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Review articles

Antihypertensive and lipid lowering treatment in stroke prevention : current state and future

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Abstract

Diabetes mellitus, arterial hypertension, smoking are major stroke risk factors. The role of hypercholesterolemia in stroke has not been established yet. In patients with type 2 diabetes mellitus there is evidence that intensive glucose lowering therapy diminishes the risk of microvascular complications. In all patients with stroke or transient ischemic attack (TIA), blood pressure should be lowered irrespectively of the baseline level with either diuretics, angiotensin converting enzyme (ACE) inhibitors, beta-blockers, or calcium antagonists. The role of angiotensin II (AT2) receptor blockers has not been established so far. In general terms a global approach to management of patients with vascular risk factors should be developed. An extended follow-up of randomised trials on preventive therapy should be completed. Controlled trials comparing angiotensin receptor blockers with ACE inhibitors should be started. Further research may focus on the new lipid lowering agents, and on the comparison of single lipid lowering agent vs. combinations in stroke prevention. These efforts should help in finding the best vasoprotective strategy in stroke prevention.

Key words : Stroke ; prevention ; risk factors ; hypertension ; hyphercholesterolemia.

Stroke is the third leading cause of death worldwide and the leading cause of disability in developed countries. In developed countries the average age-adjusted incidence of stroke is 150 per 100,000 population per year, and stroke-related mortality ranges from 50 to 100 per 100,000 population per year. In United States every 53 seconds there is a new case of stroke, and every 3 minutes there is a stroke-related death. As burden of stroke is high, the risk factors of stroke should be well determined, searched, and treated. Stroke risk factors can be divided into non-modifiable and modifiable. The non-modifiable risk factors are the following : age, race, sex, and family history of stroke or TIA. Each decade after the age of 55 years was shown to double the risk of stroke (1). Stroke incidence is the highest in Blacks (233/100,000), followed by Hispanics (196/100,000), and Whites (93/100,000) (2). Stroke is more prevalent in men (58.8-92.6/1000) than in women (32.2-61.2/1000) (3). Paternal history of stroke or TIA was shown to increase the risk of stroke by 2.4 (95% CI, 0.96-6.03), while maternal by 1.4 (0.6-3.25) (4). Among the most common modifiable risk factors there are hypertension, tobacco smoking, diabetes, atrial fibrillation, and hypercholesterolemia. Hypertension was shown to increase the relative risk of stroke by up to 4-fold, and smoking by 1.8-fold, and diabetes up to 6-fold (5, 6). Atrial fibrillation rises the risk of stroke from 2.6 to 4-fold (7). The role of hyperlipidemia in stroke is still debated, but indirect evidence favors its influence on stroke recurrence (8).

As major prevention trials and meta-analyses on hypertension and hypercholesterolemia have recently been published we will concentrate on these two stroke risk factors.

The relative risk of stroke rises proportionately to the level of systolic blood pressure for both ischemic and hemorrhagic stroke. This effect is more pronounced in the hemorrhagic stroke with relative risk reaching almost 8 for systolic pressure higher than 160 mm Hg, while the relative risk of ischemic stroke approaches 4 for the same blood pressure range (9). The difference in the risk of death of vascular causes such as stroke, or ischemic heart disease associated with a given absolute difference in usual blood pressure was shown to be about the same down to at least 115 mm Hg systolic blood pressure (SBP) and 75 mm Hg diastolic blood pressure (DBP). At ages 40-69 years, each difference of 20 mm Hg usual SBP, or 10 mm Hg usual DBP, caused more than a two-fold increase in the stroke death rate. Lowering the usual SBP by 20 mm Hg decreased stroke related mortality in all strokes and in all major etiological subtypes of stroke such as subarachnoid hemorrhage, intracerebral hemorrhage, and ischemic stroke (10). A large scale randomized prevention study (Heart Outcomes Prevention Evaluation Study - HOPE) was performed on almost 10,000 high vascular risk patients (i.e. with coronary artery disease, ischemic

stroke, or peripheral artery disease and additional risk factor such as hypertension, hyperlipidemia, smoking or microlabuminuria). This trial tested an angiotensin converting enzyme inhibitor (ACEI) - ramipril 10 mg vs. placebo in preventing myocardial infarction, ischemic stroke or vascular death irrespectively of baseline blood pressure levels, and showed that mean blood pressure reduction of 9/4 mm Hg (SBP/DBP) yielded the relative risk of stroke of 0.68 (95% CI, 0.56-0.84) (11). Another trial tested a different ACEI – perindopril 4 mg vs. placebo with additional randomization into indapamide vs. placebo in 6105 patients with a history of stroke, TIA, or amaurosis fugax. The primary endpoint was a fatal or non-fatal stroke. Combination therapy with perindopril and indapamide reduced the risk of stroke by 43% (30-54%) and at the same time it reduced blood pressure by 12/5 mm Hg, while single drug therapy did not changed the risk of stroke and reduced blood pressure by 5/3 mm Hg. Without any blood pressure entry criterion, and with an average blood pressure reduction of 3/1 mm Hg the relative risk of stroke in the perindopril arm was lowered by 28% (17-38%) when compared to placebo. This effect was more evident in hemorrhagic stroke with the risk lowered by 50% (26-67%), when compared to risk reduction of 24% (10-35%) in ischemic stroke. It is important to note, that in this trial the effects of treatment were irrespective of the presence or the absence of hypertension. In hypertensive group the risk of stroke was lowered by 32% (17-44%), when in normotensive group it was lowered by 27% (8-42%) (12). The ACEIs are the most widely studied treatment modalities nowadays. What is the most efficacious treatment – this question remains the most difficult one to answer. According to a recent systematic review β-blockers or diuretics when compared to placebo or no treatment yielded a 35% relative risk reduction with a net difference on SBP/DBP of 13/6 mm Hg. The ACEIs vs. placebo or no treatment showed a benefit of 28% in lowering the risk of stroke (net blood pressure difference of 5/2 mm Hg), and calcium-blockers vs. placebo or no treatment yielded the risk reduction of 0.61 with a net difference of blood pressure of 10/5 mm Hg (13). When comparing different age groups the effect of antihypertensive treatment was most pronounced in those younger than 60 years (RRR of 40% ; 95% CI, 26-52%). The mean baseline systolic blood pressure seemed not to influence this effect. Knowing that multiple agents exert their beneficial effect in lowering the risk of stroke, and some of them may have some pleiotropic effects (ACEI) it seems prudent to compare these agents. Diuretics were shown to be more efficacious than beta-blockers (RRR 31% ; 95% CI, 3-51%, p = 0.04) (14). Composite data from 5 randomised trials (n = 46,000 ; net difference of blood pressure of 2/1 mm Hg) showed that beta-blockers and/or diuretics were more efficient than ACEI (RR 0.91 ; 95% CI, 0.83-0.99) (13). Ten randomized trials tested beta-blockers and/or diuretics vs. calcium blockers (n= 68,000 ; net blood pressure difference of 1/1 mm Hg), and the results were slightly in favour for the latter (RR 1.08 ; 95% CI, 0.99-1.16). The composite results of 4 randomized trials (n = 23,000) showed an advantage of calcium-blockers over ACEI with RR of 0.89 (95% CI, 0.80-0.99) (net blood pressure difference of 1/1 mm Hg). When comparing the more intensive vs. less intensive antihypertensive treatment (3 randomized trials, n = 20,000) the more intensive approach was more efficient with RR= 0.80 (95% CI, 0.65-0.99) (13). Lowering of SBP (net difference in SBP) was shown to proportionately increase the relative risk reduction of stroke (13). The results of the prevention trials on new antihypertensive agents, especially those linked to the angiotensin system (Angiotensin II receptor blockers - ARB). The Losartan Intervention For Endpoint reduction in hypertension study (LIFE) compared losartan vs. atenolol in 9193 patients with essential hypertension, and found a RR of stroke of 0.75 (0.63-0.89) (15). The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial compared valsartan vs. amlodypine in 15245 patients with treated and untreated hypertension. Valsartan was slightly less efficient in preventing strokes with HR of 1.15 (95% CI, 0.98-1.35) (16). The Study on Cognition and Prognosis in the Elderly (SCOPE) examined candesartan vs. placebo in elderly patients with mildly to moderately elevated blood pressure in reducing the rate of cardiovascular events, cognitive decline and dementia. There were 4937 elderly patients with hypertension, and treatment with candesartan was shown to modestly decrease the rate of stroke (RR= 0.24 ; -0.7-42.1) (17).

Considering all these data, one may ask where we are right now with the practical guidelines for stroke prevention with antihyperstensive agents ? In primary prevention normal blood pressure limit was established at the level < 149/<90 mm Hg, and < 130/< 85 in diabetics. The normal blood pressure values should be achieved first with lifestyle modification, and later with medical treatment. In secondary stroke prevention a blood pressure lowering irrespectively of baseline level is recommended. Diuretics and or ACEI are suggested as agents of choice (18). However, in patients with severe large artery stenosis, especially bilateral carotid stenosis, intensive blood pressure lowering as a measure of secondary prevention of stroke should be better studied and introduced with caution if at all (19, 20). There are currently 3 ongoing randomized studies on ARB and stroke prevention. The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) compares telmisartan 80 mg & ramipril 10 mg vs. monotherapies + placebo in the

prevention of stroke, myocardial infarction, CVD death, and hospitalization for cardiac failure in patients older than 55 years with coronary artery disease, ischemic stroke or TIA, peripheral artery disease, or diabetes mellitus (21). The other trial TRANSCEND compares telmisartan 80 mg vs. placebo in ACEI intolerant patients with the same risk factors and endpoints as ONTARGET (21). Prevention Regimen For Effectively avoiding Second Strokes Study (PROFESS) is a randomised, parallel group, double-blind, double-dummy, placebo controlled study on stroke prevention in patients over 55 years of age who have had a stroke within 90 days. There are 15,500 patients to be randomized. Half of the active group participants will receive combintaion of acetylosalicylic acid and dipiridamole and telmisartan, while the other half will receive Clopidogrel, Aspirin, and telmisartan. The placebo group will also be divided into a half receiveing combination of acetylosalicylic acid and dipiridamole and placebo, and the other half receiving Clopidogrel, Aspirin, and Placebo. The primary outcome is time to first recurrent stroke (22).

A correlation between increased blood total cholesterol levels and risk of myocardial infarction is well known (23, 24). The association between cholesterol levels and stroke occurrence is debated in the literature. In the Framingham cohort no connection was found between the levels of cholesterol and the incidence of stroke (23). In young women, a positive correlation between total cholesterol levels and stroke-related mortality was observed, while in elderly subjects, an inverse correlation between these parameters was found (24). The combined analysis showed no significant association between the increased level of serum cholesterol and stroke rate, except for those younger than 45 years (26, 27). This analysis did not stratify into stroke subgroups and thus a positive association with ischemic stroke might be counterbalanced by a negative association with hemorrhagic stroke. This was confirmed in another study where a positive correlation between total cholesterol levels and ischemic stroke risk, was demonstrated. The serum cholesterol levels above 7.23 mmol/l increased the risk of death from ischemic stroke (28). One overview showed a trend toward decreased risk of ischemic stroke in subjects with decreased cholesterol level (29). A positive correlation between very high total cholesterol levels > 8 mmol/l, and the risk of non-hemorrhagic stroke was demonstrated in a different study (30).

The Heart Protection Study tested the effectiveness of simvastatin in patients with coronary disease, other occlusive disease or diabetes and LDL cholesterol levels at least 3.5 mmol/l.8 (31). A 24% reduction in the rate of all-cause mortality, fatal or non-fatal vascular events between simvastatin and placebo groups was shown. There was a 25% reduction in the all stroke incidence rate and a 30% reduction in the ischemic stroke incidence rate. Transient ischemic attacks were also significantly less frequent in the simvastatin vs. placebo group (2% vs. 2.4%). In this trial, there was a subgroup of patients with the history of cerebrovascular disease without coronary heart disease. However, there was no stratification for the past medical events thus yielding the interpretation of the effects of simvastatin in subgroups untrustworthy. In this subgroup, a 21% relative risk reduction of major vascular events was demonstrated. However, no effect of simvastatin on stroke recurrence was observed.

A few metaanalyses on lipid lowering and coronary prevention were published in the past decade. One included all randomized trials, published between 1966 and 2001, testing statins, resins, fibrates, niacin, surgical interventions, and diet (32). There were ten primary and 28 secondary prevention trials. This analysis showed a significant, 17% relative risk reduction of stroke incidence. There was no significant heterogeneity between trials either in intervention tested (primary vs. secondary prevention) or type of lipid lowering therapy examined. When analyzing subgroups, only statins yielded a significant, 24% relative risk reduction 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% relative risk reduction of stroke. However, the incidence of fatal strokes was not influenced by lipid lowering therapy. Lipid lowering therapy did not change the incidence of hemorrhagic stroke. A strong evidence for the role of cholesterol in stroke comes with the documented correlation of stroke incidence and the degree of cholesterol reduction, baseline cholesterol level and final cholesterol level. The final cholesterol level around 6 mmol/l (232 mmol/l), achieved with lipid lowering therapy, separated between absence and presence of stroke risk reduction.

The other and most recent systematic review analyzed all randomised trials testing statin drugs published before 2003. The relative risk reduction for stroke 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). No increase in hemorrhagic strokes was observed. Statin effect was closely linked to LDL-C reduction. Each 10% reduction in LDL-C reduced the risk of all strokes by 15.6% (95% CI, 6.7-23.6) (33).

In one metaanalysis an additive effect of acetylosalicylic acid and pravastatin was studied. Five randomised trials of secondary prevention with pravastatin 40 mg/d and acetylosalicylic acid (73 900 patient-years of observation) were included. Pravastatin and acetylosalicylic acid when compared to placebo reduced the relative risk of ischemic stroke by 39%. The combination of pravastatin and acetylosalicylic acid was shown to

be more efficient than aspirin alone (relative risk reduction of 29%), and than pravastatin alone (RRR=31%) (34).

Results of Collaborative Atorvastatin Diabetes Study (CARDS) have been released recently. This study evaluated the effectiveness of atorvastatin 10 mg daily vs. placebo in the primary prevention of coronary artery disease and stroke in patients with type 2 diabetes without raised cholesterol levels. There were 2838 patients randomised into treatment or placebo arms. The relative risk of stroke was lowered by 52% in the atorvastatin arm (RR = 48% ; 95% CI, 11-69%) (35).

According to the recent recommendations cholesterol lowering therapy is recommended in primary stroke prevention in high risk patients with coronary artery disease, hypertension or diabetes mellitus. All patients with a history of ischemic stroke or TIA may be considered for statin therapy, which may be started already during the hospitalization (18, 36).

We are now waiting for the results of a randomized trial titled Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL). This trial evaluates the effects of atorvastatin 80 mg/day in secondary prevention of stroke in patients without history of coronary artery disease. A total of 4732 patients have been enrolled. The results of this trial are of great importance as it is the first study primarily designed to prospectively evaluate the effect of statin treatment in secondary stroke prevention (37).

To summarize we would like to state that a global approach to management of patients with vascular risk factors should be developed. An extended follow-up of randomised trials on preventive therapy should be completed. Controlled trials comparing angiotensin receptor blockers with ACE inhibitors should be started. Further research may focus on the new lipid lowering agents, and on the comparison of single lipid lowering agent vs. combinations in stroke prevention. These efforts should help in finding the best vasoprotective strategy in stroke prevention.

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