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UTILISATION ANALYSIS OF ANTIHYPERTENSIVE DRUGS IN BOSNIA AND HERZEGOVINA FOR THE TIME-PERIOD 2013–2015

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ABSTRACT

Objective: Expenditures for drugs are increasingly burdening already insufficient funds for health protection. This is especially evident in less developed European countries such as Bosnia and Herzegovina. The question is whether such analyses can help save funds for financing treatment for diseases, with an emphasis on a more rational choice of drug for appropriate indication, whereby clinical complications of hypertension would be prevented and patients would have quality of their lives improved. ***Aim:*** Focus of research has been set on analysis of use of antihypertensive drugs in Bosnia and Herzegovina in the time-period January 2013–March 2015. Use of all drugs for treatment of hypertension in that time-period in the country has been shown in an unbiased manner. ***Methods:*** The study is designed as retrospective-prospective comparative research of use of antihypertensive drugs in BiH in a certain time-period. Data are collected from relevant drug utilisation database which has been established in Bosnia and Herzegovina since 2013. ***Results:*** We have calculated financial expenditure for prescribed antihypertensives in the time- period of 2013, 2014 and Q1 2015. Use of antihypertensives at the country level for this time-period is BAM 200,242,218. At the country level, physicians are most often opting for combination therapy: ACE inhibitors + diuretics (20.2%) and ACE inhibitors + Ca channel antagonists (18.0%). ***Conclusion:*** In this research, it has been shown that modern drugs are used for treatment of hypertension in Bosnia and Herzegovina. These drugs are used in the same order as they are prescribed in developed countries.

Key words: pharmacoeconomics, hypertension, antihypertensive drugs, rational therapy.

1. INTRODUCTION

Treatment costs are rising due to increasingly greater choice of new drugs on the market, and these new drugs are usually more expensive. On the other hand, cost of drugs is also affected by the fact that life expectancy has increased and that chronic diseases represent increasingly more dominant part of costs for pharmacotherapy and treatment in general (1). Most common chronic disease of modern man is hypertension (2) which represents the main health problem in the world, with high incidence in general population. According to data of the World Health Organization, some 30-50% of adult population has hypertension. Prevalence of hypertension is expected to increase by 60% in 2025 (29.2%-1.56 billion people) relative to 26.4% (972 billion people) in the year 2000 (3).

According to the latest classification criteria of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC), arterial hypertension is defined by values of arterial pressure above 140/90 mmHg measured in doctor's office by means of a calibrated mercury sphygmo-

manometer. In accordance with these criteria, hypertension is classified into categories displayed in Table 1, with subdivision of values of systolic pressure less than 140 mmHg, and diastolic pressure less than 90 mmHg (4).

Category	Systolic pressure (mmHg)	Diastolic pressure (mmHg)
Optimal pressure	<120	<80
Normal pressure	120-129	80-84
High normal pressure	130-139	85-89
Grade I AHT (mild)	140-159	90-99
Grade II AHT (moderate)	160-179	100-109
Grade III AHT (severe)	≥180	≥110

Table 1. Classification of hypertension according to ESC/ESH, 2007

Inadequately treated hypertension eventually results in onset of clinical complications of hypertension (cerebrovascular insult, left ventricular hypertrophy, angina pectoris, myocardial infarction, heart failure, nephropathies, retinopathies), which require high additional treatment costs (5).

Hypertension is the cause of many clinical complications which are especially related to the function of heart and blood vessels in the brain, kidneys and eyes. Consequences of uncontrolled development of hypertension are reflected in onset of complications, i.e. new diseases such as: angina pectoris, myocardial infarction, cerebrovascular disease, nephropathies, retinopathies which disable many young people with work ability (6). This is why it is necessary to control hypertension and to treat it adequately. Long-term studies have shown that untreated hypertension or inadequately treated hypertension increases the frequency of complications significantly. Considering that this is a risk factor that can be modified, treatment for arterial hypertension must be approached in an adequate manner. Available guidelines for AHT treatment are in use; they are based on recommendations of various professional associations with the purpose of achieving simpler and better-quality treatment (7). Bosnia and Herzegovina belongs to a group of countries with high risk of cardiovascular diseases. Five leading causes of death by circulatory system diseases in 2009 were the same as in previous years: stroke (163), cardiomyopathy (142), cardiac arrest (146), acute myocardial infarction (121) and atherosclerosis (170), which is greatly influenced by the presence of risk factors such as improper diet, hypertension, smoking, physical inactivity etc.

Costs of hypertension treatment in other countries are quite uneven; the costs refer to expenses for drugs, visits to family physicians and hospital expenses. There is a positive correlation between higher expenses (direct and indirect) and severe arterial hypertension (AHT) in comparison to those occurring in cases of mild and moderate degree of AHT. Monitoring drug use represents an important indicator of public health which, in correlation with other indicators, is necessary for getting the whole picture of health and also for the ability to plan health care.

2. AIM

Aim of this study is to determine use of antihypertensive drugs and to analyze the values as per quantities and paid prescriptions of dispensed antihypertensive drugs at the level of state of Bosnia and Herzegovina; and based on that, to recommend measures for improvement of treatment of patients with hypertension along with application of a more rational therapy.

3. METHOD

The study is designed as retrospective-prospective comparative research of use of antihypertensive drugs in BiH in a certain time-period. Data are collected from IMS (Intercontinental Marketing Service) base. Bosnia and Herzegovina is part of the IMS network since 2013.

IMS (Intercontinental Marketing Service) is the leading company which provides service information related to health industry worldwide. This is the most complex database in the healthcare system based on which all participants in this system (health funds and ministries, pharmaceutical companies, hospitals, pharmacies) can plan their business policy. This base provides data on use of all drugs at both global as country level, through all segments of the system, based on individual products and doses for all drug forms (8).

The analysis included retrospectively years 2013 and 2014, and prospectively year 2015, and also time-periods:

- Years in the entirety;
- Semesters;
- Quarters of year;
- Months individually;
- Selected drugs - antihypertensives.

According to ATC classification, drugs in group C affect the cardiovascular system.

Drugs are chosen - antihypertensives which are most often prescribed and at the same time represent drugs in following groups as monotherapy: *β-adrenergic receptor blockers; ACE inhibitors; Ca channel antagonists; diuretics;* and as a fixed combination therapy: *β-adrenergic receptor blockers + diuretics; ACE inhibitors + Cachannel antagonists; ACE inhibitors + diuretics; Ca channel antagonists + angiotensin II receptor antagonists; angiotensin II receptor antagonists; angiotensin II receptor antagonists + diuretics; α and β adrenergic receptorblockers.*

Statistical methods

Statistical analysis of data was performed using licensed statistical program SPSS 15.0 for Windows, Microsoft Excel 2004 and SAS version 9.1. Collected data were analyzed at the level of descriptive statistics via measures of central tendency (arithmetic mean and median) and measures of variability (standard deviation and standard error). Qualitative variables have been tested using $\chi 2$ test or Fisher's exact test. Link between variables has been examined using Pearson correlation coefficient. The test used to determine prediction of increase of use of antihypertensive drugs is Damped trend exponential smoothing (SAS program). All analyses have been estimated at the level of statistical significance of $p< 0.05$ or 95% confidence interval.

4. RESULTS

Structure of analyzed data

The study of analysis of use of antihypertensive drugs in Bosnia and Herzegovina for the time-period of years 2013 and 2014, and first quarter (Q1) of 2015 included 190 registered drugs with blood pressure lowering effects. Drugs are manufactured by 35 different pharmaceutical companies.

According to presence on the drug market in Bosnia and Herzegovina, domestic firms have 43% of the market or BAM 88,105,970 (Bosnalijek and Farmavita), while the remainder belongs to foreign companies.

Presence of certain therapeutic sub-groups

Most often prescribed is combination therapy: ACE inhibitors + diuretics with 20.2% of presence in relation to total use of antihypertensive drugs in the time-period 2013.-Q1 2015. Combination therapy ACE inhibitors + Ca channel antagonists has a presence of 18.0% in relation to total use of antihypertensive drugs in the time-period 2013.-Q12015.

At the same time, 6.1% of total amount of funds for antihypertensive therapy was spent on therapy with angiotensin II receptor antagonists and diuretics in the time period 2013–Q12015.

Combination therapy: Ca channel antagonists + angiotensin II receptor antagonists had a minimal presence, with only 0.2% of total use.

Of individual drugs, according to the amount of spent funds, most often prescribed were preparations from therapeutic sub-group ACE inhibitors (17.4%), β-adrenergic receptor blockers (10.7%) and Ca channel antagonists (13.2%), while diuretics were present at 4.3% (Figure 1).

Trend of use of antihypertensive drugs according to therapeutic sub-groups is displayed in Figure 2. In the

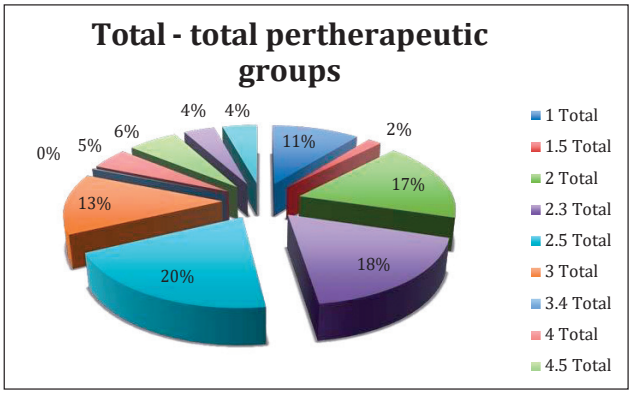

Figure 1. Total – total according to therapeutic subgroups (1 β-adrenergic receptor blockers; 1.5 β-adrenergic receptor blockers + diuretics; 2 ACE inhibitors; 2.3 ACE inhibitors + Ca channel antagonists; 2.5 ACE inhibitors + diuretics; 3 Ca channel antagonists; 3.4 Ca channel antagonists + angiotensin II receptor antagonists; 4 angiotensin II receptor antagonists; 4.5 angiotensin II receptor antagonists + diuretics; 6 α and β adrenergic receptor blockers; 7 diuretics;) Total – use of antihypertensive drugs according to therapeutic sub-groups as per months in a year (2013, 2014, Q1 2015)

graphic display, sudden increase is evident in use of drugs belonging to the group of ACE inhibitors, ACE inhibitors + diuretics and β receptor blockers in December 2013 and 2014.

Prediction of rise in use of antihypertensive drugs

Quantity of certain groups of antihypertensive drugs in relation to use of same drugs in previous time-period can be predicted statistically.

Prediction of all subgroups of antihypertensive therapy has been examined. Figures 3, 4 and 5 show prediction of increase following a period of linear values for: Ca channel antagonists + angiotensin II receptor antagonists; angiotensin II receptor antagonists; angiotensin II receptor antagonists + diuretics.

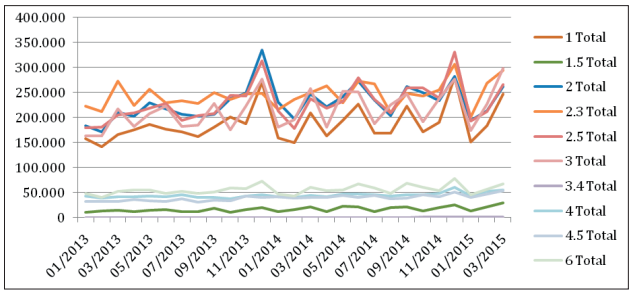

Figure 2. Total – use of antihypertensive drugs according to therapeutic sub-groups as per months in a year (2013, 2014, 2015) (1 β-adrenergic receptor blockers; 1.5 β- adrenergic receptor blockers + diuretics; 2 ACE inhibitors; 2.3 ACE inhibitors + Ca channel antagonists; 2.5 ACE inhibitors + diuretics; 3 Ca channels antagonists; 3.4 Ca channelantagonists + angiotensin II receptor antagonists; 4 angiotensin II receptor antagonists; 4.5 angiotensin II receptor antagonists + diuretics; 6 α and β adrenergic receptor blockers; 7 diuretics;)

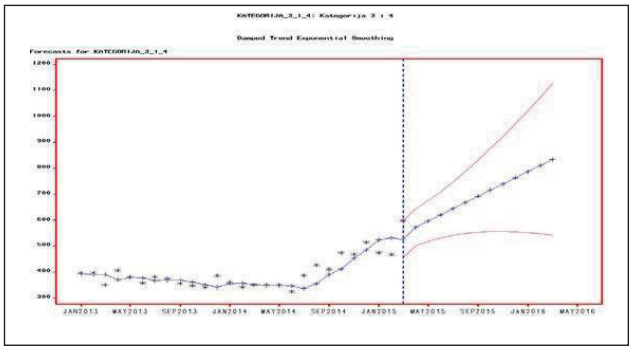

Figure 3. Prediction of use of Ca channel antagonists+ angiotensin II receptor antagonists; Damped trend exponential smoothing; p<0.001

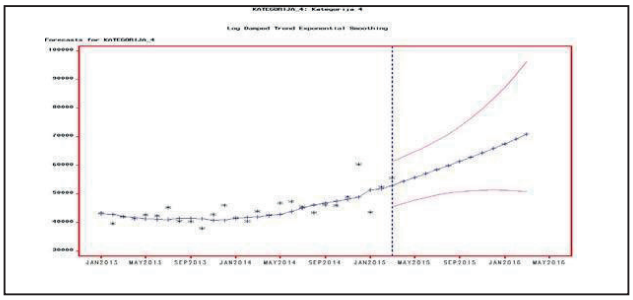

Figure 4. Prediction of use of angiotensin II receptor antagonists; Damped trend exponential smoothing; p<0.001.

5. DISCUSSION

Review of results of conducted research

Conducted research represents pharmacoeconomic analysis at the state level of Bosnia and Herzegovina; the aim was to determine use of antihypertensive drugs and possibilities for rationalization of application of this therapy. Data from IMS base were collected and analyzed.

Analyses of use of antihypertensive drugs in Bosnia and Herzegovina for the time-period 2013 and 2014 and first quarter (Q1) of 2015 included 190 registered drugs with blood pressure lowering effects. Drugs are manufactured by 35 different international and domestic pharmaceutical companies.

According to presence on antihypertensive drug market in Bosnia and Herzegovina, domestic firms have 43% of the market or BAM 88,105,970 (Bosnalijek and Farmavita), while

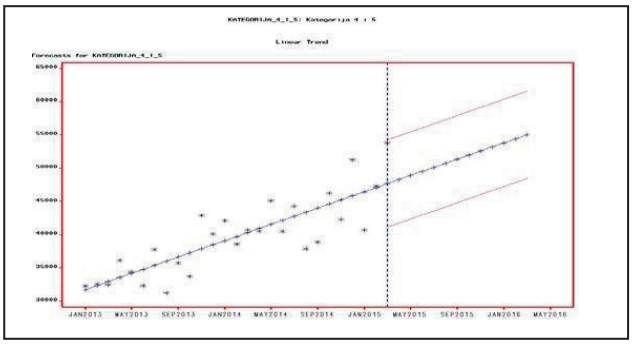

Figure 5. Prediction of use of angiotensin II receptor antagonists + diuretics; Damped trend exponential smoothing; p<0.001.

the remainder–56% or BAM 112,136,248 BAM belongs to foreign companies. Total BiH drug market regarding marketing of drugs is significantly smaller than markets of Slovenia, Croatia and Serbia. However, inspection of the list of top ten manufacturers as regards marketing of prescription drugs in BiH shows that there are merely three drug manufactures in BiH on the list: Bosnalijek, Farmavita and Hemofarm.

Although therapeutic possibilities for treatment of hypertension are numerous, it's still not easy to explain why there's no progress in control of hypertension as the most important cause of onset of cardiovascular diseases which are the leading cause of death.

Modern guidelines for treatment of hypertension are based on application of diuretics as drugs of choice for hypertension without damage to organs and application of antihypertensives of second generation in patients with hypertonic illness who have diabetes and organ damage (9, 10). Difference between American and European guidelines exists solely in the fact that when deciding on therapy, European experts pay greater attention to total cardiovascular risk and systolic blood pressure (11).

Fisher and associates have shown with their study that only 40% of physicians adhere to recommended guidelines, and they have calculated that if correctly applied, savings made in regard to prescribing antihypertensives would amount to at least USD 11.6 million (12).

NICE - analyses determined that for most people, Ca channel blockers are the most cost-effective option for initial treatment of arterial hypertension (13).

JNC 8 (Eighth Joint National Committee) in 2013 has published new guidelines for treatment of arterial hypertension in adults (14).

In accordance with contemporary guidelines for treatment of hypertension, we can make a comment on results of our research.

Statistical analysis of data related to use of antihypertensive drugs according to therapeutic groups for 2013 and 2014 and first quarter of 2015 in Bosnia and Herzegovina shows that combination therapies were most often used: ACE inhibitors + diuretics (20.2%) and ACE inhibitors + Ca channel antagonists (18.0%). Of individual drugs, according to the amount of spent funds, most often prescribed were preparations from therapeutic sub-group ACE inhibitors (17.4%), β-adrenergic receptor blockers (10.7%) and Ca channel antagonists (13.2%), while diuretics were present at 4.3%.

Compared to contemporary studies, our results are fully in accordance with the results of other authors. Špinar J. at al. have reviewed recommendations for combination therapy and fixed combinations in treatment of hypertension, according to the guidelines of ESH/ESC and CSH from 2013. Most often recommended are double combinations which include ACE inhibitors + Ca channel antagonists; angiotensin II receptor antagonists + diuretics; Ca channel antagonists + diuretics (15).

Combination therapy which implies fixed doses of ACE inhibitors with diuretics or ACE inhibitors with Ca channel antagonists is the most often used therapy in Bosnia and Herzegovina according to total use for the time-period 2013–Q1 2015. This is another proof of availability and use of modern antihypertensive therapy in our country.

Quarterly analysis regarding trend of use of antihypertensive drugs according to therapeutic sub-groups shows a sudden increase in use of drugs belonging to the group of ACE inhibitors, ACE inhibitors + diuretics and β receptor blockers in December 2013 and 2014.

This unevenness in use of drugs pertaining to a chronic disease that is hypertension is most likely a reflection of business policy related to tender procedures of procurement of drugs in hospitals.

According to the Report of the Agency for Medicinal Products and Medical Devices of Bosnia and Herzegovina from 2013, total turnover of drugs for each group of drugs from ATC classification amounted to BAM 526,773,698.5. Of that amount, the largest percentage, 21%, goes to drugs in group C–drugs for cardiovascular system (16).

We have calculated financial expenditure for prescribed antihypertensives in the time- period of 2013, 2014 and Q1 2015. Use of antihypertensives at the country level for this time-period is BAM 200,242,218.

In this study, prospective analysis was performed regarding use of antihypertensive drugs in relation to the trend of use of these drugs during analyzed time-period (January 2013.–March 2015). Method of drug use utilized records of previous use of certain drugs in order to project future needs. This is the most precise methods, provided that data sources are accurate, complete and correctly adjusted for periods without reserves and expected changes in demand and use.

Quantity of certain groups of antihypertensive drugs in relation to use of the same drugs in the previous time-period can be predicted statistically.

Prediction of all subgroups of antihypertensive therapy has been examined. Prediction of increase following a period of linear values for: Ca channel antagonists + angiotensin II receptor antagonists; angiotensin II receptor antagonists; angiotensin II receptor antagonists + diuretics has been shown.

Prediction of other analyzed drugs based on use has not yielded a statistically significant trend of increase for future time-period.

Predicted use of drugs which belong to combination therapy: Ca channel antagonists + angiotensin II receptor antagonists; angiotensin II receptor antagonists + diuretics, or to mono therapy of angiotensin II receptor antagonists cannot be appraised as rational. These are second-line therapeutic drugs according to the recommendations of guidelines for treatment of hypertension (17).

Pharmacoeconomics is an important instrument of drugs/health policy in order to ensure that the money hasn't been spent irrationally.

6. CONCLUSION

Focus of the research has been set on pharmacoeconomic analysis of use of antihypertensive drugs in Bosnia and Herzegovina for the time-period January 2013 - March 2015. Use of all drugs for treatment of hypertension in that time-period in the country has been shown in an unbiased manner. Results are comparable to results of other research where the same methodology was applied.

In this research, it has been shown that modern drugs are used for treatment of hypertension in Bosnia and Herzegovina. These drugs are used in the same order as they are prescribed in developed countries.

At the country level, physicians are most often opting for combination therapy: ACE inhibitors + diuretics (20.2%) and ACE inhibitors + Ca channel antagonists (18.0%).

Sudden increase of use of drugs belonging to the group of ACE inhibitors, ACE inhibitors + diuretics and β receptor blockers in December 2013 and 2014 is most likely a reflection of business policy related to tender procedures of procurement of drugs in hospitals as it cannot be related to chronic nature of the disease.

Systematic approach of drug use monitoring increases quality of prescribing drugs and ensures a rational therapy for certain indication.

- Author's contribution: all authors contributed equally in the preparation of the manuscript.
- Conflict of interest: none declared.

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