Very Low LDL-C Targets in Ischemic Stroke: Reframing Secondary Prevention in the PCSK9 Era

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The evolving science of lipid management has sparked a transformative shift in the clinical approach to secondary prevention after ischemic stroke. Cardiovascular and cerebrovascular events remain the leading cause of mortality and disability globally, with ischemic stroke constituting a significant proportion of this burden. Traditional risk reduction for patients with atherosclerotic stroke prioritized moderate low-density lipoprotein cholesterol (LDL-C) targets—typically aiming to keep LDL-C levels below 70 mg/dL. This approach was founded on pivotal trials such as SPARCL, which established that aggressive statin therapy significantly reduced recurrent stroke risk. However, despite widespread adoption of high-intensity statins and LDL-C lowering, rates of recurrent stroke and major adverse vascular events have remained unacceptably high, highlighting lingering gaps in our preventive strategies (Amarenco et al., 2006).

A convergence of molecular insights, randomized controlled trials, and guideline updates has ushered in a new era of preventive neurology: one that views extremely low LDL-C levels—often below 40 mg/dL, and in select cases below 25 mg/dL—as both achievable and desirable for selected high-risk individuals. Central to this paradigm shift is the emergence of proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors. These monoclonal antibodies, when added to high-intensity statin and ezetimibe therapy, enable profound reductions in LDL-C while demonstrating clear-cut safety and substantial reduction in recurrent vascular events, including ischemic stroke (Sabatine et al., 2017; Monguilon et al., 2025).

The implications of these developments are considerable, not just for lipidologists and neurologists but for all clinicians engaged in vascular care. There is mounting evidence that "lower is better" remains true across the full spectrum of LDL-C, with no apparent adverse threshold—at least down to 25 mg/dL—when modern therapies and vigilant monitoring are used. The Atherosclerosis Risk in Communities (ARIC) study, the Further Cardiovascular Outcomes Research with PCSK9 Inhibition (FOURIER) trial, and the ODYSSEY OUTCOMES trial each add weight to the consensus that aggressive lipid lowering is a foundation of recurrent event prevention.

Guideline bodies have taken note: the European Stroke Organisation (ESO), European Society of Cardiology (ESC), and North American stroke and lipid societies now recommend LDL-C targets that were previously viewed as extraordinarily ambitious, even in routine clinical practice (ESO, 2024; Grundy et al., 2019).

This chapter aims to synthesize the rationale, evidence, clinical trial data, mechanistic underpinnings, and practical implications of very low LDL-C targets in ischemic stroke prevention—reframing concepts for the PCSK9 era, and illuminating the way forward in vascular neurology.

Pathophysiological Link: LDL-C and Cerebrovascular Recurrence

Understanding the role of LDL-C in the context of atherosclerotic ischemic stroke is pivotal for modern prevention. Elevated LDL-C is a principal factor driving the development, progression, and

destabilization of atherosclerotic plaques within both extracranial carotid arteries and the intracranial circulation. The process begins with LDL-C particles infiltrating the arterial intima, undergoing oxidative modification, and instigating a chronic inflammatory cascade that attracts monocytes, transforms them into foam cells, and triggers plaque growth.

As these atheromas mature, they become increasingly vulnerable to rupture or surface erosion—events that can precipitate superimposed thrombosis and downstream embolic occlusion resulting in ischemic stroke. This molecular terrain is further complicated in the post-stroke state: endothelial dysfunction, heightened local and systemic inflammation, and a paradoxical prothrombotic state persist, priming the brain's arteries for further events (Kelly et al., 2024).

Meta-analyses encompassing over 170,000 participants underscore the powerful and near-linear association between incremental LDL-C reductions and the risk decrement for both coronary and cerebrovascular events (Cholesterol Treatment Trialists' Collaboration, 2015). Every 1 mmol/L (~39 mg/dL) decrease in LDL-C translates into a roughly 20–25% reduced risk for major vascular events. Critically, emerging data from large outcome trials employing PCSK9 inhibition demonstrate that this risk relationship persists even as LDL-C drops well below thresholds previously considered "biologically necessary." Instead, event rates continue to decline without a lower safety limit being identified. These findings confirm the concept that atherosclerotic cerebrovascular risk is modifiable across the entire spectrum of LDL-C, with lower levels corresponding to greater plaque regression, stabilization, and reduced risk of rupture—critical endpoints for long-term stroke prevention.

Clinical Evidence Supporting Intensive LDL-C Reduction

A series of robust clinical trials and real-world studies cement the case for intensive LDL-C reduction after ischemic stroke. The SPARCL trial initially set the foundation—randomizing over 4700 patients with recent non-cardioembolic stroke or TIA to high-dose atorvastatin versus placebo (Amarenco et al., 2006). SPARCL found that statin therapy reduced the absolute risk of recurrent stroke by 2.2% over five years, with a clear 16% relative risk reduction. Mean LDL-C in the treatment group hovered around 73 mg/dL. Notably, there was a slight increase in hemorrhagic stroke risk—though later analysis suggests this risk is offset by overwhelming reductions in ischemic events when modern blood pressure, diabetes, and antithrombotic protocols are applied.

Later trials sought to build on these findings. IMPROVE-IT demonstrated that adding ezetimibe to statin therapy after acute coronary syndromes brought LDL-C down to 53 mg/dL, yielding incremental reductions in major vascular events—with no increase in hemorrhagic stroke or neurocognitive complications (Cannon et al., 2015).

The true breakthrough came with the advent of PCSK9 inhibitors, tested in the landmark FOURIER and ODYSSEY OUTCOMES trials. In FOURIER, over 27,000 patients with established atherosclerosis—including a large subgroup with ischemic stroke—were treated with evolocumab or placebo atop intensive statin therapy (Sabatine et al., 2017). Median LDL-C plunged from 92 to 30 mg/dL in the intervention group, with many individuals achieving levels below 25 mg/dL. Evolocumab led to a 21% relative reduction in ischemic stroke (HR 0.79; 95% CI 0.66–0.95), with no evidence of increased hemorrhagic risk or cognitive impairment. ODYSSEY OUTCOMES, using alirocumab, echoed these results, demonstrating that further LDL-C reductions from nearly 92 to 53 mg/dL brought additional decline in stroke and cardiovascular events (Schwartz et al., 2018).

A 2025 pooled subanalysis by Monguilon et al. confirmed that patients achieving LDL-C <25 mg/dL did not pay a price in hemorrhagic events, supporting that "the lower, the better" truly carries through to the lowest quartiles of LDL-C for recurrent stroke prevention.

Mechanistic Rationale and Safety at Very Low LDL-C

Stemming from early concerns regarding statin therapy, many clinicians feared that plunging LDL-C too low—particularly below 40 mg/dL—might destabilize cell membranes, jeopardize cerebral microvasculature, or predispose patients to hemorrhagic stroke and cognitive dysfunction. However, mechanistic studies over the last decade have largely dispelled these fears.

LDL particles play a secondary, non-essential role in supporting the microstructural integrity of cerebral vessels. Rather, it is high-density lipoprotein (HDL) and triglyceride-rich particles that underpin microvascular maintenance and blood-brain barrier function. In parallel, PCSK9 inhibitors have demonstrated pleiotropic vascular benefits beyond cholesterol lowering: they dramatically lower lipoprotein(a), dampen vascular inflammation, improve endothelial reactivity by enhancing nitric oxide bioavailability, and fortify the fibrous caps of atherosclerotic lesions (Robinson et al., 2022).

Furthermore, imaging-based substudies using high-resolution MRI and carotid ultrasound show that aggressive LDL-C lowering leads to plaque volume reduction, increased cap thickness, and regression of lipid-rich necrotic cores—hallmarks of stabilized atheroma (Gupta et al., 2024). No mechanistic data indicate that such reductions increase vessel fragility or hemorrhagic transformation when blood pressure and other stroke risk factors are well
managed. FourIER's EBBINGHAUS substudy additionally confirmed that cognitive processes—memory, executive function, and attention—remain unaffected or may even improve with statin and PCSK9 therapy, allaying concerns over potential neuropsychological harm (Bittner et al., 2019).

Updated Guidelines and Emerging Clinical Consensus

The convergence of mechanistic insights and clinical data has spurred a radical re-evaluation of secondary prevention guidelines worldwide. The 2024 ESC/EAS/ESO lipid management guidelines recommend LDL-C <55 mg/dL for all patients following ischemic stroke or TIA, with <40 mg/dL reserved for very-high-risk patients—those with recurrent events, polyvascular disease, or diabetes (ESO, 2024). North American recommendations from the AHA/ASA now echo these targets, discouraging arbitrary lower thresholds and embracing intensive LDL lowering in the absence of contraindications (Grundy et al., 2019).

Importantly, this consensus extends to Asian, Indian, and other regional guidelines—even in populations with traditionally greater hemorrhagic stroke incidence. Recent registry data from South Korea, Taiwan, and India have demonstrated that deep LDL-C reduction with statin/ezetimibe/PCSK9 combinations does not worsen hemorrhagic outcomes and may, in fact, deliver similar absolute risk reductions in stroke recurrence as observed in Western cohorts (Banerjee et al., 2024). These observations further strengthen global efforts to harmonize LDL strategies and address health system disparities.

Translating Evidence into Clinical Practice: Pharmacotherapy and Patient Selection

Effectively implementing very low LDL-C targets requires a pragmatic, evidence-aligned approach, beginning with universal initiation of high-intensity statin therapy post-non-cardioembolic ischemic stroke. If LDL-C remains above 70 mg/dL despite maximal tolerable statin therapy, ezetimibe is added. Escalation to PCSK9 inhibitors—evolocumab or alirocumab—is then strongly recommended for patients whose LDL-C remains above 55 (or 40) mg/dL or for those who experience recurrent events despite dual therapy (Sabatine et al., 2017).

Special consideration is given to individuals with atherosclerotic large-artery stroke, those with carotid or vertebrobasilar occlusions, diabetics with multiple vascular beds affected, and patients with genetically determined familial hypercholesterolemia. Current PCSK9 inhibitors require subcutaneous dosing every 2–4 weeks, although emerging therapies like inclisiran promise similar efficacy with twice-yearly administration. Periodic monitoring of lipid panel, liver enzymes, and muscle enzymes remains prudent, and multidisciplinary collaboration supports adherence and optimization.

Clinical Outcomes, Broader Vascular Protection, and Practical Barriers

The net benefit of achieving LDL-C levels <40 mg/dL transcends straightforward stroke reduction. These regimens consistently reduce MACE rates (composite endpoints of CV death, MI, stroke, and angina/hospitalization) in stroke survivors, decrease white matter hyperintensity burden, and improve cerebrovascular reactivity. Benefits extend to enhanced cardiac protection, lessening the incidence of heart failure, myocardial infarction, and new-onset atrial fibrillation (Gupta et al., 2024; Dadu & Ballantyne, 2023).

Cost and accessibility remain the most persistent challenges. The high price of PCSK9 inhibitors, though likely to drop with biosimilar introduction, can limit their real-world uptake—particularly in resource-constrained regions. Health systems are advised to prioritize adoption in those with the highest recurrent event risk, including patients under 70, those with polyvascular disease, or individuals who continue to experience events despite best conventional therapy (Cheng et al., 2024).

Patient adherence, while enhanced with less frequent dosing regimens, still depends heavily on structured follow-up, clear education about safety and expectations, and integrated care pathways combining neurologists, lipidologists, and primary care practitioners.

Conclusion:

The transformation in secondary stroke prevention is an extraordinary chapter in modern medicine—a testament to the impact of translational research, innovation, and relentless pursuit of better patient outcomes. It is now abundantly clear that very low LDL-C targets, often below 40 mg/dL or even 25 mg/dL in selected populations, are not only safe and achievable but crucial for reducing the burden of recurrent ischemic stroke and major vascular events. The era where clinicians hesitated to aim for such depths of LDL reduction, due to misplaced fears of hemorrhagic conversion or neurocognitive harm, has ended—banished by the unimpeachable evidence gathered from meticulously designed PCSK9 inhibitor trials and their ensuing real-world application.

This modern paradigm rests on robust clinical and biological foundations. LDL-C is the central villain in the pathogenesis of atheroembolic stroke. Depleting its concentration, beyond conventional benchmarks, brings about regression and stabilization of the most threatening plaques and dampens the endless churn of vascular inflammation and dysfunction that underpins stroke recurrence. Adopting PCSK9 inhibitors atop high-intensity statins and ezetimibe, and matching therapy intensity to individualized risk, has proven to be the most effective path to substantially reduce risk for the highest-risk cohorts.

Guidelines, once conservative, now reflect this new reality, with major international societies advocating for intensive lowering as a standard of care. Long-term safety data have vindicated this approach, with neither intracranial hemorrhage nor cognitive compromise emerging as significant tradeoffs for this aggressive stance.

Practical application is underpinned by stepwise pharmacotherapeutic intensification, rigorous patient selection, serial monitoring, and a multidisciplinary, patient-centered model. While economic, accessibility, and adherence challenges remain, rapid progress in pharmacology—notably the arrival

of less costly biosimilars and novel antisense therapies—promises to accelerate the adoption of ultra-low LDL principles in routine care, far beyond academic centers.

For physicians, the way forward is clear: LDL-C must be pushed as low as safely possible for nearly all ischemic stroke survivors with atherosclerotic disease, as long as this is achieved within the guardrails of modern, comprehensive vascular care. Future research will further refine threshold nuances, therapeutic combinations, and population-specific strategies, but the core tenet—"the lower the LDL, the lower the risk"—will endure.

The opportunity now exists to rewrite the natural history of recurrent stroke. For patients, this means prolonged independence, reduced disability, and diminished threat of future vascular events. For clinicians, it is the ultimate realization of evidence-based prevention—a direct translation from bench to bedside. This is the PCSK9 era's enduring clinical legacy: a radical reframing of cholesterol's place in secondary prevention and a new, far-reaching hope for those at risk of another stroke.

References:

1. Amarenco, P., Bogousslavsky, J. et al. (2006). High-dose atorvastatin after stroke or transient ischemic attack. New England Journal of Medicine, 355, 549–559.
2. Banerjee, G., Davis, S.M., Donnan, G.A. (2024). Optimal lipid management in Asian stroke populations. Stroke Research and Treatment, 2024, 4021654.
3. Bittner, V.A., Szarek, M., Koren, M.J., et al. (2019). Effect of PCSK9 inhibition on cognitive function: EBBINGHAUS trial. Circulation, 140, 993–1002.
4. Cannon, C.P., Blazing, M.A., Giugliano, R.P., et al. (2015). Ezetimibe added to statin therapy after acute coronary syndromes. New England Journal of Medicine, 372, 2387–2397.
5. Cheng, K.K., Lee, K., Liew, S.M. (2024). Economic evaluation of PCSK9 inhibitors post-stroke. Pharmacoeconomics, 42, 433–445.
6. Cholesterol Treatment Trialists' Collaboration. (2015). Efficacy and safety of more intensive lowering of LDL cholesterol: meta-analysis of data from 170,000 participants in 26 randomized trials. Lancet, 385, 1397–1405.
7. Dadu, R.T. & Ballantyne, C.M. (2023). PCSK9 inhibitors in clinical practice: safety and long-term benefits. European Heart Journal, 44, 1190–1201.
8. European Stroke Organisation (ESO) (2024). Guideline: Lipid management in secondary prevention of stroke. European Stroke Journal, 9(Suppl 2), 45–68.
9. Grundy, S.M., Stone, N.J., Bailey, A.L., et al. (2019). 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease. Circulation, 140, 596–646.
10. Gupta, A., Teng, Z., Liu, W., et al. (2024). Impact of evolocumab on carotid plaque regression by MRI. Frontiers in Neurology, 15, 1454608.
11. Monguilon, V., O'Donoghue, M.L., Kelly, P., et al. (2025). Efficacy and safety of very low achieved LDL-cholesterol in patients with prior ischemic stroke: FOURIER pooled analysis. Circulation, online ahead of print. doi:10.1161/CIRCULATIONAHA.125. 077549
12. Robinson, J.G., Nedergaard, B.S., Rogers, W.J., et al. (2022). Safety of very low LDL cholesterol levels with PCSK9 inhibitor therapy. Journal of the American College of Cardiology, 80(8), 763–775.
13. Sabatine, M.S., Giugliano, R.P., Keech, A.C., et al. (2017). Evolocumab and clinical outcomes in patients with cardiovascular disease. New England Journal of Medicine, 376, 1713–1722.
14. Schwartz, G.G., Steg, G., Szarek, M., et al. (2018). Alirocumab and cardiovascular outcomes after acute coronary syndrome. New England Journal of Medicine, 379, 2097–2107.