



Recent updates in dyslipidemia management: perspectives in stroke-specific situation

Woo-Keun Seo¹, Mersedeh Bahr Hosseini², Oh Young Bang¹, David S. Liebeskind²

¹Department of Neurology and Stroke Center, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

²Department of Neurology and Comprehensive Stroke Center, UCLA, Los Angeles, CA, USA

Received: January 1, 2020

Revised: February 3, 2020

Accepted: February 5, 2020

Corresponding author:

Woo-Keun Seo

Department of Neurology
and Stroke Center, Samsung
Medical Center, Sungkyunkwan
University School of Medicine,
81 Irwon-ro, Gangnam-gu,
Seoul 06351, Korea

Tel: +82-2-3410-0799

E-mail: mcastenosis@gmail.com

ABSTRACT

Managing dyslipidemia in stroke is essential. During the past several decades, monumental changes in dyslipidemia management have occurred, resulting in improvement in outcomes of patients with cardiovascular disease (CVD). The mainstay of the changes has been related to statin therapy, which prevents recurrence of vascular events in patients with established CVD. Very recently proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors have introduced a highly efficient level of lipid lowering practice into cardiovascular field. Vast evidence has established and validated the beneficial effects of statin and PCSK-9 inhibitors in CVD. In addition, there have been extensive changes in guidelines pertaining to dyslipidemia management of CVD patients. However, assessing the direct benefits of these agents, specifically and primarily in patients with stroke, has been less of a focus of clinical studies leaving many unanswered questions open. This review covers the current and available evidence and clinical practice guidelines addressing lipid-lowering therapy in stroke. Furthermore, several specific issues related to lipid-lowering therapies in stroke will be addressed such as statin-related risk of hemorrhagic stroke, statin use in non-atherosclerotic stroke subtype, and non-statin lipid-lowering therapies.

Keywords: Dyslipidemias; Hydroxymethylglutaryl-CoA reductase inhibitors; Stroke

INTRODUCTION

Dyslipidemia is an established risk factor for cardiovascular diseases (CVDs) and stroke, and appropriate management of elevated low-density lipoprotein cholesterol (LDL-C) levels, a known atherogenic risk factor, is crucial to reduce the risk of atherosclerotic vascular events and death. Although historically a strong link between high cholesterol and CVD was suggested by various epidemiological studies [1], the vast majority of knowledge about the association appeared after the introduction of lovastatin, the first 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitor. Statin therapy in clinical practice provided a major contribu-

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0/>).

tion to our understanding of the role that high cholesterol plays in development of CVD and also the beneficial effects of cholesterol lowering on recurrence of CVD [2]. Due to the uncertainty in the role of lipid-lowering therapies for stroke prevention [3], active management of dyslipidemia in stroke started only in mid-2006, after the publication of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial [4]. Usually, stroke and coronary artery disease share the universal nature of the end-organ ischemic disease. However, several distinctive features in stroke delayed the use of active lipid-lowering therapy, unlike in coronary artery disease and other vascular diseases, including: heterogeneity of etiologies, the inverse relationship of cholesterol level with hemorrhagic stroke, and lack of high-level evidences for the effect of lipid-lowering therapy in patients with stroke.

Unfortunately, SPARCL remains one of the few randomized clinical trials specifically assessing dyslipidemia management in stroke patients since its publication more than a decade ago. However, a considerable real-world clinical practice change in dyslipidemia management for stroke patients has already taken place despite the limited evidence in the form of randomized clinical trials. Hereby, we review the recent advances in dyslipidemia management with an emphasis on stroke-specific circumstances.

CURRENT EVIDENCES AND GUIDELINES

Clinical trials of statins for dyslipidemia management in stroke

Stroke is one of the major vascular events in clinical trials investigating lipid-lowering therapies. However, clinical trials to test the effect of lipid management in stroke patients were rarely conducted. The Heart Protection Study (HPS) is a randomized clinical trial assessing the effect of simvastatin 40mg versus placebo performed in 20,536 patients with a history of coronary artery disease, other occlusive arterial diseases, or diabetes mellitus [5]. HPS revealed that simvastatin reduced the risk for all-cause mortality (relative risk reduction [RRR] 17%), coronary events (RRR 27%), and stroke (RRR 25%). Simvastatin reduced major vascular events in every subgroup irrespective of the index vascular events or risk factors. These definite and consistent results strongly supported the role of statin therapy in high-risk patients with atherosclerotic vascular disease. The *post hoc* analysis of the HPS revealed the preventive effect of statins against all vascular events in a subgroup with prior stroke. Simvastatin re-

duced major coronary events, revascularization, and major vascular events in both groups with and without previous stroke history. But, simvastatin failed to show a significant benefit over placebo for the prevention of stroke recurrence in a subgroup with prior stroke [6]. The negative association persisted regardless of the type (ischemic and hemorrhagic) or severity (severe-to-fatal and mild-to-moderate) of cerebrovascular event. The unexpected results were attributed to a long interval between the index event and randomization (mean 4.3 years). Considering that the risk of recurrent stroke among stroke survivors is highest during the early period, the exclusion of acute stroke patients could have resulted in underestimation of statin's benefits. In addition, the robustness of the results was questioned as rate of stroke was not assessed as a primary outcome in HPS.

The most notable impactful randomized clinical trial specifically investigating the relationship between statin and rate of stroke recurrence was SPARCL [7]. This prospective randomized controlled trial enrolled a total of 4,731 stroke patients with LDL-C levels between 100 and 190 mg/dL and randomized them into atorvastatin 80 mg and placebo and compared the risk of recurrent stroke between them for 5 years of follow-up. The results, although marginal for their primary endpoint of combined fatal or nonfatal strokes, were clear and robust. High dose atorvastatin therapy reduced the relative risk of stroke by 16% ($P=0.03$; 95% confidence interval [CI], 0.71 to 0.99) and the risk of secondary outcomes of stroke and transient ischemic attack (TIA) by 23% ($P<0.001$), and TIA alone by 26% ($P=0.004$). However, the absolute benefit of atorvastatin in reducing risk of stroke was small (absolute risk reduction [ARR] of 1.9% for 5 years, number needed to treat of 52), and it only reduced the risk of fatal stroke (RRR of 43%; $P=0.03$) with no significant effect on nonfatal stroke reduction ($P=0.11$). Furthermore, the survival benefit was not apparent and the atorvastatin group had a slightly higher risk of hemorrhagic stroke (2.3% vs. 1.4%).

Despite the clear benefit of statin therapy on stroke recurrence, SPARCL left several unsolved questions revolving around risk of hemorrhagic stroke associated with statins, an appropriate level of LDL reduction for stroke prevention particularly in patients with LDL-C level of <100 mg/dL at the time of stroke, and recommended dose of statin.

Subsequently, the *post hoc* analysis of SPARCL attempted to answer some these questions by revealing that atorvastatin significantly reduced the risk of combined fatal and nonfatal strokes only in patients with $\geq 50\%$ LDL-C reduction [7]. This beneficial effect was approximately twice the observed

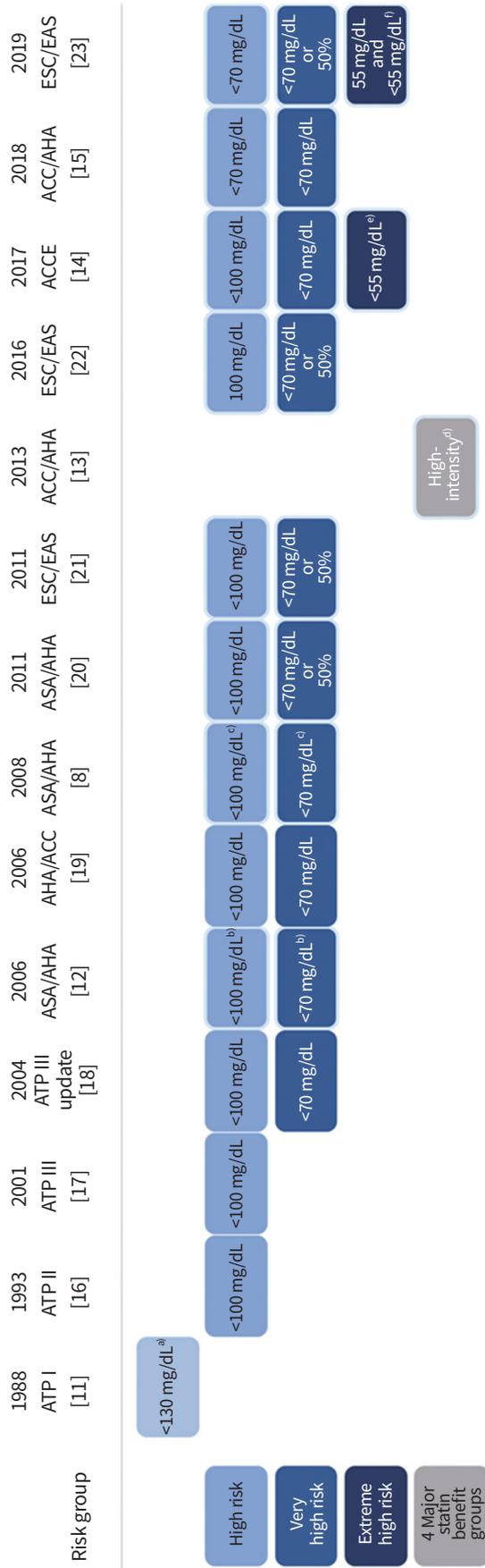


Fig. 1. Trend of changes in target low-density lipoprotein cholesterol (LDL-C) goals for secondary stroke prevention in the major clinical practice guidelines. ATP, Adult Treatment Panel; ASA, American Stroke Association; AHA, American Heart Association; ESC, European Society of Cardiology; EAS, European Atherosclerosis Society; ACC, American College of Cardiology; ACCE, American College of Clinical Endocrinology. ^a Borderline-high level; ^b Statin treatment was recommended to reduce the risk of vascular events; ^c Statin treatment was recommended to reduce the risk of stroke and cardiovascular events; ^d Definition of high-intensity statin therapy is daily dose lowers LDL-C by approximately 50% or more; ^e This is the first guideline, which comments 'extreme high-risk group' and LDL-C target <55 mg/dL; ^f For patients with atherosclerotic cardiovascular disease who experience a secondary vascular event within 2 years while taking maximally tolerated statin-based therapy, an LDL-C goal of <40 mg/dL may be considered. This is the first guideline that recommend considering LDL-C target <40 mg/dL.

effect of statins in the prespecified intention to treat analysis (31% vs. 16%) with a statistically nonsignificant increase in hemorrhagic stroke.

Nevertheless, SPARCL was the first high-level evidence supporting statin therapy in stroke patients and its results pushed the clinical practice guideline to announce the need for statin therapy to prevent recurrent stroke [8]. In addition, SPARCL reawakened our concern about the risk of statin-induced hemorrhagic stroke by showing an elevated risk of hemorrhagic stroke by 1.7-fold in the adjusted model [9]. The statin-related hemorrhagic stroke risk was apparent only in the subgroup with small vessel disease or hemorrhagic stroke and the hemorrhagic stroke risk was not correlated with on-treatment LDL-C level, warranting further investigation.

The second most notable randomized clinical trial directly assessing the role of statin use for stroke prevention was the Japan Statin Treatment Against Recurrent stroke (J-STARS). J-STARS was a randomized, open-label clinical trial comparing low potency statin (pravastatin 10 mg) versus control group [10]. This study set a target sample size as 3,000 but terminated prematurely after the randomization of 1,589 patients. The pravastatin group somewhat showed improved lipid profiles compared to control group, but total recurrence rate of stroke and TIA, which was their primary end-point, occurred similarly in both groups. However, in a subgroup with atherothrombotic stroke, pravastatin reduced the risk of recurrent stroke and TIA. Comparing J-STARS and SPARCL, the most crucial difference between the two was the intensity of statin therapy. In the SPARCL trial, the atorvastatin group showed an average of 53.7% reduction in LDL-C level from baseline. However, the pravastatin group in J-STARS showed only a 19.7% reduction of LDL-C from the baseline level. The difference in the magnitude of LDL-C reduction likely explains the conflicting result, emphasizing the importance of substantial LDL-C reduction to below at least 50% of baseline in secondary stroke prevention.

Clinical practice guidelines for dyslipidemia management for stroke patients

Clinical practice guidelines for dyslipidemia management have dramatically changed in the recent decades (Fig. 1) [8,11-23]. In terms of primary prevention of CVD, the first Adult Treatment Panel for National Cholesterol Education Program (NCEP-ATP I) published in 1988 recommended an LDL-C target level of <130 mg/dL for prevention of coronary artery disease [11]. Subsequently, published guidelines further refined the risk group of vascular events, and gradually lowered the target LDL-C levels. Finally, in 2019, the European Society of Cardiology announced that a $\geq 50\%$ LDL-C reduction from baseline and an absolute LDL-C treatment goal of <55 mg/dL is recommended for very high-risk patients [24].

The trend in the management of dyslipidemia for secondary CVD and stroke prevention has similarly changed towards a more restricted treatment goal. In 2006, before the publication of the SPARCL trial, stroke was not considered a vascular risk factor. Therefore, in 2006, the American Stroke Association guideline recommended that stroke patients should be managed for dyslipidemia according to primary prevention guidelines (i.e., to prevent coronary artery disease or other vascular diseases) [12]. However, in 2008 the results of SPARCL trial enforced a change in American Heart Association (AHA) guidelines to recommend intensive statin treatment for ischemic stroke patients with absolute LDL-C treatment goal of <100 mg/dL which was revised in 2018 guidelines to a stricter goal of achieving $\geq 50\%$ reduction in LDL-C levels with absolute LDL level of <70 mg/dL [8].

Finally, the American College of Cardiology guideline published in 2013, followed by 2018 AHA guidelines, considered stroke as one of atherosclerotic cardiovascular disease (ASCVD) [13].

STROKE SPECIFIC DYSLIPIDEMIA MANAGEMENT

Acute stroke period or early lipid-lowering therapy in stroke patients

Studies of statin therapy in hyperacute and acute post-stroke periods have undertaken two different approaches for assessing the benefits of early statin therapy: (1) assessment of the pleiotropic neuroprotective effect of statins in hyperacute stages of stroke reducing the final infarct size and (2) investigating the secondary preventive benefits of statins in lowering the early risk of recurrent strokes. Statins have been

shown to carry substantial neuroprotective effects alleviating the neuronal injuries via regulating inflammation in preclinical models of acute cerebral ischemia [25-28]. Other neuroprotective effects of statin therapy including augmentation of cerebral blood flow by increasing nitric oxygen production, decrease of glutamate excitotoxicity, neurogenesis, and angiogenesis have also been demonstrated by multiple preclinical studies [29-34].

In parallel to these preclinical evidence of statin-induced neuroprotection, case-control human studies and epidemiologic studies have explored similar effects [35-37]. Ni Chroinin et al. [35] explored the impact of early statin therapy on acute stroke patients using a population-based cohort study. Post-stroke statin therapy initiated shortly after stroke onset significantly improved early and late survival rates (odds ratio for death 0.12 at 7 day, 0.19 at 90 days, and 0.26 at 1 year) independent of stroke recurrence rate. Moreover, they observed similar survival benefits in patients with statin therapy initiated before the stroke onset. Subsequent studies reproduced the survival benefit of early statin therapy showing improvement of functional outcomes in patients treated with statins prior to stroke onset [35,38,39].

Several controlled clinical trials have addressed the second distinct feature of acute statin therapy by investigating the beneficial effects of early statin therapy on stroke prevention. The effects of very early use of rosuvastatin in preventing recurrence of ischemic stroke (EUREKA) trial tested the effect of rosuvastatin 20 mg on acute atherosclerotic stroke patients within 48 hours from the onset [40]. The trial prematurely terminated at enrollments of 316 patients, reporting inconclusive results for new ischemic lesions (the primary end-point; relative risk, 0.83; 95% CI, 0.53 to 1.30). The clinical events (stroke or TIA) were numerically more common in placebo group (4.4%) compared to rosuvastatin group (0.6%); however, it did not reach statistical significance ($P=0.067$). Surprisingly, early rosuvastatin therapy was significantly associated with a lower risk of hemorrhagic transformation compared to control (4.4% vs. 14.5%, $P=0.007$). The authors attributed their results to neuroprotective effect of early statin therapy against microvascular injury.

Another clinical trial with 44 acute stroke patients similarly supported this hypothesis [41]. In this study, acute stroke patients were randomized into the in-hospital early versus delayed statin therapy and compared the profiles of inflammatory markers between the two groups. They demonstrated that patients receiving early in-hospital statin therapy had better inflammatory profiles, including lower tumor necrosis

factor- α , interleukin 6, and vascular cell adhesion molecule-1, indicating the anti-inflammatory effects of statins. This ameliorative effect of statin was also translated to better neurological and functional outcomes.

Similarly, a recent meta-analysis summarized the effect of statin therapy in acute stroke patients by reviewing 70 articles, including eight randomized controlled trials [42]. According to this study, statin therapy started before or during admission consistently improved functional outcome and lowered mortality and statin withdrawal after stroke onset aggravated functional outcome [42].

The beneficial results from early statin therapy have not been consistent across clinical trials. The Administration of Statin on Acute Ischemic Stroke Patient (ASSORT), a clinical trial comparing functional outcomes between early (<24 hours) and delayed statin treatment (7 days), failed to disclose any difference in the distribution of modified Rankin scale at 90 days in 257 non-cardioembolic acute stroke patients [43]. Although a potential signal of efficacy was observed in subgroup analysis of patients with atheroembolic stroke, authors accounted the administration of low doses statin therapy in the trial (atorvastatin 20 mg/day, pitavastatin 4 mg/day, or rosuvastatin 5 mg/day) for their overall negative results.

Therefore, based on the available evidence there is no reason to delay the initiation of high intensity statin therapy in acute stroke patients.

Atrial fibrillation associated stroke

Atrial fibrillation (AF) provokes about a quarter of all ischemic strokes and shares the same risk factors as coronary artery disease including left ventricular hypertrophy, obesity, and hypertension. Furthermore, each component of CHA₂DS₂-VASc, which represents thromboembolic risk in AF, is also a risk factor for atherosclerotic arterial diseases. Therefore, statins may reduce thromboembolic risks in patients with AF or even have inhibitory effects on AF development. However, not much work has been performed investigating the risk alleviating effects of statins on AF and there are no clear guidelines regarding long term statin therapy in strokes related to AF [44].

On the other hand, a nationwide study using the Taiwan National Health Insurance Research Database revealed that statin therapy improved in-hospital and long-term survival by 26% irrespective of demographic features, CHADS₂ score, or stroke severity during a median follow-up of 2.4 years [45]. Also, in some observational studies, statin therapy has been

shown to improve survival and functional outcomes of patients with cardioembolic strokes associated with AF despite no evidence of any preventive effect on stroke recurrence [46-48]. The survival benefits shown by these studies could be explained by the pleiotropic statin-induced neuroprotection including anti-inflammatory and collateral enhancing effects of early and pre-stroke statin therapy [45,49].

Hemorrhagic stroke

The SPARCL trial reported an overall significant increased risk of hemorrhagic stroke by 68% in statin arm and the small subgroup of patients with hemorrhagic stroke at entry seemed not to benefit from statins [9]. The *post hoc* analysis of the trial looking at patients with $\geq 50\%$ LDL-C reduction showed a statistically non-significant increase in hemorrhagic stroke and no LDL-C threshold below which the risk of brain hemorrhage was increased. This non-significant result was attributed to loss of power due to division of the study participants to three groups of LDL-C reduction level.

Previous large-scale studies have also indicated an associations between low serum LDL and increased risk of hemorrhagic stroke [50,51]. Patients with small vessel disease or those with prior history of hemorrhage had a higher risk for hemorrhagic stroke [9].

In contrast, a meta-analysis performed on 16 observational studies investigating the impact of statins on hemorrhagic stroke risk revealed that pre-stroke or in-hospital early statin therapy in hemorrhagic stroke patients improved survival and functional outcomes at 3 months from the stroke onset [52]. Another systematic review and meta-analyses investigating the effect of statins on risk of recurrent hemorrhage failed to show any effect on rate of recurrent hemorrhage in patients taking statins, although there was a non-significant trend towards an increased hemorrhage risk among ischemic stroke patients [53,54].

To summarize, despite the evidence relating statin therapy to increased risk of hemorrhagic stroke, the possible net benefit of acute statin therapy in all stroke patients seems to outweigh the concerns although large randomized clinical trials specifically assessing benefits of statins in hemorrhagic strokes are warranted.

Cerebral small vessel diseases

Similar to statins in AF related strokes, not much work has been done on effects of statins in patients with small vessel disease presenting with lacunar infarction and white matter hyperintensities [55]. The SPARCL subgroup analysis of pa-

tients with small vessel disease revealed the persistent beneficial effects of intensive statin therapy in this subgroup [56]. Statin also delayed the progression of cerebral white matter hyperintensities in hypertensive elderly patients or patients with middle cerebral artery stenosis [55,57]. However, the association between statin therapy and white matter changes was negative in *post hoc* analysis of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) trial [58]. Therefore, further studies are required to demonstrate the relationship between white matter changes and statin therapy.

Cancer-related stroke

Cancer-related stroke is an emerging stroke subtype related to hypercoagulability, and cancer patients are at higher risk for stroke [59]. Stroke associated with cancer has high mortality [59], and anticancer treatment are often put on hold after stroke. So, various efforts have been made to find a treatment suitable for cancer-related stroke, and statin therapy is one of them. The anticancer property of statins as part of their pleiotropic protective effect has been elicited both *in vitro* and *in vivo* [60]. In terms of human studies, Kim et al. [61] investigated benefit of statins in patients with cancer accompanied by stroke using multicenter stroke registries and nationwide health insurance database. They matched the patients using statins to non-statin users with propensity score (PS) and demonstrated that statin improved survival in a dose-dependent manner. Their external validation set composed of a nation-wide health insurance service database, and subgroup analyses strongly supported the robustness of their results. In this study, the impact of statin was similar between lung cancer and other types of cancer.

In addition to its anti-cancer properties, statins have been used for stroke prevention in patients with head and neck cancer due to a strong association between neck radiation therapy and severe carotid stenosis. Addison et al. [62] reviewed the data of consecutive head and neck cancer patients with radiation therapy (n=1,011) and compared the incidence of stroke or TIA according to statin therapy at the time of irradiation. In this study, statin therapy reduced the risk of stroke and TIA with a hazard ratio of 0.4. An analysis of the health insurance database of Quebec (n=5,718) drew a similar result [63]. Statin therapy after neck irradiation improved survival and reduced the risk of stroke without critical adverse effects. In contrast, Lee et al. [64] reported the futility of statin therapy in a similar patient population, even with an effort to avoid selection bias by PS matching analysis using the Taiwanese health insurance database.

APPROPRIATE TARGET FOR DYSLIPIDEMIA MANAGEMENT IN STROKE

Appropriate target LDL-C level for stroke prevention

The primary target for the management of dyslipidemia in CVD prevention is the LDL-C level considering that atherosclerosis is the main underlying pathophysiology of CVD. The most recent AHA guidelines recommend LDL-C levels of <70 mg/dL in patients with clinical ASCVD including stroke and TIA. However, only about a third of stroke events are due to atherosclerotic origin highlighting the paucity of evidence addressing the ideal target blood level for LDL-C in stroke patients according to the stroke etiology.

In addition to achieving a specific target levels of LDL-C, the amount of LDL-C reduction in each individual is of paramount importance in stroke reduction. As previously discussed, the *post hoc* analysis of SPARCL revealed that atorvastatin reduced the risk of stroke only in patients with $\geq 50\%$ LDL reduction and the benefits of atorvastatin was most pronounced in subgroups of patients with evidence of atherosclerosis such as carotid stenosis or large artery disease. Similarly, a meta-analysis by Amarenco and Labreuche [65] in 2009 demonstrated that every 1 mmol/L (approximately 40 mg/dL) reduction in LDL-C produces a 21.1% reduction of stroke risk in a meta-analysis.

In a meta-regression study of 23 clinical trials, Shin et al. [54] demonstrated a significant correlation between stroke risk and achieved LDL-C level. Furthermore, the stroke prevention effect of lipid-lowering therapy has been shown to persist monotonously at an LDL-C level below 50 mg/dL without any floor effect while the achieved LDL-C level had no association with hemorrhagic stroke [54].

While the above trials included all types of strokes, Treat Stroke to Target (TST) trial was designed to specifically investigate the atherosclerotic stroke risk comparing the strategies of maintaining LDL-C level below 100 mg/dL versus 70 mg/dL [66]. The TST trial revealed that patients with recent ischemic stroke or TIA with evidence of atherosclerotic disease had a fewer major cardiovascular events with a target LDL-C level of less than 70 mg/dL compared to those assigned to a target of 90 to 110 mg/dL [67]. The LDL-C goal in this trial was achieved by increasing the statin dose or addition of ezetimibe to statins. The result support the target LDL-C level of <70 mg/dL in stroke patients with atherosclerotic disease.

Non-statin LDL lowering therapies and non-LDL targets
Although statins remain the most crucial medications for

dyslipidemia management, to achieve the target LDL-C level of less than 70 mg/dL, they are often insufficient requiring addition of non-statin therapies. A study has revealed that doubling the dose of statins only yields 6% of additional LDL-C reduction [68]. In addition, intolerance to high intensity statins in forms of myalgia, fatigue, or transaminitis is another common reason to use non-statin lipid therapy as an adjunct or alternative therapy to statins. The main non-statin lipid therapies have been ezetimibe and very recently proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors.

The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) evaluated the effect of ezetimibe combined with simvastatin compared to simvastatin alone in patients with the acute coronary syndrome [69]. IMPROVE-IT trial assessed the additional LDL-lowering benefits of ezetimibe and demonstrated a 6.4% RRR in combined risk of subsequent heart attack, stroke, cardiovascular death, rehospitalization for unstable angina and revascularization procedures.

Another family of medications that have been recently introduced to clinical practice are monoclonal antibodies inhibiting PCSK-9 inhibitors such as alirocumab and evolocumab. These highly potent lipid therapies can achieve up to 60% reduction in LDL-C level producing a significant reduction in composite cardiovascular risks [70,71].

The most notable clinical trial assessing the benefits of PCSK-9 inhibitor evolocumab in atherosclerotic cardiovascular prevention was Further Cardiovascular Outcomes Research with PCSK-9 Inhibition in Subjects with Elevated Risk (FOURIER). FOURIER enrolled 27,564 patients with ASCVD and LDL-C levels of more than 70 mg/dL while on high to medium intensity statin therapy. In addition to reducing the composite risk of cardiovascular death/myocardial infarction/stroke as their primary endpoint, evolocumab also reduced the risk of ischemic stroke by 78% (ARR of 0.4% and number needed to treat of 250) and stroke or TIA by 80% (ARR of 0.5%, and number needed to treat of 200) in average of 2.2 follow-up years. LDL-C level was reduced to a median of 30 mg/dL (interquartile range, 19 to 46) in 48 weeks with no increased risk of hemorrhagic stroke contradicting prior evidence associating very low levels of LDL to hemorrhage risk.

It is important to note that only 20% of FOURIER patients had history of stroke or TIA at entry. Therefore, direct beneficial effects of PCSK-9 inhibitors on stroke prevention in patients with stroke or TIA cannot be fully assessed based on these trials. Overall, the size of benefit of PCSK-9 inhibitors and ezetimibe therapy for stroke prevention has been shown

to be comparable to that of coronary artery disease highlighting the need for further large clinical trials specifically designed for stroke patients [69-71]. Furthermore, all studies of non-statin lipid therapies have tested these medications as an adjunct to statins stressing the need to investigate the beneficial effects of these medications as monotherapy particularly in patients intolerant of statins.

To address this need, a meta-regression analysis of 49 trials included 312,175 participants from 49 trials compared the effect of statin versus non-statin lipid-lowering therapy [72]. The authors found that both statin and non-statin therapy were associated with a similar impact on the rates of vascular events as long as the target LDL-C level is achieved independent on the type of lipid lowering therapy [72].

In addition to ezetimibe and PCSK-9 inhibitors, numerous new lipid-lowering therapies focusing on different mechanisms of action or targeting different lipids than LDL-C are under development. Furthermore, the time interval from the conceptualization of the new therapy to its development and subsequent release to market is rapidly shortening. For example, the first PCSK-9 monoclonal antibody trial in humans was conducted in less than 10 years following the first report of PCSK-9 gene abnormality in 2003 indicating a gain of function in carriers of the gene resulting in an increased risk of coronary heart disease [73,74].

Amongst the most noteworthy of these new emerging lipid lowering therapies are inclisiran, a long active RNA interference (RNAi) that inhibits PCSK-9, and anacetrapib, a cholesteryl ester transfer protein (CETP) inhibitors that finally passed through the long tunnel of CETP inhibitors failures. CETP inhibitors enhance high-density lipoprotein-mediated reverse cholesterol transport and, theoretically, remove the cholesterol from atherosclerotic plaques. Although the former CETP inhibitors discarded due to unexpected adverse effects, anacetrapib in addition to high intensity statins reduced the risk of coronary artery disease by 9% [75]. Angiopoietin-like gene (*ANGPTL*) is another focused target for dyslipidemia management [76-78]. *ANGPTL* secretes a protein that modulates triacylglycerol homeostasis with dual activity on both LDL-C and triglycerides levels.

Other non-LDL lipid targets for CVD prevention have been lipoprotein-a (Lp(a)) and triglycerides. Lp(a), a modified form of LDL-C, is a known risk enhancing factor for ASCVD at levels >50 mg/dL. Therapeutic targeting of Lp(a) has been a topic of many anecdotal reports and observational studies and, historically, niacin and fibrates have been used to lower the Lp(a) level with only modest effects and no proven CVD pre-

ventive benefits [79]. Currently there is no clear guideline regarding the management of high Lp(a) levels particularly in stroke patients with no other identifiable risk factors.

The role of triglycerides as risk enhancing factor for stroke remains controversial although excess triglycerides are carried in the form of very low density lipoprotein (VLDL) which known to be atherogenic at higher levels. In a large prospective cohort study following 13,956 participants for incidence of ischemic stroke, authors demonstrated that the cumulative incidence of ischemic stroke increased with increasing levels of non-fasting triglycerides above 89 mg/dL [80]. Similarly, a meta regression analysis reported a statistically significant association between baseline triglyceride levels and stroke risk (adjusted relative risk, 1.05 per 10 mg/dL increase; 95% CI, 1.03 to 1.07). Currently, guidelines recommend initiation of statin therapy to treat very high levels of triglycerides ≥ 500 mg/dL and only treat moderate level (170 to 500) in patients with high risk of atherosclerotic cardiovascular risk [81].

CONCLUSION

Abundant evidence has supported the importance of lipid-lowering therapy in cardiovascular risk reduction, however, there are still unanswered questions regarding the optimal management of dyslipidemia in stroke patients. Currently, statin therapy is the gold standard for secondary stroke prevention in all patients with stroke and an intensive statin therapy with tighter LDL-C targets should be used for patients with stroke of atherosclerotic origin. Lipid-lowering therapy should be initiated as soon as possible after an acute stroke event with statins used as the first choice of therapy. If maximally tolerable statin therapy fails to achieve target goal, combination therapy, or switching to other lipid-lowering therapies is recommended.

Large randomized clinical trials are warranted to further assess the stroke preventive benefits of different types of lipid lowering therapies, ideal LDL-C targets in patients with strokes of different etiologies, roles of other lipids, and lowering their levels in stroke patients.

CONFLICTS OF INTEREST

Woo-Keun Seo received honoraria for lectures from Pfizer, Sanofi-Aventis, Otsuka Korea, Dong-A Pharmaceutical Co. Ltd., Beyer, Daewoong Pharmaceutical Co. Ltd., Daiichi Sankyo Korea Co. Ltd., Boryung Pharmaceutical, a study grant

from Daiichi Sankyo Korea Co. Ltd., a consulting fee from OBELAB Inc., and a stock option from JLK INSPECTION.

ORCID

Woo-Keun Seo <https://orcid.org/0000-0002-4004-8434>
Mersedeh Bahr Hosseini <https://orcid.org/0000-0003-3049-4542>
Oh Young Bang <https://orcid.org/0000-0002-7962-8751>
David S. Liebeskind <https://orcid.org/0000-0002-5109-8736>

AUTHOR CONTRIBUTIONS

Conception or design: WKS, MBH, OYB, DSL.

Acquisition, analysis, or interpretation of data: WKS, MBH, OYB, DSL.

Drafting the work or revising: WKS, MBH.

Final approval of the manuscript: MBH, OYB, DSL.

REFERENCES

1. Sharrett AR, Ballantyne CM, Coady SA, Heiss G, Sorlie PD, Catellier D, et al. Coronary heart disease prediction from lipoprotein cholesterol levels, triglycerides, lipoprotein(a), apolipoproteins A-I and B, and HDL density sub-fractions: the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation* 2001;104:1108-13.
2. Endo A. The discovery and development of HMG-CoA reductase inhibitors. *J Lipid Res* 1992;33:1569-82.
3. Shahar E, Chambless LE, Rosamond WD, Boland LL, Ballantyne CM, McGovern PG, et al. Plasma lipid profile and incident ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) study. *Stroke* 2003;34:623-31.
4. Amarenco P, Bogousslavsky J, Callahan A 3rd, Goldstein LB, Hennerici M, Rudolph AE, et al. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med* 2006;355:549-59.
5. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7-22.
6. Collins R, Armitage J, Parish S, Sleight P, Peto R; Heart Protection Study Collaborative Group. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20536 people with cerebrovascular disease or other high-risk conditions. *Lancet* 2004;363: 757-67.
7. Amarenco P, Goldstein LB, Szarek M, Sillesen H, Rudolph AE, Callahan A 3rd, et al. Effects of intense low-density li-

- poprotein cholesterol reduction in patients with stroke or transient ischemic attack: the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial. *Stroke* 2007;38:3198-204.
8. Adams RJ, Albers G, Alberts MJ, Benavente O, Furie K, Goldstein LB, et al. Update to the AHA/ASA recommendations for the prevention of stroke in patients with stroke and transient ischemic attack. *Stroke* 2008;39:1647-52.
 9. Goldstein LB, Amarenco P, Szarek M, Callahan A 3rd, Hennerici M, Silleesen H, et al. Hemorrhagic stroke in the stroke prevention by aggressive reduction in cholesterol levels study. *Neurology* 2008;70(24 Pt 2):2364-70.
 10. Hosomi N, Nagai Y, Kohriyama T, Ohtsuki T, Aoki S, Nezu T, et al. The Japan Statin Treatment Against Recurrent Stroke (J-STARS): a multicenter, randomized, open-label, parallel-group study. *EBioMedicine* 2015;2:1071-8.
 11. Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. The expert panel. *Arch Intern Med* 1988;148:36-69.
 12. Sacco RL, Adams R, Albers G, Alberts MJ, Benavente O, Furie K, et al. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke. Co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. *Stroke* 2006;37:577-617.
 13. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;129(25 Suppl 2):S1-45.
 14. Jellinger PS, Handelsman Y, Rosenblit PD, Bloomgarden ZT, Fonseca VA, Garber AJ, et al. American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease. *Endocr Pract* 2017;23(Suppl 2):1-87.
 15. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *J Am Coll Cardiol* 2019;73:e285-350.
 16. Summary of the second report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel II). *JAMA* 1993;269:3015-23.
 17. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of The National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA* 2001;285:2486-97.
 18. Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004;110:227-39.
 19. Smith SC Jr, Allen J, Blair SN, Bonow RO, Brass LM, Fonarow GC, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. *Circulation* 2006;113:2363-72.
 20. Furie KL, Kasner SE, Adams RJ, Albers GW, Bush RL, Fagan SC, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2011;42:227-76.
 21. European Association for Cardiovascular Prevention & Rehabilitation, Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, et al. ESC/EAS guidelines for the management of dyslipidaemias: the task force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Eur Heart J* 2011;32:1769-818.
 22. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, et al. 2016 ESC/EAS guidelines for the management of dyslipidaemias. *Eur Heart J* 2016;37:2999-3058.
 23. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020;41:111-88.
 24. Corrigendum. *Eur Heart J* 2019 Nov 14 [Epub]. <https://doi.org/10.1093/eurheartj/ehz826>.
 25. Laufs U, Liao JK. Rapid effects of statins: from prophylaxis to therapy for ischemic stroke. *Arterioscler Thromb Vasc Biol* 2003;23:156-7.
 26. Amin-Hanjani S, Stagliano NE, Yamada M, Huang PL, Liao

- JK, Moskowitz MA. Mevastatin, an HMG-CoA reductase inhibitor, reduces stroke damage and upregulates endothelial nitric oxide synthase in mice. *Stroke* 2001;32:980-6.
27. Sironi L, Cimino M, Guerrini U, Calvio AM, Lodetti B, Asdente M, et al. Treatment with statins after induction of focal ischemia in rats reduces the extent of brain damage. *Arterioscler Thromb Vasc Biol* 2003;23:322-7.
 28. Berger C, Xia F, Maurer MH, Schwab S. Neuroprotection by pravastatin in acute ischemic stroke in rats. *Brain Res Rev* 2008;58:48-56.
 29. Zhang L, Zhang ZG, Liu XS, Hozeska-Solgot A, Chopp M. The PI3K/Akt pathway mediates the neuroprotective effect of atorvastatin in extending thrombolytic therapy after embolic stroke in the rat. *Arterioscler Thromb Vasc Biol* 2007;27:2470-5.
 30. Chen J, Zhang ZG, Li Y, Wang Y, Wang L, Jiang H, et al. Statins induce angiogenesis, neurogenesis, and synaptogenesis after stroke. *Ann Neurol* 2003;53:743-51.
 31. Kawashima S, Yamashita T, Miwa Y, Ozaki M, Namiki M, Hirase T, et al. HMG-CoA reductase inhibitor has protective effects against stroke events in stroke-prone spontaneously hypertensive rats. *Stroke*. 2003;34:157-63.
 32. Lu D, Qu C, Goussev A, Jiang H, Lu C, Schallert T, et al. Statins increase neurogenesis in the dentate gyrus, reduce delayed neuronal death in the hippocampal CA3 region, and improve spatial learning in rat after traumatic brain injury. *J Neurotrauma* 2007;24:1132-46.
 33. Bosel J, Gandor F, Harms C, Synowitz M, Harms U, Djoufack PC, et al. Neuroprotective effects of atorvastatin against glutamate-induced excitotoxicity in primary cortical neurones. *J Neurochem* 2005;92:1386-98.
 34. Laufs U, Gertz K, Huang P, Nickenig G, Bohm M, Dirnagl U, et al. Atorvastatin upregulates type III nitric oxide synthase in thrombocytes, decreases platelet activation, and protects from cerebral ischemia in normocholesterolemic mice. *Stroke* 2000;31:2442-9.
 35. Ni Chroinin D, Callaly EL, Duggan J, Merwick A, Hannon N, Sheehan O, et al. Association between acute statin therapy, survival, and improved functional outcome after ischemic stroke: the North Dublin Population Stroke Study. *Stroke* 2011;42:1021-9.
 36. Moonis M, Kane K, Schwiderski U, Sandage BW, Fisher M. HMG-CoA reductase inhibitors improve acute ischemic stroke outcome. *Stroke* 2005;36:1298-300.
 37. Montaner J, Chacon P, Krupinski J, Rubio F, Millan M, Molina CA, et al. Simvastatin in the acute phase of ischemic stroke: a safety and efficacy pilot trial. *Eur J Neurol* 2008;15:82-90.
 38. Choi JC, Lee JS, Park TH, Cho YJ, Park JM, Kang K, et al. Effect of pre-stroke statin use on stroke severity and early functional recovery: a retrospective cohort study. *BMC Neurol* 2015;15:120.
 39. Al-Khaled M, Matthis C, Eggers J. Statin treatment in patients with acute ischemic stroke. *Int J Stroke* 2014;9:597-601.
 40. Heo JH, Song D, Nam HS, Kim EY, Kim YD, Lee KY, et al. Effect and safety of rosuvastatin in acute ischemic stroke. *J Stroke* 2016;18:87-95.
 41. Tuttolomondo A, Di Raimondo D, Pecoraro R, Maida C, Arnao V, Della Corte V, et al. Early high-dosage atorvastatin treatment improved serum immune-inflammatory markers and functional outcome in acute ischemic strokes classified as large artery atherosclerotic stroke: a randomized trial. *Medicine (Baltimore)* 2016;95:e3186.
 42. Hong KS, Lee JS. Statins in acute ischemic stroke: a systematic review. *J Stroke* 2015;17:282-301.
 43. Yoshimura S, Uchida K, Daimon T, Takashima R, Kimura K, Morimoto T, et al. Randomized controlled trial of early versus delayed statin therapy in patients with acute ischemic stroke: ASSORT Trial (Administration of Statin on Acute Ischemic Stroke Patient). *Stroke* 2017;48:3057-63.
 44. Rahimi K, Emberson J, McGale P, Majoni W, Merhi A, Asselbergs FW, et al. Effect of statins on atrial fibrillation: collaborative meta-analysis of published and unpublished evidence from randomized controlled trials. *BMJ* 2011;342:d1250.
 45. Wu YL, Saver JL, Chen PC, Lee JD, Wang HH, Rao NM, et al. Effect of statin use on clinical outcomes in ischemic stroke patients with atrial fibrillation. *Medicine (Baltimore)* 2017;96:e5918.
 46. Choi JY, Seo WK, Kang SH, Jung JM, Cho KH, Yu S, et al. Statins improve survival in patients with cardioembolic stroke. *Stroke* 2014;45:1849-52.
 47. Ntaios G, Papavasileiou V, Makaritsis K, Milionis H, Manios E, Michel P, et al. Statin treatment is associated with improved prognosis in patients with AF-related stroke. *Int J Cardiol* 2014;177:129-33.
 48. Choi KH, Seo WK, Park MS, Kim JT, Chung JW, Bang OY, et al. Effect of statin therapy on outcomes of patients with acute ischemic stroke and atrial fibrillation. *J Am Heart Assoc* 2019;8:e013941.
 49. Lee MJ, Bang OY, Kim SJ, Kim GM, Chung CS, Lee KH, et al. Role of statin in atrial fibrillation-related stroke: an angiographic study for collateral flow. *Cerebrovasc Dis* 2014;37:77-84.

50. Iso H, Jacobs DR Jr, Wentworth D, Neaton JD, Cohen JD. Serum cholesterol levels and six-year mortality from stroke in 350,977 men screened for the multiple risk factor intervention trial. *N Engl J Med* 1989;320:904-10.
51. Ebrahim S, Sung J, Song YM, Ferrer RL, Lawlor DA, Davey Smith G. Serum cholesterol, haemorrhagic stroke, ischaemic stroke, and myocardial infarction: Korean national health system prospective cohort study. *BMJ* 2006;333:22.
52. Jung JM, Choi JY, Kim HJ, Seo WK. Statin use in spontaneous intracerebral hemorrhage: a systematic review and meta-analysis. *Int J Stroke* 2015;10 Suppl A100:10-7.
53. Ziff OJ, Banerjee G, Ambler G, Werring DJ. Statins and the risk of intracerebral haemorrhage in patients with stroke: systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry* 2019;90:75-83.
54. Shin J, Chung JW, Jang HS, Lee J, Hong KS, Bang OY, et al. Achieved low-density lipoprotein cholesterol level and stroke risk: a meta-analysis of 23 randomised trials. *Eur J Prev Cardiol* 2019 Feb 20 [Epub]. <https://doi.org/10.1177/2047487319830503>.
55. Zhang H, Cui Y, Zhao Y, Dong Y, Duan D, Wang J, et al. Effects of sartans and low-dose statins on cerebral white matter hyperintensities and cognitive function in older patients with hypertension: a randomized, double-blind and placebo-controlled clinical trial. *Hypertens Res* 2019;42:717-29.
56. Amarenco P, Benavente O, Goldstein LB, Callahan A 3rd, Sillesen H, Hennerici MG, et al. Results of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial by stroke subtypes. *Stroke* 2009;40:1405-9.
57. Mok VC, Lam WW, Fan YH, Wong A, Ng PW, Tsoi TH, et al. Effects of statins on the progression of cerebral white matter lesion: post hoc analysis of the ROCAS (Regression of Cerebral Artery Stenosis) study. *J Neurol* 2009;256:750-7.
58. ten Dam VH, van den Heuvel DM, van Buchem MA, Westendorp RG, Bollen EL, Ford I, et al. Effect of pravastatin on cerebral infarcts and white matter lesions. *Neurology* 2005;64:1807-9.
59. Jang HS, Choi J, Shin J, Chung JW, Bang OY, Kim GM, et al. The long-term effect of cancer on incident stroke: a nationwide population-based cohort study in Korea. *Front Neurol* 2019;10:52.
60. Boudreau DM, Yu O, Johnson J. Statin use and cancer risk: a comprehensive review. *Expert Opin Drug Saf* 2010;9:603-21.
61. Kim YS, Park MS, Lee JH, Chung JW, Lee MJ, Kim CK, et al. Effect of statins on survival following stroke in patients with cancer. *Front Neurol* 2018;9:205.
62. Addison D, Lawler PR, Emami H, Janjua SA, Staziaki PV, Hallett TR, et al. Incidental statin use and the risk of stroke or transient ischemic attack after radiotherapy for head and neck cancer. *J Stroke* 2018;20:71-9.
63. Boulet J, Pena J, Hulten EA, Neilan TG, Dragomir A, Freeman C, et al. Statin use and risk of vascular events among cancer patients after radiotherapy to the thorax, head, and neck. *J Am Heart Assoc* 2019;8:e005996.
64. Lee BC, Lin CL, Tsai HH, Kao CH. Statin and the risk of ischemic stroke or transient ischemic attack in head and neck cancer patients with radiotherapy. *J Stroke* 2018;20:413-4.
65. Amarenco P, Labreuche J. Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention. *Lancet Neurol* 2009;8:453-63.
66. Amarenco P, Kim JS, Labreuche J, Giroud M, Lee BC, Mahagne MH, et al. Treat stroke to target trial design: first trial comparing two LDL targets in patients with atherothrombotic strokes. *Eur Stroke J* 2019;4:271-80.
67. Amarenco P, Kim JS, Labreuche J, Charles H, Abtan J, Bejot Y, et al. A comparison of two LDL cholesterol targets after ischemic stroke. *N Engl J Med* 2020;382:9.
68. Nodari S, Rocca P, Saporetti A, Bettari L, Foresti AL, Tanghe E, et al. The combination of ezetimibe and statin: a new treatment for hypercholesterolemia. *Heart Int* 2007;3:12.
69. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015;372:2387-97.
70. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med* 2018;379:2097-107.
71. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017;376:1713-22.
72. Silverman MG, Ference BA, Im K, Wiviott SD, Giugliano RP, Grundy SM, et al. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. *JAMA* 2016;316:1289-97.
73. Abifadel M, Varret M, Rabes JP, Allard D, Ouguerram K, Devillers M, et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. *Nat Genet* 2003;34:154-6.

PRECISION AND FUTURE MEDICINE

Management of dyslipidemia in stroke

74. Stein EA, Mellis S, Yancopoulos GD, Stahl N, Logan D, Smith WB, et al. Effect of a monoclonal antibody to PCSK9 on LDL cholesterol. *N Engl J Med* 2012;366:1108-18.
75. HPS3/TIMI55-REVEAL Collaborative Group, Bowman L, Hopewell JC, Chen F, Wallendszus K, Stevens W, et al. Effects of anacetrapib in patients with atherosclerotic vascular disease. *N Engl J Med* 2017;377:1217-27.
76. Graham MJ, Lee RG, Brandt TA, Tai LJ, Fu W, Peralta R, et al. Cardiovascular and metabolic effects of ANGPTL3 antisense oligonucleotides. *N Engl J Med* 2017;377:222-32.
77. Dewey FE, Gusarova V, O'Dushlaine C, Gottesman O, Trejos J, Hunt C, et al. Inactivating variants in ANGPTL4 and risk of coronary artery disease. *N Engl J Med* 2016;374:1123-33.
78. Dewey FE, Gusarova V, Dunbar RL, O'Dushlaine C, Schurmann C, Gottesman O, et al. Genetic and pharmacologic inactivation of ANGPTL3 and cardiovascular disease. *N Engl J Med* 2017;377:211-21.
79. van Zwol W, Rimbert A, Kuivenhoven JA. The future of lipid-lowering therapy. *J Clin Med* 2019;8:1085.
80. Freiberg JJ, Tybjaerg-Hansen A, Jensen JS, Nordestgaard BG. Nonfasting triglycerides and risk of ischemic stroke in the general population. *JAMA* 2008;300:2142-52.
81. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Circulation* 2019;139:e1082-143.