RELATIONSHIP BETWEEN GENERIC COMPETITION AND GENERIC UTILIZATION OF CARDIOVASCULAR MEDICINES MONOPRODUCTS IN BULGARIA

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Summary. In Bulgaria CV medicines utilization has changed the latest years. Previous studies show that the generic competition leads to change in the market. The goal of the study is to analyze the impact of introduction of new generic substances in the positive drug lists on the reference value of reimbursed cardiovascular (CV) medicines and changes in consumption.

It is a retrospective and observational analysis of the changes of monoproducts acting on cardiovascular system for the period 2009–2013 years. On total 48 INN out of 12 ATC groups were included in the analysis and 48 INN with the 595 trademarks available on the Bulgarian market were analyzed for the changes in utilization.

The changes within the therapeutic groups with new generic molecules entrance in Positive Drug List (PDL) are different but generally, the generic competition leads to decrease of reference price per DDD thus affecting positively the utilization. The decrease is more than two fold in the therapeutic groups of ACE inhibitors, AT angiotensin receptor blockers, and antihyperlipidemic. In the group of well-established cardiovascular glycosides and antiarrhythmic medicines' prices remain stable. The number of the new generic medicines included in PDL is the highest for the group of ACE inhibitors, AT angiotensin receptor blockers, and statins. The changes in utilization as DDD/1000 inh/day follow the market rules and decrease of price of the products often leads to the higher utilization, especially for therapeutic groups ACE inhibitors, AT angiotensin receptor blockers, statins.

The study confirms that the generic and therapeutic competition lead to significant price decrease and change the trends in the CV medicines consumption.

Key words: cardiovascular medicines, generic medicines, medicines prices, reference pricing, DDD/1000 inh/ day

Introduction

Healthcare expenditures in Europe, as in most of the developed world, continue to rise. Governments regulate pharmaceutical markets to protect public health, secure patient access to safe and effective medicines, improve the quality of care, and control pharmaceutical expenditures.[1]

Pricing of generic medicines in European Union member states is an area of national responsibility. To date, little is known about how generic medicine pricing policies vary between countries, about the incentives that policies create for various stakeholders (e.g., industry, regulatory authorities, health care payers, physicians, pharmacists and patients).[2] The European experience indicates that the generic medicines industry is able to deliver competitive prices if it is ensured a high volume of the pharmaceutical market.[3] In price regulated systems, regulation may lower prices of originator and generic medicines, but appears to remove incentives for additional price reductions beyond those imposed by regulation and stimulate parallel trade.[4] Patient use of medicines is driven by disease prevalence, treatment guidelines, availability and affordability. There is a little doubt that given their affordability, generic medicines have increased patient access to and use of medicines.[5]

Cardiovascular diseases (CVD) are the main cause of the disease burden (illness and death) in

Europe (23% of all the disease burden) and the second main cause of the disease burden in those EU countries with very low child and adult mortality (17%). Of the total cost of CVD in the EU, around 57% is due to health care costs, 21% due to productivity losses and 22% due to informal care of people with CVD.[6]

For twenty years the market shows significant increase of 117.4% (41.39/90 DDD/1000 inhabitants/day) in antihypertensive drug consumption. In 1994 ACE inhibitors, calcium antagonists, and β-blockers increased significantly (P .0001), whereas diuretics were still the most commonly prescribed. Nifedipine and captopril were the most used among calcium antagonists and ACE inhibitors.[7]

Use of lipid lowering agents varied among countries (in 2003, highest in Ireland and Norway, and lowest in Italy), but increased in all countries (between 2000 and 2003 by 274% in Ireland and by 56% in France). Statins dominated the markets in all countries, although fibrates remained strong in France and Belgium (approximately 25% of all lipid lowering agents)[8]

In Bulgaria cardiovascular (CV) medicines utilization has changed the latest years. Previous study shows that the generic competition leads to changes in the market.The generic medicines decrease the price level; increase the competition, and when they are reimbursed save public funds. Some studies show that not only generic but also therapeutic competitors in terms of new molecules introduction within the same therapeutic class influences the same particularities of the market and medicines utilization.[9, 10]

Analysis of the changes in utilization, measured in DDD and prices of reimbursed cardiovascular medicines in Bulgaria (ACE inhibitors, HMG-CoA reductase inhibitors and inhibitors of AT-receptors) during 2005-2007 revealed that all therapeutic groups performed an increase in the total utilization measured in DDD for the observed period. The total utilization of ACE inhibitors increased from 73.76 to 95.55, and to 137.7 DDD/1000 inh/day. For the group of statins the total utilization increased from 2.57 to 3.96, and to 5.26 DDD/1000 inh/day, while in the groups of sartanes increased from 1.89 to 3.81 and to 5.73.

The other study shows that consumption of different forms of enalapril was significantly higher in comparison with the other ACE-inhibitors and was increasing during the observed years (72.56-87.03-98.88 DID). When the therapeutic competitors cilazapril and benazepril appeared in 2006, the overall prescribing of ACE inhibitors increased from 79 to 102 DDD/1000 inh/day, and in 2007 it again increased up to 111 DDD/1000 inh/day. Similar trends are observed for the sartans pharmacology group but they are not so evident[9,11,12]

Many new molecules as therapeutic and generic alternatives were introduced on market after 2007 that stimulate our study to analyze the impact of their introduction in the reimbursement system on the prices and utilization of the reimbursed cardiovascular (CV) medicines (monoproducts) during the period 2009-2013 years.

Materials and methods

It is a retrospective and observational analysis of the changes in reference prices per DDD (based on lowest retail market price per DDD) of monoproducts acting on cardiovascular system for the period 09.2009-09.2013 in Bulgaria. All prices are expressed in national currency at the exchange rate 1 Euro = 1.958 BGN

The annexes of the Positive drug list (PDL)[13], which include all reimbursed medicines, were systematically reviewed and all therapeutic groups belonging to ATC C were analyzed for the following changes – new molecules inclusion, new generic products, new concentrations and dosage forms, changes in reference price. The utilization in DDD/1000inh/ day was calculated using the sales data and DDD of the products according to established from WHO formulas:

DDD/1000inh/day = ((Sales data in mg/ DDD)/(N inhabitans*365)) x 1000

Sales data were provided from Bulgarian Drug Agency (BDA).On total 48 INN out of 12 ATC groups were included in the analysis and 48 INN with the 595 trademarks were analyzed for the changes in utilization.

T-test were performed to analyze the statistical significance in the observed changes.

Table 1. *Reference price per DDD and DDD/1000 inh/ day for Digoxin*

INN	Reference price perDDD (BGN)					DDD/1000 inh/ day				
Digoxin	**2009**	**2010**	**2011**	**2012**	**2013**	**2009**	**2010**	**2011**	**2012**	**2013**
	0.0754	0.0754	0.0754	0.073	0.073	3.63	9.21	3.61	3.43	6.52

Table 2. *Reference price per DDD and DDD/1000 inh/ day for Propafenon and Amiodaron*

	Reference price per DDD (BGN)					DDD/1000 inh/ day				
	2009	**2010**	**2011**	**2012**	**2013**	**2009**	**2010**	**2011**	**2012**	**2013**
Propafenon	0.4457	0.4457	0.4457	0.2975	0.2975	1.68	2.24	1.70	2.40	3.75
Amiodarone	0.2187	0.21867	0.21867	0.21167	0.2117	3.47	4.80	2.92	3.29	4.08

Results

In the group of cardiac glycosides only digoxin is included with no changes in the trade names and dosage forms till 2013. Therefore, the changes in reference price per DDD decreased insignificantly with 0.002 BGN in 2012. DDD/1000 inh/day increase in this period from 3.63 to 6.52 that is statistically significant ($p<0.05$).

Propafenone and amiodarone as anti-arrhythmic medicines are constant as number of dosage forms and trade names, but the reference price of propafenon significantly decreased nearly twice in 2012 from 0,4457 to 0.2975 BGN per DDD ($p<0.05$), while for amiodarone the decrease is insignificant. Regarding to utilization data between 2009 and 2013, we observe huge fluctuations.

Among the antistenocardic medicines isosorbide dinitrate has not changed the reference price significantly, while isosorbide monohydrate after the introduction of one new competitor with 1

Table 3. *Number of dosage forms and trade names, reference price per DDD, DDD/1000 inh/ day for the group of antistenocardic medicines*

<table>
<tr><th rowspan="2">INN</th><th rowspan="2">API mg</th><th colspan="5">Number of dosage forms</th><th colspan="5">Reference price per DDD (BGN)</th><th colspan="5">DDD/1000 inh/ day</th></tr>
<tr><th>2009</th><th>2010</th><th>2011</th><th>2012</th><th>2013</th><th>2009</th><th>2010</th><th>2011</th><th>2012</th><th>2013</th><th>2009</th><th>2010</th><th>2011</th><th>2012</th><th>2013</th></tr>
<tr><td rowspan="4">Isosorbite dinitrate</td><td>5</td><td>1</td><td>1</td><td>1</td><td>1</td><td>1</td><td rowspan="4">0.3337</td><td rowspan="4">0.333</td><td rowspan="4">0.333</td><td rowspan="4">0.323</td><td rowspan="4">0.323</td><td rowspan="4">4.17</td><td rowspan="4">6.65</td><td rowspan="4">4.01</td><td rowspan="4">4.53</td><td rowspan="4">4.57</td></tr>
<tr><td>10</td><td>1</td><td>1</td><td>1</td><td>1</td><td>1</td></tr>
<tr><td>20</td><td>1</td><td>2</td><td>2</td><td>2</td><td>2</td></tr>
<tr><td>120</td><td>1</td><td>1</td><td>1</td><td>1</td><td>1</td></tr>
<tr><td rowspan="3">Isosorbite mononitrate</td><td>20</td><td>1</td><td>1</td><td>1</td><td>1</td><td>1</td><td rowspan="3">0.3211</td><td rowspan="3">0.321</td><td rowspan="3">0.321</td><td rowspan="3">0.311</td><td rowspan="3">0.281</td><td rowspan="3">2.47</td><td rowspan="3">2.97</td><td rowspan="3">3.43</td><td rowspan="3">2.54</td><td rowspan="3">3.22</td></tr>
<tr><td>40</td><td>2</td><td>2</td><td>2</td><td>2</td><td>3</td></tr>
<tr><td>60</td><td>2</td><td>2</td><td>2</td><td>2</td><td>3</td></tr>
<tr><td rowspan="2">Trimetazidine</td><td>20</td><td>2</td><td>2</td><td>2</td><td>2</td><td>2</td><td rowspan="2">0.4637</td><td rowspan="2">0.463</td><td rowspan="2">0.264</td><td rowspan="2">0.256</td><td rowspan="2">0.230</td><td rowspan="2">10.84</td><td rowspan="2">14.09</td><td rowspan="2">9.41</td><td rowspan="2">12.73</td><td rowspan="2">15.74</td></tr>
<tr><td>35</td><td>1</td><td>1</td><td>4</td><td>5</td><td>8</td></tr>
</table>

Table 4. Reference price per DDD and DDD/1000 inh/day for the group of antagonists of imidazole receptors

INN	Reference price per DDD (BGN)					DDD/1000 inh/ day				
	2009	2010	2011	2012	2013	2009	2010	2011	2012	2013
Moxonidine	0.3885	0.3885	0.3883	0.319	0.314	1.27	0.02	1.95	3.20	4.70
Rilmenidine	0.658	0.658	0.52633	0.42333	0.42	0.51	0.02	0.75	1.31	2.00

dosage form decrease its price in 2013 in comparison with 2009 from 0,3211 to 0.2811 BGN per DDD ($p<0.05$). The inclusion of 4 and 7 new trade names for trimetazidine in 2012 and 2013, respectively has led to double decrease in reference price per DDD ($p<0.05$). In the same time its utilization increase from 9.41DDD/1000 inh /day to 12.73 DDD/1000 inh/day and to 15.74 DDD/1000 inh /day in 2012 and 2013 respectively ($p<0.05$).

To antagonists of imidazole receptors was added and 1 new trade name for rilmenidine that also decrease its reference price in 2012 from 0,6580to 0.42333 BGN per DDD ($p<0.05$). No changes in the number of trade names and dosage forms of monoxidine are observed but its reference price also decreased significantly in the observed period from 0,3885 to 0.314 BGN per DDD ($p<0.05$). Utilization of medicines has increased until 2013 especially that of moxonidine.

One new trade name and dosage form within the INN doxazosin of the group of peripheral alfa-adreno antagonists have been included in PDL, leading insignificantly decrease of the reference price per DDD from 0.2373 to 0.2307 BGN in 2013.The utilization of DDD/1000 inh /daily is increased insignificantly from 2.17 to 2.80 in 2013.

Within the group of diuretics is observed not only generic but also therapeutic competition

Table 5. Number of dosage forms and trade names, reference price per DDD, DDD/1000 inh/ day for the group of diuretics

INN	API, mg	Number of dosage forms					Reference price per DDD (BGN)					DDD/1000 inh/day				
		2009	2010	2011	2012	2013	2009	2010	2011	2012	2013	2009	2010	2011	2012	2013
Hydrochlorothiazide	25	2	2	2	3	3	0.17	0.173	0.173	0.168	0.168	8.6	8.22	4.49	4.21	5.26
Indapamide	1,5	5	5	5	9	10	0.18	0.182	0.178	0.173	0.141	6.07	10.1	5.48	4.54	6.93
	2,5	3	3	3	3	3										
Torasemide	5,0			1	2	3			0.599	0.582	0.582			0.01	0.02	0.04
Spironolacton	25	2	2	2	2	2	0.003	0.003	0.003	0.003	0.003	2.83	4.45	2.84	3.37	3.9
	50	1	1	1	1	1										
	100	1	1	1	1	1										

Table 6. Number of dosage forms and trade names, reference price per DDD, DDD/1000 inh/ day for the group of beta blockers

INN	API, mg	Number of dosage forms					Reference price per DDD (BGN)					DDD/1000 inh/ day				
		2009	2010	2011	2012	2013	2009	2010	2011	2012	2013	2009	2010	2011	2012	2013
Propranolol	20					1	0.210	0.21	0.277	0.269	0.27	2.42	3.44	2.16	2.84	3.01
	25	1	1	1	1											
	40	1	1	1	1	1										
Metoprolol	25	1	2	2	2	2	0.216	0.216	0.216	0.216	0.21	8.55	12	7.3	9.57	9.69
	50	7	8	8	10	10										
	100	7	8	8	10	10										
	200	1	1	1	1	2										
Atenolol	25	2	2	2	2	2	0.126	0.126	0.126	0.126	0.12	8.55	12	7.3	9.57	9.69
	50	3	3	3	3	3										
Bisopro-lollhemi-fumarate	2,5	1	1	1	2	3	0.243	0.243	0.211	0.211	0.16	0	0.03	0.82	2.06	3.04
	5	5	5	6	8	10										
	10	5	5	6	8	10										
Nebivolol	5	3	3	3	12	12	0.64	0.64	0.426	0.426	0.27	2.45	5.15	6.43	9.71	13.86
Carvedilol	6,25	9	9	9	10	10	0.315	0.315	0.315	0.315	0.32	3.66	4.03	2.67	2.81	2.97
	12,5	8	8	8	9	9										
	25	8	8	8	9	9										
Sotalolhy-drochlorid	80	2	2	2	2	1	0.272	0.272	0.272	0.272	0.25	0.94	1.41	0.94	1.18	1.52
	160	2	2	2	2	2										

with the introduction of torasemid. It was included in the PDL in 2011 and its price slowly started to decrease in 2013 from 0.5995 to 0.5815 per DDD. At the same time utilization increase from 0.01 (DDD/1000inh /day) to 0,04 (DDD/1000inh /day) in 2013. Five new trade names of indapamide in 5 dosage forms were included since 2013 performing significant decrease in price per DDD from 0.1823 to 0.1413 BGN. One new trade name of hydrochlorothiazide was included in 2013 decreasing the price per DDD insignificantly and for spironolactone no changes were observed. The utilization in DDD/1000 inh/day shows small increase from 6.07 to 6.83 and from 2.83 to 3.90 for Indapamide and Spironolacton respectively. In the 2011, when Torasemide is included in PDL, utilization of hydrochlorothiazide has decreased significantly ($p<0.005$).

The group of peripheral vasodilators comprises of 3 INN namely pentoxifyllyn, nicergoline and naftidrofuryl with relatively limited number of changes in trade names and dosage forms but significant change in reference price per DDD during 2009-2013 for pentoxifyllin from 0.6150 to 0.4667 BGN. Within the studied period the consumption of peripheral vasodilators increased slowly. The change is significant for nicergoline to 3.62 DDD/1000 inh/daily simultaneously with the inclusion of new generic medicines in 2011.

Within the group of beta blockers are included 6 INNs with very dynamic changes. The older and well established molecules as propranolol, atenolol, sotalol and metoprolol changed their particularities in small ranges. For bisoprolol,

Table 7. *Number of dosage forms and trade names, reference price per DDD, DDD/1000 inh/day for the group of Ca-antagonists*

INN	API, mg	Number of dosage forms					Reference price per DDD (BGN)					DDD/1000 inh/ day				
		2009	2010	2011	2012	2013	2009	2010	2011	2012	2013	2009	2010	2011	2012	2013
Amlodipine	5	11	11	11	14	15	0.113	0.113	0.113	0.054	0.054	12.64	21.83	21.3	22.41	27.98
	10	10	10	10	13	14										
Felodipine	2,5	2	2	2	2	2	0.236	0.236	0.236	0.229	0.21	7.51	9.28	5.31	5.86	6.10
	5	6	6	6	7	7										
	10	4	4	4	4	4										
Nifedipine	10	1	1	1	1	1	0.15	0.150	0.150	0.146	0.146	8.75	10.04	6.08	6.03	6.73
	20	3	3	3	3	3										
	30	1	1	1	1	1										
Lercanidipine	10	1	2	2	4	4	1.081	0.290	0.237	0.23	0.23	0.00	0.60	2.12	5.82	9.76
	20		1	1	3	3										
Verapamil Hydrochlorid	40	3	3	3	3	3	0.237	0.237	0.237	0.23	0.23	5.92	12.35	6.02	6.27	7.85
	80	4	4	4	4	4										
	120	2	2	2	2	2										
	240	3	3	3	3	3										
Diltiazem	60	4	4	4	4	4	0.215	0.215	0.215	0.208	0.208	1.74	2.10	1.32	1.25	1.41
	90	3	3	3	3	3										

nebivilol, and carvedilol the number of reimbursed trade names and dosage forms increased from 5 to 10, from 3 to 12, and from 9 to 10 respectively. This lead to significant decrease in reference price per DDD for the first 2 molecules from 0.2427 to 0.1800 BGN and from 0.640 to 0.2437 BGN respectively. The utilization of beta blockers increase for all products within the group in the observed period. The most significant change is observed for Nebivolol - from 2.45 (DDD/1000 inh/day) to 13, 86 (DDD/1000 inh/day).

The group of Ca-antagonists includes 6 INNs. New generic competitors and dosage forms entered the PDL for amlodipine and lercanidipine (in 2013). The reference price of all INNs decreased, but significant were the changes for amlodipine from 0.1133 to 0.0537 BGN and lercanidinipine from 1.0807 to 0.2018 BGN per DDD. The utilization increases for amlodipine (12.64 DDD/1000inh/day to 27.98 DDD/1000inh/day), lercanidipine (0.01- DDD/1000inh/day to 9.76 DDD/1000inh/day), and verapamil (5.92 DDD/1000inh/day to 7.85 DDD/1000inh/daily). The utilization in the observed period decreased insignificantly for the other medicines in the group of Ca-antagonists.

ACE inhibitors are the largest CV group with 7 INN and for all of them except fosinopril and quinapril new generic names and dosage forms were included into the PDL during the observed period. The latter led to significant price per DDD decrease for all INNs ($p<0.05$).The utilization of ACE inhibitors shows different variations within the observed period - decrease in 2010-2011 and after that in 2012-2013 increase for the most of them (except fosinopril and trandolapril).

AT receptor antagonists (sartans) are relatively new therapeutic group with 6 INN and 2 of them (irbesartan and olmesartan) were included in PDL in 2012 and 2013, respectively meaning that they are considered as therapeutic competitors for all other products. New generic products were included for all other INNs as follows 2 for losartan, 11 for valsartan, 9 for candesartan, and 6 for telmisartan thus making the group one of the most competitive. As a result, for all INNs the price per DDD decreased significantly with the exception of telmisartan and of the both newly included INNs. The data show increase in utilization in 2009-2010. After 2010 we found different changes – for Losartan and Valsartan decreased every year were observed, for Candesartan and Telmisartanan increased is recorded. The highest change is for Valsartan- decreased from 43.24 DDD/1000 inh/ day to 14.10 DDD/1000 inh/ day. Telmisartan increased utilization significantly from 1.81 DDD/1000 inh/day to 7.04 DDD/1000 inh/day.

Table 8. *Number of dosage forms and trade names, reference price per DDD, DDD/1000 inh/ day for the group of ACE inhibitors*

INN	API, mg	Number of dosage forms					Reference price per DDD (BGN)					DDD/1000 inh/ day				
		2009	2010	2011	2012	2013	2009	2010	2011	2012	2013	2009	2010	2011	2012	2013
Enalapril maleate	5	8	8	8	8	8	0.0824	0.082	0.082	0.077	0.077	88.84	98.3	52.64	48.79	54.42
	10	8	8	8	9	9										
	20	7	7	7	8	8										
Lisinopril	2,5	1	1	1	1	1	0.1905	0.191	0.191	0.185	0.168	9.22	13.4	11.70	14.75	16.53
	5	5	6	6	6	6										
	10	7	8	8	8	8										
	20	6	7	7	7	7										
Perindopril	4				1	4	0.4437	0.444	0.183	0.177	0.177	4.64	6.36	3.97	4.77	5.71
	5	1	1	1	1	2										
	8				1	4										
	10	1	1	1	1	2										
Ramipril	2,5	1	1	1	1	1	0.1222	0.122	0.112	0.108	0.074	10.32	15.3	12.48	16.70	22.62
	5	5	5	5	7	10										
	10	3	3	4	7	9										
Quinapril	10	2	2	2	2	2	0.3073	0.307	0.307	0.343	0.191	1.32	1.32	0.67	0.73	0.91
	20	2	2	2	2	2										
Fosinopril	10	3	3	3	3	3	0.25	0.25	0.25	0.215	0.215	4.50	2.75	1.46	1.92	1.90
	20	3	3	3	3	3										
Trandolapril	0,5	1	1	1	1	1	0.3143	0.314	0.269	0.255	0.255	1.47	1.90	1.09	1.12	1.06
	2	2	2	2	3	3										
	4	1	1	1	2	2										

Table 9. *Number of dosage forms and trade names, reference price per DDD, DDD/1000 inh/day for the group of sartans*

INN	API, mg	Number of dosage forms					Reference value per DDD (BGN)					DDD/1000 inh/ day				
		2009	**2010**	**2011**	**2012**	**2013**	**2009**	**2010**	**2011**	**2012**	**2013**	**2009**	**2010**	**2011**	**2012**	**2013**
Losartan	**50**	4	4	4	6	6	0.308	0.301	0.280	0.245	0.237	7.23	8.42	4.68	6.34	6.24
	100				1	2										
Valsartan	**80**			1	1	3	0.452	0.376	0.275	0.267	0.264	43.2	39.08	31.62	24.32	14.10
	160	2	3	4	7	13										
	320															
Irbesartan	**75**					1			0.548	0.372	0.250			1.5	2.0	4.0
	150			2	3	5										
	300			2	3	5										
Candesartan	**8**	1	1	2	3	8	0.619	0.619	0.208	0.201	0.154	0.39	1.26	1.47	2.45	3.83
	16	1	1	2	3	10										
	32				1	5										
Telmisartan	**40**				2	2	0.026	0.026	0.026	0.369	0.256	1.81	3.76	2.61	4.50	7.04
	80	1	1	1	7	7										
Olmesartan	**20**					1					0.748					3.04
	40					1										

In the group of anti-hyperlipidemic statins no new INNs were included in the PDL, only 3 new generic for simvastatins, 1 for fluvastatin, 8 for atorvastatin, 10 for rosuvastatin and 2for fenofibrate were included in 2013. The prices decreased for all molecules significantly ($p<0.05$), except the price of lovastatin. The highest change in the consumption was observed for Rosuvastatin -from 1.04 DDD/1000 inh/day to 9.11 DDD/1000 inh/day, as well as, the number of new generic medicines is the highest for Rosuvastatin.

Comparison of the changes in prices and utilization is almost simultaneously. The utilization depends on price, changes in prices, generic competitors' entrance and new alternatives in clinical practice, but there are probably many other factors influencing the changes. This fact is confirmed by the simultaneous trends in changes in the reference price for DDD and utilization in DDD/1000 inh/day (Figure 1–4).

Utilization in DDD/1000 inh/day in 2009 is the highest for Enalapril and Valsartan and the smallest for Lercanidipine and Candesartan. The number of the new generic medicines included in PDL is the highest for the group of ACE inhibitors, AT angiotensin receptor blockers, and statins. The significant changes are observed for Ramipril, Telmisartan, Rosuvastatin, Amlodipine, and Lercanidipine concerning prices and utilization. The results from the applied t-test show that between 2009 - 2013 years the greatest difference in the utilization is found for the group of peripheral vasodilators, and the smallest is for the group of diuretics.

Discussion

The changes within the therapeutic groups with new generic molecules entrance in Positive

Table 10. *Number of dosage forms and trade names, reference price per DDD, DDD/1000 inh/ day for the group of statins and fenofibrate*

INN	API, mg	Number of dosage forms					Reference price per DDD (BGN)					DDD/1000 inh/ day				
		2009	2010	2011	2012	2013	2009	2010	2011	2012	2013	2009	2010	2011	2012	2013
Simvastatin	10	8	9	9	11	11	0.451	0.451	0.415	0.215	0.215	4.50	8.07	6.10	6.83	6.93
	20	11	11	11	13	14										
	30	1	1	1	1											
	40	9	9	9	11	10										
	80	1	1	1	1	1										
Lovastatin	20	3	3	3	3	3	0.513	0.513	0.513	0.497	0.497	0,34	0,35	0.16	0.12	0.12
	40	2	2	2	2	2										
Fluvastatin	80	2	2	2	2	3	0.749	0.749	0.749	0.726	0.679	0.55	0.78	0.45	0.40	0.34
Atorvastatin	10	4	4	4	11	12	0.515	0.515	0.423	0.366	0.141	3.36	4.88	3.25	5.30	8.31
	20	4	4	5	12	12										
	40	2	2	2	4	6										
	80	1	1	1	1	1										
Rosuvastatin	5				1	2	1.476	1.476	0.561	0.395	0.291	1.04	1.95	2.00	5.03	9.11
	10	1	1	1	9	11										
	15				1	1										
	20	1	1	1	9	11										
	30				1	1										
	40				2	3										
Fenofibrate	160	1	1	1	2	2	0.652	0.652	0.520	0.504	0.504	1.10	1.66	1.05	1.51	1.83
	200	1	1	1	1	2										

Drug List generally favor the generic competition and let to decrease of reference price. The decrease is more than two fold in the therapeutic groups of ACE inhibitors, AT angiotensin receptor blockers, and antihyperlipidemic. In the group of well-established cardiovascular glycosides and antiarrhythmic medicines, the prices remain almost stable. The prices decrease is more evident in 2013 probably as result of the legislative changes introduced in the period and activity of the National Council of pricing and reimbursement created in 2013.

The National consensus for antihypertensive medicines prescribing, based on scientific evidences, recommends β-blockers, diuretics, Ca-antagonists, ACE-inhibitors, and sartans as first line monotherapy. The above mentioned therapeutic groups are with highest utilization in Bulgaria that support the compliance with the guidelines. This means that medicines consumption is in regard with the scientific evidences and the latest pharmacotherapeutic recommendations.[14]

The high number of the new generic products as INNs and trademarks included between

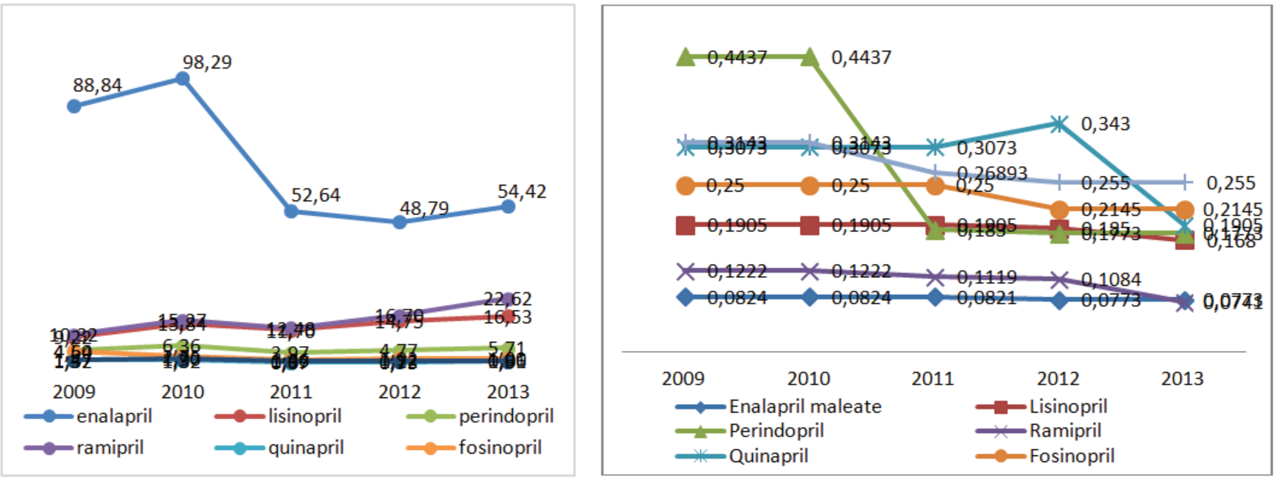

Fig. 1. Changes in reference price and DDD/1000 inh/day in the group of ACE-inhibitors

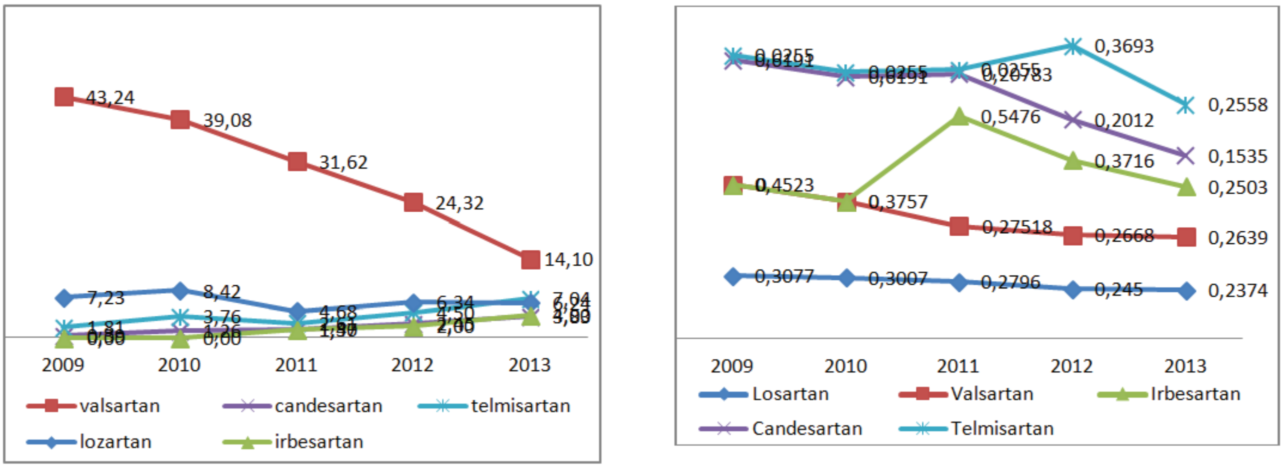

Fig. 2. Changes in prices and utilization in DDD/1000 inh/day in the group of sartans

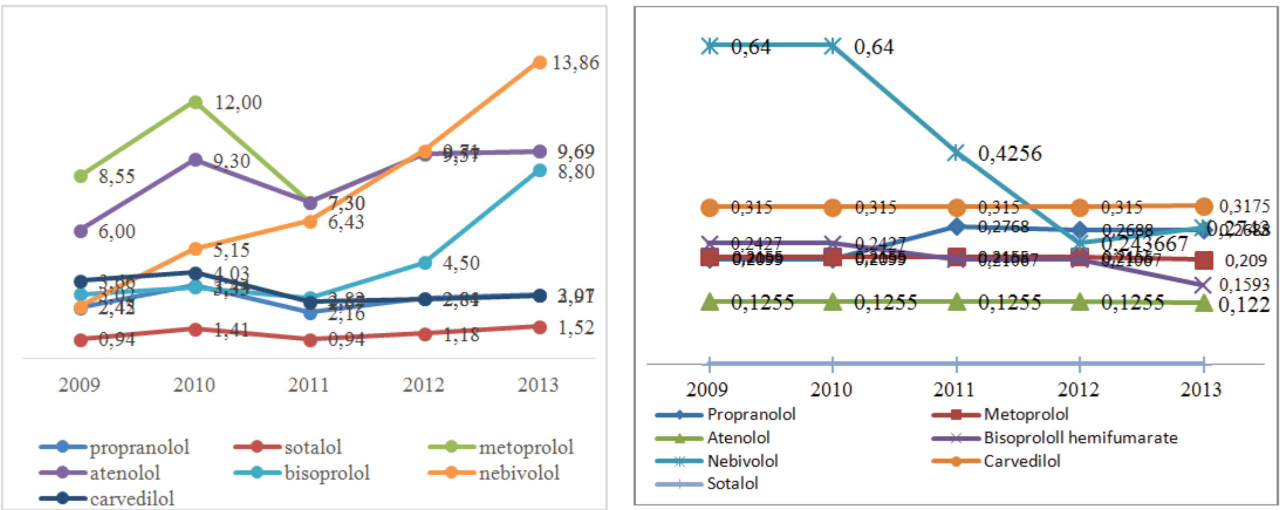

Fig. 3. Changes in prices and utilization in DDD/1000 inh/day in the group of β-blockers

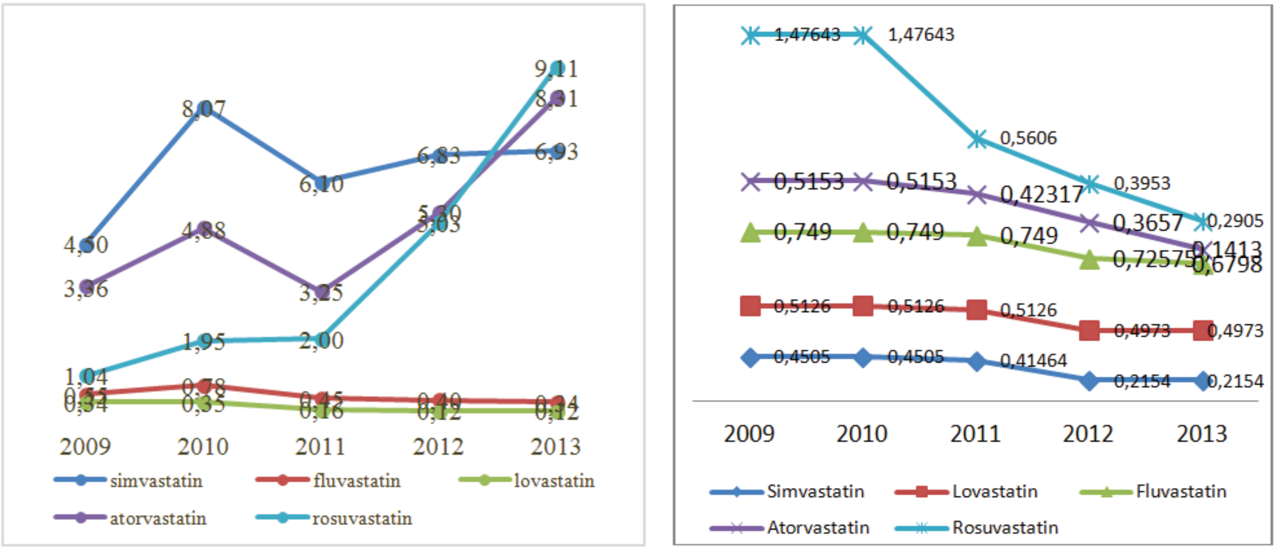

Fig. 4. Changes in prices and utilization in DDD/1000 inh./daily in the group of statins

2009–2013 years suggest that there are effective measures for generic competition and therapeutic competition stimulation in the country. The changes in reference price per DDD and utilization as DDD/1000 inh/day follow let decrease of price of the products and often increase utilization, especially for the new and dynamic therapeutic groups (ACE inhibitors, AT angiotensin receptor blockers, statins).

Conclusion

The study confirms that the generic and therapeutic competition lead to significant price decrease, and simultaneously change medicines utilization. Other factors also play an important role in the process, as legislation price control measures. The therapeutic and generic competition is one of the most important factors influencing changes in price and utilization of the CV medicines.

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