

Cost effectiveness analysis of antihypertensive drugs usage by combination of ACEI–diuretic and ARB–diuretic in outpatient hypertension therapy at Leuwiliang regional general hospital Bogor 2015

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Abstract. Hypertension is a cardiovascular disease that can lead to increased morbidity and mortality. The prevalence of hypertension in Indonesia is 7.6 (Riskesdas 2007) in 2013 increased to 9.5. Therapy of hypertensive takes a long time and expensive. This study to determine the effectiveness of drug combination and cost effectiveness of combination therapy of antihypertensive drugs ACEI-Diuretic and ARB-Diuretic in outpatient of hypertension at RSUD Leuwiliang Bogor 2015. This study was a cohort design to measure the effectiveness and Cost Effectiveness Analysis to measure the efficiency of cost of antihypertensive combination drugs ACEI-Diuretic and ARB-Diuretic. The data for this study were collected prospectively from medical record of outpatient hypertensive visit to Leuwiliang Regional General Hospital Bogor June-December 2015. The samples size were 70 patients with hypertension who meet the inclusion and exclusion criteria and were divided into 2 groups. Each group consisted of 35 hypertensive patients, each receiving combination antihypertensive drugs and observed for 3 months. Results showed that the antihypertensive combination drug of ACEI-Diuretic controlled blood pressure 91.1% and unit cost IDR 837.670- Combined ARB-Diuretic controlled blood pressure 76.4% and unit cost IDR 1.133.520,-. This means that the combination drug ACEI-Diuretic is more effective and efficient than the ARB-Diuretic combination. The combination drug ACEI-Diuretic is more effective and efficient than the ARB-Diuretic combination, evidenced by the value of ACER 837.670 and the value of ICER -233.585.

1. Introduction

Hypertension is a non-communicable disease that needs to be controlled, because this disease can threaten human life, sometimes without symptoms so it was often called the silent killer. Hypertension is characterized by increased systolic blood pressure greater than 140 mmHg and diastolic blood pressure greater than 90 mmHg [1]. Patients with hypertension tend to be at risk for cardiovascular disease, this disease is the main cause of death in Indonesia. The results of basic health research (RISKESDAS) in 2007 showed the prevalence of national hypertension reached 31.7%, in 2013 the figure decreased to 26.5% [2]. Prolonged arterial hypertension

can damage blood vessels in the kidneys, the heart and brain, and can increase the incidence of renal failure, coronary heart disease, heart failure and stroke [3].

According to the JNC VII 2003 obtained the national prevalence of 5.3 % (for male 6 % and and 4.7 %, female), rural (5.6 %) are higher than urban areas (5.1 %). Handling of hypertension begins with the modification of patterns of life, This is one way to control blood pressure, subsequent handling based on The Seventh of the Joint National Committee (JNC7) On Prevention, Detection, Evaluation, and Treatment of

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High Blood Pressure with drug therapy antihypertension single or combination of both [5].

The Combined antihypertensive drugs are given if a single antihypertension has not been able to achieve a controlled therapeutic target. The combination often used to control hypertension is ACEI-Diuretics and ARB-Diuretics. Effective treatment with minimal costs is the hope of hypertension therapy. To meet this expectation, research on drug effectiveness and cost-effectiveness of oral antihypertensive drug use is needed by conducting pharmacoeconomic analysis. In this study carried out on hypertensive patients outpatient at Leuwiliang Regional General Hospital Bogor.

The problem in the treatment of hypertension are:

- Hypertension needs treatment continuously so that it becomes a burden to the family, the Government and State. During treatment with a single drug has not yet reached the optimum effect, needs to be given a

combination of antihypertensive drugs to control blood pressure.

- Not yet known effectiveness of each combination of antihypertensive drugs (ACEI-Diuretic and ARB-Diuretic) used in the treatment of hypertensive patients at Leuwiliang Regional General Hospital Bogor in the period June-December 2015. And it is not yet known which combination is more efficient between the two combinations drugs (ACEI-Diuretics and ARB-Diuretics) used in the treatment of hypertensive patients at the Leuwiliang Bogor Regional General Hospital in the period June-December 2015.

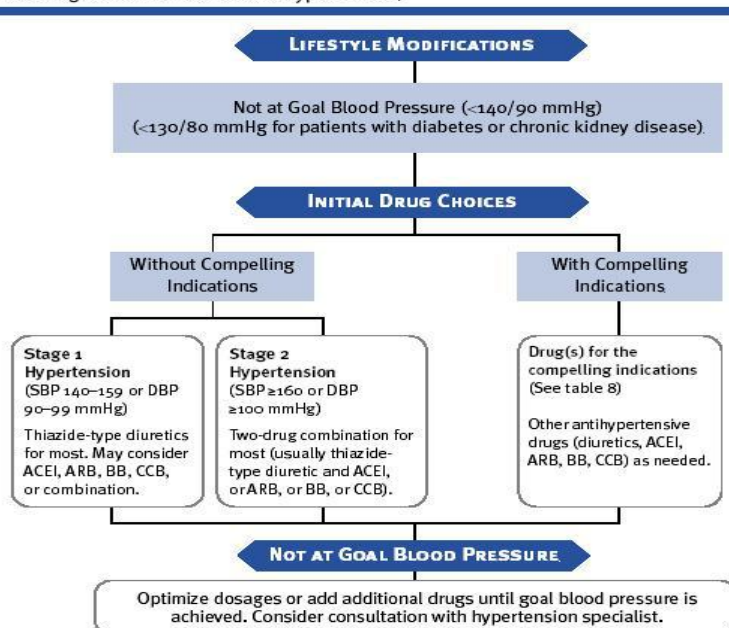
- Not yet known the unit cost (unit cost) each antihypertensive combination drugs (ACEI-Diuretic and ARB-Diuretic) used in the treatment of patients of hypertension sufferers at Leuwiliang Regional General Hospital Bogor Period June-December 2015 is unknown.

Classification Of Hypertension

The Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (JNC) USA, Classification (JNC VII 2003) [5]

Characteristic	SISTOLIC (mmHg)	DIASTOLIC (mmHg)
Normal	< 120	< 80
Pre-Hypertension	120 – 139	80 – 89
Hypertension		
Stadium 1	140 – 159	90 – 99
Stadium 2	>/= 160	>/= 100

Figure 1. Algorithm for treatment of hypertension.



DBP, diastolic blood pressure; SBP, systolic blood pressure.

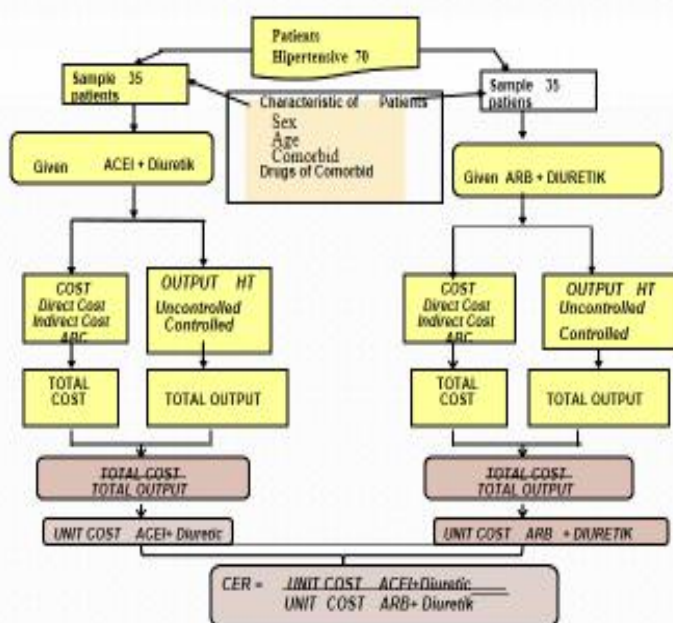
Drug abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CCB, calcium channel blocker.

2. Objectives

This study was to determine the drugs effectiveness, and cost effectiveness in the treatment of hypertension patients in outpatient who use antihypertensive drugs

combinations (ACEI-Diuretic and ARB-Diuretic) at Leuwiliang Regional General Hospital Bogor Period June-December 2015.

The Framework of Research Concept



Note:

ACEI = Angiotensin Converting Enzyme Inhibitor
ARB = Angiotensin Receptor Blokera,
ABC = Activity Based Costing
CER = Cost Effectiveness Ratio

3. Methodology

This Study was conducted in Leuwiliang Regional General Hospital Bogor from June-December 2015. This Study uses two designs i.e.

1. To review the effectiveness of the drug using a cohort design by doing observation and measurement against a prospective outpatient hypertensive from June-December 2015. We collected 70 hypertensive outpatient who meet the criteria for inclusion and exclusion. Every
2. hypertensive outpatient observed during 3 months.

3. We conduct cost effectiveness analysis to examine cost effectiveness in treatment of hypertension.

Inclusion Criteria

- Hypertensive outpatients in Leuwiliang Regional General Hospital Bogor June-December 2015
- Hypertensive outpatients who first time never did control for a period longer than 2 weeks (associated with drug bioavailability).
- Age 30-65years (productive age)
- Willing to be the subject of research

- The patient who following treatment for 3 months

Exclusion Criteria

- Hypertensive inpatients who are hospitalized
- Drugs use instead of antihypertensive drugs combination of ACEI-Diuretic and ARB-Diuretic
- Patients who consumed more salt than 1500 mg/day and coffee consumption of 300 mg/day
- Pregnant and lactating women

Materials

Antihypertensive drug combination (combination of two groups)

1. Antihypertensive drug combination of ACEI-Diuretic, there are two drugs in one of combinations (Lisinopril + Furosemide)
2. Antihypertensive drug combination of ARB-Diuretic, there are two drugs in one of combinations (Losartan + Furosemide)

Tools and materials for the laboratory Examination for comorbidities

The data collected

- 1). Data treatment (drug effectiveness) of hypertensive patient who admitted

Tools used include:

- Stethoscope-Littmann Classic II SE inchi 71 28 cm
- Sphygmomanometer Riester Reg. No. KL 0502190139, data and results of the anamnesis
- Other Physical examination tools

- 2). Data for the study of Economics (medical expenses) the results of the interviews with the patient through the questionnaire, the instrument used a questionnaire.

The Data Analysis

- a. To find out the effectiveness of medications by conducting an analysis below;

- 1). Analysis of univariate data for estimating the distribution of each variable.

- 2) Chi Square analysis for estimating the relationship between the independent variable with dependent variable [8].

b. To perform cost analysis using the Pharmacoeconomic method that is Cost Effectiveness Analysis (CEA) with perspective patients. CEA costs are taken into account direct costs, indirect costs and costs intangible.

CEA is a pharmacoeconomic analysis that compares cost-effectiveness between 2 treatments whose results or outcomes are assessed from natural units, CEA does not need to be in monetary form. Enough on the natural unit. The natural unit can be, blood pressure, life-saving, blood sugar levels, cholesterol and so on. The end result is in the form of cost effectiveness ratio (ACER = an average Cost ACER = health care cost (in monetary) / clinical outcome (in natural units) Effective Ratio)

To compare two alternative drugs that are better, we can calculate the additional costs and effectiveness we get (ICER = incremental cost effective ratio) $ICER = \frac{Cost A - Cost B \text{ (in monetary)}}{Effect A - Effect B \text{ (in\%)}}$.with this ICER Formula we can see how much extra costs are needed to get the effect of replacing drug A to drug B

3. Result

The characteristics of hypertensive outpatients based on sex, age, education, work, blood pressure, comorbidities, the use antihypertensive drugs combination ACEI-Diuretic and ARB-Diuretic at Leuwiliang Regional general Hospital Bogor 2015 during the period from June to December, 2015 is as follows the sex of the majority of women, ages ranging from 45-65 years, education at most colleges and universities, the work of civil servants and private employees, systolic blood pressure ranged from 160 - 200 mmHg, diastolic blood pressure ranged between 90-100 mmHg, comorbidities most with type 2 diabetes mellitus, hyperlipidemia, osteoarthritis, followed by dyspepsia and vertigo

Table 1. The relationship between the Antihypertensive drugs combination with controlled of blood pressure on treatment hypertensive outpatients at Leuwiliang Regional General Hospital Bogor period June-December 2015

Antihypertensive Drug Combination	Blood Pressure				Total	
	Controlled		Uncontrolled		N	%
	N	%	N	%		
ACEI-Diuretic	31	91.1	3	8.9	34	100
ARB-Diuretic	26	76.4	10	23.6	36	100

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The table above shows that patients who received combination drug therapy ACEI-Diuretics, controlled blood pressure by up to 91.1 %. While the outpatient

hypertensive who received ARB-Diuretic combination therapy, controlled blood pressure 76.4%.

Table 2. The relationship between comorbidities with the effectiveness of therapy Antihypertensive combination drugs A and combination drugs B treatment of Hypertensive outpatients at Leuwiliang General Hospital Bogor Period June-December 2018

Comorbidities	Antihypertensive Combination drug A						Antihypertensive Combination drug B					
	Cont		Uncont		Total		Cont		Uncont		Total	
	N	%	N	%	N	%	N	%	N	%	N	%
Hyperlipidemia	12	34.3	0	0	12	34.3	8	22.9	4	11.3	12	34.2
DM type 2	10	28.6	0	0	10	28.6	6	17.4	2	5.7	8	23.1
Osteoarthritis	6	17.1	0	0	6	17.1	5	14.3	2	5.7	7	20.0
Dyspepsia	4	11.4	0	0	4	11.4	3	8.6	2	5.7	5	14.3
Vertigo	2	5.7	1	2.9	3	8.6	2	5.7	1	2.7	3	8.4
Total	34	97.1	1	2.9	35	100	24	68.9	11	31.1	35	100

Note: A= ACEI-Diuretic B= ARB-Diuretic Cont=Controlled Uncont=Uncontrolled

The above table showed that hypertensive patients with comorbidities who received antihypertensive drugs combination ACEI-Diuretic are DM tipe2, hiperlipidemia, osteoarthritis, dyspepsia, and vertigo respectively. However, treatment with ACEI-Diuretic hypertension disease controlled up to about

97%. While hypertension patients with comorbidities who received the antihypertensive drugs combination ARB-Diuretic, that most of the DM type 2, hyperlipidemia and osteoarthritis, following dyspepsia, the effect achieved is the is the control of blood pressure up to 69 %.

Table 3. The Distribution Of Direct Costs on Hypertensive Outpatients Using Antihypertensive Combination drugs ACEI-Diuretic and ARB-Diuretic at Regional General Hospital Leuwiliang Bogor Period June-December 2015

No.	The Components Of Direct Cost	Group ADC A (IDR)	Group ADC B (IDR)
1.	Cost of antihypertensive combination drugs	4.050.000.00	4.800.500.00
2.	Cost of Comorbidities drugs	5.169.400.00	6.123.000.00
3.	Cost of Laboratory	4.211.100.00	4.520.000.00
4.	Cost of examination	6.120.200.00	6.850.000.00
	Total of direct cost	19.550.700.00	22.293.500.00

Note:

ACD A= Antihypertensive combination drugs ACEI-Diuretic

ACD B= Antihypertensive combination drugs ARB-Diuretic

In the above table shows that the patients who received treatment with antihypertensive combination drugs of ACEI-Diuretic, which costs the most in the components of direct costs is the cost of examination,

Cost of drugs comorbidities and costs of antihypertensive combination drug, on patients treated with antihypertensive drugs combination ARB-Diuretic, which costs the most the direct cost component is also the cost of the examination and the comorbidities drug costs and antihypertensive combination drug costs.

Table 4. The Distribution Of Indirect Costs on Hypertensive Outpatients Using Antihypertensive Combination drugs ACEI-Diuretic and ARB-Diuretic at Leuwiliang Regional General Hospital Bogor Period June-December 2015

No.	The Components Of Direct Cost	Group ADC A (IDR)	Group ADC B (IDR)
1.	Cost of transportation	684.000.00	768.000.00
2.	Cost of accommodation	1.400.000.00	1.550.000.00
3.	Cost of loss of productive time	4.333.326.00	4.960.000.00
	Total of Indirect cost	6.417.326.00	7.178.000.00

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Note:

ACD A= Antihypertensive combination drugs ACEI-Diuretic

ACD B= Antihypertensive combination drugs ARB-Diuretic

The data from Table 4 shows that patients who received treatment with antihypertensive combination drugs of ACEI-Diuretic, which costs the most in the components of indirect costs is the cost of loss of

productive time, on patients treated with antihypertensive drugs combination ARB-Diuretics, which costs the most the indirect cost component is the cost of loss of Productive time.

Table 5.The distribution costs on hypertensive outpatients using antihypertensive drugs combination ACEI-Diuretic and ARB-Diuretic at Leuwiliang Regional General Hospital Bogor Period June-December 2015

ACD	Direct Cost (IDR)	Indirect Cost (IDR)	Total Cost (IDR)	Patients with Controlled BP	Unit Cost (IDR)
ACEI-Diuretic	19.550.400	6.417.326	25.967.726	31 (91%)	837.670
ARB-Diuretic	22.293.500	7.178.000	29.471.500	26 (76%)	1.133.520

Note: BP = Blood Pressure

The table above shows that patients who received treatment with the antihypertensive combinations drugs ACEI- Diuretic controlled their blood pressure as much as 31 people (91%) compared to patients who received treatment with the antihypertensive combinations drugs ARB-Diuretic and controlled blood pressure just 26 people (76%). The antihypertensive combination drugs ACEI-Diuretic is more effective in controlled blood pressure compare ARB-Diuretic. The Unit Cost Combination drugs ACEI-Diuretic IDR 837.670, while unit cost combination drugs ARB-Diuretic IDR 1.133.520,-. The antihypertensive combination drugs ACEI-Diuretic is more efficient, as evidenced by as evidenced by unit cost, where the combination of ACEI-Diuretic unit costs is lower than the ARB-Diuretic combination drugs.

$$ACER \text{ for ACEI-Diuretic} = 25967726/31 = 837.670$$

$$ACER \text{ for ARB-Diuretic} = 29471500/26 = 1.133.520$$

The smallest ratio is a combination of ACEI-Diuretic, this means that the combination drug chosen is a small ratio, the results of this study, the smallest one is ACEI-Diuretic

To compare the two drugs are better alternatives, can be calculated the additional cost and effectiveness that we get (ICER = incremental cost effective ratio)

$$ICER = \text{Cost A} - \text{Cost B (in monetary)} / \text{Effect A} - \text{Effect B (in\%)}$$

$$ICER = (\text{Cost ACEI-Diuretic}) - (\text{Cost ARB-Diuretic}) / (\text{Effect ACEI-Diuretic}) - (\text{Effect ARB-Diuretic})$$

$$ICER = 25967726 - 29471500 / 91 - 76 = - 233,585$$

Sensitivity analysis

Sensitivity analysis is a simulation if the group of patients receiving ARB-Diuretic combination drugs is replaced with a combination of ACEI-Diuretic drugs

which reaches 35 (100%) patients be controlled blood pressure [16].

4 Discussion

In this study, the hypertensive patients are dominated by female. This study was same with previous study about gender of hypertensive patients from study Department of Health [1]. Hormonal changes of woman in menopausal phase of women around 50s, where the average median age – women menopause that is 50 years old, as in women who have not experienced menopause hormone estrogen protected role in raising levels of HDL. A high HDL cholesterol levels is a protective factor in preventing the occurrence of atherosclerosis processes which in turn will occur resulting in a narrowing of the arteries of hypertension [11].

Based on age, the hypertensive outpatient at Leuwiliang Regional General Hospital Bogor are dominated between 46 – 55 years and 55 years old. Age has correlation with decreasing elasticity of blood vessel and increasing systolic blood pressure and declining of aortic volume which lead hypertension. The hypertensive outpatient has another following diseases: type 2 diabetes mellitus, hyperlipidemia, osteoarthritis, vertigo, and dyspepsia.

Bivariat analysis results from patients with drug therapy combinations ACEI–Diuretic showed that diagnosis result of hypertension with blood pressure, diseases of companion remains under control means disease companion does not affect treatment with the Antihypertension combination drugs ACEI–Diuretic and ARB-Diuretic [12]. The Chi Square analysis results indicate that the ACEI–Diuretic is more

effective than ARB-Diuretic is characterized by his higher learning outcomes.

In this study, comparing cost analysis between antihypertensive combination drugs of ACEI-Diuretic with ARB-Diuretic. Cost analysis is done in the form of total cost of merging the direct costs and indirect costs from each combination. Then do cost analysis in Pharmacoeconomic i.e. Cost Effectiveness Analysis (CEA) on both the drug combination of antihypertensive by comparing the total cost with the effectiveness of the therapy are achieved[17].

The research results obtained from the total direct costs for the combination of ACEI – Diuretic IDR 19.550.400,- as for the combination of ARB-Diuretic IDR 22.293.500,-. This is due to the price of the drug combination antihypertension ARB-Diuretic is more expensive compared to the other combinations of antihypertensive drugs ACEI-Diuretic. While the indirect costs On this research indirect costs include the cost of transportation patients, accommodation costs and the cost of the loss of productive time.

From research results obtained total indirect costs for the combination of ACEI – Diuretic IDR 6.417.326,-, as for the combination of ARB-Diuretic IDR 7.178.000,-. The total indirect cost for ARB-Diuretic drug combination is greater because it is influenced by various variables including the value of productive time.

The cost-effectiveness ratio (CER) is the lowest cost between the unit cost of the ACEI-Diuretic drug combination with the unit cost of the ARB-diuretic combination drug. Unit costs are obtained from the total costs compared to therapeutic output, namely the number of patients with controlled blood pressure.

This study showed that combination drug of ACEI-Diuretic has the lowest unit cost compared with drug combination of ARB-Diuretic. And patients with controlled blood pressure as much as 91% compared with combination antihypertensive drugs ARB - Diuretics Controlled blood pressure only (76%)

Effectivity, hypertensive outpatients at Leuwiliang Regional General Hospital Bogor Period June-December 2015, who received antihypertensive drug combination ACEI-Diuretic is more effective than the combination of ARB-Diuretics. this is evidenced by the number of patients whose blood pressure controlled. In the table 4, showed that value of unit cost of antihypertensive combination drugs ACEI - Diuretics is IDR 837.670,- lower than combination drugs of ARB-Diuretic IDR 1.133.520,-. Antihypertensive combination drugs ACEI-Diuretic are also more efficient than combination antihypertensive drugs

ARB-Diuretic. This finding is supported by the results of research Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension (Accomplish) in the United States in 2003. In that study, showed The combination of ACEI - diuretic which is a combination of drugs recommended by JNC VII 2003 [14].

4. Conclusions

The conclusions from the results of this research it can be concluded that:

- Patients who receive antihypertensive combination drugs of ACEI – Diuretic is more effective compared to antihypertensive combination drugs of ARB – diuretic at Leuwiliang Regional General Hospital Bogor period June-December 2015
- Unit cost of antihypertensive drug combination of ACEI – diuretic lower than antihypertensive drug combination of ARB – Diuretic at Leuwiliang Regional General Hospital Bogor period June-December 2015
- Patients who receive antihypertensive drug combination drugs of ACEI – Diuretic is more efficient compared to antihypertensive combination drugs of ARB – Diuretic at Leuwiliang Regional General Hospital Bogor period June-December 2015
- Patients who receive antihypertensive combination drugs ACEI-Diuretic more effective and more efficient (Cost effectiveness) compared to ARB – Diuretic evidenced by the value of ACER 837.670 and the value of ICER -233.585, at Leuwiliang Regional General Hospital Bogor period June-December 2015

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