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Original Study

Analysis of Drug Consumption From The Group of Angiotensin II Receptor Blockers in The Republic of Serbia in The Period 2012-2021

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SUMMARY

Introduction: High blood pressure is the leading factor in the development of cardiovascular diseases and premature death of patients worldwide. Angiotensin II receptor blockers (ARBs) have been proven to be highly effective in both lowering arterial hypertension and preventing cardiovascular outcomes.

Aim: The aim of this study was to analyze the consumption of drugs from the group of angiotensin II receptor blockers in the Republic of Serbia in the period from 2012 to 2021, as well as to examine the relationship between the price of these medications and their consumption.

Material and Method: Drug consumption was monitored using the ATC/DDD methodology, as well as using the DU 90% method. The connection between drug consumption and price was examined by linear regression at the level of statistical significance of 0.05.

Results: Analyzing the consumption of the examined group of drugs, the most prescribed ones include valsartan, losartan, telmisartan, irbesartan, as well as their combinations with hydrochlorothiazide. Compared to Finland and Norway, the consumption of these medications was two to twelve times higher than in our country. Since 2018, the combination of valsartan-sacubitril drugs has been present in Serbia, and the expenditure on this fixed combination has been continuously increasing.

Conclusion: The consumption of ARB drugs is increasing and shows a negative correlation with their price. Due to their better efficiency, reduced toxicity and faster achievement of the therapeutic goal, preference should be given to fixed doses of these drugs rather than monocomponents.

Keywords: Cardiovascular Diseases, Hypertension, Defined Daily Dose

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INTRODUCTION

High blood pressure is the leading contributor to the development of cardiovascular diseases and premature mortality worldwide [1, 2]. Nearly one billion people live with hypertension, and it is estimated to cause more than three million deaths each year owing to its high prevalence and the wide range of cardiovascular, renal, and neurological complications it precipitates [3, 4]. It is estimated that during the year 2020, eighteen million people died from complications of cardiovascular diseases (CVD) (32% of all deaths that year) [5]. The Republic of Serbia ranks among the countries with a high prevalence of hypertension, where in 2013 every third person had prehypertension (33.1%), and almost every second person had hypertension (49.3%). During the same year, 57.8% of people with hypertension were taking antihypertensive therapy, while only a third of patients had blood pressure within normal values [6]. Hypertension is a multifactorial disease that includes a complex interaction of various genetic, environmental, socioeconomic and psychological factors that affect multiple organ systems and, with a cumulative effect, and produce a lifetime risk of developing high blood pressure that exceeds 90% [7, 8].

Effective antihypertensive therapy markedly reduces the risk of CVD [9, 10]. Management begins with non pharmacological measures—healthy diet, reduced sodium intake, smoking cessation, moderated alcohol consumption, and regular physical activity to achieve ideal body weight [11]. Pharmacological therapy has been shown to be very effective both in lowering blood pressure and in preventing CVD complications in most patients. First line agents include diuretics, β adrenergic blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and calcium channel blockers [7]. A small number of patients can achieve the satisfactory decrease in blood pressure values using only monotherapy, and therefore most of them require combining antihypertensive drugs [12, 13].

The renin-angiotensin-aldosterone system (RAAS) significantly affects the development of hypertension, and therefore, ACE inhibitors and ARBs are recommended as a suitable first choice for antihypertensive therapy [14]. ARBs are widely used because they are well tolerated, efficacious, and confer proven renal protection [15]. In order to improve the therapeutic effect, ARBs can be combined with either diuretics or calcium channel blockers as these fixed combinations show better compliance with a reduced number of adverse reactions to drugs ,which lead to a better quality of life for patients [16, 17].

In the Republic of Serbia, ACE inhibitors are among the most frequently prescribed antihypertensives [18]. A study that analyzed the use of antihypertensive drugs in Novi Sad, during 2011 and 2012, showed an uneven representation of first-choice drugs, where the use of ARBs was very low compared to the practices that exist in countries with a more developed pharmacotherapeutic approach, such as Norway and Finland [19, 20]. The abovementioned facts impose the need for further analysis of the consumption of this group of drugs in Serbia, especially emphasizing the high prevalence and risks that hypertension carries [20].

AIM

The aim of this study was to analyze the consumption of drugs from the group of angiotensin II receptor blockers in the Republic of Serbia in the period from 2012 to 2021, as well as to examine the relationship between the price of these medications and their consumption.

MATERIAL AND METHODS

This academic research was conducted as a retrospective, Phase IV pharmacoeconomic study.

Data on drug consumption and pricing in the Republic of Serbia for the period from 2012 to 2021, were obtained from the official website of the Agency for Medicines and Medical Devices (ALIMS) of the Republic of Serbia [21]. The consumption of drugs is monitored by the internationally accepted ATC/DDD methodology, as well as using the DU 90% method.

Defined Daily Dose (DDD) is a statistical unit used to measure drug consumption. It represents the assumed average daily dose of a drug used by an adult and is independent of the drug's price, packaging, or formulation. The number of DDD/1000 inhabitants per day provides insight into how many inhabitants (1000) used a certain drug and were exposed

to its effects during the day [22]. The ATC/DDD system is designed to monitor and research the use of medicines, as well as to present and compare statistics on the consumption of drugs at the national and international level in order to improve the quality of their use [21]. The DU 90% method ranks drugs according to total DDDs and determines how many drugs are in 90% of the total use and provides a representation of the medicines that most affect the health of the observed group of patients [23].

Anatomical-Therapeutic-Chemical (ATC) classification is based on a combination of seven alphanumeric characters that indicate the International Nonproprietary Name (INN) of the medication. In this system substances are divided into different groups according to their chemical, pharmacological and therapeutic properties. According to the ATC classification, drugs from the group of angiotensin II receptor blockers belong to group C09 [21]. Drug consumption was expressed in the number of defined daily doses per 1000 inhabitants per day (DDD/1000 inhabitants/day or DDD TID) [22]. Drug prices were expressed in euros (€) per 1 DDD to enable international comparison.

Statistical data processing was performed using SPSS version 21.0 (IBM, Chicago, IL, USA). Results are presented as absolute values and percentages. Each series of drug use over time was examined by linear regression at a statistical significance level of 0.05.

The obtained results are presented in tables.

RESULTS

An analysis of the expenditure trends for monocomponent angiotensin II receptor

2012		2013		2014	
INN (DDD/TID)	%	INN (DDD/TID)	%	INN (DDD/TID)	%
C09C (11.73)	100.00	C09C (13.16)	100.00	C09C (11.73)	100.00
losartan (8.25)	70.40	losartan (9.93)	75.45	losartan (8.25)	70.40
valsartan (2.50)	21.33	valsartan (2.22)	16.87	valsartan (2.50)	21.33
DU90% - 5/2	91.73	DU90% - 6/2	92.32	DU90% - 5/2	91.73
2015		**2016**		**2017**	
INN (DDD/TID)	%	INN (DDD/TID)	%	INN (DDD/TID)	%
C09C (22,90)	100.00	C09C (23.47)	100.00	C09C (21.80)	100.00
losartan (13.91)	60.74	losartan (11.27)	48.01	losartan (8.93)	40.96
valsartan (5.94)	25.94	valsartan (7.99)	34.04	valsartan (8.71)	39.95
telmisartan (2.21)	9.65	telmisartan (2.96)	12.61	telmisartan (3.40)	15.60
DU90% - 6/3	96.33	DU90% - 5/3	94.66	DU90% - 5/3	96.51
2018		**2019**		**2020**	
INN (DDD/TID)	%	INN (DDD/TID)	%	INN (DDD/TID)	%
C09C (28.85)	100.00	C09C (22.10)	100.00	C09C (35.54)	100.00
valsartan (12.06)	41.80	losartan (10.39)	47.01	losartan (15.27)	42.96
losartan (10.90)	37.78	telmisartan (5.79)	26.20	valsartan (9.51)	26.76
telmisartan (4.48)	15.53	valsartan (4.04)	18.28	telmisartan (8.03)	22.59
DU90% - 5/3	95.11	DU90% - 5/3	91.49	DU90% - 5/3	92.31
2021					
INN (DDD/TID)	%				
C09C (30.35)	100.00				
valsartan (11.01)	36.29				
losartan (10.39)	34.24				
telmisartan (6.00)	19.77				
DU90% - 5/3	90.30				

Table 1. Overview of drug consumption from the group: angiotensin II receptor blockers, monocomponent (C09C) within the DU90% segment in Serbia, in the period 2012 - 2021, presented as the number of DDD/1000 inhabitants/day (DDD/TID) and as a percentage (%) of the total consumption in group C09C

INN - International Nonproprietary Name
DDD/TID - number of defined daily doses per 1000 inhabitants per day
DU90% - segment of drug use 90%
C09C - angiotensin II receptor blockers, monocomponent

Table 2. Overview of drug consumption from the group: angiotensin II receptor blockers, fixed combinations (C09D) within the DU90% segment in Serbia, in the period 2012 - 2021, presented as the number of DDD/1000 inhabitants/day (DDD/TID) and as a percentage (%) of the total consumption in group C09D

INN - International Nonproprietary Name
DDD/TID - number of defined daily doses per 1000 inhabitants per day
DU90% - segment of drug use 90%
C09D - angiotensin II receptor blockers, fixed combinations

2012	
INN (DDD/TID)	%
C09D (1.72)	100.00
losartan, hydrochlorothiazide (0.99)	57.56
valsartan, hydrochlorothiazide (0.54)	31.39
telmisartan, hydrochlorothiazide (0.16)	9.30
DU90% - 5/3	98.25

2013	
INN (DDD/TID)	%
C09D (2.09)	100.00
losartan, hydrochlorothiazide (1.10)	52.63
valsartan, hydrochlorothiazide (0.73)	34.93
telmisartan, hydrochlorothiazide (0.15)	7.18
DU90% - 6/3	94.74

2014	
INN (DDD/TID)	%
C09D (3.43)	100.00
losartan, hydrochlorothiazide (1.97)	57.43
valsartan, hydrochlorothiazide (1.25)	36.44
DU90% - 6/2	93.87

2015	
INN (DDD/TID)	%
C09D (5.76)	100.00
losartan, hydrochlorothiazide (2.58)	44.79
valsartan, hydrochlorothiazide (2.35)	40.80
irbesartan, hydrochlorothiazide (0.47)	8.16
DU90% - 5/3	93.75

2016	
INN (DDD/TID)	%
C09D (8.77)	100.00
valsartan, hydrochlorothiazide (4.02)	45.84
losartan, hydrochlorothiazide (3.51)	40.02
irbesartan, hydrochlorothiazide (0.61)	6.95
DU90% - 5/3	92.81

2017	
INN (DDD/TID)	%
C09D (9.86)	100.00
losartan, hydrochlorothiazide (4.19)	42.49
valsartan, hydrochlorothiazide (4.13)	41.89
telmisartan, hydrochlorothiazide (0.94)	9.53
DU90% - 5/3	93.91

2018	
INN (DDD/TID)	%
C09D (11.46)	100.00
valsartan, hydrochlorothiazide (5.75)	50.17
losartan, hydrochlorothiazide (3.56)	31.06
telmisartan, hydrochlorothiazide (1.25)	10.90
DU90% - 6/3	92.13

2019	
INN (DDD/TID)	%
C09D (14.89)	100.00
valsartan, hydrochlorothiazide (8.46)	56.82
losartan, hydrochlorothiazide (3.82)	25.65
telmisartan, hydrochlorothiazide (1.41)	7.72
DU90% - 6/3	90.19

2020	
INN (DDD/TID)	%
C09D (12.54)	100,00
valsartan, hydrochlorothiazide (5.23)	41.71
losartan, hydrochlorothiazide (4.37)	38.85
telmisartan, hydrochlorothiazide (1.87)	14.91
DU90% - 6/3	95.47

2021	
INN (DDD/TID)	%
C09D (12.32)	100.00
valsartan, hydrochlorothiazide (4.68)	37.99
losartan, hydrochlorothiazide (4.02)	32.63
telmisartan, hydrochlorothiazide (1.76)	14.28
irbesartan, hydrochlorothiazide (0.98)	7.95
DU90% - 6/4	92.85

blockers reveals a consistent increase in their prescription over the study period. Valsartan, losartan, and telmisartan were the three most frequently used medications throughout the entire ten-year span [21].

According to Table 2, the drugs that accounted for 90% of total consumption within the C09D group were primarily fixed-dose combinations of losartan, valsartan, telmisartan and irbesartan with the thiazide diuretic hydrochlorothiazide [21].

Data presented in Table 3 indicate a statistically significant relationship between the price and consumption of several monocomponent drugs, including valsartan, irbesartan, telmisartan, and olmesartan medoxomil. The observed negative correlation suggests that a reduction in the price of these medications over the ten-year period contributed to an increase in their usage. Also, table

INN	2012 DDD/TID	2021 DDD/TID	Change in use (%)	Beta	Statistical significance
losartan	8.25	10.39	25.94	-0.508	0.134
valsartan	2.50	11.01	340.40	-0.783	0.007[x]
irbesartan	0.19*	2.64	1289.47	-0.774	0.014[x]
candesartan	0.01	0.01**	0.00	0.459	0.541
telmisartan	0.80	6.00	650.00	-0.747	0.013[x]
olmesartan medoxomil	0.16	0.29	81.25	-0.827	0.003[x]
losartan, hydrochlorothiazide	0.99	4.02	306.06	-0.814	0.004[x]
valsartan, hydrochlorothiazide	0.54	4.68	766.67	-0.810	0.004[x]
irbesartan, hydrochlorothiazide	0.09*	0.98	988.89	-0.894	0.001[x]
candesartan, hydrochlorothiazide	0.01	0.01**	0.00		
telmisartan, hydrochlorothiazide	0.16	1.76	1000.00	-0.819	0.004[x]
valsartan, amlodipine	0.02	0.35	1650.00	-0.745	0.013[x]
valsartan, sakubitril	0.01***	0.52	5100.00	-0.986	0.014[x]

Table 3. Changes in the use of drugs from the group angiotensin II receptor blockers monocomponent and angiotensin II receptor blockers fixed combinations between 2012 and 2021 shown in percentages and the correlation between the price and consumption of these drugs

INN - International Nonproprietary Name
DDD/TID - number of defined daily doses per 1000 inhabitants per day
***** - calculated from 2013
****** - calculated until 2015
******* - calculated from 2018
[x] - statistically significant

3 presents data on fixed-dose combinations, where a statistically significant correlation was observed between price and consumption for almost all drugs in this category [21].

A comparison of drug prices between the first and last year of the study, which is shown in table 4, it was concluded that the price of all drugs has decreased. The most significant reduction was observed for telmisartan, with a price decrease of 73.53%, while the smallest change was recorded for the fixed-dose combination of valsartan with sacubitril [21].

DISCUSSION

Between 2012 and 2021 in the Republic of Serbia, overall utilisation within ATC group C09 (agents acting on the renin–angiotensin–aldosterone system, RAAS) was dominated by monocomponent ACE inhibitors (subgroup C09A). Their share, however, declined gradually as consumption of other C09 subclasses grew [21].

Use of monocomponent ARBs in Serbia was two to five fold lower than in Finland, where losartan and candesartan are both widely prescribed [21, 24]. Finland's higher ARB uptake is partly attributed to the lower incidence of bradykinin mediated adverse effects compared with ACE inhibitors; ARBs are 1.8 % less likely to be discontinued for intolerance over 4.1 years of therapy [25].

Evidence supports this broader adoption. Reboldi et al. showed that RAAS acting drugs reduce the risk of myocardial infarction

INN	2012 Price in euros	2021 Price in euros	Change in price (%)
losartan	0.24	0.10	-58.33
valsartan	0.30	0.14	-53.33
irbesartan	0.25*	0.09	-64.00
candesartan	0.29	0.14**	-51.73
telmisartan	0.34	0.09	-73.53
olmesartan medoxomil	0.61	0.29	-52.46
losartan, hydrochlorothiazide	0.30	0.13	-56.67
valsartan, hydrochlorothiazide	0.38	0.13	-65.79
irbesartan, hydrochlorothiazide	0.36*	0.12	-66.67
candesartan, hydrochlorothiazide	0.49	0.24**	-51.02
telmisartan, hydrochlorothiazide	0.48	0.15	-68.75
valsartan, amlodipine	0.66	0.26	-60.61
valsartan, sakubitril	2.19***	2.10	-4.11

Table 4. Changes in the price of drugs from the group angiotensin II receptor blockers monocomponent and angiotensin II receptor blockers fixed combinations between 2012 and 2021 shown in percentages

INN - International Nonproprietary Name
***** - calculated from 2013
****** - calculated until 2015
******* - calculated from 2018

and stroke more effectively than other antihypertensive classes, and that ARBs may surpass ACE inhibitors in stroke prevention [26].

Consistent with these data, the 2018 European hypertension guidelines recommend initiating therapy with fixed dose combinations, ideally two drugs in a single tablet [27]. For this reason there is a significant increase in the consumption, as well as monocomponent and fixed combinations of ARBs with diuretics, calcium channel blockers and neprilysin inhibitors, from 2012 to 2021. In numerous studies, it has been proven that the advantages of combined therapy are better efficiency, reduced development of drug resistance and occurrence of side effects; because of this, fixed combinations have become the standard for the treatment of several diseases, which certainly includes hypertension [28].

Analyzing the data and comparing the usage of these drugs in the first and last year of the examined period, we observed significant changes. From 2012 to 2021 the consumption of valsartan-amlodipine combination increased by 1650%. The use of this drug, during the examined period, grew both in Serbia and in Finland, where it had the highest use among combinations containing calcium channel blockers [24]. The most dramatic change was observed with the sacubitril–valsartan fixed combination, which saw a 5,100% increase in consumption over the same period. This sharp rise is likely due to the high clinical efficacy of this medication. According to the study that was done by John et al. a comparison of the effectiveness of drugs from the group of ACE inhibitors-enalapril and the combination of drugs sacubitril-valsartan was made, where it was concluded that the use of the drug sacubitril-valsartan leads to a reduced mortality rate and hospitalization of patients suffering from heart failure [29].

Compared to countries with well-developed pharmacotherapy practices, such as the Republic of Finland and the Kingdom of Norway, the consumption of fixed combinations of angiotensin II receptor blockers, depending on the year, was two to twelve times higher than in the Republic of Serbia. This variation in antihypertensive drug utilization may be attributed to the continued preference for ACE inhibitors in Serbia, despite the more favorable safety profile of ARBs. Notably, ARBs are associated with a lower incidence of adverse effects, such as bradykinin-mediated cough, which often leads to better treatment adherence. Furthermore, current clinical guidelines advocate initiating antihypertensive therapy with fixed-dose combinations, highlighting the need to align prescribing practices with evidence-based recommendations and internationally recognized therapeutic standards [24, 27, 30].

CONCLUSION

In the Republic of Serbia, an increase in the consumption of drugs from the group of angiotensin II receptor blockers was observed during the period from 2012 to 2021, with the most commonly used drugs being valsartan, losartan, telmisartan, irbesartan, as well as their combinations with hydrochlorothiazide.

A correlation was observed between the consumption and the price of certain drugs such as valsartan, irbesartan, telmisartan and olmesartan medoxomil, as well as their fixed combinations with diuretics, amlodipine and sacubitril. The reduction in the price of these drugs is followed by an increase in their consumption. This finding is significant because the mentioned drug combinations are commonly used in the management of arterial hypertension and the treatment of heart failure, and therefore belong to the most frequently prescribed medications. Understanding the relationship between drug price and consumption helps to highlight the economic factors that may influence the accessibility of these essential therapies for patients.

Since 2018., there has been data on the consumption of fixed combination valsartan and sacubitril, and from year to year there was a continuous increase in the consumption of this drug, which correlates with the decrease in its price. This upward trend correlates with a decrease in the drug's price over the same period. The observed pattern suggests a more consistent implementation of contemporary treatment guidelines for heart failure, in which the sacubitril–valsartan combination is recommended as a standard therapy. Furthermore, the reduced cost of the medication enhances its accessibility, thereby contributing to improved patient adherence and more effec-

tive disease management.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

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Analiza potrošnje lekova iz grupe blokatora receptora angiotenzina II u Republici Srbiji u periodu 2012-2021. godine

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KRATAK SADRŽAJ

Uvod: Povišen krvni pritisak predstavlja vodeći i najvažniji faktor rizika za nastanak kardiovaskularnih oboljenja i prerane smrti pacijenata širom sveta. Farmakološka terapija se pokazala veoma efikasnom kako u snižavanju arterijske hipertenzije tako i u prevenciji ishoda kardiovaskularnih bolesti. Među najefikasnijim lekovima izdvojili su se preparati iz grupe inhibitora receptora angiotenzina II.
Cilj: Cilj rada je bila analiza potrošnje lekova iz grupe antagonista receptora angiotenzina II u Republici Srbiji u periodu od 2012. do 2021. godine, kao i ispitivanje povezanosti cene navedenih preparata i njihove potrošnje.
Materijal i metode: Potrošnja lekova je praćena ATC/DDD metodologijom, kao i upotrebom DU 90% metode. Povezanost potrošnje i cene lekova ispitana je linearnom regresijom na nivou statističke značajnosti od 0,05.
Rezultati: Analizom potrošnje ispitivane grupe lekova, u najpropisivanije spadaju valsartan, losartan, telmisartan, irbesartan, kao i nihove kombinacije sa hidrohlortijazidom. U poređenju sa Republikom Finskom i Kraljevinom Norveškom, potrošnja posmatranih preparata je u zavisnosti od godine bila dva do dvanaest puta viša nego u našoj državi. Od 2018. godine u Republici Srbiji prisutna je kombinacija lekova valsartan-sakubitril i iz godine u godinu se kontinuirano beleži povećanje potrošnje ovog preparata.
Zaključak: Potrošnja lekova iz grupe blokatora receptora angiotenzina II je u porastu i korelira sa padom njihove cene. Zbog bolje efikasnosti, smanjene toksičnosti i bržeg dostizanja terapijskog cilja, prednost je potrebno dati fiksnim kombinacijama pomenutih lekova u odnosu na monokomponentne preparate.

Ključne reči: kardiovaskularna oboljenja, hipertenzija, definisana dnevna doza

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