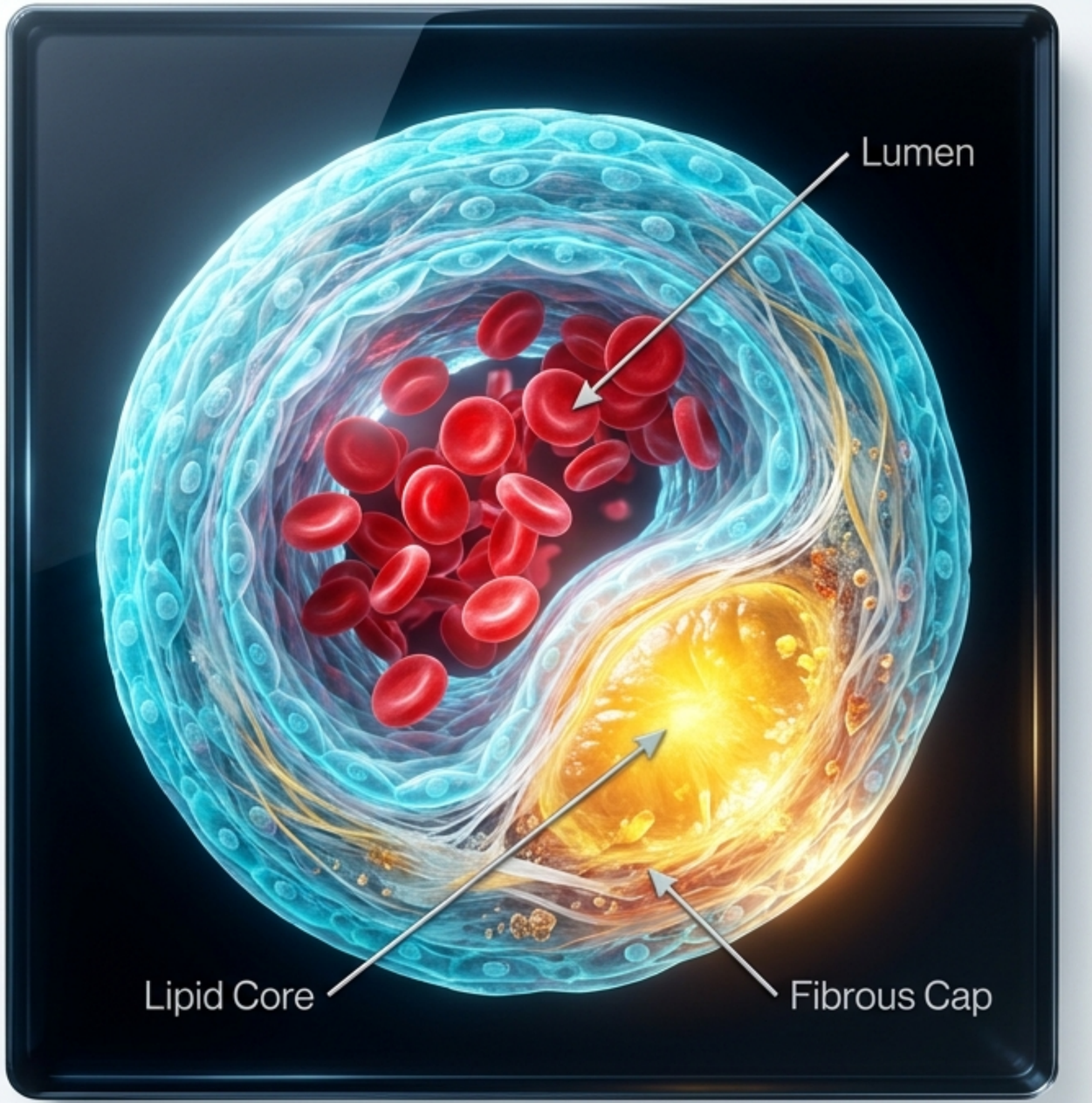
The Anatomy of a Medical Paradox

Can dietary patterns influence coronary geometry and plaque phenotype beyond what fasting ApoB captures?

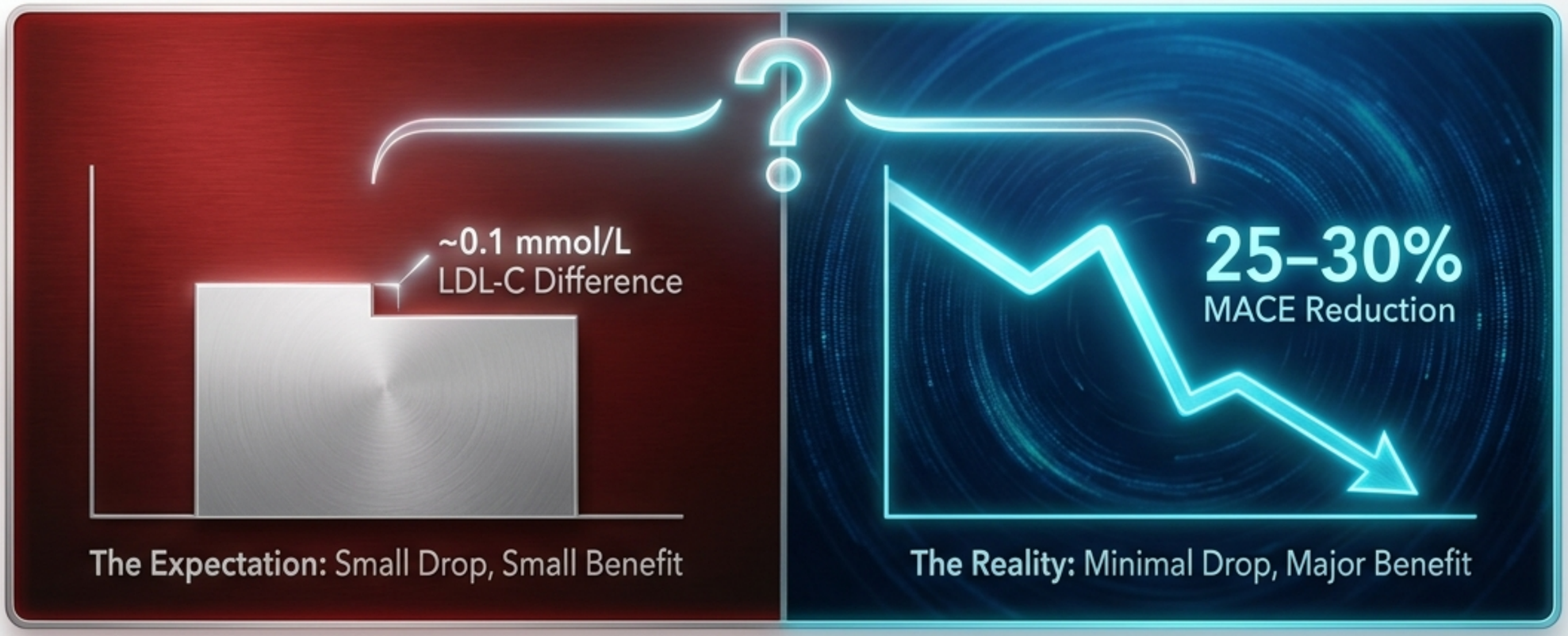
A visual investigation of the complementary biological pathways of diet and lipid-lowering pharmacotherapy.



The Event-Lipid Discordance

The Expectation: Based on standard pharmacologic meta-analyses, a small LDL-C drop should yield a small clinical benefit.

The Reality: Mediterranean dietary trials (PREDIMED, CORDIOPREV) report major event reductions (25–30%) despite minimal fasting LDL-C separation between arms.



The Lyon Anomaly: The Lyon Diet Heart Study reduced recurrent events dramatically with virtually no lipid difference between arms.

Untangling the Four Propositions

Proven

Diet improves vascular endpoints.
(Supported across multiple models and clinical trials).

Plausible

The improvement is not fully captured by a single fasting ApoB measurement.
(Supported by postprandial and functional observations).

Untested

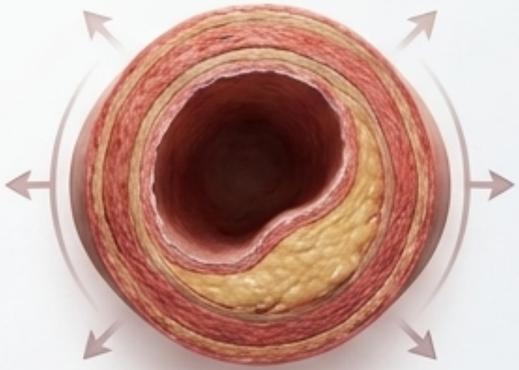
The improvement would persist if longitudinal ApoB exposure were experimentally matched.
(No trial has done this).

Unsupported

Diet delivers more lumen widening or plaque stability per unit of ApoB reduction than intensive pharmacotherapy.
(No evidence).

The Three Axes of Arterial Change

An intervention can improve composition without shrinking volume, or widen the lumen without dissolving plaque. A single measurement axis cannot capture the whole truth.



Axis 1: Plaque Volume

Percent Atheroma Volume.
Visible to IVUS / CCTA.

Axis 2: Lumen Caliber

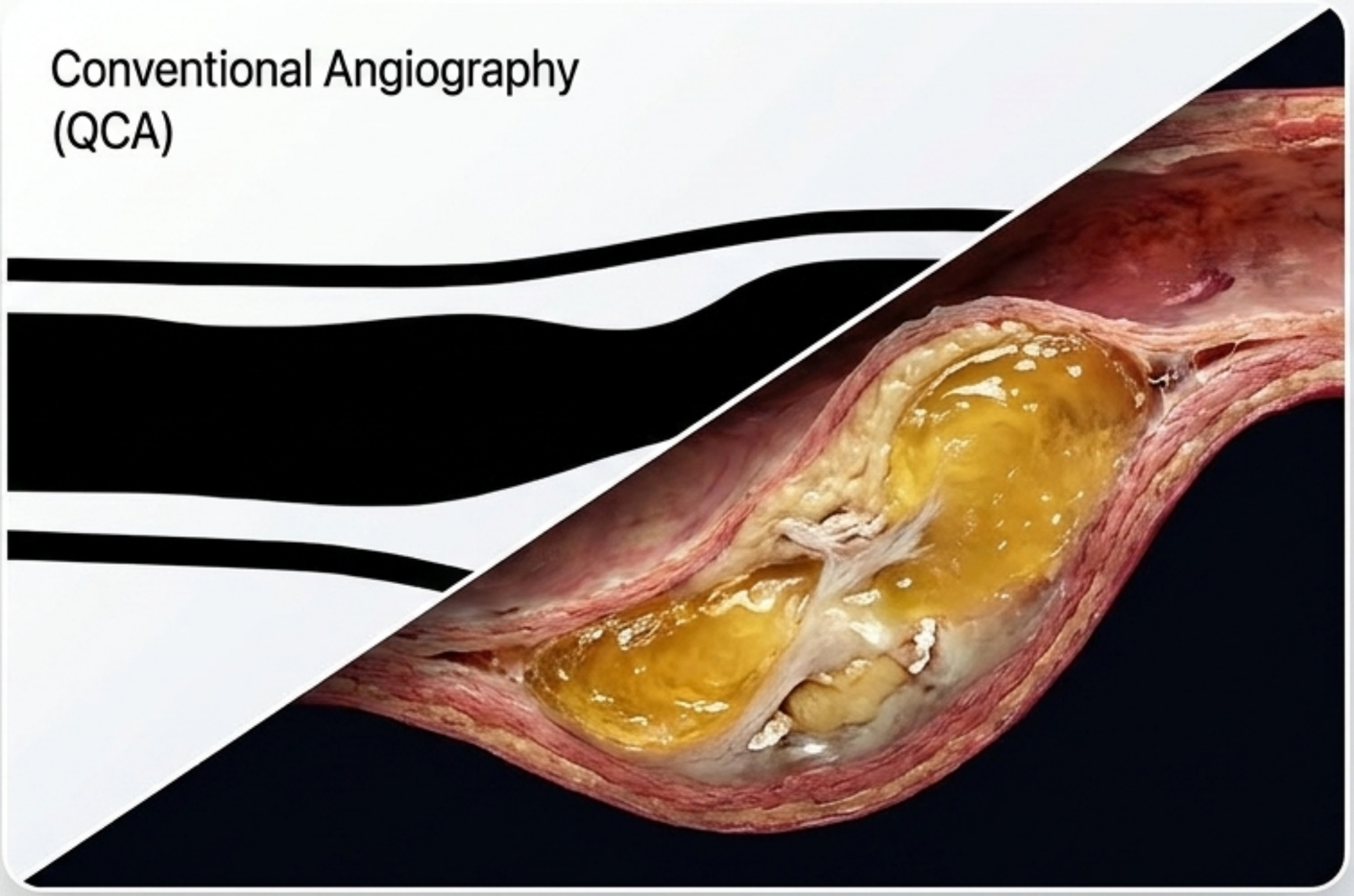
Minimal Lumen Diameter.
Visible to QCA.

Axis 3: Plaque Composition

Low-Attenuation Plaque.
Visible to OCT / NIRS.

The Illusion of Luminology and Glagov Remodeling

The Blind Spot: Conventional angiography (QCA) only images the dye filling the lumen. It is completely blind to the vessel wall.

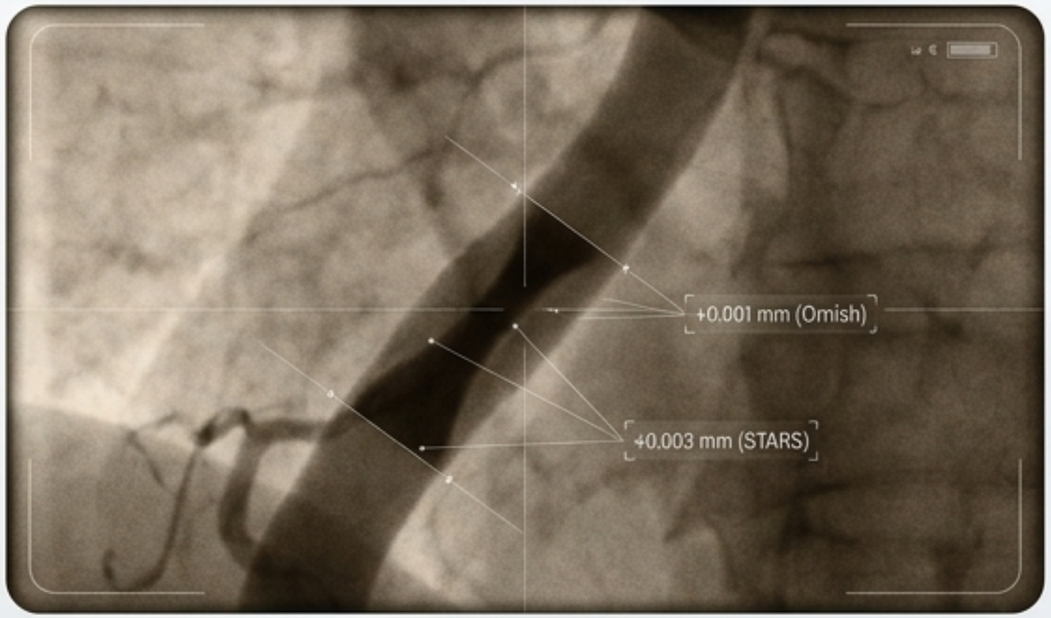


Glagov's Compensation: As plaque accumulates, the artery expands outward. The lumen remains preserved until the plaque occupies ~40% of the internal area.

The Error: Early trials equated preserved lumen with disease regression, missing the hidden outward growth.

Historical Clues vs. Modern Reality

The 1990s (QCA)



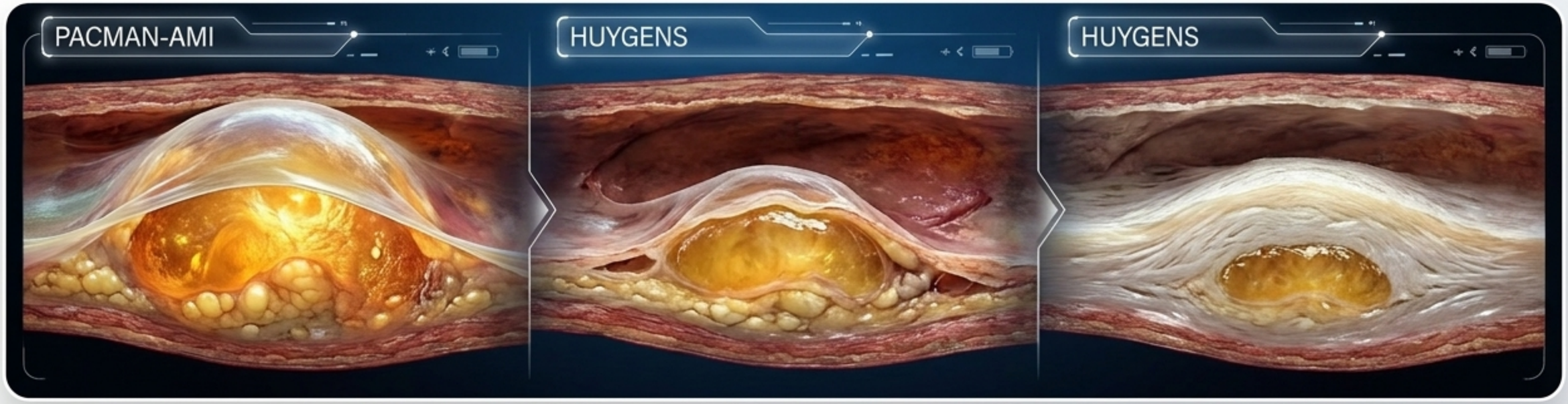
Early intensive lifestyle trials showed relative preservation of lumen caliber against control-group narrowing, not convincing average widening.

The 2020s (CCTA)

DISCO-CT, testing an intensive diet/lifestyle program added to optimal medical therapy, found no difference in total plaque burden (+1.0% vs +1.1%). The diet arm actually saw maximum lumen diameter shrink by 3.1%.

The Pharmacologic Benchmark

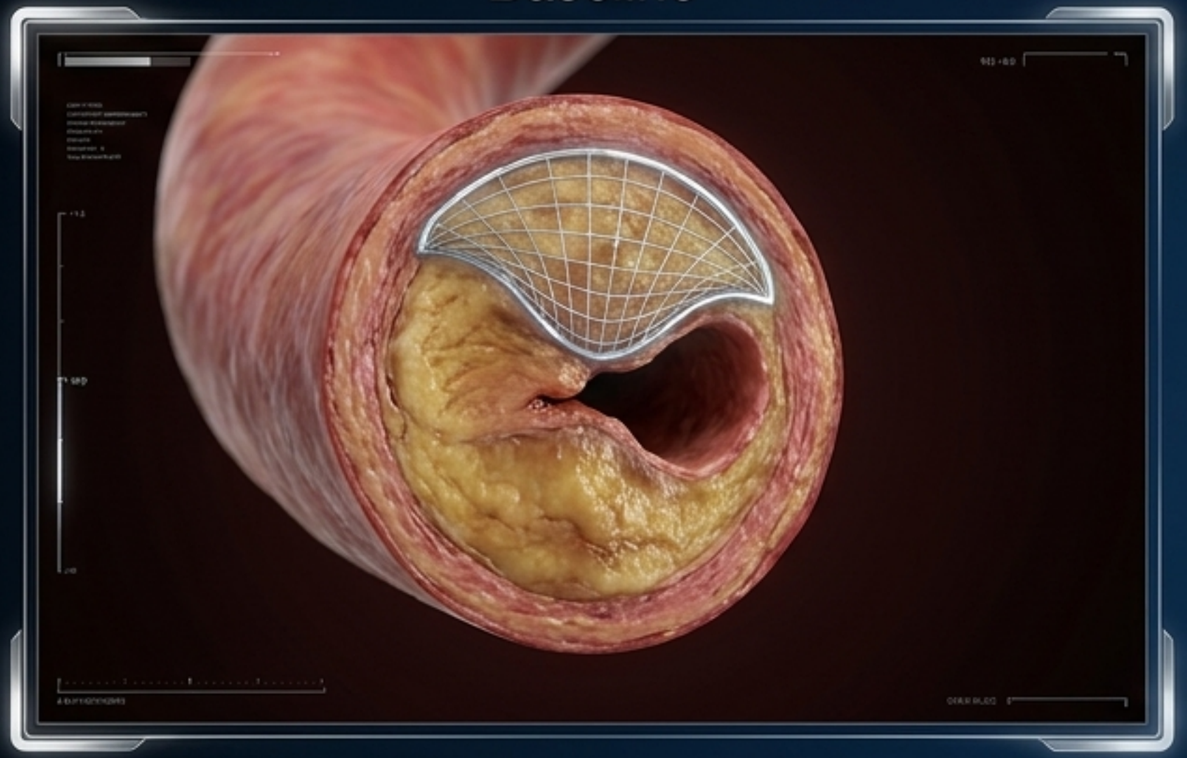
- The Myth: Drugs shrink plaque; diet stabilizes it.
- The Reality: Intensive ApoB lowering (achieving LDL-C ~23–28 mg/dL) orchestrates profound structural repair.



Dual Action: Trials like PACMAN-AMI and HUYGENS prove intensive drugs not only reduce Percent Atheroma Volume, but actively deplete the lipid core and vastly thicken the fibrous cap. Whatever diet adds, it does not fill a compositional gap left open by drugs.

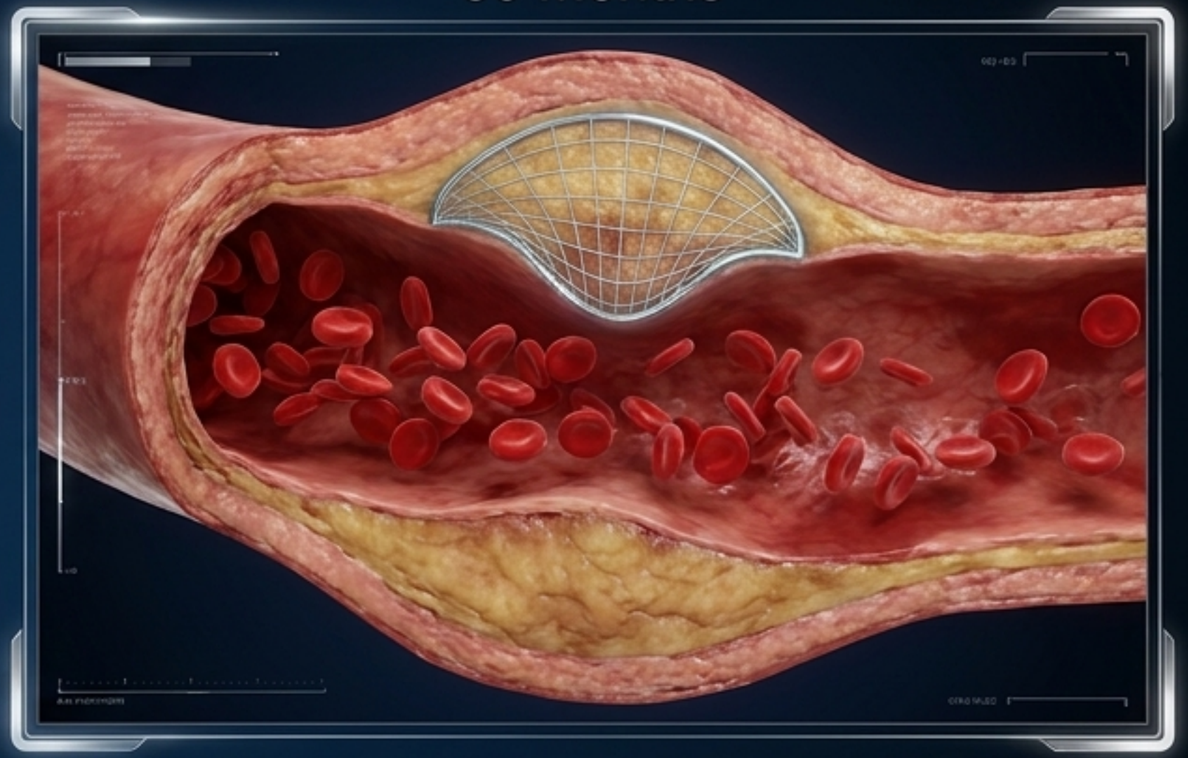
The Primate Paradox: Geometric Dissociation

Baseline



The Williams Macaque Experiment: After 30 months of plasma lipid lowering, coronary artery and lumen cross-sectional areas were approximately twice as large.

30 Months

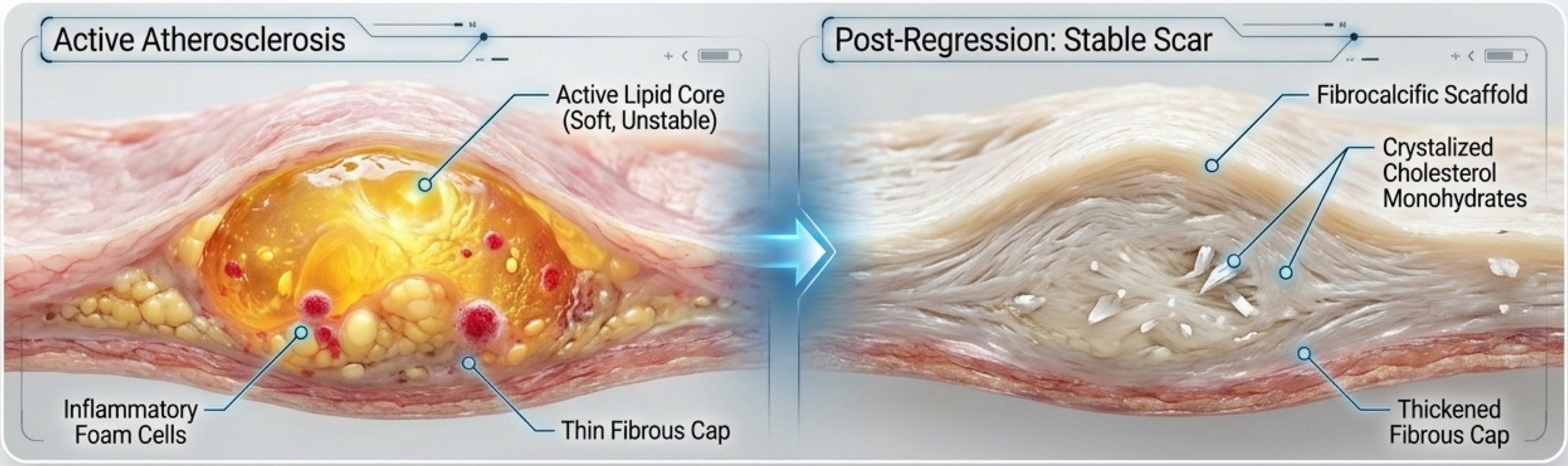


The Catch: There was no statistically significant difference in plaque area.

The Mechanism: The artery remodeled and widened the roadway, rather than dissolving the obstruction.

The Scaffold Persists

Advanced atherosclerosis features two compartments: a metabolically active lipid core and a structural fibrocalcific scaffold.



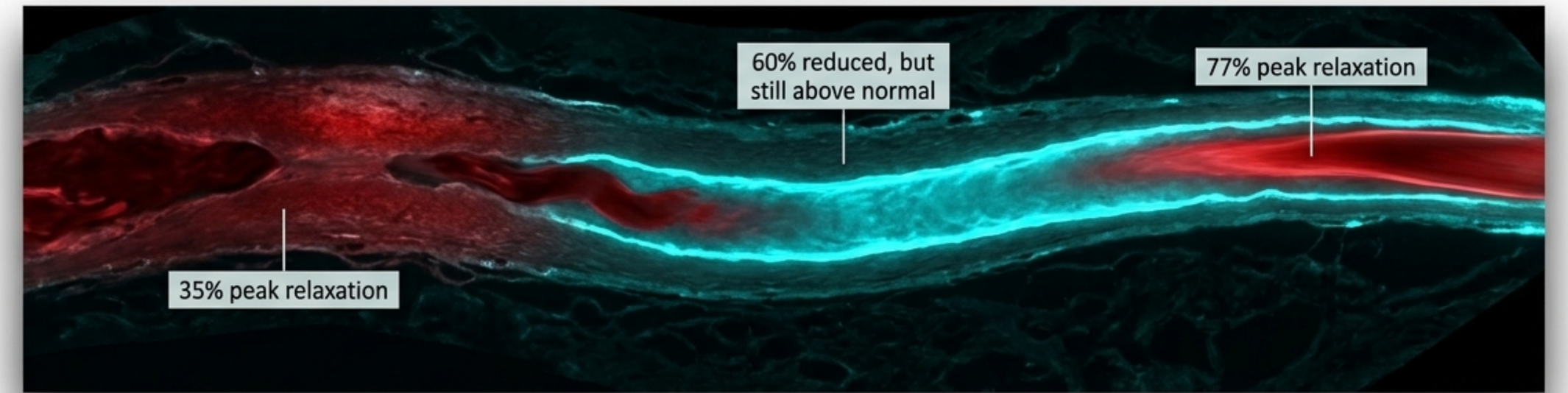
When particle burden drops, the lipid drains and necrotic debris resolves.

However, the fibrous tissue condenses and calcifies into a permanent scar. Total plaque volume remains, but the danger is neutralized.

The persistent scaffold stabilizes the vessel, neutralizing the risk of rupture despite the remaining plaque volume.

Function Normalizes Before Structure

- The **Harrison Experiment**: In primate iliac arteries, diet-induced regression restored endothelium-dependent relaxation to **perfectly normal** levels.
- The **Structural Lag**: This complete functional recovery occurred even though intimal thickening remained many times above normal.
- Relieving the endothelium of its lipid burden restores **nitric oxide function faster** than the body can dissolve the physical lesion.



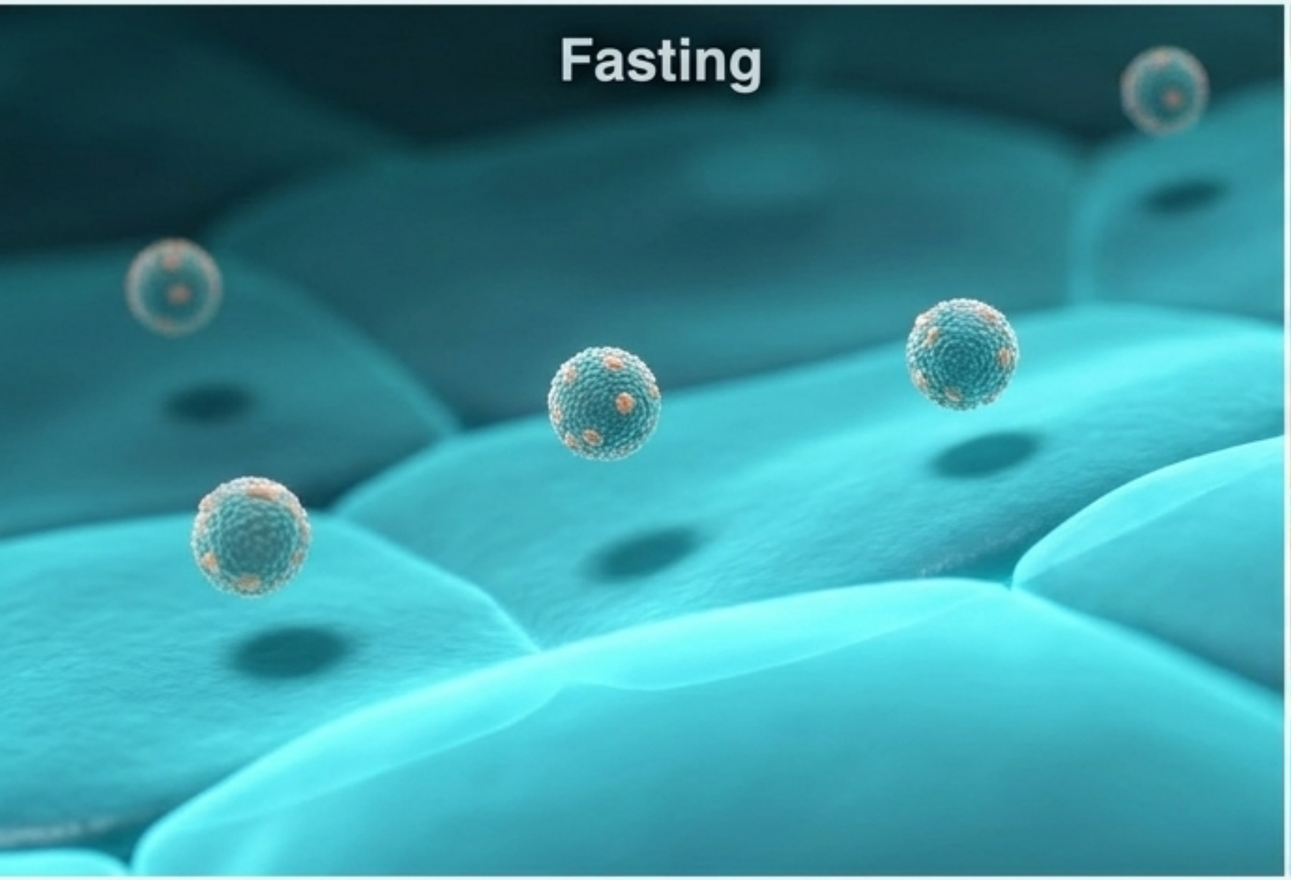
Evidence Mapping: Playing Different Games

The historical dietary literature and the modern pharmacologic literature rarely overlap in their chosen endpoints.

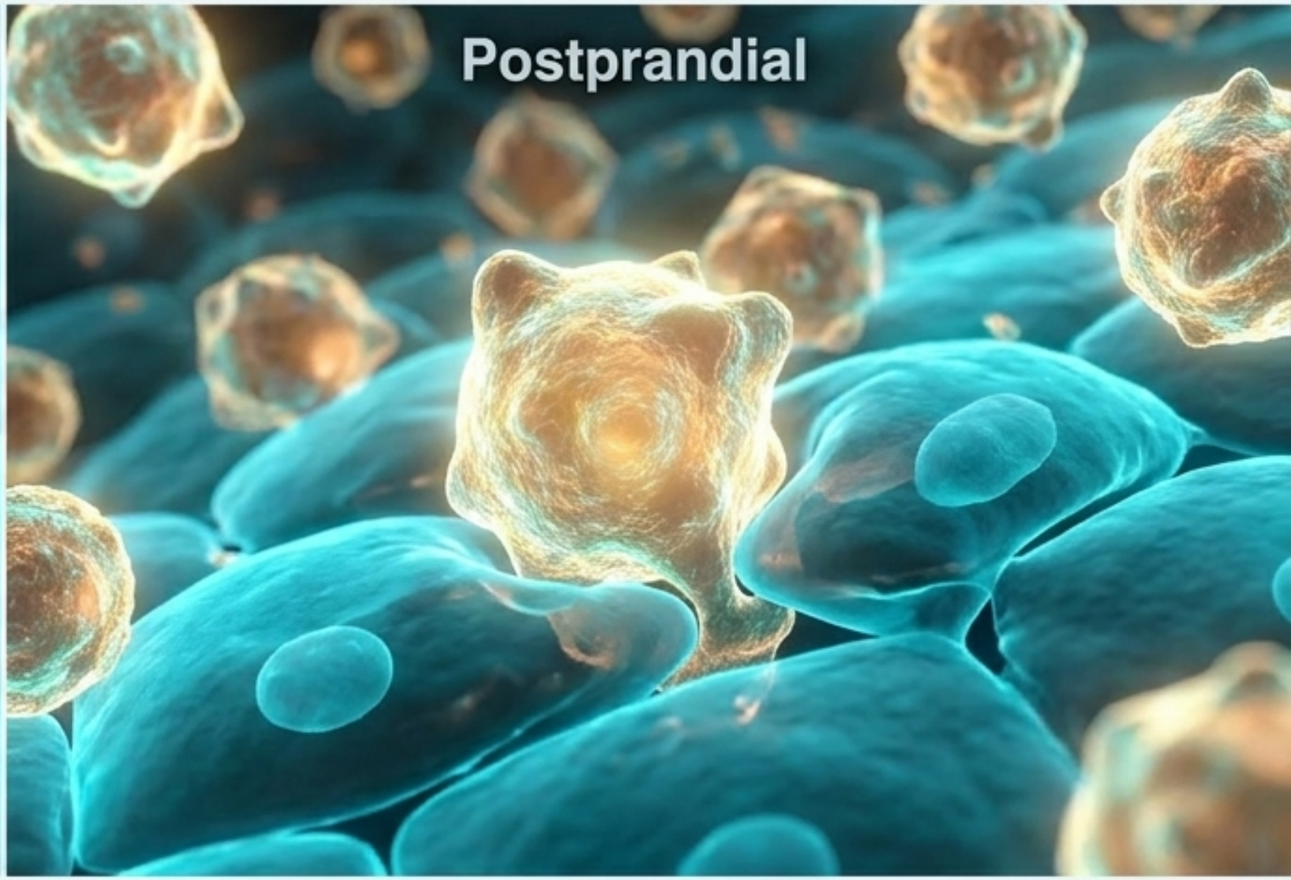
- Each discipline is strongest where the other is completely silent.
- Diet and drugs are not competing for the same mechanism; they are targeting different layers of vascular biology.

The Blind Spot: Postprandial Remnant Exposure

- Fasting lipid panels measure the bloodstream at its quietest metabolic hour.
- A high-fat meal induces transient endothelial dysfunction and floods the system with triglyceride-rich remnants.
- Dietary modifications can drastically reduce this postprandial bombardment, lowering total daily arterial exposure in ways a fasting test completely ignores.



Fasting State



Postprandial State

The Inflammatory Overlay

The CANTOS Proof: Targeted inhibition of the IL-1β inflammatory pathway reduced cardiovascular events by 15%—with absolutely zero reduction in LDL-C.

This establishes that downstream inflammatory modulation is a validated, independent therapeutic target.

Plant-forward and Mediterranean diets have been shown to reduce circulating immune-cell activation and inflammatory biomarkers like hsCRP, providing a plausible non-ApoB mechanism for event reduction.

Hemodynamics: Modifying the Channel

- Vasomotor Tone: Endothelial nitric oxide release can relax smooth muscle, widening the lumen in minutes without altering plasma lipoproteins or plaque mass.
- Blood Pressure: In randomized trials, angiographic progression was attenuated purely through blood pressure reduction, with no change in cholesterol.
- Hemodynamic shifts manipulate the physical geometry of the vessel, directly improving blood flow independent of ApoB retention.

The Mechanisms Taxonomy

Most dietary mechanisms conventionally labeled “beyond ApoB” actually fall into the interacting middle tier.

Diet modifies how much damage a given burden of retained particles produces, rather than operating entirely outside the laws of lipid biology.

ApoB-Mediated

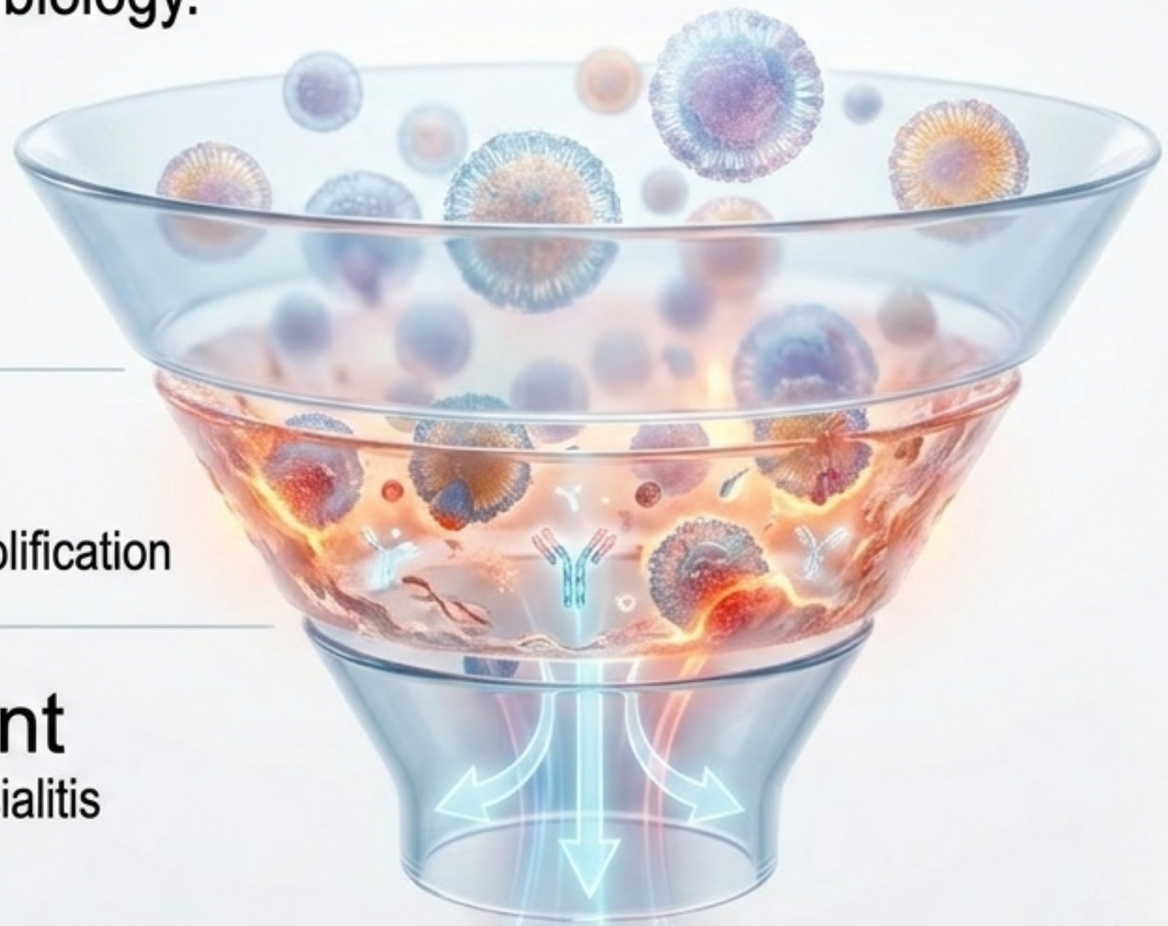
Fasting ApoB, Postprandial Remnants

ApoB-Interacting

Arterial Retention, Oxidation, Inflammatory Amplification

Potentially Independent

Vasomotor Tone, Blood Pressure, Xenosialitis

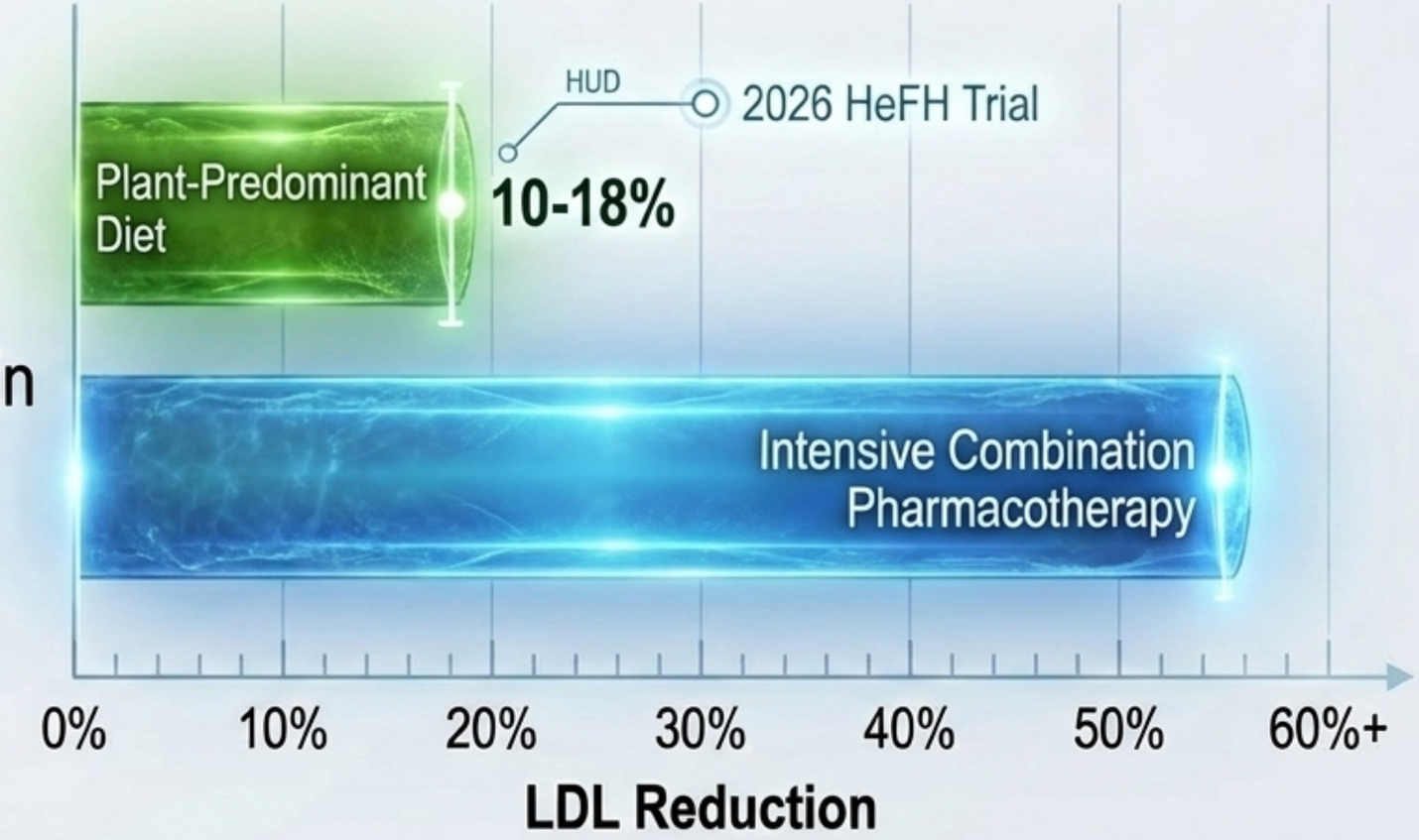


The True Dietary Lipid Effect

The Data: Pooled randomized trials and rigorous controlled-feeding studies (HeFH) demonstrate that plant-predominant diets lower LDL-C by roughly 10% to 18%.

The Context: While highly beneficial, this is numerically dwarfed by intensive combination pharmacotherapy.

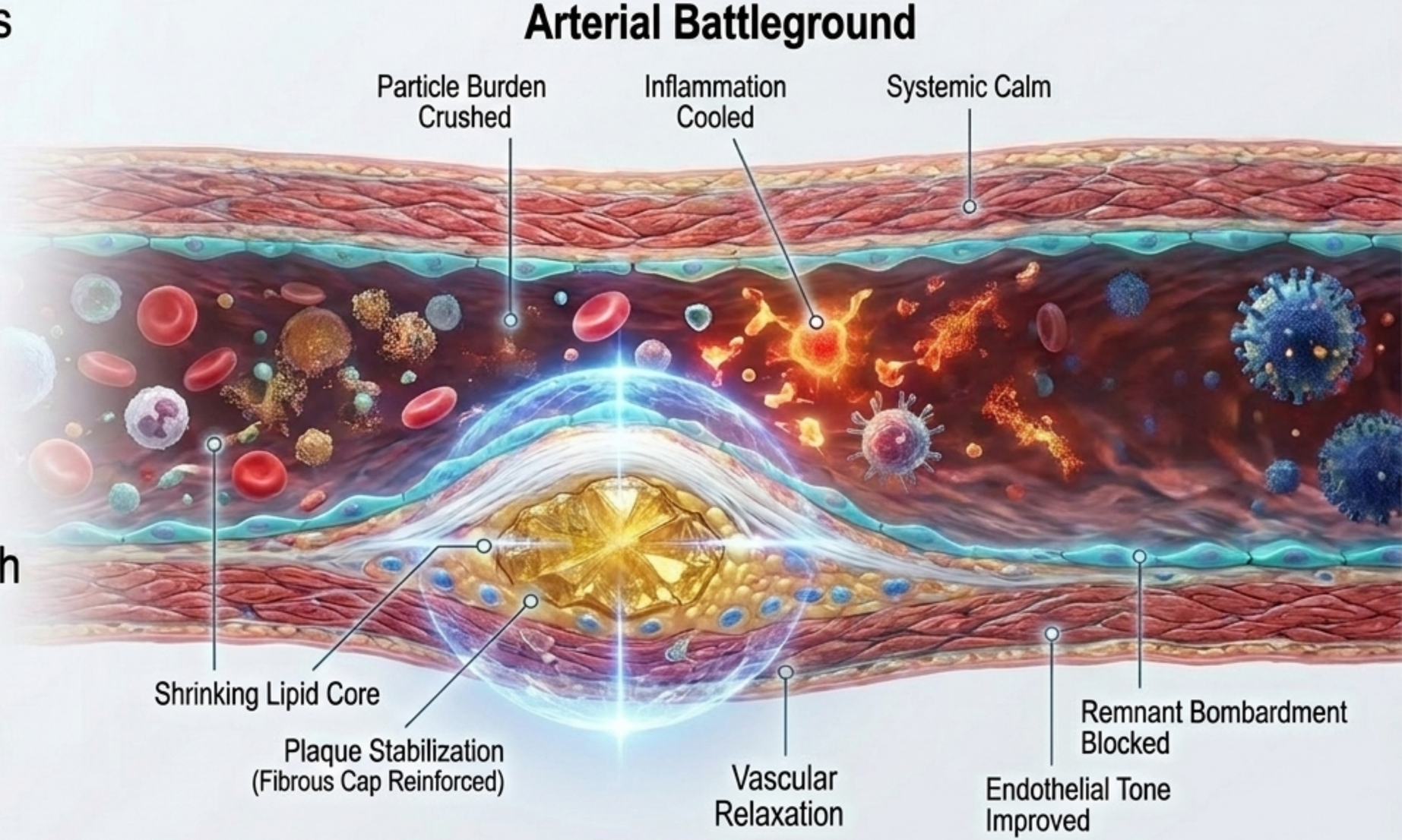
The Conclusion: If diet achieves massive event reductions (as seen in Mediterranean trials), the math requires mechanisms operatinms operating outside just the 10-18% drop in fasting LDL-C.



The Unified Complementary Model

Diet and indicated lipid-lowering therapy are complementary, not competing.

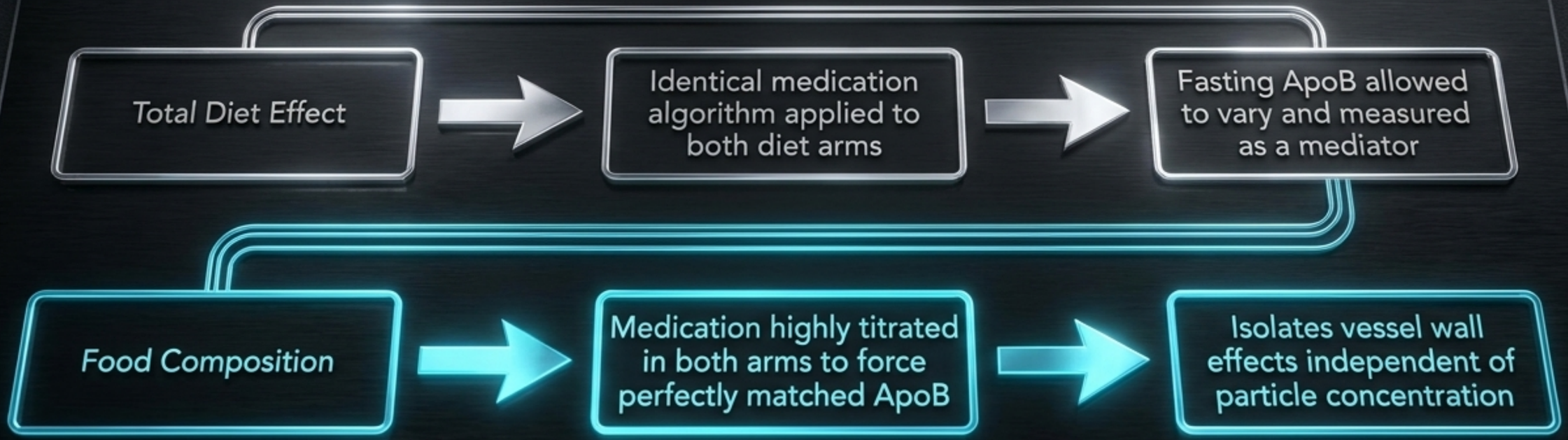
- **Pharmacotherapy** does the heavy lifting of crushing particle burden, shrinking lipid cores, and physically stabilizing the plaque.
- **Diet** adds a systemic overlay: cooling fiery inflammatory signals, relaxing vascular smooth muscle, improving endothelial tone, and limiting postprandial remnant bombardment.



The Unfinished Business: Ideal Trial Architectures

The exact partition of benefit remains unmeasured because the defining trials do not exist.

Future CCTA/IVUS imaging trials must standardize background pharmacotherapy, repeatedly measure ApoB exposure, and utilize objective biomarkers of dietary adherence.



Synergy Over Supremacy

Current evidence strongly supports cumulative ApoB reduction as the primary driver of atherosclerotic arrest.

However, dietary patterns profoundly influence vascular biology through tone, inflammation, and remodeling—mechanisms missed by fasting panels and volumetric imaging alike.

The optimal treatment of coronary disease requires mastering both the physics of the particle and the biology of the vessel wall.