



**RESEARCH ARTICLE**

**Improvement Ejection Fraction and Quality of Life in Patient with Systolic Heart Failure by Adding Valsartan to Combination Therapy ACE Inhibitor and Furosemide**

**Rachma HP<sup>\*1</sup>, Hendrawan D<sup>2</sup>, Saifurrohman<sup>3</sup>**

<sup>1</sup>*Study Program of Pharmacy Faculty of Medicine Brawijaya University, Malang- Indonesia.*

<sup>2,3</sup>*Cardiovascular Department, dr Saiful Anwar General Hospital Malang, Faculty of Medicine Brawijaya University, Malang- Indonesia.*

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**ABSTRACT**

Heart failure is a clinical syndrome caused by the inability of the heart to pump sufficient blood to meet the metabolic needs of the body. One of the therapies that can be used as the therapy is the addition valsaran on combination therapy (ACE inhibitor and furosemide). Addition of valsartan on the treatment containing ACE inhibitor, blocks the effects of Angiotensin II generated by pathways other than renin and ACE, such as CAGE (chymotrypsin-like angiotensin generating enzyme) or chymase. This study was designed to examined improvement ejection fraction and quality of life in patient with systolic heart failure by adding valsartan to combination therapy ACE Inhibitor and furosemide. This study has been conducted at ambulatory clinic dr Saiful Anwar General Hospital Malang during 2 month. The design of this study is observational prospective with analysis descriptive. Patient who have experienced decreased ejection fraction, elderly patient (60-75 years), AHA stage C were eligible in this research. This study found that there is an increase in ejection fraction at month 0 and second month, which is significantly different ( $p = 0,000$ ). Patient also experienced significant improvement in quality of life between month 0 and the second month. Addition valsartan to combination therapy ACE Inhibitor and furosemide improve ejection fraction and quality of life patient with systolic heart failure.

**KEYWORDS**

Heart Failure, Ejection Fraction, Valsartan, ACE Inhibitor, Furosemide

**INTRODUCTION**

Heart failure can be defined as a condition that heart is unable to pump blood throughout the body. Heart failure is the final stage of the entire heart disease and cause of increasing morbidity and mortality. Worldwide, the number of sufferers of the disease is steadily growing.

In 2000, the American Heart Association estimates there are 4.7 million people suffer from heart failure in the United States and there were 550,000 new cases are reported each year. Based on statistical data of hospitals in Indonesia in 2006, cardiovascular disease is the leading cause of death, where the highest 3,23% due to heart failure.<sup>2,4,7,20</sup>

Cardiac disease is a complex pathophysiological conditions, that's need proper management therapy for the patient. Management therapy for heart failure include therapy pharmacologic and

**\*Address for Correspondence:**

**Hananditia Rachma Pramestutie**

Study Program of Pharmacy Faculty of Medicine,

Brawijaya University

Malang- Indonesia

E-Mail Id: [hananditia@ub.ac.id](mailto:hananditia@ub.ac.id)

non pharmacologic. The goals of management therapy for heart failure patient's are to improve patient's quality of life, reduce symptoms, slow progression of the disease process and prolong survival. Therapy pharmacologic for heart failure include diuretics, ACE inhibitors, Angiotensin II receptor blockers,  $\beta$  blockers, aldosterone antagonists, digoxin and vasodilator. Therapy non pharmacologic include change life style patient which is reduce body weigh and diligent exercising.<sup>4,20,21</sup>

One therapies that can be used as the therapy for heart failure, is the addition valsartan on combination therapy ACE inhibitor and furosemide. Addition of valsartan on the treatment containing ACE inhibitor, blocks the effects of Angiotensin II generated by pathways other than renin and ACE, such as CAGE (chymotrypsin-like angiotensin generating enzyme) or chymase. This combination can significantly improve ejection fraction (EF).<sup>33,42</sup>

## **MATERIALS AND METHODS**

### **Patients**

The design of this study is observational prospective with analysis descriptive. This study has been conducted at ambulatory clinic dr Saiful Anwar General Hospital Malang during 2 month, during the period December 2010 until January 2012. Patient who have experienced decreased ejection fraction ( $\leq 40\%$ ), male or female, elderly patient (60 – 75 years). Samples taken by quota sampling. From the results of the calculation according to the formula, it takes sample of 30 patients.

Inclusion criteria of this study is patient's heart failure with American Heart Association (AHA) class C, patients who experience chronic heart failure without existence of acute heart failure during last 6 weeks and get basic therapy (ACE inhibitors and furosemide) which remained at least for 6 months, patients get combination therapy (ACE inhibitors and furosemide) for 6 months with a dose vary according of the needs of each patients, patients who indicated use valsartan (ARB) therapy.

Exclusion criteria of this research is patients who already or obtained valsartan therapy or the other ARB before an examination conducted LVEF, patient with hypokalemia or hyperkalemia, patients who have level of serum creatinin  $> 2,5$  mg/dL, cardiogenic syok, hypotension (SBP  $< 100$  mmHg), acute astma and COPD, patients who uses a pacemaker.

All patient who complied with inclusion criteria was collect, then given an explanation for they willingness involved in this study. After that all patients asked to fill out and sign the information consent, then undergo laboratory examination to check serum electrolyte levels and examination echocardiography to get baseline of EF. Patient also prompted to fill quality of life questionnaire with guide officers who have been selected by researchers and already know the purpose and manner of taking questionnaire. Examination echocardiography, level of serum electrolite and fill out quality of live questionnaire at month 0 and second month. In this study examination echocardiography conducted by 2 doctors who are expert in echocardiography. For the examination of the quality of life taken from Minnesota Living with Heart Failure Questionnaire. This questionnaire consists of 9 question. Where each question consists of score of 0,1,2,3,4 and 5. The question presented in the questionnaire of quality of life of patients heart failure belongs as a negative question. If the patient is experiencing an increase in quality of life, then the number of scores in this questionnaire is getting smaller.

### **Statistical Analysis**

Data analyse in this study uses shapiro wilk test and wilcoxon test. Shapiro wilk test used to see data distribution of ejection fraction and quality of life, distribution data is normal when  $p > 0,05$ . For knowing mean LVEF difference and quality of life at month 0 and second month, we use wilcoxon test, data significant different when  $p < 0,05$ .

## RESULT AND DISCUSSION

### Data Demographic

Data heart failure patient undergoing treatment ambulatory clinic dr Saiful Anwar General Hospital Malang since Desember 2010 until Januari 2012, obtained by prospective from medical record. In this study obtained the number of sample as much as 30 patients, where the patients have met inclusion and exclusion criteria. Data demographic of this study are gender, age and comorbid (table 1). For the gender, most are male. As for age, most of the subject is at the age 71 – 75 years old. And for comorbid most patients are sustaines hypertension.

Table 1: Demographic Data

Variable	Patient (n=30)	p
Gender		
Male	17 (56,67%)	0,465
Female	13 (43,33%)	
Age		
60 – 65 years	8 (26,67%)	0,670
66 – 70 years	10 (33,33%)	
71 – 75 years	12 (40%)	
Commorbid		
Hypertension	9 (30%)	0,940
Diabetes Mellitus	7 (23,33%)	
Hypertension+ Diabetes Mellitus	7 (23,33%)	
Coronary Heart Disease	7 (23,33%)	

### Ejection Fraction

One of the main parameters measurement in this study is ejection fraction (EF). Ejection fraction can be measure by using echocardiographic mechine. Normal value of ejection fraction is

53% to 72%. In this study there are 28 patients experienced improved ejection fraction, 2 patients with ejection fraction data constant and 1 patient decreased ejection fraction. Test used to knowing the difference ejection fraction of patient who received addition valsartan to combination therapy (ACE inhibitor and furosemide) at month 0 until second month, used wilcoxn test. Based on test results obtained that there is an increase in ejection fraction at month 0 and second month, which is significantly different ( $p = 0,000$ ). (Figure 1).

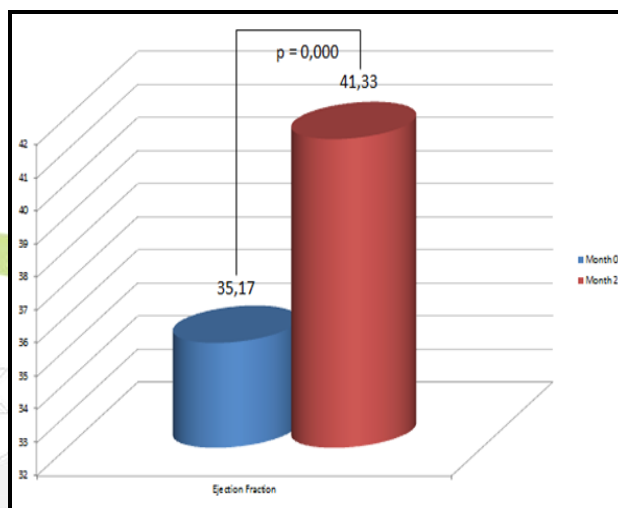


Figure 1: The difference results in ejection fraction at 0 month to second month

### Quality of Life

Measurement of the quality of life in this study using questionnaire assessment of the quality of life of patients with heart failure. This questionnaire is quoted from the Minnesota Living with Heart Failure Questionnaire of Quality of life by Hulsmann, Berger and Sturm (2002), where this questionnaire has been on test validity and reability. Almost all patients experience improvement the quality of life that is marked by the presence of a decrease in the total value of the questionnaire in second month. Wilcoxon test used to know the existence of differences in the quality of life at the time of the month 0 compared to second month. Based on test results obtained that there is an increase in quality of life at month 0 and second month, which is significantly different ( $p = 0,000$ ). (Figure 2).

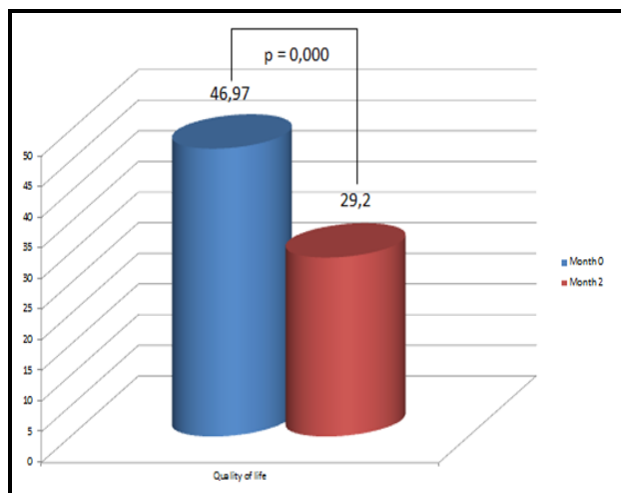


Figure 2: The difference results in quality of life at 0 month to second month

### Side Effect

Side effects that often occur in the additional valsartan therapy on the therapy contain ACE inhibitor is hyperkalemia and hypotension. Based on the study results, there was not found patients who suffered side effects hyperkalemia and hypotension.

### DISCUSSION

A prospective observational study using a descriptive analysis for presence of influence adding valsartan to combination therapy (ACE inhibitor and furosemide) to improve ejection fraction and the quality of life in patient heart failure in ambulatory clinic dr Saiful Anwar General Hospital Malang retrieve data as much as 30 patients. Large sample as many as 30 patients have been determined based on the calculation of large samples.

Data demographic of this study are gender, age and comorbid. Patient demographic data can be seen in table 1. Heart failure patients in these study are mostly men. At the age of 65 years, the incidence of heart failure in men greater than women. It's caused the incidence of coronary heart disease larger in men. Thus, an increased survival patient with coronary heart disease or with a history of myocardial infarction tending to increase risk of the occurrence of heart failure.<sup>4</sup>

The majority age of heart failure patient from this study is 71 – 75 years old. The majority of heart failure patients are geriatrics patient. The condition of heart failure will rise 1-3% in the population with increasing age and bad prognosis. The incidence of heart failure occurs in about 10% of patients aged over 75 years old and about 2% in patient aged 40 to 59 years old.<sup>4</sup>

Background of this study is to examined improvement ejection fraction and quality of life in patient with systolic heart failure by adding valsartan to combination therapy ACE Inhibitor and furosemide in 2 month. Adding valsartan to combination therapy ACE inhibitor and furosemide have researched in animal and human. The combination can decrease mortality and morbidity in patient with chronic heart failure and left ventricular systolic impairment.

Test used to knowing the difference ejection fraction of patient who received addition valsartan to combination therapy (ACE inhibitor and furosemide) at month 0 until second month, used wilcoxn test. Based on test results obtained that there is an increase in ejection fraction at month 0 and second month, which is significantly different ( $p = 0,000$ ). Improved ejection fraction at month 0 until second month caused by combination valsartan and ACE inhibitor can inhibit the renin angiotensin aldosterone system thus inhibiting the formation of angiotensin II. It's will reduce peripheral vascular resistance and caused decrease ejection fraction.<sup>40,42</sup>

The decline of ejection fraction in heart failure patients due to several mechanism, that is increase sympathetic tone, increase renin angiotensin and vascular smooth muscle alteration. Increase sympathetic tone will cause renal vasoconstriction so that will lead to Na retention and lead to increased peripheral vascular resistance. An increase in renin angiotensin also caused Na retention and lead to increased peripheral vascular resistance. Vascular smooth muscle alteration can caused increased peripheral vascular resistance. All of

this mechanism can decrease ejection fraction.<sup>33,40,42</sup>

Addition furosemide in this study can improve the function of ejection fraction. Combination valsartan, ACE inhibitor and furosemide can improve ejection fraction by reduce load of the heart. Improved ejection fraction can also be influence by adherence patient in taken medicine.<sup>42</sup> If patient adherence in taken medicine, the effect of such drugs would be felt.

Patient also fill quality of life questionnaire that adopted from Minnesota Living with Heart Failure Quality of life Questionnaire by Hulsmann, Berger and Sturm. Charging this questionnaire also to know the effectiveness of the addition of valsartan therapy on therapeutic containing ACE inhibitor. The question presented in the questionnaire of quality of life in patients heart failure belongs as a negative question. If the patient is experiencing an increase in quality of life, then the number of scores in this questionnaire is getting smaller. From total score on quality of life questionnaire, all of patient in this study suffered decline scores. This means entire patient experience increased quality of life.

On the CHARM added, giving a combination of candesartan high doses 32 mg/day and ACE inhibitor in heart failure patient NYHA stage II and LVEF  $\leq 40\%$  can improved quality of life. Improvement quality of life conducted in 2, 4 and 12 month. In second month CHARM added, there are significantly improvement quality of life. In this study improving quality of life in patients who get additional therapy valsartan comparable with improvement of ejection fraction.

Several patient in this study having improved quality of life but aren't followed by repair of ejection fraction. The improvement of the quality of life that isn't accompanied by improved ejection fraction caused examination of ejection fraction are examination depends on operator, so allowing the examination of less precise. In this study examination echocardiography conducted by 2 doctors who are expert in echocardiography. Result ejection

fraction by 2 doctors performed the kappa test to find out the value of ejection fraction patient either in the 0 month and second month.

Question contained in the quality of life questionnaire is a question which consists of question that related with changing of symptoms in the patients condition and changes in patients psychic. A slight change of symptoms and psychic patient after getting additional therapy valsartan to combination therapy (ACE inhibitor and furosemide), will be easy perceived by the patient so that will affect in filling a questionnaire of quality of life in second month.

Side effects that may occur from additional valsartan to combination therapy (ACE inhibitor and furosemide) is hypotension nad hyperkalemia. In this study didn't found symptom and side effect in patient. To monitor any side effect hypotension, should be done blood pressure screening every week. For hyperkalemia should be done routinely once every six month to monitor side effect in patient.

Weakness of this study is the sample was in small numbers and examination ejection fraction conducted within 2 month. This study ignores variations dose furosemide and ACE inhibitor that given to each patient because the dose is individualization.

## CONCLUSION

Adding valsartan to combination therapy ACE inhibitor and furosemide improve ejection fraction and quality of life patient with systolic heart failure.

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