

Therapy of Hypertension in Primary Prevention of Stroke – Possibility so Far Not Used

Widimský J.

Department of Cardiology – IKEM, Prague, Czech Republic

SUMMARY

Many studies proved that pharmacological treatment of systolic-diastolic hypertension and isolated systolic hypertension in the elderly have led to the significant decrease of stroke prevalence by more than 40% within several years. The prevalence of strokes decreased in the Czech Republic during the period 1985–2002 by more than 40%, which creates roughly two-thirds decrease of rate of strokes observed in the USA. Nevertheless, we cannot be satisfied with the antihypertensive therapy in the Czech Republic, because only 18% of the patients are effectively controlled, which means BP < 140/90 mmHg. Insufficiently intensive treatment is caused first of all by the low use of combination treatment. From the prognostic point of view, the level of the systolic pressure in subjects older than 50 years is more significant than the level of diastolic pressure. The risk of stroke increases already from the systolic blood pressure level 115 mmHg almost linearly. Calcium channel blockers or diuretics are the most suitable drugs for the treatment of isolated systolic pressure in the elderly. The risk of stroke is also increased in subjects with excessive rise of BP in the morning hours. Therefore it is necessary to use entirely the drugs acting for 24 hours in the treatment of hypertension in the elderly. The trials from the last years (HOPE study, PROGRESS study) demonstrated also that the lowering of blood pressure decreases the prevalence of strokes not only in hypertonics but also in normotonics in primary and secondary prevention. The literary data show that 27% of ischaemic cerebrovascular events and 57% of cerebral haemorrhages that occurred in the "treated" hypertonics were due to insufficiently treated hypertension. Missing therapy of hypertension is responsible for 22.8% of strokes in males and 25.4% in females. From the above-mentioned data we can find large reserve and potential for further significant decrease of strokes among the population.

Key words: hypertension in elderly, systolic hypertension, strokes, primary prevention of strokes, hypertension control.

Čas. Lék. čes., 2004, 143, pp. 657–663.

The prevalence of systolic-diastolic hypertension, but also isolated systolic hypertension is in the elderly substantially higher than in the younger age groups. American trial NHANES III reports that hypertension in the USA is present in 60% of older white population (1). Kannel et. al. 1981 (2) report the following hypertension type distribution in 65–89 year old hypertensive patients: 60% have isolated systolic hypertension, 30% systolic-diastolic hypertension and 10% isolated diastolic hypertension. Isolated systolic hypertension is defined by systolic pressure 140 mmHg or higher and by normal diastolic pressure – e.g. lower than 90 mmHg (3).

The prevalence of isolated systolic hypertension is according to Staessen et. al. 1990 (4) 5% in age group 60–69 years, 12.6% in age group 70–79 years and 23.6% in age group 80–89 years.

In the patients with isolated systolic hypertension the blood pressure amplitude is increased, sign of decreased elasticity of arteries, which is even a better predictor of cardiovascular risk than systolic and diastolic pressure itself (5, 6).

Relative risk of cardiovascular diseases is higher in the elderly than in young people and it holds for every level of the blood pressure. Though absolute probability of cardiovascular disease is significantly higher in older hypertonics, the same level of blood pressure decrease in the elderly has bigger therapeutic impact in shorter time than in younger hypertonics. Nevertheless contradictions had existed about this issue and even in the 80s in our medical journals it could be found the statement that in the therapy of hypertension "less means often more".

In the 80s some of the physicians were aware of antihypertensive therapy which could worsen the prognosis of hypertension in the elderly. This awareness originated from few case

histories describing the onset of complications of hypertension in relation to antihypertensive therapy. It became clear that in most cases it was incorrect therapy, using medication which led to severe blood decrease in orthostatic position. Also cerebrovascular complications are known since the time when ganglioplegics (e.g. hexametonium) as a monotherapy of hypertension had been used (7). From the later medication, guanethidin monotherapy had been accompanied by these complications. This type of therapy should never be used in older hypertonics.

Systolic pressure is a predictor of future stroke and ischaemic heart disease, heart failure and all-cause mortality with higher significance than diastolic pressure (8).

Systolic pressure appeared to be the best individual predictor of coronary and cerebrovascular events in the Cardiovascular Health Trial comprising 5,888 subjects at the age of 65 years and older (9).

Ischaemic strokes represent 80% of total strokes, haemorrhagic ones only 20%. Embolic heart events, atherosclerosis of the large vessels (carotic atherosclerosis) and minor vessels diseases represent the mechanisms of ischaemic strokes and less frequent mechanisms are arterial dissection, hematological diseases and other conditions. Cerebral haemorrhage and sub-arachnoideal haemorrhage represent haemorrhagic strokes.

Non modifiable risk factors are age, male sex and genetic factors. Modifiable factors are according to the ISH document from 2003 (10) increased blood pressure (systolic pressure higher than 115 mmHg is the most important), which is responsible for 60% of the total risk of strokes in the population.

Other factors are smoking, abuse of alcohol, obesity, diabetes mellitus, carotic atherosclerosis, atrial fibrillation and others.

However, at the beginning of the 90s, large studies on antihypertensive treatment in the elderly were published: British trial – MRC trial 1992 (11), Swedish trial – STOP trial 1991 (12) and American trial on isolated systolic hypertension-called SHEP 1991 (13). Table 1 shows the results of 5 studies on therapy of hypertension in the elderly, in analysis according to MacMahon and Rodgers 1993 (14). This analysis also comprises the analyses of the subgroups of older hypertensives from previous studies from the 80s, e.g. Australian trial on the mild hypertension 1981 (15), study of Coop and Warrender 1986 (16) or EWHPE trial (European Working Party on High Blood Pressure in the Elderly Trial) 1985 (17).

The studies of antihypertensive therapy of the elderly comprised in the Table 1 contain the data from 12,483 patients older than 60 in total. The difference in the systolic pressure between the treated and control group was 12–14 mmHg, the difference in diastolic pressure 5–6 mm Hg. The prevalence of coronary events, strokes and deaths caused by vascular disorders was significantly lower in this trial due to pharmacotherapy.

Table 2 shows the comparison of two studies on therapy of the isolated systolic hypertension in the elderly – SHEP trial (13) and SYST-EUR trial (18) and the 2 studies on systolic-diastolic hypertension in the elderly – STOP trial (12) and MRC trial 1992 (11) published mostly in the 90s. SHEP trial (13) and SYST-EUR trial (18) were the first trials showing the great significance of the drug therapy of isolated systolic hypertension in the elderly.

Till the end of 80s it had been generally accepted that normal systolic pressure was defined as the sum of 100 + age, so in 70 years old patient the systolic 170 mmHg had been considered normal. The study on the therapy of isolated systolic hypertension persuaded the physicians about the significance of the systolic blood pressure normalisation. Since the 90s, systolic blood pressure lower 140 mmHg is considered normal also in the elderly and the old people.

The antihypertensive therapy of the elderly represents also the effective prevention of heart failure and coronary events in the elderly (Tab. 2). Nevertheless the studies on antihypertensive therapy underestimate the real impact of antihypertensive therapy in that the patients with concomitant diseases and the patients with more severe hypertension requiring a therapy usually have not been included into these studies (19). Moreover it should be emphasized that therapy has usually been started in the subjects from control placebo group when further increase of blood pressure could not be tolerated from ethical reasons and due to not ideal patients adherence to therapy in the mentioned studies.

Patients with the combination of hypertension and diabetes have the greatest benefit from well controlled systolic pressure. The significance of the aggressive antihypertensive therapy in the primary prevention of strokes is shown by the results of UKPDS 39 trial (20) that compared the intensive antihypertensive therapy with less intensive therapy (Tab. 3). The difference in blood pressure between both treatment groups was 10/5 mmHg; nevertheless the difference in the prevalence of fatal strokes was 56% and chronic heart failure was present by 58% less frequently in intensively treated group of type 2 diabetics with hypertension (20).

In 2004, Lawes et al. (21) published a meta-analysis of more than 40 randomised studies on the influence of blood pressure decrease on the risk of strokes. Meta-analysis comprised more than 188,000 participants and ca 6,800 strokes. The results of the meta-analysis showed that in northern America, western Europe and Asian-Pacific region every decrease of the systolic pressure by 10 mmHg led to the lower risk of strokes of one third in the age group 60–79 years (21). This rule holds for both sexes, various geographic regions, various types of strokes, either fatal or non-fatal.

Lawes et al. (21) confirmed at the same time *that the relation of blood pressure and risk of stroke is continuous at least to the blood pressure level of 115/75 mmHg.* This relation is dependent on age, but positive correlations exist even in 8th life decade. The data of the randomised studies in persons with average age of 70 show as well that systolic blood pressure

Tab. 1. The results of five trials on hypertension in the older persons by Mac Mahon and Rodgers 1993

Risks	Therapy	Controls	Decrease of risk
strokes	288	438	■ 34% ■ 2p<0.0001
fatal strokes	78	120	■ 19%
IHD	346	438	■ 2p<0.05
fatal coronary events	208	279	■ 23%
vascular deaths	382	494	■ 2p<0.001

Tab. 2. Treatment of hypertension of older people (review of large studies on antihypertensive treatment)

Name of study	STOP	MRC	SHEP	SYST-EUR
n	1627	4396	4736	4695
age	70–84	65–74	60–80	60–85
mean BP at the beginning	195/102	185/91	170/77	174/86
RR of strokes	0.58	0.75	0.67	0.58
RR of IHD	0.87	0.81	0.73	0.73
RR of risk failure	0.49	not stated	0.45	0.76
RR of all c-v events	0.60	0.83	0.68	0.73

RR – relative risk, IHD – ischemic heart disease, c-v – cardiovascular

Tab. 3. Study UKPDS 38: a comparison of intensive and less intensive treatment of hypertension in diabetes mellitus

	Intensive therapy	Less intensive therapy
average blood pressure	144/82 mmHg	154/87 mmHg
deaths due to diabetes	relative risk lower in the group with intensive therapy	
fatal strokes	-32%	p=0.019
heart failure	-56%	p=0.044
	-58%	p=0.0043

decrease by 10 mmHg leads to lowered risk of stroke roughly by one-third.

Table 4 shows the relative mortality risk of stroke for cases with systolic blood pressure decrease by 20 mmHg. Usual systolic BP (blood pressure) is >115 mmHg (21). As seen from Table 4, decrease of systolic BP leads to a lower risk of stroke for all age groups. The effect of various antihypertensive drugs appeared to be quite similar, but blood pressure decrease was of greater benefit. The results of meta-analysis indicate that blood pressure lowering and its maintenance on low level is more important than the choice of antihypertensive medication.

Tab. 4. Relative risk of mortality due to strokes for systolic blood pressure 20 mmHg lower (Usual systolic pressure BP >115 mmHg)

Age group	N – number of deaths	Relative risk
40–49	414	0.36
50–59	1372	0.38
60–69	2939	0.43
70–79	4327	0.50
80–89	2636	0.67

But already the data from Prospective Study Collaborators from 2002 (22), based on the analysis of more than 1 million cases did not show any value of blood pressure, under which vascular mortality rate would increase. For example, overall mortality was only half in population with systolic BP 120 mmHg compared with systolic blood pressure 140 mmHg.

Isolated systolic hypertension is treated in the same way as systolic-diastolic hypertension in the elderly. The treatment is started by non-pharmacological treatment.

There are some specific aspects of treatment of hypertension in the elderly:

- we begin with a small dose of drug
- we use the lower doses of the drugs, usually half of doses used in the treatment of hypertension in the middle-aged patients
- blood pressure should be decreased slowly, not more than 10 mmHg per month
- drugs acting for 24 hours should be used
- the number of tablets should be minimized
- laboratory follow-ups are necessary
- comorbidity should be taken in consideration when deciding on treatment

Because sensitivity of baroreceptors is often damaged in older hypertonics and the renal function is lowered, the patients are at higher risk of postural hypotension and volume depletion (23). Hypotensive drugs that can cause postural hypotension should not be used in the older hypertonics – peripheral adrenergic blockers, prazosin, guanetidin, labetalol and high doses

of diuretics (23). Centrally acting alpha-2-agonists may worsen the cognitive functions.

On principle, we do not administer:

- drugs that can cause orthostatic hypotension
- drugs that can deteriorate accompanying illnesses
- drugs that may lead to the worsening of cognitive functions

We also do not use non-retarded or insufficiently retarded nifedipine in the treatment of hypertension in older people, not even in the treatment of hypertensive crisis (23, 4). Nifedipin is known to increase the risk of IHD by activating sympathetic nervous system and renin-angiotensin system. On the other hand, there is no objection against using of fully retarded nifedipine, acting for 24 hours.

BLOOD PRESSURE INCREASE IN MORNING HOURS

The demand to use only drugs acting for 24 hours is based on the fact that most strokes and myocardial infarctions occur between 6AM and 12AM during the 24-hour cycle. It is also shown from the results of CONVINCENCE study from 2003 (25) which compared the treatment with retarded verapamil with the treatment with atenolol or hydrochlorothiazide. The increased occurrence of ischaemic and haemorrhagic stroke, sudden death and myocardial infarction in the morning hours is caused by the increase of sympathetic activity, decreased fibrinolysis and increased platelet aggregation (23).

The latest study by Kario et al. 2003 (26) proved that excessive rise of the morning blood pressure is very important aspect for the genesis of stroke. These authors (26) calculated the difference between the mean systolic BP during the first two hours after awakening and the lowest systolic BP during night, using the method of ambulatory 24hour BP monitoring. The older hypertonics in the upper decile of difference between the lowest nocturnal systolic BP and systolic BP during the first two hours after awakening (55 mmHg and more) had higher incidence of silent brain infarcts (19% vs. 7.3%, p=0.004) compared with other patients with lower morning rise to blood pressure.

INSUFFICIENT CONTROL OF BLOOD PRESSURE IN MORNING HOURS THUS MAY LEAD TO FURTHER SIGNIFICANT INCREASE IN THE RISK OF STROKE EVENTS

Higher BP can be easily found out by the home blood pressure measurement. If morning BP is higher than 140/90 mmHg, it is necessary to increase the effectivity of antihypertensive treatment by medication that can guarantee the therapeutical effect for at least 24 hours (27).

HOW TO EVALUATE 24-HOUR CONTROL OF BLOOD PRESSURE?

Methods for assessment of medication's capability to provide 24-hour BP control are as follows:

- BP measuring at the end of the dosing period in morning hours (before the patient takes the next daily dose of the drug)
- morning home BP measurement (enables BP measuring at the end of dosing period in so called "through period" and assures relatively standard conditions)
- 24-hour ambulatory BP monitoring (Holter)

Isolated systolic hypertension is treated in the same way as systolic-diastolic hypertension in older persons. The treatment is started with non-pharmacological approaches.

Requirement for 24-hour activity of antihypertensive drugs is important. At the end of the dosage period blood pressure's decrease should represent at least 50% of hypotensive effect achieved during the peak activity of the drug. It is known that strokes arise the most often during the morning hours when sympathetic activity and thrombogenic properties of blood escalate. In the treatment of hypertension, the drugs with 24-hour activity are preferred because the patients' treatment adherence is better and control of hypertension is continuous (medication with short-acting antihypertensives is unsuitable). Systolic BP is mostly lowered with low doses of thiazide diuretics, as well as with indapamide or metipamide and with long-acting dihydropyridine calcium channel blockers. We also present the list of drugs that may have favourable effect on the concomitant diseases and complications (23) in Table 5.

Tab. 5. Drugs that can have favourable effect on concomitant diseases or complications (modification by the 6th report of JNC)

angina pectoris	beta-blockers, long-acting calcium channel blockers
atrial fibrillation, atrial tachycardia	beta-blockers, verapamil or diltiazem
type II diabetes mellitus, without proteinuria	ACE inhibitors, AT ₁ blockers
chronic heart failure	metoprolol, bisoprolol, carvedilol
migraine	hydrophilic beta-blockers, verapamil, or diltiazem
osteoporosis	thiazide diuretics
prostate hypertrophy	alpha-blockers
renal failure (pay attention to renovascular hypertension and creatinin 265 µmol/l and higher)	ACE inhibitors, AT ₁ blockers
perioperative hypertension	beta-blockers

SIGNIFICANCE OF BLOOD PRESSURE LOWERING IN NORMOTONICS IN PRIMARY AND SECONDARY PREVENTION OF STROKES

Blood pressure lowering in primary prevention of strokes is effective not only in hypertonics but also in normotonics. As it was already stated according to epidemiological studies, the risk of stroke increases from BP 110/70 mmHg. The first study that proved the significance of blood pressure lowering in primary prevention in normotonics was HOPE study (28, 29).

HOPE study (28, 29) analyzed the influence of treatment with ramipril on prevalence of cerebral vascular events. The study recruited 9,279 patients at the age ≥55 with concomitant ischaemic heart disease, diabetes or ischaemic disease of the lower

extremities or the patients after stroke and with another risk factor. In HOPE study, ramipril 10 mg or placebo were added to the treatment of patients in with a risk. The results of the study are shown in Table 6.

Tab. 6. Result of the HOPE study – prevention of strokes

	Ramipril n=4645	Placebo n=4652	Relative risk
all stroke events	156	226	0.68 (0.56–0.84)
nonfatal stroke events	139	182	0.76 (0.61–0.94)
fatal stroke events	17	44	0.39 (0.22–0.67)

As seen in Table 6, prevalence of all strokes was lowered by 32% ($p < 0.0002$), prevalence of the fatal strokes was lowered by 61%.

The main surprising finding of HOPE study was the fact that favourable effect was observed even in the patients with normal BP. HOPE study proved the significance of blood pressure lowering even in normotonics in terms of primary prevention of strokes.

Similar finding was observed also in the PROGRESS study (30) that detected the significance of blood pressure lowering for secondary prevention of strokes.

The active treatment in PROGRESS study (30) (perindopril +indapamide) led to statistically significant reduction of stroke recurrences by 28% (95% CI, 17–38%, $p < 0.0001$). Some difference was apparent already in the first year and increased during further course of the study. Stroke recurrences in some subgroups of patients are shown in Table 7.

Tab. 7. Recurrences of stroke events in the PROGRESS study on the basis of case history

	Active treatment n	Placebo n	Relative risk (95% CI)
hypertonics	163	235	0.67 (0.5–0.81)
patients without hypertension	144	185	0.78 (0.63–0.97)
diabetes mellitus	48	65	0.67 (0.46–0.98)
patients without diabetes	259	355	0.72 (0.62–0.85)
ischemic stroke	236	307	0.76 (0.64–0.90)
hemorrhagic stroke	28	49	0.52 (0.33–0.83)
TIA/amaurosis	333	449	0.66 (0.42–1.02)
sum	307	420	0.72 (0.62–0.83)

As seen in Table 7, the active treatment in PROGRESS study (30) prevented stroke recurrences both in hypertonics and in patients without hypertension. Secondary preventive effect of treatment was achieved in the patients with history of haemorrhagic stroke.

Studies HOPE (28) and PROGRESS (30) are complementary to each other. HOPE study (30) showed possibilities of primary prevention of strokes. PROGRESS study (30) showed possibilities of primary prevention of coronary events, HOPE study (30) showed possibilities of secondary prevention of coronary attacks.

WHAT IS THE AGE LIMIT OF HYPERTENSION TREATMENT?

Pharmacological treatment of hypertension is recommended in older people in the age group of 60–80 years. For the present,

there is no evidence about effectivity and safety of pharmacological antihypertensive treatment of persons older than 80 years. Guyeffier et al. (31) performed a meta-analysis of the studies dealing with the treatment of hypertension in very old people. The results of this meta-analysis showed that the treatment of hypertension in very old people (older than 80 years) on the one hand could bring about a significant reduction of strokes by 36%, it could also decrease significantly the prevalence of heart failure, but on the other hand the all-cause mortality was not significantly influenced, on the contrary, trend towards insignificant increase of overall mortality by 14% was observed.

The results of the pilot study HYVET (32) showed similar results as the above-mentioned meta-analysis. Just 66% lowering of strokes due to the treatment with diuretic bendroflumethiasid ($p=0.02$) was significant. Decrease of prevalence of strokes by lisinopril was not statistically significant (32). If difference between all actively treated patients (with diuretics or ACE inhibitors) and untreated group was analyzed, then the difference in terms of lowering of risk of stroke was significant and made 53% (32). Mortality from other diseases showed only a trend towards the risk increase, because only 15 patients died of other diseases (32). Simply said, it is not clear whether prevention from stroke on the one hand is not associated with an increase of death risk due to other causes than cerebrovascular ones on the other hand.

According to the authors of the study, the results of this pilot study prove the necessity of performing the large study HYVET, because their results are based on a small sample. The pilot study proved feasibility and eligibility of such study.

LIMITS OF RECOMMENDATIONS

Favourable impact of hypertension treatment cannot be fully generalized.

Mostly older persons without other serious diseases were recruited to the large studies of antihypertensive treatment – which could be selection bias.

Especially in patients with other serious illnesses that shorten the life expectancy or markedly limit quality of life, the physician must individually assess the possible benefit of antihypertensive treatment.

CONTROL OF SYSTOLIC HYPERTENSION IN THE POPULATION

On the basis of the results of NHANES III register, the inadequate control of systolic BP in hypertonics older than 65 is the main cause of inadequate hypertension control in the population in the USA (33).

Normalization of diastolic BP is easier than normalization of systolic BP. The results of the series of studies, lastly of LIFE study (34), demonstrated that decrease of systolic BP to the values ≤ 140 mmHg was achieved only in 49% of losartan group of patients and in 46% of atenolol group. Normalization of diastolic pressure was achieved in LIFE study in 89% in both treated groups. The best results were obtained in VALUE study in which systolic pressure normalization was achieved in more than 70% of hypertonics.

COMBINATION TREATMENT

On principle, drugs from various classes should be combined, which provides an additive antihypertensive effect. The comparison of hypertension control in the population from six districts participating in MONICA programme together with outpatient department for hypertension of Department of preventive cardiology IKEM Prague showed the achievement of the target BP values ($<140/<90$ mmHg) in 38.1% of the population but in 75.1% patients treated at the specialized outpatient department in IKEM Prague (35). The control of systolic pressure was also much more successful – 74% vs. 46% ($p=0.001$). The difference was caused by far more frequent use of combination of 3 or more antihypertensives at the Department of preventive cardiology IKEM than in the population (47.5% vs. 17.7%) (35). Worse control of hypertension in population is also due to popularity of monotherapy among general practitioners, not only in this country but also in France or Great Britain. But monotherapy may normalize BP only in 30–40% of hypertonics (23).

Thus therapy of hypertension represents quite fundamental possibility of radical decrease of mortality caused by strokes. In the USA since the 50s, there has been a decrease of cerebrovascular mortality by 60%. This decrease was caused first of all by lowered prevalence of vascular cerebral events, to a lesser extent by lowering mortality of strokes already arisen.

But it is necessary to remind that the rate of cerebrovascular mortality started to drop in the USA much sooner than effective antihypertensive therapy had been discovered. Nevertheless the introduction of this treatment sharply accelerated the decrease of rate of cerebrovascular mortality. The American data clearly prove the significance of antihypertensive treatment for the lowering of cerebrovascular mortality. Finnish data also show that drop of cerebrovascular mortality went hand in hand with improved control of hypertension in the population. In the Czech Republic, rate of mortality due to strokes did not change in the 70s and at the beginning of the 80s and remained high (one of the highest in the world), and just in half of the 80s it began to drop (36). Nevertheless this decrease continued the whole 10 years, so that till 2002 cerebrovascular mortality decreased in the males by 42.2% compared with 1985 and similarly in the females by 40.9%, which is delightful and probably reflecting the improved control of hypertension also in population in this country, as it is proved by the data by Cífková et al. (37).

The influence on blood pressure lowering in primary prevention of strokes can be summarized as follows:

Blood pressure decrease lowers the risk of strokes roughly by one-third in various high-risk groups.

Blood pressure lowering helps not only to the hypertonics, but also to the high-risk patients with normal BP.

The studies show that 5 main classes of antihypertensives (diuretics, beta-blockers, ACE inhibitors, calcium channel blockers and AT₁ blockers) are effective both in blood pressure lowering and in lowering the risk of strokes.

Diuretics are at least as effective as the other antihypertensives in the prevention of strokes.

Lowering of systolic hypertension leads to the same decrease of risk of strokes in the middle-aged people, older and old people.

THE RELATIONSHIP OF UNTREATED HYPERTENSION OR INADEQUATELY TREATED HYPERTENSION TO THE ONSET OF STROKE

There are studies that show that hypertension is not controlled properly in a great many patients after stroke (38). These authors ascertained that BP levels higher than 140 mmHg and 90 mmHg were found out in 78% of patients with ischaemic cerebral vascular events, in 85% of patients with cerebral hemorrhage and in 65% of hypertonics without strokes.

In the opinion of these authors, 27% of ischaemic cerebral vascular events and 57% cases of cerebral haemorrhage, that appeared in "treated" hypertonics were caused by not intensively enough treated hypertension (39).

The mistakes in therapeutical procedure that could be associated with onset of stroke were found out in 44% of hypertonics in Great Britain in the medical practice of the general practitioners. The most frequent doctors' mistake was lack of systematic therapy after detection of hypertension. The most common mistake the patients made was continuing smoking and missing body weight reduction. Moreover, a portion of patients interrupt the therapy due to lack of sufficient motivation for the treatment, the other portion do not take drugs regularly or do not take them at all.

That is to say, there is no correlation between symptoms and severity of hypertension. Significant portion of patients also interrupt treatment after normalization of BP with erroneous idea of complete health restoring. The interruption of treatment due to the adverse reactions occurs in 10–15% patients.

Klungel et al. 1999 (39) followed the effectivity of hypertension control in the treated hypertonics. They selected 2,616 hypertonics from the population of about 450,000 males and females older than 20 years. They ascertained that prevalence of strokes was significantly higher during 4.6 years in untreated hypertonics compared with treated hypertonics.

Percentage of cases of stroke due to lack of hypertension treatment was 22.8% in the males and 25.4% in the females.

THERAPEUTICAL GOALS

The European guidelines for the treatment of hypertension (4) recommend to reach the normalization of blood pressure, i. e. its lowering on the level less than 140/90 mmHg also in the elderly, both in systolic-diastolic hypertension and in isolated systolic hypertension. In patients with diabetes mellitus, the target levels of blood pressure are even lower ($\leq 130/80$ mmHg).

The result of the studies HOPE (28) and PROGRESS (30) show that it is necessary to try to decrease blood pressure also in normotonics, at least in those with high normal BP.

The goal is not only BP lowering, but also slowing down of development or even regression of organ manifestation and influencing of further course of vascular complications of hypertension.

The prognosis of hypertension depends more on the level of BP during the treatment than on the level of BP before the treatment. The lower blood pressure is achieved during the antihypertensive treatment, the better prognosis for the patient. There are also other risk factors of cerebrovascular events including smoking (increases the risk about twice), diabetes mellitus, obesity, alcohol intake and physical inactivity. There are no proofs about influence of non-pharmacological therapy

on occurrence of strokes even though there are no doubts about its benefit. Main problem of non-pharmacological therapy in this country and in the world that still remains is unsatisfactory adherence of significant portion of the patients to this form of therapy. But it is known that excessive consumption of alcohol increases the risk of stroke. Alcohol intake should be limited to 20–30 g per day in the males and to 10–20 g per day in the females or in males with a small body habitus.

In summary, the primary prevention of strokes is based first of all on the treatment of hypertension. The risk is also lowered by abstinence from smoking, limiting alcohol consumption, reduction in body weight in the obese people and increase of physical activity.

Treatment of hypertension is the most effective form of the primary prevention of vascular cerebral events.

Abbreviations

BP	–	blood pressure
IKEM	–	Institute of Clinical and Experimental Medicine, Prague
ISH	–	International Society of Hypertension
JNC	–	Joint National Committee

REFERENCES

1. **Burt, V. L., Whelton, P., Roccella, E. J. et al.:** Prevalence of hypertension in the US adult population: results from the third National Health and Nutrition Examination Survey, 1988-1991. *Hypertension*, 1995, 25, pp. 305-313.
2. **Kannel, W. B., Wolf, P. A., McGee, D. L. et al.:** Systolic blood pressure, arterial rigidity and stroke. The Framingham study. *JAMA*, 1981, 245, pp. 1225-1228.
3. Guidelines Committee. 2003 European Society of Hypertension – European Society of Cardiology guidelines for the management of arterial hypertension. *J. Hypertens.*, 2003, 21, pp. 1011-1053.
4. **Staessen, J., Amery, A., Fagard, R.:** Editorial review: isolated systolic hypertension in the elderly. *J. Hypertens.*, 1990, 8, pp. 393-405.
5. **Madhavan, S., Ooi, W. L., Cohen, H., Alderman, M. H.:** Relation of pulse pressure and blood pressure reduction to the incidence of myocardial infarction. *Hypertension*, 1994, 23, pp. 395-401.
6. **Franklin, S. S., Khan, S. A., Wong, N. D. et al.:** Is pulse pressure useful in predicting risk for coronary heart disease? The Framingham Heart Study. *Circulation*, 1999, 100, s. 354-360.
7. **Widimský, J.:** 50 let historie léčby hypertenze. Praha, Triton, 2001, 159 p. (in Czech)
8. National High Blood Pressure Education Program Working Group. National High Blood Pressure Education Program working group report on hypertension in the elderly. *Hypertension*, 1994, 23, pp. 275-285.
9. **Psaty, B. M., Furberg, C. D., Kuller, L. H. et al.:** Association between blood pressure level and the risk of myocardial infarction, stroke, and total mortality. *Arch. Intern. Med.*, 2001, 161, pp. 1183-1192.
10. International Society of Hypertension Writing Group. International Society of Hypertension (ISH): Statement on blood pressure lowering and stroke prevention. *J. Hypertens.*, 2003, 21, pp. 651-663.
11. MRC Working Party: Medical Research Council trial of treatment of hypertension in older adults: principal results. *Br. Med. J.*, 1992, 304, pp. 405-412.
12. **Dahlöf, B., Lindholm, L. H., Hansson, L. et al.:** Morbidity and mortality in the Swedish trial in Old Patients with Hypertension. (STOP- Hypertension). *Lancet*, 1991, 338, pp. 1281-1285.
13. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA*, 1991, 265, pp. 3255-3264.
14. **MacMahon, S., Rodgers, A.:** The effects of blood pressure reduction in older patients: an overview of five randomised controlled trials in elderly hypertensives. *Clin. Exp. Hypertens.*, 1993, 15, pp. 967-978.
15. The Management Committee Treatment of mild hypertension in the elderly: a study initiated and administered by the National Heart Foundation of Australia. *Med. J. Aust.*, 1981, 2, pp. 398-402.
16. **Coope, J., Warrander, T. S.:** Randomised trial of treatment of hypertension in elderly patients in primary care. *Br. Med. J.*, 1986, 293, pp. 1145-1152.
17. **Amery, A., Birkenhäger, W., Brixko, P. et al.:** Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly Trial. *Lancet*, 1985, 1, pp. 1349-1354.

18. **Staessen, J. A., Fagard, R., Thijs, L. et al.:** For the Systolic Hypertension-Europe (Syst-Eur) Trial Investigators. Morbidity and mortality in the placebo-controlled European Trial on Isolated Systolic Hypertension in the Elderly. *Lancet*, 1997, 360, pp. 757-764.
19. **Linjer, E., Hansson, L.:** Underestimation of the true benefits of antihypertensive treatment: an assessment of some important sources of error. *J. Hypertens.*, 1997, 15, pp. 221-225.
20. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylurea or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes: UKPDS 33. *Lancet*, 1998, 352, pp. 837-853.
21. **Lawes, C. M. M., Bennett, D. A., Feigin, V. L., Rodgers, A.:** Blood pressure and stroke. An overview of published reviews. *Stroke*, 2004, 35, pp. 776-785.
22. Prospective Studies Collaborators. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*, 2002, 360, pp. 1903-1913.
23. **Widimský, J. et al.:** Hypertenze. Praha, Triton, 2004, 590 p. (in Czech)
24. **Grossman, E., Messerli, F., Kowey, P.:** Should a moratorium be placed on sublingual nifedipine capsules given for hypertensive emergencies and pseudoemergencies? *JAMA*, 1996, 276, pp. 1328-1331.
25. **Black, H. R., Elliott, W. J., Grandits, G. et al.:** For the CONVINC Research Group. Principal results of the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial. *JAMA*, 2003, 289, pp. 2073-2082.
26. **Kario, K., Pickering, T. G., Umeda, Y. et al.:** Morning surge in blood pressure as a predictor of silent and clinical cerebrovascular disease in elderly hypertensives: a prospective study. *Circulation*, 2003, 107, pp. 1401-1405.
27. **Kaplan, N. M.:** Morning surge in blood pressure. *Circulation*, 2003, 107, s. 1347.
28. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high risk patients. *N. Engl. J. Med.*, 2000, 342, pp. 145-153.
29. **Bosch, J., Yusuf, S., Pogue, J. et al.:** On behalf of the HOPE Investigators. Use of ramipril in preventing stroke: double blind randomised trial. *Br. Med. J.*, 2002, 324, pp. 699-702.
30. PROGRESS Collaborative Group. Randomised trial of perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. *Lancet*, 2001, 358, pp. 1033-1041.
31. **Gueyffier, F., Bulpitt, Ch., Boissel, J.-P., et al.:** For the INDANA Group. Antihypertensive drugs in very old people: a subgroup meta-analysis of randomised controlled trials. *Lancet*, 1999, 353, pp. 793-796.
32. **Bulpitt, C. J., Beckett, N. S., Cooke, J. et al.:** On behalf of Hypertension in the Very Elderly Trial (HYVET) Working Group. Results from the pilot study for Hypertension in the Very Elderly Trial. *J. Hypertens.*, 2003, 21, pp. 2409-2417.
33. **Hyman, D. J., Pavlik, V. N.:** Characteristics of patients with uncontrolled hypertension in the United States. *N. Engl. J. Med.*, 2001, 345, pp. 479-486.
34. **Dahlöf, B., Devereux, R. B., Kjeldsen, S. E. et al.:** For the LIFE study group. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomized trial against atenolol. *Lancet*, 2002, 359, pp. 995-1003.
35. **Jozífová, M., Cífková, R., Škodová, Z. et al.:** Porovnání léčby hypertenze a rizikového profilu hypertoniků v obecné populaci a na specializovaném pracovišti. *Cor Vasa*, 2003, 45, pp. 533-541.
36. **Škodová, Z., Piša, Z., Poledne, R. et al.:** Pokles úmrtnosti na kardiovaskulární onemocnění v České republice v období 1984-1993 a jeho možné příčiny. *Čas. Lék. čes.*, 1997, 136, pp. 373-379.
37. **Cífková, R. et al.:** Decreased prevalence and improved control of hypertension in the Czech Republic. *J. Hypertens.*, 1999, 12, 95A (Abstract).
38. **Klungel, O. H., Kaplan, R. C., Heckbert, S. R. et al.:** Control of blood pressure and risk of stroke among pharmacologically treated hypertensive patients. *Stroke*, 2000, 31, pp. 420-424.
39. **Klungel, O. H., Stricker, B. H. C., Paes, A. H. P. et al.:** Excess stroke among hypertensive men and women attributable to undertreatment of hypertension. *Stroke*, 1999, 30, pp. 1312-1318.
40. **Klungel, O. H., Heckbert, S. R., Longstreth, W. T. Jr. et al.:** Antihypertensive drug therapies and the risk of ischemic stroke. *Arch. Intern. Med.*, 2001, 161, pp. 37-43.

Address for correspondence:
Prof. Jiří Widimský, MD, DSc., FESC
Department of Cardiology – IKEM
146 21 Prague 4, Vídeňská 1958/9
Czech Republic
E-mail: widimsky@post.cz

Translation: Oldřich Louthan