SIMULATION ANALYSIS OF TERAPEUTIC OUTCOMES REGARDING CHRONIC HEART FAILURE WHEN USING BETA BLOCKERS

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Abstract

Cardiovascular (CV) diseases have become the most important cause for mortality in developed countries. This indicates that they also significantly influence the quality of life and represent an important social and economic burden. As national registers for such diseases are not available in all countries and/or for all CV diseases and because of the fact that statistical data are for small populations not very reliable in the paper three phase modelling structure is suggested with which different important aspects of hypertension and chronic heart failure (CHF) can be evaluated on the basis of combination of data from different sources. Mentioned structure enables the observation of hypertension and CHF prevalence (simulation results of the first and second phase), while in combination with demographic data also quantitative prediction of observed patients is possible. In the third phase information of treatment expenses and population data in Slovenia was added. In this way social and economic burden was estimated in the form of expected patients' number regarding their age and year treatment expenses. In addition also treatment efficacy of drugs with beta blockers is evaluated. The simulation results show that observed drugs are justified also from economical point of view. Finally the extrapolation of results to the countries with similar social and demographic situation is suggested.

Keywords: Hypertension, Congestive Heart Failure, Beta-blockers, Economic Burden.

Presenting Author's biography

Maja Atanasijević-Kunc. She received B.Sc., M.Sc. and Ph.D. degrees from the Faculty of Electrical Engineering, University of Ljubljana, Slovenia where she is currently associated professor. Her research interests include modelling and simulation of dynamical systems and control systems analysis and design, especially of MIMO-systems.

1 Introduction

Cardiovascular (CV) diseases (e.g. hypertension, heart diseases, chronic heart failure) were not very frequent illness a century ago. At the beginning of the 20th century CV diseases were the cause of mortality in less than 10% of deaths. Over the century the number increased to over 50% looking from worldwide perspective [1].

Regarding recent findings it can be expected that several important factors will contribute to a further increase of CV diseases. In developed countries people live longer and population is getting older. The second reason is very fast increase of obesity and diabetes which are conditions that usually lead to hypertension and other cardiovascular diseases. Due to longer working time it is important to take into account also stress and a lack of physical activities. Very significant risk is also smoking, especially in younger population [2-4].

Hypertension (high blood pressure) is one of the most important reasons for an adult to visit a doctor [5]. It can lead to different complications. Lowering the blood pressure with antihypertensive treatment was proven through several trials to reduce the risk for the development of cardiovascular diseases and to decrease the number of complications.

Chronic heart failure is the end stage of cardiac disease being a consequence of hypertension and heart disease. The heart is not able any more to deliver blood in enough quantities to organs and tissues. Patients with chronic heart failure have symptoms like breathlessness, fatigue and fluid retention (peripheral oedema) as a direct consequence. This condition not only significantly affects quality of life of those patients, but is connected also with high mortality (one patient out of five die in one year) and frequent hospitalizations (around one third of patients is hospitalized in a period of one year after the first hospitalization) [6].

Beta-adrenergic receptor blockers (beta blockers - BB) were introduced to market in 1950s. In the following decades their usage was extended to the treatment of variety diseases, mainly cardiovascular. Notable number of clinical trials confirmed their role in the treatment of hypertension, myocardial infarction, angina pectoris, chronic heart failure. The clinical trials confirmed that beta blockers are reducing mortality and the risk for new cardiovascular events (e.g. myocardial infarction, stroke, …). They also became a drug of choice for treatment of hypertension [7-10].

In patients with chronic heart failure beta-blockers are part of the standard therapy together with other groups of medicines for reduction of hospitalizations due to worsening of heart failure and for reduction of mortality.

It is interesting that although beta blockers are present in the treatment of different cardiovascular diseases for decades, the actual use in clinical practice vary from country to country and from one disease to another. Comparison of the use of beta blockers in the treatment of chronic heart failure among different European countries have shown that only 25% to up to 78% of patients were treated with beta blockers [11, 12].

In the paper we have tried to evaluate therapeutic outcomes regarding heart failure when using beta blockers. The corresponding mathematical model was developed with which it is possible to predict the number of patients with hypertension, chronic heart failure and their combinations, as well as to estimate economical burden and optimal treatment outcomes which can not be neglected taking into account the increase of CV diseases. The simulation results are calculated for Slovenia and extrapolation is also suggested for the countries with similar demographic and social situation. Resembling results can be expected in practically all EU countries.

The paper is organized in the following manner. In the next section the structure of developed mathematical model is presented. Then simulation results are illustrated which can, in combination with estimated treatment expenses, give the evaluation of overall social and economical burden of observed patients. The paper ends with concluding remarks and some ideas for future work.

2 Modelling structure

As already mentioned, the aim of presented study was to fulfill several goals. It should enable the estimation of patients number with hypertension and their connection with the patients who experienced different health complications. The influence to chronic heart failure in observed population is presented in the third section. In some countries registers for such diseases are available, but in many areas they do not exist, or their statistical value is, due to small number of observed patients, very low.

As these diseases are strongly correlated with patient's age, also this time dimension – namely patients' age, not only time, should be taken into account.

Modelling results should, in addition, enable also the evaluation of social and economic burden of observed diseases, what is important for governments, insurance companies, hospitals and also for each individual regarding educational aspects with which serious health complications can be prevented.

To meet all mentioned goals mathematical model was developed as presented in Fig. 1.

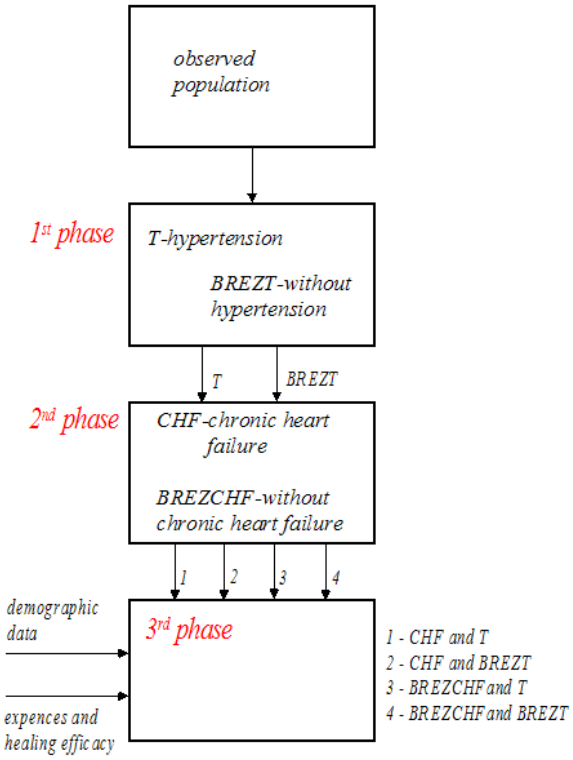

Fig.1 Proposed model structure

It consists of three main design phases. In the frame of the first phase dynamical structure is described with two output signals representing percentage distribution (prevalence) of the patients with hypertension (T) and those who are healthy regarding this disease (BREZT). Hypertension is defined as blood pressure higher than 140/90 mm Hg or taking antihypertensive medications [13]. Input signal is unity step indicating the beginning of problem observation, namely at the birth. Observation time is 95 years regarding patients' age.

Modelling has started with observation of statistical data as illustrated in Table 1 [14]. For simplification reasons the average regarding both sexes was taken into account.

High-order (11th order) nonlinear dynamical structure with different time constants containing also delay time was identified. Such disease is namely very rare in the youth (before the age of 20).

In the second phase the model was extended with the dynamic structure describing the development of chronic heart failure [15] (Table 2). Dynamic properties depend also on the group from which the patients are coming from (Fig. 1).

In the USA research has shown [16] that hypertension is in 10% of cases the reason for heart failure. In Italy this number is increased to 15.8% [17]. The efficacy of several dynamic structures was evaluated, but the final decision was made regarding also good matching with the number of patients in different countries of European Union [11, 18]. The result is dynamic structure of the 13th order with time delays.

Table 1: Prevalence of hypertension

age [years]	men [%]	women [%]	average [%]
20-34	11.1	5.8	8.45
35-44	21.3	18.1	19.7
45-54	34.1	34.0	34.05
55-64	46.6	55.5	51.05
65-74	60.9	74.0	67.45
75 and more	69.2	83.4	76.3

Table 2: Prevalence of chronic heart failure

age [years]	men [%]	women [%]	average [%]
45-54	0,3	0,2	0.25
55-64	1,4	0,9	1.15
65-74	4,5	3,6	4.05
75-84	10,9	9,9	10.4

In the third modelling phase the information was added regarding demographic data in Slovenia [19]. In Fig. 2 population of Slovenia is illustrated in 2003. Combination of prevalence with population number gives the number of patients regarding their age as illustrated in the next section.

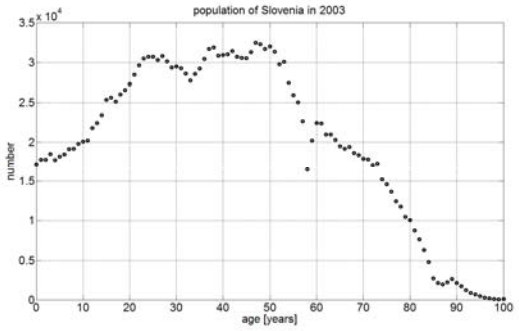

Fig.2 Number of people in Slovenia

Obtained results were, in this last phase, combined also with the estimated expenses connected with

treatment of observed patients, namely needed drugs, hospitalization and mortality. In this way year economical burden was presented regarding observed diseases. Developed structure enabled also the evaluation of antihypertensive effects regarding the decrease of observed cardiovascular complications, which is illustrated through simulation results in the next session.

As similar results as in Slovenia can be expected in the countries with resembling social, demographic and economic situations (most of EU countries) [20], also extrapolation of the results is suggested, which can be applied in such situations.

Simulation was realized using Matlab with Simulink [21, 22].

3 Simulation results

As already mentioned, in the first modelling phase the development of hypertension, regarding patients' age has been defined. Simulation result (percentage patients' distribution) is illustrated in Fig. 3, where it is also indicated that good matching was achieved for the average distribution in different age intervals.

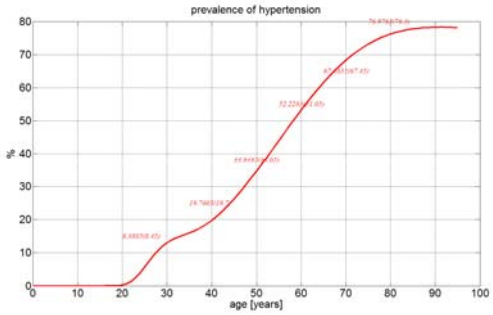

Fig.3 Prevalence of hypertension

In the third phase this result was combined with the population counting in Slovenia in 2003 (Fig. 2). So the number of patients with hypertension, regarding their age was estimated (Fig. 4).

It came out that in Slovenia live over 526 000 people with high blood pressure and this represents 26.4% of the whole population.

It is important to point out that sometimes confusing description regarding percentage prevalence of this chronic disease is given. Such misleading information can arise from the fact that the time window, for which calculation is realized, is not very clearly defined. In Fig. 5 it is possible to observe how the start time of observation influence a percentage distribution of patients with hypertension, which can for the same population vary from 26.4% to over 78% if only older population is taken into account.

For evaluation purposes hypertension prevalence was combined also with demographic data of Germany and Great Britain and for all three countries also the number of patients is in good matching with statistical data [18, 23, 24].

In the second design phase serious health complications were observed. In Fig. 6 prevalence distribution of the patients with chronic heart failure is presented. Here it is also possible to differ those, who suffer from CHF and hypertension.

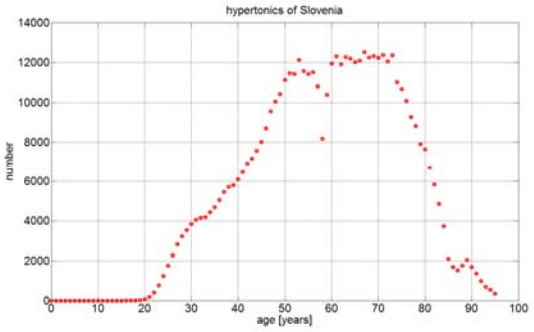

Fig.4 Number of patients with hypertension

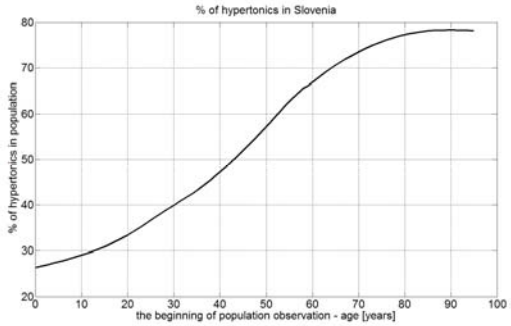

Fig.5 Percentage of hypertonics regarding the start-time observation

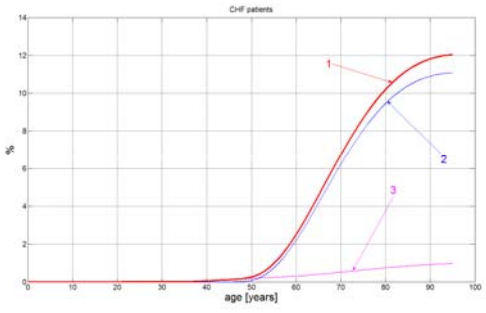

Fig.6 Prevalence of chronic heart failure (1-all CHF patients, 2-patients without hypertension and with CHF, 3-patients with hypertension and CHF)

Again prevalence was in the third phase combined with population number (Fig. 2) and patients' number regarding their age was calculated as presented in Fig.

7. In Slovenia there are over 29800 CHF patients, or 1.5% of population experience CHF each year.

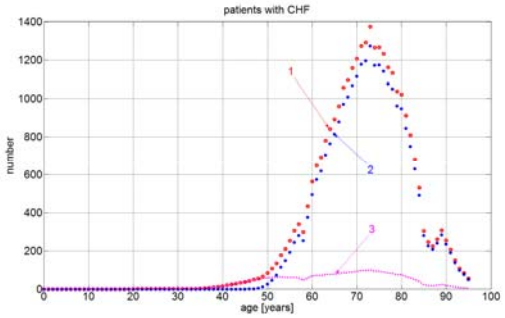

Fig.7 Number of patients with CHF (1-all patients, 2-patients without hypertension and with CHF, 3-patients with hypertension and CHF)

Regarding the patients who have only high blood pressure an average price for optimal year treatment was evaluated for the most frequently used beta blockers. For one patient it is estimated that €51.49 per year is needed [25]. It can therefore be expected that in Slovenia for this group of patients economic burden is almost €27 million per year.

Expenses for CHF patients can arise from numerous reasons. In the present study the following were taken into account:

- the usage of beta blockers,
- other needed drugs,
- hospitalization and
- mortality.

Regarding other needed drugs, hospitalization, mortality and also, when evaluating treatment efficacy, it is important to differ from which group the patients are. The situations are different regarding how serious is patient's condition. To distinguish among them NYHA (New York Heart Association) classification was accepted and average circumstances were taken into account, where 38% of patients are in the first group, 34% in the second, 23% in the third and 5% (where situation is the most serious) in the fourth.

Regarding treatment efficacy it was first supposed that all patients are healed with beta blockers and later on this situation was compared with the one where beta blockers would not be used (statistical data of placebo results were taken into account). On the basis of obtained results the efficacy of beta blockers can be presented.

First it can be expected that optimal drug treatment of patients with hypertension would prevent 40% of cases where CHF is developed or with other words, each year around 1200 CHF patients less would be expected in Slovenia.

In Fig. 8 year mortality regarding patient's age is shown, indicating that during one year over 2600 people die because of CHF in Slovenia.

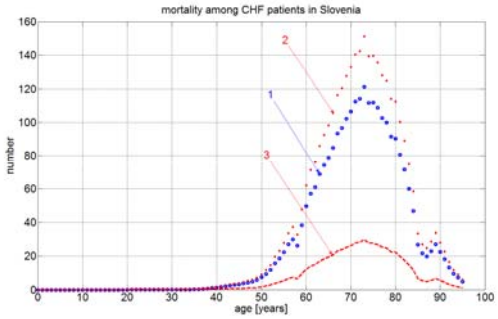

Fig.8 Number of patients with CHF who die each year in Slovenia (1-patients are treated with BB, 2-patients are not treated with BB, 3-the difference between both situations)

Their contribution to economic burden depends on their age. It is important if they are from the group of active people (it was taken into account that in average in Slovenia people are retired at age of 59) or not. It is also important for how many years would the patient need to work. Also the information regarding the degree of unemployed population was taken into account. Expenses were calculated regarding patients' ages (*i=0, ... ,95*) using the following relation:

$$N(i) = N_m(i) * as * dwa * (1 - du) * f_x$$

where $N_m(i)$ is evaluated number of deaths at certain age, *as* is an average salary, *dwa* is a degree of working activity, *du* is a degree of unemployment [14] and f_x is 1 if observed person was active, otherwise it is 0. Results for Slovenia are illustrated in Fig. 9.

Year expenses in Slovenia due to mortality are for CHF patients €163 000.

Regarding model prediction in Slovenia each year over 25 600 hospitalizations are expected in CHF patients for what almost €81 million is needed. Economic burden regarding hospitalization is illustarted in Fig. 10.

When observing the economic burden of drugs with beta blockers it is important to take into account that 40% of CHF patients from NYHA I group are using this medicine and all from other three groups. Year expenses for this group of drugs are therefore €1.9 million each year.

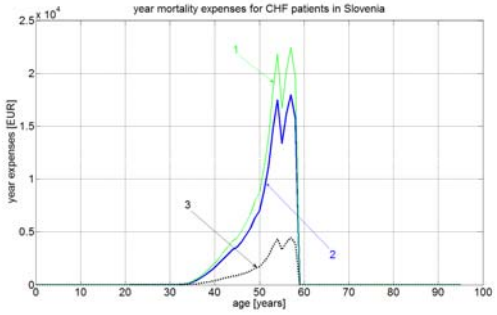

Fig.9 Year mortality expenses in EUR for CHF patients in Slovenia (1-patients are not treated with BB, 2-patients are treated with BB, 3-the difference between both situations)

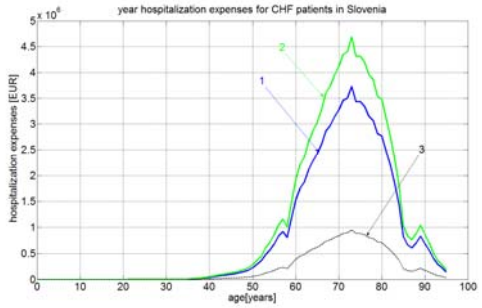

Fig.10 Year hospitalization expenses in EUR for CHF patients in Slovenia (1-patients are treated with BB, 2-patients are not treated with BB, 3-the difference between both situations)

In addition to beta blockers general guidelines suggest also the usage of additional drugs regarding from which of mentioned NYHA group the patients are. For these drugs almost €7.5 million is needed per year.

As mentioned, treatment efficacy when using beta blockers was evaluated regarding the assumption that these drugs decrease mortality and hospitalization. Graphically estimated influence is illustrated in Figs. 8 – 10.

It can be expected that without the usage of beta blockers each year 650 CHF patients more would die in Slovenia, what represent the burden of around €40000 per year.

The number of hospitalizations would be increased for almost 6600, for which additional €21 million would be used each year.

Regarding all mentioned expenses the investment to the usage of beta blockers seems to be justified also from the economical point of view, as approximately €19 million can be saved per year.

4 Conclusions

In the paper modelling and simulation results are presented, illustrating the prevalence and the number of patients with hypertension, chronic heart failure and all possible combinations of these two diseases. Taking into account that in Slovenia live 2 million people, it can be expected that in the population of million people with social and demographic situations which are characteristic for developed regions, around 264000 have high blood pressure. Maximum number of patients can be expected among the people who are 50 to 70 years old. Year expenses for medicaments with beta blockers for this group of patients were estimated to be around €13.5 million.

The number of patients with chronic heart failure is estimated to be 15000 each year in the population of one million people. Taking into account that their health condition is not the same, they have been divided into four groups due to NYHA classification what further enabled the estimation of needed treatment, hospitalization and expected mortality among these groups and finally also financial burden.

Regarding model predictions it can be expected that for each million of people there are approximately 12800 hospitalizations per year what represent the financial burden of almost €41 million.

In addition, financial burden are also expenses for drugs. Again observing the group of 1 million people, for CHF-patients €4.7 million is needed each year in addition to antihypertensive treatment.

Mortality of CHF patients is relatively high as it can be expected that in a group of million people each year die over 1300 people, what represent economic burden of approximately €81500 per year.

Model predictions also warn that in the case when drugs with beta blockers are not used the increase of hospitalizations and mortality can be expected among CHF patients and as a consequence also overall expenses would be increased for almost €10 million. To be more precise it can be expected 3300 hospitalizations more per year and over 300 CHF patients more would die in such circumstances in the group of 1 million of people.

As hypertension has negative influence also to the other CV diseases additional savings can in general be expected. Estimation of these potential savings will be the goal of our further work together with the observation how population aging influences health condition in developed regions. This is of course very important as it can be expected that in the developed countries the average population oldness would be drastically increased in the next few decades.

5 References

[1] J. W. Levenson, P. J. Skerrett, J. M. Gaziano, Reducing the global burden of cardiovascular disease: the role of risk factors, *Prev Cardiol*., vol. 5, pp. 188-99, 2002.

[2] R. O. Bonow, L. A. Smaha, S. C. Smith, et al., World Heart day 2002, The international burden of cardiovascular disease: responding to emerging global epidemic, *Circulation,* vol. 106, pp. 1602-5, 2002.

[3] M. Atanasijević-Kunc, J. Drinovec, S. Ručigaj, A. Mrhar, Modelling of the risk factors and chronic diseases that influence the development of serious health complications, *Slovenian Medical Journal*, pp. 487-98, 2008.

[4] M. Atanasijević-Kunc, J. Drinovec, S. Ručigaj, A. Mrhar: Modeling the influence of risk factors and chronic diseases on the development of strokes and peripheral arterial-vascular disease, *Simulation Modelling Practice and Theory*, pp. 998-1013, 2008.

[5] E. Amrosioni, Pharmacoeconomic challenges in disease management of hypertension, *J hypertens*, vol. 19 (suppl 3), pp. S33–S40, 2001.

[6] W. Rosamond, K. Flegal, K. Furie, A. Go, et al., Heart disease and stroke statistics—2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee, *Circulation*, vol. 117, pp. 25–146, 2008.

[7] C. S. Wiysonge, H. Bradley, B. M. Mayosi, R. Maroney, A. Mbewu, L. H. Opie, J. Volmink, Beta–blockers for hypertension, *Cochrane Database of Systematic Reviews 2007*, Issue 1. Art. No.: CD002003. DOI: 10.1002/14651858.CD002003.pub2.

[8] L. H. Lindholm, B. Carlberg, O. Samuelsson, Should β blockers remain first choice in the treatment of primary hypertension? A meta–analysis, *Lancet 2005*; 366: pp. 1545–53.

[9] B. M. Psaty, N. L. Smith, D. S. Siscovick, T. D. Koepsell, et al, Health outcomes associated with hypertensive therapies used as first–line agents, A systemic review and meta–analysis, *JAMA 1997*; 277: pp. 739–45.

[10] N. Khan, A. Mc Alister, Re–examining the efficacy of β–blockers for the treatment of hypertension: a meta–analysis, *CMAJ 2006*; 174: pp. 1737–42.

[11] J. G. F. Cleland, K. Swedberg, F. Follath, et al. The EuroHeart Failure survey programme – a survey on the quality of care among patients with heart failure in Europe, Part 1: patient characteristics and diagnosis, *European Heart Journal*, vol. 24, pp. 442–63, 2003.

[12] The study group of diagnosis of the working group on heart failure of the European Society of cardiology, The EuroHeart Failure survey programme – a survey on the quality of care among patients with heart failure in Europe, Part 2: treatment, *European Heart Journal*, vol. 24, pp. 464–75, 2003.

[13] K. L. Ong, B. M. Y. Cheung, Y. B. Man, C. P. Lau, K. S. L. Lam: Prevalence, Awareness, Treatment, and Control of Hypertension Among United States Adults 1999–2004, *Hypertension*, pp. 49-69, 2007.

[14] T. Thom, N. Haase, W. Rosamond, V. Howard, et al., Heart disease and stroke statistics - 2006 update. A report from the American Heart Association statistics committee and stroke statistics subcommittee, *Circulation* published online Jan 11, 2006. DOI:10.1161/CIRCULATIONAHA.105.171600

[15] Prevalence of heart failure, British heart foundation statistics database, Office of National Statistics, England and Wales, 1998, General practice study, <<www.heartstats.org>>, (1. 11. 2008)

[16] J. He, L. G.Ogden, L. A. Bazzano, S. Vupputuri, C. Loria, P. K. Whelton, Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study, *Arch Intern Med.,* Apr 9;161(7), pp. 996-100, 2001.

[17] G. Fabbri, M. Gorini, A. P. Maggioni, G. Cacciatore, A. Di Lenarda, Italian Network on Congestive Heart Failure: ten-year experience, *G Ital Cardiol* (Rome), Oct;7(10), pp. 689-94, 2006.

[18] R. Nehru, The Cardiovascular Disorders Market Outlook to 2012, *Reuters Insight*, 2008.

[19] Statistical Office of the Republic of Slovenia, <http://www.stat.si/eng/index.asp>, (13. 5. 2010).

[20] B. Ameer, Extending Worldwide Clinical Pharmacology Education Through a Pricing Approach, *J. Clin. Pharmacology*, pp. 982-986, 2005.

[21] Mathworks. *Using Matlab version 7*. The Mathworks Inc., 2005.

[22] Simulink, *User's Guide,* The MathWorks Inc. 2005.

[23] H. Löwel, C. Meisinger, M. Heier, H. Hymer, D. Alte, H. Völzke, Epidemiology of hypertension in Germany, Selected results of population-representative cross-sectional studies, *Dtsch Med Wochenschr*, Nov 17;131(46), pp.2586-91, 2006.

[24] U. S. Census Bureau, International Data Base, Population, by Age and Sex, United

Kingdom/2007, <http://www.census.gov/cgi-bin/ipc/idbsprd>, (28.9.2008).

[25] Recept (Prescription), Bilten o zdravilih iz obveznega zdravstvenega zavarovanja (Bulletin of drugs from mandatory health insurence), in Slovene, 5(1), 2007.