LIPID LOWERING TREATMENT IN SECONDARY STROKE PREVENTION

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SUMMARY – Secondary preventive measures such as measuring serum cholesterol levels and treatment of hypercholesterolemia with statins, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are insufficiently used in patients with acute stroke or transient ischemic attack, although statins offer potential benefits for reducing the incidence and improving the prognosis of stroke. Besides lipid lowering, statins could have additional effects such as improvement of endothelial-dependent flow-mediated vasodilatation, modulating inflammatory response, decreasing clot formation, and decreasing platelet adherence to ruptured plaque, thus stabilizing the atherosclerotic plaque. Other antiatherosclerotic properties of statins include reduction of inflammatory cell accumulation in atherosclerotic plaques, inhibition of vascular smooth muscle cell proliferation, inhibition of platelet function, and improvement of vascular endothelial function. Randomized clinical trials and evidence based medicine support the role of statin therapy in preventing ischemic stroke in patients at risk of cerebrovascular disease.

Key words: Cerebrovascular accident – prevention and control; Cerebrovascular accident – etiology; Lipoproteins – drug effects; Hypercholesterolemia – drug therapy; Risk factors; Anticholesteremic agents

Introduction

Secondary prevention embraces treatment and rehabilitation of stroke patients and patients who have experienced transient ischemic attack (TIA), and detection and treatment of the population at a high risk of developing stroke, in order to prevent stroke occurrence. It can prolong overall survival, improve the quality of life, decrease the need of surgical procedures, and reduce the incidence of subsequent strokes. Secondary prevention also comprises changing of lifestyle: quitting smoking, increasing physical activity, reducing body weight, changing dietary habits, treatment of concomitant diseases such as hypertension, diabetes, elevated plasma lipids, cardiac diseases, atrial fibrillation, prescribing drugs for secondary prevention of ischemic stroke, and surgical interventions such as carotid endarterectomy and angioplasty.1-3

The role of cholesterol levels as a risk factor for ischemic stroke is controversial. Although elevated cholesterol levels have been associated with coronary heart disease, the evidence for the role of cholesterol in stroke is less well defined. Previous results on the association of raised serum cholesterol levels and stroke were inconsistent. Some of them indicated a significant positive correlation4,5, whereas others showed no such correlation6,7. Studies on the prevention of ischemic heart disease with statins clearly show reductions in overall mortality, cardiovascular mortality, acute myocardial infarction and other coronary events as well as in the risk of ischemic stroke8,9. There is no comparable information on patients with recent ischemic stroke or TIA, even though myocardial infarction is the main cause of death in ischemic stroke survivors and patients who suffered a TIA.6,8

Patients with ischemic stroke of other etiologies, except for stroke in the young or other unusual causes, are patients with a high vascular risk (cardiac and cerebral) due to the stroke, age and other vascular risk factors, therefore they should be treated with statins, at least from the point of view of primary prevention of ischemic heart disease (IHD). Statins would be indicated in secondary prevention of

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atherothrombotic stroke, and in cardioembolic and lacunar stroke associated with clinical or silent atherosclerosis (IHD, peripheral artery disease)\textsuperscript{10,11}.

Secondary preventive measures such as measuring serum cholesterol levels and treatment with statins are inadequately used in patients with acute stroke or TIA\textsuperscript{12,13}. The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, statins, reduce the number of strokes by decreasing the rate of atherothrombotic strokes, cardioembolic strokes secondary to IHD, and lacunar strokes related to atherothrombosis and microatheromas.

The benefits of statins in stroke may be due to a combination of mechanisms. Statins lower cholesterol levels and reduce the progression of atherosclerotic plaque formation in carotid arteries as well as the incidence of emboli from cardiac, aortic and carotid sites. Furthermore, statins may produce independent effects such as improving cerebral blood flow and reducing inflammation and oxidative stress, which could limit the size of ischemic lesion.

Statins offer potential benefits by reducing the incidence and improving the prognosis of stroke\textsuperscript{12,13}. Treatment with HMG-CoA reductase inhibitors is associated with plaque stabilization and even regression of atheromatous plaque in carotid arteries\textsuperscript{14}. Statins also inhibit the coagulation cascade at various levels, e.g., activation of prothrombin, factor V, factor X and tissue factor release in response to vascular injury. The inhibition of fibrinolysis occurs secondary to the inhibition of plasmin generation. Treatment with HMG-CoA reductase inhibitors reduces the risk of myocardial infarction, stroke, and vascular death in patients with coronary artery disease (CAD). Treatment should be initiated in all patients with an ischemic stroke or TIA who have evidence of or high risk for developing CAD over the next years if their cholesterol concentration is >5.0 mmol/L or low-density lipoprotein cholesterol (LDL-C) exceeds 3.0 mmol/L\textsuperscript{15}.

Hypercholesterolemia is a risk factor for nonhemorrhagic or ischemic stroke. The majority of nonlacunar ischemic strokes are caused by thromboemboli arising from atheromatous disease outside the brain, either from the carotid artery, the aortic arch, or the heart, where hypercholesterolemia is an important risk factor for the development of atherosclerosis.CAD causes ischemic left ventricular dysfunction, postinfarction wall motion abnormalities, and atrial fibrillation, all of which significantly increase stroke risk. The reduction of CAD with cholesterol-lowering therapy should lead to reduction in the incidence of ischemic stroke. Although it is likely that statins\textsuperscript{13} reduce preecerebral and large-vessel cerebral atherosclerosis, direct evidence is not yet available to assess differential effects of statin therapy on various subtypes of ischemic stroke. It is yet unidentified whether statin therapy reduces small-vessel lipohyalinosis and thus prevents lacunar stroke. Many clinical “lacunes” are not due to lipohyalinosis but to artery-to-artery embolization.

Since hypertension and diabetes mellitus are frequently associated with hypercholesterolemia, statin therapy may improve the small-vessel atherosclerotic effects of these risk factors for lacunar infarction.

### Clinical Trials of Statins and Stroke

Hypercholesterolemia as an important risk factor for stroke has been supported by recent prospective placebo-controlled clinical trials with various statins. HMG CoA reductase inhibitors have been shown to be effective lipid lowering agents and are able to significantly reduce cardiovascular mortality and morbidity in patients at risk of cardiovascular disease. In the Framingham study positive correlation was found between the occurrence of stroke and elevated levels of cholesterol in men aged 50-59, if cholesterol level was more than 6.24 mmol/L\textsuperscript{15}.

Stroke was a specified end point in the Cholesterol and Recurrent Events (CARE) trial of 40 mg of pravastatin daily versus placebo in 4159 patients with a history of myocardial infarction but with average cholesterol levels\textsuperscript{17}. Pravastatin significantly reduced stroke incidence by 31%, without an increase in the risk of hemorrhagic stroke.

**Post hoc analysis of the Scandinavian Simvastatin Survival Study (4S)\textsuperscript{17},** which examined the effects of 20 to 40 mg daily of simvastatin in patients with known coronary artery disease, also showed a similar significant reduction in stroke incidence in the treatment group without hemorrhagic complications.

The clinical benefit of statins in preventing ischemic stroke in secondary prevention trials is supported by two recent meta-analyses reporting that statin therapy significantly lowers stroke risk by approximately 30%-31\textsuperscript{12,13}. These meta-analyses suggest that statin therapy can reduce stroke risk in patients with evidence of vascular disease by an extent comparable to that of aspirin.

The Pravastatin, Lipids, and Atherosclerosis in the Carotids II (PLAC-II) study\textsuperscript{18} demonstrated a significant 35% reduction in carotid intimal-medial thickness on B-mode ultrasound.

The Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) trial compared the effects of pravastatin 40 mg once daily on mortality due to coronary heart disease (the primary end point) with the effects of placebo.\textsuperscript{19}
among 9014 patients with a history of myocardial infarction or unstable angina. The risk reduction for total stroke (fatal and nonfatal) in the LIPID trial was 19% with pravastatin compared with placebo, but pravastatin had no effect on hemorrhagic stroke.\(^{20}\)

In the aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolemia (ASAP) trial, the carotid intima-media thickness (IMT) as measured by quantitative B-mode ultrasound decreased (-0.031 mm) in the atorvastatin group (80 mg daily) after 2 years, whereas in the simvastatin group (40 mg daily) it increased (0.036 mm) in 325 patients with familial hypercholesterolemia.\(^{20}\)

In the Heart Protection Study (HPS) allocation to 40 mg simvastatin daily significantly reduced all-cause mortality chiefly due to a definite 17% proportional reduction in the death rate from vascular causes in 20,536 high-risk individuals. In the simvastatin group there was a significant 25% proportional reduction in the incidence rate of first stroke. This was mainly due to a definite 30% proportional reduction in the incidence rate of strokes attributed to ischemic stroke, while there was no apparent difference in hemorrhagic stroke. Also, there was a significant reduction in the numbers of participants who had at least one episode of transient cerebral ischemia.\(^{23}\)

The Collaborative Atorvastatin Diabetes Study (CARDS) was a multicenter randomized placebo-controlled trial testing the efficacy of atorvastatin in primary prevention of cardiovascular disease in type 2 diabetes. Assessed separately, acute coronary disease events were reduced by 36%, coronary revascularizations by 31%, and the rate of stroke by 48%. Atorvastatin reduced the death rate by 27%. Results of the study showed atorvastatin 10 mg daily to be safe and efficacious in reducing the risk of first cardiovascular disease events, including stroke, in patients with type 2 diabetes without high LDL-C.\(^{23}\)

Although most of the recent studies showed a beneficial effect of statins in reducing stroke risk, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) in 10,355 older participants with well-controlled hypertension and moderately elevated LDL-C receiving either pravastatin 40 mg daily or usual care showed that all-cause mortality was similar for both groups. Pravastatin reduced neither all-cause mortality nor coronary heart disease significantly when compared with usual care.\(^{24}\)

Considering the prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA), a multicenter randomized controlled trial, showed that atorvastatin 10 mg daily lowered total serum cholesterol by about 1.3 mmol/L compared with placebo at 12 months, and by 1.1 mmol/L after 3-year follow-up.\(^{24}\)

In a recently published meta-analysis of 164 short-term randomized placebo-controlled trials of six statins and LDL cholesterol reduction, 58 randomized trials of cholesterol lowering by any means and ischemic heart disease events, and nine cohort studies and the same 58 trials on stroke, it is concluded that statins can lower LDL-C concentration by a mean of 1.8 mmol/L, which reduces the risk of ischemic heart disease events by about 60% and of stroke by only 17%. In subjects with the existing vascular disease the reduction of stroke is 36%.\(^{25}\)

In conclusion, it seems that there is a statistical link between elevated LDL-C or decreased high-density lipoprotein cholesterol and ischemic stroke, and a reduction in vascular risk with statins in randomized trials in patients with coronary heart disease. Also, there is evidence for a decreased plaque progression under statins, and pooled analyses of primary and secondary prevention trials showing that reduction of total serum cholesterol reduces the incidence of stroke, especially at the highest rate of cholesterol reduction, and in patients with the highest risk of stroke.\(^{14}\)

### Statins and Hypercholesterolemia

Atherosclerosis is a chronic inflammatory disorder characterized by the presence of monocytes or macrophages and T-lymphocytes in the atherosclerotic plaque as well as the proliferation of smooth muscle cells, elaboration of extracellular matrix, and neovascularization.

Statin therapy transforms a number of atherosclerotic plaque components, thus rendering stability of the plaque and making rupture and thrombosis less likely.

Pravastatin has been shown to directly influence cholesterol synthesis in macrophages in vivo and in vitro, potentially reducing cholesterol accumulation within these cells.\(^{25}\) By reducing macrophage activity in the plaque, it is likely to attenuate macrophage activation, which has been shown to be associated with plaque instability.\(^{26}\) Macrophages have been implicated in the pathophysiology of acute vascular syndromes by producing enzymes, including members of the metalloproteinase family (interstitial collagenase, gelatinase, and stromelysin) that weaken the plaque cap, making disruption more likely.\(^{27}\)

Among the many other products elaborated by macrophages is tissue factor, a membrane-bound glycoprotein that
plays an integral role in the extrinsic pathway of blood coagulation. It appears that statins have direct antiatherosclerotic effects on the arterial wall, probably through a reduction in the synthesis of intermediates in cholesterol metabolism, such as isoprenoids, compounds that have been implicated in the control of cell proliferation.

Additionally, statins have been shown to modulate immune function and to alter regulation of DNA transcription, to regulate natural-killer cell cytotoxicity, and to inhibit antibody-dependent cellular cytotoxicity. Statin therapy appears to modulate immune cell activation within the plaque, and may attenuate cellular recruitment and reduce the inflammatory responses that lead to plaque instability.

Endothelium-derived relaxing factor or nitric oxide (NO) is produced under basal conditions and mediates endothelium-dependent relaxation in response to a number of stimuli such as platelet activation, shear stress, and concentrations of thrombin, serotonin, and catecholamines. Endothelium-dependent relaxation is reduced in atherosclerosis and hypercholesterolemia, and it appears that LDL is the major determinant of this phenomenon.

LDL is oxidized in vascular endothelial cells to oxidized LDL, which is toxic to the endothelial cell. Oxidized LDL appears to cause endothelial dysfunction through inactivation of NO by oxygen-derived free radicals, and reduced transcription and destabilization of NO synthase mRNA. The dysfunctional endothelial cell promotes platelet adhesion, macrophage migration, vasoconstriction, leukocyte adhesion, and thrombosis.

Statins may have beneficial effects on vascular physiology that may be independent of their effects on cholesterol reduction. Adjunctive effects of statins may help explain the significant recent reduction in both coronary and cerebrovascular events. These favorable modulations in the vascular setting occur not only in the coronary bed but also in the aorta, carotids, and intracranial vasculature.

**Statins against Thrombosis**

Platelets contribute to both atherosclerosis and thrombosis, and play a major role in the pathophysiology of thromboembolic cerebrovascular disease. Enhanced platelet aggregation has been demonstrated in stroke, and increases in the mean platelet volume and a reduction in platelet count have been documented in both acute and nonacute phases of cerebral ischemia, and appear to precede and contribute to the acute event.

Increased thromboxane biosynthesis has been described in patients with acute coronary, and cerebral ischemic syndromes, indicating platelet activation in these conditions. Hypercholesterolemia is accompanied by hypersensitivity to various aggregating agents and an increased platelet cell membrane cholesterol content. It is evident that lowering cholesterol reduces the tendency of platelets to aggregate. The mechanism underlying the effect of statin therapy on platelet function is unclear but may be through decreased platelet thromboxane production. Plasma membrane and cytosolic calcium level of platelets appear to be altered in hypercholesterolemic states, perhaps increasing platelet reactivity.

In addition to the effect on platelets, hypercholesterolemia is also associated with an enhanced thrombotic and a reduced fibrinolytic state that can be reversed by lowering LDL.

Acute ischemic stroke has also been shown to be associated with elevation of prothrombotic markers such as fibrinogen, plasminogen activator inhibitor-1 activity, and increased levels of thrombin-antithrombin III complex. Data suggest that the link between hypercholesterolemia, thrombosis, and ischemic stroke may be more important than previously realized and that this aberrant thrombotic-fibrinolytic balance can be normalized with cholesterol-lowering statin therapy.

Statins inhibit HMG-CoA reductase, a rate-limiting enzyme in cholesterol synthesis leading to a depletion of intracellular cholesterol in hepatocytes, which induces up-regulation of hepatic LDL receptors and in turn promotes lowering of LDL levels.

Statins also improve endothelial function leading to vascular tone normalization, hemorheologic stress reduction, and restoration of the thrombotic-fibrinolytic balance.

**Conclusion**

The use of statins in patients with vascular disease has been shown to lower the incidence of stroke. Statins exhibit a number of antiatherosclerotic and antiinflammatory properties that are likely to underlie the recently observed reductions in cerebrovascular disease by reducing the inflammatory, proliferative, and thrombogenic processes in the plaque, making it less likely to rupture. Additionally, they reverse the endothelial dysfunction and platelet activation accompanying hypercholesterolemia, and may reduce the tendency to thrombosis. There is evidence for a decreased plaque progression under statins, and pooled analyses of primary and secondary prevention trials showing that reduction of total serum cholesterol decreases the incidence of stroke, especially at the highest rate of cholesterol reduction and in patients with the highest risk of stroke.
Statins appear to make the plaque more stable and less likely to undergo thrombotic disruption, and also improve the endothelial dysfunction that accompanies hypercholesterolemia and reduce the associated hemorheologic stress. Finally, statin therapy has a beneficial impact on both platelet and coagulation abnormalities that are associated with hypercholesterolemia and that appear to be important in the pathophysiology of thromboembolic stroke.

Pravastatin therapy is associated with a reduction in the size of aortic atheroma, which is an independent risk factor for stroke. Left ventricular dysfunction after acute myocardial infarction is associated with an increased risk of stroke and HMG-CoA reductase inhibitors may indirectly decrease the incidence of stroke by reducing coronary events. Most of these effects are independent of the cholesterol-lowering effects of HMG-CoA reductase inhibitors.

The reduction in stroke may not be solely related to cholesterol or low-density lipoprotein reduction but may involve effects of the nonsterol mechanisms on endothelial cells, macrophages, platelets, and smooth muscle cells. Currently the best evidence for stroke prevention is with pravastatin and simvastatin. These statins play an essential part in secondary prevention of ischemic stroke, together with antiplatelet agents, anticoagulants, angiotensin-converting enzyme inhibitors and treatment of other vascular risk factors.

Pravastatin reduces the risk of stroke in patients with coronary artery disease and average cholesterol levels, and simvastatin reduces the risk of the combined endpoint of stroke and TIA.

Elevated apolipoprotein B (apoB) is known to be an important risk factor for coronary heart disease, and dysregulation of the metabolism of apoB-containing lipoproteins is involved in the progression of atherosclerosis. Statins reduce circulating concentrations of atherogenic apoB-containing lipoproteins by decreasing the production of VLDL in the liver.

It seems that besides the cholesterol lowering potential statins may improve endothelial-dependent flow-mediated vasodilation by increasing the bioavailability of NO. They may stabilize the plaque by modulating the inflammatory response within the vessel wall. They also may decrease clot formation by decreasing the platelet adhesion to the ruptured plaque and by acting on the extrinsic coagulation cascade pathway.

Statins possess anti-inflammatory properties, as evidenced by their ability to reduce the accumulation of inflammatory cells in atherosclerotic plaques; they inhibit vascular smooth muscle cell proliferation and platelet function, and improve vascular endothelial function through augmentation of NO generation. At present, clinical trials and basic science evidence support the role of statin therapy in preventing ischemic stroke. Further work is required to address the specific effects of statins within the cerebral vasculature and to define patient subgroups with or at risk of cerebrovascular disease that may benefit from statin therapy.

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Sažetak

LIJEČENJE SNIŽAVANJEM MASTI U SEKUNDARNOJ PREVENCIJI MOŽDANOG UDARA

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Mjere sekundarne prevencije, kao što su mjerenje serumskih razina kolesterolna i liječenje hiperkolesterolemije statinima, inhibitorima reduktaze 3-hidroksi-3-metilglutaril koenzima A (HMG-CoA), nedovoljno se primjenjuju u bolesnika s akutnim moždanim udarom ili prolaznim ishemijskim ispadom, iako statini nude moguće koristi u snižavanju incidencije i poboljšanju prognoze moždanog udara. Uza snižavanje masti, statini bi mogli imati i dodatne učinke, kao što je poboljšanje o endotelu ovisne i protokom posredovane vazodilatacije, moduliranje upalnog odgovora, smanjeno stvaranje ugrušaka, te smanjeno prijanjene trombocita uz rasprenu plak, stabilizirajući time aterosklerotski plak. Ostala antiaterosklerotska svojstva statina uključuju smanjeno nakupljanje upalnih stanica u aterosklerotskom plaku, suzbijanje proliferacije krvožilnih glatkomišićnih stanica, suzbijanje funkcije trombocita, te poboljšanje funkcije krvožilnog endotela. Randomizirana klinička istraživanja i medicina zasnovana na dokazima govore u prilog uloge liječenja statinima u sprječavanju ishemijskog moždanog udara u bolesnika s rizikom za cerebrovaskularnu bolest.

Ključne riječi: Cerebrovaskularni incident — prevencija i kontrola; Cerebrovaskularni incident — etiologija; Lipoproteini — ušteda lijekova; Hiperkolesterolemija — terapija lijekovima; Čimbenici rizika; Antiškolesteremični lijekovi