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Cerebrovascular Disease and Stroke (S Silverman, Section Editor)

Management of Hyperlipidemia After Stroke

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Abstract

Purpose of review Hyperlipidemia is a key therapeutic target for stroke risk modification. The goal of this review is to highlight available treatment options and review their efficacy in the setting of general cardiovascular disease and after most subtypes of ischemic stroke and hemorrhagic stroke.
Recent findings Statins remain first-line in the management of hyperlipidemia to prevent stroke. In recent trials of patients with pre-existing atherosclerotic vascular disease, new agents, most notably PCSK9 inhibitors and ezetimibe, added additional stroke risk reduction when combined with statins.
Summary Risk of stroke can be significantly reduced by understanding that hyperlipidemia is a key therapeutic target, particularly in patients with cardiovascular disease, and by identifying patients who may benefit from aggressive LDL-C reduction with statins ± novel agents.

Introduction

Cardiovascular diseases, including stroke, are the leading cause of mortality worldwide [1]. Stroke incidence is stable in low- and moderate-income countries but decreasing in high-income countries [2]. Improved cardiovascular risk factor control is driving much of this trend [3]. Hyperlipidemia is associated with a 28% increased risk of ischemic stroke, placing it behind hypertension, diabetes, and smoking as a key risk factor for stroke and identifying it as an important therapeutic target for risk modification [3].

The relationship between blood lipids and stroke, both ischemic and intracerebral hemorrhage (ICH), is

Table 1. Chart summarizing therapies to treat hyperlipidemia and effect on stroke

LDL-C Modification	
Statins	• First line therapy in primary and secondary prevention [13●, 16●, 17-20] • Reduce LDL-C by 55-60% at highest-intensity dosing [8, 21●, 22●] • Total stroke risk decreased by 16% with every 39 mg/dl reduction in LDL-C [8] • Minimal risk of side effects in randomized trials [22●, 23] • ICH risk far outweighed by ischemic stroke risk reduction [24●]
Red yeast rice	• Not recommended [25]
PCSK9 inhibitors	• Reduce LDL-C by 50-60% [26-28] • Powerful additive effect when combined with statins [26-28] • PCSK9 inhibitor + statin versus placebo + statin reduced risk of ischemic stroke by 25-27% [29●●, 30●●] • No significant side effect difference between group [29●●, 30●●] • ICH risk far outweighed by ischemic stroke risk reduction [29●●, 30●●]
Ezetimibe	• Reduced LDL-C by 16 mg/dl compared to placebo [31] • Ezetimibe + statin versus placebo + statin reduced risk of composite of cardiovascular outcomes by 6% [31] • Risk of ischemic stroke reduced by 21% [31] • No significant side effect difference between groups [31] • ICH risk outweighed by ischemic stroke risk reduction [31]
HDL-C and Triglycerides Modification	
Omega-3 fatty acids	• Icosapent ethyl (IE) reduced triglycerides by 18% compared to placebo [32●] • IE + statin versus placebo + statin reduced risk of composite of cardiovascular outcomes by 26% [32●] • Risk of ischemic stroke reduced by 21% [32●] • IE was associated with atrial fibrillation/flutter and trend toward serious bleeding but not ICH [32●] • Mineral oil (the placebo) may have been harmful [32●] • Other Omega-3 trials were mostly negative [33-36]
Fibrates	• Role in stroke prevention unclear [5, 37]
Niacin	• Role in stroke prevention unclear [38-40]
CETP inhibitors	• No current role in stroke prevention [41, 42]
Inflammation Modification	
Canakinumab	• Reduces inflammatory markers but not LDL-C [43●] • Canakinumab + statin versus placebo + statin reduced risk of composite of cardiovascular outcomes by 15% [43●] • Stroke risk not affected [43●] • Associated with sepsis and fatal infection, lower risk of cancer mortality [43●]

complex. Total cholesterol is predominantly low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C): total cholesterol = LDL-C + HDL-C + triglycerides/5. In population-based studies, these lipids play varying roles in the pathogenesis of each stroke subtype. Total cholesterol is weakly associated with ischemic stroke and inversely related to ICH, while high HDL-C appears protective against ischemic stroke [2–4]. Triglycerides have an unclear relationship with stroke, but recent research indicates that high triglycerides are a marker of increased remnant cholesterol particles which promote atherosclerosis and atherothrombosis [2, 5–7].

Currently, LDL-C is the most useful blood lipid marker to predict stroke risk. The odds of ischemic stroke increase with LDL-C, particularly in the large vessel atherosclerosis subtype, while therapies which reduce LDL-C reduce stroke risk [2, 8–12].

Statins powerfully reduce LDL-C and are proven to reduce stroke risk, but our most potent statins have been available for about 20 years, and patients on maximal statin therapy remain at risk of cardiovascular events [5, 13•, 14, 15, 16•]. New therapies are emerging to answer this need, particularly inhibitors of proprotein convertase subtilisin–kexin type 9 (PCSK9) and ezetimibe, both of which reduce LDL-C.

Therapies to treat dyslipidemia and reduce stroke risk

This section will discuss treatments for dyslipidemia to reduce stroke risk, focusing on therapies which predominantly modify LDL-C, HDL-C, triglycerides, and inflammation. Table 1 below summarizes these medications.

Lifestyle: physical activity, exercise, diet, weight loss

Lifestyle interventions decrease stroke risk, but the mechanisms underlying the reduced risk are multiple and not plainly due to modification of lipid profiles [16•, 17–19].

Statins

Mechanistically, statins inhibit HMG-CoA reductase, modify vascular risk primarily via reduction of LDL-C, and reduce LDL-C by 55–60% at highest-intensity dosing [8, 21•, 22•]. Aggressively lowering LDL-C is typically more beneficial: every 39 mg/dl reduction in LDL-C reduces risk of stroke by 16%, and no LDL-C threshold has been identified below which patients experience harm rather than benefit [8, 21•, 24•]. Statins are first-line therapy in both primary and secondary prevention guidelines [13•, 16•, 17–20]. However, some patients remain at high risk of cardiovascular events despite statin therapy and may benefit from adjunctive therapies, which is discussed below [5, 13•, 16•, 20].

There is widespread, but typically unfounded, concern about statin-related adverse effects [21•, 22•, 23, 44]. Unblinded trials attribute adverse effects to statins far more commonly than blinded trials [23]. Inappropriate statin discontinuation due to these worries appears to cause harm, therefore, a brief discussion of common statin-related concerns is warranted [45–48].

Intracerebral hemorrhage (ICH): Discussed below.

Cognition, cancer, mortality, and other conditions: There is no evidence that statins increase risk of cognitive dysfunction at any dose or when very low LDL-C levels are achieved when statins are combined with PCSK9

inhibitors or ezetimibe [22•, 29••, 30••, 31, 44, 49]. Additionally, statins do not increase risk of non-vascular mortality, cancer incidence, cancer death, peripheral neuropathy, renal dysfunction, cataracts, erectile dysfunction, or tendonitis [21•, 22•, 44].

Diabetes: Statins slightly increase the risk of diabetes, predominantly in patients already at high risk of diabetes, but statin therapy prevents about 3.5 to 5 cardiovascular events, including stroke, for every new case of diabetes [21•, 22•, 44].

Muscle symptoms: Muscle symptoms are often erroneously attributed to statins in unblinded studies and community settings [22•, 23, 44]. In blinded RCTs, there is at most a 1% difference in the incidence of muscle symptoms between statin and placebo groups [22•, 23, 44]. Statins increase the risk of myopathy by about 1 patient per 1000–10,000 per year, and rhabdomyolysis is even rarer [22•]. Statins are not associated with cardiomyopathy [22•].

Liver considerations: Mild transaminase elevation occurs in about 1% of patients on statins but is typically not clinically significant [22•]. Statin-associated severe hepatotoxicity is exceedingly rare [22•, 44]. Statins are contraindicated in patients with active liver disease, but appear generally safe in patients with chronic liver disease [22•].

Red yeast rice

Red yeast rice (RYR) is a supplement, not a pharmaceutical, and is therefore not held to rigorous standards. Commonly marketed RYR products demonstrate a lack of uniformity, widely varying levels of ingredients, and the possibility of contamination and harm [25].

PCSK9 inhibitors

Early studies demonstrated that inhibitors of proprotein convertase subtilisin–kexin type 9 (PCSK9) reduce LDL-C by approximately 50–60%, decrease cardiovascular risk similarly to statins, and produce a powerful additive effect when combined with statins [26–28].

In 2017, evolocumab was compared against placebo in the FOURIER trial for a median follow-up of 2.2 years in patients with atherosclerotic cardiovascular disease (including 19% of patients with previous ischemic stroke) already on statin therapy with LDL-C > 70 mg/dl [29••]. Evolocumab reduced LDL-C by 59% compared to placebo, achieving a median LDL-C after 48 weeks of 30 mg/dl; 42% of patients achieved LDL-C < 25 mg/dl. In the evolocumab arm, risk of the composite of cardiovascular outcomes was reduced by 20% ($p < 0.001$) and total stroke by 21% ($p = 0.01$), which was driven by a 25% risk reduction in ischemic stroke but a nonsignificant increase in ICH [29••]. Adverse events were similar between treatment groups.

In 2018, alirocumab was compared against placebo in the ODYSSEY OUTCOMES trial for a median follow-up of 2.8 years in patients with a previous acute coronary syndrome (3.2% of enrolled patients had a previous stroke) already on maximally tolerated statin therapy with LDL-C > 70 mg/dl [30••]. Treatment reduced LDL-C by 55% compared to

placebo, achieving a mean LDL-C of 53 mg/dl in the on-treatment analysis. In the alirocumab arm, risk of the composite of cardiovascular outcomes was reduced by 15% ($p < 0.001$) and ischemic stroke by a significant 27% (CI, 0.57–0.93) without increase in hemorrhagic stroke risk. Adverse events were similar between treatment groups.

Ezetimibe

Ezetimibe inhibits cholesterol absorption from the gastrointestinal tract. The IMPROVE-IT study compared simvastatin 40 mg daily plus either ezetimibe 10 mg daily or placebo in patients with a recent acute coronary syndrome and LDL-C 50–125 mg/dl [31]. Patients with stroke or transient ischemic attack (TIA) were excluded from the trial. After a median of 6 years of follow-up, ezetimibe lowered LDL-C by about 16 mg/dl to a mean LDL-C of 54 mg/dl, decreased risk of the composite of cardiovascular outcomes by 6% ($p = 0.016$), and decreased total stroke risk by 14% ($p = 0.05$), which was driven by a 21% risk reduction in ischemic stroke ($p = 0.008$) with a nonsignificant increased risk of ICH. Adverse events were similar between groups.

Modification of HDL-C and triglycerides

Statins are first-line therapy in both primary and secondary prevention guidelines [13•, 16•, 17–20]. However, patients with residual triglyceride elevation and/or low HDL-C despite effective statin therapy seem to represent a particularly high-risk group which may benefit from adjunctive therapies [5].

Omega-3 fatty acids (also called n-3 fatty acids)

Icosapent ethyl, a highly purified eicosapentaenoic acid (EPA) ethyl ester, was recently compared against placebo in the REDUCE-IT trial at a dose of 2 g twice daily in patients with established cardiovascular disease or diabetes already on statin therapy with LDL-C 41–100 mg/dl (median LDL-C 75 mg/dl) and elevated serum triglycerides with level 135–499 mg/dl [32•]. After a median follow-up of 4.9 years, treatment reduced triglyceride levels by 18% from baseline and slightly increased LDL-C by 3.1%. Icosapent ethyl reduced the risk of the composite of cardiovascular outcomes by 26% ($p < 0.001$) and specifically reduced the risk of total stroke by 28% ($p = 0.01$). Treatment was associated with higher rates of atrial fibrillation or flutter and a nonsignificant trend toward serious bleeding events but no difference in rates of ICH.

JELIS, an earlier trial of EPA, also showed cardiovascular benefit [36]. Other trials of omega-3 fatty acids have been negative, however [33–35]. Why did REDUCE-IT find such robust benefit in the face of previous omega-3 disappointments? Possible explanations include the formulation (EPA may be more effective than other omega-3 fatty acids), the relatively large dose, the pharmaceutical grade of this omega-3 rather than a supplement-grade, and the possibility that the placebo used—mineral oil—actually caused harm and thus spuriously improved the profile of icosapent ethyl [32•, 33–35, 50]. Another large trial of omega-3 fatty acids, STRENGTH, is ongoing [51].

Fibrates

Fibrates reduce cardiovascular events in monotherapy trials, but statins are superior first-line therapy [5]. There is a suggestion that statin-treated diabetic patients with high residual triglyceride levels (> 204 mg/dl) and low HDL-C have reduced cardiovascular events with adjunctive fibrate therapy [52]. This is being studied further [37].

Niacin

Recently, two large trials evaluating the combination of niacin and statin versus statin alone were negative [38, 40]. However, subgroup analysis of these trials hints at a possible role for niacin as adjunctive therapy in high-risk patients with residual elevation of triglycerides and low HDL-C despite statin therapy (similar to fibrate therapy above) [39].

Cholesteryl ester transfer protein (CETP) inhibitors

Anacetrapib modestly decreased LDL-C, increased HDL-C by 104%, and reduced coronary events by 9% compared to placebo when added to statin therapy [41]. However, the manufacturer decided against seeking regulatory approval of anacetrapib [42]. Other trials of CETP inhibitors were negative despite similarly large effect on HDL-C [53, 54].

Inflammation

Canakinumab

The CANTOS trial compared canakinumab, a monoclonal antibody targeting interleukin-1β, to placebo in patients already on statin therapy with prior myocardial infarction and high-sensitivity C-reactive protein (hsCRP) > 2 mg/L. [43•] The optimal dose of canakinumab substantially decreased hsCRP, reduced risk of the vascular composite outcome by 15% ($p = 0.021$) without lowering stroke risk, and did not affect blood lipid levels. Canakinumab was associated with greater risk of sepsis and fatal infection, reduced platelet counts without increased bleeding risk, and significantly lower risk of cancer mortality. This trial confirmed that inflammation plays a key role in atherosclerosis and atherothrombosis, and it offered an alternative avenue for reducing cardiovascular risk independent of lipid level modification [5, 43•, 55–57].

Stroke subtypes and dyslipidemia management

Of all strokes, 87% are ischemic, 10% are intracerebral hemorrhage (ICH, often called hemorrhagic stroke), and 3% are subarachnoid hemorrhage [2]. Ischemic strokes are often categorized by stroke mechanism using the TOAST criteria (Trial of ORG 10172 in Acute Stroke Treatment) [58]. A recent study estimated that, of all ischemic strokes, 23% are due to large vessel disease, 22% to small

vessel disease, 22% to cardioembolism, 3% to other determined cause, and 26% to undetermined cause [58]. Other studies have found similar results [59].

The most common causes of spontaneous ICH (hemorrhagic stroke) are deep perforator arteriopathy and cerebral amyloid angiopathy (CAA), both of which predominantly affect small vessels [60]. While there is some overlap between these two ICH etiologies, lobar hemorrhage more frequently affects older patients, has high risk of recurrence, and is often caused by CAA, whereas deep ICH commonly affects younger patients, has lower risk of recurrence, and is frequently caused by small vessel arteriopathy, which is etiologically similar to ischemic small vessel disease [60, 61].

This section will examine the evidence for lipid-lowering therapy based on stroke subtype.

Large vessel disease

High-intensity statin therapy is first-line treatment in patients of all ages with large vessel disease (LVD), including in patients > 75 years [8, 13•, 21•, 62]. In patients enrolled in SPARCL with ischemic stroke due to LVD as their entry event, atorvastatin 80 mg daily reduced total stroke (ischemic + hemorrhagic) risk by 40% compared to placebo [63, 64]. Adjunctive therapies could be employed with statin therapy in patients with symptomatic extracranial or intracranial atherosclerosis, particularly in patients who have recurrent ischemic stroke or TIA despite maximally tolerated statin therapy with LDL-C > 70 mg/dl. A PCSK9 inhibitor or ezetimibe should be considered initially for adjunctive therapy [13•, 16•, 20, 29••, 30••, 31]. In patients with residual elevation of triglycerides, the omega-3 fatty acid icosapent ethyl might be considered [32•]. The anti-inflammatory agent canakinumab might be considered if hsCRP is elevated, but this medication has an uncertain role in stroke prevention as it did not decrease stroke risk in CANTOS [43•].

Small vessel disease

In patients enrolled in SPARCL with ischemic stroke secondary to small vessel disease (SVD), atorvastatin 80 mg daily versus placebo reduced risk of recurrent ischemic stroke by 24% (95% CI, 0.57–1.02) and total stroke by 16% (95% CI, 0.64–1.11) at a cost of increased risk of ICH [64]. However, multivariate analysis did not implicate high-intensity statin therapy as an independent predictor of ICH in patients with SVD [62, 64]. Furthermore, SVD increases risk of long-term combined cerebrovascular and coronary events approximately as much as LVD [65]. Therefore, it would be reasonable to treat SVD patients similarly to LVD patients as described immediately above: high-intensity statin therapy initially, potentially followed by adjunctive therapy with either a PCSK9 inhibitor or ezetimibe if LDL-C > 70 mg/dl.

Cardioembolic stroke

SPARCL excluded patients with atrial fibrillation and other cardiac sources of embolism, leading to uncertainty about the benefit of statins in patients

with ischemic stroke secondary to atrial fibrillation [63]. However, recent data indicates that patients with atrial fibrillation benefit as much from lipid-lowering therapy as patients with LVD or SVD [66•]. Multiple mechanisms may be at play here. Elevated LDL-C was found to be an independent predictor of stroke risk in patients with atrial fibrillation [12]. Statins robustly lower LDL-C, but also have pleiotropic effects independent of lipid-lowering which may reduce stroke risk [67]. Furthermore, statins appear to reduce the likelihood of developing both incident atrial fibrillation and recurrent atrial fibrillation after a previous episode of atrial fibrillation [68–70].

Stroke of undetermined cause

In patients enrolled in SPARCL with ischemic stroke of unknown or other cause, atorvastatin 80 mg daily versus placebo reduced risk of total stroke (ischemic + hemorrhagic) by 20% (95% CI, 0.62–1.27) [64]. A recent study estimated that 26% of strokes are of uncertain cause, but with close follow-up, many of these strokes are found to have been caused by occult LVD or paroxysmal atrial fibrillation [58, 59]. Therefore, treatment with a high-intensity statin is warranted if the mechanism of stroke is unknown.

Transient ischemic attack

Patients enrolled in SPARCL with a transient ischemic attack (TIA) had a nonsignificant 20% risk reduction (95% CI, 0.60–1.24) in total stroke with atorvastatin [64]. Initiation of high-intensity statin therapy after TIA is reasonable as the 1-year and 5-year risk of stroke after TIA is considerable [71, 72].

Intracerebral hemorrhage

There is little data concerning lipid-lowering therapy in patients with prior intracerebral hemorrhage (ICH) [22•]. Only 93 of the 4731 patients in SPARCL had an ICH as their enrollment event [63]. Eighty-eight patients suffered an ICH during the trial, and two of the factors found to significantly increase risk of ICH were ICH as the entry event and randomization to atorvastatin rather than placebo [64, 73]. Given this very small sample size and the lack of patient-level information concerning the crucial detail of ICH location (lobar versus deep), reaching any definitive conclusions is difficult [63, 64, 73]. However, the suggestion of risk is consistent with other research: statins have antithrombotic properties; statins are associated with increased cerebral microbleed burden, particularly cortically; microbleed burden is associated with increased risk of ICH; and secondary prevention RCTs after ischemic stroke have demonstrated a modestly increased risk of ICH with lipid-lowering therapy [24•, 67, 74, 75].
This leads to a frequently encountered clinical scenario: is there a net benefit of lipid-lowering therapy after ICH in patients perceived to be at risk for ischemic events? A decision model published in 2011 recommended avoidance of statin therapy in all patients after lobar ICH and *consideration* of statin therapy in patients after deep ICH only in the setting of very high

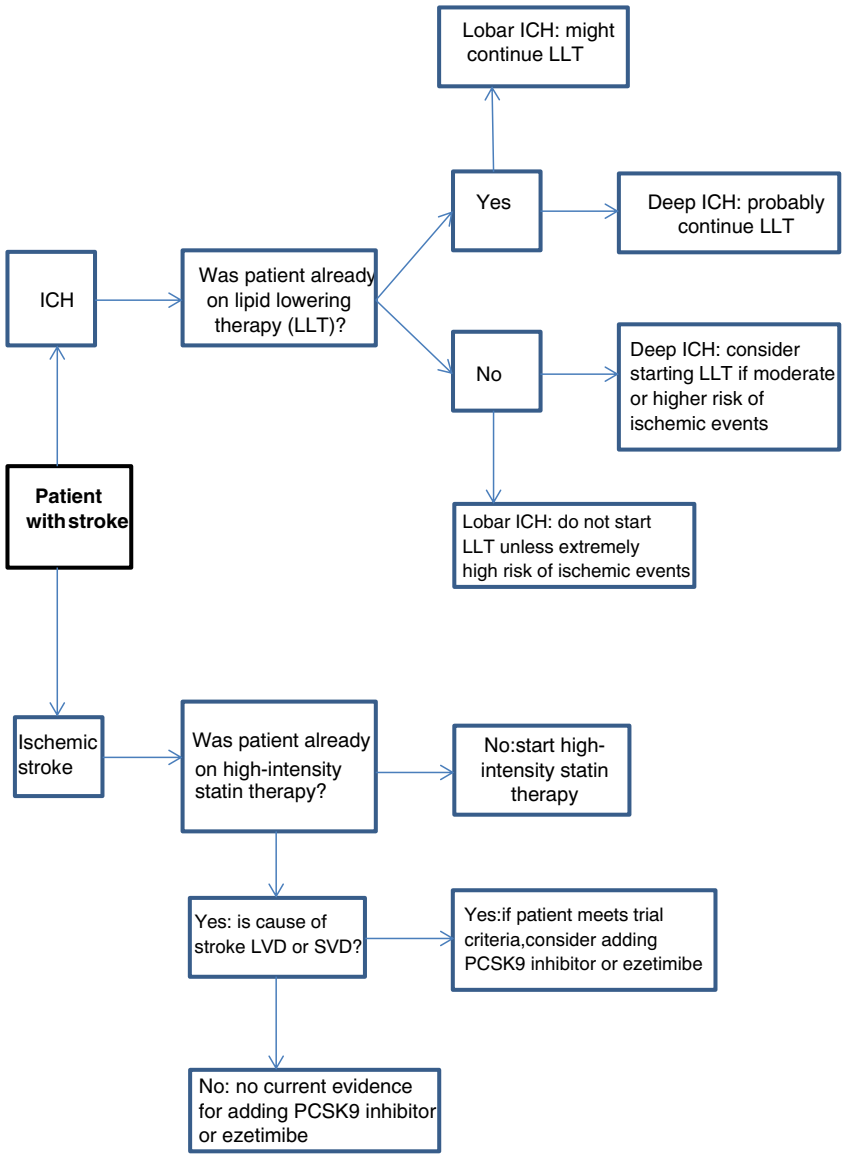

Fig. 1. Flowchart offering suggestions for dyslipidemia management after stroke or TIA.

cardiovascular disease risk [76]. These recommendations were echoed by several editorials [73, 77, 78].

New information has since become available. First, continuing statin therapy after ICH may be associated with improved outcomes while discontinuing statin therapy after ICH may be associated with worse outcomes [79, 80]. Second, annual risk of ICH recurrence after ICH may be smaller than we previously thought: about 1.5–2% after deep ICH and 6–7% after lobar ICH, but risk seems to decrease substantially after the first year [81, 82•, 83, 84]. Third, the annual risk of ischemic events after ICH may be substantially higher than we previously thought, particularly after deep ICH [82•, 83, 84].

Therefore, in patients already taking a statin who present with any ICH, it may be reasonable to continue the statin if the risk of ischemic events is significant. In patients not taking a statin who present with deep ICH, both the relatively higher risk of ischemic events and the relatively lower risk of ICH recurrence in this ICH subtype might warrant initiating statin therapy in patients at high risk of ischemic events. In patients not taking a statin who present with lobar ICH, both the relatively lower risk of ischemic events and the relatively higher risk of ICH recurrence in this ICH subtype should lead to caution about initiating statin therapy, particularly in the first year when risk of ICH recurrence is highest.
Figure 1 provides a flowchart with suggestions for dyslipidemia management after stroke or TIA.

Addressing common concerns: advanced age, low LDL-C, and perceived risk of ICH without history of ICH

Clinical scenarios frequently arise in which there is uncertainty about whether to continue, initiate, or discontinue lipid-lowering therapy. This section will discuss several common situations and concerns.

Advanced age

Statins are quite safe in elderly patients, with low risk of myopathy and drug-drug interactions and no discernible risk of cognitive dysfunction, even with very low LDL-C levels when statins are combined with PCSK9 inhibitors or ezetimibe [22•, 29••, 30••, 31, 44, 49]. Statins substantially reduce the risk of major vascular events and total stroke in patients of all ages, with only a mild decrease in effectiveness with advancing age, including in patients > 75 years [21•]. This benefit has mostly been identified in the setting of secondary prevention; there is currently uncertainty regarding the net benefit of statins in primary prevention in the oldest patients [21•, 85, 86]. These patients are being enrolled in the STAREE trial [87].
More recent secondary prevention studies utilizing combination therapy (statin + medication versus statin alone) showed no reduction in treatment effect in patients > 65 years (FOURIER, ODYSSEY OUTCOMES) or in patients > 75 years (IMPROVE-IT) [29••, 30••, 31].

Low LDL-C

Multiple population-based studies have implicated low LDL-C as a risk factor for ICH [88, 89]. However, RCTs of LDL-C lowering therapies have not agreed with these observational studies. RCTs have consistently shown that in trials of primary prevention, secondary prevention, statin versus placebo, more intensive versus less intensive statin therapy, and combination therapy with statin + medication versus statin alone, neither baseline LDL-C nor degree of LDL-C reduction is

predictive of ICH, even at very low-achieved LDL-C [8, 24•, 29••, 30••, 31, 41, 63, 64].

Perceived risk of ICH without history of ICH

Concerning primary prevention, there is no evidence from RCTs that statins increase the risk of ICH [24•]. Furthermore, a recent huge population-based study primarily of primary prevention patients found that more intensive statin therapy actually decreases risk of ICH [90•].

In secondary prevention, increased risk of ICH with statin therapy was found in the Heart Protection Study and in SPARCL [63, 91]. In SPARCL, a secondary prevention trial after stroke or TIA, atorvastatin 80 mg daily versus placebo was associated with a 22% reduced risk of ischemic stroke, a small but significant increased risk of ICH, and an overall 16% reduced risk of total stroke ($p = 0.03$) [63]. A large meta-analysis of statin trials, which did not include SPARCL, reached a very similar conclusion [8]. These trials were unable to identify any threshold at which LDL-C was "too low" or reduced "too far," finding no evidence that baseline LDL-C or degree of LDL-C reduction is associated with ICH [8, 63, 64].

Recent combination therapy trials, all described previously, reduced LDL-C levels even further [29••, 30••, 31, 41]. A new meta-analysis which evaluates these recent trials and previous statin-only trials is very reassuring: lipid-lowering therapy is not associated with ICH in primary prevention trials; lipid-lowering therapy is very modestly associated with ICH in secondary prevention trials (OR, 1.18; 95% CI, 1.00–1.38); baseline LDL-C and degree of LDL-C lowering do not explain the increased risk of ICH in secondary prevention trials; ischemic stroke prevention with lipid-lowering therapy significantly and substantially exceeds risk of ICH, thus greatly favoring aggressive LDL-C reduction in secondary prevention [24•].

Emerging therapies and future directions

Lipid-lowering medications that have been on the market for decades continue to prove their worth, while recently approved therapies show promise. Looking forward, we should first emphasize prescription of and adherence to first-line therapy, statins, and knowledgeably address concerns when they arise, keeping in mind that patients can suffer harm as a result of inappropriate statin discontinuation [45, 92]. Second, the ongoing STAREE trial will hopefully address the uncertainty regarding statin therapy for primary prevention in elderly patients [87]. Third, incorporating ezetimibe and PCSK9 inhibitors as adjunctive therapies to statins has the potential to reduce stroke risk, particularly after ischemic stroke due to LVD and perhaps SVD [13•, 16•, 20, 29••, 30••, 31]. Fourth, continued follow-up of patients on combination therapy will be necessary to assess the long-term safety and benefit of pharmacologically achieved very low LDL-C levels. Fifth, hopefully, we will soon reach a conclusion regarding the role of omega-3 fatty acids, particularly EPA, which has now shown cardiovascular benefit in two trials, while other trials of omega-3 fatty acids were negative

[32•, 33–36]. Last, identification of blood markers for stroke subtypes more specific than LDL-C could significantly change both the diagnosis and management of stroke.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflict 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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