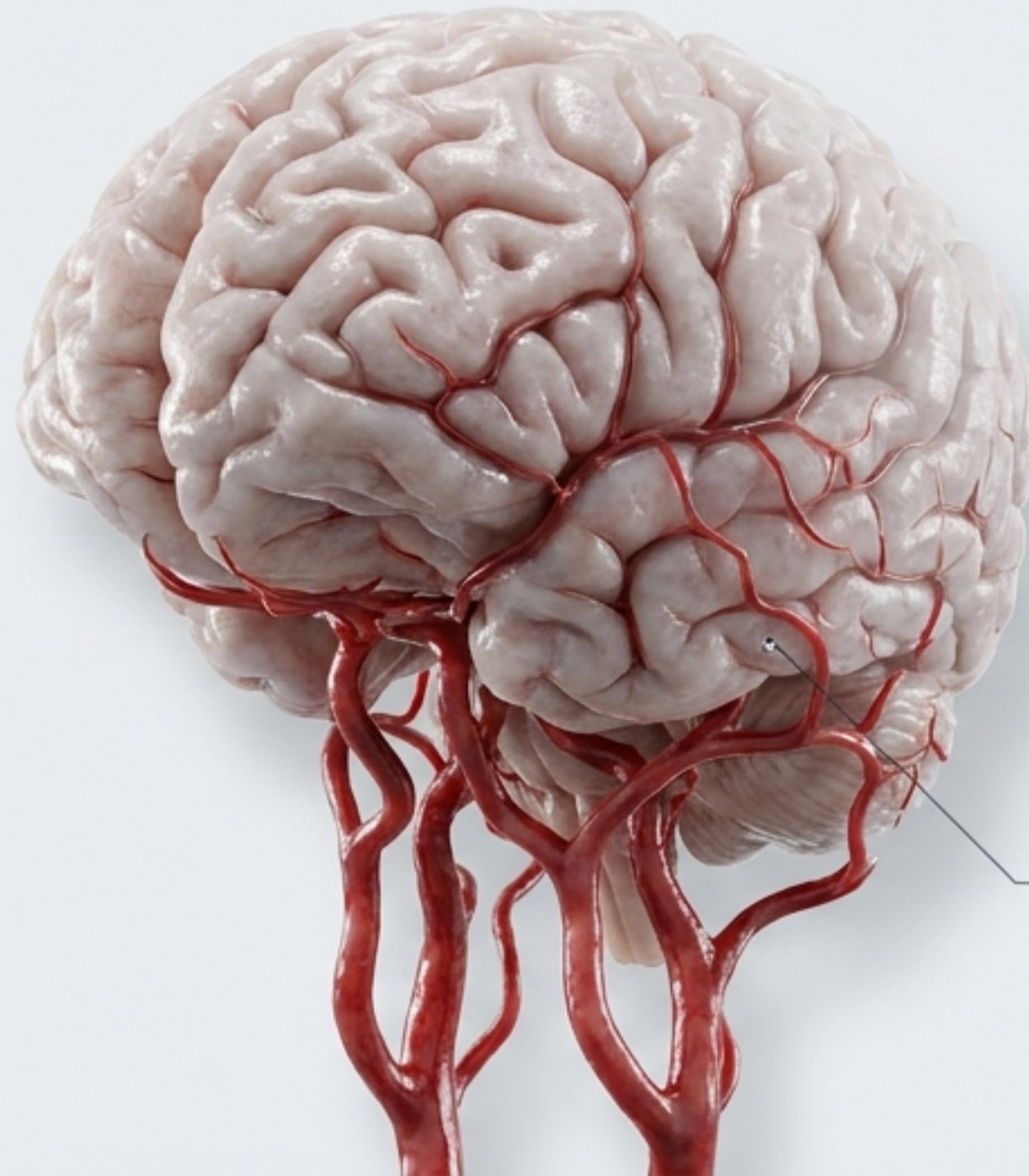


The Cardiorenal-Cerebral Axis

Apolipoprotein B-Driven Atherosclerosis as a Causal Basis for Alzheimer's Disease



A Synthesis of Mendelian
Randomization, Longitudinal
Imaging, and Neuropathology

The Usual Suspect: The Neurocentric Model

The Assumption

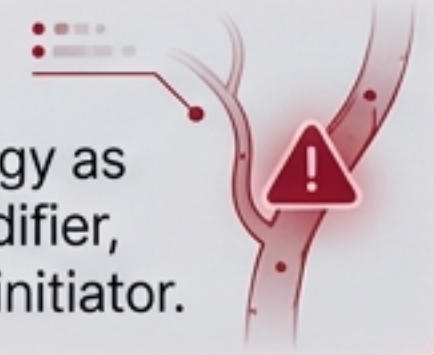
Alzheimer's is primarily initiated by the overproduction or misfolding of amyloid- β .

The Treatment Focus

Remove the proteinopathy to halt cognitive decline.

The Blind Spot

Treats systemic vascular pathology as merely a frequent secondary modifier, ignoring its role as the upstream initiator.



The Target:
Amyloid- β & Tau

The Reality of the Aged Brain: Mixed Pathology is the Rule

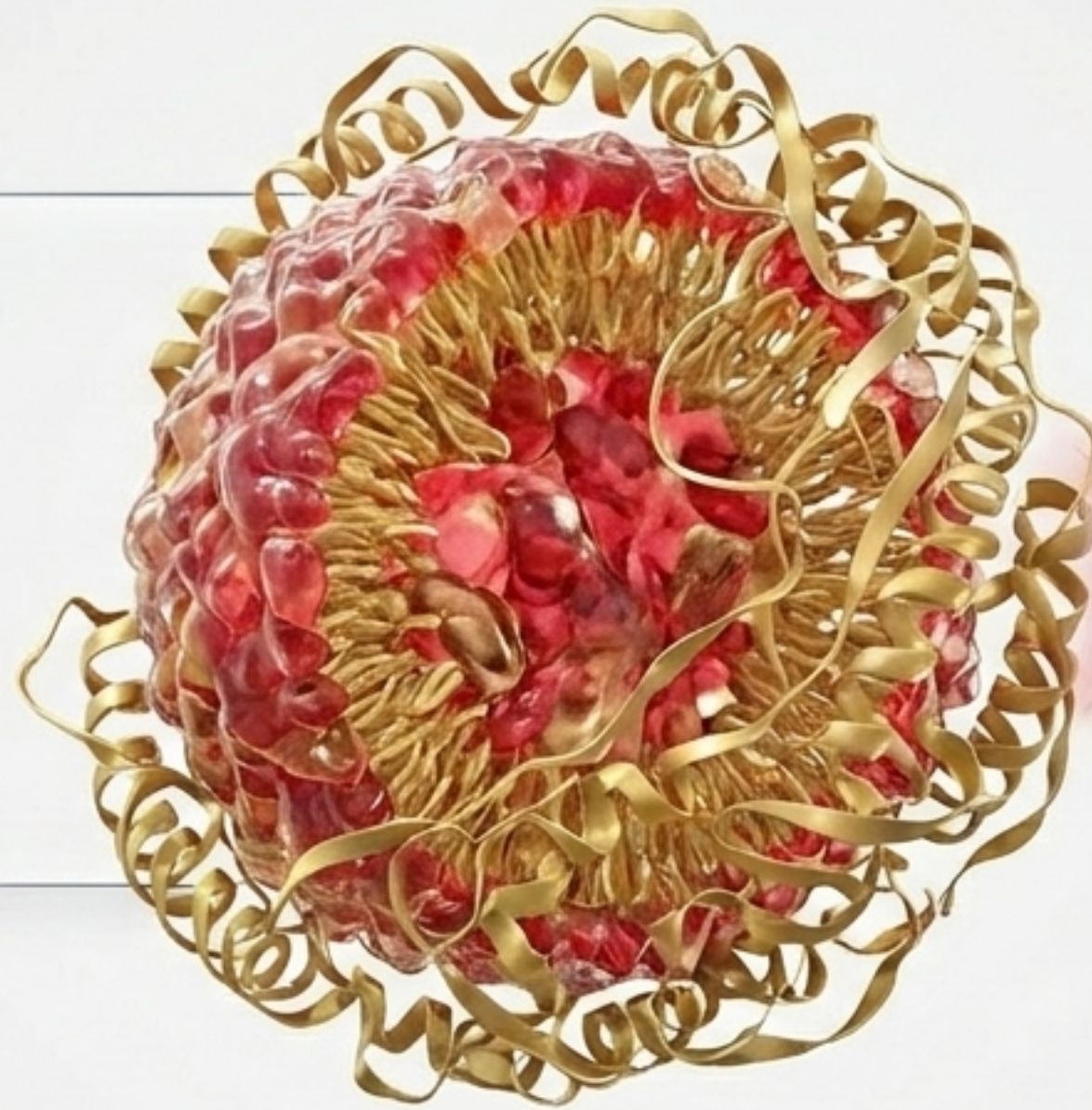
Community-based autopsy studies prove the categorical distinction between pure Alzheimer's and vascular dementia is empirically untenable.

	Alzheimer's Disease	Vascular Dementia	Mixed Dementia
Primary proteinopathy	A β /Tau	Minimal/Absent	Extensive A β & Tau
Vascular lesions	Often present (CAA)	Large infarcts, WMH	Combined vascular & proteinopathic
Hemodynamics	Reduced CBF	Focal ischemia	Chronic hypoperfusion + stiffness
Lipid driver	ApoB link via injury	Strong LDL-C/ApoB	Lifelong high ApoB burden

The Mastermind: Apolipoprotein B (ApoB)

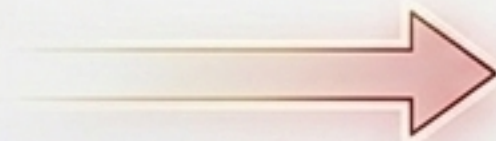
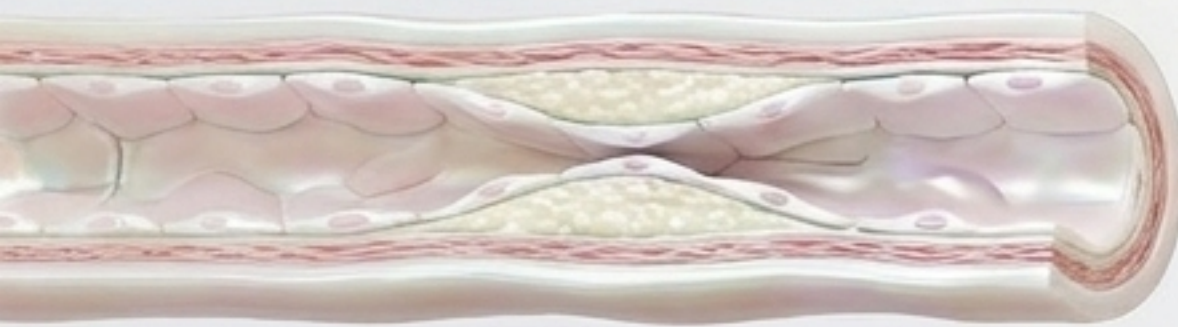
Core Thesis:

Alzheimer's disease is, in a substantial subset of patients, the late-stage neurological manifestation of decades-long vascular-lipid-inflammatory injury.



HUD
HOR

apoB-100
Structural Protein



Elevated ApoB Particles → Subendothelial Retention



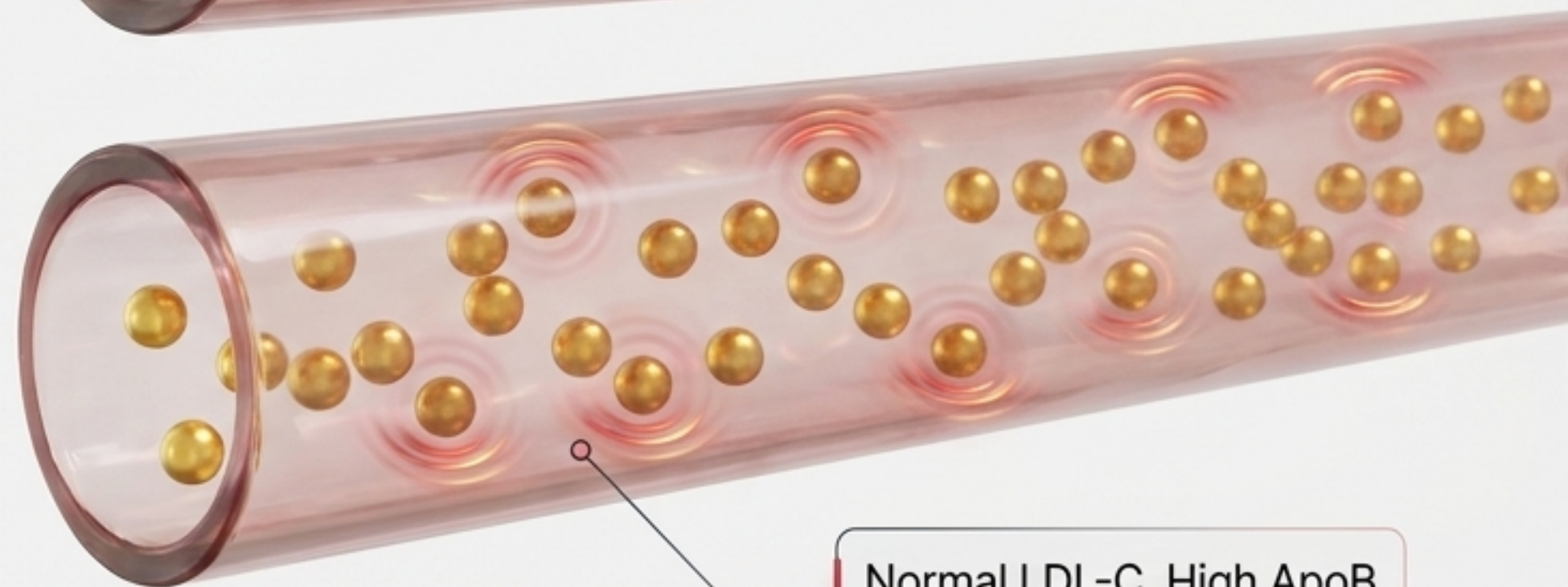
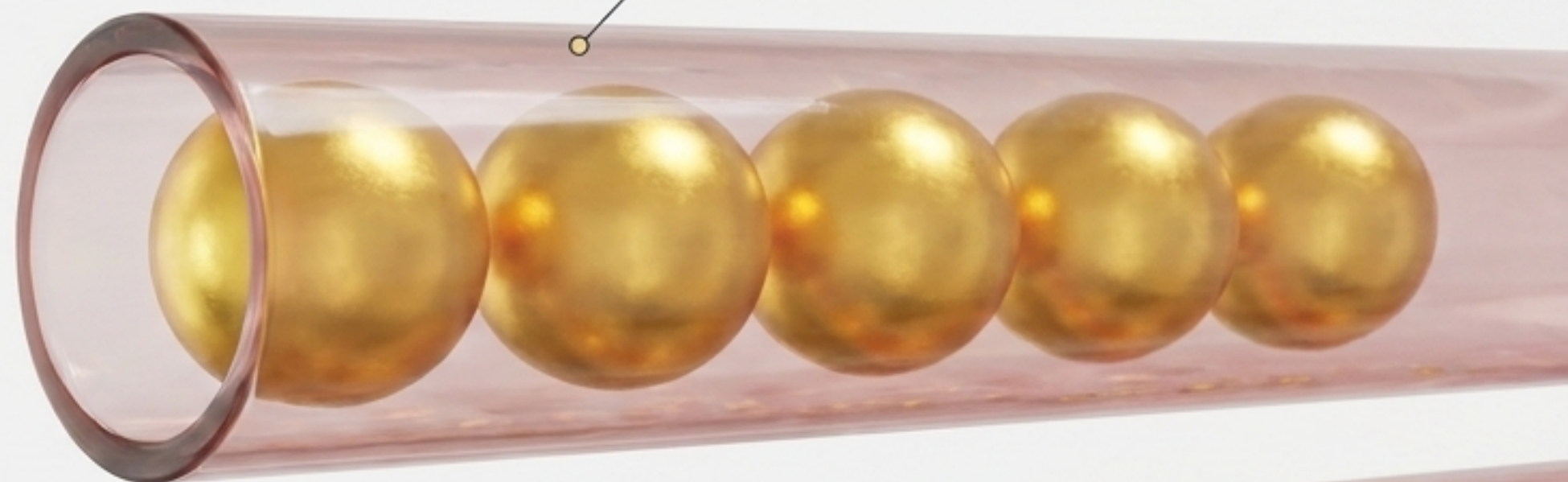
Why Count Matters More Than Mass

Key Insight:

The probability of a lipoprotein particle entering the arterial intima and being retained is a function of particle concentration, not the cholesterol mass inside the particle.

Takeaway:

When ApoB is conditioned upon, LDL-C loses its independent causal information for atherosclerotic disease.



High LDL-C, Low ApoB
(Low Particle Count)

Normal LDL-C, High ApoB
(High Particle Count)

The Lipid Biomarker Showdown

LDL-C

- Measures cholesterol mass.
- **Flaw:** Misses risk in discordance.

Non-HDL-C

- Practical surrogate for total atherogenic burden (LDL, VLDL, IDL, Lp(a)).

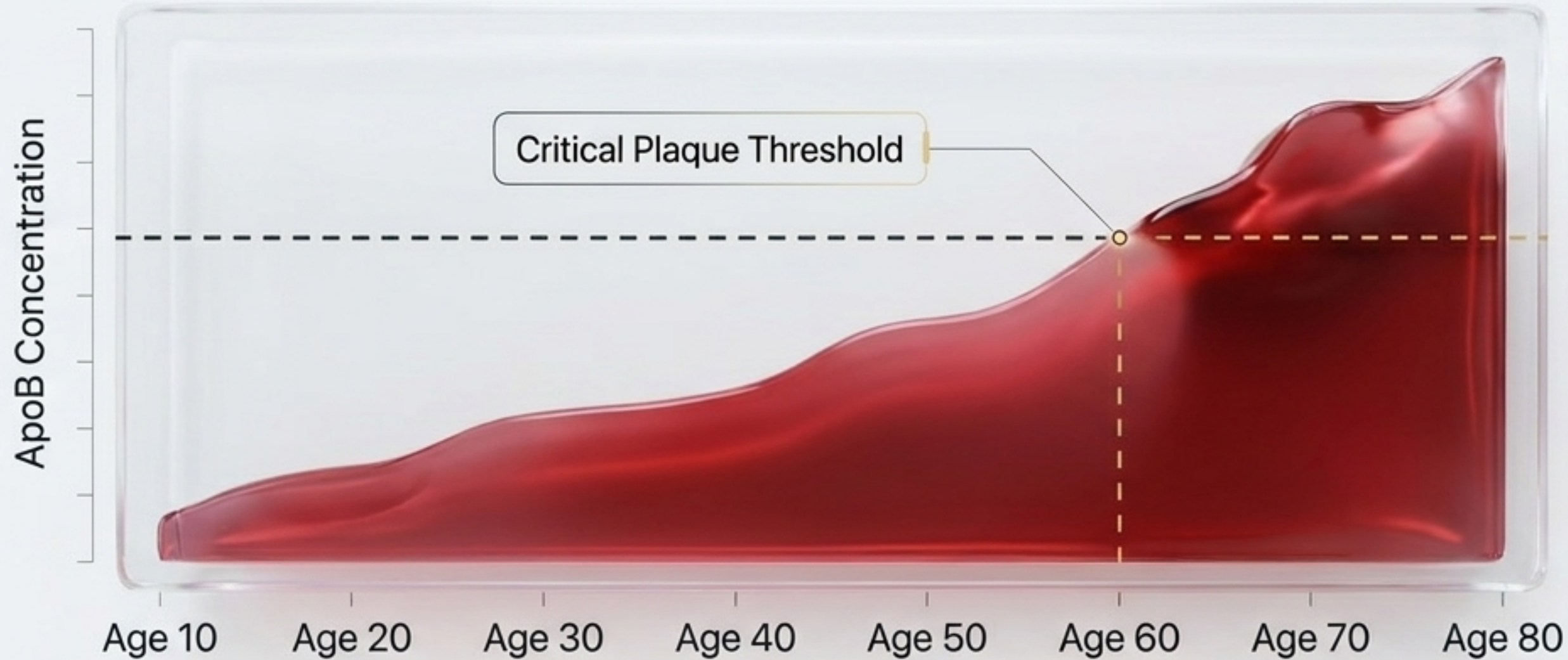
Lp(a)

- LDL-like particle with apolipoprotein(a).
- **Trait:** Independent, pro-thrombotic genetic risk factor.

ApoB

- Total count of atherogenic particles.
- **Status:** The superior predictor of particle retention and lifetime vascular injury.

The Weapon: Cumulative Exposure (ApoB-Years)



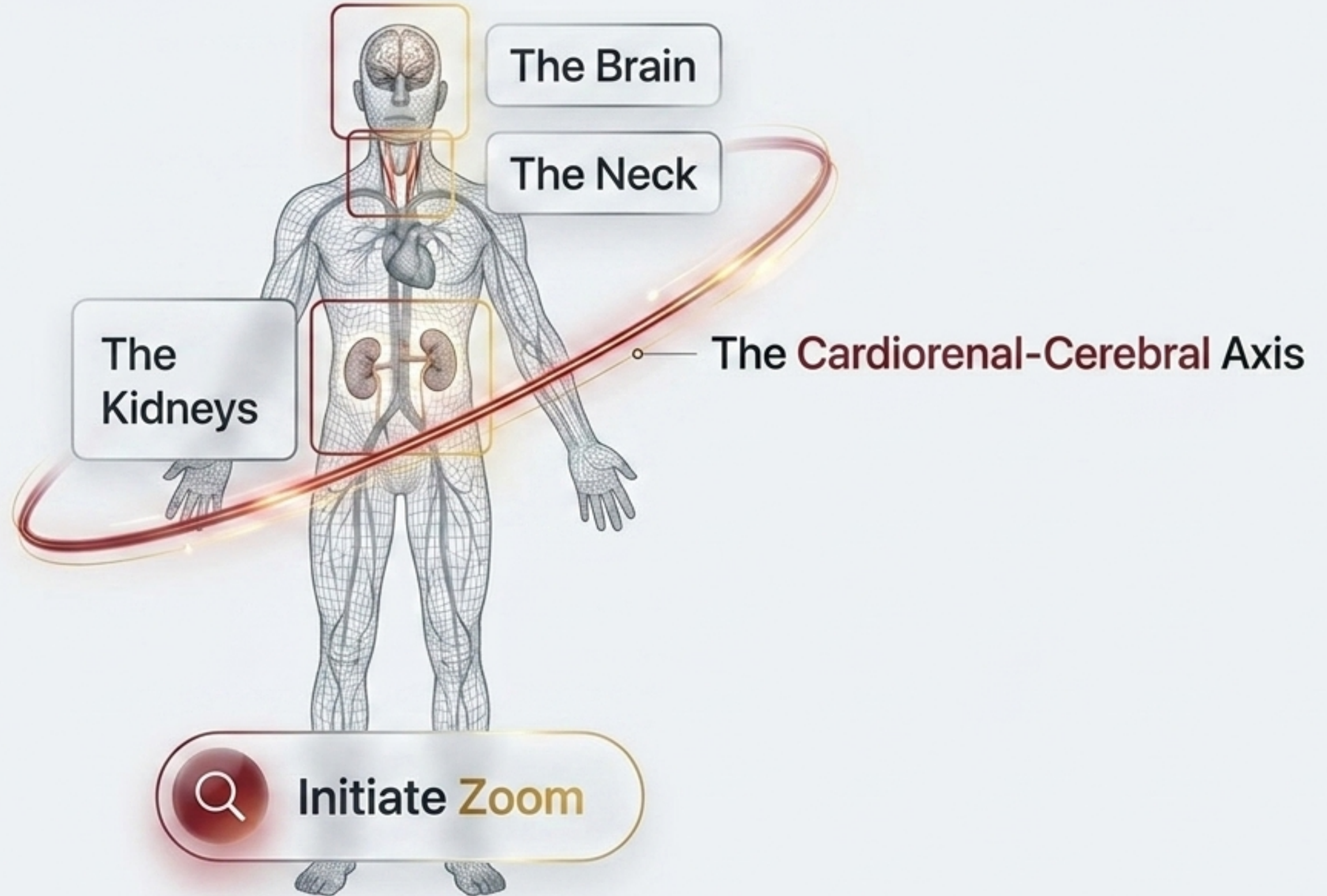
- Atherogenesis begins in childhood. Risk is driven by the **integral of ApoB** over time.
- Mid-life or late-life measurements are insufficient. Total lifetime exposure dictates the injury.



Subendothelial Retention
→ Oxidative Modification
& Inflammation

Act III: The Anatomical Journey

Atherosclerosis is a systemic disease, but local anatomy dictates the nature of the neurological damage.



Renal Station: The Pressure Generator

Anatomy Focus

Aortic orifice / proximal one-third of the main renal artery.

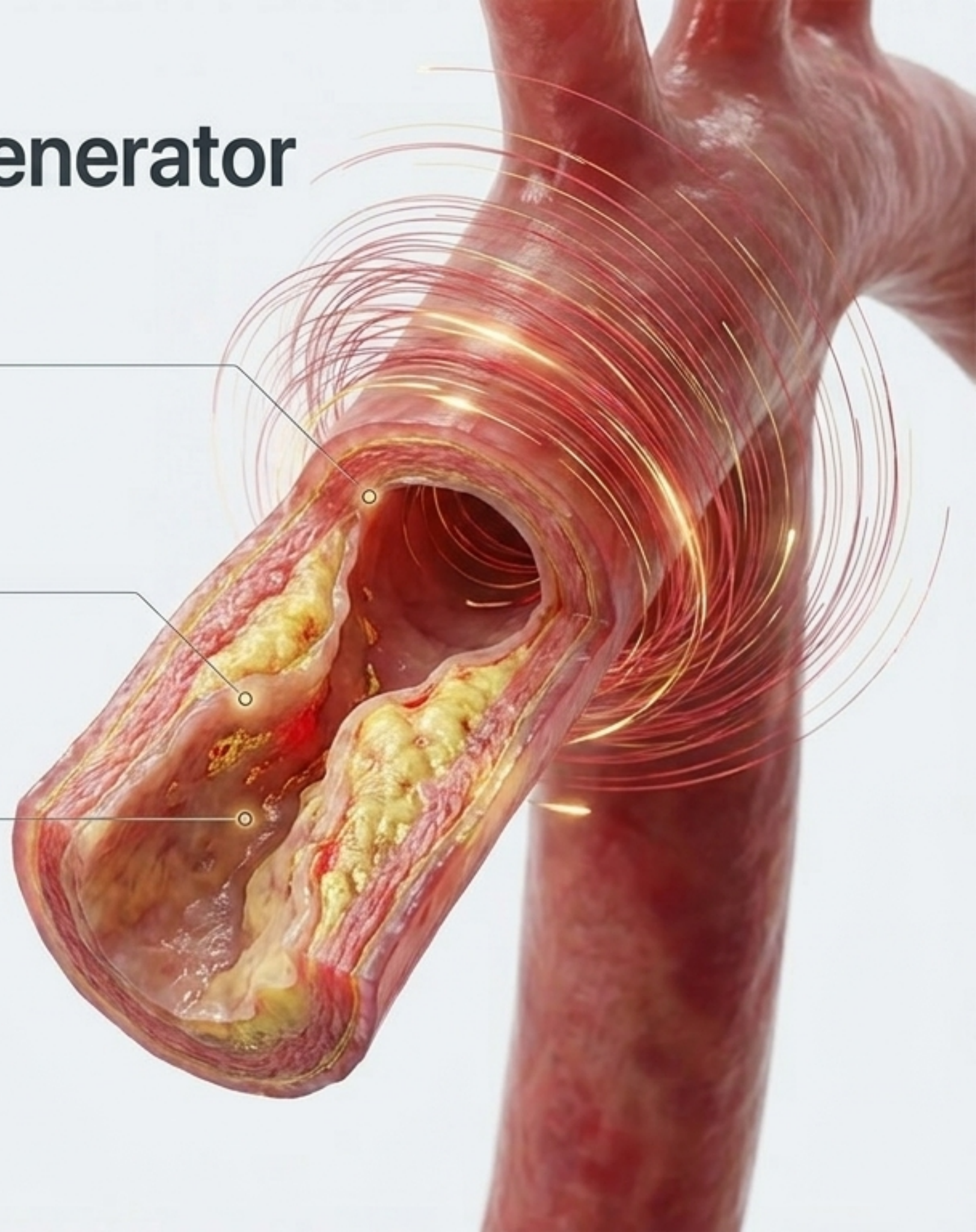
Mechanism

Atherosclerotic Renal Artery Stenosis (RAS) activates the renin-angiotensin-aldosterone system.

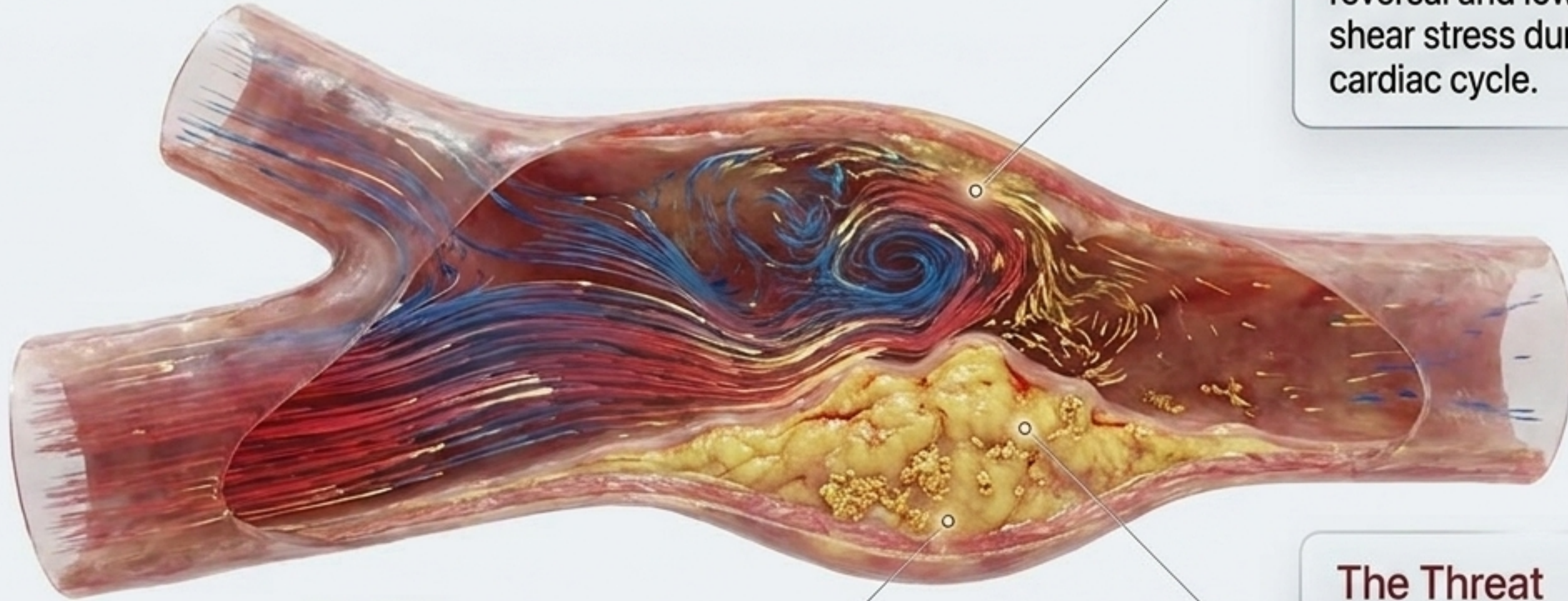
Consequence

Secondary hypertension. Chronic high pressure accelerates damage to delicate cerebral microvasculature.

Target: Chronic Kidney Disease - Independent driver of systemic inflammation and uremic endothelial toxicity.



Carotid Station: The Embolic Engine



Hemodynamics



Complex geometry causes flow reversal and low/oscillatory wall shear stress during the cardiac cycle.

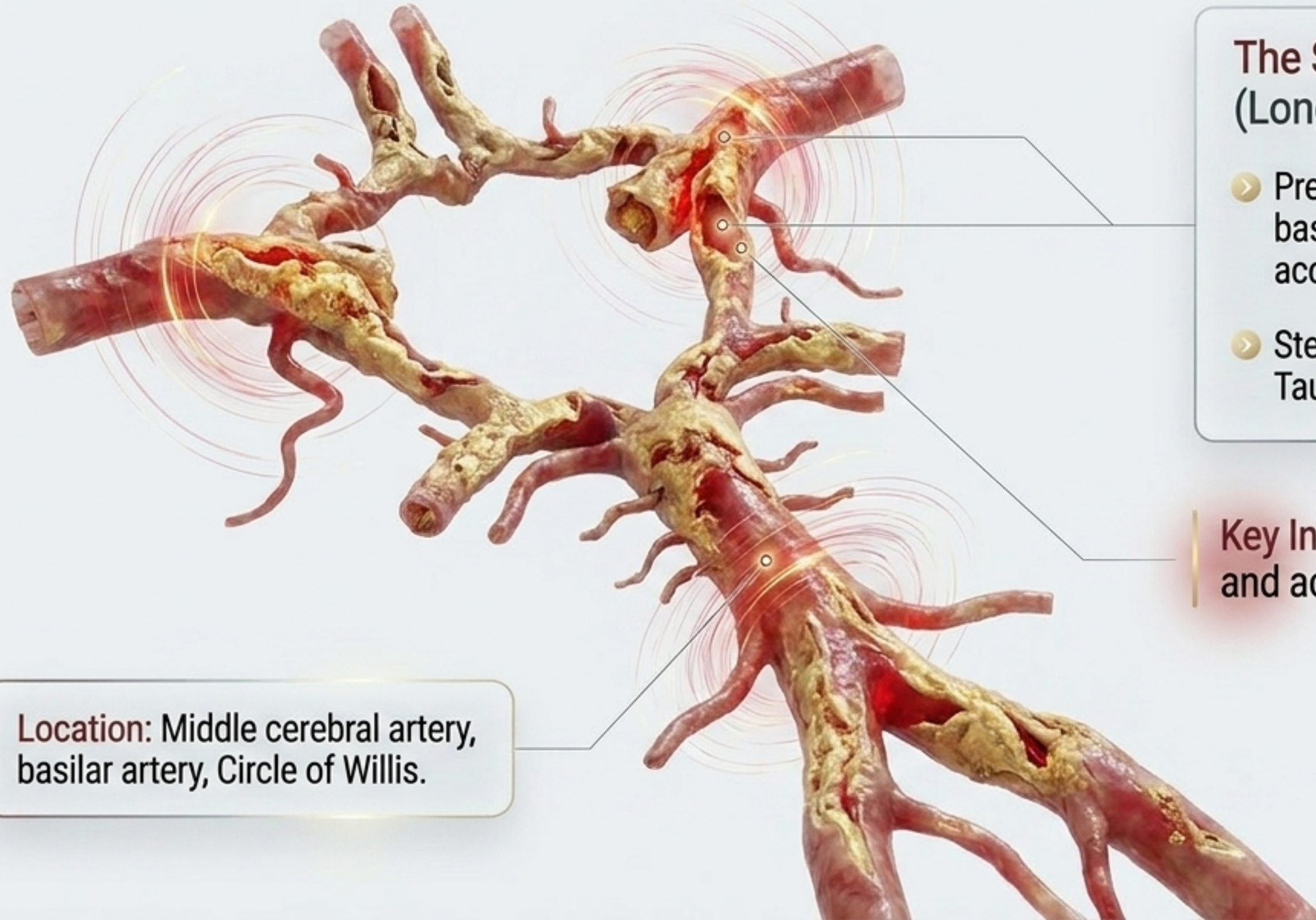
Clinical Consequence

Recurrent microemboli, lacunar infarction, and microbleeds — the core substrates of Vascular Cognitive Impairment.

The Threat

High-velocity flow dislodges thrombi from ulcerated plaques.

Intracranial Station: The Ground Zero for Proteinopathy



The Smoking Gun (Longitudinal PET Evidence)

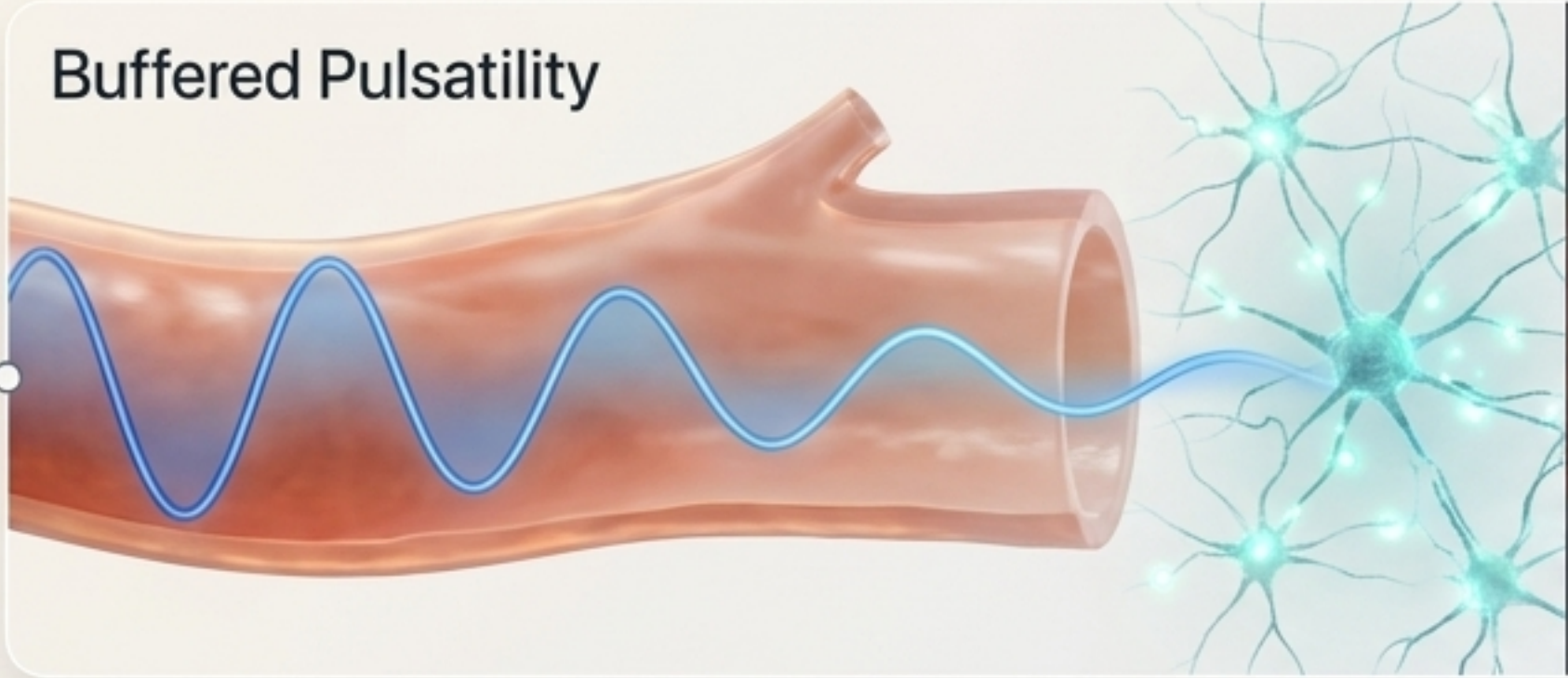
- Presence of any ICAD stenosis at baseline predicts greater Amyloid- β accumulation over 4 years.
- Stenosis in ≥ 2 arteries predicts greater Tau deposition over 2 years.

Key Inference: Vascular injury precedes and accelerates protein deposition.

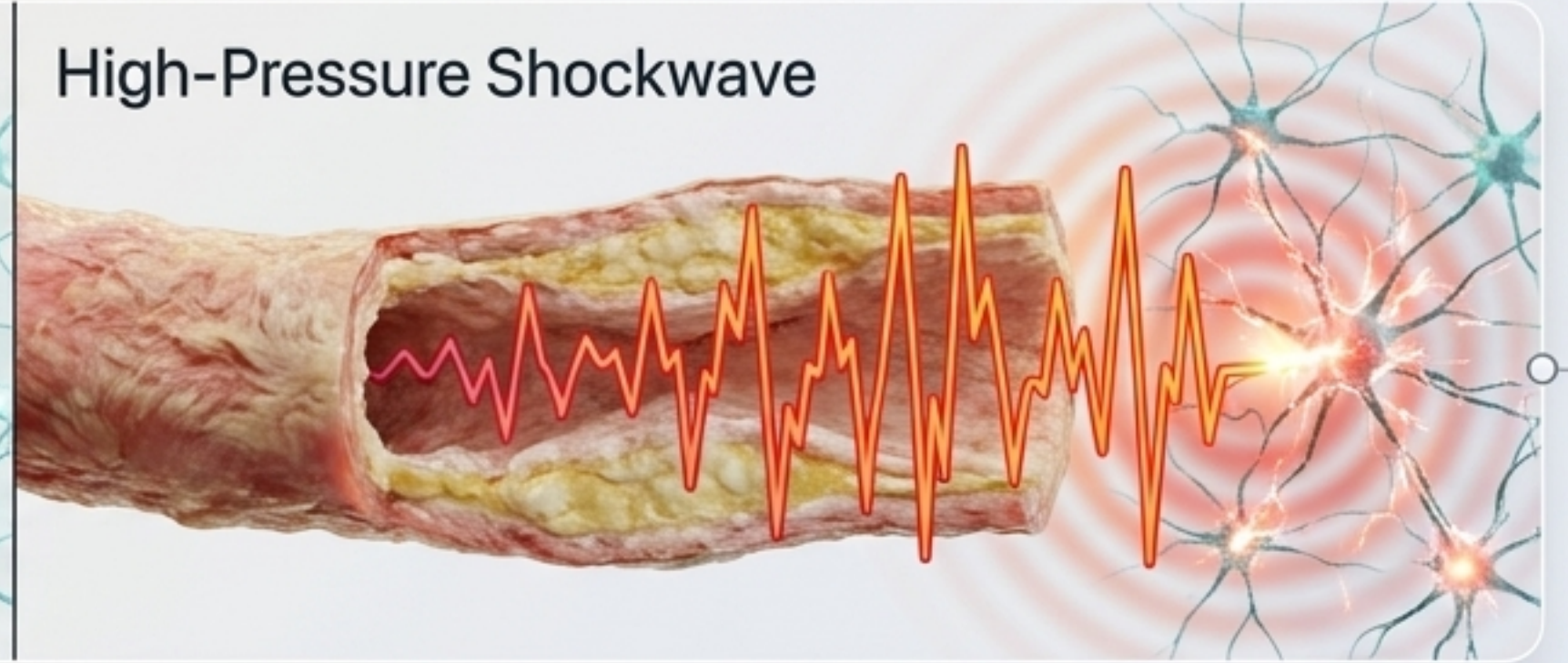
Location: Middle cerebral artery, basilar artery, Circle of Willis.

The Hemodynamic Shockwave

Buffered Pulsatility



High-Pressure Shockwave



Mechanism:

Arterial stiffness in the proximal aorta and carotids transmits unbuffered, high-pressure pulsatility directly into the low-resistance cerebral microvasculature.

Result:

Chronic hypoperfusion, metabolic stress, and activation of the NLRP3 inflammasome.

Carotid artery, Slide 7



Endothelial Activation & Narrowing → Hyper-pulsatility & Hypoperfusion

Breaching the Blood-Brain Barrier

The Genetic Bridge:

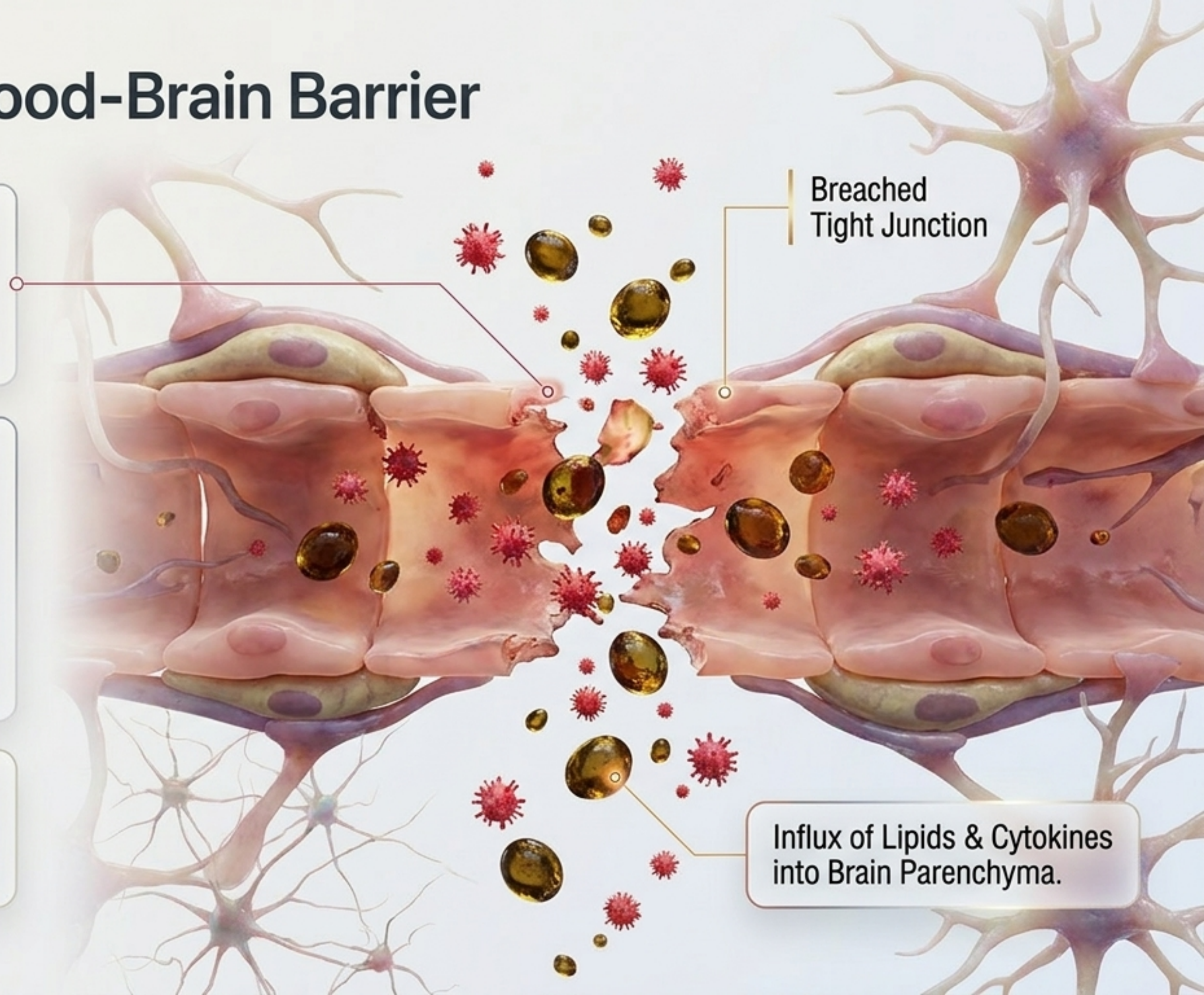
Enter the APOE ϵ 4 allele (the largest common genetic risk factor for late-onset AD).

Mechanism:

APOE ϵ 4 operates substantially through cerebrovascular pathways, causing blood-brain barrier breakdown that precedes and predicts cognitive decline independently of amyloid and tau.

Synthesis:

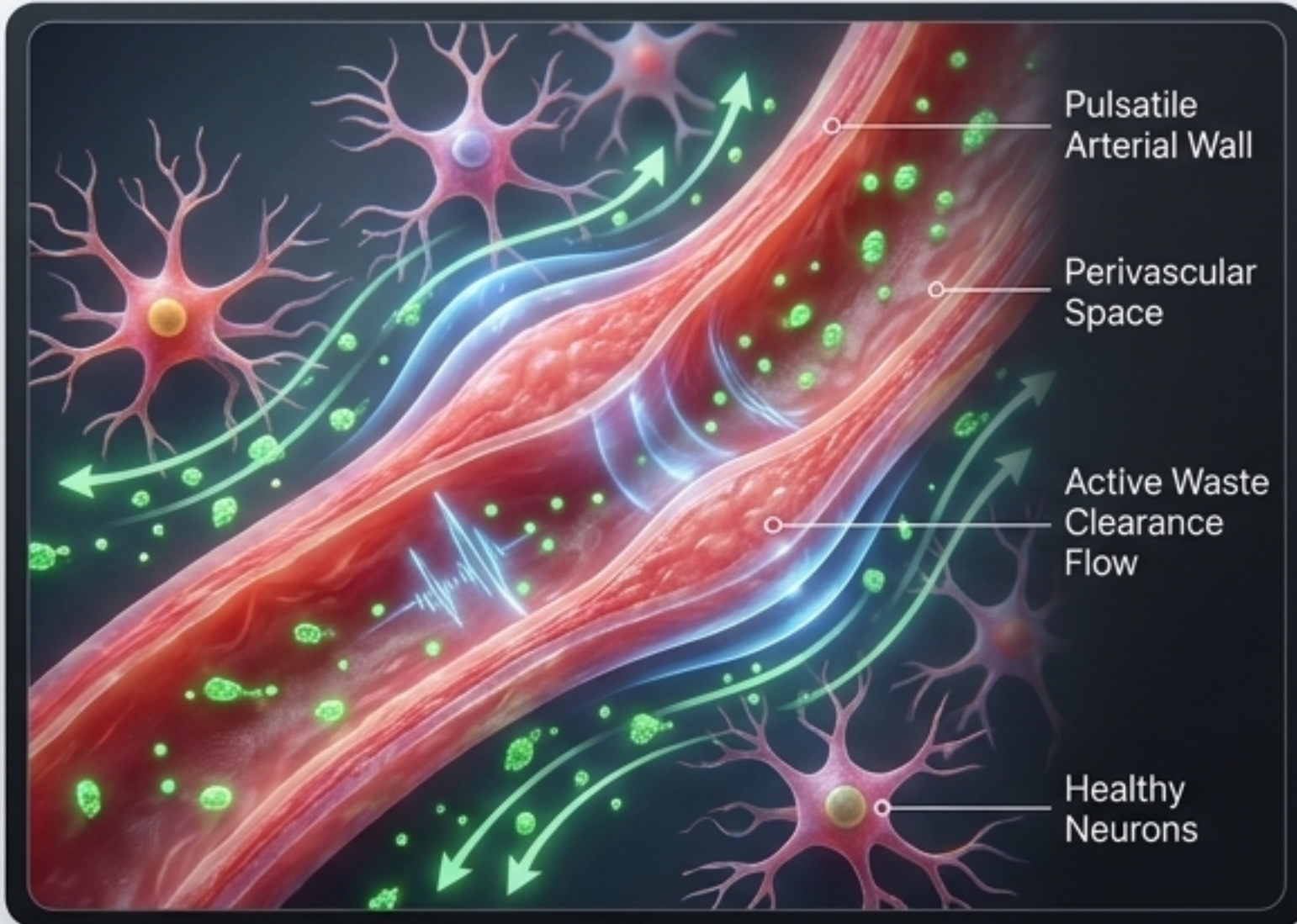
Genetic risk and vascular risk are intertwined, not competing.



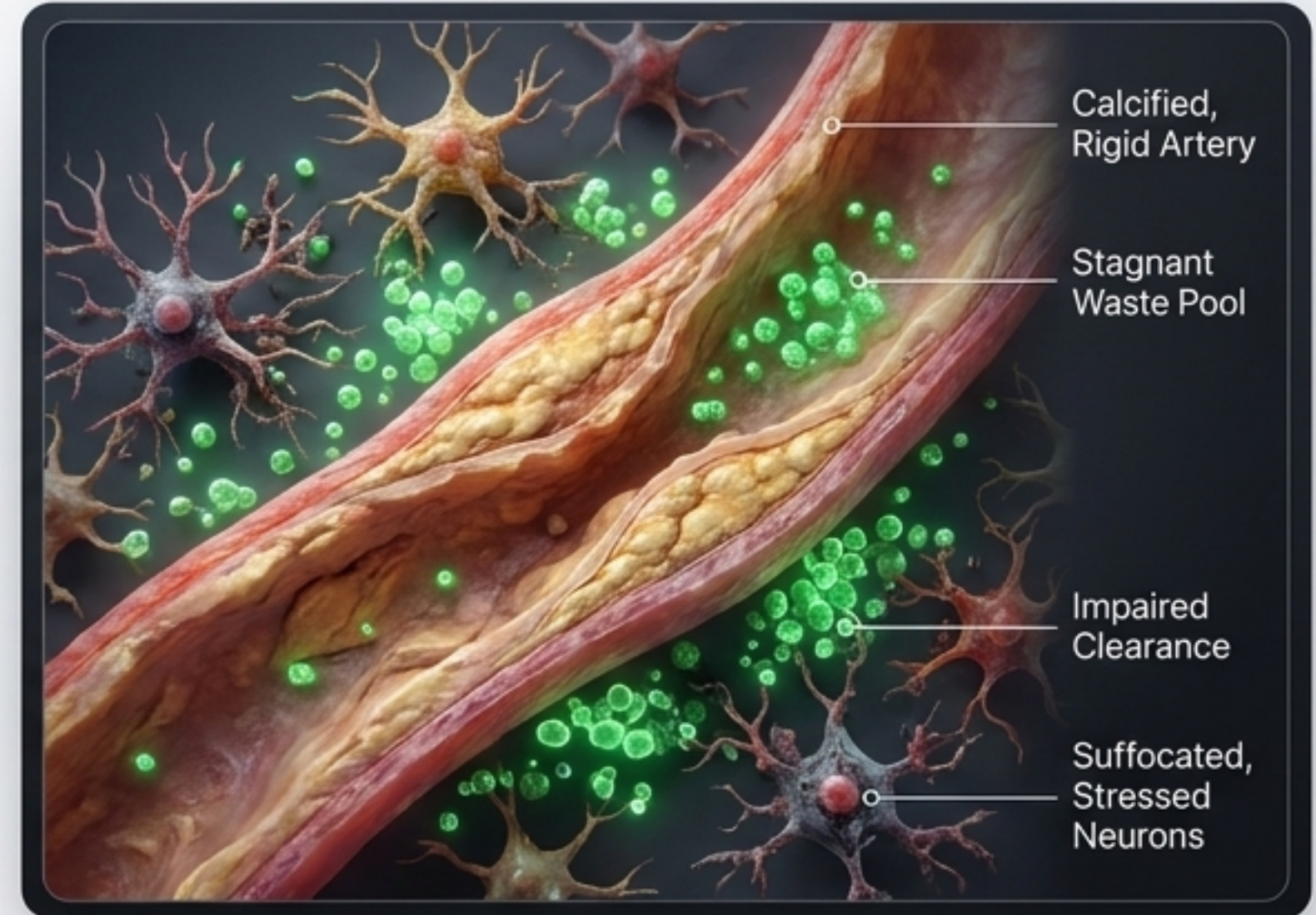
Breached
Tight Junction

Influx of Lipids & Cytokines
into Brain Parenchyma.

Glymphatic Failure: The Broken Trash Compactor



Active Clearance (Pulsatile Pump)



Clearance Failure (Stiffened Artery)

≡ **The Physiology:** The brain's glymphatic waste clearance system is physically driven by arterial pulsatility.

⚡ **The Pathology:** When atherosclerosis stiffens the arteries, the pump breaks.

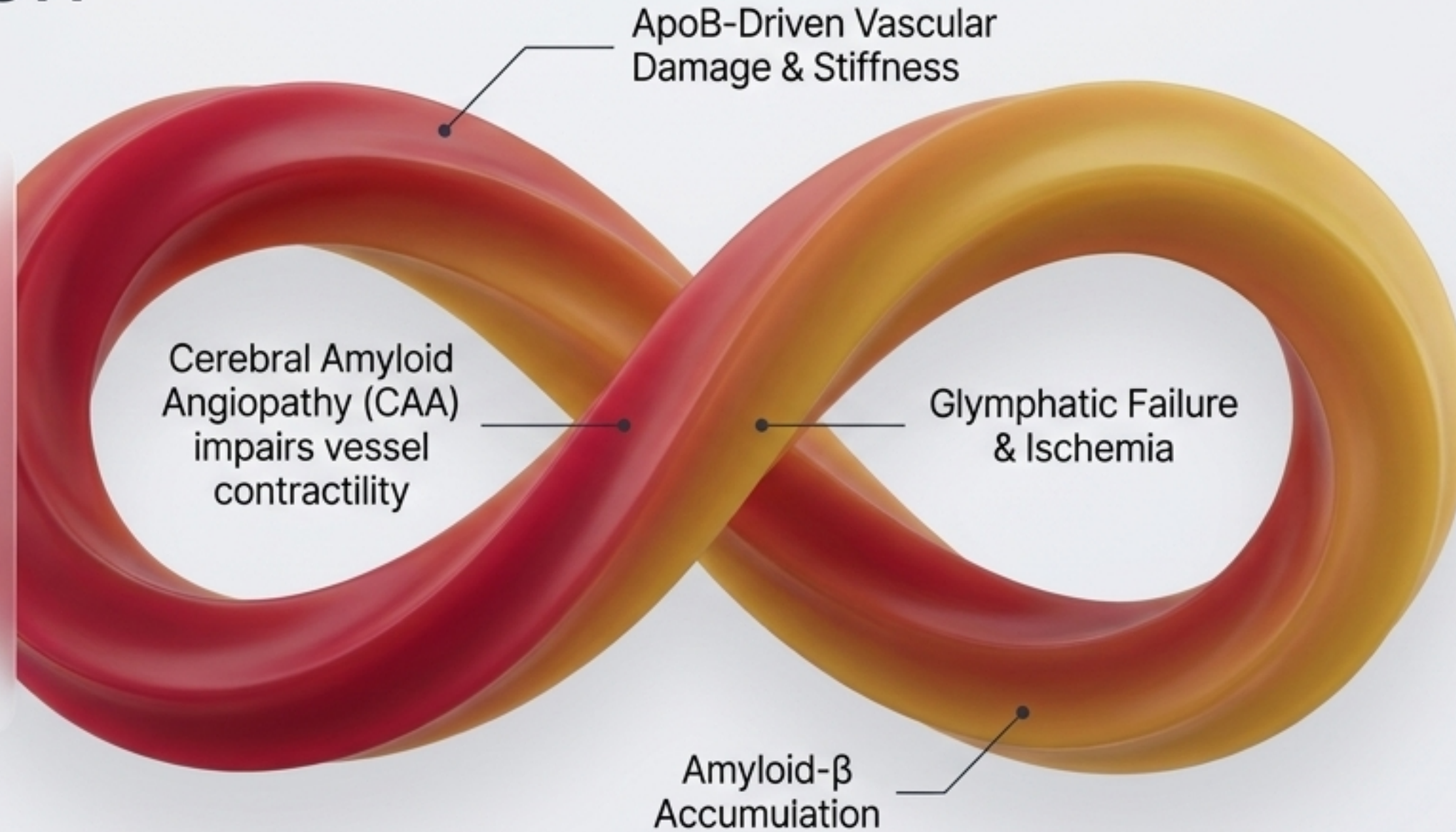
⊖ **The Result:** Neurotoxic proteins (Amyloid- β and Tau) accumulate due to impaired clearance, not just overproduction.

The Fatal Loop: Amplification, Not Exclusion

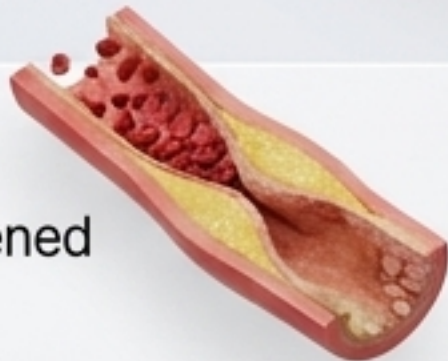
The Aha Moment:
Amyloid is not merely
downstream debris.

Vascular damage promotes
Amyloid accumulation,
which physically coats the
vessels (CAA), causing
more vascular damage and
neuroinflammation.

They bidirectionally amplify.



Heavily diseased,
calcified, and stiffened
artery, Slide 12



Impaired Glymphatic Clearance \leftrightarrow Amyloid/Tau Accumulation



Reconciling with the 2024 NIA-AA Criteria

The Current Standard

The 2024 criteria define AD biologically by core amyloid and tau biomarkers, independent of clinical syndrome.

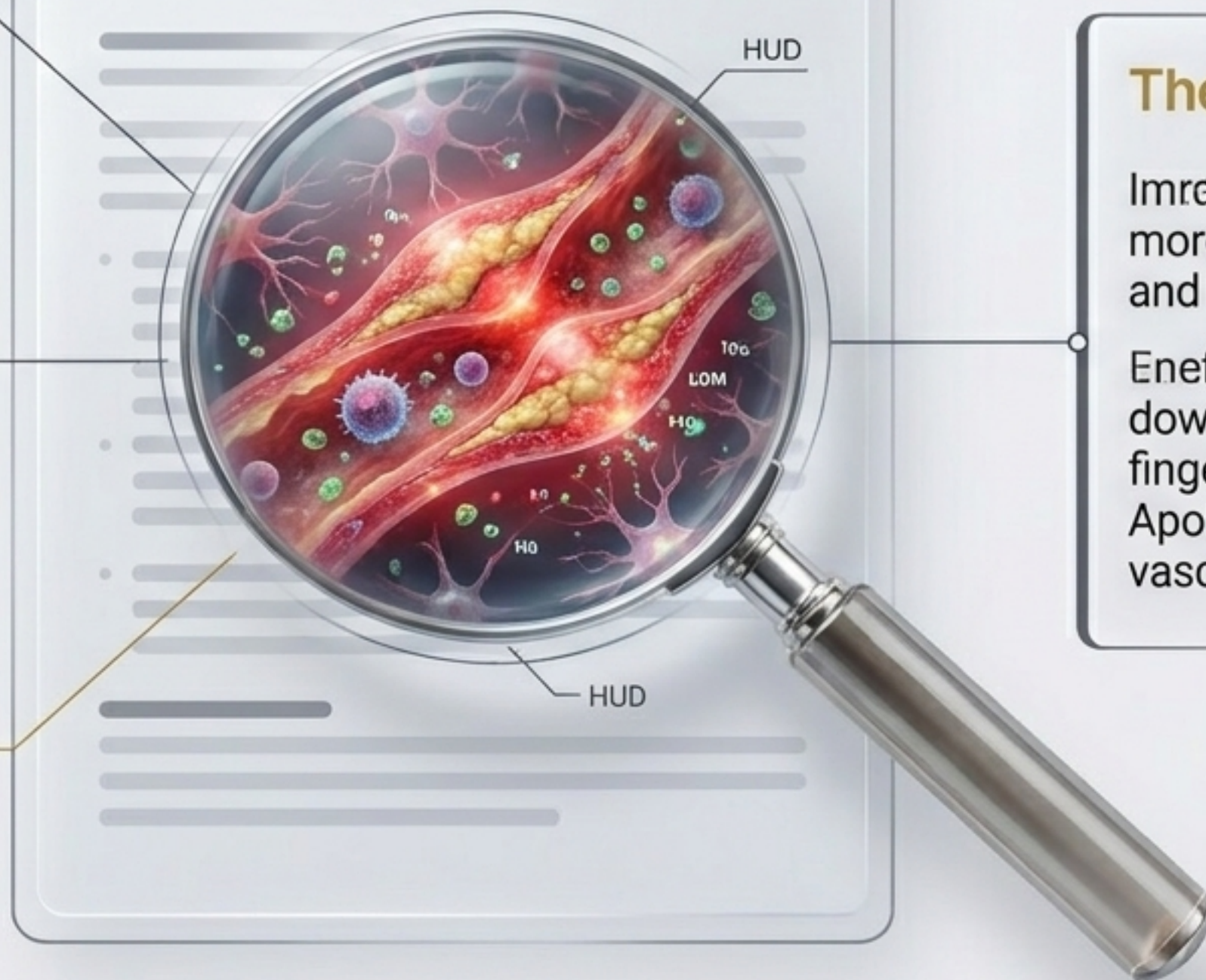
The Clarification

These criteria are a diagnostic framework, not an etiologic claim.

The Synthesis

Defining AD by its downstream biomarker fingerprint is fully compatible with attributing that fingerprint to decades of upstream ApoB-driven cerebrovascular injury.

2024 NIA-AA Revised Criteria



The Synthesis

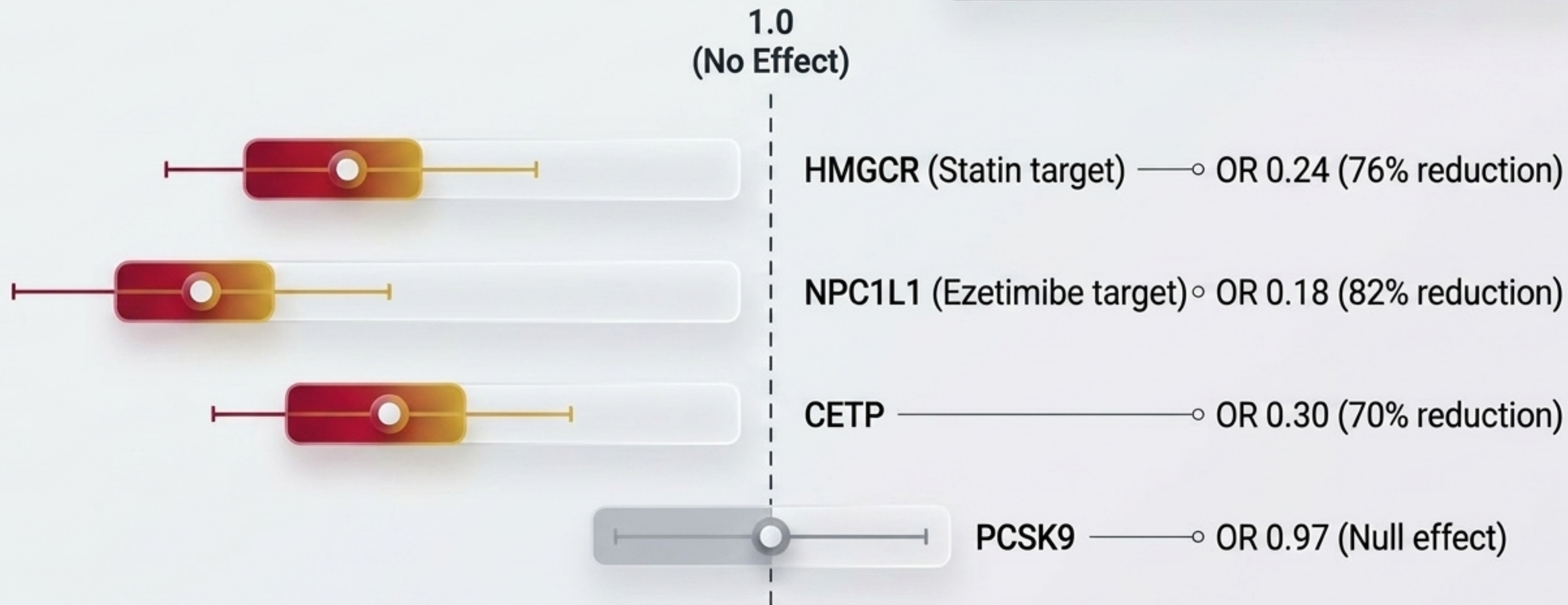
Imrdining AD by its morostroatic cytokine, and ciherstenicy.

Enefining AD by its downstream biomarker fingerprint is in decades ApoB-driven cerebrovascular.


The Ultimate Trial: Mendelian Randomization

The Method:

Leveraging random genetic assortment to mimic lifelong randomized controlled trials. Data from >1 million individuals.



Note: PCSK9 null effect points to target-specific cerebrovascular biology rather than a universal lipid mechanism.



Isolating the ApoB Signal

UK Biobank & IGAP Evidence

- **The Evidence:** Univariable two-sample MR shows genetically higher **ApoB** is associated with **shortened healthspan** and possibly increased risk for **Alzheimer's disease**.
- **Multivariable MR Insight:** When conditioned on **LDL-C**, ApoB retains its association with shortened healthspan, while **LDL-C** drops to null.
- **Scientific Caveat:** Supportive but preliminary causal evidence specifically for the **AD endpoint**, awaiting replication against strict 2024 biomarker-confirmed AD outcomes.

Evaluating the Evidence: Diagnostic Warning Lights



ApoB is so strongly causal for **fatal heart attacks/strokes** that genetically high-ApoB individuals who would have developed **AD** are removed from the population before **AD** can manifest. This artificially attenuates the lipid-**AD** signal in datasets.

Genetic variants may affect outcomes through **alternate pathways** (robustly tested via MR-Egger and weighted medians).

MR measures **lifelong genetic exposure**, meaning its **vast effect sizes** exceed what can be achieved with late-life pills.

Reconciling the Counterarguments

Counterargument 1: The Late-Life Low-Cholesterol Paradox

Observation: Low cholesterol in ages 75+ is linked to higher dementia risk.

- **The Reality (Reverse Causation):** Preclinical dementia causes years of unintentional weight loss, frailty, and hepatic synthetic dysfunction, lowering cholesterol as a **result of the disease, not a cause.**

Counterargument 2: Anti-Amyloid mAbs Work

Observation: Monoclonal antibodies slow decline by 27-36%.

- **The Reality:** We accept this! Removing amyloid provides **robust clinical benefit**, proving amyloid is not merely vascular debris. However, **late-stage incremental slowing is not upstream prevention.**

The Intervention Imperative: Time is the Target

Late-Life Intervention (Age 70+)

Mid-Life Prevention (Age 45)

Age 45

Structural Failure

Neurofibrillary Tangles

Mature Plaques

Cognitive Decline

Cognitive Decline

Fractured Neuronal Connections

Healthy Arterial Substrate

Clear Cerebrovascular Flow

Preserved Cognitive Function

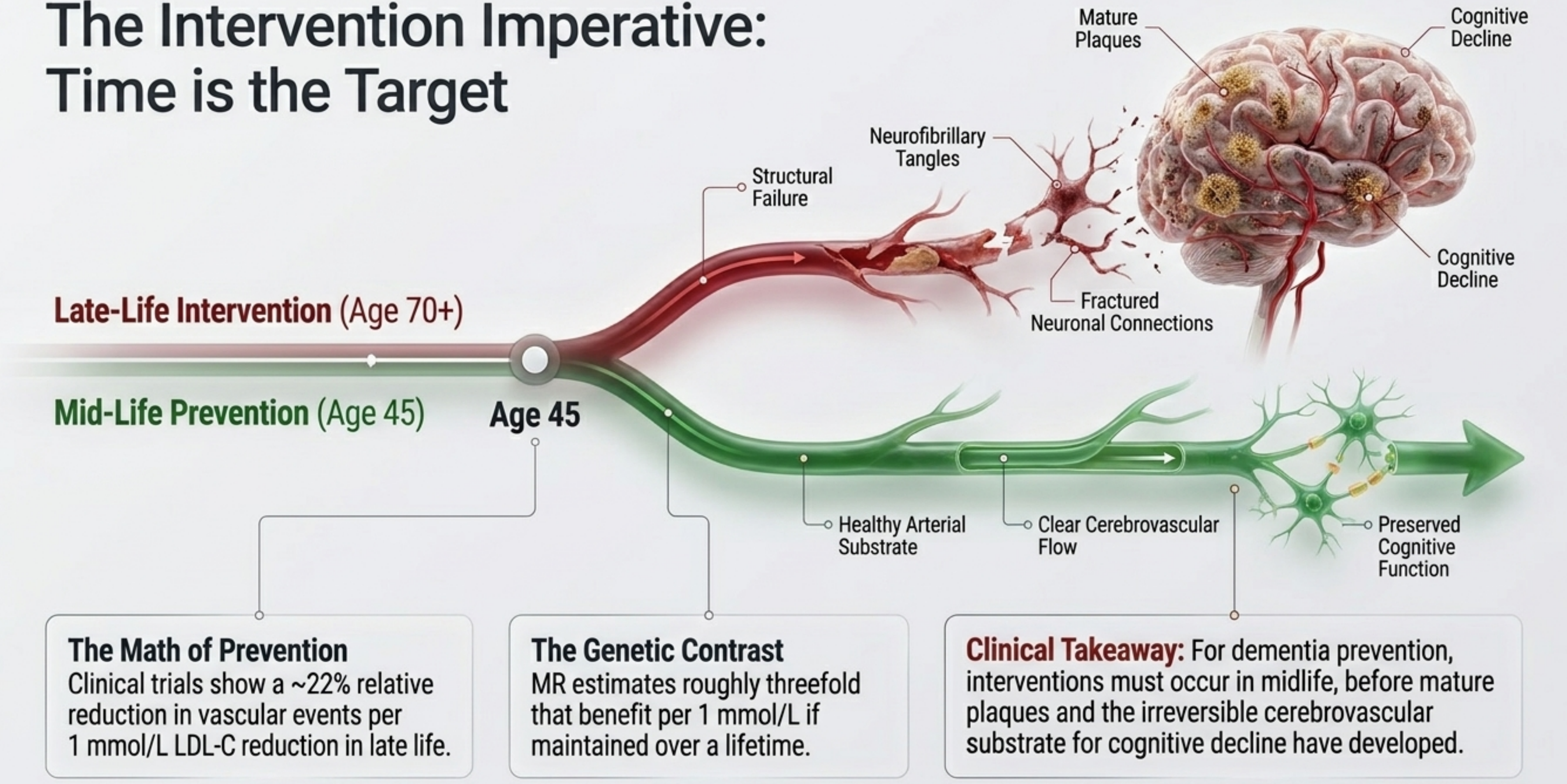
The Math of Prevention

Clinical trials show a ~22% relative reduction in vascular events per 1 mmol/L LDL-C reduction in late life.

The Genetic Contrast

MR estimates roughly threefold that benefit per 1 mmol/L if maintained over a lifetime.

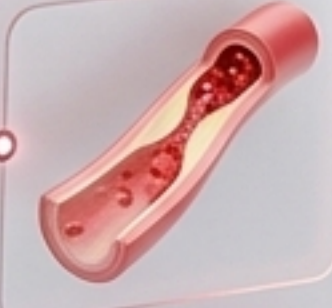
Clinical Takeaway: For dementia prevention, interventions must occur in midlife, before mature plaques and the irreversible cerebrovascular substrate for cognitive decline have developed.




The Proof of Concept: Vascular Trials Save Cognition

SPRINT MIND

Action: Intensive blood-pressure control (target SBP <120 mmHg).



Result: Reduced the composite of MCI or probable dementia (HR 0.85) and reduced MCI specifically (HR 0.81).



FINGER Trial

Action: 2-year multidomain intervention (diet, exercise, cognitive training, vascular risk monitoring).












Result: Improved cognitive composite scores versus control in at-risk older adults.



Synthesis: Modifying systemic vascular risk directly modifies brain destiny

The Dietary Arsenal: Modulating ApoB at the Source

Insight: High-quality plant-forward diets reduce ApoB, improve endothelial function, and modulate the gut microbiome.

Dietary Pattern	Key Components	Effect on ApoB	Effect on Inflammation	Dementia Risk
Healthful Plant-Based (hPDI)	Whole plants/legumes	Decreased 	Decreased 	21% Lower Incidence
Mediterranean (PREDIMED)	Olive oil/plants/fish	Decreased 	Decreased 	Lower
MIND Diet	Plants/berries/fish	Decreased 	Decreased 	Lower
Unhealthy Plant-Based (uPDI)	Refined grains/sweets	Neutral	Increased 	26% Higher Incidence
Western	Red meat/refined sugars	Increased 	Increased 	Higher

The Path Forward: Testing the Lifelong Protection Hypothesis

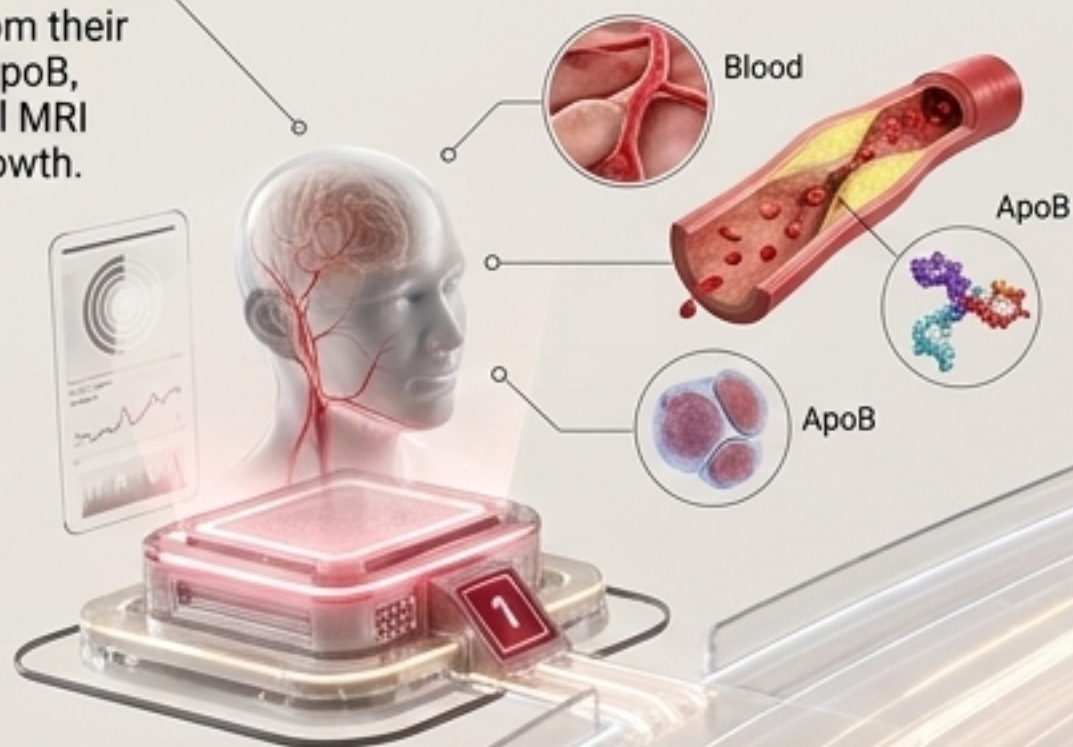
Mid-Life Prevention Trials

Randomized trials testing early, aggressive ApoB lowering, stratified by APOE ϵ 4 status and baseline cerebrovascular burden.



Longitudinal Life-Course Tracking

Follow individuals from their 30s/40s with serial ApoB, Lp(a), and vessel-wall MRI to monitor plaque growth.



Advanced Imaging Protocols

Map how vascular injury precedes protein accumulation using amyloid/tau-PET and perivascular-diffusivity proxies of glymphatic function.

The Paradigm Realigned

Final Thesis:

Alzheimer's disease is not solely a disorder of rogue proteins. It is the tragic, late-stage manifestation of decades of **vascular-lipid-inflammatory injury**.

Amyloid biology is a necessary component of the disease, and late-stage protein-targeted therapy is crucial.



The Call to Action:

True prevention demands we look **decades upstream**.

By relentlessly targeting lifelong exposure to **ApoB** starting in midlife, we have the biological mechanism to **fundamentally rewrite** the trajectory of cognitive decline.