Original Research Article

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

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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 (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 the changes in prices and utilization after the inclusion in the positive drug list (PDL).
Results: 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. Many new generic molecules as FDC entrance the PDL and generally, the generic competition leads to decrease of the reference price. The decrease is significant in the new therapeutic groups. The changes in utilization calculated as DDD(defined daily dose)/1000 inhabitans/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 in Bulgaria the generic and therapeutic competition has increased between 2009-2013 years. It leads to the significant price decrease and change 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

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 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] more patients are treated with two or more antihypertensive drugs. Combination therapy is used in approximately 75% [4] of patients with hypertension. Combination therapy included the selection of two-drug combinations which reduce the blood pressure (BP) and exhibit excellent tolerability. [4]

The conception for combination therapy includes treatment with two, or more active pharmaceutical ingredients (API). They could be administered in a fixed-dose combination (or separately) pill. It helps of patients with hypertension to reach target blood pressure [5,6]. The studies confirms that it also leads to cost savings and better compliance with the prescribed therapy [7, 8].

Treatment by 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 CCB. [9] A recent study has shown that ACE-Inhibitors are more efficacious than ARBs in decreasing peripheral oedema associated with CCB therapy. [10]. Meta-analysis of 42 trials (10,968 participants) with the goal quantify 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 other diseases (like diabetes) can be treated with a therapy 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 which observe combination therapy instead of monotherapy shows improved rates of blood pressure control and less time to achieve 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 for management of hypertension and initial therapy in Bulgaria using the 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%. As far to ACE-inhibitors, they are most frequently used in males than females - 29% vs 26%. Therefore the use of CV medicines is different depending on the gender of the patients. In Bulgaria CT, especially FC was preferred as initial AHT 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 compare hypertension therapy in Bulgaria and Serbia. The results shows that patients in Bulgaria are often treated by 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]. 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**).

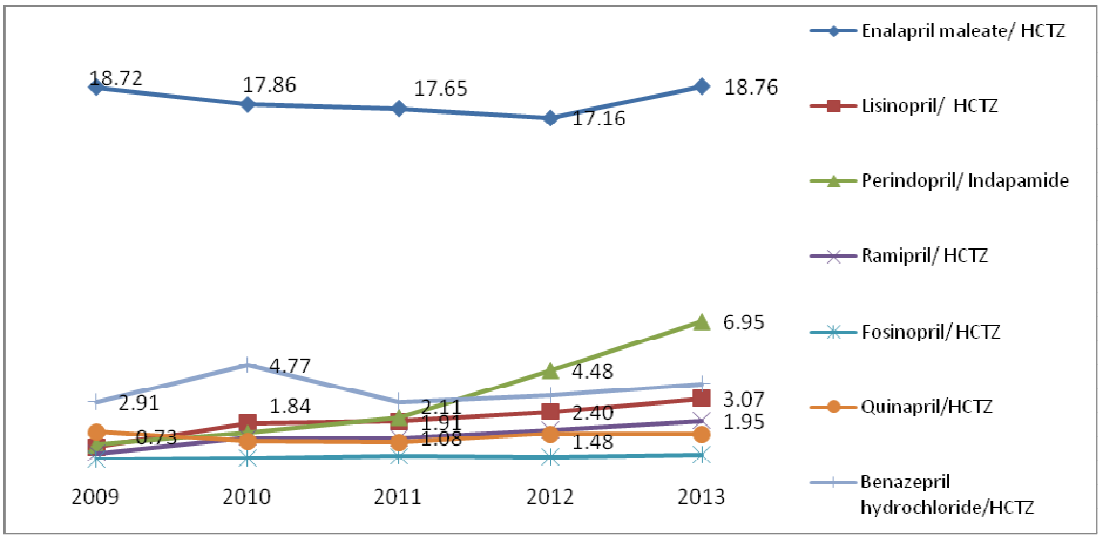

Figure 1: Changes in DDD/1000 inh/day for the group of ACE-inhibitors and diuretic

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/1000inh/day. The new generics included in PDL encourage generic competition. For the combination Perindopril/ Indapamide the utilization increases significantly 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					
	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 which leads to increased generic and therapeutic competition. Exception is the FDC Benazepril/HCTZ 20/25 mg - no included new products and no changes in reference price. The utilization increased insignificantly.

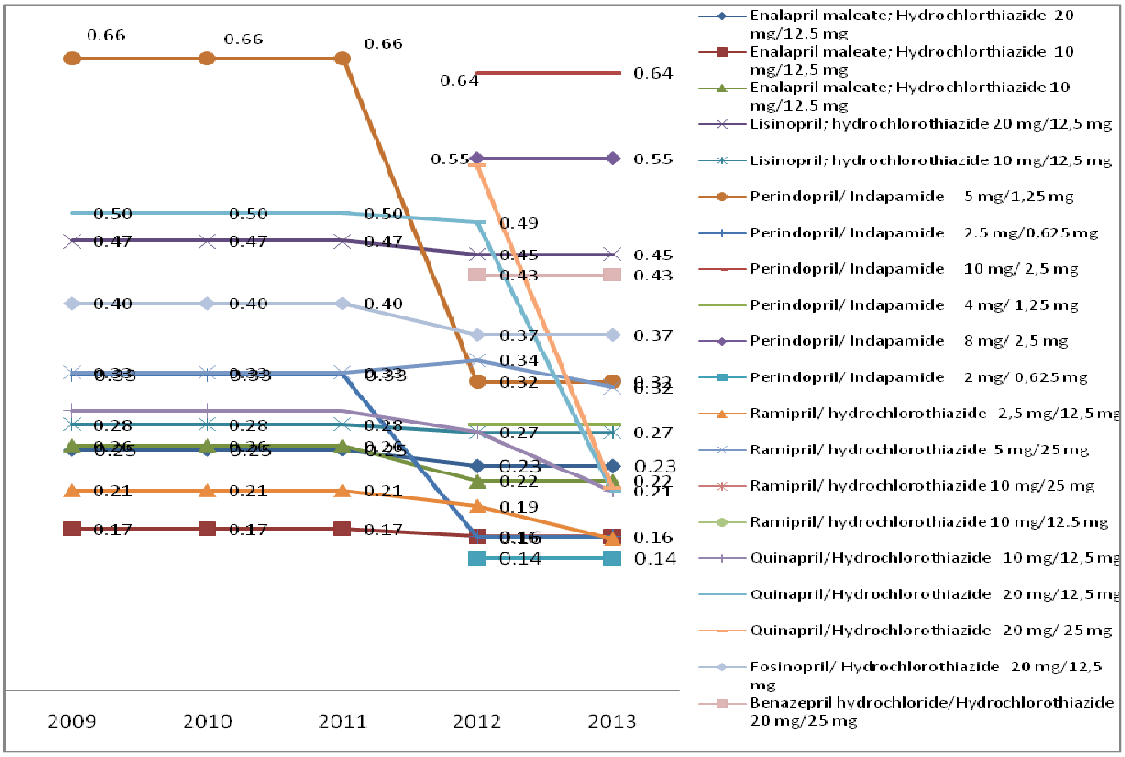

Figure 2: Changes in reference price per DDD for the group of ACE-inhibitors and diuretic

FDCs of ACE- inhibitor and calcium channel blocker diminish number of exhibited adverse event of CCB - legs oedema. The combination of calcium-channel blockers and ACE inhibitors could have a synergistic effect. The results shows 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 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**). The reference price per DDD decreases for all FDCs and it is the most obviously for the combinations of Perindopril/ Amlodipine. New trademarks increase competition, resulting in a decrease of the reference value and increased consumption.

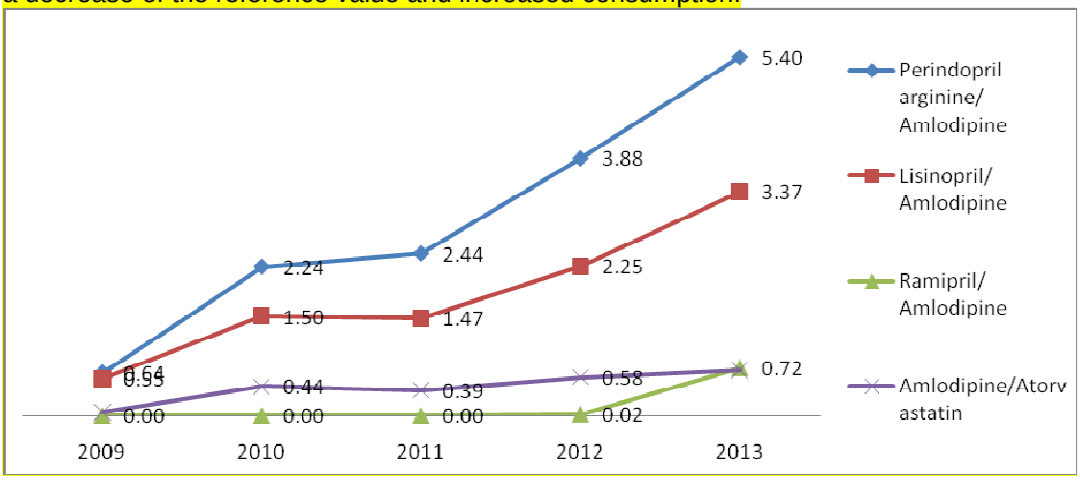

Figure 3: Changes in DDD/1000 inh/day for group of ACE-inhibitors and Ca-antagonists

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					

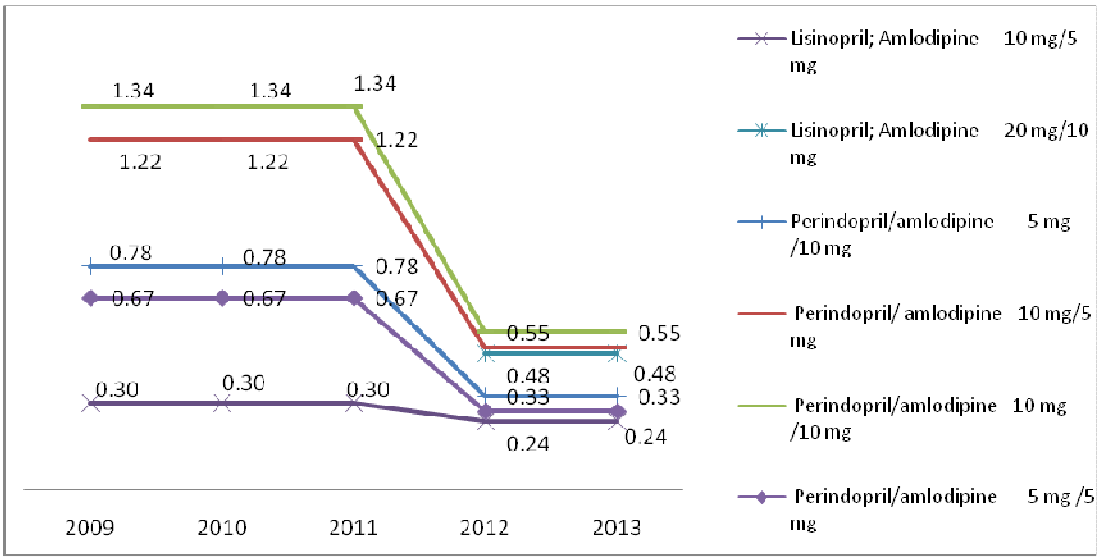

Figure 4: Changes in reference price per DDD for the group of ACE-inhibitor and Ca-antagonist

The combination renin–angiotensin–aldosterone system (RAAS) inhibitor and a diuretic in low-doses shows higher reduction of blood pressure and response than the medicines administered separately as well as compensate the increased plasma renin activity provoked by the diuretic.[22, 23, 24, 25]. 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 groups. 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					
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					

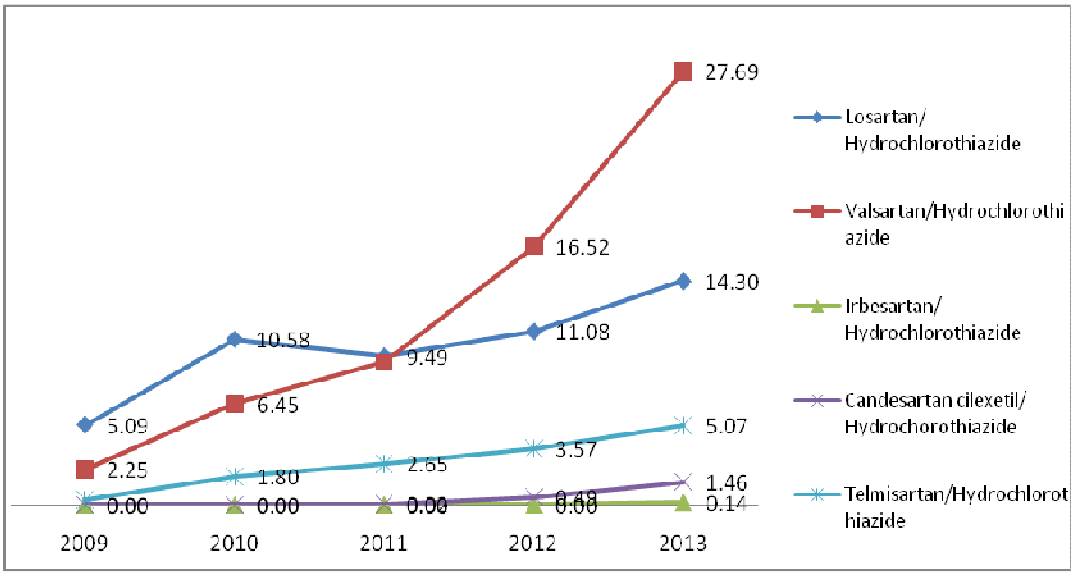

Figure 5: Changes in DDD/1000 inh/day in the group of sartans and diuretics

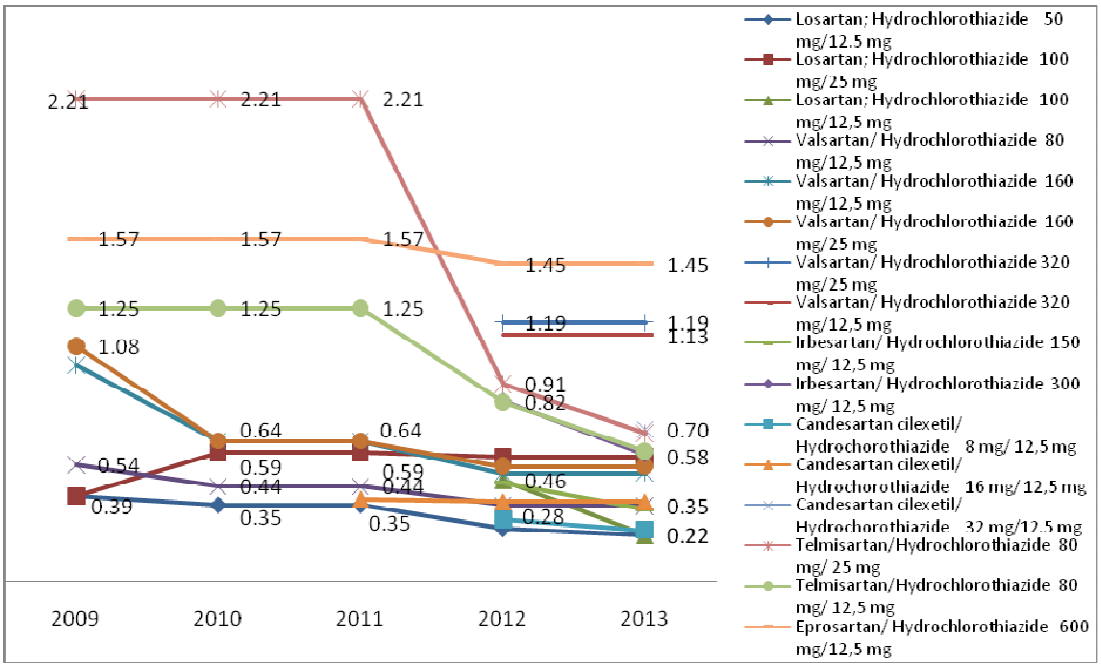

Figure 6: Changes in reference price per DDD in the group of sartans and diuretics

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

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 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]. The study showed that monotherapy with either agent was more effective than placebo, but that when combination therapy was used, the beneficial effects were greater than when either agent was 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 (**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.

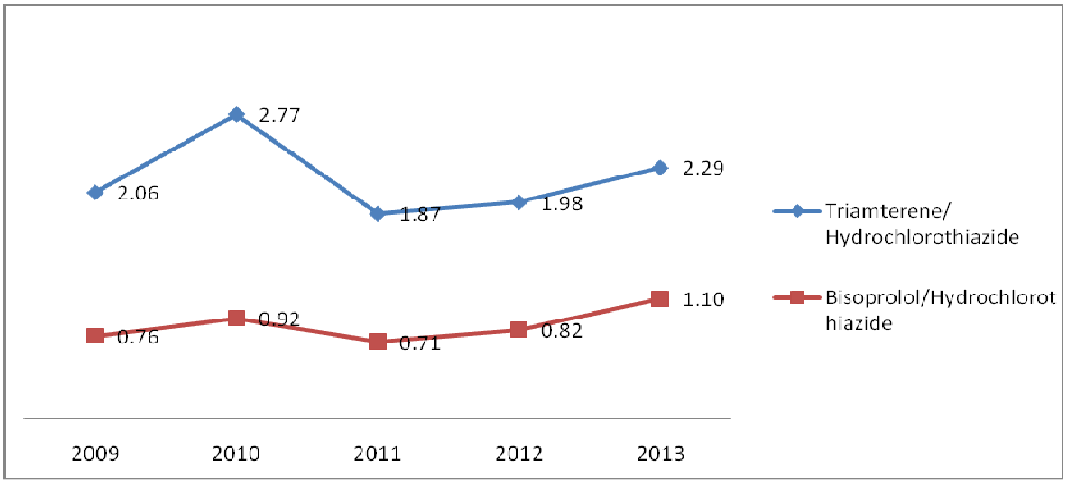

Figure 7: Changes in DDD/1000 inh/day for the group of β-blockers/ diuretic and combination of two diuretics

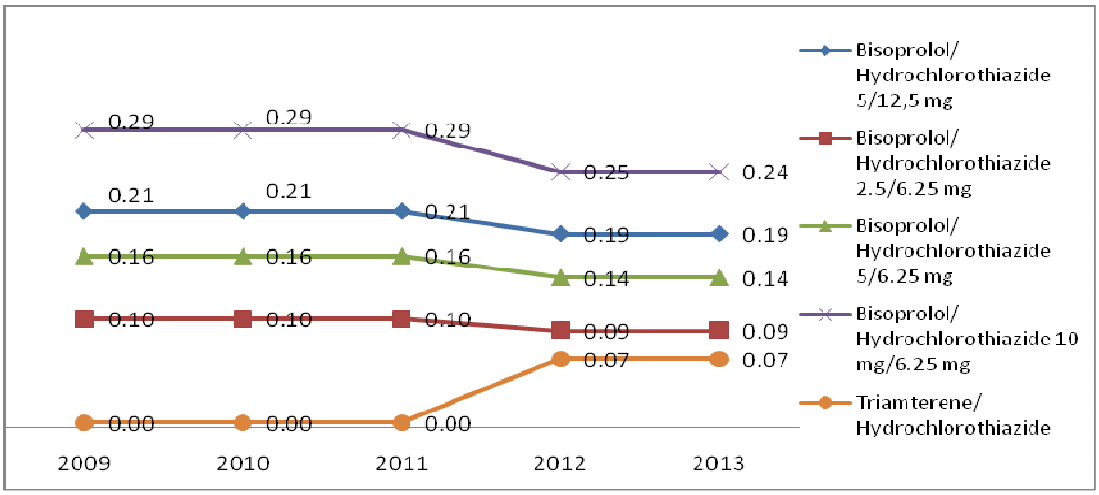

Figure 8: Changes in reference price for FDC of β-blockers/diuretic and two diuretics

The 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 information of how utilization of expensive medicines compares with that of less expensive.

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 either 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 more desirable in Bulgaria and the first choice for monotherapy. [16] Our study confirms that in combination therapy 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 FDC were underused compared with the monotherapy. Monotherapy was prescribed more frequently in low/moderate risk. In patients with high/very high risk the CT were used more often. Our study confirms that last few years the utilization of FDCs has increases which is a result from the high number of reimbursed medicines included in PDL and the increasing competition. We proved also that last years there is inverse relationship between the high price per DDD and utilization of medicines in Bulgaria. In study for 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. For the newer dynamic groups with many new dosage forms and new trademarks included in the reimbursement, the reference price has decreased significantly.

The results from the T-test shows that there are no statistically significant changes in the utilization and reference prices. In the analysis were compared DDD/1000 inh/day and reference price per DDD for each 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. Despite the great change in the utilization for some of the products included

in PDL, as a whole there are no statistically significant differences between 2009 - 2013 year for the groups. The same is found in regards to the variations of the reference value. The reference value 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 of physicians. If the doctors treats hypertension using 2 or 3 mono products, the patients can't choose 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. [31,32, 33]

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 to FC therapy. 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. [34]

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 [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.

The study was prepared with the information provided by BDA for calculation of DDD/1000 inh/day. It gives the opportunity for comparison of the changes for all products marketed in Bulgaria. The information for the changes in reference price per DDD is published in official internet site on The National Council on Prices and Reimbursement of Medicinal Products. [35].

In Bulgaria it is the first study comparing DDD/1000 inh/day, reference price per DDD, and number of the approved trademarks and generic medicines for fixed doses combinations between 2009 - 2013. Limitation of the study is calculation of DDD only using DDD/1000 inh/day. The WHO is approved also DDDs per inhabitant per year for estimation of the average days for treatment annually of each inhabitant.

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 the 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.

COMPETING INTERESTS

Authors have declared that no competing interests exist

AUTHORS' CONTRIBUTIONS

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

LIST OF 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

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