Novel aspects of cardiovascular prevention as of 2005

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Among all European Union members, Slovakia has some of the highest cardiovascular morbidity and mortality. Therefore, the evaluation of efficacy and effectiveness of preventive measures regarding cardiovascular diseases is of particular interest for this country. In the present paper we review the current evidence in this field.

On a *population* level, there are some efficacious strategies, e.g. salt reduction and antismoking measures.

On the *individual* level, we analyze several issues: 1. The need to view cardiovascular risk factors not as categorical entities but rather as continuous variables. 2. We emphasize the need to evaluate in each patient the global cardiovascular risk. Although it is challenging to do, integration of guidelines might be instrumental in preventing the omission of one risk factor while treating another one. 3. In the last section of the paper we discuss the role of different pharmacological agents both in the *primary* and *secondary* prevention of circulatory diseases.

Key words: Cardiovascular diseases – Risk factors – Primary prevention – Secondary prevention

FODOR GJ, KOTREC M, TURTON P. **Prevratné pohľady na kardiovaskulárnu prevenciu v roku 2005.** Cardiol 2006;15(2):89–95

Slovensko patrí medzi krajiny Európskej únie s najvyšším výskytom srdcovocievnych ochorení a úmrtí. Preto má analýza účinnosti a uplatniteľnosti (efficacy and effectiveness) preventívnych opatrení v kardiovaskulárnej medicíne pre Slovensko osobitne dôležitý význam. V prezentovanej práci sa zaoberáme hodnotením súčasných poznatkov v tejto oblasti.

Na *populačnej* úrovni existuje niekoľko účinných stratégií, ako sú napríklad redukcia obsahu soli v potravinách alebo protifajčiarske opatrenia.

Na *individualnej* úrovni sa zameriavame na tri okruhy otázok: 1. Potreba nazerania na kardiovaskulárne rizikové faktory nie ako na kategorické, ale skôr ako na kontinuálne premenné. 2. Zdôrazňovanie potreby hodnotenia globálneho kardiovaskulárneho rizika u každého pacienta. V tejto súvislosti by integrácia liečebných odporúčaní mohla pomôcť predchádzať situáciam, kedy popri liečbe jedného rizikového faktora sa prehliada prítomnosť ďalšieho. 3. V záverečnej časti práce sa diskutuje o úlohe rôznych farmakologických preparátov tak v *primárnej* ako aj *sekundárnej* prevencii srdcovocievnych ochorení.

Kľúčové slová: srdcovocievne ochorenia – rizikové faktory – primárna prevencia – sekundárna prevencia

Introduction

Cardiovascular (CV) disease, including myocardial infarction, stroke and peripheral vascular disease, is the main cause of death in Slovakia. In 2002, Slovakia was fourth out of twenty-five European Union members in the mortality from circulatory diseases (after the three Baltic republics). For comparison, Spain with its 187.5 cardiovascular deaths/100 000 population had the lowest cardiovascular mortality in European Union, mortality from circulatory diseases in Czech Republic was 456/100.000 population, whereas in Slovakia it was 527.7/100.000 population, which is higher than the average cardiovascular mortality in the whole EU, including its 10 new members (450.5/100.000 population) (*European health for all database (HFA-DB), World Health Organization Regional Office for Europe. http://www.euro.who.int/hfadb. Accessed on November 15, 2005*). It is well established that the reduction of key cardiovascular risk factors results in reduction of morbidity and mortality from circulatory diseases (1 – 3). Experience from countries which successfully reduced cardiovascular morbidity and mortality indicate that the strategies which brought the epidemic of these diseases under control are complex. Recent data from Ireland (*unpublished, presented at the 45th Annual Conference on CV Disease Epidemiology and Prevention, April – May 2005, Washington DC*) estimate that 55% of the mortality fall was attributed to treatment of individuals, while approximately 43% of the mortality fall was attributable to population risk factor changes, in particular due to reduction of smoking (26.4%), cholesterol (25.4%) and blood pressure control (4.8%). At the same

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time, there had been an adverse impact on cardiovascular mortality caused by increasing prevalence of obesity, diabetes and physical inactivity.

In the present paper we aim to summarize the current evidence for cardiovascular prevention, and outline some of the novel aspects of the primary and secondary prevention.

Prevention in population setting

An important question to answer is how much of the cardiovascular risk reduction can be achieved through counseling and behavioral modification, and which of these "life style" changes have proven efficacy and effectiveness.

One of the few success stories of life style modification is antismoking intervention. In Canada, the prevalence of smokers has dramatically declined in the past 20 years – from 35 to 20% (*Canadian Tobacco Use Monitoring Survey, http://www.hc-sc.gc.ca, accessed on November 15, 2005*). This success has been achieved mostly through societal pressure, e.g. taxation and legislation (4, 5).

In contrast, the situation is much worse if we are assessing the efficacy and effectiveness of nutritional counseling and effort to increase physical activity. The failure of our nutritional policy is obvious if we look at the epidemic of obesity. We have a robust database documenting that in the real-life situation nutritional counseling has minimal effect on blood cholesterol level (6). This meta-analysis of 19 randomized trials studying the efficacy of dietary counseling on cholesterol levels in the community setting showed a mean reduction in total cholesterol of 3% if the subjects were to follow the American Heart Association step 1 diet (< 30% of total energy intake as fat, with 8 – 10% as saturated fat; ratio of polyunsaturated to saturated fatty acid > 1.0; cholesterol intake < 300 mg/day; and energy intake to achieve desirable body weight), and of 5.6% if AHA step 2 diet (< 30% of total energy intake as fat, with 7% or less as saturated fat; ratio of polyunsaturated to saturated fatty acid >1.4; cholesterol intake < 200 mg/day; and energy intake to achieve desirable body weight).

The *efficacy* of the low fat diet was analyzed recently by Studer et al (7). This systematic review of seventeen randomized trials failed to show any effect of these diets on overall mortality. Moreover, the *effectiveness* of nutritional counseling is questioned also by the highly authoritative U.S. Task Force for Preventive Services (USTPS). After systematic review of the relevant literature the USTPS concluded that the evidence of the effectiveness of nutritional counseling is such that they are unable to recommend for or against counseling (8).

Also counseling of hypertensive patients to adhere to a low salt diet and reduce body weight is lacking effectiveness. More than 80% of sodium intake is involuntary due to high salt content of processed food. The complete failure to achieve significant long term weight reduction in most overweight patients is a fact well known to every practicing physician.

Notwithstanding, the European Society of Hypertension Guidelines suggest that patients with grade 2 hypertension [systolic blood pressure (SBP) 160 – 179/diastolic blood pressure (DBP) 100 – 109] with one to two CV risk factors should be treated with lifestyle modification for as long as several months prior to the starting of drug treatment (9). The U.S. NCEP Adult Treatment Panel III (10) recommends also a two-step approach to high cholesterol management: Drug therapy is recommended only after an appropriate trial of dietary therapy to reduce LDL cholesterol (~ 3 months) has been tried. Also, in patients with metabolic syndrome, lifestyle changes (i.e. weight reduction and increased physical activity) are recommended before drug therapy for treatment of the metabolic risk factors is required.

The Treatment of Mild Hypertension Study (TOMHS) (11) compared six antihypertensive interventions for the treatment of mild hypertension. All 902 participants, aged 45 to 69 years with mild hypertension (DBP < 100 mmHg) received sustained nutritional-hygienic advice to reduce weight, dietary sodium intake, and alcohol intake, and increase physical activity. On top of that, they were randomly allocated to take placebo or an active treatment – one of five antihypertensive drug classes (diuretics, beta-blockers, calcium channel blockers, ACE-inhibitors, or alfa-blockers). After a minimum period of 4 year follow-up blood pressure reduction was marked in all six groups, but significantly greater in participants on active antihypertensive treatment than in the placebo group. What is even more important is the finding that despite only mild hypertension of the participants the active antihypertensive therapy was more effective in preventing cardiovascular and other clinical events than was nutritional-hygienic treatment alone.

Prevention on the individual level

Turning now our attention to the clinical approach of primary and secondary prevention of cardiovascular diseases in individual patients we also face a number of problems.

1. There is a tendency to view risk factors as categorical entities rather than continuous variables. For example, let us have a look at the issue of hypertension. The

cardiovascular risk increases with increasing blood pressure across the whole range of values. Thus, SBP of 132 mmHg represents a higher risk than 130 mmHg. Nevertheless, the hypertensive disease by definition starts at 140 mm Hg SBP while a person with 139 mm Hg SBP is "normotensive".

There is growing evidence that death from both ischemic heart diseases and stroke increases progressively and linearly, without any evidence of a threshold, down to at least 115 mmHg SBP and 75 mmHg DBP (12).

MacMahon et al (13) pointed out in a recent paper: "…the only rationale for maintenance of a discrete, blood pressure-based definition of hypertension would be proof that blood pressure lowering regimens were ineffective in non-hypertensive individuals. However, clear evidence now shows that several blood pressure-lowering drugs reduce the risks of major vascular events in a broad range of non-hypertensive with high-risk disorders….." This is the lesson we have learned from the HOPE (14) and EUROPA (15) trials and *pari passu* from the Heart Protection Study (16) where statin administration prevented a significant number of cardiovascular events regardless what was the level of LDL in the study subjects.

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII) (17) addressed this issue by introducing a new classification of hypertension with a new category "prehypertension" for the individuals with blood pressure (BP) ranging from 120 – 139 mmHg SBP, and/or 80 – 89 mmHg DBP. This aims for easy identification of those individuals in whom an early intervention by healthy lifestyle could reduce blood pressure and thus prevent its progression to hypertensive levels.

Moreover, the MRFIT trial (18) that screened and followed-up 356 222 men aged 35 to 57 years, free of a history of hospitalization for myocardial infarction, showed a continuous, graded relationship between the total plasma cholesterol concentration and coronary heart disease events and mortality. In other words, the relationship between serum cholesterol and coronary heart disease is not a threshold one, but rather a continuous one.

2. Another important issue is that the current clinical practice guidelines address hypertension, dyslipidemia, and diabetes *separately*. The risk of this approach is that it may inadvertently lead to labeling patients as solely "diabetic", "hypercholesterolemic", or "hypertensive", not realizing that the majority of patients with an unfavorable cardiovascular profile have more than one risk factor. Separate management guidelines for various risk factors should be replaced with integrated ones. It is important to pay particular attention to those with more than one risk factor. As Jackson et al recently suggested, moderate reductions in several risk factors may be more effective than a large reduction in one (3).

3. Efficacy of drug therapy on reduction of cardiovascular risk factors, and more importantly the beneficial effect on mortality, has been proven by a number of randomized clinical trials (14, 16, 19, 20).

In this context we are going to assess several drug groups that are currently the mainstay of evidence- based preventive interventions. Tabular summary of the efficacy of the main drug groups in primary and secondary cardiovascular prevention can be seen in **Table 1**.

Table 1 Efficacy of different drug classes in primary and secondary cardiovascular disease prevention

	Primary prevention of cardiovascular diseases	Secondary prevention of cardiovascular diseases
Aspirin	+*	+++
	USPSTF (35)	Antithrombotic Trialists'
	Women's Health Study (37)	Collaboration (34)
ACE-inhibitors	?	+++
		HOPE (14)
		EUROPA (15)
Beta-Blockers	0	+++
	MRC Working Party (30)	Yusuf S, et al, 1985 (28)
	IPPPSH (31)	ISIS-1 (29)
	HAPPHY (32)	
	ASCOT-BPLA (33)	
Statins	+++	+++
	ASCOT-LLA (19)	HPS (16)
	WOSCOPS (21)	4S (20)
	AFCAPS/TexCAPS (22)	LIPID (23)
		CARE (38)

+ Efficacy proven with some limitations; +++ Strong evidence shown; 0 Efficacy not shown; ? Efficacy not known; * Effective in patients at high risk for CHD, and women > 65 years of age

Statins

Until now, there have been three major clinical trials studying the efficacy of statins in *primary* coronary heart disease prevention. The 4 S Study in 1994 (20) and the West of Scotland Coronary Prevention Study (WOSCOPS), published in 1995 (21) became landmark studies. Until then, all lipid lowering trials using non-statin drugs had shown an increase in mortality from non-cardiovascular causes. In WOSCOPS, 40 mg of pravastatin daily administered to 6 595 men with hypercholesterolemia and without prior evidence of myocardial infarction or cardiac revascularization not only had favourable effects on the lipid profile, but it also decreased cardiovascular mortality by 32% and all-cause mortality by 22%. In the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCPAS/TexCAPS) (22), lovastatin, 20 to 40 mg

daily administered to 5 608 men and 997 women without coronary heart disease, resulted in a 37% reduction in the risk for first acute major coronary events, defined as fatal or nonfatal myocardial infarction, unstable angina, or sudden cardiac death. The number of deaths was low and the study was not powerful enough to detect the differences in mortality. This study was the first primary prevention trial to demonstrate risk reduction from lipid modification in generally healthy men and women without clinical evidence of cardiovascular disease and with total and LDL cholesterol levels similar to those in the general population (5.7 and 3.9 mmol, respectively).

The third major trial studying statins in the primary prevention of coronary heart disease is the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA) (19). 10 305 hypertensive patients with moderate risk of developing cardiovascular events and non-fasting total cholesterol concentrations of 6.5 mmol/l or less were randomly assigned additional atorvastatin 10 mg or placebo. The trial had to be stopped after 3.3 years due to the significant benefit of statins – they led to a 36% reduction in primary endpoint (non-fatal MI plus fatal CHD). Probably due to early discontinuation of the trial, there was no significant reduction in all-cause and cardiovascular mortality, although the trend was observed.

There are numerous trials proving the benefits of statins also in *secondary* prevention for coronary heart disease. The 4S trial (20) evaluated 4 444 patients with established coronary heart disease and baseline total cholesterol levels between 5.5 and 8.0 mmol/l. The patients were randomized to simvastatin 20 to 40 mg daily, or a placebo. At the end of 5.4 years a significant reduction in total mortality, major coronary events, coronary deaths, revascularization procedures, and fatal plus non-fatal cerebrovascular events was noted in those receiving simvastatin.

The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study (23) randomly assigned to therapy with pravastatin or a placebo 9 014 men and women with history of recent myocardial infarction and total cholesterol levels 4.0 to 7.0 mmol/l. The study had to be stopped prematurely because, when compared to the placebo, pravastatin significantly reduced death from coronary heart disease, total mortality, stroke, need for bypass surgery, and fatal and nonfatal myocardial infarction. Moreover, as proven by the MRC/BHF Heart Protection Study (HPS) (16), adding simvastatin to the existing treatment in patients with coronary artery disease, other vascular disease, or diabetes, irrespective of their cholesterol levels, can produce a significant reduction in total mortality, mediated mainly through the reduction in coronary deaths. The importance of the study is in the fact that it extends the knowledge of the benefits of statins to a broader population, i.e. all patients with vascular disease, including those with "low" and "normal" lipid levels.

A systematic review of the effects of numerous different antilipidemic agents and diet on mortality involving almost 280 000 participants, performed by Studer et al (7) has shown that only statins and N-3 fatty acids are efficacious in reducing the risk of overall and cardiac mortality in patients with or without coronary heart disease.

Similarly, a meta-analysis by Cheung and colleagues (24) showed that statins reduce coronary events, strokes, and all-cause mortality without increasing non-coronary mortality. This benefit was found in both genders, hypertensives and normotensives, diabetics and nondiabetics.

ACE-inhibitors

It is well known that ACE-inhibitors reduce mortality, hospitalization and progression of heart failure in patients with left ventricle systolic dysfunction with or without congestive heart failure symptoms (25, 26).

The question is, however, if ACE-inhibitors improve cardiovascular outcomes also in patients *without established heart failure*. The HOPE trial (14) studying the efficacy of ACE-inhibitors in high-risk patients without left ventricular dysfunction has shown significant reduction in the rates of cardiovascular death, myocardial infarction, and stroke. This benefit was initially thought to be independent of the reduction of blood pressure, as only a minor portion of the patients were hypertensive at baseline, and the mean reduction of blood pressure with ramipril was very small (3.3/1.4 mmHg). However, the HOPE Substudy (27) showed that the main benefit was truly achieved through the BP reduction. The reason for this discrepancy is the fact that the study patients took their medication at bedtime, and BP was measured 10-18 hours later. The HOPE Substudy analyzed 24-hour ambulatory BP monitorings from 38 patients recorded while participating in the HOPE study and showed that the BP reduction originally reported in the HOPE trial (3.3/1.4 mmHg) had been underestimated.

The EUROPA study (15) had similar design to that of the HOPE study except that its 13 655 patients with stable coronary heart disease had no heart failure or substantial hypertension. After the mean follow-up of 4.2 years, perindopril reduced cardiovascular mortality by 14 % and total mortality by 11%.

Beta-blockers

The beneficial effects of long-term (28) and early (29) beta-blockade on mortality in *secondary* prevention in post-myocardial infarction patients have been known for several decades. The question is whether we can expect similar beneficial effects in *primary* prevention of coronary artery disease. In other words, do beta blockers have cardioprotective effects in hypertensive patients without established coronary artery disease? There have been several studies looking into this. The Medical Research Council Trial of Treatment of Hypertension in Older Adults (30) evaluated the efficacy of beta blockers (atenolol 50 mg/d or placebo) and diuretics (amilorid 2.5 mg/d + hydrochlorothiazide 25 mg/d or placebo) to reduce cardiovascular morbidity and mortality in hypertensive older adults. After the mean follow-up of 5.8 years and after adjusting for baseline characteristics the diuretic group reduced risk of stroke, coronary events, and all cardiovascular events compared with the placebo group. The atenolol group showed no significant reduction in these end points. Similarly, the International Prospective Primary Prevention Study in Hypertension (IPPPSH) (31) and the Heart Attack Primary Prevention in Hypertension trial (HAPPHY) (32) failed to show additional benefits of beta blockers over other antihypertensive drugs in primary prevention of coronary heart disease in hypertensive patients. The recently published ASCOT-BPLA (33) study also showed the failure of atenolol-based regimen in cardiovascular event prevention in hypertensive patients in comparison to an amlodipine-based regimen.

Thus, we know that beta blockers have a clear beneficial effect when used for secondary prevention in patients after myocardial infarction. Its benefit in primary prevention of coronary heart disease in patients with arterial hypertension was not proven.

Aspirin

The efficacy of aspirin in the secondary prevention of cardiovascular disease is generally well recognized. Antithrombotic Trialists' Collaboration Group (34) conducted a meta-analysis of 287 studies involving more than 210 000 high-risk patients. The meta-analysis confirmed that aspirin (or another oral antiplatelet drug) reduced the combined outcome of any serious vascular event (ie, non-fatal myocardial infarction, non-fatal stroke, or vascular death) by one quarter, non-fatal myocardial infarction by one third, non-fatal stroke by one quarter, and vascular mortality by one sixth. The authors also showed that low dose aspirin (75 – 150 mg daily) is effective in the long term management, but higher loading dose of at least 150 mg should be considered in an acute setting.

The effect of aspirin in primary cardiovascular prevention is more complex. The meta-analysis by U.S. Preventive Services Task Force (35) found a beneficial potential of aspirin for patients without previous history of cardiovascular disease but at high risk for developing coronary heart disease in the next five years. Patients at low risk for coronary artery disease, however, do not benefit from primary prevention with aspirin and may be even harmed because the risk of adverse events may exceed the benefit. After this meta-analysis had been published, the U.S. Preventive Task Force (35) and American Heart Association (36) recommend aspirin for men and women whose 10-year risk of a first coronary event is 10% or greater.

Since three of five trials studied in the above meta-analysis evaluated men exclusively, and only a small portion of vascular events occurred in women, Ridker with colleagues (37) conducted a large, two-by-two factorial trial – the Women's Health Study – evaluating the balance of risks and benefits of low-dose aspirin (100 mg every other day) and vitamin E (600 IU every other day) in the primary prevention of cardiovascular disease and cancer in women. In this trial, involving almost 40 000 women, aspirin use was associated with non-significant reduction in the risk of myocardial infarction, significant reduction of ischemic stroke by 24%, and no effect on all-cause mortality. Women older than 65 years of age benefited more than did younger women – aspirin in older women reduced the risk for both myocardial infarction and ischemic stroke. Adverse events included a possible increased risk for hemorrhagic stroke and a definite increased risk for major gastrointestinal bleeding by 40%. The balance between benefit and harm is therefore very delicate, and any decision about the use of aspirin in primary prevention must be made after a thorough consideration and discussion with the patient.

Summary

Prevention of cardiovascular diseases can be advanced by appropriate public health measures as well as detection and treatment of high risk patients.

At the population level, efficacy and effectiveness of various preventive measures should be the guiding principle while developing the relevant interventions. Some of these strategies are successful (antismoking campaigns), others less so, e.g. nutritional interventions.

At the individual level four drug categories (aspirin, ACE-inhibitors, beta-blockers and statins) have proven efficacy in secondary prevention of CVDs while statins and aspirin are efficacious in primary prevention as well.

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