

The Stroke Begins Outside the Brain

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Abstract

An ischemic stroke is a neurological emergency, yet the vessel occlusion may be the end of a process that began years earlier in the intestine, liver, heart, vascular wall or coagulation system. This paper presents a multi-compartment model of stroke causation. It distinguishes lipid retention and plaque development from the immediate thrombotic or embolic event, and asks when impaired sterol handling may contribute to the former without directly accounting for the latter.

The systemic origins of vascular injury

For a substantial subset of ischemic strokes, the causal history starts outside the brain, but a systemic model becomes credible only when it predicts the vascular mechanism.

The phrase “fat cannot be processed” is too vague for causal medicine. Dietary triglycerides normally enter circulation through chylomicrons, while intestinal NPC1L1 and ABCG5/ABCG8 transporters govern sterol uptake and exclusion. The liver redistributes cholesterol in lipoproteins and removes sterol through biliary secretion and bile-acid conversion. Each step has different pathological consequences. Atherogenic apoB-containing particles infiltrate susceptible arterial walls; retained lipoproteins may provoke inflammatory responses and plaque formation. None of this implies that undigested fat collects directly within a brain artery.

A useful model includes five paths: intestinal sterol entry; hepatic lipoprotein production and clearance; endothelial retention of apoB particles; plaque destabilization and platelet-rich thrombosis; and cardioembolism or small-vessel injury arising through separate mechanisms. Rare ABCG5/8 disorders establish that abnormal absorption and biliary excretion can be clinically consequential, but most ischemic strokes are not caused by sitosterolemia. The model therefore treats abnormal clearance as one potential contributor to atherosclerotic stroke, not a unifying explanation for intracranial embolism, dissection or atrial fibrillation.

Sterols, particles, plaques and emboli

A sophisticated vascular account must distinguish the source of plaque from the source of the clot. The atheroma develops in a particular arterial environment under sustained exposure to retained lipoproteins, local injury and immune-cell recruitment. A plaque may remain clinically silent until rupture or erosion produces thrombosis, or it may cause critical narrowing without an acute rupture. By contrast, an embolus produced in a fibrillating atrium can occlude a cerebral vessel without needing substantial atherosclerotic plaque in that artery. Bile-acid handling is potentially relevant upstream of lipoprotein biology; it does not by itself explain cardiac rhythm, coagulation or the anatomy of embolization. This nested-cause framework protects both conventional knowledge and original inquiry.

Consider two people with similar LDL-cholesterol values. One has an elevated apoB particle count and progressive carotid plaque; the other develops an embolic stroke from atrial fibrillation without important large-artery atherosclerosis. Only the first case directly tests the proposed bridge from cholesterol transport to the arterial lesion. Treating both as evidence that a bile defect caused stroke destroys the anatomical precision required for the thesis. This distinction does not diminish a broader idea: lipid handling may contribute materially to the vulnerability that precedes some ischemic events. It identifies where the contribution should be measurable.

The experimental chain would measure sterol metabolism, apoB, bile-acid species, hepatic disease and plaque morphology before the event whenever possible. A prospective cohort should record antihypertensive and lipid-lowering treatment, kidney function, diabetes and smoking. Event adjudicators who do not know the metabolic results should classify stroke mechanism using vessel and cardiac investigations. Then the central prediction is straightforward: clearance-related phenotypes should preferentially predict atherothrombotic burden, not emboli from unrelated causes.

Intestinal sterol entry, hepatobiliary cholesterol handling, apoB-particle circulation, plaque retention and endothelial activation form one conceivable sequence. A separate sequence begins with atrial fibrillation or ventricular injury and ends in cardioembolism. These mechanisms can coexist without being reducible to a single “fat-processing” defect. The stronger controversial proposition is not that all strokes are biliary; it is that undermeasured sterol-handling abnormalities could explain part of the residual risk of atherothrombotic events even after standard lipid measures are taken into account.

Which stroke mechanism should respond?

A future paper ought also to address reversibility. If the upstream abnormality is corrected, do plaque development or event rates change, and over what timescale? Short-term modification of a bile-acid concentration is not equivalent to reversing a complex plaque. Mechanisms that took years to produce a lesion will often resist interpretation through brief nutritional experiments. The conceptual advance is a layered causal theory, not the suggestion that a single metabolic measurement can stand in for vascular imaging.

The distinction between clearance and atherogenic exposure. Even a strong association between biliary variables and stroke would require explanation of how altered transport changes the number, duration or characteristics of particles capable of entering arterial walls. A fall in total serum cholesterol after a digestive intervention would not isolate this pathway if weight, diet, medication and insulin sensitivity changed simultaneously. Measurements of apoB, plant sterols when indicated, bile-acid metabolism and lesion-specific imaging could help separate the stages. A causal model predicts the direction of each effect in advance, rather than selecting favorable markers afterward.

Anatomy as a negative control. A useful negative-control outcome would be a stroke mechanism that has no credible direct dependence on long-term plaque retention, such as certain dissections. If a candidate biomarker predicted dissection and large-artery atherosclerosis equally after adjustment, it might be acting as a nonspecific illness or age marker rather than a specific cholesterol-clearance mechanism. This would not make the biomarker useless, but it would undercut the narrow causal thesis. Likewise, an association appearing only after an infarct could reflect acute tissue injury or the

accompanying stress response.

The clinical horizon. Treatment of the acute occlusion, investigation of its source and modification of chronic risk operate on very different clocks. A novel enterohepatic strategy might eventually act on years-long plaque biology; it cannot be expected to reopen an occluded brain artery in minutes. Preserving this time distinction permits a bold systemic hypothesis without compromising the life-saving value of rapid stroke care.

The decisive cohort would obtain sterol and bile-acid measurements before stroke, record serial apoB and plaque morphology, and classify events by blinded imaging review. The hypothesis predicts greater specificity for large-artery atherosclerosis than for unrelated dissection or primary cardiac embolism. An association equally strong across every stroke subtype would argue against the proposed pathway and toward a nonspecific risk marker.

What would distinguish the hypotheses? Evidence for ABCG5/ABCG8 dysfunction or major sterol abnormalities would support a sterol-handling component in an unusual case. Evidence for a left atrial appendage thrombus, atrial fibrillation or a spontaneous cervical artery dissection would favor alternative proximate causes. A convincing explanatory model must identify the stage at which each factor acts, not simply claim that the last event was “downstream.”

The clinically important counterexample

Imagine two otherwise similar patients with large-artery disease. One has a marked apoB burden and a progressive carotid plaque; the other has a stable plaque but develops a new embolic event from a cardiac source. A theory about impaired cholesterol clearance should predict much more about the first course than the second. This is not a concession that the theory is unimportant. It is an essential sharpening of its proposed domain. A biologically specific hypothesis can win by identifying a substantial subset of cases that are currently grouped with heterogeneous others. Conversely, if a laboratory measure taken in the hospital after the stroke is interpreted as proof of a years-long metabolic problem, time order has been lost. Acute inflammation, reduced oral intake, hospitalization and treatment may all change the analyte. The more persuasive design samples before disease and adjudicates the event afterward. A genuine enterohepatic contribution would likely take the form of altered plaque risk and susceptibility to thrombosis, not a claim that poor fat digestion physically sends intact dietary lipids into brain vessels.

The decisive contrast is anatomical

An investigator could use plaque imaging as an intermediate outcome to connect lipid-handling abnormalities to the tissue in which they are expected to matter. If an abnormal sterol signature correlates with atherosclerotic disease in one arterial bed but no others, the anatomical pattern deserves explanation. Differences in shear, vessel diameter, age and local inflammation may shape that distribution. By contrast, an association with stroke based only on discharge codes risks hiding substantial diagnostic heterogeneity. Stroke subtype adjudication should be independent of experimental biomarker data, with the source and timing of each measurement recorded. The evidence would become much more persuasive if abnormal clearance preceded plaque formation and if a treatment addressing that pathway subsequently affected lesion progression without relying solely on a change in serum concentration. The dramatic causal thesis should be argued through those intermediate events rather than by treating a distant antecedent as equivalent to the final clot.

It would be disproved as a general thesis by stroke subgroups in which plaque biology is irrelevant. Lacunar infarction related to arteriolosclerosis, atrial-fibrillation-associated embolism, and arterial dissection have different proximate mechanisms. Even in atherosclerotic disease, serum cholesterol concentration, apoB burden, hypertension, diabetes, smoking and inherited factors may better explain risk than a presumed bile-flow defect. The distinction between circulating lipoprotein particles and fat malabsorption is indispensable.

The practical research question is not “does bile blockage cause stroke?” but “which measurable transport phenotype predicts which stroke mechanism after standard risk factors are considered?” Useful measures include apoB, lipoprotein phenotype, relevant genetic findings, hepatic disease when clinically indicated, carotid and intracranial imaging, cardiac rhythm evaluation and stroke-territory concordance. No dietary cleanse should be substituted for acute stroke reperfusion assessment or proven secondary prevention.

Sources and research leads

1. [Sitosterolemia: a review and update of pathophysiology, clinical spectrum, diagnosis, and management](#)
2. [Sitosterolemia: Twenty Years of Discovery of ABCG5 ABCG8](#)
3. [Recent Advances in the Digestive, Metabolic and Therapeutic Effects of FXR and FGF19](#)

Additional clinical guideline: [2026 AHA/ASA Guideline for the Early Management of Acute Ischemic Stroke](#)

Editorial status: Third-pass conceptual research manuscript. The argument has been individually strengthened and shared boilerplate removed. Original reference leads were retained; a complete independent source-by-source scholarly verification has not been performed. No new clinical trial data are presented.