Analysis of Drug Effectiveness and Efficiency of Use of Amlodipine-Captopril Combination Compared to Amlodipine-Valsoartan in the X Hospital Patients of Bogor

Ferry Effendi*, Sri Septiani, and Leny Fitri Lubis
Department of Pharmacy, Sekolah Tinggi Teknologi Industri dan Farmasi Bogor, Jl Kumbang No23, Bogor, Indonesia, 16151

*ferry@sttif.ac.id

Abstract. Prevalence of people with hypertension are increased with the increasingly cost of health, especially the cost of drug and hypertension including disease with long life medication therefore, we need cost effectiveness analysis for hypertension in order to assist in making effectiveness the drug selection decisions by benefit and cost. This study aim to find out difference of cost-effectiveness between amlodipine-captopril combination and amlodipine-valsartan on hypertension inpatient with BPJS in X Hospital of Bogor. Cost effectiveness analysis was conducted through payers perspective namely BPJS from direct medical cost. The output is patient blood pressure after medication with antihypertensives. Cost effectiveness analysis using value of ACER based difference on ratio between cost with output. Based on sociodemography hypertension inpatient most widely male sex (57.8%), age 56-65 years old (33.3%), housewife profession (36.7%), and last education in elementary school (33.3%). Result revealed there's difference of effectivity therapy and there's difference of cost effectiveness between amlodipine-captopril combination and amlodipine-valsartan combination, based on ACER value of amlodipine-captopril combination was Rp.19.361,9 and it is smaller than value ACER of amlodipine-valsartan combination was Rp 27.655,8. Indicating that amlodipine-captopril combination more effective and more cost-effective than amlodipine-valsartan.

1. Introduction
Based on the 2018 Basic Health Research, there was an increase in the prevalence of non-communicable diseases, one of which was hypertension from 25.8% to 34.1% and was the most non-communicable disease case during 2018, namely hypertension with a diagnosis of 185,857 patients[1].

Hypertension is a silent killer where sufferers are often not aware of any disorders or symptoms[2]. The overall goal is to reduce morbidity and death. The goal of hypertension therapy is prevention of complications, decreased cardiovascular, cerebrovascular, and renovascular events, in other words. Based on JNC VIII the blood pressure target that must be achieved at age <60 years is ≤140 / 90 mmHg, and the age of 60 years is ≤150 / 90 mmHg while for patients with diabetes or with chronic kidney disease (chronic kidney disease / CKD) the target blood pressure is 130/80 mmHg[3].

Hypertension is an increase in systolic blood pressure of more than 140 mmHg and diastolic blood pressure of more than 90 mHg at two measurements with an interval of five minutes in a state of sufficient rest / calm [4].
About 31% of the population has blood pressure > 140/90 mmHg. Blood pressure rises with age, and hypertension is common in older people. Chances of someone suffering from hypertension at the age of ≥ 55 years, despite having normal blood pressure, is 90%. Most people suffer from prehypertension before finally being diagnosed with hypertension where the diagnosis occurs in the third to fifth decade of life. [5]

In most patients, the cause of hypertension is unknown (essential or primary hypertension). This causes primary hypertension can not be cured but can be controlled. There are only a few patients who are known to cause hypertension (secondary hypertension). The mechanisms that contribute to primary hypertension have been identified. Genetic factors play a role in the development of this type of hypertension which is seen in patients suffering from hypertension also have familial relationships that also suffer from hypertension [5]

There are many risk factors for habits that can cause an increase in blood pressure, including eating foods that contain too much fat and salt and eating less fruits and vegetables, often consuming alcohol, lack of physical activity and exercise, and stress. This habit factor is strongly influenced by community work and living conditions [6]

Blood pressure is influenced by cardiac output and peripheral pressure. Various factors that affect cardiac output and peripheral pressure will affect blood pressure such as high salt intake, genetic factors, stress, obesity, endothelial factors. Increased blood pressure in primary hypertension is influenced by several genetic factors that cause changes in the kidneys and cell membranes, sympathetic nerve activity and renin, angiotensin which affects the hemodynamic state, sodium intake and sodium metabolism in the kidneys as well as obesity and endothelial factors [7]

The main goal of hypertension treatment is to achieve and maintain blood pressure targets. If the blood pressure target is not achieved within one month of treatment, an increase in the initial drug dose or by adding a second drug from one of the classes (thiazide diuretics, CCB, ACEI, or ARB) [8]

Patients receive a combination, because blood pressure in the majority of hypertensive patients cannot be controlled using only 1 hypertension drug, so two or more other antihypertensive drugs from different classes of medication are needed [9]

The cost of health services, especially medicine costs, has risen sharply in the last few decades, and this trend is likely to continue. This is due to the increased use of drugs and the presence of new drugs that are more expensive and the application of sophisticated technology. Increasing health care costs is increasingly difficult to overcome by the ability to provide government and community funds. Studies that study this are known as pharmacoconomics [10]

Pharmacoeconomics is very important in helping efforts to control drug costs, especially in the application of the National Health Insurance (JKN) organized by the Social Security Organizing Agency or BPJS. In drug selection, the efficacy and safety factor (safety and efficacy) is one important consideration, but economic considerations become very important [11]

Pharmacoeconomics is needed because of limited resources, where the most important thing is how to provide effective medicine with available funds, allocating available resources efficiently, patient needs where from the patient's point of view and private and public insurance service providers are minimal costs possible [12]

The methodology used in making drug selection decisions that are both cost-effective and cost effective is cost-effectiveness analysis. In general, cost effectiveness analysis is defined as analytical and mathematical procedures used to assist in choosing an action to be carried out from various alternatives that exist [13]

Cost effectiveness analysis is quite simple and is widely used for pharmacoeconomic studies to compare two or more health interventions that give different magnitudes of effects. With an analysis that measures both costs and outcomes, users can determine the most efficient form of health intervention requiring the lowest cost for the treatment outcome that the intervention is aiming at. In other words, CEA can be used to choose health interventions that provide the highest value with limited funds [14]
Effectiveness is the benefit of an intervention or treatment that is calculated in certain units. Measurement of cost benefits expressed in terms of: Case that is successfully treated; Proportion of side effects; Long disappearance of clinical symptoms[15]

Various kinds of antihypertensives are used to treat hypertension at X Hospital. However, the choice for antihypertensive therapy combination that is often used in hospitalization is a combination of amlodipine 10 mg-captopril 25 mg and a combination of amlodipine 10 mg-valsartan 160 mg. Based on data from January - December 2018 recorded 45 patients who used a combination of amlodipine 10 mg-captopril 25 mg and 46 patients who used a combination of amlodipine 10 mg-valsartan 160 mg.

The effectiveness and cost efficiency of amlodipine 10 mg-captopril 25 mg combination and amlodipine 10 mg-valsartan 160 mg combination in the management of hypertension in X Hospital hospitalization is not yet known, so this research needs to be done to find out more effective and efficient hypertension treatment in hypertensive patients treated at X Hospital BPJS users.

2. Material and methods
This research is an observational or non-experimental research with a descriptive analytic design and in the form of a cross-sectional analysis by looking at secondary data taken from medical record data. Data was collected using a retrospective approach that is using the medical record data of hypertensive patients using BPJS and undergoing hospitalization at X Hospital during the January-December 2018 period.

This study is a pharmacoconomics study by conducting a comparative study of the cost of treating hypertension between an antihypertensive combination of amlodipine 10 mg-captopril 25 mg with a combination of amlodipine 10 mg-valsartan 160 mg and comparing the effectiveness of each of these antihypertensive combinations. The calculation of costs is reviewed from the perspective of the BPJS on direct medical costs (direct medical costs), namely the cost of using antihypertensive drugs, doctor's service costs, and treatment costs during antihypertensive drug administration.

The method for analyzing data uses two methods namely statistical data analysis and pharmacoconomics analysis. Data analysis was performed using the Statistical Package for the Social sciences program 24.

In this research the method used is Cost Effectiveness Analysis (CEA). Cost effectiveness analysis based on the results of the value of ACER (Average Cost Effectiveness Ratio). The data obtained were analyzed for each patient and the total cost data were classified according to the antihypertensive combination obtained and calculated by ACER which is the average of the direct treatment costs of each treatment according to their class divided by the% effectiveness of therapy used using the following formula:

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\text{ACER} = \frac{\text{Total of medication cost}}{\text{Effectiveness(clinical outcomes)}} \tag{1}
\]

3. Result and Discussion

| Variable       | Amlodipine-Captopril | Amlodipine-Valsartan | Total |
|----------------|----------------------|----------------------|-------|
|                | N   | %    | N   | %    | N   | %    |
| Age (years)    |     |      |     |      |     |      |
| 26-35          | 4   | 8.9% | 2   | 4.4% | 6   | 6.7% |
| 36-45          | 8   | 17.8%| 10  | 22.2%| 18  | 20%  |
| 46-55          | 11  | 24.4%| 13  | 28.9%| 24  | 26.7%|
| 56-65          | 15  | 33.3%| 15  | 33.3%| 30  | 33.3%|
| > 65           | 7   | 15.6%| 5   | 11.1%| 12  | 13.3%|
| Gender         |     |      |     |      |     |      |
| Male           | 22  | 48.9%| 30  | 66.7%| 52  | 57.8%|
| Girl           | 23  | 51.1%| 15  | 33.3%| 38  | 42.2%|
Table 1 shows that the group of patients with the most hypertension was at the age of 56-65 years as many as 30 patients (33.3%), aged 46-55 years as many as 24 patients (26.7%), aged 36-45 years 18 patients (20%) aged more than 65 years were 12 patients (13.3%) and the least were at 26-35 as many as 6 patients (6.7%). This can be due to the increased incidence of hypertension in the age group above 46 years, because with increasing age blood pressure increases due to calcification of the vessel wall [5].

Hypertension is more common in male patients as many as 52 patients (57.8%) compared to 38 female patients (42.2%). Apart from smoking habits or unhealthy lifestyles this can also be caused by hormonal differences, because the hormone testosterone is water retention so the possibility of men affected by hypertension is greater than women.

The occupations that suffered the most from hypertension were housewife in 33 patients (36.7%) followed by entrepreneurs in 25 patients (27.8%), employees and drivers in 12 patients (13.3%), laborers in 9 patients (10%), Civil and teachers as many as 8 patients (8.9%), did not work as many as 2 patients (2.2%) and the least were farmers as much as 1 patient (1.1%). This can be caused by many factors such as the use of birth control pills, older age causes fewer estrogen hormones so that they are more at risk of developing hypertension.

Patients with the most hypertension were patients with the most recent education, namely elementary school (elementary school) as many as 30 patients (33.3%), high school as many as 27 patients (30%), followed by junior high school (first secondary school) as many as 23 patients (25.6%), Bachelor as many as 8 patients (8.9%), and at least that is not schooling as much as 2 patients (2.2%).

Table 2. Relationship of Output / Effectiveness with Patients Receiving Amlodipine-Captopril and Amlodipine-Valsartan Antihypertensive Combination Therapy in Hypertension Patients at X Hospital in 2018.

| Variabel Efektivitas | Amlodipine-Captopril | Amlodipine-Valsartan | Total |
|-----------------------|----------------------|----------------------|-------|
|                       | N   | %   | N   | %   | N   | %   |
| Under Control         | 35  | 53.8% | 30  | 46.2% | 65  | 100% |
| Uncontrollable        | 10  | 40%  | 15  | 60%  | 25  | 100% |

Effectiveness is the success of hypertension treatment to reach blood pressure levels toward the target after the patient gets antihypertensive therapy. Effectiveness is obtained by calculating the blood pressure of patients who reach the target divided by the number of patients using the therapy.

Based on the table above, the patients with the most controlled blood pressure were the patients receiving amlodipine-captopril combination therapy, as many as 53.8% or 35 patients and 10 patients with uncontrolled blood pressure while the patients with amlodipine-valsartan combination therapy were 46.2 % or as many as 30 patients are stressed his blood was controlled and 15 patients had blood
pressure out of control. This proves that the amlodipine-captopril combination is more effective than the amlodipine-valsartan combination in BPJS outpatient hypertensive patients at X Hospital.

Data analysis using Pearson Chi Square statistical tests processed with Statistical Product and Service Solution (SPSS) 24 For Windows produced a significance value of 0.039. Because p (0.039) <α (0.05), H0 is accepted, this means that there is a significant relationship between patients given amlodipine-captopril and amlodipine-valsartan antihypertensive therapy with output / effectiveness.

Table 3. Direct Medical Cost Patients Hypertension Using The Therapeutic Combination of Amlodipine-Captopril at X Hospital in 2018.

| Direct Medical Cost | Price (Rp) | Average Cost per patient (Rp) |
|---------------------|------------|-------------------------------|
| Inpatient fee       | 29,550,000 | 656,666,7                     |
| Hypertension Drug Costs | 36,075    | 801,7                         |
| Maintenance costs   | 38,200,000 | 848,888,9                     |
| Total cost          | 67,786,075 | 1,506,357,2                   |

Calculation of direct medic costs for hypertensive patients undergoing hospitalization at X Hospital in 2018 can be seen in the table above. There are three components of costs, namely the cost of antihypertensive drugs, hospitalization costs, and the cost of care during hospitalization that includes doctor fees, nursing care costs, and laboratory costs. The total direct medical cost for using the combination of amlodipine-captopril for 45 patients is Rp. 67,786,075, - with an average direct medical cost per patient that is Rp. 1,506,357, -

Table 4. Direct Medical Cost Patients Hypertension Using Therapeutic Combinations of Amlodipine-Valsartan at X Hospital in 2018

| Direct Medical Cost | Price (Rp) | Average Cost per patient (Rp) |
|---------------------|------------|-------------------------------|
| Inpatient fee       | 35,400,000 | 786,666,6                     |
| Hypertension Drug Costs | 208,804   | 4,640                         |
| Maintenance costs   | 47,400,000 | 1,053,333,3                   |
| Total cost          | 83,008,804 | 1,844,640                     |

Table 4 illustrates the total direct medicinal costs for user therapy for amlodipine-valsartan combination user therapy. The total direct medical cost for using the combination of amlodipine-valsartan for 45 patients is Rp. 83,008,804, - with an average direct medical cost per patient that is Rp. 1,844,640, -

Table 5. Calculation Unit Cost of a Combination of The Antihypertensive Drug Amlodipine-Captopril and Amlodipine-Valsartan at X Hospital in 2018

| Drug Combination     | Total Cost (C) | Outcomes/ Efektivness (E) | Unit Cost (C/E) |
|----------------------|----------------|---------------------------|-----------------|
| Amlodipine-Captopril | 1,506,357      | 35                        | 43,038,8        |
| Amlodipine-Valsartan | 1,844,640      | 30                        | 61,488          |

From the table above shows that the unit cost of patients receiving amlodipine-captopril combination therapy is Rp. 43,038, - lower than patients receiving amlodipine-valsartan combination therapy, which is Rp61,488, -

Table 6. Calculation ACER of a Combination of The Antihypertensive Drug Amlodipine-Captopril and Amlodipine-Valsartan at X Hospital in 2018

| Drug Combination     | Total Cost (C) | Outcomes/ Efektivness (E) | ACER (C/E) |
|----------------------|----------------|---------------------------|------------|
| Amlodipine-Captopril | 1,506,357      | 77,8 %                     | 19,361     |
| Amlodipine-Valsartan | 1,844,640      | 66,7 %                     | 27,655     |
Cost effectiveness research is expressed in the form of ACER obtained by comparing the average cost of various treatment patterns with the effectiveness of the treatment pattern to achieve the expected blood pressure (outcome or effectiveness). ACER value can be used as a criterion, an intervention is said to be cost-effectiveness is the lowest cost per unit effectiveness, in other words the ACER value is the lowest[13].

The ACER value shows that for every 1% increase in effectiveness it takes a cost of ACER. For example in the amlodipine-captopril combination, it means that each 1% increase in the effectiveness of the combination requires a cost of Rp. 19,361,-. Based on table 10, the highest ACER value is shown by the combination of the drug amlodipine-valsartan, which is Rp. 27,655,- and the lowest value of ACER is the amlodipine-captopril combination, which is Rp.19,361,- The smaller the ACER value, the more cost-effective the drug, so it can be concluded that the combination of amlodipine-captopril is the most cost-effective or efficient drug for antihypertensive therapy in hospitalized patients in X hospitals.

4. Conclusion

Patients with hypertension were hospitalized most male sex (57.8%), based on age at most 56-65 years (33.3%), based on the most occupations namely housewife (36.7%) , and based on the most recent education the most are elementary schools (33.3%).

Outcome / effectiveness on the use of amlodipine-captopril antihypertensive combination that is equal to 53.8% while the effectiveness of the amlodipine-valsartan antihypertensive combination is 46.2%, this means that the amlodipine-captopril combination is more effective compared to the amlodipine-valsartan combination in hypertensive patients by 46.2% hospitalized at X Hospital.

Based on ACER value of amlodipine-captopril antihypertensive combination is Rp 19,361,-while in amlodipine-valsartan antihypertensive combination is Rp 27,655,- So that the amlodipine-captopril combination is more efficient compared to the amlodipine-valsartan combination in patients with hypertension inpatient at X Hospital.

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