Biotechnology & Biotechnological Equipment

ISSN: 1310-2818 (Print) 1314-3530 (Online) Journal homepage: https://www.tandfonline.com/loi/tbeq20

The Cost-Effectiveness of Hypertension Pharmacotherapy in Serbia: A Markov Model

Dragana Lakić, Guenka Petrova, Nataša Bogavac-Stanojević, Zorana Jelić-Ivanović & Mitja Kos

To cite this article: Dragana Lakić, Guenka Petrova, Nataša Bogavac-Stanojević, Zorana Jelić-Ivanović & Mitja Kos (2012) The Cost-Effectiveness of Hypertension Pharmacotherapy in Serbia: A Markov Model, Biotechnology & Biotechnological Equipment, 26:3, 3066-3072, DOI: 10.5504/BBEQ.2012.0009

To link to this article: https://doi.org/10.5504/BBEQ.2012.0009

ARTICLE
BIOECONOMICS
DOI: 10.5504/BBEQ.2012.0009

THE COST-EFFECTIVENESS OF HYPERTENSION PHARMACOTHERAPY IN SERBIA: A MARKOV MODEL

Dragana Lakić[1], Guenka Petrova[2], Nataša Bogavac-Stanojević[1], Zorana Jelić-Ivanović[1], Mitja Kos[3]
[1]University of Belgrade, Faculty of Pharmacy, Belgrade, Serbia
[2]Medical University – Sofia, Faculty of Pharmacy, Sofia, Bulgaria
[3]University of Ljubljana, Faculty of Pharmacy, Ljubljana, Slovenia
Correspondence to: Dragana Lakić
E-mail: dlakic@pharmacy.bg.ac.rs

ABSTRACT

To date there is no Markov model to evaluate the cost-effectiveness of antihypertensive pharmacotherapies at national level in developing countries. The aim of our study was to evaluate different antihypertensives and determine their cost-effectiveness as monotherapy treatment in primary care in Serbia.

We developed a Markov model to estimate quality-adjusted life years (QALY), lifetime costs and incremental cost-effectiveness of different antihypertensive medicines used in the clinical practice in Serbia (diuretic, beta blocker, Ca channel blocker and ACE inhibitors) to strategy "no intervention". Cohort of 55-year-old patients with hypertension (systolic and diastolic blood pressure ≥140 and 90 mmHg), without cardiovascular complications was run through the model. Acute myocardial infarction, angina pectoris, heart failure, stroke, and total mortality were observed as outcomes. The time horizon was over a lifetime, and the perspective was that of a third-party payer. Annual discount rate of 5% was applied to all future costs and effects.

The results showed small differences in QALY in strategies ACE inhibitor, beta blockers, and diuretic. The incremental cost-effectiveness ratio (ICER) for diuretic, compared to no intervention, was €74.27/QALY. The ICER for beta blocker compared to diuretic was €75.58/QALY. ACE inhibitor was extended dominated by diuretic and beta blocker, while Ca channel blocker had higher costs and less effectiveness compared to all previous strategies. The results of the probabilistic sensitivity analysis showed that application of antihypertensive therapy is cost-effective even at small values of willingness to pay.

It could be concluded that for individuals aged 55 the diuretics are the most cost-effective strategy to start monotherapy of hypertension.

Biotechnol. & Biotechnol. Eq. 2012, **26**(3), 3066-3072

Keywords: hypertension, cost-effectiveness, pharmacotherapy, Markov model, Serbia

Conflict of interest: Authors declare no conflict of interest

Introduction

Hypertension (HT) is an important challenge to public health. According to statistics, in 2000 over one quarter of the adult population worldwide suffered from HT. It has been predicted that by 2025 this proportion will reach nearly 30% (29). HT is one of the major risk factors for ischemic heart disease, cerebrovascular diseases, diseases of peripheral arteries and other cardiovascular disease (CVD) complications. The effectiveness of antihypertensive therapies is well established and documented in terms of risk reduction for stroke and other CVD events (17, 18, 42). The European Society of Hypertension and the European Society of Cardiology stated in their guidelines that all antihypertensive therapies can be considered as first-line choice drugs (34). Accordingly, the costs of antihypertensive pharmacotherapy and CVD complications have become extremely important (6). CVDs can pose a great burden on any healthcare system. In 2003 the cost of CVD in the European Union was almost 105 billion euros, or 12% of the total healthcare expenditure (31).

Economic evaluation in health care is defined as the comparative analysis of alternative options in terms of their costs and consequences (14). Different cost models have been created for evaluation of the cost and cost-effectiveness of hypertension pharmacotherapy. Lloyd et al. (32) created a burden-of-disease model and estimated that in the UK, in general, 16 million adults have blood pressure in the range of 140/90−160/95 mm Hg and above and that 58,000 major cardiovascular events per year occur in these patients. Hansson et al. (22) 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 calculated that 1.26 billion euros could be saved if HT management achieved blood pressure targets. Flack et al. (15) developed a model to estimate the number of cases and costs of myocardial infarction, stroke and congestive heart failure and, in doing so, discovered that inadequate control resulted in 39,702 cardiovascular events and 8,374 deaths thus leading to $964 million of direct medical expenditure.

The Markov decision model, a powerful analytical tool in economic evaluations, allows modelling of patients' preferences and costs over patients' lifetime. Markov models have been constructed for the evaluation of the cost-effectiveness of

different antihypertensive medicines and therapies, an example being angiotensin-converting enzyme (ACE) inhibitors (5).

To date there is no Markov model to evaluate the cost-effectiveness of antihypertensive pharmacotherapies at a national level in developing countries. The purpose of this study was to create a Markov model and to determine the cost-effectiveness of different antihypertensive pharmacotherapies in a primary care setting in Serbia. The point of view of the analysis is that of a third-party payer over a life-time horizon. The study is important from the perspective of financing institutions in order to make the consequences of the current pharmacotherapeutic approaches in countries with scarce resources and limited therapy choice as clear as possible.

Materials and Methods

Model and strategies

The hypothetical cohort of 1000 55-year-old patients with HT (systolic and diastolic blood pressure ≥140 and 90 mmHg, respectively), without CVD complications (angina pectoris (AP), acute myocardial infarction (AMI), heart failure (HF) and/or stroke) or left ventricular hypertrophy, with a cholesterol level of less than 200 mg/dL and a HDL-c level above 60 mg/dL was run through the model from the starting point.

Comparator strategies were antihypertensive therapies used in the clinical practice in Serbia (diuretics, beta blockers, Ca channel antagonists and ACE inhibitors), as either mono- or combination therapy. Combination therapy (di- and tri-therapy) was modeled according to the clinical practice. For example, monotherapy with an ACE inhibitor meant inclusion of a diuretic (di-therapy) and a beta blocker as tri-therapy (1, 27, 34). All therapeutic strategies were compared with the "no intervention" strategy, in other words patients not receiving any therapy.

A Markov model was created which took into account the previously published analyses of the prescribing practice and cost of HT in Serbia (1, 27) as well as analyses of clinical trials of different pharmacotherapies. Previously published pharmacoeconomic studies (41, 52) were adapted in a way to reflect the current clinical practice in Serbia (di-therapy and tri-therapy). A Markov model was constructed using TreeAge Healthcare module version 1.5.2 (TreeAge Software INC., Williamstown, USA). The model consists of 9 defined health states (**Fig. 1**) identical to all strategies except for "no intervention". At the beginning patients were assumed not to have any cardiovascular comorbidity. The arrows show cohort movement through the model. At any point in time a patient can be in only one of the states.

The cycle length that determined the stay of the cohort in a particular stage was defined to last 6 months. During this period the patient could be in only one of the defined states. The 6-month period was chosen under the assumption that it is possible to develop only one complication during that period and that add-in therapy takes place every six months.

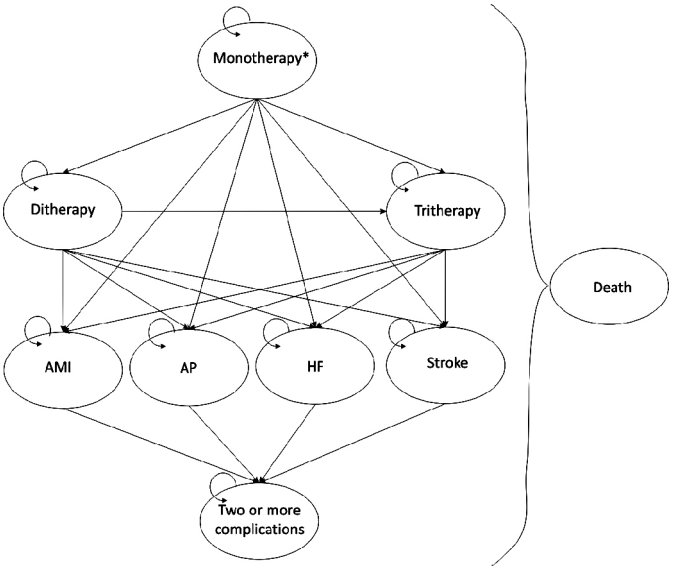

Fig. 1. Bubble diagram for health states in the Markov model. * in the case of "no intervention" there are no mono-, di- or tri- therapies. AMI – acute myocardial infarction; AP – angina pectoris; HF – heart failure.

Complications of HT (AMI, AP, HF or stroke and their combinations) and total mortality were observed as outcomes. Other CVD complications were not included in the model due to inadequate data in the literature.

The time-horizon of the study was the lifetime of the patient or 100 years of age due to the assumption that 99% of the cohort would die at that age.

Probabilities

Patient transition through the model was defined by transition probabilities describing the likelihood of moving within states over each model cycle. All probabilities were calculated from large prospective studies using the formula: $p = 1 - exp\{-rt\}$, where p is the probability, r is the rate and t is the time period of interest (3, 45). The transition probability for cardiovascular events (AMI, AP) and mortality after AMI, AP for "no intervention" was calculated from the Serbian Acute Coronary Syndrome Registry (24) depending on the age of the subject. Due to the unavailability of the probability data for HF and stroke, we assumed the same probability as for AMI. The probability of dying from a non-CVD event was based on Serbian life expectancy tables which depend on age (26). Six-month transition probabilities for the cohort are shown in the Appendix (see the Supplementary Appendix available at www.diagnosisp.com) with the corresponding references (2, 4, 8, 10, 11, 12, 13, 19, 21, 23, 24, 26, 28, 44, 50, 51, 53).

Patient adherence to the therapy was also included in the model. Meta-analysis of the effects of different blood-pressure-lowering drugs showed a very similar discontinuation rate between all antihypertensive drugs. About three-quarters of all patients remained on their assigned treatments at the end of the follow-up (mean 4.9 years) (42). The STOP-Hypertension-2 trial (20) showed that there was no difference in patient adherence to therapy and the non-adherence rate was

37.7%, 37.7%, 33.8% and 38.7% for diuretics, beta blockers, Ca channel antagonists and ACE inhibitors, respectively, for a 60-month follow-up period. We calculated six-month probabilities using the above formula and non-adherence data from STOP-Hypertension-2 trial.

Costs

Only direct medical costs were taken into consideration. Costs of medicines, office visits to physicians, hospitalisations and surgical interventions were expressed in euros (€) using the 2009 average exchange rate to convert the Serbian dinar to the € (€1 = 94.12 RSD). All costs were taken from the Serbian Republic Institute for Health Insurance (RIHI) price list and are summarised in **Table 1**. Given the current legislation, it was assumed that the patient had six visits to a GP and two, to a cardiologist per year.

TABLE 1

Costs used in the model (2009 values)

Comparator	Value (€)
Diuretic (furosemide)	5.57
Beta blocker (metoprolol)	18.13
Ca channel blocker (amlodipine)	19.97
ACE inhibitor (enalapril)	15.10
Statins (simvastatin)	18.78
Ticlopidine	60.22
Clopidogrel	79.58
Warfarin	11.32
Acenocoumarol	7.05
Hospital day (intensive cardiovascular surgery)	56.03
Hospital day (general cardiovascular surgery)	20.88
Rehabilition stroke – 1 day	12.22
Rehabilition acute myocardial infraction/angina pectoris – 1 day	11.16
Visit to general practitioner (every 2 months)	4.90
Visit to cardiologist (once in 6 months)	1.99
Acute miocardial infarction event	3204.23
Angina pectoris event	3196.18
Heart failure event	3575.49
Stroke event	2346.41
Two or more complications	6160.16

For base case analysis the medicine's cost was for the most commonly used medicine from the given therapeutic class in a defined daily dose (for example, enalapril 20 mg daily). Drug utilization data were obtained from the RIHI.

The costs of complications were calculated as the sum of hospitalisation cost, cost of surgical intervention [coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA)], cost of medication administered and costs for rehabilitation.

The average number of hospital days spent in intensive care units were 7.81, 9.06, 9.00 and 10.00 for AP, AMI, HF and strokes, respectively (25). The rehabilitation patients spent on average 2, 3, 3 and 4 weeks per cycle for AP, AMI, HF and strokes, respectively.

The cost of an AMI event includes application of streptokinase (in 13% of patients), heparin (21%), lidocaine (15.4%), amiodarone (9.8%), dopamine (10.4%), CABG intervention (26%), cost of PTCA with drug-eluting stent implantation (74%), complete blood analysis with additional analysis of C-reactive protein, creatine kinase, myoglobin and troponin; echocardiogram, electrocardiogram, coronary angiography with the application of intravenous anesthetic, hospitalisation days (7.81) and an ergometric test one month after the AMI event and rehabilitation for three weeks. AP event costs include cost of CABG intervention (in 26% of patients), cost of PTCA with drug-eluting stent implantation (74%), complete blood analysis with additional analysis, the same as in the case of an AMI event, echocardiogram, electrocardiogram, coronary angiography with the application of intravenous anesthetic, hospitalisation days (9.06) and an ergometric test one month after the AMI event and rehabilitation for two weeks. The costs of HF include cost of CABG intervention (in 18% of patients), cost of PTCA with drug-eluting stent implantation (49%) valve surgery (20%), cost of pacemaker (10%), complete blood analysis with additional analysis of troponin, natriuretic peptide and renal function, echocardiogram, electrocardiogram, chest X-ray, ergometric test, coronary angiography with the application of intravenous anesthetic, 10 hospitalisation days and rehabilitation for three weeks. The costs of stroke include application of fibrinolytic recombinant tissue-type plasminogen activator within 3 hours of the cerebrovascular event at a dose of 0.9 mg per kg of body weight, the use of antipyretics, anxiolytics, anticonvulsants and antibiotics (to prevent urinary infections), neurological examination, brain CT, magnetic resonance imaging of the head, anticoagulant therapy (heparin and its derivatives in the stationary settings), measurement of pro-thrombin time after the introduction of thrombolytic therapy, electroencephalography, transcranial doppler, 10 hospitalisation days and rehabilitation for four weeks.

Utilities

The utility measurement included in the analysis was quality-adjusted life years (QALY). QALY can have a value between 0 and 1, where 0 represents death and 1 represents a health state equal to perfect health. Due to the unavailability of utility values in Serbia, we obtained utility data from the Harvard cost-effectiveness analysis registry database (7). The same database and adequately extracted data from the database have been used by previous cost-effectiveness studies conducted in Canada (52) and the UK (41). During analysis utility loss from the adverse effects of treatment was not taken into account, because most of the published cost-effectivenesss studies assumed minimal loss (0.01 or less) (7, 41). In cases of combined therapy utility was obtained by multiplying monotherapy utilities, for example di-therapy on a diuretic and a beta blocker resulted in a utility value of 0.9492, obtained as the product of the utility value associated with the diuretic

(0.9494) and the utility value associated with the beta blocker (0.9998). The same applies to two or more complications. Utility values used in the model are summarised in **Table 2**.

Cost-effectiveness analysis

Analyses were performed from a third-party payer perspective. The RIHI is the leading health care payer responsible for the health care of almost all the Serbian population (7.5 million inhabitants). An annual discount rate of 5% was applied to all future costs and effects (47).

The results of the analysis are presented as incremental cost-effectiveness ratio (ICER) which represents additional costs per additional effectiveness of each alternative strategy compared to "no intervention" or another strategy. Due to the fact that Serbia does not have an established ICER threshold for acceptance, we used WHO-CHOICE (CHOosing Interventions that are Cost-Effective) methodology. Strategies that have cost effectiveness ratios below three times the GDP per capita are cost-effective, while strategies that have ratios below GDP per capita are highly cost-effective (40). In 2008 the GDP per capita was €4546.5, or US$6647.

The uncertainty of the model was tested through probabilistic sensitivity analysis using Monte-Carlo simulation. Ten thousand simulations were performed. In every simulation, each input parameter (probability, cost and utility) was sampled from the defined distribution of that parameter. The distributions were chosen based on the previously published work by Briggs et al. (3). Due to the fact that the costs are constrained to be positive, we used gamma distribution to represent uncertainty associated with this parameter. For utilities we chose a uniform distribution between the given ranges (**Table 2**). Since probabilities are bounded by 0 and 1 we used Dirichlet distribution to describe probabilities for the given events. Results from the probabilistic sensitivity analysis are reported as cost-effectiveness acceptability curves (33).

TABLE 2

Utility used in the Markov model

Utility for the given state	Value (QALY)	Range (QALY)
No intervention	0.8580	0.7440 – 1.0000
Monotherapy with diuretic	0.9494	0.8484 – 1.0000
Monotherapy with beta blocker	0.9998	0.9998 – 1.0000
Monotherapy with Ca channel blocker	0.8517	0.7385 – 0.9927
Monotherapy with ACE inhibitor	0.9234	0.8480 – 0.9988
Acute myocardial infarction	0.7571	0.6900 – 0.9700
Angina pectoris	0.8567	0.6900 - 0.9700
Heart failure	0.6800	0.3000 – 0.9700
Stroke	0.6070	0.3500 – 0.8550
Two or more complications	0.4750	0.3646 – 0.5609
Death	0	

Results and Discussion

Table 3 shows the lifelong predictions of costs, QALYs and cost-effectiveness. There were small differences in QALYs between ACE inhibitor, beta blocker and diuretic strategies. The marginal effectiveness for the diuretic strategy compared with "no intervention" was 5.10 QALY and that of the beta blocker strategy compared with the diuretic strategy was 0.73 QALY. The ICER for the diuretic strategy compared to "no intervention" was just €74.27/QALY. The ICER for the beta blocker strategy compared to the diuretic strategy was €75.58/QALY. The Ca channel blocker was dominated, meaning that the strategy had higher costs and less effectiveness compared to the other strategies.

ACE inhibitors were excluded from the analysis due to extended (or weak) dominance, meaning that ACE inhibitors were dominated by a linear combination of diuretics and beta blockers.

TABLE 3

Results for base-case analysis (cost and effectiveness are discounted at 5% per year)

Comparator	Cost (€)	Δ Cost (€)	Effectiveness (QALY)	Δ Effectiveness (QALY)	C/E (€/QALY)	ICER (€/QALY)
No intervention	699.0		8.67		80.64	
Diuretic	1078.0	379.0	13.77	5.10	78.28	74.27
ACE inhibitor	1112.6	34.6	13.82	0.05	80.49	679.96
Beta blocker	1136.7	24.1	14.55	0.73	78.13	33.20
Ca channel blocker	1142.9	6.2	12.25	- 2.29	93.26	dominated
Results after the exclusion of dominated options (simple or extended)						
No intervention	699.0		8.67		80.64	
Diuretic	1078.0	379.0	13.77	5.10	78.28	74.27
Beta blocker	1136.7	58.7	14.55	0.78	78.13	75.58

Δ = difference in; QALY= quality adjusted life years; ICER = incremental cost-effectiveness ratio

Strategies that had the best cost effectiveness ratio formed an efficiency frontier. These were "no intervention", diuretics and beta blockers. Dominated strategies (simple or extended) lay on the left of the efficiency frontier. Graphical representation of the efficiency frontier is given in **Fig. 2**.

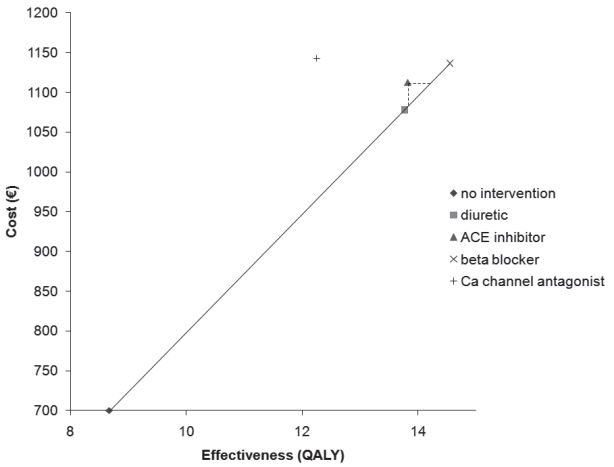

Fig. 2. Efficiency frontier for comparator strategies for treatment of patients with arterial hypertension.

As the Monte Carlo simulation was used, probabilistic sensitivity analysis was performed. Application of antihypertensive therapy was cost-effective even at minimal willingness to pay (less than €200/QALY). Cost-effectiveness acceptability curves in **Fig. 3** show the probability that the antihypertensive strategies were cost effective for different wilingness to pay thresholds for a QALY. The y-axis curve intercepts were above zero, indicating that in a small percentage of cases antihypertensive strategies could even be cost saving (for diuretics, beta blockers, calcium ion channel blockers and ACE inhibitors in 11.34%, 13.33%, 17.93% and 7.23% of the cases, respectively). Three cost-effectiveness acceptability curves (diuretics, beta blockers and ACE inhibitors) had very similar probabilties of being cost-effective.

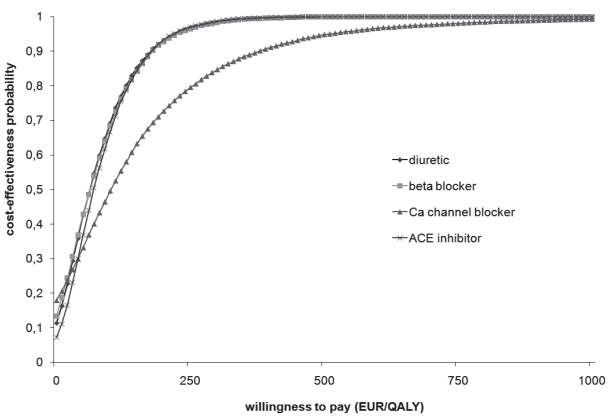

Fig. 3. Cost-effectiveness acceptability curve indicating the probability that the antihypertensive therapy is cost effective compared to "no treatment" at different willingness to pay.

The results of the cost-effectiveness evaluation suggest that antihypertensive treatment has gain in QALY compared to "no intervention". The differences between treatments are small, except in the case of Ca channel blockers, compared to other antihypertensive therapies. The results of our study are in agreement with results from the pharmacoeconomic study conducted in Germany (16) and Spain (35). From the perspective of the national health insurance funds, antihypertensive treatment prolongs patients' life and affects patients' quality of life with relatively modest increase in the health care expenditure compared to "no intervention".

In our study, antihypertensive treatment (regardless of the anatomical therapeutic chemical (ATC) group of medicines) was a highly cost-effective intervention, with the cost-effectivness ratio falling far below the chosen threshold (40). Similar results were demonstrated by Montgomery et al. (39) where the antihypertensive treatment for low-risk men and women aged 50-59 were £1010 and £1917 per QALY, compared to untreated individuals.

We show that the use of diuretics is the most cost-effective strategy to start hypertensive therapy. Pharmacoeconomic evaluations in the UK (41), Canada (52), Spain (35) and Greece (49) showed that the most cost-effective strategy as first-line therapy was thiazide diuretics. In all of the countries diuretics were the least costly strategy; in some cases the cost of diuretics was lower than the "no intervention" strategy (US$ 3163 for diuretic vs. US$ 4189 for "no intervention" for males aged 55 having a 150 mmHg systolic blood pressure) (52). The difference between our study and the abovementioned studies is that we included the sulfonamide diuretic furosemide in our analysis based on the prescribing practice in Serbia (1, 27), while other studies focused on thiazide diuretics. We assumed the same efficacy for all drugs in a given drug class. If the cost of thiazide diuretic was included in the pharmacoeconomic evaluation instead of sulfonamide diuretics, the ICER for diuretics would have been even smaller, as the cost of hidrochlortiazide therapy is lower than that of furosemide therapySerbian recomendations (38) are consistent with those of the European Society of Hypertension and the European Society of Cardiology (34) and recommend usage of all major classes of antihypertensive agents for the initiation and maintenance of antihypertensive treatment either as monotherapy or in combination. On the other hand, JNC-7 guidelines (9) and British Hypertension Society guidelines (54) recommend thiazide-type diuretics as the preferred initial agent. Diuretics are used sparsely in Serbia; in 2009 only 10% of all antihypertensive medications prescribed were diuretics, of which 70% where loop diuretics (1, 27). In Serbia and some neighbouring countries ACE inhibitors are frequently prescribed (1, 27, 36). The results of this cost-effectiveness study suggest that ACE inhibitors are not a cost-effective strategy. They are a less effective and more costly option compared to diuretics. The cost-effectiveness of ACE inhibitors as first-line antihypertensive therapy has been estimated using a Markov model in a Canadian population (43). The results of this study showed that the QALY gain in patients on ACE inhibitors was very small and that ACE

inhibitors had an unfavorable ICER (almost 1 million US$ per QALY) when compared with conventional therapy, beta blockers or diuretics.

According to the Serbian guidelines for arterial hypertension, the Framingham risk score (FRS) and Systematic Coronary Risk Evaluation (SCORE) can both be used to determine absolute CVD risk. The guidelines postulated that the SCORE system was the perfered one. However, in our previous work (30) we examined the accuracy and applicability of the FRS to the Serbian population. The accuracy of FRS in a study of 385 participants was 85.4%. After internal validation of the results in which the jack-knife method was used, the jack-knifed coefficients implied that there was little over-expresion in the estimated predictive accuracy of the FRS model.

All analysed antihypertensive medications are on the RIHI reimbursement list. For the majority of medications the patients only have to pay € 0.53 per prescription. There are only a few drugs that cost more. One is carvedilol (€ 1.60 per dispensed drug).

The cost-effectiveness ratio obtained in our study had a lower value than that found in studies conducted in the more economically developed European countries. This can be explained by the lower costs of antihypertensive medication, labour costs, hospital days and surgical intervention in Serbia than in developed European countries.

Considering the incidence of hypertension in a 55- to 64-year-old patient cohort and the percentage of patients adherent to their therapy (37), it can be expected that there would be 114,000 new hypertensive patients in 2011. If the current trend in antihypertensive drug utilisation is maintained, an increase in RIHI expenditures of about 5% (€ 5.6 milion) in 2011 could be expected.

To our knowledge this is the first Markov model focusing on all available therapeutic approaches for hypertension pharmacotherapy in Serbia. Accordingly it has several limitations.

In the literature there is a lack of studies that directly (head-to-head) compare the effects of antihypertensive therapy. We found a few meta-analyses that examined the health outcomes associated with various antihypertensive treatments (46, 48, 55). However, inadequate data for the numerous probabilities were used in the models. Therefore, the effectiveness of the antihypertensive therapies used in the models is based on indirect comparisons which can cause an error in the assessment of results of antihypertensive drugs. The same method was used in other pharmacoeconomic studies conducted in the UK and Canada (41, 52). Due to the lack of adequate studies, we conducted a sensitivity analysis. It was performed on a cohort of patients aged 55. The obtained results should not be extrapolated to younger or to older patients, since several pharmacoeconomic studies have shown that ICER values (regardless of strategy) are significantly higher in younger patients, and significantly lower in older patients when compared with the patients chosen as subjects in the analyzed cohort (16, 35, 39, 41).

The Markov model in our study included only major HT CVD complications including AMI, AP, HF and stroke. It did not include other HT complications such as diabetes or renal failure. On the basis of these differences the model can be explained by differences in the results of the analysis in relation to NICE's (National Institute of Clinical Excellence) model (41).

Conclusions

Based on the results of cost-effectiveness we concluded that all types of antihypertensive medicines increased the life expectancy of patients with HT. The highest gain was seen in patients receiving diuretics. For individuals aged 55 diuretics are the most cost-effective strategy to start hypertensive monotherapy in Serbia, which is in accordance with the available medicines and their market prices. Despite local guidelines recommending all antihypertensive agents as first-line therapy, prescribing solely diuretics would be more cost-effective.

Acknowledgements

The work was supported by the Ministry of Science and Environmental Protection of the Republic of Serbia (project No. 175035). The funding agreement ensured the authors independence in designing the study, interpreting the data, writing, and publishing the report. The authors are grateful to Dr. David R. Jones for help in editing the manuscript.

REFERENCES

1. **Andrić V., Lakić D., Petrova G.** (2009) Arh. Farm., **59**, 13-26.
2. **Black H.R., Elliott W.J., Grandits G., et al.** (2003) JAMA, **289**(16), 2073-2082.
3. **Briggs A., Claxton K., Sculpher M.** (2006) Decision modeling for economic evaluation, Oxford University Press, New York, pp. 51-120.
4. **Brown M.J., Palmer C.R., Castaigne A., et al.** (2000) Lancet, **356**(9227), 366-372.
5. **Campbell H.M., Boardman K.D., Dodd M.A., Raisch D.W.** (2007) Ann. Pharmacother., **41**, 1101-1110.
6. **Carroll C.A., Coen M.M., Piepho R.W.** (2003) Ann. Pharmacother., **37**, 327-331.
7. **CEA Registry**, https://research.tufts-nemc.org/cear/Default.aspx (Accessed: 16.02.2011)
8. **Cheung C.M., Tsoi T.H., Hon S.F.K., et al.** (2007) Hong Kong Med. J., **13**(2), 95-99.
9. **Chobanian A.V., Bakris G.L., Black H.R., et al.** (2003) JAMA., **289**, 2560-2572.
10. **Cohn J., Johnson G., Ziesche S., et al.** (1991) N. Engl. J. Med., **395**(5), 303-310.
11. **D'Agostino R.B., Russell M.W., Huse D.M., et al.** (2000) Am. Heart J., **139**(2), 272-281.

12. **Dahlof B., Devereux R.B., Kjeldsen S.E., et al.** (2002) Lancet, **359**(9311), 995-1003.
13. **Dahlof B., Sever P.S., Poulter N.R., et al.** (2005) Lancet, **366**(9489), 895-906.
14. **Drummond M.F., Sculpher M.J., Torrance G.W., et al.** (2005) Methods for the Economic Evaluation of Health Care Programmes, 3rd Ed, Oxford University Press, New York, p. 9.
15. **Flack J.M., Casciano R., Casciano J., et al.** (2002) Manag. Care. Interface., **15**, 28-36.
16. **Gandjour A, Stock S.** (2007) Health Policy, **83**, 257-267.
17. **Gueyffier F., Boissel J.P., Boutitie F., et al.** (1997) Stroke, **28**, 2557-2562.
18. **Gueyffier F., Boutitie F., Boissel J.P., Pocock S., Coope J., Cutler J., et al.** (1997) Ann. Intern. Med., **126**, 761-777.
19. **Hansson L., Hedner T., Lund-Johansen P., et al.** (2000) Lancet, **356**(9227), 359-365.
20. **Hansson L., Lindholm L.H., Ekborn T., Dahlöf B., Lanke J., Scherstén B., et al.** (1999) Lancet, **354**, 1751-1756.
21. **Hansson L., Lindholm L.H., Niskannen L., et al.** (1999) Lancet, **353**(9153), 611-616.
22. **Hansson L., Lloyd A., Anderson P., et al.** (2002) Blood. Press., **11**, 35-45.
23. **Hjalmarson A., Goldstein S., Fagerberg B., et al.** (2000) JAMA, **283**(10), 1295-302.
24. **Institute of Public Health of Serbia** (2009) Incidence and mortality of acute coronary syndrome in Serbia 2008, Belgrade, Serbia.
25. **Institute of Public Health of Serbia.** Monitoring of the quality of health care - selected indicators in Serbia 2005-2009, http://www.batut.org.rs/index.php?content=61 (Accessed: 28.09.2010) (In Serbian)
26. **Institute of Statistics of Republic of Serbia.** Detailed mortality tables, http://webrzs.stat.gov.rs/axd/stanovnistvo/izbor.htm (Accessed: 28.09.2010) (In Serbian)
27. **Ivannova A., Lakić D., Andrić V., et al.** (2009) Pharm. Pract., **7**, 108-112.
28. **Julius S., Kjeldsen S.E., Weber M., et al.** (2004) Lancet, **363**(9426), 2022-2031.
29. **Kaerney P.M., Whelton M., Reynolds K., et al.** (2005) Lancet, **365**, 217-223.
30. **Lakic D., Bogavac-Stanojevic N., Jelic-Ivanovic Z., et al.** (2010) Value. Health., **13**, 770-777.
31. **Leal J., Luengo-Fernandez R., Gray A., et al.** (2006) Eur. Heart. J., **27**, 1610-1619.
32. **Lloyd A., Schmieder C., Marchant N.** (2003) Pharmacoeconomics, **21**(Suppl. 1), 33-41.
33. **Lothgren M., Zethraeus N.** (2000) Health. Econ., **9**, 623-630.
34. **Mancia G., De Backer G., Dominiczak A., et al.** (2007) J. Hypertens., **25**, 1105-1187.
35. **Mar J., Rodriguez-Artalejo F.** (2001) J. Hypertens., **19**, 149-155.
36. **Marković B.B., Kranjčević K., Stojanović-Špehar S., et al.** (2009) Coll. Antropol., **33**, 71-76.
37. **Ministry of Health of Republic of Serbia** (2006) Health survey of the Republic of Serbia 2006, Final Report, http://www.zdravlje.gov.rs/showpage.php?id=142 (Accessed: 10.07.2010) (In Serbian)
38. **Ministry of Health of Republic of Serbia** (2011) Arterial hypertension – guidelines, http://www.zdravlje.gov.rs/showpage.php?id=145 (Accessed: 12.05.2011) (In Serbian)
39. **Montgomery A.A., Fahey T., Ben-Shlomo Y., et al.** (2003) J. Hypertens., **21**, 1753-1759.
40. **Murray C.J.L., Lauer J.A., Hutubessy R.C.W., et al.** (2003) Lancet, **361**, 717-725.
41. **National Collaborating Centre for Chronic Conditions** (2006) Hypertension: Management in Adults in Primary Care: Pharmacological Update, Royal College of Physicians, London.
42. **Neal B., MacMahon S., Chapman N.** (2000) Lancet, **356**, 1955-1964.
43. **Nordmann A.J., Krahn M., Logan A.G., et al.** (2003) Pharmacoeconomics, **21**, 573-585.
44. **Pepine C.J., Handberg E.M., Cooper-DeHoff R.M., et al.** (2003) JAMA, **290**(21), 2805-2816.
45. **Petiti D.** (2000) Meta-Analysis, Decision Analysis and Cost-Effectiveness Analysis, 2nd Ed., Oxford University Press, New York, p. 145-155.
46. **Psaty B.M., Lumley T., Furberg C.D., et al.** (2003) JAMA, **289**, 2534-2544.
47. **Shaffer P.A., Haddix A.C.** (1996) In: Prevention Effectiveness: A Guide to Decision Analysis and Economic Evaluation (A.C. Haddix, S.M. Teutsch, P.A. Shaffer, D.O. Dunet, Eds.), Oxford University Press, New York, 76-84.
48. **Staessen J.A., Wang J.G., Thijs L.** (2003) J. Hypertens., **21**, 1055-1076.
49. **Stafilas P.C., Serafidid P.A., Lasaridis A.N., et al.** (2005) Am. J. Hypertens., **18**, 1233-1240.
50. **The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group** (2002) JAMA, **288**(23), 2981-2997.
51. **The SOLVD investigators** (1991) N. Engl. J. Med., **395**(5), 293-302.
52. **Tran K., Ho C., Noorani H.Z., et al.** (2007) Thiazide diuretics as first-line treatment for hypertension: meta-analysis and economic evaluation [Technology report number 95], Canadian Agency for Drugs and Technologies in Health, Ottawa.
53. **Weber M.A., Bakris G.L., Jamerson K., et al.** (2010) J. Am. Coll. Cardiol., **56**(1), 77-85.
54. **Williams B., Poulter N.R., Brown M.J., et al.** (2004) J. Hum. Hypertens., **18**, 139-185.
55. **Wright J.M., Musini V.M.** (2009) Cochrane Database of Systematic Reviews, **3**, Art. No.: CD001841.DOI: 10.1002/14651858.CD001841.pub2.