

## Cost-Effectiveness Analysis of Antihypertensive Combination Treatment in Chronic Kidney Disease Outpatients with Hypertension

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### Abstract

The expense of managing CKD patients ranks second highest behind cardiovascular illness, with hypertension being the primary contributor to renal impairment. Maximizing the efficiency of therapeutic expenditures is essential. This study is to evaluate the cost-effectiveness of the combination of amlodipine 10 mg - candesartan 16 mg compared to the combination of candesartan 16 mg - furosemide 40 mg in patients with chronic kidney disease and hypertension. The research employed a non-experimental observational cohort design. The study was performed at both a private and a governmental hospital in Yogyakarta, Indonesia. Data were gathered retroactively using complete sampling. The inclusion criteria comprised outpatients with CKD-hypertension from January 2019 to October 2022, aged 18 years or older, who were undergoing combination therapy. The efficacy of therapy was evaluated by determining the number of samples achieving therapeutic objectives after 2 to 4 weeks. The mean expenditure was derived from monthly antihypertensive costs. The analysis of cost-effectiveness employed the Average Cost-Effectiveness Ratio (ACER) and the Incremental Cost-Effectiveness Ratio (ICER). The study comprised 50 samples, with 51% male participants and 66% aged 60 or older. Amlodipine and candesartan demonstrated superior efficacy (77%) and a reduced average cost of 101,095 IDR. The ACER for amlodipine and candesartan was 1,306 IDR, whereas for furosemide and candesartan it was 1,571 IDR. The amalgamation of amlodipine and candesartan is more economically advantageous than furosemide and candesartan.

**Keywords:** Amlodipine, Candesartan, Chronic kidney disease, Cost-effectiveness analysis, Furosemide, Hypertension.

## Analisis Efektivitas Biaya Kombinasi Antihipertensi pada Pasien Gagal Ginjal Kronis dengan Hipertensi

### Abstrak

Biaya perawatan pasien gagal ginjal kronis (GGK) adalah yang tertinggi kedua setelah penyakit jantung, dengan hipertensi sebagai penyebab utama kerusakan ginjal. Mengoptimalkan biaya terapi sangatlah penting. Penelitian ini bertujuan untuk mengetahui efektivitas biaya dari kombinasi amlodipin 10 mg - candesartan 16 mg dibandingkan dengan candesartan 16 mg - furosemid 40 mg pada pasien GGK dengan hipertensi. Penelitian ini menggunakan desain observasional non-eksperimental kohort. Penelitian dilakukan di sebuah rumah sakit swasta dan juga rumah sakit umum di Yogyakarta, Indonesia. Data dikumpulkan secara retrospektif melalui total sampling. Kriteria inklusi adalah pasien rawat jalan GGK-hipertensi pada periode Januari 2019 hingga Oktober 2022, berusia  $\geq 18$  tahun, dan menerima terapi kombinasi. Efektivitas terapi dinilai dengan menghitung jumlah sampel yang mencapai target terapi setelah 2-4 minggu. Biaya rata-rata didasarkan pada biaya antihipertensi bulanan. Efektivitas biaya dianalisis dengan menggunakan *Average Cost-Effectiveness Ratio* (ACER) dan *Incremental Cost-Effectiveness Ratio* (ICER). Penelitian ini melibatkan 50 sampel, dengan 51% laki-laki dan 66% berusia  $\geq 60$  tahun. amlodipin dan candesartan memiliki efektivitas yang lebih tinggi (77%) dan rata-rata biaya yang lebih rendah (Rp. 101.095). ACER untuk amlodipin dan candesartan adalah Rp. 1.306, sedangkan untuk furosemide dan candesartan adalah Rp. 1.571. Kombinasi amlodipin dan candesartan lebih hemat biaya dibandingkan furosemid dan candesartan.

**Kata Kunci:** Amlodipin, Candesartan, Gagal ginjal kronis, analisis efektivitas biaya, furosemide, hipertensi.

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## 1. Introduction

In order to maintain blood pressure, erythrocyte production, and calcium levels, the kidneys produce hormones and enzymes.<sup>1</sup> Hypertension has been a major cause of kidney failure and a concomitant condition in recent years.<sup>2</sup> According to RISKESDAS (2018), the prevalence of CKD in patients aged 15 and older is as high as 0.43% in Yogyakarta Province. According to reports, Yogyakarta has a higher prevalence of hypertension (11.01%) than the national average (8.8%).<sup>3</sup>

A multitude of characteristics, such as age, gender, race, degree of education, economic condition, employment status, marital status, then lifestyle, among others, can affect CKD in people with hypertension.<sup>4</sup> Chronic hypertension can increase the risk of CKD because it damages the kidneys' blood vessels. According to JNC 8, the therapeutic aim for hypertensive individuals with chronic kidney failure (CKD) is to attain a blood pressure below 140/90 mmHg, with a target attainment timeframe of between two and four weeks.<sup>5</sup>

Angiotensin Receptor Blockers (ARB) and Angiotensin-converting-enzyme inhibitors (ACE-i) constitute the primary therapeutic interventions for CKD accompanied with hypertension. Diuretics, including thiazide and loop diuretics, together with ACE-i or ARB and Calcium Channel Blockers (CCB), are the advised combination therapy for hypertensive individuals with kidney disease, according to KDIGO (2021). Diuretics and Renin-Angiotensin-Aldosterone System (RAAS) antagonists, both of which are ARB/ACE-i, work together to reduce blood pressure because they are effective in treating edema and excess salt while also preventing ARB/ACE-i activation, which can occasionally result in blood vessel vasoconstriction. One medication alone is frequently insufficient to regulate blood pressure.<sup>6</sup> JNC 8 supports combination therapy, stating that while a single therapy is allowed as a first resort, a combination is advised if blood pressure deviates too much from the target.<sup>7</sup>

According to the Social Security Administrator for Health's (BPJS Kesehatan) cost coverage, heart illness is the most expensive condition in Indonesia, with chronic kidney disease coming in second. According to data from BPJS Kesehatan, 1.4 million kidney failure cases occurred in 2014, costing 2.2 trillion IDR. Up until the third quarter of 2015, 1.2 million kidney failure cases were funded by BPJS Kesehatan, costing 1.6 trillion IDR.<sup>8</sup> Long-term, even lifetime, hypertension therapy resulted in a high medical cost burden.<sup>9</sup>

According to a study by Muchtar, Tjitrosantoso, and Bodhi (2015), the most common combination of antihypertensive medications used in CKD patients at

RSUP Prof. Dr. R. D. Kandou Manado is ACE-i and diuretic (17.2%), followed by ARB and CCB (13.8%). The cost-effectiveness of antihypertensive medications was not examined in this study, though.<sup>10</sup> Baroroh & Sari (2017) examined the cost-effectiveness of treating hypertensive patients with a combination of antihypertensive medications, such as amlodipine and candesartan or diltiazem and candesartan. The combined usage of amlodipine - candesartan demonstrated superior therapeutic efficacy (58,33%) over the combination of diltiazem - candesartan (22.22%). This combination also obtained an ICER value of approximately 23,187.40 IDR, indicating that it is more cost-effective than the comparison.<sup>11</sup> The study did not examine the cost-effectiveness of the antihypertensive combination in patients with CKD. The use of additional antihypertensive combinations, such as amlodipine and candesartan or candesartan and furosemide, was also examined in our study. This is what makes our study unique. This study's antihypertensive selection complied with JNC 8. The ACE-i/ARB group, which can be administered in conjunction with CCBs or thiazides, is the suggested combination antihypertensive medication for CKD patients with concomitant hypertension, according to JNC 8. Additionally, according to KDIGO (2021), diuretics can be used as thiazide or loop diuretics, with or without ACE-i, ARB, or CCB. Therefore, in CKD patients with concomitant hypertension, the intention of this study was to determine the cost-effectiveness between amlodipine and candesartan versus furosemide and candesartan as a combination therapy.

## 2. Methods

### 2.1. Design

Observational cohort that is non-experimental and uses medical records to gather data retrospectively. Direct medical expenses for CKD patients with hypertension in the form of antihypertensive medication expenditures were the costs that were investigated in this study.

### 2.2. Assessment

The study, which was ethically free and registered under the number 160/EC-KPK FKIK UMY/VII/2022, was carried out in a public hospital in Yogyakarta from September to December 2022 using medical record data of all outpatients diagnosed with CKD – hypertension for the January 2019 – October 2022 period. There were 67 patients in the population. The Purposive Sampling Method was utilized in this investigation. Fifty patients' samples were included in the inclusion criteria. Outpatients with CKD-hypertension, those

who were at least eighteen years of age, those who had taken amlodipine-candesartan and furosemide – candesartan together, and those who took blood pressure readings two to four weeks after taking the antihypertensive were all eligible. Incomplete medical record data and patients who switched antihypertensives during the trial period were the exclusion criteria. The number of samples that achieve the therapeutic target  $<140/90$  mmHg following therapy using both combinations for 2-4 weeks was used to determine the therapy's efficacy. The average costs, on the other hand, are direct medical expenses in the form of medication prices that the patient uses, namely a combination of 10 mg of amlodipine and either 16 mg of candesartan or 40 mg of furosemide. Each medication purchased costs 10 mg of amlodipine (183.15 IDR), 16 mg of candesartan (2,053.5 IDR), and 40 mg of furosemide (278 IDR). The Average Cost-Effectiveness Ratio (ACER) and, if required, the Incremental Cost-Effectiveness Ratio (ICER) formulas were used to compute the cost-effectiveness analysis. An intervention's costs and results are compared to determine the ACER, whereas the difference between the costs and results of the two therapies under study is used to compute the ICER.

This study applies SPSS software alongside pharmacoeconomic analyses to ascertain whether blood pressure baseline, blood pressure reduces, and average medication costs exhibited significant variation among patients. The chi-square test, the independent t-test for normally distributed data, and the Mann-Whitney test for data that is not normally distributed.

### 3. Result

Male patients made up the majority of the patient population, according to earlier research by Felicia & Meizly (2017). With 34 male patients (51%) and 33 female patients (49%), Table 1's results were not significantly different. According to the International Society of Hypertension (2020), patient characteristics based on initial blood pressure are broken down into multiple groups.<sup>12</sup> Additionally, Table 2 shows the distribution of initial blood pressure data for patients taking amlodipine, candesartan, furosemide, and candesar-

tan together. According to the findings, most people who used amlodipine and candesartan together had an initial blood pressure no less than 160/100 mmHg (16 individuals). In contrast, the initial blood pressure of the majority of furosemide and candesartan users (20 individuals) was 140-159/90-99 mmHg. A Chi-Square test was then used to determine whether the variables were correlated and whether there were any significant differences. The p-value in this study was 0.010, indicating a significant difference between the two combinations since certain patients, particularly those with blood pressure  $<140/90$  mmHg, had distinct baseline starting points.

Table 3 shows the efficacy of treatment in both combinations. 77% of patients who took amlodipine and candesartan successfully met the goal, compared to 72% who took candesartan and furosemide. As indicated in Table 4, the average cost was determined by adding up all of the patient's antihypertensive drug expenses over the course of a month. Candesartan and amlodipine together have a lower average cost than candesartan plus furosemide because amlodipine is less expensive. The Mann-Whitney U test used to examine the data on the average cost of antihypertension for both combinations. The p-value was 0.010, signifying a statistically significant disparity in the average cost of the two pairings.

### 4. Discussion

This study is to evaluate the cost-effectiveness of the amlodipine – candesartan combination medication vs the furosemide-candesartan regimen for chronic kidney disease patients with concurrent hypertension. The features of patients, categorized by age and gender, exhibited minimal differences, consistent with previous research findings.<sup>13</sup> A study by Putri et al. (2014) indicated that the proportion of female patients was higher (52.4%) than that of male patients; similarly, research by Ingenida et al. in 2024 reported that the sample was predominantly composed of female patients with hypertension (68.62%).<sup>9,14</sup> RISKESDAS (2018) elucidates that hypertension predominantly affects women due to more frequent exposure to stressors, which elevate adrenaline levels, resulting in va-

**Table 1.** Characteristics based on Gender and Age

Characteristic	Quantity of Patients (n)	Percentage (%)
<b>Gender</b>		
Man	34	51
Woman	33	49
<b>Age</b>		
18-29 years	0	0
30-59 years	23	34
$\geq 60$ years	44	66

**Table 2.** Characteristics Based on Initial Blood Pressure

No	Initial Blood Pressure (mmHg)	Number of Patients (n)		p value
		amlodipine 10 mg – candesartan 16 mg	furosemide 40 mg – candesartan 16 mg	
1	<130/85	1	1	<b>0.010*</b>
2	130-139/85-89	2	1	
3	140-159/90-99	12	20	
4	≥160/100	16	14	
	<b>Total</b>	<b>31</b>	<b>36</b>	

\*The standard p-value is < 0,05, which indicates that there is a significant difference

soconstriction and therefore elevated blood pressure. Men are at an elevated risk of chronic kidney disease and hypertension due to their more erratic lifestyle choices.

The Joint National Committee (JNC) 8 has categorized hypertension patients into three age categories start from 18–29 years, then 30–59 years, and 60 years or older. The majority of patients with CKD and hypertension were aged 60 years or older (66%), consistent with prior research by Lilis in 2014 at PKU Muhammadiyah Hospital Yogyakarta, which indicated that majority of respondents aove 55 years, comprising 18 individuals (47.4%). This finding aligns with Ingenida et al. (2024), which reported the highest patient numbers in the 46-55 and 56-65 year age brackets.<sup>15,16</sup> A significant influencing element is renal function, which diminishes with advancing age, leading to renal function problems in certain older persons.<sup>17</sup>

Administering combination therapy to hypertension patients is strongly advised due to its synergistic effects and potential to mitigate the negative effects of individual medications.<sup>18</sup> The results mentioned earlier aligns with the research conducted by Tri Wulandari (2019), which identified that the most prevalent and effective combination of antihypertensives comprises the CCB and ARB groups (86.7%).<sup>19</sup> Baroroh and Sari (2017) indicated that the therapeutic efficacy of the amlodipine and candesartan combination (58.33%) surpassed that of the diltiazem and candesartan combination (22.22%). Calcium channel blockers (CCB) can rapidly lower blood pressure, while angiotensin receptor blockers (ARB) mitigate the adverse effects associated with CCB. KDIGO (2021) asserts that the ARB cohort can diminish the likelihood of renal failure

and significant cardiovascular incidents. The combination of loop diuretics and ARB is indicated for individuals with hypertension associated with chronic CKD, as loop diuretics are typically employed to decrease glomerular filtration rate (GFR), particularly in patients with edema.<sup>20</sup>

Upon assessing the reduction in both systolic and diastolic blood pressure, the data will ascertain whether a significant difference exists in the average decrease of systolic blood pressure, employing the Mann-Whitney test due to the non-normal distribution of one of the combinations. The p-value derived from the average reduction in systolic blood pressure was 0.021 (<0.05), indicating a significant difference between those two combinations. The mean decrease in diastolic blood pressure was evaluated using the independent T-test, providing that both datasets demonstrated a normal distribution and the p-value was 0.180 (>0.05), signifying no significant difference between these combinations. This outcome differs marginally from the prior study conducted by Dian et al. in 2019, which reported a p-value of 0.178 for the mean reduction in systolic blood pressure. The p-value for the mean reduction of diastolic blood pressure was 0.527, indicating no significant difference in the reduction of systolic and diastolic blood pressure in hypertensive – CKD patients.<sup>21</sup>

Baroroh and Sari (2017) reported that the mean direct healthcare expenditures for antihypertensive treatment with a combination of amlodipine – candesartan over three months was 341,479 IDR ± 187,609 IDR, which was significantly lower than the costs associated with diltiazem and candesartan, totaling 812,966 IDR ± 224,713 IDR. Additionally, this analysis yielded a p-value of 0.000 for the average cost of antihypertensives,

**Table 3.** Average Decrease and Therapeutic Effectiveness in Systolic Blood Pressure and Diastolic Blood Pressure

Medicine Type	Quantity of Patients (n)	Quantity of Patients Reaches Target (n)	Therapy Effectiveness (%)	SBP + SD Reduction (mmHg)	DBP + SD reduction (mmHg)
amlodipine 10 mg – candesartan 16 mg	31	24	77	39 ± 18.04	13.09 ± 11.17
furosemide 40 mg – candesartan 16 mg	36	26	72	28.42 ± 16.09	18.11 ± 14.6
	p-value			<b>0.021*</b>	<b>0.180</b>

\*The standard p-value is < 0,05, which indicates that there is a significant difference



**Table 4.** Average Expense and ACER Value

Medicine Type	Number of Samples (n)	Therapeutic Effectiveness (%)	Mean Expense $\pm$ SD (IDR)	ACER Value (IDR)
amlodipine 10 mg and candesartan 16 mg	24	77	101,095 IDR $\pm$ 27,730 IDR	1,306 IDR
furosemide 40 mg and candesartan 16 mg	26	72	113,439 IDR $\pm$ 32,737 IDR	1,571 IDR
p-value			0.010*	

\*The standard p-value is  $< 0,05$ , which indicates that there is a significant difference

indicating a substantial difference in average expenses between the combinations, consistent with the findings of the current research. This research presented the cost-effectiveness analysis through ACER and ICER values. However, ICER is no longer employed in this study as this computation is applicable only when treatments have elevated costs and outputs. ICER computes the incremental costs associated with each 1% rise in patient output.

The therapeutic combination of amlodipine and candesartan yields an ACER value of 1,306 IDR, whereas the combination of candesartan and furosemide results in an ACER value of 1,571 IDR. Consequently, the most economically efficient therapeutic intervention identified in this investigation was a combination of amlodipine and candesartan. A lower ACER value of a therapy indicates more cost-effectiveness. A minimal ACER signifies economical medication with substantial efficacy. A prior investigation by Baroroh and Sari (2017) corroborates these findings, indicating that amlodipine and candesartan exhibited superior efficacy (58.33%) at a reduced cost of approximately 1,168,443 IDR, compared to an alternative treatment with a therapeutic efficacy of merely 22.22% and an average expense of 2,005,766 IDR, thereby demonstrating that the amlodipine and candesartan combination is more cost-effective. The findings of this study will aid in the selection of medicines that are both efficacious and economically viable.

## 5. Conclusion

The ACER Value of the combination of amlodipine 10 mg and candesartan 16 mg is lower (1,306 IDR) compared to of the comparison, which is considered the most effective combination therapy for optimal clinical outcomes in CKD outpatients with hypertension. As a result, this implies that candesartan and amlodipine are more cost-effective.

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## Conflict of Interest

The authors declare no conflicts of interest related to this work.

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