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Original Article

COST-EFFECTIVENESS OF BETA BLOCKERS AND THE SURVIVAL OF THE PATIENTS WITH HEART FAILURE IN THE CARDIOLOGY CENTER IN TIRANA

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ABSTRACT

Objective: To evaluate the survival of the patients with heart failure in the Cardiology Center in Tirana, to evaluate the cost effectiveness of carvedilol versus metoprolol.

Methods: 239 patients (pts) suffering chronic heart failure of different aetiologies, on traditional treatment for heart failure (angiotensin-converting enzyme inhibitors, diuretics, digoxin), with ejection fraction<50%, in NYHA class II-IV, were randomised to carvedilol 6.25-25 mg/day, or metoprolol 50-100 mg/day, or nebivolol 5 mg/day or treated only with the traditional treatment for they have contraindications regarding the use of β–blockers, followed for a two-year period.

Results: There were included 239 patients of mild, moderate and severe heart failure, NYHA II-IV, with the fraction of ejection<50 hospitalized in the University clinic of cardiology of Tirana, followed for a two-year period; 83 patients (34.7%) were treated with Carvedilol; 70 patients (29.2%) were treated with metoprolol, 21 patients were treated with nebivolol (8.7%), and 65 patients (27.1%) were treated only with the traditional therapy (TTh).

Conclusion: The use of carvedilol along with the traditional therapy of heart failure assures a higher survival rate and a lower hospitalization rate but an increase of cost of treatment of 216 €a year compared to metoprolol in addition with traditional therapy.

Keywords: Chronic heart failure, Carvedilol, Metoprolol, Survival rate.

INTRODUCTION

The use of beta-blockers has been shown to improve survival in patients with chronic heart failure (CHF) and the benefit of the three agents, carvedilol [1, 2] metoprolol [1, 3] and bisoprolol, [4, 5] was demonstrated. The COMET study showed that carvedilol reduced mortality compared to metoprolol tartrate in patients with mild-moderate heart failure and left ventricular systolic dysfunction [4]. These drugs block beta1-adrenergic receptors, but only carvedilol blocks $beta_2$-and $alpha_1$-adrenergic receptors and have at the same time antiproliferative, antioxidant, and anti-endothelin actions [6, 7].

The comprehensive adrenergic blockade of carvedilol leads to a greater sympatho-inhibitory effect than metoprolol [8-10]. At the same time carvedilol, but not metoprolol leads to persistent beta-blockade beyond its plasma elimination, due to binding to an allosteric site of human β-adrenoceptors with slower kinetics [11]. Carvedilol significantly decreases systemic blood pressure, pulmonary artery pressure, and pulmonary capillary wedge pressure because of the vasodilatation that occurs with blocking of β -receptors. Blocking of ß-receptors reduces the heart rate and increases diastolic filling time [12].

Our aim was to estimate the effects in survival of two treatments of heart failure; carvedilol β_1, β_2 β-blocker and metoprolol selective β_1–blocker. The average daily costs of hospitalization and the costs of the treatment were calculated. It was the first time that a cost-effectiveness study between β-blockers was performed in the national clinic of cardiology in Tirana, Albania (QSUT).

MATERIALS AND METHODS

In the double blind prospective study were included 239 patients of mild, moderate and severe heart failure, NYHA II-IV, with the fraction of ejection less than 50%, hospitalized in the University Clinic of Cardiology of Tirana, followed for a two-year period. According to the type of their medication, the patients were divided in four groups.

First group: traditional therapy+carvedilol (*6.25-25 mg/d*);

Second group: traditional therapy+metoprolol(*50-100 mg/d*);

Third group: traditional therapy+nebivolol, (*5 mg/d*);

Fourth group and at the same time control group: only traditional therapy, TTh (Diuretics, ACEI/ARB, Digoxin)

Written informed consent was obtained from all patients. In a three months time period an echocardiography examination over the patients under study was performed.

To have a larger view of the necessary economic values for the treatment of CHF, the annual costs of treatment must be calculated.

It was calculated the daily cost of drugs for every patient, daily cost of medical analysis and tests for every patient, days of standing in the hospital and the value of hospital secondary expenses.

The hospital cost for every patient was calculated; at the same time using the daily cost of drugs for every patient, we are able to find the cost of the treatment for the period out of the hospital for every patient.

The total of the hospital costs for every patient with respective out of hospital costs per patient, gives us the annual cost of every patient. To all cost values found we have given the averages.

We have studied the average annual cost for the two types of treatment schemes (Traditional treatment+Carvedilol; Traditional treatment+ Metoprolol) and we have to find the difference between them.

Statistical methods like ANOVA, Kaplan-Meir Curves, Cox Regression were applied. [13-19]

Exclusion criteria

Patients diagnosed with acute myocardial infarction or unstable angina in two previous months, with valvular disease, with untreated arrhythmia, or patents who had undergone a major surgical procedure within three months, patients with systolic blood pressure of more than 160 or less than 85 mm Hg or diastolic blood pressure of more than 100 mm Hg; patients with a heart rate of less than 68 beats per minute, or patients with clinically important hepatic or renal disease, were excluded from our study.

RESULTS

There were included 239 patients of mild, moderate and severe heart failure, NYHA II-IV, with the fraction of ejection<50 hospitalized in the University clinic of cardiology of Tirana, followed for a two-year period; 83 patients (34.7%) were treated with Carvedilol; 70 patients (29.2%) were treated with metoprolol, 21 patients were treated with nebivolol (8.7%), and 65 patients (27.1%) were treated only with the traditional therapy (TTh).

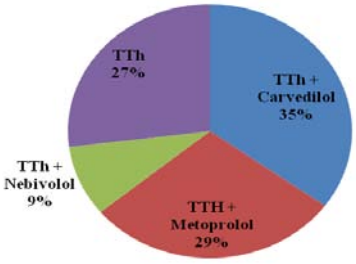

Fig. 1: The patient`s percentage treated in each group

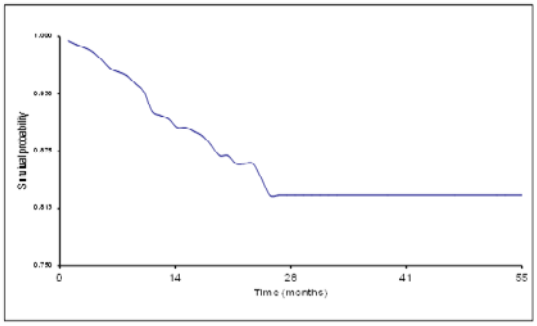

Fig. 2: The Kaplan–Meier model for all patients

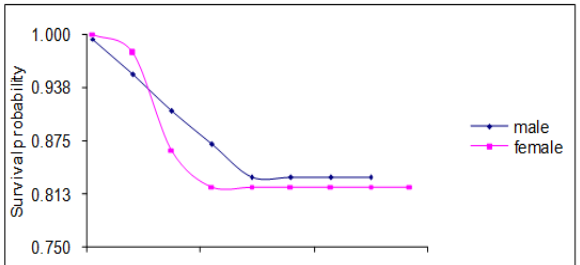

Fig. 3: The Survival Function (Kaplan–Meier model) according to the gender

Survival Function (Kaplan–Meier model) according the gender has clearly shown that male (blue line) has a higher probability to survive.

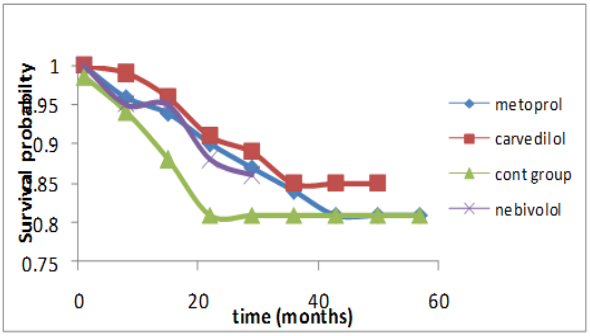

Fig. 4: The survival function (kaplan–meier model) according to the type of medication

Table 1: Medications used for each group

Treatment	Type of therapy in (%)				p-value
	Carvedilol (n=83(34.7%)	Metoprolol n=70(29.2%)	Nebovolol n=21(8.7%)	Control group n=65(27.1%)	
Diuretics	50 (60.2)	42 (51.2)	18 (85.7)	46 (70.1)	0.007
Aldosteron Antagonists	9 (10.8)	21(30.2)	3 (14.2)	52 (80.0)	0.027
ACE-inh	63 (75.9)	62 (88.4)	16 (76.9)	48 (73.8)	0.013
ARBs	15 (18.0)	5 (6.9)	5 (23.8)	10 (15.4)	0.041
Digitalis	23 (27.7)	16 (23.3)	3 (14.2)	32 (49.2)	0.037
Antiarrhythmics	0 (0.0)	0 (0.0)	0 (0.0)	17 (26.2)	0.001
Nitrites	7 (8.4)	18 (25.6)	3 (14.2)	21 (25.3)	0.005
B-Blockers	83 (100.0)	70 (100.0)	21 (100.0)	0 (0.0)	<0.001
Anticoagulants	23 (27.7)	11 (16.9)	1(4.7)	21 (32.3)	0.001
Aspirin	37 (44.6)	47 (67.4)	4 (19.0)	37 (56.9)	0.001

Mean age of First group: traditional therapy (TTh)+carvedilol, was 59.6 years±9.86; Mean age of Second group: TTh+metoprolol, 58.5 years±10.3, Mean age of Third group: traditional therapy+Nebivolol, mean age 62 years±9.36Mean age of Fourth group: only TTh(Diuretics, ACEI/ARB, Digoxin) was 63.9±10.3, without any statistical difference between them (p=0.071).

Table 2: The NYHA and the number of deaths in each group

Characteristics	Type of therapy n (%)				p-value
	Carvedilol n=83(34.7%)	Metoprololn=70(29.2%)	Nebovolol n=21(8.7%)	Control group n=65(27.1%)	
NYHA II	34 (41.0)	33 (47.1)	11 (52.4)	22 (33.7)	0.116
NYHA III	29 (35.0)	29 (41.9)	9 (42.9)	28 (42.5)	0.089
NYHA IV	20 (24.0)	8 (11.4)	1 (4.8)	15 (23.8)	0.001
EF (mean±SD)	0.42±0.09	0.47±0.10	0.44±0.11	0.42±0.83	0.234
Nr of deaths	5 (6.0)	8 (11.4)	0 (0.0)	10 (15.4)	0.001

The number of deaths was higher in the control group, 10 (15.4%), in Metoprolol group was 8 (11.4%), and in Carvedilol group was 5(6%); p=0.001. There were not deaths in Nebivolol group. The number of patients in this group is smaller than the other groups. (21 patients only). The function of survival was performed with KAPLAN-Meier method for the entire sample as well as for special subgroups to compare them.

Based to this results, we conclude that patients who have use Carvedilol in addition with traditional therapy have a higher probability to survive. They are followed from the patients who had used Metoprolol in addition with traditional therapy. The lower probability to survive was for the fourth group (they do not use β-blocker),The Cox model of the Hazard Function was built taking into consideration the factors which influence the risk of death such as age, gender, etiology of dilatation, type of treatment.

Table 3: The Cox's model results of the Hazard Function controlled for gender and type of treatment.

Controlled Cox regression for gender, diagnose and treatment					
Variables	**Haz, Ratio**	**Std, Err,**	**P>|z|**	**CI95%**	
Gender-female	1.14	0.496	0.075	0.489	1.678
Gender-male	1	reference			
TTh+Metoprolol	0.89	0.383	0.072	0.344	1.053
TTh+Carvedilol	0.82	0.313	0.041	0.283	1.680
TTh+Nebivolol	0.96	0.643	0.047	0.270	0.999
TTh	1	reference			

As it is shown above females have 14% higher probability of death compared to males. However, this is not highly significant (p=0.075). All combined treatments are advantageous compared to the traditional treatment. Patients who take Carvedilol alongside the traditional treatment have the highest advantage (18% lower hazard of death compared to the traditional treatment). Patients who take metoprolol alongside the traditional treatment have 11% lower hazard of death compared to those who are treated with the traditional medication. However, this is not highly significant p=0.072. Finally,patients who take Nebivolol have only a slight advantage compared to those who are treated with the traditional medication with only 4% lower hazard of death. This is status ally significant p=0.047. We cannot however, compare various treatments among themselves; we can only compare different treatments with the reference group-the traditional treatment.

Another indicator with economic importance, that at the same time express the effectiveness of the treatment was the Average days of hospital stand, reflected below.

Table 4: The average length of hospital stay (days)

S. No.	Type of treatment	Average length of hospital stay (days)
1.	Treatment with metoprolol	12.25
2.	Treatment with carvedilol	10.48

Average days of hospital stay for Metoprolol group were 12.25days/year, Average days of hospital stay for Carvedilol group were 10.48days/year.

Estimation of costs

The effectiveness of beta-blockers in patients with heart failure was demonstrated in some studies. However, the cost effectiveness of them remains to be established. To have a larger view of the necessary economic values for the treatment of CHF, the annual costs of treatment needs to be calculated. It was calculated the daily cost of drugs for every patient, daily cost of medical analysis and tests for every patient, and the value of hospital secondary expenses.

The Average hospital daily cost for the patient in lek is higher of 423lek(3.02 €) compared with the Average hospital daily cost with Metoprolol Group and 458 lek(3.27 €) more than Control Group.

The total of the hospital costs for every patient with respective out of hospital costs per patient, gives us the annual cost of every patient. We have studied the average annual cost for the two types of treatment schemes (Traditional treatment+Carvedilol; Traditional treatment+ Metoprolol) and we have found the difference between them.

Table 5: The average hospital daily cost for patients for carvedilol, metoprolol and control group(TTh)

Groups according medication	Hospital cost for patient/day
Carvedilol Group	2736lek±52 (19.54 €)
Metoprolol Group	2313lek±64 (16.52 €)
Control Group(TTh)	2278 lek±88(16.27 €)

Exchange rate 1euro=140lek

Table 6: The average of annual cost for carvedilol, metoprolol groups

S. No.	The Average of annual Cost	Value	Difference between groups
1	Metoprolol Group	54713 lek (390.8€)	30277 lek (216.26 €)
2	Carvedilol Group	84990 lek (607.07€)	

1euro=140lek, The average annual cost of treatment with TTh+carvedilol is 30277lek (216€) more expensive than the average annual cost of TTh+metoprolol.

DISCUSSION

The COMET study showed that carvedilol reduced mortality compared to metoprolol tartrate in patients with mild-moderate heart failure and left ventricular systolic dysfunction [4].

Our study confirms this conclusion. Patients treated with carvedilol 18% less chance of death compared to the control group (p=0.041). Patients who take metoprolol have11% less chance of death compared to the control group (p=0.072, without statistical difference). In the two multi center studies [20, 21] treatments with

metoprolol for 12 to 18 months or with bisoprolol for 4 to 44 months, was associated with fewer hospitalizations.

Our study indicates that, carvedilol therapy was associated with a reduction in hospitalization for cardiovascular causes compared with metoprolol therapy. The decrease in hospitalizations for cardiovascular causes seen with carvedilol in our study reaffirms these earlier observations.

We consider as a limitation of our study the small number of patients evaluated. It can seem that the study is limited only in one city, but the patients enrolled are representative of the whole country and not just of the Tirana city because this is the greatest cardiology center in Albania.

CONCLUSION

The findings of this study suggest the superiority of carvedilol compared to metoprolol

in terms of efficacy and cost-effectiveness. The use of carvedilol along with the traditional therapy of heart failure patients assures a higher survival rate and a lower hospitalization rate (-1.77days of hospitalization for patient), but an increase of 216 € more a year when compared to the medication of metoprolol in addition with the traditional therapy.

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CONFLICT OF INTERESTS

The authors declare no conflicts of interest regarding the content of this article

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