

CLINICAL STUDY

Costs related to medical treatment for common cardiovascular risk factors

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Abstract: *Aim:* The aim of this study was to evaluate the direct and indirect costs of selected cardiovascular diseases, namely hypertension (HT), metabolic syndrome (MS) and diabetes mellitus (DM) in the Slovak Republic.

Methods and results: This study analyzes the data of 1,000 patients, randomly selected from NEMESYS database (10,300 patients). Average direct pharmacotherapeutic costs of hypertension per year were 257 € in men and 264 € in women. Costs of metabolic syndrome were 334 € in men and 321 € in women. Finally, the costs of diabetes mellitus were 392 € in men and 384 € in women. The most expensive pharmacotherapy was used in patients with a combination of all three diagnoses (HT+MS+DM), namely 452 € in men and 455 € in women. Indirect costs represent an even more serious financial burden. The highest indirect costs were in patients with diabetes mellitus, namely 5,227 € in men and 5,365 € in women.

Conclusions: The study proved the assumption of increasing the direct pharmacotherapeutic costs in correlation with the increased severity of disease. The gender differences on the other hand, were smaller in patients with more serious conditions. The indirect costs represented the greatest financial burden, and were 13 to 17 times higher than the direct pharmacotherapeutic costs (Tab. 4, Ref. 17). Full Text in free PDF www.bmj.sk.
Key words: direct costs, indirect costs, pharmacotherapy, hypertension, metabolic syndrome, diabetes mellitus.

Cardiovascular (CV) diseases are one of the most frequent causes of death in Europe (1). The cost of CV diseases in European Union is estimated to be as high as 169 billion € yearly. The average yearly costs per patient are calculated at 372 €. Plenty of pharmacoeconomic studies are analyzing the costs of cardiovascular diseases in Slovakia, but none of them projected exact data considering all related costs.

CV diseases cause more than half of all deaths in Europe, which means around 4.35 million of deaths yearly in 52 states of the European part of World Health Organization (WHO) and more than 1.9 million of deaths yearly in European Union (2). Around 40 % of inhabitants in Slovakia suffer from increased blood pressure – hypertension. This is 10 % more than the world average. High blood pressure increases the cardiovascular risk as well as chances of cardiovascular death, heart attack, stroke, and heart failure. (3) The basic aim of hypertension treatment is to decrease and control the patient's blood pressure in long term and keep it as close as possible to normal levels. This approach intends to reduce the cardiovascular risk. The first step usually lies in lifestyle correction (more exercise, diet, salt restriction, etc.)

If these interventions are not enough to control the blood pressure, pharmacotherapy is indicated. Once initiated, such medical therapy is often set for life. The doctor's challenge is to set up an individually tailored hypertension therapy providing a continuous long-term blood pressure control well tolerated by the patient and causing minimal adverse effects.

The cost of hypertension medical treatment represents a significant financial burden. For example, yearly costs of hypertension treatment in USA exceed 66 billion dollars. (4) The average patient with hypertension needs 2–3 drugs of different ATC classes for reliable long-term hypertension control (5). Some core triggers of hypertension can be influenced without medical therapy. A very important one is obesity. Approximately half of all adults from developed countries suffer from obesity. The most dangerous type of obesity is the abdominal obesity, which is characteristic by the deposit of fat tissue around the waist. Patients with this type of obesity are at twice the risk of developing hypertension. Hypertension is considered a dangerous comorbidity of diabetes mellitus. It is diagnosed in 20–60 % of diabetic patients. The prevalence of hypertension among diabetic patients depends on age, body weight, race, and diabetes type. High prevalence of hypertension in diabetes type II patients can be explained by central obesity and increased sympathetic stimulation or overproduction of catecholamines. Essential hypertension has recently been considered a part of the metabolic syndrome. The direct relationship between metabolic syndrome and the increased risk of diabetes mellitus has been known for more than 30 years. In clinical practice, the relevance of metabolic syndrome has in-

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creased after the finding that it increases the risk of coronary, cardiovascular and overall mortality rates more than 3 times (6).

The prevalence of metabolic syndrome is close to 25 % in developed industrialized countries. It is increasing with age. After the age of 60, the prevalence is greater than 40 %. Costs of medical treatment for metabolic syndrome are comparable to medical costs used for treating some types of cancer, dependence on drugs, or AIDS (7).

Currently, we are witnessing a worldwide explosion of new cases of diabetes mellitus. Seventy-five percent of diabetic patients die because of cardiovascular diseases (8). Since 1980, the number of diabetic patients in Slovakia has almost doubled (9). In 2004, we registered 287 034 patients. The majority were women, namely 161 588, and we registered 125 716 men. Most probably, it is correlated with the average life expectancy, which is longer in women than in men (10). The increasing numbers of patients with hypertension, metabolic syndrome, and diabetes mellitus obviously lead to increased direct medical treatment costs. The diagnosis, proper management and prevention of these diseases as well as other chronic diseases have several serious overall economic impacts.

Background

This analysis is based on the NEMESYS study and it uses the same pool of patients. We analyzed 1,000 patients randomly selected from total NEMESYS basic pool of 10,300 patients. Patient's data were collected from out-patient offices of 54 General Practitioners. They were randomly selected from the entire Slovakian territory irrespective of their geographic location. The only exclusion criterion of selected GP offices was their willingness to cooperate. In each office, we investigated 200 patients. In our particular subanalysis, we randomly picked out five offices with 200 patients from the basic database, i.e. a total of 1,000 patients.

Observed parameters

Only the fully cooperating patients were involved. They provided informed consents (allowing us using their personal data) and they were given project information. After recording their characteristics in respect of age, gender, height and weight, and waist circumferences (measured at the joint of spina iliaca anterior superior where the waist is widest) their blood pressure was measured by standard method. From their anamneses we tracked their smoking habits (smoker, non-smoker, ex-smoker for more than two years), hypertension (diagnosed, undiagnosed, treated, untreated, controlled, uncontrolled) and diabetes mellitus (diagnosed, undiagnosed, treated, untreated, controlled, uncontrolled, type I or type II). From blood draw, we registered lipid spectrum (total cholesterol, HDL, LDL and TAG). We used only the data recorded in documents in the past six months. If the patient refused the blood draw and there were no previous data, we entered this fact as "data unavailable" into the protocols.

All actual medical treatments were recorded, namely both,

prescriptions and other long-term treatments of their chronic diseases, except for antibiotic therapy.

Basic characteristics

There were 572 women and 428 men involved in the pharmaco-economic analysis. The set of patients can be characterized as an adult population with a wide age range (from 18 to 91 years of age) with average age of 54 in men and 55.6 in women. Obesity was common. They had slightly increased levels of total cholesterol and LDL cholesterol, as well as relatively high levels of glycemia with glucose metabolic disorder frequently proved by GPs at outpatient clinics. Average glycemic level was 5.84 mmol/l in women, and 5.99 mmol/l in men. As we expected, there were significant gender differences between smokers. Women smoked less. Only 72 (13.3 %) women admitted to being smokers, compared to 107 (25 %) men. There were several statistically significant gender differences in monitored parameters. From the clinical point of view, the most important were the differences in lipid profile and smoking habits.

Methods

Calculating the direct medical costs of selected cardiovascular diseases

The basic goal of this analysis was to calculate the direct medical costs of arterial hypertension, metabolic syndrome, and diabetes mellitus. The costs were evaluated separately per diagnosis as well as together in intersections of multiple diagnoses (hypertension plus diabetes, etc.). The medical costs of selected treatment are expressed in direct monetary units (€). Its contribution can be expressed either in monetary units or in special unit of clinical merit (for example mortality, morbidity, disability, drugs utilization, need of operation, need of transplantation, quality of life, etc.).

Direct costs represent all prescriptions, services and other resources covering the medical interventions, pharmacologic procedures or dealing with unforeseen side effects or temporary and long-term medical complications. *Direct medical costs* include the costs of examinations, drugs, stocks, medical staff and medical equipment (11).

In our particular case, we defined direct medical costs as the costs of medical drugs used for medical therapeutic intervention relating to cardiovascular diseases and monitored complications, namely metabolic syndrome and diabetes mellitus.

The analysis includes all drugs belonging to following ATC categories: entire category *C Cardiovascular system drugs* (C01-C10), selected sub categories of main category *B Blood and hemoplastic organs* (B01, B02, B03, B04) and sub categories of A10 – Antidiabetics from main category *A Digestive tract and metabolism disorders*.

All drugs were recorded with their use (long-term, chronic usage) as well as actual prescriptions. From this basic record, all drugs belonging to the above-mentioned ATC categories were separately analyzed. To each drug, the average monthly therapy

Tab. 1. Calculation of the number of working employees in SR for 2006.

Employment rate (age range 15–64)	59.40 %
Number of inhabitants (age range 15–64)	3 875 360
Calculated number of working employees	2 301 964

Tab. 2. Productivity calculation in SR for 2006.

GDP in 2006	42 994 000 €
Working employees in 2006	2 301 964
Per 1 person per year	18 677 €
Per 1 person per day	51 €

Tab. 3. Data used for calculation of indirect costs.

	2006	€
Average salary	Monthly	623
	Yearly	7 473
	Daily	30
Net patient income	Monthly	484
	Yearly	5 814
	Daily	24
Direct State income from taxes	Monthly	357
	Yearly	4 285
	Daily	17
Indirect state income (Productivity)	Monthly	1 556
	Yearly	18 677
	Daily	51

costs were added according to their therapeutic recommendations. The financial values were calculated for one-year therapy. The financial costs were calculated from retail (pharmacy) prices of each package. The retail prices were applied according to the categorized list of drugs, food supplements and medical devices reimbursed by public health insurance valid from January 1, 2006 to March 31, 2006. The categorized list was approved by the Division of Categorization, Pricing and Drug Policy of Slovak Ministry of Health.

The following example is showing the logical flow of calculations of direct medical costs covering the pharmacotherapy: ACE inhibitor **Diroton**, ATC code C09AA03, this drug falls into our analytical database according to its ATC code, and the recommended therapeutic dose is 10 mg once a day (morning). Packages contain 28x10mg tablets with retail price of 9.61 €, which means 0.34 € daily. The monthly therapy was calculated for average of 30 days, representing 10.2 €, while the yearly calculation is 10.2 € x 12 = 122.4 €.

For each patient we summed all drug costs calculated according to this method getting one sum representing the total direct medical cost covering a yearly treatment of patient. The patients were divided into two basic groups according to gender, and then additionally divided into subgroups according to diagnoses: A (arterial hypertension), B (metabolic syndrome), and C (diabetes mellitus). Separately we analyzed the conjunctions of patients with multiple diagnoses: A+B, A+C, B+C, A+B+C. For each

group and subgroup, we calculated the average financial values of therapies. These values were compared.

Calculating the indirect medical costs of selected cardiovascular diseases

Indirect costs represent the productivity losses caused by the reduced count of active working days, which has an impact on the national economic earnings. Its is calculated from the duration of sick leave, decreased performance due to health problems, disability or early death due to serious disease. For several disease types, the indirect costs represent a significantly higher financial burden than the direct medical costs. Beside the indirect costs, the *indirect contribution* is often measured. It means the potential increase in economic productivity enabled by preventing early deaths and disability as well as by minimizing the negative impacts of diseases. The most frequently used method of measuring the indirect costs is the evaluation of human capital. It is based on the calculation of achievable gross income of sick patients affected by the disease, who could have worked instead of being on sick leave, disabled or dying early.

For the indirect cost calculation, the 2006 data were used while the NEMESYS project was performed in the first quarter of 2006. The average monthly salary in 2006 was in amount of 622.75 € based upon the data from the Slovak Statistical Office. By using tax formulas valid in 2006, the following monthly data were calculated: Average monthly net income was 484.5 € and *average monthly direct state* income was 367.5 €. The average monthly direct state income was determined as the sum of payroll taxes contributed by employees to the state budget (83.5 €), income taxes paid by employee (54.7 €), and payroll taxes paid by employer (219.3 €). Indirect costs (productivity) can be estimated from the ratio of GDP and number of working employees in Slovak Republic. The exact data on the number of working employees as for 2006 in SR was not available at the time of our analysis. Available was the employment rate in the age group of 15–64, namely 59.4 %. The missing number of working employees was extrapolated from the number of inhabitants in Slovakia of the same age range based on information from the Slovak Statistical Office. The logical flow is described in Table 1.

Indirect income, respectively the potential State loss in 2006 was 18 677.3 € per person per year, which represents an amount of 51.2 € daily (Tab. 2).

For the calculation of indirect cost, also other data were needed. In 2006, the average duration of sick leave was 38.67 days. The average yearly sickness allowance for one patient was in amount of 2,530 €, which represents an amount of 6.9 € per day. The full data needed for the calculation of indirect costs are assembled in Table 3.

Data from the Slovak Social Insurance Office were used to determine the average duration of sick leave. With the help of Slovak Social Insurance Office, we filtered the needed data by diagnoses, gender and age groups. According to these data, we calculated the average duration of sick leave in days per diagnosis. For this analysis, we used two diagnoses: hypertension and diabetes mellitus. The evaluation of average duration of sick leave

due to metabolic syndrome was complicated, because there is no such diagnosis in the insurance office database. A special hypothesis was created, by which metabolic syndrome was placed between hypertension and diabetes mellitus according to its characteristics in respect of the severity of disease and complications. There is a common link between metabolic syndrome and hypertension. The majority of patients with metabolic syndrome have increased blood pressure (in our analysis 93% of all patients). They can be characterized as hypertonic patients with a complication. Most of metabolic patients have insulin resistance, some kind of pre-diabetes state, often progressing into diabetes mellitus type II. In our analysis, 41 % of metabolic patients have diabetes mellitus. Some studies report 83 % of insulin resistance among patients with type II diabetes (12). The average duration of sick leave due to metabolic syndrome was based on the average numbers of days of absence from work due to hypertension and diabetes mellitus.

Results

The total pool of 1,000 analyzed patients was randomly selected from the database of NEMESYS project containing 10,300 participants. In the first step, the participants were split by gender because we expected significant gender differences in the calculated cost results. In the next step, separate groups were created according to selected diseases. Average yearly direct medical pharmacotherapeutic costs of hypertension (group A) were in amount of 257 € in men and 263 € in women. The overall costs of women were higher by 2.66 %. Average yearly direct medical costs of pharmacotherapy of metabolic syndrome (group B) were in amount of 334 € in men and 321 € in women (3.89 % gender difference). In line with our expectations, the average yearly direct medical pharmacotherapeutic costs were highest in the diabetes mellitus group (group C), namely in amount of 392 € in men and 384 € in women (2.01 % gender difference). The average yearly direct medical costs were analyzed in detail by examining the intersections of participants with combined diseases as follows: Patients with hypertension and metabolic syn-

drome (group A+B) yielded values of 354 € in men and 350 € in women (gender difference 1.27 %); patients with hypertension and diabetes mellitus (group A+C) yielded values of 452 € in men and 442 € in women (gender difference 3.77 %); the double combination with the highest financial burden, i.e. the combined group of metabolic syndrome and diabetes mellitus (group B+C) yielded a burden of 408 € in men and 424 € in women (gender difference 2.48 %). Our basic hypothesis was that the more serious the disease (or disease combination) the higher the medical costs of its treatment. This was supported by calculations of the burden of triple combination. The medical costs of patients with all three selected diseases, namely hypertension, metabolic syndrome and diabetes mellitus (group A+B+C) were in amount of 452 € in men and 455 € in women (gender difference 0.68%). The financial value of 452 € in the male A+B+C group was equal to the value of double combination in the B+C group. The reason is that in the B+C group, all men had also hypertension, while some women with DM and MS who had no hypertension.

Table 4 gives a summary of yearly indirect costs for analyzed diseases. The lowest indirect costs evaluated for patients with hypertension were in amount of 4,493 € in men and 4,741 € in women (gender difference 5.52 %). The highest indirect yearly costs were found to be expended in respect of diabetes mellitus as they amounted to 5,961 € in men and 5,980 € in women (gender difference only 0.33 %). The indirect costs of metabolic syndrome calculated according our assumptions (average duration of sick leave due to hypertension and diabetes mellitus) were in amount of 5,227 € in men and 5,365 € in women (gender difference 2.65 %).

Discussion

Direct medical pharmacotherapeutic costs for an average hypertonic patient are in amount of 260 € per year while a patient with metabolic syndrome needs an amount of 327 €. The costs for a patient with MS are higher by 26 %. The highest amounts of yearly costs are those for patients with diabetes mel-

Tab. 4. Indirect costs of selected cardiovascular diseases.

	Patients with HT		Patients with MS		Patients with DM	
	Men	Women	Men	Women	Men	Women
Annual aggregate of sick leave duration (in days)	45.3	47.8	52.7	54.1	60.1	60.3
Costs of sick leave (in €)	314	331	365	375	417	418
Direct state loss of income-tax revenue (in €)	789	833	918	943	1.047	1.051
Indirect state loss of income-tax revenue due to decreased productivity (in €)	2.319	2.447	2.697	2.769	3.076	3.086
Financial loss of patient (in €)	1.071	1.130	1.246	1.279	1.420	1.425
Total losses (state+patient) (in €)	4.493	4.741	5.227	5.365	5.961	5.980

litus, with an average of 388 €. This is 50 % more than for hypertensive patient and 18.5 % more than for patients with metabolic syndrome. A similar analysis was performed from the basic database of NEMESYS using 8,679 patients. This analysis compared the pharmacotherapeutic costs for hypertension, metabolic syndrome and diabetes mellitus. The combined daily costs (hypertension & dislipidemy) were higher by 0.15 € compared to those for metabolic syndrome patients (DDD 1.15 € vs 1 € in group without MS). This is only 14.5 % more than in our main analysis, which involved also drugs from other ATC codes (13). The same database has also been used for a pilot analysis investigating the economic burden of obesity (14). In this particular study, the total pharmacotherapeutic costs per patients were in a range from 453 € to 677 €. The pharmacotherapeutic costs of hypertension, dislipidemy and diabetes mellitus represented 67.2 % (394 €) in age range of 50–59. In age range of 70–79 years it was the lowest, namely 51 % (331 €). If we compare this interval of selected costs of pharmacotherapy with the interval we have analyzed, i.e. 260 € to 388 € for direct costs of pharmacotherapy, we see definite similarities. Interesting finding during the comparison of results between the costs of targeted diseases was that there was a certain decreasing trend of gender differences in connection with increasing seriousness of diseases. While in the group of patients with hypertension, the direct medical costs for women were higher by 2.66 %, in the metabolic syndrome group, the direct medical costs for men were higher by 3.89 %. In the group of patients with diabetes mellitus, the gender difference was only 2 %. As we further compared the patients with multiple diagnoses, the lowest gender difference was in the group of patients with the most serious combination of diseases (group A+B+C). The same conclusion was made by the comparison of gender differences of indirect costs. The largest gender difference was in patients with hypertension (5.52 %), and the lowest difference was in patients with diabetes mellitus (only 0.33 %). The clinical study CODE-2 has described the total medical costs of DM type II patients. Patients without complications had costs in value of 1,505 €. The medical costs for patients with micro and macrovascular complications reach 5,226 €. Total costs of DM in NEMESYS subanalysis are in range of 6,307 € to 6 373 €, which is 20 % more than the costs of most complicated patients with DM in CODE-2 analysis. One of the explanations could be that the CODE-2 study was performed in 1998. If we counted just with an average cost increase by 5 % yearly, because of newer, more expensive and more available treatment, we could get the same average values in NEMESYS already after a six-year period.

One of the most important outcomes of our costs subanalysis was the estimation of metabolic syndrome. It is easy to neither diagnose nor target the patients with metabolic syndrome. These patients cannot be filtered from the databases of insurance companies, hospitals, family doctors or majority specialists. It is because there is no official diagnosis such as metabolic syndrome, by which these patients could be clearly identified. They can be identified and diagnosed just by detailed analysis of several patients data as gender (while there are different criteria

form men and women), blood pressure, lipid blood levels and glycemia, including one uncommon parameter, namely waist circumference.

The outcomes of metabolic syndrome costs from the NEMESYS subanalysis can be compared with some clinical studies performed worldwide. One pharmaco-economic study from western Italy monitored a pool of 4,974 patients. The patient's inclusion criteria were to have at least one prescription of combination of oral antidiabetes drug, cholesterol-lowering drug and antihypertensive drug in a period of 2001–2003. Along with this monitored group, one control group was selected with a similar size, gender and age structure. The prevalence of metabolic syndrome was 49.5 %. Pharmaco-economic analyses were calculated based on international ATC codes classification ICD-9 from 2003. The average yearly direct costs for a patient with metabolic syndrome were 1,522 €. Of that, 558 € were direct medical costs for pharmacotherapy and 964 € direct hospitalization costs. In the control group, the average yearly costs were 361 € while 155 € of that covered pharmacotherapy and 206 € covered hospitalization (16). In comparison, we identified yearly average medical drug costs in amount of 327 €, which represents 58 % of similar costs identified in Italy. The explanation of this 40 % difference could lie in different drug prices and different medical approaches to metabolic syndrome treatment.

Another pharmaco-economic study was performed by Medco. It investigated metabolic syndrome costs in USA from 2002 to 2004. Medco's analysis reviewed the prescribed drugs for approximately 2 million adult patients aged 20 or older. Those categorized with metabolic syndrome were taking medications for at least three of the risk factors associated with the syndrome – diabetes, abnormal cholesterol and hypertension. Average yearly costs of total pharmacotherapy (all drugs taken by patient) were 4,116 \$. This was 4.2 times higher than the costs of pharmacotherapy of patients without metabolic syndrome. The costs of pharmacotherapy used for metabolic syndrome treatment were around 40 % of total costs 1,160 € (17). Compared to our results this value is 4 times higher.

Conclusions

There is a significant association between the direct medical pharmacotherapeutic costs and seriousness of disease. The more complex the cardiovascular disease the higher its treatment costs. Direct costs expended on pharmacotherapy of our most complicated patients with diabetes mellitus were 50 % higher than the costs expended on hypertension, and 18 % higher than the costs of patients with metabolic syndrome. At the same time, decreasing gender differences were observed. Differences between men and women in direct medical therapy costs were decreasing with the severity or complexity of the disease. For the most complicated patients with combination of hypertension, metabolic syndrome and diabetes mellitus, the gender difference was only 3 € in full yearly therapy.

The indirect costs represented a financial burden, which was 13 to 17 times (from hypertension to diabetes mellitus type 2)

higher than that of direct pharmacotherapeutic costs. In practice, this means that direct medical costs are only the visible tip of the iceberg and have to be added to the costs that are hidden beneath and usually underestimated and undercontrolled despite the fact that they are much higher. The indirect costs of hospitalization, productivity losses, absence from work due to sickness leave or disability represent a much higher financial burden for the society than is apparent from most analyses, reports and forecasts primarily focused on “expensive” pharmacotherapy.

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