Effect of Candesartan Usage on Uric Acid Levels

(*Pengaruh Penggunaan Candesartan Terhadap Kadar Asam Urat*)

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ABSTRACT

Cardiovascular disease is caused by disorders of the heart and blood vessels. One of the risk factors for cardiovascular disease is hyperuricemia, which indicates a high uric acid level in the blood, namely ≥ 7.0 mg / dL in men and ≥ 6.0 mg/ dL in women. Candesartan is one of the main line therapies that are widely used in cardiovascular patients which in previous studies were known to affect uric acid levels. This study aims to determine the effect of using candesartan on uric acid levels in cardiovascular patients for 3 months. This study uses a cross-sectional study with a prospective approach that is by examining uric acid levels before and after three months using candesartan and analyzed using SPSS statistical test Paired test. Of the 32 total samples that met in the inclusion and exclusion criteria were 19 patients, the results showed an increase in uric acid levels with a significant value of 0,012 ($p = \leq 0.05$). So it can be concluded that the average uric acid level of patients before using candesartan was 5.44 mg / dL, and the average uric acid level after using candesartan for three months was 6.30 mg / dL which means that the used of 8 mg candesartan for three months had a significant effect on the increase in uric acid levels in cardiovascular patients.

INTRODUCTION

Cardiovascular disease is caused by disorders in the heart and blood vessels like hypertension, stroke, coronary heart disease, dyslipidemia, and diabetes mellitus (American Diabetes Association 2015). This disease can be caused by several factors, such as obesity, smoking, high-fat foods consumption, lack of activity, and heredity (Martiningsih and Haris 2019). Cardiovascular disease is also one of the leading causes of death worldwide. There were 17,3 million people who died of this disease in 2008; this number is expected to increase to more than 23,3 million people by 2030 (Kumar Arun 2014). Based on the doctor's diagnosis in Indonesia, it was known that the prevalence of heart disease was 1,5% and hypertension was 8,4% in 2018 (Ministry of Health of Indonesia, 2018).

Angiotensin II receptor blocker (ARB) is one of the first-line therapies used to cure heart disease and hypertension by blocking angiotensin III type 1 (AT1R) of blood vessels but not inhibiting angiotensin-converting enzymes in order to avoid the increase of bradykinin associated with vasodilation that is caused by angiotensin enzyme inhibitors (Nieradko-Iwanicka 2018). Some ARB are also known to have side effects on uric acid levels, increasing or decreasing uric acid levels in the blood. Candesartan is one of the drug classes that affects uric acid levels (Nishida et al., 2013). According to (Rayner et al. 2006) candesartan was known to increase average uric acid levels from 25 patients in 24 weeks, from 0,46 mg/dL to 0,48mg/dL. Meanwhile, based on the research result conducted by (Nishida et al. 2013), candesartan was known to be able to increase uric acid levels significantly for 12 weeks which was indicated by a trans-stimulatory effect on the URATI transporter. Therefore, knowing the role of candesartan in uric acid levels can also be useful in determining the usage of patients with hyperuricemia.

Antihypertensives ARB is used in Undata Palu Regional Public Hospital, where candesartan is more dominant than other ARB groups. It is known that Angiotensin II receptor blockers (ARB) were 4.025 prescriptions from 1.692 patients, and candesartan was especially used for 3.121 prescriptions from 2018 to 2020 for 1.146 patients in 2018. Based on the research background above and previous unclear research about the effect on uric acid levels, the researcher is interested in researching The Effect of Candesartan Usage on Uric Acid Levels.

MATERIAL AND METHODS

Materials

The research is conducted by examining the patient's uric acid levels before and after three months usage of candesartan in Cardiac Polyclinic in Undata Palu Regional Public Hospital during the period November 2019 – March 2020. The tool used is Easy Touch 3 in 1.

Methods

The research is conducted by using cross-sectional study with retrospective data collection techniques. The population in this research is all patients with cardiovascular disease who receive candesartan therapies in Undata Palu Regional Public Hospital in Cardiac Polyclinic during the period of November 2019 – March 2020. This research type is conducted by purposive sampling technique based on exclusion and inclusion criteria. The inclusion criteria in this research is patients who receive candesartan, patients with the age ≥18 years old and patients who are willing to participate in the research. Meanwhile the exclusion criteria is patients who use therapies that can affect uric acid levels, patients who pass away during treatment, and patients who suffer hyperuricemia. The collected data is then analyzed by using univariate and bivariate analysis. Univariate analysis is used to know the distribution of independent variables and dependent variable. Bivariate analysis was used to know the relationship between independent variables and dependent variable by using paired sample t-test statistical test (Nishida et al. 2013). This research has been approved by Ethics Committee of Tadulako University Medical Faculty (Number : 2157 / UN 28.1.30 / KL / 2020).

RESULTS AND DISCUSSION

Based on the research result conducted in Undata Palu Regional Public Hospital during the period of November 2019 to February 2020, it was known that the total patients who received candesartan were 35 patients. 32 patients of them fulfilled the requirements to be analyzed further. Patients who had no complete uric acid levels examination data were not further analyzed because they received referrals to other hospitals and passed away during the treatment. Angiotensin II Receptor Blockers (ARB) is one of the main therapy lines used for hypertensive patients, which this drug class also has clinical effect to patients with cardiovascular disease (Munger 2011). Cardiovascular disease could be affected by some factors such as age, gender, education level, smoking or not, etc (Martiningsih and Haris 2019; N Medayanti et al. 2018). Based on the research result conducted in Undata Palu Regional Public Hospital to patients who receive candesartan therapies, the details of age, gender, education, and occupation are as below in Table 1.

Table 1. Patient's demographic characteristics who receive candesartan therapies in Undata Palu Regional Public Hospital.

Patient's Characteristic	Total (n=32)	Percentage (%)
Age		
15-24 years old	0	0
25-34 years old	0	0
35-44 years old	1	3,125
45-54 years old	2	6,25
55-64 years old	11	34,375
65-74 years old	15	46,875

>75 years old	3	9,375
Gender		
Man	16	50
Women	16	50
Education		
Never Had Schooling	0	0
Ungraduate from Primary School / MI	0	0
Graduate from Primary School / MI	2	6,25
Graduate from Junior High School / MTS	3	9,375
Graduate from Senior High School / MA	11	34,375
Graduate from Associate Degree to Bachelor's Degree	16	50
Occupation		
Unemployed	17	53,125
School	0	0
Government Employees / Indonesian State Army / State-Owned Enterprises / Regional Owned Enterprises	10	31,25
Private employees	1	3,125
Entrepreneur	4	12,5

Table 1 shows that the patients who receive candesartan therapies are mostly found between the age of 65 – 74 years old (46,875%) and 55 – 64 years old (34,375%). This is consistent with the research conducted by Gikas et al (2016) who stated that patients with the age above 50 years old are most susceptible to cardiovascular disease compared to patients with the age below 50 years old. Similar results are also found by Delima, Mihardja and Siswoyo (2009) which stated that the risk of suffering from heart disease increased to more than 2,2 times at the age of 55 years old and 2,49 times at the age of 75 years old. Age factor is one of the risks of cardiovascular disease. Getting older could cause the heart muscles to stiffen and thickened (Fadlilah, Sucipto, and Amestiasih 2019). Moreover, getting older also increased total cholesterol levels and the occurrence of build-up plaque in blood vessels causes blood vessels narrow resulting in disrupted blood flow (Ghani, Susilawati, and Novriani 2016).

Based on gender, the usage of candesartan to men and women is equal (50% : 50%). It indicates that gender difference does not affect the risk of cardiovascular disease. This result is different from the research conducted by (Martiningsih and Haris 2019) and (Fadlilah, Sucipto, and Amestiasih 2019) which showed that there were 23 (28,4%) men and 58 women (71,6%). Meanwhile there were total respondents of 56 (70,9%) men and 23 (29,1%) women in the research conducted by (Fadlilah, Sucipto, and Amestiasih 2019). Meanwhile, even though there is a difference of respondent type between men and women in those two researches, it is known that the risk of cardiovascular disease does not have a significant difference. Men are known to have bigger risk from suffering cardiovascular disease due to unhealthy lifestyle like smoking and consuming more alcohol than women. Nevertheless, women after

entering menopause also have the same risk of suffering from cardiovascular disease with men. This is caused by the amount of hormone estrogen produced will decrease as getting older and will decrease significantly after entering menopause. Hormone estrogen is known able to protect cardiovascular system with the presence of genomic and non-genomic mechanisms. At menopause period, decreased production of estrogen would cause structural and functional change to cardiovascular system, such as endothelial dysfunction, increased adrenergic status, obesity visceral, and systemic inflammation which leaded to hypertension, impaired glucose tolerance, lipid profile abnormalities, and insulin resistance (Jackson 2008).

Based on occupation, table 1 shows that the incidence rate of cardiovascular disease mostly occurs to 17 unemployed patients (53,125%), which is consisted of housewives and retirees. This is consistent with the research conducted by (Jamayanti et al. 2020) which showed more than 50% from unemployed patients. This was caused by the lack of activity of this job status which could affect systolic blood pressure resulting in obesity especially to men. Furthermore, the lack of activity could increase the risk of suffering from cardiovascular disease for 1,47 times (Ghani, Susilawati, and Novriani 2016). Table 1 also shows that the number of cardiovascular disease incidence was mostly in patients who did not work as many as 17 patients (53.125%), where in this group were housewives (IRT) and retirees. This result is comparable with research (Jamayanti et al. 2020) where more than 50% of the patients who did not work. This incident is because the status of this job causes a lack of activity which can affect systolic blood pressure, which can lead to obesity, especially in men. In addition, the lack of activity can increase the risk of cardiovascular disease by 1.47 times (Ghani, Susilawati, and Novriani 2016).

Based on clinical manifestations (Table 2), it is known that chest pain is the most complained clinical manifestations from patients who suffer from cardiovascular disease which is 56,25%. Chest pain is one of the main syndromes of cardiovascular disease caused by decreased coronary blood flow towards heart muscles in which this chest pain starts from the chest area and spreads to the arm (Ridwan, Yusni, and Nurkhalis 2020). According to Kabo (2014) in Ramadini 2018, chest pain was caused by the blockage in arteries by more than 75% and additional heart burden due to excessive activities so that the patients would tend to be weaker and insomnia (Nurani, Setyorini, and Rifai 2018). Hard to breathe was also one of the most found clinical manifestations in patients who suffered from cardiovascular disease, which hard to breathe could be connected to chest pain due to inadequate ventilation from inspiration and expiration (Alamsyah et al. 2019). Hard to breathe could also be caused by fluid build-up in the alveoli which caused blood pump in the heart to be not optimal so that the oxygen supply was reduced (Nirmalasari 2017).

Table 2. Clinical manifestations of patients who suffer from cardiovascular disease using candesartan in Undata Palu Regional Public Hospital

Clinical Manifestations	Total Patients (n=32)	Percentage (%)
Chest pain	18	56,25
Hard to breathe	11	34,375
Weak	8	25
Headache	7	21,875
Tired easily	6	18,75
Tension in the head	6	18,75
Heart palpitations	3	9,375
Blurred vision	1	3,125
Insomnia	1	3,125
Anxious	1	3,125

Table 3. Diagnosis of patients who suffer from cardiovascular disease who receive Candesartan therapies in Undata Palu Regional Public Hospital

Diagnosis	Total (n = 32)	Percentage (%)
Single cardiovascular disease	12	37,5
Single cardiovascular disease + Kidney stones	1	3,125
2 Cardiovascular diseases	10	31,25
2 Cardiovascular diseases + BPH	1	3,125
3 Cardiovascular diseases	8	25

*BPH: Benign Prostatic Hyperplasia.

Based on Table 3, it is known that the patients who are diagnosed of a single cardiovascular disease are mostly found, followed by patients who suffer from two or three cardiovascular diseases. Coronary Artery Disease (CAD), Hypertensive Heart Disease (HHD), Anti Phospholipid Syndrome (APS), and Congestive Heart Failure (CHF) are the most found diagnosis in patients who are diagnosed with cardiovascular disease. CAD, or Coronary Heart Disease (CHD) or coronary heart was one of the most found cardiovascular diseases caused by a build-up of plaque on the walls of the arteries so that the oxygen supply to the heart muscle becomes disrupted (Ghani, Susilawati, and Novriani 2016), which could be suffered up to a lifetime resulting in drastic decline to the patient's health status. CAD is shown by clinical manifestations like angina and infark miokard (Wantiyah, Saputra, and Deviantony 2020). HHD is a systolic and diastolic abnormality, left ventricular hypertrophy disorder indicated by a thickening of the left ventricle to minimize pressure on the ventricular walls caused by increased blood pressure (Drazner 2011). APS is a complex and systemic autoimmune disease due to the presence of antiphospholipid antibodies (aPL) associated with arterial and venous thrombosis and repeated fetal loss. aPL was known to play a role in atherosclerosis from endothelial activity that could form lesions in heart

valves from the inflammatory process of aPL deposition process so that APS was known able to affect thrombotic immunity mediated heart where valvulopathies and CAD where the clinical manifestations occurred (Kolitz et al. 2019). CHF or congestive heart failure is right and left heart failure in which the heart can no longer pump blood to meet the needs of the body and was characterized by several symptoms such as dyspnea, orthopnea, ascites, weight gain, and insomnia (Fachrunnisa, Nurchayati, and Arneliawati 2015).

Uric acid can affect the angiotensin aldosterone renin system and reactive oxygen species lane, inhibiting nitric oxide synthesis, autonomic dysfunction, and increasing blood pressure. Uric acid is also able to cause cardiovascular conditions to worsen. Several researches stated that the higher the uric acid levels, the more cardiovascular disease worsens. This is caused by the relationship between uric acid and atherosclerosis. It was known that uric acid had a massive effect on atherosclerosis plaque, which would increase platelet adhesion and thrombus formation (Muiesan et al. 2016) due to oxidative stress during uric acid synthesis and veins or blood vessels transporter disruption (Kuwabara 2016). Uric acid would also be able to make the condition of cardiovascular disease to be worsened due to its effect on atherosclerosis which uric acid releases protein -1,25 and interleukin-1b (LL-1b) chemokine monocytes, interleukin-6 (LL-6), and factor-a tumor necrosis (TNF-a), and induced vascular endothelial cell damage which would result in increased Low-Density Lipoprotein (LDL) oxidation (Setiasih and Marfianti 2014). Based on the research conducted by Tian et al. (2018), uric acid was included in the risk factor of early onset CAD incidence. It was also related to the severity of cardiovascular disease, uric acid levels could also trigger dysregulation of glucose binding. Besides that, high uric acid levels could become a consideration to do heart transplantation because uric acid could indicate the CHF severity level associated with inflammation (Khan et al. 2017).

Based on the research result in Table 4, it is known that the most consumed drugs by patients who suffer from cardiovascular disease besides candesartan are bisoprolol (68,75%), clopidogrel (46,875%), lansoprazole (43,75%), amlodipine (34,375%), and isosorbide dinitrate (31,25%). Bisoprolol was one of the β-blocker classes that was cardioselective in low dosages. It inhibited the release of renal renin, negative chronotropic and inotropic in the heart resulting in decreased cardiac output (Dipiro et al. 2015). β-blocker classes were known to increase uric acid levels with unknown mechanisms (Choi et al. 2012). The combination of β-blocker and nitrate could be used to reduce the side effects resulting from nitrate, i.e., tachycardia and increased heart strength. Isosorbide dinitrate is one of the nitrate groups that works by relaxing smooth muscle, resulting in vasoditalation and decreased heart size, decreased peripheral resistance and blood pressure, and reduced oxygen demand (Katzung and Trevor 2015).

Table 4. Drugs usage profile of cardiovascular disease patients who receive candesartan therapies in Undata Palu Regional Public Hospital

Therapy Class	Drug Class	Drug Name	Total Drugs (n=32)	Percentage (%)
Cardiovascular Drugs	Angiotensin II receptor blockers	Candesartan	32	100
	Beta-blockers	Bisoprolol	22	68.75
	Antiplatelet	Clopidogrel	15	46.875
		Acetylsalicylic acid	8	25
	Calcium channel blockers	Amlodipine	11	34.375
	Nitrate	Isosorbide dinitrate	10	31.25
		Nitroglycerin	2	6.25
	ACE inhibitors	Ramipril	1	3.125
		Captopril	1	3.125
Antidiabetics	Biguanide	Metformin	5	15.625
	Sulfonylurea	Glimepiride	4	12.5
Antibiotics	Cephalosporin	Cefixime	1	3.125
	Makrolide	Azithromycin	1	3.125
Anti hyperlipidemia	Statin	Simvastatin	7	21.875
		Atorvastatin	1	3.125
	Fibrates	Fenofibrate	1	3.125
Cough medicine	Mucolytic	N-acetylcysteine	2	6.25
	Antitussive	Codein	1	3.125
Anti-asthmatic, bronchodilators, and anti-allergic	Corticosteroids and beta 2-agonists	Budesonide and formoterol fumarate	1	3.125
		Salbutamol	1	3.125
	Antihistamines	Cetirizine	1	3.125
	Derivate xanthin	Theophylline	1	3.125
Analgesic, antipyretic, and antiinflammatory	Non-steroid anti-inflammatory	Meloxicam	4	12.5
	Corticosteroids	Methylprednisolone	2	6.25
Antireflux dan antiulcer	Proton pump inhibitors	Lansoprazole	14	43.75
Supplement and hormone therapy	Vitamin	Vitamin B1, B6, dan B12	7	21.875
	Hormone therapy	Estradiol and norgestrel	1	3.125
Antidepressant	Benzodiazepine	Alprazolam	5	15.625
GABA analog	Anticonvulsants	Gabapentin	1	3.125
Antifungal	CYP3A4 inhibitor	Ketoconazole	1	3.125

Clopidogrel was classified into antiplatelet drugs, which needed CYP2C19 enzymes to be metabolized from prodrug to platelet blockers active metabolites by blocking ADP receptor to prevent platelet aggregation, which was commonly used for ischemia, prevent stroke, and restenosis due to the placement of coronary stents (Katzung and Trevor 2015). Clopidogrel therapy did not affect uric acid levels, but aspirin was known to increase uric acid levels in patients (Zhang et al. 2017).

Lansoprazole was classified into weakly alkaline lipophilic proton pump inhibitor drugs class, which diffused into parietal cells and worked by inhibiting hydrogen potassium adenosine triphosphatase

inside parietal cells in the stomach so that gastric acid secretion became inhibited (Dipiro et al. 2015). Drugs class of proton pump inhibitor was known not to affect uric acid levels (Pichholiya et al. 2016). Different from CCB drug class in which, this drug class was uricosuric, which could affect uric acid levels by inhibiting renal urate uptake by URAT1 transporter (Hori et al. 2018). One of this drugs class was amlodipine, included in Calcium Channel Blockers (CCB) antihypertensive drugs class which worked by inhibiting calcium entry into extracellular cells resulting in smooth muscle and heart muscle relaxation, and also caused vasodilatation and low blood pressure (Dipiro et al. 2015).

Based on the research conducted, it is known that the uric acid levels of patients who suffer from cardiovascular disease using candesartan therapy as shown in the table 5.

Table 5. Evaluation of uric acid levels of patients who suffer from cardiovascular disease before and after three months of receiving candesartan therapy in Undata Palu Regional Public Hospital.

Drugs	Uric Acid Levels						SD	t	p
	Baseline (n=32)			Evaluation (n=32)					
	Low	Normal	High	Low	Normal	High			
Candesartan	2	17	13	-	13	19	1,36	-2,79	0,012

*n = Total patients

Table 6. Descriptive data of uric acid levels of patients suffering from cardiovascular disease before and after three months of candesartan therapy in Palu Undata Regional Public Hospital.

Descriptive	Baseline	Evaluation
Mean	5,44	6,30
Median	5,50	6,20
Mode	5,0	4,7
Maximum	7,0	9,60
Minimum	3,10	4,50
Quartile	1,40	2,60

Based on Table 5 and 6, it is known that there are 13 patients with high uric acid levels out of 32 patients before three months of usage of candesartan therapy, and therefore, those patients don't meet the requirements for further testing. The data of Paired T Test from 19 patients who meet the requirements for further testing shows a significant difference in the patient's uric acid levels before and after using candesartan for 12 weeks with significant value of 0,012 or *p=<0,05*. This result is consistent with previous research, which stated that the usage of 8 mg candesartan was able to increase uric acid levels in hypertensive patients for 12 weeks (Manolis J et al., 2000; Nishida et al. 2013).

Angiotensin II Receptor Blockers was known able to give a different result to uric acid levels of each drugs. Some of this drugs class were able to lower uric acid levels. Meanwhile some others were able

to increase uric acid levels due to the difference of chemical structure and variability to URATI receptor which became the target of antihyperuricemia therapy. Those were the main transporters influenced in reabsorption and excretion of uric acid in the kidneys and also became the target of antihyperuricemia therapy (Wolff et al. 2015). Candesartan was one of the ARB drugs class known able to increase uric acid levels because the transtimulation effect to URATI has a high concentration compared to stimulation effect so that it was able to increase uric acid levels in the body (Dezki 2016). Besides that, there were some factors that could affect uric acid levels, such as healthy lifestyles like consuming high purines food and drinks i.e. alcohol, offal, anchovy, shellfish, and crab, the disease suffered, and drugs usage (Flaurensia, Kussoy, and Wowiling 2019).

CONCLUSION

Average uric acid levels of patients before using candesartan is 5,44 mg/dL and after using candesartan for three months becomes 6,30 mg/dL. 3 months usage of candesartan have a significant difference to increased uric acid levels to patients who suffer from cardiovascular disease.

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CONFLICT OF INTEREST

The authors declare no conflict of interest

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