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Abbreviations: ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; AsxCS, Asymptomatic carotid artery stenosis; CARUSO, CARotid plaqUe StabilizatiOn and regression with evolocumab; CAS, Carotid artery stenting; CEA, Carotid endarterectomy; cIMT, Carotid intima-media thickness; CI, Confidence interval; CRP, C-reactive protein; CV, Cardiovascular; CVD, Cardiovascular disease; FOURIER, Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects with Elevated Risk; GSM, Grey-scale medium; HR, Hazard ratio; IBS, Integrated back scatter; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial; LDL-C, Low-density lipoprotein cholesterol; MI, Myocardial infarction; NAFLD, Non-alcoholic fatty liver disease; NASCET, North American Symptomatic Carotid Endarterectomy Trial; ODYSSEY OUTCOMES, Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab; OR, Odds ratio; PCSK9, Proprotein convertase subtilisin/kexin type 9; RCT, Randomized controlled trial; SCS, Symptomatic carotid artery stenosis; SPARCL, Stroke Prevention by Aggressive Reduction in Cholesterol Levels; TIA, Transient ischemic attack; WMD, Weighted mean difference.

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ABSTRACT

International guidelines strongly recommend statins alone or in combination with other lipid-lowering agents to lower low-density lipoprotein cholesterol (LDL-C) levels for patients with asymptomatic/symptomatic carotid stenosis (AsxCS/SCS). Lowering LDL-C levels is associated with significant reductions in transient ischemic attack, stroke, cardiovascular (CV) event and death rates. The aim of this multi-disciplinary overview is to summarize the benefits and risks associated with lowering LDL-C with statins or non-statin medications for Asx/SCS patients. The cerebrovascular and CV beneficial effects associated with statins, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and other non-statin lipid-lowering agents (*e.g.* fibrates, ezetimibe) are reviewed. The use of statins and PCSK9 inhibitors is associated with several beneficial effects for Asx/SCS patients, including carotid plaque stabilization and reduction of stroke rates. Ezetimibe and fibrates are associated with smaller reductions in stroke rates. The side-effects resulting from statin and PCSK9 inhibitor use are also highlighted.
The benefits associated with lowering LDL-C with statins or non-statin lipid lowering agents (*e.g.* PCSK9 inhibitors) outweigh the risks and potential side-effects. Irrespective of their LDL-C levels, all Asx/SCS patients should receive high-dose statin treatment±ezetimibe or PCSK9 inhibitors for reduction not only of LDL-C levels, but also of stroke, cardiovascular mortality and coronary event rates.

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A positive correlation has been found between low-density lipoprotein cholesterol (LDL-C) levels and stroke risk. A systematic review and meta-analysis that included >90,000 individuals participating in 26 randomized controlled trials (RCTs) demonstrated that statin treatment significantly reduced the incidence of stroke.[1] Each 10% reduction in LDL-C levels reduced the risk of all strokes (*e.g.*, ischemic, fatal/non-fatal, disabling, *etc.*) by 15.6% (95% confidence interval [CI]: 6.7–23.6%) without an increase in hemorrhagic strokes (odds ratio [OR]: 0.90; 95% CI: 0.65–1.22).[1] Another meta-analysis (14 trials; 90,056 participants) showed that statin treatment was associated with a significant 17% proportional reduction in the incidence of first fatal or nonfatal stroke of any type (hemorrhagic, ischemic, or of unknown type; 1340 *vs* 1617 events, for statin *vs* placebo, respectively; 95% CI: 12–22%, $p < 0.0001$) per mmol/l lower LDL-C.[2] A third, larger meta-analysis ($n = 24$ RCTs; 165,792 patients) demonstrated that each 1 (one) mmol/l (39 mg/dl) decrease in LDL-C levels was associated with a 21.1% relative risk reduction of stroke (95% CI: 6.3–33.5; $p = 0.009$).[3] Based on these data, international guidelines provide a strong recommendation for statin treatment in patients with asymptomatic (AsxCS) or symptomatic (SCS) carotid artery stenosis for long-term prevention of stroke, myocardial infarction (MI) and cardiovascular (CV) event rates.[4–7]

SCS is defined as the development of carotid-territory focal neurologic symptoms in the presence of an ipsilateral >50% internal carotid artery stenosis according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria.[7] Such symptoms include contralateral weakness of the face, upper and/or lower extremity; contralateral sensory deficit or paresthesia of the face, upper and/or lower extremity; or transient ipsilateral blindness [amaurosis fugax]).[7] AsxCS is defined as the presence of >50% internal carotid artery stenosis in the absence of carotid-territory neurologic symptoms.[7]

Statins are an essential component in the management of patients with carotid artery stenosis, whether they are managed conservatively or scheduled to undergo a carotid intervention.[8] Besides reducing stroke risk and cardiovascular event rates, there is evidence that statins also significantly reduce perioperative/periprocedural morbidity and mortality rates, as well as coronary events when these patients undergo carotid endarterectomy (CEA) or carotid artery stenting (CAS).[4–8] Thus, statin use is mandatory in AsxCS/SCS patients.

Besides their multiple beneficial effects, statin use is sometimes associated with side-effects. These side-effects may lead to statin discontinuation and consequently suboptimal CV disease (CVD) risk reduction. The present narrative review will discuss the benefits and drawbacks associated with statins used for LDL-C lowering in patients with AsxCS/SCS. It will also discuss the benefits and drawbacks of novel LDL-C lowering drugs used in patients with AsxCS/SCS, namely the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, as well as other lipid-lowering agents (*e.g.*, ezetimibe).

Benefits associated with statin use

A number of beneficial actions have been reported for patients with AsxCS/SCS receiving statins whether managed conservatively or undergoing an intervention (Table 1). At the molecular level, statins improve endothelial function, reduce LDL-C oxidation, increase nitric oxide

Table 1
Potential benefits associated with statin use in patients with carotid artery stenosis whether managed conservatively or offered an intervention.

Potential benefits associated with statin use
a. Conservative management
1. Stabilization of carotid plaques[4,8]
2. Reduction of intima-media thickness progression rates[4,8]
3. Reduction of stroke/death rates[4,8]
4. Reduction of myocardial infarction/cardiovascular event rates[4,8]
5. Improvement in renal function[31]
6. Reduction of contrast-induced nephropathy rates[29,30]
b. Surgical/endovascular management
1. Improvement in perioperative/periprocedural mortality/morbidity rates[20–23]
2. Reduction of perioperative/periprocedural and long-term transient ischemic attack/stroke rates[20–23]
3. Reduction of perioperative/periprocedural and long-term cardiovascular event and death rates[20–23]
4. Improvement in postoperative renal dysfunction[20–23]

production and inhibit the migration of macrophages as well as smooth muscle cell proliferation, thus stabilizing the carotid atherosclerotic plaque.[9–11] Statins also possess anti-inflammatory actions, *e.g.*, reduction of C-reactive protein (CRP), inflammatory/proinflammatory cytokines (such as interleukin-6 and 8) and adhesion molecule levels.[9–11] Furthermore, statins decrease platelet activity, enhance fibrinolysis and have considerable beneficial effects on carotid plaque composition and volume.[9–11] The beneficial effects of statins may be monitored by the increase in carotid plaque echogenicity using ultrasound and grey scale median (GSM) or integrated back scatter (IBS).[12] Statin treatment resulted in a significant reduction in carotid intima-media thickness (cIMT) and plaque progression rates.[8,13] Statins may also induce plaque regression.[13–15] Besides modulation of plaque progression, statins improve carotid plaque stability and reduce the risk of stroke and combined CVD events in AsxCS/SCS patients.[7,14] All-cause and cardiac mortality in AsxCS patients are very high.[16] Therefore, high-dose statin treatment is essential in these patients to reduce overall CVD mortality.

In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial, 4731 patients with a recent stroke/transient ischemic attack (TIA), LDL-C levels between 100 and 190 mg/dl (2.6–4.9 mmol/l) and no known coronary heart disease were randomly assigned to atorvastatin 80 mg/day *vs* placebo.[17] The mean LDL-C level during the trial was 73 mg/dl (1.9 mmol/l) for atorvastatin and 129 mg/dl (3.3 mmol/l) for placebo. During a median follow-up of 4.9 years, atorvastatin use was associated with a 5-year absolute reduction in stroke risk of 2.2% (265 *vs* 311 fatal or non-fatal strokes; 11.2 *vs* 13.1%, for atorvastatin *vs* placebo, respectively; adjusted hazard ratio [HR]: 0.84; 95% CI: 0.71–0.99; $p = 0.03$), despite an increase in hemorrhagic strokes (55 *vs* 33 strokes, respectively; adjusted HR: 1.66; 95% CI: 1.08–2.55; $p < 0.05$).[17] Patients with ≥50% LDL-C reduction had a 31% reduction in all-stroke risk (HR: 0.69; 95% CI: 0.55–0.87; $p = 0.0016$), including a 33% reduction in ischemic stroke (HR: 0.67; 95% CI: 0.52–0.86; $p = 0.0018$) without a significant increase in hemorrhagic stroke (HR: 1.04; 95% CI: 0.61–1.78; $p = 0.8864$).[18] In the subgroup of patients with carotid stenosis ($n = 1007$ of 4731 patients), atorvastatin reduced the risk of stroke by 33% (HR: 0.67; 95% CI: 0.47–0.94; $p = 0.02$) and the risk of TIA/stroke by 34% (HR: 0.66; 95% CI: 0.50–0.89; $p = 0.005$).[19]

Statins are also associated with several beneficial actions in AsxCS/SCS patients offered a carotid intervention. A detailed description of the benefits associated with statin use is beyond the scope of this review and are discussed in detail elsewhere.[20–23] Briefly, these include (among others) reduction in perioperative/periprocedural and long-term stroke/MI/death rates, as well as reduction of long-term restenosis rates in patients undergoing CEA/CAS.[20–23] Statin users undergoing carotid artery revascularization procedures ($n = 7893$) had almost 25% lower 1-year major adverse cardiac and cerebrovascular events compared with statin non-users (adjusted HR: 0.76; 95% CI: 0.70–0.83; $p < 0.001$).[24] These beneficial actions associated with statin use were observed regardless of the type of carotid revascularization procedure (CEA or CAS), symptomatic status or statin dosage.[24] Despite these multiple beneficial actions, up to 50% of patients may not be on routine statin treatment.[25,26]

In addition to reducing perioperative/periprocedural and long-term stroke/MI/death rates, statins have a beneficial effect on several other potential complications of carotid interventions.[27–31] For example, there is evidence that statins are associated with a reduced incidence of venous thromboembolism[27,28] as well as the development of contrast-induced nephropathy[29,30] in carotid patients undergoing CEA/CAS. Statins also improve microalbuminuria, hypertension and arterial stiffness.[31] These effects probably contribute to the reduction in vascular events.

Drawbacks associated with statin use

Statin intolerance and statin-associated adverse events may occur in up to 20% of patients.[32,33] Up to a third of patients on statins may present with statin-associated muscle symptoms; these include muscle weakness, muscle aches, stiffness, soreness, tenderness and muscle cramps.[32,33] Muscle myositis and rhabdomyolysis occur extremely rarely (<2/1000,000 statin users).[32,33] Statin-associated muscle symptoms often lead to drug discontinuation resulting in suboptimal CVD risk reduction in these patients.

Options for statin-intolerant patients include reduction of dose, change in statin formulation, alternate-day statin treatment and combination therapy with ezetimibe and PCSK9 inhibitors.[32,33] The strategies available to overcome statin intolerance are discussed in detail elsewhere.[34]

Liver toxicity and elevations in serum aspartate (AST) and alanine (ALT) aminotransferase activity are adverse effects that can occur with statin treatment.[35] Liver abnormalities caused by statin treatment vary from asymptomatic elevations of ALT and AST (which are generally moderate and temporary) to cholestatic or mixed hepatitis and liver injury.[35] On the other hand, conflicting evidence has recently been published.[36] A meta-analysis ($n = 14$ studies; 1,247,503 participants) demonstrated that statins may reduce the risk of developing non-alcoholic fatty liver disease (NAFLD; OR: 0.69; 95% CI: 0.57–0.84; $p = 0.0002$), as well as ALT (weighted mean difference [WMD]: −27.28; 95% CI: −43.06 to −11.51; $p = 0.0007$), AST (WMD: −10.99; 95% CI: −18.17 to −3.81; $p = 0.003$) and gamma-glutamyl transferase levels (WMD: −23.40; 95% CI: −31.82 to −14.98; $p < 0.00001$) in patients presenting with NAFLD at baseline.[36] The results from this meta-analysis suggest that statins may benefit liver function.

Another drawback of statin treatment is the increased risk of new-onset diabetes mellitus associated with statins.[37,38] This association is observed with all investigated statins (hydrophilic or lipophilic) and possibly represents a class effect.[37,38] However, the risk of new-onset diabetes with statins is much lower than with β-blockers, diuretics, niacin or steroids, thus rendering statin discontinuation due to fear for the development of new-onset diabetes rather unnecessary.[37,38] There may also be a deterioration of glycemic control in patients with diabetes.[39]

Even a brief discontinuation of statins might be harmful.[40] Abrupt stopping of statins might increase the risk of vascular events and CVD mortality.[40] The mechanisms implicated in the adverse effects in case of statin discontinuation include deterioration in endothelial function, elimination of the anti-inflammatory, antithrombotic and vasculoprotective effects of statins and consequently the development of adverse cardiovascular outcomes.[40,41] Therefore, statins should not be discontinued, especially in high risk patients, except for a very good reason.[40]

Benefits associated with PCSK9 inhibitor use

PCSK9 inhibitors is a 'novel' class of monoclonal antibodies that reduce LDL-C levels. PCSK9 inhibitors bind and inhibit circulating PCSK9,

a proteolytic enzyme that indirectly regulates serum LDL-C by causing the destruction of LDL receptors on the surface of liver hepatocytes.[42] By inhibiting circulating PCSK9, this results in increased LDL-C receptors and therefore a decrease in serum LDL-C.[42] Preliminary evidence suggests that, besides their ability to reduce LDL-C levels, PCSK9 inhibitors stabilize the vulnerable carotid atherosclerotic plaques[43,44] and reduce arterial wall inflammation[45] in patients with AsxCS/SCS. PCSK9 inhibitors were also reported to reduce carotid stiffness and improve cIMT in patients with familial hypercholesterolemia.[46,47]

In the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial, 27,564 patients with established atherosclerotic disease already on statin therapy were randomized to a PCSK9 inhibitor, evolocumab, or placebo (Fig. 1).[48,49] The median LDL-C levels of both groups at randomization was 2.4 mmol/l (interquartile range: 2.1–2.8). After 4 weeks, the mean percentage reduction in LDL-C levels with evolocumab was 55.6% (95% CI: 54.4–56.9; $p < 0.001$) compared with placebo to a median concentration of 0.8 mmol/L (interquartile range, 0.5–1.2). The difference between treatment groups persisted throughout the trial follow-up (56.3%; 95% CI: 54.5–58.2; $p < 0.001$) with a median LDL-C at 48 weeks of 0.8 (0.5–1.2) mmol/l in the evolocumab group.[48,49] After a median follow-up of 2.2 years, 469/27,564 patients (1.7%) experienced a total of 503 strokes of which 421 (84%) were ischemic. Evolocumab significantly reduced all-strokes and ischemic strokes with no difference in hemorrhagic strokes (Fig. 1).[48,49] Therefore, in FOURIER a more aggressive LDL-C lowering to a median of 30 (interquartile range: 19–46) mg/dl (or 0.78 [interquartile range: 0.49–1.2] mmol/l) was paralleled with a greater reduction in ischemic and all strokes, without an increase in hemorrhagic strokes.[48,49]

Similar results were obtained in the Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab (ODYSSEY OUTCOMES) trial (Fig. 2).[50] The ODYSSEY OUTCOMES trial compared alirocumab 75 mg administered subcutaneously every 2 weeks *vs* placebo in 18,924 patients with recent acute coronary syndrome. All patients of both groups should have LDL-C levels ≥70 mg/dl (1.8 mmol/l) at study entry. After a median follow-up of 2.8 years, alirocumab reduced the risk of any stroke and ischemic stroke without increasing hemorrhagic stroke (Fig. 2).[50] The treatment effect appeared greater for patients with higher baseline LDL-C, suggesting that patients with a higher risk at baseline have a larger benefit with alirocumab.[50] These results once again suggest that intensive LDL-C lowering with statins plus PCSK9 inhibitors reduces the risk of ischemic stroke.

PCSK9 inhibitors exert their effects on carotid plaque size and volume by regression of carotid plaque lipid content and neovasculature.[51,52] The regression in plaque composition and concurrent plaque stabilization may be an additional mechanism responsible for the reductions in cerebrovascular and CVD events.[51,52]

A recent systematic review and meta-analysis ($n = 28$ RCTs; 89,115 participants) compared the efficacy of PCSK9 inhibitors *vs* ezetimibe and *vs* placebo on clinical and lipid-lowering outcomes.[53] Compared with placebo, PCSK9 inhibitors significantly reduced the incidence of stroke (relative risk [RR]: 0.75; 95% CI: 0.66–0.86; $p < 0.0001$), MI (RR: 0.81; 95% CI: 0.76–0.87; $p < 0.00001$) and major adverse CVD events (MACEs; RR: 0.83; 95% CI: 0.79–0.88; $p < 0.00001$).[53] However, there was no difference in MACEs between PCSK9 inhibitors and ezetimibe (RR: 0.70; 95%: CI: 0.40–1.20; $p = 0.20$).[53] Secondary analyses showed that PCSK9 inhibitors were not superior to ezetimibe in preventing stroke (RR: 0.38; 95% CI: 0.09–1.69; $p = 0.20$), MI (RR: 0.95; 95% CI: 0.47–1.90; $p = 0.88$) and CVD death (RR: 0.44; 95% CI: 0.14–1.43; $p = 0.17$).[53]

The addition of a PCSK9 inhibitor to statin therapy appears to have a beneficial effect in patients undergoing CAS.[54] Patients initiated on a PCSK9 inhibitor (besides their standard statin treatment) before undergoing CAS had a significant reduction in new ischemic lesions on diffusion-weighted imaging compared with patients only receiving standard statin treatment (11.5 *vs* 41.2%, respectively; $p = 0.029$).[54] Preliminary evidence suggests that preoperative administration of PCSK9 inhibitors stabilize carotid plaques and reduce perioperative complications in patients undergoing CAS.[55] The beneficial effects of PCSK9 inhibitors on carotid plaque composition and regression will be investigated in the on-going CARotid plaqUe StabilizatiOn and regression with evolocumab (CARUSO) study.[56]

Drawbacks associated with PCSK9 inhibitor use

PCSK9 inhibitors are well-tolerated and safe with only mild side-effects reported.[57–59] These include mild injection-site reactions and nasopharyngitis. PCSK9 inhibitors are not associated with hepatotoxicity,

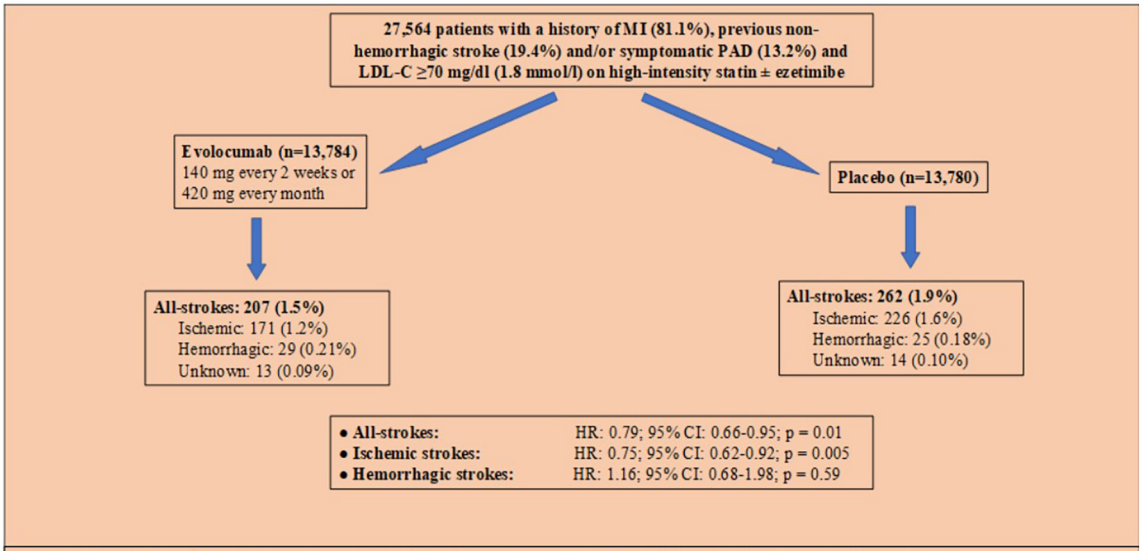

Fig. 1. Design and stroke outcomes in the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial.[48,49]

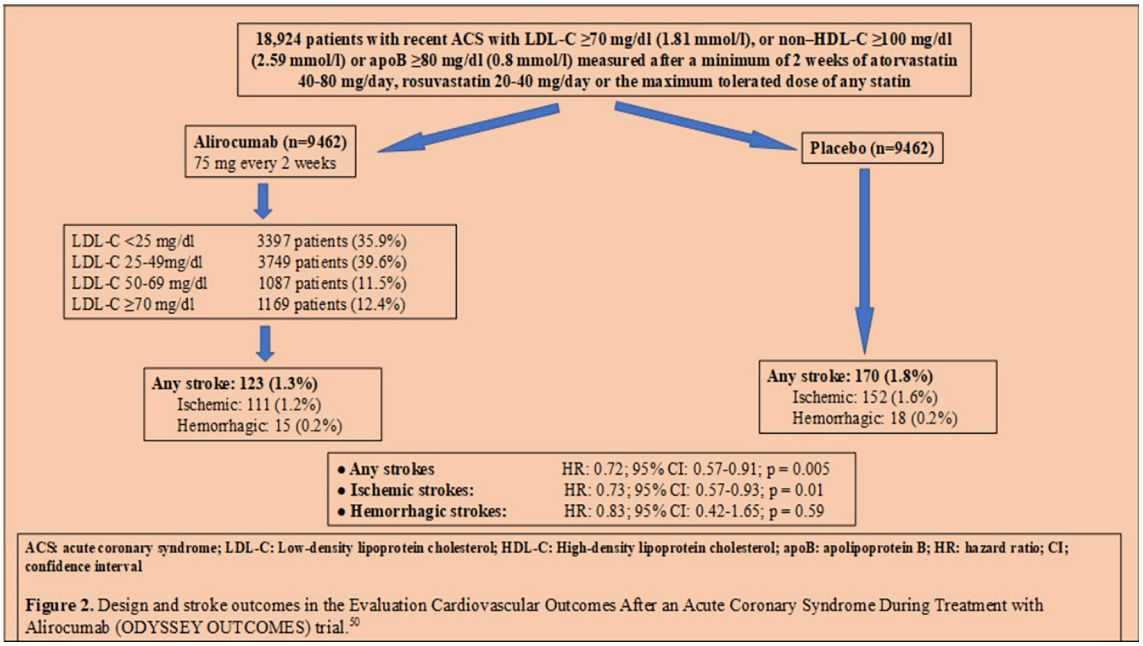

Fig. 2. Design and stroke outcomes in the Evaluation Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab (ODYSSEY OUTCOMES) trial.[50]

muscle-related complaints or increase in muscle/liver enzymes.[57–59] They have no clinically significant drug-drug interactions and no increased risk of cognitive impairment. Their main drawback is their high cost (around $5850/year).[57]

Benefits associated with other lipid-lowering agents

A population-based cohort study from South Korea investigated the long-term clinical efficacy of fenofibrate and/or omega-3 fatty acid use with regards to mortality and CVD outcomes in type 2 diabetic patients ($n = 10{,}114$; 5057 fenofibrate users *vs* 5057 non-users).[60] CVD death (1.8 *vs* 3.1 per 1000 person-years; HR 0.59; 95% CI: 0.352–0.987; $p = 0.0446$), all-cause death (7.6 *vs* 15.3 per 1000 person-years; HR: 0.437; 95% CI: 0.340–0.562; $p < 0.0001$), and stroke (6.5 *vs* 8.6 per 1000 person-years; HR: 0.621; 95% CI: 0.463–0.833; $p = 0.0015$) were significantly lower in the fenofibrate group. Furthermore, when outcomes were stratified in quartiles for duration of fenofibrate use, the benefit for stroke increased even more for patients with fenofibrate use >486 days (HR: 0.347; 95% CI: 0.226–0.532; $p < 0.0001$).[60]

In a prespecified analysis of the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), 18,144 patients with LDL-C 50–125 mg/dl were randomized to simvastatin/ezetimibe *vs* simvastatin/placebo following an acute coronary syndrome.[61] Outcomes were stratified by the presence/absence of diabetes mellitus.[61] In diabetic patients, the addition of ezetimibe resulted in a 39% reduction in the incidence of ischemic stroke (HR: 0.61; 95% CI: 0.46–0.82; $p = 0.001$), whereas no significant difference was observed for non-diabetic patients (HR: 0.91; 95% CI: 0.74–1.13; $p = 0.399$).[61] Ezetimibe further reduces vascular events when added to statin therapy.[62]

The combination of 2 lipid-lowering drugs into a single pill improves patient adherence to lipid-lowering treatment compared with 2 separate drugs.[63] A single-pill statin/ezetimibe combination was initiated in 5351 and a two-pill combination in 2881 patients. At 1 year, patients prescribed a single-pill combination had an 87% (95% CI: 75–99%) greater odds of being highly adherent and a 79% (95% CI: 72–84%) lower odds of being poorly adherent to treatment.[63] A higher adherence translated to a 55% reduced risk of cardiovascular outcomes compared with a low adherence.[63]

A meta-analysis of 78 trials ($n = 266{,}973$ patients; cumulative exposure: 946,582 person-years; mean follow-up: 3.5 years) was performed to determine the effects of various cholesterol lowering treatments on the risk of stroke and its relationship with the extent of cholesterol lowering.[64] Information regarding total stroke (*i.e.* fatal and non-fatal) was available for 123,293 patients allocated to an active cholesterol-lowering treatment and 131,219 controls.[64] Overall, 2993 individuals suffered a stroke in the treated group *vs* 3724 in the control group (2.4 *vs* 2.8%, respectively; OR: 0.88; 95% CI: 0.83–0.94; $p < 0.001$). Statins significantly reduced the risk of total stroke by 15% (OR: 0.85; 95% CI: 0.78–0.92; $p < 0.001$), while fibrates did not (OR: 0.98; 95% CI: 0.86–1.12; $p = 0.788$) and neither did other cholesterol lowering drugs (OR: 0.81; 95% CI: 0.61–1.08; $p = 0.155$) or non-pharmacological treatments (*e.g.*, ileal bypass surgery; OR: 0.92; 95% CI: 0.44–1.93; $p = 0.830$).[64] It was concluded that the reduction of stroke by cholesterol-lowering treatment is proportional to the percent of cholesterol lowering with an adjusted relative risk of 0.8% reduction for each 1% decrease in total cholesterol.[64] Such benefit is mainly attributed to the reduction of LDL-C levels.[62]

Conclusions

Statins have an established role in both the conservative and the surgical/interventional management of patients with carotid artery stenosis. Their use in vascular patients is supported by guidelines with Level I Evidence.[4–7] Potential drawbacks are the statin-related adverse effects, namely muscle aches and liver toxicity. These adverse effects are usually benign, but may lead to drug discontinuation in a considerable percentage of vascular patients.[32,33] Such discontinuation may be associated with an increased risk of a vascular event.[32,33]

PCSK9 inhibitors are promising agents which are also associated with pleiotropic benefits besides LDL-C lowering. PCSK9 inhibitors are safe and well-tolerated. Their major drawback is their high cost. Future research should aim at generic or oral formulations of PCSK9 inhibitors. In 5 years, PCSK9 inhibitors, on top of statin therapy or possibly even as a monotherapy, could play a key role in the management of AsxCS/SCS patients.

The reduction in stroke rates is proportional to the reduction of LDL-C levels achieved by different lipid-lowering agents. Patients with carotid stenosis achieve further reductions in stroke rates.

The benefits associated with lowering LDL-C with statins or non-statin lipid lowering agents (*e.g.*, PCSK9 inhibitors) outweigh the risks and potential side-effects. Irrespective of their LDL-C levels, all carotid patients should receive high-dose statin treatment ± ezetimibe or PCSK9 inhibitors for reduction not only of LDL-C levels, but also of stroke, CVD mortality and coronary event rates.

Conflicts of interest

Dimitri P. Mikhailidis has given talks, acted as a Consultant or attended conferences sponsored by Amgen and Novo Nordisk. Jonathan Golledge has received honoraria for speaking by Amgen and Bayer. Seemant Chaturvedi is a Consultant to Astra Zeneca. The other authors have no conflicts of interest.

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