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Review

Dyslipidemia Treatment and Cerebrovascular Disease: Evidence Regarding the Mechanism of Stroke

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ABSTRACT

Dyslipidemia stands as a significant risk factor for stroke, on par with the impact of hypertension, diabetes, and smoking. While the role of dyslipidemia is firmly established in the context of coronary artery disease, its influence on strokes remains somewhat enigmatic. This complexity likely arises from the diverse mechanisms underpinning strokes, which encompass a heterogeneous spectrum (hemorrhagic and ischemic; large artery atherosclerosis, small vessel occlusion, cardioembolism, and etc.). The extent to which lipid-lowering treatments affect stroke outcomes may vary depending on the specific stroke subtype. For instance, in cases of large artery atherosclerosis (LAA), the optimal target level of low-density lipoprotein cholesterol (LDL-C) is relatively clear. However, when dealing with other stroke subtypes like small vessel occlusion or cardioembolism, the appropriate LDL-C target remains uncertain. Furthermore, reperfusion therapy has emerged as the foremost treatment for acute ischemic stroke. Nevertheless, the precise relationship between LDL-C levels and outcomes in patients undergoing reperfusion therapy remains shrouded in uncertainty. Consequently, we have undertaken an in-depth exploration of the existing evidence supporting the utilization of lipid-lowering medications such as statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. Our objective is to elucidate their role in secondary stroke prevention and the management of dyslipidemia across the various stroke subtypes.

Keywords: Dyslipidemia; Stroke; Disease prevention, secondary; Low-density lipoprotein

INTRODUCTION

Dyslipidemia stands as a significant risk factor for stroke, following hypertension, diabetes, and smoking.[1] Lowering cholesterol levels has been associated with both primary and secondary prevention of cerebrovascular diseases.[2] The current guidelines for lowering low-density lipoprotein cholesterol (LDL-C) emphasize the "lower is better" approach to mitigate the occurrence or recurrence of atherosclerotic ischemic stroke.[2]

Statins play a crucial role in preventing atherosclerotic disease due to their lipid-lowering attributes and potential additional benefits.[3] However, a significant number of patients fail to

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attain the recommended LDL-C targets, often due to insufficient dosing or an elevated risk of adverse effects associated with high-dose statin treatments.[4] Consequently, the consideration of incorporating non-statin therapies, such as ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9), becomes pertinent.[5] Furthermore, stroke is a heterogeneous condition with various etiologies, thus the extent to which lipid-lowering treatments affect stroke outcomes may vary depending on the specific stroke subtypes.[6]

This review aims to outline the available evidence regarding the effectiveness of 1) lipid-lowering medications in ischemic stroke patients, including statins, ezetimibe, and PCSK9 inhibitors, in the context of secondary stroke prevention, 2) strategies and consideration of lipid lowering in ischemic stroke patients, and 3) the management of dyslipidemia for each distinct subtypes of stroke.

LOWERING LDL-C FOR REDUCING ISCHEMIC STROKE

The correlation between blood lipids and stroke has been subject to thorough investigation, as evidenced by studies.[7-9] LDL-C stands out as a particularly valuable serum lipid marker for gauging stroke risk.[2] Meta-analyses have compellingly demonstrated that interventions involving lipid-lowering therapy, specifically through the use of statins, yield a significant 22% decrease in major vascular events for every 1 mmol/L reduction in LDL-C. This reduction encompasses a 21% decrease in relative risk associated with ischemic stroke per 1 mmol/L decline in LDL-C.[10] With these findings in mind, LDL-C has been adopted as the target parameter for risk management and treatment.

1. Statins

Statins, known as 3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) reductase inhibitors, reduces endogenous cholesterol biosynthesis and increases the expression of LDL receptors leading to LDL-C uptake and clearance.[11] High-intensity statin therapy reduces LDL-C by ≥50%, and moderate-intensity therapy reduces it by 30%–50%.[12]

The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial was a prospective, double-blind, placebo-controlled international study conducted at 205 centers. It involved 4,731 patients, with 67% having experienced ischemic stroke, 31% transient ischemic attack (TIA), and 2% hemorrhagic stroke. These patients, all without a history of coronary heart disease, were recruited and randomized.[13] Among them, 2,365 received atorvastatin 80 mg per day, while 2,366 received a placebo. The follow-up period extended to an average of 4.9 years. The results showed that the atorvastatin group exhibited a 16% reduction in the risk of cardiovascular events (95% confidence interval [CI], 0.71–0.99; p=0.03). The incidence of hemorrhagic stroke was higher in the atorvastatin group, with 55 cases, as opposed to 33 cases in the placebo group. According to the post-hoc analysis, in comparison to patients with increased or unchanged LDL-C levels, those with a ≥50% reduction in LDL-C level experienced a 31% decrease in stroke risk (95% CI, 0.55–0.87; p=0.0016) and a 33% reduction in ischemic stroke (p=0.0018). Remarkably, these benefits were achieved without an increase in the risk of intracranial hemorrhage (ICH).[14] Furthermore, expanding efficacy to reduce subsequent vascular events revealed that atorvastatin 80mg prevented over twice the total compared to initial events. This highlights its potential in reducing both initial and subsequent cardiovascular risks.[15]

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JLA Journal of Lipid and Atherosclerosis

2. Non-statins

Ezetimibe

Ezetimibe effectively reduces LDL-C levels by inhibiting cholesterol absorption within the gastrointestinal tract. This mechanism of action results in a decreased supply of cholesterol to the liver. In response to this reduced influx of cholesterol, the liver initiates an upregulation of LDL receptor expression. Consequently, this upregulation enhances the clearance of LDL from the bloodstream, contributing to the overall reduction of LDL-C levels.[16]

The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE IT) was a prospective, double-blind, placebo-controlled international trial that enrolled 18,144 patients with acute coronary syndrome. These patients were randomly assigned to 2 groups. One group received a combination of ezetimibe (10 mg daily) and simvastatin (40 mg daily), while the other group received a placebo alongside simvastatin (40 mg daily). The trial spanned an average of 6 years, during which various outcomes were assessed. Results from the trial revealed that the group receiving ezetimibe and simvastatin experienced a notable 6% reduction in cardiovascular disease risk, a 14% decrease in overall stroke risk, and a substantial 21% decrease in ischemic stroke risk. Remarkably, these benefits were achieved without an increase in the risk of ICH. Adverse effects were consistent across both treatment groups.[17]

Subsequent analysis delved into patients with a history of stroke within the IMPROVE IT trial (n=641, 3.5%). Among this subgroup, those treated with ezetimibe exhibited a remarkable 21% reduction in ischemic stroke risk (hazard ratio [HR], 0.79; 95% CI, 0.67–0.94; p=0.008). However, it's important to note that there was a non-significant increase in hemorrhagic stroke risk (HR, 1.38; 95% CI, 0.93–2.04; p=0.11) within the same group.[18]

The *post hoc* analysis of the Treat Stroke to Target (TST) study aimed to investigate the comparative impacts of dual therapy involving a statin and ezetimibe and the individual use of either ezetimibe or a statin as monotherapy. The primary objectives were to assess their effectiveness in attaining the desired LDL-C levels and in lowering the occurrence of significant vascular events.[19] Among patients undergoing dual therapy, including both statin and ezetimibe, the attained LDL-C levels were 66.2 mg/dL. In contrast, those on statin monotherapy achieved an LDL-C level of 64.1 mg/dL. The study's primary objective was met with lower target group, showcasing a reduction in the primary outcome compared to the group targeting higher LDL-C levels (HR, 0.60; 95% CI, 0.39–0.91; p=0.016). However, this reduction was not observed during statin monotherapy (HR, 0.92; 95% CI, 0.70–1.20; p=0.52). It is important to note that this reduction in the primary outcome was achieved without a notable increase in the occurrence of intracranial bleeding. Hence, as per current guidelines, if the desired goals are not attained within 4–6 weeks using the highest tolerated dose of a statin alone, the recommendation is to consider combining it with ezetimibe.[20]

PCSK9 inhibitor

PCSK9 is synthesized in hepatocytes, subsequently released into the bloodstream, and regulates the expression of LDL-C receptors by binding to receptors carrying LDL-C in the blood. The recently developed PCSK9 inhibitor operates by inhibiting PCSK9 activation through the application of monoclonal antibodies. This inhibition disrupts the PCSK9 mechanism, leading to the absorption and degradation of LDL-C receptors within hepatocytes. Consequently, this process enhances the rate at which LDL-C receptors are recycled, ultimately resulting in a reduction of LDL-C levels.[2]

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The Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial was a randomized, double-blind, and placebo-controlled study. This trial was conducted among patients with atherosclerotic cardiovascular disease, which also included 19% of patients with a history of ischemic stroke. The trial specifically focused on individuals whose LDL-C levels exceeded 70 mg/dL.[21] Patients were randomly assigned to receive evolocumab (either 140 mg every 2 weeks or 420 mg monthly) or placebo, and median duration of follow-up was 2.2 years. The evolocumab lowered LDL-C by 59% from the baseline and maintained it at 30 mg/dL until 48 weeks after administration. The primary efficacy endpoint, a composite measure encompassing cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization, occurred in 9.8% of the evolocumab-treated group and 11.3% of the placebo group (HR, 0.85; 95% CI, 0.79–0.92; p<0.001). This suggests a substantial reduction in risk among those receiving evolocumab. Furthermore, there was a 21% decrease in overall stroke risk and a 25% reduction in ischemic stroke risk within the evolocumab group when compared to the placebo group. It is significant to note that the risk of ICH did not show an increase, and adverse effects were found to be comparable across the various treatment groups.

The Evaluation of Cardiovascular Outcomes after an Acute Coronary Syndrome during Treatment with Alirocumab (ODYSSEY OUTCOMES) trial was carried out among patients who had experienced acute coronary syndrome, which included 3.2% of patients with a history of stroke. These patients exhibited LDL-C levels exceeding 70 mg/dL despite receiving the highest tolerable intensity of statin treatment.[22] Alirocumab intervention led to a significant reduction in LDL-C levels, effectively lowering it by 55% from the baseline. During the course of treatment, the mean LDL-C level reached 53 mg/dL. The alirocumab group experienced a 15% decrease in the risk of composite cardiovascular events, and the risk of ischemic stroke was significantly reduced by 27%. Importantly, there was no observed increase in the risk of hemorrhagic stroke within the alirocumab group. Adverse effects were consistent and comparable across the different treatment groups.

In general, PCSK9 inhibitors lead to a substantial reduction of 50-60% in LDL-C levels from the baseline. They also exhibit the ability to lower the risk of cardiovascular disease. Notably, when combined with statins, PCSK9 inhibitors demonstrate a robust additive effect. Hence, the inclusion of PCSK9 inhibitors as a potential strategy could be considered for stroke patients, especially when the desired LDL-C goal is not achieved through existing treatments or when optimal intensity of statin therapy isn't feasible. This approach offers an alternative pathway to manage LDL-C levels and mitigate cardiovascular risk in stroke patients.[20]

3. Bempedoic acid

Bempedoic acid functions as an adenosine triphosphate (ATP) citrate lyase inhibitor, akin to statins, by diminishing hepatic cholesterol synthesis and elevating LDL receptor expression, facilitating the uptake and clearance of LDL-C.[23] Notably, bempedoic acid, a prodrug primarily activated in the liver with minimal activation in peripheral tissues like skeletal muscle, presents a lower risk of muscle-related adverse events, such as myalgia, in comparison to statins.[24]

The Cholesterol Lowering via Bempedoic Acid (ECT1002), an ACL-Inhibiting Regimen (CLEAR) trial, a prospective, double-blind, placebo-controlled study, enrolled 13,970 patients characterized by statin intolerance, high cardiovascular risk, or a history of cardiovascular events.[23] Participants were randomly assigned to receive either bempedoic acid (180 mg daily)

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or placebo, with a median follow-up duration of 40.6 months. After 6 months, bempedoic acid reduced LDL-C by 21.1% from the baseline. The primary endpoint, a composite measure including death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization, occurred in 11.7% of the bempedoic acid-treated group versus 13.3% of the placebo group (HR, 0.87; 95% CI, 0.79–0.96; p=0.004). However, bempedoic acid did not show significant effects on fatal or nonfatal stroke (HR, 0.85; 95% CI, 0.67–1.07; p=0.16). It is important to note that the incidences of gout and cholelithiasis were higher with bempedoic acid than with placebo (3.1% vs. 2.1% and 2.2% vs. 1.2%, respectively). Further research is warranted to fully understand the impact of bempedoic acid on stroke patients.

TWO STRATEGIES FOR LIPID LOWERING IN STROKE PATIENTS

1. High dose statin considering the pleiotropic effects

Statins have demonstrated pleiotropic effects, including an anti-atherogenic impact that enhances the production of nitric oxide, diminishes endothelin production, and curbs vascular smooth muscle cell proliferation within vessel walls. These effects also extend to reducing lipid content in atherosclerotic plaques and enhancing their stability. Moreover, statins exhibit anti-inflammatory properties, boosting tissue plasminogen activator (tPA) while reducing tissue factor and plasminogen activator inhibitor-1.[2]

After the administration of statins, atherosclerotic plaques demonstrated a reduction in size, accompanied by an increase in the gray scale mean. This change indicates a shift toward more stabilized plaque characteristics.[25] Likewise, the use of high-dose statins led to a decrease in macrophage presence and an increase in smooth muscle cells. These findings were supported by pathological studies involving samples from carotid artery endarterectomy (CEA) procedures.[26] Furthermore, the reduction in inflammation following statin use was corroborated by positron emission tomography after high-dose statin administration.[27]

In the realm of carotid revascularization, the benefits of statin use have been explored extensively. A retrospective cohort study encompassing individuals aged ≥66 years who underwent CEA or stenting evaluated the impact of pre-procedural and persistent statin use. Pre-procedural statin use exhibited a 24% risk reduction in the composite outcome of stroke, myocardial infarction, or death within the first year, and persistent long-term statin use showed a 25% risk reduction for this composite outcome over 5 years. These findings advocate for the integration of statins in patients undergoing carotid revascularization.[1]

As the number of stroke patients taking statins continues to rise, there is increasing focus on the potential benefits of statin pretreatment. Among individuals with LAA, statin pretreatment has exhibited notable advantages, including lower mortality rates and a decrease in the frequency of early stroke recurrence compared to those not receiving statins.[28] This phenomenon could potentially be attributed to the observation that individuals who undergo statin pretreatment tend to display fewer microembolic signals in cases of LAA-related strokes. This reduction in microembolic signals might stem from the anti-thrombotic and anti-inflammatory properties of statins, which could impede the formation of such signals.[29] Another effect of statin pretreatment is its potential to enhance collateralization during acute ischemic stroke. Collateralization, in this context, refers to the development of alternative blood pathways that can help maintain adequate blood flow to regions affected by blocked

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arteries. By promoting improved collateralization, statin pretreatment might potentially mitigate the impact of restricted blood flow and minimize the severity of resulting damage.[30]

Based on these findings, the recommendation has been to promptly initiate high-dose statin treatment upon admission for stroke and to continue this regimen throughout the follow-up period for patients with ischemic stroke. However, the current guideline has evolved, now emphasizing the target management of LDL-C for secondary prevention, based on the following results.

2. Target LDL-C for secondary stroke prevention

TST study was a randomized, parallel-group, event-driven trial conducted at 61 sites in France and 16 sites in South Korea. It focused on 2,860 patients who had experienced a stroke or TIA and displayed evidence of cerebrovascular or cardiac atherosclerosis. The participants were divided into two groups: the lower target group aiming for an LDL-C level below 70 mg/dL, and the higher target group with an LDL-C level ranging from 90 to 110 mg/dL. The study followed these patients for a median duration of 3.5 years.[31] The results showed that the mean achieved LDL-C level was 65 mg/dL in the lower-target group and 96 mg/dL in the higher-target group. Remarkably, the lower-target group exhibited a 22% reduction in major vascular events (95% CI, 0.61–0.98; p=0.04). There was no significant difference in the incidence of ICH between the 2 groups (HR, 1.38; 95% CI, 0.68–2.82).

Drawing insights from these trials, the 2021 American Heart Association/American Stroke Association (AHA/ASA) guidelines made a recommendation. Specifically, they advised aiming to reduce LDL-C levels to 70 mg/dL as a goal, utilizing either high-intensity statin therapy or the highest tolerated statin therapy. This guideline holds relevance for individuals diagnosed with stroke attributed to LAA.[20] In cases of acute ischemic stroke, anticipating the pleiotropic effects of statins and promptly initiating high-dose statin treatment seems reasonable. However, for the long-term secondary prevention of cerebral infarction, it appears most crucial to establish a target for LDL-C levels and adeptly adjust various medications accordingly to meet that goal. Since stroke stems from a variety of underlying causes, the specific mechanism of the stroke and the treatment context must be taken into account when addressing target goal for LDL-C lowering.

TREATMENT CONSIDERING STROKE MECHANISMS

Stroke is a diverse medical condition encompassing various etiologies, including both hemorrhagic and ischemic subtypes.[32] Hemorrhagic stroke (HS) comprises subtypes such as subarachnoid, intracerebral, and subdural bleeding.[33] Moreover, ischemic stroke can stem from different mechanisms, categorized as LAA, small vessel disease (SVD), cardioembolism (CE), stroke with other determined etiology (e.g., vasculitis, genetic disorder), and stroke with undetermined etiology.[34]

In the context of cerebral atherosclerosis, there is a notable prevalence of intracranial atherosclerosis (ICAS) in Asian populations compared to Western populations. ICAS is linked to a wider range of mechanisms, characterized by distinct lesion patterns observed on diffusion-weighted imaging: 1) local branch occlusion, 2) artery-to-artery embolism, 3) in situ thrombosis, and 4) hemodynamic. Conversely, extracranial atherosclerosis (ECAS) is primarily attributed to artery-to-artery embolism.[35]

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1. Large artery atherosclerosis

ICAS

Limited research has been conducted on lipid-lowering therapies specifically targeting ICAS. [1] One such study, the "Intensive Statin Treatment in Acute Ischemic Stroke Patients with Intracranial Atherosclerosis: a High-Resolution Magnetic Resonance Imaging study" (STAMINA-MRI Study), aimed to address this gap. This study focused on statin-naïve patients who had experienced an ischemic stroke with symptomatic ICAS (>50% stenosis) in the proximal sections of the middle cerebral artery (MCA), basilar artery (BA), or intracranial segment of the internal carotid artery (ICA).

During the study, participants were administered either atorvastatin (40 to 80 mg) or rosuvastatin (20 mg) for a duration of 6 months. High-resolution magnetic resonance imaging (HR-MRI) scans were performed both before and after the statin treatment. The study results indicated that the application of statin treatment yielded significant positive outcomes: 1) Notable reduction in plaque accumulation (32.07±39.15 vs. 17.06±34.53 mm^3, p=0.013), 2) Decrease in wall area index (7.5±4.3 vs. 5.9±4.1, p=0.016) and 3) Reduction in the degree of stenosis (76.5±20.2 vs. 64.1±21.3%, p=0.195). These findings collectively highlight the beneficial impact of statin treatment on the reduction of plaque accumulation, improvement in wall area index, and mitigation of stenosis degree in patients with symptomatic ICAS following an acute ischemic stroke.

However, strokes occurring in patients with ICAS are attributed to a range of mechanisms, encompassing atherosclerotic steno-occlusion, perforator occlusion, artery-to-artery embolism, and hemodynamic impairment. This diversity underscores the complexity of the condition. Various studies have indicated that risk factors and vessel wall pathology may vary depending on the specific mechanism involved.[36] In such instances, there is an observed correlation between perforator occlusion and the presence of longer plaques within the main blood vessel.[37] Addressing this connection, interventions aimed at reducing the plaque burden could potentially offer benefits in terms of decreasing both the existing plaque load and the risk of future strokes in individuals with ICAS marked by perforator occlusion. The therapeutic effects of statins may also vary based on the specific types of ICAS mechanisms.[38] However, given that ICAS is considered a medical condition rather than a context for actively conducting endovascular interventions, as demonstrated by the outcomes of previous intervention trials, the emphasis on reducing atherosclerotic burden becomes paramount.[39] This focus on reducing atherosclerosis becomes even more crucial than in other vascular beds where stenting procedures are routinely carried out.

ECAS

In contrast to ICAS, several randomized controlled studies have been conducted to assess the impact of statin therapy in patients with ECAS. In a subgroup analysis of the SPARCL trial, individuals with carotid stenosis who were treated with atorvastatin exhibited a 33% reduction in their stroke risk (95% CI, 0.47–0.94; p=0.02) and a 34% reduction in the risk of TIA or stroke (95% CI, 0.50–0.89; p=0.005).[40] Additionally, the Japan Statin Treatment Against Recurrent Stroke (JSTAR) trial, a multicenter, randomized, open-label, parallel-group study, enrolled 1,578 patients with non-cardioembolic ischemic stroke. Within this study, patients were administered either pravastatin (10 mg/day) or assigned to the control group. Pravastatin treatment demonstrated a reduction in stroke recurrence among patients with LAA (HR, 0.33; 95% CI, 0.15–0.74; p=0.0047), while no similar effect was observed in those with other stroke subtypes.[41] Moreover, in the TST trial, the superiority of the lower

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target strategy over the higher target strategy was evident in the French population; however, this benefit did not manifest when South Korean patients were analyzed separately. This discrepancy could potentially be attributed to the comparatively lower occurrence of ECAS among Asians in comparison to their French counterparts, resulting in a higher incidence of ICAS or SVD among South Koreans.[42]

The current guidelines advocate for an LDL-C goal of 70 mg/dL in cases of the LAA stroke subtype[20]; however, it is important to note that the LDL-C goal should be tailored to the individual circumstances of each stroke patient. Recent European guidelines propose a target of less than 55 mg/dL for patients with the LAA stroke subtype who face recurrent cardiovascular events or possess a high recurrence risk. Additionally, for individuals in extremely high-risk categories, a target LDL-C goal of less than 40 mg/dL is recommended.[12] Despite the potential for hemorrhagic stroke when using dual antiplatelet therapy and high-intensity statins, attaining the desired LDL level remains effective in the prevention of secondary strokes and other cardiovascular incidents. Ezetimibe and PCSK9 inhibitors did not exhibit an elevated risk of hemorrhagic stroke in studies such as IMPROVE IT and FOURIER, suggesting that these alternatives could be considered if the risk of ICH is elevated, and the target LDL-C is not achieved.

Carotid artery stenting represents a significant strategy for addressing ECAS. Nevertheless, a substantial number of patients encounter a phenomenon known as in-stent restenosis, which is closely linked to instances of stented-territory infarction. Notably, the levels of LDL-C beyond the 12-month mark emerge as an independent predictive factor for occurrences of stented-territory infarction and in-stent restenosis post carotid artery stenting. Those who managed to maintain their LDL-C levels within the targeted range exhibited a decreased likelihood of stroke recurrence.[43]

2. SVD

SVD constitutes a pathological progression frequently intertwined with atherosclerosis and pivotal cardiovascular risk factors, including hypertension, hyperlipidemia, and the aging process. This condition manifests through various forms, such as lacunar infarction (LI), white matter hyperintensities (WMHs), cerebral microbleeds (CMBs), and even ICH.[1] There exists a body of evidence examining the impacts of statins across diverse categories of SVD.

LI

LI typically arises from deep perforating arterial disease and displays pathological characteristics distinguished by lipohyalinosis or fibrinoid degeneration, instead of substantial lipid accumulations within the vessel walls. [44] However, in instances involving patients with non-stenotic atherosclerosis, localized atheromas have the potential to obstruct the orifice of the perforator, leading to the development of LI. This phenomenon is defined as branch atheromatous disease (BAD).[1]

In a particular study, it was observed that larger lacunar lesions (ranging from 8 to 20 mm on magnetic resonance imaging), likely attributed to microatheroma, demonstrated an association with LDL-C levels (prevalence ratio=1.27 per standard deviation; 95% CI, 1.06–1.52). Conversely, smaller lesions (≤7 mm), possibly arising from lipohyalinosis, did not exhibit such a correlation.[45] A retrospective study involving 2,742 stroke patients, including 281 pre-stroke statin users (10.2%), utilized logistic regression analyses to reveal a link between statin treatment and favorable functional outcomes among patients with LI (odds

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JLA Journal of Lipid and Atherosclerosis

ratio [OR], 2.28; 95% CI, 1.15–4.52). It is suggested that statins could potentially enhance cerebral endothelial function in this subset of patients.[1]

WMH

The impact of statins on the progression of WMH has yielded conflicting results. In a *post hoc* analysis of the Regression of Cerebral Artery Stenosis (ROCAS) study, the effects of statins on WMH progression were examined. In this study, 208 subjects were randomized into either the placebo group (n=102) or the simvastatin 20 mg daily group (n=106). After a 2-year follow-up period, no significant alteration in WMH volume was observed between the statin and placebo groups.[46]

Conversely, a recent *post hoc* analysis of the Systolic Blood Pressure Intervention Trial Memory and Cognition in Decreased Hypertension (SPRINT-MIND) trial unveiled that consistent use of statin medications was associated with a nearly 2.5-fold increase in the likelihood of WMH progression over a span of 4 years (adjusted OR, 2.30; 95% CI, 1.11–4.77; p=0.025). This phenomenon might arise from statins interacting with low-density lipoprotein receptor-related protein 1 (LRP1), a transmembrane receptor present in various neuronal tissues. LRP1 plays a pivotal role in mitigating atherogenesis, supporting neuronal integrity, and clearing myelin debris. However, statin therapy has been linked to a reduction in LRP1 levels.[47] Consequently, the activation of LRP1 in neurons could diminish due to statin intake, leading to a decline in its advantageous effects and potentially resulting in an increase in WMH observable through brain MRI scans.

CMBs

CMBs stem from the accumulation of amyloid and lipid hyaline within arterioles, contributing to the disruption of the blood-brain barrier and the subsequent deposition of hemosiderin around blood vessels.[48] CMBs serve as significant biomarkers, aiding in the prediction of cerebral hemorrhage incidents or recurrences. [49] Furthermore, it's important to distinguish between different types of CMBs based on their location. Lobar CMBs are associated with amyloid deposition in the cortical blood vessels, while deep CMBs are linked to the presence of hypertensive arteriopathy. This differentiation provides insights into the underlying mechanisms and pathological processes driving the development of CMBs in distinct regions of the brain.[50]

A prior study demonstrated a negative association between LDL-C levels and the occurrence of incident.[51] However, there exists no substantial evidence implicating statins as a risk factor for the development of CMBs. A recent meta-analysis delved into the connection between the utilization of statins and the emergence of CMBs.[52] The outcomes of this analysis indicated that statin usage exhibited no significant correlation with CMBs in either unadjusted (OR, 1.15; 95% CI, 0.76–1.74) or adjusted analyses (OR, 1.09; 95% CI, 0.64–1.86). The statin use displayed a more pronounced association with the presence of lobar CMBs in the unadjusted analysis (OR, 2.01; 95% CI, 1.48–2.72), although this effect did not remain significant in the adjusted analysis (OR, 2.26; 95% CI, 0.86–5.91). This emphasizes the complexity of the relationship between statins and different types of CMBs, which may be influenced by various factors and requires further investigation for a comprehensive understanding.

3. Cardioembolism

Cardioembolic stroke constitutes a substantial portion, ranging from 31% to 38%, of all ischemic strokes. This type of stroke can be triggered by different factors, including atrial

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fibrillation (AF), myocardial infarction, dilated or congestive cardiomyopathy, and the presence of a thrombus within the left ventricular wall. These diverse cardiovascular sources can lead to the formation of emboli that travel to the brain, resulting in a cardioembolic stroke.[53] The understanding of the impact of statins on cardioembolic stroke is limited, mainly because patients with AF and other underlying causes of cardioembolism were intentionally excluded from the SPARCL trial. As a result, there is a lack of comprehensive data regarding the specific effects of statins in this subset of patients who experience stroke due to cardioembolic factors.[54]

Nonetheless, there is evidence to consider regarding the potential benefits of lipid-lowering therapy in patients with AF, mirroring findings observed in cases of LAA and SVD. A retrospective study demonstrated these advantages, suggesting that lipid-lowering therapy could have similar benefits in AF patients.[55] This could be attributed to the multifaceted effects of statins, as AF is known to increase CD40 expression and enhance platelet adhesion to the endocardium. Simvastatin has shown efficacy in modulating this expression, thereby potentially reducing the risk of intra-atrial thrombus formation.[56] The Korean nationwide ATrial fibrillaTionEvaluatioN regisTry in Ischemic strOke patieNts (K-ATTENTION) study, which focused on AF related stroke, found that the use of high-intensity statins was associated with a lower risk of 3-year mortality from any cause, stroke, acute coronary syndrome, or major bleeding compared to low-to-moderate statin use. Furthermore, there was no significant difference in major bleeding between the 2 groups.[57] Recent findings from a meta-analysis of observational studies also indicated that statin use effect on the reduction of mortality rate and did not elevate the risk of major bleeding in cardioembolic stroke (relative risk, 0.35; 95% CI, 0.06–2.16).[58,59]

Hence, it is imperative not to postpone the treatment of dyslipidemia even in cases of the cardioembolic stroke subtype. Initiating a regimen of statin therapy exceeding moderate intensity and striving to achieve an LDL-C level of less than 70 mg/dL following an acute stroke can be considered. Furthermore, the prescription of statins becomes especially crucial when a patient presents with concomitant atherosclerotic cardiovascular diseases. This approach underscores the importance of proactive lipid management in stroke patients, with tailored treatment strategies to mitigate the risk factors associated with cardioembolic stroke.

4. Acute reperfusion therapy

Reperfusion therapy stands out as the most effective treatment for AIS.[60] However, the relationship between LDL-C levels and outcomes in AIS patients who underwent reperfusion therapy remains uncertain. There is limited clarity on how LDL-C impacts individuals who have undergone reperfusion therapy for AIS.[61]

Some retrospective studies have indicated that a reduction in LDL-C levels during hospitalization in AIS patients who received reperfusion therapy, whether through intravenous (IV) tPA or endovascular treatment (EVT), is significantly linked to unfavorable functional outcomes after 90 days.[62,63] This connection could be due to lower cholesterol levels potentially affecting the neuronal membrane's electronic balance, leading to compromised neuronal cells' ability to withstand acute ischemic stress-related hyperosmolarity and acidosis.[61,64] Furthermore, cholesterol has been associated with shielding against oxidative stress and aiding in the remyelination process of penumbra tissue following reperfusion therapy.[61] Building on this theme, a study focusing on patients with emergent large vessel occlusion who underwent EVT aimed to ascertain the association

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between lipid profiles and EVT prognosis. The findings demonstrated that higher total cholesterol levels were linked to favorable outcomes three months after EVT, particularly among patients with CE etiology and complete recanalization.[61]

In a *post hoc* analysis of the Stroke Treatment With Acute Reperfusion and Simvastatin (STARS) trial, it was discovered that patients who were administered tPA displayed a positive response to simvastatin treatment. This was evident in a higher proportion of patients experiencing significant neurological recovery (OR, 4.14; 95% CI, 1.18–14.4; p=0.02). This finding underscores the potential benefits of simvastatin in conjunction with tPA therapy for enhancing neurological outcomes.[65] Moreover, recent meta-analytical research suggests that utilizing statins during hospitalization after IV tPA is not only safe but also holds the potential to positively influence clinical results. This in-hospital statin usage was correlated with a decreased risk of symptomatic ICH (OR, 0.46; 95% CI, 0.21–1.00; p=0.045) as well as any ICH occurrence (OR, 0.51; 95% CI, 0.27–0.98; p=0.04).[66] Administering statins earlier after the administration of IV tPA has been linked to improved outcomes. According to current guidelines, initiating statin treatment during the admission of stroke patients is recommended for optimal management.

5. Hemorrhagic stroke

Considering the pivotal role of cholesterol in cell membrane structural integrity, diminished cholesterol levels might pose a potential risk for ICH. This is attributed to the potential weakening of the endothelial lining due to reduced cholesterol, consequently fostering arterial vulnerability and subsequent hemorrhage.[67] Several epidemiological investigations have underscored an inverse correlation between levels of LDL-C and the likelihood of ICH.[68] In a recent meta-analysis, findings revealed that a mere 10 mg/dL escalation in LDL-C corresponded to a 3% reduction in ICH risk (95% CI, 0.95–0.98).[1]

The SPARCL trial revealed that patients undergoing statin treatment experienced a notable increase (HR, 1.66; 95% CI, 1.08–2.55) in the risk of ICH.[69] However, upon further investigation, it was determined that independent risk factors for hemorrhagic stroke encompassed male gender, hypertension, advancing age, and the presence of hemorrhagic or small vessel stroke at the commencement of the study (entry). Low levels of LDL-C were not identified as an independent risk factor.[54] Additionally, within the context of the TST trial, sub-analysis findings did not exhibit a significant variance in the occurrence of hemorrhagic stroke between groups with lower and higher target levels.[70]

However, a consensus on the most effective approach to managing dyslipidemia after hemorrhagic stroke is currently lacking, primarily due to the limited number of RCTs directly addressing statin use in these patients. The conflicting risks, involving the potential for an increased propensity for ICH versus preventing subsequent ischemic cardiovascular events, add complexity to determining the optimal strategy for dyslipidemia management post-ICH.[71] This dilemma emphasizes the need for a careful and individualized approach. The decision on whether to continue statin therapy in patients with a history of ICH should take into consideration various factors, including the initial indication for statin use (primary versus secondary prevention and the severity of atherosclerotic disease), the estimated individual risk of ICH recurrence based on ICH location/cause (lobar versus deep, and the burden of lobar CMBs or cortical superficial siderosis), and the delicate balance between the risks of ischemic cardiovascular events and hemorrhagic events. This nuanced decision-making process underscores the importance of a thorough assessment and personalized risk-benefit analysis for each patient.[71]

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Therefore, when a patient possesses a history of ICH or displays multiple microbleeds on brain imaging, considering alternatives such as opting for moderate-intensity statin therapy or exploring the use of ezetimibe instead of high-intensity statin.[2] Additionally, emphasizing rigorous blood pressure control is highly likely to yield the most advantageous results, especially for patients at high risk for ICH.

CONCLUSION

Statin, ezetimibe, and PCSK9 inhibitors could be considered to stroke patients for secondary prevention. However, the roles of blood lipids and lipid-lowering therapies differ among stroke subtypes (**Fig. 1**). Statin use is probably useful in ICAS, but the effect may be less robust or inconsistent than in ECAS. "high dose statin" and "low LDL-C targets" can be the most reasonable strategy in patients with ECAS. Based on the evidence that medical treatment is important in patients with ICAS, further studies are needed to investigate the effects of statins as considering of various mechanisms of stroke in ICAS. For SVDs, statins do not appear to increase the risk of further stroke, probably because statins have various pleiotropic effects beyond the lipid-lowering effect. However, if patient has a high risk of bleeding tendency (prior history of ICH or multiple CMBs at the lobar area), considering alternatives such as opting for moderate-intensity statin therapy or exploring the use of ezetimibe instead of high-intensity statin could be considered. For CE stroke, statin can potentially affect to reduce mortality, especially when a patient presents with concomitant atherosclerotic cardiovascular diseases. Although the relationship between dyslipidemia and acute reperfusion therapy remains uncertain, the use of statins in these patients has been linked to improved outcomes. Further studies are needed to establish appropriate LDL-C target levels for different stroke subtypes.

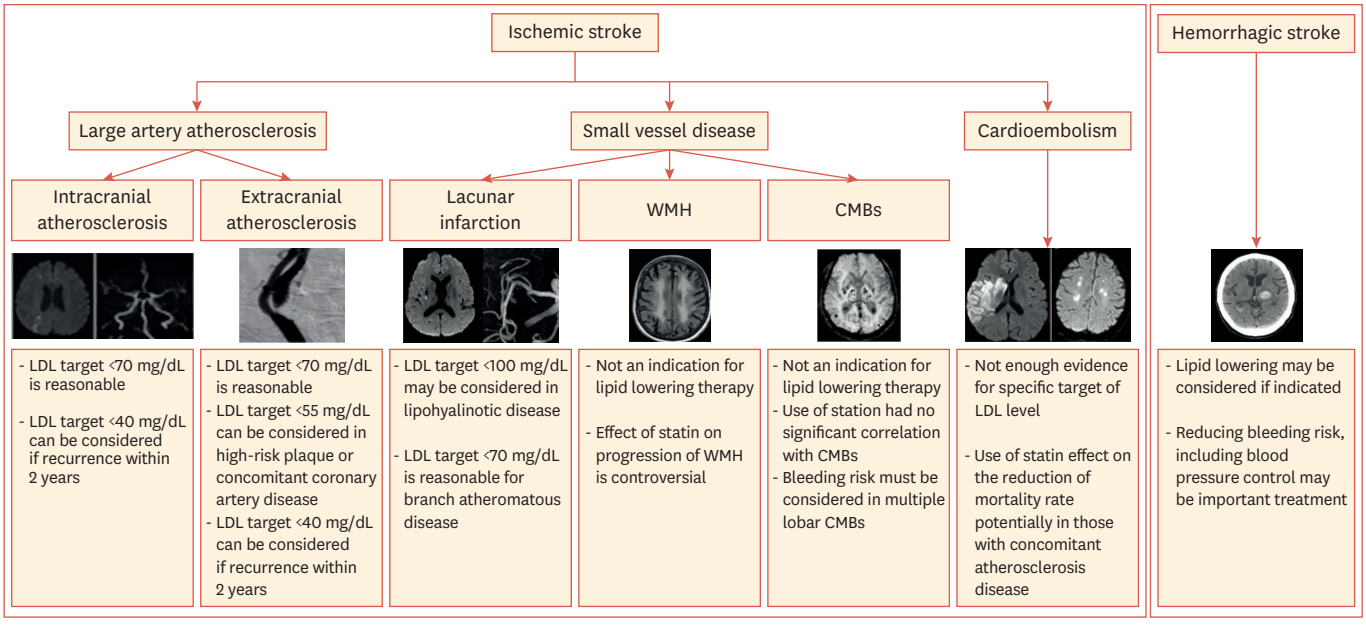

Fig. 1. Secondary prevention of stroke and the management of dyslipidemia depending on the stroke subtypes.
LDL, low-density lipoprotein; WMH, white matter hyperintensity; CMB, cerebral microbleed.

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