HYPERTENSION AND COMMON COMPLICATIONS – ANALYSIS OF THE AMBULATORY TREATMENT COST

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SUMMARY

Aim: Retrospective analysis of the prescribing practice and cost of ambulatory treatment of hypertension and its common complications – heart failure, sequelae of cerebrovascular disease, and angina pectoris.

Methods: Analysis of 3,240 reimbursable ambulatory prescriptions for hypertension, heart failure, sequelae of cerebrovascular disease and angina pectoris according to the complexity of the therapy and frequency of the prescribed medicines. Modeling and calculation of the expected monthly cost for outpatient therapy by using the "decision tree model". Sensitivity analysis is performed within the ±30% interval.

Results: 65% of the prescription were for the hypertension, and 35% for the observed complications. 1,297 prescriptions for hypertension include one medicine, 647 include two medicines, and only 8% of prescriptions were for three medicines. ACE inhibitors have been prescribed in 41% of all hypertension prescriptions, followed by beta-blockers (19%), Ca channel blockers (16%), diuretics (15%) etc. The prescriptions for hypertension complications are more diverse as therapeutic groups. The expected monthly cost of prescribed medicines per patient with hypertension alone is 6.90 € and in case of complications it is 10.71 € according to the prevalence of the complexity of therapy, and weighted monthly cost of medicines. The overall ambulatory cost is expected to be around 148 million € per year for near 1.5 million patients with 44% reimbursement. The cost of the therapy is sensitive more to changes in the medicine's prices than to its complexity.

Conclusion: This study is a first step in providing information for evidence-based cost containment measures or policy decisions at ambulatory level in Bulgaria and for the assessment of the share of complications' therapy on the overall hypertension cost.

INTRODUCTION

High blood pressure is the most common chronic medical problem and hypertension is an important public-health challenge world-wide. Overall, 26.4% of the adult population in 2000 had hypertension and it is expected that 26.1% of women, and 29.2% of men will have this condition by 2025 year worldwide (1). In Europe the hypertension was found to be more prevalent than in USA and Canada and poor controlled (2–5). Hypertension is a major global economic burden because of an increased risk for cardiovascular events and inadequately controlled high blood pressure raises the medical, economic, and human costs.

Age-standardized mortality rate for cardiovascular diseases is 554.0 per 100,000 Bulgarian population (6) and hypertension is the leading cause for death (108.1 per 100, 000) (7) and its complication leads to age-standardized annual event rate from 915 to 30 per 100, 000 people all over the world (8, 9). The high social and medical importance of hypertension underlines the economic impact of the therapy of hypertensive patients at national and international level.

There have not been found studies on the cost of hypertension therapy in Bulgaria and this stimulated us to perform the current study. In 2004 the National Health Insurance Fund published information that the hypertension is one of the leading 10 diagnoses accounting for near 20 million € expenditures per year. Till then no such information was publicly available (10). In addition to the cost analysis we also want to explore the impact of the hypertension medication therapy. The problem is important from the point of view of the financing institutions in order to make them understand the variables influencing the changes in the hypertension therapy cost.

BACKGROUND OF THE PROBLEM

Researchers are studying the social and economic impact of hypertension at national level in many different ways (11–15). They calculate the direct and indirect cost of hypertension and/or complications cost, analyze prescribing practice and changes in cost of therapy, as well as create different cost models.

The costs for antihypertensive drugs in France are calculated as 258 €per patient per year and will further increase (16, 17). In UK the monthly costs of the antihypertensive drugs was found £23.44 (18). The hypertension expenditures in Italy represent 42.7% of total expenditure for medicines, followed by cost for hospital admission (28.4%) (19). In Latin America the amount allocated for hypertension in 2007 was estimated at US$ 2,486,145,132 that is 6% to 8% of the total health budget (20).

If only drug acquisition costs are considered, there are marked differences among antihypertensive drug classes (21). Total costs for management of hypertension of elderly patients depend on therapeutic class (22). The medical and human costs of treating preventable conditions such as stroke, heart failure, and end-stage renal disease could be reduced by appropriate antihypertensive treatment (23), and patient's switch from a previous antihypertensive class is an important factor (24).

There are some published studies examining the costs for using certain therapeutic groups. The thiazide diuretics alone or in combination remained the most commonly prescribed drugs in 56% of all patients in Nigeria (25). The prescribing of calcium channel blockers, and ACE-inhibitors was found 51% and 24% respectively (26). Pharmacoeconomic analyses have confirmed the cost effectiveness of conventional hypertension therapy, usually involving diuretics or β-blockers, compared with the new strategies (27). The currently preferred pharmacological treatment options for hypertension are the angiotensin-converting enzyme inhibitors, whilst β-blockers provide other-line treatment options for hypertension (28). Some authors consider that β-blockers should not remain the first choice in the treatment of primary hypertension (29).

Different cost models have been built for the evaluation of the variations in the treatment approaches. Lloyd A, et al. create a burden-of-disease model and estimated that in the UK in general 16 million adults have blood pressure in the range 140/90−160/95 mm Hg and above, and that 58,000 major cardiovascular events per year occur in these patients (3). The achievement of target blood pressure will reduce the expenditures by pound 97.2 million per year at 2000/01 prices. Hansson L. et al. estimated the burden of failing to achieve targets for blood pressure control in France, Germany, Italy, Sweden and the UK by constructing a cost of illness model and estimated that 1.26 billion €could be spared if hypertension management did achieve blood pressure targets (4). Flack JM. et al. develop a model to estimate the number of cases and costs of myocardial infarction, stroke, and congestive heart failure and discover that inadequate control result in 39,702 cardiovascular events and 8,374 deaths, thus leading to $964 million direct medical expenditures (30).

It is undoubtful that the changes in prescription patterns have tremendous impact on hypertension cost as well as on the other health care resources (31). However often physicians did not adhere to guidelines when initiating treatment of patients with co-morbidities (32).

In summary the cost of hypertension and its complications differs among the countries and prescription practice is one of the important factors. Modeling the influence of the hypertension therapy with respect to its cost allows us to analyze simultaneously the effect of prescribing differences and complexity of the therapy on the hypertension cost. We did not find such a study for the Bulgarian therapeutic practice and this stimulated our interest in the topic.

GOAL AND STUDY QUESTIONS

The aim of this study is to analyze the relation among the prescribing practice and the cost of ambulatory treatment of arterial hypertension and its common complications in Bulgaria.

Discussed are the following study questions:
- Is the hypertension prescribing practice consistent with the treatment guidelines?
- What is the burden of hypertension cost for the population and third party payer?

MATERIALS AND METHODS

The study is a retrospective analysis of the ambulatory prescriptions for hypertensive patients from the point of view of patients and health insurance fund for one year time horizon.

Prescribing Practice Analysis

To analyze the prescribing practice a prescription sample size was determined to satisfy the values for α 0.05 and a study power of 0.80. The size of 250 prescriptions per diagnosis satisfies the stated criteria. The 3,240 reimbursable prescriptions were retrospectively collected in 3 geographically representative urbanized regions in Bulgaria covering near 40% of the population of the country in 2006 year. Out of approximately 1,000 pharmacies 100 allocated in different geographically representative areas of the observed regions were selected for search in databases in order to collect prescriptions with conditions meeting definition of the International classification of diseases (ICD) (33), as follows: hypertensive heart disease and essential hypertension (ICD codes I.10; I.11); heart failure (ICD code I.50); sequelae of cerebrovascular disease (ICD code I.69), and unstable angina pectoris (ICD code I. 20). Out of the collected 3,240 prescriptions, 2,106 (65%) were those for hypertension and 1,134 (35%) for its common complications, as follows: 300 prescriptions for heart failure, 361 for sequelae of cerebrovascular disease, and 473 for angina pectoris (Table 1). The prescriptions were systematized and analyzed according to the complexity of the therapy – monotherapy, ditherapy, and therapy with 3 medicines ("threetherapy"), as well as frequency of the prescribed medicines as therapeutic class; INN; and trade name.

Prescription Cost Calculation

For every particular medicine the officially published price to be reimbursed and co-payment contribution was gathered (34). Within the prescription sample we calculated the relative share, as percentage and probability, of the prescribed trade names of medicines for every disease under consideration. To match the differences in the probability of prescribed trade names and respective prices the weighed monthly cost per prescription was calculated by using the following formula:

$$\text{WMC per prescription} = \Sigma\ (q_1 \times c_1 \times p_1 + q_2 \times c_2 \times p_2 + \ldots + q_i \times c_i \times p_i)\ /\ \text{number of prescriptions}$$

where:

WMC - weighed monthly cost

$q_{1, 2..., i}$ – quantity prescribed for the monthly therapy;

$c_{1, 2..., i}$ - corresponding unit reimbursement price;

$p_{1, 2..., i}$ - probability of prescribed trade name as share of the prescription sample.

where "i" is the serial number of the trade name prescribes (for example if there are 5 trade names the i=5).

The same calculation was repeated for the co-payment.

Modeling the Costs of Ambulatory Therapy

The "decision tree model" (TreeAge Pro 2007; TreeAge Software, Inc., Williamstown, Massachusetts) was build corresponding to the complexity of the therapy, probability of the observed complications and weighed monthly cost of the therapy (Fig. 1).

The starting point in the "decisions tree" is the presence of hypertension and complications. The first chance node refers to the probability of having hypertension alone or the observed complications occurrence. The second chance node represents the complexity of the hypertension therapy, as defined by the number of prescribed medicines per prescription. For the hypertension with complication the second chance node presents the probability values of the observed 3 types of complications and the third chance nodes are presenting the probability of the complexity of the therapy for complications. At the end of the model was inserted the weighed monthly reimbursement cost per patient or per health insurance fund in Euro and expected model cost was calculated by multiplying the weighed monthly cost with the probability of being on particular therapy and summarizing for every branch of the decision tree (35).

Sensitivity Analysis

To examine the influence of the complications and weighed monthly cost on the ambulatory hypertension cost we performed a one way sensitivity analysis by varying the weighed monthly cost and probability of the hypertension and its complications within the ±30% interval.

Table 1. *Distribution of the collected prescriptions according to the disease, complexity of the therapy and related weighted monthly cost*

Disease/type of therapy	Number of prescriptions	%	Weighted monthly costs €	Weighted monthly costs paid by NHIF[1] €	Co-payment by patient (weighted monthly costs) €
AH[2] – Total parameters value	2,106	100	6.93	2.44	4.49
Monotherapy	1,297	61	5.00	1.75	3.25
Ditherapy	647	31	9.16	3.30	5.86
"Three" therapy	162	8	13.01	4.35	8.66
AH complication – Total	1,134	100	10.77	3.96	6.81
Total for AP[3]	473	100	11.91	4.40	7.51
AP-mono	317	67	9.22	3.40	5.82
AP-di	117	25	16.54	6.14	10.40
AP "three"	39	8	19.98	7.39	12.59
Total for SCD[4]	361	100	13.65	5.11	8.54
SCD -mono	237	66	9.75	3.68	6.08
SCD -di	93	26	20.60	7.63	12.97
SCD -three	31	8	23.22	8.73	14.49
Total for HF [5]	300	100	5.40	1.88	3.52
HF-mono	191	64	3.58	1.19	2.39
HF-di	75	25	7.84	2.51	5.33
HF "three"	34	11	10.40	4.43	5.97
Total cost (AH+complications)			17.71	6.40	11.30

Abbreviations used:

[1] NHIF – National health insurance fund;

[2] AH – arterial hypertension;

[3] AP – angina pectoris;

[4] SCD – sequellae of cerebrovascular disease;

[5] HF – heart failure;

[6] WMC – weighed monthly cost;
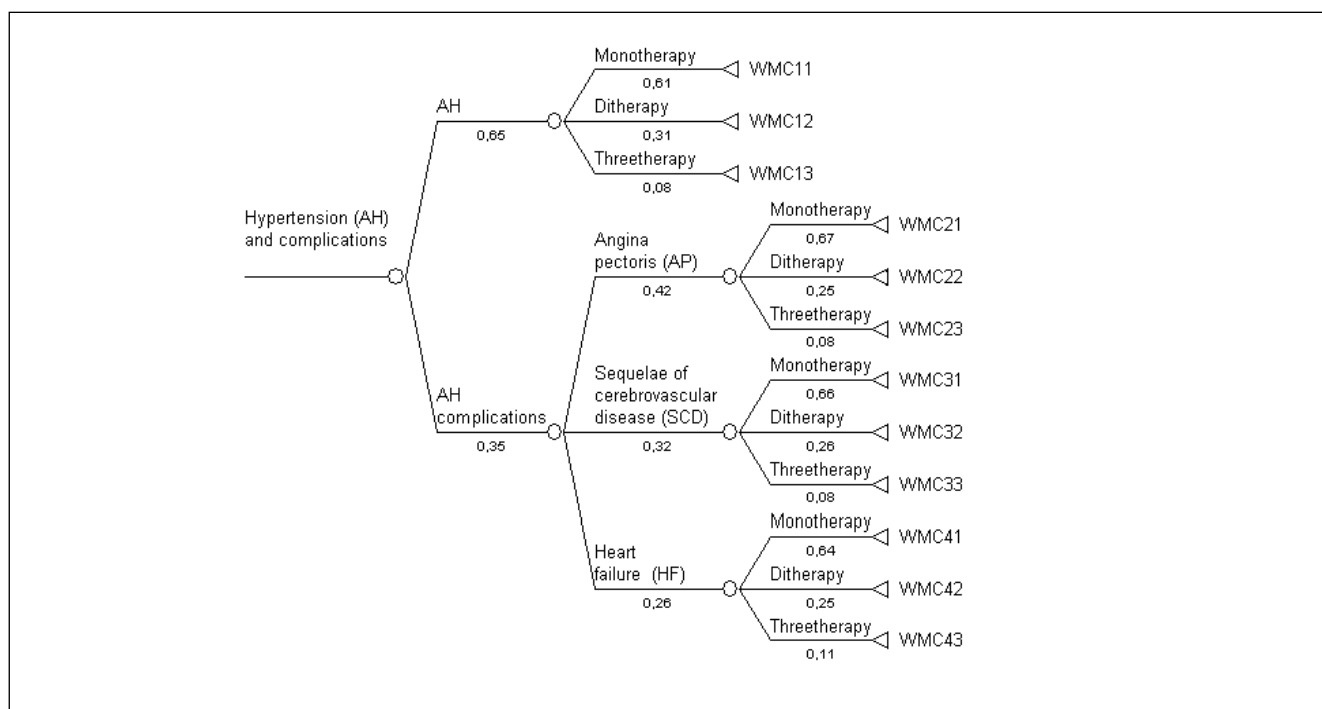
[7] AH – arterial hypertension

Fig. 1. *Model structure for the cost calculation of hypertension therapy and its observed complications.*
AH – arterial hypertension, AP – angina pectoris, SCD – sequelae of cerebrovascular disease, HF – heart failure, WMC – weighed monthly cost, P – probability of complication as part of the total prescription sample.

RESULTS

Results of the Prescribing Practice Analysis

The distribution of prescriptions according to the disease code shows that 35% of them are for the observed complications. The cardiac complications lead with 15% angina pectoris and near 9% heart failure. Sequelae of cerebrovascular disease are the second complication with 11% among the collected prescriptions (see Fig. 1, Table 1). For the hypertension patients 1,297 prescriptions include one medicine (61%), while 647 include two medicines (31%) and only 8% of the observed patients were treated with three medicines (162 prescriptions).

It is necessary to note that according to the existing reimbursement rules no more than 3 medicines could be prescribed per patient per diagnosis for a monthly therapy and that every prescription is only for one diagnosis. Prescriptions with one medicine were found in 67% of patients with angina pectoris, 66% with sequelae of cerebrovascular disease and 64% for heart failure. The relative share of the di-therapy is on average 25.5% (range 25%–31%) among all the prescriptions, while the therapy with three medicines have been observed in 10% (8%–11%) of the prescriptions on average (see Table 1).

According to the therapeutic class the ACE inhibitors have been prescribed in 41% of all prescriptions for hypertension, followed by β-blockers (19%), Ca channel blockers (16%), diuretics (15%) etc. (Fig. 2). Among the ACE inhibitors enalapril was prescribed in 68% of all prescriptions, followed by perindopril (10%) and trandalopril (9%). All other authorized for sale ACE inhibitors
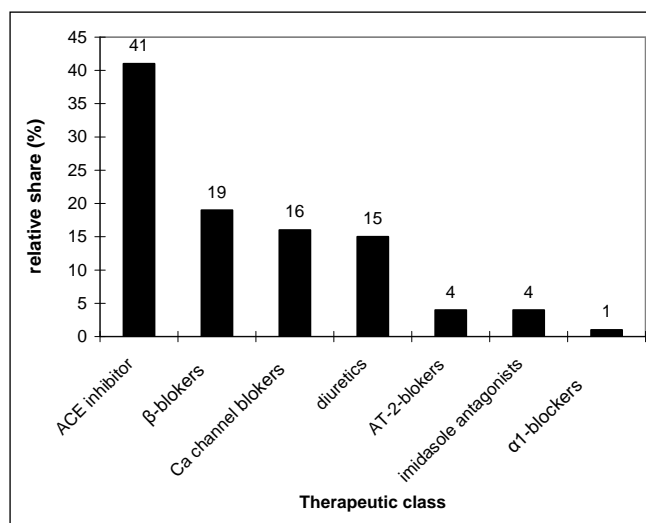

Fig. 2. *The relative share (%) of prescribed medicines for hypertension therapy by therapeutic groups in the selected sample.*

as lisinopril, ramipril and fosinopril accounts for the rest 13%. The second choice in the hypertension therapy is the combination with diuretic. The combinations of enalapril and dehydratin have been observed in the 38% of all prescriptions. ACE inhibitors and Ca channel blockers were prescribed less frequently, mainly as combination of enalapril and nifedipine (28%), and then follows combination of metoprolol and indapamid (12%). Therapy with 3 medicines includes β-blocker or Ca channel blocker prescribed

with ACE inhibitor and diuretic, respectively in 35% and 28% of all prescription. The relatively new therapeutic groups recommended for hypertension therapy as AT 2 blockers and α 1 blockers have been prescribed in a limited number of prescriptions (1%–4%). The prescribed fixed dose combinations among the reimbursable prescriptions have not been found because they are not included in the reimbursement list.

Analysis of prescriptions for the observed hypertension complications has not revealed so strongly leading therapeutic group as first choice therapy (Fig. 3). Vasodilatators (ATC N06BX) were prescribed in 21% of the prescriptions followed by antianginous (ATC C01DA) drugs (18%), β-blockers (ATC C07AA 13%), ACE-inhibitors (ATC C09AA – 10%) etc. Among the prescriptions for heart failure the classical combination of diuretic and cardiac glycosides were preferred in almost 85% of all cases. For sequelae of cerebrovascular disease therapy vasodilators and nootropic agents were the preferred di-therapy, and the addition of anti agregants to them was found to be the classic approach for the three-therapy. The therapy of angina pectoris relies mainly on combination of Ca channel blocker and antianginous agent, or ACE-inhibitor, diuretic and antianginous agent (Fig. 3).

Results of the Calculation of the Weighted Monthly Cost of Hypertension Therapy

The variations in the prescribing habits, as well as the differences in the prices of the prescribed medicines leads to the different structure of the weighed monthly cost of analyzed diagnoses as presented in Table 1.

Hypertension weighted monthly monotherapy cost was near 5 €, ditherapy was near 9 and therapy with 3 medicines was found to be near 13 €. The most expensive to treat are the sequelae of cerebrovascular disease therapy (10 € for monotherapy, 21 for di- and 23 for the three- therapy), followed by angina pectoris, hypertension without complications and heart failure.

It was observed that the reimbursed part of the cost of all diseases account on average for 40% (29%–42%). The reimbursed part increases when the therapy becomes more complicated. Also it was observed that in case of di- and/or "three" therapy there was a tendency for inclusion of lower price products that lead to the overall decrease in the weighted monthly cost of therapy.

Modeling the Cost of Hypertension Therapy from the Patient and Insurance Institution Point of View

After inserting the probability of having prescription for either hypertension or some of the observed complications and their weighed monthly therapy costs the model calculated the expected cost of hypertension alone according to the probability of mono-, di- and three- therapies, as well as the cost of every particular complication according to the complexity of the therapy, and their probabilities. Then the total model expected cost of having hypertension with or without any of the complication was calculated based on the probabilities of their appearance within the prescriptions sample.

For one patient the expected cost of hypertension alone is 6.90 € per month according to the prevalence of the complexity of therapy and weighted monthly cost of prescribed medicines. Considering the complexity of the therapy the monthly model expected cost of angina pectoris is 11.84 €, 13.58 € costs the therapy of sequelae of cerebrovascular disease, and 5.37 € is the cost of heart failure. The expected cost of the second chance node of having complications is 10.71 €

Variety of the co-payment exists in the reimbursement drug list (34) for the medicines prescribed for therapy of hypertension and its complications. Because of that the expected cost of the
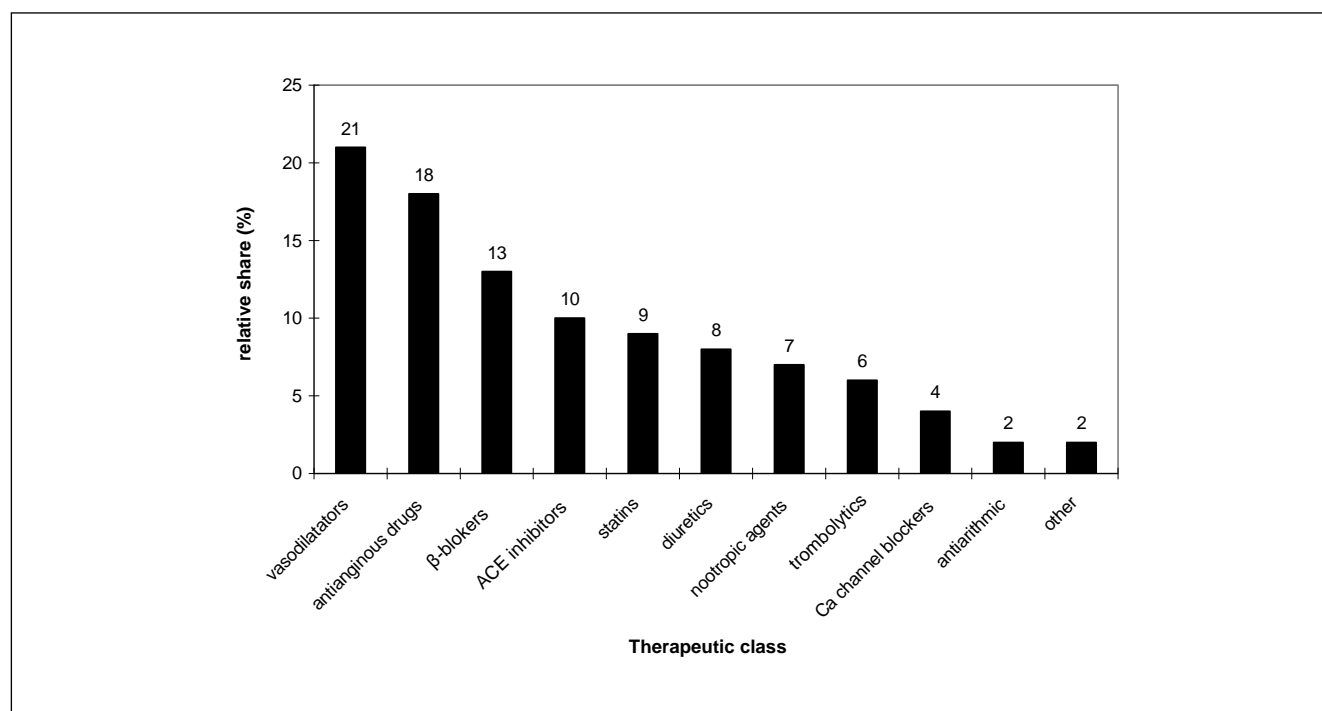

Fig. 3. *The relative share (%) of prescribed medicines for hypertension complications therapy by therapeutic groups in the selected sample.*

reimbursable part of the hypertension cost was calculated separately. The reimbursed part of the hypertension cost alone according to the model is 44% (3.04 €out of 6.90 €). For the observed complications, as well as for the whole second chance node the reimbursed part is 51%. Thus for hypertension and complications the reimbursed part is 47% (3.90 out of 8.23 €).

There are around 1.5 million patients with hypertension in Bulgaria (36). If the prescribing patterns and complexity of the therapy follows the same tendency as described by the model the total cost of hypertension will be 148 million €per year including the complication therapy cost.

Sensitivity Analysis

To match the differences among the medicines prices and the theoretical possibility to have any of the observed complications interval for the sensitivity analysis was established a ±30% around the WMC and probability of complication appearance (Table 2) (35). From the one-way sensitivity analysis it is evident that the changes in the medicines prices that could lead to the increase or decrease in the weighted monthly cost have a greater impact on the total model cost of hypertension and its complications (model cost in a base case is 8.23 and is varying among 10.70 and 5.76 €). By varying only the probability of having or not complication the total model cost did not change significantly (model cost in a base case is 8.23 and is varying among 8.98 and 7.49 €).

DISCUSSION

This is the first ever study that is modeling the hypertension cost for the Bulgarian therapeutic practice which is influenced by the prescribing habits, complexity of the therapy and probability of complications appearance. The model could be used by the financing institutions for further analysis of the influence of hospitalization, or other factors influencing the hypertension cost. The model that was created is based on the prescribing habits probability and possibility of choice of particular medicines in the therapy of hypertension and its common complications.

The model is just an illustration how to present and calculate in a simple way the cost of therapy.

Considering the stated study questions the results from our study could be discussed from different points of view.

In our study the ACE inhibitors prevail in the hypertension therapy and this corresponds with some of the suggestions made by Gerbrandt (37). Because the ACE inhibitors are the relatively homogeneous group in terms of efficacy and time course of action, we consider that their wider usage as first line therapy is mainly due to their lower cost (38). In this study we observed that usage of well established old generics and classic thiazide diuretic prevails. Further analysis should be done on the gap in total treatment cost associated with older versus newer antihypertensive drugs (39).

The higher prevalence of monotherapy, especially for hypertension is partly in contradiction with the therapeutic guidelines but it might be due to diagnosing the earlier stages of disease, or factors connected with the patients' compliance that have not been studied.

The calculation of the weighted monthly cost for the hypertension therapy and its complication shows that there is a tendency towards low priced drug prescribing, as well as generic prescribing whenever such an option exists. This might be explained not only by the generic drug oriented policy but also by preferences of the health insurance institution. The conclusion is partly true for the therapy of the complications. It is noted that the level of reimbursement is very low and the burden of hypertension for the patients is very high but the reimbursement increases when the therapy becomes more complex and expensive and that is a positive finding, regarding the health insurance policy.

Our study shows that the cost of sequelae of cerebrovascular complications was higher, followed by the cost for angina pectoris therapy, probably due to the seriousness of this condition. Investing in their ambulatory therapy might lead to the decrease in the health care resource utilization and hence future hospitalization cost.

The appropriateness of the hypertension therapy should be carefully reviewed by the national health authorities, not only from the point of view of the relevance to the therapeutic guidelines but

Table 2. *Results of the one way sensitivity analysis within ±30% interval around the base case for weight monthly cost or probability of the complexity of therapy*

	AH (%)	Complications (%)	WMC [6] AH	WMC Complications	Final model cost
Base case	65	35	6.90	10.71	8.23
Results of the one way sensitivity analysis					
Varying WMC (+30%); p=constant	650	35	8.97	13.93	10.70
Varying WMC (-30%); p=constant	65	35	4.83	7.50	5.76
WMC=constant; varying p AH[7] (+30%)	85	15	6.90	10.71	7.49
WMC=constant; varying p AH (-30%)	46	54	6.90	10.71	8.98
WMC=constant; varying p complications (+30%)	47	53	6.90	10.71	8.90
WMC=constant; varying p complications (-30%)	75	25	6.90	10.71	7.83

For abbreviations see p. 225.

also from the point of view of sufficient financing at the primary level, because it might have a positive impact on the other health care sectors. There are some expert opinions that near 400,000 hypertonic patients did not received adequate treatment or did not receive treatment at all (40). At the population level, severe hypertension leads to considerable losses in terms of years of life lost, years of work lost, and costs, but the overall impact of mild hypertension is much more limited. That's why the analyses of the ambulatory therapy of hypertension and its complications are important for the health institutions because they provide the arguments for strengthening the control on prescribing practice and changes in the financing.

At last the study provides evidences that the changes in the medicines prices, that are affecting the weighted monthly costs, influenced the hypertension cost to a greater extent than the complexity of the therapy. It could be a result of the high sensitiveness of the population and market towards the prices of the medicines. By trying to estimate the economic burden of hypertension and hypertension-related diseases at ambulatory level we made a first step in providing information for evidence-based cost containment measures or policy decisions at ambulatory level.

Limitations

The study possesses some main limitations. By focusing only on the reimbursable prescriptions we miss the medicines and respectively the patients that are using fixed dose combinations or other medicines that have not been reimbursed during the observed period. This might have an impact on hypertension cost because pharmaceutical companies are having lower prices for the combinations but no information was found on relative share of the prescribed combinations. We also recognize that the observed complications could be due to other reasons than hypertension. To overcome this limitation was determined such a big interval for the sensitivity analysis. It covers the variety of pricing approaches and the price differences among the generic and original products, as well as mono- and combination products.

The second limitation is the usage of the prescriptions as a main source of information. There is a possibility for some patients to use not only one pharmacy and thus we could miss the whole picture for those patients. This is the reason also for the third limitation. We assume that the patients are not changing their therapy for one year and did not change the pharmacies when we calculate at the end the expected yearly cost.

Limits stated by the insurance fund to prescribe only three medicines per patient per ICD code could also affect the overall treatment practice but they are valid for all the cases.

CONCLUSIONS

Hypertension is a costly disease alone or due to its complication for patients and third party payers at the ambulatory level in Bulgaria. The study confirms the results of similar analysis in other countries that the ACE inhibitors have become a first line choice for hypertension therapy mainly due to their lower price in our case as well.

It was found that the level of reimbursement is very low and the burden of hypertension for the patients is very high but the reimbursement increases when the therapy becomes more complex and expensive that is a positive finding, regarding the health insurance policy. The sensitivity analysis reveals that the changes in the prices of medicines affect more the overall ambulatory hypertension cost than the complexity of the therapy and its complications.

Inclusion of the probability of common complications in the calculations of the ambulatory hypertension cost is important for clarifying their impact on the health care expenditures. This study is the first step in providing information for evidence based cost containment measures or policy decisions at ambulatory level in Bulgaria.

Conflict of interest: There is no conflict of interest of the authors.

REFERENCES

1. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. Lancet. 2005 Jan 15-21;365(9455):217-23.
2. Wolf-Maier K, Cooper RS, Banegas JR, Giampaoli S, Hense HW, Joffres M, et al. Hypertension prevalence and blood pressure levels in 6 European countries, Canada, and the United States. JAMA. 2003 May 14;289(18):2363-9.
3. Lloyd A, Schmieder C, Marchant N. Financial and health costs of uncontrolled blood pressure in the United Kingdom. Pharmacoeconomics. 2003;21 Suppl 1:33-41.
4. Hansson L, Lloyd A, Anderson P, Kopp Z. Excess morbidity and cost of failure to achieve targets for blood pressure control in Europe. Blood Press. 2002;11(1):35-45.
5. Thomson R, Greenaway J, Chinn DJ, Wood R, Rodgers H. The impact of implementing national hypertension guidelines on prevalence and workload in primary care: a population-based survey of older people. J Hum Hypertens. 2005 Sep;19(9):683–9.
6. World Health Organization [homepage on the Internet]. Core health indicators [cited 2009 Jun 4]. Available from: http://www.who.int/whosis/database/core/core_select_process.cfm.
7. National Statistic Institute of Bulgaria [homepage on the Internet]. Reasons for death 2007 [cited 2009 Jun 4]. Available from: http://www.nsi.bg/SocialActivities/Health.htm. (In Bulgarian.)
8. Sans S, Kesteloot H, Kromhout D; Task Force of the European Society of Cardiology on Cardiovascular Mortality and Morbidity Statistics in Europe. The burden of cardiovascular diseases mortality in Europe. Eur Heart J. 1997 Aug;18(8):1231-48.
9. Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakangas AM, Pajak A. Myocardial infarction and coronary deaths in the World Health Organization MONICA project: Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. Circulation. 1994 Jul;90(1):583-612.
10. National Health Insurance Fund [homepage on the Internet]. An annual report for the National Health Insurance Fund activities for 2004 [cited 2009 Jun 4]. Available from: http://www.nhif.bg/downloads/Otchet_2004.pdf. (In Bulgarian.)
11. Johannesson M, Le Lorier J. How to assess the economics of hypertension control programmes. J Hum Hypertens. 1996 Feb;10 Suppl 1: S93-4.
12. Marković BB, Kranjcević K, Reiner Z, Blazeković SN, Spehar SS. Drug therapy of cardiovascular risk factors: guidelines versus reality in primary health care service. Croat Med J. 2005 Dec;46(6):984-9.
13. Kwaśniewska M, Bielecki W, Drygas W. Sociodemographic and clinical determinants of quality of life in urban population of Poland. Cent Eur J Public Health. 2004 Jun;12(2):63-8.
14. Panagiotakos DB, Pitsavos Ch, Chrysohoou Ch, Stefanadis Ch, Toutouzas P. The role of traditional mediterranean type of diet and lifestyle, in the development of acute coronary syndromes: preliminary results from CARDIO 2000 study. Cent Eur J Public Health. 2002 Jun;10(1-2):11-5.
15. Kopczyński J, Wojtyniak B, Goryński P, Lewandowski Z. The future of chronic diseases. Cent Eur J Public Health. 2001 Feb;9(1):3-13.

16. Tibi-Levy Y, de Pouvourville G, Westerloppe J, Bamberger M. The cost of treating high blood pressure in general practice in France. Eur J Health Econ. 2008 Aug;9(3):229-36.
17. Marques-Vidal P, Montaye M, Ruidavets JB, Amouyel P, Ferrielres J. Evolution and cost trends of antihypertensive and hypolipidaemic drug treatment in France. Cardiovasc Drugs Ther. 2003 Mar;17(2):175-89.
18. Shiner T, Simons L, Parkinson H, Khanbhai A, Karthikeyan VJ, Nandhara G, et al. The financial cost of optimising blood pressure control. J Hum Hypertens. 2005 Jan;19(1):83-4. Erratum in: J Hum Hypertens. 2005 Oct;19(10):849.
19. Degli Esposti E, Berto P, Ruffo P, Buda S, Degli Esposti L, Sturani A; Pandora Study Group. The PANDORA project: results of the cost of illness analysis. J Hum Hypertens. 2001 May;15(5):329-34.
20. Arredondo A, Zúñiga A. Epidemiologic changes and economic burden of hypertension in Latin America: evidence from Mexico. Am J Hypertens. 2006 Jun;19(6):553-9.
21. Wilson TW, Chockalingam A, Quest DW. Pharmacoeconomics of hypertension control: basic principles of economic evaluation. J Hum Hypertens. 1996 Feb;10 Suppl 2:S19-22.
22. Linjer E, Hedner T, Jönsson B, Ekbom T, Lindholm LH, Dahlöf B, et al; Stop-2 Hypertension Group. Cost analysis of different pharmacological treatment strategies in elderly hypertensives. Blood Press. 2005;14(2):107- 13.
23. Elliott WJ. The economic impact of hypertension. J Clin Hypertens (Greenwich). 2003 May-Jun;5(3 Suppl 2):3-13.
24. Chen K, Chiou CF, Plauschinat CA, Frech F, Harper A, Dubois R. Patient satisfaction with antihypertensive therapy. J Hum Hypertens. 2005 Oct;19(10):793-9.
25. Adigun AQ, Ishola DA, Akintomide AO, Ajayi AA. Shifting trends in the pharmacologic treatment of hypertension in a Nigerian tertiary hospital: a real-world evaluation of the efficacy, safety, rationality and pharmacoeconomics of old and newer antihypertensive drugs. J Hum Hypertens. 2003 Apr;17(4):277-85.
26. Wang YR, Alexander GC, Stafford RS. Outpatient hypertension treatment, treatment intensification, and control in Western Europe and the United States. Arch Intern Med. 2007 Jan 22;167(2):141-7. Erratum in: Arch Intern Med. 2007 Apr 9;167(7):648.
27. Ambrosioni E. Pharmacoeconomics of hypertension management: the place of combination therapy. Pharmacoeconomics. 2001;19(4):337-47.
28. Palmer A, Chambers S. Disease overview - hypertension. Drugs Context. 2006;2(13):561-72.
29. Lindholm LH, Carlberg B, Samuelsson O. Should β blockers remain first choice in the treatment of primary hypertension? A meta-analysis. Lancet. 2005 Oct 29-Nov 4;366(9496):1545-53.
30. Flack JM, Casciano R, Casciano J, Doyle J, Arikian S, Tang S, et al. Cardiovascular disease costs associated with uncontrolled hypertension. Manag Care Interface. 2002 Nov;15(11): 28-36.
31. Hodgson TA, Cai L. Medical care expenditures for hypertension, its complications, and its comorbidities. Med Care. 2001 Jun;39(6):599-615.
32. Mehta SS, Wilcox CS, Schulman KA. Treatment of hypertension in patients with comorbidities: results from the study of hypertensive prescribing practices (SHyPP). Am J Hypertens. 1999 Apr;12(4 Pt 1):333-40.
33. World Health Organization [homepage on the Internet]. International Statistical Classification of Diseases and Related Health Problems. 10th Revision [cited 2007 Jun 11]. Available from: www.who.int/classifications/apps/icd/icd10online/navi.htm..
34. National health insurance fund [homepage on the Internet]. Amendment 2 to "Instruction for usage of drug list of NHIF (Amendment 11 of National Agreement 2006, State Gazette 106/2005) in force from 01 September 2006-work version for-pharmacy [cited 2009 Jun 4]. Available from: http://www.nhif.bg/bg/default.phtml?w=800&h=570. (In Bulgarian.)
35. Elliot R, Payne K. Essentials of economic evaluation in healthcare. 1st ed. London: Pharmaceutical Press; 2005.
36. World Health Organization [homepage on the Internet]. European Health for All database (HFA-DB) [cited 2009 Jun 4]. Available from:http://data.euro.who.int/hfadb/.
37. Gerbrandt KR,Yedinak KC. Formulary management of ACE inhibitors. Pharmacoeconomics. 1996 Dec;10(6):594-613.
38. Nordmann AJ, Krahn M, Logan AG, Naglie G, Detsky AS. The cost effectiveness of ACE inhibitors as first-line antihypertensive therapy. Pharmacoeconomics. 2003;21(8):573-85.
39. Payne KA, Caro JJ. Evaluating the true cost of hypertension management: evidence from actual practice. Expert Rev Pharmacoecon Outcomes Res. 2004 Apr;4(2):179-87.
40. International Healthcare and Health Insurance Institute [homepage on the Internet]. Bulgaria. Review and strategy for National Healthcare. Sofia, September 2004 [cited 2009 Jun 4]. Available from: http://www.zdrave.net/document/services/health_policy/Health%20strategy_05-10_BG.pdf. (In Bulgarian.)