

Review Article

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Palm Tocotrienol-Rich Vitamin E In CADASIL And Cerebral Small-Vessel Disease: From Neurovascular Mechanistic Promise to Clinical Futility And Next-Generation Disease-Modifying Investigation

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ABSTRACT

Palm-derived tocotrienols have attracted sustained interest as nutraceutical candidates for cardiometabolic disease because experimental studies suggest effects on cholesterol synthesis, oxidative stress, inflammation, endothelial biology, and metabolic signalling. However, the clinical evidence for conventional lipid lowering is substantially less consistent than mechanistic narratives often imply. This critical qualitative literature review examines the apparent discrepancy between biological plausibility and human clinical outcomes. Contemporary randomized evidence does not support a reproducible, clinically substantial reduction in low-density lipoprotein cholesterol, total cholesterol, or triglycerides across populations and formulations, although selected studies report improvements in high-density lipoprotein cholesterol, inflammatory biomarkers, oxidative stress, insulin resistance, or related metabolic endpoints. Interpretation is complicated by heterogeneity in tocotrienol isomers, palm tocotrienol-rich fraction composition, α -tocopherol content, formulation, dose, bioavailability, participant phenotype, background diet, concomitant pharmacotherapy, and outcome selection. We therefore propose a “lipid-centric versus pleiotropic” model. Under the lipid-centric model, current evidence is insufficient to position tocotrienols as alternatives to established LDL-lowering therapy. Under the pleiotropic model, their antioxidant, anti-inflammatory, metabolic, and potentially endothelial actions remain biologically and clinically interesting but require stronger translational validation. Future trials should employ standardized preparations, pharmacokinetic verification, contemporary lipoprotein phenotyping, vascular-function measurements, adequate treatment duration, documented background therapy, and ultimately cardiovascular outcomes.

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Introduction

CADASIL is a paradigmatic inherited cerebral small-vessel disease (CSVD) because a defined molecular lesion can be followed across several biological levels, from a NOTCH3 variant to vascular wall pathology, white-matter damage, stroke, cognitive decline and disability. Pathogenic variants most often alter the number of cysteine residues within epidermal growth factor-like repeats of the NOTCH3 extracellular domain, and the disease classically manifests with migraine, recurrent subcortical ischemic events, mood or psychiatric symptoms, executive dysfunction and progressive functional impairment. Contemporary population genetics has also shown that cysteine-altering NOTCH3 variants are more common and more variably penetrant than the historical picture of a uniformly severe familial disorder suggested, creating a spectrum that ranges from nonpenetrance or mild MRI abnormalities to classical CADASIL [1-5].

This expanded spectrum has sharpened rather than weakened the importance of CADASIL as a translational model. Variant position and aggregation propensity contribute to clinical heterogeneity, and high-risk variants are associated with earlier stroke and faster radiological progression. NOTCH3 extracellular-domain deposition is not merely a diagnostic histological curiosity:

recent studies connect greater aggregation burden with more severe vascular and imaging phenotypes, while experimental work indicates that mutant and wild-type NOTCH3 extracellular domains can co-aggregate and drive arterial pathology. These findings position abnormal NOTCH3 protein accumulation upstream of many of the endothelial, inflammatory and white-matter abnormalities observed later in the disease course [6-10].

Despite increasing molecular precision, CADASIL still lacks a proven disease-modifying treatment. Current clinical care therefore relies on individualized management of vascular risk factors, cautious use of conventional stroke-prevention strategies, rehabilitation and symptom-directed treatment. The American Heart Association scientific statement on inherited central nervous system small-vessel diseases emphasizes the absence of high-quality evidence for a therapy that changes the underlying CADASIL disease trajectory, and recent clinical reviews continue to identify this as the principal therapeutic gap [11-13].

Tocotrienol-rich vitamin E emerged as an attractive candidate because its proposed actions overlap several downstream mechanisms implicated in CSVD. Tocotrienols share the chromanol ring of tocopherols but possess an unsaturated isoprenoid side chain that influences membrane behavior, metabolism and tissue distribution. Palm-derived tocotrienol-rich fractions typically contain multiple tocotrienol isomers and some tocopherol. Preclinical literature has linked tocotrienols to

free-radical scavenging, reduced lipid peroxidation, modulation of nuclear factor-kappa B signaling, mitochondrial protection, anti-apoptotic effects and attenuation of neuroinflammation. These mechanisms are relevant to an arteriopathy in which oxidative stress, endothelial dysfunction, blood-brain barrier (BBB) disruption and neurovascular-unit failure may magnify tissue injury [14-18].

The translational problem is that biological plausibility is not equivalent to clinical efficacy. Tocotrienol pharmacokinetic studies demonstrate oral absorption but also show marked variation among formulations and isomers, while randomized trials in non-CADASIL populations produce heterogeneous changes in circulating inflammatory and oxidative biomarkers. A compound can therefore alter systemic redox biology without necessarily reaching the relevant cerebral microvascular compartment at a sufficient concentration or modifying the causal lesion in a NOTCH3 proteinopathy [19,20].

The decisive contemporary development was the T3CAD trial, published in 2026. In this randomized, double-blind, placebo-controlled study, 51 genetically confirmed CADASIL patients received a tocotrienol-rich vitamin E complex or placebo for 24 months. The primary composite endpoint was treatment failure, defined by stroke occurrence, disability progression or cognitive decline. Treatment failure occurred in 68.0% of participants receiving active treatment and 61.5% receiving placebo; Bayesian analysis met prespecified futility criteria, and no significant benefit was detected in secondary clinical or exploratory MRI outcomes. Safety was acceptable, but the trial did not support disease modification in the treated population [21].

This negative trial does not make the tocotrienol question scientifically irrelevant. On the contrary, it creates a rare opportunity to ask why a biologically credible downstream intervention failed in a genetically defined human arteriopathy. The central interpretive issue is whether tocotrienols were targeting a pathway that is causal enough, early enough and accessible enough to change longitudinal disease progression. The present qualitative literature review therefore examines the NOTCH3-to-tissue-injury cascade, the role of neurovascular oxidative and inflammatory amplification, the distinction between neuroprotection and vasculoprotection, tocotrienol pharmacology, the T3CAD findings, emerging biomarkers and the design principles required for next-generation CADASIL trials.

Literature Review: Conceptual and Theoretical Foundations

The modern molecular model of CADASIL begins with NOTCH3 rather than with nonspecific ischemia. NOTCH3 is expressed prominently in vascular smooth-muscle cells and pericytes, where it participates in mural-cell differentiation and vascular homeostasis. Most pathogenic CADASIL variants create an odd number of cysteines in an extracellular epidermal growth factor-like repeat, favoring aberrant folding, extracellular-domain accumulation and granular osmiophilic material in small arterial walls. Clinical reviews published since 2020 consistently describe CADASIL as a diffuse non-atherosclerotic, non-amyloid angiopathy of small and medium penetrating vessels rather than as a primary neurodegenerative condition [22-23].

Genotype matters because the location of a cysteine-altering variant influences both aggregation and phenotype. UK and international cohort studies show that variants within EGFr domains 1-6 are associated with earlier stroke and more severe disease than many variants located more distally. The same biological gradient is

visible in tissue: proximal high-risk variants tend to produce a larger NOTCH3 aggregation burden in skin and brain vasculature. A three-tier concept of high-, moderate- and lower-risk NOTCH3 variant categories has therefore become useful for prognosis and trial enrichment rather than treating all pathogenic variants as equivalent [24].

Experimental work by Dupré and colleagues provides particularly important causal evidence. In CADASIL mouse models, vascular pathology tracked the burden of NOTCH3 extracellular-domain aggregates more closely than changes in canonical NOTCH3-regulated gene expression. Wild-type and mutant extracellular domains co-aggregated, and reducing wild-type NOTCH3 in the mutant background attenuated vascular aggregation and pathology. This supports a neomorphic or toxic aggregation mechanism and implies that interventions acting directly on NOTCH3 production, aggregation or clearance may be more disease proximal than interventions targeting downstream oxidative stress alone.

The second conceptual layer is the neurovascular unit. Brain homeostasis depends on coordinated signaling among endothelial cells, vascular smooth-muscle cells, pericytes, astrocytes, neurons, oligodendrocytes and extracellular matrix. Endothelial cells regulate nitric oxide, vascular tone, leukocyte trafficking, thrombosis and BBB permeability, while mural cells maintain microvascular structure and reactivity. Across CSVD, endothelial dysfunction has emerged as a central process that couples vessel disease to parenchymal injury, although contemporary work also cautions against reducing pathogenesis to the endothelium alone [25-28].

CADASIL is especially instructive because its upstream mural-cell pathology can converge on downstream mechanisms shared with sporadic CSVD. Chronic vessel-wall dysfunction can impair vasoreactivity and autoregulation, increase pulsatile stress, alter perfusion and disturb endothelial signaling. In 2026, experimental work on the common Asian NOTCH3-R544C variant showed endothelial inflammatory activation, impaired migration and lipid dysregulation, providing additional evidence that endothelial pathology can participate in a disease historically viewed mainly through vascular smooth-muscle cells [29]. These data do not prove that endothelial dysfunction is the initiating lesion, but they place it firmly within the propagation phase of NOTCH3 vasculopathy.

BBB dysfunction is another important bridge between vascular and tissue pathology. The BBB is a highly regulated multicellular interface, and its disruption permits abnormal flux of plasma proteins, water, iron-associated products and inflammatory mediators into vulnerable tissue. Direct CADASIL evidence includes MRI-associated iron leakage consistent with barrier disruption, whereas broader CSVD research indicates that BBB dysfunction can precede or accompany lesion progression and cognitive decline [30-32]. The implication is that barrier failure may amplify white-matter damage even if it is not the first event in the causal sequence.

A 2026 synthesis further positions BBB disruption as a dynamic hub linking endothelial injury, neuroinflammation, lipid dysregulation and impaired perivascular clearance in CSVD. This perspective strengthens the rationale for mechanism-matched BBB and endothelial biomarkers, while also underscoring that a downstream barrier effect should not be equated with correction of the initiating NOTCH3 lesion in CADASIL [33].

Oxidative stress fits naturally into this network. Reactive oxygen species can reduce nitric-oxide bioavailability, modify membrane lipids and proteins, injure endothelial mitochondria, destabilize tight junctions and activate redox-sensitive inflammatory pathways. Neuroinflammation then feeds back through cytokines, microglial activation, astrocyte responses and further oxidative injury. Reviews of sporadic CSVD increasingly conceptualize oxidative stress, inflammation and endothelial dysfunction as interacting modules rather than independent causes [34,35]. This systems view is important for tocotrienols because an antioxidant may reduce one amplification loop without changing the upstream vascular proteinopathy.

Interstitial-fluid and perivascular-clearance abnormalities add another layer. Enlarged perivascular spaces are common MRI markers in CSVD and may reflect altered fluid transport, vessel-wall remodeling or other tissue changes rather than a direct measurement of glymphatic flow. Nevertheless, diffusion-based studies suggest that increased extracellular free water and reduced perivascular diffusion indices can precede or accompany white-matter lesion progression. In CADASIL, impaired cerebral interstitial-fluid dynamics have been demonstrated using advanced diffusion approaches, supporting the possibility that chronic arteriopathy perturbs both perfusion and fluid exchange [36-39].

White-matter injury is the anatomical substrate through which these vascular processes become cognitive and functional disease. CADASIL typically produces diffuse white-matter hyperintensities, lacunes, microbleeds, enlarged perivascular spaces and brain atrophy. Longitudinal MRI studies show measurable progression over two years, and diffusion metrics can change even in younger or premanifest carriers. High-risk NOTCH3 variants are associated with faster progression of stroke, mean skeletonized mean diffusivity and lacune burden, demonstrating that quantitative MRI can capture disease evolution within a time horizon suitable for clinical trials [40].

Cognitive impairment in CADASIL is not well represented by a single global score. Executive dysfunction, processing-speed decline and network disconnection often occur before severe global dementia. Multimodal neuroimaging has shown default-mode-network structural, metabolic and functional abnormalities linked to cognitive performance, while Japanese registry data associate lacunes, microbleeds and white-matter lesion severity with poorer cognition [41,42]. These findings matter for therapeutic trials because a composite endpoint that relies on insensitive cognitive thresholds may miss biologically meaningful early change.

Disease staging has therefore become a major advance. The 2025 NOTCH3-SVD staging system spans premanifest disease through end-stage disability and was validated across large international cohorts. Stages correlate with imaging injury, cognition, neurofilament light chain and long-term outcomes, yet many participants remain in the same categorical stage over two years. This combination slow categorical transition but measurable continuous biomarker change strongly argues for stage-informed enrollment and quantitative surrogate outcomes in early-phase studies [43].

Blood biomarkers may complement imaging. Plasma neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP) are elevated in CADASIL and have been associated with prevalent and incident stroke phenotypes; longitudinal work further supports serum NfL as a candidate marker of evolving neuroaxonal injury

[44,45]. In broader CSVD, biomarker studies increasingly examine endothelial, inflammatory and neuroaxonal signals, while circulating PECAM-1 has been linked to lesion burden, cognitive decline and incident dementia in prospective cohorts [46,47]. These biomarkers are promising for monitoring but remain downstream and nonspecific, so they should not be mistaken for direct measures of NOTCH3 target engagement.

Recent syntheses published in 2025-2026 reinforce the need for multimodal biomarker panels rather than reliance on any single analyte. Reviews integrating neuroimaging, blood and cerebrospinal-fluid evidence emphasize that candidate markers differ in biological proximity and disease specificity; accordingly, combining endothelial or vascular markers with NfL/GFAP and quantitative MRI may improve phenotyping and longitudinal monitoring, although prospective validation in monogenic CSVD remains necessary [48-50].

The imaging field has also become more standardized. STRIVE-2 updated definitions and research standards for small-vessel disease neuroimaging, emphasizing conventional lesions together with quantitative tissue and diffusion measures. Free-water imaging is particularly relevant because elevated free water in normal-appearing tissue can predict later FLAIR white-matter hyperintensity progression, and BBB disruption and free water are associated with worse cognition in chronic cerebrovascular disease [51,52]. These methods create an opportunity to detect biologically earlier effects than stroke or disability endpoints.

Against this disease architecture, tocotrienol pharmacology must be examined carefully. Tocotrienols differ from tocopherols in the unsaturation of the isoprenoid side chain, which affects transport and membrane behavior. Human pharmacokinetic studies demonstrate meaningful variation by isomer, dose, food conditions and formulation; annatto-derived preparations can show different exposure profiles from palm-derived tocotrienol-rich fractions. Consequently, evidence for one formulation cannot automatically be generalized to another, and plasma exposure does not prove sufficient concentration in the brain microvasculature.

Preclinical evidence for neuroprotection is extensive but disease-nonspecific. Systematic and scoping reviews describe antioxidant, anti-inflammatory, mitochondrial, anti-apoptotic and gene-regulatory effects of tocotrienol-rich fractions in neuronal cell systems and animal models. Tocotrienols also improved learning-related outcomes in a high-fat/high-sucrose mouse model, illustrating biological activity under metabolic stress rather than under genetically determined NOTCH3 arteriopathy [53]. Human brain-health evidence is much smaller and heterogeneous, with a 2025 randomized study of rice-derived tocotrienols reporting selected cognitive benefits in healthy adults with subjective memory concerns but providing no direct evidence for cerebral small-vessel disease modification [54].

Human inflammatory evidence is similarly mixed. A meta-analysis of randomized tocotrienol trials found that an apparent C-reactive-protein reduction was driven heavily by a single delta-tocotrienol study, while pooled effects on interleukin-6, tumor necrosis factor- α and malondialdehyde were not significant. A randomized trial in type 2 diabetes reported favorable changes in glycemic, inflammatory and oxidative biomarkers with delta-tocotrienol, confirming that human biological activity is possible but not demonstrating cerebral target engagement. The translation from systemic biomarker change to NOTCH3-related microangiopathy

therefore remained an untested assumption until T3CAD.

Method

This article was designed as a qualitative literature review rather than a systematic literature review. Its objective was explanatory synthesis: to integrate recent genetic, vascular, imaging, biomarker, pharmacological and randomized clinical evidence into a coherent translational framework. It was not intended to estimate pooled effect sizes, produce a PRISMA-based exhaustive retrieval claim or rank evidence through a formal systematic risk-of-bias instrument. The methodological choice reflects the review question, which concerns relationships among mechanisms operating at different causal levels rather than a single narrowly defined intervention-outcome comparison.

The evidence base emphasized peer-reviewed journal articles published from January 2020 through October 2026. Searches were conducted primarily in PubMed/MEDLINE and were supplemented by targeted citation chaining using combinations of CADASIL, NOTCH3, cerebral small-vessel disease, tocotrienol, vitamin E, oxidative stress, neuroinflammation, endothelial dysfunction, blood-brain barrier, white matter, glymphatic or interstitial fluid, MRI, neurofilament light chain, cognition, stroke and clinical trial. Recent authoritative scientific statements, narrative reviews and scoping or systematic reviews were used to contextualize primary studies, while direct human CADASIL evidence was prioritized whenever available.

A translational evidence hierarchy was applied during synthesis. Tier 1 consisted of randomized or longitudinal human CADASIL data. Tier 2 consisted of cross-sectional human CADASIL biomarker, imaging, genetic and pathological studies. Tier 3 consisted of human sporadic-CSVD studies that interrogated mechanisms shared with CADASIL. Tier 4 consisted of human tocotrienol pharmacokinetic or supplementation studies outside CADASIL. Tier 5 consisted of experimental and preclinical tocotrienol evidence. This hierarchy was not a formal grading system; it was an interpretive safeguard against allowing abundant preclinical evidence to outweigh sparse disease-specific human evidence.

Three analytical distinctions guided data interpretation. First, an association with disease severity was not assumed to demonstrate causal priority. Second, systemic biological activity was not considered equivalent to cerebral or neurovascular target engagement. Third, neuroprotection and vasculoprotection were treated as mechanistic categories, whereas disease modification was reserved for evidence of sustained alteration in the longitudinal natural history of CADASIL. This distinction was essential because a treatment may reduce oxidative injury yet fail to alter

NOTCH3 aggregation, stroke risk, MRI progression or disability.

Thematic synthesis proceeded across six domains: upstream NOTCH3 proteinopathy; neurovascular-unit and BBB dysfunction; oxidative and inflammatory amplification; interstitial-fluid and white-matter injury; tocotrienol pharmacology and biological plausibility; and clinical translation through T3CAD and next-generation trial design. Contradictory findings were retained and used analytically rather than excluded. In particular, positive mechanistic and biomarker evidence for tocotrienols was interpreted together with, not separately from, the negative randomized CADASIL trial.

The final reference set was restricted to publications from 2020 to 2026 and includes only sources cited in the manuscript. DOI links are provided to improve traceability and access. Because the review is qualitative, the findings should be interpreted as a structured scholarly synthesis rather than an exhaustive systematic inventory of every publication within the date range.

Results: Thematic Findings

The first theme was that CADASIL is best understood as an upstream vascular proteinopathy with downstream neurovascular consequences. Population studies demonstrate a broad NOTCH3 phenotype, but tissue and genotype studies consistently show that variant location and aggregation propensity influence severity. This provides a mechanistic basis for separating proximal disease biology from later oxidative or inflammatory consequences.

The second theme was that oxidative stress, inflammation, endothelial dysfunction and BBB injury form a plausible amplification network but are not yet proven to be the initiating lesion in CADASIL. Evidence from CSVD and CADASIL supports endothelial impairment, barrier leakage, mitochondrial oxidative injury and inflammatory signaling, while recent NOTCH3-R544C experimental findings extend this network to endothelial migration and lipid homeostasis. This supports therapeutic interest in redox biology but also limits claims that antioxidant treatment directly corrects CADASIL pathogenesis.

A proposed mechanistic cascade in Figure 1 separates the initiating NOTCH3 proteinopathy from downstream vascular, inflammatory, and tissue-level consequences. This distinction is central to interpreting tocotrienol evidence because the compound is most plausibly linked to downstream redox, inflammatory, mitochondrial, and endothelial processes rather than to direct removal or correction of NOTCH3 extracellular-domain aggregates.

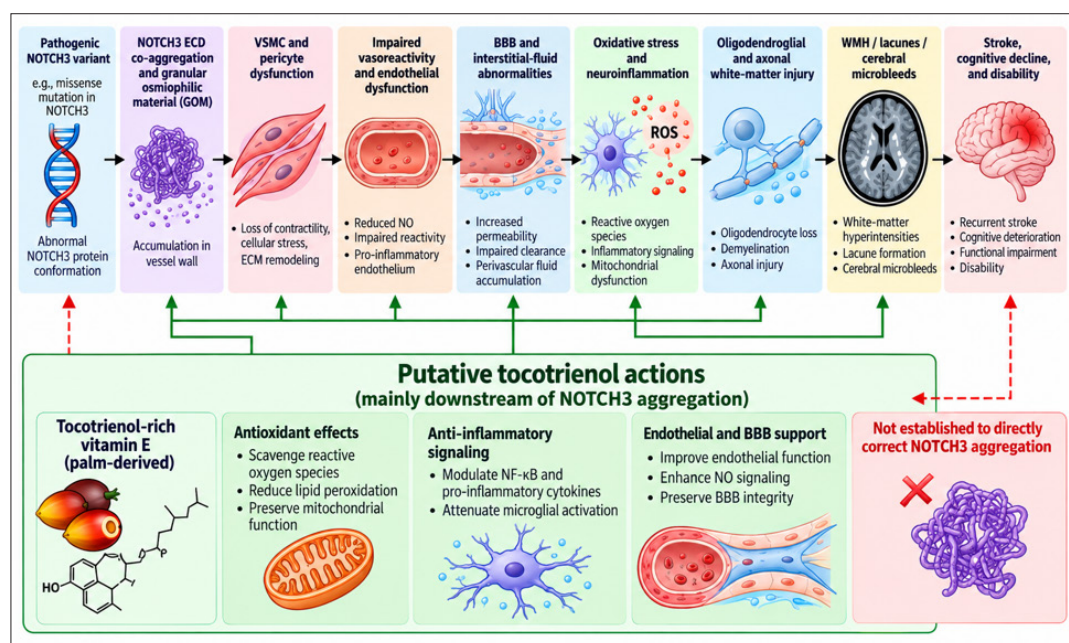


Figure 1: Multilevel Pathobiological Cascade of Cadasil and Putative Tocotrienol Intervention Points

Figure 1 shows that the schematic should be read from left to right as a causal hierarchy rather than as a claim that every step is strictly linear. Feedback loops undoubtedly occur among endothelial dysfunction, BBB leakage, oxidative stress and inflammation. Nevertheless, the upstream location of NOTCH3 aggregation provides an important therapeutic benchmark: demonstrating antioxidant activity is not the same as demonstrating disease modification.

The third theme concerned fluid and white-matter homeostasis. Perivascular-space abnormalities, increased extracellular free water and altered diffusion signatures suggest that chronic small-vessel pathology affects interstitial transport as well as perfusion. In CADASIL, advanced diffusion metrics indicate impaired interstitial-fluid dynamics; in sporadic disease, free-water elevations can precede conversion of normal-appearing tissue to FLAIR-visible lesions. These findings favor biomarkers that capture active tissue injury rather than only fixed lesion burden.

The fourth theme was the mismatch between tocotrienol mechanistic evidence and disease-specific clinical evidence. Preclinical literature supports antioxidant and anti-inflammatory actions, and human studies demonstrate oral exposure and selected systemic biomarker effects. Yet formulation-dependent pharmacokinetics, limited direct brain exposure data and heterogeneity in human responses weaken the inferential chain from supplementation to cerebral small-vessel modification.

The fifth and most important theme was the T3CAD result. The randomized trial enrolled 51 genetically confirmed patients and tested a tocotrienol-rich vitamin E complex for 24 months. Treatment failure occurred more often numerically in the active group than in placebo, Bayesian futility criteria were met and no meaningful advantage appeared in secondary or exploratory MRI outcomes, although safety was favorable. This is direct evidence against disease-modifying efficacy for the tested regimen in a population with established CADASIL and must dominate interpretation of tocotrienol claims in this specific disease.

The sixth theme was that negative efficacy does not identify the exact point of failure in the translational chain. The intervention may have failed because oxidative stress was too downstream, because the relevant neurovascular compartment was insufficiently exposed, because irreversible structural injury was already advanced, because the formulation or dose was suboptimal, or because the endpoints were insensitive. A clinical futility result integrates all of these possibilities. It therefore justifies a negative efficacy conclusion but not a precise mechanistic conclusion about which upstream or pharmacological step failed.

The seventh theme was that disease stage and genotype are now measurable enough to support more efficient trial designs. The NOTCH3-SVD staging system spans premanifest to end-stage disease, while two-year longitudinal imaging shows that high-risk NOTCH3 variants progress more rapidly and that diffusion measures can change in premanifest individuals. Symptomatic progression studies also demonstrate that categorical clinical deterioration is slow and variable, reinforcing the need for enriched populations and continuous biomarkers [55].

The eighth theme concerned the clinical spectrum. CSVD affects more than stroke and global cognition, with overviews of systematic reviews and large biobank analyses identifying broader neuropsychiatric and functional phenotypes. Nevertheless, evidence strength varies across manifestations and imaging markers, and CADASIL-specific trials should avoid overly broad composites that combine events with different biological meanings [56].

The ninth theme was that biomarker panels are more informative when matched to the causal level of the intervention. NfL and GFAP reflect downstream neuroaxonal or glial injury, BBB and free-water imaging reflect tissue and barrier physiology, and NOTCH3 aggregation measures are closer to the upstream disease substrate. A future intervention directed at NOTCH3 should therefore be evaluated with a proximal target-engagement marker plus sensitive imaging and clinical outcomes rather than with inflammatory markers alone.

Discussion and Analysis

The central question raised by T3CAD is not whether tocotrienols possess antioxidant activity. That proposition is supported by substantial experimental work and selected human biomarker studies. The more demanding question is whether those activities occupy a causally dominant position in established CADASIL. The current evidence suggests they do not, at least not to an extent sufficient for the tested tocotrienol-rich formulation to alter 24-month clinical progression. This distinction is the foundation of a more disciplined interpretation of nutraceutical and bioactive-compound research.

A useful causal model separates CADASIL into upstream, intermediate and downstream layers. The upstream layer comprises pathogenic NOTCH3 variation and abnormal extracellular-domain aggregation. The intermediate layer comprises mural-cell dysfunction, altered vessel mechanics, endothelial dysfunction, impaired autoregulation, BBB disturbance and abnormal tissue-fluid exchange. The downstream layer comprises oxidative and inflammatory amplification, oligodendroglial and axonal injury, lacunes, white-matter disconnection, stroke, cognitive impairment and disability. These layers interact bidirectionally, but they are not therapeutically equivalent. A downstream modifier may reduce injury while leaving the initiating process unchanged.

This layered model explains why neuroprotection, vasculoprotection and disease modification must be separated. Neuroprotection concerns neurons, axons, oligodendrocytes, synapses and metabolic resilience. Vasculoprotection concerns endothelial integrity, smooth-muscle and pericyte function, perfusion, BBB stability and vascular reactivity. Disease modification is an evidential claim about natural history. A treatment can plausibly protect mitochondria or reduce inflammatory signaling and still fail to reduce stroke, MRI progression or disability. Conversely, an upstream therapy might slow structural progression before patients perceive symptomatic improvement.

Figure 2 distinguishes neuroprotection, vasculoprotection and disease modification. The first two describe plausible biological effects; the third requires longitudinal evidence that the natural history of CADASIL has been altered. This distinction is necessary when interpreting an intervention such as tocotrienol-rich vitamin E, for which mechanistic evidence is stronger than disease-specific efficacy evidence.

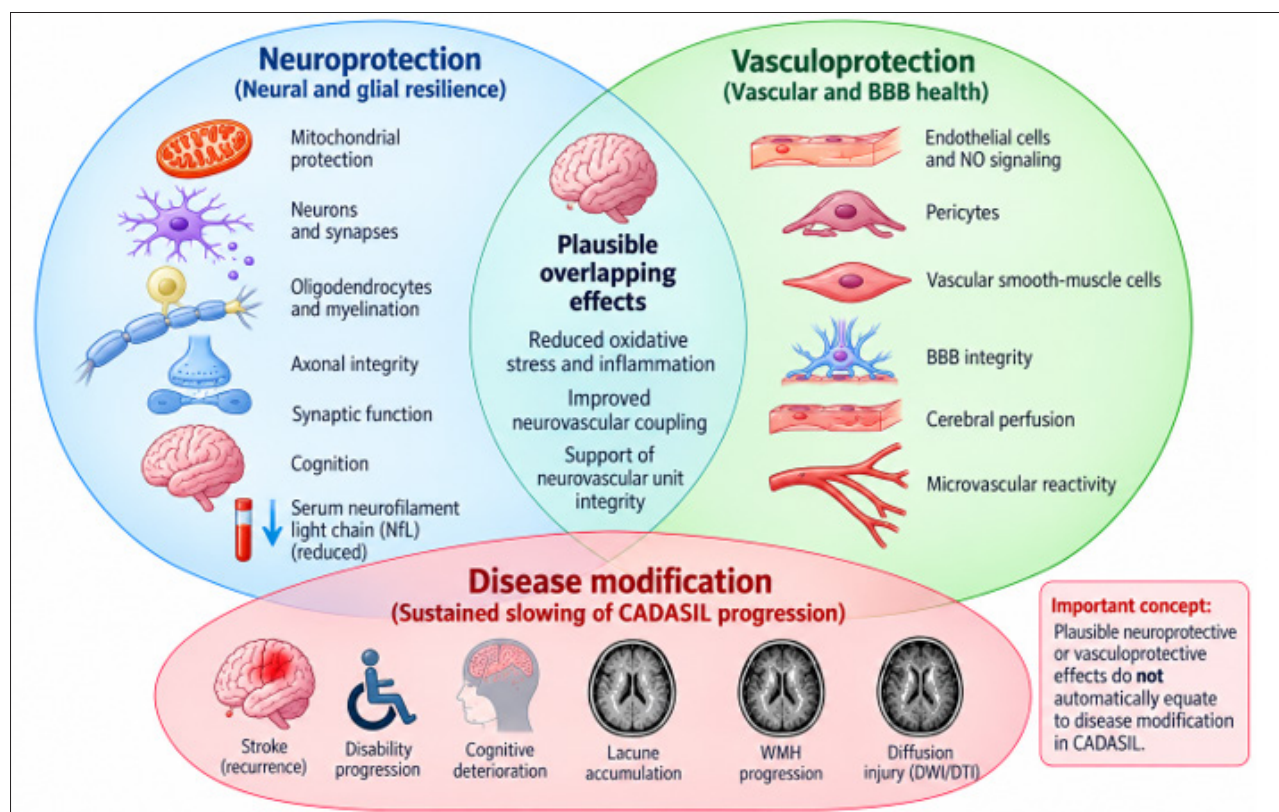


Figure 2: Neuroprotection, Vasculoprotection and Disease Modification As Distinct Evidential Domains

Figure 2 illustrates that neuroprotective outcomes may include reduced neuroaxonal injury or better cognitive-network resilience, whereas vasculoprotective outcomes may involve BBB integrity, perfusion or endothelial function. A treatment becomes disease modifying only when these biological effects translate into sustained slowing of clinically or structurally meaningful progression.

Tocotrienols occupy the first two categories more comfortably than the third. Experimental reviews consistently identify antioxidant and anti-inflammatory effects, and animal models suggest cognitive or neuronal benefits. Yet these models frequently involve metabolic, toxic or neurodegenerative insults that differ markedly from NOTCH3 proteinopathy. The fact that tocotrienols are active in oxidative models therefore establishes mechanism, not indication.

The human evidence also illustrates why target engagement matters. A randomized diabetes study demonstrated reductions in oxidative and inflammatory biomarkers with delta-tocotrienol, while meta-analysis across trials found inconsistent effects on interleukin-6, tumor necrosis factor-alpha and malondialdehyde. Even if such systemic changes are genuine, they leave unresolved whether the relevant small penetrating arteries, endothelial cells, pericytes and white-matter compartments receive sufficient active exposure.

Pharmacokinetics is therefore not a peripheral technical issue. Different tocotrienol isomers and formulations achieve different

exposure profiles, and the evidence base often treats ‘tocotrienol’ as if it were one uniform pharmacological entity. Sharif et al. showed meaningful differences between annatto-based and palm-derived preparations. For CADASIL, the key unknown is not merely plasma concentration but concentration and biological activity at the neurovascular unit. Future mechanistic studies should measure exposure, adherence and a mechanism-matched pharmacodynamic response before advancing to a large efficacy design.

The T3CAD result should be interpreted specifically. It provides evidence that the tested formulation did not produce clinically meaningful disease modification in a cohort with established CADASIL over 24 months. It does not establish that every tocotrienol isomer is inactive, that oxidative stress is irrelevant, or that premanifest intervention must fail. However, the burden of proof has shifted. Any renewed CADASIL tocotrienol program must now explain why a different formulation, dose, disease stage or endpoint is expected to overcome a randomized futility result rather than simply restating preclinical antioxidant mechanisms.

Figure 3 presents a translational evidence ladder. Tocotrienol-rich vitamin E has comparatively strong evidence for chemical antioxidant activity and substantial preclinical neuroprotection, moderate but heterogeneous evidence for human systemic pharmacokinetics and biomarkers, limited direct evidence for cerebral target engagement, and negative randomized evidence for clinically meaningful CADASIL disease modification.

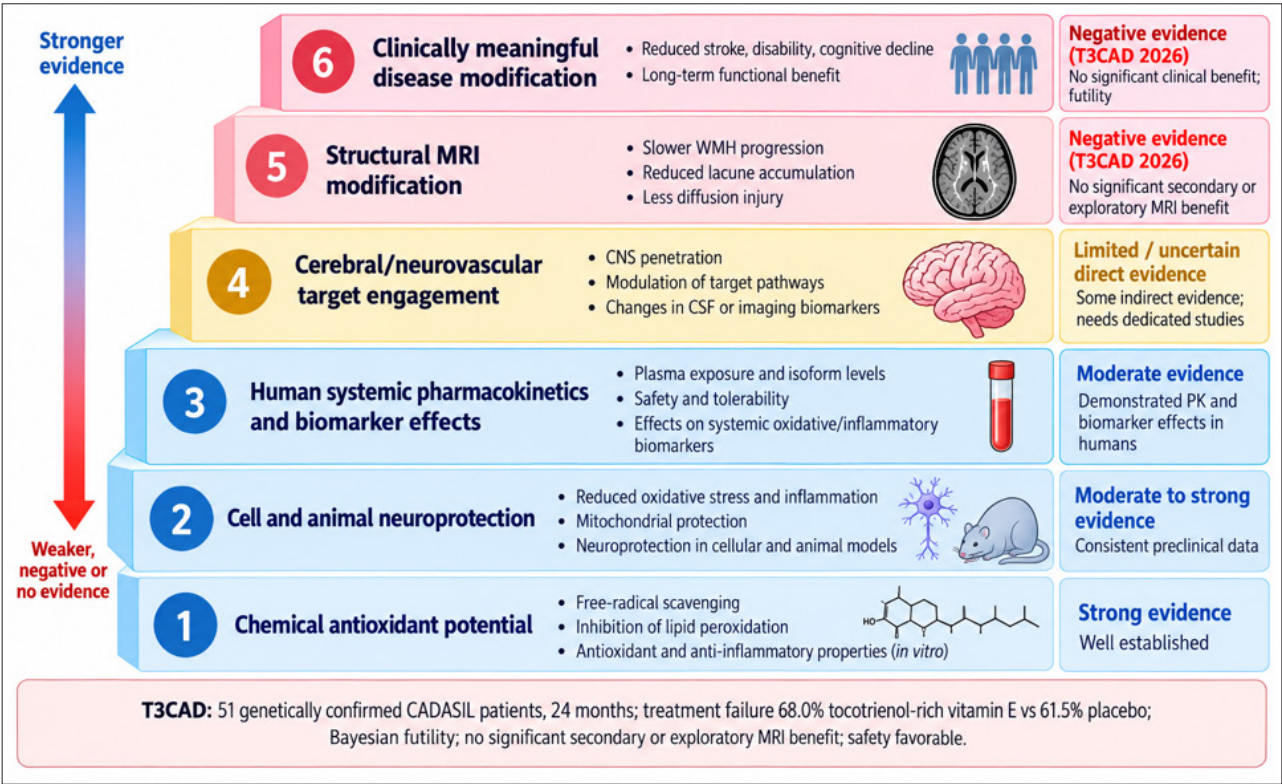


Figure 3: Tocotrienol Translational Evidence Ladders From Chemical Activity to Clinical Disease Modification

Figure 3 illustrates that the central gap is therefore not the absence of any biological effect, but the failure to establish a continuous evidence chain from exposure to cerebral target engagement, to structural modification, to clinical benefit. Future studies should be designed to resolve each rung rather than infer the highest rung from evidence at the lowest.

Disease stage is the most plausible place to explore a genuinely new hypothesis, but it should not become an unfalsifiable rescue explanation. Earlier treatment makes biological sense because lacunes and established white-matter disconnection are not easily reversed. The NOTCH3-SVD staging system, quantitative diffusion MRI and high-risk genotype categories now permit earlier disease to be defined objectively rather than by age alone. An early-stage trial would therefore need prespecified evidence that the selected target is active before irreversible injury and a biomarker sensitive to change within the intended duration.

Genotype-informed enrichment can improve power but introduces tradeoffs. High-risk variants show faster stroke and imaging progression, so preferential enrollment could increase event rates and make a rare-disease trial more efficient. Yet narrow enrichment would reduce generalizability to moderate-risk variants and to the broader NOTCH3 spectrum observed in population cohorts. Adaptive or Bayesian designs can partly manage this tension by allowing probability-based decisions and subgroup expansion, but they must be prespecified to avoid post hoc rescue of ineffective interventions.

Outcome selection is equally important. Stroke and major disability are clinically meaningful but may occur too infrequently for small early-stage studies. Global cognitive scores are vulnerable to ceiling effects, practice effects and domain insensitivity. Quantitative Diffusion Markers, Including Mean Skeletonized Mean Diffusivity (MSMD) and Peak Width of Skeletonized Mean Diffusivity (PSMD), together with lacune volume, free-water measures, BBB imaging and NfL, may offer greater sensitivity, although none should be treated as a validated surrogate for clinical benefit without further evidence. STRIVE-2 provides a framework for standardized imaging, while CADASIL-specific longitudinal data support mean skeletonized mean diffusivity and lacune burden as promising trial measures.

Recent biomarker reviews support this multimodal approach by emphasizing that imaging, circulating and cerebrospinal-fluid measures capture different levels of the CSVD cascade and should be interpreted jointly rather than as interchangeable surrogates. Such integration may improve trial sensitivity, but candidate biomarkers still require disease-specific validation before they can substitute for clinically meaningful outcomes.

A strong next-generation design would therefore use a causal sequence rather than a single endpoint. First, demonstrate adequate exposure. Second, demonstrate target engagement using a biomarker matched to the therapy. Third, show a favorable effect on a sensitive structural or physiological marker. Fourth, confirm consistency with clinical outcomes over longer follow-up. This staged logic allows early futility decisions and avoids investing in a definitive trial when the therapy has not crossed basic mechanistic thresholds.

Figure 4 proposes a next-generation CADASIL trial architecture that begins with biological staging and genotype enrichment, then requires pharmacological exposure and target engagement before sensitive imaging and clinical outcomes are interpreted. The final analytical layer uses Bayesian or adaptive principles to support early futility decisions in a rare, slowly progressive disease.

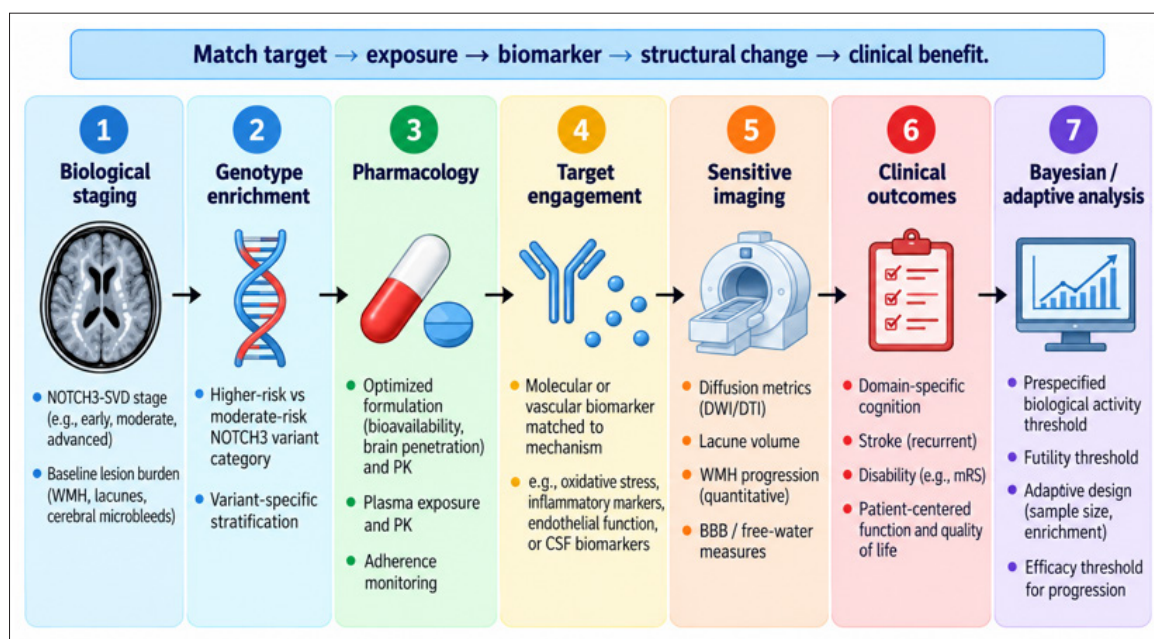


Figure 4: Proposed next-generation CADASIL disease-modifying trial architecture

Figure 4 illustrates that this architecture is intended to prevent another common translational failure: reaching a negative clinical endpoint without knowing whether the drug ever engaged the intended cerebral target. By sequencing exposure, pharmacodynamics, structural change, and clinical benefit, the design can identify where the translational chain succeeds or fails.

The emerging NOTCH3 aggregation literature suggests what a more proximal strategy might look like. If abnormal extracellular-domain accumulation is a major driver, then lowering NOTCH3 production, preventing mutant/wild-type co-aggregation or enhancing vascular clearance may be more disease specific than generic antioxidant treatment. These strategies remain investigational and could carry safety risks because NOTCH3 has normal vascular functions, but they align the therapeutic target more closely with the causal substrate.

Combination therapy is also conceptually attractive. An upstream NOTCH3-directed agent could reduce the primary vascular protein burden while a downstream vasculoprotective or neuroprotective compound could limit oxidative-inflammatory amplification. Tocotrienols might theoretically fit the second role better than the first. However, combination therapy should not be adopted merely because a single downstream agent failed; each component should demonstrate independent target engagement and a rational relationship to disease stage before combination efficacy is tested.

The CADASIL experience also has implications for sporadic CSVD. Both conditions can display endothelial dysfunction, BBB leakage, oxidative stress, inflammation, interstitial-fluid abnormalities, white-matter damage and cognitive impairment. This convergence makes CADASIL a useful human model of how chronic microvascular dysfunction injures brain tissue [57]. Yet the initiating biology differs. Sporadic disease is typically driven by ageing, hypertension, arterial stiffness, metabolic disease, smoking, renal dysfunction and complex polygenic susceptibility, whereas CADASIL begins with NOTCH3 pathology.

Accordingly, therapeutic extrapolation must be bounded. A treatment that fails in CADASIL could still work in sporadic CSVD if its target is more proximal to the sporadic disease mechanism. Conversely, a successful NOTCH3-directed therapy might have little value in hypertension-related arteriolosclerosis. The correct translational use of CADASIL is therefore to illuminate shared downstream microvascular biology while preserving etiological distinctions.

The broader CSVD literature reinforces the importance of such distinctions. Endothelial dysfunction, BBB abnormalities and oxidative-inflammatory signaling are recurrent themes across recent reviews, but disease-specific treatment remains elusive despite a large mechanistic literature. This pattern mirrors the tocotrienol story: identifying a plausible pathway is easier than proving that pathway is sufficiently causal, druggable and modifiable in humans.

The negative T3CAD trial also provides an ethical lesson for scientific communication. Tocotrienol-rich products are readily perceived as benign nutritional supplements, which can encourage clinical claims that exceed evidence. Safety and efficacy are separate domains. T3CAD suggests acceptable tolerability, but tolerability cannot be presented as proof of benefit. Patients with a rare progressive genetic disorder are particularly vulnerable to therapeutic overstatement, so reviews should clearly distinguish investigational rationale from established care. At the same time, a negative trial should not be framed as a failure of science. Publication of futility is valuable because it prevents repeated investment in an unsupported disease-modification claim, sharpens hypotheses and identifies measurement problems. T3CAD also illustrates the usefulness of Bayesian rare-disease methods, where posterior probabilities can support transparent futility decisions even with small samples. The unexpectedly high event rate in the placebo group further shows why contemporary natural-history data are essential for prior assumptions and sample-size planning.

Natural-history work is now sufficiently mature to improve this process. Longitudinal studies quantify two-year MRI change, clinical trajectory studies characterize progression in symptomatic disease, staging systems locate individuals along the disease continuum, and blood biomarkers provide repeatable measures of neuroaxonal injury. Integrating these elements should reduce the uncertainty that affected earlier trial designs.

Finally, the current evidence argues for a change in the language used to describe tocotrienols in CADASIL. Terms such as ‘promising disease-modifying therapy’ are no longer justified without qualification. A more accurate description is ‘a biologically plausible downstream neurovascular modifier that failed to demonstrate disease modification in the first randomized CADASIL trial.’ This formulation preserves the legitimate mechanistic literature while respecting the highest-level disease-specific evidence.

Evidence Synthesis and Trial-Design Implications

Table 1 synthesizes the evidence hierarchy supporting the interpretation of tocotrienol-rich vitamin E in CADASIL. The table is intended as a qualitative comparison of evidential proximity and confidence rather than a formal GRADE assessment, with greatest weight assigned to disease-specific human data and the least weight to extrapolated mechanistic plausibility.

Table 1: Evidence Hierarchy for Tocotrienol-Rich Vitamin E in CADASIL

Evidence domain	Representative evidence	Interpretation	Confidence
NOTCH3 disease biology	Aggregation, variant-risk and staging studies	Strong evidence that CADASIL is an upstream vascular proteinopathy	High
Tocotrienol mechanisms	Preclinical antioxidant, anti-inflammatory and neuroprotective studies	Biological plausibility, but mostly disease-nonspecific	Moderate
Human pharmacology	Formulation-dependent PK and systemic biomarker changes	Oral exposure is established; cerebral target engagement remains uncertain	Moderate
CADASIL randomized efficacy	T3CAD 24-month randomized trial	No demonstrated reduction in clinical progression or exploratory MRI outcomes	High
Future role	Earlier-stage, target-engagement or adjunctive studies	Requires a materially new hypothesis and mechanism-matched biomarkers	Hypothesis-generating

As Table 1 demonstrates, the evidence base is intentionally asymmetrical: NOTCH3 disease biology and the randomized T3CAD efficacy result provide comparatively high-confidence disease-specific evidence, whereas tocotrienol mechanisms and human pharmacology remain supportive but indirect. Any future CADASIL role for tocotrienols is therefore hypothesis-generating and requires a materially different, mechanism-verified strategy rather than repetition of the prior efficacy claim.

Table 2 maps candidate endpoints to the causal level they are intended to measure. This framework is useful because an intervention should first be evaluated with biomarkers proximal to its hypothesized mechanism and then linked to structural and clinical outcomes, rather than treating all biomarkers as equivalent evidence of disease modification.

Table 2: Candidate Outcome Framework for Next-Generation CADASIL Trials

Causal level	Candidate measure	Strength	Limitation
Proximal disease biology	NOTCH3 aggregation / deposition marker	Mechanistically specific	Requires validated scalable assay
Neurovascular physiology	BBB permeability, vascular reactivity, endothelial marker	Mechanism matched	Method standardization needed
Tissue injury	Mean/peak-width skeletonized mean diffusivity (MSMD/PSMD), free water, lacune volume, WMH volume	Sensitive to progression	Surrogacy for clinical benefit not fully established
Neuroaxonal injury	Serum NfL / GFAP	Repeatable and accessible	Nonspecific to CADASIL mechanism
Clinical outcome	Stroke, cognition, disability, patient-centered function	Direct patient relevance	Slow change and limited power in rare disease

Table 2 also highlights an important limitation of current trial science: highly accessible downstream measures such as NfL or GFAP are not specific to NOTCH3 pathology, whereas more proximal NOTCH3 aggregation measures are mechanistically informative but are not yet validated as scalable surrogate endpoints. A credible next-generation trial should therefore combine proximal target engagement with sensitive MRI and patient-relevant clinical outcomes.

Strengths and Limitations

A major strength of this review is the integration of genetics, vascular pathology, neuroimaging, biomarkers, pharmacology and randomized clinical evidence within a single causal framework. However, as a qualitative literature review, it does not claim exhaustive retrieval or formal risk-of-bias grading, and mechanistic evidence from sporadic CSVD or non-CADASIL tocotrienol studies cannot be treated as direct evidence for NOTCH3-associated disease. Several proposed biomarkers also lack validated surrogate status, while the effects of tocotrienol exposure beyond the 24-month T3CAD horizon remain uncertain. The conclusions should therefore be interpreted as a translational synthesis anchored by disease-specific randomized evidence rather than as a quantitative estimate of treatment effect.

Conclusion and Future Directions

CADASIL illustrates both the power and the difficulty of translational neurovascular research. The causal chain begins with pathogenic NOTCH3 variation and abnormal vascular extracellular-domain accumulation, then expands through mural-cell dysfunction, endothelial and BBB abnormalities, impaired perfusion and fluid homeostasis, oxidative-inflammatory amplification, white-matter injury, stroke and cognitive decline. Contemporary genetics, pathology, MRI and biomarker research now support a much more granular view of this sequence than was available even a few years ago.

Within that sequence, tocotrienol-rich vitamin E remains mechanistically interesting but clinically unproven as a disease modifier. Experimental and selected human studies support antioxidant, anti-inflammatory and neuroprotective actions, and

the available randomized CADASIL trial indicates acceptable tolerability. Yet T3CAD did not reduce the composite clinical progression endpoint and did not demonstrate secondary or exploratory MRI benefit. Current evidence therefore does not support tocotrienol-rich vitamin E as an established disease-modifying treatment for CADASIL.

The most important consequence of the trial is methodological. Future studies should match intervention level to disease stage and endpoint. Earlier or premanifest disease can now be defined using NOTCH3-SVD staging, genotype-risk categories and quantitative diffusion MRI. Candidate therapies should demonstrate exposure and target engagement before large efficacy testing. MRI markers, NfL/GFAP and other downstream biomarkers can improve sensitivity, but therapies aimed at proximal NOTCH3 pathology will require equally proximal pharmacodynamic measures.

For tocotrienols specifically, any renewed CADASIL investigation should be hypothesis driven rather than repetition driven. A distinct formulation, earlier disease stage or adjunctive role would require evidence explaining why the new strategy differs materially from T3CAD. More broadly, the field should pursue therapies that reduce NOTCH3 aggregation or its direct vascular consequences while considering downstream neurovascular protection as a complementary rather than substitutive approach.

CADASIL also offers lessons for sporadic CSVD, but those lessons should remain mechanistic rather than simplistic. Shared endothelial, BBB, oxidative, inflammatory and white-matter processes make CADASIL a valuable model of microvascular brain injury, yet monogenic NOTCH3 vasculopathy is not equivalent to hypertension- or ageing-related small-vessel disease. Translational rigor therefore requires both connection and restraint. The path toward a true disease-modifying era will depend less on the attractiveness of a mechanism and more on demonstrating, step by step, that the intervention reaches the right target, at the right stage, changes the right biology and ultimately changes the patient’s disease trajectory.

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