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Research Article

Study of Lisinopril in Heart Failure Patients

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Abstract.
Heart failure is a progressive clinical syndrome that results in structural or functional abnormalities of the heart that disrupt the heart's performance in pumping blood. The clinical manifestations are shortness of breath and cardiomegaly. The purpose of the study was to determine the Lisinopril therapy (dose, route of administration, frequency) in heart failure patients at the hospitalized installation of Sidoarjo Hospital. The method of collecting the data was retrospectively by health medical records at Sidoarjo Hospital from January 1 until December 31, 2020. The results showed that the health medical records sample got inclusion criteria of 20 patients. Heart failure was suffered by 12 patients (60%) male patients and 8 female patients (40%). The highest age range was 56- 65 years, with 8 patients (40%). In patients with the pattern of using combination 2, there were 9 patients (33%), combination 3 had 9 patients (33%), and combination 4 had 9 patients (33%). The highest combination of 2 was Lisinopril (1x 10 mg) po + Bisoprolol (1x 2.5 mg) po. There were 2 patients (22%). The highest combination of 3 was Lisinopril (1x5 mg) po + Bisoprolol (1x 2.5 mg) po + Furosemide (1 x 20 mg) iv. There were 2 patients (22%). The highest combination of 4 was Lisinopril (1x 10 mg) po + Bisoprolol (1x 2.5 mg) po + Furosemide (3x 40 mg) iv + Spironolactone (1x 25 mg) po. There were 3 patients (33%). The results show that there are 16 patterns of using switch therapy.

Keywords: lisinopril, heart failure, hospitalization

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1. INTRODUCTION

Heart failure is an abnormality of the structure or function of the heart that causes impaired heart function in pumping blood, which in turn leads to progressive clinical disease (1). Heart failure is influenced by systolic dysfunction (HfrEF), a condition of impaired contraction in pumping blood due to weak myocardial contractility, and diastolic dysfunction (HfpEF), a condition of impaired relaxation in filling blood into the ventricles due to thickening of the ventricular wall (1).

The pathophysiology of heart failure begins with a decrease in cardiac output which causes the heart to be unable to pump blood normally so that the heart performs a compensatory mechanism were neurohormonal activation, hemodynamic load, and increased wall stress, which aims to increase cardiac output. In the long term can lead

to a worse prognosis of heart failure was cardiac remodeling (2). Cardiac remodeling is a change in ventricular mass, composition, and volume as well as an overall change in geometry so that the heart's shape is less elliptical and more rounded (1).

Based on PERKI 2020 guidelines and *ESC (European Society of Cardiology) 2016 guidelines*, anti-remodeling therapy for heart failure patients (HfrEF) given in combination with the first ACE inhibitors to reduce the workload of the heart, then beta blocker to reduce heart rate, then an aldosterone antagonist (spironolactone) in heart failure patients (persistent EF < 35%). The addition of diuretics (Furosemide) only in patients who had symptoms was shortness of breath and congestion (3) (4). Based on the guidelines of the ESC (European Society of Cardiology) 2021, therapy for heart failure can be given all of combination ACE inhibitors, beta blockers, aldosterone antagonists (Spironolactone), and SGLT 2 Inhibitor (5). Based on the JNC 8 guidelines, heart failure therapy is given a combination of ACE inhibitors, beta blockers, diuretics, and spironolactone, in this case (6). There are differences in the guidelines PERKI 2020 and ESC 2016 that the provision of diuretic therapy can be given to all patients with heart failure, not only patients who had symptoms was shortness of breath and congestion.

ACE inhibitors act as left ventricular antihypertensive and anti-remodeling agents. The mechanism of action of ACE inhibitors prevents the formation of Angiotensin II so that there is no vasoconstriction and an increase in aldosterone as a trigger for increased blood pressure and fluid retention which can result in hypertension and ventricular remodeling (7). Lisinopril is one of the ACE inhibitors which is water soluble, has a long half-life, and is an active drug ester (does not need to be metabolized by the liver) (8).

Based on research Lisinopril can prevent and weaken myocardial hypertrophy and prevent changes in myocardial contractility (9). In journal citations Lisinopril, one of the ACE inhibitors, has safety and effectiveness in lowering blood pressure and treating heart failure, which is supported by a quality randomized controlled trial (RCT) and the 1999 ATLAS study, ALLHAT 2002 (10).

2. MATERIALS AND METHODS

This study is observational because the researchers did not give treatment to the sample. The research design was made descriptively and data were collected retrospectively. The inclusion criteria in this study were heart failure patients who received Lisinopril therapy at Sidoarjo Hospital using data collection sheets, master tables, clinical data, laboratory data, and supporting data.

3. RESULTS

Table 1: Demographic data of heart failure patients.

Characteristics N=20	Amount	Percentage (%)
Gender		
Man	12	60%
Woman	8	40%
Total	**20**	**100%**
Age (Ministry of Health 2019)		
36-45 Years	1	5
46-55 Years	6	30
56-65 Years	8	40
>65 Years	5	25
Total	**20**	**100%**

Table 2: Concomitant diagnoses of heart failure patients.

Types of diseases	Number of Patients	Percentage (%)
SKA (Acute Coronary Syndrome)	14	26
Atrial Fibrillation	8	15
Heart Valve Abnormalities	4	7
Cardiogenic Shock	1	2
Left Ventricle Thrombus	1	2
Ischemic Cardiomyopathy	1	2
Hypertension	2	4
Deep Vein Thrombosis	1	2
CV/ Stroke	1	2
Diabetes mellitus	6	11
Pneumonia	4	8
Pulmonary Edema	1	2
Thrombocytopenia	1	2
Dyslipidemia	2	4
Kidney failure	2	4
Hypokalemia	1	2
Hyperuricemia	1	2
Hyponatremia	1	2
Total	**52**	**100%**

***One patient can have more than one comorbid diagnosis**

***One patient can have more than one risk factor**

***One patient can have more than one therapy**

Table 3: Risk Factors for Heart Failure Patients.

Risk Factor	Number of Patients	Percentage (%)
Hypertension	12	48
Diabetes mellitus	9	36
Acute Coronary Syndrome	2	8
CVA/Stroke	1	4
Smoke	1	4
Total	**25**	**100%**

Table 4: Therapeutic Use Pattern.

Therapy Pattern	Number of Patients	Percentage (%)
Single	0	0
2 combination	9	33
3 combination	9	33
4 combination	9	33
Total	**27**	**100%**

Table 5: Combination therapy pattern.

COMBINATION OF TWO	Amount
ACE inhibitor + loop diuretic	
Lisinopril (1x 10 mg) po + Furosemide (3x20 mg) iv	1
Lisinopril (1x5 mg) po+ Furosemide pump (3mcg/kgBW/min)	1
Lisinopril (1x5 mg) po + Furosemide (1x40 mg) po	1
Lisinopril (1x 5 mg) po + Furosemide (1 x 20 mg) iv	1
ACE Inhibitor + Beta blocker	
Lisinopril (1x 10 mg) po + Bisoprolol (1x 2.5 mg) po	2
Lisinopril (1x2.5 mg) po + Bisoprolol (1x 2.5 mg) po	2
ACE Inhibitor + CCB	
Lisinopril (1x 5 mg) po + Amlodipine (1x 10 mg) po	1
Total	**9**

4. DISCUSSION

Based on Health Medical Record data from heart failure patients at the Sidoarjo Hospital for the period January 1 until December 31, 2020, there were 20 samples of inclusion criteria for heart failure patients who received Lisinopril therapy.

Table 1 showed demographic data based on gender distribution in 20 heart failure patients with Lisinopril therapy for the period January to December 2020. The male patients are 12 patients (60%) more than the female patients were 8 patients (40%).

Table 6

COMBINATIONS OF THREE	Amount
ACE Inhibitor + Beta blocker + Loop diuretic	
Lisinopril (1x 5 mg) po + Bisoprolol (1x 2.5 mg) po + Furosemide (1x 20 mg) iv	2
Lisinopril (1x 5 mg) po + Bisoprolol (1x 2.5 mg) po + Furosemide (1x 40 mg) po	1
Lisinopril (1x20 mg) po + Bisoprolol (1x 2.5 mg) po+ Furosemide (3x 20mg) iv	1
Lisinopril (1x 2.5 mg) po + Bisoprolol (1x 2.5 mg) po + Furosemide (2x 20 mg) iv	1
Lisinopril (1x 10 mg) po + Bisoprolol (1x 2.5 mg) po + Furosemide (6x 20 mg) iv	1
ACE Inhibitor + Loop Diuretic + CCB	
Lisinopril (1x 10 mg) po + Furosemide (3x20 mg) po+ Nifedipine (1x30 mg) po	1
ACE Inhibitor + Beta blocker + Aldosterone antagonist	
Lisinopril (1x 5 mg) po + Bisoprolol (1x 2.5 mg) po + Spironolactone (1x 25 mg) po	1
ACE inhibitor + loop diuretic + aldosterone antagonist	
Lisinopril (1x 2.5 mg) po + Furosemide (2x 20 mg) iv + Spironolactone (1x 25 mg) po	1
Total	**9**

Table 7

COMBINATIONS OF FOUR	Amount
ACE Inhibitor + Beta blocker + Loop diuretic + Aldosterone antagonist	
Lisinopril (1x10 mg) po + Bisoprolol (1x 2.5 mg) po+ Furosemide (2x 20 mg) iv + Spironolactone (1x 25 mg) po	1
Lisinopril (1x 10 mg) po + Bisoprolol (1x 2.5 mg) po + Furosemide (1x 20 mg) iv+Spironolactone (1x 25 mg) po	1
Lisinopril (1x 10 mg) po + Bisoprolol (1x 2.5 mg) po + Furosemide (3x 40 mg) iv + Spironolactone (1x 25 mg) po	3
Lisinopril (1x10 mg) po + Bisoprolol (1x 2.5 mg) po + Furosemide (3x20 mg) iv + Spironolactone (1x 25 mg) po	1
Lisinopril (1x 10 mg) po + Bisoprolol (1x 2.5 mg) po + Furosemide pump (3 amp/24 hours) + Spironolactone (1x 25 mg) po	1
Lisinopril (1x20 mg) po + Bisoprolol (1x 2.5 mg) po + Furosemide (3x 20mg) iv + Spironolactone (1x 25 mg) po	1
Lisinopril (1x 2.5 mg) po + Bisoprolol (1x2.5mg) po + Furosemide (1x 40 mg) po + Spironolactone (1x 25 mg) po	1
Total	**9**

Cardiovascular disease in men tends to be higher, this condition is influenced by unhealthy male lifestyles such as smoking habits and alcohol consumption compared to women (11). In productive women, they have a lower risk because the hormone estrogen plays an important role in protecting blood vessels from damage that triggers atherosclerosis by controlling increased levels of cholesterol, especially low-density lipoprotein, however, protection by this hormone lasts as long as women are not menopausal (12).

Patient demographic data by age, the most range of age were 56-65 years with 8 patients (40%). Physiologically, increasing age will cause physiological changes in the heart including, the heart muscle will become stiffer, the heart wall will thicken, and the structure of the blood vessels will undergo changes that cause the blood vessels to be less elastic and increase systolic pressure, of course, this will result in an increased risk of cardiovascular disease (13).

Data on the guarantor status of heart failure patients with Lisinopril therapy for the period January-December 2020 obtained as many as 19 patients (95%) using BPJS services and 1 patient (5%) using public services. BPJS is a legal entity formed by the government to provide certainty of protection and welfare for all Indonesian people. specifically for health problems. So pharmacoeconomic aspects can be achieved by providing efficient treatment without reducing the effectiveness of therapy.

Table 2 showed a list of comorbidities in 20 heart failure patients at Sidoarjo Hospital. The most common comorbidities were Acute Coronary Syndrome (ACS) as many as 14 patients (26%). The cause of the acute coronary syndrome is acute rupture, fissure, or erosion of an unstable atherosclerotic plaque followed by subsequent thrombus formation that impairs distal blood flow (14). If the myocardium of the heart cannot be supplied with blood due to plaque blockage, it will cause a systolic function disorder that ends in heart failure (15).

Table 3 showed a list of risk factors for heart failure patients. Based on the results of the study, the most case history in heart failure patients was hypertension in 12 patients (48%), and found 1 patient (4%) with smoking as a risk factor. Hypertension causes systolic and diastolic disturbances in the heart. Systolic disorders can occur if hypertension is a risk factor for acute myocardial infarction resulting in impaired left ventricular systolic function. In addition, diastolic disorders can occur due to hypertension causing left ventricular hypertrophy (16). Smoking habits can also reduce the function of arterial vasodilation through a decrease in the ability of nitric oxide. Nicotine will stimulate the proliferation of endothelial cells and smooth muscle cells including cardiomyocytes. Cardiomyocyte proliferation will eventually lead to left ventricular hypertrophy (17).

Another study explains that smoking is a risk factor for left ventricular hypertrophy, systolic dysfunction, and the incidence of heart failure hospitalization (18).

The results of the study, dosage regimen of Lisinopril consisted of (1x 2.5 mg) po, (1x 5 mg) po, (1x 10 mg) po, and (1x 20 mg) po, in this case, is following *guidelines* PERKI 2020 which describe the initial dose range for heart failure therapy is (1x 2.5 mg) po - (1x 5 mg) po and the target dose range (1x 20 mg) po-(1x 40 mg) po (3). Lisinopril is given at night, this is consistent with a 24-hour study that the renin-angiotensin-aldosterone system, which is the main target of Lisinopril therapy, peaks at night, at bedtime (19).

Table 4 showed that there was only a pattern of using combination therapy in heart failure patients for the period January 1 to December 31, 2020, for as many as 27 patients. Heart failure therapy is not given in a single dose but given in combination, in this case, it is following the guidelines for heart failure therapy.

Table 5 showed the pattern of combination therapy for heart failure patients at Sidoarjo Hospital for the period January 1 - December 31, 2020. The combination 2 were 9 patients (33%), the combination 3 were 9 patients (33%), and the combination 4 were 9 patients (33%). The most combination therapy 2 was Lisinopril dose (1x 2.5 mg) po/(1x 10 mg) po and Bisoprolol (1x 2.5 mg) po. Lisinopril therapy is given as antihypertensive and anti-remodeling in heart failure patients by preventing the formation of Angiotensin II (20). Bisoprolol therapy is added to reduce heart rate and cardiac output by blocking beta 1 receptors in the heart so that the heart works more slowly and lowers blood pressure (21). Bisoprolol has a beneficial effect on patients with heart failure and atrial fibrillation by preventing left ventricular remodeling and increasing the left ventricular ejection fraction (LVEF). The most combination therapy 3 is Lisinopril (1x 5 mg) po + Bisoprolol (1x 2.5 mg) po + Furosemide (1x20 mg) iv. Furosemide therapy is given to patients with shortness of breath and congestion (3). In the results of the study, it was found that patients with chest x-ray examination had cardiomegaly, pulmonary edema, and the mechanism of action of inhibiting (Na+, K+, Cl2-) in the loop of Henle there by reducing NaCl reabsorption, this condition will cause diuresis and end up with a decrease in blood pressure (22). The most combination therapy 4 was Lisinopril (1x 10 mg) po + Bisoprolol (1x 2.5 mg) po + Furosemide (3x 40 mg) iv + Spironolactone (1x 25 mg) po. Spironolactone therapy in patients with heart failure is given when patients with persistent heart failure (EF<35%) have been given ACE inhibitor and beta-blocker therapy. The mechanism of action of Spironolactone is by blocking aldosterone thereby preventing the formation of water and sodium retention which prevents cardiac remodeling (3).

The pattern of switching drugs in patients with heart failure from January 1 to December 31, 2020, there are 16 switching patterns. The pattern of turnover in question includes changing the type of therapy and drug combination therapy. The pattern of changing the same type of therapy consists of ACE inhibitor (Captopril→Lisinopril), the aim is to *switching* is the frequency of giving Lisinopril less and minimizing the occurrence of side effects of dry cough from Captopril, because the duration of action of Lisinopril is longer than Captopril so that in this case it is easier for elderly patients to take the drug (10). Switching CCB therapy to ACE inhibitors (Nifedipine → Lisinopril), a research journal stated that ACE *Inhibitor* (Lisinopril) is more effective for treating cardiovascular disease compared to CCB (Nifedipine). In addition, routine use of ACE inhibitors in combination with low-dose diuretics and beta blockers is recommended as antihypertensive therapy (23). Change therapy (Lisinopril → Ramipril) therapy was changed from a fellow ACE *Inhibitor*, due to the duration of action of Ramipril which has a longer half-life than Lisinopril, so the use of ACE inhibitors with a long duration of action is intended to prolong the effect medicine (24). Switching therapy (Lisinopril → Candesartan), Candesartan is an ARB, this is an alternative therapy for patients who have a history of angioedema while receiving ACE inhibitors (Lisinopril) (1). As for examples of switching patterns patient received combination therapy Lisinopril (1x 2.5 mg) po + Bisoprolol (1x 2.5 mg) po + Furosemide (2x 20 mg) iv but on the next day the patient received only 2 combination therapy because the patient's condition improved and there were no symptoms of shortness of breath, reduced edema, so furosemide therapy was discontinued.

Length of Hospital Admission (MRS) of heart failure patients at the Sidoarjo Hospital is divided into four categories, there is 1 patient with MRS (1-3 days), (4-6 days) 10 patients, (7-9 days) 7 patients, (> 9 days) as many as 2 patients. The length of treatment depends on the patient's condition which indicates that they were getting better, so they take home and treated as an outpatient with frequent check-ups at the cardiac clinic.

The condition of heart failure patients who have received Lisinopril while undergoing treatment at the Sidoarjo Hospital with condition improved but is still under the control of the cardiac polyclinic as many as 19 patients and 1 patient died. The patient's condition can be seen by monitoring the symptoms felt by the patient and clinical data such as BP, pulse, RR, temperature, and GCS values.

The weakness of this study is the incompleteness of data from the patient's medical record which can affect the results of data analysis. It is necessary to complete the recording of medical records so that it can make it easier for further researchers to obtain more accurate data.

5. CONCLUSION

1. The use of Lisinopril combination 2 was 9 patients (33%), combination 3 was 9 patients (33%), combination 4 was 9 patients (33%).

2. The most used combination 2 was Lisinopril (1x 10 mg) po + Bisoprolol (1x 2.5 mg) po as many as 2 patients (22%). The most common 3 combinations were Lisinopril (1x5 mg) po + Bisoprolol (1x 2.5 mg) po + Furosemide (1 x 20 mg) iv in 2 patients (22%). The most combination 4 was Lisinopril (1x 10 mg) po + Bisoprolol (1x 2.5 mg) po + Furosemide (3x 40 mg) iv + Spironolactone (1x 25 mg) po in 3 patients (33 %).

3. The use of switches there are 16 patterns.

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