



## Patterns of prescription antihypertensive drug utilization and adherence to treatment guidelines in the city of Novi Sad

Praksa propisivanja lekova protiv povišenog krvnog pritiska u Novom Sadu i usklađenost sa farmakoterapijskim smernicama

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### Abstract

**Background/Aim.** Hypertension is one of the leading causes of cardiovascular morbidity and mortality and more than a half of all health insurance expenditures for reimbursed medicines are allocated to antihypertensive drugs in Serbia. The aim of this study was to identify the antihypertensive drug utilization patterns among hypertensive outpatients in the city of Novi Sad, Serbia, determine the adherence to clinical guidelines and address the economic aspects of current prescribing practices. **Methods.** This retrospective observational study was conducted in Novi Sad over a period of six months. The data on the number of packages, size their, and retail price of antihypertensives issued on prescription in outpatients with the diagnosis of essential arterial hypertension was collected from all state-owned pharmacies in Novi Sad. Drug consumption was analyzed using the Anatomical Therapeutic Chemical (ATC)/ defined daily dose (DDD) methodology. **Results.** Total consumption of antihypertensives issued on prescription over a 6-month period in the city of Novi sad, Serbia was 283.48 DDD *per* 1,000 inhabitants *per* day (DID). Angiotensin converting enzyme inhibitors (ACEi) were most commonly prescribed

drugs, and were used 3 times more often than calcium channel blockers and 5 times more than beta-blockers. The consumption of diuretics and angiotensin receptor antagonists was low within all the groups of outpatients. Both national and international guidelines state superiority and effectiveness of diuretics in treatment of hypertension in the elderly, but their consumption was unreasonable low despite the fact that over 70% of all antihypertensive drugs in the city of Novi Sad were dispensed in people aged > 60. The use of more expensive ACEi was observed despite the guidelines deeming all the drugs of this class equally effective in treatment of hypertension. **Conclusion.** Large differences in utilization of different groups of antihypertensive agents were noted in this study. Underutilization of valuable, efficacious, and cost-effective thiazide diuretics and overuse of expensive ACE inhibitors is unjustifiable. There is a potential for large savings with switching to low-price ACEi, modeling the practice of Scandinavian countries.

**Key words:** antihypertensive agents; serbia; cost-benefit analysis; economics, pharmaceutical; drug utilization review.

### Apstrakt

**Uvod/Cilj.** Hipertenzija je jedan od vodećih uzroka kardiovaskularnog morbiditeta i mortaliteta u Srbiji, te više od polovine troškova za lekove na teret osiguranja odlazi na antihipertenzivne lekove. Cilj ove studije bio je analiza strukture upotrebe antihipertenzivnih lekova kod hipertenzivnih vanbolničkih pacijenata u Novom Sadu, usklađenosti sa farmakoterapijskim uputstvima i ekonomskih aspekta trenutne prakse propisivanja. **Metode.** Podaci o prometu i potrošnji antihipertenzivnih lekova propisanih kod vanbolničkih pacijenata sa dijagnozom esencijalne arterijske hipertenzije u šestomesečnom pe-

riodu prikupljeni su u državnim apotekama u Novom Sadu. Lekovi su klasifikovani prema anatomsko-terapijsko-hemijskoj klasifikaciji lekova i izračunate definisane dnevne doze (DID) na hiljadu stanovnika na dan. **Rezultati.** Ukupna potrošnja antihipertenzivnih lekova izdatih na recept u periodu od šest meseci u Novom Sadu bila je 283,48 DID. Najčešće korištena grupa lekova bili su inhibitori angiotenzin konvertujućeg enzima (ACEi), koji su propisivani tri puta češće od kalcijumskih antagonista i pet puta više od beta blokatora. Iako uputstva za lečenje hipertenzije navode da su svi ACEi jednako efikasni, primećena je upotreba skupljih ACEi. Upotreba diuretika i antagonista receptora angiotenzina bila je niska u posma-

trantom periodu. Farmakoterapijska uputstva naglašavaju prednost i efikasnost diuretika u lečenju hipertenzije kod starijih osoba, ali njihova potrošnja bila je neopravdano niska, uprkos činjenici da je preko 70% svih antihipertenzivnih lekova u Novom Sadu propisana pacijentima starijim od 60 godina. **Zaključak.** Ovo ispitivanje pokazalo je velike razlike u propisivanju različitih grupa antihipertenzivnih lekova. Nedovoljno korišćenje tiazidnih diuretika, lekova sa najboljim

odnosom koristi i troškova i upotreba skupih ACE inhibitora je neopravdana. Postoji mogućnost za značajne uštede sa racionalnijom upotrebom ACEi, po uzoru na skandinavske zemlje.

**Ključne reči:**  
antihipertenzivi; srbija; troškovi-korist, analiza; farmakoekonomika; lekovi, korišćenje, izveštaji.

## Introduction

Cardiovascular diseases (CVD) are a leading cause of morbidity and mortality in the Republic of Serbia<sup>1</sup>. Hypertension has been recognized for decades as a major risk factor for heart failure, coronary heart disease, myocardial infarction and stroke<sup>2</sup>. However, many other factors contributing to CVD such as obesity, smoking, physical inactivity and high cholesterol levels are also widely present among Serbian people with over a half of population having some of the risk factors listed above<sup>3,4</sup>. Therefore, it is not surprising that CVD accounted for 53.7% of deaths in Serbia in 2012<sup>4</sup>. According to the Institute of Public Health of Serbia reports, the overall prevalence of hypertension in Serbia is 33%<sup>5</sup>. Reducing blood pressure is one of the most cost-effective methods to reduce CVD morbidity and mortality<sup>6</sup>. Despite the life style changes, treatment of hypertension relies mostly on medications, and cardiovascular drug utilization therapy consumes a huge amount of financial resources<sup>7</sup>. In Serbia, 55.5% of all health insurance expenditures for reimbursed medicines are allocated to antihypertensive drugs<sup>8</sup>. Previous studies showed that there may be certain inadequacies in the treatment of arterial hypertension in Serbia. Inappropriate use of drug resources exacerbates the problem of plummeting drug expenditure, often without contributing to improved patient outcomes<sup>9</sup>. Research conducted in 2006 showed that among patients being treated for hypertension in the city of Novi Sad only 20.9% had blood pressure within the desired range<sup>10</sup> which points to the need for evaluation of prescribing practices among Serbian physicians.

This study was designed to identify the antihypertensive drug utilization patterns among outpatients in the city of Novi Sad, Serbia, with essential arterial hypertension, to determine the adherence to clinical guidelines, address the economic aspects of current prescribing practices and to estimate the potential for drug-cost savings if more rational prescribing practices were employed. Rational prescribing would in this case mean using less expensive angiotensin converting enzyme inhibitors (ACEi) as in Scandinavian countries, with developed pharmacotherapeutic practice.

## Methods

This retrospective observational study was conducted in the city of Novi Sad (estimated population 350,000) from September 2011 to February 2012. The data on the number of packages, size of packages, and retail price of

antihypertensive drugs issued on prescription were collected from all state-owned pharmacies in the city of Novi Sad. A report from state-owned pharmacies includes data on diagnosis, age and sex of the patients and price of drug package (in dinars - DIN). Conversion of prices to euros was done according to the National Bank of Serbia exchange rates on February 29, 2012 (EUR = 110.2 DIN). Since antihypertensive drugs are also used in treatment of other cardiovascular diseases, only drugs issued on International Classification of Diseases (ICD) code I10 (essential arterial hypertension) were included in this study. Drug consumption was analyzed using the Anatomical Therapeutic Chemical (ATC) classification of World Health Organization (WHO) Collaborating Center for Drug Statistics and Methodology<sup>11</sup>. Utilization rates were calculated as defined daily dose (DDD) *per* 1,000 inhabitants *per* day (DID). Drug utilization (DU90%) methodology was also used. The DU90% profile is a simple method that reflects the number of drugs that account for 90% of drug prescriptions. High quality of prescribing is associated with the use of a relatively limited number of pharmaceutical products within a drug group. The number of products in the DU90% segment and adherence to prescription guidelines serve as general quality indicators<sup>12</sup>. The price *per* DDD for each specific drug utilized and the mean total price *per* DDD were also calculated. The impact of adjusting the patterns of ACE inhibitors use to that of Scandinavian countries and direct drug costs of current and of the adjusted pattern were calculated. Possible drug-cost savings were estimated as the difference between the potential and current use. The data on the patterns of consumption of ACE inhibitors in Finland and Norway was extracted from the databases of the representative national authorities. The actual prescription patterns were compared to the current Serbian National Guidelines, 2009 Guidelines of the European Society of Cardiology and European Society of Hypertension (ESC/ESH), 2003 American Society of Hypertension Guidelines and 2011 British National Institute for Clinical Excellence (NICE) Guidelines for Treatment of Hypertension.

## Results

Over a 6-month period in the city of Novi Sad, Serbia, a total of 670,477 packages of medication were issued for treatment of hypertension – 85% of all cardiovascular drugs dispensed. Up to 2013, including our study period, prescription drugs were available for reimbursement only in state owned pharmacies. Total utilization of antihypertensives issued on prescription was 283.48 DID (Table 1). More medication

was prescribed to female outpatients, but no substantial differences in the structure of different groups of antihypertensives were observed between sexes. The use of antihypertensive medication increased with patients age, with over 70% being prescribed to patients over the age of 60 (Figure 1). ACE inhibitors were most commonly prescribed

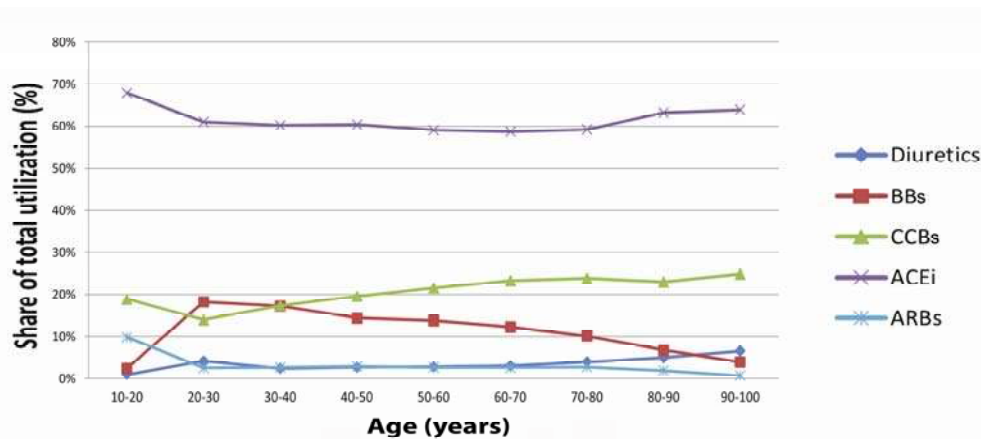
drugs in all age groups, followed by calcium channel blockers (CCBs), and beta-blocking agents (BBs). The consumption of diuretics and angiotensin II receptor blockers (ARBs) was low in all the groups of patients.

Sixteen drugs were within DU90%, accounting for 255.65 DID (Table 2). Amlodipine was most commonly used

**Table 1**  
**Consumption of the main groups of antihypertensive agents according to sex of patients**

ATC group	Male		Female		Total	
	DID (n)	Share (%)	DID (n)	Share (%)	DID (n)	Share (%)
C03	3.62	3.19	6.28	3.70	9.90	3.49
C07	12.52	11.03	20.36	11.98	32.87	11.60
C08	26.83	23.64	37.72	22.18	64.55	22.77
C09A	58.37	51.42	84.98	50.00	143.35	50.57
C09B	9.42	8.30	15.77	9.28	25.19	8.88
C09C	2.52	2.22	4.41	2.59	6.93	2.44
C09D	0.24	0.21	0.45	0.27	0.69	0.24
Total	113.52	100.00	169.97	100.00	283.48	100.0

**C03 – diuretics, C07 – beta blocking agents; C08 – calcium channel blockers; C09A – angiotensin converting enzyme inhibitors, C09B – angiotensin converting enzyme inhibitors, combinations; C09C – angiotensin II receptor antagonists; C09D – angiotensin II receptor antagonists, combinations; ATC – anatomical therapeutic clinical; DID – defined daily dose per 1,000 inhabitants per day.**



**Fig. 1 – Trends in the use of the main groups of antihypertensives according to age of patients.**  
BBs – beta blocking agents; CCBs – calcium channel blockers; ACEi – angiotensin-converting enzyme inhibitors; ARBs – angiotensin II receptors antagonists.

**Table 2**  
**Consumption of antihypertensives – DU90% profile expressed in the number of DDD/1,000 inh/day (DID), share, average price per DDD (in Euros), and patient co-payment**

No	ATC	INN	DDD [n]	DDD [%]	Price per DDD [€]	Co-payment (%)
1	C08CA01	amlodipin	52.51	18.5	0.06	/
2	C09AA02	ramipril	39.42	13.9	0.06	/
3	C09AA05	enalapril	38.56	13.6	0.07	/
4	C09AA09	fosinopril	22.12	7.8	0.15	35
5	C07AB02	metoprolol	18.32	6.5	0.09	/
6	C09AA08	cilazapril	15.57	5.5	0.11	35
7	C09AA01	captopril	15.12	5.3	0.09	/
8	C09AA03	lisinopril	8.50	3.0	0.06	/
9	C09BA02	enalapril/HCTZ <sup>1</sup>	7.47	2.6	0.11	/ <sup>2</sup>
10	C09BA05	ramipril/HCTZ	7.35	2.6	0.11	/ <sup>2</sup>
11	C07AB07	bisoprolol	7.05	2.5	0.10	/
12	C08CA05	nifedipin	6.38	2.3	0.06	/ <sup>2</sup>
13	C09DA01	losartan	5.61	2.0	0.11	25
14	C09BA09	fosinopril/HCTZ	4.82	1.7	0.18	30
15	C08DB01	diltiazem	3.49	1.2	0.17	/
16	C09BA03	lisinopril/HCTZ	3.36	1.2	0.10	/ <sup>2</sup>
Within DU90% 1–16			255.65	90.2	0.10	8
Beyond DU90% 17–42			27.84	9.8	0.13	24
Total N = 42			283.48	100.00	0.12	19

<sup>1</sup>HCTZ – hydrochlorothiazide; <sup>2</sup>limited reimbursement (fixed combinations available for reimbursement after 3 months of treatment with single preparations); DDD – defined daily dose; ATC – anatomical therapeutic clinical; INN – international nonproprietary names; DU90% – drug utilization 90%.

and made up more than 18% of the total consumption and two more drugs of the same class, nifedipine and diltiazem were within DU90%. Metoprolol was the most commonly used beta-blocker, followed by bisoprolol. Out of 16 drugs in DU90% profile, 10 were ACEi or ACEi and combinations. Neither thiazide diuretics, nor ARB were within DU90%, as thiazide diuretics and combinations altogether comprised 2.4% and ARB comprised 2.6% (losartan 2.0%, other ARB 0.6%). The average price *per* DDD within the DU90% segment was 0.10 Euro/DDD, whereas for the antihypertensives beyond the DU90% segment the average

price/DDD was 0.13 Euro/DDD. Direct drug cost of antihypertensive medication distributed was more than 1.5 million euro (Figure 2). Utilization and expenditure share were similar for the majority of drugs, and drugs within the DU90% segment had better utilization-expenditure ratio, especially amlodipine, enalapril and ramipril (Figure 3). A potential change in the use of ramipril and enalapril and corresponding decrease in the use of expensive ACE (i.e. fosinopril) provided a resulting net potential for direct drug-cost savings of 175,000 euro over a 6-month period in the city of Novi Sad (Table 3).

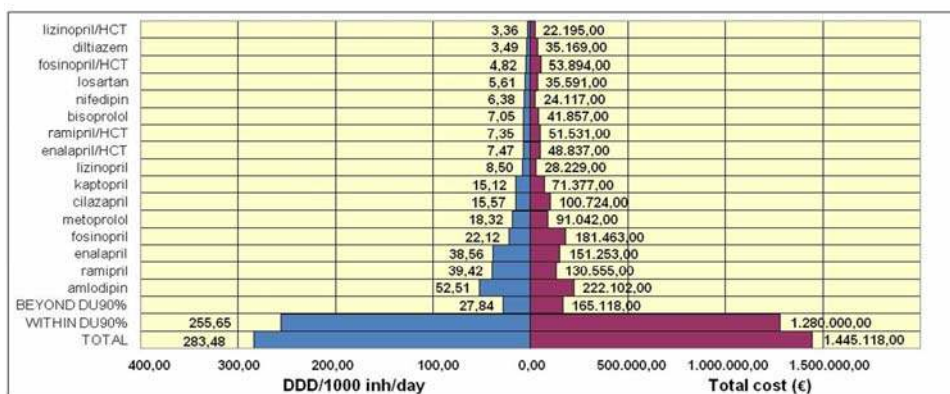


Fig. 2 – Drug utilization (DU90%) segment – utilization and expenditure comparison. DDD – defined daily dose.

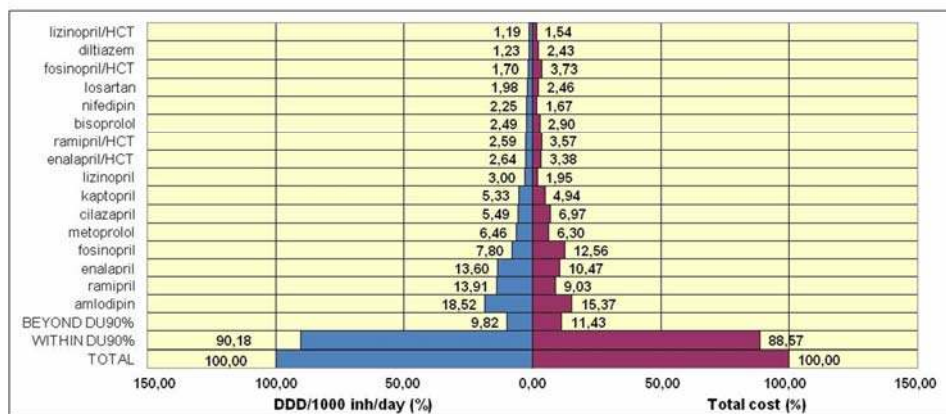


Fig. 3 – Drug utilization (DU90%) segment – comparison of utilization and expenditure share. DDD – defined daily dose.

Table 3

The impact of adjusting angiotensin converting enzyme inhibitors (ACEi) prescribing to that of Scandinavian countries - current total use in Novi Sad, Serbia (DID) and direct drug cost (in Euros), pattern ACEi prescribing adjusted to Scandinavian countries and potential savings over a 6-month period.

Drug (INN)	Price <i>per</i> DDD (€)	Current ACEi use in Novi Sad			Adjusted ACEi use*		
		DID	Share (%)	Cost (€)	Share (%)	Cost (€)	Savings (€)
Captopril	0.09	15.12	10.6	71,377	0.6	3,886	67,491
Enalapril	0.07	38.56	26.9	151,253	25.6	143,596	7,657
Lizinopril	0.06	8.50	5.9	28,229	4.7	22,467	5,762
Perindopril	0.11	1.60	1.1	9,534	4.5	38,346	-28,812
Ramipril	0.06	39.42	27.5	130,555	64.5	305,808	-175,254
Quinapril	0.11	2.30	1.6	15,692	0.2	1,588	14,104
Cilazapril	0.11	15.57	10.9	100,724	/	/	100,724
Fosinopril	0.15	22.12	15.5	181,463	/	/	181,463
Zofenopril	0.19	0.17	0.1	1,975	/	/	1,975
Total		143.19	100.0	688,827	100.0	515,691	175,111

\*adjusted to the structure of use of ACE inhibitors in Scandinavian countries.

ATC – anatomical therapeutic clinical; DDD – defined daily dose; DID – defined daily dose *per* 1,000 inhabitants *per* day;

INN – international nonproprietary names.

## Discussion

Both Serbian and ESC/ESH guidelines state that all the available antihypertensive classes are suitable for hypertension management<sup>13,14</sup>, so individual patient needs and comorbidities, as well as on economic aspects should be critical when determining preferential antihypertensive drugs. Despite neither of the main types of antihypertensives being favored in clinical guidelines, ACEi were the most commonly used drug group, used 3 times more than CCBs, 5 times more than BBs and 20 times more than diuretics. Vast usage of ACEi also reflected the DU90% profile – out of 16 drugs within DU90%, 9 were ACEi. Beneficial effects of ACEi in hypertensive patients have been well documented and in British NICE guidelines they are recommended as first line treatment of hypertensive patients under 55 years of age<sup>15</sup>. ACEi do not only lower blood pressure, but also have vasoprotective, antiatherogenic effect and improve prognosis of CVD, lower the incidence of myocardial infarction and stroke<sup>16,17</sup>. No difference in efficacy has been documented between different drugs in the ACEi group, nor clinical guidelines favor specific ACEi, yet clinicians in Serbia prescribed extensive amounts of fosinopril and cilazapril, with two times higher price *per* DDD than, for example, enalapril. Fosinopril with less than 8% of total utilization accounted for nearly 13% of total spending. Fund reimburses 65% of costs for these drugs; the rest needs to be compensated by patients<sup>18,19</sup>. Multiple studies<sup>20–22</sup> emphasized that higher prescription copayments were associated with poor compliance. The reasons for prescribing more expensive ACEi despite no proved clinical benefit are probably a combination of tendency of the physician to use a wide palette of drugs, inclination towards newer drugs and marketing pharmaceutical campaigns<sup>23</sup>. There are differences in the use of ACEi between Serbia and Scandinavian countries. In Norway and Finland, ACEi and combinations are also the primary drug class used, but they account for around 20–30% of all drug utilized, a share much smaller than in the city of Novi Sad<sup>24,25</sup>.

Most patients require two or more antihypertensive drugs to achieve blood pressure control<sup>21</sup>. Fixed combinations of antihypertensives (ACEi or ARBs with diuretics or CCBs) allow combination therapy with a higher patient compliance and thus better control of hypertension compared to multiple drugs administration. These drugs, mainly ARBs and diuretics combinations are widely used in Scandinavian countries such as Norway and Finland, with well-developed pharmacotherapeutic practice<sup>24,25</sup>. Utilization of these drug types is much lower in Serbia, especially for ARBs combinations. Many factors limit their use in Serbia, since a fixed combination of antihypertensives can be reimbursed only after a failure to achieve blood pressure control with a 3-month combination therapy with single drug preparation and copayment ranges from 25% [(most ACEi and hydrochlorothiazide (HCTZ)] to 70% (telmisartan and HCTZ)<sup>18,19</sup>. CCBs were also widely utilized in hypertensive patients, amlodipine being the most commonly prescribed drug. CCBs utilization is probably associated with demographic characteristics of the city of Novi Sad, where 40% of inhabitants are older than 50, and guidelines recommend cal-

cium channel blockers in treatment of hypertension in people over the age of 55. A higher usage of BBs was observed in people under 40, which is in accordance with the national guidelines<sup>13</sup>, where BBs are the drugs of choice in case of hypertension associated with increased sympathetic tone, mostly observed in younger people. A lower usage of BBs in older population may be due to the fact that many of comorbidities in senior population are a contraindication for use of these drugs.

Both national and international guidelines state superiority and effectiveness of diuretics<sup>13–15,26</sup> in treatment of hypertension in the elderly, but their consumption was unreasonable low despite the fact that over 70% of all antihypertensive drugs in the city of Novi Sad were dispensed to people > 60. The elderly are more likely to have developed organ damage related to hypertension or to have heart failure or diabetes as concomitant conditions, and thiazide diuretics, drugs with the highest cost-effect index, which are at least as effective as BBs and ACEi in reducing cardiovascular events (CVEs) in patients with hypertension, and that are more effective in reducing stroke<sup>27</sup> accounted for 2.4% of total consumption. A study conducted in the city of Niš region of Serbia<sup>28</sup> also demonstrated underutilization of diuretics which emphasizes the need to undertake efforts to change this practice in Serbia. In 1995, a total utilization of diuretics was similar to today's (10.221 DID in 1990 vs 9.9 in 2012), even though CVD drugs were used in much smaller extent<sup>29</sup>. In the last 25 years, the use of CVD drugs in the city of Novi Sad has doubled, yet the consumption of diuretics stayed the same. The use of thiazides in the city of Novi Sad, Serbia is low in comparison to the neighboring Croatia<sup>30</sup>, as well as western countries. A share of thiazides in all drugs utilized in treatment of hypertension ranges from 7.8% in Sweden, 6.8% in Netherlands to 25.0% in Denmark<sup>31</sup>. The American Society of Hypertension guidelines<sup>26</sup> recommend thiazides as initial treatment of non-complicated hypertension and thiazide accounted for 14% of total utilization in the USA in 2012<sup>32</sup>.

Our analysis indicates that there is a substantial potential for savings if Serbian physicians prescribe low-cost ACEi more frequently, modeling the practice of Scandinavian countries. An increase in ramipril and enalapril consumption with an equivalent decrease in the use of more expensive ACEi, could result in the yearly savings around 350,000 euros in the city of Novi Sad alone. If we extrapolate these results to the national level, since in Serbia, in 2012, 44 million euro worth of ACEi were distributed<sup>33</sup>, the savings worth 5.5 million euros could be provided. In Serbia, drugs for therapy are used much more than drugs for the prevention of CVDs, such as serum lipid-reducing drugs. The study that compared the use of lipid reducing drugs in Serbia and Scandinavian countries<sup>34</sup> has shown that the mortality rate for CVDs and the use of serum lipid-reducing drugs have an inverse relationship. Numerous obstacles to lipid-lowering treatment are present in Serbia, as the Republic Health Fund has a very stringent criteria for refunding the cost of statins. A saving provided with changes in ACEi patterns could be redistributed and widen the indications for statin reimburse-

ment, and make lipid-lowering drugs available for primary prevention of cardiovascular diseases.

The limitations of our study that should be mentioned are imposed by the type of data used which contained no information on compliance and actual consumption.

### Conclusion

Despite the guidelines stating that all available antihypertensive classes are suitable for hypertension management this study demonstrates substantial differences in utilization of different groups of antihypertensive agents in the city of Novi Sad. Irrational prescribing and preference to more

expensive drugs have been reported in the city of Novi Sad. Underutilization of valuable, efficacious, and cost-effective thiazide diuretics and over the use of expensive ACE inhibitors is unjustifiable. The modeling structure of the use of ACE inhibitors in Scandinavian countries could produce substantial savings and significantly reduce pressure on already limited health resources without negative effect on treatment outcomes.

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