Research article/Raziskovalni prispevek

SOME PHARMACOECONOMIC ASPECTS OF CONGESTIVE HEART FAILURE IN SLOVENIA

NEKATERI FARMAKOEKONOMSKI VIDIKI SRČNEGA POPUŠČANJA V SLOVENIJI

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Prispelo 2003-08-19, sprejeto 2004-02-10; ZDRAV VESTN 2004; 73: 53–7

Key words: *congestive heart failure; therapy; epidemiology; pharmacoeconomics*

Abstract – Background. *Congestive heart failure is a fatal disease. In view of its increasing frequency, primarily in the developed world and its aging population, it is becoming a major economic burden for the health care and whole society.*

Methods. *A meta-analysis of effectiveness of convertase inhibitors and beta-blockers in the treatment of congestive heart failure was made. Based on epidemiological data collected in the region Bela krajina, we theoretically calculated the prevalence of congestive heart failure in Slovenia, visits at specialist doctors in a year, and determined hospitalization level. Also, we calculated the annual costs for each individual patient according to the classification made by the New York Heart Association (NYHA), total therapy costs for all patients with heart failure in Slovenia, the share of these costs in the total health care expenditures in Slovenia and in the gross national product.*

Results. *Meta-analysis revealed effectiveness of the treatment of patients with heart failure with convertase inhibitors and beta-blockers with regard to reduced mortality as well as reduction of number of hospitalizations. Based on the epidemiological data from the region Bela krajina, the calculated prevalence of heart failure in the Slovene population was 1.11%, and the heart failure hospitalization level 1.37%. The annual costs of treatment of an individual patient with heart failure are increasing with progressive NYHA classes and amount to SIT 147,000.00 in NYHA class I, and SIT 1,672,000.00 in NYHA IV. Total costs of optimum treatment of the 40,000 patients with heart failure would in Slovenia amount to SIT 22,559,570,750.00, accounting for 7.07% of total health care expenditures and 0.56% of the gross national product.*

Conclusions. *Prevalence of heart failure increases with age and is a considerable economic burden for the society.*

Ključne besede: *srčno popuščanje; zdravljenje; epidemiologija; farmakoekonomika*

Izvleček – Izhodišča. *Srčno popuščanje spada med usodne bolezni. Zaradi vse večje pogostosti, predvsem v razvitejšem delu sveta s starajočim se prebivalstvom, postaja pomembna obremenitev za zdravstvo in družbo.*

Metode. *Napravljena je bila metaanaliza učinkovitosti konvertaznih zaviralcev in blokatorjev receptorjev beta pri srčnem popuščanju. Na osnovi epidemioloških podatkov na področju Bela krajina so avtorji teoretično izračunali prevalenco srčnega popuščanja v celotni Sloveniji, število letnih obiskov pri specialistu in poiskali stopnjo hospitalizacije. Na osnovi dobljenih epidemioloških podatkov so izračunali delež stroškov za posameznega bolnika s srčnim popuščanjem letno glede na klasifikacijo po njujorškem kardiološkem združenju, celokupne stroške za vse bolnike s srčnim popuščanjem v Sloveniji, delež v celotnih stroških za zdravstveno varstvo ter del bruto nacionalnega dohodka.*

Rezultati. *Metaanaliza je pokazala uspešnost pri zdravljenju bolnikov s srčnim popuščanjem pri uporabi konvertaznih zaviralcev in blokatorjev receptorjev beta tako glede manjše smrtnosti kot hospitalizacije. Na osnovi epidemioloških podatkov področja Bela krajina je bila izračunana prevalenca srčnega popuščanja med slovenskim prebivalstvom 1,11%, stopnja hospitalizacije zaradi srčnega popuščanja pa 1,37%. Letni stroški zdravljenja pri posameznem bolniku s srčnim popuščanjem po razredih klasifikacije njujorškega kardiološkega združenja naraščajo in veljajo v razredu I 147.000,00 SIT, v razredu IV pa 1.672.000,00 SIT. Celokupni stroški idealnega zdravljenja vseh 40.000 bolnikov s srčnim popuščanjem v Sloveniji bi znašali 22.559.570.750,00 SIT, to bi pomenilo 7,07% sredstev za zdravstveno varstvo in 0,56% bruto nacionalnega prihodka.*

Zaključki. *Prevalenca srčnega popuščanja se povečuje s starostjo in pomeni znatno ekonomsko obremenitev za družbo.*

Introduction

Heart (or cardiac) failure is the pathophysiological state, which is usually, but not always, caused by a defect in myocardial contraction, that is, by myocardial failure (1). It should be distinguished from circulatory failure, in which in inadequate cardiac output is due to an abnormality of some component of the circulation – the heart, the blood volume, the concen-

tration of oxygenated hemoglobin in the arterial blood, or the vascular bed.

A Working Group convened by the National Heart, Lung, and Blood Institute defines (2) and describes heart failure as follows: Heart failure occurs when an abnormality of cardiac function causes the heart to fail to pump blood at the rate required by the metabolizing tissues or when the heart can do so only with an elevated filling pressure. The heart's inability to pump a sufficient amount of blood to meet the needs of the body tissues may be due to insufficient of defective cardiac filling and/or impaired contraction and emptying. Compensatory mechanisms increase blood volume and raise cardiac filling pressures, heart rate, and cardiac muscle mass to maintain the heart's pumping function and cause redistribution of blood flow. Eventually, however, despite these compensatory mechanisms, the ability of the heart to contract and relax declines progressively, and the heart failure worsens.

Heart failure is a fatal disease and the public is becoming increasingly aware of it as a distinctive problem in industrially developed countries with an aging population. Heart failure is the final phase of all heart diseases and the major cause of morbidity and mortality related to these diseases. It is estimated that it is the primary admission diagnosis for 5% hospitalizations to internal medicine departments, i. e. more than 100,000 hospitalizations yearly in UK and over 2.5 million in USA. In Great Britain, it has surpassed myocardial infarction as the primary admission diagnosis, while in USA, heart failure is the most common primary admission diagnosis in patients older than 65 years. It is estimated that in USA, in the coming 8 years, the possibility for a person aged 70 years and over to be hospitalized due to heart failure, will be about 15%. Reports from several other countries revealed that the complete costs for caring of patients with heart failure account for 1 to 2% of total health care expenditures (3).

The total incidence of heart failure is 1–4/1000 inhabitants, and in elderly population aged from 65 to 89 years, the incidence is from 3.5 and 27/1000. The total prevalence of left ventricular dysfunction in the elderly aged from 75 to 86 years is 10.8% (3, 4).

The quality of life of patients with heart failure is very poor and similar to the quality of life of patients with severest forms of malignant diseases. The same may be claimed for the prognosis of the condition (Table 1) (5, 6, 7, 8).

Table 1. *Progression of heart failure according to NYHA classification and related annual mortality.*

Razpr. 1. *Napredovanje srčnega popuščanja po klasifikaciji njujorškega združenja za bolezni srca (NYHA) in pripadajoča letna umrljivost.*

NYHA class Razred NYHA	Progression into higher class (%) Napredovanje v višji razred (%)	Annual mortality (%) Letna umrljivost (%)
I	20	4
II	30	5–15
III	40	20–50
IV		30–70

In the United States, heart failure causes the death of about 200,000 patients yearly. The annual costs for the treatment of patients with heart failure amount to over 38 billion dollars. Although a remarkable progress has been made in the prevention of cardiovascular diseases with the use of statins, acetylsalicylic acid and beta-blockers; the treatment of these diseases with antihypertensive drugs, and in part antiarrhythmic, anticoagulant and fibrinolytic agents; with the discovering of heart failure at its early stages by utilizing ultrasound diagnostics: and consequently, the treatment of these patients during the last 20 years with diuretics, convertase inhibitors, beta-blockers and aldosterone antagonists – heart failure remains a difficult field to manage for the health care and entire society. However, the major burden falls upon the patient and his family (7, 9, 10).

In view of lack of statistical data on the presence of heart failure in the population of Slovenia, we aimed in a prospective epidemiological and pharmacoeconomic study to establish the incidence of heart failure in a small region in Slovenia. Based on the data obtained in this region and taking into account several restrictions, we prepared a generalization for Slovenia overall. It was our objective to carry out a meta-analysis for medicines that prolong life of patients with heart failure. By means of a decision tree, we planned to prepare clinical pathways for patients with heart failure and calculated costs of diagnostic procedures and therapy. We intended to calculate total annual costs of treatment of patients with heart failure, as well as the share of these costs in the total health care expenditures in Slovenia and in the gross domestic product.

Methods

Meta-analysis for ACE inhibitors was found in literature (11–16), while we conducted the meta-analysis for beta-blockers. We collected studies from databases MEDLINE and OVID. In both meta-analyses, we included trials that comprised more than 1000 patients and lasted at least one year. The effects of ACE inhibitors were compared with the effects of symptomatic treatment in the placebo group that received diuretics and digitalis glycosides and anti-arrhythmic agents, if needed. The meta-analysis of effectiveness of beta-blockers comprised patients treated with this group of drugs and additionally with ACE inhibitors and all other symptomatic medicines. Patients in the placebo groups were given all the enumerated medicines except the beta-blockers.

The results of meta-analysis were presented by the odds ratio and corresponding 95% confidence interval. If the adds ratio was less than 1, the effectiveness of the specific drug in the tested group was proven in comparison to the placebo group. The confidence interval gives an indication of the statistical significance of the result; if it comprises the values smaller than 1, the result is statistically significant, however, if the confidence interval includes the value 1, the result is statistically not significant. Effectiveness or ineffectiveness was primarily assessed with regard to mortality, hospitalization and in some trials with regard to recurrent myocardial infarction. We excluded all the trials that were not prospective or they lacked a mortality end point. Mentel-Haenszel method was used as statistical method (17).

The epidemiological field study was conducted in the region Bela krajina because of the compactness and relative seclusiveness of the region, as well as its distance from the capital Ljubljana. We determined the prevalence of heart failure in symptomatic patients aged 40 years and older, more precisely in those who sought medical help in general outpatient clinics, specialist outpatient clinics or were hospitalized from 1 October until 31 December 2001. Data on the population structure were obtained from the Statistical Office of the Republic of Slovenia (18), while data on mortality, the number of patients per one doctor and number of all visits at the doctor, were found in the Annual health statistics report for the year 2000 (19). From the collected statistical data, we made a theoretical calculation of the total number of patients with heart failure in the Slovene population.

We prepared an algorithm for the clinical pathway and annual management of 1000 patients with heart failure, based on the guidelines and recommendations for the management of patients with heart failure. From the data obtained, we calculated theoretical annual costs of optimum management of all Slovene patients with heart failure and presented these costs

as the share in total health care expenditures in Slovenia and in the gross national product.
The costs were divided into direct medical costs (costs for general practitioner, specialist cardiologist, diagnostic procedures, medication, hospitalization), direct non-medical costs (travel costs), and in-direct costs (sick leave costs), as well as with regard to NYHA class.

Results

The results of the meta-analysis of effectiveness of ACE inhibitors in patients with heart failure are shown in Table 2 (11–16).

Table 2. *Meta-analysis of effectiveness of ACE-inhibitor therapy in patients with heart failure in studies SAVE, AIRE, TRACE and SOLVD, in comparison to effectiveness of therapy without ACE inhibitors in patients with heart failure.*

Razpr. 2. *Metaanaliza učinkovitosti zdravljenja bolnikov s srčnim popuščanjem z zaviralci ACE pri raziskavah SAVE, AIRE, TRACE in SOLVD v primerjavi z bolniki, zdravljenimi brez zaviralcev ACE.*

Variable Spremenljivka	Events Dogodki ACE n 6391 štev.	Placebo 6372	Odds ratio (95% confidence interval) Razmerje verjetnosti (95% interval zaupanja)	Significance (p) Significantnost (p)
Death Smrt	1467 (23.0%)	1710 (26.8%)	0.80 (0.74–0.87)	< 0.0001
Recurrent infarction Ponovni infarkt	571 (8.9%)	703 (11.0%)	0.79 (0.70–0.89)	0.0001
HF rehospitalization Ponovna hospitalizacija zaradi SP	876 (13.7%)	1202 (18.9%)	0.67 (0.61–0.74)	< 0.0001
Death/recurrent infarction Smrt/ponovni infarkt	1725 (27.0%)	2043 (32.1%)	0.77 (0.72–0.84)	< 0.0001
Death/HF hospitalization Smrt/Ponovna hospitalizacija zaradi SP	1962 (30.7%)	2354 (36.9%)	0.74 (0.69–0.80)	< 0.0001
Death/MI/HF rehospitalization Smrt/MI/Ponovna hospitalizacija zaradi SP	2161 (33.8%)	2610 (41.0%)	0.72 (0.67–0.78)	< 0.0001

HF – heart failure, SP – srčno popuščanje
MI – myocardial infarction, MI – miokardni infarkt

The results of meta-analysis of effectiveness of beta-blockers in patients with heart failure are shown in Table 3 (20, 21, 22).
Table 4 shows the number of patients with heart failure according to their age decade who were diagnosed in a period of three months in the region Bela krajina.
In specialist outpatient clinics, we found documentation for 3 patients with heart failure aged from 40 to 49 years, 3 patients aged from 50 to 59 years, 10 patients aged from 60 to 69 years, 9 patients aged from 70 to 79 years and 10 patients aged from 80 to 89 years.
Figure 1 shows the prevalence of patients with heart failure in Bela krajina distributed according to gender and age groups, based on Table 4.
Table 5 shows the calculated data for prevalence of patients with heart failure in Slovenia, distributed according to gender and age.
It is our estimation that in Slovenia, the total number of patients treated for heart failure is about 20,000. It is known from

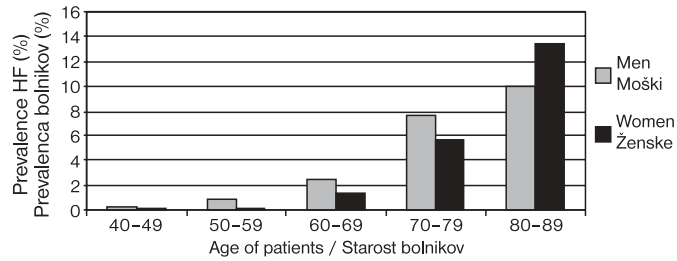

Figure 1. *Prevalence of patients with heart failure in Bela krajina, distributed according to gender and age groups.*

Sl. 1. *Prevalenca bolnikov s srčnim popuščanjem v Beli krajini, porazdeljenih po spolu in starosrnih skupinah.*

Table 4. *Distribution of registered patients with heart failure according to gender and age decades in the region Bela krajina.*

Razpr. 4. *Porazdelitev registriranih bolnikov s popuščanjem srca po spolu in desetletjih v Beli krajini.*

	40–49	50–59	60–69	70–79	80–89	>90
Males Moški	7	15	31	54	15	1
Females Ženske	4	2	19	73	58	14
Total Skupaj	11	17	50	127	73	15

Table 5. *The calculated prevalence of symptomatic patients with heart failure (classes II, III, IV) in Slovenia, distributed according to gender and ages.*

Razpr. 5. *Izračunana prevalenca simptomatskih bolnikov s srčnim popuščanjem (razredi II, III, IV) v Sloveniji, porazdeljena po spolu in starosti.*

	40–49	50–59	60–69	70–79	80–89	>90
Males Moški	502.41	1145.51	2351.95	3835.76	1146.52	79.95
Females Ženske	291.08	169.33	1496.20	5081.54	4047.00	974.76
Total Skupaj	793.49	1314.84	3848.15	8917.30	5193.52	1054.71

literature that left ventricular dysfunction is at least twice as frequent as symptomatic heart failure, or defined with clinical criteria – about half of the patients with known left ventricular dysfunction have no symptoms or signs of heart failure. In view of this, we can draw a conclusion that in addition to the treated patients, there is a similar number of non-diagnosed patients, and, the total number of patients in Slovenia that would require treatment for heart failure is approximately 40,000.
The prevalence of symptomatic heart failure in the Slovene population is 1.17% or 11.7/1000 inhabitants yearly (13.4/1000 women and 9.9/1000 men).
The share of patients with heart failure in Slovenia who are treated in specialist outpatient clinics is 11.95% or 119.5/1000 patients yearly (109.5/1000 women and 138.2/1000 men).
The hospitalization rate of patients with heart failure is 1.37% or 13.7/1000 patients yearly (5.8/1000 women and 24.4/1000 men).
Hospitalization in the region Bela krajina is significantly lower than in the whole Slovenia; a total of 0.6/1000 inhabitants yearly (0.3/1000 women and 1.0/1000 men).
Annual costs of optimum treatment of 1000 patients with heart failure in Slovenia are presented in Table 6.

Table 3. *Meta-analysis of efficacy of beta-blocker therapy in comparison to efficacy of therapy without beta-blockers in patients with heart failure.*

Razpr. 3. *Metaanaliza učinkovitosti zdravljenja bolnikov s srčnim popuščanjem z blokatorji receptorjev beta v primerjavi z bolniki, zdravljenimi brez blokatorjev receptorjev beta.*

Study Študija	Mortality Umrljivost			Mortality/Hospitalization Umrljivost/hospitalizacija		
	Drug / Zdravilo Event/All Dogodek/vsi	Placebo / Placebo	OR (95% CI) Event/Al Dogodek/vsi	Drug / Zdravilo Event/All Dogodek/vsi	Placebo / Placebo	OR (95% CI)
Anderson	5/25 (20.0%)	6/25 (24.0%)	0.79 (0.22–2.81)			
Engelmeier	1/9 (11.1%)	2/16 (12.5%)	0.88 (0.08–10.14)			
MDC	23/194 (11.9%)	21/189 (11.1%)	1.08 (0.57–2.04)	48/194a (24.7%)	61/189 (32.3%)	0.69 (0.46–1.04)
Fisher	1/25 (4.0%)	2/25 (8.0%)	0.48 (0.06–3.54)			
CIBIS	53/320 (16.6%)	67/321 (20.9%)	0.75 (0.52–1.09)	88/320a (27.5%)	115/321 (35.8%)	0.68 (0.50–0.92)
Bristow	4/105 (3.8%)	2/34 (5.9%)	0.63 (0.12–3.22)			
Krum	3/33 (9.1%)	2/16 (12.5%)	0.70 (0.12–4.11)	8/33a (24.2%)	6/16 (37.5%)	0.53 (0.17–1.63)
PRECISE	6/133 (4.5%)	11/145 (7.6%)	0.58 (0.24–1.38)			
US Carvedilol	22/696 (3.2%)	31/398 (7.8%)	0.39 (0.25–0.61)	110/696a (15.8%)	98/398 (24.6%)	0.57 (0.44–0.75)
Carvedilol efficacy	2/70 (2.9%)	2/35 (5.7%)	0.49 (0.08–2.72)			
Colucci	2/232 (0.9%)	5/134 (3.7%)	0.22 (0.07–0.68)	10/232a (4.3%)	12/134 (9.0%)	0.46 (0.22–0.95)
Australia – New Zaeland HF Group	20/207 (9.7%)	26/208 (12.5%)	0.75 (0.42–1.33)	104/207b (50.2%)	131/208 (63.0%)	0.59 (0.42–0.84)
CIBIS II	156/1327 (11.8%)	228/1320 (17.3%)	0.64 (0.52–0.78)	388/1327a (29.2%)	463/1320 (35.1%)	0.76 (0.66–0.89)
MERIT–HF	145/1990 (7.3%)	217/2001 (10.8%)	0.65 (0.53–0.79)	641/1990b (32.2%)	767/2001 (38.3%)	0.76 (0.68–0.86)
CAPRICORN	116/975 (11.9%)	151/984 (15.3%)	0.74 (0.59–0.95)	340/975a (34.9%)	367/984 (37.3%)	0.90 (0.75–1.08)
COPERNICUS	130/1156 (11.2%)	190/1133 (16.8%)	0.63 (0.51–0.78)	425/1156b (36.8%)	507/1133 (44.7%)	0.72 (0.62–0.84)
TOTAL / SKUPAJ	689/7497 (9.2%)	963/6984 (13.8%)	0.66 (0.59–0.73)	2162/7130 (30.3%)	2527/6704 (37.7%)	0,75 (0.70–0.80)

OR (95% CI) is odds ratio (95% confidence interval)
OR (95% CI) je razmerje verjetnosti (95% interval zaupanja)

Table 6. *Distribution of expenses for optimum therapy in 1000 patients with heart failure in Slovenia.*

Razpr. 6. *Porazdelitev stroškov pri optimalnem zdravljenju 1000 bolnikov s srčnim popuščanjem v Sloveniji.*

Type of expenses Vrsta stroškov	Service Storitev	Price (SIT) Cena (SIT)	Share (%) Delež (%)
Direct medical costs Neposredni medicinski stroški	General practitioner Splošni zdravnik	9,372,457.00	1.66
	Specialist cardiologist Specialist kardiolog	5,088,969.00	0.90
	Diagnostic services Diagnostične storitve	24,753,778.00	4.39
	Medicines Zdravila	101,342,780.26	17.99
	Hospitalization Hospitalizacija	384,024,271.00	68.15
Total Skupaj		524,582,255.26	93.09
Direct non-medical costs Neposredni nemedicinski stroški	Travel costs Potni stroški	19,257,990.00	3.42
Indirect costs Posredni stroški	Sick leave Bolniški stalež	19,649,023.50	3.49
Total Skupaj		563,489,286.76	100.00

The annual costs per patient with heart failure in Slovenia, with regard to NYHA class are shown in Figure 2.
Optimum treatment of all 40,000 patients with heart failure in Slovenia (20,000 symptomatic from NYHA classes II-IV and 20,000 asymptomatic from NYHA class I) would cost 22,559,570,750.00 SIT. This would account for 7.07% of total health care expenditures in Slovenia for the year 2000 and for 0.56% of the gross national product.

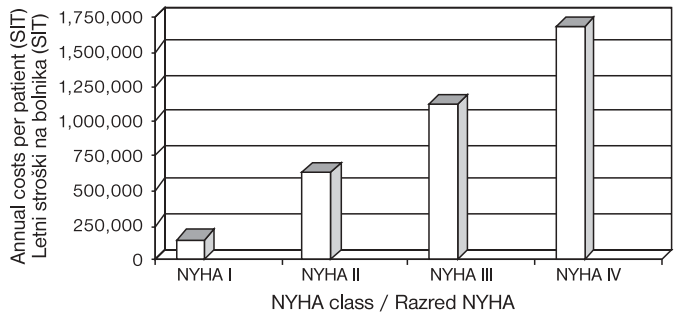

Figure 2. *Annual costs per patient with heart failure in Slovenia with regard to NYHA class.*

Sl. 2. *Letni stroški na posameznega bolnika s srčnim popuščanjem v Sloveniji po razredu NYHA.*

Discussion

The meta-analysis of ACE inhibitors and beta-blockers revealed effectiveness of both drug groups in the treatment of patients with heart failure (23, 24). Therapy recommendations and guidelines by most important institutions do not, as yet, include aldosterone antagonists as the recommended drug group in the majority of patients. European guidelines predict the use of aldosterone antagonists in NYHA classes III and IV for survival improvement. If ACE inhibitors are not well tolerated, they are replaced with angiotensin-II receptor antagonists (25, 26, 27).
The epidemiological part of our study included only patients with heart failure classified as NYHA classes II-IV and not patients of class I who had no symptoms and signs and did not visit a doctor or were diagnosed for heart failure.
The geographic region Bela krajina is particularly suitable to be statistically analyzed as it is well manageable due to the fact that most patients are treated in the clinic in the nearest town Novo mesto, and only a few need to go to a hospital in Ljubljana. In outpatient general and family medical centers, as well as in specialist cardiologist practices, transparency is assured. The majority of doctors, including the specialists and hospital in Novo mesto cooperated very well and all data are therefore credible. A generalization made of three-month data to one year is completely justified, while generalization of the studied population segment made to the whole Slovene po-

pulation has more limits, despite of its similar age structure. Due to the facts that patients with heart failure NYHA class I were not included in the study, and the educational structure of the population in Bela krajina is below the Slovene average, we could predict lower medical awareness of this population. In view of this, our theoretical calculation of the prevalence of heart failure in Slovenia is the lowest possible, however, it may well be twice as high. A convincing proof of that prediction is also the significantly lower hospitalization frequency of patients with heart failure in Bela krajina in comparison to the population of total Slovenia.

The theoretical calculation for the prevalence of heart failure in the whole Slovenia is consistent with epidemiological data worldwide, particularly with those with the lowest figures which retrospectively proves that such generalization has been justified.

Pharmacoeconomic analysis revealed the great economic burden from the treatment of heart failure in Slovenia. The calculation is theoretical, with the projection that all patients in Slovenia are treated according to current guidelines. Unfortunately, in reality, management of heart failure in Slovenia and in the most developed countries does not follow these guidelines. It is estimated that optimum management is ensured for 30 to 55% of patients, at the most. Patients themselves frequently ignore the signs and symptoms of the illness, which rarely remains undertreated or patients themselves decide to withdraw therapy (2, 27, 28).

Heart failure is a progressively worsening and fatal disease affecting the patient and his family, while it is a considerable economic burden for the society. Knowing that leads us to employment of preventive measures, early detection and timely treatment (2, 3, 6, 29).

Conclusions

1. The meta-analysis revealed effectiveness of the treatment of patients with heart failure with ACE inhibitors and beta-blockers.
2. The calculated prevalence of heart failure among Slovene adults is 1.17%, while the hospitalization level due to heart failure is 1.37% yearly.
3. Total annuals costs for the treatment of one patient with heart failure amount for NYHA class I to 147,000.00 SIT, class II to 630,000.00 SIT, class III to 1,122,000.00 SIT and class IV to 1,672,000.00 SIT yearly.
4. The total costs of optimum treatment of 40,000 patients with heart failure in Slovenia would amount to 22,559,570,750.00 SIT, that accounts for 7.07% of total health care expenditures in Slovenia in the year 2000 and 0.56% of the gross national product.
5. The major part of expenditures of optimum treatment are direct medical costs that account for 93% of total expense, of which the main part (68%) is hospitalization, followed by 18% for drugs, 4.5% for diagnostic services, and only 1.5% for the general practitioner and 1% for the specialist. All other costs comprise sick leave and travel costs.

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