

THE METABOLIC-TO- THROMBOTIC CONTINUUM OF ISCHEMIC STROKE

Hepatic lipoprotein regulation, carotid plaque homeostasis, and the transition to cerebral arterial occlusion

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ABSTRACT

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Background. Atherosclerotic ischemic stroke represents the culmination of chronic vascular pathology and an often abrupt loss of cerebral blood supply. Metabolic explanations have frequently emphasized blood cholesterol concentration without distinguishing lipoprotein production, receptor-mediated clearance, arterial retention, plaque maintenance, and the acute thrombotic event. Interest in bile-acid signaling and lipid-derived inflammatory mediators raises a further question: whether hepatobiliary physiology contributes to stroke causation independently of established atherogenic particle exposure.

Objective. To construct a falsifiable, stroke-specific causal framework integrating systemic lipid regulation, local carotid plaque biology, thromboinflammatory conversion, and cerebral perfusion; to rank supporting evidence according to its ability to establish human causation; and to evaluate the narrower liver–bile hypothesis against competing explanations.

Approach. This critical narrative synthesis prioritizes randomized clinical outcomes, human genetic studies, prospective carotid imaging, human tissue analyses, and mechanistic interventions. It is not a registered or exhaustive systematic review. Associations are not interpreted as causal simply because they are temporally proximal, statistically strong, or mechanistically attractive.

Synthesis. The most defensible sequence for plaque-related stroke comprises prolonged apoB-containing lipoprotein exposure; arterial retention and atherosclerosis; impaired plaque maintenance and vulnerability; local thrombosis or embolization; and downstream cerebral ischemia. Randomized evidence demonstrates that lipid lowering, selected antiplatelet regimens, and treatment of appropriately selected symptomatic carotid lesions reduce clinical events. Imaging studies identify intraplaque hemorrhage and fibrous-cap abnormalities as predictors of ipsilateral stroke, while experiments implicate cholesterol efflux, efferocytosis, ceramide signaling, and immune–platelet interactions in lesion behavior. Bile-acid pathways modify cholesterol homeostasis and experimental atherosclerosis or thrombosis, but independent prevention of human ischemic stroke through bile-acid manipulation has not been shown.

Conclusion. The metabolic origins of atherosclerotic stroke are best framed as a multi-stage interaction between systemic atherogenic particle regulation, local arterial-wall injury, and event-level hemostasis. Impaired bile digestion is not an established general cause. Prospective, subtype-specific research is needed to determine whether defined bile-acid or ceramide signatures contribute information or causal effects beyond apoB, plaque phenotype, and conventional vascular risk.

Keywords: ischemic stroke; atherothrombosis; carotid plaque; apoB; LDL clearance; intraplaque hemorrhage; macrophage efferocytosis; bile acids; FXR; TGR5; causal inference.

Introduction: the difference between a metabolic vulnerability and a stroke

Atherosclerotic ischemic stroke is often experienced as a sudden event: weakness, loss of speech, or visual disturbance appears within minutes. Its antecedents, however, may be decades old. The cerebral infarction is the immediate result of insufficient delivery of oxygenated blood, whereas the vulnerability that makes the event possible often develops through prolonged interactions among circulating lipoproteins, arterial-wall cells, inflammation, vessel geometry, and hemostasis. Treating all of those processes as a single entity obscures both causal explanation and prevention.

The starting proposition of this paper is narrow. A subset of ischemic strokes is attributable to atherosclerotic disease in extracranial or intracranial arteries, sometimes through plaque-related thrombosis or artery-to-artery embolization. Many others arise from atrial fibrillation, penetrating-artery disease, dissection, or alternative mechanisms. A theory of hepatic cholesterol regulation can illuminate the former without explaining the latter. Contemporary secondary-prevention guidance explicitly calls for etiologic evaluation and mechanism-specific treatment [2].

The central issue is not whether lipids matter; that question has strong causal answers. The issue is *which lipid-related process matters at which stage*. Cholesterol is an essential component of membranes and steroid synthesis. Atherosclerosis is not caused by cholesterol existing in the body but by sustained arterial exposure to particles capable of entering and being retained in the intima, particularly apoB-containing lipoproteins [1]. The biological importance of retained particles differs from the triggers that make a mature lesion thrombogenic. A plaque may narrow an artery without rupturing, rupture without causing a major infarct, or generate an embolus while producing less than 50% luminal narrowing.

The additional hepatobiliary hypothesis deserves examination because the liver simultaneously synthesizes cholesterol, packages lipids into VLDL, removes LDL and remnants, converts cholesterol to bile acids, and participates in biliary sterol disposal. The intestine contributes absorption, sterol exclusion, and enterohepatic bile-acid signaling. These pathways may influence atherogenic exposure. Yet inadequate bile delivery ordinarily impairs intestinal fat absorption; it does not produce a circulating stream of unprocessed dietary fat that directly lodges within cerebral arteries. Confusing these mechanisms weakens an otherwise plausible systemic account of stroke.

We therefore propose a **metabolic-to-thrombotic continuum** as an explanatory framework, not a new clinical diagnosis. Its purpose is to locate established causes, plausible mediators, predictive markers, and consequences of the stroke within one coherent model. The key question is always counterfactual: would modifying a proposed mechanism *before* the event reduce the occurrence of the relevant stroke subtype?

Scope, methods, and evidence hierarchy

This article is a critical narrative synthesis, not an original experimental study, meta-analysis, or PRISMA-compliant systematic review. It draws on landmark randomized outcome trials, contemporary prevention guidance, human carotid imaging cohorts, genetic and clinical lipid evidence, and selected mechanistic investigations published by the cutoff date. Original reports were preferred when a specific effect estimate or mechanism was discussed. Selected studies were verified against publisher, PubMed, or open-access records. The literature selection was purposive rather than exhaustive; no claim is made that every qualifying study has been identified.

Evidence is organized into four tiers. **Tier I** comprises randomized trials reporting actual stroke or vascular outcomes and convergent human genetic evidence. **Tier II** comprises prospective longitudinal studies showing that an exposure or plaque feature precedes a subsequent ischemic event. **Tier III** comprises human cross-sectional tissue, imaging, or biomarker associations. **Tier IV** comprises

mechanistic cell and animal interventions without direct validation in human stroke prevention. This ordering does not mean lower-tier experiments are unimportant. They often establish biological mechanisms more clearly than observation can. It means that mechanisms must not be promoted into proven explanations for the occurrence of human strokes without the necessary translational evidence.

Three outcome distinctions are applied throughout. A biomarker associated with **atherosclerotic burden** is not automatically a predictor of **future plaque-related stroke**. A treatment improving **plaque imaging** is not automatically proven to reduce **clinical cerebral infarction**. A substance reducing **brain infarct size after arterial occlusion** is not automatically an agent that prevents **arterial occlusion**. These distinctions are particularly important when evaluating bile acids, ceramides, endothelial signaling, and inflammation.

1. Define the stroke before constructing its metabolic cause

The large-artery atherosclerotic pathway concerns lesions in vessels supplying the brain, including extracranial carotid arteries and intracranial arteries. A stroke can follow local thrombosis at a plaque, embolization of plaque-associated thrombus, or severe stenosis with inadequate downstream perfusion. The alternative mechanisms are not variants of the same lipid pathway. Atrial fibrillation can create a left-atrial thrombus that embolizes to the brain without a carotid lesion. Lacunar infarction often reflects abnormalities in small penetrating arteries, with hypertension and arteriolar pathology especially important. Intracerebral hemorrhage is an altogether different endpoint in which vessel rupture, not arterial blockage, is central.

This classification has direct evidentiary consequences. Anticoagulation is effective for appropriate atrial-fibrillation-related stroke prevention, whereas antiplatelet therapy is used for selected noncardioembolic mechanisms [2,22]. Blood-pressure treatment reduces

recurrent stroke across relevant populations [20], and the SPS3 trial specifically addressed patients with MRI-confirmed lacunar infarction [23]. These results would be inexplicable under a universal hypothesis that all ischemic strokes originate in impaired bile-mediated digestion or LDL clearance. They are readily accommodated by a multiple-pathway model.

Even atherosclerotic carotid disease is not synonymous with the stroke mechanism. A patient may have visible plaque but suffer a simultaneous cardioembolic event. Establishing ipsilateral vascular territory, infarct pattern, competing sources, and relevant clinical history is essential. High-risk plaque features in nonstenotic carotid disease are more common ipsilateral to embolic stroke of undetermined source than contralaterally, but that asymmetry does not prove that every lesion caused the index infarct [8]. A good causal framework permits uncertainty where the clinical evidence cannot assign the embolus to a specific source.

2. Systemic lipid regulation: production, clearance, and cumulative particle exposure

2.1 ApoB particles, not undigested dietary fat

The most strongly supported metabolic contributor to atherosclerotic disease is prolonged exposure to apoB-containing lipoproteins. LDL, cholesterol-bearing remnants of triglyceride-rich lipoproteins, and lipoprotein(a) can enter susceptible arterial regions and be retained by matrix interactions. Local inflammation and macrophage lipid loading follow. Experimental, genetic, epidemiological, and pharmacological evidence converge on the causal importance of retained atherogenic particles [1]. Cholesterol mass and particle number are related but distinct. A person may have apparently moderate LDL-C yet elevated apoB because each particle carries less cholesterol, as can occur in insulin-resistant dyslipidemia.

The liver regulates both sides of this exposure. Hepatic VLDL secretion places apoB100-containing particles into the circulation; subsequent intravascular remodeling yields remnants and LDL. Hepatic LDL receptors recognize LDL and selected remnant particles, inter-

nalize them, and often recycle to remove further particles. PCSK9 can redirect LDL receptors toward degradation, thereby reducing functional receptor availability. Excessive production and impaired clearance can coexist. The observed blood concentration cannot, by itself, identify which is dominant.

An instructive approximation is **particle concentration $\approx$ particle input rate / fractional clearance rate** under simplified steady-state conditions. This is not a validated stroke-risk equation; it highlights why a normal rate of production can still produce high plasma LDL when clearance falls. Over decades, the more relevant arterial exposure is the integrated concentration over time, modified by arterial susceptibility and other conditions. One isolated lipid measurement cannot reconstruct that history.

Insulin resistance introduces a particularly common acquired disturbance. Increased fatty-acid delivery from adipose tissue, altered hepatic lipogenesis, greater VLDL secretion, and disturbed lipoprotein-lipase/remnant pathways may increase the number and persistence of circulating apoB-containing particles. Triglyceride concentration becomes a marker of altered particle metabolism, not proof that triglyceride droplets themselves are directly forming a cerebral embolus. Cholesterol-rich remnants can contribute to arterial lipid retention [25]. Hypothyroidism and nephrotic syndrome are additional secondary causes of dyslipidemia; they illustrate that the liver's clearance behavior can be influenced by endocrine or renal disease elsewhere in the body.

2.2 Why causal intervention matters

The SPARCL trial randomized 4,731 patients with recent stroke or TIA to atorvastatin 80 mg or placebo; recurrent fatal or nonfatal stroke occurred in 11.2% versus 13.1% over a median 4.9 years [4]. The trial also detected a hemorrhagic-stroke signal, emphasizing the importance of distinguishing stroke categories and individual risk. Treat Stroke to Target assigned 2,860 patients with atherosclerotic stroke or TIA to lower or higher LDL-C targets; the primary *composite cardiovascular* outcome occurred in 8.5% versus 10.9% [5]. These percentages are not isolated ischemic-stroke rates.

FOURIER adds mechanistic relevance because the intervention directly increases effective hepatic LDL clearance through PCSK9 inhibition. In 27,564 high-risk participants with established atherosclerotic cardiovascular disease receiving statins, evolocumab reduced ischemic stroke from 1.6% to 1.2% over a median 2.2 years (HR 0.75, 95% CI 0.62–0.92) [6]. This supports a causally important role for atherogenic lipoprotein exposure. It does not prove that every prevented stroke originated from a carotid plaque, nor that every benefit was due to one specific imaging change.

2.3 The sterol-excretion exception that sharpens the theory

Sitosterolemia provides a rare human example in which defective intestinal and biliary sterol transport produces premature atherosclerotic disease. Biallelic pathogenic variants affecting ABCG5 or ABCG8 cause excess plant-sterol absorption and inadequate biliary excretion [19]. Its importance lies in demonstrating that sterol transport physiology can be causally relevant to human arterial disease. The disorder does *not* demonstrate that ordinary dietary seed-oil fatty acids accumulate because bile production is poor. Plant sterols and polyunsaturated fatty acids are different molecular classes. Generalizing from the rare transporter defect to the entire population would be unsound.

3. From atherogenic exposure to a vulnerable carotid plaque

Arterial-wall susceptibility and local hemodynamics influence where apoB particles accumulate. A plaque is a living tissue compartment containing lipid droplets, cholesterol crystals, macrophages, smooth-muscle cells, extracellular matrix, and sometimes newly formed microvessels. Its danger is not exhausted by the percentage of stenosis. A relatively modest lesion may develop features associated with thromboembolism, while a larger lesion may remain clinically silent during a given follow-up period.

Prospective carotid MRI offers especially important human evidence. An individual-patient meta-analysis pooled seven cohorts including 696 people with carotid disease. MRI-detected intraplaque

hemorrhage predicted subsequent ipsilateral ischemic stroke in symptomatic disease (HR 10.2; 95% CI 4.6–22.5) and, with greater uncertainty, asymptomatic disease (HR 7.9; 95% CI 1.3–47.6) [7]. These are cohort-specific hazard ratios, not universal individual risk predictions. A 2025 systematic review in embolic stroke of undetermined source found high-risk nonstenotic plaques in approximately 31% of ipsilateral carotid arteries versus 14% contralaterally [8]. The difference suggests a potential embolic source even with less than 50% narrowing, while alternative cardiac causes remain possible.

Intraplaque hemorrhage deserves particular emphasis because it may introduce an independent internal source of cholesterol-rich material. Fragile neovessels can leak red blood cells into the lesion; membrane cholesterol and hemoglobin-related products then add to local lipid and oxidative burdens. In a carotid MRI substudy of AIM-HIGH, plaques with intraplaque hemorrhage gained lipid content at approximately 1.2 percentage points per year while plaques without hemorrhage lost approximately 1.0 point per year, despite intensive background lipid lowering [13]. This does not mean systemic lipid treatment has failed. It means the local lesion may continue remodeling through mechanisms not fully captured by the current LDL-C measurement.

Serial MRI provides complementary evidence for modifiability. In a prospective study, lipid-rich necrotic core volume fell from 60.4 to 37.4 mm³ over three years among 33 participants with measurable baseline core and complete follow-up [14]. The finding is encouraging but should not be described as an observed reduction in stroke incidence. The internal plaque composition may change before overall vessel narrowing meaningfully regresses. Equally, lesions with persistent hemorrhage may remain high risk even after blood lipids improve.

4. Plaque maintenance as a second lipid-clearance problem

The liver is not the only location at which lipid handling matters. Within an established plaque, macrophages must balance uptake of modified particles and cellular debris against storage, metabolic processing, and cholesterol export. ABCA1 and ABCG1 support cholesterol efflux toward apoA-I and HDL-associated acceptors. This cellular transfer is not identical to complete removal of cholesterol from the body: subsequent transport and excretion remain necessary. When incoming lipid exceeds effective removal, macrophage lipid burden rises.

A 2025 *Journal of Clinical Investigation* study identified Listerin as a regulator of ABCA1 stability. In experimental systems, oxidized LDL favored lysosomal degradation of ABCA1; Listerin helped preserve the transporter. Macrophage-specific loss of Listerin worsened plaque lipid accumulation and necrotic features in mice, whereas enhanced expression had protective effects [12]. This supports a mechanism by which the plaque environment may undermine its own cholesterol export capacity. It does not establish a clinically effective macrophage-directed stroke-prevention therapy.

A second maintenance function is efferocytosis, the engulfment and processing of dying cells. Failed efferocytosis permits dead-cell accumulation, secondary necrosis, and inflammatory remodeling. In human carotid specimens, proteolytic cleavage of the macrophage receptor MerTK correlated with plaque necrosis and ischemic symptoms. In atherosclerosis-prone mice engineered to resist MerTK cleavage, plaques exhibited improved efferocytosis, smaller necrotic cores, and thicker fibrous caps [11]. The experiment demonstrates a plausible causal mechanism for plaque composition. It cannot specify how much of human stroke incidence would be prevented by targeting MerTK.

These systems interact. A macrophage engulfing an apoptotic foam cell acquires additional cholesterol and must dispose of it. Enhancing engulfment without preserving lipid processing could create a different form of cellular overload. Equally, efficient cholesterol

efflux does not guarantee that dying cells will be recognized and removed. The novel proposition is that **persistent plaque vulnerability may reflect a mismatch between ongoing lipid and debris inputs and the lesion's capacity for coordinated removal and tissue repair.**

Recent human plaque analyses strengthen the rationale while underscoring limitations. A 2026 exploratory lipidomics study compared 14 vulnerable and 14 nonvulnerable carotid specimens, reporting enrichment of ceramides and related lipid classes in vulnerable tissue [15]. A separate 2026 study identified macrophage signatures associated with secondary composite cardiovascular events after endarterectomy [16]. Neither result proves that the measured cell states or lipid species caused a subsequent ipsilateral stroke. The removed lesion is no longer present during follow-up, and postoperative outcomes may reflect systemic susceptibility or disease elsewhere. These are important leads rather than validated clinical tests.

5. Thrombotic conversion: the distinct event that blocks cerebral blood flow

An atherosclerotic lesion may exist without a clinically important clot. Acute ischemia can arise when plaque rupture or endothelial erosion exposes thrombogenic structures to circulating blood. Platelets adhere and activate; tissue factor facilitates factor VII-dependent coagulation; thrombin promotes platelet activation and fibrin formation. An enlarging thrombus may obstruct the source artery or release an embolus into the internal carotid and cerebral circulation. Severe fixed stenosis can alternatively threaten perfusion when compensatory vascular reserve is exhausted.

This final step is not the same as the preceding decades of lipoprotein accumulation. The embolus is commonly composed of fibrin, platelets, red blood cells, and other clot constituents. It need not be a fragment of solid cholesterol. Clinically successful antiplatelet intervention is therefore a separate test of causality. In CHANCE, a selected population with minor ischemic stroke or high-risk TIA treated

within 24 hours had a 90-day recurrent-stroke rate of 8.2% with a short initial course of aspirin plus clopidogrel followed by clopidogrel, versus 11.7% with aspirin alone [21]. That trial does not justify long-term dual antiplatelet therapy for every stroke phenotype.

Inflammatory activation and neutrophil extracellular traps may influence thrombus formation or persistence, but the causal importance of individual pathways for human carotid embolization remains incompletely defined. A molecular marker discovered in a clot removed after stroke cannot automatically be assigned a role in initiating that clot. Local plaque tissue factor, blood-flow geometry, platelet behavior, and systemic inflammatory state may interact, but their relative contributions vary. Recent infection is associated with a transiently elevated probability of ischemic stroke in case-cross-over studies; ARIC observed its strongest association within fourteen days of hospitalization for infection [24]. That finding does not identify carotid rupture as the mechanism in each case. Infection can also influence cardiac rhythm, systemic perfusion, and other stroke pathways.

The practical distinction is between the **chronic risk substrate**, the **local plaque event**, and the **acute systemic state**. A person may possess a vulnerable carotid lesion for years without stroke. An acute disturbance can modify the likelihood of thrombus propagation or critically reduced downstream perfusion, but it is generally not possible to reconstruct a unique molecular trigger for an individual stroke from post-event biomarkers alone.

6. Clinical intervention as a set of causal experiments

Randomized outcomes are especially valuable because they test whether disrupting a proposed pathway prevents real vascular events. The results of several landmark studies, however, should not be collapsed into a single pooled treatment effect: populations, follow-up, endpoints, and stroke mechanisms differ.

Intervention or pathway	Trial / cohort	Outcome and interpretation
Intensive statin therapy	SPARCL, n=4,731	Recurrent stroke 11.2% versus 13.1% over median 4.9 years; hemorrhagic-stroke signal requires qualification [4].
Lower LDL-C target	Treat Stroke to Target, n=2,860	Primary cardiovascular composite 8.5% versus 10.9% over median 3.5 years; not isolated stroke rates [5].
PCSK9 inhibition	FOURIER, n=27,564	Ischemic stroke 1.2% versus 1.6% over median 2.2 years [6].
BP-lowering regimen	PROGRESS, n=6,105	Recurrent stroke approximately 10% versus 14% over four years [20].
Early selected antiplatelet regimen	CHANCE, n=5,170	Recurrent stroke 8.2% versus 11.7% at 90 days [21].
Symptomatic severe carotid intervention	NASCET, n=659 in severe-stratum report	Ipsilateral stroke 9% versus 26% at two years with surgery plus care versus care alone [9].
Anticoagulation in AF	AVERROES, n=5,599	Stroke/systemic embolism 1.6% versus 3.7% per year with apixaban versus aspirin [22].

The NASCET comparison is particularly revealing. Among selected patients with recently symptomatic 70–99% carotid narrowing, removal of the local plaque dramatically reduced subsequent ipsilateral strokes [9]. The intervention did not require first correcting hepatic cholesterol metabolism. This does not refute metabolic contributions to plaque formation; it shows that the immediate treatable lesion can be a separate causal component. Modern treatment decisions must not use the historical absolute effect unchanged, because medical therapy and procedural techniques have evolved. In CREST-2, intensive medical therapy produced relatively low four-year event rates among selected patients with *asymptomatic* severe carotid narrowing; stenting and endarterectomy had different comparisons against medical therapy and different procedural risks [10]. These are not interchangeable clinical scenarios.

Negative trials further clarify the causal argument. Low-dose colchicine in CONVINCED did not significantly reduce its primary recurrent vascular composite after noncardioembolic stroke, despite a numerically favorable point estimate [26]. The result does not make inflammation irrelevant; it shows that a plausible anti-inflammatory intervention and an unselected heterogeneous population need not generate a demonstrable stroke benefit. Likewise, the SPS3 trial's more intensive blood-pressure target did not achieve statistical sig-

nificance for total recurrent stroke, although the direction of effect favored lower pressure and hemorrhagic stroke declined [23]. A valid pathway does not guarantee benefit from every intervention, at every time, in every patient.

7. The liver–bile hypothesis: what survives a strict causal test?

The hepatobiliary system participates in cholesterol homeostasis but is not a single-direction disposal pipe. Hepatocytes manufacture and secrete VLDL, remove apoB-containing particles through receptors, synthesize cholesterol, convert a portion into bile acids, and secrete neutral sterols into bile. The intestinal–hepatic circulation recycles most bile acids. FXR-mediated intestinal signaling through FGF19 feeds back on hepatic bile-acid synthesis. These systems can affect circulating lipoprotein concentrations without any overt bile duct obstruction.

The critical distinction is that **poor bile delivery to the intestine and inefficient hepatic LDL clearance are not the same defect**. Lack of luminal bile ordinarily reduces absorption of many lipids and fat-soluble vitamins. It does not create free dietary fats that deposit directly within cerebral arteries. Severe cholestasis can also produce unusual cholesterol-rich lipoproteins such as apoB-free lipoprotein X, making conventional cholesterol measurements misleading. The relevant vascular exposure for atherogenesis is the nature and number of circulating particles, not total cholesterol mass alone.

Bile-acid signaling nevertheless has compelling experimental implications. In 2021, Wu and colleagues demonstrated that intestinal FXR activity affected SMPD3-mediated ceramide generation and atherosclerosis in ApoE-deficient mice. Intestinal FXR deficiency or treatment with an FXR antagonist reduced circulating ceramides and plaque; restoring SMPD3 or a relevant ceramide attenuated protection [17]. The study supplies intervention-level evidence for an

experimental pathway, including partial molecular mediation. It does not show that obstructed bile flow causes human carotid strokes.

A separate 2025 study by Qi and colleagues demonstrated that deoxycholic acid (DCA), a microbiome-derived secondary bile acid, could inhibit platelet activation through TGR5-mediated cAMP/PKA signaling. The investigators included human platelet experiments and mechanistic mouse studies of atherothrombosis, with emphasis on coronary disease [18]. This is a plausible connection to the acute coagulation stage. But it has not established that low endogenous DCA causes carotid plaque thrombosis, nor that increasing DCA prevents human ischemic stroke. DCA has context-dependent effects and can be harmful in other settings; it must not be interpreted as a general-purpose protective supplement.

The two bile-related pathways are distinct. Intestinal FXR–SMPD3 regulates ceramide production under experimental conditions; platelet TGR5 influences platelet signaling. A favorable result for one bile acid in one tissue cannot be generalized to all bile acids or to a simple rule that more bile is better. The human plaque ceramide findings [15] and the experimental intestinal FXR results [17] are convergent clues, *not* a single validated liver-to-carotid causal chain. Tissue ceramides may be generated locally, taken up from circulation, or altered as a consequence of inflammatory remodeling. Post-stroke blood samples introduce further reverse-causality risk.

Thus, the strongest bile-related proposition is that hepatobiliary signaling **may modify** known atherosclerotic or thrombotic pathways. The strongest established metabolic proposition is that prolonged apoB exposure **causally contributes** to atherosclerosis and to a subset of ischemic strokes. Confusing those levels of certainty would diminish the value of the review.

8. A causal diagram that can be falsified

The continuum is best modeled as several linked but nonidentical processes. Upstream hormonal, genetic, dietary, renal, and metabolic influences change hepatic production and clearance of athero-

genic particles. Cumulative particle exposure contributes to carotid and intracranial plaque. Within established plaque, hemorrhage, cholesterol efflux, efferocytosis, and inflammation modify vulnerability. Plaque-surface disruption and coagulation can then produce embolic occlusion. Simultaneously, collateral blood flow and systemic hemodynamics determine whether arterial disease results in irreversible brain injury. Other stroke mechanisms, including atrial fibrillation, enter the diagram through separate pathways.

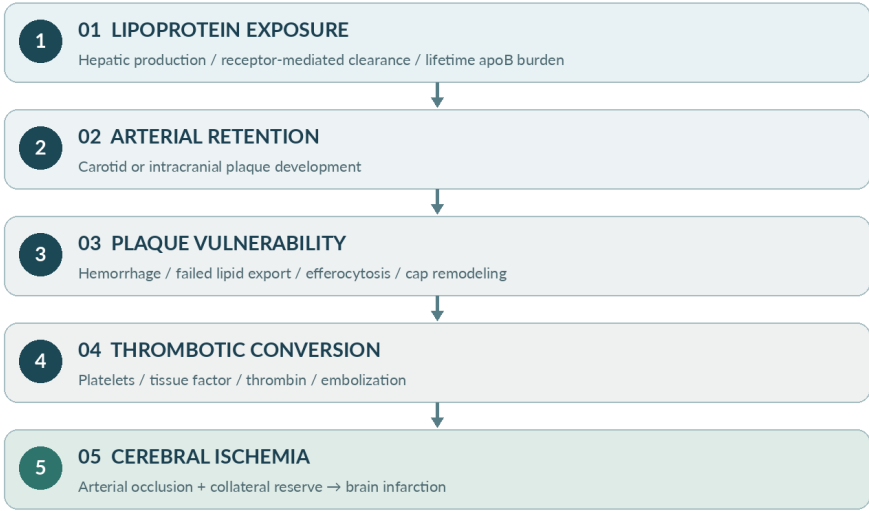


Figure 1. Stroke-specific metabolic-to-thrombotic causal framework. The diagram presents the core atherothrombotic sequence; proposed bile-acid modifiers are evaluated separately in the text.

A useful formal distinction is between *total causal effects* and *direct effects conditional on downstream mediators*. Suppose a bile-acid species alters ceramide metabolism, which changes plaque vulnerability. Adjusting statistically for ceramides might remove part of the very signal one wishes to measure. Conversely, failing to account for insulin resistance, medication exposure, or liver disease could produce a spurious bile-acid association. Causal modeling requires an explicitly specified directed acyclic graph and prespecified adjustment sets; indiscriminate adjustment is not a substitute for identifying the question.

The temporal dimension is equally important. A bile-acid or inflammatory biomarker collected after a stroke may be a cause, a correlated marker, or a consequence of acute brain injury. Stronger evi-

dence would require its measurement before the event, repeated assessment of its stability, and stroke-subtype adjudication. The relevant outcome should be territorial ischemic stroke or other carefully defined atherothrombotic events, not simply all-cause cardiovascular disease.

9. Four competing causal explanations

The model should confront serious alternatives, not merely collect confirming studies.

Model A: systemic apoB burden as the dominant upstream driver. Most of the long-term association between altered hepatic metabolism and atherosclerotic stroke is explained by increased number or lifetime residence of apoB particles. This model is supported by convergent genetics and LDL-lowering interventions [1,4–6]. The biliary pathway might influence LDL indirectly but add little independent explanatory value once particle exposure is quantified.

Model B: plaque-local failure of lipid and debris clearance. After plaque formation, intraplaque bleeding and altered macrophage function sustain injury even when circulating LDL falls. Prospective MRI observations [7,13], MerTK experiments [11], and ABCA1-related work [12] make this credible. Yet the extent to which these pathways causally determine future human stroke, independent of plaque structure, is unproven.

Model C: systemic thromboinflammatory susceptibility. Temporary inflammation, platelet activation, infection, or coagulation changes affect whether an existing lesion forms an occlusive thrombus. Human infection timing [24] and clinical antiplatelet benefit [21] support the broad concept. Specific mediators such as NETs or DCA–TGR5 signaling remain less secure as independent human stroke causes.

Model D: shared-cause and reverse-causality explanation. Metabolic abnormalities in bile acids, ceramides, or cytokines may reflect insulin resistance, hepatobiliary disease, plaque inflammation, or the cerebral event itself. They could predict outcomes without being

the optimal intervention target. A cross-sectional difference in a post-stroke blood sample cannot discriminate this model from the more ambitious causal claims.

These explanations are not mutually exclusive. Multiple pathways may operate in the same patient. The purpose of separating them is to avoid assigning every abnormal marker a distinct causal role. Evidence of an association becomes informative only when temporality, confounding, mediation, and competing stroke mechanisms have been evaluated.

10. Research agenda: what would establish an independent bile-related stroke pathway?

A serious test should be prospective, stroke-subtype-specific, and externally validated. A candidate design would recruit adults with clinically identified carotid or intracranial atherosclerosis, using a prospective observational cohort nested within routine cerebrovascular care. Baseline measurements would include apoB, LDL-C, triglyceride-rich remnant metrics, Lp(a), glycemic and renal status, thyroid and liver indices, and medication exposure. A targeted metabolomic panel would quantify individual primary, secondary, conjugated, and unconjugated bile acids alongside selected ceramide species; C4 and FGF19 could index components of bile-acid synthesis feedback. Carotid plaque features would be characterized using clinically appropriate imaging, including IPH, ulceration, and stenosis.

The **primary clinical endpoint** should be adjudicated new ischemic stroke in the vascular territory supplied by the relevant diseased artery. Secondary outcomes could include TIA, imaging progression, other ischemic stroke subtypes, and myocardial events. Each event would require infarct-pattern review, vascular evaluation, and appropriate cardiac investigation so that an incident atrial-fibrillation embolus was not incorrectly attributed to carotid plaque. Pre-event biomarker measurement is essential; repeated sampling would help determine whether a hypothesized bile-acid exposure precedes progression or varies only with illness.

Analysis should begin with established predictors—age, sex, smoking, blood pressure, diabetes, kidney disease, apoB, Lp(a), and prior symptoms—then assess whether bile-acid or ceramide measurements add calibrated predictive value. The analysis should report absolute risk, discrimination, calibration, and external performance rather than relying only on statistically significant odds ratios. A second, separately prespecified causal analysis should model mediators and confounders explicitly. Adjusting for plaque features when estimating an upstream total causal effect may remove a mechanism through which the exposure operates; conversely, omitting them when asking about independent prediction can exaggerate incremental value.

Mechanistic experiments should follow the human findings, not replace them. Candidate bile-acid species would be tested at physiologically relevant free concentrations and with appropriate carrier proteins. Receptor dependence could be assessed through FXR, TGR5, and platelet or macrophage pathway perturbations. Importantly, an effect on mouse aortic plaque or coronary thrombosis would not be reported as equivalent to preventing human carotid stroke. Only a credible combination of temporality, molecular mediation, dose specificity, and ultimately clinical intervention would justify elevating the pathway to an established cause.

Prespecified falsification criteria should include: no association of baseline bile-acid signatures with subsequent territorial stroke; absence of reproducible incremental prediction after established factors; inconsistent receptor-mediated effects at physiological concentrations; or successful modulation of a molecular biomarker without corresponding improvement in a clinically relevant endpoint. A null result for a defined bile-acid pathway would not invalidate apoB causality or the entire continuum; it would narrow the role assigned to that particular modifier.

11. Clinical meaning without therapeutic overreach

The framework helps separate the questions clinicians must answer. The lipid profile—including selective apoB and Lp(a) measurement—describes aspects of systemic atherogenic exposure. Carotid and intracranial imaging describes local arterial disease. MRI infarct location and cardiac evaluation help establish the probable source of the embolus or perfusion failure. Each addresses a different stage of the continuum. No single biomarker establishes all three.

For a patient with established atherosclerotic ischemic stroke, evidence-based secondary prevention—including appropriate lipid treatment, blood-pressure management, antithrombotic therapy, smoking cessation, and selected revascularization—has clinical outcome evidence [2]. Acute focal neurological symptoms remain a medical emergency requiring immediate stroke evaluation; the 2026 AHA/ASA acute ischemic stroke guideline addresses thrombolysis and endovascular treatment in eligible patients [3]. The present framework is not a reason to defer those interventions while investigating metabolic causes.

Equally, the novel biochemical leads do not justify prescribing bile-acid supplements, manipulating DCA, interrupting indicated antiplatelet or lipid-lowering treatment, or attempting prolonged fasting or dehydration as a strategy to prevent stroke. In particular, acute hypovolemia or large blood-pressure changes may worsen perfusion in selected patients with severe flow-limiting cerebral arterial disease. The correct intervention depends on the established stroke mechanism, contraindications, and individual clinical circumstances.

12. Limitations and unresolved problems

Several limitations constrain the interpretation. This is a narrative synthesis rather than an exhaustive systematic review, and publication or selection bias may shape the apparent strength of new mechanistic findings. Much of the most detailed carotid tissue biology comes from endarterectomy specimens; these patients are highly se-

lected and the tissue is usually collected after neurological symptoms. Ex vivo expression signatures cannot establish the direction of causation. Small lipidomic studies may overfit plaque-vulnerability labels and require independent replication. Substantial results from mouse aorta or coronary thrombosis cannot be assumed to transfer to the human carotid circulation. Imaging-defined plaque stabilization and reduction of a composite cardiovascular endpoint are not identical to prevention of a new ipsilateral ischemic stroke.

The model is also incomplete by design. It does not fully address cerebral amyloid angiopathy, hemorrhagic stroke, cervical dissection, cerebral venous thrombosis, inherited arteriopathies, or cardioembolism. Small-vessel disease may share metabolic risk factors but requires distinct vessel-wall models. Finally, acute event timing may be stochastic or contingent on local micro-events that currently cannot be measured prospectively. There is no validated clinical test that predicts the day on which a particular carotid plaque will rupture.

Conclusion

Atherosclerotic ischemic stroke should not be reduced to either a cholesterol number or a sudden clot. It is better understood as a multistage disease process in which systemic atherogenic lipoprotein exposure helps create an arterial lesion; local cholesterol handling, cellular cleanup, hemorrhage, and inflammation influence that lesion's condition; and thrombosis, embolization, and cerebral perfusion determine whether neurological infarction occurs. The contributions of these stages differ among patients and cannot be generalized to all stroke subtypes.

The liver is causally important because it regulates atherogenic particle production and clearance. The most robust metabolic claim is that excessive cumulative apoB-containing particle exposure contributes to atherosclerotic vascular disease, and that interventions lowering this exposure reduce ischemic strokes in appropriately selected populations. Bile-acid synthesis and signaling intersect with cholesterol homeostasis and possess experimentally interesting

links to ceramide production and platelet activity. Yet an independent, clinically important human bile-acid-to-carotid-stroke causal chain remains unproven. Impaired digestion of fat is not an established explanation for the formation of cerebral arterial emboli.

The useful advance is therefore not a universal liver-first theory, but a falsifiable **metabolic-to-thrombotic continuum** with separate causal claims at each stage. Future investigations should prioritize prospectively measured exposures, territory-specific ischemic endpoints, competing-source adjudication, and interventions that demonstrate real stroke prevention rather than biomarker change alone.

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