JFSP Vol.11, No.2, May-August 2025, Page: 147-155
pISSN: 2549-9068, eISSN: 2579-4558
Jurnal Farmasi Sains dan Praktis
(JFSP)
http://journal.unimma.ac.id/index.php/pharmacy

COST-EFFECTIVENESS ANALYSIS OF AMLODIPINE AND CANDESARTAN USE IN TYPE 2 DIABETES MELLITUS PATIENTS WITH COMORBID HYPERTENSION IN YOGYAKARTA, INDONESIA

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https://doi.org/10.31603/pharmacy.v%vi%i.13353

Article info:
Submitted : 22-03-2025
Revised : 09-05-2025
Accepted : 29-08-2025

Publisher:
Universitas Muhammadiyah Magelang

ABSTRACT
Type 2 diabetes mellitus, often accompanied by comorbid hypertension, necessitates expensive and prolonged treatment. Therefore, conducting a cost-effectiveness analysis is crucial to identify the most economically viable option by comparing the costs and therapeutic efficacy of amlodipine and candesartan in patients with type 2 diabetes mellitus and comorbid hypertension in Yogyakarta, Indonesia. This research aims to analyze therapy costs and effectiveness using pharmacoeconomic assessment, specifically calculating ACER (Average Cost-Effectiveness Ratio) and ICER (Incremental Cost-Effectiveness Ratio) values. The study uses a quantitative approach with retrospective data collection from patient medical records through total sampling. This research gathered data from 149 medical records. The cost-effectiveness analysis based on ACER values revealed the following: amlodipine 5 mg cost IDR 86; amlodipine 10 mg cost IDR 51; candesartan 8 mg cost IDR 571; candesartan 16 mg cost IDR 727. The ICER value of amlodipine 5 mg – candesartan 8 mg cost IDR 1,527; amlodipine 5 mg – candesartan 16 mg cost IDR 2,192; amlodipine 10 mg – candesartan 8 mg cost IDR –8454; amlodipin 10 mg – candesartan 16 mg cost IDR –5,979. The therapy is considered cost-effective when the ACER value is low, and the negative value of ICER indicates that the treatment has lower costs with greater effectiveness. So, using amlodipine 10 mg is the most cost-effective approach for reducing blood pressure in type 2 diabetes mellitus patients with comorbid hypertension in Yogyakarta, Indonesia.

Keywords: amlodipine; candesartan; cost effective; hypertension; type 2 diabetes mellitus

1. INTRODUCTION

Diabetes is a long-term condition resulting from a failure to produce insulin in the pancreas or an insufficient use of the produced insulin by the body (WHO, 2021). There are four different forms of diabetes: gestational diabetes, type 2 diabetes, type 1 diabetes, and diabetes specificity (ADA, 2022). As many as 90–95% of diabetes cases worldwide are caused by type 2 diabetes mellitus (WHO, 2019). Then, the prevalence of diabetes in Indonesia is 10.6%, affecting 19.47 million out of 179.72 million people (Pahlevi, 2021). Yogyakarta has the highest prevalence at 3.1% (Kemenkes, 2020). It is predicted to increase due to changes in people's lifestyle patterns (Chrisniati et al., 2017).

Diabetes mellitus is a metabolic disorder that occurs when the body struggles to regulate blood sugar levels due to problems with insulin production, insulin resistance, or both. Insulin resistance is a condition in which insulin cannot effectively promote the absorption and utilization of glucose in the body. As a result, insulin resistance may increase the risk of type 2 diabetes, atherosclerosis, hypertension, and polycystic ovary syndrome (PCOS) (Bhavya & Sanjay, 2022). Patients with diabetes are frequently diagnosed with hypertension; it affects 10% to 30% of those with type 1 diabetes and 60% of those with type 2 diabetes. Two out of three diabetic patients have comorbid hypertension (ADA, 2022). Hypertension is diagnosed in adults aged 18 and above when systolic blood pressure is at least 140 mmHg and/or diastolic blood pressure is at least 90 mmHg across multiple readings (Unger et al., 2020). According to (Whelton et al., 2018), consistently elevated blood pressure measurements above the normal range indicate a diagnosis of hypertension. Antihypertensive therapy aims to decrease blood pressure below the target level (Unger et al., 2020). According to hypertension treatment in diabetic patients, the primary single therapy consists of Angiotensin Receptor blockers, called ARBs; Angiotensin-converting enzyme inhibitors, called ACEIs; Calcium Channel Blockers, called CCBs; and Thiazide diuretics (ADA, 2022).

The CEO of BPJS claims that hypertension at IDR 12.1 trillion is the primary reason for healthcare referral costs, followed by diabetes mellitus, at IDR 9.2 trillion. The total cost of chronic medications totaling IDR 19.5 trillion is dominated by high-cost medications, such as those for diabetes mellitus and hypertension, accounting for 78% (BPJS, 2017). Type 2 diabetes mellitus is often accompanied by hypertension, necessitating excessive costs and long-term therapy. Therefore, pharmacoeconomic analysis is needed to make therapy decisions. Due to the significant variation in the prices of antihypertensive drugs, it is crucial to consider the effectiveness of therapy in terms of cost and pharmacology (Nurhikma et al., 2019). Pharmacoeconomic analysis, such as cost-effectiveness analysis (CEA) is used to assess the economic impact of a drug therapy or health intervention (Refasi et al., 2018). Direct medical costs include expenses related to healthcare, such as medication and non-drug interventions (Fautrel et al., 2020).

Cost-effectiveness analysis is commonly used to compare therapy options based on treatment success. The cost-effectiveness ratio, or C/E ratio, is used in cost-effectiveness analysis. The Average Cost-Effectiveness Ratio, also called ACER, and the Incremental Cost-Effectiveness Ratio, called ICER, can be computed to evaluate cost-effectiveness outcomes. This research becomes the first study that evaluates the cost-effectiveness between amlodipine and candesartan in patients with diabetes mellitus with comorbid hypertension, using the ACER and ICER approaches, which can be the basis for making more effective therapeutic decisions. Studies on the treatment of hypertension in type 2 diabetes mellitus have been conducted, but evidence on the cost-effectiveness of amlodipine and candesartan is limited. So, this research aimed determine therapy effectiveness, average therapy costs, and cost-effectiveness analysis of using amlodipine and candesartan in type 2 diabetes mellitus patients with comorbid hypertension in Yogyakarta, Indonesia, based on the ACER and the ICER values.

2. METHOD

This study was quantitative and utilized both descriptive analysis and an observational design. Data analysis utilized pharmacoeconomic methods, specifically cost-effectiveness analysis, calculating therapy cost-effectiveness, average therapy costs, and ACER. The research was conducted at the medical records departments of General Hospital and Privat Hospital from August to October 2022. Data collection involved retrospective records of type 2 diabetes mellitus patients with comorbid hypertension.

The study's participants were people with type 2 diabetes who also had hypertension. One hundred forty-nine patient records meeting the inclusion and exclusion criteria were selected using the total sampling technique. Inclusion criteria encompassed type 2 diabetes mellitus patients with comorbid hypertension, outpatient status, patients undergoing single therapy with amlodipine 5 mg, amlodipine 10 mg, candesartan 8 mg, and candesartan 16 mg, patients aged ≥ 18 years, patients whose blood pressure was measured after therapy and achieved target therapy in less than one month. Exclusion criteria included unreadable or incomplete medical records and patients not returning for blood pressure measurement after amlodipine and candesartan therapy.

The data collection instrument used was an observation sheet containing medical record numbers, patient names, patient with ICD-10 with code E11 and I10, gender, age, blood pressure data of patients with diabetes mellitus before and after taking antihypertensive drugs, types of antihypertensive drugs used, administration frequency, blood pressure measurement dates, or outpatient visit dates, and direct medical costs of amlodipine and candesartan. The research preparation phase involved drafting the research proposal, obtaining Ethical Clearance from the Ethical Committee of FKIK UMY No. 061/EC-EXEM-KEPK FKIK UMY/VII/2022, Ethical Committee of Wates Regional Public Hospital No. KEPK/106/RS/VII/2022, Ethical Committee of PKU Muhammadiyah Yogyakarta Hospital No. 1775/PI.24.2/VII/2022, and preparing the observation sheets. The implementation phase included collecting data on the usage of amlodipine and candesartan in type 2 diabetes mellitus patients with comorbid hypertension, following the research instrument. The reporting phase involved analyzing cost-effectiveness by calculating therapy cost-effectiveness, average therapy costs, and ACER and compiling the research results.

3. RESULT AND DISCUSSION

3.1. Distribution of Respondent Characteristics

The study results related to the number of respondents who experienced diabetes mellitus with comorbid hypertension in Yogyakarta showed 149 respondents. The distribution of respondent characteristics is shown in **Table 1.**

Table 1. Distribution of Respondent Characteristic

Characteristics of respondent	N	Percentage (%)
Gender		
Male	75	50.3
Female	74	49.7
Total	149	100.0
Age		
Less than 45 years old	4	2.7
More than equal to 45 years old	145	97.3
Total	149	100.0
Therapy		
Amlodipine 5 mg	16	10.7
Amlodipine 10 mg	56	37.6
Candesartan 8 mg	29	19.5
Candesartan 16 mg	48	32.2
Total	149	100.0

According to **Table 1**, the distribution of gender characteristics indicates that male patients dominate with 75 patients at 50.3%, while female patients amounted to 74 patients at 49.7%. It shows that patients with diabetes mellitus with comorbid hypertension are dominated by males. According to research, this has been validated by (Whelton et al., 2018), which states that males are more at risk of hypertension than women. Regarding (Arum, 2019), males are more at risk of hypertension due to hormonal differences, namely not having the hormone estrogen-like women, which can function as protection against hypertension and its complications. Therefore, males tend to be at risk of hypertension caused by changes in blood vessels that stiffen at around 30 years of age, triggering an increase in blood pressure (Candra et al., 2022). In addition, unhealthy lifestyle choices contribute to why male patients are at risk of hypertension (Baroroh & Sari, 2018).

According to age characteristics, four patients were aged <45 years (2.7%), and 145 patients were aged ≥45 (97.3%). All patients experience high blood pressure at the age of ≥45 years. It causes diabetes mellitus patients with comorbid hypertension to have a 3.6 times higher risk at the age of ≥45 years (Dedefo et al., 2018). The number of diabetes mellitus patients with comorbid hypertension increases with age or is more prevalent in older patients (Stiadi et al., 2020). It is in line with research conducted by (Orbayinah et al., 2024), which states that a person's quality of life will decrease with age. It triggers a decrease in the function of organs, including the heart, which works harder to circulate blood throughout the body, so it often causes an increase in blood pressure in elderly patients (Dedullah et al., 2015).

Concerning the therapy used by the patient, sixteen patients (10.7%) used amlodipine 5 mg, 56 patients (37.6%) used amlodipine 10 mg, 29 patients (19.5%) used candesartan 8 mg, and 48 patients (32.2%) used candesartan 16 mg. Amlodipine and candesartan are the most widely used hypertension therapies in patients with diabetes mellitus with comorbid hypertension when compared with other antihypertensive therapies (Cahyaningsih & Wicaksono, 2020). More than half of the patients use candesartan according to the therapy usage pattern. ARB-class antihypertensives (candesartan) have lower side effects than other antihypertensives (Restyana, A. Probosiwi, 2018). Common side effects in CCB-class (amlodipine) include peripheral edema (Ahadiah et al., 2020). The decrease in blood pressure resulting from peripheral edema due to CCB usage can be addressed by using ARB to lower blood pressure without side effects, as ARB (candesartan) is neuroprotective (Wulandari, 2019). However, amlodipine usage accounts for almost half of the total sample size. It aligns with a systematic review analyzing cost-effectiveness results from 76 studies, showing that amlodipine is the most widely used CCB-class antihypertensive (Park et al., 2017).

3.2. Cost Analysis

Cost analysis was conducted on the most commonly prescribed antihypertensive drugs for patients with diabetes mellitus with comorbid hypertension, such as amlodipine and candesartan. This analysis was conducted to evaluate the average costs incurred by patients. The results of the cost analysis can be presented in **Table 2.**

Table 2. Cost of Using Amlodipine and Candesartan

Therapy	N	N (effective)	Cost average ± SD (IDR)
Amlodipine 5 mg	16	7	3,781±769
Amlodipine 10 mg	56	39	3,566±1,813
Candesartan 8 mg	29	19	37,380±22,367
Candesartan 16 mg	48	30	45,420±19,294
Total	149	95	

In **Table 2**, the average therapy cost for seven patients using amlodipine 5 mg was IDR. 3,781±769, for 39 patients using amlodipine 10 mg was IDR. 3,566±1,813, for 19 patients using candesartan 8 mg was IDR 37,380±22,367, and for 30 patients using candesartan 16 mg was IDR 45,420±19,294. Direct medical costs in this research include the costs of amlodipine and candesartan obtained from the Maximum Retail Price (MRP) of amlodipine and candesartan in 2022. The cost required for hypertension therapy per day is IDR 153 for amlodipine 5 mg, IDR 183 for amlodipine 10 mg, IDR 2,035 for candesartan 8 mg, and IDR 2,054 for candesartan 16 mg. It is reinforced by the study conducted by (Riannur et al., 2020), which explains that CCB-group drugs, including amlodipine, are known to have lower prices than ARB-group drugs, such as candesartan. This result also aligns with a study that found amlodipine at IDR 613,816 has a lower average cost compared to candesartan at IDR 886,736 (Perawati et al., 2021).

3.2. Effectiveness Analysis

Effectiveness analysis is critical to determine the most effective therapy in the treatment of hypertension in patients with diabetes mellitus. The results of the effectiveness analysis are shown in **Table 3.**

Table 3. Effectiveness of Using Amlodipine and Candesartan

Therapy	N	N (effective)	Percentage (%)
Amlodipine 5 mg	16	7	43.8
Amlodipine 10 mg	56	39	69.6
Candesartan 8 mg	29	19	65.5
Candesartan 16 mg	48	30	62.5
Total	149		

Regarding therapy effectiveness of amlodipine and candesartan based on **Table 3**, the effectiveness calculation showed that 7 out of 16 patients (43.8%) were effective using amlodipine 5 mg, 39 out of 56 patients (69.6%) were effective using amlodipine 10 mg, 19 out of 29 patients (65.5%) were effective using candesartan 8 mg, and 30 out of 48 patients (62.5%) were effective using candesartan 16 mg. Therapy was considered effective if it achieves blood pressure targets of <140/90 mmHg within less than one month (De Boer et al., 2017). Some factors that cause ineffective therapy and uncontrolled blood pressure are individual bioavailability factors such as pharmacokinetics and pharmacodynamics (Wardani & Yuswantina, 2023). Therapy effectiveness is determined by the ratio of patients achieving therapy targets to the total patients receiving the medication multiplied by 100%. Amlodipine is the most commonly used therapy for the management of hypertension comorbidity in patients with type 2 diabetes (Cahyaningsih et al., 2023). It aligns with the research findings that therapy effectiveness in diabetes patients with comorbid hypertension indicates amlodipine 10 mg (80.64%) is higher than candesartan 16 mg (35.48%) (Perawati et al., 2021). Amlodipine has a fast onset of action in lowering blood pressure. It also has a long half-life, good bioavailability, and a lengthy duration of action, allowing for once-a-day administration (Restyana, A. Probosiwi, 2018). Another study mentioned that calcium channel-blocking drugs (CCBs), such as amlodipine, are very effective because they act on vascular smooth muscle and heart muscle. Amlodipine can reduce cardiac output, thereby reducing blood volume and blood pressure (Mazaya et al., 2020).

3.3. Cost-Effectiveness Analysis

3.3.1. ACER (Average Cost-Effectiveness Ratio)

ACER calculation is the ratio between total cost and therapeutic effectiveness. By comparing ACER values, it can be determined which therapy alternative has a lower cost for each outcome achieved. In other words, ACER shows the average cost required to obtain one

outcome in therapy (Laloan et al., 2019). The results of the ACER calculation are presented in **Table 4.**

Table 4. Average Cost-Effectiveness Ratio

Therapy	C (IDR)	E (%)	ACER (IDR)
Amlodipine 5 mg	3,781	43.8	86
Amlodipine 10 mg	3,566	69.6	51
Candesartan 8 mg	37,380	65.5	571
Candesartan 16 mg	45,420	62.5	727

C : Cost of therapy
E : Effectiveness of therapy

According to ACER calculation ACER values of IDR 86 for amlodipine 5 mg, IDR 51 for amlodipine 10 mg, IDR 571 for candesartan 8 mg, and IDR 727 for candesartan 16 mg. The calculation of ACER is used to determine how much money is needed for every one percent of therapy effectiveness, calculated by dividing the average therapy cost (IDR) by therapy effectiveness (%). A therapy can be considered cost-effective if it has a lower ACER value compared to other therapies. Amlodipine 10 mg has the lowest ACER value, making the CCB group (amlodipine) more cost-effective than candesartan, with amlodipine 10 mg being the most cost-effective. These results align with a systematic review indicating that the CCB therapy group (amlodipine) provides better cost-effectiveness than the ARB therapy group (candesartan) (Park et al., 2017). Another study also mentioned that amlodipine provides better cost-effectiveness than candesartan with an ACER value of amlodipine of IDR 156,441.92 and an ACER value of candesartan of IDR 166,527.78 (Akbar et al., 2024).

3.3.2. ICER (Incremental Cost-Effectiveness Ratio)

The ICER calculation is a calculation to determine the additional cost required for each one-unit change in effectiveness. It will help facilitate decision-making regarding more cost-effective treatment alternatives. The calculation results of ICER are shown in **Table 5.**

Table 5. Incremental Cost-Effectiveness Ratio

Therapy	C (IDR)	E (%)	ICER (IDR)
Amlodpin 5 mg - Candesartan 8 mg	-33,599	-22%	1,527
Amlodipin 5 mg - Candesartan 16 mg	-41,639	-19%	2,192
Amlodipin 10 mg - Candesartan 8 mg	-33,814	4%	-8,454
Amlodipin 10 mg - Candesartan 16 mg	-41,854	7%	-5,979

C : Cost of therapy
E : Effectiveness of therapy

The ICER calculation for amlodipine 5 mg - candesartan 8 mg is IDR 1,527 and for amlodipine 5 mg-candesartan 16 mg is IDR 2,192. A positive ICER value in quadrant III indicates that amlodipine 5 mg therapy is less cost-effective compared to candesartan 8 mg and candesartan 16 mg. Amlodipine 10 mg in comparison to candesartan 8 mg is negative 8,454, and amlodipine 10 mg in comparison to candesartan 16 mg is negative 5,979, indicating negative ICER values which signify that amlodipine 10 mg is more cost-effective compared to candesartan 8 mg and candesartan 16 mg. To enhance the effectiveness of amlodipine therapy, a cost of IDR 2,324 is required (Madania et al., 2022). It is in line with research by (Anggraini et al., 2023), which states that amlodipine 10 mg is more cost-effective in hypertensive patients with type II DM with an ICER-IDR value 223,246.40. The smaller the ICER value indicates that the therapy is more effective so that it can be a consideration for therapy.

4. CONCLUSION

Based on the cost-effectiveness analysis, amlodipine belongs to the CCB class is more cost-effective than candesartan, which is part of the ARB class, in patients with type 2 diabetes mellitus with comorbid hypertension, and amlodipine 10 mg is the most effective option to decrease blood pressure. Thus, this can be the basis for considering their use to maximize therapy while reducing the burden of effective and efficient health costs.

5. ACKNOWLEDGMENT

The authors sincerely thank Universitas Muhammadiyah Yogyakarta for supporting this research.

6. CONFLICT OF INTEREST

The authors confirmed that they had no conflict of interest.

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