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Amlodipine-Candesartan Combination: A Cost-Effective Strategy for Successful Therapy of Hypertension

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ABSTRACT: Introduction: The combination of amlodipine and candesartan can have a better effect, although the cost-effectiveness analysis was not yet determined. This research aimed to establish the Incremental Cost-Effectiveness Ratio (ICER) value among outpatients with hypertension who used amlodipine-candesartan. Method: This research was a descriptive study that retrospectively gathered data from medical records . Medical records data focused on information for hypertensive patients at Universitas Andalas Hospital in 2021. This study compared the standard treatment involving amlodipine-candesartan and sole amlodipine, next to calculate the ICER using cost-effectiveness analysis. Results: Out of the total population of 284, as many as 73 patients were involved in this study. Among these, 21 patients (28.77%) were treated with amlodipine alone, while 52 (71.23%) received an amlodipine-candesartan combination. The Incremental Cost-Effectiveness Ratio (ICER) for reducing systolic blood pressure was IDR 74,738.10 per one mmHg decrease in the northeast quadrant of the cost-effectiveness chart. The ICER for lowering diastolic blood pressure was IDR 205,918.24 per one mmHg decrease in the northeast quadrant on the cost-effectiveness chart. Conclusion: The cost of the amlodipine-candesartan combination yields superior effects; however, warranting a probabilistic sensitivity analysis to determine its ICER robustness is essential for its effective implementation.

Keywords: **amlodipine; antihypertension; candesartan; cost-effectiveness analysis; incremental cost-effectiveness ratio.**

Introduction

Hypertension therapy has the main goal; reducing the effects of high blood pressure and preventing complications [1]. Treating hypertension is a prolonged endeavor with a significant likelihood of complications arising [2]. These two things will have an impact on the costs incurred by patients. While undergoing hypertension therapy, patients will require a lot of money. The high prevalence and severity or chronic nature of hypertension will create an even greater economic burden for patients and the health care system. Hypertension is associated with a large economic burden for individuals and the population [3]. The estimated annual direct and indirect costs of hypertension in the United States are $47.3 billion and $3.9 billion, respectively. Meanwhile, the average cost for one adult hypertensive patient treated per year is an average of $733 [4].

The prevalence of hypertension in Indonesia is quite high, as 34.11% at age ≥18 years. Based on Basic Health Research conducted in 2018, as many as 25.16% of the population of West Sumatra aged ≥ 18 years suffer from hypertension [5]. This large amount is a multiplier factor that can increase public spending.

Based on research by Sohn et al (2017), the amlodipine-candesartan combination provided a significantly greater difference in blood pressure reduction compared to single therapy using amlodipine after 8 weeks of therapy [6]. Amlodipine-candesartan combination therapy for eight weeks can reduce blood pressure by 27.9/18.6 mmHg [6]. For single amlodipine therapy, there was a reduction in blood pressure of 25.7/14.7 mmHg [7]. Previous research showed that the amlodipine-candesartan combination therapy is more cost-effective than the amlodipine-ramipril combination [8]. The effectiveness of combination therapy in lowering blood pressure is better than single therapy. However, combination therapy can also increase the total cost of treatment. This will burden society, especially those with lower

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middle-class economies [9–11].

Combining antihypertensive agents can enhance the overall blood pressure-lowering effect. By comparing combination therapy to monotherapy, researchers can assess whether the addition of candesartan to amlodipine offers superior control over blood pressure levels, particularly in patients whose hypertension is not adequately controlled by a single agent. Beside, comparing the combination therapy with monotherapy helps determine if the additional benefits in blood pressure reduction justify any increased costs. This analysis is crucial for healthcare systems to decide which treatments to endorse and subsidize.

Antihypertension has different effectiveness, and hypertension therapy requires large medical costs due to the long treatment period. The cost and effectiveness of antihypertensives should be considered in selecting antihypertensives [12]. Based on the description above, it is necessary to carry out a cost-effectiveness analysis of hypertension therapy. That way, the costs incurred by patients and the state will be reduced [13,14]. This research is a pharmacoeconomic study that compares the cost–effectiveness of the amlodipine-candesartan combination compare to sole amlodipine at Universitas Andalas Hospital. This study aimed to see the trend in the effectiveness of using amlodipine and candesartan combination therapy compared to amlodipine alone by calculating the ICER and next to see its position on the cost-effectiveness curve.

Methods

Materials

The data used in this study is medical record data of hypertensive patients at Universitas Andalas Hospital in 2021. This data was then cross-checked with billing data in the hospital management information system (SIM-RS).

Research Design, Target Population, and Location

This research was a descriptive study-based health economics evaluation through retrospective data collection. In this study, we refer to the standardized CHEERS 2022 that is available on the Equator network [13,15]. The research was conducted at Universitas Andalas Hospital. The target of this research is hypertensive patients who refill their medication at the Universitas Andalas hospital. This study compared amlodipine 5mg-candesartan 8mg (intervention) with amlodipine 5mg alone (comparator). Sampling was conducted non-randomly using a purposive sampling technique, where samples that met the inclusion criteria were used as research samples.

Inclusion and Exclusion Criteria

The inclusion criteria in this study were outpatient hypertensive stage 2 patients undergoing therapy in 2021 who had insurance. Outpatient hypertensive patients receive amlodipine therapy or the amlodipine-candesartan combination. These patients undergo routine control for at least three months. The range of age of the patients were 15-64 years. The treatment duration of 3 months is intended to see the effect of therapy in patients referred back. They would refill the drug at the hospital after the third month. We excluded patients with incomplete medical record data, pregnant, patients with comorbidities and patients who died during treatment.

Perspective, Time Horizon, and Index Year

The cost perspective used is the hospital perspective (health care perspective). The cost calculated is the fee paid to the hospital. This cost component is the direct medical cost which consists of hospital administration costs, medicines, laboratory tests, and doctor visits. This research looked at time horizon progress data for three months in 2021. The index year was set in 2021.

Currency and Discount Rate

The currency used is Rupiah (IDR). Because it is in the same fiscal year, no discount cost and effect is applied in this study [13,15].

Cost-Effect Variables

The data taken is then entered into the data collection sheet. The data collected included: Patient sociodemographic data: gender, age, educational level, and occupation. Second, patient clinical data: type of antihypertensive given, disease diagnosis, and therapy outcomes (changes in blood pressure, whether systolic or diastolic). Third, direct cost data: includes administrative costs, treatment costs, support costs, and medicines costs that categorize to total direct costs [15,16].

Data Analysis

A compare means analysis was conducted for data on the average value between the two groups. The independent T Test then used to calculate the average and the univariate relationship between the dependent and independent variables. Meanwhile, group data will be tested statistically using Chi-square [17]. After obtaining the base-case data, a pharmacoeconomic analysis was carried out to get the Incremental Cost-Effectiveness Ratio (ICER) value.

Theory/Calculation

The cost-effect analysis in economic evaluation assesses the ICER of new interventions and comparators. The ICER value was calculated using the formula [13,16,18]:

$$ICER = \frac{\text{incremental cost}}{\text{incremental effect}}$$

$$ICER = \frac{\text{intervention cost} \quad \text{comparator cost}}{\text{intervention effect} \quad \text{comparator effect}}$$

$$ICER = \frac{\text{amlodipine} \quad \text{candesartan cost} \quad \text{amlodipine cost}}{\text{amlodipine} \quad \text{candesartan effect} \quad \text{amlodipin effect}}$$

The difference in cost and effectiveness of the two interventions can be seen through the cost-effectiveness plane (CE Plane), which consists of four quadrants. The effectiveness of the new intervention (comination of amlodipine-candesartan) is better than the comparator's and the costs required by the recent intervention are also cheaper than the cost of the comparator, then in this condition, the new intervention would be chosen [4,13].

Result and Discussion

After being selected according to the inclusion and exclusion criteria, as 73 patients in the included criteria, consisted of 30 male and 43 female. The sociodemographic description of hypertensive patients can be seen in Table 1.

The research sample had an age range of 25 to 64 years. The *Riskesdas* data also shows that the below the age range , the smaller the percentage affected by hypertension [5,19].

The research results obtained show that the smaller the age range, the smaller the percentage of people affected by hypertension [20]. The cause of the increasing number of cases of hypertension with increasing age is due to the risk of collagen buildup in the smooth muscle layer. This causes the walls of the arteries to thicken and makes the blood vessels narrow, then the blood vessels will become

Table 1. A chi-square analysis to determine the relationship between patient characteristics and antihypertensive treatment

Characteristics		Antihypertensive groups (%)		Number of patients (%)	p *value*
		Amlodipine	Amlodipine + Candesartan		
Age (year)	25-34	0	2 (3.85)	2 (2.74)	0.254
	35-44	0	7 (13.46)	7 (9.59)	
	45-54	9 (42.86)	18 (34.62)	27 (36.99)	
	55-64	12 (57.14)	25 (48.08)	37 (50.68)	
Gender	Male	7 (33.33)	23 (44.23)	30 (41.10)	0.399
	Female	14 (66.67)	29 (55.77)	43 (58.90)	
Education	Elementary	3 (14.29)	3 (5.77)	6 (8.22)	0.318
	Junior	2 (9.52)	5 (9.62)	7 (9.59)	
	Senior	6 (28.57)	18 (34.62)	24 (32.88)	
	Diploma	2 (9.52)	1 (1.92)	3 (4.11)	
	Bachelor	6 (28.57)	11 (21.15)	17 (23.29)	
	Refuse to mention	2 (9.52)	14 (26.92)	16 (21.92)	
Occupation	Civil servant	6 (28.57)	11 (21.15)	17 (23.29)	0.827
	Private sector	2 (9.52)	3 (5.77)	5 (6.85)	
	Retiree	2 (9.52)	2 (3.85)	4 (5.48)	
	Home maker	6 (28.57)	17 (32.69)	23 (31.50)	
	Farm	1 (4.76)	3 (5.77)	4 (5.48)	
	Refuse to mention	4 (19.05)	16 (30.77)	20 (32.88)	

Table 2. Blood measurements data of hypertensive patients

Antihypertensive drugs	Systolic (mmHg±SD)		p value		Diastolic (mmHg±SD)		p value	
	Initial	Post-treatment	Initial	Post-treatment	Initial	Post-treatment	Initial	Post-treatment
Amlodipine	145 (±25.16)	131.14 (±12.11)	1.01	1.12	85.38 (±21.22)	76.14 (±10.10)	0.90	0.91
Amlodipin-Candesartan	152.56 (±24.29)	133.85 (±11.19)			86.54 (±10.15)	75.54 (±9.23)		

stiff. Stiff blood vessels will cause systolic blood pressure to increase until the age of 70 years and diastolic blood pressure to increase until the age of 60 years [21]. In old age, gender will influence the risk factors for hypertension, where the risk factors will increase sharply in women [22]. This can be caused by the onset of the menopause phase. When the menopause phase occurs, estrogen levels will fall and the effects of androgens become unbalanced. This, will trigger hypertension [23]. Apart from being influenced by menopause, regular use of oral contraceptives will cause blood pressure to rise. Approximately 5% of women who take oral contraceptives regularly in the long term experience an increase in blood pressure [24]. The research found that hypertension risk increases sharply in post-menopausal women. The reduction in estrogen and the imbalance of androgens contributes to this increased risk. The use of oral contraceptives also plays a role, with about 5% of long-term users experiencing elevated blood pressure. This gender-specific information is crucial for tailoring public health interventions and awareness programs to address and manage hypertension in different demographic groups effectively.Effect parameter

The effectiveness seen in this study was reducing blood pressure [21,25]. The blood pressure seen in this study is divided into two dimensions; systolic blood pressure and diastolic blood pressure. Table 2 contains baseline blood pressure data for the amlodipine alone group and the amlodipine-candesartan combination group. In the baseline blood pressure data, it can be seen that the average initial blood pressure in the combination group, both systolic and diastolic blood pressure, was higher compared to the single group. The average initial systolic blood pressure in the combination group was quite high and almost reached 160 mmHg or stage 2 hypertension, where for stage 2 hypertension it is recommended that combination therapy be given [6].

Cost-Effectiveness Analysis

The recorded variance in average direct medical expenses and blood pressure reduction between interventions is input into the formula for calculating the Incremental Cost-Effectiveness Ratio (ICER). This research categorized blood pressure into two dimensions for streamlined analysis: a reduction in systolic and diastolic blood pressure. Consequently, two ICER values were derived: one for reducing systolic pressure and one for reducing diastolic pressure. Table 3 shows the calculation of incremental cost-effectiveness ratios for systolic and diastolic blood pressure.

The data indicates two distinct approaches to antihypertensive therapy: single drug therapy with amlodipine and amlodipine-candesartan therapy. For the single amlodipine group, there was an average decrease in diastolic blood pressure of 9.24 mmHg (SD=8.05), and for the combination therapy group, an 11 mmHg decrease in diastolic blood pressure was observed (SD=10.24). Additionally, after 8 weeks of treatment, the combination therapy was found to reduce blood pressure by 27.9 mmHg systolic and 18.6 mmHg diastolic, compared to the single therapy, which reduced blood pressure by 25.7

Table 3. The ICER value of Amlodipin-Candesartan combination

Antihipertensive drugs	Number of patients	Decrease in systolic blood pressure (mmHg±SD)	Decrease in diastolic blood pressure (mmHg±SD)	Direct medical cost (IDR)	ICER systolic	ICER Diastolic
Amlodipine	21	13.86 (±8.40)	9.24 (±8.25)	735,166.67	IDR 74,738.10 /mmHg	IDR 205,918.24 /mmHg
Amlodipine+ Candesartan	52	18.71 (±10.01)	11 (±10.24)	1,097,975.00		

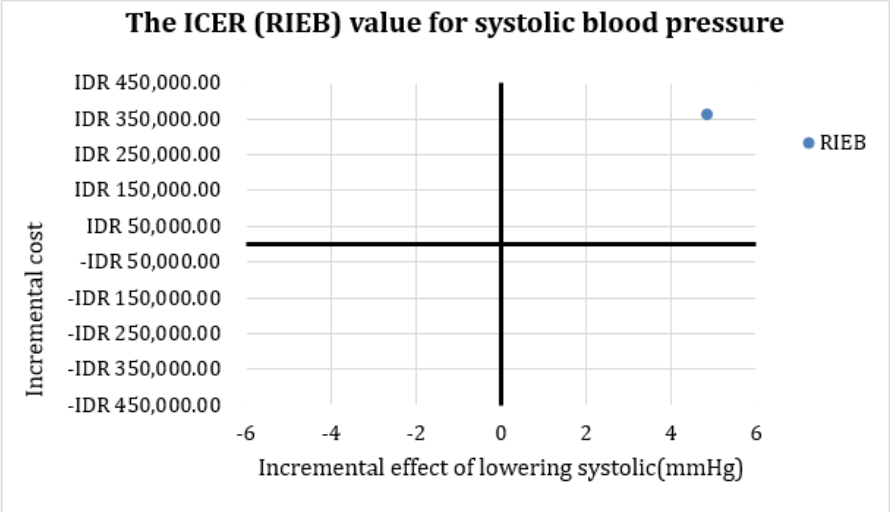

Figure 1. The ICER position of systolic blood pressure on the cost-effectiveness diagram

mmHg systolic and 14.7 mmHg diastolic. The differences between systolic and diastolic blood pressure reflect the superior effectiveness of the combination therapy over the single drug therapy in managing hypertension, evidenced by larger reductions in both systolic and diastolic blood pressure. The standard deviations (SD) provided for the reductions in diastolic blood pressure (8.05 for amlodipine alone and 10.24 for the combination) suggest variability in response among patients but do not negate the observed differences in average blood pressure reductions between the two groups. This result is confirmed by previous research which stated that the amlodipine-candesartan combination showed effective results after use at 8 weeks [6].

The ICER values for systolic and diastolic blood pressure in the cost-effectiveness diagram can be seen in Figure 1 and Figure 2.

The combination therapy demonstrated greater efficacy in reducing both systolic and diastolic blood pressure compared to single therapy with amlodipine alone, although the difference in blood pressure reduction between the two therapies was not substantial. In terms of cost-effectiveness, the Incremental Cost-Effectiveness Ratio (ICER) for reducing systolic blood pressure by an additional 1 mmHg using the combination therapy over amlodipine alone was IDR 74,738.10. This suggests that the combination therapy is more cost-effective for systolic blood pressure reduction. Furthermore, treatment with candesartan was found to be more economically efficient, with an ICER of IDR 580,993 per percentage point improvement in blood pressure, indicating a favorable balance between cost and effectiveness for the combination therapy in both systolic and diastolic blood pressure management.The ICER value for diastolic blood pressure is IDR. 205,918.24/mmHg. This means that every additional cost of IDR 205,918.24 for the combined use of amlodipine and candesartan will provide a reduction in blood pressure of 1 mmHg compared to the use of amlodipine alone. Valsartan and candesartan are antihypertensives that belong to the same group, in which the ARB (Angiotensin Receptor Blockers) group [7]. Based on research by Baroroh et al. (2019), Hence, candesartan treatment proves to be more economically efficient, exhibiting an ICER value of IDR 580,993 per percentage point improvement.

The two ICER values lie in the same quadrant 1 (northeast). Therefore, we can say that the amlodipine-candesartan combination has better effectiveness in lowering blood pressure than amlodipine alone, but also requires greater costs. According to Park's research (2017), combination therapy with nifedipine and candesartan is more cost-effective compared with candesartan or nifedipine therapy alone. The ICER value in this study falls into quadrant 2 or dominates [4]. This can happen because in Park's (2017) research, comorbidities in hypertensive patients were similar (7).

The findings underscore the importance of early intervention and targeted treatment strategies for hypertension management. Given the higher efficacy and cost-effectiveness of combination therapy, healthcare policies should consider recommending such regimens, especially for patients with severe hypertension. Public

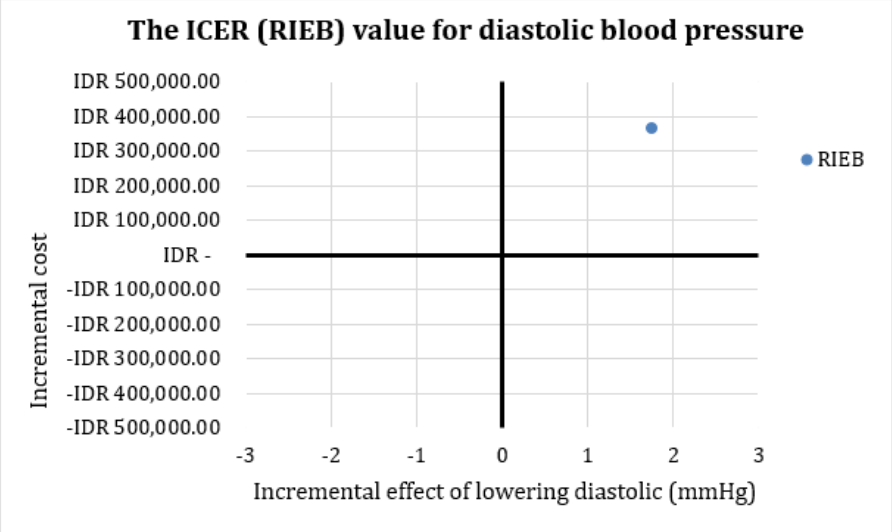

Figure 2. The ICER position of diastolic blood pressure on the cost-effectiveness diagram

health programs should also focus on educating both healthcare providers and patients about the benefits of combination therapy and the risks associated with untreated hypertension, particularly in older adults and post-menopausal women.

Strength and Limitation

This study with a clear aim and methodology, provides valuable data on the cost-effectiveness of hypertension treatments. By using a descriptive, retrospective study design, the research leverages existing medical records, allowing for the efficient gathering of data without the need for new patient enrollments. However, limitations such as the small sample size, lack of a comprehensive sensitivity analysis, and the inconclusiveness of cost-effectiveness outcomes suggest areas for future research and improvement.

Conclusion

Despite the higher cost of this therapy, its benefits in managing blood pressure suggest it could be cost-effective. The study also points out the need for a probabilistic sensitivity analysis to confirm these cost-effectiveness results. This analysis is important because it considers how different patients might react to the therapy, how well they stick to their treatment, and any changes in the cost of the medicines. By looking at both the economic and health outcomes, healthcare leaders can make informed decisions about which treatments provide the best value for money and health benefits. This research is crucial for understanding how to evaluate and choose high blood pressure treatments wisely, ensuring healthcare resources are efficiently used.

Conflict of Interest

The authors have no conflicts of interest regarding this investigation.

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Ethical Approval

This study received ethical approval from the Research Ethics Committee of the Faculty of Medicine, Universitas Andalas No. 620/UN.16.2/KEP-FK/2022.

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Author Contributions

NF designed the study, YZS and MM conducted the fieldwork, HN and MA supervised data collection in the field. NF checked conceptual variables and wrote the manuscript. All authors read and approved the final version.

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