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Original Research Article

FIXED DOSES COMBINATIONS ACTING ON CARDIOVASCULAR SYSTEM - UTILIZATION AND GENERIC COMPETITION

ABSTRACT

Aims: The goal of the study is to analyze the impact of introduction of new fixed dose combinations (FDCs) in the positive drug lists on the reference price of reimbursed cardiovascular (CV) medicines and their utilization during the period 2009-2013 years.
Study design: It is a retrospective and observational analysis of the changes in reimbursed fixed dose combinations (FDCs) acting on cardiovascular system (CVS)
Place and Duration of Study: Medical University of Sofia, Faculty of Pharmacy for the period 2009-2013 years.
Methodology: Total 18 INN in different combinations belonging to 6 anatomic therapeutic chemical (ATC) groups (ACE-inhibitor and diuretic, Ca-antagonists and ACE-inhibitors, sartan and diuretics, Ca-antagonist and statin, two diuretics, b-blocker and diuretic); 60 dosage forms, and 104 trademarks were analyzed for the changes in their prices and utilization after the inclusion in the positive drug list (PDL).
Results: Many new generic molecules as FDC entrance the PDL and generally, the generic competition leads to decrease of their reference price. The decrease is significant in the new therapeutic groups. The number of the new generic medicines included in PDL is the highest for the group of ACE -inhibitors and diuretics, angiotensin receptor blockers (AT receptor blockers, ARBs, sartans) and diuretics. The changes in utilization calculated as DDD/1000 inh/day shows the higher utilization in 2013 years for the groups of ACE inhibitors and diuretics and AT receptor blockers and diuretics (Enalapril/Hydrochlorthiazide (HCTZ), Perindopril/ Indapamide, Valsartan/HCTZ, Losartan/ HCTZ).
Conclusion: The study confirms that the generic and therapeutic competition leads to significant price decrease and change the trends in the FDC utilization in cardiology.

Keywords: cardiovascular medicines; generic medicines, medicines prices, reference pricing, fixed doses combinations, DDD/1000 inh/ day

1. INTRODUCTION

The cardiovascular diseases (CVD) are major cause of the disease burden (illness and death) in Europe (23% of whole 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

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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. [1].

Study in Bulgaria shows that cardiovascular risk is high in a large proportion of Bulgarian urban population, especially in men aged over 65. A representative sample of Bulgarian urban population (n=3810, response rate 68.3%) from five Bulgarian cities was included in a cross-sectional observation study performed in the period 2005-2007. Nearly a quarter of the sample had a total cardiovascular risk of over 10% (SCORE ≥ 10%), whereas 10.1% of the sample had excessively high cardiovascular risk (SCORE ≥ 15%). In the 65-75 age group, the prevalence of men with excessively high risk was 46.6%, compared with 6.0% in women. [2].

In order to reach the target blood pressure (BP) recommended by current treatment guidelines [3] a large majority of patients require simultaneous administration of two or more antihypertensive drugs. Combination therapy is necessary in approximately 75% of patients with hypertension. Rational combination therapy begins with the selection of two-drug combinations that exhibit additive BP reduction, excellent tolerability and a demonstrated ability to reduce cardiovascular endpoints in long-term clinical trials. [4].

Combination therapy is a treatment with two, or more active pharmaceutical ingredients (API) administered separately, or in a fixed-dose combination (FCD) pill and is necessary for many patients with hypertension to reach target blood pressure [5, 6]. Additional benefits may include cost savings and better compliance. [7, 8].

The combination therapy offers number of advantages compared to monotherapy; part of this effect is a result of the higher percentage of patients with lowered BP (blood pressure). The combination therapy acts in different directions and can influence the compensatory mechanisms induced by one of the drugs. This is the reason why some patients, who fail to respond to two individual agents administered as monotherapy, frequently respond to a combination of both agents. Some combinations of antihypertensive agents exhibit additive or even synergic effect.

The high-risk patients with hypertension and diabetes can be treated with a combination of two drugs (ACE inhibitor, ARB and diuretic or ACE inhibitor and Calcium channel blocker). In this way, the remote compliance of patients will be improved and therefore cardiovascular morbidity and mortality will be decreased. [9]. In many cases, combination therapy improves rates of blood pressure control and requires less time to achieve target blood pressure [1,10,11] with equivalent [12] or with better tolerated [13] drugs than higher-dose monotherapy.

Study for management of hypertension and initial therapy has been organized in Bulgaria as prospective, observational, non-interventional using data from 770 geographically diverse primary care cities (77% GPs, 23% cardiologists). Monotherapy was started in 1550 (26.4%) and combination therapy (CT) in 4328 (73.6%) patients. 1003 (17.1%) patients were on fixed dose combination (FDC) alone, and 3325 (56.6%) on free combinations (FC). The most frequently used FDC and FC were angiotensin receptor blockers and diuretics (54%, resp. 28%). Diuretics, b-blockers, angiotensin receptor blockers were more frequently used in females than in males - 22%, 47%, 22%, resp. 19%, 42%, 19%, unlike ACE-inhibitors - 29% vs 26%. In Bulgaria CT, especially FC was preferred as initial AHT than monotherapy. FDC were underused. Monotherapy was prescribed more frequently in low/moderate risk, CT in high/very high risk. B- blockers were used as initial therapy unjustified frequently [14].

Other study shows that patients with arterial hypertension in Bulgaria are most often on monotherapy (61% in Bulgaria vs 6% in Serbia), as well as those with complications (66% vs 0% Serbia). In both countries the first choice of therapy are the ACE inhibitors (37.01% in Serbia and 41% in Bulgaria) and then follows the calcium antagonists, beta-blockers, and diuretics [15].

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Fixed dose combinations as initial therapy may lead to improved compliance of patients and reduced cardiovascular morbidity and mortality. [16]. The latest years many new FDCs, especially in cardiology were introduced on Bulgarian market.

The objective of this study is to analyze the impact of introduction of new fixed dose combinations (FDCs) in the positive drug lists on the reference price of reimbursed cardiovascular (CV) medicines and their utilization during the period 2009-2013 years.

2. MATERIAL AND METHODS

It is a retrospective and observational analysis of the changes in reference price per defined daily dose (DDD), based on lowest retail market price per DDD of FDCs acting on cardiovascular system for the period 2009-2013 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), which include all reimbursed medicines, were systematically reviewed and therapeutic groups including ACE - inhibitors and diuretics, ACE-inhibitors and Ca-antagonists, statin and diuretic, b-blocker and diuretic, two diuretics, sartans and diuretics. All of the FDCs were analyzed for the following changes – new active pharmaceutical ingredients (API) inclusion, new generic products, new concentrations and dosage forms entering the PDL.

The utilization in DDD/1000 inh/day was calculated using the sales data provided by BDA (Bulgarian Drug Agency) and DDD of the products according to established from WHO formulas:

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

According to formula approved by WHO for DDD/1000 inh/day and the methodology accepted by ESAC (European Surveillance of Antimicrobial Consumption) for calculation of the utilization of FDC the DDD of the active substance which is leading in the combination (according to ATC-code), was used to calculate DDD/1000 inh/day for FDCs in cardiology.

18 FDCs included in PDL were included in the analysis. The whole number of the dosage forms is 60 and 104 trademarks marketed in Bulgaria were analyzed for the changes in utilization.

T-test was applied for statistical significance of the changes based on the average value of reference price per DDD and DDD/1000 inh/day.

3. RESULTS AND DISCUSSION

Reimbursed combinations between ACE-inhibitor and diuretic are the largest group with the highest number of dosage forms and generics. For the combination Enalapril/ Hydrochlorothiazide (HCTZ) we observed decrease in the reference price for all of dosage forms (**Figure 2**). The utilization of combinations increased in a small range and remain very high from 18.72 DDD/1000 inh/day to 18.76 DDD/1000 inh/day (**Figure1**).

Figure 1: Changes in DDD/1000 inh/day for the group of ACE-inhibitors and diuretic

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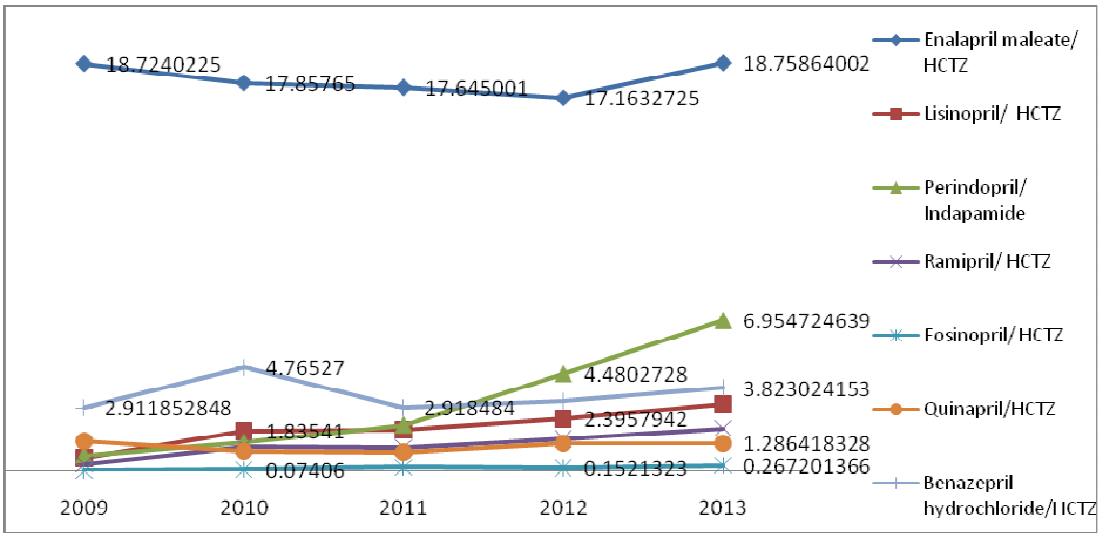

For the combination, Lisinopril/HCTZ the reference price decreased in 2012 and new trademarks were included in PDL. The utilization has increased significantly from 0.61 to 3.07 DDD/1000 inh/day. The utilization increases significantly for the combination Perindopril/ Indapamide within the observed period from 0,73 to 6,95 DDD/1000 inh/day. The reference price also decreased significantly and 4 new dosage forms were included in PDL in 2012 (**Table 1, Figure 2**).

Table 1: Number of dosage forms and trade names of FDCs ACE-inhibitor and diuretic

INN	API, mg	Number of dosage forms					Number of trade names				
		2009	2010	2011	2012	2013	2009	2010	2011	2012	2013
Enalapril maleate/ HCTZ	20/12,5	4	4	4	4	4	4	4	4	4	4
	10/12,5	1	2	2	2	2					
	10 /25	1	2	2	2	2					
Lisinopril/ HCTZ	20/12,5	1	1	1	1	3	1	1	1	1	3
	10/12,5	1	1	1	1	3					
Perindopril/ Indapamide	5/1,25	1	1	1	1	2	1	1	1	4	6
	2.5/0,625	1	1	1	1	1					
	10 2,5	-	-	-	2	2					
	4 /1,25	-	-	-	1	5					
	8 / 2,5	-	-	-	1	1					
	2/0,625	-	-	-	2	3					
Ramipril/ HCTZ	2,5 /12,5	4	4	4	1	3	5	5	5	3	5
	5 /25	4	4	4	3	4					
	10 /25	-	-	-	-	1					

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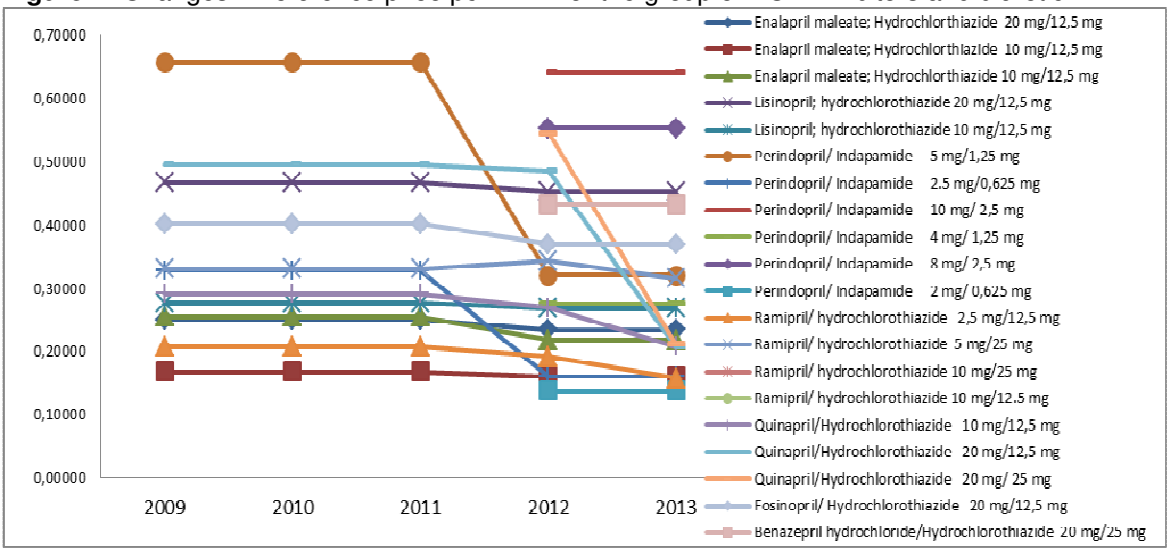
	10 /12.5	-	-	-	-	1					
Quinapril/ HCTZ	**10/12,5**	1	1	1	3	4	1	1	1	3	4
	20/12,5	1	1	1	3	4					
	20 / 25	-	-	-	1	2					
Fosinopril / HCTZ	**20/12,5**	1	1	1	2	2	1	1	1	2	2
Benazepril / HCTZ	**20/25**	-	-	-	2	2	-	-	-	2	2

For the other combinations the same changes in utilization and reference value per DDD has been observed. New dosage forms were included in PDL within the period 2009-2013 years. Exception is the FDC Benazepril/HCTZ 20/25 mg from the group - no included new products and no changes in reference price. The utilization increased insignificantly.

Figure 2: Changes in reference price per DDD for the group of ACE-inhibitors and diuretic



FDCs of ACE- inhibitor and calcium channel blocker diminishes the extent of one of the most frequent adverse effect of CCB - legs oedema. ACE inhibitors blunt the stimulation of the renin angiotensin-aldosterone axis that may result from this diuretic effect. These agents also inhibit the central sympathetic stimulation that may result from calcium antagonist–associated vasodilatation, although both classes of drugs are potent vasodilators [17,18]. We observed the changes in reference price and the utilization for 3 combinations between ACE inhibitors and Ca channel blockers included in PDL (**Table 2**). The increase of utilization for FDCs Lisinopril/ Amlodipine and Perindopril/ Amlodipine is significant -from 0.55 DDD/1000 inh/day to 3.37 DDD/1000 inh/day and from 0.64 to 5.40 DDD/1000 inh/ day respectively (**Figure 3**).

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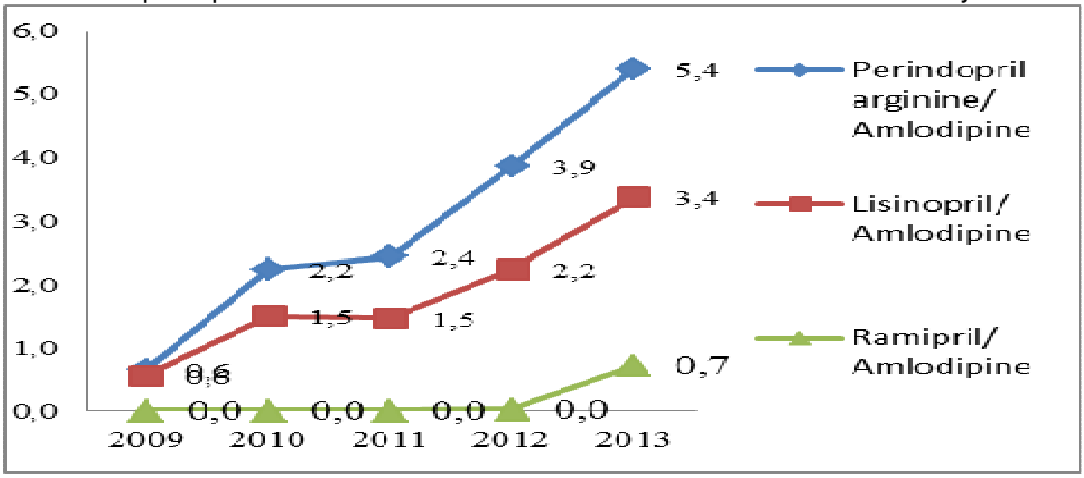
Figure 3: Changes in DDD/1000 inh/day for group of ACE-inhibitors and Ca-antagonists

The reference price per DDD decreases for all FDCs and it is the most obviously for the



combinations of Perindopril/ Amlodipine. The reference price per DDD decreases from 1,222 to 0,497 for the combination 10 mg perindopril/5 mg amlodipine and from 1,33600 to 0,550 for the combination 10 mg perindopril/10mg amlodipine between 2009-2013 years (**Figure 4)**.

Table 2: Number of dosage forms and trade names of FDCs Ca-antagonists/ACE-inhibitors

INN	API, mg	Number of dosage forms					Number of trade names				
		2009	2010	2011	2012	2013	2009	2010	2011	2012	2013
Lisinopril/ Amlodipin	10/5	1	1	1	1	1	1	1	1	1	1
	20/10	-	-	-	1	1					
	20 /5					1					
Perindopril arginine/ Amlodipin	5 /10	1	1	1	1	1	1	1	1	1	2
	10 /5	1	1	1	1	1					
	10 /10	1	1	1	1	1					
	5 /5	1	1	1	1	1					
	4/5	-	-	-	-	1					
	4 /10	-	-	-	-	1					
	8 /5	-	-	-	-	1					
	8 /10	-	-	-	-	1					
Ramipril/ Amlodipin	5/5	-	-	-	-	2	-	-	-	-	2
	10/5	-	-	-	-	1					
	10/10	-	-	-	-	1					

Figure 4: Changes in reference price per DDD for the group of ACE-inhibitor and Ca-antagonist

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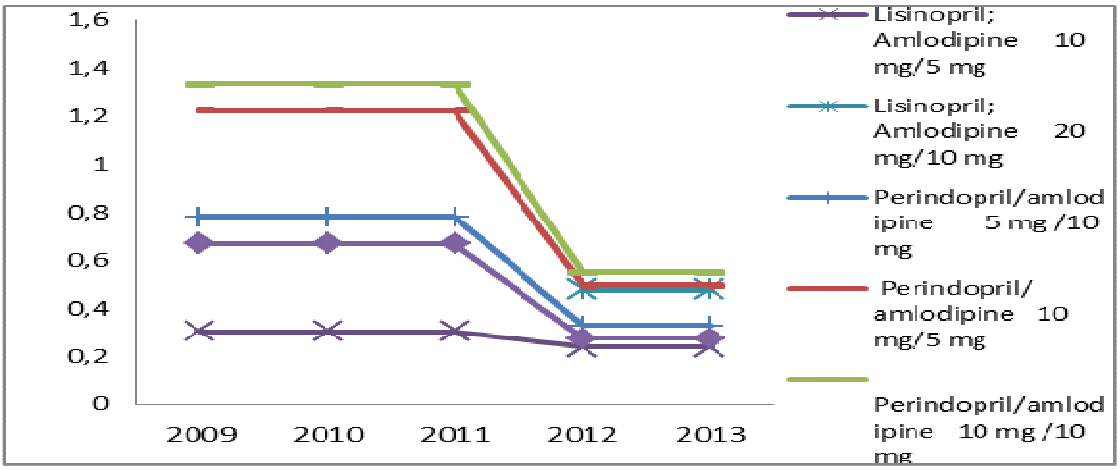

Renin–angiotensin–aldosterone system (RAAS) inhibitor and a diuretic combination will offset the diuretic-induced increase in plasma renin activity. The salt loss will be added to the antihypertensive effect of RAAS blocker. Besides, an ARB will also attenuate the metabolic effects of thiazide diuretics like hypokalemia and hyperglycemia. Several studies have demonstrated the antihypertensive effectiveness of this combination in low doses, showing substantially greater reductions in BP and higher response rates than either of the treatments alone. [19] During the observed period, the group containing sartan and diuretic was developed greatly. High number of dosage forms, trademarks and new international non-proprietary name (INN) were included. For combination, Valsartan/ HCTZ 8 new trademarks were included in PDL, and for combination, Candesartan/HCTZ 5 new trademarks were included (**Table 3**). The total number of 43 new generic medicines were included in the group during 2009-2013. The results shows that it is one of the most dynamic group. The Included new medicines leads to decrease of the reference price per DDD and increase of the utilization (**Figure 5; Figure 6**). The most significant decrease in reference price is for Telmisartan/HCTZ 80 mg/ 25 mg (from 2,208 to 0.581), Telmisartan/ HCTZ 80 mg/12,5 mg (from 1,253 to 0.495), Valsartan/ HCTZ 160 mg/25 mg (from 1,077to 0.512).The changes in utilization of Valsartan/ HCTZ are significant - from 2,25 to 27.69 DDD/1000 inh/ day.

Table 3: Number of dosage forms and trade names of FDC including sartan and diuretics

INN	API, mg	Number of dosage forms					Number of trade names				
		2009	2010	2011	2012	2013	2009	2010	2011	2012	2013
Losartan/ HCTZ	50/12.5	2	2	2	5	6	2	2	2	5	6
	100 /25	1	1	1	1	1					
	100 /12,5	-	-	-	1	1					
Valsartan/ HCTZ	80/12,5	1	2	2	1	3	3	4	4	7	11
	160 /12,5	3	4	4	6	9					
	160 /25	3	4	4	5	8					
	320 /25	-	-	-	1	1					
	320 /12,5	-	-	-	1	1					

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Irbesartan/ HCTZ	150 / 12,5	-	-	-	1	3	-	-	-	1	3
	300 / 12,5	-	-	-	1	3					
Candesartan cilexetil/ HCTZ	8 / 12,5	-	-	-	3	4	-	-	1	4	6
	16 / 12,5	-	-	1	4	6					
	32 /12.5	-	-	-	-	2					
	32 /25	-	-	-	-	1					
Telmisartan/ HCTZ	80 / 25	1	1	1	1	3	1	1	1	1	3
	80 / 12,5	1	1	1	1	3					

Figure 5: Changes in DDD/1000 inh/day in the group of sartans and diuretics

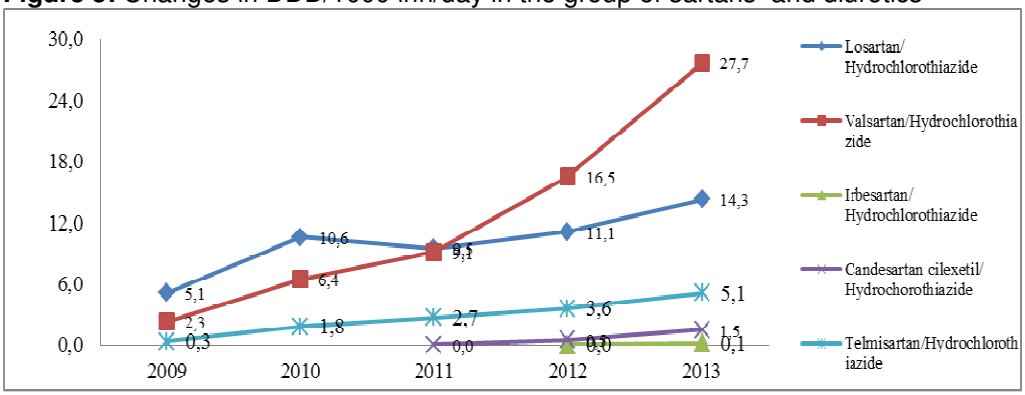

Figure 6: Changes in reference price per DDD in the group of sartans and diuretics

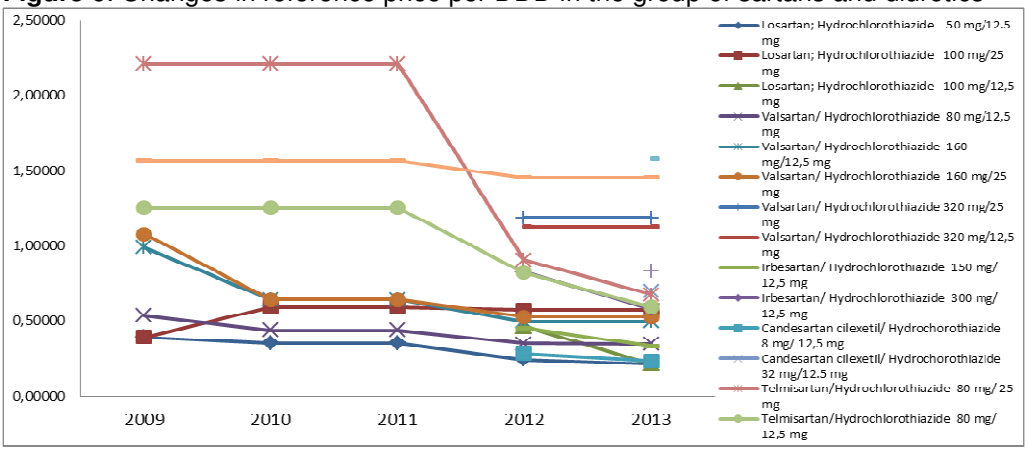

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Table 4: Number of dosage forms and tradenames, reference price per DDD, DDD/1000 inh/day (BGN) for the group of Ca-antagonist and statin

INN	API, mg	Number of dosage forms					Number of trade names				
		2009	2010	2011	2012	2013	2009	2010	2011	2012	2013
Amlodipine/ Atorvastatin	5 /10	1	1	1	2	3	1	1	1	2	3
	10 /10	1	1	1	2	3					
	20 /5	-	-	-	1	1					
	20 /10	-	-	-	1	1					
	10 /5	-	-	-	-	1					

INN	API, mg	Reference price per DDD (BGN)					DDD reference	DDD/1000 inh/ day (BGN)				
		2009	2010	2011	2012	2013		2009	2010	2011	2012	2013
Amlodipine/ Atorvastatin	5 /10	0,37097	0,3709	0,3709	0,2365	0.1138	20	0.05	0.44	0.39	0.58	0.69
	10 /10	0,48427	0,4842	0,4842	0,2901	0.1675						
	20 /5	-	-	-	0,4193	0.1740						
	20 /10	-	-	-	0,4730	0.2276						
	10 /5	-	-	-	-	0.1138						

Ca- antagonist and antihyperlipidemic (statin) combination is from INNs Amlodipine and Atorvastatin. In 2012, the reference price decreased and new dosage forms of FDC were included into the PDL. The number of registered trademarks is increasing. In 2013, reference price per DDD decreased and the utilization increased (**Table 4**).

The rationale for combining beta blockers with diuretics is two fold: beta blockers blunt the increase in the plasma renin level that is induced by diuretics, and diuretics decrease the sodium and water retention that is caused by beta blockers. [20]. When used in combination with bisoprolol, hydrochlorothiazide (6.25 mg) did not cause low potassium level or any adverse effects on the lipid profile.In the group of b-blocker and diuretic we observed the changes in reference price per DDD for the combinations of bisoprolol/ HCTZ. The utilization of combinations has increased insignificantly within observed period from 0.76 to 1.1 DDD/1000 inh/day regardless the changes in reference price (**Figure 7**; **Figure 8)**. In 2012 new dosage form and trademark were included in PDL (**Table 5**). In the same year reference price per DDD decreases for all combinations of bisoprolol/HCTZ (**Figure 8**).

Table 5: Number of dosage forms and tradenames for the combinations of β-blocker and diuretic

INN	API, mg	Number of dosage forms					Number of trade names				
		2009	2010	2011	2012	2013	2009	2010	2011	2012	2013
Bisoprolol/ HCTZ	5/12,5 mg	1	1	1	2	2	2	2	2	3	3
	2.5/6.25 mg	1	1	1	1	1					
	5/6.25 mg	1	1	1	1	1					
	10/6.25 mg	1	1	1	1	1					

The combination of two diuretics Triamterene and Hydrochlorothiazide has been studied also. There are no included new dosage forms and trademarks within observed period. DDD/1000 inh/day has increased slightly and reference price per DDD has increased also between 2009-2013 years.

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Figure 7: Changes in DDD/1000 inh/day for the group of β-blockers/ diuretic and combination of two diuretics

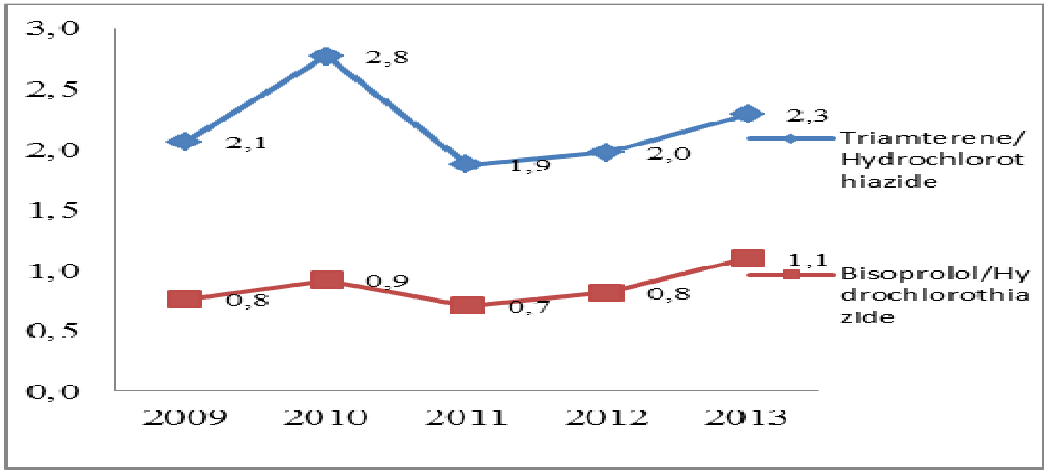
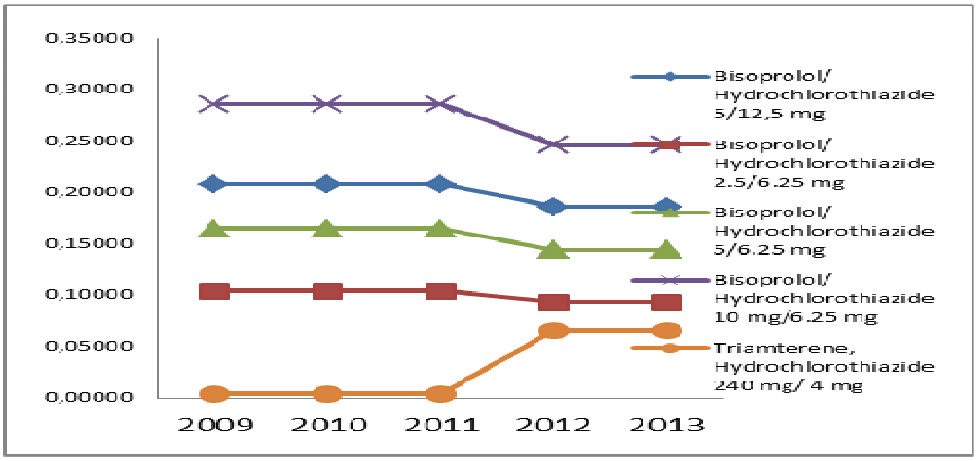


Figure 8: Changes in reference price for FDC of β-blockers/diuretic and two diuretics



The presence of many fixed-dose combinations of antihypertensive medicines is convenient for the clinical practice.Studies have shown that FDC of ACE inhibitor–diuretic achieves blood pressure control in approximately 80 percent of patients. The results were obtained in one of the larger double-blind, placebo-controlled trials. Antihypertensive drug combinations containing an ACE inhibitor and a lower dose of hydrochlorothiazide are more desirable [21, 22]. Our study confirms this results and ACE inhibitor/diuretic combination was one of the most often used with increasing generic competition and decrease in prices.

The results shows that there are various changes in utilization and reference price per DDD observed for the FDC in cardiology. The relationship between the cost per DDD and the utilized DDD/1000 inh/day provides indication of how utilization of more expensive medicines compares with that of less expensive.

The reference price has decreased significantly in 2012 and many new medicines are included in PDL. In this period, legislative changes were introduced and National Council

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on Prices and Reimbursement of Medicinal Products was created. For the newer dynamic groups with many new dosage forms and new trademarks included in the reimbursement, the reference price has decreased significantly.

Within the observed period, the use in DDD/1000 inh/day has increased in all therapeutic groups, but the greatest increases were marked for the FDC of Valsartan/HCTZ, Losartan/ HCTZ and Perindopril / Indapamide.

The study proves inverse relationship between the high price per DDD and utilization of medicines. Other factors also influence the medicines utilization - changes in price, generic competitors used as alternatives in clinical practice, preferences of physicians. If the doctors treats hypertension using 2 or 3 mono products, the patients can't substitute other medicines in the retail pharmacy in Bulgaria. Many studies confirm that utilization of FDC improves compliance of the patients and decreases cost for treatment of the disease and consequences of bad control.

The National consensus for antihypertensive medicines utilization recommended combinations with proven effectiveness and tolerability as are the:

- Thiazide or loop diuretics and β-blockers;
- Thiazide or loop diuretics and ACE inhibitors or ARB
- Beta blockers and α receptor blockers
- Beta blockers and Ca channel blockers
- ACE inhibitors and Ca channel blockers [9].

The current analysis shows that all mentioned therapeutic groups noted increasing utilization in the latest years. This means that medicines utilization follows the scientific evidences and the latest pharmacotherapeutic recommendations.

The high number of the new generic products as INNs and trademarks included between 2009-2013 years suggest that there are effective measures for generic competition and therapeutic competition stimulation in the country. When the reference price per DDD is decreasing the utilization as DDD/1000 inh/day is increasing, especially for the new and dynamic therapeutic groups. The therapeutic and generic competition is one of leading factors influencing the changes in price and utilization of CV medicines FDCs.

CONCLUSION

The study confirms that in Bulgaria the utilization of newer cardiovascular fixed dose combinations has increases due to decrease of the reference price per DDD and the growing number of the approved new generic medicines and new dosage forms. This is an indicator that treatment is based on the recent standards and guidelines for the treatment of cardiovascular disease.

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