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Effect of Combination Therapy of Multiple Antihypertensive Drugs with Diuretics on Kidney Function in Congestive Heart Failure Patients

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Abstract
Congestive heart failure is the inability of the heart to pump adequate blood that can cause kidney problems. Congestive heart failure causes fluid buildup or edema. This can be overcome by administering diuretics that act on the kidneys by removing fluid retention. This study aims to determine patients' sociodemographic and clinical characteristics and evaluate kidney function in patients receiving antihypertensive combination therapy with diuretics. **Method:** This research is observational, with a cohort study design and a retrospective approach. **Result:** The number of samples that met the criteria were 52 patients with sociodemographic characteristics, which were dominated by women as much as 61.5%, aged over 65 years 44.2%, high school education level 55.8%, and worked as IRT (Housewife) 48.1 %. While the clinical characteristics of patients based on length of stay were the most three days 36.5%, and 40-47 kg body weight 19.2%. Of the 52 patients receiving antihypertensive combination therapy with diuretics, 25% (13 people) had normal kidney function, 40% (21 people) had mild kidney impairment, and 35% (18 people) had moderate kidney impairment. **Conclusion:** based on statistical analysis, antihypertensive drugs with diuretics had no significant effect on kidney function.

Keywords: *antihypertensive, diuretics, heart failure, kidney function*

Introduction

Congestive heart failure is a condition in which the heart is unable to pump sufficient blood to meet the body's needs [1]. Heart failure is a complex collection of symptoms in which a patient has symptoms of heart failure (typical shortness of breath at rest or during activities with or without fatigue) signs of fluid retention (pulmonary congestion or ankle edema), and objective evidence of structural disturbances or cardiac function at rest [2].

Based on basic health research (RISKESDAS 2018), the prevalence of heart disease based on a doctor's diagnosis in people of all ages in 2018 was 1.5%, the highest incidence occurred in North Kalimantan Province with a rate of 2.2%, and the lowest occurred in the Province of NTT with a rate of 0.7% [3]. According to the Data and Information Center of the Ministry of Health of the Republic of Indonesia (KEMENKES RI), the prevalence of heart failure sufferers in West Sumatra Province, based on a doctor's diagnosis, the estimated number of people with heart failure is 4,456 people (0.13%), and based on diagnosis or symptoms of 10,283 people (0.3%) [4]. Based on Basic Health Research (RIKESDAS 2007) the prevalence of heart disease in Solok City is 6.2% based on a diagnosis by a health worker or with symptoms [5].

Different therapies are also given depending on the stage of congestive heart failure. In stage A patients, single therapy is given Angiotensin Converting Enzyme Inhibitor (ACEI) or Angiotensin Receptor Bocker (ARB) because the patient's condition is not too severe. Stage B is given a combination of ACEI and Beta Blocker; stage C is given a combination of several drugs such as ACEI, beta-blockers, diuretics, digoxin or other alternatives ARB, Spironolactone, Nitrates, and Hydralazine, while in stage D given drugs such as stages A, B, C plus IV inotropic (digoxin) infusion for palliative therapy [6].

Administration of Angiotensin Receptor Blockers with diuretics may result in increased, decreased, or no change in potassium levels, although logically, adding Angiotensin Receptor Blockers to treatment with diuretics is more likely to increase potassium, and vice versa. Potassium levels should be routinely monitored when Angiotensin Receptor Blockers are used in patients with heart failure, renal impairment, or the elderly [7].

In combination of ARB with furosemide, where ARB can increase potassium levels while furosemide

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decreases potassium levels, the interaction effect is unclear, but the possibility of interaction may occur. ARB combination with Hydrochlorothiazide where ARB increases potassium levels while Hydrochlorothiazide decreases potassium levels. The combination of ARBs with spironolactone can increase potassium levels in the blood, with the potential for dangerous interactions to occur [8]. Drugs excreted mainly through the kidneys will accumulate with impaired kidney function and can cause toxic effects or worsen the patient's kidney condition [9]. Blood chemistry (urea, creatinine, and electrolytes) should be checked prior to therapy, one week to two weeks after initial therapy, and at each dose titration [10].

From the discussion above, the researchers wanted to know the use of a combination of antihypertensive drugs with diuretics on kidney function in patients with Congestive Heart Failure at M. Natsir Solok Hospital. Because these cases are often found in the hospital, however, no research has been conducted regarding the use of antihypertensive and diuretic drug therapy, especially in looking at the impact on patient's kidney function. This study aims to determine the sociodemographic and clinical characteristics of patients with congestive heart failure, identify and compare the kidney function of patients with congestive heart failure who received combination antihypertensive therapy with diuretics, and examine the effect of these drugs on kidney function in patients with congestive heart failure.

Method

This research is observational, with a cohort study design and a retrospective approach. The study population was stage C congestive heart failure patients treated at M. Natsir Hospital in 2018. The sampling method used was purposive sampling, namely all samples that met the study inclusion criteria, namely all inpatients with a diagnosis of Stage C congestive heart failure (according to AHA 2013) who received combination therapy of antihypertensive drugs with diuretics at the M. Natsir Solok Hospital. Exclusion criteria were patients with heart failure who had incomplete medical record data and patients who died during treatment. Data were collected from patient medical records for the 2018 period. The data needed in this study included: administrative data, sociodemographic data, clinical data, and supporting data (laboratory data and patient creatinine clearance calculations) as well as treatment data. The collected data were analyzed descriptively in qualitative and quantitative forms. Qualitative data consisted of sociodemographic and clinical characteristics of heart failure patients. Meanwhile, quantitative data is in the form of data obtained from the laboratory results of heart failure patients. Then the data were analyzed using Chi-square.

This study focused on patients with stage C congestive heart failure who received antihypertensive combination therapy for the Angiotensin Receptor Blocker, Angiotensin Converting Enzyme Inhibitor, and Beta Blocker classes with diuretics without seeing other therapies.

Results

After data collection, the total population of stage C congestive heart failure patients has obtained as many as 67 patients during the 2018 period. The number of samples that met the inclusion criteria was 52 patients and 15 patients met the exclusion criteria.

Patient Sociodemographic Characteristics

The data shown in Table 1 is data on the distribution of sociodemographic characteristics of Stage C congestive heart failure patients with a gender category dominated by 32 female patients (61.5%) and 20 male patients (38.5%). This research is in line with research conducted by Sami in 2018 which found that women more than men suffer from heart failure [17]. Men have a higher risk than women of having an attack earlier in life due to many risk factors that are not willing to change, such as smoking, alcohol, and lower HDL levels [36]. According to Husaini (2011), the prevalence of heart failure is higher in men than in women [18]. Based on the results of a study conducted by Rosa (2015) where the number of male sufferers was 60 patients (54%) and 51 female patients (46%) [34]. Women produce the hormone estrogen, which can act as cardioprotective in several ways, namely inhibiting NADPH so that it can block the rate of oxidation, reduce the risk of inflammation, reduce afterload pressure by inhibiting calcineurin, has an antiapoptotic effect, maintains cardiomyocytes longer, stimulates the growth of mesenchymal cells in heart failure patient, exerts a vasodilating effect on blood vessel walls, as well as an atheroprotective effect related to inhibition of smooth muscle cell proliferation, and the hormone estrogen can reduce LDL, lipoprotein, and total cholesterol levels and increase HDL [19]. Analysis of the chi-square test between sex and kidney function obtained $p = 0.735$ (> 0.05), meaning

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no significant relationship exists between gender and kidney function in patients with congestive heart failure. This could be due to differences in lifestyle habits between men and women, such as men smoking and consuming alcoholic beverages.

Table 1 Sociodemographic Characteristics Data of Patients with Renal Function

Characteristics	Category	n	%	Kidney Function		
				Normal	Progress	Decrease
Gender	Male	20	38,5	4	9	7
	Female	32	61,5	7	11	14
Age	17-25	1	1,9	0	1	0
	26-35	1	1,9	0	1	0
	36-45	5	9,6	5	0	0
	46-55	10	19,2	4	2	4
	56-65	12	23,1	1	6	5
	>65	23	44,2	1	10	12
Education	SD (elementary school)	9	17,3	1	3	5
	SMP (junior high school)	3	5,8	0	1	2
	SMA (senior high school)	29	55,8	5	12	12
	PT (college)	11	21,2	5	4	2
Occupation	PNS (civil servant)	5	9,6	3	2	0
	Swasta (private)	9	17,3	1	5	3
	IRT (housewife)	25	48,1	4	8	13
	Others	13	25,0	3	5	5

Based on the age category of heart failure patients in Table 1, it can be seen that the highest number of patients with congestive heart failure were aged > 65 as many as 23 people (44.2%) while the least were in the age range 17-25 years as many as 1 person (1 .9%) and 26-35 years old as much as 1 person (1.9%). As people get older, a person will be at risk of heart failure due to decreased heart function. The American College of Cardiology Founder and American Heart Association (2013) states that the possibility of Congestive Heart Failure will increase with age [20]. In developing countries, the median age of patients with Congestive Heart Failure is 75 years [21]. This is supported by research conducted by Harikatang et al., (2016) that the age group with the most heart failure respondents studied was the 60-70-year-old group where this age constituted 50% of the total number of respondents [22]. If related to gender, women aged over 65 years have the possibility of having a congestive heart failure attack because, in old age, women have experienced menopause so they produce less estrogen hormone. Estrogen is a hormone that is cardioprotective. This further increases the likelihood of suffering from congestive heart failure [18]. In the analysis of the Chi-Square Test between age and kidney function, the value of p=0.001 (<0.05) means that there is a significant relationship between age and kidney function in heart failure patients. This means that age can influence the patient's kidney function. In accordance with the theory, the older a person is, the less the function of the organs of the body, one of which is the function of the kidneys.

Based on the education category of heart failure patients on table 1, it can be seen that the highest number of heart failure patients were at the end of high school education with 29 people (55.8%). This research is in line with research conducted by Sami (2018) that the highest final education level is high school with a total of 57 people (44.53%). This may be due to the patient's lack of knowledge about any things that can damage the condition of kidney function. In addition, the patient is less concerned about kidney care. In the bivariate analysis, it was found that p = 0.408 (> 0.05), which means that there is no significant relationship between education and kidney function. This research is in line with the research of Sri Sitiaga (2015) that there is no relationship between education and impaired kidney function [23].

Based on the occupational category, which can be seen in Table 1, the highest number of heart failure sufferers were patients who worked as IRT (housewives), namely 25 people (48.1%) and the lowest number were civil servant jobs, 5 people (9.6%). According to most heart failure sufferers based on gender category, namely women. Women primarily work as housewives. So women have bigger household responsibilities than men, which has a negative impact on health recovery [24]. Low income will be related to the utilization of health

services and prevention. Some people do not use the existing health service because they could not afford medicine or pay for transportation [25]. Based on the bivariate test, the value of p = 0.258 (> 0.05) was obtained, which means that there was no significant relationship between work and kidney function.

Clinical Characteristics Data

Table 2 Data on Clinical Characteristics of Patients with Kidney Function

Characteristics	Category	n	%	Kidney Function		
				Normal	Progress	Decrease
Treatment Length	2 days	2	3,8	1	1	0
	3 days	19	36,5	2	9	8
	4 days	10	19,2	2	4	4
	5 days	6	11,5	3	2	1
	6 days	9	17,3	2	2	5
	7 days	6	11,5	1	2	4
Weight	40-47	10	19,2	0	4	6
	48-54	4	7,7	0	1	3
	55-65	23	44,2	6	9	8
	66-70	9	17,3	3	3	3
	>70	6	11,5	2	3	1

Based on the category of length of stay shown in table 2, it can be seen that heart failure patients were treated the longest for 3 days, namely 19 people (36.5%), followed by 4 days for 10 people (19.2%) and the least was 2 days. namely as many as 2 people (3.8%). This study is in line with research conducted by Ananda (2009), namely the number of patients who were most hospitalized for 3-10 days (26). Based on the bivariate test, the value of p = 0.668 (> 0.05) was obtained, which means that there was no significant relationship between length of stay and kidney function in congestive heart failure patients.

Based on the weight category, which can be seen in Table 2, the highest number of patients with congestive heart failure were patients with a body weight in the range of 55-65 kg, 23 people (44.2%). One of the risk factors for congestive heart failure is excess body weight. Based on the chi-square test, the value of p = 0.446 (> 0.05) was obtained, which means that there is no significant relationship between body weight and kidney function.

Data on the Degree of Kidney Failure

Based on the results in Figure 1, patients with congestive heart failure who received antihypertensive combination therapy with diuretics were divided into three groups based on kidney function: patients with normal kidney function, mild kidney failure, and moderate kidney failure. Of the 52 patients, 25% (13 people) had normal kidney function, 40% (21 people) experienced mild kidney failure, and 35% (18 people) had moderate kidney failure. This was seen based on the changes in the patient's creatinine clearance before and after receiving a combination of antihypertensive therapy with diuretics. A literature review obtained data from 80,098 patients treated for heart failure, who experienced a decrease in kidney function by 63%; the rate of decline in kidney function was proportional to the increase in mortality. For every increase in serum creatinine level of 0.5 mg/dl, there was an increase in mortality rate of 15% [27].

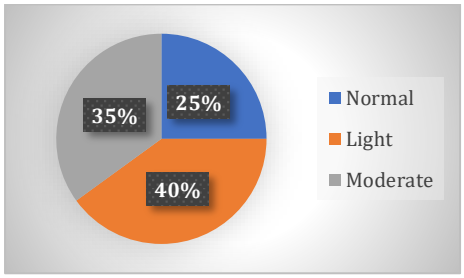

Figure 1 Degree of kidney failure in congestive heart failure patients

Medication Data

From all the data that included inclusion, it turned out that there were 5 groups of different drug combinations. First there is a combination of diuretics and ARBs (Angiotensin Receptor Blockers), diuretics and Beta Blockers, combinations of diuretics and ACEIs (Angiotensin Coverting Enzyme Inhibitors), combinations of diuretics, Beta Blockers and ACEI (Angiotensin Coverting Enzyme Inhibitors), and a combination of diuretics, ARBs (Angiotensin Receptors Blockers), and ACEI (Angiotensin Covering Enzyme Inhibitors).

Table 3 Distribution of the number of diuretics used at the M.Natsir Solok Hospital

Diuretic	n	Percentage
Furosemide	34	65,4
Spironolactone	18	34,6

From Table 3, it can be seen that there are 2 types of diuretics used in M. Natsir Hospital, namely loop Henle diuretic (furosemide) and potassium-sparing diuretic (spironolactone). Furosemide was used in 65.4% (34 patients) while 34.6% (18 patients) used spironolactone. This is in line with Juwita's research (2019) where more heart failure patients used furosemide [35]. According to the theory, combinations often prescribed are Henle's loop diuretics (furosemide) and potassium sparingly (spironolactone). Because of their greater effectiveness, loop diuretics, such as furosemide, are the mainstay of diuretic therapy in HF. Henle's loop diuretics produce a more intense and rapid diuresis than thiazides, resulting in a more prolonged diuresis. However, it is less effective in patients with impaired renal function. In practice, the dose of loop diuretics should be as low as possible, in order to maintain a euvolemia state. Limiting the amount of sodium and water, monitoring daily weight, and avoiding NSAID use are all critical in preventing salt and water retention [28].

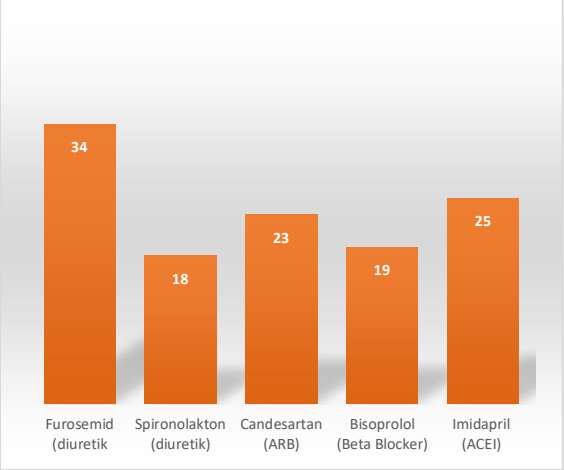

Figure 2 Distribution of medication use in patients with congestive heart failure

Based on Figure 2, it can be seen that the number of drugs that are often used to treat congestive heart failure patients is the ACEI group (imidapril) in 25 patients. Then there was the ARB group (candesartan) in 23 patients and the beta blocker group (bisoprolol) in 19 patients. The use of combinations of ACEI and diuretics is the least used combination. Several studies have also reported interactions between ACEI and furosemide. Renal failure and events of acute renal failure can arise from the concurrent use of these two drugs. Therefore, it is necessary to observe the renal function of patients on this drug combination [29]. For each group of data, an analysis was performed of changes in kidney function after receiving drug therapy by observing kidney function parameters including urea and serum creatinine. The serum creatinine value was converted to a clear creatinine value using the Cockroft and Gault equation.

Data on the Use of Diuretics on Kidney Function in Patients

Based on the results in Table 4, the data obtained were analyzed using SPSS software to process statistical data. First, the normality test was carried out using the Shapiro-Wilk test, which obtained a p value> 0.05, which means that the data was normally distributed except for testing the urea value in combinations of diuretics, beta-blockers and ACEI, the data were not normally distributed with a p-value <0.05. For normally distributed data, it was continued with the Paired T-test and obtained a p value> 0.05, for data that was not normally distributed, followed by the Wilcoxon test, it also obtained a p> 0.05 value. It can be concluded that there is no significant difference between the labor data before and after receiving treatment. Means there is no effect of the drug on the patient's kidney function.

Combination of ARB with furosemide, in which ARB can increase potassium levels while furosemide decreases potassium levels. ARB combination with Hydrochlorothiazide where ARB increases potassium levels while Hydrochlorothiazide decreases potassium levels. The combination of ARB with spironolactone, both drugs can increase potassium levels in the blood, and potentially harmful interactions occur [8]. Administration of ARBs with diuretics can cause an increase, decrease, or no change in potassium levels at all, although it is logical to add ARBs to treatment with diuretics more likely to increase potassium, and vice versa. Potassium levels should be routinely monitored when ARBs are used in patients with heart failure, renal impairment, or the elderly.

The ARB group works by inhibiting the action of the enzyme converting angiotensin I to angiotensin II, causing aldosterone to decrease.

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Decreased angiotensin II and aldosterone can attenuate the deleterious effects of neurohormones including ventricular remodeling, myocardial fibrosis, myocyte apoptosis, cardiac hypertrophy, NE release, vasoconstriction, and salt and water retention. Angiotensin receptor blockers may occasionally cause worsening of renal function, hyperkalemia, symptomatic hypotension, and cough. Therefore, this class of drugs is only given to patients with adequate kidney function and normal potassium levels [30]. This research is in line with research conducted by Surya (2013), that there is no significant difference in all parameters that determine kidney function. It can be interpreted that the use of ACE inhibitors and diuretics does not worsen kidney function in congestive heart failure patients, both with normal and impaired kidney function [31].

Table 4 Significant differences in labor data before and after acceptance of therapy

Data	Diuretic and ARB		Diuretic and Beta Blocker		Diuretic and ACEI		Diuretic, Beta Blocker, and ACEI			Diuretic, ARB and ACEI	
	N[a]	P[b]	N[a]	P[b]	N[a]	P[b]	N[a]	P[b]	P[c]	N[a]	P[b]
Ureum	0,304	0,474	0,067	0,133	0,432	0,298	0,009		1,000	0,895	0,857
CrSr	0,090	0,462	0,083	0,834	0,796	0,337	0,104	0,445		0,149	0,987
Crcl	0,223	0,581	0,662	0,476	0,464	0,407	0,893	0,906		0,805	0,643

[a]*shapiro-wilk*
[b]*Paired T-test*
[c]*Wilcoxon*

If ACEI is combined with diuretics such as thiazides and spironolactone, hyperkalemia can occur. If an ACEI must be combined with a diuretic, then furosemide is an option compared to thiazides and spironolactone [32]. However, the combination of furosemide and ACEI are some examples of drugs that damage kidney function. This combination can reduce GFR, causing an increase in serum keratinin values, which is one of the parameters to assess kidney function [30]. Before using ACEI and the furosemide class of drugs, it is recommended to do a kidney function and electrolyte examination. In addition, during treatment should be monitored for side effects of ACEI. This condition is more common in patients with impaired renal function, and adjusting the dose of ACEI is necessary. Although ACEIs have a unique role in some forms of kidney disease, including chronic kidney disease, they sometimes cause impaired kidney function that can progress and cause severity [33].

Conclusion

1. Sociodemographic characteristics of heart failure patients who received a combination of drugs with diuretics were mostly women 61.5%, aged more than 65 years 44.2%, the highest education level was high school 55.8% and work as an IRT (housewife) 48, 1%. While the clinical characteristics of patients based on length of stay were the most 3 days 36.5%, body weight 40-47kg 19.2%.
2. Of the 52 patients who received combination antihypertensive therapy with diuretics, 25% (13 people) had normal kidney function, 40% (21 people) had mild kidney impairment, and 35% (18 people) had moderate kidney impairment.
3. Based on statistical analysis of antihypertensive drugs with diuretic drugs in testing the values of urea, creatinine and creatinine clearance before and after congestive heart failure patients obtained p value> 0.05, which means there is no significant difference between the values before and after treatment. This means that the drugs given do not affect kidney function in patients with congestive heart failure.

Authors' Contribution

RY, SD, research design; RY, ANP, data collector in the Hospital; RY, SD, ANP, analyze data; RY, ANP, wrote the manuscript; and all authors have read and approved the final manuscript.

Competing Interests

The author states that there is no competing interest in conducting this research.

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