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IMPACT OF DISCOUNTING IN PHARMACOECONOMIC MODELING. A CASE STUDY

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ABSTRACT

Discounting adjusts future costs and benefits in terms of their present value. The purpose of this study was to present the effect of discounting on Markov model prepared for the evaluation of the different antihypertensive treatments in Serbia.

The Markov model consisting of eight states with the cycle length of six months was constructed. Comparator strategies were diuretic, beta blocker, calcium channel blocker and ACE inhibitors. All therapeutic strategies were compared with strategy "no intervention". Complications of hypertension (acute myocardial infraction, angina pectoris or stroke alone or in combinations) and total mortality were observed as outcomes. Time horizon of the study was lifetime of the patient or 100 years old, due to assumption that 99% of the cohort would die at that age. Analyses were performed from the third-party payer perspective. Annual discount rate of 5% was applied at all future costs and effects.

Undiscounted results showed that patients who started treatment with a beta blocker had the highest life expectancy (49.00 QALY) and being the most cost-effective strategy (ICER = €46.63/QALY compared to no intervention). In the case of discounting the highest gain in the QALY had patients who were on beta blocker, 23.7 QALY. After the discounting cost-effective strategies were ACE inhibitor (ICER = €253.08/QALY compared to no intervention) and diuretic (ICER = €262.54/QALY compared to no intervention).

The results of the study showed that the discounting could change the choice of cost-effective therapeutic strategy.

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Keywords: Markov model, discounting, antihypertensive medication

Introduction

Cost-effectiveness has become "the fourth hurdle" presented in front of the medicines in order to bring them to the market (10). Modeling is considered as vital part of the pharmacoeconomic studies. The model represents a simplified picture of reality, and is used when it is not possible to conduct economic evaluations parallel with the clinical study or is not possible to obtain long term data for the expected clinical results. The clinical trials for obtaining marketing authorization are focused on medicines safety and efficacy, and are not created with the intention of collecting data on costs, as well as on effectiveness. Most clinical studies has a limited number of comparative strategies (usually two, rarely more) and short follow-up (3). When costs or benefits of treatment occur over a long period of time, it is necessary to take into account the time preference for money and benefits. Discounting adjusts future costs and expresses all costs and monetary benefits in terms of their present value (8).

The purpose of this study was to present the effect of discounting on pharmacoeconomic model prepared for the cost-effectiveness evaluation of the different antihypertensive treatments in the prevention of cardiovascular disease (CVD) complications in primary care in Serbia. The study question was: what is the impact of discounting on the choice of cost-effective therapeutic strategy?

Materials and Methods

Model and strategies

The therapy of the hypothetical cohort of 55 years old patients with hypertension (systolic and diastolic blood pressure ≥140 and 90 mmHg, respectively), without other CVD complications or risk factors was modeled. Comparator strategies were antihypertensive groups of medicines present in clinical practice (diuretic, beta blocker, calcium channel antagonist and ACE inhibitors). All therapeutic strategies were compared with strategy "no intervention", to cover the patients who for any reason are not compliant with their therapy. Combined therapy was modeled according to clinical practice (11), e.g. monotherapy with ACE inhibitor meant inclusion of diuretic (di-therapy) and beta blocker as tri-therapy.

A Markov model was constructed using the TreeAge Healthcare module version 1.5.2 (TreeAge Software, INC., Williamstown, Massachusetts, USA). The model consists of 8 defined health states (**Fig. 1**) identical in structure to all strategies except for no intervention (due to no adherence to therapy, there are no mono-, di- or tri-therapy states). At the start patients are assumed not to have any cardiovascular co-morbidity. 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 was defined to last 6 months and during this period a patient can be in only one of the defined states. The half-year length was chosen under the assumption that it is possible to have only one complication during that period, and that add-in therapy takes place every six months.

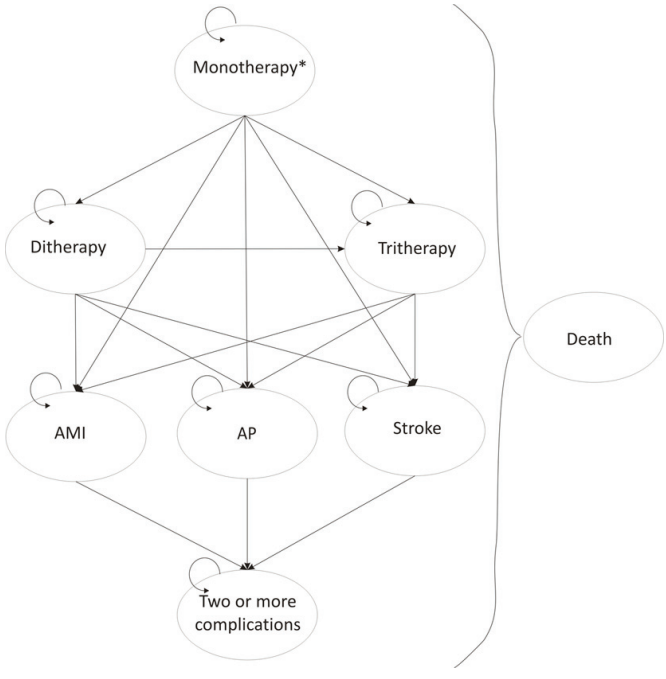

Fig. 1. Bubble diagram for health states in Markov model. * in case of no intervention there are no mono-, di- or tri-therapy. AH – arterial hypertension; AMI – acute miocardial infraction; AP – angina pectoris.

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

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

Probabilities

The transition of the patients through the model was defined by transition probabilities, describing the likelihood of moving within states over each model cycle. All probabilities were calculated from the 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 (1, 8).

Costs

Costs of medications, office visits to physicians, hospitalizations and surgical interventions were expressed in Euro (€) using the average exchange rate during 2009 to convert Serbian dinar to € (€1 = 94.12 RSD) (4). All costs were taken from the Republic Institute for Health Insurance (RIHI) price list and are summarized in **Table 1**. According to current legislation it is assumed that a patient has six visits to a GP and two, to a cardiologist per year. For base case analysis the medicines cost was for the most commonly used medicines from the given therapeutic class in the defined daily dose (e.g. enalapril 20 mg daily). Drug utilization data were obtained from the RIHI. The costs for complications were calculated as a sum of hospitalization cost, cost of surgical intervention (CABG or PTCA) and costs for rehabilitation. Average numbers of hospital days spent at intensive care unit were 7.81, 9.06 and 10.00 (6), while at rehabilitation the patients averagely spent 3, 2 and 4 weeks per cycle for AMI, AP and stroke, respectively (expert opinion).

TABLE 1

Costs and utilities used in the model. All costs are presented in euro in 2009 values

Variable	**Value**
Cost per 6-month cycles	***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 miocardial infraction/angina pectoris – 1 day	11.16
visit to general practictioner (every 2 months)	4.90
visit to cardiologist (once in 6 months)	1.99
acute miocardial infraction event	3204.23
angina pectoris event	3196.18
stroke event	2346.41
two or more complications	5831.21
Utility for the given state	***Value (QALY)***
no intervention	0.8580
monotherapy with diuretic	0.9494
monotherapy with beta blocker	0.9998
monotherapy with Ca channel blocker	0.8517
monotherapy with ACE inhibitor	0.9234
acute miocardial infraction	0.7571
angina pectoris	0.8567
stroke	0.6070
two or more complications	0.4750
death	0

Utilities

Utility measure included in the analysis was quality-adjusted life years (QALY). QALY can have values between 0 and 1,

TABLE 2

Results for undiscounted costs and effects

Comparator	cost (€)	Δ cost (€)	effectiveness (QALY)	Δ effectiveness (QALY)	C/E (€/QALY)	ICER (€/QALY)
No intervention	867.7		16.42		52.85	
ACE inhibitor	2284.2	1416.5	45.98	29.56	49.68	47.92
Diuretic	2315.1	30.9	42.94	- 3.04	53.91	dominated
Ca channel blocker	2372.0	87.8	39.95	- 6.03	59.37	dominated
Beta blocker	2386.8	102.6	49.00	3.02	48.72	33.97

TABLE 3

Results for discounted costs and effects (discount rate: 5% per year)

Comparator	cost (€)	Δ cost (€)	effectiveness (QALY)	Δ effectiveness (QALY)	C/E (€/QALY)	ICER (€/QALY)
No intervention	484.7		11.67		41.53	
ACE inhibitor	1000.6	515.8	13.71	2.03	72.98	253.08
Diuretic	1033.4	32.8	13.76	0.05	75.13	680.66
Beta blocker	1076.9	76.3	13.51	- 0.25	79.68	dominated
Ca channel blocker	1092.1	15.3	11.25	- 2.51	97.10	dominated

where 0 represents death and 1 represents health state equal to perfect health. Due to unavailable utility values for Serbia, we obtained utility data from the Harvard cost-effectiveness analysis registry database (2). In cases of combined therapy or two or more complications utility was obtained by multiplying individual utilities. Utility values used in the model are summarized in **Table 1**.

Cost-effectiveness analysis

Analyses were performed from the third-party payer perspective, RIHI, the leading health care payer, responsible for health care of almost the entire Serbian population (7.5 million). Annual discount rate of 5% was applied at all future costs and effects (5).

Results and Discussion

The results from the undiscounted cost-effectiveness analysis are given in **Table 2**. The gain in QALY in strategies that include a medicine was significantly higher than in the strategy of "no intervention". Patients who started treatment with beta blocker had the highest life expectancy measured in 49 QALY, in the case of undiscounted results. After the incremental cost-effectiveness analysis, strategies, diuretic and Ca channel blocker were dominated, meaning that they had a negative gain in QALY compared to the previous strategy (higher costs and lower effectiveness of the strategy). Strategy ACE inhibitor was extended dominated, meaning that the next strategy, beta blocker, was more effective (higher gain in QALY) with the lower ICER value compared to ACE inhibitor.

The results from the pharmacoeconomic evaluation after the discounting of the costs and effects (the 5% per annum for both costs and effects) were different compared to the undiscounted results. In the case of discounting the highest gain in the QALY had patients who were on beta blocker, 23.7 QALY. The results of the cost-effectiveness analysis for the discounted costs and effects are given in **Table 3**.

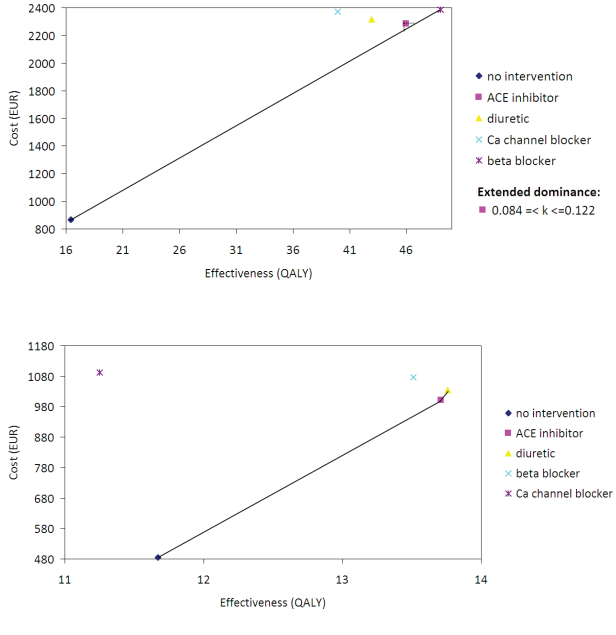

Fig. 2. Efficiency frontier for comparator strategies for treatment of patients with arterial hypertension: **A)** undiscounted results; **B)** discounted results (5%/year).

Graphical reperesentation of the undiscounted and discounted results is given in **Fig. 2**. The difference in results was seen on the efficiency frontier, which represents the

optimal strategies for treatment of hypertension. The slope of the frontier is the ICER value for the given strategy. In the case of the undiscounted results the efficiency frontier consisted of only two strategies: no intervention and beta blocker (**Fig. 2a**). The efficiency frontier for discounted results (**Fig. 2b**) consisted of three strategies: no intervention, ACE inhibitor and beta blocker.

The results of this study showed great differences in the base-case analysis in the cost-effectiveness study, after discounting was employed. As shown in **Table 2** and **Table 3**, discounting increased the cost/QALY ratio in all strategies that employed antihypertensive therapy (on average by 50%). It has been observed in earlier works that higher discount rates increased cost/QALYs regardless of the intervention considered. Lundkvist and collegues showed that cost/QALY as a result of cost-effectiveness analysis in prevention of nonfatal stroke, was almost doubled after the discount rate changed from 0% to 5%, €8867/QALY vs. €16063/QALY, respectively (7).

Interestigly, the ranking of the strategies was changed after the discounting. In case of undiscounted results, only beta blocker was a cost-effective antihypertensive startegy (ICER value of €46.62/QALY), while in discounted results beta blocker was dominated by diuretic and ACE inhibitor. On the other hand, diuretic was a dominated strategy when the discount rate was 0%, but when the discount rate changed to 5% it had an ICER value of €680.66/QALY. This can be explanied by the fact that discounting dampens the relative importance of costs and benefits occurring in future. As discount rates rise, future benefits and costs become less and less important when compared with benefits and costs occurring at present. The effects of discounting are more pronounced for strategies where benefits (and/or cost offsets) occur later (9).

Conclusions

This study showed that discounting could change the choice of cost-effective therapeutic strategy and change the order in ranking of the antihypertensive strategies in the prevention of CVD complications.

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