Cholesterol, carotid artery disease and stroke: what the vascular specialist needs to know

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Abstract: Hypercholesterolemia is a risk factor for carotid artery stenosis and stroke. Statins are the main drugs for the management of hypercholesterolemia and they are strongly recommended by international guidelines for the management of vascular patients. The present review will focus on the associations between cholesterol, carotid artery stenosis and stroke and will cover several topics, including the conservative and perioperative/periprocedural management of carotid patients, the effect of statins on contrast-induced nephropathy developing after endovascular carotid interventions, the role of statin loading prior to endovascular procedures, as well as the indirect beneficial effects of statin treatment on renal function. It will also discuss the topics of statin intolerance and alternative cholesterol-lowering options for statin-intolerant vascular patients. Cholesterol levels play a prognostic role in carotid patients with regards to both short- and long-term stroke and mortality rates. Physicians should keep in mind the pivotal role of cholesterol levels in determining cardiovascular outcomes and the pleiotropic beneficial effects associated with statin use and should not miss the opportunity for cardiovascular risk reduction with aggressive statin treatment.

Keywords: Cholesterol; statins; carotid artery stenosis; stroke

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Introduction

In 2017, the European Society for Vascular Surgery (ESVS) Writing Group (1) updated the 2009 ESVS guidelines (2) regarding the management of patients with atherosclerotic carotid and vertebral artery disease. The 2017 ESVS Guideline committee (1) adopted the prevention classification proposed by the Institute of Work and Health (3). According to this classification (3), primary prevention aims to prevent carotid and vertebral disease from ever developing, secondary prevention aims at reducing the clinical impact of asymptomatic carotid and vertebral artery stenoses [i.e., from causing a transient ischaemic attack (TIA) or stroke], while the goal of tertiary prevention is to reduce the risk of recurrent TIA or stroke in patients who present with a TIA or stroke secondary to

carotid or vertebral artery stenoses. The ESVS Guidelines only dealt with secondary and tertiary prevention; primary prevention was outside the scope of these guidelines (1).

Several risk factors have been identified for the development of vascular disease, among others smoking, hypertension, hypercholesterolemia/hyperlipidemia, obesity and diabetes mellitus (1,2). Statins are the first-line agents for the treatment of hypercholesterolemia (4-6). Besides their cholesterol-lowering action, statins have pleiotropic effects (7-9), some of which will be discussed subsequently.

We undertook a critical review of the literature aiming at issues related with cholesterol, carotid artery disease and stroke which are of interest to vascular surgeons/vascular specialists/stroke physicians.

Methods

PubMed/MedLine was searched until December 1, 2019 for reports looking into the association between cholesterol, carotid artery stenosis and stroke. By use of the search terms "cholesterol AND carotid", this produced 6,008 items. Case reports, brief communications, letters to the Editor and Editorials were excluded.

The title and abstract of all these articles were read by one of the authors (KI Paraskevas). When relevant, the full-text article was retrieved. The reference lists of the full-text articles were manually searched for additional studies, which were also considered. Only reports in English were considered.

The identified studies were included in our review if they covered at least one of the following three topics: (I) statins and conservative management of carotid stenosis, (II) statins and surgical/endovascular management of carotid stenosis, and/or (III) effects of high *vs.* moderate statin dose on patients with carotid stenosis. We also briefly discuss the various available options for the statin intolerant patients.

Results

Statins exert several effects on patients with carotid stenosis whether managed conservatively or scheduled for carotid endarterectomy (CEA)/carotid artery stenting (CAS). These effects include reduction in stroke/TIA and death rates, as well as reduction in myocardial infarction (MI) and cardiac event rates. Statins also exert a number of miscellaneous beneficial effects on these patients (e.g., improvement of renal function).

A discussion of the beneficial effects of statin treatment on patients with carotid artery stenosis is presented.

Effects of statins on patients with carotid stenosis managed conservatively

Statins are essential in the conservative management of patients with carotid artery stenosis (10). At the molecular level, statins increase nitric oxide production, improve endothelial function, reduce low-density lipoprotein cholesterol (LDL-C) oxidation, inhibit the migration of macrophages and smooth muscle cell proliferation, thus stabilizing the carotid atherosclerotic plaque (11-13). Statins exert several anti-inflammatory actions, namely they reduce C-reactive protein levels, inflammatory and proinflammatory cytokines (e.g., interleukins 6 and 8) and adhesion molecules; they also decrease platelet activity and enhance fibrinolysis (11-13). Initiation of statin treatment in patients with carotid artery stenosis leads to a rapid improvement in carotid adventitial angiogenesis/carotid plaque neovascularization (14) and has considerable beneficial effects on carotid plaque composition and volume (15,16). Statin administration in these patients not only lowers the risk of vascular events and cardiac death, but also reduces carotid intima media thickness progression rates (11). It has been hypothesized that statins may lead to carotid plaque regression (17,18). However, even if intensive statin treatment does not cause carotid plaque regression, achieving LDL-C levels <70 mg/dL is associated with a reduction in progression rates of carotid artery atherosclerosis (19).

Besides a risk factor for carotid stenosis, dyslipidemia is a risk factor for ischemic stroke (20). Elevated LDL-C levels appear to increase the risk of ischemic stroke and some other stroke subtypes (e.g., lacunar and cardioembolic strokes) (20). Statins are strongly indicated in patients with carotid stenosis to reduce strokes not only of carotid, but also of other origin. A subgroup analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial (n=4,731 patients; mean follow-up: 4.9 years) demonstrated that intensive lipid lowering with atorvastatin (80 mg/day *vs.* placebo) reduces the risk of both cerebrovascular and cardiovascular events in patients both with and without carotid stenosis (21). However, patients with carotid stenosis may have greater benefit (21). In SPARCL, there was also a reduction in coronary events, despite the fact that none of the SPARCL participants had no clinically evident coronary artery disease (CAD) at entry into the trial (22). Optimal control was defined as

LDL-C <70 mg/dL, high-density lipoprotein cholesterol (HDL-C) >50 mg/dL, triglyceride levels <150 mg/dL and a systolic to diastolic blood pressure rate of 120/80 mmHg. The risk of stroke decreased in proportion to the number of risk factors controlled. For those achieving control of 1, 2, 3 and 4 factors the risk of stroke decreased by 2%, 22%, 38% and 65%, respectively (22). Statin treatment is associated with a reduced stroke risk in patients with carotid stenosis suffering a TIA (23). Although the stroke risk is not eliminated, carotid patients receiving statin treatment are less likely to experience a moderate or severe stroke (24).

The role of aggressive lipid-lowering treatment for carotid patients after a carotid-related ischemic stroke is not firmly established. A study from Taiwan investigated the influence of total cholesterol levels on 5-year outcomes of ischemic stroke patients with high-grade internal carotid artery stenosis and post-stroke functional dependence (25). Of 196 acute ischemic stroke patients with high-grade internal carotid stenosis, 117 (59.7%) had ≥200 mg/dL and 79 (40.3%) had <200 mg/dL total cholesterol levels at admission. In multivariate Cox regression analysis and after adjustment for clinical predictors of adverse outcomes, lower total cholesterol levels were a significant predictor of 5-year mortality (HR: 1.88; 95% CI: 1.09–3.23; P=0.023) (25). This association prompted the authors to support that aggressive treatment of hyperlipidemia should be carefully considered in ischemic stroke patients with high-grade carotid stenosis and post-stroke functional dependence, although they admitted that it could reduce the risk of atherosclerotic cardiovascular diseases and stroke recurrence in some stroke patients (25).

Effects of statins on patients undergoing CEA/CAS

Besides the conservative management, statins are also essential in the perioperative/periprocedural period of carotid patients undergoing CEA/CAS (26,27). Statins reduce fatal/non-fatal MIs, ventricular tachyarrhythmias, acute congestive heart failure and cardiac death in those patients. Furthermore, by stabilizing carotid plaques (10-13), statins are associated with reduced perioperative TIA and stroke rates. Statins are also associated with reduced recurrent carotid stenosis and long-term stroke/mortality rates (26,27).

Pre-interventional statin treatment has a protective effect against peri-interventional stroke, MI or death in patients treated with CEA/CAS (26,28). Pre-interventional use of statins not only reduces cardiovascular events and mortality, but may also have an important effect on the anatomic durability of CEA (29). Statin pretreatment reduces the incidence of periprocedural complications after CAS dose-dependently; the higher the statin dosage pre-procedurally the lower the incidence of periprocedural complications (30).

Statins are safe agents, with muscle and liver toxicity being the main adverse effects (31,32). Other adverse effects are much less common and include gastrointestinal adverse effects (e.g., nausea, dyspepsia, flatulence and diarrhea/constipation), skin side-effects (e.g., alopecia, rash, lichenoid eruption, etc), central nervous adverse effects (e.g., depression, insomnia, headaches) and erectile dysfunction (31,32). New-onset diabetes is another major adverse effect (31,32). Overall, however, the benefits associated with statin use by far outweigh their possible side-effects.

Effect of high-dose statin treatment on strokes rates

According to the 2018 ESVS carotid guidelines (1), statin therapy is recommended for the prevention of long-term stroke, MIs and other cardiovascular events in patients with symptomatic carotid disease. This a strong recommendation (Class I; Level of Evidence: A). Furthermore, it is recommended that patients start statin therapy prior to endarterectomy or stenting and that statins should not be stopped during the perioperative period and should be continued long-term (Class I; Level of Evidence: B) (1).

It is of paramount importance that patients with carotid artery stenosis do not just receive "any" statin dosage, but the maximal tolerated dosage (33). In the Treating to New Targets (TNT) Study (34), 10,001 patients with documented coronary disease were randomized to atorvastatin 10 *vs.* 80 mg/day and were followed-up for a median of 4.9 years. Mean LDL-C levels during the study were 101 mg/dL in the 10 mg group and 77 mg/dL in the 80 mg group. Patients in the high-dosage group demonstrated a 25% reduction in stroke rates compared with the low-dosage group (HR: 0.75; 95% CI: 0.59–0.86; P=0.021) (34). Cerebrovascular events (TIA or fatal/non-fatal stroke) were reduced by 23% in the 80 mg group (HR: 0.77; 95% CI: 0.64–0.93; P=0.007). Each 1 mg/dL reduction in LDL-C was associated with a 0.6% relative risk reduction in cerebrovascular events (P=0.002) and a 0.5% relative risk reduction in stroke (P=0.041). The conclusion reached was that aggressive treatment of LDL-C with 80 mg/day atorvastatin reduces both ischemic stroke and cerebrovascular events by an additional 20–25%

compared with the 10 mg/day dose, without an increase in hemorrhagic strokes (34).

These findings were verified by a meta-analysis of individual participant data from 21 randomized trials (n=129,526 patients; median follow-up: 4.8 years) of more *vs.* less intensive statin therapy (35). This meta-analysis showed that aggressive statin treatment was associated with a 16% further reduction in the incidence of ischemic stroke compared with less intensive statin treatment (relative risk: 0.84; 95% CI: 0.71–0.88; P=0.005) (35). Consequently, vascular surgeons should ensure that carotid patients receive the maximal tolerated statin dosage (33).

Aggressive LDL-C level reduction using intensive lipid-lowering therapy with statins is essential after a TIA or an ischemic stroke. The recent Treat Stroke to Target study compared outcomes in patients with an ischemic stroke in the previous 3 months or a TIA within the previous 15 days having achieved LDL-C levels of <70 mg/dL (1.8 mmol/L) *vs.* 90–110 mg/dL (2.3-2.8 mmol/L) (36). All patients had evidence of cerebrovascular or coronary atherosclerosis and received a statin and/or ezetimibe. The composite primary end-point (ischemic stroke, MI, new symptoms leading to urgent coronary or carotid revascularization or death from cardiovascular causes) occurred in fewer patients in the lower compared with the higher LDL-C target group (8.5% *vs.* 10.9%, respectively; adjusted HR: 0.78; 95% CI: 0.61–0.98; P=0.04) (36). On the other hand, the incidence of intracranial hemorrhage and newly diagnosed diabetes mellitus did not differ between the two groups (36). This study demonstrated the importance of intensive lipid-lowering treatment with high-dosage statins for reduction of the risk of secondary cardiovascular events in patients after an ischemic stroke (36). Stroke or TIA patients at very high vascular risk who do not achieve adequate LDL-C lowering with maximal tolerated statin dose may be eligible for more intensive cholesterol lowering treatment with protein convertase subtilisin-kexin type 9 (PCSK9) inhibitors (4,37).

Miscellaneous effects of statins on patients with carotid stenosis

Besides the above-mentioned actions, routine statins administration in carotid patients may be associated with several beneficial effects, such as:

(I) Improved renal function: besides reducing carotid intima media thickness progression rates (38,39), statin treatment improves renal function in vascular patients (39,40). This is important as renal function *per se* predicts vascular risk (41). Vascular patients often have impaired renal function; statins can improve proteinuria and glomerular filtration loss in patients with impaired kidney function (42). By improving renal function, statins reduce cardiovascular disease risk and delay the progression of chronic kidney disease (42).

(II) Statin loading dose: a statin loading dose before vascular interventions (e.g., peripheral endovascular interventions or carotid artery stenting) is associated with several benefits with regards to cardiovascular outcomes, total mortality and/or contrast-induced acute kidney injury (43,44). In the Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty-9 Clopidogrel and Atorvastatin Treatment During Carotid Artery Stenting (ARMYDA-9 CAROTID) Study (43), patients were randomized to receive an atorvastatin 80 mg loading dose given a mean of 12 h before carotid intervention with an additional 40-mg dose approximately 2 h before the procedure *vs.* no statin reload. The 1-month incidence of TIA/stroke or new ischemic lesions on cerebral DW-MRI was 18.4% in patients with an atorvastatin reload *vs.* 35% in the no statin reload arm (P=0.031) (43). Thus, a statin loading dose should be considered before any carotid intervention to improve cardiovascular outcomes.

(III) Statins and contrast-induced nephropathy (CIN): CIN is increasingly being reported following endovascular procedures (45-47). CIN is not only associated with prolonged hospitalization, but also with increased cardiovascular/renal morbidity and all-cause mortality (48,49). Due to their nephroprotective effects, statins may reduce the occurrence of CIN in carotid patients undergoing endovascular interventions (45-47). This effect is coupled with reduction of cardiovascular disease risk and improved morbidity and mortality rates.

A study from China aiming to investigate the optimal dose of atorvastatin for the treatment of CIN randomized 76 patients undergoing elective CAS to 3 different doses of atorvastatin [low dose: 20 mg (n=30); intermediate dose: 40 mg (n=24); high dose: 60 mg (n=22)] (50). The incidence of CIN in the high-dose group was significantly lower than the intermediate or the low-dose groups (0 *vs.* 8.3% *vs.* 13.3%, respectively; for all associations, P<0.05) (50).

Statin intolerant patients: what options are available?

According to the 2019 European Society of Cardiology/ European Atherosclerosis Society (ESC/EAS) guidelines for the management of dyslipidaemias (4), for individuals at very high cardiovascular risk, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (55 mg/dL) is strongly recommended both in primary (Class I; Level of Evidence: A) and in secondary prevention (Class I; Level of Evidence: A). For LDL-C lowering, a high-intensity statin up to the highest tolerated dose is recommended (Class I; Level of Evidence: A) (4). If the goals are not achieved with the maximum tolerated dose of a statin, combination with ezetimibe (Class I; Level of Evidence: B) or with a PCSK9 inhibitor is recommended (Class: I; Level of Evidence: A) (4). In patients who experience a second vascular event within 2 years (not necessarily of the same type as the first event) while taking maximally tolerated statin-based therapy, the ESC/EAS guidelines suggest that an LDL-C goal <1.0 mmol/L (<40 mg/dL) may be considered (4).

As more and more stringent LDL-C targets are pursued, statin intolerance will be observed in an increasing number of patients. Statin discontinuation because of statin intolerance or related side-effects may be harmful and lead to adverse outcomes (51). In case of statin intolerance, several options may be available. These include switching to a different statin, reducing statin dosing, alternate day statin dosing, use of lipid-lowering drugs other than statins (e.g., ezetimibe, bile acid sequestrants and fibrates, alone or in combination) or use of PCSK9 inhibitors (52).

Several recent randomized controlled trials have evaluated the effects of LDL-C lowering by PCSK9 inhibitors [e.g., the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial (53,54), the Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy (ODYSSEY LONG TERM) trial (55), the Open-label Study of long-term Evaluation against LDL Cholesterol (OSLER) trial (56) and the Study of PCSK9 Inhibition and the Reduction of Vascular Events (SPIRE) (57)]. All these studies showed that LDL-C lowering with PCSK-9 inhibitors was coupled with a significant reduction in MI, stroke and cardiovascular event rates (53-57). These promising results suggest that PCSK-9 inhibitors may gradually become key pharmacological agents for the management of cardiovascular patients and the reduction of MI and stroke rates.

Conclusions

Cholesterol levels play a pivotal role in the carotid patients not only for the progression of carotid artery stenosis, but also for the development of cerebrovascular symptoms and overall cardiovascular risk. Statins comprise the gold standard for the management of carotid patients and should be initiated immediately upon establishment of the diagnosis of carotid artery stenosis (58). Physicians should keep in mind the pleiotropic beneficial effects associated with statin use and should not miss the opportunity for cardiovascular risk reduction with aggressive statin treatment.

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