

Conservative and Device Treatments for Chronic Heart Failure: Comparative Research

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Abstract

Being a very common condition among the whole population of the world, often leading a life-threatening illness and having high risk and mortality rate, chronic heart failure (CHF) is also a major public health problem for the world. Our goal is to investigate what has been achieved in the treatment of CHF patients with a left ventricular ejection fraction (LVEF) <40% recent years. In recent years, it is revealed that BNP has been crucial in the pathogenesis of heart disease. Due to this reason, we tried to investigate the results of the complex medical treatment method performed with the combination of sacubitril/alsartan which angiotensin is receptor neprilysin inhibitor in CHF patients. We also investigated the device treatment methods used in the treatment of these patients, particularly the cardiac resynchronization therapy. Finally, we investigated the results of the complex medical treatment method performed with the combination of sacubitril/valsartan which is angiotensin receptor neprilysin inhibitor in comparison with the those of the cardiac resynchronization therapy.

Keywords: Chronic heart failure; Neprilysin inhibitor/sacubitril and valsartan; Cardiac resynchronization therapy

aldosterone secretion, antihypertensive and antifibrotic effects, lipolysis and mitochondrial biogenesis can be attributed to these effects of natriuretic peptides in the organism [8].

Introduction

Heart failure is a clinical syndrome characterized by typical symptoms (e.g. dyspnoea, swelling of the heel and fatigue) accompanied by signs of structural or functional abnormalities (e.g. high intravascular venous pressure, pulmonary edema, and peripheral edema) in the heart [1,2]. According to data provided in 2017, 26 million people worldwide suffer from heart failure [3,4]. This number is increasing every year for a number of reasons all over the world. These reasons include especially malnutrition and obesity, diabetes mellitus that is increasing every year, increase in smoking, hypertension, and an increase of alcohol consumption. Thus, it is estimated that the number of patients suffering from heart failure only in the United States will rise to 8 million by 2030. Generally, most patients with heart failure die in the first 5 years after the diagnosis [5].

In the pathophysiology of chronic heart failure – there is a complicated complex of disorders of the cardiovascular and neurohormonal system leading to the development of stagnant manifestations [6]. There is a balance between vasodilator and vasoconstrictor neurohormonal systems in practically healthy individuals [6]. In recent years, a number of studies have been conducted to investigate the pathogenetic role of natriuretic peptides in the pathogenicity of heart failure. Thus, natriuretic peptides play a role in regulating the activity of cardiovascular, skeletal, nervous, reproductive and other systems by activating transmembrane quanyl cyclases and by increasing their intracellular concentration [7]. The activity of natriuretic peptides, in particular BNP, causes a number of significant cardiac and renal effects. This effect is widely mentioned in an article by Kobalava Z, Kotovskaya Y, Averkov O and others in 2016. Decline of arterial blood pressure, vasodilation, increased diuresis and natriuresis, increase in soft tissue filtration, decrease in renin and

Literature Review

Atrial natriuretic peptide (ANP) is essentially stored as a propeptide in atrial pellets and enters the bloodstream in response to atrial tension [7]. B-type natriuretic peptide is also found in atrial pellets, but also it reaches a high level in the ventricle of heart during its intensive work. Such cases are most commonly seen in the patients with congestive heart failure [7]. An article written by James L. Januzzi, referring to the natriuretic peptides, indicates that BNP and pro-BNP have an important role in medicine in recent years. In particular, there is a significant role in both diagnosis and evaluation of heart failure. Therefore, at present, both BNP and NT-pro BNP are tested worldwide to evaluate patients with suspected or confirmed HF, as well as their role in managing disease progression.

Due to the development of tests for the measurement of natriuretic peptides these important biomarkers have started to be regarded as biological mediators of the cardiovascular system and are important clinical solutions for diagnostic and prognostic evaluation of patients with heart failure nowadays. Generally, after the BNP and pro-BNP test being began, the approach to the diagnosis and evaluation of heart failure has changed. Additionally, this article shows that taking BNP as a therapeutic target to achieve better treatment of heart failure patients may lead to some changes in modern cardiology [9].

Another article in this regard shows that the measurement of natriuretic peptides and its use as in addition to echocardiography are of great importance for the evaluation of clinical manifestations for the diagnosis of HF in patients suffering from dyspnoea. After the appropriate diagnosis, the plasma concentration measured in each patient reflects its current hemodynamic status and predicts its future clinical outcomes [10]. In another study on the diagnostic accuracy of

natriuretic peptides in heart failure in 2015, the following results were obtained. In this meta-analysis, 15263 test results were used in 37 coronary studies [10]. In general, the correct diagnosis is difficult in the patients with the possibility of heart failure and it is approved only in 40-50% cases. Many studies on heart failure diagnosis showed that during the diagnosis of heart failure the measurement of natriuretic peptide levels in plasma, along with collection of the patient's history, clinical examinations and conventional examinations (chest x-ray, etc.) increases the number of symptoms diagnosed correctly. Therefore, in the international guidelines of recent years on the diagnosis and treatment of heart failure it is recommended that these indicators should be used during diagnosis [10].

In 2012, the European Society of Cardiology adopted the B-type natriuretic peptide level ≤ 100 ng/l in plasma and N terminal pro-natriuretic peptide level ≤ 300 ng/l in the heart failure guidelines [10]. Studies have shown that there is no statistical difference between the measurement of BNP or that of NT proBNP in plasma for diagnostic accuracy. The use of these measurements in patients with acute heart failure can help diagnose or reject a diagnosis quickly [10]. Thus, the following results have been achieved as a result of this meta-analysis. Measuring the level of the natriuretic peptide will decrease the need for echocardiography in patients with the natriuretic peptide in plasma being under the normal rate and thus, result in cost savings. At the same time, it will also help to detect non-cardiac patients more quickly [10].

The articles on this subject show that there are important relationships between BNP and lipid metabolism. In addition, patients with normal body weight and patients suffering from obesity are reported to have different regulators of the secretion and activity of natriuretic peptides. The obesity pandemic is the leading cause of increased morbidity and mortality worldwide. Obesity is a risk factor for arterial hypertension, hyperlipidemia, diabetes and left ventricular hypertrophy. These indicators are also a risk factor for chronic heart failure [11]. The available data indicate that there is a correlation between BNP and NT-proBNP and body mass index. Increased body weight adversely affects the BNP and pro BNP levels. Reduced NP levels, in turn, have a negative effect on heart failure.

Treatment Methods for Chronic Heart Failure

Classical conservative treatment of chronic heart failure

Currently, the use of many new medications and device treatments has been started to treat patients with chronic heart failure [12]. Modern principles of current treatment techniques are based on the pathogenic concept that develops as a result of the long-term activation of the CHF neurohormonal system. This is primarily the renin-angiotensin-aldosterone and sympathetic-adrenal systems, which are considered as pathogens of high activity in patients with poorly predicted chronic heart failure. From a theoretical point of view, the combined use of different groups of neurohormonal modulators may provide additional advantages as a result of more complete neurohormonal blockade in the treatment of patients with chronic heart failure. The essence of such a concept is quite simple, the higher the degree of different levels of neurohumoral regulation, the better the result [12].

In recent years, the use of angiotensin-reducing enzyme inhibitors, beta-blockers, in combination with cardiac glycosides and diuretics, has been routinely used in the treatment of patients with CHF. Thus,

ACEI has been a major drug regulator for RAAS components for a long time, which has, in fact, improved not only the clinical course of the disease, but also the prognosis of patients with CHF. The mechanism of the ACE inhibitors has been widely studied in recent years. The ACEI has a double blockade: the formation of angiotensin II (AII) and the destruction of bradykinin, showing its effect through nitrogen oxide and vascular prostanoid. It has also been discovered that ACEI cannot adequately adjust the RAAS activity during long-term use, even when using its maximum doses [12].

The guidelines of the European Society of Cardiology should be followed correctly in the treatment of patients with CHF decompensation and severe edema. Along with medication, control over nutrition, the amount of water and salt taken by the patient, should be strengthened. It is recommended that the daily dose of the salt taken by patients should not be more than 2-3 gms and the daily amount of liquid taken should not exceed 750-800 ml in aggravated disease duration [13]. Diuretic is the basis of severe edema - the treatment of hyperhydration. Diuretics are a drug group that plays a key role in the accumulation of fluid in the body, the recovery of patients with severe edema, and the improvement of the quality of life of the patients.

Although diuretics do not affect the prognosis of the CHF and the progression of the disease, with their help the burden of the large and smaller blood circulation is reduced, dyspnea and edema with excess fluid is removed and the quality of life of the patients is improved. In the case of severe decompensation, inadequate administration of diuretics decreases the quality of treatment and can further aggravate the condition of the patients. So, the low doses increase edema and dyspnea, as well as high doses can lead to the hypotension, electrolyte disorders and complications such as dangerous arrhythmias [13].

In general, dehydration treatment is carried out in two - active and depressive stages. In the active phase, which is the initial stage of treatment, the amount of urine extracted from the body should not exceed the amount of liquid taken more than 0.8-1 lts. If this amount exceeds 2.5 lts, it will result in the excessive RAAS and SAS activation, so "ricochet effect", which makes it even more difficult to treat the disease. Effectiveness of dehydration treatment can also be monitored by controlling body weight. If the weight of the patient decreases by one kilogram per day, this indicates that the dehydration therapy has a good effect [13]. Therefore, if there is no reflection in the treatment of all patients with CHF, diuretics should be initiated from the first days at the appropriate dosage according to the guidelines. Of course, this treatment should be done in combination with the ACEI (ARB) and AA (MRA) [13].

In the treatment of these patients, extensions in life survival were recorded after initiating the use of β -blockers, angiotensin converter enzyme inhibitors, angiotensin receptor neprilysin inhibitor, hydralazine plus nitrate and aldosterone antagonists. However, there is little evidence of positive effect of diuretic treatment on life survival. Currently, the use of a new drug, the neprilysin inhibitor, has been widely used in the treatment of CHF. Angiotensin converter enzyme inhibitors or angiotensin receptor blockers may be substituted by an optimally dose of angiotensin receptor neprilysin inhibitor in the treatment of II-III functional class (NYHA) heart failure and chronic symptomatic patients with adequate blood pressure. In this case, the angiotensin receptor neprilysin inhibitor should not be given within 36 hours after the last dose of angiotensin converter enzyme inhibitors [14]. Despite the short-term beneficial effects of the drugs used in the treatment of heart failure, the absence of a positive effect on long-term

outcomes has led to the study of regulatory authorities, clinical practice guidelines, morbidity and mortality rates and thus, the adoption of therapeutic guidelines for heart failure [2,15].

Guidelines of the European Society of Cardiology in 2016 also show that ACEI reduce the mortality and morbidity in the patients with HFrEF. Thus, its use is recommended in the treatment of all symptomatic heart failure [2]. While using ACEI, it should be titrated to achieve adequate inhibition of the renin-angiotensin-aldosterone system (RAAS) [2]. In clinical practice, there is evidence that many patients have received ACEI in suboptimal doses [2]. Also, ACFI is recommended for the patients with asymptomatic systolic dysfunction of the left ventricle in order to reduce heart failure symptoms, hospitalization and risk of death due to heart failure [2].

Diuretics should be tested for patients with signs of degrade and decompensation. There is an agreement that beta blockers and ACEI are complementary and that they can be initiated together after the HFrEF has been diagnosed. There is no evidence to favor the initiation of treatment with beta-blocker prior to commencement of ACEI. Beta-blockers should be initiated in clinically stable patients with low doses and should gradually be titrated to a maximum tolerable dose. In patients admitted to the hospital because of acute heart failure, beta-blockers can be started with caution in the hospital after stabilizing the patient's condition [2]. The meta-analysis of individual patient data in all key research done with beta-blockers in HFrEF patients has showed that beta-blockers do not have any benefit to reduce hospitalization and mortality in the subgroup of HFrEF patients with atrial fibrillation [2,16].

Other drug groups used in the treatment of heart failure may include mineralocorticoid receptor antagonists. This group of preparations - spironolactone and eplerenone - blocks receptors that bind aldosterone and other nearby steroid hormones (e.g. corticosteroids, androgens). Spironolactone or eplerenone is recommended for all symptomatic patients (despite ACEI and beta-blockers treatment), especially in HFrEF patients with LVEF \leq 35%, to reduce the mortality rate and the hospitalization of heart failure [2]. Care should be taken when MRA are used in patients with renal failure and potassium level >5.0 mmol/L in plasma. In such cases, the level of potassium in the plasma and the renal function should be checked regularly in accordance with the clinical condition of the patient [2].

In the guidelines of the European Society of Cardiology in 2016, diuretic is a prime concern in the treatment of heart failure. Doses of diuretics are selected as a result of clinical observations [17]. The progressive condition of patients with chronic heart failure, such as the occurrence of edema or increased edema, dyspnea and signs of stagnation in the lungs, are associated with the slowing down of fluid in body. Diuretics are recommended for all patients with stagnation symptoms and complaints, regardless of the ejection fraction [18].

Diuretics in the treatment of chronic heart failure can be conditionally divided into three main groups:

1. Thiazide and thiazide-like diuretics (with poor diuretic effect)
2. Loop diuretics with strong effect
3. Potassium-sparing diuretics

The 2016 guidelines also emphasize that although diuretics are advised to reduce the load and symptoms in patients with HFrEF, their effect on reduce in mortality and morbidity has not been investigated in randomized studies [2]. According to the Cochrane meta-analysis,

in patients with chronic heart failure, loop and thiazide group diuretics reduce the risk of death and deterioration and increase physical activity compared to placebo [2]. During treatment with torsemide, cardiac measurements were reduced in all subgroups regardless of etiology and weight. These advantages of torsemide are explained by its additional effects on RAAS and SAS, and the good compliance of patients with diuretics treatment. The use of torsemide in the treatment of patients with chronic heart failure can lead to high survival of patients [19].

In addition, the guidelines show that new therapeutic agents and neutral endopeptidase systems, angiotensin receptor nephritis inhibitor, that affect RAAS have been developed [2]. It is noted that the degradation of NP, bradykinin and other peptides slows down when neprilysin is inhibited. Highly cyclical A (ANP) and B (BNP) type natriuretic peptide build up physiological effects by combining with NP-receptors and increasing cGMP, thereby increase diuretics, natriuresis, myocardial discharge and anti-remodeling [2]. An anticoagulant therapy in the treatment of chronic heart failure is usually initiated in patients with atrial fibrillation. The guidelines of the European Society of Cardiology in 2016 indicate that patients with HFrEF who has also with atherosclerosis or venous thromboembolism should have anticoagulant admission [2]. It is also noted that non-dihydropyridine calcium-channel blockers (CCB) are not instructed for the treatment of patients with HFrEF. The use of diltiazem and verapamil in patients with HFrEF is indicated to be dangerous. There is evidence of the safety of amlodipine and felodipine in patients with HFrEF and they may only be used with absolute indications [2].

According to the information we have received from the world literature, it is clear that in recent years a number of achievements have been made in the treatment of chronic heart failure. One of them is the addition of sacubitril/valsartan complex which is an angiotensin receptor and a neprilysin inhibitor to the existing therapeutic remedies for heart failure with low ejection fraction.

The use of sacubitril/valsartan in conservative treatment of chronic heart failure

In recent years, a new drug has been used in the conservative treatment of chronic heart failure patients with low ejection fraction. Thus, in the Paradigm-HF study, a detailed combination of sacubitril/valsartan was found to have a positive effect on the treatment of chronic heart failure patients with low ejection fraction. Numerous studies have been conducted on the research of this new drug, and the research is still ongoing. In the Paradigm-HF study, being one of such studies, it has been found that conservative treatment with sacubitril/valsartan is more beneficial than the treatment method with enalapril and endogenous natriuretic peptides reduce recurrence and mortality rates in heart failure patients with low ejection fraction [20].

Thus, the degradation of NP, bradykinin and other peptides is slowed down when neprilysin is inhibited. Highly cyclical A (ANP) and B (BNP) type natriuretic peptide build up physiological effects by combining with NP-receptors and increasing cGMP, thereby increase diuretics, natriuresis, myocardial discharge and anti-remodeling. ANP and BNP inhibit renin and aldosterone secretion. Affecting RAAS, it reduces vasoconstriction, sodium and water in the body and myocardial hypertrophy [2].

In a study involving 8442 patients with II-IV functional class heart failure, the following findings have been reported: in a study covering patients with low ejection fraction heart failure both angiotensin II and

sacubitril/valsartan which is neprilysin inhibitor have been found to be more effective in reducing the risk of death and re-hospitalization cases due to heart failure or other cardiovascular causes compared to enalapril. Besides reducing the risk of death, it is also found that sacubitril/valsartan combination reduces the symptoms of heart failure and the physical limitations of the disease. The advantages of this new drug were observed in patients with heart failure who took all the other known drugs (beta-blockers and mineralocorticoid receptor antagonists) to improve survival [20].

As a result of the study, the effect of sacubitril/valsartan in reducing the risk of death and re-hospitalization in patients with heart failure is higher than that of enalapril alone, which is angiotensin receptor. Regarding cardiovascular death, the beneficial effects of sacubitril/valsartan compared to enalapril are at least as great as the effect of long-term treatment of placebo with enalapril. This finding is a strong indication that joint inhibition of angiotensin receptor and neprilysin in patients with chronic heart failure is superior to the inhibition of renin-angiotensin system [20]. The data provided in the research published in 2016 suggests that the long-term activity of the natriuretic peptide system, along with blocking the renin-angiotensin-aldosterone system, can provide therapeutic results in the treatment of HFrEF patients.

In general, a series of studies on the use of sacubitril/valsartan combination in the treatment of heart failure have been conducted. In another study, angioedema formation characteristics of enalapril which is angiotensin converting enzyme inhibitor and used in the treatment of heart failure patients with low ejection fraction have been investigated comparatively with the those of angiotensin II and sacubitril/valsartan which is neprilysin inhibitor. Thus, inhibition of ACE, and co-inhibition of ACE and neprilysin, may increase the risk of angioedema, this was an adverse event of special interest. This study demonstrated significant clinical benefits for sacubitril/valsartan (an angiotensin receptor neprilysin inhibitor) versus the angiotensin-converting enzyme inhibitor (ACEI) enalapril in patients with heart failure with reduced ejection fraction.

In the study covering randomly selected 10513 patients, confirmed event was experienced by 15 patients (0.14%) in enalapril run-in, by 10 patients in sacubitril/valsartan run-in and respectively by 10 (0.24%) and 19 (0.45%) patients in the corresponding randomized arms during the double-blind phase. The frequency of confirmed angioedema was higher in black patients. Most events were mild. Only five patients required hospitalization, and none required mechanical airway support. So, there was no-marked excess risk of angioedema with sacubitril/valsartan versus enalapril.

In general, the frequency of angioedema in black patients is higher than in other patients. The number of confirmed events in this study was low [21]. In another study we considered it was investigated how many of the patients with chronic heart failure were suitable for the use of sacubitril/valsartan. The findings show that sacubitril/valsartan is more effective than enalapril in some patients with heart failure. It is not clear which part of the heart failure patients is suitable for sacubitril/valsartan. But sacubitril/valsartan is a significant improvement in the management of symptoms of patients with HFrEF. The results of this study showed that when selective criteria for PARADIGM-HF were applied strictly, more than 25 percent of patients with HFrEF could be eligible for sacubitril/valsartan in the end [22].

In another study, the prevalence of pre-diabetes condition among patients with HFrEF and the consequences of this condition in the progression of the disease were investigated. During this study, 8399 patients were monitored. During this study, dysglycemia was found to be intense among the DAFUC patients and it has been discovered that this condition often results in unpleasant cardiovascular events. Compared with patients with HbA1c <6.0%, more complications were found in patients with pre-diabetes condition during the study. Regardless of the glycemic status of the patients, sacubitril/valsartan showed superior results compared to enalapril [23].

Heart failure and diabetes are two major epidemics of the modern age [23]. Diabetics is considered a risk factor for heart failure, but there are few studies that investigate the relationship between them [23]. In a study conducted in 2018, the role of sacubitril/valsartan in the treatment of sleep apnoea syndrome in patients with chronic heart failure was investigated sleep-disordered breathing is a highly prevalent co - morbidity in these patients and can play a detrimental role in the pathophysiology course of chronic heart failure. Approximately 76% of patients with HFrEF may experience Sleep-disordered breathing. The best way to manage sleep-disordered breathing in chronic heart failure is still a matter of debate [24].

Sacubitril and valsartan are good candidates for correcting sleep-disordered breathing (SDB) of chronic heart failure patients because their known mechanisms of action are likely to counteract the pathophysiology of sleep-disordered breathing in chronic heart failure [24]. Sacubitril-valsartan has been included in the 2016 European Society of Cardiology guidelines as an alternative to angiotensin - converting enzyme inhibitors to further reduce the risk of progression of CHF, CHF hospitalization, and death in ambulatory patients.

From the studies we have considered, the use of sacubitril/valsartan is one of the most important achievements in the treatment of chronic heart failure. Thus, with the use of sacubitril/valsartan, pathogenetic treatment of chronic heart failure has been completed. This has led to new studies on the use of device therapy in treating chronic heart failure.

Discussion

Device treatment of chronic heart failure

Along with the drug treatment of chronic heart failure, the device treatment is also highly developed. The implantations of cardiac defibrillators and cardiac resynchronization treatment have been widely used worldwide in recent years. ICDs are mainly used in the treatment of bradycardia, in order to prevent lowering of heartbeat and associated complications. Also, these devices are effective in preventing complications associated with ventricular arrhythmia, which are considered to be potentially deadly complications. Thus, some anti-arrhythmic drugs may reduce the risk of mortality and sudden deaths, but they cannot reduce the overall mortality rate. In some cases, these drugs themselves also cause some adverse effects in the course of the disease [2]. In such cases, ICD implantation may be used. However, the use of ICD in serious patients who are unlikely to live for more than one year is inappropriate. They are unable to obtain significant benefits from this treatment method [25-27].

The purpose of the ICD implantation, the implantation process, the possible complications (mainly inappropriate shocks) associated with the activation of the device, as well as the cases when the device is needed to cancel (terminal status) or remove (infection, rehabilitation

of the left ventricle) should be explained beforehand to the patients to whom this method of treatment is recommended [2]. Other device therapy is the resynchronization treatment method of the heart. The information obtained in this field also indicates that the cardiac resynchronization treatment improves cardiac activity, symptoms and general condition of the patients in the correctly selected patients, reduces the incidence of re-illness and the rate of death [2,28].

In moderate-to-severe patients with heart failure, treatment can lead to improved quality of life in two thirds of patients and to the prolongation of life in one-third [2]. However, all patients do not respond to the cardiac resynchronization treatment. A number of features can affect the course of the disease following the treatment method and the mortality indicator. Because of myocardial scar tissue in patients with ischemic etiology, this treatment progresses less in the left ventricular function. And this reduces the likelihood of beneficial remodeling during cardiac resynchronization treatment in such patients [2]. In some studies, investigating the results of the cardiac resynchronization treatment in men and women, it can be understood that women may react more positively than men due to their small size and heart size [2].

The information on the forms of the cardiac resynchronization treatment given in the 2016 European Society of Cardiology guidelines indicates that in the comparison of the recurrence of illness and the rate of death there is no significant difference between the used devices (CRT-P and CRT-D) during the cardiac resynchronization treatment. In recent years, extensive use of CRTs has led to the need to conduct research aimed at clarifying whether it can be used in different rhythms than the sinus rhythm. Some of these studies have investigated the conduct of CRT in patients with atrial fibrillation. In these studies, CRT was compared with the pharmacological therapies in patients with atrial fibrillation and contradictory results have been made [2].

In the 2016 European Society of Cardiology guidelines it is also noted that there is no benefit from CRT compared to ICD. It has also shown that, when the biventricular injuries are 98%, the prognosis of the improvement of patients with CRT decreases. In general, patients with a large myocardial infarction may have little improvement in the function of the left ventricle with CRT implantation [2]. In general, a number of new drugs and device treatments have been invented in recent years on the treatment of heart failure. And this raises the question of which of these treatments is superior in some cases. Several investigations are also being carried out in connection with such cases.

One of these studies is research by Zaca in 2018. In this study, comparison of sacubitril/valsartan with ICD was conducted in HFrEF patients. As a result of this study, it has been understood that sacubitril/valsartan prolongs life spending at lower costs compared to ICD, and ultimately it has been concluded that medical treatment is more economically viable [29]. So, the results of this model indicate that sacubitril/valsartan prolongs life with lower costs compared to ICD in HFrEF patients. Sensitivity analysis also confirms the economic effectiveness of sacubitril/valsartan in most tested cases [29].

Conclusion

Thus, when examining studies in world literature, we can see that both complex conservative treatment methods including sacubitril/valsartan covering all pathogenic rhinitis (SAS, renin-angiotensin-aldosterone, natriuretic peptide), and device therapy have been widely studied in the treatment of HFrEF patients. However, only a few

studies have been conducted in the comparative studies of these treatments. As the patients undergo surgery during CRT, they may have surgery-related trauma or complications, so in world literature, patients are advised to be informed about this beforehand. Furthermore, patients treated in this way are forced to stop their labor activity even for a short period of time. Moreover, the CRTs are far more expensive than conservative treatment. Complex medication therapy with sacubitril/valsartan can be financially cheaper and can improve patient complaints and functional class performance without any trauma. It is both medical and economically beneficial.

Conflicts of Interest

There are no conflicts of interest for the present study.

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