

Stroke Prevention in Patients With Arterial Hypertension

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Abstract: Stroke is a pressing medical and social problem worldwide and in Uzbekistan due to its prevalence and severe consequences. In our country, every 1.5 minutes a stroke develops for the first time in one person, and at least 450 thousand new cases of this disease occur per year [1]. The cost of treating one patient with a stroke in Russia is 127 thousand rubles per year. Of those who survive, 15-30% remain disabled, which is a serious consequence not only for the patients themselves, but also for their environment. As a result, prevention of primary and prevention of recurrent stroke remain among the most pressing and studied issues of modern angioneurology.

Keyword: vascular dementia, cardiovascular diseases, arterial hypertension, vascular surgical treatment.

Activities aimed at primary prevention of stroke are based on the population-based social strategy for the prevention of cerebrovascular diseases at the state level, referred to as the mass strategy, and medical prevention, or high-risk strategy [2]. The later developed comprehensive approach to stroke prevention includes a population-based strategy, a high-risk strategy, and secondary prevention [3]. Secondary prevention primarily involves preventing recurrent stroke, as well as activities aimed at preventing, early detection, and correction of other cardiac and cerebral complications of the post-stroke period. It is known that the probability of developing a recurrent stroke in individuals who have already suffered a stroke or transient ischemic attack is 9 times higher than in the population. The population strategy is aimed at informing the population about modifiable risk factors associated with lifestyle and the possibility of their correction. The high-risk strategy involves early detection of patients from high-risk groups with subsequent preventive drug and (if necessary) vascular surgical treatment.

In terms of its impact on the risk of premature death from cardiovascular diseases, arterial hypertension (AH) ranks first among modifiable risk factors. At the same time, AH and atrial fibrillation contribute most to the development of acute cerebrovascular pathology, while smoking, hyperlipidemia and diabetes mellitus (DM) contribute most to the development of acute myocardial infarction. With an increase in DBP by every 10 mm Hg, the risk of stroke increases by 1.95 times (Prospective Studies Collaboration, 1995). For every 10 mmHg increase in systolic blood pressure (SBP), starting from 115 mmHg, stroke mortality doubles [4]. The greatest risk is observed in patients with increased pulse BP [5].

AG affects all structural and functional levels of the vascular system of the brain, triggering a whole complex of both adaptive and destructive changes in the main, regional vessels and microcirculatory bed [6, 7].

The effect of hypertension on the brain is manifested by multiple changes in the neurovascular unit at both the macro- and micro levels.

At the macro level, instability of blood pressure leads to a breakdown in the autoregulation of cerebral blood flow, the appearance of miliary aneurysms, the development of hypertensive stenosis of cerebral vessels, activation of endothelial dysfunction and acceleration of the atherosclerotic process. At the micro level, chronic inflammation reactions, autoimmune reactions are activated, mitochondrial dysfunction and lipid peroxidation reactions increase.

Thus, pathological processes in the vascular bed lead to damage to the brain tissue with the formation of hypertensive angioencephalopathy [8]. Decompensation of hypertensive angioencephalopathy is manifested by the development of acute vascular catastrophe and/or vascular dementia [9]. In this regard, antihypertensive therapy is the most important direction of primary prevention of stroke in people under 80 years of age. Most studies demonstrate a reduction in the risk of stroke by 30–40% with a moderate decrease in blood pressure, which implies 10–12 mm Hg for SBP and 5–6 mm Hg for DBP [10, 11]. The evidence base for the effectiveness of antihypertensive therapy for the prevention of stroke in old age (over 80 years) is less convincing [12]. The use of antihypertensive drugs in old age is limited by the high risk of adverse events and requires careful titration of dosages [13], which does not exclude hypertension from the list of the most important modifiable risk factors for stroke at this age.

Antihypertensive therapy is the basis of not only primary, but also secondary stroke prevention in patients suffering from hypertension [14]. The results of meta-analyses indicate a 19% reduction in the relative risk of recurrent stroke in patients receiving adequate antihypertensive therapy. However, excessive reduction of blood pressure in people who have had a stroke can worsen cerebral circulatory failure, which requires an individual approach when choosing a treatment regimen, taking into account not only the degree of hypertension, but also the nature of the stroke, the degree of stenosis of the carotid arteries, and existing cardiac pathology.

For patients with chronic cerebrovascular insufficiency who have experienced acute ischemic episodes, the following target SBP levels are recommended:

- 160–145 mm Hg with stage III hypertension and bilateral carotid stenosis $\geq 70\%$;
- 145–135 mm Hg with stage II hypertension and unilateral carotid stenosis $\geq 70\%$;
- 135–120 mm Hg is the minimum possible blood pressure for patients with stage I hypertension, high normal blood pressure and no significant damage to the main arteries of the head.

In patients who have suffered a hemorrhagic stroke, it is advisable to achieve actual normalization of blood pressure, since in this case the frequency of repeated strokes is linearly dependent on the blood pressure level [15].

The main principles of antihypertensive therapy are: a combination of antihypertensive drugs and non-drug methods of correcting blood pressure, individual selection of drugs taking into account concomitant factors, gradual reduction of blood pressure to the target level, orientation of the patient to long-term use of drugs, correction of concomitant risk factors [16].

Despite the high level of evidence for the preventive value of antihypertensive therapy in combination with lifestyle modification (defined in the 2011 EFNS guidelines as class I, level A) [17], this approach to stroke prevention often does not produce the expected results due to low patient adherence to physician recommendations [18, 19].

For drug correction of hypertension, diuretics, calcium antagonists, ACE (angiotensin-converting enzyme) inhibitors, angiotensin II receptor antagonists, α -blockers, and centrally acting drugs are used [20].

In most cases, target BP levels can be achieved with a combination of 2 antihypertensive drugs; monotherapy effective in 20–30% of patients with hypertension [21]. Monotherapy can be used in patients with stage I hypertension and low/moderate risk. After a stroke, any antihypertensive drug can be used; the most convincing evidence base is available for a combination of ACE inhibitors and diuretics (PROGRESS, 2006) [22].

Antihypertensive drugs from the ACE inhibitor and angiotensin-renin receptor blocker groups are currently considered the drugs of choice for secondary stroke prevention (level of evidence I) [23]. These two groups of drugs reduce the frequency of recurrent strokes not only in hypertensive patients, but also in normotensive patients due to the pleiotropy of the drugs.

The PROGRESS study [24] examined the possibility of preventing recurrent stroke when taking ACE inhibitors in 6105 patients (mean age 64 years, baseline blood pressure averaged 147/86 mm Hg) with a history of transient ischemic attack or who had suffered a minor stroke in the previous 5 years. The total number of cases of stroke, myocardial infarction, and death from cardiovascular diseases decreased by 26% compared with the control group.

The antihypertensive effect of ACE inhibitors is based on their ability to suppress the activity of angiotensin - I -converting enzyme (ACE kinase II), which controls the rate of angiotensin II synthesis, i.e. inhibition of RAAS activity. By inhibiting RAAS activity, ACE inhibitors reduce the formation of angiotensin II (AT II), helping to reduce the vasoconstrictor and aggregation effect, and aldosterone secretion. The antihypertensive effect of ACE inhibitors is based on their direct effect on the cardiovascular system through improvement of blood rheological parameters: viscosity, platelet and erythrocyte aggregation activity.

All ACE inhibitors have cardio- , angio- , nephroprotective and metabolic effects. Cardioprotective effects are manifested in the restoration of the balance between the myocardium's need for oxygen and its supply, a decrease in pre- and afterload on the left ventricle, a decrease in its volume and mass, a slowdown in remodeling , a decrease in sympathetic stimulation, and an antiarrhythmic effect.

The angioprotective effect is due to a direct antiatherogenic effect, antiproliferative and antimigration effect on the smooth muscle cells of the vascular wall, improvement of endothelial function, antiplatelet effect, and enhancement of endogenous fibrinolysis .

The nephroprotective effect is characterized by a decrease in intraglomerular hypertension, an increase in the glomerular filtration rate, an increase in sodium uresis and a decrease in potassium uresis , a decrease in proteinuria, and an increase in diuresis.

The main metabolic effects of ACE inhibitors are increased breakdown of very low-density lipoproteins, decreased synthesis of triglycerides, increased synthesis of high-density lipoprotein cholesterol, increased sensitivity of cellular receptors to insulin, and increased glucose consumption.

The multidisciplinary action of ACE inhibitors allows them to be considered the “gold standard” in the treatment of cardiovascular diseases.

Currently, more than 20 ACE inhibitors are known . In the context of preventive treatment of stroke, preference is given to prolonged-action ACE inhibitors , which include fosinopril (Monopril), lisinopril , enalapril , ramipril , perindopril , etc.

lipophilicity index fosinopril allows to significantly suppress the effects of the tissue form of ACE, slow down the processes of pathological remodeling in target organs and reduce the incidence of side effects (cough). In addition, Monopril , unlike other ACE inhibitors , has a dual compensatory elimination pathway (liver and kidneys), so Monopril is the drug of choice in elderly patients with liver and kidney disease.

The antihypertensive effect of fosinopril occurs 1–3 hours after oral administration, the peak action (maximum concentration of the drug in the blood) is 6 hours, the half-life is 12–13 hours, and the duration of action is 34 hours. Steady-state therapeutic levels of fosinopril in the blood are achieved in 2–3 days with regular administration of the drug at a dose of 10 mg x 2 times a day . Fosinopril causes dilation of arterioles and veins, which is accompanied by a decrease in SBP and DBP by 15%.

The efficacy of different doses of fosinopril (10, 40, and 80 mg/ day) was studied in a multicenter, placebo-controlled trial in 220 patients with mild to moderate hypertension (DBP 95–115 mm Hg). If monotherapy was ineffective after 4 weeks , chlorthalidone 25 mg/ day was added . A significant decrease in SBP was observed with all doses of fosinopril , and DBP was significantly reduced only

with doses of 40 and 80 mg/ day . The proportion of patients who did not require a diuretic was 46% in the placebo group and 41, 58, and 57% in the groups receiving fosinopril at doses of 10, 40, and 80 mg/ day , respectively. The achieved effect was maintained in all groups during long-term therapy. The drug was well tolerated, with only 9 patients refusing to continue therapy due to side effects [25].

Fosinopril effectively reduces blood pressure not only at rest, but also under stress, both physical and mental [26]. A study using daily blood pressure monitoring and a bicycle ergometric (BEM) test demonstrated that even a small dose of fosinopril (20 mg/ day) for 45–60 days can achieve a significant reduction in blood pressure. A decrease in SBP by 13.5 mm Hg and DBP by 9.7 mm Hg was noted, with blood pressure levels decreasing both during the day and at night [27]. As with other ACE inhibitors , the effectiveness of fosinopril increases when combined with thiazide diuretics. When comparing the efficacy of fosinopril at a dose of 20 mg/ day , hydrochlorothiazide – 12.5 mg/ day , their combination and placebo in patients with moderate hypertension (DBP 95–110 mm Hg), it turned out that combination therapy is superior in efficacy to both drugs prescribed as monotherapy [28]. The efficacy and safety of fosinopril were confirmed in the Russian open multicenter post-marketing study FLAG. 2829 patients with hypertension of I and II degrees were examined. The target reduction in blood pressure with fosinopril by the 3rd month of therapy was achieved in 62.1% of patients. In 43.4% of patients, fosinopril was used at a dose of 10 mg/ day , in 20.4% – at the same dose in combination with a diuretic, 28.5% received 20 mg of fosinopril in combination with a diuretic and 7.7% – monotherapy with 20 mg of fosinopril . Adverse effects were noted in only 8.3% of patients, and the probability of their development did not depend on the dose of fosinopril , and with combination therapy the risk increased [29]. As demonstrated in the PHYLLIS study (The Plaque Hypertension Lipid-Lowering Italian Study), fosinopril, even as monotherapy , has an anti-atherosclerotic effect, although certainly to a lesser extent than statins .

Thus, ACE inhibitors are a large group of drugs with multicomponent antihypertensive efficacy and good tolerability. There is convincing evidence that ACE inhibitors can improve the long-term prognosis in patients with hypertension, especially in combination with diabetes and atherogenic dyslipidemia . Monopril is a drug with proven hypotensive efficacy and protective properties in relation to target organ damage. The drug is well tolerated. The use of original ACE inhibitors (Monopril) is a promising direction for stroke prevention in patients with hypertension.

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