ABSTRACT
Objective: To compare the prescribing practice and pharmacotherapy outpatient cost of hypertension and its common complications between two neighboring countries, Bulgaria and Serbia. The study questions focus on consistency of the prescribing practice with the treatment guidelines; comparability of the treatment patterns among both countries, and burden of hypertension cost to the population and third party payer in the countries under consideration.
Methods: Retrospective study, one year time horizon is for outpatient therapy.
Results: Patients with arterial hypertension in Bulgaria are most often on monotherapy (61% vs 6% in Serbia), as well as those with complications (66% vs 0% Serbia). In both countries the first choice of therapy are the ACE inhibitors (37.01% in Serbia and 41% in Bulgaria) and then follows the calcium antagonists, beta-blockers, and diuretics. The weighed monthly cost of hypertension and complicated hypertension is almost doubled in Serbia (12.56 vs 8.23 EUR for hypertension, and 13.39 vs 8.23 EUR) and prevailing part is reimbursed (88% vs 44% in Bulgaria).
Conclusion: Our study confirms that hypertension and its complications therapy consumes a huge amount of financial resources. In both countries under consideration the therapy is corresponding with the European treatment guidelines. The international cost comparisons are possible but they depend on many external factors as the regulatory measures, prescribing habits and reimbursement policy and should be analysed within this framework.

Cardiovascular diseases were the leading cause of mortality in Serbia in 2006, with 57.6% of all deaths, and women (53.9%) died more often than men.\(^1\) Age-standardized mortality rate for cardiovascular diseases is 554.0 per 100,000 Bulgarian population\(^2\) and hypertension is also among the leading causes for death (108.1 per 100,000).\(^3\) Hypertension complication leads to age-standardized annual event rate from 9.15 to 30 per 100,000 people all over the world.\(^4,5\) Premature death and disability due to cardiovascular diseases represent significant economic and social burden to any country, which is recognized by European Society of Hypertension.\(^6\)

Studying the hypertension prescribing practice is important not only from the therapeutic point of view but also from the economic point, especially when it is connected with the cost of the complications.

The aim of this study is to compare the prescribing practice and pharmacotherapy outpatient cost of hypertension and its common complications between two neighbouring countries Bulgaria and Serbia.

Study questions:
- Is the hypertension prescribing practice in both countries consistent with the treatment guidelines?
- Are the treatment patterns comparable among both countries?
- What is the burden of hypertension cost to the population and third party payer in the countries under consideration?

The studies are the retrospective ones, the point of view is that of the outpatient therapy and time horizon is for one year.

In Serbia the total number of patient with hypertension, codes I10-I11 was 2764 while in Bulgaria the whole sample is including 3240 patients. Patients without complications of hypertension were 1856 in Serbia and 2106 in Bulgaria that represent 67.15% and 65% respectively. Patients with complicated hypertension were 908, or 32.85% in Serbia and 1134 (35%) in Bulgaria.

**METHODS**

The studies in the two countries were organized consecutively and independently following the same methodological approach and then the results were compared.

A one year retrospective study from the point of view of health care systems in Bulgaria and Serbia was performed in 2006.

A prescription sample size was determined to satisfy the values for alpha 0.05 and a study power of 0.80. The size of 250 prescriptions per diagnosis satisfies the stated criteria.

**Prescribing practice analysis**

In Bulgaria on a retrospective random basis were collected 3240 reimbursable prescriptions in 2006 year from the pharmacies databases working under National health insurance fund (NHIF) conditions. In Serbia the information database of the Republic Institute of Health Insurance (RIHI) was used as a source of the analysis. The list of all insured persons according, that betake medications on 12 or more prescriptions per year (depict on chronic disease and regular therapy) was created and out of this list the random sample of patients was collected for the following conditions defined by the International classification of diseases (ICD)\(^7\): hypertension (I10-I11) and for its complications - heart failure (I50); sequelae of cerebrovascular disease (I69); angina pectoris (I20). In Bulgaria according to NHIF rules 1 patient can receive only 1 prescription for one health condition per month including no more than 3 medicines while in Serbia there is no such a limitation.

The medicines in the collected samples were systematized and analyzed according to the following criteria:

- complexity of the therapy – mono-, di-, three-, etc.);
- frequency of the prescribed medicines as therapeutic class; international nonproprietary names; and brand name.

**Prescription cost calculation**

In the prescribing cost calculation were considered the following outcome indicators:

- total number of patients (n) by ICD diagnosis of arterial hypertension or with complicated hypertension;
- number of patients with ICD codes I10-I11(n) that except the I10-I11 possess and one or more of hypertension complications: angina pectoris (I20), myocardial infarct (I21), ischemic hard disease (I25), cardiac insufficiency (I50), insult (I69); In Bulgaria only angina pectoris, cardiac insufficiency and insult were considered for the analysis.
- frequency of patients (p) with hypertension out of all collected patients and frequency of patients with complications (p) complicated hypertension out of all patients with hypertension;
- number of patients (n) on mono-, di-, three- or poly therapy out of all patients with hypertension and out of all patients with complicated hypertension;
- frequency of monthly prescribing of trade names of medicines (p) in the groups of patients on mono-, di-, three- and poly therapy for hypertension and complicated hypertension, calculated as a number of dispensed packages of medicines per patient on mono- ; di-; three-etc- therapy;
- weighed monthly cost of pharmacotherapy (Σ) per patient on mono-, di-, three- and poly-therapy for hypertension and simple hypertension, calculated using the following formula:

\[
WMC = (Σ_1 \times p_1 + Σ_2 \times p_2 + \ldots + Σ_n \times p_n).
\]
where:

\[ \Sigma_{i, 2 \ldots i} \text{ is in Bulgaria the officially published retail price negotiated with NHIF}^9 \text{ while in Serbia is an average monthly price of package of prescribed dosage form}^9; \]
\[ p_{i, 2 \ldots i} \text{ is a frequency of monthly prescribing of the same trade name.} \]

There are a variety of the co-payment in the reimbursement drug list in Bulgaria for the medicines for hypertension therapy and its complications that impose a separated calculation for the reimbursed part of the cost and co-payment contribution. The same was also completed for the complicated hypertension.

The total cost of yearly therapy is calculated as a sum of the cost of all hypertension patients for 12 months (AHU), calculated as 12 monthly therapy costs multiplied by the number of patients with hypertension:

\[ \Sigma_{\text{AHU}} = (\Sigma_{\text{AH}} \times p_{\text{AH}} + \Sigma_{\text{CAH}} \times p_{\text{CAH}}) \times 12 \times \text{number of patients}. \]

Statistical analysis

Differences in proportions between the prescribing practice and cost of hypertension and complicated hypertension therapy in Bulgaria and Serbia were compared with the two-sided z-test for two proportions. We estimated 95% confidence intervals (CI) assuming a normal distribution. The z value and 95% confidence interval z value were analyzed using Excel.

RESULTS

In Serbia the total number of patient with hypertension, codes I10-I11 was 2764 while in Bulgaria the whole sample is including 3240 patients. Patients with out complications of hypertension were 1856 in Serbia and 2106 in Bulgaria that represent 67.15% and 65% respectively. Patients with complicated hypertension were 908, or 32.85% in Serbia and 1134 (35%) in Bulgaria.

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*p < 0.05

AH, arterial hypertension; CAH, complicated arterial hypertension; ACE, Angiotensin-Converting Enzyme; RIHI, Republic Institute of Health Insurance

Distribution of patients according to available complications is following. Angina pectoris is leading complication with 70% in Serbian sample and 42% in Bulgarian, then follows heart insufficiency (7% and 26%), ischemic heart disease (6% for Serbia no information for Bulgaria), sequelae of cerebrovascular disease (0.33% and 0.32 %), and other diagnoses 16.7% in Serbia. In
complicated hypertension prevails the mono-therapy in Bulgaria for 66%, while in Serbia 62% of patients are using more than three medicines (Table 1).

Patients with hypertension in Bulgaria are most often on mono-therapy (61% vs 6% in Serbia), as well as those with complications (66% vs 0% Serbia). The mono-therapy in hypertension treatment prevails in Bulgaria in 1296 patients while in Serbia only 118 patients are on mono therapy. Two medicines were prescribed in 30% and 29% respectively, while the three therapies prevail in Serbia with 35%. More than three medicines have been prescribed in 28% of the observed patient sample in Serbia.

In spite of the differences in the complexity of the therapy it was not observed statistically significant differences among the prescribed therapeutic classes of medicines (Table 1). In both countries the first choice of therapy are the ACE inhibitors (37.01% in Serbia and 41% in Bulgaria) and then follows the calcium antagonists, beta-blockers, and diuretics.

The weighed monthly cost of hypertension and complicated hypertension is almost doubled in Serbia (12.56 vs 8.23 Euro for hypertension, and 13.39 vs 8.23 Euro) and prevailing part is reimbursed (88% vs 44% in Bulgaria).

**DISCUSSION**

There are some estimation that the total number of patients with hypertension in Serbia is around 1 400 000, which correspond to 17.97% prevalence (7.4 million population). For Bulgaria the corresponding figure is 1.5 million hypertensive patients (7.2 million inhabitants). The number of patients with hypertension and complicated hypertension is similar in both country samples and this similarity is statistically significant (Table 1). The structure of the patients with complications differs because in Bulgaria only the 3 main complications were included in the sample, while in Serbia was considered also and other complications. The fact that there were no patients on poly therapy in Bulgaria could be explained with the health insurance fund limits to prescribe no more than 3 medicines per prescription, per diagnosis per month for a particular patient. This rule affects all the prescribing structure. The fact that patients in Bulgaria are most often on mono-therapy could be explained with the same regulation because patients receive a medicines for particular diagnoses and for the main disease as is the hypertension on the same prescription. We recognize that the marginal use of combination therapy in Bulgaria contrasts with the 2007 ESH/ESC guideline’s recommendations for hypertension therapy. There was a thorough debate among the health practitioners and NHIF in Bulgaria about the possible negative impact that this limitation could have on a proper handling with the high blood pressure and now a day are going changes in the positive drug list. There were included a combination products within it. We could not comment the final results because the process of medicines selections is still in process but we believe that it will be beneficial for the patients. In Serbia patients receive prescriptions for all diagnoses together.

The fact that there is a similar structure of the prescribing by the main therapeutic classless means that professionals’ in both countries follows the contemporary treatment guidelines. Further researches are necessary not only on cost control measures but also there on the need of physician education on rational drug therapy, and risk screening among the population. The fact that there are patients using more than 4 medicines per diagnoses in Serbia requires careful analysis.

Study results show that 55.5% of all health insurance expenditures for reimbursed medicines in Serbia are allocated on antihypertensive drugs; that was significantly higher than in the other countries. This fact underlines the significance of the cost analysis of hypertension pharmacotherapy and necessity of the strict control on antihypertensive medicines. Antihypertensive drugs accounted for more than half of the prescription drug expenditures, although only 18% of population had hypertension, according to the data. This could be commented as lack of precise epidemiological statistic for the hypertension burden and confirms the importance of the cost control measures.

Further analysis should be done in depth about the adequate control on the blood pressure and introduction of measures for patient’s education and compliance improvement, as well as study on the commitment of health care professionals. It could be kept in mind that the introduction of cost control measures could significantly increase the misuse of the medicines and therapy could failed but in any case clear evidences about the correspondence among the medicines usage and hypertension control are necessary for making any policy changes.

The prevalence of the ACE inhibitors (37%) and calcium antagonist (22%) prescribing while the diuretics usage is only 10% and 3% as mono-therapy and fix combination respectively could be explained with the existing marketing differences in terms of authorised for sale medicines as well as with the producers’ policy on the local markets.

High percentage of patients with complicated hypertension indicates late beginning of therapy, irregular general practitioner visits and low compliance.

It is authors’ opinion that better cooperation between physicians and patients would lead to arterial hypertension morbidity and mortality reduction, reduction in expenditures for patient and society, which will finally affect patient’s quality of life. Further analysis is needed.

**CONCLUSIONS**

Our study confirms that hypertension and its complications therapy consumes a huge amount of financial resources.
In both countries under consideration the therapy is corresponding with the European treatment guidelines.

We also could conclude that the international cost comparisons are possible but they depend on many external factors as the regulatory measures, prescribing habits and reimbursement policy and should be analysed within this framework.

CONFLICT OF INTEREST
None declared.

References