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Cerebrovascular Disorders (D Jamieson, Section Editor)

Statins in Ischemic Stroke Prevention: What Have We Learned in the Post-SPARCL (The Stroke Prevention by Aggressive Reduction in Cholesterol Levels) Decade?

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Abstract

Purpose of review We describe the current status of lipid-lowering therapies for ischemic stroke prevention. The SPARCL trial published in 2006 has been a landmark study in vascular neurology. The trial demonstrated that high-dose atorvastatin prevents recurrent stroke, and led the AHA/ASA to recommend statin therapy for patients with stroke or TIA of atherosclerotic origin.
Recent findings Recently, the J-STARS study demonstrated that therapy with low-dose pravastatin reduced atherothrombotic infarction incidence among patients with prior ischemic stroke. Besides, several trials have shown improved stroke outcomes with non-statin lipid-lowering medications: IMPROVE-IT with ezetimibe on top of simvastatin and PCSK9 inhibitors—FOURIER with evocolumab and ODYSSEY-OUTCOMES with alirocumab—on top of statin therapy.

Summary LDL-cholesterol remains the primary lipid treatment target for reduction of stroke risk. Randomized trials have shown that each reduction of 40 mg/dL in the level of LDL-cholesterol reduces the stroke risk by approximately one quarter, and further, reductions in LDL-cholesterol levels have shown to produce additional reductions in stroke risk. Currently, we have evidence of benefit for adding non-statin lipid-modifying therapies to statins to reduce stroke risk. Surely, these novel strategies to reduce residual lipidic risk will provide future benefits on stroke prevention.

Introduction

Currently, statins, or 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are considered the most important advance in stroke prevention since the introduction of aspirin and antihypertensive treatments [1]. In fact, a meta-analysis of randomized trials of statins in combination with other preventive strategies, including 165,792 individuals, shows that each 1 mmol/L (39 mg/dL) decrease in low-density lipoprotein cholesterol (LDL-C), equates to a reduction in relative risk [RR] for stroke of 21.1% (95% confidence interval [CI] 6.3–33.5, $p = 0.009$) [2].

A later meta-analysis of 18 randomized controlled trials that compared the effects of statins and placebo in patients at high risk for stroke revealed that statins reduced the overall incidence of stroke than placebo (odds ratio [OR] 0.80; 95% CI 0.74–0.87; $p < 0.00001$). In particular, statins showed efficacy in reducing the incidence of fatal stroke [3].

Besides, intensive-dose statin treatment seems to be more effective than standard-dose statin treatment for the prevention of strokes. A further meta-analysis revealed that for the all stroke incidences, intensive-dose statin treatment compared with placebo treatment and standard-dose statin treatment compared with placebo treatment showed a significant 21% reduction in RR (RR 0.79, 95% CI 0.71, 0.87, $p < 0.00001$) and an 18% reduction in RR (RR 0.82, 95% CI 0.73, 0.93, $p = 0.002$) in the subgroup without renal transplant recipients and patients undergoing regular hemodialysis separately. For the fatal stroke incidences, intensive-dose statin treatment compared with standard dose or placebo was effective reducing fatal stroke (RR 0.61, 95% CI 0.39, 0.96, $p = 0.03$) and the RR was 1.01 (95% CI 0.85, 1.20, $p = 0.90$) in standard-dose statin treatment compared with placebo [4].

However, until recently, there was little evidence that statin therapy reduced the risk of stroke recurrence.

Published in New England Journal of Medicine in 2006, the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial [5••] has been a landmark study in vascular neurology. It was specifically designed to investigate the effect of the reduction of cholesterol levels with a statin in secondary stroke prevention, and was the first trial to show the benefits of statin therapy in preventing recurrent stroke. The SPARCL trial has been very influential, and has formed the basis for the American Heart Association/American Stroke Association (AHA/ASA) recommendation for statin therapy in patients with prior stroke and transient ischemic attack (TIA) [6••].

The SPARCL trial

The SPARCL [5••] was a prospective, double-blind, placebo-controlled international trial conducted at 205 centers in which 4731 patients with a history of non-disabling stroke or TIA in the preceding 1–6 months and with no coronary heart disease (CHD) or hypercholesterolemia were randomized. Subjects were enrolled between September 1998 and March 2001. Patients received either atorvastatin 80 mg per day ($n = 2365$) or placebo ($n = 2366$) and were followed for an average of 4.9 years.

The primary endpoint was the incidence of fatal or nonfatal stroke. A number of cardiovascular (CV) events were also measured as secondary outcomes. LDL-C levels were similar between the two groups at baseline and decreased by 53% in the atorvastatin group while remaining unchanged in the placebo group at 1 month after randomization.

During the follow-up period, 265 patients (11.2%) receiving atorvastatin and 311 patients (13.1%) receiving placebo had a fatal or nonfatal stroke and represented a RR reduction of 16% ($p = 0.03$, 95% CI; 0.71–0.99). This effect was driven predominately by reduced adjusted RR of fatal stroke which was decreased by 43% ($p = 0.03$), whereas atorvastatin had no significant effect on nonfatal stroke reduction ($p = 0.11$).

Finally, the number needed to treat (NNT) with atorvastatin to prevent one stroke was 46 patients over 5 years. In comparison, for example, the NNT of aspirin, a first-line medical therapy for secondary stroke prevention, is 143 patients per year to prevent one recurrent ischemic stroke [7].

Based on the SPARCL trial findings, the AHA/ASA guidelines [6••] for the prevention of stroke in patients with ischemic stroke recommended high-intensity statin therapy for patients with TIA or ischemic stroke presumed to be of atherosclerotic origin to reduce the risk of stroke and CV events (Table 1).

Subgroup analysis of the SPARCL trial

In the following years, multiple publications consisting of subgroup analyses originated from SPARCL. Although not predefined in the original study and inadequately powered, these post hoc studies suggested answers to important clinical questions, generated new hypothesis and strengthened (or weakened) previous theories of statin use in stroke patients [7].

Age

In this post hoc analysis of the SPARCL study [8], the patient cohort was divided into an elderly group (≥ 65 years) and a younger group. The study included 2249 patients in the elderly group, with a mean age of 72.4 years. The risk of stroke and

Table 1. 2014 AHA/ASA Guidelines: Recommendations on dislipidemia in patients with ischemic stroke

1. Statin therapy with intensive lipid-lowering effects is recommended to reduce risk of stroke and cardiovascular events among patients with ischemic stroke or TIA presumed to be of atherosclerotic origin and an LDL-C level ≥ 100 mg/dL with or without evidence for other clinical ASCVD *(Class I; Level of Evidence B)*. (Revised recommendation)
2. Statin therapy with intensive lipid-lowering effects is recommended to reduce risk of stroke and cardiovascular events among patients with ischemic stroke or TIA presumed to be of atherosclerotic origin, an LDL-C level < 100 mg/dL, and no evidence for other clinical ASCVD *(Class I; Level of Evidence C)*. (New recommendation)*
3. Patients with ischemic stroke or TIA and other comorbid ASCVD should be otherwise managed according to the 2013 ACC/AHA cholesterol guidelines, which include lifestyle modification, dietary recommendations, and medication recommendations *(Class I; Level of Evidence A)*. (Revised recommendation)

ASCVD, Atherosclerotic cardiovascular disease *Added to be consistent with the 2013 ACC/AHA cholesterol guideline but to indicate a lower level of evidence when LDL-C is < 100 mg/dL

TIA (Hazard ratio-HR- 0.79, $p = 0.01$), major coronary events (HR 0.68, $p = 0.035$), any coronary disease event (HR 0.61, $p = 0.0006$), and revascularization procedures (HR 0.55, $p = 0.0005$) was clearly reduced in the elderly group.

Gender

To assess the impact of gender, a secondary analysis of endpoints in men and women was also attempted. Although stroke risk factor profiles from the SPARCL baseline data differed for men and women, a secondary analysis did not find any differences in statin treatment effects or adverse reactions [7, 9]. There were no sex by treatment interactions for the combined risk of nonfatal and fatal stroke (treatment HR = 0.84, 95% CI 0.68, 1.02 in men versus HR = 0.84, 95% CI 0.63, 1.11 in women; treatment x sex interaction $p = 0.99$) and other secondary end-points.

Stroke subtypes

Among 4731 participants included in the SPACL trial, 4728 had information regarding entry event subtype with 15.8% classified as having large vessel disease ($n = 749$), 29.8% small vessel disease ($n = 1409$), 21.5% ischemic stroke of unknown cause ($n = 1017$), 30.9% TIA ($n = 1460$), and 2% hemorrhagic stroke ($n = 93$).

Authors found no difference in the efficacy of treatment for either the primary end point (LVD HR 0.70, 95% CI 0.49 to 1.02, TIA HR 0.81, CI 0.57 to 1.17, SVD HR 0.85, CI 0.64 to 1.12, unknown cause HR 0.87, CI 0.61 to 1.24, HS HR 3.24, CI 1.01 to 10.4; p for heterogeneity = 0.421), or mayor CV events [MCVEs] (p for heterogeneity = 0.360) based on subtype of the index event. *Authors concluded that* atorvastatin 80 mg/day was similarly efficacious in preventing strokes and other CV events, irrespective of baseline ischemic stroke subtype [10].

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Patients with carotid stenosis

Carotid artery evaluation was not required by the SPARCL protocol, but 4278 (90.4%) of the SPARCL subjects underwent carotid imaging by the local investigators at the time of patient randomization [5••].

Of the total SPARCL population, 1007 were documented as having carotid stenosis at baseline, 3271 did not, and the status of 453 was unknown. In the group with carotid artery stenosis, treatment with atorvastatin was associated with a 33% reduction in the risk of any stroke (HR 0.67, 95% CI, 0.47–0.94; $p = 0.02$), and a 43% reduction in risk of major coronary events (HR 0.57, 95% CI, 0.32–1.00; $p = 0.05$). Later carotid revascularization was reduced by 56% (HR 0.44, 95% CI, 0.24–0.79; $p = 0.006$) in the group randomized to atorvastatin [11].

In the group with carotid stenosis, the absolute risk reduction for stroke was 1% per year (number needed-to-treat [NNT] = 20 in 5 years), and considering all CV events, the annual risk reduction exceeded 2.5% per year (NNT = 8 in 5 years). Interestingly, authors pointed out that this benefit was comparable to performing carotid endarterectomy in asymptomatic patients but without the risks of surgery and with the additional benefits of reduced CV events [12].

Patients with more intense lipid lowering

This post hoc analysis of the SPARCL trial [13] revealed that achieving an LDL-C level of < 70 mg/dL was related to a 28% reduction in risk of stroke (HR, 0.72;

95% CI, 0.59–0.89; $p = 0.0018$) without a significant rise in the risk of hemorrhagic stroke (HR, 1.28; 95% CI,0.78–2.09; $p = 0.3358$). In addition, stroke and TIA patients with ≥ 50% reduction in LDL-C had a 31% reduction in stroke risk (HR, 0.69, 95% CI, 0.55 to 0.87, $p = 0.0016$), a 33% reduction in ischemic stroke ($p = 0.0018$) and a 37% reduction in major coronary events ($p = 0.0323$), with no statistically significant increase in hemorrhagic stroke ($p = 0.8864$).

In this paper, authors concluded that those having ≥ 50% reduction would have the greatest reductions in stroke and other vascular events.

Patients with optimal levels of LDL-C, HDL-C, triglycerides, and BP

In this subanalysis [14], authors assessed the relative contributions of on-treatment LDL-C and high-density lipoprotein cholesterol (HDL-C), triglycerides, and blood pressure (BP) control on the risk of recurrent stroke or major CV events in patients with stroke using the SPARCL population.

After 4.9 years, at each level of LDL-C reduction, subjects with HDL-C value above the median or systolic BP (SBP) below the median had greater reductions in stroke and major CV events and those with a reduction in triglycerides above the median or diastolic BP (DBP) below the median showed similar trends. In a further exploratory analysis, optimal control was defined as LDL-C < 70 mg/dL, HDL-C > 50 mg/dL, triglycerides < 150 mg/dL, and SBP/DBP < 120/80 mmHg. The risk of stroke decreased with as the level of control increased (HR [95% CI] 0.98 [0.76 to 1.27], 0.78 [0.61 to 0.99], 0.62 [0.46 to 0.84], and 0.35 [0.13 to 0.96]) for those achieving optimal control of 1, 2, 3, or 4 factors as compared to none, respectively. Results were similar for major CV events. In summary, authors found a cumulative effect of achieving optimal levels of LDL-C, HDL-C, triglycerides, and BP on the risk of recurrent stroke and major CV events. The protective effect of having a higher HDL-C was maintained at low levels of LDL-C.

Patients with lower baseline HDL-C

In this subanalysis of SPARCL [15], authors explored the relative contributions of baseline SBP and DBP and lipoproteins on the risk of recurrent stroke or first major CV events (MCVE) and their potential impact on the benefit of statin treatment.

After 4.9 years of follow-up, there were 575 primary end points (fatal and nonfatal stroke), including 491 ischemic strokes, and 740 MCVEs. Cox regression models analysis showed a trend ($p > 0.05$ and $p < 0.10$) for higher SBP but not DBP to be associated with an outcome stroke with only SBP associated with MCVE. Only baseline low HDL-C was associated with an outcome stroke. Baseline HDL-C, triglycerides, and LDL/HDL ratio were each associated with MCVEs.

Thus, HDL was the strongest baseline lipoprotein predictor of stroke risk, with each standard deviation (SD) increase in baseline HDL-C level being associated with a 13% reduction in the risk of recurrent stroke. This finding indicated that HDL-C could be a potential target for stroke prevention therapy.

Authors concluded that in SPARCL population, only lower baseline HDL-C predicted the risk of recurrent stroke with HDL-C, triglycerides, and LDL/HDL ratio associated with MCVE.

Patients with diabetes

In this secondary analysis of the SPARCL trial [16], authors explored the effects of treatment in subjects with type 2 diabetes mellitus (T2DM) or metabolic syndrome (MetS).

From the 4731 subjects enrolled in the SPARCL trial, patients were classified as having T2DM at enrollment ($n = 794$), MetS retrospectively ($n = 642$), or neither diabetes nor MetS ($n = 3295$, the reference group) based on data collected at baseline. Subjects with T2DM had increased risks of stroke (HR 1.62; 95% CI, 1.33–1.98; $p < .001$), major CV events (HR = 1.66; 95% CI, 1.39–1.97; $p < .001$), and revascularization procedures (HR = 2.39; 95% CI, 1.78–3.19; $p < .001$) compared with the reference group. Subjects with MetS were not at increased risk for stroke ($p = .78$) or major CV events ($p = .38$) but more frequently had revascularization procedures (HR = 1.78; 95% CI, 1.26–2.5; $p = .001$). There were no treatment × subgroup interactions for the SPARCL primary end point ($p = .47$). Authors concluded that the SPARCL subjects with T2DM were at higher risk for recurrent stroke and CV events. This exploratory analysis found no difference in the effect of statin treatment in reducing these events in subjects with or without T2DM or MetS.

Patients with atherogenic dyslipidemia

Treatment with statins reduces the rate of CV events in high-risk patients, but residual risk persists. At least part of that risk may be attributable to atherogenic dyslipidemia characterized by low HDL-C (≤ 40 mg/dL) and high triglycerides (triglycerides ≥ 150 mg/dL).

In this exploratory analysis [17], authors studied subjects with stroke or TIA in the Prevention of Cerebrovascular and CV Events of Ischemic Origin With Terutroban in Patients With a History of Ischemic Stroke or Transient Ischemic Attack (PERFORM; $n = 19,100$) [18] and SPARCL ($n = 4731$) trials who were treated with a statin and who had HDL-C and triglycerides measurements 3 months after randomization ($n = 10,498$ and 2900, respectively). The primary outcome measure for this exploratory analysis was the occurrence of MCVEs (nonfatal myocardial infarction, nonfatal stroke, or CV death).

A total of 10% of subjects in PERFORM and 9% in SPARCL had atherogenic dyslipidemia after ≥ 3 months on start statin therapy. After a follow-up of 2.3 years (PERFORM) and 4.9 years (SPARCL), a MCVE occurred in 1123 and 485 patients in the 2 trials, respectively. The risk of MCVEs was higher in subjects with versus those without atherogenic dyslipidemia in both PERFORM (HR, 1.36; 95% CI, 1.14–1.63) and SPARCL (HR, 1.40; 95% CI, 1.06–1.85). The association was attenuated after multivariable adjustment (HR, 1.23; 95% CI, 1.03–1.48 in PERFORM and HR, 1.24; 95% CI, 0.93–1.65 in SPARCL). Time-varying analysis confirmed these findings.

Authors concluded that the presence of atherogenic dyslipidemia was associated with higher residual CV risk in PERFORM and SPARCL subjects with stroke or TIA receiving statin therapy.

A post hoc analysis of the SPARCL trial found that treatment with atorvastatin was independently associated with an increased risk of hemorrhagic stroke ($n = 55$ [2.3%] for statin treatment versus $n = 33$ [1.4%] for placebo; HR, 1.66; 95% CI, 1.08–2.55). This was particularly true of subjects enrolled with an index hemorrhagic stroke who had a 5-fold increase in risk of recurrent

hemorrhage [19]. A similar observation was seen in the subset of 3200 patients who had stroke before randomization in the Heart Protection Study (HPS), in which there was a 91% relative rise in risk of hemorrhagic stroke in patients assigned to statin treatment [20]. In this regard, the ASA/AHA guidelines recommend: "Given the higher risk of hemorrhagic stroke with statin treatment observed among survivors of a stroke or TIA in SPARCL and the HPS, a history of intracerebral hemorrhage may identify a subset of stroke patients with greater hemorrhagic propensity in whom statins should be used very judiciously, if at al" [6••].

Other landmark statin trials in secondary stroke prevention

The Heart Protection Study (HPS) [20]

Evidence for the benefit of statin therapy in secondary stroke prevention in patients with previous cerebrovascular disease was first provided by the HPS. A total of 20,536 patients with a high risk of vascular events were included in the HPS. The mean duration of follow-up was 5.0 years for all randomized participants. Simvastatin treatment significantly reduced the risk of vascular events (RR reduction 24%, $p < 0.00001$) and those events that cause strokes (RR reduction 27%, $p < 0.00001$). The HPS included 3280 randomly chosen stroke patients (none with TIAs) and 1822 stroke patients without established CHD. In all stroke patients, there was a 19% RR reduction of MCVEs, and in the stroke patients without established CHD, the reduction in the risk of MCVEs was 23%. However, the HPS did not find a reduction in stroke risk among patients with recurrent cerebrovascular disease (10.4% of patients in the statin group had a recurrent stroke as compared with 10.5% of patients in the placebo group). Therefore, in patients with a prior stroke, statins likely reduced the incidence of coronary events, but there was no proof that statins reduced the incidence of recurrent strokes.

The Japan Statin Treatment Against Recurrent Stroke (J-STARS) study [21•]

In the J-STARS, a total of 1578 Japanese men and women aged 45 to 80 years with previous non-cardioembolic ischemic stroke and total cholesterol concentration between 180 and 240 mg/dL were randomly assigned to open-label pravastatin 10 mg per day or to control (no statin, but non-statin drugs were allowed) and followed for a mean of 4.9 years. The primary outcome, any cerebrovascular event, similarly occurred in both groups: 2.56%/year in the low-dose pravastatin group versus 2.65%/year in the control group (adjusted HR 0.97, 95% CI: 0.73 to 1.29). Allocation to pravastatin was however associated with a lower incidence of ischemic stroke due to atherothrombosis compared to control (0.21 vs 0.64% per year, adjusted HR 0.33, 0.15 to 0.74; $p = 0.0047$) without increasing intracranial hemorrhage (0.29 vs 0.31% per year, adjusted HR 1.00, 0.45 to 2.22) or mortality (1.11 vs 0.90% per

year, adjusted HR 1.23, 0.79 to 1.93). Therefore, among Japanese patients with prior ischemic stroke, low-dose pravastatin did not prevent recurrent cerebrovascular events, although it did prevent atherothrombotic infarction.

J-STARS substudies

Differences of early or late pravastatin treatment

The J-STARS study enrolled patients with non-cardioembolic ischemic stroke patients within 1 month to 3 years after initial events. In this subanalysis [22], authors evaluated differences of early (within 6 months) or late (after 6 months) pravastatin treatment benefits on the incidence of stroke or TIA, as well as atherothrombotic stroke and the other subtypes. Authors found that the rate of atherothrombotic stroke was lower in the pravastatin group compared to controls in the early cohort (0.24 vs. 0.88%/year, $p = 0.01$) but not in the late cohort (0.17 vs. 0.39%/year, $p = 0.29$). However, this difference of pravastatin effect on atherothrombotic stroke was not significantly interacted by the early or late cohort ($p = 0.59$). The incidence rates of other stroke subtype were not different in between pravastatin and control groups despite the timing of entry. Authors concluded that pravastatin was likely to reduce atherothrombotic stroke in patients enrolled within 6 months after stroke onset. However, the clinical efficacy for prevention of recurrent stroke was not conclusive with earlier statin treatment.

Desirable LDL-C levels for preventing stroke recurrence

To define desirable target LDL-C levels for the prevention of stroke recurrence, a post hoc analysis was performed in the J-STARS study [23]. The postrandomized LDL-C levels until the last observation were 104.1 ± 19.3 mg/dL in the pravastatin group and 126.1 ± 20.6 mg/dL in the control group. The adjusted HRs for stroke and TIA and all vascular events decreased in the postrandomized LDL-C level of 80 to 100 mg/dL ($P = 0.23$ and 0.25 for the trend, respectively). The adjusted HR for atherothrombotic infarction significantly reduced with the usage of statin after adjusting baseline LDL-C levels (HR, 0.39; 95% CI, 0.19–0.83). The adjusted HR for atherothrombotic infarction and intracranial hemorrhage were similar among the postrandomized LDL-C level subgroups ($P = 0.50$ and 0.37 for the trend, respectively). The adjusted HR for lacunar infarction decreased in the postrandomized LDL-C level of 100 to 120 mg/dL (HR, 0.45; 95% CI, 0.20–0.99; $p = 0.41$ for the trend). Authors concluded that the composite risk of stroke and TIA reduced in the postrandomized LDL-C level of 80 to 100 mg/dL after adjusting for statin usage.

Cumulative effect of LDL-C and CRP levels on recurrent stroke and TIA

In this subanalysis [24], authors investigated the relative contribution of on-treatment LDL-C and C-reactive protein (CRP) to the risk of recurrent stroke and TIA. During the follow-up, patients with on treatment LDL-C < 120 mg/dL showed 29% reduction in recurrent stroke and TIA than those with LDL –C ≥ 120 mg/dL (event rate 2.20 vs. 3.11 per 100 person-years, HR 0.71, 95% CI 0.50–0.99, $p = 0.048$). Patients with CRP < 1 mg/L had 32% reduction

compared with that of patients with CRP ≥ 1 mg/L (event rate 2.26 vs. 3.40 per 100 person-years; HR 0.68, 95% CI 0.48–0.96, $p = 0.031$). Although LDL-C and CRP levels were not correlated in individual patients, those who achieved both LDL-C < 120 mg/dL and CRP < 1 mg/L showed 51% reduction compared with that of patients with LDL-C ≥ 120 mg/dL and CRP ≥ 1 mg/L (event rate 2.02 vs. 4.19 per 100 person-years; HR 0.49, 95% CI 0.31–0.79). Authors concluded that the control of both LDL–C and CRP levels appears to be effective for preventing recurrent stroke and TIA in patients with non-cardiogenic ischemic stroke.

Non-statin lipid-lowering medications: new evidence for stroke prevention

As we have shown, statins are the first-line treatment to lower LDL-C in ischemic stroke prevention; however, some high CV risk patients may have inadequate responses to statin therapy or are intolerant of statins, and may need additional and/or alternative non-statin therapies to further reduce their LDL-C levels. Moreover, although statins are highly effective, even those who have achieved significant LDL-C reductions with intensive statin therapy may still experience CV events, referred to as 'residual risk'. This risk is particularly high in certain patients such as those with diabetes and atherosclerosis affecting multiple vascular beds (e.g., cerebrovascular, peripheral vascular as well as coronary) [25]. In fact, with an optimized reduction of elevated LDL-C levels with statins, the risk for CV diseases can be reduced by 30%, indicating a residual remaining risk of 70% for the development and progression of CV diseases [26].

Recently, several randomized controlled trials have shown improved CV disease and stroke outcomes with non-statin lipid-lowering medications: ezetimibe on top of simvastatin [27••] and monoclonal antibodies that inhibit proprotein convertase subtilisin/kexin type 9 (PCSK9)—evocolumab and alirocumab—on top of statin therapy [28••, 29••].

Published in 2015, the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) trial [26] showed for the first time that if you added non-statin therapy ezetimibe on top of a statin, you had a further lowering of LDL-C and a further diminution on CV risk. The addition of ezetimibe to statin therapy lowered LDL-C levels from 70 to 54 mg/dL and significantly reduced major CV events. In extending this concept further in a trial evaluating the effect of evolucumab, a PCSK9 inhibitor, on long-term CV disease events, authors found consistent reductions in rates of CV events across the range of baseline LDL–C levels. There was a 22% reduction in the risk of the key secondary end point among the patients in the lowest quartile for baseline LDL–C level, in whom evolocumab lowered the median LDL–C level from 73 to 22 mg/dL [28••]. These observations align well with the effects of evolocumab on coronary atherosclerotic plaque volume in the Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound (GLAGOV) trial [30•] and show that continued CV benefit can be accrued even when LDL –C levels are reduced to 20 to 25 mg/dL a range that is well below current targets [28••].

Nevertheless, in 2008, the publication of the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) study had created uncertainty about the efficacy of the therapy with ezetimibe.

In this trial including patients with familial hypercholesterolemia, the therapy with ezetimibe added to 80 mg of simvastatin led to greater reductions in LDL-C levels as compared with simvastatin alone. However, it had a neutral effect on the surrogate endpoint of carotid intima-media thickness. Therefore, the trial also showed that characterization of clinical outcomes regarding lipid-lowering agents based on surrogate biomarker studies not designed to assess CV disease outcomes may be misleading [31].

In the IMPROVE-IT [27••], an additional reduction in LDL-C levels with the addition of ezetimibe, a cholesterol-absorption inhibitor, to a statin significantly reduced CV event rate, as compared with statin monotherapy. Ezetimibe targets the Niemann–Pick C1–like 1 (NPC1L1) protein, thereby reducing absorption of cholesterol from the intestine. When added to statins, ezetimibe reduces LDL-C levels by an additional 23 to 24%, on average [32].

The IMPROVE-IT evaluated the use of ezetimibe in addition to 40 mg of simvastatin daily in 18,144 post-acute coronary syndrome patients with LDL-C levels of 50 mg/dL to 125 mg/dL. In this secondary prevention population, the addition of ezetimibe to statin therapy reduced the absolute risk of CV events—primarily nonfatal myocardial infarction or stroke—by 2% over the course of 7 years. The event rate for the primary end point was 32.7% in the simvastatin-ezetimibe group, as compared with 34.7% in the simvastatin-monotherapy group (HR 0.936; 95% CI 0.89 to 0.99; $p = 0.016$), with no increased risk of adverse events.

In the overall population, a nonsignificant reduction occurred in the first event of stroke of any type with the addition of ezetimibe to simvastatin compared with simvastatin monotherapy with rates of 4.2 versus 4.8%, respectively (HR, 0.86; 95% CI, 0.73–1.00; $p = 0.052$). Ischemic stroke as a first event was significantly reduced by 21% with ezetimibe/simvastatin compared with placebo/simvastatin (3.4 vs 4.1%; HR, 0.79; 95% CI, 0.67–0.94; $p = 0.008$). However, a nonsignificant but greater number of hemorrhagic strokes occurred with ezetimibe/simvastatin versus placebo/simvastatin (0.8 vs 0.6%; HR, 1.38; 95% CI, 0.93–2.04; $p = 0.11$).

In a further subanalysis of the IMPROVE-IT [32] with a focus on patients with a stroke before randomization, authors found that patients who had experienced a stroke prior to randomization were at a higher risk of recurrence and demonstrated an absolute risk reduction of 8.6% for stroke of any etiology (10.2% versus 18.8%; NNT = 12; HR, 0.60; 95% CI, 0.38–0.95; $p = 0.030$) and 7.6% for ischemic stroke (8.7 vs 16.3%; NNT = 13; HR, 0.52; 95% CI, 0.31–0.86; $p = 0.011$) with ezetimibe added to simvastatin therapy. Therefore, the addition of ezetimibe to simvastatin in patients stabilized after acute coronary syndrome reduces the frequency of ischemic stroke, with a particularly large effect seen in patients with a prior stroke.

The magnitude of benefit from the simvastatin-ezetimibe combination on stroke is similar to that seen in statin trials when adjusted for the degree of LDL-C lowering. With a between-group difference in LDL-C of 17 mg/dL, the relative reduction in ischemic stroke per millimole of LDL-C reduction with ezetimibe in IMPROVE-IT was 25% compared with a 21% reduction seen with statin

monotherapy previous meta-analysis [1]. The consistency of these findings supports the benefit of LDL-C lowering on stroke prevention through a non-statin mechanism [33].

PCSK9 inhibitors

Recently the Food and Drug Administration approved two novel medications for LDL-C reduction: Evolocumab and Alirocumab. These agents target and inactivate PCSK9, a hepatic protease that attaches and internalizes LDL receptors into lysosomes hence promoting their destruction. Suppressing PCSK9 activity leads to decreased LDL receptor degradation, therefore, increasing LDL receptor expression on the hepatocyte surface and resulting in increased clearance of LDL-C from the blood stream [34].

In phase II and III clinical trials, PCSK9 inhibitors have been shown to reduce LDL-C levels by as much as 60% to 70% when administered as monotherapy or as an add-on treatment to statins and other lipid-lowering therapies [34].

More recently, two important trials evaluating the effect of PCSK9 inhibitors on long-term CV disease events have been published: FOURIER (Further cardiovascular outcomes research with PCSK9 inhibition in subjects with elevated risk) [28••] for Evolocumab and ODYSSEY-OUTCOMES (ODYSSEY outcomes: Evaluation of cardiovascular outcomes after an acute coronary syndrome during treatment with alirocumab) [29••] for Alirocumab.

The FOURIER trial included 27,564 patients with atherosclerotic CV disease and LDL-C levels of 70 mg/dL or higher who were receiving statin therapy. Patients were randomly assigned to receive evolocumab (either 140 mg every 2 weeks or 420 mg monthly) or matching placebo as subcutaneous injections. The primary efficacy end point was the composite of CV death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. The key secondary efficacy end point was the composite of CV death, myocardial infarction, or stroke. The median duration of follow-up was 2.2 years. Relative to placebo, evolocumab treatment significantly reduced the risk of the primary end point (1344 patients [9.8%] vs. 1563 patients [11.3%]; HR, 0.85; 95% CI, 0.79 to 0.92; $p < 0.001$) and the key secondary end point (816 [5.9%] vs. 1013 [7.4%]; HR, 0.80; 95% CI, 0.73 to 0.88; $p < 0.001$) with no difference in CV disease death or all-cause death. Likewise, evolocumab significantly reduced the risk of stroke. Stroke occurred in 207 patients (1.5%) in the evolocumab group and in 262 patients (1.9%) in the placebo group (HR, 0.79; 95% CI, 0.66 to 0.95; $p = 0.01$). Notably, there were no relevant side effects found under treatment with evolocumab including screening for neurocognitive events and the development of neutralizing antibodies [28••].

The ODYSSEY OUTCOMES trial included 18,924 patients who had an acute coronary syndrome 1 to 12 months earlier, had a LDL-C level of at least 70 mg/dL, a non-HDL-C level of at least 100 mg/dL, or an apolipoprotein B level of at least 80 mg/dL, and were receiving statin therapy at a high-intensity dose or at the maximum tolerated dose. Patients were randomly assigned to receive alirocumab subcutaneously at a dose of 75 mg (9462 patients) or matching placebo (9462 patients) every 2 weeks. The dose of alirocumab was adjusted under blinded conditions to target an LDL-C level of 25 to 50 mg/dL. The primary end point was a composite of death from CHD nonfatal myocardial infarction, fatal or

nonfatal ischemic stroke, or unstable angina requiring hospitalization. The median duration of follow-up was 2.8 years. A composite primary end-point event occurred in 903 patients (9.5%) in the alirocumab group and in 1052 patients (11.1%) in the placebo group (HR, 0.85; 95% CI, 0.78 to 0.93; $p < 0.001$). A total of 334 patients (3.5%) in the alirocumab group and 392 patients (4.1%) in the placebo group died (HR, 0.85; 95% CI, 0.73 to 0.98). The risk of fatal and nonfatal ischemic stroke was lower among patients treated with alirocumab than among those who received placebo. Stroke occurred in 111 patients (1.2%) in the alirocumab group and in 152 patients (1.6%) in the placebo group (HR, 0.73; 95% CI, 0.57 to 0.93; $p < 0.01$). The incidence of adverse events and of laboratory abnormalities was similar in the alirocumab group and the placebo group, with the exception of local injection-site reaction [29••].

Regarding safety, in randomized clinical trials, PCSK9 inhibitors have showed a favorable safety profile. Nevertheless, initially, two meta-analyses showed that the use of PCSK9 inhibitors was associated with a significantly increased incidence of neurocognitive adverse effects compared to controls. These results raised initial concern about the effect of PCSK9 inhibitors and led to a recommendation of the US Food and Drug Administration in 2014 to perform a long-term trial prospectively evaluating neurocognitive function [35]. The evaluating PCSK9 binding antibody influence on cognitive health in high cardiovascular risk subjects (EBBINGHAUS) study prospectively assessed cognitive function using formal tests and showed no effect on cognitive function in patients randomized to evolocumab compared to placebo [36]. Moreover, no significant differences in neurocognitive adverse effect rates were found between alirocumab vs. controls [37]. Finally, a recent meta-analysis, including a larger number of trials, showed no significant differences between the PCSK9 inhibitor and the control arm on neurocognitive outcomes [35].

The recently released American College of Cardiology/American Heart Association (ACC/AHA) multisociety Guideline on the Management of Blood Cholesterol 2018 [38••], updates the 2013 guideline, and emphasizes a more intensive approach based on these recent controlled trials who demonstrated LDL-C 'lower is better' and safe to very low levels. The new guidelines include a stepped approach to escalating statin therapy, adding ezetimibe if lipid levels remain high, and finally to introducing a PCSK9 inhibitor if further reduction is required (Table 2).

Novel therapies

Currently, novel agents are on the horizon, which have shown to lead to a significant decrease in other lipoprotein fractions. Combining a statin with these agents can help achieve lipid goals. Thus, lipid lowering through these therapeutic agents offers a novel strategy to reduce residual risk of atherosclerotic CV events, and will likely provide future benefits on stroke prevention.

In the recently reported Randomized Evaluation of the Effects of Anacetrapib through Lipid Modification (REVEAL) trial [39], among patients with atherosclerotic vascular disease who were receiving intensive statin therapy, the use of anacetrapib (an inhibitor of cholesteryl ester transfer protein (CETP) which raises HDL-C levels and also reduces LDL-C levels)- resulted in a lower incidence of major coronary events than the use of placebo (10.8 vs.11.8%; rate ratio, 0.91; 95%CI:, 0.85 to 0.97; $p = 0.004$). Nevertheless, the

Table 2. Main 2018 ACC/AHA recommendations for statin therapy use in patients with ASCVD

COR	LOE	Recommendations
I	A	In patients who are 75 years of age or younger with clinical ASCVD,* high-intensity statin therapy should be initiated or continued with the aim of achieving a 50% or greater reduction in LDL-C levels.
I	A	In patients with clinical ASCVD in whom high-intensity statin therapy is contraindicated or who experience statin-associated side effects, moderate-intensity statin therapy should be initiated or continued with the aim of achieving a 30% to 49% reduction in LDL-C levels.
I	B-NR	In patients with clinical ASCVD who are judged to be very high risk and *considered for PCSK9 inhibitor therapy,* maximally tolerated LDL-C lowering therapy should include maximally tolerated statin therapy and ezetimibe.
IIa	ASR	In patients with clinical ASCVD who are judged to be very high risk and who are on maximally tolerated LDL-C lowering therapy with LDL-C 70 mg/dL (≥ 1.8 mmol/L) or higher or a non–HDL-C level of 100 mg/dL (≥ 2.6 mmol/L) or higher, it is reasonable to add a PCSK9 inhibitor following a clinician–patient discussion about the net benefit, safety, and cost.
IIa	B-R	In patients with clinical ASCVD who are on maximally tolerated statin therapy and are judged to be at very high risk and have an LDL-C level of 70 mg/dL (≥ 1.8 mmol/L) or higher, it is reasonable to add ezetimibe therapy.
IIa	B-R	In patients older than 75 years of age with clinical ASCVD, it is reasonable to initiate moderate- or high-intensity statin therapy after evaluation of the potential for ASCVD risk reduction, adverse effects, and drug–drug interactions, as well as patient frailty and patient preferences.
IIa	C-LD	In patients older than 75 years of age who are tolerating high-intensity statin therapy, it is reasonable to continue high-intensity statin therapy after evaluation of the potential for ASCVD risk reduction, adverse effects, and drug-drug interactions, as well as patient frailty and patient preferences.
IIb	B-R	In patients with clinical ASCVD who are receiving maximally tolerated statin therapy and whose LDL-C level remains 70 mg/dL (≥ 1.8 mmol/L) or higher, it may be reasonable to add ezetimibe.

ASCVD, Atherosclerotic cardiovascular disease
COR, Class of Recommendation
LOE, Level of Evidence
Clinical ASCVD includes stroke, transient ischemic attack (TIA), of atherosclerotic origin and acute coronary syndrome (ACS), those with history of myocardial infarction (MI), stable or unstable angina or coronary or other arterial revascularization, or peripheral artery disease (PAD) including aortic aneurysm

between-group difference in the rate of the secondary composite outcome of major atherosclerotic events (i.e., myocardial infarction, coronary death, or presumed ischemic stroke) was not significant (rate ratio, 0.93; 95% CI, 0.86 to 1.00; $p = 0.052$). Consequently, the effect of anacetrapib on presumed ischemic stroke (rate ratio, 0.99; 95% CI, 0.87 to 1.12) was not formally tested.

On the contrary, recently, high doses (4-g daily) of the omega-3 oil eicosapentaenoic acid (EPA) have shown a large benefit on CV events including stroke.

The Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT) [40] was a multicenter, randomized, double-blind, placebo-controlled trial that included 8179 patients with established CV disease (70.7%) or with diabetes and other risk factors, who had been receiving statin therapy and who had a fasting triglyceride level of 135 to 499 mg per deciliter and a LDL-C level of 41 to 100 mg per deciliter. The patients were randomly assigned to receive 2 g of icosapent ethyl twice daily (total daily dose, 4 g) or placebo. After a median follow-up of 4.9 years, there was an approximately

25% RR reduction in the primary endpoint of first occurrence of a major adverse CV event (a primary end-point event occurred in 17.2% of the patients in the icosapent ethyl group, as compared with 22.0% of the patients in the placebo group (HR 0.75; 95% CI, 0.68 to 0.83; $p < 0.001$). The risk of the secondary end point fatal or nonfatal stroke was also significantly lower, by 28% (HR 0.72 CI 0.55 to 0.3; P 0.01), in the icosapent ethyl group than in the placebo group.

Conclusions

The SPARCL trial published in 2006 has been a landmark study in vascular neurology. The trial demonstrated for the first time that high-dose atorvastatin prevents recurrent stroke, and led the AHA/ASA to recommend statin therapy for patients with stroke or TIA of atherosclerotic origin. Multiple post hoc analyses of different subgroups followed the SPARCL study and suggested answers to important clinical questions. Later, the J-STARS study also demonstrated that therapy with low-dose pravastatin reduced atherothrombotic infarction incidence among patients with prior ischemic stroke. Recently, several trials have shown improved stroke outcomes with non-statin lipid-lowering medications: IMPROVE-IT with ezetimibe on top of simvastatin and PCSK9 inhibitors—FOURIER with evocolumab and ODYSSEY-OUTCOMES with alirocumab—on top of statin therapy. The recently released ACC/AHA guideline emphasizes a more intensive approach based on these trials who demonstrated LDL-C 'lower is better' and safe to very low levels. The new guidelines include a stepped approach to escalating statin therapy, adding ezetimibe if lipid levels remain high, and finally to introducing a PCSK9 inhibitor if further reduction is required.

In summary, currently we know that statin-based lipid-lowering is effective both for primary and secondary prevention of ischemic stroke and randomized trials have shown that each reduction of 40 mg/dL in the level of LDL-C reduces the stroke risk by approximately one quarter and further reductions in LDL-C levels have shown to produce additional reductions in stroke risk. Besides, now we have evidence of benefit for adding non-statin lipid-modifying therapies to statins to reduce stroke risk. Surely, these and novel strategies to reduce residual lipidic risk will provide future benefits on stroke prevention.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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