THE ROLE OF NEW ANTIHYPERTENSIVE DRUGS IN STROKE PREVENTION

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SUMMARY – There is no doubt that treatment of hypertension has a significant role in the prevention of stroke. Recently published data from large, randomized clinical trials show that lowering of blood pressure is associated with a significant decrease in the risk of stroke. Reduction in the risk of stroke varies from approximately one quarter to approximately one third, depending on the study. Furthermore, besides blood pressure lowering it seems that the use of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers and calcium antagonists could provide some additional beneficial effects. ACE inhibitors and angiotensin receptor blockers could improve endothelial function, cardiac and vascular remodeling, thus retarding the progression of atherosclerosis. Calcium antagonists, especially the highly lipophilic ones, may have some antioxidant properties. They reduce the oxidation of low-density lipoprotein (LDL) cholesterol and its influx into the arterial wall. Amlodipine, lacidipine or nifedipine suppress platelet production in hypertensive patients. Therefore, ACE inhibitors, angiotensin receptor blockers and calcium antagonists could be potential antiatherosclerotic agents. Considering all these data, it could be assumed that a wider use of these drug classes could significantly improve our ability to prevent all vascular diseases, stroke in particular. Data from recently published large randomized clinical trials shed bright light on stroke prevention in the forthcoming future.

Key words: *Blood pressure – drug effects; Cerebrovascular accident – prevention and control; Hypertension – drug therapy; Antihypertensive agents – therapeutic use*

Introduction

Stroke is defined by the World Health Organization (WHO) as a clinical syndrome of rapid onset of focal (or global, as in subarachnoid hemorrhage) cerebral deficit lasting for more than 24 h or leading to death, with no apparent cause other than a vascular one. Stroke can be ischemic, accounting for approximately 80%, or hemorrhagic (primary intracerebral hemorrhage and subarachnoid hemorrhage), accounting for approximately 20% of all strokes in Caucasian populations. Stroke is a major public health burden worldwide. It is one of the three most common causes of death and disability all over the world. Most of all strokes are probably due to atherosclerosis and changes that atherosclerosis produces on arterial tree and on the heart. Therefore, hypertension as the most common vascular risk factor is considered as one of the most important risk factors for stroke.

Although there has been great improvement in stroke treatment in recent years, the prevention of stroke still has a pivotal role in the approach to stroke[1,2].

In this paper, results of clinical trials dealing with the treatment of hypertension in stroke prevention will be presented, with special emphasis on the potential new beneficial actions of some groups of antihypertensives (angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and calcium channel blockers).

Hypertension is one of the most potent risk factors for first ever and recurrent stroke. Lowering of blood pressure has been known for years to reduce the risk of first stroke. Bloore pressure lowering for primary prevention of stroke could be undertaken using a variety of therapeutic agents:

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beta-blockers, ACE inhibitors, angiotensin receptor blockers, calcium antagonists, diuretics, etc. The choice of first line antihypertensive drug is still difficult.

Results of Published Studies

The ALLHAT trial showed in 33,357 participants with hypertension no difference in combined fatal coronary heart disease or nonfatal myocardial infarction among the groups treated with a thiazide-type diuretic chlorthalidone (12.5 to 25 mg/d), calcium entry blocker amlodipine (2.5 to 10 mg/d) or ACE inhibitor lisinopril (10 to 40 mg/d). The lisinopril group had a higher stroke rate than the chlorthalidone group (6.3% *vs* 5.6%). The authors suggest the use of thiazide-type diuretics because they are superior in preventing 1 or more major forms of cardiovascular disease and are less expensive. Therefore, they should be preferred for first-step antihypertensive therapy[3].

The PROGRESS trial showed that the relative risk reduction by about 25% was associated with a decrease of 9 mm in systolic and 4 mm in diastolic blood pressure[4]. In the PROGRESS trial a combination of perindopril and indapamide as well as perindopril alone were tested. The reduction in the risk of stroke was approximately of the size that could be predicted from epidemiologic observations, meaning that there probably was no additional effect of the drugs tested over and above their blood pressure lowering effect[2].

However, recent clinical evidence reveal ACE inhibitors as potent agents in preventing ischemic events and in blocking an array of ischemic processes, including atherogenesis[5,6]. It seems that ACE inhibitors and probably angiotensin receptor blockers could improve endothelial function, cardiac and vascular remodeling, retard the anatomic progression of atherosclerosis, and reduce the risk of myocardial infarction, stroke, and cardiovascular death[7].

The first trial that showed other potential beneficial effects of ACE inhibitors beyond blood pressure reduction was the Heart Outcomes Prevention Evaluation (HOPE) trial. The HOPE trial showed in 9297 high risk patients that lowering of systolic blood pressure by only 3.3 mm Hg and of diastolic blood pressure by only 1.4 mm Hg using ramipril 10 mg once daily *per os* caused a relative stroke risk reduction by 32% as compared with placebo. The high percentage of stroke risk reduction was supposed to be due to independent, additional effect of ramipril besides blood pressure lowering[8].

The Losartan Intervention For Endpoint Reduction in Hypertension Study (LIFE) did not show any difference in 9193 participants aged 55-80 years with essential hypertension in blood pressure lowering between the angiotensin receptor blocker losartan and atenolol, however, a 25% reduction of the relative risk of stroke was observed in the losartan group during the follow-up period of 4.8 years. The results of this study may imply that the angiotensin receptor blocker losartan could confer benefits beyond the blood pressure reduction[9].

The Study on Cognition and Prognosis in the Elderly (SCOPE) randomized 4964 elderly patients with mild to moderate hypertension to the angiotensin receptor blocker candesartan or placebo, and followed them up for 4.5 years. The candesartan group showed a 10.9% reduction in the relative risk of stroke, myocardial infarction or death. The candesartan-based treatment reduced nonfatal stroke by 27.8% and all stroke by 23.6%. The large reduction of nonfatal and all stroke could implicate that the angiotensin receptor blocker candesartan could have some additional effects in stroke prevention besides blood pressure lowering[10].

On the other hand, calcium antagonists, especially the highly lipophilic ones, amlodipine nad lacidipine, may have some antioxidant properties. These drugs reduce the oxidation of LDL cholesterol and its influx into the arterial wall, and reduce atherosclerotic lesions in animals. Platelet production is suppressed by amlodipine, lacidipine or nifedipine in hypertensive patients. Thus, selective calcium antagonists could be potential antiatherosclerotic agents[11].

New evidence from longterm clinical trials of calcium antagonists indicate that these drugs can reduce the rate of atherosclerosis progression in hypertensive and coronary heart disease patients. In the Regression Growth Evaluation Statin Study (REGRESS), coadministration of the calcium antagonist amlodipine or nifedipine with pravastatin caused a significant reduction in the occurrence of new angiographic lesions[12,13].

In the Verapamil in Hypertension and Atherosclerosis Study (VHAS), verapamil was more effective than chlorthalidone in promoting regression of thicker carotid lesions in parallel with a reduction in the incidence of cardiovascular events[14].

In the Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT), amlodipine slowed the progression of early coronary atherosclerosis in patients with coronary artery disease[6].

In a subprotocol of the Interventions as a Goal in the Hypertension Treatment (INSIGHT) study, nifedipine gastrointestinal-transport-system (GITS) significantly decreased intima media thickness as compared with coamilozide (hydrochlorothiazide + amiloride)[15].

The European Lacidipine Study on Atherosclerosis (ELSA) was a randomized, double-blind trial in 2334 patients with hypertension comparing the effects of a 4-year treatment with either lacidipine or atenolol on the intima media thickness (IMT) in distal walls of common carotids and bifurcations. Although clinical blood pressure reductions were identical with both therapies, the yearly IMT progression rate was 0.0145 and 0.0087 mmg/year in the atenolol- and lacidipine-treated patients, respectively, yielding a 40% reduction in the latter. Patients with plaque progression were significantly less common, and those with plaque regression significantly more common in the lacidipine group. There was no significant difference between the two therapies in cardiovascular events, although the relative risk of stroke, major cardiovascular events and mortality showed a trend favoring lacidipine[16].

In recently published overviews of trials comparing active treatment regimens with placebo, the overview of placebo controlled trials of ACE inhibitors (four trials, 12,124 patients, mostly with coronary heart disease) has revealed reductions in stroke (30%), coronary heart disease (20%), and major cardiovascular events (21%). The overview of placebo controlled trials of calcium antagonists (two trials, 5520 patients, mostly with hypertension) has shown reductions in stroke (39%) and major cardiovascular events (28%). The authors conclude that strong evidence for benefits of ACE inhibitors and calcium antagonists is provided by the overviews of placebo controlled trials[17].

Blood pressure lowering for primary and secondary prevention of stroke should be undertaken using a variety of therapeutic agents, however, it seems that ACE inhibitors, angiotensin receptor blockers and calcium antagonists could have some additional beneficial effects on stroke prevention besides blood pressure reduction[18].

Blood pressure control must take due consideration of the adverse effects in some patients. Generally, the lower the blood pressure the better, with target levels of blood pressure in a vast majority of patients and healthy individuals below 130/70 or 120/80 mm Hg to minimize the occurrence of stroke and other cardiovascular complications, providing that adverse effects are acceptable to the patient[2,19].

Recently, it has been shown that blood pressure reduction in the acute phase of stroke has detrimental effects[20]. Therefore, blood pressure reduction should be delayed until the acute phase of stroke has resolved. Then blood pressure lowering should probably be introduced at a slow pace.

Conclusion

Nowadays, there is no doubt that treatment of hypertension has a significant role in primary and secondary prevention of stroke. Data from recently published large, randomized, clinical trials convincingly show that blood pressure lowering is associated with a significant reduction in the risk of stroke. Furthermore, it seems that the use of ACE inhibitors, angiotensin receptor blockers and calcium antagonists could provide some additional beneficial effects besides blood pressure and cholesterol lowering.

ACE inhibitors and angiotensin receptor blockers could improve endothelial function, cardiac and vascular remodeling, and retard the anatomic progression of atherosclerosis. Calcium antagonists, especially the highly lipophilic ones, may have some antioxidant properties. They reduce the oxidation of LDL cholesterol and its influx into the arterial wall, thus reducing atherosclerotic lesions in animals. Amlodipine, lacidipine or nifedipine suppress platelet production in hypertensive patients. Thus, selective calcium antagonists could be potential antiatherosclerotic agents.

Taking into account all these data, it could be supposed that a wider use of these drug classes could significantly improve our ability to prevent all vascular diseases, stroke in particular. Published recommendations for stroke treatment[21] could significantly improve and unify stroke treatment and prevention. The data from large randomized clinical trials shed bright light on stroke prevention in the forthcoming future.

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Sažetak

ULOGA NOVIH ANTIHIPERTENZIVNIH LIJEKOVA U PREVENCIJI MOŽDANOG UDARA

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Liječenje hipertenzije nesumnjivo ima značajnu ulogu u prevenciji moždanog udara. Podaci iz nedavno objavljenih velikih randomiziranih kliničkih studija pokazuju da je snižavanje krvnog tlaka povezano sa značajnim smanjenjem rizika nastanka moždanog udara. Smanjenje rizika nastanka moždanog udara kreće se od jedne trećine do jedne četvrtine, ovisno o studiji. Nadalje, izgleda da bi primjena inhibitora ACE, blokatora angiotenzinskih receptora i kalcijevih antagonista uza snižavanje krvnog tlaka mogla imati i neke dodatne povoljne učinke. Inhibitori ACE i blokatori angiotenzinskih receptora mogli bi poboljšavati funkciju endotela i kardiovaskularno preoblikovanje, te na taj način usporavati proces ateroskleroze. Kalcijevi antagonisti, a naročito visoko lipofilni, mogli bi imati antioksidativna svojstva. Oni smanjuju oksidaciju LDL kolesterola i ulazak LDL kolesterola u arterijsku stijenku. Amlodipin, lacidipin i nifedipin suzbijaju funkcije trombocita kod hipertenzivnih bolesnika. Stoga bi inhibitori ACE, blokatori angiotenzinskih receptora i kalcijevi antagonisti mogli biti i potencijalni antiaterosklerotski lijekovi. Uzimajući u obzir sve podatke moglo bi se pretpostaviti da bi ove skupine lijekova mogle značajno unaprijediti mogućnost prevencije krvožilnih bolesti, a pogotovo moždanog udara. Podaci iz nedavno objavljenih velikih randomiziranih kliničkih studija bacaju novu svjetlost na prevenciju moždanog udara u skoroj budućnosti.

Ključne riječi: *Krvni tlak – učinci lijekova; Cerebrovaskularni ispad – prevencija i kontrola; Hipertenzija – terapija lijekovima; Antihipertenzivni lijekovi – terapijska primjena*