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Fixed Doses Combinations Acting on Cardiovascular System - Utilization and Generic Competition

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Authors' contributions

This work was carried out in collaboration with all authors. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Aims: To analyze the impact of introduction of new fixed dose combinations (FDCs) in the Positive drug list on both the reference price and the utilization of reimbursed cardiovascular (CV) medicines.
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.
Methodology: On total 18 INNs (international nonproprietary name) 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 changes in the prices and utilization after the inclusion in the Positive drug list (PDL).
Results: The number of the new generic medicines included in PDL is highest for the group of ACE

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-inhibitors and diuretics, angiotensin receptor blockers (AT receptor blockers, ARBs, sartans) and diuretics. Many new generic molecules as FDCs enter the PDL, thus leading to decrease in the reference price, because of generic competition. The decrease is significant in the new therapeutic groups. The changes in utilization calculated as defined daily dose (DDD)/1000 inhabitants/day show higher utilization in 2013 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 in Bulgaria the generic and therapeutic competition has increased during 2009-2013. It leads to significant price decrease and changes in the trends in utilization of the FDC in cardiology.

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

ABBREVIATIONS

ACE : Angiotensin-converting enzyme
AHT : Antihypertensive therapy
API : Active pharmaceutical ingredient
ARB : Angiotensin receptor blockers, sartans,
AT : Receptor blockers
ATC : Anatomic therapeutic chemical
BDA : Bulgarian Drug Agency
BP : Blood pressure
CCB : Calcium channel blockers
GPs : General Practitioners
CT : Combination therapy
CV : Cardiovascular
CVD : Cardiovascular diseases
CVS : Cardiovascular system
DDD : Defined daily dose
DRI : Direct renin inhibitors
ESAC : European Surveillance of Antimicrobial Consumption
FC : Free combinations
FDC : Fixed dose combinations
HCTZ : Hydrochlorthiazide
INN : International nonproprietary name
PDL : Positive Drug List
RAAS : Renin–angiotensin–aldosterone system
WHO : World Health Organization

1. INTRODUCTION

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

As the current guidelines recommend [3] patients in advanced hypertension stages should be treated with two or more antihypertensive drugs. Combination therapy is used in approximately 75% [4] of patients with hypertension. Combination therapy reduce the blood pressure (BP) and exhibit excellent tolerability [4].

The concept of combination therapy is based on treatment with two, or more active pharmaceutical ingredients (API). They could be administered in a fixed-dose combination (FDC) or separately. It is proved that the combination therapy in the majority of patients with hypertension is effective in reaching target blood pressure [5,6]. The studies confirm that it leads also to cost savings and better compliance with the prescribed therapy [7,8].

Treatment with combination therapy offers some advantages compared to monotherapy. The combination therapy sometimes can influence the compensatory mechanisms induced by one of the drugs and prevents the adverse reactions. Some combinations of antihypertensive agents could exhibit additive or synergic effect. Additive decrease of the blood pressure is documented with the combination of an ACE-Inhibitor, ARB, or DRI (direct renin inhibitors) with a calcium channel blockers (CCB) [9]. A recent study has shown that ACE-Inhibitors are more efficacious

than ARBs in decreasing peripheral edema associated with CCB therapy [10]. Meta-analysis of 42 trials (10,968 participants) quantifies the incremental effect of combining drugs from any classes (thiazides, beta-blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers) over 1 drug alone and the results from combining drugs with doubling dose. The extra blood pressure reduction from combining of drugs from 2 different classes is approximately 5 times greater than doubling the dose of the drug used as monotherapy [11].

The high-risk patients with hypertension and accompanying diseases (like diabetes) can be treated with combining two drugs (ACE inhibitor, ARB and diuretic or ACE inhibitor and Calcium channel blocker) to achieve better result in control of blood pressure with a low rate of side effects. The compliance of patients will be improved and cardiovascular morbidity and mortality, costs and patient adverse events will be decreased [12]. The studies for combination therapy showed improved rates of blood pressure control and less time to achieve the target blood pressure [1,13,14], lower incidence results from the adverse effects, fewer patient visits, and reduced cost to the health care system [14].

Study on the management of hypertension based on data from 770 geographically diverse primary care cities (77% GPs, 23% cardiologists) found that 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%. ACE-inhibitors are the more frequently used in males than females - 29% vs 26%, showing that CV medicines utilization could vary depending on the patient's gender. In Bulgaria CT, especially FC was preferred as initial hypertension therapy than monotherapy. Monotherapy was prescribed more frequently in low/moderate risk, CT in high/very high risk. B-blockers were used as initial therapy unjustified frequently [15].

Other study compares hypertension therapy in Bulgaria and Serbia. The results show that patients in Bulgaria are often treated with 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), followed by the calcium antagonists, beta-blockers, and diuretics [16].

Fixed dose combinations as initial therapy may lead to improved compliance of patients and reduced cardiovascular morbidity and mortality [17]. In the latest years many new FDCs, especially in cardiology, were introduced on the 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 and utilization of reimbursed cardiovascular (CV) medicines during 2009-2013 years.

2. MATERIALS AND METHODS

It is a retrospective and observational analysis for the period 2009-2013 performed in Bulgaria. Changes in reference price per defined daily dose (DDD) were observed. The reference price is the lowest retail market price per DDD of FDCs acting on cardiovascular system. All prices are expressed in national currency at the exchange rate 1 Euro = 1.958 BGN.

Systematically was reviewed the Positive drug list (PDL), which include all reimbursed medicines. The observed combinations are from the therapeutic groups of 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 is calculated in DDD/1000 inh/day according to established World Health Organization (WHO) formulas:

$$\text{DDD/1000inh/day} = \left(\left(\text{Sales data in mg}/\text{DDD}\right)/\left(\text{N inhabitans}*365\right)\right) \times 1000$$

Sales data are provided by BDA (Bulgarian Drug Agency) and DDD of the products were derived from WHO website. We use 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. Only the DDD of the active substance leading in the combination (according to ATC-code) was considered.

18 FDCs included in PDL presented in 60 dosage forms out of 104 trademarks were analyzed for the changes in reference price and 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

Combinations of ACE-inhibitor and diuretic are the largest group with the highest number of dosage forms and generics included into the PDL. For the combination Enalapril/ Hydrochlorothiazide (HCTZ) we observed decrease in the reference price for all of dosage forms (Fig. 2). The utilization of combinations increased from 18.72 DDD/1000 inh/day to 18.76 DDD/1000 inh/day and remain very high in comparison with the other ACE inhibitors/ diuretics combinations (Fig.1).

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

Table 1. Number of dosage forms and trade names of FDCs of 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					
	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

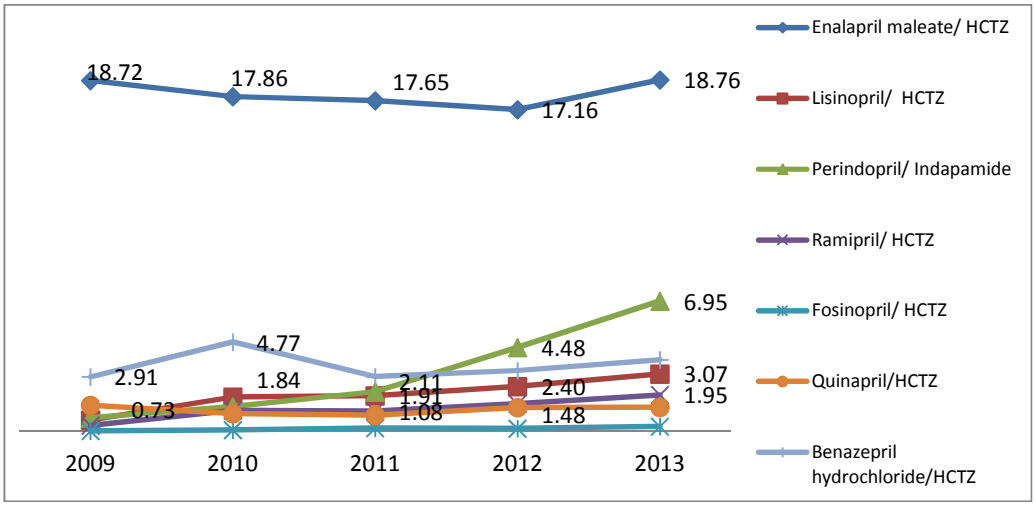

Fig. 1. Changes in DDD/1000 inh/day for FDCs of ACE-inhibitors and diuretic

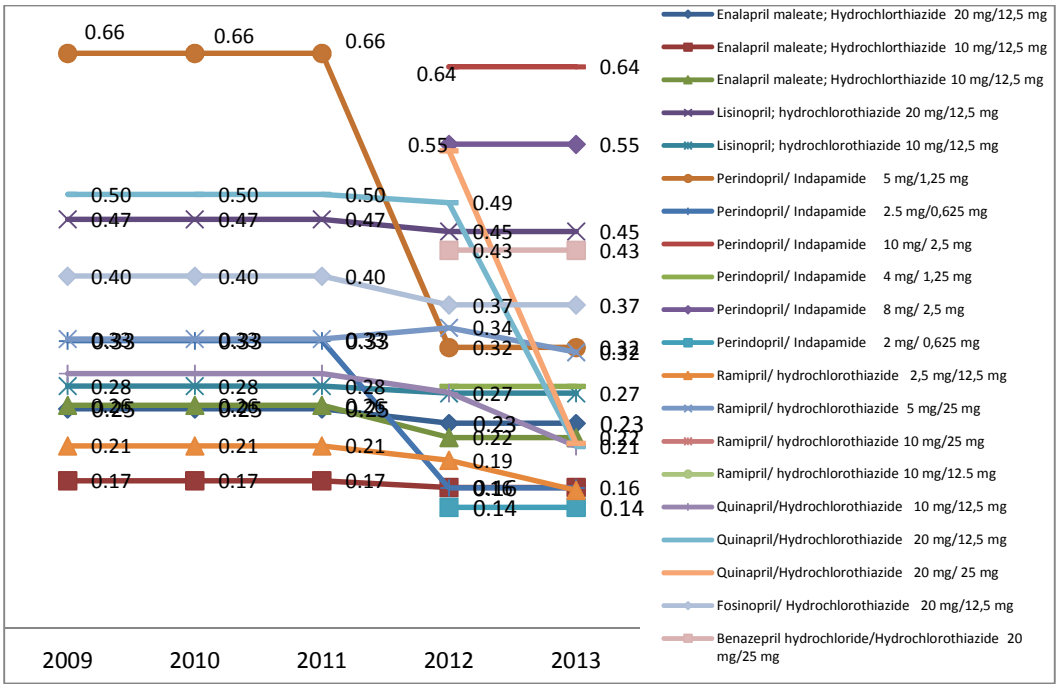

Fig. 2. Changes in reference price per DDD for the FDCs of ACE-inhibitors and diuretic

For the other combinations similar changes in utilization and reference price per DDD were observed. New dosage forms included in PDL within the period let to increased generic and therapeutic competition. Exception is the FDC Benazepril/HCTZ 20/25 mg for which there is no new products and no changes in reference price. The utilization increased insignificantly.

FDCs of ACE- inhibitor and calcium channel blocker diminish numerous adverse event of CCB as for example the legs edema. The combination of calcium-channel blockers and ACE inhibitors could have a synergistic effect. The results show that the combination of nitrendipine and captopril appears to be a very effective and well-tolerated for the treatment of mild to moderate primary hypertension [18,19,20,21]. We observed the changes in reference price and the utilization for 3 FDCs of ACE inhibitors and Ca channel blockers included in PDL (Table 2). The increase in utilization of

FDCs of Lisinopril/ Amlodipine and Perindopril/ Amlodipine is significant (0.55 DDD/1000 inh/day to 3.37 DDD/1000 inh/day and 0.64 to 5.40 DDD/1000 inh/ day respectively (Fig. 3). The reference price per DDD decreases for all FDCs and it is the most obviously for the combinations of Perindopril/ Amlodipine. The high number of new trademarks increases competition, resulting in a decrease of the reference price from one side and to increased consumption on the other side.

Table 2. Number of dosage forms and trade names of FDCs of 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					

Table 3. Number of dosage forms and trade names of FDCs of 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					
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					

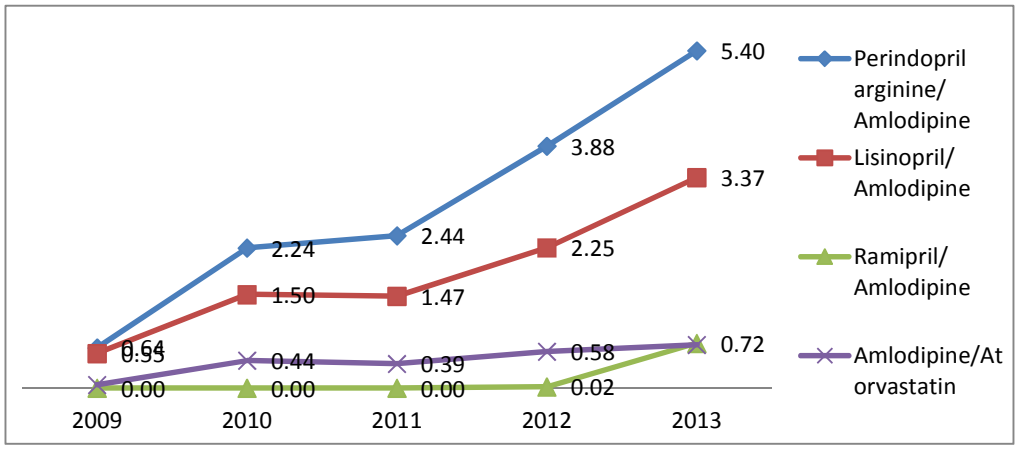

Fig. 3. Changes in DDD/1000 inh/day for group of ACE-inhibitors and Ca-antagonists

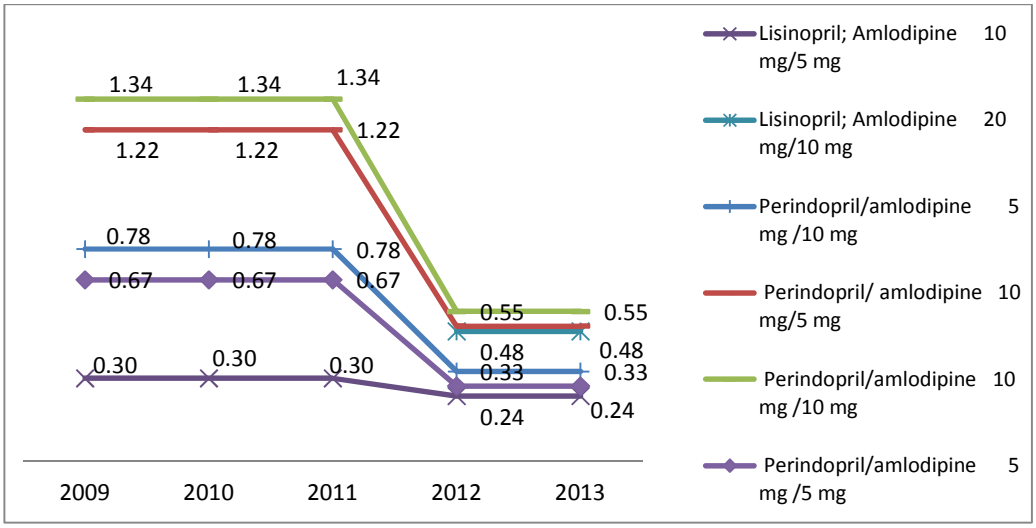

Fig. 4. Changes in reference price per DDD for the FDCs of ACE-inhibitor and Ca-antagonist

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 (Fig. 4).

FDC of renin–angiotensin–aldosterone system (RAAS) inhibitor and a diuretic in low-doses shows higher reduction of blood pressure and response to therapy than both APIs administered separately. It also compensates the increased plasma renin activity provoked by the diuretic [22,23,24,25]. During the observed period FDCs of sartan and diuretic performed steady increase in their dosage forms, trademarks and new international non-proprietary name (INN). For FDC of Valsartan/HCTZ 8 new trademarks were included in PDL, and for combination, Candesartan/HCTZ 5 new trademarks were included (Table 3). On total 43 new generic medicines were included in the group during 2009 - 2013. The results show that it is one of the most dynamic groups. The higher number of new generic forms leads to decrease of the reference price per DDD and increase of the utilization (Fig. 5; Fig. 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.

The reference price and utilization are significantly impacted from the high number of new products included in PDL within

observed period and for all products it is decreasing.

For the FDC of Amlodipine and Atorvastatin after the introduction of new dosage forms in PDL the reference price per DDD decreased in 2012 and 2013 while the utilization has increased (Table 4).

The combination of beta blockers and diuretics blunt the increase in the plasma renin level that is induced by diuretics, and decreases water retention caused by beta blockers [26]. Studies showed that monotherapy with either agent was more effective than placebo. If the combination therapy is used, the beneficial effect would have been greater than that of either agent used alone [27]. 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 (Fig. 7; Fig. 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 (Fig. 8).

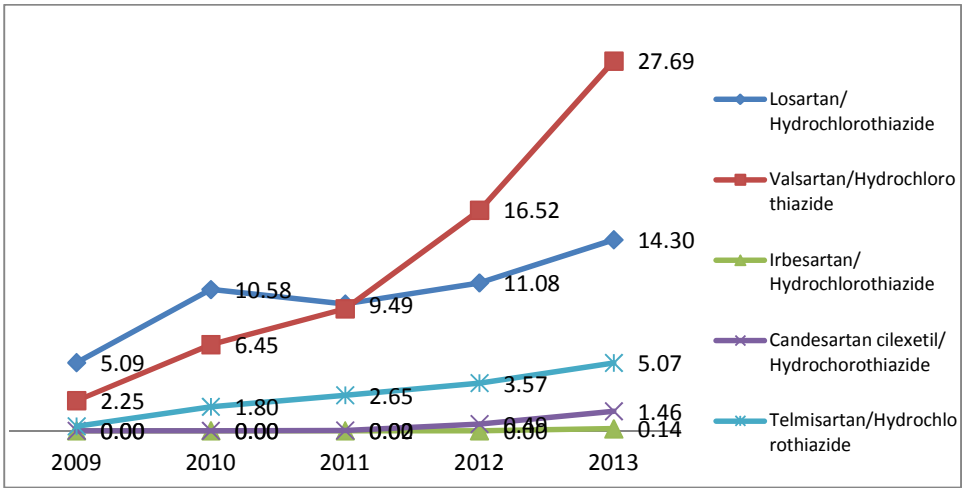

Fig. 5. Changes in utilization in DDD/1000 inh/day of FDCs of sartans and diuretics

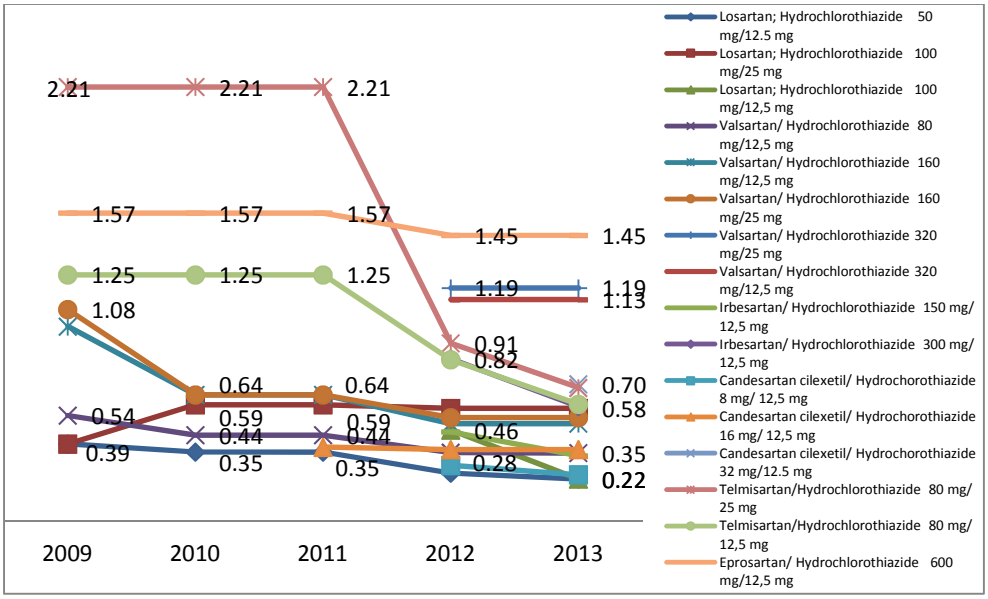

Fig. 6. Changes in reference price per DDD of FDCs of sartans and diuretics

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	DDD/1000 inh/ day (BGN)				
		2009	2010	2011	2012	2013	reference	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						

Table 5. Number of dosage forms and tradenames for the FDCs 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					

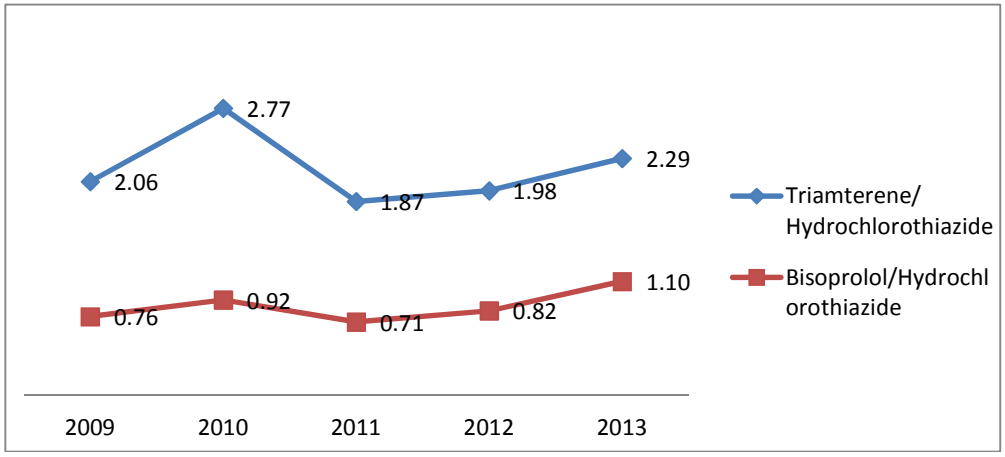

Fig. 7. Changes in utilization in DDD/1000 inh/day for FDC of β-blockers/ diuretic and combination of two diuretics

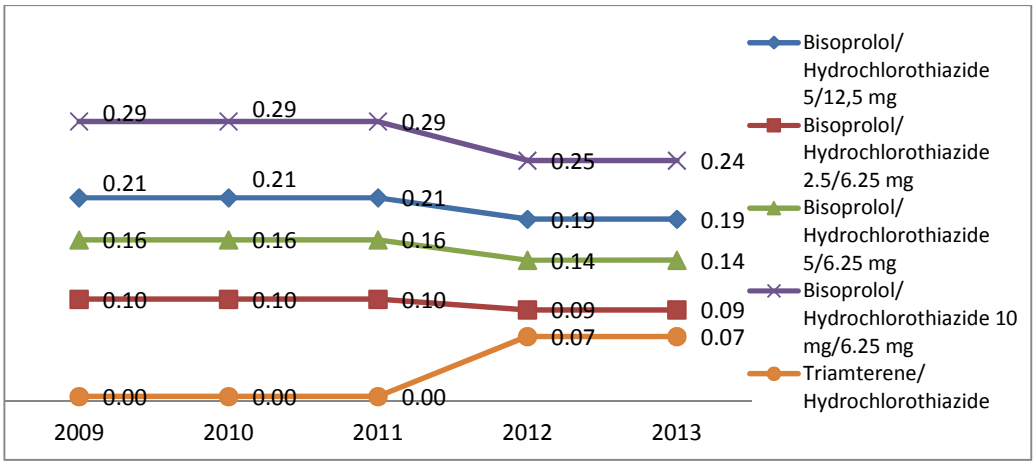

Fig. 8. Changes in reference price for FDC of β-blockers/diuretic and two diuretics

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. The variations in reference price per DDD are not so significant between 2009-2013 years.

There are various changes in utilization and reference price per DDD in the cardiology medicines. The relationship between the cost per DDD and the utilized DDD/1000 inh/day provides information of how the utilization of expensive medicines compares with that of less expensive.

Other studies have shown that FDC of ACE inhibitor–diuretic achieves therapeutic control and improve the blood pressure in approximately 80 percent of patients [28,29]. The results were proved in multicenter, double-blind, placebo-controlled trial. The lower doses of hydrochlorothiazide both alone or in combination with lisinopril were equipotent with higher doses and were free of metabolic side effects [28]. Antihypertensive drug combinations containing ACE- inhibitor and lower dose of hydrochlorothiazide are preferred in Bulgaria as the first choice for monotherapy [16]. Our study confirms that the combination therapy with ACE-inhibitors/diuretics and statins/diuretic were most preferred. 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 results from the other study [15] shows that in Bulgaria FDCs were underused compared with the monotherapy. Monotherapy was prescribed more frequently in low/ moderate risk patients. In patients with high/very high risk, the CT was used more often. Our study confirms that during the latest years the utilization of FDCs has increased which is a result from the high number of reimbursed medicines included in PDL and the increasing competition. We proved also that there is an inverse relationship between the price per DDD and utilization of medicines in Bulgaria. In a study from South Africa the same results are reported for antipsychotic, antidepressant, hypnotic and anxiolytic drugs [30].

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 on Prices and Reimbursement of Medicinal Products was created. The reference price has decreased significantly mainly for the newer dynamic groups with many new dosage forms and new trademarks included in PDL [31].

The results from T-test shows that there are many statistically significant changes in the utilization and reference prices. In the analysis were compared DDD/1000 inh/day and reference price per DDD for every group between 2009 - 2013. The highest change in utilization is found for the group of ACE - inhibitors and Ca antagonists, $p = 0.113$. The highest change in reference price is found for the group of ACE - inhibitors and Ca antagonists, $p= 0.167$ and b-blocker/ diuretic (we observe combination bisoprolol/HCTZ only), $p= 0.113$. Similar are the results for the variations of the reference price. The reference price reduces significantly for some products, but within the group it is not statistically significant.

Other factors that influence the medicines utilization could be changes in price, generic competitors used as alternatives in clinical practice, preferences and prescribing habits of the physicians. Many studies confirm that utilization of FDC improves compliance of the patients and decreases the cost of therapy for the cardiovascular diseases and their consequences in case of bad control [32,33,34].

The patients treated with FDCs had better persistence (42.5% higher; $P < 0.002$) and compliance (22.1% higher; $P < 0.001$), compared with the patients who were switched from FDCs. The higher compliance rate (22.1%) is associated with lower costs for hypertension-related health care ($P < 0.001$) and reduction in hypertension-related expenditures as a whole. [35].

The National consensus for antihypertensive medicines utilization recommends 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 [12].

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.

This is the first Bulgarian study comparing the utilization in DDD/1000 inh/day, reference price per DDD, and the number of the approved trademarks and generic medicines of FDCs during 2009 - 2013. Limitation of the study is the calculation of utilization when only DDD of the leading substance is used [36].

The high number of the new generic products as INNs and trademarks included during 2009-2013 suggests 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 the leading factors influencing the changes in price and utilization of CV medicines FDCs.

4. CONCLUSION

The study confirms that in Bulgaria the utilization of newer cardiovascular fixed dose combinations has increased due to decreasing 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. It also confirms that the generic entrance let to competitive pharmaceutical market.

COMPETING INTERESTS

Authors have declared that no competing interests exist

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