

Why Stroke Cannot Be Treated as One Disease

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Abstract

“Stroke” describes a clinical syndrome, not a single etiology. Ischemic arterial occlusion, intracranial hemorrhage, cerebral venous thrombosis and stroke mimics require different reasoning and sometimes mutually incompatible treatments. This paper argues that any root-cause theory of stroke must be partitioned by mechanism before it can be evaluated.

One name conceals multiple vascular causes

The word “stroke” hides multiple diseases with different initiating mechanisms, and research that pools them can erase real subtype-specific metabolic signals.

For ischemic disease the relevant etiologies include large-artery atherosclerosis, cardioembolism, small-vessel occlusion, arterial dissection, prothrombotic disorders and other determined or undetermined causes. Even within one broad category, a proximal embolus and local in-situ thrombosis imply different preventive strategies. The central distinction is between predisposition, vessel event and brain response: hypertension can increase small-vessel risk; atrial fibrillation can generate emboli; infarct size and collateral flow shape outcome.

A terrain-based explanation can contribute if it identifies a measurable upstream exposure that maps onto a recognized phenotype. For example, cholesterol-handling abnormalities are more directly relevant to atherosclerotic mechanisms than to traumatic dissection. An infection-associated cardiomyopathy may lead to cardioembolism, whereas a retinal vascular event may signal systemic risk without revealing the precise causal pathway. Mechanism-specific thinking prevents one attractive explanation from becoming universal.

Why mechanism-specific prevention matters

Classification is not just taxonomy; it predicts different interventions. Large-artery disease may motivate evaluation of local stenosis and plaque, atrial fibrillation may require anticoagulation, and hemorrhagic stroke makes some antithrombotic interventions immediately hazardous. Small-vessel pathology is strongly shaped by longstanding vascular risk, while dissection involves a lesion in the arterial wall. There are also mixed-mechanism patients: an older person can have carotid plaque and intermittent atrial fibrillation together. The clinician must determine which abnormality explains the current event and whether both require prevention. An inclusive systems theory should make this differentiation easier, not erase it.

The category “stroke” bundles events whose final shared feature is inadequate blood supply, not events with a universal initiating defect. Large-artery atherosclerosis requires attention to plaque, artery-to-artery embolism and stenosis. Cardioembolic disease asks about atrial fibrillation, ventricular thrombus and structural heart disorders. Small-vessel infarction may reflect longstanding blood-pressure effects in penetrating arteries. Dissection introduces mechanical vessel-wall injury, and inflammatory or hypercoagulable states produce still other pathways. This diversity is not a reason to abandon systemic theory; it is a requirement for system-specific predictions.

The proposed biliary and lipid hypotheses might have a defined role within atherothrombotic stroke, perhaps by modifying apoB exposure or inflammatory plaque biology. They may have less explanatory power in a young patient with vertebral dissection or an older patient with a documented intracardiac clot. A rigorous synthesis should estimate how frequently each pathway is implicated before generalizing to the whole stroke population.

Atherosclerotic occlusion, atrial-fibrillation embolism, lacunar infarction, dissection and intracerebral hemorrhage share clinical urgency but not one pathogenesis. A metabolite that correlates with large-artery plaque may be irrelevant to dissection; a drug preventing cardioembolism may not prevent artery-to-artery thrombosis. The Institute's argument should challenge studies that use stroke as a homogeneous endpoint while still respecting the diagnostic value of the syndrome in emergency care.

The cost of pooled stroke cohorts

Treatment also depends on mechanism and time. A person with atrial fibrillation may require anticoagulation for prevention, whereas a person with large-artery plaque may require a different combination of therapies and risk-factor management. These clinical distinctions are not merely procedural details; they are evidence that the causal pathways have different actionable nodes. A universal upstream story that predicts the same treatment for every stroke is inferior to a pluralistic model that can actually guide care.

Three superficially similar examples. A patient with carotid plaque and ipsilateral cortical infarction illustrates a plausible artery-to-artery pathway. A patient with abrupt multifocal infarcts and atrial fibrillation suggests a cardiac embolic source. A patient with a small deep infarct and chronic hypertension raises a different penetrating-vessel mechanism. These are hypothetical contrasts, not descriptions of actual patients. They demonstrate why a single metabolic pattern might be relevant to one mechanism and peripheral to another.

Classification is imperfect. Stroke etiologies are often assigned under uncertainty, and multiple potential causes may coexist. Atherosclerosis and atrial fibrillation are common enough for the same person to have both. Research must distinguish “possible,” “probable” and “demonstrated” causal attribution, preferably through blinded adjudication and sensitivity analyses. Otherwise a putative biliary marker may appear to predict a subtype merely because the classification itself incorporated correlated risk factors.

A prediction with clinical value. If altered sterol disposal preferentially predicts progressive atherosclerotic plaque and events in related territories, but not unrelated mechanisms, it could help

select patients for mechanistic study. If it predicts all stroke phenotypes without an identified common pathway, confounding becomes a stronger explanation. The practical value of stroke heterogeneity is that it gives original terrain theories a rigorous opportunity to be right about something specific rather than wrong about everything.

Reanalyze cohorts by adjudicated mechanism, incident versus recurrent events, lesion territory and time from onset to sampling. Seek interactions instead of a single pooled association. If a proposed biliary or lipid signature predicts only plaque-driven events, that selective result strengthens the theory. A pooled null result would not necessarily refute a genuine subtype effect, but post hoc subgroup mining would still need replication.

A good stress test for any proposed unified mechanism is whether it explains a cerebral venous thrombosis, deep small-vessel lacune and embolic cortical infarct equally well. If the explanation changes definitions to encompass all three, it has probably ceased to discriminate. The value of a model depends on excluding some alternatives in addition to explaining those it favors.

A pooled answer can conceal opposite mechanisms

A study of a hypothetical blood biomarker may find little association with the general label of ischemic stroke. On closer inspection, the association might be strong in extracranial atherosclerosis, absent in atrial-fibrillation embolism and opposite in certain unusual etiologies. The pooled statistic conceals this because the outcome includes events generated by different biological machinery. That result is not sufficient proof of subgroup causality; after-the-fact slicing of data can create chance discoveries. The correct way forward is to propose the interaction in advance and reproduce it in an independently adjudicated cohort. Stroke severity also needs separation from stroke occurrence. A compound that correlates with larger infarcts could affect collateral flow or inflammatory secondary injury without having caused the original arterial occlusion. These are distinct and potentially valuable findings, but each asks a different research question. A new metabolic stroke theory should be judged by how specifically it predicts anatomy, mechanism and timing, not by the number of vascular outcomes it can be made to mention.

What subtype-sensitive research could reveal

Classification errors can erase true metabolic signals. If a study groups patients by the broad label of ischemic stroke, a transport phenotype relevant to plaque formation may be diluted by many cases caused by arrhythmia or dissection. Conversely, selectively reclassifying events after observing the biomarker may create an artificial subgroup that appears to confirm the hypothesis. The safeguard is to define etiologic categories and analytic plans before examining the candidate marker. A well-characterized cohort could identify both the circumstances in which the proposed pathway predicts an event and those in which it demonstrably does not. Showing that a biliary phenotype has little association with a mechanism it should not affect is valuable evidence of specificity. Systems explanations should welcome such negative-control comparisons because they transform a broad causal slogan into a predictive, limited and potentially useful theory.

Stroke-like deficits can result from seizures, hypoglycemia, migraine and functional neurological symptoms. Conversely, a normal initial CT may fail to visualize an early ischemic infarct; the scan's

clinical role includes excluding hemorrhage and assessing reperfusion candidacy. A convincing alternate diagnosis must explain localization and time course, not simply coexist with a negative early scan.

Every future ABSURD stroke paper should state the lesion's vascular territory, likely occlusion mechanism, the relevant evidence and the uncertainty. The most humane consequence of better theoretical classification is faster recognition of situations where immediate stroke evaluation remains necessary. Exploratory explanations and emergency treatment must never compete for time.

Sources and research leads

1. [Navigating the clinical landscape of artery of Percheron infarction: A systematic review](#)
2. [Sitosterolemia: a review and update of pathophysiology, clinical spectrum, diagnosis, and management](#)

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.