



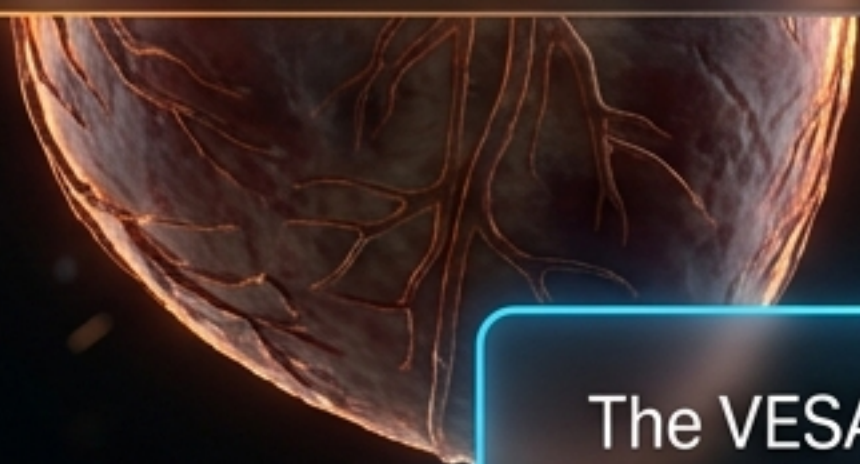
Preventing your first heart attack

by Peter Megdal PhD



THE CONSENSUS

For thirty years, cardiology agreed: if a heart attack has already happened, aggressive cholesterol lowering is strictly necessary.

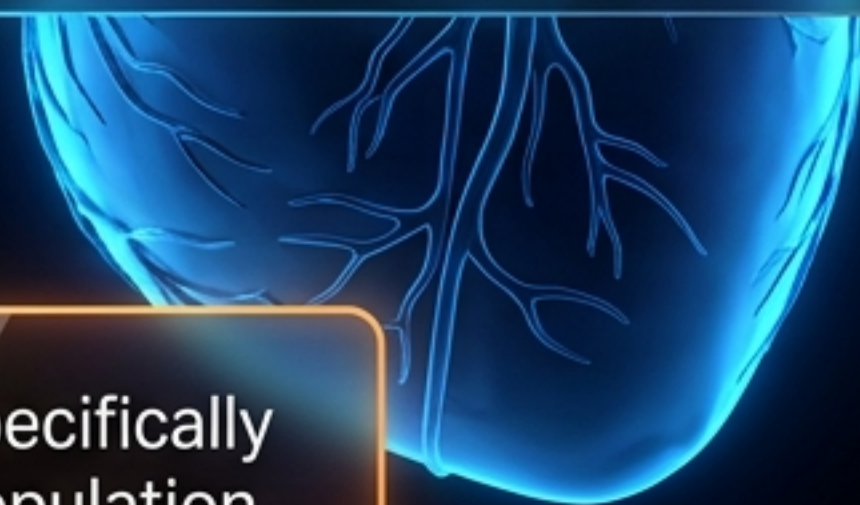


The VESALIUS-CV trial was designed specifically to answer this question in a high-risk population.



THE UNANSWERED QUESTION

The debate remained centered on the untouched heart. Is it worth deploying intensive, aggressive therapies before the first event ever occurs?



COHORT

12,257 adults across
33 countries.

Evolocumab
(140 mg bi-weekly injection)

RISK PROFILE

High risk (diabetes or
documented atherosclerosis),
but strictly zero previous
heart attacks or strokes.

4.6 Years Median Follow-Up

BASELINE TREATMENT

~87% already on a statin
(68% high-intensity).

Placebo

THE BASELINE PROBLEM

Despite statins, median
baseline LDL-C remained
elevated at ~122 mg/dL.

LDL-C Cut by >50%

Dropped from ~122 mg/dL
to ~45 mg/dL

36% Drop

In first heart attacks

25% Drop

In 3-point MACE
(heart attack, stroke,
or coronary death)

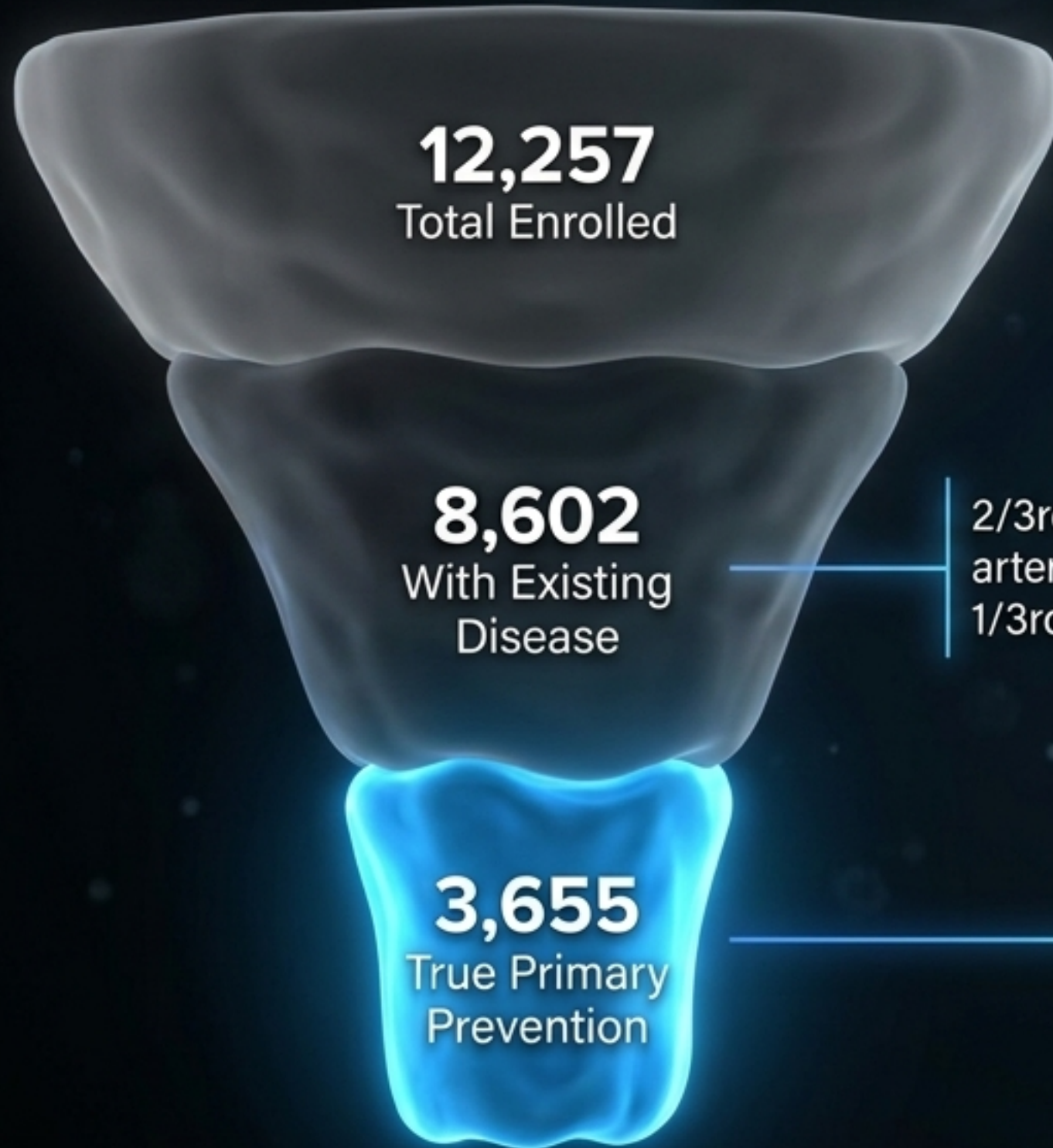
19% Drop

In 4-point MACE
(adding ischemia-driven
revascularization)

Context: The Stroke Caveat

While strokes trended down by roughly 20%, the result did not reach statistical significance to rule out chance. The heart attack finding, however, is definitively solid.

The Funnel of Truth



2/3rds already had visible artery disease, and nearly 1/3rd already had a stent.

THE REALITY

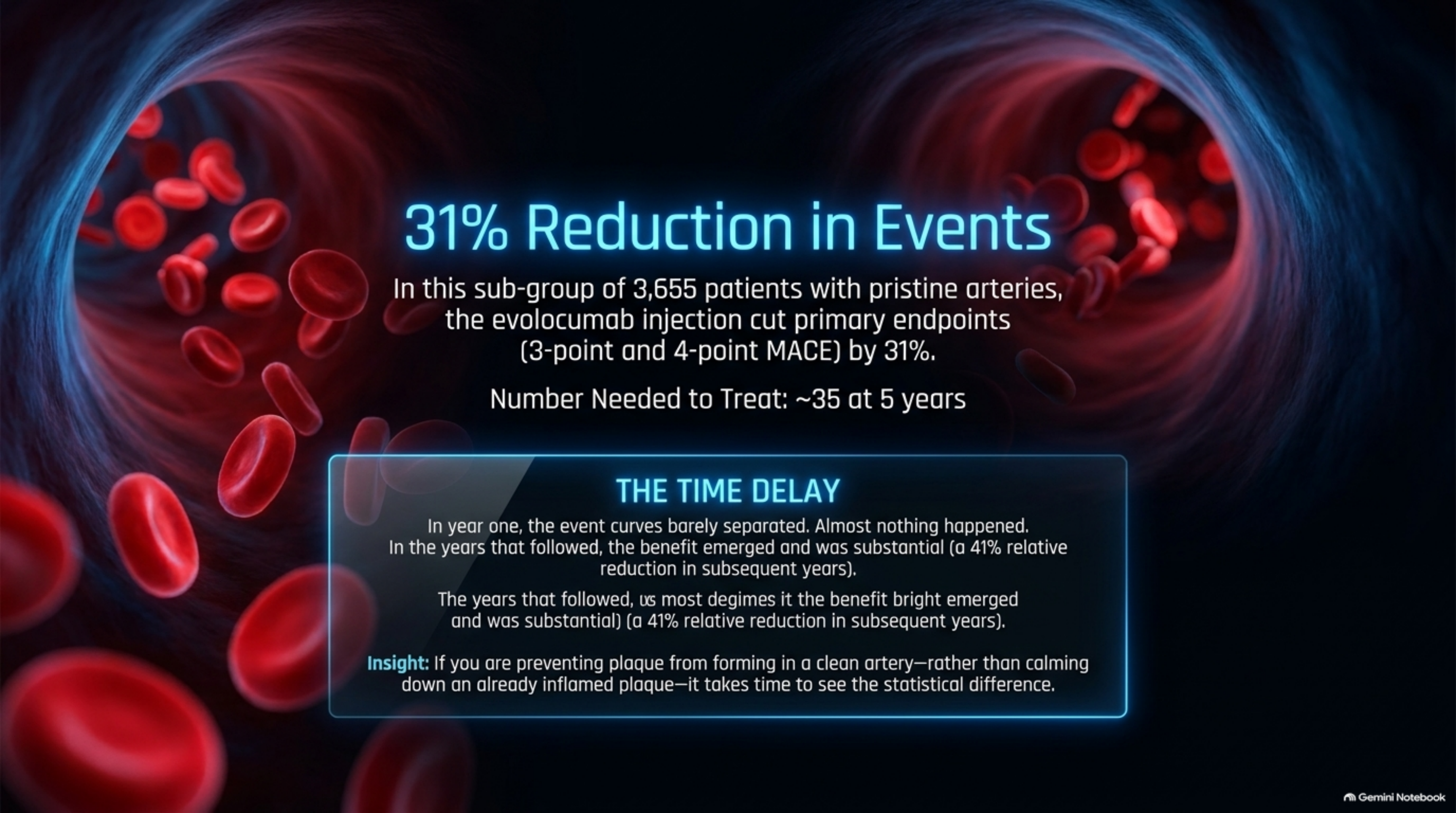
"No prior events" is technically true but misleading.

Most doctors consider patients with stents and visible plaque to be secondary prevention patients.

The genuinely new territory was the 3,655 patients at the bottom of the funnel.

PROFILE OF THE 3,655

- Diabetes diagnosis
- No prior arterial revascularization
- No stenosis $\geq 50\%$
- Coronary calcium score < 100



31% Reduction in Events

In this sub-group of 3,655 patients with pristine arteries, the evolocumab injection cut primary endpoints (3-point and 4-point MACE) by 31%.

Number Needed to Treat: ~35 at 5 years

THE TIME DELAY

In year one, the event curves barely separated. Almost nothing happened. In the years that followed, the benefit emerged and was substantial (a 41% relative reduction in subsequent years).

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Insight: If you are preventing plaque from forming in a clean artery—rather than calming down an already inflamed plaque—it takes time to see the statistical difference.

Cholesterol does not float loose in the blood. It must be carried inside particles. Every atherogenic particle is tagged with a single protein: Apolipoprotein B (ApoB).

LDL-C = THE CARGO

This measures the total mass of cholesterol being carried.



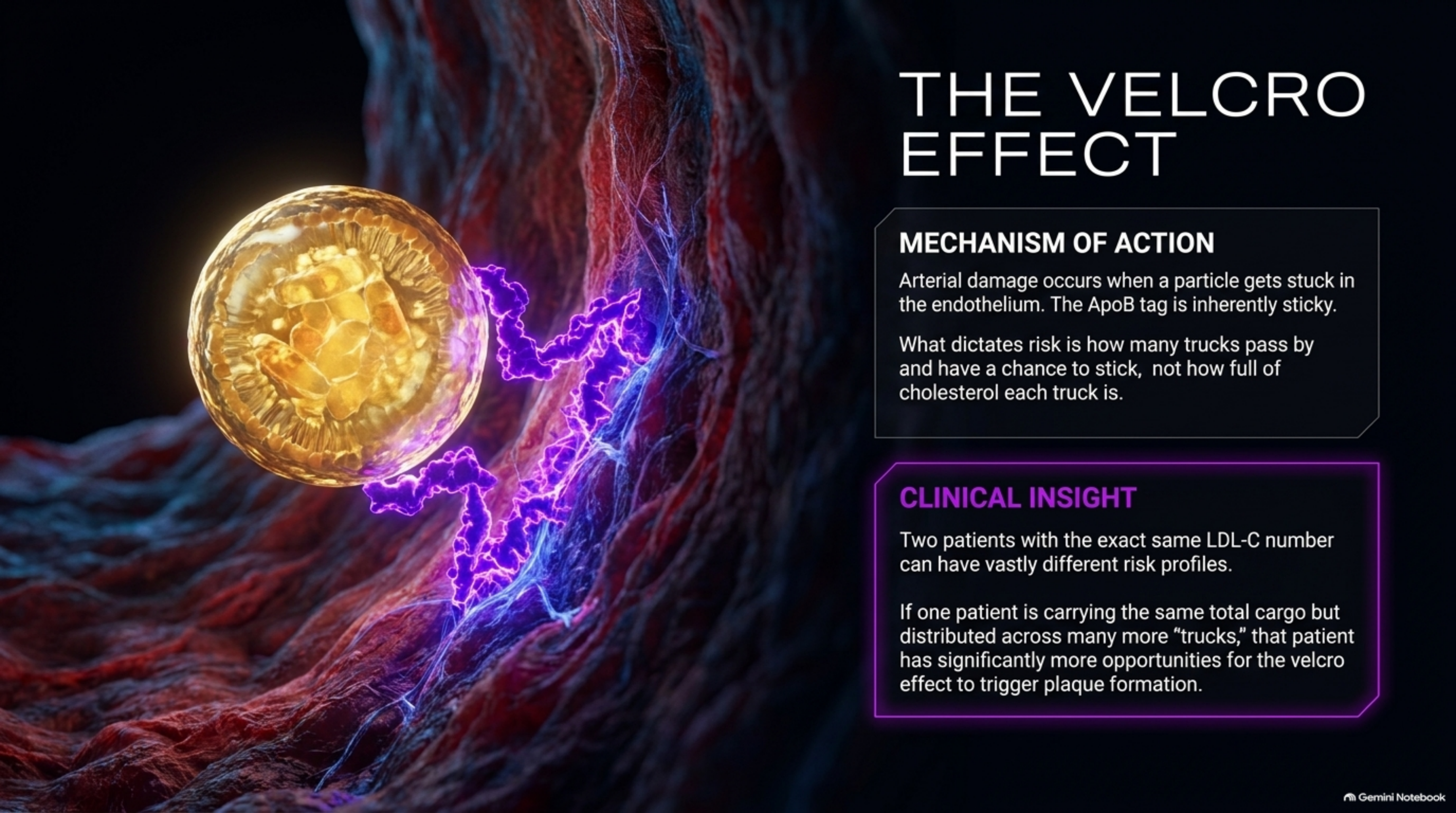
ApoB = THE DELIVERY TRUCKS

This counts the total number of particles carrying the cargo.

(ApoB 100 mg/dL roughly equals $1.1\text{--}1.2 \times 10^{16}$ particles per liter).



Measuring ApoB is essentially counting the exact number of atherogenic trucks on the highway.



THE VELCRO EFFECT

MECHANISM OF ACTION

Arterial damage occurs when a particle gets stuck in the endothelium. The ApoB tag is inherently sticky.

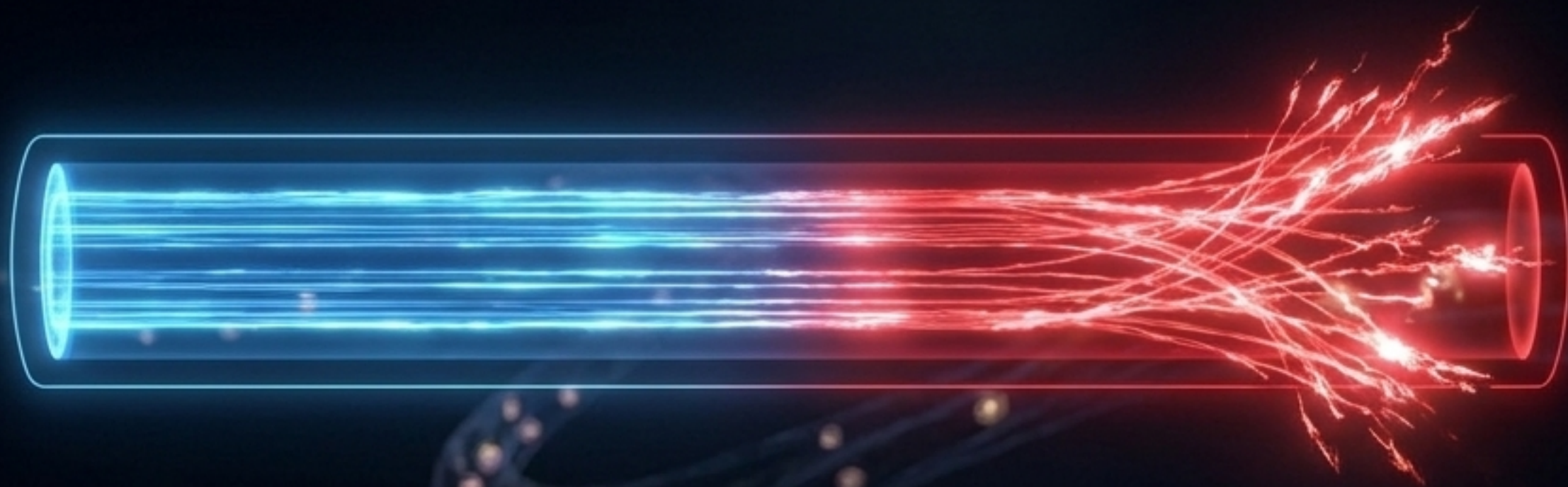
What dictates risk is how many trucks pass by and have a chance to stick, not how full of cholesterol each truck is.

CLINICAL INSIGHT

Two patients with the exact same LDL-C number can have vastly different risk profiles.

If one patient is carrying the same total cargo but distributed across many more “trucks,” that patient has significantly more opportunities for the velcro effect to trigger plaque formation.

LDL and ApoB
Tightly Coupled



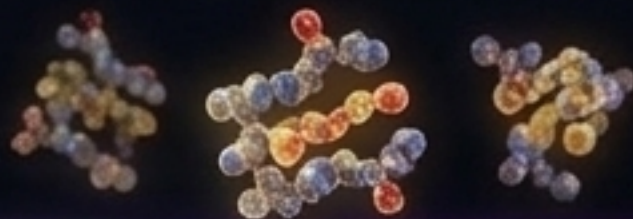
Drastic
Decoupling

LDL-C is usually an estimate, not a direct measurement.
It breaks down and diverges from reality exactly when clinical
decisions are hardest. the more game ot ol decisions are hardest.

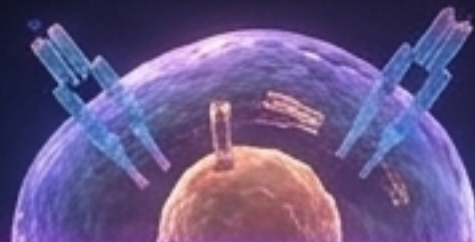
THE DISCORDANCE CHECKLIST

Patients can have a "normal" LDL-C but dangerously high ApoB (more particles than the cholesterol mass implies) in the presence of:

High Triglycerides
(>200 mg/dL)



Diabetes and
Insulin Resistance

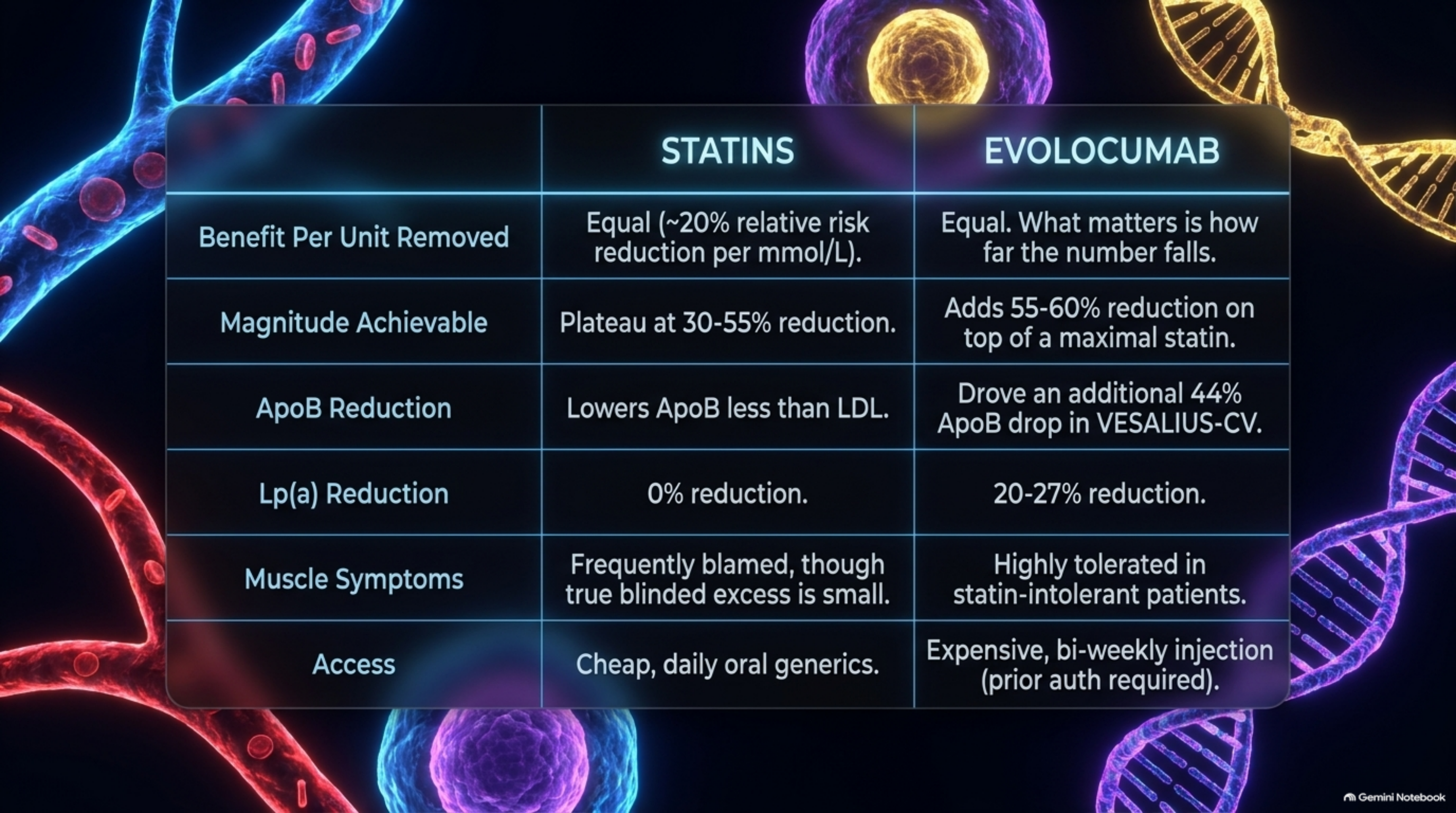


Obesity and
Older Age



Statin Treatment
(Statins lower cholesterol mass
proportionally more than they
lower particle count)





	STATINS	EVOLOCUMAB
Benefit Per Unit Removed	Equal (~20% relative risk reduction per mmol/L).	Equal. What matters is how far the number falls.
Magnitude Achievable	Plateau at 30-55% reduction.	Adds 55-60% reduction on top of a maximal statin.
ApoB Reduction	Lowers ApoB less than LDL.	Drove an additional 44% ApoB drop in VESALIUS-CV.
Lp(a) Reduction	0% reduction.	20-27% reduction.
Muscle Symptoms	Frequently blamed, though true blinded excess is small.	Highly tolerated in statin-intolerant patients.
Access	Cheap, daily oral generics.	Expensive, bi-weekly injection (prior auth required).

THE BIOLOGICAL CEILING

Statins work by forcing the liver to create more LDL receptors. However, the body pushes back. Statins also trigger the release of PCSK9, a protein that destroys those very receptors.

REMOVING THE BRAKE

Evolocumab is a PCSK9 inhibitor. It eliminates the body's pushback, allowing the receptors to survive and clear particles continuously.



THE SYNTHESIS

The statin comes first—it is the foundational, cheap, evidence-backed oral therapy. The injection is the sledgehammer required when the statin hits its biological ceiling and residual risk remains.

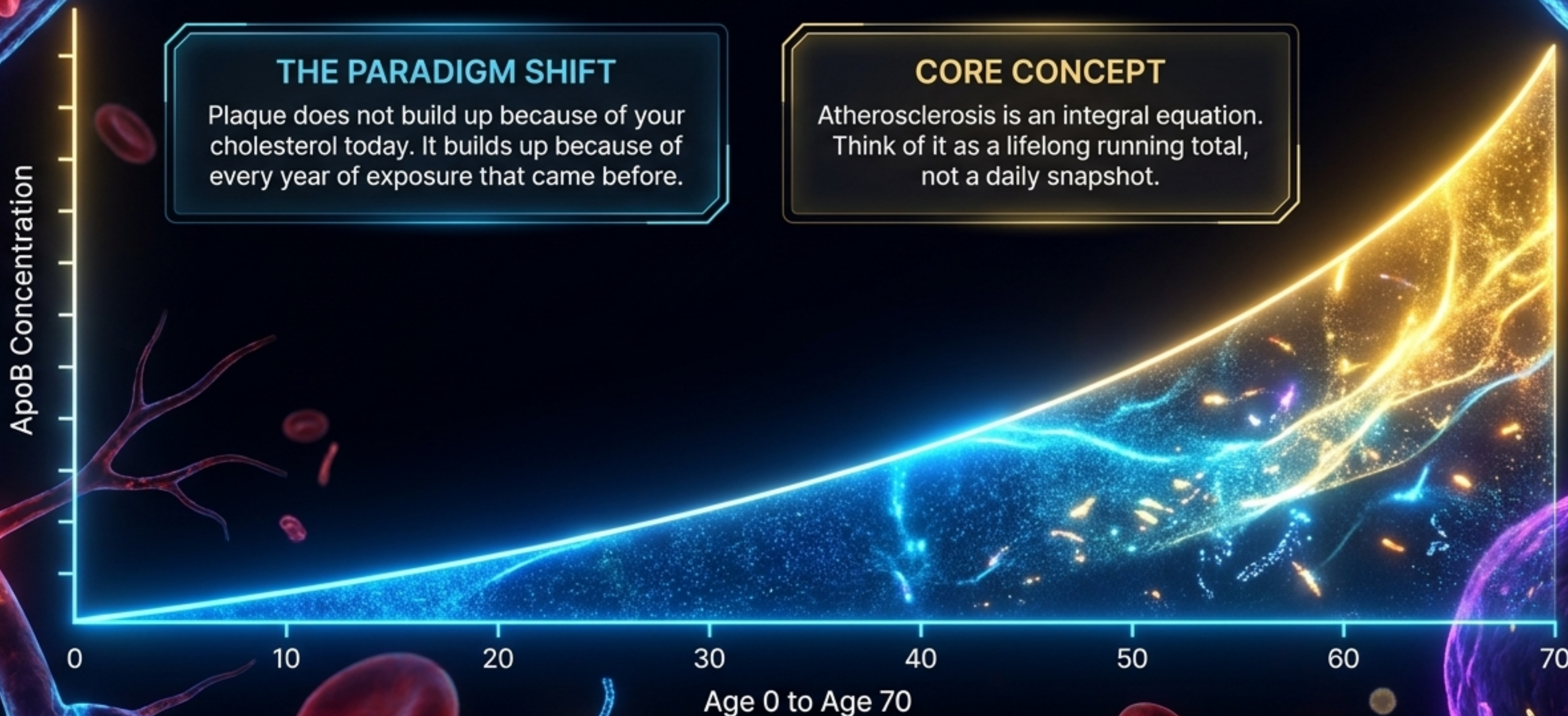
The Unifying Framework: Cumulative ApoB Exposure

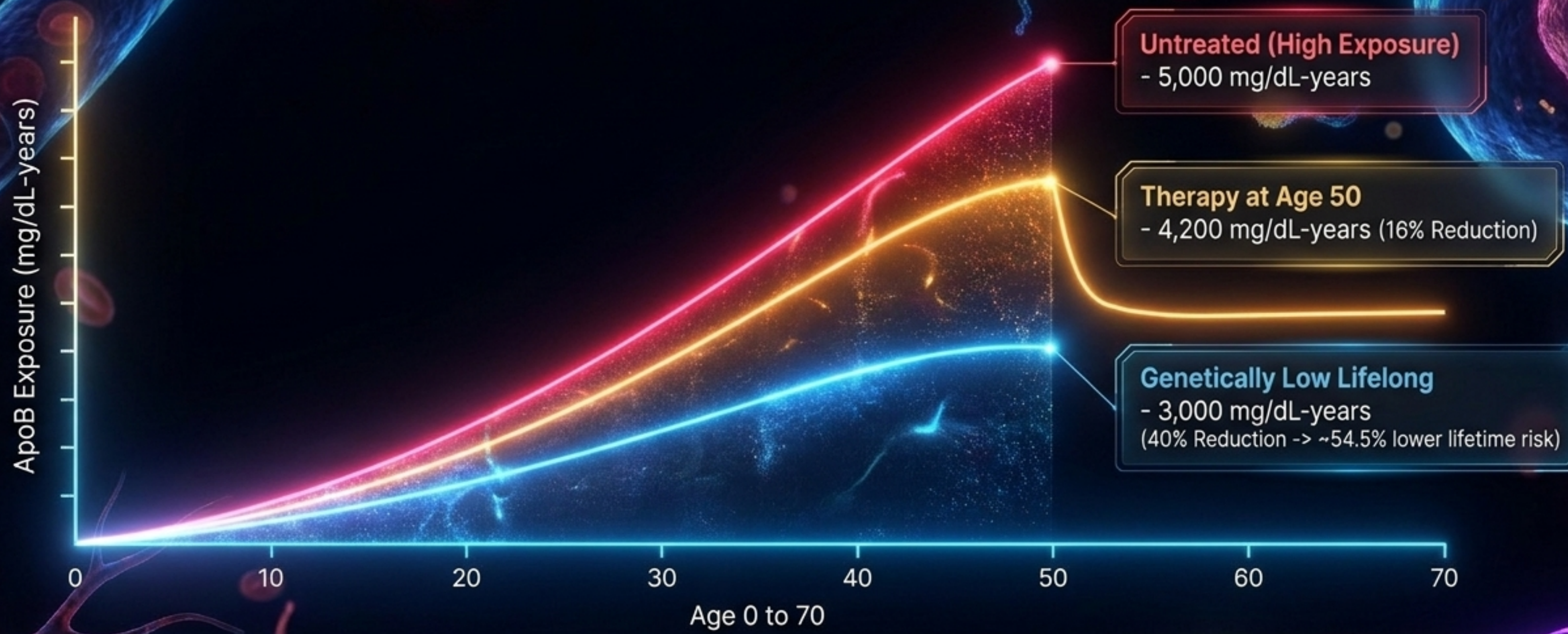
THE PARADIGM SHIFT

Plaque does not build up because of your cholesterol today. It builds up because of every year of exposure that came before.

CORE CONCEPT

Atherosclerosis is an integral equation. Think of it as a lifelong running total, not a daily snapshot.





THE POWER OF TIME

Duration is an active variable in risk. Starting treatment at age 40 does fundamentally more good than starting at 55, even if the daily pill is exactly the same, because you are intercepting the area under the curve earlier.

Re-evaluating Reference Values

Guidelines are not 'grades' for a test. They are context-dependent thresholds.

Established Disease (Very High Risk)

LDL < 55 mg/dL | ApoB < 60 mg/dL

High Risk (Multiple factors, subclinical plaque)

LDL < 70 mg/dL | ApoB < 70 mg/dL

Borderline / Intermediate Risk

LDL < 100 mg/dL | ApoB < 90 mg/dL

Note: The numbers do not perfectly match. An LDL of 70 corresponds to a population-median ApoB closer to 60, not 70. Guideline pairings are not percentile-equivalent.

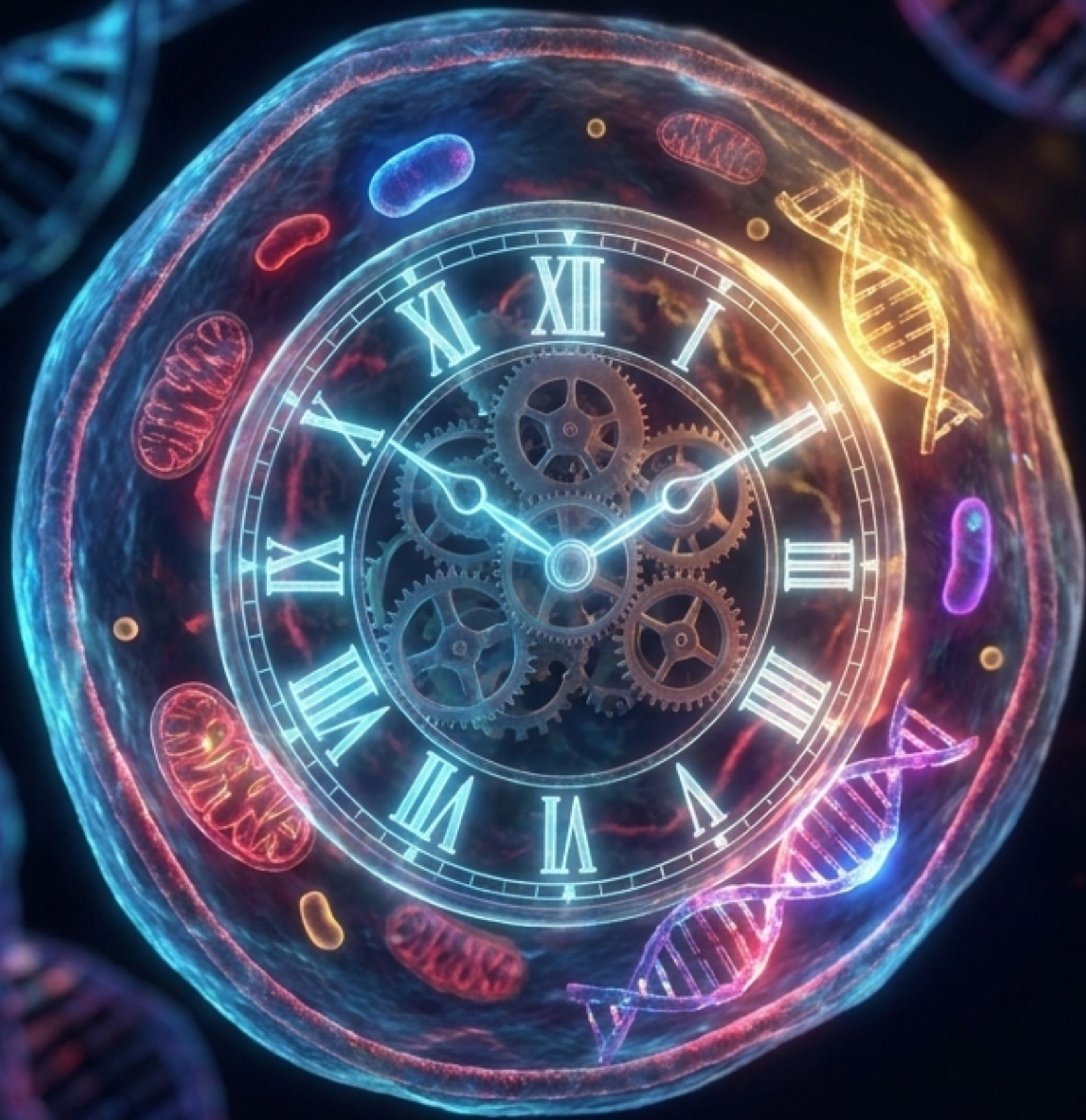
What Primary Prevention Looks Like Now

STEP 1: Measure the right things.

- Check Lp(a) at least once in a lifetime (≥ 125 nmol/L or 50 mg/dL is risk-enhancing).
- Measure ApoB directly when triglycerides exceed 200 mg/dL, in diabetic patients, or when achieved LDL-C is below 70 mg/dL.

STEP 2: Stratify with selective imaging.

- Use a coronary calcium score (CAC) to clarify the clinical picture.
- A CAC score of 100+ or a stenosis of $>50\%$ means the patient is no longer a primary prevention case—the disease is already established.



STEP 3: Escalate according to circumstance.

If a high-risk patient (resembling the VESALIUS-CV cohort) remains above target despite optimized statins, adding a PCSK9 inhibitor is now heavily validated to prevent first events.

STEP 4: Treat duration as an active variable

When you start matters just as much as how far the number falls. Pharmacotherapy should be considered in young adulthood if LDL-C is ≥ 160 mg/dL or a strong family history is present. Stop waiting for the risk to manifest.

CORE WARNING: The trial does NOT mean everyone gets an injection.

LIMITATIONS

DEMOGRAPHICS

The VESALIUS-CV population was 93% White, limiting broad generalization.

MONOTHERAPY UNPROVEN

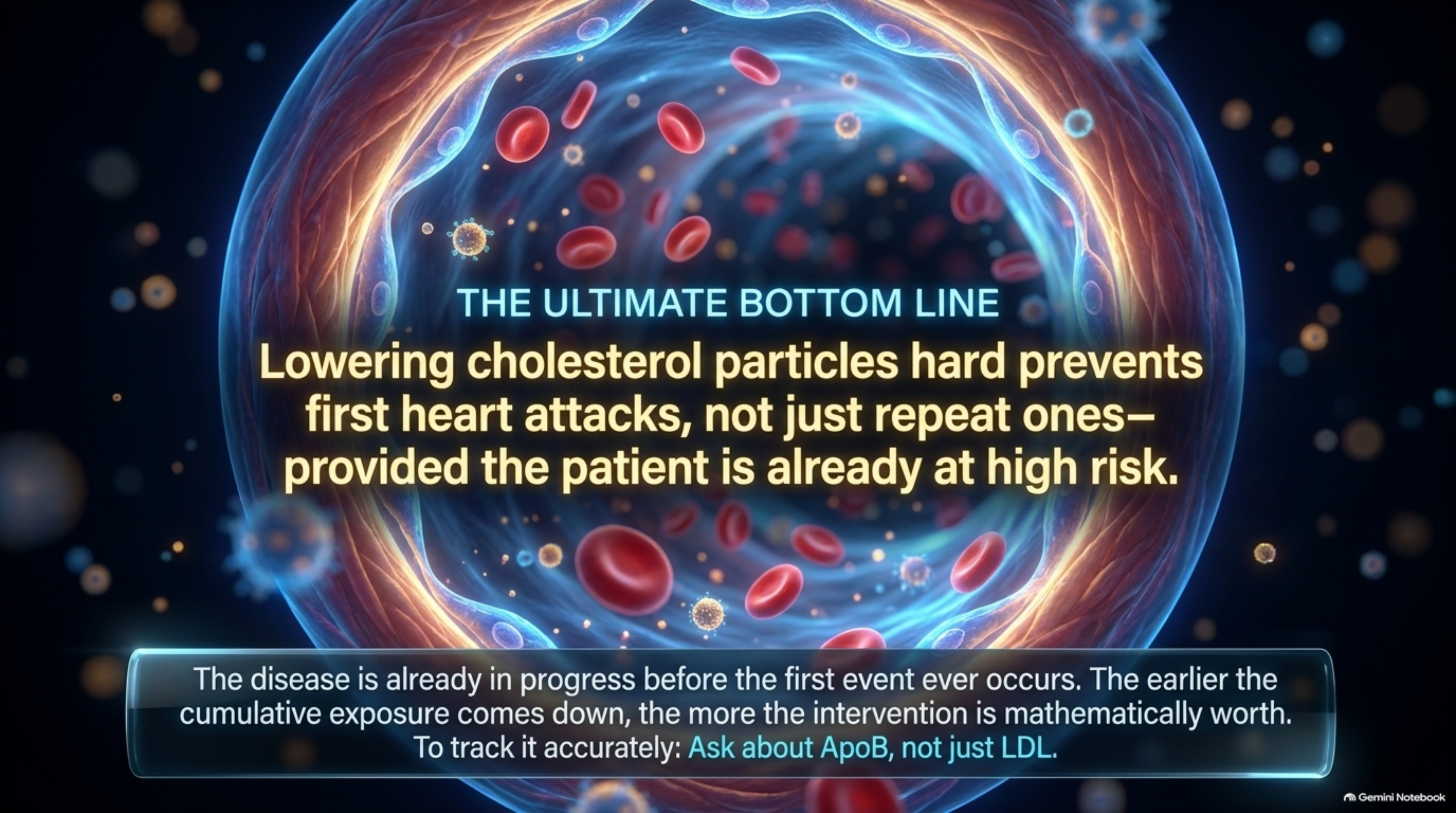
Too few people in the trial were off statins to definitively prove the shot works perfectly on its own in primary prevention.

RISK PROFILE

The trial validates escalation in high-risk individuals. Nothing in the data suggests an average-risk person with ordinary cholesterol needs an injection.

THE MATH IS CONCEPTUAL

The “ApoB-years” cumulative framework is highly useful, but it has not yet been validated into an exact mathematical clinical calculator.

A stylized illustration of a blood vessel, possibly an artery, shown in cross-section. The vessel wall is depicted with blue and orange wavy lines, suggesting a textured or inflamed surface. Inside the vessel, numerous red blood cells are visible as red, biconcave discs. Scattered throughout the vessel lumen are several small, yellowish, spherical particles, representing cholesterol or lipoproteins. The background is dark blue with faint, out-of-focus light spots.

THE ULTIMATE BOTTOM LINE
**Lowering cholesterol particles hard prevents
first heart attacks, not just repeat ones—
provided the patient is already at high risk.**

The disease is already in progress before the first event ever occurs. The earlier the cumulative exposure comes down, the more the intervention is mathematically worth.
To track it accurately: **Ask about ApoB, not just LDL.**