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Original Study

Outcomes of Beta-Blocker Pharmacotherapy In Patients With Heart Failure

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SUMMARY

Introduction: Heart failure is characterized by a high prevalence both in our country and in the world. Patients with heart failure have an impaired quality of life, are prone to re-hospitalization and have a higher mortality rate. Adequate pharmacotherapy should be set in a proper manner and in accordance with the latest knowledge.
Aim: The aim of the research was to examine the role of beta blockers in patients with HF (ischemic and non-ischemic etiology) as one of the key drugs in their treatment.
Material and Methods: The criteria for the inclusion of patients in the study was an established ejection fraction lower than 30%, they were divided depending into two equal groups, one with ischemic and other with non-ischemic heart failure. Thirty patients participated in the study. Data on beta blocker therapy and treatment outcomes were observed and compared with the recommendations given by the guidelines of the European Society of Cardiology.
Results: The study included more men than women. The largest number of patients were treated with bisoprolol, followed by metoprolol and carvedilol. Regardless of the etiology of heart failure the majority of the patients were treated with a dose of 2.5 miligrams of bisoprolol. Atrial fibrillation was present in slightly less than a third of patients, disregarding the etiology of HF. In the three-year follow-up of our patients, 46.4% died from non-ischemic cardiomyopathy, or 13.2% from ischemic cardiomyopathy.
Conclusion: Most patients were on appropriate beta-blocker therapy according to guidelines. Atrial fibrillation has been confirmed as a poor prognostic parameter. A three-year follow-up of our patients showed a high percentage of deaths, but no association of beta-blocker dose with poor outcomes.

Keywords: Bisoprolol, Metoprolol, Carvedilol, Guideline, Atrial Fibrillation

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INTRODUCTION

According to International Classification of Diseases 10th Revision (ICD-10), heart failure (HF) is a clinical syndrome caused by many diseases, characterized by the inability of the heart to pump an adequate amount of blood according to the needs of the organs and tissues, at rest and with effort, despite normal blood flow to the heart. By etiology, HF can be divided into ischemic (verified coronary disease) and non-ischemic (valvular, hypertensive, as a result of arrhythmias, congenital heart defects, radiation and chemotherapy, after myocarditis, infectious, caused by drugs, infiltrative, due to pericarditis, metabolic, idiopathic cardiomyopathy) [1].

Today, approximately 60 million people worldwide are thought to be diagnosed with HF with an annual incidence of 3/1000. Mortality as a result of HF is high and ranges from 15 to 60% annually. Nowadays, HF is the most common discharge diagnosis in people over 65 [1]. Considering the number of people suffering from HF, it is considered a global pandemic [2]. Approximately 1-2% of the adult population in Western countries suffer from HF, and its prevalence increases with age and is over 10% among people over 70 years old [3]. Since there is no accurate data on the number of people suffering from HF in Serbia, the data on the number of people suffering from diseases of the heart and blood vessels, which in a significant percentage contribute to the occurrence of HF, are given. The number of deaths from diseases of the heart and blood vessels in Serbia was 52102 (23788 of them were men, while 20314 were women). Women (54.3%) died more often than men (45.7%) from this group of diseases. Ischemic heart and cerebrovascular diseases are the leading cause of death in this group of diseases [4].

The quality of life of these individuals is reduced to varying degrees, and the final outcome is poor, with a survival rate worse than that of colon, breast, or prostate cancer. The economic effect of this disease is no less significant, the total costs of HF measured in 197 countries are estimated at about 108 billion dollars per year [5].

In the developed world and in our country, the leading cause of HF is coronary heart disease (about 70% of cases), followed by arterial hypertension (53-66% of cases), tachyarrhythmia, most often atrial fibrillation (21-42%), followed by cardiomyopathy (10%) and valvular heart disease (10%). Among the causes are endocrine diseases (diabetes in about 40% of cases, hypothyroidism, hyperthyroidism, pheochromocytoma, increased growth hormone production, adrenal insufficiency, Cushing's syndrome), viral infections (often undiagnosed), toxins (alcohol, cocaine, mercury, cobalt, arsenic), drugs (cytostatics, antiarrhythmics, calcium channel blockers, nonsteroidal anti-inflammatory drugs), kidney failure (in about 30% of cases), amyloidosis, sarcoidosis, hemochromatosis, connective tissue diseases, thiamine, selenium, carnitine deficiency, HIV infection [3,6,7]. Identification of different pathologies should be part of the diagnostic procedure in order to determine an adequate therapeutic protocol.

In the last decade, the therapeutic approach to HF has undergone major changes. The modern therapeutic approach implies not only the improvement of symptoms, but also the prevention of the transition of asymptomatic cardiac dysfunction to symptomatic HF, stopping the progression of HF and reducing mortality. Blockers of beta adrenergic receptors are the most commomly used and prescribed drugs in modern cardiology. The have changed how we perceive treatment and the natural history of a number of diseases of the heart and blood vessels. Today, they are used in the treatment of all forms of ischemic heart disease, they are the most important drugs in the treatment of patients after myocardial infarction, hypertension, arrhythmia, congestive HF, hypertrophic cardiomyopathy. Beta blockers can be defined as drugs that have an antagonistic effect on the action of catecholamines (adrenaline and noradrenaline), by blocking structures called beta adrenergic receptors. This action of beta receptor blockers occurs through competitive antagonism. With the development of the third generation of beta blockers, which are characterized by strong vasodilator properties, significant success was achieved in the treatment of HF [6,8]. The European Association for Heart Failure has given standards for the treatment of HF in accordance with the accreditation criteria of the European Association of Cardiology, according to which only four beta-blockers can be used in the treatment of HF. These are carvediolol, metoprolol succinate, nebivolol and bisoprolol. The last two of the listed retain their selectivity even at high doses.

AIM

The aim of the research was to examine the role of beta blockers in patients with HF (ischemic and non-ischemic etiology) as one of the key drugs in their treatment.

MATERIAL AND METHODS

The case series was designed as an academic, prospective, non-interventional study. The patients were monitored for three years (from 2017 to 2019), and the data was collected at the Polyclinic Kovačević in Novi Sad, Republic of Serbia. The criteria for the inclusion of patients in the study was an established ejection fraction of less than 30%. In addition to beta blockers, all patients also received other drugs that are recommended by the current guides. Patients were divided into two large groups depending on the etiology of HF: ischemic (clearly verified significant coronary disease) and non-ischemic. The analysis included 30 patients (11 female and 19 male). Fifteen patients had non-ischemic and 15 ischemic cardiomyopathy, with an ejection fraction less than or equal to 30%.

In the mentioned period, beta blocker therapy was analyzed: type of beta blocker, dose, titration. At the same time, the following were monitored: mortality, the number of hospitalizations/rehospitalizations due to cardiac decompensation and the associated occurrence of atrial fibrillation. Findings were compared with relevant current guidelines (2021 heart failure guidelines) [9].

RESULTS

In the studied sample of 30 patients with HF, there were 19 (63.3%) men and 11 (36.7%) women, as shown in Figure 1.

The largest number of patients were treated with bisoprolol (64.5% in ischemic cardiomyopathy and 57.7% in non-ischemic cardiomyopathy), followed by metoprolol (29% in ischemic and 30.8% in non-ischemic cardiomyopathy) and carvedilol (it was not prescribed in ischemic cardiomyopathy and 3.9% in non-ischemic cardiomyopathy). Patients who did not receive beta blocker therapy are represented in 6.5% in ischemic or 7.7% in non-ischemic cardiomyopathy. The percentage representation of individual beta blockers is shown in Figure 2.

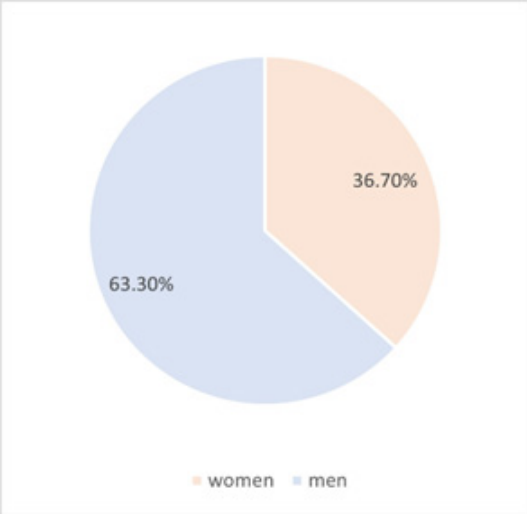

Figure 1. Percentage of HF among genders

The largest number of patients were treated with a dose of 2.5 mg of bisoprolol regardless of the etiology of HF (32.3% in non-ischemic and 30.8 in ischemic cardiomyopathy). A dose of 5 mg was given to 22.6% of patients in the ischemic, resp. 15.4% of patients in non-ischemic cardiomyopathy. With the smallest dose of bisoprolol (1.25 mg), 9.7% of ischemic patients were treated, or 11.5% of patients with non-ischemic cardiomyopathy. Metoprolol succinate in a dose of 47.5 mg was used in the treatment of ischemic cardiomyopathy in 3.2%, and in a dose of 90 mg in 19.4% of cases. A dose of 47.5 mg in non-ischemic cardiomyopathy is present in 15.4%, and a dose of 90 mg in 7.7% of patients. Metoprolol tartrate in doses of 75 and 100 mg was given to 3.2% of patients with ischemic cardiomyopathy, while 3.9% of patients with non-ischemic HF were treated with doses of 50 and 100 mg. Carvedilol was not prescribed to patients with ischemic HF, while 3.9% of patients with non-ischemic HF recived carvedilol at a dose of 12.5 mg. The doses of beta-blockers administered to the observed patients are shown in Table 1.

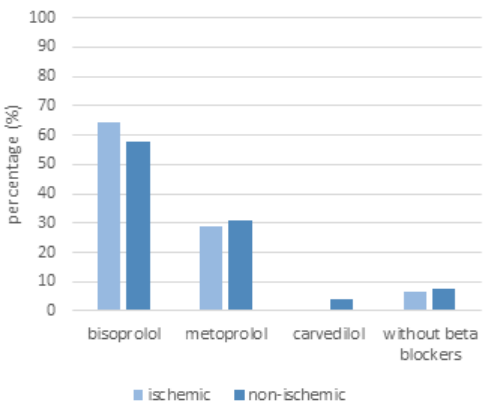

Figure 2. Percentage representation of certain beta blockers

Table 1. Beta blocker doses

Drug	Dose (mg)	Patients with ischemic cardiomyopathy (%)	Patients with non-ischemic cardiomyopathy (%)
bisoprolol	1.25	9.7	11.5
	2.5	32.3	30.8
	5	22.6	15.4
metoprolol succinate	47.5	3.2	15.4
	90	19.4	7.7
metoprolol tartarate	50	0	3.9
	75	3.2	0
	100	3.2	3.9
carvedilol	12.5	0	3.9
Without drugs	0	6.4	11.4

Atrial fibrillation was present in slightly less than a third of patients, regardless of the etiology of HF. Practically the same percentage occurred in patients with ischemic and non-ischemic HF (Table 2).

In the three-year follow-up of our patients, 46.4% died from non-ischemic cardiomyopathy, or 13.2% from ischemic cardiomyopathy (Table 3).

DISCUSSION

Beta blockers regulate the increased tone of adrenaline in HF which is a hyperadrenergic state. It is caused by a decrease in cardiac output, leads to a reaction of the body in the form of neurohumoral activation, remodeling of the left ventricle and oxidative stress, which has a negative effect on the body. Medicinal therapy of HF is aimed at regulating the body's excessive response to reduced cardiac output. That is why beta blocker therapy is important. It is basically a solution to a paradox, which is that drugs with a negative inotropic effect can help improve contractility. The first reaction of the body to the decreased cardiac output is an increase in the concentration of adrenaline and noradrenaline which via beta receptors (primarily beta-1 receptors) increase contractility and have a positive inotropic effect. This is a desirable and positive reaction of the organism that becomes bad over time. The number of beta receptors increases (more beta-1, and less beta-2 and alpha receptors) because the need for adrenaline increases. Due to an excessive number of beta signals to which the cell can no longer respond, there is a drop in myocardial contractility, which represents a negative phase in the body's reaction to reduced cardiac output. Beta blockers reduce this increased reaction of the body by blocking beta receptors, and thus the number of signals is normalized and the cell recovers. Cell recovery takes 10-15 days, which is why beta blockers are used in small doses at the beginning of HF therapy. That dose is increased after 10 to 15 days. Small doses of beta blockers are used at the beginning of therapy, in order to avoid side effects that occur with the use of higher doses. In the three-year follow-up of patients, beta blockers were used in more than 98% of cases, which is in accordance with current valid guidelines on the treatment of HF. Beta blockers have been shown to be useful because: they protect against the proarrhythmic effect of catecholamines, inhibit the renin-angiotensin-aldosterone system, slow down the pulse and reduce cardiac output, reduce oxygen con-

Table 2. Atrial fibrillation in HF

Ischemic cardiomiopathy		Non-ischemic cardiomiopathy	
Number of patients	15	Number of patients	15
Patients with atrial fibrilation	5	Patients with atrial fibrilation	4
Deceased	0	Deceased	3
Mortality	0%	Mortality	75%

Table 3. Mortality and survival rate

	Ischemic	Non-ischemic
Mortality rate	13.2%	46.4%
Survival rate	86.8%	53.6%

sumption - anti-ischemic effect, reduce end-diastolic volume and end-diastolic pressure, increase the ejection fraction, prevent further remodeling of the left ventricle.

Bisoprolol and metoprolol succinate were used most often. Carvedilol was the least used in therapy, although its additional positive effects such as antioxidant activity [8] or alpha blockade are known (useful for elderly patients). A small percentage of patients (about 7%) did not receive a beta blocker in therapy. The probable explanation lies in the low blood pressure of these patients and the impossibility of applying beta blockers in such clinical situations, as well as global respiratory insufficiency in one of the patients. This probable explanation has no support in today's modern understanding of HF. Concomitant diseases are not a sufficient reason for discontinuation of beta-blocker therapy. Not taking these drugs in HF is to the detriment of the patient. The use of metoprolol tartrate in HF is not supported by clinical studies or current guidelines. The explanation is not reasonable and probably lies in the automaticity of prescribing this drug as well as its long-standing presence on the market, ie the habits of doctors and patients.

Today, four beta blockers are considered to be used in HF: bisoprolol, carvedilol, long-acting metoprolol, and nebivolol. In patients with HF, dose titration of beta blockers is necessary. It starts with a small dose that is successively increased (every two weeks) depending on the patient's clinical condition, frequency and blood pressure [9].

In case of deterioration of the patient's condition, it is necessary to reduce or stop the dose of beta blockers and increase the dose of diuretics. If ACE inhibitors were also used in the therapy, we will omit their application so that beta blockers can be administered without interruption. Evidence was provided in the CIBIS II study that established the use of beta blockers in HF (NYHA class III/IV). What is interesting in this study is that the trial was stopped much earlier, after one year and three months, because treatment with beta blockers significantly reduced all causes of mortality, so it was inhumane to leave patients without beta blockers. The study showed a significant survival and reduction of all events after (sudden death, death due to pump dysfunction and rhythm disturbance) administration of bisoprolol. It has also been shown that doses should be maintained at the level tolerated by the patient, but aim for target doses, as well as a significant increase in mortality with the cessation of bisoprolol administration. Based on the conducted research, it was determined that the maintenance of the dose of bisoprolol is based on the individual tolerance of each patient and that a small dose is better than none [9].

In our work, atrial fibrillation was represented almost equally in patients with ischemic and non-ischemic HF (NYHA III/IV), which coincides with the results of large studies. According to the data of other authors, atrial fibrillation is common in advanced HF, but its association with mortality is controversial. In our study, three nonischemic cardiomyopathy patients out of four with atrial fibrillation (75%) died during the 3-year follow-up. Our findings are consistent with those of large studies where atrial fibrillation has been shown to be a poor prognostic sign in patients with HF. This study showed that in patients with ischemic and non-ischemic cardiomyopathy and atrial fibrillation, it is an independent risk factor for reduced survival [11].

Limitations of this study include the small sample size and the suboptimal titration of beta blocker doses. The target doses were not achieved due to concerns about bradycardia and hypotension. Future research should incorporate a larger cohort to provide a more definitive assessment of the association between beta blocker use and adverse outcomes in patients with HF.

CONCLUSION

More men than women with HF participated in our study, and the majority (98%) were on beta blocker therapy. Beta-blocker dose titration was followed according to current guidelines. The target dose of beta-blockers was not reached in our patients with HF, which is consistent with the results of other authors. Atrial fibrillation was a poor prognostic sign in our patients with HF (75% mortality in nonischemic cardiomyopathy), very frequent rehospitalizations were noted (19 times in ischemic and 18 times in nonischemic cardiomyopathy). Three-year follow-up of our patients showed a high percentage of deaths (46.4% in non-ischemic and 13.2% in ischemic cardiomyopathy), but no association of beta-blocker dose with poor outcomes.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

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Ishodi farmakoterapije beta blokatorima kod pacijenata sa srčanom insuficijencijom

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KRATAK SADRŽAJ

Uvod: Srčanu insuficijenciju odlikuje visoka prevalencija kako kod nas, tako i u svetu. Pacijenti sa srčanom insuficijencijom imaju narušen kvalitet života, skloni su rehospitalizaciji i imaju visok mortalitet. Adekvatna farmakoterapija treba da bude postavljena na pravilan način i u skladu sa najnovijim saznanjima.
Cilj: Cilj istraživanja bio je da se ispita uloga beta blokatora kod pacijenata sa HF (ishemične i neishemične etiologije) kao jednih od ključnih lekova u njihovom lečenju.
Materijal i metode: Kriterijum za uključivanje pacijenata u studiju bio je utvrđena ejekciona frakcija manja od 30%, a podeljeni su u zavisnosti od etiologije u dve jednake grupe na one sa ishemijskom i one sa neishemijskom srčanom slabošću. U studiji je učestvovalo 30 pacijenata. Posmatrani su podaci o terapiji beta blokatorima i ishodima lečenja i poređeni sa preporukama datim smernicama Evropskog udruženja kardiologa.
Rezultati: U ispitanom uzorku bilo je više muškaraca. Najveći broj pacijenata bio je na terapiji bisoprololom, potom metoprololom i karvedilolom. Najveći broj pacijenata lečen je sa dozom od 2,5 mg bisoprolola bez obzira na etiologiju srčane insuficijencije. Atrijalna fibrilacija bila je zastupljena u nešto manje od trećine pacijanata bez obzira na etiologiju HF. U trogodišnjem praćenju naših pacijenata umrlo je 46,4% od neishemijske kardiomiopatije, odnosno 13,2% od ishemijske kardiomiopatije.
Zaključak: Većina pacijenata je bila na odgovarajućoj terapiji beta blokatorima u skladu sa smernicama. Atrijalna fibrilacija je potvrđena kao loš prognostički parametar. Trogodišnjim praćenjem naših pacijenata zabeležen je visok procenat umrlih, ali ne i povezanost doze beta blokatora sa lošim ishodima.

Ključne reči: bisoprolol, metoprolol, karvedilol, smernica, atrijalna fibrilacija

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