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Characteristics of Patients with Heart Failure Improved Ejection Fraction (HFiEF) in Outpatient Cardiology Clinic Karangasem Regional Hospital

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Abstract: ***Background: Current heart failure guidelines based on ejection fraction only classify patients as preserved, midrange, and reduced ejection fraction. Meanwhile, there are patients with improved ejection fraction. There are not many studies and data regarding this heart failure subset. Method: Of all chronic heart failure patients who underwent echocardiography examinations in outpatient cardiology clinic Karangasem Regional Hospital from November 2019 to June 2020, 16 patients met the criteria for HFiEF (baseline EF 40% and increased to >40% 1 year later). Characteristics of patients with HFiEF were found more in male sex, younger age, with etiologic coronary artery disease, without diabetes mellitus, and without heart rhythm disturbances. All patients have received therapy according to Guideline - Directed Medical Therapy (GDMT) with the mostly used β - blocker is bisoprolol reaching 50% of the target dose, ACE - inhibitor is ramipril which reached 100% of the target dose, ARB are candesartan and valsartan reaching <50% of the target dose and MRA is spironolactone which given 50% of the target dose. Conclusion: HFiEF is a subset of HF with different characteristics from HFrEF and HFpEF. Patients with HFiEF have better outcomes than other subsets and therefore require a larger number of studies of these patients to determine appropriate management.***

Keywords: heart failure, improved ejection fraction.

1. Introduction

Heart failure (HF) is a clinical syndrome characterized by a group of symptoms (dyspnea, orthopnea, swelling of the lower extremities) and signs (elevated jugular venous pressure, pulmonary congestion) which are often caused by structural and/or functional cardiac abnormalities resulting in decreased cardiac output and/or increased intracardiac pressure. [1]This is a common long - term condition; affects 26 million people worldwide, and in many countries population - based studies show that heart failure occurs in 1 - 2% of the general population. [2]In Indonesia, the prevalence of heart failure in 2015 was 0.13% or an estimated 229, 696 people, while based on a doctor's diagnosis/symptoms it was 0.3% or an estimated 530, 068 people. [3]

Current guidelines tend to use the term heart failure to refer to patients with chronic heart failure (CHF) whose symptoms can be assessed according to the New York Heart Association (NYHA) functional classification. [4] The main terminology describing HF is based on left ventricular ejection fraction (LVEF) measurements. HF comprises a wide variety of patients, from those with an LVEF ≥50% referred to as *HF with preserved ejection fraction* (HFpEF)] and those with reduced LVEF <40% referred to as *HF with reduced ejection fraction* (HFrEF)]. Patients with an LVEF in the 40 - 49% range which is now defined as (HFmrEF) *HF with mid - range ejection fraction*. [5]

It is now recognized that a subset of patients with HFpEF previously had HFrEF. [2] Patients with elevated EF who were previously included in HFrEF are now referred to as the *HF improved ejection fraction* (HFiEF). [5, 6] In 2011, Punnoose et al reported that nearly 70% of patients with symptomatic HFpEF had recovered from a previously low ejection fraction (EF). These patients are clinically different from those with HFpEF and are more similar to the HFrEF population to which they were originally included. A further study found that HFiEF was associated with a better biomarker profile, quality of life, and reduced symptoms compared to the HFrEF and HFpEF groups, but still experienced significant rehospitalization rates, suggesting a persistent risk of HF. [7]

2. Methods

This was a retrospective study, as we reviewed the medical records of adult (age ≥18 years) outpatients who received care between November 2019 to June 2020 Cardiology Clinic Karangasem Regional Hospital by cardiologists. Medical records were reviewed for symptoms, signs, comorbidities, heart rhythm disturbances and treatment of HF, as well as the first reported *Left Ventricular Ejection Fraction* (LVEF), LVEF documentation one year later, and the causes of HF. The diagnosis of HF was verified based on physician examination of symptoms, signs, and guideline - based treatment for HF.

Based on the index echocardiography findings, patients were classified into those with HFrEF (LVEF ≤40%), HFmrEF (LVEF between 40% and <50%), and HFpEF (LVEF ≥50%). All patients given schedule to control everyone month regarding the condition of the patients. Follow - up echocardiography was done 1 year later. Among patients with HFrEF at the first visit, those whose LVEF improved to >40% were considered to have HFiEF, whereas those with LVEF ≤40% were considered to have persistent HFrEF.

In terms of medication, this study assessed the used of β - blockers, ACE - inhibitor and MRA as the corner stone of HF therapy according to the recommendation of the current guidelines. The use of β - blockers for HF treatment was defined as a prescription for carvedilol, bisoprolol, or nebivolol. Use of ACE - inhibitor was a prescription of ramipril, while an angiotensin II receptor blocker was defined as a prescription for candesartan or valsartan if the ACE - inhibitor is contraindicated. And the use of MRA for HF treatment was defined as a prescription for spironolactone. Each of the medication name and dose were evaluated in the year following diagnosis of HFiEF. Low - and high - dose of each medication were defined as those with <50%, 50% and 100% of the target dose, respectively. The target dose was based on the clinical guideline.

Table 1: Dose of drugs in heart failure reduced ejection fraction [5]

	Starting dose (mg)	Target dose (mg)
ACE - i		
Captopril	6, 25 *t. i. d*	50 *t. i. d*
Enalapril	2, 5 *b. i. d*	10 - 20 *b. i. d*
Lisinopril	2, 5 - 5 *o. d*	20 - 35 *o. d*
Ramipril	2, 5 *o. d*	10 *o. d*
Trandolapril	0, 5 *o. d*	4 *o. d*
Beta - blocker		
Bisoprolol	1, 25 *o. d*	10 *o. d*
Carvedilol	3, 125 *b. i. d*	25 *b. i. d*
Metoprolol succinate	12, 5 - 25 *o. d*	200 *o. d*
Nebivolol	1, 25 *o. d*	10 *o. d*
ARB		
Candesartan	4 - 8 *o. d*	32 *o. d*
Valsartan	40 *b. i. d*	160 *b. i. d*
Losartan	50 *o. d*	150 *o. d*
MRA		
Eplerenone	25 *o. d*	50 *o. d*
Spironolactone	25 *o. d*	50 *o. d*
ARNI		
Sacubitril/valsartan	49/51 *b. i. d*	97/103 *b. i. d*

3. Result and Discussion

3.1 Result

Of all patients with CHF whose data were obtained and analyzed from medical records, a total of 16 patients met the criteria. Based on demography68.75% were male and 31.25% were female. Most of the patients with HFiEF were in age of 51 - 60 years (43.75%), followed by age over 60 years (37.50%), age 40 - 50 years (12.50 %) and age less than 40 years (6.25%).

The most common etiology of patients with HFiEF were *coronary artery disease* (CAD) (81.25%), *hypertensive heart disease* (HHD) (12.50%) and *dilated cardiomyopathy* (DCM) (6, 25%).75.00%patients had no comorbidities, 12.5% had comorbidities with chronic kidney disease (CKD), 6.25% had Type 2 DM, and 6, 25% with hyperthyroidism.

75% patients with HFiEF did not have heart rhythm abnormalities, while another 6.25% with premature ventricular contraction (PVC) and 18.75% others with atrial fibrillation (AF). This study also found the incidence of hospitalization in patients with HFiEF during the one year observation period. A total of 50% of the patients had never been hospitalized, 37.50% were hospitalized one time, and only 12.40% were hospitalized more than one time. All patients have received medical therapy in accordance with Guideline - Directed Medical Therapy (GDMT) for HFrEF, namely administration of angiotensin - converting enzyme inhibitors (ACE - I) or angiotensin receptor blockers (ARBs), beta blockers (β blockers), and aldosterone antagonists (MRA).), but only 6.25% patient received all of the medications 100% according to the target dose.

Table 2: Characteristics of therapy in HFiEF patients

	Percentage (%)
ACE - i	
Ramipril	
<50%	6, 25
50%	18, 75
100%	31, 25
Beta - blocker	
Bisoprolol	
<50%	25
50%	68, 75
100%	6, 25
ARB	
Candesartan	
<50%	12, 50
50%	0
100%	0
Valsartan	
<50%	25
50%	6, 25
100%	0
MRA	
Spironolactone	
<50%	0
50%	87, 50
100%	12, 50

3.2 Discussion

In this comprehensive analysis of HFiEF, we investigated the clinical characteristics of the patients. This study demonstrates that there is potential for myocardial recovery in certain patients in an outpatient setting and identifies patients with heart failure who are more likely to experience a substantial improvement in LVEF over time.

Patients with HFiEF were found predominantly men, younger in age, with etiology of coronary artery disease, without any heart rhythm disturbances and comorbidities such as diabetes mellitus and kidney disease. This patient also had lower rate of hospitalization.

The exact mechanism underlying LVEF improvement in patients with HFiEF is unclear but available evidence suggests that neurohormonal involvement and cardiac electrical activity lead to a reverse remodelling process. Previous studies have shown that in MRI, the amount of damaged but viable myocardium is an independent predictor of left ventricular reverse remodelling, as seen with an increase in LVEF after beta - blocker therapy. [8, 9]

Reverse remodeling is an effective process of recovery from heart failure, which is phenotypically characterized by decreased ventricular mass and volume, reduced wall thickness and increased ejection fraction. [9] This reversal process generally occurs as a result of either medical treatment or the installation of a device. [10]

Acute activation of the renin angiotensin aldosterone (RAA) system that occurs in patients with heart failure can overcome the body's hemodynamic disturbances, but continuous activation can induce cardiac fibrosis, cellular necrosis and induce cardiomyocyte hypertrophy. One therapy that can induce reverse remodelling is to block the angiotensin converting enzyme (ACE) signaling pathway. The same thing was obtained with the administration of an angiotensin receptor blocker (ARB). [8, 11]

Rehospitalizations are a matter of constant concern because after the diagnosis of heart failure was made in outpatients, 83% of patients had been hospitalized at least once and 43% at least four times. In this study it was found that the majority of patients with HFiEF had fewer episodes of hospitalization, in accordance with the study of Gula et al, with a study subject of 787 hospitalized patients with heart failure, there were fewer rehospitalizations in patients with HFiEF compared to patients with both HFrEF and HFpEF. [11] It also has been mentioned that patients with HFiEF have better clinical outcomes compared to patients with HFrEF and HFpEF. Several prospective cohorts of HFiEF have reported a higher survival rate of 80% - 90% compared to patients with HFrEF who only have a 65% - 75% survival rate. [12]

The study of Basuray et al. showed that patients with HFiEF were still at higher risk of worsening and reverting to HFrEF compared to the healthy population. Factors associated with recurrence of HFrEF in patients with HFiEF include discontinuation of heart failure therapy, older age, longer duration of heart failure, lower LVEF, LBBB, slower heart rate, hypertension and lower glomerular filtration rate (GFR). [13] These findings provide a rationale for continuing medical or device therapy for HFiEF patients. This recommendation is consistent with other previous studies showing that discontinuation of medical therapy is associated with recurrence of LV dysfunction in patients who have previously experienced improvement or recovery in EF. [11, 14]

4. Conclusion

Many studies on HFiEF have been conducted with mixed results regarding positive and negative predictors of LVEF improvement. Clinical management remains a challenge because current guidelines only provide recommendations for patients with HFrEF and HFpEF, which may not address the different clinical and biochemical profiles of patients with HFiEF. Discontinuation of previously administered medical therapy increases the risk of recurrence of reduced LVEF in the majority of patients with HEiEF, so patients are advised to continue treatment even after improvement in LVEF.

5. Conflict of Interest

There is no conflict of interests in this study

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