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Comparative Economic and Clinical Utility of Adding Candesartan for Hypertension Management

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ABSTRACT: Antihypertensive medications entail significant expenses due to their long-term usage. Hence, careful consideration of drug selection criteria, including efficacy and cost, is essential. This study aimed to evaluate the benefits of hypertension therapy and the non-medical costs incurred by patients using cost-utility analysis (CUA). Method: This research was a prospective study. The incremental Cost-Utility Ratio (ICUR) of antihypertensive treatment was calculated using cost-utility data obtained through EQ-5D-5L questionnaires from outpatients at Universitas Andalas Hospital in January- March 2023 who met the inclusion and exclusion criteria. The costs used were from a patient perspective, consisting of direct medical and nonmedical costs. This study compared standard treatment (amlodipine) with the addition of candesartan. Results: The number of respondents in this study was 67, consisting of 23 respondents (34.33%) using amlodipine alone and 44 respondents (65.67%) using the amlodipine-candesartan combination. The ICUR value obtained was IDR 7,318,674/QALY. The difference in the average utility value of the amlodipine-candesartan combination with amlodipine alone is -0.02, and the difference in cost is -IDR12,224. Based on the cost-utility diagram, the amlodipine-candesartan combination group is included in the southwest

quadrant (quadrant III), which illustrates that the cost required for the amlodipine-candesartan combination group is lower than the cost of the amlodipine single treatment group and the outcome is also not better (slightly lower or the same). Conclusion: It was recommended to prioritize using amlodipine alone for hypertension management, as it provides similar outcomes to the amlodipine-candesartan combination while incurring lower costs.

Keywords: hypertension; utility; cost-utility analysis; candesartan.

Introduction

Hypertension, high or increased blood pressure, is a condition in which the blood vessels experience a continuous increase in pressure [1]. Hypertension is when the patient's systolic blood pressure is more than 140 mmHg, and diastolic pressure is more than 90 mmHg [2]. According to the JNC-8 report, the target blood pressure for adults aged 60 years or older is 150/90 mmHg, while it is 140/90 mmHg for those aged 30 to 59 years [3]. The optimal blood pressure of a normal adult is currently defined as less than 120/80 mmHg [4,5].

Hypertension, a prevalent cardiovascular disease, continues to see a rising global incidence, with over 11.64 million individuals estimated to be affected. In 2017, standard blood pressure measurement screening was carried out, showing that 34.5% of the 69,307 people screened in Indonesia suffered from hypertension. Of these, 20% were untreated, and 63% of those receiving antihypertensive drugs had uncontrolled blood pressure [6]. The increase in the prevalence of hypertension in Indonesia showed an increase at the beginning of 2018 to 34.1% (from 26.5% in 2013) [6]. Based on the results of blood measurements from Indonesia Basic Health Research (Rikesdas) in 2018, the prevalence of hypertension in the population aged 18 years and over in Indonesia was 34.11%. West Sumatra

ranked at the top of the 10 most common types of disease; in Padang City, there were 49,512 cases in 2020 [7]. According to data from Universitas Andalas Hospital, hypertension was in the top 3 most cases occurring at



*Corresponding Author: Najmiatul Fitria Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy. Universitas Andalas. Padang. Indonesia.25163 | Email: najmiatulfitria@phar.unand.ac.id Universitas Andalas Hospital of 1720 cases in 2022 [8].

Utility is defined as expected value. Quality of life (QoL) includes physical and psychological values and is a useful parameter for evaluating the usefulness of medical care. QoL 1.0 indicates perfect condition, while QoL 0 indicates death [9,10]. QoL is also used to identify various problems that may affect patients. This information can be communicated to future patients to help them anticipate and understand the consequences of their disease and its treatment [11]. In addition, QoL is also important for medical decision-making because QoL is a predictor of treatment success and is therefore important for prognostics [12]. QoL estimation types, such as EQ-5D, are often used in cost-effectiveness analysis. The instrument widely used to measure QoL weight is the EuroQoL (EQ-5D) instrument [10,13,14]. The EQ-5D-5L is more sensitive in patients with severe health conditions and less sensitive in groups with milder health conditions [14,15]. The EQ-5D-5L value set has been developed in 18 countries, including Indonesia [10]. Additionally, the EQ-5D-5L provides predetermined values for QALY calculations using a societal perspective, which is the preferred perspective in health economics (11). The EQ-5D-5L instrument is followed by a self-assessment of overall health status on the visual analog scale (EQ VAS). The score of the EQ VAS ranges from 0 (worst imaginable health condition) to 100 (best imaginable health condition) [13].

The average direct medical costs incurred by hypertensive patients on amlodipine monotherapy per month were IDR 68.660 and IDR 784.716 for patients who received the amlodipine-candesartan combination for 3 months [8]. Antihypertensive drugs are a category of drugs that are classified as vital with high costs due to their long-term use and high volume of use. Therefore, consideration is needed in their selection, both in terms of effectiveness and drug price. The relationship between the quality of life of hypertensive patients and direct medical and non-medical costs can be seen using cost-utility analysis carried out on patients using the amlodipinecandesartan combination with amlodipine alone. Costutility analysis (CUA) is the most appropriate method to use when comparing life-prolonging treatment programs and alternatives with serious side effects [16,17]. The CUA results are expressed in a cost-utility ratio (C:U ratio). This ratio is often translated as a cost per QALY gained or another health condition utility measure [8].

Given the high costs and long-term use of antihypertensive drugs, evaluating their Cost-Effectiveness is Crucial. Cost-utility analysis (CUA) is a method used to compare the cost and health outcomes of different regimens, providing a cost per quality-adjusted life year (QALY) gained. This study aims to assess the benefits of hypertension therapy and the non-medical costs incurred by patients using CUA. The study looked to provide insights into the most cost-effective treatment strategies for managing hypertension by comparing the effectiveness and costs of amlodipine-therapy combination with amlodipine monotherapy.

Methods

Materials

The EQ-5D-5L questionnaire was the primary tool for evaluating health-related quality of life (HRQoL). It includes five dimensions—mobility, self-care, usual activities, pain/discomfort, and anxiety/depression each with five levels of severity. Patient medical records are essential for providing clinical data, such as diagnosis, treatment regimens, and health outcomes. Additionally, cost data is crucial and includes direct medical costs (e.g., medication, hospital visits, and procedures) and nonmedical costs (e.g., transportation, accommodation, and out-of-pocket expenses).

Research Design, Target Population, and Location

The research was conducted at Universitas Andalas Hospital, Padang City, in January- March 2023. This observational research design used a study-descriptive design. The data collection technique was carried out prospectively and confirmed in medical records of hypertension outpatients. Sampling was purposively done, and 69 patient data were obtained for further analysis. This study compared amlodipine alone with the amlodipinecandesartan combination.

Inclusion and Exclusion Criteria

The inclusion criteria in this study were outpatients aged 15-64 years (productive age), receiving antihypertension amlodipine alone or a combination of amlodipine-candesartan, and outpatients diagnosed with hypertension for at least 3 months. Meanwhile, hypertensive patients who were pregnant, had incomplete data, were not willing to be interviewed, and patients who died while undergoing hypertension therapy were excluded from this study.

Perspective, Time Horizon, and Index Year

The cost perspective in this research is the patient's perspective; the costs calculated are direct medical costs paid to the hospital and direct non-medical costs. The sample of this study is a portion of the population of outpatients diagnosed with hypertension in February 2023 who met the inclusion and exclusion criteria. The time horizon is determined in 1 month of treatment.

Currency and Discount Rate

The currency used is Rupiah (IDR). Because it is in the same fiscal year, no discount cost and effect were applied to this study.

Cost-Utility Variables

The variable costs used here are direct medical costs in medicines, doctor visits, screening, and treating complications and non-direct. Utility data was used by filling out the EQ-5D-5L questionnaire. Meanwhile, the effect variable consists of blood pressure (mmHg).

Data Analysis

Data analysis began by calculating the utility based on the EQ-5D-5L, which patients filled out, and then calculating the average decrease in utility value for each group of amlodipine or amlodipine-candesartan in percentage form. A normality test was carried out first for each dependent variable. The non-parametric was tested using the Kruskal-Wallis test, while parametric was tested using One-way ANOVA. The categorical variables will be tested with chisquare. The p-value < 0.05 was declared as a result that has a significant effect. Furthermore, a cost analysis was carried out, consisting of direct and non-direct medical costs. The ICUR value is determined based on the value of each utility parameter

Result and Discussion

Sociodemographic Parameter

This study aimed to investigate the sociodemographic characteristics of patients undergoing different antihypertensive treatments. By examining variables such as gender, education level, occupation, and place of residence, the analysis sought to determine whether there were any significant differences among the treatment groups. Table 1 presents sociodemographic characteristics in amlodipine and amlodipine-candesartan groups.

Based on the Chi-Square variable test, it was found that the p-value was > 0.05 in the gender, highest education, occupation, and place of residence groups, so it could be concluded that there were no significant

Characteristic	Amlodipine (N = 23)		Amlodipine- Candesartan (N = 44)		Total		- nyaluo	
characteristic	N	%	Ν	%	N	%	p value	
Age, year (Mean±SD)	57.43 ±6.373		56.11 ± 5.723		67	100%	0.391 ª	
Gender								
Men	9	39.1%	16	36.36%	25	37.31%	1 000 h	
Women	14	60.9%	28	63.64%	42	62.69%	1.000 5	
Education level								
Low	3	13.0%	15	34.09%	18	26.87%		
Middle	8	34.8%	17	38.64%	25	37.31%	0.076 ^b	
High	12	52.2%	12	27.27%	24	35.82%		
Occupation/ Work								
Working	16	69.6%	28	63.64%	44	65.67%	0.020 h	
Not working	7	30.4%	16	36.36%	23	34.33%	0.830 *	
Residential								
Region A	1	4.3%	3	6.82%	4	5.97%		
Region B	16	69.6%	30	68.18%	46	68.66%	0.917 ^b	
Region C	6	26.1%	11	25.00%	17	25.37%		

Table 1. Sociodemographic characteristics in amlodipine and amlodipine-candesartan groups.

^a = Compare-means;

^b = Chi-Square;

Region A = Pariaman, Koto Tangah, Padang Utara and Nanggalo, Region B = Padang Barat, Kuranji and Pauh, Region C = Padang Selatan, Lubuk Begalung, and Lubuk Kilangan

Component	Amlodipine (N = 23)		Amlodipine-can	p-value		
-	Mean	SD	Mean	SD		
Utility						
Utility	0.93	0.11	0.91	0.12	0.56 °	
VAS						
VAS	79.13	13.87	81.39	15.33	0.56 ^e	
VAS = Visual analog scale, ^e =	One Way ANOVA					

 Table 2. Comparison of utility values, VAS, and blood pressure differences for the antihypertensives group.

differences for each treatment group. Based on data on respondents' characteristics according to place of residence, respondents in this study were dominated by respondents who lived in Region B at 68.66%, followed by Region C in the second position. The gender group was dominated by 62.69% women and 37.31% male patients. Final education is divided into three categories: low (not schooled, Elementary School), medium (Junior High School, Senior High School), and high (Graduate and Postgraduate). Judging from their latest education, most respondents fall into the secondary education and higher education groups. In the sociodemographic picture, it was found that there was no significant difference between the recipients of amlodipine alone or the combination of amlodipine-candesartan. It can be assumed that there is no relationship between sociodemographic characteristics and the antihypertension received.

Utility Parameter

The utility of antihypertension therapy observed in this study resulted from converting the utility values that patients filled in on the EQ-5D-5L questionnaire. Table $\underline{2}$. shows a comparison of utility values, VAS, and blood pressure differences for the antihypertensives group.

The results of the One-Way ANOVA analysis showed a p-value ≥ 0.05 , which was 0.560. It can be concluded that there is no significant difference in utility between the two groups in terms of quality of life. The average VAS score of respondents was 80.62; this is in line with the results of research conducted by Hamida et al. (2019), which obtaned a VAS score or hypertensve patents (79.4 \pm 12.4). The average VAS value n respondents who used amlodipine alone was 79.13 and 81.386 in patients who used amlodipine-candesartan combination therapy. The mean VAS value data shows that hypertensve patents who used amlodipine alone were included in the group wth good VAS scores and the amlodpne-candesartan combination group with very good scores.

Cost Analysis

In this study, a cost analysis was carried out for the types of antidiabetics to see the difference in costs for using the two antihypertensive combinations, both direct medical costs and non-direct costs. Direct medical costs include administrative costs, medical medical support, and medicines; non-direct services, costs include transportation and food costs [8,18], as seen in Table 3. The average direct medical costs incurred by the group using amlodipine alone were higher compared to the group using the amlodipine-candesartan combination, which was caused by the unequal number of BPJS classes of respondents in each antihypertensive group [7,8]. The direct non-medical costs incurred by the two groups did not have a significant difference, where the single amlodipine group incurred an average of direct nonmedical costs of IDR 36,826 and IDR 39,864 for the group using the amlodipine-candesartan combination.

Table 3. Average cost of antihypertensive group.

Antihypertension	Number of Patients	Direct medical cost (IDR)	Non-direct medical cost (IDR)	Total cost (IDR)
Amlodipine	23	96,739 (±65,150)	36,826 (±33,543)	133,565 (±78,748)
Amlodipine Candesartan	44	81,477 (±64,046)	39,864 (±38,354)	121,341 (±86,397)

Antihypertensive	Number of patients	Utility	Cost (IDR)	ICUR (IDR/QALY)	
Amlodipine	23	0.927	133.565	7 040 674	
Amlodipine Candesartan	44	0.906	121.341	/.318.6/4	

Table 4. Incremental cost-utility ratio	value.
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value of IDR 7,318,674/QALY is obtained for the increase in quality-of-life years (QALYs), which is the cost of improving a patient's quality of life in one year for the use of the amlodipine-candesartan combination [19]. This also aligns with previous research at the same hospital, which assessed ICER values for changes in systole and diastole in hypertensive patients. The combination therapy was more effective in reducing systolic and diastolic blood pressure than amlodipine alone, although the difference in blood pressure reduction was insignificant. In terms of cost-effectiveness, the Incremental Cost-Effectiveness Ratio (ICER) for reducing systolic blood pressure by an additional 1 mmHg with the combination therapy over amlodipine alone was IDR 74,738.10, indicating that the combination therapy is more cost-effective for systolic blood pressure reduction. Additionally, treatment with candesartan proved to be more economically efficient, with an ICER of IDR 580,993 per percentage point improvement in blood pressure, demonstrating a favorable cost-effectiveness balance for the combination therapy in managing both systolic and diastolic blood pressure. The

ICER for diastolic blood pressure reduction was IDR 205,918.24 per mmHg [8].

Incremental Cost-Utility Ratio (ICUR)

The incremental cost-ICUR Ratio (ICUR) compares the cost-effectiveness of different media interventions by measuring the additional costs per additional unit of health benefits, often quantified as quality-adjusted life years (ways). In this study, ICUR determines whether the higher cost of the amlodipine-candesartan combination is justified by its improved health outcomes compared to single amlodipine. Table 4 presents the ICUR value.

The average difference between the utility value of the amlodipine-candesartan combination and amlodipine alone is -0.02, and the cost difference is -IDR 12,224, with the ICER value of IDR 7,318,674/ QALY. Based on the cost-utility diagram, the amlodipine-candesartan combination group falls into quadrant 3 (southwest). The position of the ICUR value in quadrant III illustrates that the costs required for the amlodipine-candesartan combination group are lower than the costs of the single



Cost utility plane Amlodipine-Candesartan

Figure 1. Utility diagram of an antihypertensive cost of single amlodipine and a combination of amlodipine-candesartan.

amlodipine treatment group, and the outcomes are also not better (slightly lower or the same). Meanwhile, another publication revealed that the two ICER systolic and diastolic blood pressure values lie in the same quadrant 1 (northeast). Therefore, we can say that the amlodipinecandesartan combination has better effectiveness in lowering blood pressure than amlodipine alone but also requires greater costs [8].

Although the quadrant locations of the results of these two studies are different, the similarity of the incremental costs that lie in the northeast and southwest quadrants of the cost-utility plane can be understood as the Magnitude of the Ratio, where both quadrants indicate a change in costs and effectiveness. In the Northeast, the intervention is more costly but more effective, while in the Southwest, it is less costly but less effective. The ICER/ ICUR, in both cases, provides a ratio that reflects the trade-off between cost and effectiveness. The intervention may be deemed cost-effective if the ICER/ICUR is within an acceptable range (below the WTP threshold).

The ICER/ICUR helps understand the value of an intervention in both scenarios. It provides a standardized way to assess whether the additional effectiveness (or reduced effectiveness in the southwest quadrant) is worth the additional cost (or cost savings) [17,20,21]. The similarity of ICER/ICURs in the northeast and southwest quadrants lies in their role in evaluating the trade-off between costs and effectiveness, helping decision-makers assess the value of healthcare interventions under different circumstances [22,23].

Strengths and limitations

This study has several strengths, including a comprehensive cost analysis that considers both direct medical costs based on package pricing and claims costs, providing a thorough understanding of the financial aspects of hypertension treatment. The data collection was prospective and confirmed through medical records, ensuring accuracy. The study offers a detailed overview of the patient population by examining sociodemographic characteristics. It compares the efficacy and costs of two antihypertensive treatments, offering valuable insights into their relative cost-effectiveness. The use of the EQ-5D-5L questionnaire to measure utility and calculate the Incremental Cost-Utility Ratio (ICUR) provides a nuanced evaluation of treatment outcomes in terms of qualityadjusted life years (QALYs). However, the study has some limitations. The findings are not generalizable to other healthcare providers, as the study was limited to patients at Universitas Andalas Hospital in Padang City. The short

time horizon of one month may not capture long-term costs and outcomes. No discounting of costs and effects was applied, which may impact the accuracy of the costeffectiveness analysis over longer periods.

Conclusion

The ICUR value obtained was IDR 7,318,674 utility for the increase in quality years of life (QALYs) using the amlodipine-candesartan combination. The difference in the average utility value of the amlodipinecandesartan combination with amlodipine alone is -0.02, and the difference in cost is IDR 12,224. Based on the cost-utility diagram, the amlodipinecandesartan combination group is included in the southwest quadrant (quadrant III), which illustrates that the cost required for the Amlodipine-Candesartan combination group is lower than the cost of the Amlodipine single treatment group and the outcome is also not better (slightly lower or the same).

Ethical Approval

This research was conducted at Andalas University Hospital, making ethical clearance (ethical clearance) at the Research Ethics Committee of the Faculty of Medicine, Universitas Andalas No. 1111/ UN.16.2/KEP-FK/2023

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Competing Interest

The author(s) declare no conflict of interest regarding this manuscript. No funding was provided for this study.

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Author Contributions

NF designed the study. NAR conducted the fieldwork. NF and DAJ supervised data collection in the field. NF checked conceptual variables and wrote the manuscript. TN checked the statistical value. AM checked the cost evaluation part. All authors read and approved the final version.

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