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Recommendations for lipid modification in patients with ischemic stroke or transient ischemic attack: A clinical guide by the Hellenic Stroke Organization and the Hellenic Atherosclerosis Society

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Abstract

This document presents the consensus recommendations of the Hellenic Stroke Organization and the Hellenic Atherosclerosis Society for lipid modification in patients with ischemic stroke or transient ischemic attack. This clinical guide summarizes the current literature on lipid management and can be of assistance to the physicians treating stroke patients in clinical practice.

Keywords

Recommendations, lipid modification, ischemic stroke, low-density lipoproteins, Hellenic Stroke Organization and the Hellenic Atherosclerosis Society

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Introduction

Stroke remains one of the leading causes of death and a major cause of long-term disability in most developed countries worldwide, despite the significant progress in prevention and acute treatment. In Greece, the annual incidence of stroke in subjects aged 45–84 years was 319.4 per 100,000 people, with an overall 28-day case fatality of 26.6% according to a population-based study.[1] Patients with ischemic stroke commonly suffer from other major cardiovascular (CV) events due to increased prevalence of multiple CV risk factors. Among them, dyslipidemia is one of the most important risk factors prevailing in up to 28% of patients with ischemic stroke.[2] Dyslipidemia is the basic underlying mechanism of atherothrombosis and a common risk factor of ischemic stroke irrespective of the underlying pathogenetic mechanisms and increasing the risk for future CV events.[3] As such, patients with previous ischemic stroke tend to have significantly increased risk for stroke recurrence, major CV events, and higher mortality.[3] Therefore, implementation of optimal secondary CV prevention strategies is warranted. Nevertheless, stroke is associated with increased economic burden due to treatment and poststroke care, with high direct (hospital care, medications, medical visits, outpatient rehabilitation, and orthopedic aids) and indirect (income loss due to absence from work) costs.[4]

The Hellenic Stroke Organization (HSO) and the Hellenic Atherosclerosis Society (HAS) are actively involved in the prevention and management of CV diseases, including stroke, promoting education, and excellence in the field. The development and publication of clinical recommendations adapted to the Hellenic National Health System is an important tool to support these goals and may serve as a useful clinical guide for physicians who treat stroke patients in clinical practice, such as internists, general practitioners, neurologists, cardiologists, etc. The present consensus paper puts forward the HSO and HAS clinical recommendations for the management of dyslipidemia in patients with ischemic stroke or transient ischemic attack (TIA).

Methods

The Board of Directors of the HSO and HAS considered several Greek experts in the field as potential leaders of the working group and unanimously selected the first two authors (DS and GN). After accepting the invitation, the first two authors assembled the core working group which consisted of experienced stroke scientists and experts in atherosclerosis and clinical lipidology (DS, GN, EL, HM) who set the preliminary recommendations of the clinical guide, based on a non-systematic literature search for meta-analyses, clinical trials, and case cohort series on lipid modification strategies in patients with previous ischemic stroke. The core working group prepared the first draft of the document. At the second stage, a larger group of Greek stroke scientists, clinical lipidologists, and dietitians serving in Greece or abroad were invited to comment on and critically contribute to the first draft. After several rounds of constructive discussions and modifications of the first draft, the working group reached to full agreement among its members on every recommendation and concluded to the final draft. Due to restricted resources and given that the members of the working group serve in several countries in Europe and given the current travel restrictions due to the COVID-19 pandemic we did not organize joint meetings in person. The working group did not include nurse and patient representative. No funding or sponsorship or any kind of support was obtained to support the development of this document.

Quality of evidence

To evaluate the quality of the existing evidence and build the recommendations we used the grading system of the American College of Chest Physicians[5] which had been previously used in other HSO clinical recommendations.[6–8] This system classifies recommendations as strong (Grade 1) or weak (Grade 2), based on the possible benefits, risks, burdens, and cost. Additionally, the quality of evidence was classified as high (Level A), moderate (Level B), or low (Level C) according to the study design, the consistency of the results, and the directness of the evidence (Table 1).

Recommendations

Lifestyle modification should be recommended to all patients with ischemic stroke or TIA (1B)

Table 1. Levels of evidence and grades of recommendations

Level of evidence
Level A: randomized trials without significant restrictions or conclusive evidence from observational studies Level B: randomized trials with significant restrictions or strong evidence from observational studies Level C: observational studies on patient series or expert opinions
Grade of recommendation
1: The recommendation is powerful as the benefit of the selection clearly outweighs the risk (or vice versa) 2: The recommendation is weak as it is not clear if the benefit of the selection outweighs the risk

The initial non-pharmacological approach is very important in patients at very high risk of future CV events, such as stroke or TIA patients, increasing the potential of a better physician-to-patient interaction, and adherence to treatment.

Diet modification is a basic component of the non-pharmacological approach in patients with previous CV event. Patients with ischemic stroke should avoid saturated fat (<10% of total energy intake) and trans fatty acids (<1% of total energy intake).[9] Dietary fat should be provided in the form of unsaturated and especially omega-3 polyunsaturated fatty acids mainly by vegetable oils, fish, and nuts. A total fat intake higher than 35% of total energy intake should be avoided, especially for people with mild to moderate hypercholesterolemia. Recently, one study including 92,978 individuals from two prospective cohort studies, showed that higher intake of olive oil was associated with 14% lower risk of CV events [pooled hazard ratio (HR): 0.86; 95% confidence interval (CI): 0.79–0.94].[10] Additionally, olive oil, which is the basic compound of the Mediterranean diet, has been shown to significantly reduce CV mortality among patients at high risk of CV events.[11] These patients should also be encouraged to adhere to Mediterranean diet by increasing the intake of fish, whole grain products, and especially vegetables, fruits, and legumes which are related with a significant reduction in low-density lipoprotein cholesterol (LDL-C).[12] In a meta-analysis of four randomized controlled trials (RCTs) including 12,293 patients at high risk of CV events, adherence to Mediterranean diet was associated with a significant reduction in the risk of the composite outcome of CV mortality and stroke [relative risk (RR): 0.55, 95% CI: 0.39, 0.76].[13] Similarly, a meta-analysis of 20 prospective cohort studies involving 682,149 participants showed that Mediterranean diet was associated with lower risk of ischemic stroke (RR 0.86, 95% CI 0.81–0.91; 9 studies) and hemorrhagic stroke (RR 0.83, 95% CI 0.74–0.93; 8 studies).[14]

Adherence to the Mediterranean diet should be accompanied with salt intake restriction, which follows a linear correlation to arterial pressure reduction, resulting to a significant reduction in stroke and coronary event rates.[15]

Patients with previous CV events or stroke should be encouraged to quit smoking[16] and be physically active. One study including 1072 smokers at the time of ischemic stroke showed that patients who quitted smoking had a significant reduction of the five-year risk of CV events (15.7% vs. 22.6%, HR 0.66, 95% CI 0.48–0.90).[17]

Early after stroke, apart from rehabilitation strategies, a physical exercise program should be designed due to the beneficial effects in neurological disability and the metabolic parameters.[18] Especially, after stroke two exercise strategies, a gradually increasing in intensity exercise with a constant 30-min duration and a low-intensity exercise, gradually increasing in duration to up to 60 min have been shown to have beneficial effects in blood pressure and lipid parameters, instead of the conventional therapeutic exercise consisting mainly of strength, balance, and range of motion activities.[19]

Despite a general perspective of the beneficial effect of mild red wine consumption, patients with previous stroke should be encouraged to quit alcohol due to a linear correlation of alcohol intake with an increased risk of stroke (RR: 1.27; 95% CI: 1.13–1.43) and intracerebral hemorrhage (RR: 1.58; 95% CI: 1.36–1.84).[20]

Patients with ischemic stroke or TIA should receive lipid-modifying treatment with high-intensity statin (1A)

The Heart Protection Study (HPS) was the first large-scale randomized controlled trial of simvastatin in secondary prevention to include patients with cerebrovascular disease as per protocol (Table 2). HPS showed that statin treatment significantly reduced the rate of major CV events and stroke.[21] In the group of patients with previous stroke, treatment with simvastatin had no effect on stroke recurrence rate, but was associated with a significant reduction of major vascular events by 20% (24.7% vs. 29.8%; $p = 0.001$) irrespective of the stroke subtype.[22] Later on, two large randomized control trials of statins in non-cardioembolic stroke patients showed significant reduction in stroke recurrence and CV events, namely the Japan Statin Treatment Against Recurrent Stroke (J-STARS)[9] and the Stroke Prevention by Aggressive Reduction of Cholesterol Levels (SPARCL).[10]

The J-STARS study included Chinese patients with a non-cardioembolic stroke who were allocated to low pravastatin dose or placebo. Patients in the pravastatin treatment arm showed a significant reduction in atherothrombotic stroke recurrence rate (0.21 vs. 0.64%/year, HR: 0.33, 95% CI: 0.15–0.74), but with no effect on total strokes and TIAs.[23] In the SPARCL study, patients with a previous non-cardioembolic stroke who had been treated with atorvastatin 80 mg daily had an absolute 2.2% risk reduction for fatal and nonfatal stroke (HR: 0.84; 95% CI: 0.71–0.99), while major CV events were reduced by 3.5% (HR: 0.80; 95% CI: 0.69–0.92) compared to placebo.[24] In this study, atorvastatin had no effect on mortality but patients on active treatment had a significant increase (HR: 1.66; 95%CI: 1.08–2.55) in the risk of ICH.[24] An exploratory analysis of the SPARCL trial showed that high-dose atorvastatin was similarly efficacious in preventing strokes and other CV events, irrespective of baseline stroke or ischemic stroke subtype.[25]

Table 2. Secondary prevention trials of hypolipidemic therapy including patients with stroke as per protocol

Study	Patients no.	Stroke patients no.	Treatment	Age, years (mean)	Follow-up, years (mean)	Baseline LDL-C, mg/dL (mean)	On treatment LDL-C, mg/dL (mean)	Ischemic stroke events (treatment/no treatment)
HPS, 2004	20,536	3280	Simvastatin	65	5.0	132	93	100/122
SPARCL, 2006	4731	4731	Atorvastatin	63	4.9	133	73	218/274
J-STARS, 2015	1578	1578	Pravastatin	66	4.9	130	104	62/66
FOURIER, 2017	27,564	5337	Evolocumab	63	2.2	86	30	171/226
TST, 2019	2860	2860	Statin ± Ezetimibe	67	3.5	135	65	120/139

HPS: Heart Protection Study; SPARCL: Stroke Prevention by Aggressive Reduction in Cholesterol Levels; J-STARS: Japan Statin Treatment Against Recurrent Stroke; FOURIER: Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk; TST: Treat Stroke to Target.

Recently, the Treat Stroke to Target (TST) trial showed that after an ischemic stroke with evidence of atherosclerosis, patients who were intensively treated to reach a LDL-C target of <70 mg/dL (1.8 mmol/L, mean LDL-C: 65 mg/dL, 1.7 mmol/L) had significantly lower risk of major CV events and death (HR: 0.78; 95% CI: 0.61–0.98) compared to those with higher LDL-C levels (target range of 90–110 mg/dL, 2.3–2.8 mmol/L; mean LDL-C 96 mg/dL, 2.5 mmol/L)[26] (Table 2). An exploratory analysis of this study in a Caucasian population confirmed these results and additionally revealed a significant effect of intensive LDL-C lowering on the reduction of cerebral infarction or cerebral/carotid revascularization.[27] A recent network meta-analysis on statin therapy in secondary stroke prevention including nine RCTs showed that among 10,394 patients with previous stroke, statin treatment was associated with an absolute risk reduction (ARR) of 1.6% on ischemic stroke recurrence [odds ratio (OR): 0.81; 95% CI: 0.70–0.93].[28] Similarly, in these patients statin treatment was associated with an ARR of 5.4% in major CV events (OR: 0.75; 95% CI: 0.69–0.83).[28] Apart from RCTs supporting a significant benefit of statin therapy in non-cardioembolic strokes, observational studies including patients with cardioembolic strokes related to atrial fibrillation (AF) suggest an important role of statins in this population. In one Greek observational study, statin treatment was an independent predictor of major CV events (HR: 0.44, 95% CI: 0.22–0.88) and mortality (HR: 0.49, 95% CI: 0.26–0.92).[29] Similarly, observational studies, showed that statin treatment after a cardio-embolic AF-related stroke was an independent predictor of 5-year survival (HR: 0.52; $p = 0.005$) in Caucasian[30] and 3-year survival in Chinese population (HR: 0.237; 95% CI: 0.080–0.703 for low-potency statin; HR: 0.158; 95% CI: 0.037–0.686 for high-potency statin).[31]

Patients with ischemic stroke or TIA should be treated with an LDL-C target < 55 mg/dL (1.4 mmol/L) and at least 50% reduction of baseline LDL-C levels. LDL-C levels should be monitored to reach the target after six to eight weeks (1B)

Ischemic stroke is a heterogeneous syndrome which may result from different causes like atherosclerosis, small vessel disease, cardiogenic embolism, and others.[32] Regardless of the underlying cause, the vast majority of stroke patients are at very high risk for further CV events. In the Athens Stroke Registry, the 5-year cumulative probability of composite CV events was 38.1% and 38.2% for patients with embolic stroke of undetermined source (ESUS) and cardioembolic strokes, respectively, and 29.8, 28.2, and 24.3% for atherosclerotic, lacunar, and strokes of miscellaneous etiology, respectively.[33] In a recent meta-analysis of four primary and four secondary stroke prevention trials LDL-C had a strong linear relationship with the risk of stroke recurrence ($p = 0.03$).[34] Among 18,144 patients with recent acute coronary artery syndrome included in the IMPROVE-IT trial, those treated with simvastatin 40 mg in combination with ezetimibe 10 mg reached a median LDL-C level of 53.7 mg/dL (1.4 mmol/L) and experienced significantly less major CV events than patients treated with simvastatin monotherapy who reached a median LDL-C level of 69.5 mg/dL (1.8 mmol/L).[35] In an exploratory analysis of 641 patients with previous stroke, the combination of simvastatin and ezetimibe, which resulted in LDL-C levels < 55 mg/dL 1.4 (mmol/L), significantly reduced the risk for stroke recurrence by 8.6% [10.2% vs.

18.8%; number needed to treat (NNT) = 12; HR: 0.60; 95% CI: 0.38–0.95].[36] Similarly, the FOURIER trial (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk, FOURIER), which included 27,564 patients with prior stroke or coronary or peripheral artery disease followed for up to 2.2 years, showed that LDL-C decrease to a median of 30 mg/dL (0.8 mmol/L) significantly reduced all major CV outcomes (HR: 0.85; 95% CI: 0.79–0.92) and stroke on follow-up (HR: 0.79; 95% CI: 0.66–0.95) on follow-up.[37] In the exploratory analysis of 5337 patients with stroke, LDL-C lowering to 30 mg/dL (0.8 mmol/L) resulted in a significant reduction of all CV events and death (HR: 0.85; 95% CI: 0.72–1.00), while the effect of evolocumab on stroke was consistent despite the presence or absence of a previous cerebrovascular events (p *for* interaction = 0.22).[38] In addition, another exploratory analysis of FOURIER trial showed a monotonic relationship between achieved LDL-C and major CV events, with LDL-C levels reaching to 19 mg/dL (0.5 mmol/L) without any adverse events.[39] Similarly, the ODYSSEY–OUTCOMES trial (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab), which included 18,924 patients with a recent acute coronary syndrome followed over a median of 2.8 years showed that a reduction of LDL-C < 53 mg/dL (1.4 mmol/L), was correlated with a significant reduction of the primary composite outcome of any CV event and death (HR: 0.85; 95% CI: 0.78–0.93) and the rates of fatal and nonfatal ischemic stroke (HR: 0.73; 95% CI: 0.57–0.93).[40] A recent exploratory analysis of the ODYSSEY OUTCOMES trial showed that this effect of alirocumab on stroke prevention was consistent independently of the history of previous cerebrovascular event (*p* for interaction 0.37) or the baseline LDL-C (p *for* interaction 0.31).[41] Notably, the treatment effect on stroke was numerically greater in patients with higher baseline LDL cholesterol levels (>100 mg/dL, 2.6 mmol/L). Even in patients achieving very low LDL-C (<25 mg/dL, 0.65 mmol/L) there was no increase in the risk of hemorrhagic stroke.[41] These data point toward a log-linear relationship of stroke reduction attributed to LDL-C lowering, independently of the drug of choice.[42]

LDL-C levels should be monitored to reach the target of <55 mg/dL (1.4 mmol/L) six to eight weeks after the initiation of a lipid-modifying therapy, in order to assure the highest drug efficacy depending on its intensity. The intensity of the lipid-modifying agents differs from drug to drug category (Table 3).

In patients with previous ischemic stroke or TIA who do not achieve the recommended LDL-C targets under the highest tolerated statin dose, ezetimibe should be added (1A)

The IMPROVE-IT trial[35] demonstrated a significant reduction in the incidence of ischemic stroke (HR: 0.79, 95% CI: 0.79–0.94) in patients with an acute coronary syndrome, when ezetimibe was added to the standard simvastatin regimen. Patients with a history of previous stroke ($n = 641$) experienced an ARR by 8.6% for any stroke (10.2 vs.18.8%; NNT = 12; HR: 0.60; 95% CI: 0.38–0.95) and 7.6% for ischemic stroke (8.7 vs.16.3%; NNT = 13; HR: 0.52; 95% CI: 0.31–0.86).[36]

Table 3. Intensity of lipid-modifying agents

Lipid-modifying agent	Average LDL-C reduction (%)
Moderate intensity statin	30
High intensity statin	50
High intensity statin plus ezetimibe	65
PCSK9 inhibitor	60
PCSK9 inhibitor plus high intensity statin	75
PCSK9 inhibitor plus high intensity statin and ezetimibe	85

LDL-C: low-density lipoprotein cholesterol.

In patients with ischemic stroke or TIA who do not achieve the recommended LDL-C targets under the highest tolerated dosage of statin and ezetimibe, a PCSK9-inhibitor should be added (1A)

In two randomized controlled trials[37,40] investigating the efficacy and safety of add-on therapy with a PCSK9 inhibitor (evolocumab or alirocumab) in patients with established CV disease or acute coronary syndrome receiving statin therapy at the maximum tolerated dose (±ezetimibe), the incidence of the primary composite CV outcome was significantly reduced (HR: 0.85; 95% CI: 0.79–0.92 for evolocumab and HR: 0.85; 95% CI: 0.78–0.93 for alirocumab). Apart from these positive results, both studies also showed a significant reduction of ischemic stroke (HR: 0.79; 95% CI: 0.66–0.95 for evolocumab and HR: 0.73; 95% CI: 0.57–0.93 for alirocumab).[37,40] Subgroup analyses of the FOURIER and ODYSSEY OUTCOMES trials involving patients with a history of stroke confirmed a benefit in the reduction of CV events and a numerical decrease in the rate of stroke recurrence.[38,41] Taking into account the difficulties in achieving very low LDL-C levels in clinical practice, PCSK9 inhibitors

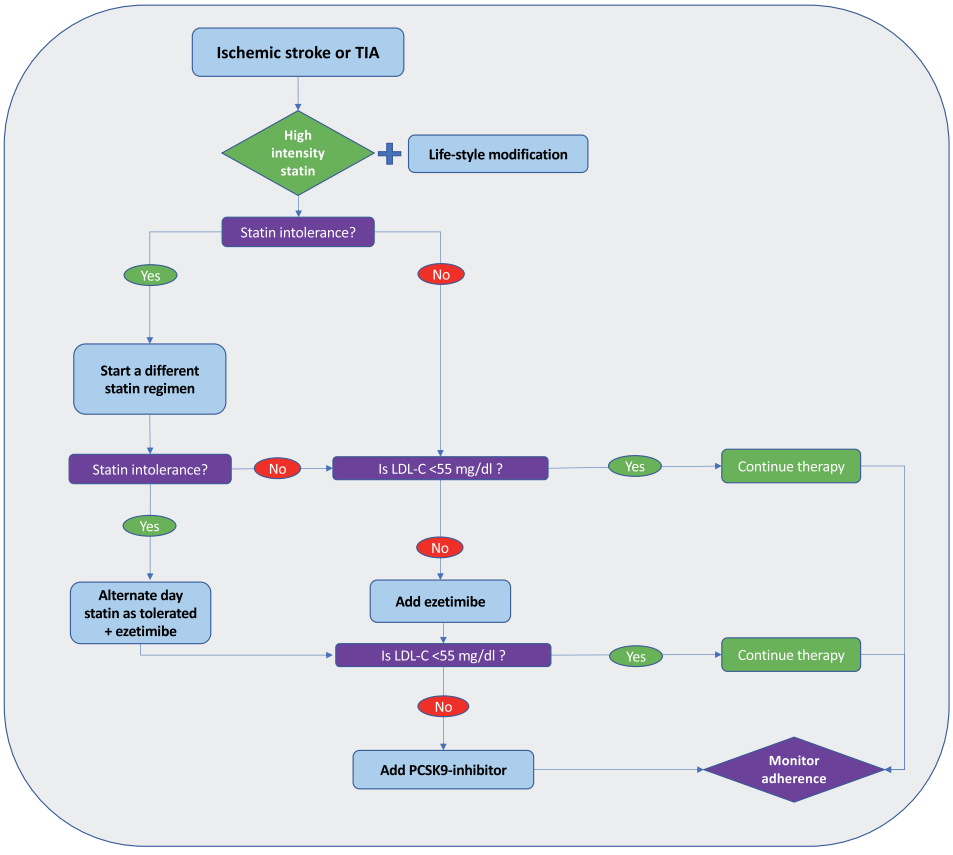
should be considered to be added on top of the maximum tolerated dose of a high-potency statin plus ezetimibe in order to achieve the desired LDL-C targets and reduce the overall CV morbidity and mortality (Figure 1).

Patients with previous ischemic stroke or TIA attributed to a specific cause that is not related to CV risk factors (such as cervical artery dissection, paradoxical embolism, infective or marantic endocarditis, atrial myxoma, and others) should not be a priori considered as very high-risk patients for future stroke and CV morbidity and mortality. Lipid modification treatment should be based on an individualized 10-year risk of new CV events, estimated by the calibrated country-specific SCORE (1B).

An ischemic stroke may not be related to CV risk factors but to other causes, such as cervical artery dissection, paradoxical embolism, infective or marantic endocarditis, atrial myxoma and others.[43] Stroke recurrence after an ischemic stroke due to artery dissection is very rare. As shown in the Cervical Artery Dissection in Stroke Study (CADISS), only 1–2% of patients with ischemic stroke due to artery dissection had a recurrent stroke, irrespective of antithrombotic treatment.[44] Similarly, patients with paradoxical embolism due to a Patent Foramen Ovale (PFO) have a very low recurrence rate even if they do not proceed to PFO closure [1.1 per 100 patient-years which is reduced to 0.53 per 100 patient-years if they proceed to PFO closure (OR: 0.43; 95% CI: 0.21–0.90)].[45] The low recurrence rates in these patients may be attributed to the low prevalence of CV risk factors. Therefore, intensive lipid-lowering therapy for secondary stroke prevention is not warranted in these patients due to lack of relevant evidence. These patients may be treated based on their individualized 10-year CV risk, estimated by the calibrated country-specific SCORE (Systematic Coronary Risk Estimator).[46]

Patients with ischemic stroke or TIA should be monitored for statin-related adverse effects. If a patient develops statin-related adverse effects, another statin regimen (lower dose of the same statin or another statin or alternate statin administration) should be used. If the adverse effects recur following change of statin regimen, statin therapy should be permanently discontinued and

Figure 1. Therapeutic algorithm of lipid-modifying treatment in patients with ischemic stroke.



ezetimibe and/or a PCSK9 inhibitor should be prescribed (2C).

The two most common statin-related adverse effects comprise statin-induced muscle and liver dysfunction which are generally mild.[47,48] Severe statin-related adverse effects are infrequent and should be further evaluated.

Muscle dysfunction appears as a broad spectrum of clinical presentation and may include from subjective myalgias and creatinine phosphokinase (CK) elevation to myopathy and rhabdomyolysis. When baseline CK levels are $>4 \times$ UNL at baseline, statin therapy should be withheld.[49] If a patient experiences muscle pain (myalgias) with mild elevation of CK ($<10 \times$ UNL) while on statin treatment, statins should be discontinued temporarily. After CK normalization, the same or another statin may be restarted at a lower dose cautiously. If a patient with otherwise normal CK levels presents with significant elevation of CK ($>10 \times$ UNL) while on statin treatment regardless of the presence of symptoms, statins should be discontinued, CK must be monitored every two weeks and reversible causes should be sought.[50] If CK levels increase again, statin therapy must be stopped and the patient should be started on ezetimibe and/or a PCSK9-inhibitor[51,52] (Figure 2). Other causes of myopathy or causes increasing the risk of statin-related muscle should always be considered[49,53] (Tables 4 and 5).

Liver dysfunction is commonly defined as an increase of serum aminotransferase activities [liver function tests (LTs): aspartate aminotransferase (AST), alanine aminotransferase (AST)]. If aminotransferase levels are $>3 \times$ the upper normal limits (UNLs), statin therapy should be discontinued, and another statin regimen must be started cautiously upon normalization of LTs. In case that LTs increase again to higher than $3 \times$ UNL, statin therapy should be stopped and the patient started on ezetimibe and/or a PCSK9-inhibitor[51,52] (Figure 2). Secondary causes for LT elevation should be ruled out especially in patients with LT increase prior to statin treatment[51] (Table 4).

Figure 2. Monitor algorithm of statins adverse effects.

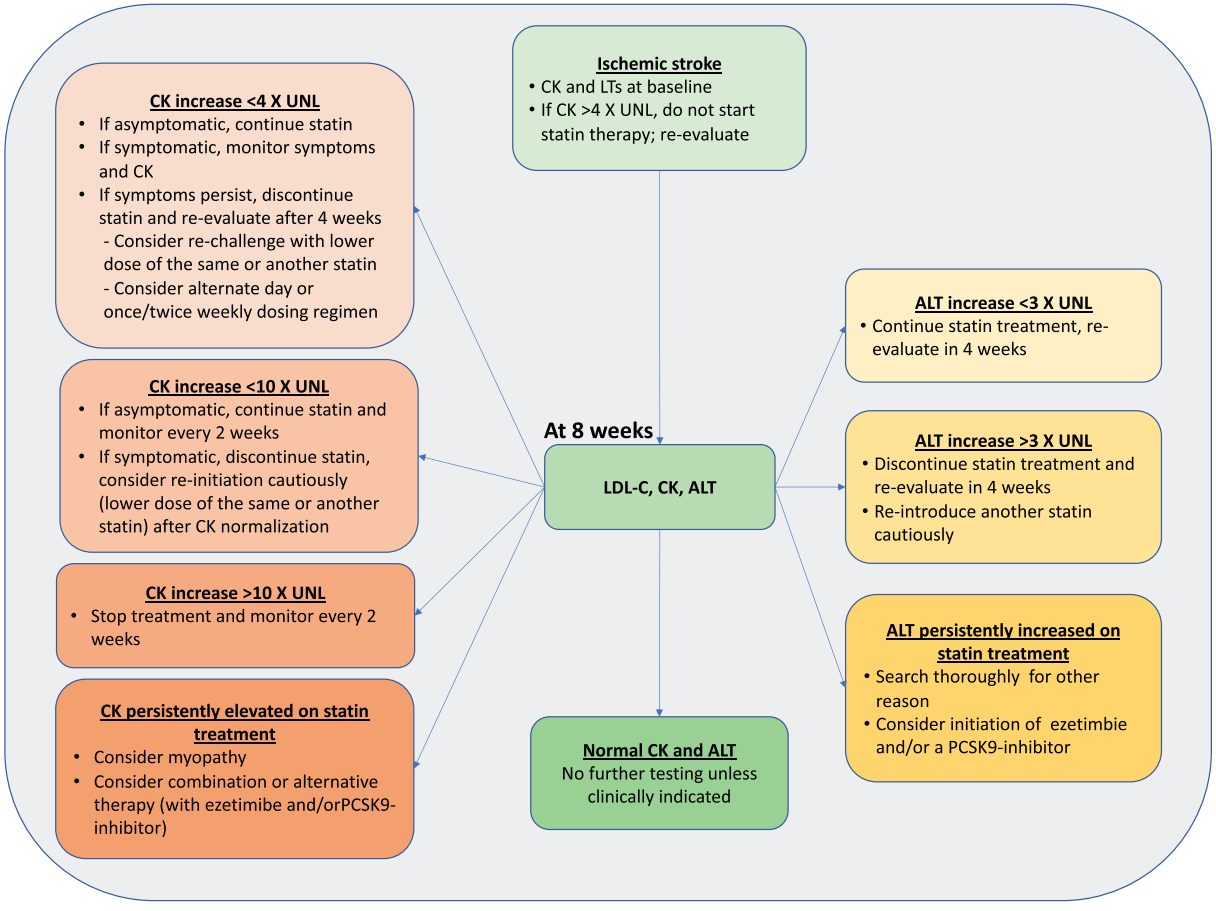


Table 4. Differential diagnosis of statin-related adverse effects

Possible causes of LT elevation	Possible causes of myopathy
Chronic HBV, HCV infection[a]	Inflammatory myopathies (polymyositis, dermatomyositis, HIV myopathy)
NAFLD	Infectious myopathies
Autoimmune liver diseases (AIH, PBC, etc.)	Endocrine myopathies—thyroid, parathyroid, adrenal, pituitary disorders
Ethanol consumption	Toxic myopathies—alcohol, corticosteroids, narcotics, Colchicine, chloroquine
Drugs	Metabolic myopathies
Herbals and supplements	Paraneoplastic myopathy
Illicit drugs	
Genetic liver diseases (Wilson disease, hemochromatosis etc.)	
Hypo-, hyperthyroidism	
Malignancies (primary/metastatic)	

[a]HCV screening of adults born from 1945 to 1980 in Greece is essential, according to the Hellenic HCV National Plan.[63]
HBV: hepatitis B virus; HCV: hepatitis C virus; NAFLD: nonalcoholic liver disease; AIH: autoimmune hepatitis; PBC: primary biliary cholangitis; LT: liver function tests.

Table 5. Risk factors for statin-induced myopathy

Advanced age (>80 years old)	Diet (excessive grapefruit or cranberry juice)
Female gender	Drugs interacting with CYP3A4 and increase
Low body mass index	serum statin concentration (e.g. antibiotics,
Liver or renal dysfunction	antifungals, calcium channel blockers,
Hypothyroidism (untreated)	antiretrovirals, antidepressants
Vigorous exercise	Single nucleotide polymorphism (SNP)
Ethanol consumption	rs4363657 in the *SLCO1B1* gene on chromosome
Major trauma	

Additionally to lipid-lowering therapy and especially in statin-intolerant patients several nutraceuticals such as Red yeast rice, Berberine, Bergamont, polyunsaturated omega-3 fatty acids, and others may play a role in dyslipidemia management.[54] Despite their effect in lipid modification, their use in patients at very high risk for future CV events is limited.

Elderly patients with ischemic stroke or TIA should be treated similar to younger patients, since the CV benefit in this population is comparable to younger patients (2C)

In the HPS study, simvastatin significantly decreased CV events or death (8.7 vs. 11.8%; $p < 0.0001$) as well as nonfatal or fatal stroke (4.3% vs. 5.7%; $p < 0.0001$) compared with placebo in 20,536 patients aged from 43 to 80 years old.[21] In the age-specific subgroup analysis, there were no significant differences in the risk reduction of major CV events between patients aged <65, 65–70 or > 70 years. In addition, a meta-analysis of 23 trials based on age categories, including 147,242 participants treated with a statin-based regimen compared with placebo or usual care, showed a 12% proportional reduction (RR: 0.88; 95% CI: 0.85–0.91) in vascular mortality per 38.7 mg/dL (1.0 mmol/L) reduction in LDL-C in patients with previous vascular disease, which was also significant in older (>75 years) patients (p trend 0.2), after excluding patients with heart failure or end-stage renal disease.[55] Although there is currently a debate about the possible association between very low LDL-C and dementia which renders a lot of physicians to be cautious treating these patients intensively, preliminary evidence did not identify a strong association.[56,57] Still further evidence is necessary to exclude any such possibility. Especially in this frail patient group, polypharmacy is an important factor of nonadherence to statin treatment.[58] Motivational interventions and patient education may enhance statin adherence and thus prevent further CV events.

The association between very low LDL levels and the risk of ICH seems weak. This putative small risk of ICH does not seem adequate to outweigh the CV benefits of lipid-modification treatment (2B)

Previous data from the SPARCL study suggested a small but significant correlation of intense statin treatment to hemorrhagic stroke (HR: 1.66; 95% CI: 1.08–2.55), which was driven especially from patients with lacunar stroke as inclusion event.[24,25] Meta-analyses of randomized and observational studies[59,60] did not find any evidence that statin treatment was associated with ICH in the general population, while recently the TST trial including 2860 patients with previous stroke or TIA[26] showed that those reaching LDL-C levels ≤70 mg/dL (1.8 mmol/L), treated in their vast majority with statins, did not appear to have a higher risk of ICH. Additionally, PCSK9-inhibitor trials[61] did not show that achieving extremely low LDL-C (lower than 19 mg/dL, 0.5 mmol/L) is associated with an elevated risk of ICH. Overall, the association between very low LDL-C levels and the risk of ICH seems weak. Moreover, a recent population-based cohort including 2728 patients with ICH and 52,964 patients with ischemic stroke showed that among patients with previous ICH the risk of future recurrence was similar between those treated with statin and those who did not (HR: 0.90; 95% CI: 0.72–1.12), while patients with previous ischemic stroke had significantly lower risk of ICH reduced by half, when treated with statins (HR: 0.53; 95% CI: 0.45–0.62). Among patients with previous stroke this association differentiate only in patients older than 80 years old, in whom statin treatment did not affect the risk of future ICH (HR: 0.82; 95% CI: 0.60–1.12).

For patients with acute ischemic stroke or TIA, it is suggested that treatment with high-intensity statins should be initiated during hospitalization as early as possible (1C)

During the early poststroke period patients have the highest recurrence risk independently of the stroke subtype.[62] The significant effect of statins in patients at very high risk of stroke and secondary CV events, taken together with their pleiotropic effects on plaque biology and stabilization[63] supports a clinical rational for very early statin initiation. Indeed, in the Athens Stroke Registry statin treatment as late as at discharge was associated with lower risk of 10-year recurrence (HR: 0.65; 95% CI: 0.39–0.97) and lower 10-year mortality rates (HR: 0.43; 95% CI: 0.29–0.61).[64] Despite these findings, the Administration of Statin on Acute Ischemic Stroke Patient (ASSORT) trial including 257 patients with non-cardioembolic stroke and dyslipidemia, treated very early with statins (within 24 h), showed that functional outcome at 90 days was not associated to early (<24 h) or late (>7 days) statin therapy initiation (odds ratio, OR: 0.84; 95% CI: 0.53–1.3).[65] The limitations of ASSORT trial, including the small number of stroke patients and the primary outcome of functional outcome, instead of CV events affect the clinical significance of this study. These results taken together with the possible favorable effect of early statin treatment after stroke or TIA, suggest that statin therapy should be initiated as soon as possible after an ischemic stroke.

Table 6. Drugs with potential interactions with statins.[44]

Itraconazole	Verapamil
Ketoconazole	Diltiazem
Posaconazole	Amlodipine
Clarithromycin	Amiodarone
Erythromycin	Grapefruit juice
Ciclosporin	Ranolazine
Danazol	Gemfibrozil

In patients with ischemic stroke or TIA, lipid-modification treatment aiming to achieve the recommended LDL-C targets should be continued lifelong (1B)

Higher adherence to statin therapy has been shown to be an independent predictor of stroke-free survival, both in patients without (HR: 0.78; 95% CI: 0.63–0.97) and with AF (HR: 0.59; 95% CI: 0.43–0.81).[66] It is recommended that statin treatment should be continued lifelong in order to reduce the stroke and overall CV risk in patients with previous stroke.

The coadministration of statins with drugs metabolized by CYP450 should be avoided due to the increased risk of adverse effects and an alternative regimen should be used (1B)

Drugs metabolized by the CYP450 may increase the adverse effects of statins (especially myopathy) and vice versa, augmenting any possible drug adverse effect. If there is no alternative, the administration of these drugs (Table 6) should be done cautiously with close monitoring for adverse events. If a short-period therapy with macrolide antibiotics or imidazole-based antifungal agents is clinically indicated, statin therapy should be temporarily withheld. Of note, azithromycin can be coadministered with statins.

Summary of recommendations	
Patients with ischemic stroke or transient ischemic attack should receive lipid-modifying treatment with high-intensity statin	1A
Patients with ischemic stroke or transient ischemic attack should be treated with an LDL-C target <55 mg/dL (1.4 mmol/L) and at least 50% reduction of baseline LDL-C levels. LDL-C levels should be monitored to reach the target after six to eight weeks	1B
In patients with previous ischemic stroke or transient ischemic attack who do not achieve the recommended LDL-C targets under the highest tolerated statin dose, ezetimibe should be added	1A
In patients with ischemic stroke or transient ischemic attack who do not achieve the recommended LDL-C targets under the highest tolerated dosage of statin and ezetimibe, a PCSK9-inhibitor should be added	1A
Patients with previous ischemic stroke or transient ischemic attack attributed to a specific cause that is not related to cardiovascular risk factors (such as cervical artery dissection, paradoxical embolism, infective or marantic endocarditis, atrial myxoma, and others) should not be a priori considered as very high-risk patients for future stroke and cardiovascular morbidity and mortality. Lipid modification treatment should be based on an individualized 10-year risk of new cardiovascular events, estimated by the calibrated country-specific SCORE	1B
Patients with ischemic stroke or transient ischemic attack should be monitored for statin-related adverse effects. If a patient develops statin-related adverse effects, another statin regimen (lower dose of the same statin or another statin or alternate statin administration) should be used. If the adverse effects recur following change of statin regimen, statin therapy should be permanently discontinued and ezetimibe and/or a PCSK9 inhibitor should be prescribed	2C
Elderly patients with ischemic stroke or transient ischemic attack should be treated similar to younger patients, since the cardiovascular benefit in this population is comparable to younger patients	2C
The association between very low LDL levels and the risk of ICH seems weak. This putative small risk of ICH does not seem adequate to outweigh the cardiovascular benefits of lipid-modification treatment	2B
For patients with acute ischemic stroke or transient ischemic attack, it is suggested that treatment with high-intensity statins should be initiated during hospitalization as early as possible	1C
In patients with ischemic stroke or transient ischemic attack, lipid-modification treatment aiming to achieve the recommended LDL-C targets should be continued lifelong	1B
The coadministration of statins with drugs metabolized by CYP450 should be avoided due to the increased risk of adverse effects and an alternative regimen should be used	1B

LDL-C: low-density lipoprotein-cholesterol; PCSK9: proprotein convertase subtilisin–kexin type 9; ICH: intracerebral hemorrhage.

Conclusion

Patients with previous ischemic stroke or TIA are at very high risk for future CV events and they should be treated intensively with the optimal lipid modifying agent. This clinical guide will help treating physicians to improve secondary stroke prevention strategies and reduce the risk of future CV events and stroke recurrence in their patients.

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