Renin-Angiotensin System Inhibition and Prevention of Stroke

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Executive Summary

Stroke is the second commonest cause of death worldwide.

Stroke can be prevented. The most important modifiable risk factor for stroke in hypertension. The reduction in strokes in meta-analysis of randomized trials of antihypertensive drugs is similar at 42%. Conventional therapy with diuretics and beta blockers was mostly used in these trials. Recent antihypertensive drugs, such as angiotensin converting enzyme inhibitors (ACE inhibitors), calcium antagonists and angiotensin receptor blockers (ARB’s) were shown to reduce the risk of total major cardiovascular events- including stroke- and larger reductions in blood pressure produced larger reductions in risk. Review of clinical trials with ACE inhibitors reveals that these agents are not very efficacious in the reduction of stroke when compared to diuretics and calcium antagonists. Two mega trials with angiotensin receptor blockers (LIFE and SCOPE) showed large reduction in risk of stroke with small reduction in blood pressure when compared to conventional therapy.

Introduction:

Stroke is the second leading cause of death in the world and disability in developed countries (1). Hypertension is the most important modifiable risk factor for stroke (2). Hypertension whether systolic, diastolic or combined
increases stroke risk. In fact when patients have hypertension, they are more likely to have a stroke than a myocardial infraction (3). There has been compelling evidence for more than 30 years that control of high blood pressure contributes to the prevention of stroke (4).

**Review of clinical trials with angiotensin converting enzyme inhibitors**

In the UK Prospective Diabetes Study 39 (5), hypertensive diabetic patients were randomized to receive either captopril or atenolol. There were no statistical differences in blood pressure reduction between the two groups. In this study no statistically significant difference was noted in stroke rates between the two groups.

The Captopril Prevention Project randomized patients to conventional treatment with beta blockers and diuretics vs captopril (6). Treatment blood pressures were significantly higher in the captopril arm and this group had a 25% higher stroke rate compared to the conventional therapy group.

The STOP-2 trial (7) comprised three treatment groups: diuretics, beta blockers or both vs ACE inhibitors or calcium antagonists. Blood pressure was lowered similarly in the three groups and no statistically significant differences were noted in the rate of strokes.

The ALLHAT study (8) compared chlorthalidone, amlodipine and lisinopril. In this study blood pressure was statistically significantly lower in the group given diuretics. The diuretic group had a lower rate of stroke than the ACE-inhibitor group but did not differ from the amlodipine group.

PROGRESS (9) was a randomized, double blind, placebo-controlled trial of perindopril 4 mg plus indapamide 2.5 mg daily in patients with a history of
stroke or transient ischemic attacks. There was a 28% relative risk reduction in favor of the perindopril based therapy. Combination therapy with perindopril plus indapamide reduced the risk of stroke more substantially than “perindopril therapy alone”; the latter showed relative risk reduction of 5% which did not reach statistical significance.

The HOPE trial (10) was a double-blind, randomized clinical trial that investigated ramipril 10 mg once daily in high risk patients who had vascular disease plus one other cardiovascular risk factor. A treatment effect of ramipril on blood pressure was noted of 4/2 mm Hg at the beginning of the study and 3/2 mm Hg at the end. The risk of any stroke was reduced by 32% with ramipril therapy. The blood pressure lowering effect of ramipril may have been understated. In the HOPE trial the drug was given at bedtime and blood pressure was measured during the day – 24-ambulatory blood pressure measurement in a small subset of patients showed a more pronounced blood pressure lowering effect during the night (11).

Review of Clinical Trials with Angiotensin Receptor Blockers

In the LIFE study (Losartan Intervention For Endpoint reduction in hypertension Study) (12). 9193 participants aged 55-80 years with essential hypertension and LVH ascertained by electrocardiography were assigned once daily losartan-based or atenolol-based antihypertensive treatment in a double-masked, randomized, parallel-group manner. Large blood pressure reductions in this population were noted in both groups (30/17 and 29/17 mm Hg in the losartan and atenolol groups respectively). Despite similar mean arterial pressure, the losartan arm experienced a stroke reduction of 25%
compared to atenolol. The stroke reduction was consistent through all subgroups (as high as 40%) and highly significant in the predetermined analysis of patients with isolated systolic hypertension (13).

The Study on COgnition and Prognosis in the Elderly (SCOPE) (14) randomized 4964 patients, aged 70-89 years, with systolic blood pressure 160-179 mm Hg, and/or diastolic blood pressure 90-99 mm Hg, to the angiotensin receptor blocker candesartan or placebo, with open-label active antihypertensive therapy added as needed (84% of the control group). Blood pressure fell by 21.7/10.8 mm Hg in the candesartan group and by 18.5/9.2 mm Hg in the control group. Candesartan-based treatment reduced non-fatal stroke by 27.8% (95% CI, 1.3 to 47.2, \( P=0.04 \)) and all stroke by 23.6% (95% CI, -0.7 to 42.1, \( P=0.056 \)).

In a predefined subgroup analysis of outcome results in 1518 patients with isolated systolic hypertension (15), 754 patients were randomized to the candesartan group and 764 patients to the control group. Over the study period, blood pressure was reduced by 22/6 mm Hg in the candesartan group and by 20/5 mm Hg in the control group. Candesartan-based therapy resulted in a significant 42% relative risk reduction in stroke in comparison with other antihypertensive treatment. There was no significant difference between the treatment groups (either in the SCOPE main study or in the subgroup with isolated systolic hypertension) with respect to cognitive function or dementia.

The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial (16) randomized 15245 patients, aged 50 years or older with treated or untreated hypertension and high risk of cardiac events, to therapy based on valsartan or amlodipine in a double-blind, parallel-group comparison. Blood
pressure was reduced by both treatments, but the effects of the amlodipine-based regimen were more pronounced, especially in the early period (blood pressure 4.0/2.1 mm Hg lower in the amlodipine group than the valsartan group after 1 month, 1.5/1.3 mm Hg after 1 year, P<0.001 between groups). The main outcome of cardiac disease did not differ between the treatment groups. In VALUE, stroke incidence was lower in the amlodipine group than in the valsartan group. Most of the excess stroke in the valsartan group appeared in the first year when the difference in blood pressure between the 2 groups was largest.

**Practical Implications**

Evidence from clinical trials shows that control of blood pressure leads to a lower risk of stroke. The reduction in strokes in meta-analysis of randomized trials of antihypertensive drugs is similar at 42% and appears rapidly after administration of therapy. In comparison of regimens based on different drug classes, the blood pressure lowering treatment trialists collaboration (17), found some differences in stroke risk, but these were of borderline significance. There was a trend towards a greater risk reduction with regimens based on diuretics or B blockers compared with regimens based on ACE inhibitors (9%[0-18]), and trends towards greater reductions with regimens based on calcium antagonists compared with those based on diuretics or B blockers (7%[-1 to 14]) or with those based on ACE inhibitors (12%[1-25]). Although modest independent effects of specific drug classes on stroke were not precluded by the investigators, the results did suggest that blood pressure lowering is a major component of the benefit conferred by the regimens investigated. Diuretics are very efficacious in reducing the risk of stroke. A
better stroke reduction was achieved with diuretics than with other antihypertensive drugs such as beta blockers and ACE inhibitors, despite similar reductions in blood pressure (17). Long-acting dihydropyridine calcium antagonist, amlodipine, was superior to ACE-inhibitor (lisinopril) and diuretic (chlorthalidone) in ALLHAT (8), and to valsartan in VALUE (16) in risk reduction of stroke.

It is possible that the favorable effect on stroke in the ARB-treated groups in both LIFE (14) and SCOPE (15) trials is related to AT1-receptor blockade (and / or AT2-receptor activation) and not just to blood pressure lowering. The small BP reduction in the treatment groups compared to the control group in both trials could not account for the large reduction in stroke incidence. The hypothesis of cerebroprotection by AT2-receptor activation has been supported by animal studies (18) that indicate neuroprotective effects by AT1-receptor blockade at concentrations not affecting blood pressure. It appears that activation of AT2-receptors by drugs that generate elevated levels of angiotensin II facilitates the recruitment of collateral vessels and increases neuronal resistance to ischemia (19). Furthermore, activation of AT2-receptors has been shown to induce vasodilatation by local synthesis of nitric oxide and prostacyclin (20). However, this hypothesis of cerebroprotection by AT2-receptor activation should be thoroughly tested by a head-to-head comparison of an ARB and ACE-inhibitor in a patient population at high risk of cerebrovascular disease.
References


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