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ROLE OF BISOPROLOL ADDING TO ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITOR AND FUROSEMIDE COMBINATION ON THE LEFT VENTRICULAR FUNCTION IN SYSTOLIC HEART FAILURE PATIENTS

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Abbreviation:
EF: Ejection Fraction,
ACE: Angiotensin Converting Enzyme

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ABSTRACT

Background: β-blocker is an established therapeutic strategy for stage C systolic heart failure based on the American Heart Association guideline, nonetheless limited studies analyzed the role of β-blocker primarily Bisoprolol adding to ACE inhibitor and furosemide combination on the left ventricular function in systolic heart failure patients.
Objectives: This study was designed to analyze the role of Bisoprolol adding to ACE inhibitor and furosemide combination on the ventricular function in patients with systolic heart failure particularly on ejection fraction and quality of life.
Subjects & Methods: 40 to 80 years old ambulatory patients (N=30) at Dr. Saiful Anwar General Hospital Malang diagnosed as stage C systolic heart failure receiving optimum dose of inhibitor ACE and furosemide combination for at least 2 months. Before Bisoprolol was added, the ejection fraction and the quality of life was observed to assess the baseline left ventricular function then re-observed after 3 months.
Results: After the adding of Bisoprolol, there were significant differences in ejection fraction (measured by echocardiography) and quality of life (measured by Minnesota quality of life living with heart failure questionnaire) with both P value equal to 0,000 (95% Confidence Interval).
Conclusions: The adding of Bisoprolol to ACE inhibitor and Furosemide combination seems to improve the left ventricular function in stage C systolic heart failure patients particularly on ejection fraction and quality of life measurements.

INTRODUCTION: Heart failure is defined as clinical syndromes (such as: short of breathing, activities limitation, or pulmonary obstruction) manifest from degradation of heart function caused by various heart diseases. This syndrome may lead to quality of life reduction with higher morbidity and mortality than other diseases [2]. American Heart Association guideline of heart failure recommend β-blocker combined with ACE Inhibitors and diuretics as an established therapeutic strategy for stage C systolic heart failure patients throughout contraindications are not found. Previous study found that this brought many benefits in morbidity and mortality if given to stabile heart failure patients [4, 5, 6].

In contrary, not many physicians confidence to prescribe β-blocker to the heart failure patients. β-blocker inhibits the surge of β adrenergic activity. The surge of β adrenergic activity in heart failure will brings deterioration conditions such as vasocontriction, sodium and water retention which lead to increase cardiac load and aggravate hypoperfusion due to inadequate ventricular ejection. β-blocker act to decrease heart rate and prolonged the ventricular filling time, then provide adequate preload at diastolic phase and improve cardiac output [4, 5, 6].

Bisoprolol is one of selective β-blocker that available in indonesia. It has prominently high β_1 affinity, low bronchoconstriction effect, and it has no intrinsic simphatomimetic activity (high bradycardia effect) and membrane stability activity therefore has minimum effect on cardiac conductance [3, 12].

The aim of this study is to analyze the role of Bisoprolol adding to ACE inhibitor and furosemide combination on the ventricular function in patients with systolic heart failure particularly on ejection fraction (EF) and quality of life.

METHODS: Research was conducted in Dr. Saiful Anwar General Hospital Malang, Indonesia between february 2011 to january 2012. This quasi-experimental study used a one group pretest-posttest design to compare the ejection fraction (by echocardiography) and quality of life (by Minessota Living with Heart Failure questionnaire) measurements before and after the adding of Bisoprolol to ACE inhibitor and furosemide combination for three months at stage C systolic heart failure patients.

40 – 80 years of age stage C systolic heart failure patients with EF reduction were included. Inclusion criterias were stabile heart failure, already received the optimum dose of ACE inhibitor and furosemide, fulfill for Bisoprolol indication. Patients were excluded if already accepted Bisoprolol before recruitment, had acute heart failure and needed positive inotropic except digoxin, comorbid condition which affect to quality of life such as mitral regurgitation and atrial fibrilation, cardiogenic shock, bradycardia (heart rate below 60 times per minute), hypotension with systolic pressure below 100 mmHg, and severe asthma.

Ejection fraction measured by two operator using echocardiography with Simpson method of measurement as a gold standard. Minessota Living with Heart Failure Questionnaire is already used worldwide to measure the quality of life of heart failure patients.

This study examined the ambulatory patients of Cardiovascular Department at Dr. Saiful Anwar General Hospital, Malang.

Patient adherence has significant contribution to the result of this study, thus this study enclosed to the high adherence patients (measured by patients adherence questionnaire).

Data Analysis: EF and quality of life are dependent variables measured in this study. Both variables show the left ventricular function. Baseline EF and quality of life were compared to those results three months after Bisoprolol addition using paired t test analysis in the Statistical Product and Service Solutions (SPSS) version 16. Normal distribution data is required for Paired t test as a parametric analysis. This is examined by Shapiro-Wilk analysis for small size sample (below 50). Wilcoxon analysis is the alternate analysis to compare baseline EF and quality of life to the endpoint if the data do not fulfill normal distribution.

RESULTS: Total patients who meet inclusion and exclusion criteria between february to October 2011 were 30 patients followed up for three months with the endpoint measurements last on January 2012.

Chi-square statistical test using SPSS 16 carried out to see the distribution of patient demographic data. Sex, age, and previous disease history respectively did not show significant differences in distribution, with the P value for those are > 0.05. Comorbid condition (previous disease history) categorized in to three group then examined by Chi-Square analysis and resulted P = 0.061.

Chi-Square analysis also conducted to determine the age (divided in to four groups in table 1) and gender differences and resulted P value 0.141 and 0.465 respectively. Patients demographic data summarized in **table 1**.

TABLE 1. PATIENTS DEMOGRAPHIC DATA

	%	P
Sex:		0.465
Male	73.3	
Female	26,7	
Age:		0.141
40 to 50 years old	13.3	
51 to 60 years old	30	
61 to 70 years old	40	
71 to 80 years old	16,7	
History of previous illness:		0.061
Hypertension	26.7	
Ischemic heart disease + HT	53.3	
Diabetes Mellitus + HT	20	

Ejection Fraction (EF): EF show the fraction of blood that ejected from the left ventricle. Normal value of EF is in the range between 53% to 72% while in heart failure EF may reduce to 50% or below. Lowest EF value at baseline was 17% while at endpoint was 24%. Highest EF value at baseline was 49% while at endpoint was 58%. Normality test for EF showed that endpoint EF data did not meet Gaussian distribution so that data analysis should used nonparametric test for two related samples that is Wilcoxon Signed Ranks Test.

Wilcoxon Signed Ranks Test results showed that baseline EF were significantly differ from endpoint EF with P value equal to 0.000 (95% Confidence Interval (CI); 0.00 to 0.27). Wilcoxon test results for EF summarized in **table 2**.

TABLE 2: WILCOXON TEST RESULTS FOR EF

	EF percentage (%)
Mean baseline	35.2 ± 8.98
Mean at 3rd months	42.8 ± 10.15
P value	0.000

EF mean at baseline and 3rd months comparison by Wilcoxon test was displayed to the bar charts in **figure 1**.

Quality of Life: Quality of life for heart failure patients measured by Minessota Living with Heart Failure questionnaire. This questionnaire consists of twenty one questions each questions contain six choices based on the symptoms frequencies which is valued 0, 1, 2, 3, 4, 5 respectively. The more frequent symptoms would provide the higher score for this questionnaire. The maximum score of this questionnaire is 105, which is explained that the heart failure condition has a very high impact to the reduction of quality of life.

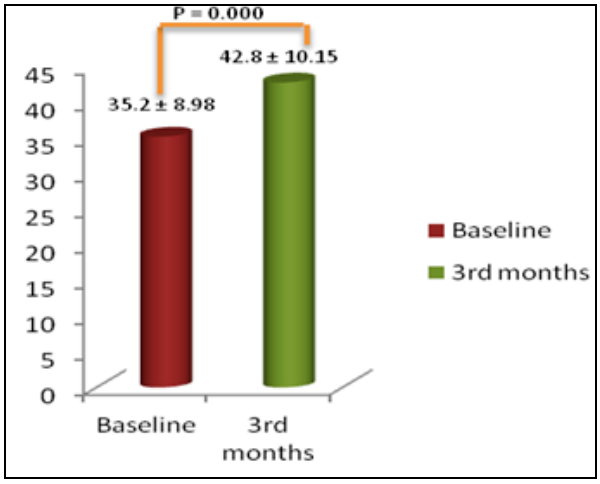

FIGURE 1: PROFILE OF BASELINE MEAN EJECTION FRACTION COMPARED TO THOSE AFTER THE ADDING OF BISOPROLOL FOR THREE MONTHS

Quality of life data taken from the the patients based on the questionnaire results in this study showed that the highest score of Minessota Living with Heart Failure Questionnaire was 70 at baseline and 64 after three months receiving Bisoprolol. While the lowest score for this questionnaire was 37 at baseline and 30 at the endpoint after the adding of Bisoprolol for three months.

Normality test for patients quality of life showed that the distribution data met Gaussian distribution (normal distribution) so that data analysis should used parametric test for two related samples that is Paired t test.

Paired t test results showed that the baseline quality of life questionnaire score were significantly differ from endpoint score with P value equal to 0.000 (95% Confidence Interval (CI); -18 to -1). Paired t test results for quality of life questionnaire score summarized in **table 3**.

TABLE 3. PAIRED T TEST RESULTS FOR SUM SCORE OF MINESSOTA LIVING WITH HEART FAILURE

	Sum Score of Minessota Living with Heart Failure
Mean baseline	54.93±9.61
Mean at 3rd months	48.27±8.57
P value	0.000

Mean of Minessota Living with Heart Failure score at baseline and 3rd months comparison by Paired t test was displayed to the bar charts in **figure 2**.

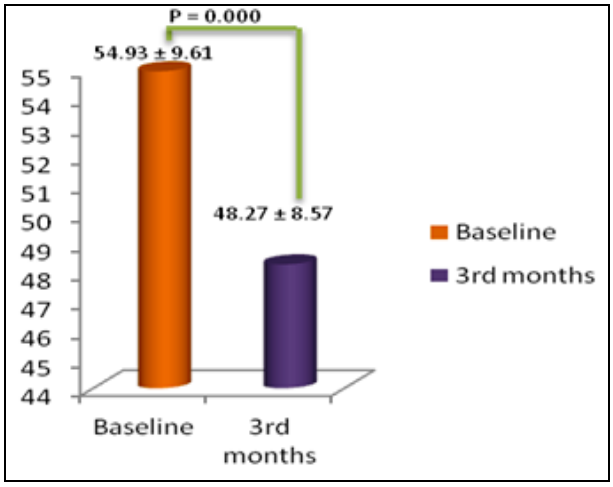

FIGURE 2: PROFILE OF MEAN SCORE OF MINESSOTA LIVING WITH HEART FAILURE QUESTIONNAIRE COMPARISON

DISCUSSION: Background setting in this study was conducted at ambulatory clinic in cardiovascular department, Dr Saiful Anwar General Hospital, Malang. Since recruited samples were ambulatory patients, many counfounding factor may had significant impact on the results. One of the method to minimize the effect of confounding factor to the results was by limiting sample recruitment only to the adherence patients.

Other confounding factors were gender, comorbid condition (history of previous chronic illness), and age. Thus Chi-Square analysis conducted to determine whether those factors impact to the examined variables such as ejection fraction and quality of life. Chi-Square analysis resulted that demographic data taken from the patients were equivalent thus no classification based on gender, comorbid condition, and age were needed in comparing variables.

Previous studies (CIBIS I, II, III) demonstrated the improvement in morbidity, mortality and length of hospitalization stay in heart failure patients who were treated with Bisoprolol. While previous studies did not analyze the role of Bisoprolol to the left ventricular function, this study primarily examined the left ventricular function due to ejection fraction and quality of life.

This study resulted that there were significantly improvement in left ventricular function which were shown in the increasing of ejection fraction (P = 0.000) and decreasing score of quality of life questionnaire (P = 0.000). This result probably delivered by the reduction of cardiac oxygen demand as a result from the decreasing of heart rate so that ischemic related symptom improved. Other mechanism of Bisoprolol in improving left ventricular function was due to the antagonistic effect of aldosteron by inhibits renin release so that decreasing in water and sodium retention which bring to the reduction of cardiac load and decrease ischemic state [9, 10, 13].

This study conducted a quasi-experimental with one group pretest-posttest design to compare the ejection fraction and quality of life measurements before and after the adding of Bisoprolol to ACE inhibitor and furosemide combination for three months at stage C systolic heart failure patients. Before the adding of Bisoprolol, the patients should had accepted an optimum dose of ACE inhibitor in order to ensure that the improvements of left ventricular function was obtained by the adding of Bisoprolol to the combination of ACE inhibitor and furosemide diuretic, since those combination had been proven to decrease heart failure morbidity and increase left ventricular ejection fraction based on the research conducted by Simon and Nishio at 2002 and 2008 respectively [12, 13].

Systolic heart failure condition usually accompanied by left ventricular hypertrophy. The left ventricular filling will be disturbed in the left ventricular hypertrophy condition. So that the cardiac afterload volume decrease then aggravated by the reduction of the left ventricular myocyte contraction. All of this condition bring to the reduction of cardiac output and hypoperfusion through all of the body thus change the cellular metabolism in to anaerob metabolism. This anaerob metabolism will lead to clinical manifestation such as fatigue due to lactic acid accumulation and this may lead to metabolic acidosis.

Left ventricular function has important role in the clinical manifestation in heart failure condition.

Ejection fraction describe the left ventricular function by measuring the fraction of the blood that ejected from the left ventricle. Ejection fraction may be derivated by this formula:

$$EF = \frac{EDV - ESV}{EDV} \times 100\%$$

(Silvestry *et al.*, 2009 [14])

A higher EF value means a higher blood fraction which is ejected from the left ventricle and by the reversed the lower EF value means a lower blood fraction which is ejected from the left ventricle and the worse left ventricular function. The reduction of cardiac output volume (EDV – ESV) due to impairment of the left ventricular ejection induce the increasing of blood volume which is left in the left ventricle after contraction phase this will aggravate the left ventricular hypertrophy.

EF can be measured by several methods. The best method which used to be a gold standard is Simpson method. This method calculates the left ventricular volume in the end of diastolic and systolic phase then develope to the formula above. This method minimize the operator error in determine the cut point of the left ventricle. This study recruited two blinded operator to examine the ejection fraction to prove the precision and accuracy.

Baseline ejection fraction from the patients then compare to themselves ejection fraction after receiving Bisoprolol for three months. Comparison method was by Wilcoxon test since the baseline ejection fraction showed non Gaussian distribution. As the results showed in table 2 there were increasing of ejection fraction between baseline and three months after the adding of Bisoprolol in most of patients. Wilcoxon test indicated that EF mean were significantly difference by 95% confidence of interval (P = 0.000). This incline trend may indicated the role of Bisoprolol in increasing left ventricular function by decreasing heart rate and promoting adequate filling phase in the left ventricle.

Heart failure condition has very high impact on the quality of life and should be examined frequently in order to predicted the worsening or improving left ventricular function. The level of heart failure impact on the quality of life usually measured by Minessota questionnaire which is contain twenty one questions each determines the frequencies of symptoms or the heart failure impact on phsycosocial life. The more heart failure impact on the quality of life, the higher score were determined. The avarage of baseline and endpoint total scores for Minnesota Living with Heart Failure questionnaire in patients then compared by paired t test analysis since data distribution was normal.

Paired t test analysis showed there were significantly difference in the score of Minnesota Living with Heart Failure questionnaire before and after the adding of Bisoprolol by 95% confidence of interval (P = 0.000). The total score of Minnesota Living with Heart Failure questionnaire tend to decrease after the adding of Bisoprolol to ACE inhibitor and furosemide for three months. This indicated that the routine adding of Bisoprolol to the combination of ACE inhibitor and furosemide may improved the quality of life in heart failure patients.

This study limitation was the ignorance of the ACE inhibitor and furosemide to the improvement of ejection fraction and quality of life since previous study noted that those combination also improve left ventricular function in heart failure. This study also consider that dose variation do not take important role in improving left ventricular function.

Further studies are needed to examine the role of dose variation in heart failure therapy to the left ventricular improvement. Better study design such as randomized control trial with the bigger sample size is needed to confirm our results. As β-blocker monotherapy is not recommended in heart failure condition, so that the single effect of β-blocker on the left ventricular function is infeasible to be examined.

CONCLUSION: Result of this prospective study showed that the routine addition of Bisoprolol to ACE inhibitor and furosemide combination may increase ejection fraction significantly by P = 0.000 and 95% confidence of interval. Bisoprolol addition to ACE inhibitor and furosemide combination may also improve quality of life in systolic heart failure patients significantly (P = 0.000 ; 95% confidence of interval) if measured by Minnesota Living with Heart Failure questionnaire.

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Conflicts of Interest: The authors declare that they have no competing interests

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