Original article

Cost Analysis of Combination Diuretic Therapy with Ace-Inhibitors to Diuretic Therapy without Ace-Inhibitors in Heart Failure Patients

Pribadi FW[1] , Dwiprahasto I[2], Thobari JA[2]

Abstract:

Background: Heart failure is the final stage of the entire heart disease and become a major health problem because of the high morbidity and mortality. Diuretic combination therapy with ACE inhibitors compared to diuretic therapy without ACE inhibitors will affect the costs and hospitalization for heart failure patients; so it can be used to study Pharmacoeconomics. *Method and Design*: This study is an analytic observational retrospective cohort study design. Researchers compared the cost analysis between groups having diuretic combination therapy with an ACE inhibitor and diuretic therapy without ACE inhibitors. Data taken with a total sampling of heart failure databases claimed prescribing health insurance between January 1, 2010 until December 31, 2011. *Results*: Out of the 377 patients of the study population, 64 patients received combination therapy with ACE inhibitors and diuretics, and 60 patients received diuretic therapy without ACE inhibitors. The analysis showed that the total cost was Rp. 4.96 million and Rp. 5.14 million; the average total inpatient days a year was 10.67 days and 7.00 days. *Conclusion*: This study showed that the diuretic combination therapy with an ACE inhibitor is more cost-effective. Further research is needed to assess the total costs and effectiveness of therapy with more number of subjects and longer periods.

Key Words: diuretics; ACE-inhibitors; heart failure; cost analysis

Introduction:

Heart failure is the final stage of the entire heart disease and to this day remains a major health problem because of the high morbidity and mortality[1]. Figures prevalence, incidence or new cases a year which is the highest frequency cause of hospitalization in patients aged 65 years or more. Figures hospital discharge increased[2,3]. Unfavorable prognosis with survival rates of 50% and 10% in a period of 5 and 10 years and also occupy about 30-35% of the total hospitalisation[4]. In addition, Case fatality rates after hospitalization within 30 days was 10.4%; whereas in 1 year was 22% and in 5 years was 42.3%[5].

In Indonesia, there was 13.396 hospitalized cases, outpatient 16,431 cases with a case fatality rate 13.42%[6]. Lodging in Central Java Province categorized in groups of heart and blood vessel disease or cardiovascular diseases such as heart disease, stroke, hypertension is the number of 833 094 cases (54.33%) with a prevalence of 0.14%, which means there are 10,000 people 14 people who suffer from heart failure[6,7].

Costs incurred for the management of heart failure was 5.9% of the total health budget in Amerika[8]. While the National Heart, Lung, and Blood Institute estimates that the total cost of heart failure in 2010 of 39.2 million dollars to the direct cost of 35.1 million dollar[9]. In developing countries, consume between 1-2% of the total health budget and two-thirds is the cost of hospitalization[10].

Given standard therapy for severe heart failure is a loop diuretic, an ACE inhibitor, digoxin, β-blocker or a combination thereof. In two RCTs

1. Fajar Wahyu Pribadi, Department of Pharmacology, The Faculty of Medicine, Jenderal Soedirman University.

2. Iwan Dwiprahasto,

3. Jarir At Thobari,
   Department of Pharmacology and Toxicology, The Faculty of Medicine, Gadjah Mada University

Corresponds to: Fajar Wahyu Pribadi, Department of Pharmacology, The Faculty of Medicine, Jenderal Soedirman University, Indonesia. **E-mail:** tarique@iium.edu.my | m.tariqur.rahman@gmail.com.
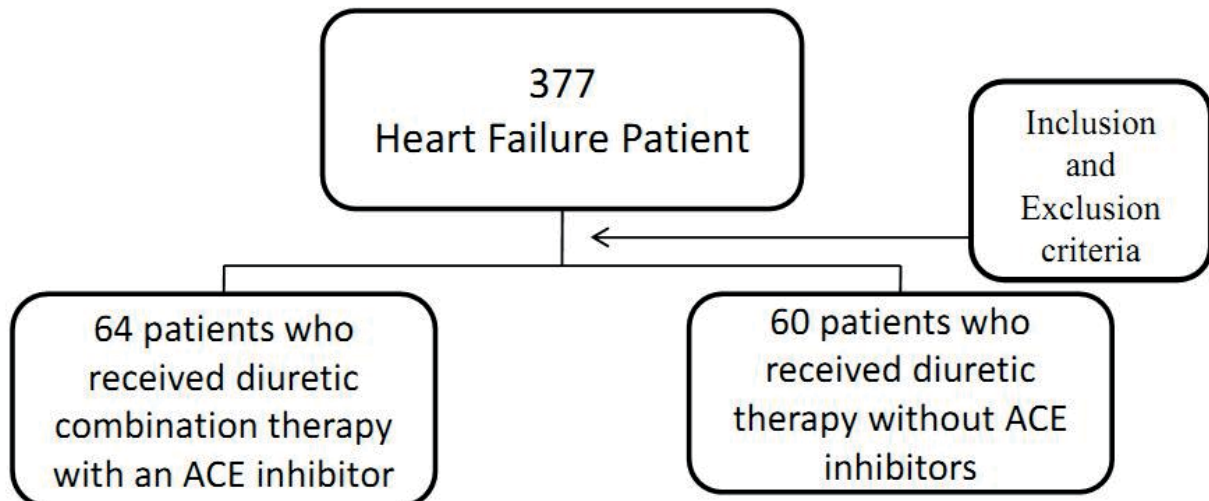
Figure 1. The selection process of the study

(CONSENSUS and SOLVD-Treatment) conducted in 2,800 patients with a diagnosis of mild to severe heart failure who were given enalapril and placebo showed the results of therapy with ACE inhibitors reduce the risk of death (RRR = Relative Risk Reduction) by 27% in CONSENSUS and 16 % in SOLVD-Treatment. In addition to the SOLVD-Treatment also showed RRR of 26% in hospital admission for worsening heart failure. This advantage arises when combined with conventional therapy[11].

In a meta-analysis of diuretic therapy showed a decrease in mortality of 75% (OR = 0:25, 95% CI 0.84% to 0:07%; p = 0:03; ARR 8.2%; NNT = 12) and an increase in exercise capacity 63% (OR = 0:37, 95% CI 0.1% to 0.64%) 12. Incremental cost-effectiveness to ACE inhibitors in the AIRE and HOPE shows an estimate of $ 2.800 / YOLS (Year of Life Saved) and $ 15,000 / YOLS, while the estimated lifetime treatment for $ 5,000 / YOLS and 8.500 / YOLS. Research on RALES get that diuretics decrease heart failure hospitalization

Table 1: Characteristics of Subjects Research

Characteristics	Total N=124	Sum (%)		p-value
		Diuretic & ACE Inhibitor (n=64) n (%)	Diuretik tanpa ACE *Inhibitor* (n=60) n (%)	
Sex				
- Female	48 (38,7)	28 (43,8)	30 (33,2)	0,234
- Male	76 (61,3)	36 (56,2)	40 (46,8)	
Age				
- < 45 year	4 (3,2)	2 (3,1)	2 (66,1)	0,668
- 45-64 year	63 (50,8)	35 (54,7)	28 (46,7)	
- > 64 year	57 (46,0)	27 (42,2)	30 (50,0)	
Room Class				
- I	75 (60,5)	40 (62,5)	35 (58,3)	0,092
- II	45 (36,3)	20 (31,3)	25 (71,7)	
- ICU	4 (3,2)	4 (6,3)	0 (0)	
Comorbid				
- No	97 (78,2)	51 (79,7)	46 (76,7)	0,684
- Yes	27 (21,8)	13 (20,3)	14 (23,3)	

Source: processed secondary Data 2012

Table 2. Normality Test

No.	Variabel	Shapiro-Wilk		
		Statistic	df	sig
1	Hospitalization Cost	0,794	124	0,000
2	Services and laboratories Cost	0,690	124	0,000
3	Drug Costs	0,643	124	0,000
4	Total Costs	0,850	124	0,000
5	CER/Day	0,763	124	0,000

Source: processed secondary Data 2012

Table 3. Long Hospitalization between diuretics and ACE inhibitor group with diuretics without ACE inhibitors

Long Hospitalization	Mean ($\pm$SD)		p
	Diuretik & ACE Inhibitor (n=64)	Diuretik without ACE Inhibitor (n=60)	
Day/ Year	7,00 (4,42)	10,67 (4,34)	0,000

Source: processed secondary Data 2012

Table 4. Bivariate Analysis Regarding the cost of diuretics and ACE inhibitor group with diuretics without ACE inhibitors

Cost	Rupiah, in Thousand (Mean $\pm$ SD)		p
	Diuretic& *ACE Inhibitor* (n=64)	Diuretic without ACE *Inhibitor* (n=60)	
Hospitalization Cost	2782,81 (2620,41)	3473,33 (2262,51)	0,001
Services and laboratories Cost	754,44 (873,22)	635,75 (661,10)	0,836
Drug Costs	1572,13 (1765,38)	859,95 (1241,72)	0,000
Total Costs	4960,72 (3677,66)	5143,06 (2920,60)	0,620

Source: processed secondary Data 2012

of 250 (663 versus 413, placebo versus diuretic)[13]. Then research the total cost of torasemide and furosemide was 1,502 DEM and DEM 1.863. While the cost effectiveness (annual cost per patient with improved NYHA class) is 3.954 DEM and DEM 7.605[14] . All of these studies was to compare between each drug with placebo. While the study was to compare between diuretic Spannheimer. Therefore, this study sought to obtain information on cost analysis diuretic combination therapy with ACE inhibitors to diuretic therapy without ACE inhibitors in heart failure patients Askes participants so that the results of this study will be used as a basis for the study of other Pharmacoeconomics.

Research methods:

This study was an observational study with retrospective cohort study design study using a database of participants claimed prescribing health insurance from PT. Askes Persero. The data used is the patient data for one year, ie between

January 2010 until December 2011, which were then followed for 1 year. The perspective adopted in this study is the perspective of payers in this case is the PT. Askes Persero. Inclusion criteria for this study is the case group participants Askes patients with a diagnosis of heart failure and age over 18 years (has entered the adult criteria), a patient undergoing diuretic combination therapy with an ACE inhibitor and diuretic therapy without ACE inhibitors, have the data about the patient in the form of : patient data (Askes ID number, date of birth, and gender), data about the prescription (prescription date, trade name drugs, drug dosage, frequency of administration, the amount of drug administered and the cost of drugs), the data and the length of hospital diagnosis in hospital . The exclusion criteria in this study include the pregnant condition, there is a diagnosis of malignancy. The results of this study were analyzed using the data processing software and presented in tabular form and narrative.

Ethical approval was taken prior study.

Research result:

Subjects Characteristics

Based on the data claimed prescribing heart failure, there were 377 patients with heart failure. The subjects of the study after the selection is based on inclusion and exclusion criteria, were allocated into two groups, the first group of cases (n = 64) who received diuretic combination therapy with an ACE inhibitor. The second was the control group (n = 60) who received diuretic therapy without ACE inhibitors

The selection process of the study are shown on Figure 1

Characteristics of subjects in each group are shown in Table 1.

Based on results of the normality test using the

Table 5. Bivariate Analysis CER between diuretics and ACE inhibitor group with diuretics without ACE inhibitors

	n	CER Rupiah, in Thousand (Mean $\pm$ SD) Day/ Year
Therapy		
- Diuretic & ACE *Inhibitor*	64	824,77 (487,61)
- Diuretic without ACE *Inhibitor*	60	468,61 (202,40)
p value		0,000
Age		
< 45 year	4	886,30 (445,79)
- Diuretic & ACE *Inhibitor*	2	927,29 (206,89)
- Diuretic without ACE *Inhibitor*	2	845,32 (739,37)
45-64 year	63	636,03 (387,17)
- Diuretic & ACE *Inhibitor*	35	748,62 (465,82)
- Diuretic without ACE *Inhibitor*	28	495,30 (184,38)
> 64 year	57	654,15 (447,63)
- Diuretic & ACE *Inhibitor*	27	915,90 (523,76)
- Diuretic without	30	418,58

ACE *Inhibitor*		(140,62)
p value		0,313
Sex		
Female	48	724,14
		(510,27)
- Diuretic & ACE *Inhibitor*	28	944,98 (564,10)
- Diuretic without ACE *Inhibitor*	20	414,96 (139,30)
Male	76	607
		(340,71)
- Diuretic & ACE *Inhibitor*	36	731,28 (403,21)
- Diuretic without ACE *Inhibitor*	40	495,43 (224,29)
p value		0,307
Comorbid		
Non Comorbid	97	672,74
		(458,15)
- Diuretic & ACE *Inhibitor*	51	861,58 (536,26)
- Diuretic without ACE *Inhibitor*	46	463,38 (207,50)
Comorbid	27	579,49
		(197,59)
- Diuretic & ACE *Inhibitor*	13	680,40 (153,47)
- Diuretic without ACE *Inhibitor*	14	485,79 (190,95)
p value		0,710

Source: processed secondary Data 2012

Shapiro-Wilk test the dependent variable in this study, namely the cost of hospitalization, cost of services and laboratories, drug costs, and the total cost, and CER / Day unknown that all the data were not normally distributed because all p values (sig) < 0.05, so that the results of this study can not be generalized and can only be inferred for research subjects. Then the analysis followed by Mann-Whitney test, while for analysis seen from age followed by the Kruskal-Wallis test. Normality test results can be seen in Table 2 below:

Effectiveness Hospitalization

Based on Table 3 it can be seen that the time of hospitalization was there are different views on the number of days in heart failure patients who use drugs diuretics and ACE inhibitors with diuretics without ACE inhibitors ($p = 0.000$) in which the number of days of hospitalization mean that using diuretics and ACE inhibitors as much as 7 days things this is less than the number of days of hospitalization average with diuretics without ACE inhibitors as many as 10.067 days.

This shows that the treatment of heart failure patients using diuretics and ACE inhibitor drugs turned out to have a higher CER compared to treatment with diuretics without ACE inhibitors, but the results of Table 3 indicate that the treatment of heart failure patients using diuretics and ACE inhibitor drugs

Tabel 6. Summary

Cost	Mean (±SD)		
	Diuretik & ACE Inhibitor (n=64)	Diuretik without ACE *Inhibitor* (n=60)	
Total Cost*	4960,72 (3677,66)	5143,06 (2920,6)	182,34
Outcome			
Day	7,00 (4,42)	10,67 (4,34)	3,67
CER			*Incremental*
CER (Day)*	824,77 (487,97)	468,61 (202,40)	356,16

*in thousand Rupiah

turned out to be the number of days average for each hospitalization is smaller than treatment with diuretics without ACE inhibitors. Both of these results it can be concluded that the use of diuretics and ACE inhibitor drugs able to reduce the number of days of hospitalization in heart failure patient by 1 day for each hospitalization.

Charge

Based on Table 4 it can be seen that the cost of hospitalization and medication costs incurred in the year between the heart failure patients using diuretics and ACE inhibitor drugs with diuretics without ACE inhibitors showed a difference (p = 0.001) at the cost of hospitalization and (p = 0.000) at the cost of drugs. While the cost of services and laboratories (p = 0.836) and total cost (p = 0.620) were issued in the year between the heart failure patients using diuretics and ACE inhibitor drugs with diuretics without ACE inhibitors showed no difference (p > 0.005)

Relationship Therapy, Hospitalization and Costs

Based on Table 5 it can be seen that the CER difference from the number of days of hospitalization for one year in patients with heart failure between the use of drugs diuretics and ACE inhibitors with diuretics without ACE inhibitors showed a significant difference (p = 0.000).

At CER analysis based on age, it can be seen that there is no difference CER seen from inpatient day for a year for each hospitalization in patients with heart failure between the ages < 45 years, 45-64 years , and more than 64 years, because all p values > 0.05.

On gender, based on table 5 it can be seen that there is no difference CER inpatient day for a year for

each hospitalization in patients with heart failure between female and male, because p values > 0.05. In comorbidities, it is known that there is no difference CER views of inpatient day for a year in patients with heart failure between the non-comorbid and comorbid, because all p values > 0.05.

Discussion:

The results showed that the subjects in this study mostly over the age of 45 years the majority of men (61.3%). These results have the same results with the NHANES study and the NHLBI who reported that the age 45 years and older have a higher prevalence of heart failure more than under the age of 45 Year[9]. In addition, the prevalence occurs in men more than women[15].

For the results obtained that the hospitalization costs incurred for hospitalization diuretic group without ACE inhibitors during the year is greater than the costs incurred for hospitalization group diuretics and ACE inhibitors during the year. This happens because of the length of stay (in days) diuretic and ACE inhibitor groups fewer than longer hospitalization diuretic group without ACE inhibitors. These results have similarities with the results of research conducted by Tilson L et al. where the standard therapy group diuretic and lowers the cost of hospitalization.

However, in these studies there was a drop of only 5%. This is probably caused by the studies conducted using specific diuretic that spironolactone[16].

At the cost of services and laboratory results, it was found that the group of diuretics and ACE inhibitors to pay more than the diuretic group without ACE inhibitors, but was not statistically

significant (p> 0.005). This occurs because the amount of the diuretic and ACE inhibitor group more than the amount of the diuretic group without ACE inhibitors. In addition, the group of diuretics and ACE inhibitors are a class rooms comparison in between class I (62.5%), class II (31.3%) and ICU (6.3%). While in the diuretic group without ACE inhibitors are a class room on the comparison between class I by 58.3%, amounting to 71.7% class II and ICU at 0%.

While the results of the cost of the drug, also found that subjects in the group of diuretics and ACE inhibitors to pay more than the diuretic group without ACE inhibitors, although it was not statistically significant (p> 0.005). This happens because there are additional costs ACE inhibitor drugs in the group of diuretics and ACE inhibitors. On the total costs incurred, it was found that the two groups nearing cost almost the same (difference of only 182.34). Diuretics without ACE inhibitor group issued a total cost of greater but not statistically significant (p> 0.005). This happens because the total cost is the sum of the cost of hospitalization, cost of services and laboratory and drug costs. Although the cost of hospitalization in the diuretic group without ACE inhibitors greater, but the cost of services and laboratory and drug costs less than the group issued a diuretic and ACE inhibitors

In the CER results consisting of CER (days / year) is divided into several outcomes, namely between the diuretic and ACE inhibitors with diuretics without ACE inhibitors, the patient's age, gender, co-morbidities. It was found that the CER (days / year) diuretic and ACE inhibitor group is greater than the diuretic group without ACE inhibitors. This happens because the average days diuretic and ACE inhibitor group is smaller than the diuretic group without ACE inhibitors.

Results of CER (days/ year) found that the largest is at age <45 years, and the smallest is at the age of 45-64 years. This happens because the average Number of patients smallest at age <45 years, and the largest is at the age of 45-64 years.

In the CER results obtained views of gender CER (days/ year) is greater in women than men. This happens because the average average days of women less than men even though statistically not significant (p> 0.005). While the results of co-morbidities seen CER (day) in the group without comorbidities greater than the group with

comorbidities. This happens because the average days /year group without comorbidities smaller than the group with comorbidities.

Another result of this study is the combination therapy showed diuretic and ACE inhibitors lower the results of inpatient day average compared to diuretic therapy without ACE inhibitors.

In connection with the above results, similar studies have been done on the ATLAS study which found that ACE inhibitors decrease hospitalization for heart failure by 24% (P = 0.002). This research was carried out for 36 months in 3164 heart failure patients. While the PEP-CHF trial conducted in 850 patients with heart failure found that ACE inhibitors decrease the rate of heart failure hospitalization for 1 year by 35% (RR = 0.65, 95% CI 0.98 to 0:43)[18].

Conclusion:

The total cost diuretic combination therapy with ACE inhibitors in patients with heart failure Askes participant in a year is Rp. 4.96072 million, -. The total cost diuretic therapy without ACE inhibitors in heart failure patients Askes participant in a year is Rp. 5.14306 million, -. Effectiveness diuretic combination therapy with ACE inhibitors in heart failure patients Askes participants judging from the total number of days hospitalized in a year is 7 days. Effectiveness diuretic therapy without ACE inhibitors in heart failure patients Askes participants judging from the total number of days hospitalized in a year is 10.67 days. ICER therapy diuretic therapy without ACE inhibitors in heart failure patients seen in total number of days hospitalized in a year is Rp. 356 160, -

Research limitations:

This study has several limitations, especially in a short period of study and number of samples are minimal. Further research is needed to assess the total costs and Effectiveness of therapy with more number of subjects and a period of over one year.

Conflict of interest: None

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