The Zero-Risk Hypothesis: Eliminating Atherosclerosis through Ultra-Low LDL-C

A critical biological and epidemiological evaluation of the substrate-dependence of ASCVD.

Designed for Clinical Review

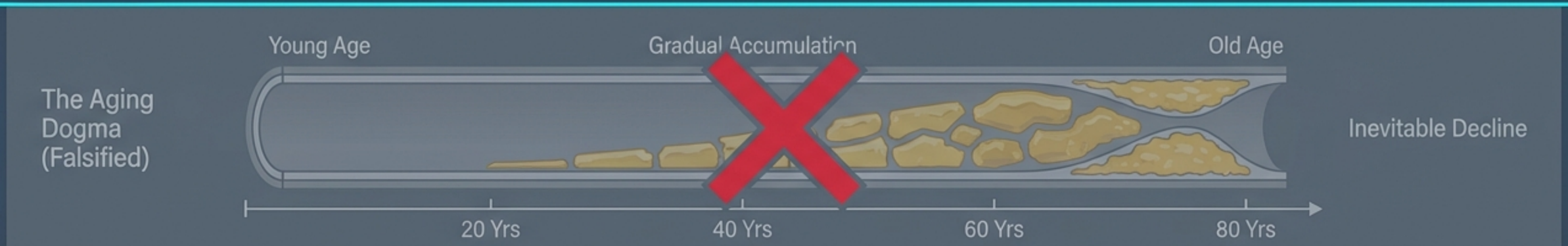
Atherosclerotic cardiovascular disease is not a chronic consequence of human senescence.

- Historically categorized as an inevitable result of aging.

- Contemporary molecular biology defines it as a biologically avoidable, substrate-dependent inflammatory pathology.

- The core premise: maintaining lifelong ultra-low low-density lipoprotein cholesterol (LDL-C ≈ 15 mg/dL) reduces the probability of disease initiation to a negligible biological zero.

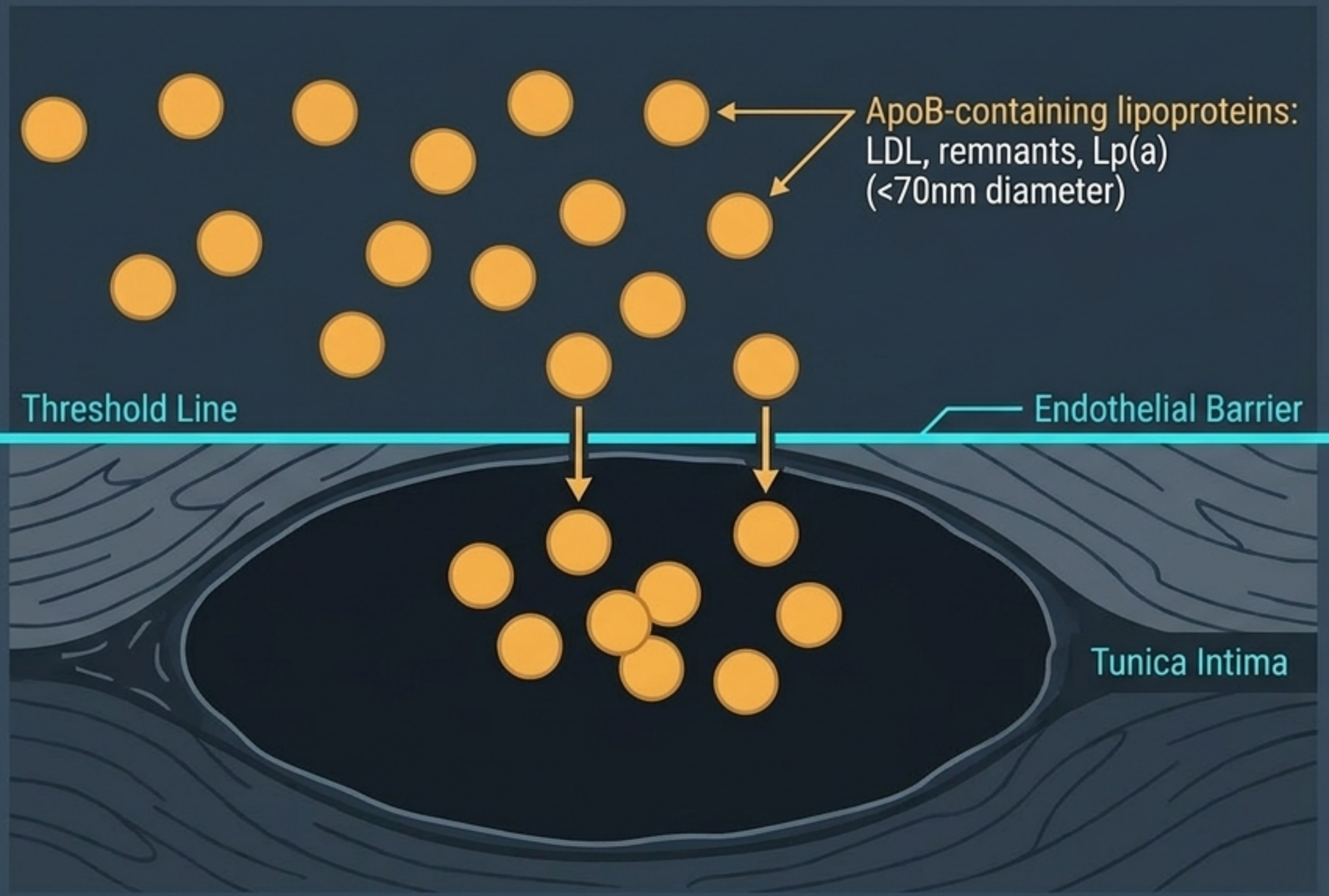
Threshold Line



The Substrate Pathology (Current Science)

Negligible Biological Zero
Avoidable Substrate
Maintenance of Ultra-Low LDL-C
Lifetime Protection

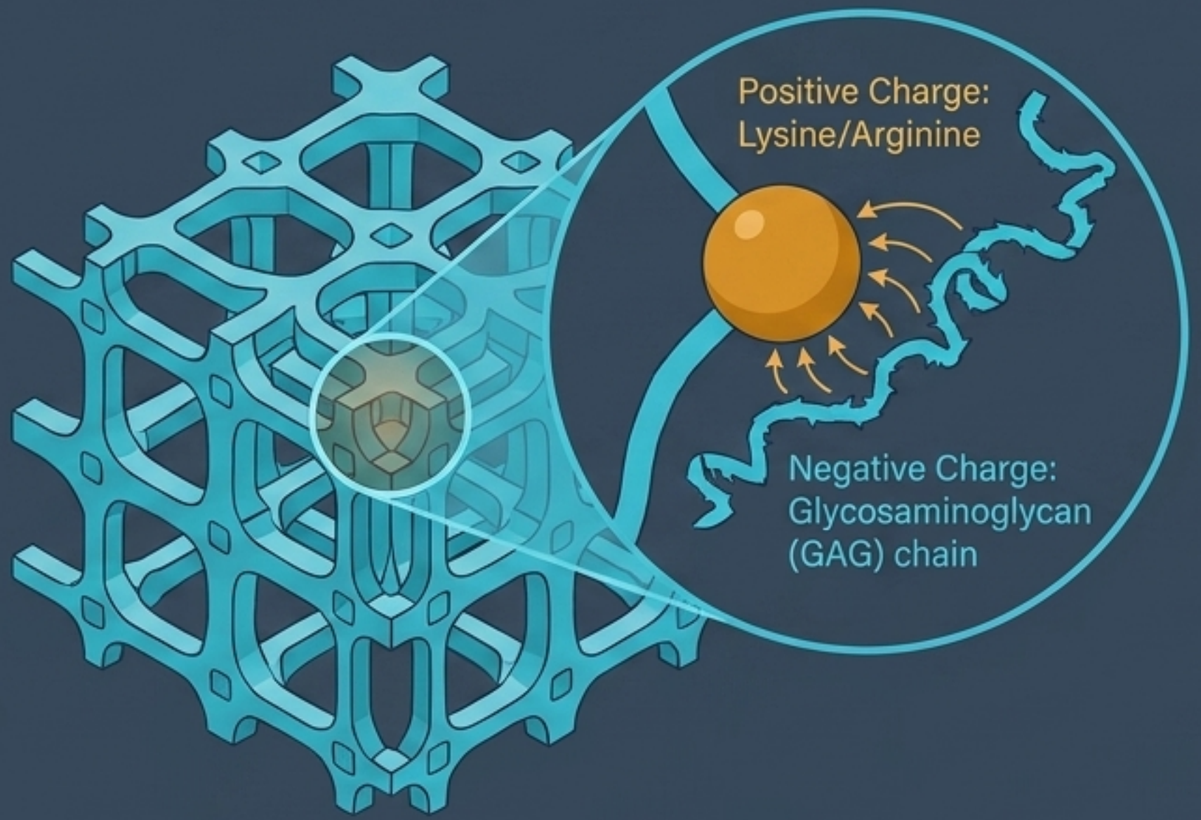
The initiation of atherogenesis requires the subendothelial retention of ApoB lipoproteins.



Key Takeaways

- Traditional models blamed direct endothelial injury.
- Current evidence confirms disease begins under an intact (though dysfunctional) endothelial barrier.
- Only particles under 70nm in diameter physically traverse the barrier into the tunica intima.

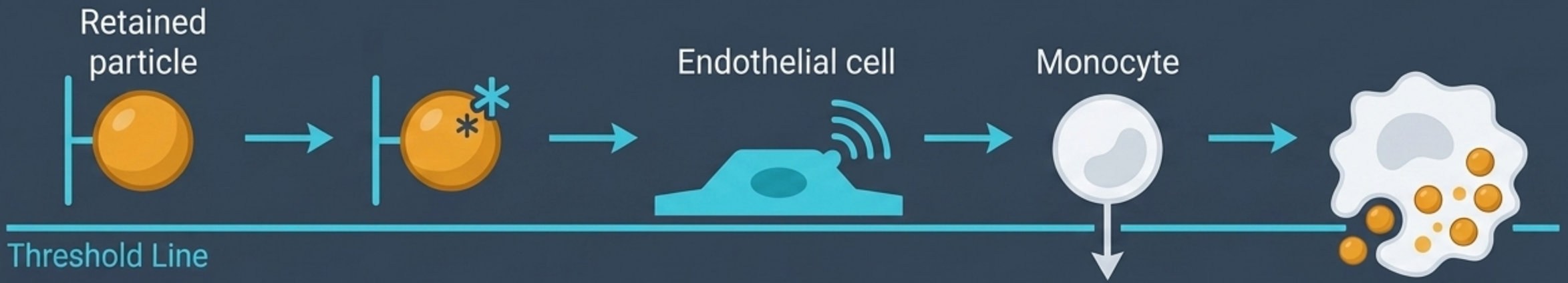
Intimal trapping is a critical electrostatic biochemical event, not passive entrapment.



Versican	Expands intimal volume, promotes particle trapping and smooth muscle cell migration.
Perlecan	Basement membrane scaffold facilitating early stage retention.
Biglycan	High affinity for ApoB; strongly correlated to the lipid-rich necrotic core.
Decorin	Modulates the fibrotic response and aggregation in the extracellular matrix.

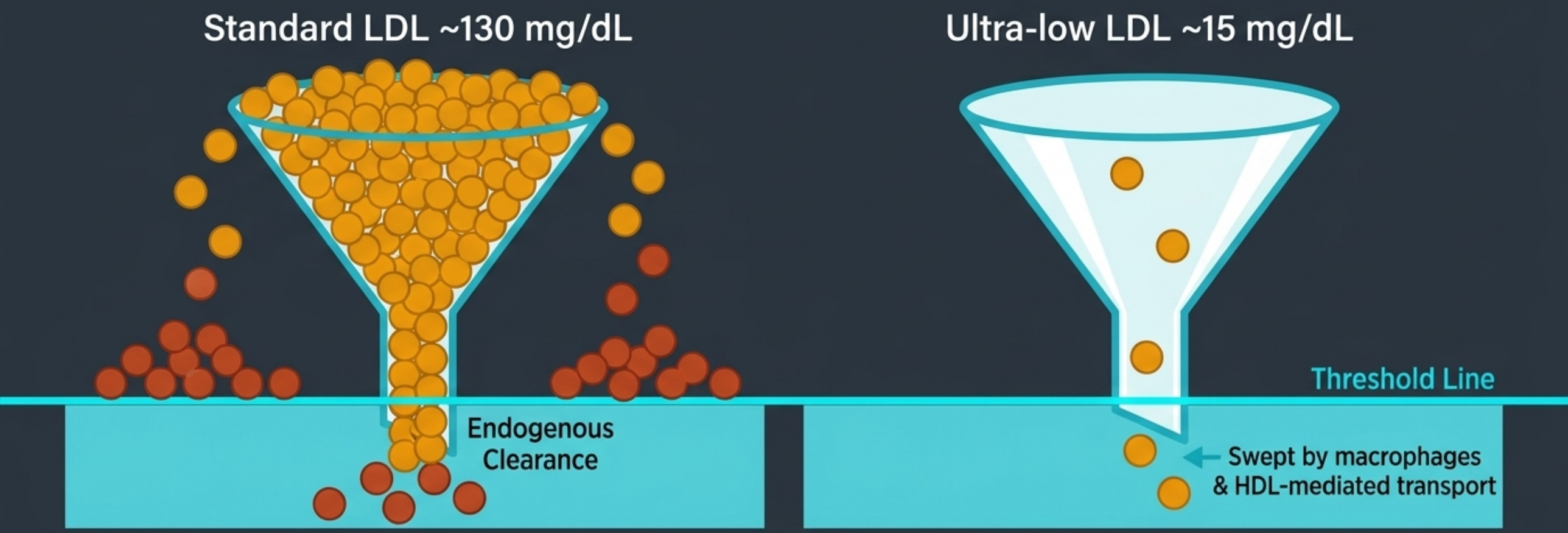
Threshold Line

Retained lipoproteins undergo pro-inflammatory modifications that trigger a maladaptive immune response.



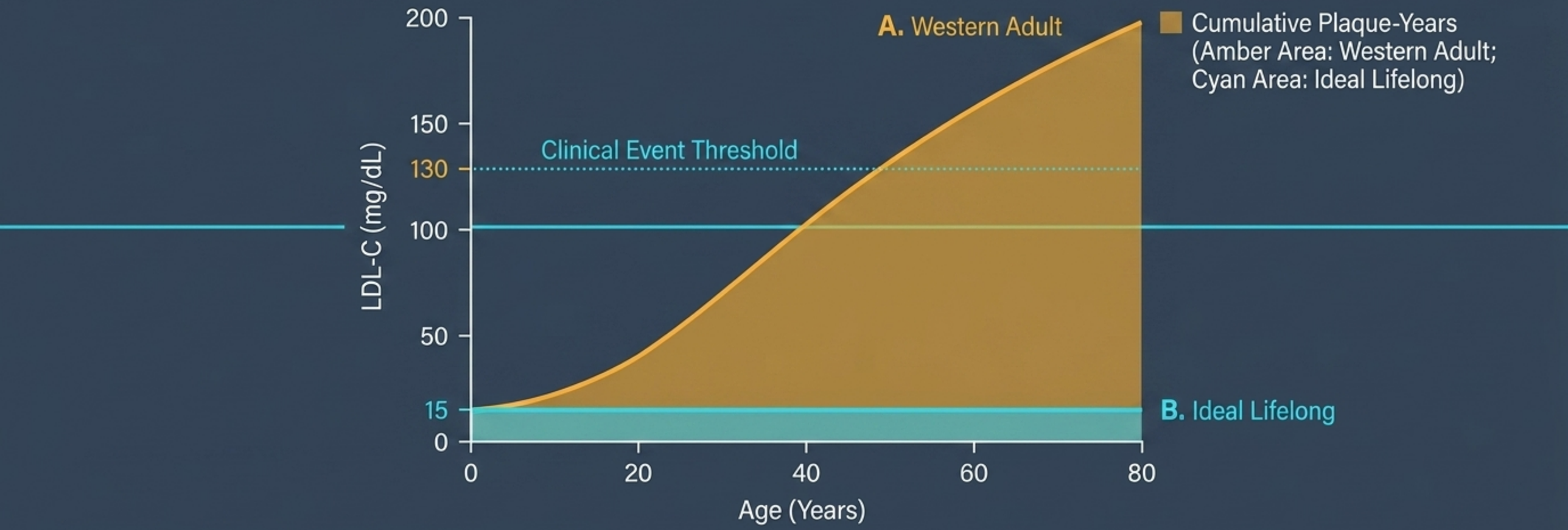
Takeaway: Retention increases residence time → Susceptibility to oxidation → Endothelial activation (VCAM-1) → Monocyte recruitment → Macrophage engulfment via scavenge → Foam cell formation.

The probability of retention is a thermodynamic function of particle concentration versus endogenous clearance.



Key Concept: In a stochastic model, if the influx of particles is sufficiently low, endogenous clearance mechanisms sweep them away before they undergo pro-inflammatory modification. The inflammatory cascade is never initiated.

Clinical risk is not dictated by current levels, but by the mathematical integral of exposure over time.



Atherosclerosis is a disease of gradual accumulation. Time to a clinical event is determined by how rapidly an individual reaches their personal plaque-year threshold.

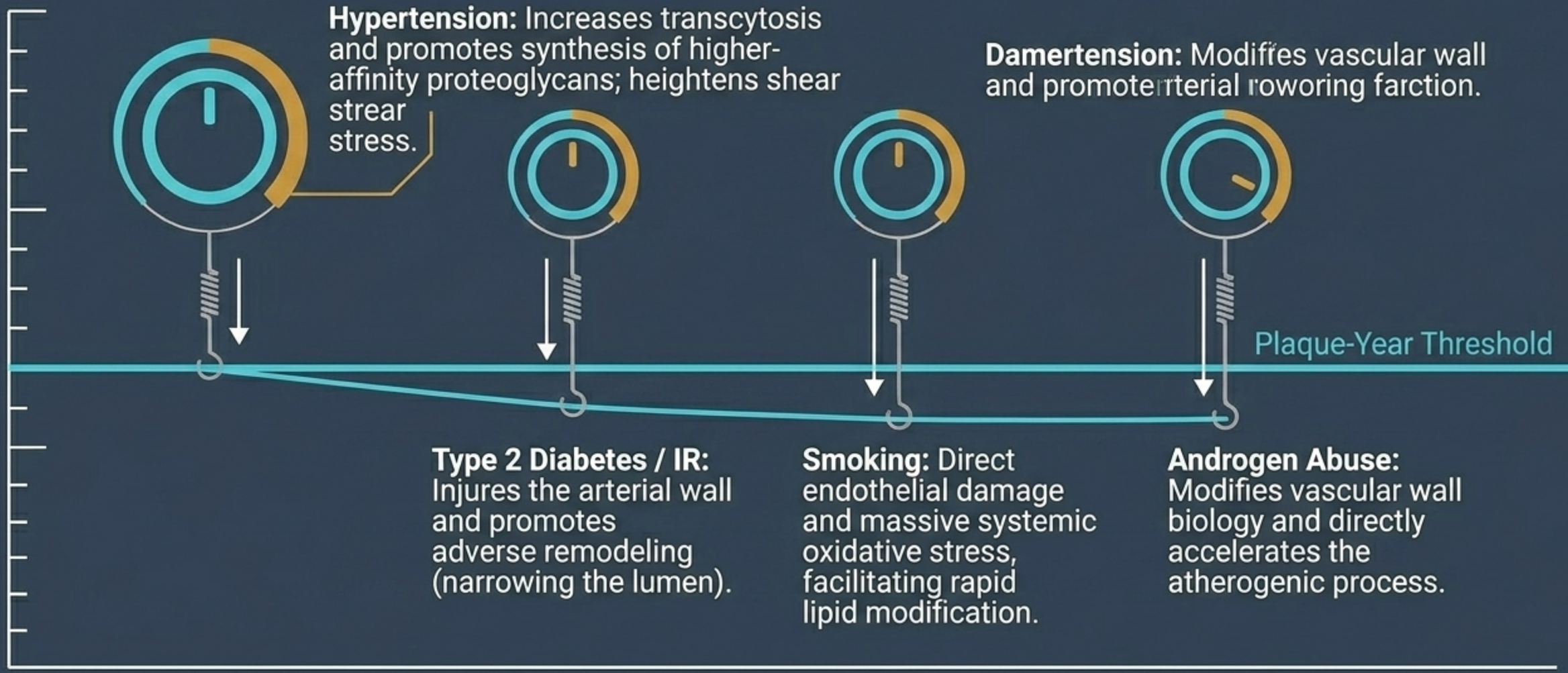
Defining the minimum cumulative exposure required to trigger clinical events.

Cumulative Exposure Threshold (mg-years)	Clinical Reality (Men)
Low-Risk Threshold	5,000 mg-years (1% probability of event).
Intermediate Threshold	7,000 mg-years (Median age for non-zero CAC, ~55).
High-Risk Threshold	8,000 mg-years (50% probability of event).
Very High-Risk Threshold	10,000 mg-years (Median age for CAC >100).

Threshold Line

Footnote: Thresholds for women are generally higher (~7,000 mg-years for 1% risk) prior to menopause due to the protective effects of estrogen on transcytosis. A lifelong LDL of 15 mg/dL for 80 years yields only 1,200 mg-years—vastly below initiation thresholds.

Secondary risk factors do not create the substrate; they lower the arterial tolerance threshold.



Genetic null models provide biological proof: no substrate, no plaque.

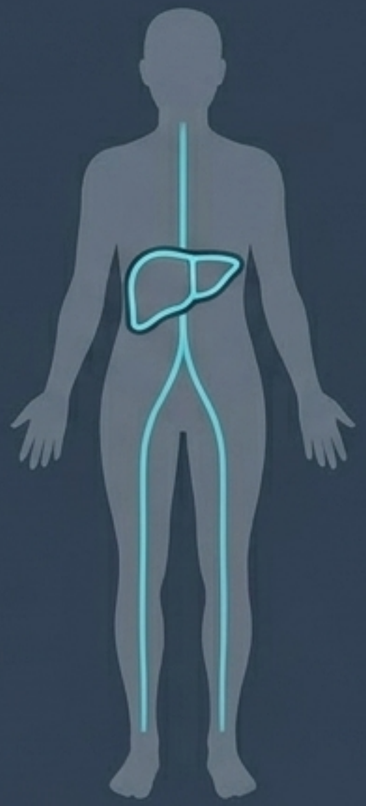
Genetic Profile	Mechanism	LDL-C Range	ASCVD Phenotype
Abetalipoproteinemia	MTTP loss-of-function (No particle assembly)	LDL <10 mg/dL	Complete absence of plaque.
Homozygous FHBL	APOB loss-of-function (Truncated proteins)	LDL <20 mg/dL	Complete absence of plaque.
PCSK9 LOF (Homozygous)	Enhanced LDLR recycling (Rapid clearance)	LDL ~15 mg/dL	Profound protection; no documented plaque.
ANGPTL3 Deficiency	Increased LPL/EL activity	Low TG and LDL	Absence of plaque in homozygous cases.

Threshold Line

PCSK9 and ANGPTL3 mutations prove ultra-low LDL-C is entirely compatible with normal human physiology.

Pathological Lows

ABL/FHBL severe non-cardiac pathology includes fat malabsorption, neuromuscular degeneration, and Vitamin E deficiency.



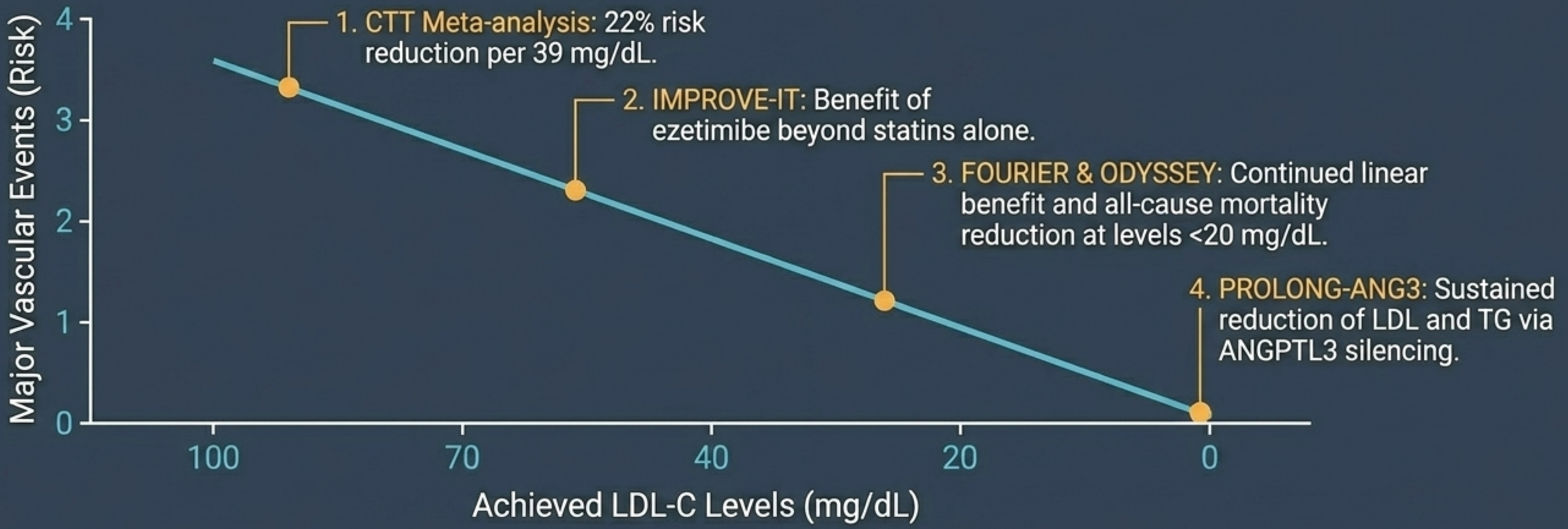
Healthy Ultra-Low

Unlike MTTP deficiency, PCSK9 Loss-of-Function (LOF) yields extreme low LDL (~15 mg/dL) safely. The first homozygous individual identified was a completely healthy, fertile woman. Heterozygous PCSK9 carriers see an 88% risk reduction over 15 years.

ANGPTL3 LOF confirms no increased hepatic fat, identifying an ideal target for long-term pharmacological mimicry.

Threshold Line

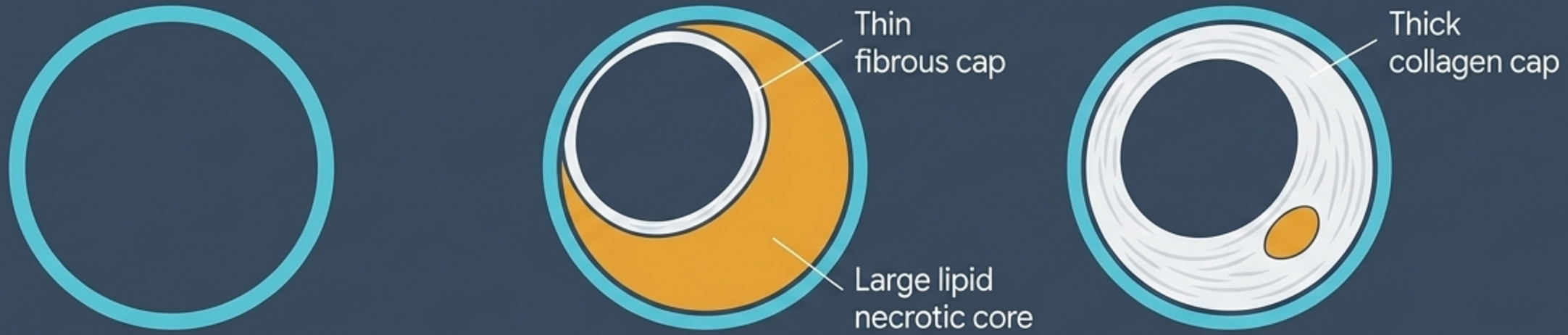
Pharmacological intervention confirms the strict linearity of benefit down to sub-physiological levels.



Conclusion: The ‘no-plateau’ observation indicates the biological drivers of atherosclerosis remain substrate-limited even at extreme pharmacological lows.

Threshold Line

Intravascular imaging (IVUS) reveals that ultra-low LDL-C forces radical structural remodeling of existing plaques.



Virgin Artery
(Lifelong <15 mg/dL)

Vulnerable Pimple
(Standard Adult)

Solid Wart
(Pharmacologically stabilized)

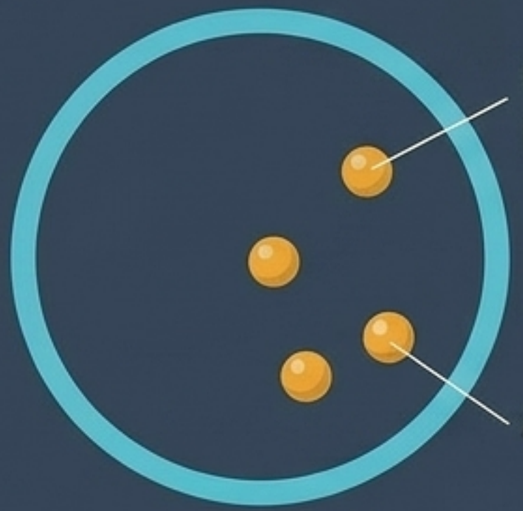
Mechanisms:

- **Regression:** Percent Atheroma Volume (PAV) reduces when LDL-C drops below 70 mg/dL.
- **Stabilization:** Extreme lows shrink the necrotic lipid core and cement the plaque with a thick collagen cap.

The **Zero-Risk Paradigm:** Early-life maintenance prevents the lipid core entirely, making 'regression' irrelevant because there is no lesion to stabilize.

Residual risk in treated patients is a reflection of irreversible structural damage, not a failure of the hypothesis.

Primary/Primordial Prevention



Clean artery + Ultra-Low LDL
= No Substrate = No Initiation

Event Horizon

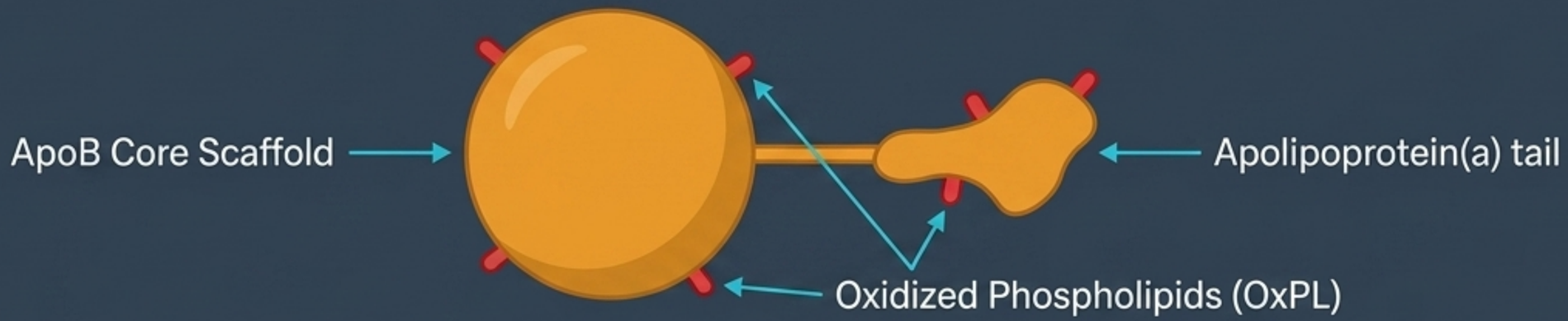
Secondary Prevention

In secondary prevention, patients achieving <15 mg/dL still experience events. Once a plaque features a necrotic core and thinned fibrous cap, it can rupture independently of current LDL-C levels due to localized mechanical stresses.

The zero-risk hypothesis is strictly about eliminating disease initiation.

Threshold Line

Lipoprotein(a) is highly atherogenic but remains structurally subordinate to the ApoB pathway.



The Counterargument	The Biological Reality
Lp(a) causes independent risk and carries highly inflammatory oxidized phospholipids (OxPL).	Every Lp(a) particle contains exactly one molecule of ApoB. In genetic null states (like ABL or homozygous FHBL) where ApoB cannot be synthesized, Lp(a) cannot be formed because the essential scaffold is missing. Lp(a) cannot initiate plaque without ApoB.

Threshold Line

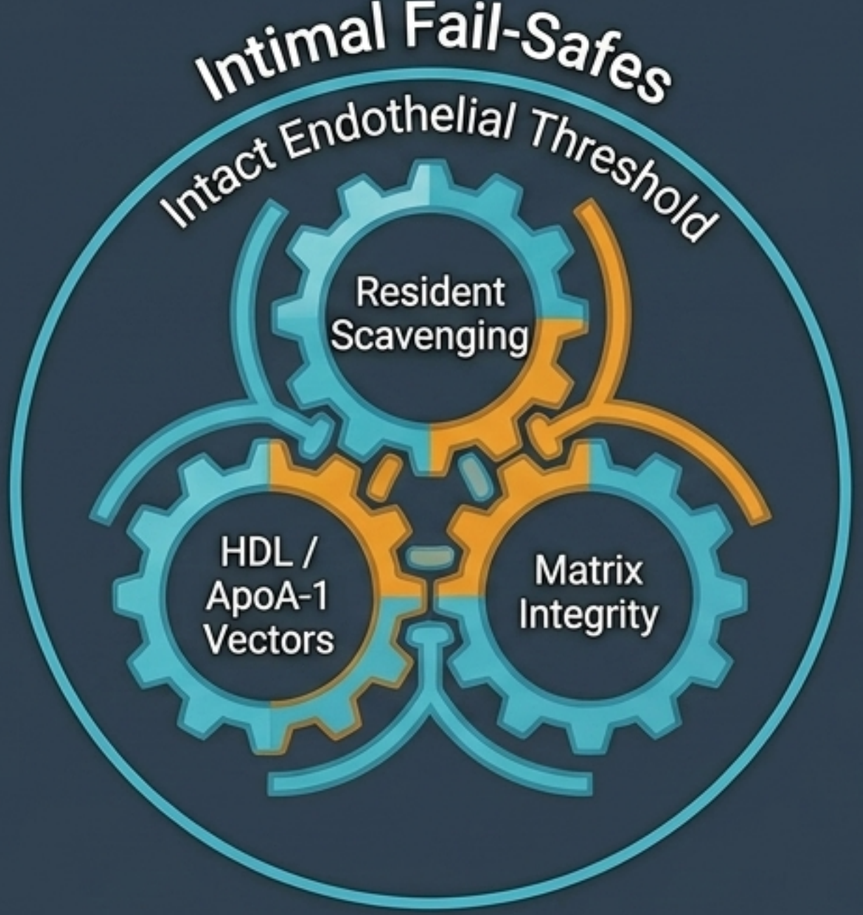
Inflammation acts strictly as a downstream potentiator, never as an independent initiator.

State 1	High Lipids + Inflammation (CANTOS study)	+ 	Massive Foam Cell creation
State 2	Severe Systemic Inflammation + ZERO Hyperlipidemia (Wild-Type Mouse Model)	+ —	Arterial wall remains completely clear

- **The Insight:** The CANTOS study proved inhibiting the IL-1β pathway reduces events. However, arterial inflammation and macrophage recruitment are the normal, expected biological responses of healthy tissue to the pathological presence of retained lipoproteins.
- **Conclusion:** Animal models confirm that severe systemic inflammation (e.g., rheumatoid arthritis models) will lower the retention threshold, but it absolutely cannot intiate atherosclerosis in the absence of hyperlipidemia.

Threshold Line

Arterial fail-safes ensure that mathematically stochastic retention remains biologically irrelevant.



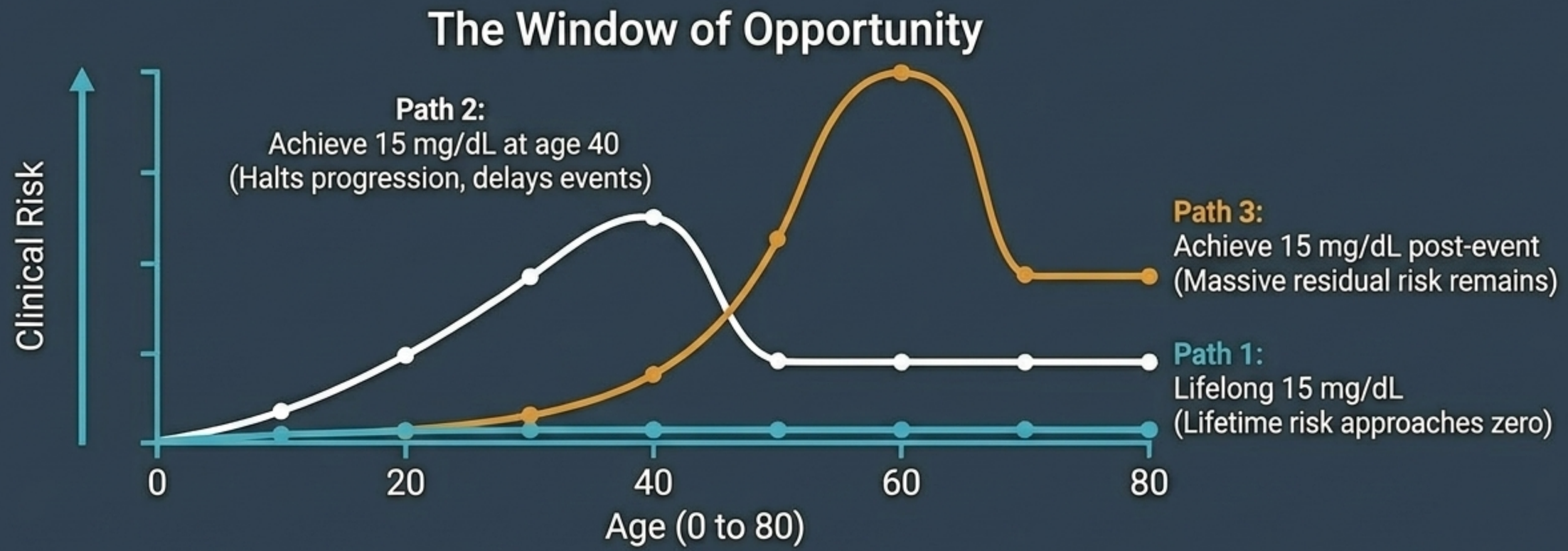
The Stochastic Limit:

At 15 mg/dL, the probability of a single particle entering and oxidizing is mathematically non-zero. However, the probability of reaching a critical focal mass is effectively zero due to robust homeostatic mechanisms:

- Resident Scavenging: Intimal macrophages clear minute traces of lipid without triggering cytokine cascades.
- HDL/ApoA-1 Vectors: Bidirectional efflux capacity easily outpaces ultra-low influx.
- Matrix Integrity: Without sustained retention, proteoglycan expansion does not occur, leaving the matrix thin and elastic.

Threshold Line

Synthesis: Atherosclerosis is an irreversible structural disease driven by a reversible chemical environment.



Core Revelation: Mendelian randomization reveals that "residual risk" is largely just a synonym for "late intervention." The age at which lowering begins dictates the maximum possible clinical benefit.

Threshold Line

Formal evaluation of the Zero-Risk Hypothesis outcomes.

The Strong Form	Lifelong LDL ≈ 15 mg/dL results in effectively zero probability of clinically meaningful atherosclerosis.	✓	**Evaluation:** Supported by human genetic null models and baseline physiological newborn levels.
The Weak Form (Asymptotic)	Risk approaches zero but never fully reaches it due to stochastic retention limits.	—	**Evaluation:** Plausible at extreme age or in states of highly abnormal severe systemic inflammation, though clinically negligible.
The Null Hypothesis	Atherosclerosis occurs at meaningful rates independent of ApoB.	✗	**Evaluation:** Refuted for the ideal phenotype; non-ApoB residual risk only applies to pre-existing mature plaques.

Threshold Line

Mapping clinical phenotypes against predicted structural burden.

Ideal Phenotype

Lifelong LDL ~15 mg/dL

Plaque Burden:
Zero/Undetectable

Event Risk:
Effectively Zero

Healthy Adult

Lifelong LDL ~70 mg/dL

Plaque Burden:
Minimal/Aging-related

Event Risk:
<1%

Western Adult

Lifelong LDL ~130 mg/dL

Plaque Burden:
Progressive/Mature

Event Risk:
High

Secondary Prevention

Achieved LDL ~15 mg/dL
(Late life)

Plaque Burden:
Stable/Calcified

Event Risk:
Significant Residual

Threshold Line

Redefining the Threshold of Human Health.

Atherosclerosis is a biologically eradicable disease.

Managing risk as an inevitable outcome of aging is clinically obsolete.

The future of cardiology relies on primordial prevention: maintaining physiological lipoprotein levels through the earliest stages of life to permanently eliminate the substrate of the world's leading killer.

The disease requires a minimum lifelong cumulative exposure. We control the exposure.