

# Cost Effectiveness Analysis of Candesartan Therapy in Comparison to Candesartan-Amlodipine Therapy on Hypertensive Outpatients

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## Abstract

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**BACKGROUND:** The achievement of optimal hypertension therapy requires cost-effective medicine. The treatment of hypertensive patients needs for long-term medication have made medical costs a prime issue in health economics.

**AIM:** This study aims to determine the cost effectiveness of candesartan therapy compared to candesartan-amlodipine therapy on hypertensive outpatients.

**METHODS:** This is a prospective cohort study that compares candesartan therapy to candesartan-amlodipine therapy at a public hospital from payers' perspective. The outcome is the percentage of targeted blood pressure decrease after three months of therapy. The cost effectiveness analysis uses the Incremental Cost Effectiveness Ratio (ICER) based on the ratio of cost difference to the outcome in both therapy groups.

**RESULTS:** As many as 111 patients participated in this research, comprising 40 candesartan therapy patients and 71 patients with the combination of candesartan-amlodipine. Of the participants, 63.96% were female, 57.66% were aged 60 or older, and 56.32% had diabetes mellitus as the most common complication. Results show that the average direct medical cost per patient for a therapy of three months with candesartan was IDR 1,050,536 ± 730,007 and IDR 760,040 ± 614,290 for a candesartan-amlodipine therapy. The mean decline of systolic and diastolic blood pressure under candesartan therapy is less than that of candesartan-amlodipine, although without any significant difference ( $p > 0.05$ ). It follows that the effectiveness of candesartan (85%) is greater than that of the candesartan-amlodipine combination (84.50%). Candesartan therapy is thereby more cost-effective with an ICER value of IDR 580,993%.

**CONCLUSION:** Hypertension therapy by candesartan is more cost-effective than candesartan-amlodipine therapy with a cost addition of IDR 580,993.

## Introduction

The widely ranging prices of various antihypertension brands of angiotensin-converting-enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) play an important role in hypertension treatment management, particularly concerning comorbidities such as diabetes and heart failure. A health service provider has to be sensible in procuring drugs and determining the most effective cost according to the financial state of the patient so as to lessen the economic burden of the patient or the health care system [1]. The treatment of hypertensive patients (HTs) requires a long-term commitment of

compliance for the patient and resources by the healthcare system. This poses an economic dilemma in countries where universal healthcare is standard [2]

Candesartan is an angiotensin II receptor antagonist antihypertensive drug with a biphenyl derivative molecular structure. The active mechanism of candesartan inhibits the renin-angiotensin-aldosterone system (RAAS) at level 1 of the angiotensin receptor (AT 1) for angiotensin II (AT II). In an RAAS reaction, AT II produces the strongest effect as vasoconstrictor. Candesartan reduces the adverse effects of angiotensin II endothelium by decreasing the release of vasoconstrictors which enhance arterial elasticity. Candesartan boasts its distinct advantage in increasing arterial elasticity when

compared to other conventional antihypertension medicine such as diuretics (Ds),  $\beta$ -blockers (BABs) and even calcium channel blockers (CCBs) [3].

A therapy with the combination of candesartan and amlodipine lowers the risk of major adverse cardiovascular events (MACEs) by 38% with a significant value of  $p = 0.025$ , compared to when the patients are simply treated with non-amlodipine and candesartan drugs [4].

Hypertension therapy takes a long time which consequently demands a great cost. The diverse effectiveness of antihypertensives and the broad price range of antihypertensive types also impact on the treatment cost. According to survey, candesartan or the combination of candesartan-amlodipine is the most common therapy or antihypertensive drug administered to hypertensive outpatients under the national health cover (JKN) at public hospitals. Considering this situation, research has been undertaken to examine the cost effectiveness of candesartan in comparison to candesartan-amlodipine in the medication of hypertensive outpatients.

## Material and Methods

This study has gained ethical approval for research number 011802023 from the Research Ethics Committee of Universitas Ahmad Dahlan. The investigation employs a prospective cohort method comparing the outcome of candesartan therapy to that of candesartan-amlodipine at a public hospital from payers' perspective. The cost effectiveness analysis utilizes the Incremental Cost Effectiveness Ratio (ICER) which is the ratio of cost difference to the outcome in both therapy groups. The calculated cost is the direct medical cost, or the average total therapy cost of hypertensive patients for three months. The assessed outcome is the targeted decline of blood pressure after three months of therapy, the proportion of patients with which is then counted against the total number of patients in each therapy group.

**Inclusion criteria:** Outpatients diagnosed with hypertension (ICD10: I10), aged  $\geq 18$ , male or female with or without another disease, consuming candesartan or candesartan-amlodipine antihypertensives, and listed as JKN / BPJS members

**Exclusion criteria:** Patients who do not ingest the same drug during observations, do not undergo regular control, or have incomplete data of medical records, blood rates and costs.

Beside using ICER, data analysis also identifies any notable difference in blood pressure decrease by t-test if the data are normally distributed, or by Mann-Whitney test if otherwise.

## Results

Hypertensive outpatients who fulfilled the inclusion criteria amounted to 111 patients, consisting of 40 patients under candesartan therapy and 71 patients under candesartan-amlodipine therapy. Detailed characteristics of the patients are described in Table 1.

**Table 1: Patient characteristics**

Characteristic	N = 111	(%)
Sex		
Male	40	36.04
Female	71	63.96
Age (years)		
< 60	47	42.34
$\geq 60$	64	57.66
Complication		
Arrhythmia	1	1.15
CHF	3	3.45
CAD	8	9.20
CKD	3	3.45
DM	49	56.32
Dyslipidemia	4	4.60
DM, Dyslipidemia	7	8.05
Gerd	2	2.30
OA	10	11.49
Non-Complication	24	21.62

CHF = Congestive Heart Failure; CAD = Chronic Artery Disease; CKD = Chronic Kidney Disease; DM = Diabetes Mellitus; Gerd = Gastro Esophageal; OA = Osteoarthritis.

### Therapy cost

The therapy cost in this research is the total direct medical cost of hypertensive outpatients under the national health cover (payers' perspective) receiving the antihypertensives candesartan and candesartan-amlodipine at a public hospital in Yogyakarta for three months from February to May 2018. The cost components in this study are antihypertensive and non-antihypertensive drug cost, administration cost, laboratory cost, and medical examination cost. The mean direct medical cost of hypertensive outpatient therapy can be seen in Table 2.

**Table 2. Average direct medical cost**

Therapy	Average cost (IDR)	p value
Candesartan	1,050,536 $\pm$ 730,007	0.005
Candesartan-Amlodipine	760,040 $\pm$ 614,290	

Table II depicts that the direct medical cost per patient for a three-month candesartan therapy amounts to IDR 1,050,536  $\pm$  730,007, greater than that of the candesartan-amlodipine combination at IDR 760,040  $\pm$  614,290. The huge standard deviation (SD) value stems from the sizeable range of the cost. The Mann-Whitney test indicates significant difference in the average total therapy cost between candesartan-amlodipine and candesartan with a p value of 0.005.

### Therapy effectiveness

The effectiveness of candesartan and candesartan-amlodipine hypertension therapy is gauged by the decrease to the targeted blood

pressure based on the Evidence-Based Guideline for the Management of High Blood Pressure in Adults (JNC VIII), as can be observed in Table 3.

**Table 3. Therapy effectiveness**

Average blood pressure decrease	Candesartan	Candesartan-Amlodipine	p value	p value (RR;95%CI)
Systole (mm/Hg)	8.50	13.24	0.259	
Diastole (mm/Hg)	5.25	5.92	0.645	
Effectiveness (%)	85.00	84.50		1.000 (1.006;0.854-1.185)

It transpires that the effectiveness of candesartan therapy for hypertensive outpatients in terms of average systolic blood pressure decline at 8.50 mm/Hg is less than that of candesartan-amlodipine at 13.24 mm/Hg. However, the Mann-Whitney test discerns no substantial distinction between candesartan and candesartan-amlodipine in this respect as  $p = 0.259$ . Similarly, the diastolic blood pressure reduction in the candesartan therapy (5.25 mm/Hg) is lower than that in the candesartan-amlodipine treatment (5.92 mm/Hg), but no meaningful disparity emerges from The Mann-Whitney test either ( $p = 0.645$ ).

The therapy effectiveness measured in this study, which is subsequently taken into account in the cost effectiveness analysis, is presented as the percentage of blood pressure loss according to target after three months of therapy. Table III points out that the therapy effectiveness of candesartan (85.00%) is greater than that of candesartan-amlodipine (84.50%).

### Cost effectiveness analysis

The cost effectiveness analysis of hypertension therapy in this research is done by ICER, which is the difference between cost and effectiveness in each hypertension therapy group, obtained by comparing the total cost to be directly spent with the output, which is the effective percentage of targeted blood pressure decrease after three months of therapy with candesartan and candesartan-amlodipine antihypertensives. The ICER value of hypertensive outpatients treated with candesartan and candesartan-amlodipine is featured in Table 4.

**Table 4. Therapy cost effectiveness**

Therapy	Average cost (IDR)	Therapy effectiveness (%)	ICER value (IDR/%)
Candesartan	1,050,536 ± 730,007	85.00	580,993
Candesartan-Amlodipine	760,040 ± 614,290	84.50	

It is notable from Table IV that the ICER value stands at IDR 580,993/%, signifying that hypertension therapy by candesartan is more cost-effective by IDR 580,993 for every percent.

## Discussion

Descriptive analysis of patient characteristics in this study reveals that the incidence rate of hypertension in female patients is greater than in their male counterparts and is 57.66% higher in patients aged 60 or above than in those under 60 years old. Following menopause, ceased production of endogenous estrogens prevents the female body from maintaining vasodilatation that controls blood pressure, thus causing the high prevalence of hypertension in women [5].

Other diseases, including chronic ones, that potentially exacerbate organ damage due to hypertension may occur as comorbidities or complications. Among patients in this research, the most frequent is diabetes mellitus (DM) at 56.32%. In DM type 2 patients, high insulin levels can accelerate the production of corticotrophin and cortisol hormones by the reins, which in turn triggers neurological stress that leads to rising blood pressure in the arteries. It can be stated that DM and hypertension have a linear relationship [6].

On average, the direct medical cost of candesartan therapy administered to a patient for three months is significantly higher than that of candesartan-amlodipine at  $p = 0.005$ . In this case, the mean total direct cost of a 3-month candesartan-amlodipine therapy is IDR 760,040 ± 614,290. Compared to other research [7] in which the average monthly cost of candesartan-amlodipine antihypertensives given to hypertensive patients with comorbidities varies between IDR 167,700 and IDR 200,280, this study found that the mean total cost ranges from IDR 297,667 to IDR 878,479 per month, affected by the cost of antihypertensives ( $p < 0.001$ ), non-antihypertensives ( $p < 0.001$ ), and the treatment of comorbidities ( $p = 0.001$ ).

On the other hand, therapy by candesartan is less effective than by the combination of candesartan-amlodipine in terms of systolic and diastolic blood pressure reduction, but the Mann-Whitney test does not indicate any marked difference between both. Nevertheless, in regard to achieving the targeted blood pressure loss after three months, the effectiveness of candesartan therapy is superior to that of candesartan-amlodipine, although not significant difference  $RR = 1.006$  (0.854-1.185). In comparison, another study [8] shows considerable decline of systolic and diastolic blood pressure following four and eight weeks of candesartan and amlodipine therapy respectively, although amlodipine and candesartan are not meaningfully dissimilar in reducing blood pressure in this context.

All in all, according to the resulting ICER, hypertensive therapy by candesartan is more cost-effective than by candesartan-amlodipine with a difference of IDR 580,993. To compare with, prior

research [9] divulges that hypertension therapy by combined candesartan-amlodipine is firmly more cost-effective than by candesartan-diltiazem with an ICER of IDR -23,187.40%.

In conclusion, hypertension therapy by candesartan is more cost-effective than by candesartan-amlodipine with an ICER value of IDR 580,993%.

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