Quality of cardiovascular drugs prescribing in Croatia 2003-2008

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Quality of Cardiovascular Drugs Prescribing in Croatia 2003–2008

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A B S T R A C T

The aim of the study was to determine cardiovascular drugs utilization and quality of prescribing in Croatia from 2003 to 2008. Data on the outpatient utilization of cardiovascular drugs in Croatia were collected during 2003–2008. Data on the size and number of packages, were obtained from Croatian institute for Health Insurance (CIHI). Based on the data obtained, the numbers of DDD and DDD per 1000 inhabitants per day (DDD/1000/day) were calculated for all cardiovascular drugs. Quality of drugs prescribing was assessing using Drug Utilization 90% (DU90%) method. Renin-angiotensin system agents showed highest share in the utilization of group C drugs, followed by calcium channel blockers. These two groups of drugs accounted for half of the overall cardiovascular drug utilization. Greatest changes were observed in the groups of renin-angiotensin system agents and hypolipemics. The number of drugs within DU90% segment increased between 2003 and 2008. In the same period Cost/DDD decreased.

Key words: *cardiovascular, drugs, prescribing, ATC/DDD methodology, Croatia*

Introduction

There is a constant rise in drug sales at the world market. In the past 12 months, a 6% rise in drug utilization was recorded at 13 leading world markets[1]. In Croatia, the group of cardiovascular drugs, i.e. group C in the Anatomical-Therapeutic-Chemical (ATC) classification of drugs, has for years been the leading group of drugs according to utilization[2,3]. At the same time, cardiovascular diseases are the leading cause of morbidity and mortality, and the leading cause of hospitalization in Croatia[4]. All these indicators pointed to the need to assess the use of cardiovascular agents and their prescribing quality by use of the WHO Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) methodology as a standard method of drug utilization monitoring at the population level, providing an insight into the real drug utilization irrespective of price, and allowing for comparison with other settings[5–8]. For these reasons, we embarked upon the present study to estimate the distribution of cardiovascular drug utilization in Croatia, and to assess the quality of cardiovascular drug prescribing at primary health care (PHC) level in Croatia. The results thus obtained were used to propose a set of most efficient measures for rationalization of cardiovascular drug utilization.

Material and Methods

Data on the outpatient utilization of cardiovascular drugs (ATC group C) in Croata were collected during, 2003, 2004, 2005, 2006, 2007 and 2008. Data on the size and number of packages, and financial data based on wholesale price were obtained from Croatian institute for Health Insurance (CIHI). All drugs were classified according to ATC system. Based on the data obtained, the numbers of DDD and DDD *per* 1000 inhabitants *per* day (DDD/1000/day) were calculated for all cardiovascular drugs using ATC indexes with DDD for 2003, 2004, 2005, 2006, 2007 and 2008[9–14].

Operational definitions:

$$\text{Number of DDDs} = \text{Number of packages sold} \times \text{DDD of the package}$$

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DDD *per* 1000 inhabitants *per* day = Total consumption in DDDs × 1000

Covered inhabitants × Days in the period of data collection (365 days – one year)

On DDD/1000/day calculation, data from the latest 2001 census were used, according to which the population of the Croatia was 4.437.460. Total outpatient utilization of ATC group C prescription drugs, utilization distribution of this drug group at secondary, tertiary and quaternary level, and consumption of individual drugs were analyzed. Utilization of drugs included in the List of Drugs of the Croatian Institute of Health Insurance (CIHI), i.e. prescription drugs, was investigated. Relations of all modifications made in drug legislation during the 2003–2008 period in Croatia, which may have influenced the quality of drug prescribing, were analyzed. The Drug Utilization 90% (DU90%) method was used as a criterion of prescribing quality[15,16]. Additional indicators of rational drug utilization were also determined, e.g., cost *per* DDD within DU90% segment (cost/DDD); cost/DDD for drugs beyond DU90% segment; and cost/DDD for all cardiovascular drugs.

Results

Renin-angiotensin system agents showed highest share in the utilization of group C drugs, followed by calcium channel blockers. These two groups of drugs accounted for half of the overall cardiovascular drug utilization. Greatest changes were observed in the groups of renin-angiotensin system agents and hypolipemics; their utilization increased from 2003 to 2008 by 150%. The greatest utilization decline was recorded in the group of cardiac agents (C01), whereas C02 group showed lowest utilization modification during the study period (Table 1).

The number of drugs within DU90% segment increased between 2003 and 2008 (Table 2 and Table 3). The number of C09 group drugs showed a rise (from 7 in 2003 to 9 in 2008). In this group, the use of lisinopril that predominated in 2003 was reduced by half, while the use of angiotensin II antagonists (II-C09C; losartan, valsartan) increased until 2008. The use of hypolipemics also showed a significant increase; in 2008, atorvastatin and simvastatin ranked second and third according to group C drug utilization.

In the same period Cost/DDD decreased.

TABLE 1
OUTPATIENT UTILIZATION OF ATC GROUP C DRUG GROUPS AT SECONDARY ATC SYSTEM LEVEL EXPRESSED AS DDD/1000/DAY IN CROATIA 2003–2008

ATC code	2003	2004	2005	2006	2007	2008
C01	31.86	30.11	29.54	32.63	26.66	26.59
C02	7.00	6.66	6.60	7.50	6.57	6.56
C03	40.40	41.11	35.85	39.86	38.78	40.81
C07	22.70	22.53	22.70	25.36	25.32	27.88
C08	55.73	56.19	59.55	64.22	69.56	76.77
C09	53.69	58.97	59.85	70.16	125.36	142.40
C10	29.99	36.09	36.03	46.21	59.41	74.62
Total	241.37	250.44	250.28	286.43	351.69	396.27

Legend: C01 – cardiac agents; C02 – antihypertensive agents; C03 – diuretics; C07 – β-blockers; C08 – calcium channel blockers; C09 – renin-angiotensin system agents; C10 – hypolipemics

Discussion

From 2003 to 2008, the number of drugs within DU90% segment increased by one agent. The number of

TABLE 2
DRUGS WITHIN DU90% SEGMENT, THEIR SHARE IN GROUP C UTILIZATION, COST *per* DEFINED DAILY DOSE (COST/DDD) EXPRESSED IN HRK WITHIN DU90% SEGMENT AND TOTAL COST/DDD IN 2003

No	2003	
	INN-generic name of drug	%
1	amlodipine	12.07
2	lisinopril	10.30
3	simvastatin	8.18
4	furosemide	7.25
5	atenolol	6.64
6	lisinopril + hydrochlorothiazide	5.90
7	isosorbide mononitrate	4.87
8	atorvastatin	3.85
9	verapamil	3.79
10	lacidipin	3.41
11	cilazapril	3.03
12	ramipril	2.98
13	doxazosin	2.74
14	propafenone	2.30
15	nifedipine	2.09
16	chlorthalidone	1.99
17	methyl digoxin	1.82
18	cilazapril + hydrochlorothiazide	1.27
19	bisoprolol	1.26
20	indapamide	1.24
21	amiodarone	1.21
22	losartan	0.92
23	losartan + hydrochlorothiazide	0.82
Total (%)		89.93
Number of drugs within DU90% segment		23
Total number of drugs**		67
Total cost/DDD		2.40
Cost/DDD within DU90% segment		2.38
Cost/DDD beyond DU90% segment		2.58

*share in total group C prescription drug utilization expressed as number of DDD/1000/day according to generic names of drugs included in the CIHI List of Drugs in particular year; **total number of group C drugs included in the CIHI List of Drugs in particular year

TABLE 3
DRUGS WITHIN DU90% SEGMENT, THEIR SHARE IN GROUP C UTILIZATION, COST *per* DEFINED DAILY DOSE (COST/DDD) EXPRESSED IN HRK WITHIN DU90% SEGMENT AND TOTAL COST/DDD IN 2008

No	2008	
	INN-generic name of drug	%
1	amlodipine	12.63
2	atorvastatin	9.14
3	simvastatin	7.80
4	lisinopril + hydrochlorothiazide	7.56
5	ramipril	7.41
6	lisinopril	7.06
7	furosemide	6.85
8	lacidipin	4.49
9	atenolol	3.17
10	isosorbide mononitrate	2.90
11	bisoprolol	2.27
12	ramipril+ hydrochlorothiazide	2.10
13	losartan + hydrochlorothiazide	1.79
14	fluvastatin	1.61
15	losartan	1.55
16	trandolapril	1.39
17	indapamide	1.32
18	doxazosin	1.31
19	cilazapril	1.30
20	propafenone	1.28
21	cilazapril + hydrochlorothiazide	1.27
22	chlorthalidone	1.27
23	methyl digoxin	1.26
24	verapamil	1.12
Total (%)		89.88
Number of drugs within DU90% segment		24
Total number of drugs**		72
Total cost/ddd		1.58
Cost/DDD within DU90% segment		1.50
Cost/DDD beyond DU90% segment		2.27

*share in total group C prescription drug utilization expressed as number of DDD/1000/day according to generic names of drugs included in the CIHI List of Drugs in particular year; **total number of group C drugs included in the CIHI List of Drugs in particular year

C01 drugs within DU90% segment was four in 2003 and three in2008, including the same agents, i.e. isosorbide mononitrate, propafenone and methyl digoxin; however, the utilization of these agents decreased significantly during the study period. The utilization of methyl digoxin was 7,05DDD/1000/day and 4,96 DDD/1000/day in 2003 and 2008, respectively. The indications for the use of this drug include acute and chronic cardiac decompensation and some supraventricular arrhythmias[17,18]. However, due to the potential side effects, primarily cardiac rhythm disturbance, digitalis glycosides are currently administered only as the fourth-choice therapy for chronic cardiac decompensation, after ACE inhibitors, β-blockers and diuretics; and for acute cardiac decompensation in the presence of peripheral hypoperfusion with congestion or pulmonary edema refractory to diuretics and vasodilators in optimal dosage[18]. Therefore, the reduced utilization of this agent is justifiable, and it is anticipated to disappear from DU90% segment in the future. Propafenone belongs to the group of antiarrhythmics, indicated for the treatment of supraventricular cardiac rhythm disturbances[19]. The use of propafenone also decreased from 8,87 DDD/1000/day in 2003 to 5,06 DDD/1000/day in 2008. Amiodarone, another antiarrhythmic, was present within DU90% segment in 2003. In addition to its potent antiarrhythmic action, thus now widely used instead of lidocaine on resuscitation, long-term use of amiodarone is associated with a number of side effects[19]. Propafenone also leads to various side effects, including exacerbation of heart failure and proarrhythmic effect as the most severe ones[19]. Although antiarrhythmic agents have their place in therapy, they should always be administered with caution. It should be noted that not all arrhythmias require treatment. Group I agents including propafenone are not recommended for use at long-term, especially in patients with coronary disease. Group III agents are considered as being safe for cardiac patients[19–24]. According to CIHI provisions, these drugs can be restrictively prescribed exclusively on the internist's recommendation[25,26]. Yet, given the high utilization of these agents, it is questionable to what extent the Croatia PHC practitioners do comply with this regulation. Comparison of our indicators with those on Scandinavian countries revealed the utilization of antiarrhythmics to be ten times lower in the latter[27,28]. Based on these scientific data, it is obvious that these agents, propafenone in particular, should not be found within DU90% segment, as they actually are in Croatia, with quite a high rate of utilization.

Isosorbide mononitrate is the third group C01 agent recorded within DU90% segment throughout the 6-year study period. During this period, the utilization of isosorbide mononitrate showed an almost twofold decline, from 18,83 DDD/1000/day in 2003 to 11,47 DDD/1000/day in 2008, still reflecting quite a high rate of utilization, yet at the level recorded in Scandinavian countries[27,28]. The indications for prescribing nitrates include prophylaxis of angina pectoris and treatment of heart failure[18]. In case of stable angina pectoris, β-adrenergic receptor blockers are therapy of choice, whereas nitrates are only used as the second- or third-choice agents[18]. Nitrates have their place in the management of acute heart failure and pulmonary edema[29–31]. However, all nitrates lead to tolerance and their long-term and frequent use is wrong[32,33]. In this context, the high utilization of isosorbide mononitrate in Croatia is a highly questionable issue. The significant reduction in the utilization of cardiac agents is in line with the respective guidelines and scientific concepts, and it is expected to continue in the future, of cardiac glycosides in particular.

The utilization of C02 group, almost exclusively referring to doxazosin, also showed a declining tendency during the study period (Table 1). Doxazosin was the only C02 group agent within DU90% segment, where it ranked high (Table 2) throughout the 6-year period, although its utilization decreased during the study period, i.e. from 6,59 DDD/1000/day in 2003 to 5,19 DDD/1000/day in 2008. Doxazosin is an -adrenergic receptor blocker (C02CA), thus belonging to the group of antihypertensive agents. However, the role of doxazosin in the management of hypertension has now been considerably reduced based on the studies demonstrating its use to be associated with a higher mortality rate in patients with heart failure. Therefore, this agent is currently used only in patients with benign prostate hyperplasia, for its relaxing effect on the prostate smooth muscle and urinary flow improvement[34–36]. Thus, this agent appears to require reclassification in the ATC system. Benign prostate hyperplasia is a common problem in elderly men; however, the utilization of doxazosin in Croatia greatly exceeds its utilization in other settings[27,28], and it can be considered neither justifiable nor appropriate.

In spite of an increase in 2004 relative to the previous year, in 2005 the utilization of diuretics decreased by 22.03% in comparison with 2003. From 2005 diuretics showed increasing trend, so utilization of C03 group in 2008 is almost the same as in 2003. During the study period, the utilization of furosemide, a potent diuretic primarily used in the management of all types of edema[37], decreased in 2005, but increased again in 2008. The utilization of chlorthalidone, primarily used as an antihypertensive agent[37], declined in study period, whereas the utilization of indapamide, firstly used in mild to moderate hypertension[17], increased. Indapamide has some advantages over chlorthalidone; however, it is more expensive, thus raising the question of rational drug prescribing[37,38]. Although diuretics yield only symptomatic effects and cannot reduce mortality when administered for the management of hypertension, they are still used as first-choice agents because of their low price, in elderly patients and for moderate, uncomplicated hypertension in particular[39,40].

Comparing the utilization of diuretics in Croatia and other settings showed it to be lower in Croatia and, although many cost-effectiveness studies prefer this group of agents for the management of hypertension[39,40].

The group of β-blockers showed an increasing utilization pattern since 2004. β-blockers play an important therapeutic role because of their efficacy in the management of arterial hypertension, coronary disease and certain arrhythmias, in secondary prevention of myocardial infarction, and for their favorable effects in cardiac failure[41,42]. Along with atenolol, bisoprolol also was present in DU90% segment throughout the 6-year study period. These two agents are selective blockers of β_1-adrenergic receptors which, while showing some pharmacokinetic variability, have very similar effects[42]. Although bisoprolol as a considerably more expensive drug can only be prescribed upon specialist's recommendation according to CIHI List of Drugs provisions, its utilization increased from 2003–2008. At the same time, the utilization of atenolol, although still exceeding the utilization of other β-blockers, declined. In the therapeutic subgroup of selective β-blockers, prescribing a more expensive drug is not justifiable because it has not yet been substantiated by professional and scientific evidence[41,42].

Utilization of calcium channel blockers as the second subgroup according to utilization in the group of cardiovascular agents showed a rising pattern until 2008. According to European guidelines[43], these agents are considered more efficient than diuretics and α-blockers in preventing the development of atherosclerosis and are therefore recommended for the treatment of angina pectoris and carotid atherosclerosis. Their greater use at the PHC level could be related to the significant reduction in the rate of hospitalization for ischemic heart disease and cerebrovascular disease. Four drugs from this group were present in DU90% segment in 2003 and three drugs in 2008. From 2003, amlodipine was the leading agent according to utilization both in the group of cardiovascular drugs and in the overall outpatient drug utilization in the Croatia. Its utilization increased from 32.26 DDD/1000/day in 2003 to 49,95 DDD/1000/day in 2008 (36% increase). The utilization of lacidipin,, increased twice during the study period (from 8.40 DDD/1000/day in 2003 to 17.77 DDD/1000/day in 2008). At the same time, the utilization of nifedipine decreased twice (from 6.31 DDD/1000/day in 2003 to 3.36 DDD/1000/day in 2008), so it was not in DU90% segment in 2008. The use of verapamil, the only selective calcium channel blocker with direct cardiac effects within DU90% segment, declined also twice (from 8.93 DDD/1000/day in 2003 to 4.43 DDD/1000/day in 2008). Because of their prolonged action and ability of baroreceptor adaptation, amlodipine and lacidipin have considerable advantages over short-acting nifedipine, which is not recommended even in hypertensive crisis anymore due to the induction of reflex tachycardia[43–45]. However, lacidipin is much more expensive than amlodipine and even more so than nifedipine. The utilization of lacidipin increased at a higher rate than that of amlodipine, while the utilization of nifedipine declined. As these three agents belong to the same therapeutic group and exert very similar or identical effects, the considerably higher rate of prescribing the most expensive drug has no grounds in professional and scientific evidence[43–45].

The subgroup of renin-angiotensin system agents (C09) showed highest utilization in the group of cardiovascular drugs. The overall utilization of C09 group showed no major modifications during the study period, however, the distribution of particular agents within this subgroup underwent significant changes, as evidenced by the number of these drugs present in DU90% segment. In 2003, seven agents were present in DU90% segment, three of them pure ACE inhibitors (C09A): lisinopril, cilazapril and ramipril; and a combinations with diuretic (C09B): (lisinopril + hydrochlorothiazide, cilazapril + hydrochlorothiazide); losartan, a pure angiotensin II antagonist (C09C); and losartan + hydrochlorothi-

azide, a combination of an angiotensin II antagonist with a diuretic (C09D). In 2008, trandolapril, and ramopril + hydrochlorothiazide joined the drugs already present in DU90% segment. During the study period, the utilization of pure ACE inhibitors increased by 27% (from 53.95 DDD/1000/day in 2003 to 74.42 DDD/1000/day in 2008). The utilization of combinations of ACE inhibitors with diuretics increased more than twice (from 21.63 DDD/1000/day in 2003 to 50.50 DDD/1000/day in 2008). The utilization of pure angiotensin II antagonists increased from 5.02 DDD/1000/day in 2003 to 9.07 DDD/1000/day in 2008. Combinations of angiotensin II antagonists with diuretics showed constant increase in utilization (3.16 DDD/1000/day in 2003, and 8.42 DDD/1000/day in 2008). ACE inhibitors currently are first-choice therapy in the management of chronic cardiac decompensation and hypertension, in diabetic patients in particular[46–48]. Members of the subgroup of pure ACE inhibitors have very similar or identical clinical effects. Consequently, WHO included enalapril in the List of Essential Medicines because of its lowest price[46]. In Croatia, however, enalapril was not present among 90% of most frequently prescribed drugs, while more expensive drugs from the same group were included. The use of angiotensin II antagonists increased. These agents are associated with less side effects and are more efficacious than ACE inhibitors only in diabetic nephropathy[47–51]. Their price is high; therefore, CIHI restricted their use only to patients that cannot tolerate ACE inhibitors, and can only be prescribed on internist's recommendation[25,26]. It remains to estimate the extent to which the increasing prescribing expensive drugs in spite of CIHI guidelines, in cases when there are as efficacious but less expensive drugs, is based on the real patient needs or on the influence of pharmaceutical industry marketing on PHC physicians or specialists.

Outpatient utilization of expensive hypolipemics rose more than twofold from 2003 to 2008. In 2003, only simvastatin was ranked third, and atorvastatin eight in DU90% segment. In 2008 these two agents ranked second and third according to utilization in the group of cardiovascular drugs. During the study period, the utilization of atorvastatin increased forefold (8.99 DDD/1000/day in 2003, and 36.17 DDD/1000/day in 2008). There are no substantial differences between these drugs, and simvastatin has a lower price *per* DDD than atorvastatin. Statins have been demonstrated to be efficient in lowering elevated serum lipid levels, cholesterol in particular, and to have a beneficial effect on decreasing morbidity and mortality from cardiovascular complications[52–54]. Because of their efficacy these drugs have been included in the List of Essential Medicines[46], however, with the same prescribing restrictions found in the CIHI List of Drugs[25,26]. Namely, due to their very high price, prescribing these drugs is indicated for secondary prevention in patients with myocardial infarction, stroke, or ultrasonography demonstrated carotid plaque, or coronary disease demonstrated by coronarography, and in diabetic patients with total cholesterol exceeding 5 mmol/L. In primary prevention, prescribing these agents is restricted to patients with total cholesterol exceeding 7 mmol/L on two laboratory tests performed three months apart, after 3-month dietary regimen[25,26]. As 25% to 75% prescription charge is paid for these drugs[25,26], the significant increase in their utilization recorded from 2003 could be related to the introduction of supplementary health insurance. A growing tendency of hypolipemic utilization is recorded all over the world[54–57]; however, it should be borne in mind that diet is the basic preventive and therapeutic measure in the management of most common hyperlipidemias[56].

Analysis of the cardiovascular drug prescribing quality and adherence to professional guidelines indicated the prescribing quality to have definitely improved. The number of drugs within DU90% segment increased, indicating a diversified, more individualized and patient adjusted therapeutic approach. Apart from doxazosin, the presence of which within 90% of most widely prescribed drugs had no professional grounds, and antiarrhythmics, propafenone in particular, other drugs were generally consistent with professional guidelines. CIHI indications were justified in case of prescribing statins and angiotensin II antagonists, considering the high price and very high utilization of these agents. The price/DDD ratio in total drug utilization and within DU90% segment was highest in 2003, which was additionally favored by the introduction of supplementary health insurance, thus exempting a great proportion of patients from paying prescription charge. This entailed considerable increase in the utilization of expensive hypolipemics. The price/ DDD ratio within DU90% segment was lower in 2008; however, the Regulations on calculating wholesale drug prices, adopted in 2004[57], reduced the prices of most very expensive drugs found within DU90% segment from 2005–2008.

Conclusion

Although showing some quality improvement, the utilization of cardiovascular agents resulting from availability of newer drugs and their introduction in the List of Drugs is not rational, suggesting that physicians in Croatia fail to comply with CIHI guidelines and mostly prescribe drugs irrespective of their price, even when there is a less expensive and as efficient agent from the same therapeutic group (e.g., lisinopril, ramipril or cilazapril instead of enalapril; lacidipin or amlodipine instead of intermediary-acting nifedipine). Introduction the Regulations on calculating wholesale drug prices, was the measure that improve farmacoeconomics indicators in Croatia.

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KVALITETA PROPISIVANJA KARDIOVASKULARNIH LIJEKOVA U REPUBLICI HRVATSKOJ OD 2003–2008

S A Ž E T A K

Cilj ovoga rada je utvrditi izvanbolničku potrošnju i kvalitetu propisivanja kardiovaskularnih lijekova na razini primarne zdravstvene zaštite od 2003–2008. godine u Republici hrvatskoj. Podaci o veličini i broju pakovanja za sve propisane kardiovaskolurane lijekove u razdoblju od 2003–2008. godine dobiveni su od Hrvatskog zavoda za zdravstveno osiguranje (HZZO). Na temelju podataka o broju pakovanja izračunat broj utrošenih definiranih dnevnih doza (DDD) i broj definiranih dnevnih doza na 1000/stanovnika/dan (DDD/1000/dan) za sve kardiovaskularne lijekove. Kvaliteta propisivanja ocjenjena je DU90% metodom. Najvećeg udjela u potrošnji kardiovaskularnih lijekova imaju pripravci s učinkom na renin-angiotenzinski sustav te zatim, blokatori kalcijevih kanala. Ove dvije skupine čine više od polovice ukupne potrošnje kardiovaskularnih lijekova. Najveće promjene u potrošnji u promatranom razdoblju bilježe skupine hipolipemika i lijekova s učinkom na rennin-angiotenzinski sustav. U promatranom rarazdoblju broj lijekova unutar DU90% segmenta je porastao, kao i kvaliteta propisivanja, dok se trošak/DDD smanjio.