

# Antihypertensive drugs utilisation and educational activities

Research Article

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**Abstract:** The mortality rate from cardiovascular diseases is high in Serbia. Analysis of antihypertensive drugs utilization is the basis for assessment of cardiovascular pharmacotherapy appropriateness. The aim of this study was to analyze the trend in antihypertensive drugs utilization among outpatients in Niš region, South Serbia compared to some Nordic countries (Norway, Sweden) and Australia as well as to analyze trends in educational and drug promotion activities directed to primary healthcare workers within the same region. Using the ATC/DDD methodology, we analyzed the utilization of antihypertensive drugs dispensed on prescription in the Nis region over the 2003 – 2007 period. The study was retrospective, based on data obtained from Central City Pharmacy Nis. Educational and drug promotion activities were noted from the records of Medical Faculty, University of Nis, and from the records of local branches of pharmaceutical companies active in Serbia. Wilcoxon's test was used in order to calculate the statistical significance of difference. A significant increase of 79.8% (153.8/ 276.6 DDD/inhabitants/day) in antihypertensive drug consumption was observed in the same period. This analysis showed there were substantial increases in the use of diuretics (134.7%), ACE inhibitors (79.5%) and calcium channel blockers (116.1%), especially amlodipin (241.2%). During the observed period, annual numbers of educational activities and of pharmaceutical sales representatives employed within the region increased for almost one fourth. This analysis pointed to a significant increase in the use of antihypertensive drugs in the Nis region, which was matched with increase in educational and drug promotion activities within the region, so that in 2006-2007 total consumption was approximate to some referential countries (Norway, Sweden).

**Keywords:** *Antihypertensive drugs • Outpatients • Defined daily dose • Drug utilization • Education*

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## 1. Introduction

Within Europe, large differences exist in mortality from cardiovascular and cerebrovascular diseases. These diseases show the highest rates in Eastern Europe, with the Russian Federation far ahead [1,2]. Serbia is not an exception, with age-standardized mortality from coronary heart disease between 110 and 172 cases per 100,000 inhabitants, and with similar mortality

from stroke (between 140 and 215 cases per 100,000 inhabitants) [1].

Monitoring drug utilization contributes greatly to the evaluation of pharmacotherapeutic attitudes in practice and to finding factors that have an effect on drug consumption [3,4]. Multiple factors influence prescribing decisions in general practice therefore, demonstrating causality in prescribing is difficult [5,6]. These factors include: national general practice education

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programs, national guidelines, Health Insurance Fund reimbursement list, expenditure, socioeconomic differences, availability, and prescribing practices [7,8]. These are known to influence prescribing and are difficult to measure and control. Furthermore, marketing and drug promotion by pharmaceutical companies have been identified as one of the main factors that influence prescribing practices. However, there are only few published quantitative studies, which have examined the relationship between marketing of pharmaceutical drugs and the use of antihypertensive drugs [9].

A trend towards predominant treatment of acute medical problems, with neglect of secondary prevention, was noted in the previous study on inpatients from a tertiary care university hospital in Kragujevac, Serbia [3]. Information about drug utilization among outpatients in Serbia is scanty and there are no available publications on the topic. Analysis of antihypertensive drug utilization is the basis for assessment of cardiovascular pharmacotherapy appropriateness.

The aim of this study was to compare and make note of trends in antihypertensive drugs utilization among outpatients in Niš region, South Serbia compared to certain Nordic countries (Norway, Sweden) and Australia, countries with high national standards and the most rational use of drugs from 2003-2007. Our aim was also to analyze trends in educational and drug promotion activities directed toward primary healthcare workers within Nis region, in the same period.

## 2. Material and Methods

The data was obtained from Nis Municipal Pharmacy, which supplies approximately 350.000 inhabitants, through the network of 25 state-owned pharmacies. All data for 2003 to 2007 was centrally collected and analyzed. The City Pharmacy Department automatic report on drugs prescribed by physicians for certain diagnoses was used as data source. The analysis included also the cost of dispensed drugs from the City Pharmacy Department.

The data was obtained by a retrospective study and expressed as a number of defined daily doses (DDD) per 1000 inhabitants/day (DID) and number of drug prescriptions for the 2003-2007 time period. All pharmaceuticals were classified according Anatomical Therapeutic Chemical (ATC) drug classification system [4]. A study was taken to analyze utilization medicines reimbursed by the Health Insurance Fund (HIF), with a focus on antihypertensive medicines. ATC/DDD methodology was used to monitor utilization of medicines. The Wilcoxon Signed Ranks Test was used

in order to calculate the significance of difference in antihypertensive drug utilization. The level of variation in drug utilization was calculated for each class of antihypertensive agents with a relative standard deviation (RSD) measure.

Educational and drug promotion activities were noted from the records of Medical Faculty, University of Nis and from the records of local branches of pharmaceutical companies active in Serbia, for the same period.

## 3. Results

The total of 14.750.342 prescriptions were analyzed, with 5.574.709 being the prescriptions of cardiovascular drugs (C1-C10) from 2003-2007 period. During the 5-year study period the total number of antihypertensive drugs prescriptions increased by 83.68% (775.661/1.424.785). The results clearly show an increase in utilization of medicine in all pharmacological groups. Total medicine utilization increased each year compared to the previous year, as follows: by 15.2, 14.3, 26.14 and 7.0%, in 2004, 2005, 2006 and 2007, respectively (Table 1). The highest utilization was observed in groups of plain ACE inhibitors (ACEi) (82.97 DID in 2003 vs. 148.88 DID in 2007). Utilization of ACEi increased by 11.6%, 21.5%, 18.1% and 12%. The next most used drugs were beta blockers (33.46 DID in 2003. and 46.56 DID in 2007) and calcium channel blockers (CCB) (26.08 DID in 2003. and 56.41 DID in 2007) (Table 1) with a constant utilization increase (Figure 1). The highest increase was observed in the groups of C03 (diuretics) (134.7%) and the lowest in the group of C07 (beta blocking agents)(39.1%). Although an increased utilization of beta blocking agents and diuretics was observed, these groups had a low share in the total of antihypertensive drugs (beta-blocking agents 13-17%, diuretics 4.9-6.5%) (Table 1).

When relative standard deviations were calculated, RSDs varied from 14.5% for beta blocking agents to 74.7% for lipid lowering agents (Figure 2). Inappropriately low utilization of lipid lowering drugs was observed, especially statins, which could be explained by the cost of the drug (0.06 DID) in 2003. However, lipid lowering drugs utilization showed a tendency to increase during the investigation period (8.2 DID) particularly in 2007, owing to reimbursements by the Republic Health Fund, as well as educational and promotional activities.

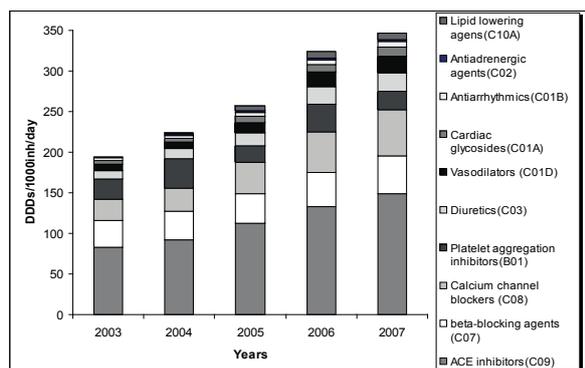
The most prescribed antihypertensive drug was enalapril which accounts for 32-44.4% of total utilization (Table 2). The use of amlodipine significantly increased by 241.2% (13.62/ 46.38 DID), during the same period and is characterized by the highest trend of increase

**Table 1.** Comparison of certain groups of cardiovascular drugs consumption during 2003- 2007.

	2003		2004		2005		2006		2007	
	DID	%	DID	%	DID	%	DID	%	DID	%
ACE inhibitors(C09)	82.9	42.56	92.5	41.22	112.4	43.80	132.8	41.03	148.8	42.93
β-Blocking agents (C07)	33.5	17.20	34.5	15.37	36.3	14.15	42.3	13.07	46.6	13.44
Calcium channel blockers (C08)	26.1	13.40	28.4	12.66	38.3	14.93	50.2	15.51	56.4	16.27
Platelet aggregation inhibitors(B01)	24.9	12.78	36.6	16.31	20.7	8.07	33.9	10.47	23.2	6.69
Diuretics(C03)	9.5	4.88	12.3	5.48	16.6	6.47	21.2	6.55	22.3	6.43
Vasodilators (C01D)	7.8	4.00	7.9	3.52	12.5	4.87	18.2	5.62	21.2	6.12
Cardiac glycosides(C01A)	5.4	2.77	5.4	2.41	7.6	2.96	9.2	2.84	11.1	3.20
Antiarrhythmics(C01B)	2.8	1.44	3.1	1.38	4.5	1.75	5.8	1.79	6.3	1.82
Antiadrenergic agents(C02)	1.8	0.92	1.6	0.71	2.1	0.82	2.3	0.71	2.5	0.72
Hypolipemic(C10A)	0.1	0.05	2.1	0.94	5.6	2.18	7.8	2.41	8.2	2.37
Total	194.8*	100	224.4	100	256.6	100	323.7	100	346.6*	100

DID - defined daily doses per 1000 inhabitants/day

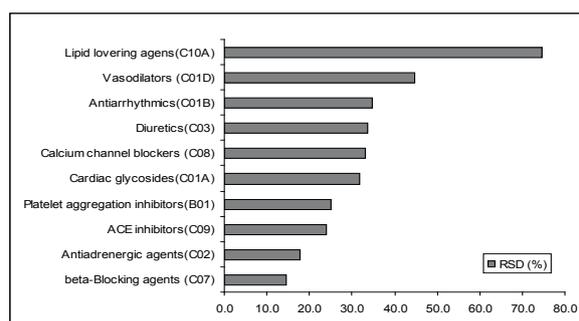
\* Consumption of drugs had a significant increase from 2003- 2007 (Wilcoxon Signed Ranks Test  $Z=2.192$   $p=0.028$ )

**Figure 1.** Comparison of certain groups of cardiovascular drugs consumption during 2003- 2007(DID).

compared to other antihypertensive drugs (Figure 3). Relative use of amlodipine use shows variation, ranging from 13.3% of all antihypertensives in 2003. to 46.4% in 2007. Besides, utilization of nifedipine almost doubled reduced in 2007 compared to 2003 (9.46/ 4.84 DID).

When relative standard deviations were calculated, RSDs varied from 9.2% for atenolol to 136 % for fosinopril (Figure 4). New ACEi (fosinopril, ramipril, lisinopril) have the highest variation because they were included in refundable medicine listings in 2005. The use of fosinopril increased tenfold in 2007 compared to 2005.

Compared to Nordic countries and Australia the use of ACEi was significantly higher in Niš, although it must be emphasized that in referential countries the use of ARB is high, while this group of medicines in Serbia was not on the refundable list in the researched period. Also we note a significantly lower use of diuretics which were the dominant group in Sweden. The utilization of CCB and BB was approximate to Nordic countries (Figure 5).

**Figure 2.** Relative standard deviation (RSD) per cardiovascular drug class.

During the observed period (2003-2007) there were 153 educational activities (at least of two working hours duration), expert meetings or symposiums in the field of cardiovascular pharmacotherapy in total; the trend of annual number of educations is shown at Figure 6. From the records of employed pharmaceutical sales representatives in local branches of pharmaceutical companies (in Niš region) we have observed an increasing trend (32 in 2003 vs. 51 in 2007), which is shown in Figure 6.

## 4. Discussion

In modern clinical practice, analyzing drug utilization is an important tool for achieving rational drug therapy in any clinical setting [9-12]. It is necessary for identification of a problem, and for following effectiveness of corrective interventions, undertaken by management of a health facility.

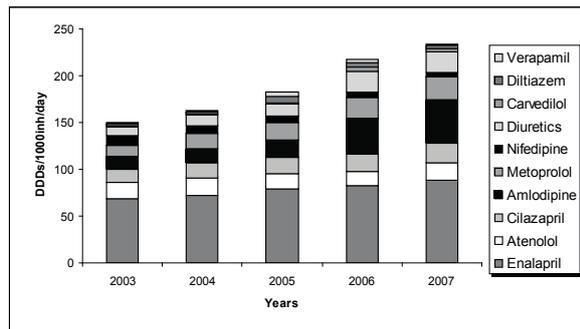
**Table 2.** Comparison of consumption of antihypertensive drugs in Nis region, 2003-2007.

	2003		2004		2005		2006		2007	
	DID	%	DID	%	DID	%	DID	%	DID	%
Enalapril	68.3	44.40	72.4	42.61	78.6	39.03	82.1	32.61	88.6	32.03
Atenolol	18.03	11.72	18.6	10.95	16.4	8.14	15.1	6.00	18.9	6.83
Cilazapril	13.8	8.97	15.4	9.06	17.8	8.84	19.2	7.63	20.8	7.52
Amlodipine	13.6	8.84	15.2	8.95	18.2	9.04	38.5	15.29	46.4	16.78
Metoprolol	12.4	8.06	16.2	9.54	18.9	9.38	21.7	8.62	23.6	8.53
Nifedipine	9.5	6.18	9.1	5.36	7.4	3.67	5.6	2.22	4.8	1.74
Diuretics	9.5	6.18	11.6	6.83	12.3	6.11	22.2	8.82	22.3	8.06
Carvedilol	1.9	1.24	0.6	0.35	0.8	0.40	4.6	1.83	3.6	1.30
Diltiazem	1.6	1.04	2.6	1.53	7.2	3.57	5.4	2.14	3.7	1.34
Verapamil	1.4	0.91	1.5	0.88	5.5	2.73	2.7	1.07	1.5	0.54
Propranolol	1.2	0.78	0.4	0.24	0.2	0.10	0.9	0.36	0.5	0.18
Metyldopa	1.2	0.78	1.1	0.65	1.6	0.79	1.7	0.68	1.8	0.65
Doxazosin	0.6	0.39	0.5	0.29	0.5	0.25	0.6	0.24	0.7	0.25
Perindopril	0.3	0.20	0.7	0.41	2.4	1.19	3.3	1.31	1.4	0.51
Lisinopril	0.2	0.13	1.2	0.71	4.4	2.18	9.7	3.85	8.5	3.07
Quinapril	0.2	0.13	1.5	0.88	2.8	1.39	6.2	2.46	5.5	1.99
Ramipril	0.1	0.07	0.9	0.53	5.2	2.58	9.8	3.89	11.4	4.12
Fosinopril	0	0.00	0.4	0.24	1.2	0.60	2.5	0.99	12.6	4.56
TOTAL	153.83*	100	169.9	100	201.4	100	251.8	100	276.6*	100

DID - defined daily doses per 1000 inhabitants/day

\* Consumption of drugs had a significant increase from 2003-2007 (Wilcoxon Signed Ranks Test,  $Z=2.240$ ,  $p=0.025$ )

**Figure 3.** Trends in consumption of same antihypertensive drugs in Nis region (2003-2007).



Our study indicated low utilization of cardiovascular drugs in Nis region, when compared with developed countries in Europe and Australia from 2003-2005. Total utilization of cardiovascular drugs in 2004 was 194.8 DID, which was (almost twice lower) much lower than in Australia (376.6 DID), Norway (317.4DID) and Sweden (383.7DID). Our data also confirmed underuse of antihypertensive drugs with the best cost/effectiveness ratio (diuretics and beta blockers). In Serbia, due to a lack of educational and promotional activities, prescribing decisions are mostly in disagreement with the Good Clinical Practice and guidelines [13].

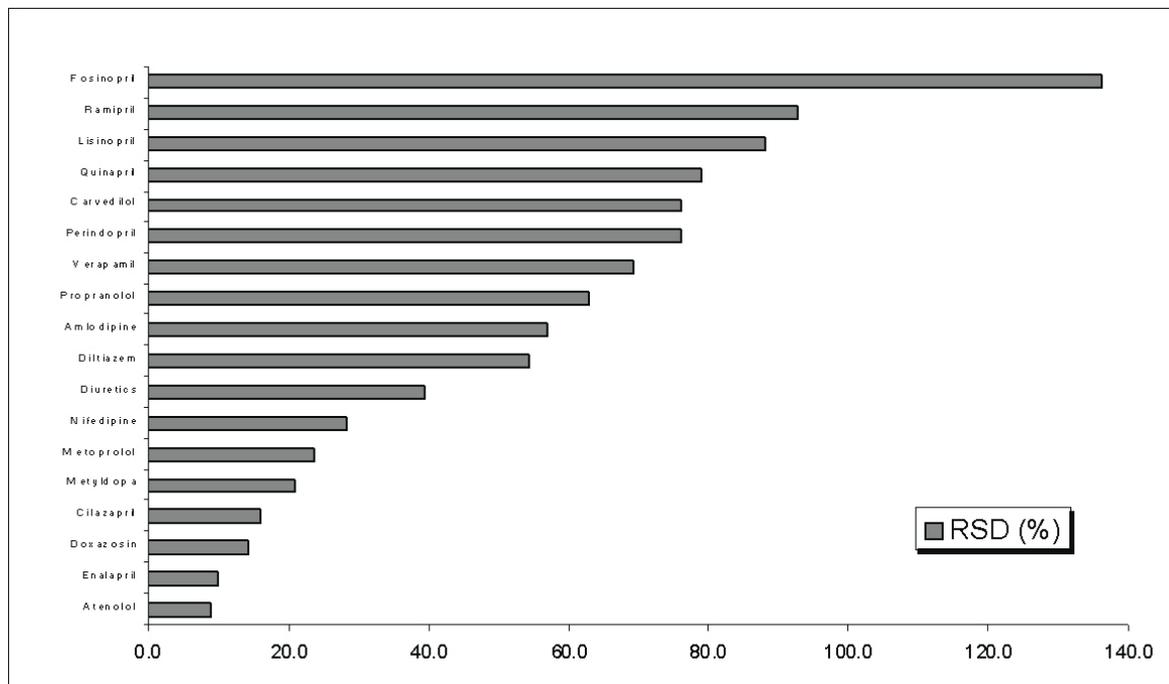
Wide qualitative differences between countries were also identified. Although other factors may play a role, it is suggested that these striking differences may be due to differences in general health policy and in the pharmaceutical markets [4,5,12-17].

Although the first drug information center (DIC)s were established decades ago in US and Europe, there is currently no DIC in Serbia nor any other source for problem oriented drug information [17]. Consequently there was a need for educational activities in order to increase the use of cardiovascular drugs.

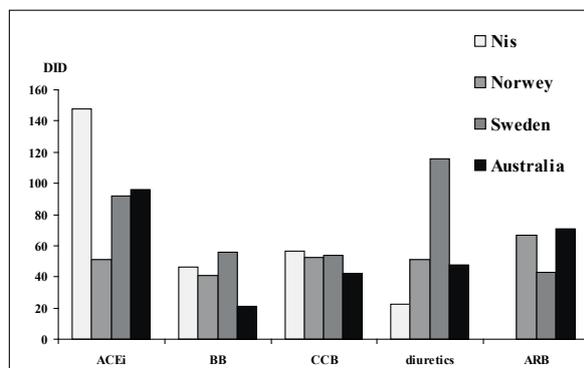
During the investigation period the total consumption of cardiovascular drugs in Nis region increased significantly in 2007, by 77.95% (194.80/346.65 DID) compared to 2003,  $p<0.05$  as it can be seen from this analysis (Table 1). This gradual increase in sales of cardiovascular drugs could indicate that the number of patients had increased.

From 2006 to 2007 there was a substantial increase in use of antihypertensive medicines in Serbia which is comparable to the increase in the referential countries [1,5,9]. In the observed period there was a trend of increase in cardiovascular pharmacotherapy educations for general practitioners, as well as an increasing number of regional representatives of pharmaceutical companies for Niš region (Figure 3). Education puts

**Figure 4.** Relative standard deviation (RSD) per antihypertensive drugs.



**Figure 5.** Comparison of consumption of antihypertensive drugs in Nis region and Nordic country (Norway, Sweden) and Australia in 2007.

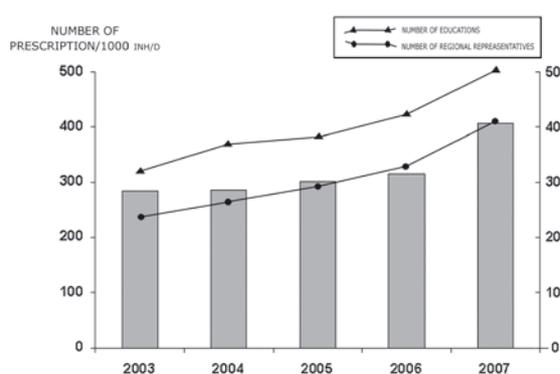


special emphasis on national and international guidelines as well as on the rational treatment of hypertension.

In the same period, per capita expenditure for health in Serbia had increased by 188.9%, from 90\$ in 2003 to 260 \$ in 2007, which created favorable environment for an increase in drug utilization as well as conditions for the extension of refundable medicines list to include more antihypertensive medicines (ramipril, fosinopril, lisinopril, quinapril, perindopril). In the same period, cost for cardiovascular drugs was increased by 284.9%, from 1.583.445€ to 7096077€.

Previous studies have indicated the negative effects of socioeconomic deprivation on health status and morbidity. Nevertheless, the economic assignment

**Figure 6.** Comparison number of prescription antihypertensive drugs and number of educations and regional representatives.



system for pharmaceutical benefits in Sweden does not take socioeconomic status into account [18].

The predominance of antihypertensive drugs in total drug utilization volume is a consequence of high cardiovascular and cerebrovascular morbidity and mortality. Out of total volume of antihypertensive drugs, the outpatients used ACEi the most, especially enalapril. This could be explained by a widening of the indications for their use in hypertension, diabetic nephropathy, heart failure, etc. In the last decade ACEi became one of the most important drugs in cardiology, taking into consideration their cardio protective and renoprotective effects [14,15,19-21]. Many clinical studies confirmed reduction in cardiovascular morbidity and mortality in

patients with use of ACEi [20,21]. Some clinical studies on use of antihypertensive drugs, conducted in Estonia, Republic of Srpska and Croatia, also found ACEi to be the most prescribed class of drugs [7,8,16,23].

Beta adrenergic receptor blockers are a class of cardiovascular drugs with registered trend for increasing consumption, by 39.1% (33.46/46.56 DID) from 2003–2007. Cardio protective and antihypertensive effects of this class of drugs justify much larger use in our patients. Beta blockers reduce mortality rate when used for primary and secondary prevention of myocardial infarction and chronic heart insufficiency [15,22]. Cardioselective beta blockers, atenolol and metoprolol were the most prescribed drugs in the population under our study (Table 2). The use of carvedilol, bisoprolol and nebivolol were found to be low in 2003, because they were not funded by state Health insurance.

The use of calcium channel blockers increased during that period, on account of amlodipine (247.9%). This drug reached second place in the list of „top ten“ drugs used in 2007. The use of amlodipine is increasing worldwide as well, due to its favorable pharmacokinetics (one time a day dosing) and efficiency in control of hypertension and prophylaxis of angina pectoris [15,21].

Our data showed very low use of diuretics (9.46 DID), especially thiazides (5.3 DID), which could be explained by an inadequate prescribing policy of the physicians in 2003. The use of diuretics was significantly increased owing to continued education physicians as well as to the extension of refundable medicines list to include diuretics and potassium-sparing agents in combination. Thiazides diuretics are fundamentals of antihypertensive therapy. They are recommended as initial pharmacotherapy in older patients with stage I or II of hypertension, or in combination with other antihypertensive drugs in patients with severe hypertension. Similar results were reported by the authors from Estonia and Bosna and Herzegovina [8,16]. Pharmacoepidemiologic analysis of outpatients' use of cardiovascular drugs in Banja Luka region (Bosnia and Herzegovina) showed similar results [23].

ALLHAT study in over 40.000 patients older than 55, in the period of 4–8 years, showed a more effective antihypertensive effect and higher reduction of cardiovascular events in patients taking thiazides, compared to calcium antagonists and ACEi [19,21,24].

In Serbia pharmacoepidemiologic surveys are scarce. Enalapril was the most prescribed cardiovascular drug, while group C takes the first place in the total consumption of medicines with 30.57% (which can be explained by its favorable price and current prescribing practices). Statins are dominant cardiovascular drugs in referential countries, which reflect adequate

pharmacotherapy attitudes, health policy and economic power of these countries [25–27]. Statin use is followed by ACEi (ramipril in Australia and Norway, lisinopril in Sweden) and ARBs (irbesartan in Australia, kandesartan in Norway), diuretics (furosemide in Australia, Norway), CCB (amlodipine in Australia, Norway), and beta blockers (metoprolol in Norway, atenolol in Australia) [14,25–32]. In Sweden, the most common drugs used were diuretics among women (104 vs 70 DDD, 8.8% of the population), while men used more ACEi (76 vs 49 DDD). Trend towards increased utilization of antihypertensive drugs was observed. In Norway, total cardiovascular medicines utilization increased each year compared to previous years, as follows: by 6.4, 5.1, 5.25 and 5.4%, in 2005, 2006, 2007 and 2008 (316.7/393.5 DID), respectively. During 1993–2006, annual volume growth in DDDs varied from 0.8 to 7.4% [27]. In Sweden antihypertensive drugs utilization increase was 114% (169.15/ 362.4 DID) in 2003–2008 period. In Australia, utilization of cardiovascular drugs increased by 6.21 and 7.9% in 2006 – 2007 (376.96/432.17 DID) and was greater than in Nordic countries [28–31]. In Nis region, utilization of antihypertensive drugs increased by 10.4, 18.5, 25.0 and 9.8%, in 2004, 2005, 2006 and 2007 (generally 15.9 DDD), respectively.

The highest utilization was observed in groups of ACEi (C09) and ARBs (99.06/124.63DID) in Norway, Sweden (62.3/92.3DID) and Australia, utilization in groups of ACEi (82.2/96.1DID) and ARBs (62.4/71.1DID), during 2005–2007 [30,31]. Actively ARBs were commonly used in Sweden (38.8DDD), mainly to treat hypertension, which accounts for 11% of all antihypertensive drugs initiated in the end of 2006. Consequently, reimbursement of ARBs was limited in Sweden from September 2008, only to patients who were unable to use ACEi or who used them as a complement to ACEi [35]. In Serbia, ARBs were not included in the list of refundable medicines in the observed period.

The lowest utilization was in the group of beta blocking agents (C07) 39.4/41.36DID) in Norway and Australia (20.8/21.36DID), while in Nis they were the third most commonly used drug (33,5/46.6 %)[27]. Measured in DDDs, the sales of cardiovascular drugs have been increasing over time and in 2008 the increase was 7 % in Norway [27], while in Nis there was an increase of 156%. Many of the factors correlated positively with cardiovascular drugs use. These factors include: national guidelines, sex, educational level, depressed mood, prescribing habits [33,34]. Cost and budget may influence the prescribing of new cardiovascular drugs, they are of secondary importance to the safety and effectiveness profile of the medicine.

Weitofte RG. et al. found rather large differences in

drug utilization for antihypertensive drugs between groups of different educational gradients in Sweden [35]. The analysis of sales data for cardiovascular drugs showed that differences in the so called “treatment traditions” were of the prime importance [36-40].

Prescription sales of antihypertensive drugs in Australia between 1993-2002 are correlated with promotional advertising and market shares. Drug promotion is one of the main factors that influence prescribing practice, but there are limited data available to quantify the relationship between drug advertising and prescription sales [9]. Advertising trends in Australia were monitored by counting the annual number of advertisements published in medical journals with the highest circulation in Australia. A national education program for general practitioners in Australia undertook at least one active educational activity (clinical audit, educational visit or case study) that was successful in improving prescribing for hypertension. The most frequent activity was clinical audit (42%), followed by academic detailing/educational visit (38%) with smaller numbers (19%) participating in case studies [5].

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## 5. Conclusion

Analysis of antihypertensive drugs use offers insight in actual prescribing practice. In general, prescribing rates of antihypertensive drugs in Nis are low compared to referential countries: Norway, Sweden and Australia in the 2003-2005 time period. This analysis pointed to a almost constant increase in use antihypertensive drugs in the Nis region owing to continued education of physicians, and an increase in numbers of pharmaceutical sales representatives, as well as to an increase in health budget per capita in Serbia, so that in 2006-2007 total consumption was approximate to referential countries (Norway, Sweden). This study will also serve as basis for further evaluation of antihypertensive drugs utilization.

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