Triple H (hypertension, hyperlipidemia, hyperglycemia) and stroke

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Abstract

Stroke is the third most frequent cause of death worldwide and the most frequent cause of permanent disability. Modification of lifestyle and risk factors treatment in the world has led to the reduction of stroke incidence and mortality of stroke. The economic burden is tremendous as well as influence on private and social life, since many patients require chronic care and long-term institutionalization. Stroke prevention begins with recognition of its risk factors by a patient and clinicians treating the patient, most patients having a stroke have multiple risk factors therefore it are of great importance to recognize all of the stroke risk factors and to educate the patient and the family how to control them.

INTRODUCTION

Stroke risk factors have been classified as traditional and novel (hyperhomocysteinemia, hypercoagulable states, and select biomarkers), and modifiable and nonmodifiable. Risk factors for cerebrovascular disease are non modifiable risk factors: age, gender, race/ethnic, genotype, previous myocardial infarction, TIA or stroke and modifiable risk factors: diabetes, hyperlipidemia, arterial hypertension, atrial fibrillation, coronary and or peripheral artery disease, obesity, physical inactivity, stress, alcohol consumption, and smoking *(1–4)*.

In order of better and faster evaluation of stroke risk factors the Framingham Stroke Risk Profile (FSRP) was developed. Authors of the FSRP were using data from 36 years follow up in the Framingham cohort and has been validated in other cohorts. The FSRP provides sex specific estimation of the probability of stroke using clinical information.

Atherosclerosis is a central pathomorphological mechanism which leads to narrowing of arterial walls throughout the body as well in brain causing cerebrovascular disease. Atherosclerosis is thought to be result from chronic inflammation and injury to the arterial wall in the peripheral or coronary vascular system. In response to endothelial injury and inflammation, oxidized lipids from LDL (low density lipoproteins) particles accumulate in the endothelial part of the vessel wall. Angiotensin II may promote the oxidation of such particles. Monocyte than infiltrate the arterial wall and differentiate into macrophages, which accumulate oxidized lipids to form foam cells. Once formed, foam cells stimulate macrophage proliferation and attraction of T-lymphocytes. T-lymphocytes in turn, induce smooth muscle proliferation in the arterial walls and collagen accumulation. The net result of the process

is the formation of a lipid-rich atherosclerotic lesion with a fibrous cap. Rupture of this lesion leads to acute vascular infarction, this ruptures and bleeding into the plaque are more frequent in diabetic patients (diabetic patients have higher perioperative risk for carotid endarcterectomy as well). In addition to atheroma formation, there is a strong evidence of increased platelet adhesion, hypercoagulability, impaired nitric oxide generation and increased free radical formation as well as altered calcium regulation in diabetic patients *(1, 5)*.

Hypertension, hyperglycemia and hyperlipidaemia are most prevalent modifiable risk factors.

Hypertension

Hypertension is the most prevalent modifiable risk factor for stroke with a prevalence of about 30% in modern western countries. The prevalence of hypertension increases with age,

The Framingham Heart Study investigators reported the lifetime risk of hypertension to be approximately 90% for men and women who were non-hypertensive at age 55 or 65 years and survived to ages 80–85 years old. A meta-analysis of one million adults enrolled in 61 observational studies concluded that death from ischemic heart disease and stroke increases

Progressively and linearly with systolic blood pressure levels as low as 115 mm Hg and diastolic 75 mm Hg upward. This study also found that for every 20 mm Hg systolic or 10 mm Hg diastolic increase in blood pressure there is a doubling of mortality from both ischemic heart disease and stroke. The authors suggest a 10 mm Hg reduction in systolic or a 5 mm Hg reduction in diastolic blood pressure would result in a 40% lower risk of stroke death and a 30% lower risk of death from ischemic heart disease or other vascular death *(5–7)*.

The United Kingdom-transient ischemic attack (TIA) trial evaluated blood pressure and risk of stroke in patients with diagnosed cerebrovascular disease and found a direct and continuous relationship between blood pressure and recurrent strokes. Their data demonstrated that a 5mm Hg lower diastolic blood pressure was associated with reduction of stroke for about one third *(8)*. Based on data such as these the 2003 Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) redefined the classification of hypertension. In the new classification, blood pressure <120/80 mm Hg was changed from »optimal« to »normal« and the new term »prehypertension« was used for a systolic blood pressure of 120–139 mm Hg and/or diastolic blood pressure of 80–89 mm Hg. The aim of this reclassification was to encourage lifestyle changes at early stages of hypertension, and reduce the incidence of stroke and heart attack. Lifestyle change includes diet, mainly eating more fruits and vegetables (meta analysis of 9 independent studies has shown that 3–5 servings per day reduces risk for stroke for 0,89) and consuming less salt, in addition to weight loss, aerobic activity and moderation of alcohol consumption. Pharmacological treatment is not recommended until systolic pressures exceed 140 mm Hg or diastolic exceeds 90 mm Hg (brain perfusion). Whereas the necessity to treat hypertension to reduce the risk of cerebrovascular events is clear, there is less clarity regarding the best choice of antihypertensive medication.

The Heart Outcomes Prevention Evaluation (HOPE) Study demonstrated improved cardiovascular outcomes with the use of the angiotensinconverting enzyme inhibitor (ACEI) ramipril beyond its ability to lower blood pressure, which was very mild in this trial (the average reduction of systolic/diastolic blood pressure was 3/2 mm Hg) *(9)*. Subsequently, the Losartan Intervention for Endpoint reduction in hypertension (LIFE) Study compared the effects the angiotensin receptor blocker (ARB) losartan with the beta-blocker atenolol on the composite end-point of cardiovascular death, stroke and myocardial infarction in patients with hypertension and left ventricular hypertrophy. When the endpoints were evaluated separately, a relative risk reduction of 25% was found in fatal and nonfatal stroke, favoring losartan over atenolol *(10)*.

The perindopril protection against recurrent stroke study (PROGRESS) was the first trial to be done solely on patients with diagnosed cerebrovascular disease. Patients with a history of stroke or TIA were randomized to placebo, perindopril or perindopril plus indapamide, a thiazide diuretic. The average blood pressure at entry was 147/86 mm Hg. The combination of indapamide and perindopril produced an average reduction in blood pressure of 12/5 mm Hg and was associated with a 43% reduction in relative risk of recurrent stroke compared with perindopril alone, which produced only a 5/3 mm Hg drop in blood pressure. This study rose the question what was responsible for the positive results- degree of reduction in blood pressure or the combination of an ACEI plus a thiazide *(11)*.

The Study on Cognition and Prognosis in the Elderly (SCOPE), elderly patients with isolated systolic hypertension were randomized to an ARB-based antihypertensive treatment with candesartan or non-ARB based treatment *(12)*.

Despite the similar degree of blood pressure lowering in the ARB arm (22/6 mm Hg) and in the non-ARB arm (20/5 mm Hg) there was a 42% relative risk reduction in stroke in the ARB arm. These results suggest that ACEI and/or ARB, especially in combination with a thiazide diuretic, may be superior to other anti-hypertensive regimens in the secondary prevention of stroke (confirmed previous results of PROGRESS).

Three randomized trials of more intensive versus less intensive blood pressure control have shown that the more intensive control of blood pressure was superior in reducing the number of strokes, however, these were primarily in diabetic patients and only targeted diastolic blood pressures- United Kingdom Prospective Diabetes study (UKPDS) *(13)*.

In The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), a thiazide

diuretic chlorthalidone was superior to a calcium channel blocker (CCB) amlodipine, alpha-receptor antagonist doxazosin, and angiotensin-coverting enzyme inhibitor (ACEI) lisinopril in preventing one or more major forms of vascular events including stroke *(14)*.

On Going Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) is comparing the ACEI ramipril versus the ARB telmisartan versus a combination of both in high-risk patients for reductions in major vascular events *(15)*.

The European Lacidipine Study on Atherosclerosis (ELSA) study was evaluating the effects of lacidipine (calcium antagonist) based treatment and beta-blocker (atenolol) based treatment on the development and progression of carotid atherosclerosis (assessed in hypertensive patients). The primary endpoint of this study was the rate of change in the thickness of the carotid artery wall, measured with B-mode ultrasound (in patients on lacidipine IMT was reduced for 40% in 5 year follow up period) *(16)*.

Valsartan Antihypertensive Long-term Use Evaluation (VALUE) study. The primary aim of the study was to determine whether lowering blood pressure with a regimen that began with the angiotensin receptor blocker (ARB) valsartan would provide a 15% risk reduction in cardiac-related morbidity and mortality when compared with similar blood pressure control with the calcium channel blocker (CCB) amlodipine. Stroke was reduced to a greater degree by amlodipine but not with statistically significance *(17)*.

Morbidity and Mortality After Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention: principal results of a prospective randomized controlled study (MOSES) has unequivocally shown that in patients with a history of cerebrovascular events, a blood pressure (BP)–lowering treatment based on eprosartan is more protective against both cerebrovascular event recurrence and cardiac complications than a treatment based on nitrendipine *(18)*.

The Secondary Prevention of Small Subcortical Strokes (SPS3) trial which is comparing different antiplatelet therapies in stroke prevention in patients with lacunar strokes is also assessing the effects of different blood pressure targets-systolic blood pressure < 150 mm Hg versus a target blood pressure < 130 mm Hg *(19)*.

The On Going Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) is comparing the ACEI ramipril versus the ARB telmisartan versus a combination of both in high-risk patients for reductions in major vascular events. The Telmisartan Randomised Assessment Study in ACE-intolerant Subjects with Cardiovascular Disease (TRANSCEND), compares telmisartan 80mg with placebo in ACEI-intolerant patients with the same risk factors and end-points as ONTARGET (20).

Effective use of antihypertensive treatments is limited by lack of awareness of hypertension in patients (prior studies have shown that only about 60% of hypertensive individuals were aware of having hypertension), once recognized effective treatment is achieved only in a minority; one third of hypertensive individuals are controlled to target blood pressure (mostly due to irregularly drugs intake).

The guidelines for treatment of hypertension in prevention of stroke state that in primary prevention of stroke, normal blood pressure limit should be set at a level lower than 149mmHg/90mmHg and lower than 130mmHg/85mmHg in diabetics. Normal blood pressure values should be reached first with modification of lifestyle, and if the former is unsuccessful a medical treatment should be considered. Currently, antihypertensive treatment is recommended for all patients who have had a TIA or a stroke. The ideal target blood pressure should be individualized according to age, sex and comorbidities. Benefit has been seen with an average blood pressure reduction of about 10/5 mm Hg. The agent of choice depends on individual patient characteristics, but ACEI and ARB in addition to a diuretic seem to be favorable in patients with stroke, based on data from the previously mentioned trials (AB/CD rule). In patients with severe pre-cerebral artery stenosis, intensive blood pressure lowering in the secondary prevention of stroke should be started with caution, if at all *(21)*.

Hyperlipidemia

Several large randomized trials of statins have demonstrated reduction of stroke risk associated with lowering lipid levels. However, observational prospective studies have not found a consistent relation between cholesterol levels and incidence of stroke. When evaluating pathomorphological mechanisms of atherosclerosis, the beneficial effects of statins on stroke risk reduction may be mediated by additional mechanisms of action such as improvement of endothelial function (regulation of heart function, blood pressure, and hyperglycemia), antioxidant properties, inhibition of inflammatory responses, immunomodulatory actions, and stabilization of atherosclerotic lesions. Although the agent used, and the dose has varied across studies, the results have been consistent, showing stroke relative risk reduction ranging approximately from 10 to 50%. Most studies included patients with concomitant coronary heart disease, therefore it is not clear enough if the benefit in stroke risk reduction was due to reduction of myocardial infarction and cardiac death *(22-24)*.

The Heart Protection Study assessed the efficacy of simvastatin in patients with coronary disease, other occlusive disease or diabetes and low-density lipoprotein (LDL) cholesterol levels of at least 3.5mmol/L in reducing vascular events. A 24% reduction in the rate of all-cause mortality, fatal or non-fatal vascular events was shown in patients treated with simvastatin when compared with those treated with placebo. A 25% reduction in total stroke incidence rate and a 30% reduction in the ischemic stroke incidence rate were observed. In the simvastatin-treated group, transient ischemic attacks were

significantly less frequent than in the placebo group (2% versus 2.4%). In this trial, there was no stratification for past medical events, thus rendering the interpretation of the effects of simvastatin in subgroups untrustworthy, as there was a subgroup of patients with the history of CVD without coronary heart disease. In this subgroup, a 21% RRR of major vascular events was demonstrated, but no effect of simvastatin on stroke recurrence was observed *(25)*.

A few meta-analyses on lipid lowering and ischemic heart disease prevention have been published in the past decade. One included all randomized trials that were published between 1966 and 2001, testing statins, resins, fibrates, niacin, surgical interventions and diet.[49] There were 10 primary and 28 secondary prevention trials. This analysis showed a significant 17% RRR of stroke incidence. There was no significant heterogeneity between trials, either in intervention tested (primary versus secondary prevention) or in the type of lipid-lowering therapy examined. When comparing different pharmacological agents, only statins yielded a significant 24% RRR of stroke. When analyzing by type of intervention, the significant effect of statins on stroke incidence was present only in secondary prevention, with a 26% RRR of stroke. Lipid-lowering therapy, however, did not influence the incidence of fatal strokes and did not change the incidence of hemorrhagic stroke. A strong evidence for the role of cholesterol in the pathogenesis of stroke is based on the correlation of stroke incidence and the degree of cholesterol reduction, baseline cholesterol level and final cholesterol level, as the target cholesterol level around 6mmol/L is the divide between absence and presence of stroke RR *(22-24)*.

Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA): Study has showed that lowering of cholesterol concentrations in individuals at high risk of cardiovascular disease improves outcome. Study has assessed benefits of cholesterol lowering in the primary prevention of coronary heart disease (CHD) in hypertensive patients who are not conventionally deemed dyslipidemic. 10 305 with non-fasting total cholesterol concentrations 6·5 mmol/L or less were randomly assigned additional atorvastatin 10 mg or placebo. These patients formed the lipid-lowering arm of the study. Atorvastatin lowered total serum cholesterol by about 1.3 mmol/L compared with placebo at 12 months, and by 1.1 mmol/L after 3 years of follow-up. The reductions in major cardiovascular events with atorvastatin are large, given the short follow-up time *(26)*.

Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S): 4444 patients with angina pectoris or previous myocardial infarction and serum cholesterol 5.5-8.0 mmol/L on a lipid-lowering diet were randomized to double-blind treatment with simvastatin or placebo over the 5.4 years. The 4S study turned out to be a milestone in cardiology and evidence-based medicine – it was clearly proven that treatment with statins changed the occurrence of events of patients with coro-

nary heart disease. There was a 24% RRR RRR of stroke during 6 years follow up period *(27)*.

The Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID): In a double-blind, randomized trial authors compared the effects of pravastatin (40 mg daily) with those of a placebo over a mean follow-up period of 6 years (9014 patients). There was a 19% RRR of stroke in pravastatin group *(28)*.

The Cholesterol and Recurrent Events (CARE) Study: 4159 subjects with average total and LDL serum cholesterol levels (mean, 209 and 139 mg/dL, respectively) who had sustained an infarction an average of 10 months before study entry and who were randomized to pravastatin 40 mg/d or placebo. Using prospectively defined criteria, the incidence of stroke, a prespecified secondary end point, and transient ischemic attack (TIA) over a median 5-year follow-up period were assessed. There was 32% reduction (95% CI, 4% to 52%, P50.03) in all-cause stroke and 27% reduction in stroke or TIA (95% CI, 4% to 44%, P50.02) *(29)*.

Stroke Prevention by Aggressive Reduction in Cholesterol Levels Study (SPARCL) was the first trial evaluating patients without concomitant coronary disease. The trial compared patients assigned to 80 mg of Atorvastatin daily with recent TIA or stroke (within 6 months of enrollment) versus placebo group. This study found absolute risk reduction in stroke rates of 2.2% (adjusted HR 0.84; 95% CI 0.71 to 0.99). This was associated with a reduction of LDL cholesterol levels of 53% (P<0.001). Although there were more hemorrhagic strokes in the atorvastatin group (55 versus 33 in the placebo group), the incidence of fatal hemorrhagic stroke was not significantly different between the groups. These results suggesting that use of statins at the time of an ischemic stroke may have beneficial effects *(30)*.

The Northern Manhattan Study found that the 90-day mortality rate was lower in patients who were taking a statin compared to those not taking it at the time of stroke (1.8% vs 10.6%, p = 0.03).

Other studies support the finding of reduced degree of stroke severity and better outcomes if lipid-lowering agents were used prior to the vascular event (also when thrombolysis was applied). Withdrawal of statin treatment at the time of an acute ischemic stroke has been related to poorer neurological outcome at 90 days. The RRR for stroke in patients on statins was 21% (OR 0.79; 95% CI: 0.73–0.85), the rate of fatal strokes was insignificantly reduced by 9% (OR 0.91; 0.76–1.10) and there was no increase in the frequency of hemorrhagic strokes. The effect of statins was closely linked to LDL-C reduction, as each 10% reduction in LDL-C reduced the risk of all strokes by 15.6% (95% CI: 6.7–23.6%).

The Collaborative Atorvastatin Diabetes Study (CARDS) evaluated the effectiveness of atorvastatin 10mg/day versus placebo in the primary prevention of coronary artery disease and stroke in 2,838 patients with type 2 diabetes without increased cholesterol levels. The RR of stroke was lowered by 52% in the group treated with atorvastatin

(RR 48%; 95% CI: 11–69%).[52] Cholesterol-lowering therapy is recommended in primary stroke prevention in high risk patients with coronary artery disease, hypertension or DM. All patients with a history of ischemic stroke or TIA may be considered for statin therapy, which may be started already during the hospitalization *(31)*.

An additive effect of ASA and pravastatin was assessed in one meta-analysis that included five randomized trials of secondary prevention with pravastatin 40mg/day and ASA (73,900 patient years of observation). The RR of ischemic stroke was reduced by 39% in patients treated with pravastatin and ASA when compared with placebo. The combination of pravastatin and ASA was shown to be more efficient than aspirin and pravastatin alone (RRR 29% and RRR 31%, respectively) *(32)*.

Practice guidelines recommend use of statins for Stroke prevention. The target total cholesterol level should be below 5,0 mm/L, LDL level varies depending on the patient's estimated risk, < 2,59 mmol/L for those with symptomatic atherosclerotic disease, and < 1,81 mmol/L for those at very high risk. Very high risk is considered when there is established cardiovascular disease and one of the following: multiple major risk factors, poorly controlled risk factors (smoking), the metabolic syndrome (mainly triglycerides >2,26 mmol/L with low high-density lipoprotein (HDL) cholesterol <1,03 mmol/L), and acute coronary syndromes.

Attention should also be paid to HDL levels. Prior studies in large cohorts have shown an inverse association between serum HDL cholesterol and stroke, it is involved in atherosclerosis and its higher levels have been related to anti-atherosclerotic and anti-inflammatory properties in animal and human studies (reduced odds of having a large-vessel stroke-OR 0.8, 95% CI 0.6 – 1). Treatment considerations include the addition of niacin or fibrates in patients with HDL <1.03 mmol/L *(22-24)*.

Hyperglycemia

Diabetes is chronic illness that requires continual medical care and patient self management education in order to prevent acute complications and to reduce the risk of long-term complications. According to last diagnostic and classification criteria classification of diabetes includes:

1. Prediabetes:
   - Impaired fasting glycemia
   - Impaired glucose tolerance
2. Diabetes mellitus type 1
3. Diabetes mellitus type 2
4. Diabetes due to other causes-genetic defects of β cells, diseases of exocrine pancreas (cystic fibrosis), drug or chemical-induced
5. Gestational diabetes

Diagnosis of diabetes should be established according to clinical signs of diabetes and blood tests (Fasting plasma glucose, Glycosylated hemoglobin, Oral glucose tolerance test).

Of patients who suffered stroke, a large proportion either has or is later diagnosed with diabetes (16-24%). Patients with diabetes are at 1.5-3 times the risk of stroke compared with general population and associated mortality and morbidity is greater than in those without this underlying condition. Even patients with metabolic syndrome component have a 1.5 fold increased risk of stroke. This is primarily due to increased proatherogenic risk factors-abnormal plasma lipid profiles, hypertension, hyperglycemia. However, other pathological features associated with diabetes, such as insulin resistance and hyperinsulinemia, also lead to atherosclerotic changes in extracranial and intracranial vessels independently of glycemia or other attendant risk factors. This is particularly expressed in smaller cerebral vessels increasing the incidence of both- overt and silent lacunar infarctions *(1-6)*.

STROKE	DIABETIC PATIENTS	NON DIABETIC PATIENTS
ischemic/hemorrhagic	10 : 1	5 : 1
risk for stroke at the age 55<	↑	↓
relative risk women/men	women > men	women < men
infratentorial stroke	frequent	Infrequent
Lacunar stroke	frequent	infrequent
Lesion volume	No difference	

Generally, vascular complications of diabetes can be separated into microvascular (diabetic nephropathy, neuropathy and retinopathy) and macrovascular (coronary disease, cerebrovascular disease, peripheral artery disease) complications. There are strong evidences of increased platelet adhesion, hypercoagulability, impaired nitric oxide generation and increased free radical formation as well as altered calcium regulation in diabetic patients. Therefore diabetes mellitus can precipitate and fasten process of atherosclerosis even in younger age. There are large clinical trials which confirmed these facts even at early stages of atherosclerosis (subclinical forms). IRAS (The Insulin Resistance Atherosclerosis study) has shown that diabetes and glucose intolerance are independent risk factors connected with increase in intima media thickness (IMT) *(33)*. SANDS trial (The Stop Atherosclerosis in Native Diabetics Study) have shown that reduction in other cerebrovascular risk factors (hypertension, hyperlipoproteinemia) can slower progression of IMT thickening in diabetic patients *(34)*. UKPDS (United Kingdom Prospective Diabetes study) has shown importance of life style modification and adequate diabetic therapy in stroke risk reduction- reduction of HbA1c for 1% reduces stroke risk for 4%. Intensive glucose control (HbA1c=7 mmol/L) with diabetic diet, peroral antidiabetic agents or insulin, particularly when instituted

early in DM, delay or prevents clinically manifest atherosclerosis (micro and macro vascular manifestations). STOP NIDDM trial (Study to Prevent Non-Insulin-Dependent Diabetes Mellitus)- in diabetic patients taking acarbosa there was very low stroke incidence (2/682 pts) *(35)*.

Observational study/Diabetes Control and Complications Intensive insulin treatment reduces any vascular incident for 41%. PROACTIVE trial (PROspective pioglitAzone Clinial Trial in macroVascular Events)- double blinded randomized study; 5238 pts, 34,5 months, 45 mg pioglitazon vs placebo). Pioglitazon reduces risk of stroke in type 2 diabetic patients at high risk for stroke *(36)*.

Correction of hypoglycemia was proven as one of the most important parameters also in therapy of acute stroke. Meta analyses have shown (32 studies) that hyperglycemia at admission (6-8 mmol/L) is predictor of worse functional outcome, as well increases 28 days mortality in previously non diabetic patients (RR 3.1 CI 95% 2.5-3.8) as well in diabetic patients(RR 1.3 CI 95% 0.5-3.4). Glucose Insulin in stroke Trial-Pilot (GIST), Insulin in Acute Ischemic stroke (INSULINFARCT), Insulin Resistance Intervention After Stroke Trial (IRIS) have shown that there are no differences in acute stroke treatment in diabetic patients, there is of great importance regulation of all metabolic parameters as well as blood glucose concentrations. In trombolysis application there is a higher risk of bleeding in diabetic patients vs normal population. About 1/5 of diabetic patients have aspirin resistance *(37-39)*.

According to the results of all mentioned studies in this review, hypertension, hypelipidemia and hyperglycemia as stroke risk factors are in interactions in the process of atherosclerosis. Primary as well as secondary prevention as well as regulating of these risk factors in acute stroke is of great importance.

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