30 HU), necrotic core, napkin-ring sign.
- **Features:** Unstable, higher absolute burden in lifelong athletes (Master@Heart). Progresses silently under positive remodeling.


Selection & Survivor Bias
Athletes who survive to masters age without early acute events inherently possess stable plaque phenotypes.
Detection Bias
Health-conscious athletes undergo cardiac imaging far more frequently than the general public.
Observed Athlete Plaque Signal
Calcification as Stabilization
Higher CAC may reflect a rapid healing/repair response to micro-injury rather than progressive atherogenesis.
The Measurement Hypothesis
The physical outward enlargement of athletic arteries reduces partial-volume effects, making existing plaque more conspicuous on CCTA.
Historical Risk
Past smoking or early-life poor diets predating the athlete's training career.

THE APOB THRESHOLD SLIDER

The Mechanical Penalty

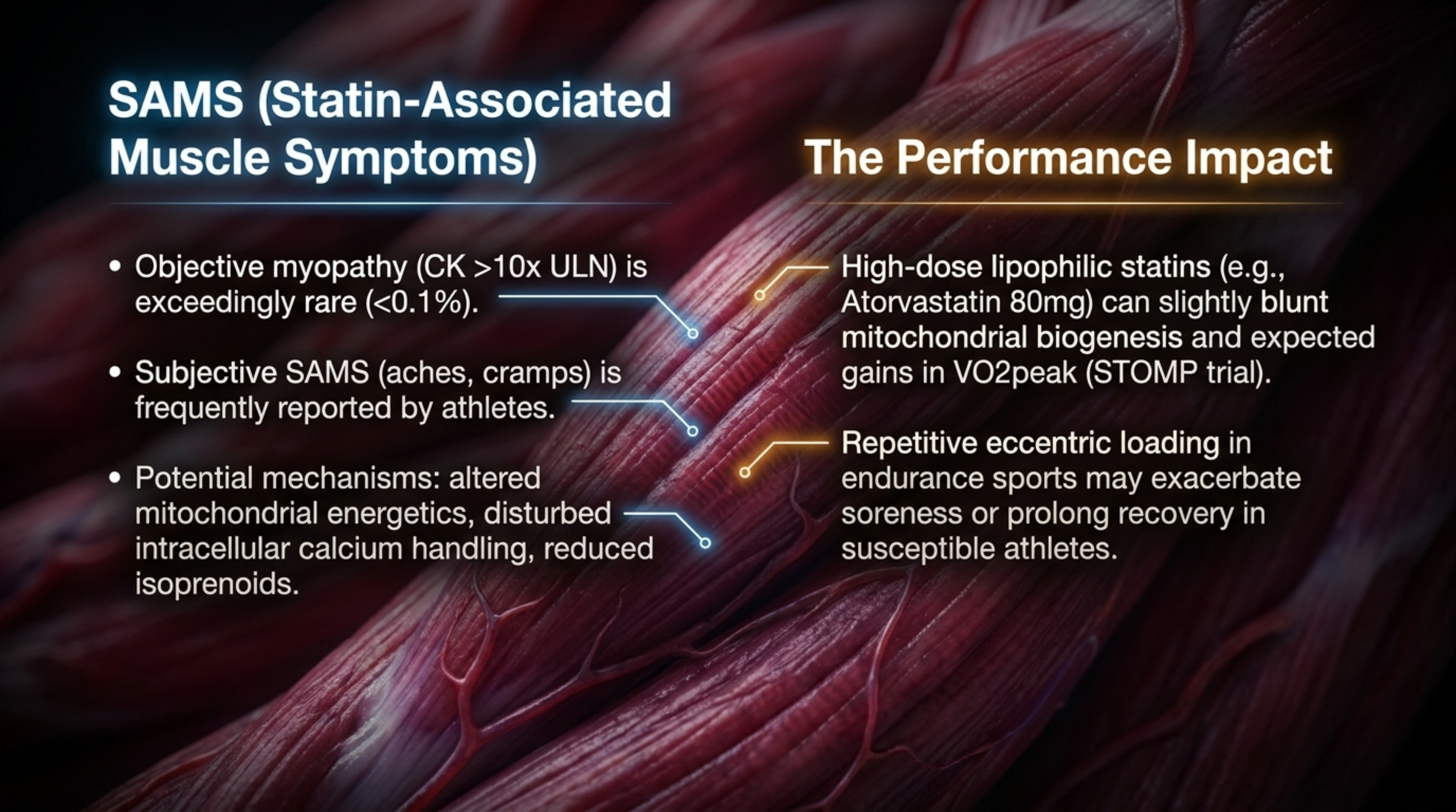
Decades of extreme cyclic strain and elevated flow velocity act as a multiplier on lipid retention.

Lowering the Threshold

Because the athletic coronary wall has a mechanically amplified propensity to trap circulating particles, the absolute concentration of ApoB required to trigger plaque formation effectively drops.

The Clinical Rationale

To maintain the exercise-induced safety buffer, it is logically necessary to aggressively drive circulating ApoB particle counts down, starving the retention engine of its substrate.



SAMS (Statin-Associated Muscle Symptoms)

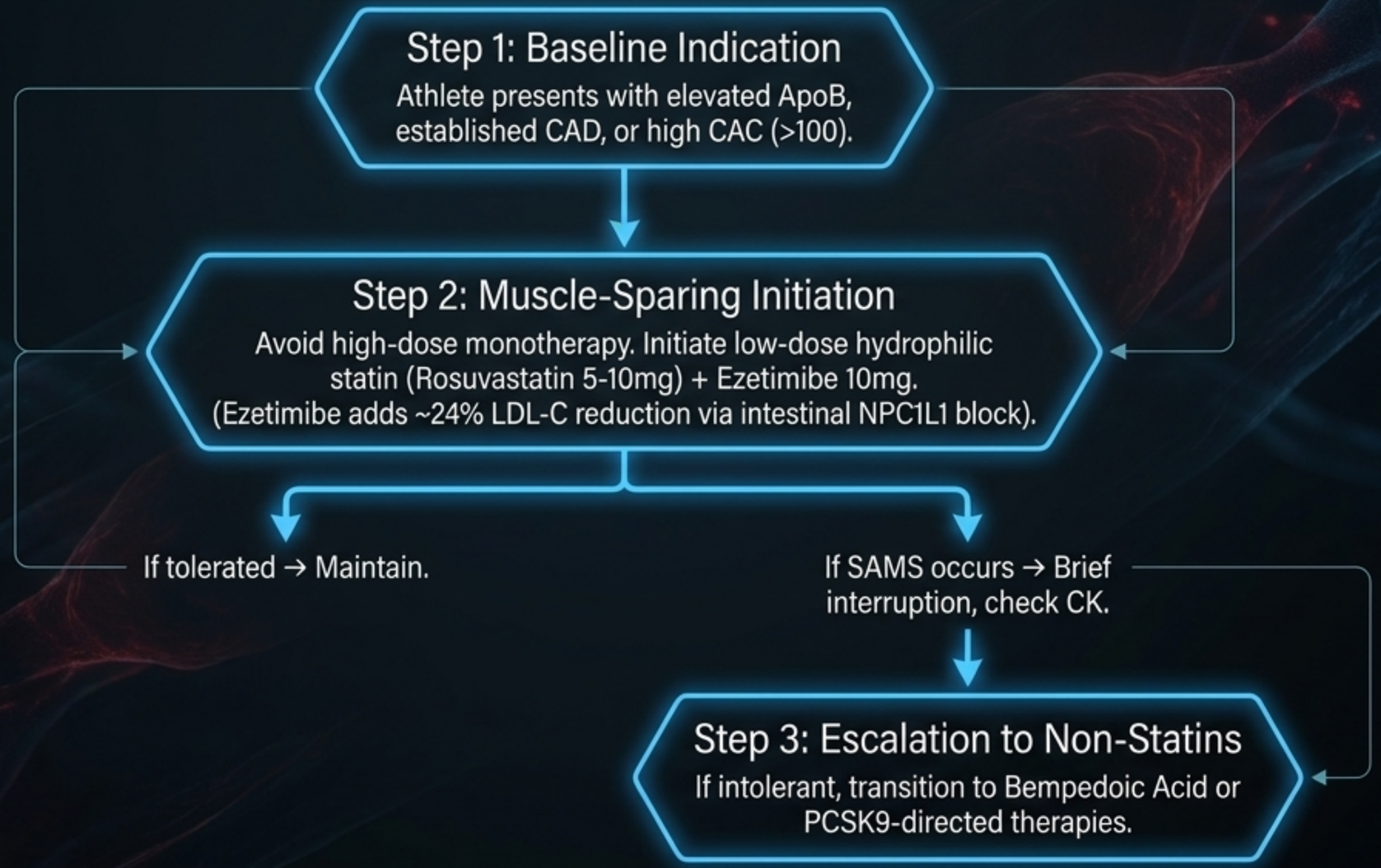
- Objective myopathy (CK >10x ULN) is exceedingly rare (<0.1%).
- Subjective SAMS (aches, cramps) is frequently reported by athletes.
- Potential mechanisms: altered mitochondrial energetics, disturbed intracellular calcium handling, reduced isoprenoids.

The Performance Impact

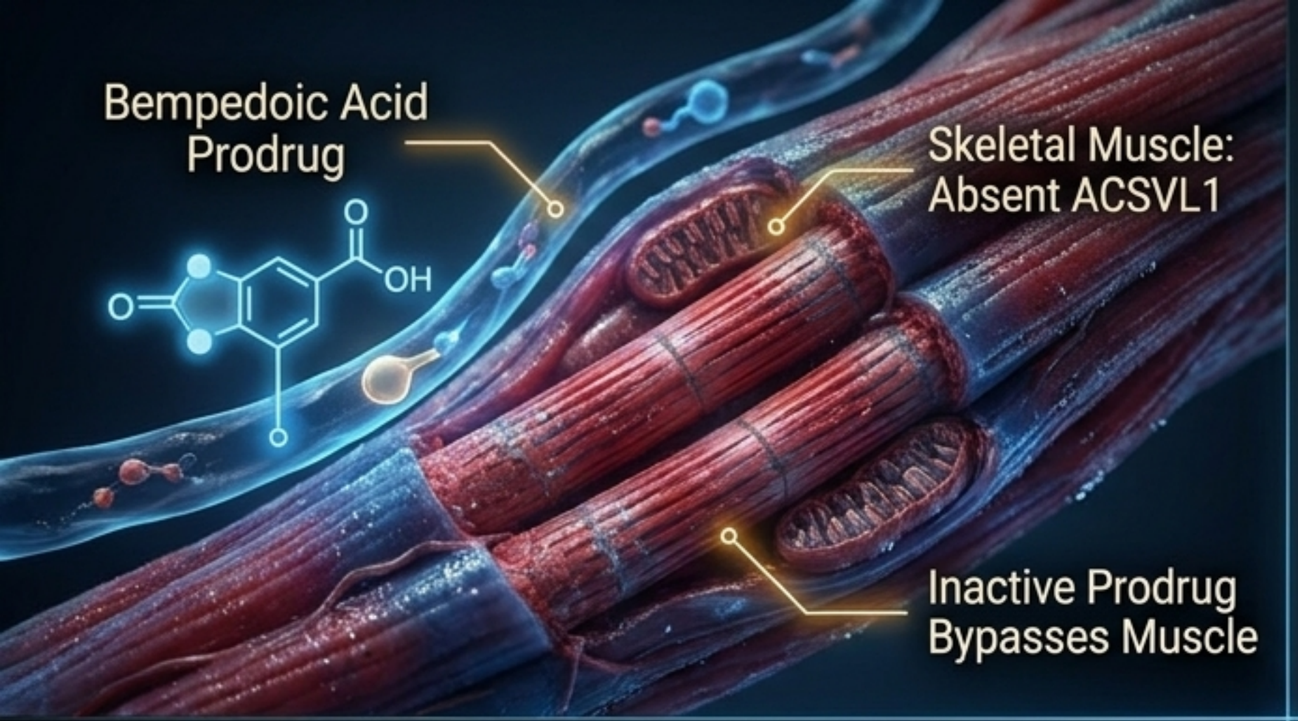
High-dose lipophilic statins (e.g., Atorvastatin 80mg) can slightly **blunt mitochondrial biogenesis** and expected gains in VO2peak (STOMP trial).

Repetitive eccentric loading in endurance sports may exacerbate soreness or prolong recovery in susceptible athletes.

Pharmacological Stepwise Strategy

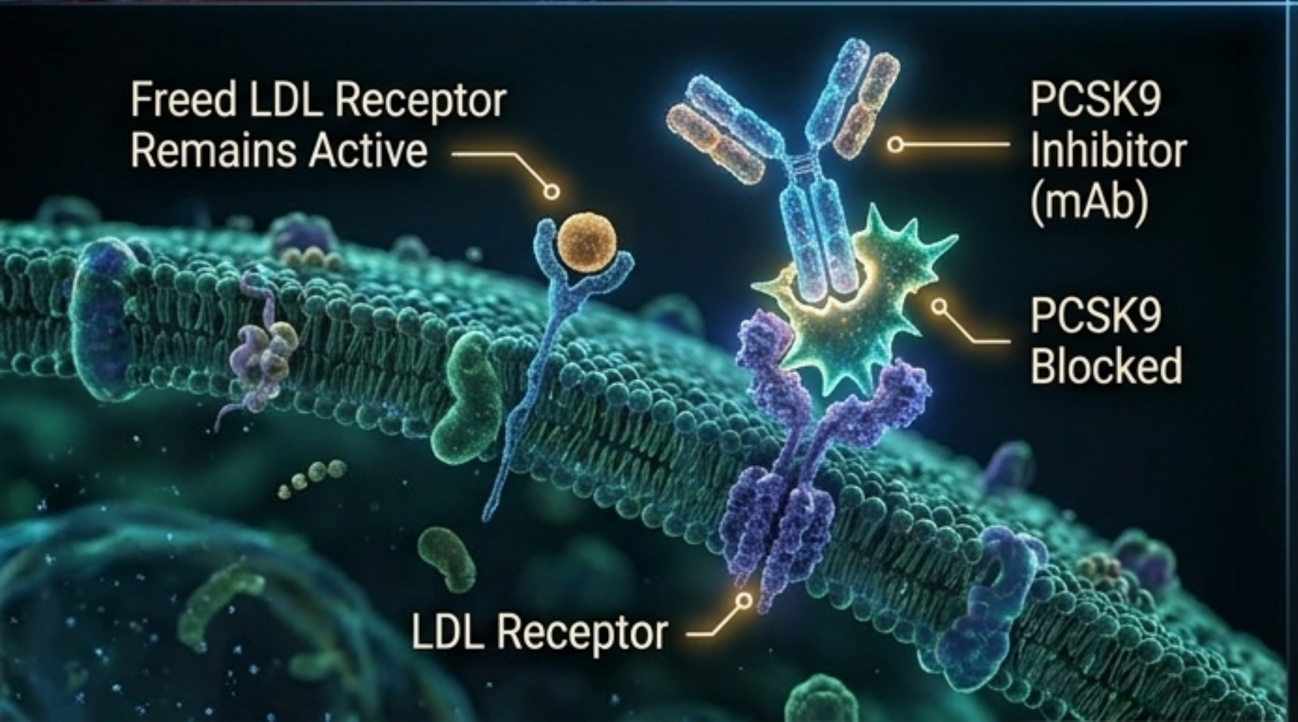


(Note: Lp(a) screening is universally recommended once for all athletes per ACC/AHA guidelines)



1. Bempedoic Acid (Oral Prodrug)

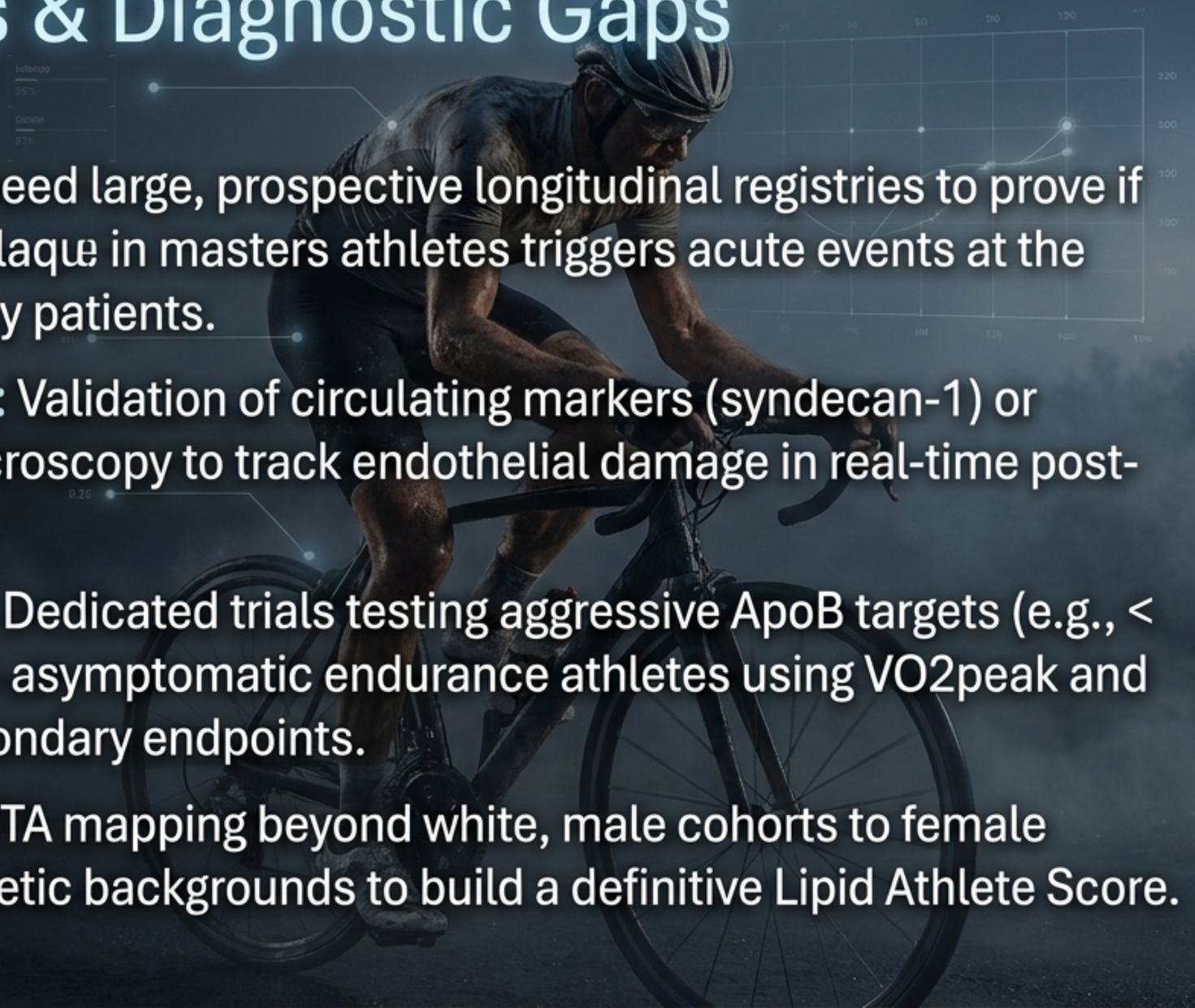
- **Mechanism**: Inhibits ATP-citrate lyase (ACLY).
- **The Athlete Advantage:** Requires activation by ACSVL1, an enzyme present in the liver but absent in skeletal muscle. It cannot be activated in myofibers, practically eliminating muscle symptoms.
- **Caveat:** Can raise uric acid (gout risk) and carries a small risk of tendon-related events.



2. PCSK9-Directed Therapies (Injectable)

- **Mechanism**: Monoclonal antibodies (Alirocumab, Evolocumab) or siRNA (Inclisiran) that prevent lysosomal degradation of hepatic LDL receptors.
- **The Athlete Advantage:** Massive LDL-C/ApoB reduction (~50-60%) with a side-effect profile practically indistinguishable from placebo regarding muscle symptoms.

Future Frontiers & Diagnostic Gaps



1. **Outcome Linkage:** We need large, prospective longitudinal registries to prove if non-calcified proximal plaque in masters athletes triggers acute events at the same rate as in sedentary patients.
2. **Glycocalyx Biomarkers:** Validation of circulating markers (syndecan-1) or sublingual dark-field microscopy to track endothelial damage in real-time post-exercise.
3. **Athlete-Specific RCTs:** Dedicated trials testing aggressive ApoB targets (e.g., < 50 mg/dL) specifically in asymptomatic endurance athletes using VO2peak and recovery kinetics as secondary endpoints.
4. **Diversity:** Expanding CCTA mapping beyond white, male cohorts to female athletes and diverse genetic backgrounds to build a definitive Lipid Athlete Score.