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# Cost Effectiveness Analysis of Hypertensive Therapy in Hypertensive Patients with Type 2 of Diabetes Mellitus at RSUD Dr. Soehadi Prijonegoro Sragen

## (*Analisis Efektivitas Biaya Terapi Hipertensi pada Pasien Hipertensi dengan Diabetes Melitus Tipe 2 di RSUD dr. Soehadi Prijonegoro Sragen*)

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## ABSTRACT

**Background:** Hypertension followed by type 2 diabetes mellitus is a major risk factor for various cardiovascular diseases and is one of the chronic degenerative diseases Hence, it requires long-lasting treatment therapy and high costs. Based on this, hypertensive patients with DM type 2 need special attention in order to get effective hypertensive therapy at minimum cost. Cost-effectiveness analysis is an analytical method for making decisions on the best alternative to the therapy used. **Objectives:** To determine the most cost-effective hypertensive therapy in hypertensive patients with DM type 2 diabetes who underwent pharmacoeconomic hospitalization with a cost-effectiveness analysis approach. **Methods:** This type of study is descriptive observational with a retrospective data collection method from January 2021 – June 2023. The data taken was 31 medical records data and bill fees that met the inclusion criteria. **Results:** The description of drug use in hypertensive patients with DM type 2 diabetes at RSUD Soehadi Prijonegoro Sragen consists of monotherapy (19.35%) and combination (80.65%). The effectiveness of monotherapy was highest in patients receiving amlodipine therapy (12.42 mmHg), while the effectiveness of the combination was highest in patients taking adalat oros + candesartan + bisoprolol + furosemide + clonidine (22,38 mmHg). From the calculation of the ACER value, it was found that the most cost-effective drug was amlodipine, which had an ACER value of Rp. 289,962 in monotherapy and amlodipine + candesartan with an ACER value of Rp. 262,626. **Conclusions:** The most widely used hypertension therapy is combination therapy; the drug with the highest effectiveness is adalat oros + candesartan + bisoprolol + furosemide + clonidine and the drug with the highest cost-effectiveness is amlodipine monotherapy and the combination of amlodipine + candesartan.



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## INTRODUCTION

Hypertension remans a health threat in Indonesia because its prevalence reached or affected 63,309,620 people in 2018 (Riskesdas, 2018). The prevalence of hypertension in Central Java experienced a significant increase from the previous year, namely 25.8% in 2013 and shot up to 37.57% in 2018. Central Java is also the province with the fourth-highest percentage of hypertension sufferers in Indonesia (Riskesdas, 2018). The prevalence of hypertension in Sragen Regency has also experienced a significant increase, from 14.5 in 2017, 25.6% in 2020, and rising to 35.9 percent in 2022 (Bepperida, 2022; Profilkes Jateng, 2021). In 2022, the prevalence of hypertension in Sragen district will reach 275,439 sufferers (Central Java Health Profile, 2021). Hypertension is the most common disease suffered by the people of Sragen Regency, followed by diabetes mellitus (Ulhaq et al., 2022).

Complications and comorbidities due to hypertension are one of the causes of death from this disease. Hypertension is a risk factor and is often a comorbidity with other NCDs, such as diabetes mellitus (DM). DM is a metabolic syndrome characterized by blood sugar levels exceeding normal. DM can be caused by abnormalities in insulin production, abnormalities in insulin function, or both. The condition of hypertension with type 2 DM is often encountered because patients with hypertension have a 1.5 times higher risk of developing type 2 DM (Petrie et al., 2018; Putra & Saraswati, 2020). The coexistence of hypertension with type 2 DM causes the risk of death to increase up to 7.2 times (Haile et al., 2022). According to research by Hurst et al (2015), hypertension with type 2 DM can increase the risk of cardiovascular disease by 41%. Hypertension with type 2 DM is also closely related to microvascular and macrovascular complications. Hypertension is a driving factor in the development of diabetic retinopathy, neuropathy and nephropathy. Hypertension can also induce atherosclerosis in type 2 DM sufferers (Stroder & Santosa, 2013).

Patients with hypertension and type 2 diabetes mellitus require lifelong hypertension therapy to control blood pressure and prevent complications (Bangol et al., 2022). However, this creates a huge economic burden. The cost of hypertension services in Indonesia continues to increase, reaching 3 trillion rupiah in 2018 (Ministry of Health of the Republic of Indonesia, 2019). Inadequate hypertension therapy in patients with coexistence of hypertension with type 2 DM can lead to other expensive catastrophic disease complications such as heart disease, stroke and kidney failure which absorb 30% of all BPJS Kesehatan funding and prolong the length of hospitalization resulting in greater medical costs. (Anjani, 2019).

The high cost of hypertension therapy for hypertensive patients with type 2 diabetes mellitus also burdens hospital finances. In research by Wusono et al. (2022) in the internal medicine clinic at Jarga

Sasameh District Hospital, it shows that this hospital suffered a loss of IDR 23,755,505 due to the difference in INA-CBGs rates and real rates for pharmaceutical components. (Wusono et al., 2022). Pharmacoeconomic analysis, such as Cost Effectiveness Analysis (CEA), is important for choosing effective therapy with minimal costs (Ministry of Health, 2013). CEA mitigates unnecessary expenditures by evaluating therapies that provide the optimal clinical outcomes at minimal costs.

## MATERIAL AND METHODS

### Materials

This study used patient medical record data collection sheets, direct medical cost data collection sheets, and medical record data for hypertensive patients with type 2 DM hospitalized at RSUD dr. Soehadi Prijonegoro Sragen in January 2021- June 2023

### Methods

This research was conducted using non-experimental or observational research methods. Data analysis uses descriptive techniques. This research uses secondary data, medical records and direct medical cost data on hypertensive patients with type 2 DM who are hospitalized at RSUD dr. Soehadi Prijonegoro Sragen from January 2021 to June 2023. Data was taken using a retrospective method and a cross-sectional approach was used to measure variables.

## RESULTS AND DISCUSSION

This study used a total sampling method with a population of 45 medical records of hypertensive patients with type 2 DM at Soehadi Prijonegoro Hospital, Sragen. A total of 14 medical record samples did not meet the inclusion criteria. The 31 samples subjected to demographic analysis, drug use profiling, analysis of the direct medical costs of hypertension therapy, and the effectiveness of hypertension therapy. The results are then used to determine hypertension therapy with the effectiveness through cost-effectiveness analysis.

Table 1. Patient demographics

| Characteristic of Patient | Number of Patients | Percentage (%) |
|---|---|---|
| **Primary Diagnosis** | | |
| Essential Hypertension | 4 | 12,9 |
| Secondary Hypertension | 27 | 87,1 |
| **Gender** | | |
| Woman | 20 | 64,52 |
| Men | 11 | 35,48 |
| **Age** | | |
| 26-35 (Early adulthood) | 2 | 6,45 |

| | | |
|---|---|---|
| 36-45 (Late adulthood) | 3 | 9,68 |
| 46-55 (Early elderly) | 14 | 45.16 |
| 56-65 (Late elderly) | 9 | 29,03 |
| 65 and above (Old human) | 3 | 9,68 |
| **Comorbidities** | | |
| Anemia | 15 | 51,72 |
| Pulmonary Edema | 4 | 13,79 |
| Hypoalbumin | 2 | 6,90 |
| Encephalopathy | 1 | 3,45 |
| Gi Hemorrhage | 1 | 3,45 |
| Hypoglycemia | 1 | 3,45 |
| Upper Respiratory Tract Infection | 1 | 3,45 |
| Nephritis | 1 | 3,45 |
| Dysphagia | 1 | 3,45 |
| Glomerular Disorders | 1 | 3,45 |
| Mitral Valve Insufficiency | 1 | 3,45 |
| **Length of Stay** | | |
| 1-2 day | 2 | 6,45 |
| 3-4 day | 6 | 19,35 |
| 5-6 day | 7 | 22,58 |
| 7-8 day | 6 | 19,35 |
| >9 day | 11 | 32,26 |

Based on the table, hospitalized patients were dominated by patients with a diagnosis of secondary hypertension (87.1%). Hypertension is often found in the 56-65 year age group with a percentage of (29.03%) and in the female gender group with a percentage of (65.42%) compared to men (35.48%). A decrease in the physiological performance of organs, abnormal lipid profiles, accumulation of collagen substances in the muscle layers of blood vessels, and menopause in women can cause this.. Most hypertensive patients experienced comorbid anemia (51.72%) and patients with pulmonary edema (13.79%). Several factors can cause anemia in hypertensive patients, namely: The effects of using hypertension therapy, such as ACEi and ARB, which can reduce the production of erythropoietin and red blood cell growth factors, uncontrolled blood pressure, long duration of hypertension, high pulse pressure, and Impaired Na–K+ ATPase activity and endothelial dysfunction which can cause peroxidation of red blood cell membrane lipids and reduce the antioxidant defense of red blood cells. Meanwhile, the length of patient stay was dominated by patients who were hospitalized for more than 9 (32,26) days. This relatively long length of stay in hospital can be caused by several factors, namely: the severity of the disease, comorbidities, ineffective therapy, patient care in the room, and hospital administration problems.

Table. 2 Overview of the use of monotherapy and combination antihypertensive drugs

| Drug Class | Name of Antihypertensive Drug | Number of Patients | Percentage (%) |
|---|---|---|---|
| **Monotherapy** | | | |
| CCB | Amlodipine | 1 | 16.67 |
| Diuretics | Furosemide | 4 | 66.67 |
| ARB | Candesartan | 1 | 16.67 |
| **Combination Therapy** | | | |
| CCB+ARB | Amlodipine + Candesartan | 2 | 8 |
| ARB+Diuretics | Candesartan + Furosemide | 3 | 12 |
| Diuretics+CCB | Furosemide + Amlodipine | 9 | 36 |
| Diuretics+Diuretics | Furosemide + Spironolactone | 2 | 8 |
| CCB+ Diuretics+ARB | Amlodipine + Furosemide + Candesartan | 1 | 4 |
| CCB+ARB+CCB | Amlodipine + Candesartan + Nicardipine | 1 | 4 |
| CCB+Diuretics+Diuretics | Amlodipine + Furosemide + Spironolactone | 1 | 4 |
| Diuretics+CCB+ACEi | Furosemide + Amlodipine + Lisinopril | 1 | 4 |
| CCB + Diuretics + ARB + Alfa Agonist | Amlodipine + Furosemide + Valsartan + Klondin | 1 | 4 |
| CCB + Diuretics + ARB + Alfa Agonist | Amlodipine + Candesartan + Uresix + Clonidine | 1 | 4 |
| Diuretics + CCB + Diuretics + CCB + ACEi | Furosemide + Amlodipine + Spironolactone + Nicardipine + Lisinopril | 1 | 4 |
| Diuretics + ARB + CCB + BB + Alfa Agonist | Furosemide + Candesartan + Adalat Oros + Bisoprolol + Clondine | 1 | 4 |
| CCB + ARB + Diuretics + CCB + Diuretics + BB + Alfa Agonist | Amlodipine + Candesartan +Uretic + Nicardipine +Spironolactone + Bisoprolol + Clonidine | 1 | 4 |

Hypertension therapy in hypertensive patients with type 2 DM at RSUD dr. Soehadi Prijonegoro Sragen is dominated by furosemide monotherapy (66.67%). The most widely used combination therapy is a combination of furosemide and amlodipine (36%). Furosemide monotherapy does not follow the recommendations of the Konsesus Penatalaksanaan Hiepertensi (2019). The recommended first-line therapy is ACEi or ARB. The recommended combination therapy is ACEi or ARB combined with diuretics or CCBs. The large use of this combination therapy can be caused by the sample being dominated by the elderly. The elderly are recommended to use CCB + diuretic combination therapy. Research by Wang (2023) shows that the use of a combination of CCB + diuretics in hypertensive patients accompanied by DM has a more dominant renoprotective effect.

Table 3. Overview of antidiabetic drug use

| Drug Class | Name of Drugs | Amount | Percentage (%) |
|---|---|---|---|
| **Monotherapy** | | | |
| Insulin Aspart | Novorapid | 19 | 73,08 |
| Insulin Glargine | Lantus soloster | 2 | 7,69 |
| Insulin Gluisine | Apidra | 1 | 3,85 |
| Sulfunilurea | Glimepiride | 3 | 7,69 |
| **Combination Therapy** | | | |
| Insulin Glargine + Insulin Aspart | Ezeline + Novorapid | 2 | 7,69 |

The most commonly antidiabetic drug used in hypertensive patients with type 2 DM at RSUD dr. Soehadi Prijonegoro Sragen was novorapid (insulin aspart), namely 19 patients (73.08%). Novorapid is a fast-acting insulin used to treat hyperglycemia in type 1 DM and type 2 DM. This finding is in line with research by Anjani (2019) which shows that insulin aspart is also the insulin most widely used in hypertensive patients with type 2 DM. Novorapid increases storage and inhibits the breakdown of glucose, fat, and amino acids.

Tabel 4. Effectiveness of hypertension therapy

| Name of Drugs | Average Decrease in Systolic (mmHg | Average Decrease in diastolic (mmHg) | Average Decrease in Systolic diastolic (mmHg) |
|---|---|---|---|
| **Monotherapy** | | | |
| Amlodipine | 11,61 ± 0,00 | 13,2 4 ± 0,00 | 12,42 ± 0,00 |
| Candesartan | 5,00 ± 0,00 | 8,00 ± 0,00 | 6,50 ± 0,00 |
| Furosemide | 10,40 ± 3,98 | 4,26 ± 6,27 | 7,33 ± 4,13 |
| **Combination Therapy** | | | |
| Amlodipine + Candesartan | 16,09 ± 4,78 | 4,88 ± 6,77 | 8,80 ± 1,00 |
| Amlodipine + Furosemide | 13,33 ± 7,35 | 8,25 ± 5,83 | 10,79 ± 6,09 |
| Furosemide + Spironolactone | 12,78 ± 6,39 | 12,26 ± 9,26 | 12,52 ± 22,05 |
| Furosemide + Candesartan | 7,03 ± 4,02 | 7,31 ± 4,02 | 7,17 ± 4,02 |
| Amlodipine + Candesartan + Furosemide | 6,96 ± 0,00 | 5,74 ± 0,00 | 6,35 ± 0,00 |
| Amlodipine + Candesartan + Nicardipine | 21,50 ± 0,00 | 0,33 ± 0,00 | 10,92 ± 0,00 |
| Amlopine + Furosemide + Lisinopril | 33,35 ± 0,00 | 7,10 ± 0,00 | 20,23 ± 0,00 |
| Amlodipine + Furosemide + Spironolactone | 27,21 ± 0,00 | 10,89 ± 0,00 | 19,05 ± 0,00 |
| Amlodipine + Candesartan, Klondin + Uresix | 22,00 ± 0,00 | 3,78 ± 0,00 | 12,89 ± 0,00 |
| Amlodipine + Clondine + Furosemide + Valsartan | 22,04 ± 0,00 | 13,48 ± 0,00 | 17,76 ± 0,00 |

| | | | |
|---|---|---|---|
| Adalat Oros + Candesartan + Bisoprolol + Furosemide + Clonidine | 26,20 ± 0,00 | 18,55 ± 0,00 | 22,38 ± 0,00 |
| Amlodipine + Candesartan + Uretic + Nicardipine + Spironolactone + Bisoprolol | 29,88 ± 0,00 | 13,31 ± 0,00 | 21,59 ± 0,00 |
| Furosemide + Amlodipine + Spironolactone + Nicardipine + Lisinopril | 21,26 ± 0,00 | 20,43 ± 0,00 | 20,85 ± 0,00 |

Description: : Highest effectiveness
: Lowest effectiveness

Amlodipine monotherapy has the highest effectiveness in reducing blood pressure in hypertensive patients with type 2 DM at RSUD Soehadi Prijonegoro Sragen, namely 12.42 mmHg. The combination therapy with the highest effectiveness is the combination of furosemide + amlodipine + spironolactone + nicardipine + lisinopril, namely 20.85 mmHg. The effectiveness of hypertension therapy can be influenced by the mechanism of action of each drug, the type of combination used, and patient demographics. In this study, the high effectiveness of amlodipine therapy is due to its pharmacodynamic and pharmacokinetic properties, such as fast duration in lowering blood pressure, having a long half-life, high bioavailability and long duration of drug action, and not being influenced by salt.

The combination therapy with the highest effectiveness in this study is the combination of adalat oros + candesartan + bisoprolol + furosemide + clonidine has a significant impact in reducing blood pressure in patients with high risks such as diabetes, kidney disorders, and hypercholesterolmia. Bisoprolol, as a beta blocker, lowers blood pressure effectively when used in combination therapy with ACEi, ARBs, CCBs, or diuretics. The combination of RAAS inhibitors and diuretics also provides additional benefits by improving the response to hypertension therapy and managing the metabolic side effects of diuretics. Furosemide, a loop diuretic, in combination with a beta blocker, has been shown to reduce the severity of diabetic nephropathy in type 1 diabetes patients receiving aggressive hypertension therapy. Clondine although currently placed as a fourth line treatment due to several side effects, this drug has the potential to stimulate NO production and cause relaxation of blood vessels and increase vasodilation effects to reduce blood pressure.

Table 5. Average direct medical cost

| Name of Drug | Average direct medical cost (Rupiah) | | | | | |
|---|---|---|---|---|---|---|
| | Medical treatment | Emergency room costs | Laboratory | Health care cost | Antihypertensive drug cost | Total |
| **Monotherapy** | | | | | | |
| Amlodipine | 1.276.000 | 267.930 | 343.000 | 1.639.297 | 880 | 3.527.107 |
| Candesartan | 1.722.000 | 177.376 | 871.000 | 479.007 | 766 | 3.250.149 |
| Furosemide | 1.075.333 | 359.321 | 992.867 | 2.152.189 | 39.466 | 4.208.495 |

| Combination Therapy | | | | | | |
|---|---|---|---|---|---|---|
| Amlodipine+ Candesartan | 536.000 | 299.207 | 689.500 | 781.906 | 3.301 | 2.309.914 |
| Amlodipine + Furosemide | 2.069.611 | 376.092 | 1.360.144 | 1.456.763 | 14.221 | 5.276.708 |
| Furosemide + Candesartan | 979.667 | 362.293 | 651.833 | 1.009.127 | 20.561 | 3.466.385 |
| Spironolactone + Furosemide | 2.442.000 | 659.934 | 1.296.000 | 1.846.453 | 13.297 | 6.257.683 |
| Amlodipine + Candesartan + Klondin+Uresix | 644.000 | 284.737 | 835.000 | 1.650.877 | 63.920 | 3.478.534 |
| Amlodipine + Candesartan + Furosemide | 1.620.000 | 559.824 | 1.420.000 | 781.906 | 79.427 | 8.509.447 |
| Amlodipine + Candesartan + Nicardipine | 1.198.000 | 880.080 | 1.556.000 | 740.643 | 101.737 | 4.476.460 |
| Amlodipine. Furosemdie + Spironolactone | 5.882.000 | 385.689 | 2.003.100 | 5.888.913 | 16.689 | 14.176.391 |
| Amlopine + Furosemide + Lisinopril | 2.845.000 | 226.309 | 1.547.500 | 2.314.444 | 20.572 | 6.953.825 |
| Amlodipine + Furosemide + Valsartan + Clonidine | 2.027.000 | 245.878 | 1.722.000 | 865.743 | 18.847 | 4.879.468 |
| Adalat Oros + Candesartan + Bisoprolol + Furosemide + Clonidine | 3.498.000 | 109.804 | 5.264.504 | 4.809.185 | 337.141 | 13.586.634 |
| Amlodipine + Candesarta + Uretic + Nicardipine + Spironolactone + Bisoprolol | 2.574.000 | 607.631 | 1.239.000 | 2.273.944 | 617.234 | 7.311.809 |
| Furosemide + Amlodipine + Spironolactone + Nicardipine + Lisinopril | 15.797.000 | 654.432 | 6.329.000 | 6.120.749 | 335.049 | 29.668.230 |

Description: : Highest direct medical cost
: Lowest direct medical cost

Direct medical costs for treating hypertension in hypertensive patients with type 2 DM at RSUD dr. Soehadi Prijonegoro Sragen vary, depending on the type of therapy given. The highest direct medical cost for monotherapy was furosemide (Rp. 4,208,495) and the lowest was candesartan (Rp. 3,527,107). The highest direct medical costs for combination therapy were furosemide + amlodipine + spironolactone + nicardipine + lisinopril (Rp. 29,668,230) and the lowest was amlodipine + candesartan

(Rp. 2,309,914). Factors that influence direct medical costs such as other complications, comorbidities, therapy for complaints experienced, severity of hypertension, number and type of medication used, length of stay in hospital.

The high direct medical costs of furosemide monotherapy can be caused by low effectiveness and longer hospital stays. The condition of patients on furosemide therapy has a history of kidney disease so they need other drug therapy to improve the general condition due to kidney disease. Meanwhile, in patients who received the drug combination regimen of furosemide + amlodipine + spironolactone + nicardipine + lisinopril, it was found that the patient had an inpatient stay of up to 19 days, which could significantly increase costs. Patients also come with high blood pressure and enter stage 3 so they need more adequate management of hypertension therapy and need longer treatment. Candesartan has lower direct medical costs than other monotherapies. Meanwhile, the combination of amlodipine + candesartan has the lowest direct medical costs among other combination therapies. This could be due to the demographics of the patient being known without having other comorbidities and the patient coming with a lower stage of hypertension or non-resistant hypertension compared to patients on other combination therapy.

Cost-effectiveness analysis is an analysis technique that compares two or more health interventions that provide different outcomes. In determining the treatment that has the lowest cost and the highest effectiveness, the data obtained is analyzed using the AEB (Cost Effectiveness Analysis) method, so that the ACER (Average Cost Effectiveness Ratio) and ICER (Incremental Cost Effectiveness Ratio) values are obtained. A drug is said to be cost-effective if the ACER value of a drug is smaller than that of other drugs. Meanwhile, the ICER value shows the additional costs to produce each unit of outcome (Kamri et al., 2021).

ACER Value can be calculated by formula

$$ACER\ (Rp) = \frac{Direct\ Medical\ Cost\ \ (Rp)}{Effectiveness\ of\ Therapy\ (mmHg)}$$

**Table. 6** ACER calculation results of hypertensive monotherapy in hypertensive patients with Type 2 DM

| Name of Drug | Average Direct Medical Cost (Rp) | Average Decrease in Systolic diastolic (mmHg) | Acer Value (Rp) | Number of Patients |
|---|---|---|---|---|
| Amlodipine | Rp3.527.107± 0,00 | 12,42 | Rp283.962 | 1 |
| Candesartan | Rp3.250.149 ± 0,00 | 6,50 | Rp500.023 | 1 |
| Furosemide | Rp4.208.495 ± Rp1.770.577 | 7,33 | Rp574.041 | 4 |

Description: : Highest ACER
: Lowest ACER

Based on this research, the most cost-effective hypertension monotherapy is amlodipine, with an ACER value of IDR 283,962. This is in line with other studies which show that amlodipine has a lower ACER value than other antihypertensive drugs. The results of this study can be used as a consideration in determining alternative treatments that can be used in hypertensive patients with type 2 DM. All monotherapy used in hypertensive patients with type 2 DM is compared with amlodipine which is the most cost-effective monotherapy (dominant option). The results of the cost-effectiveness relationship are as follows:

**Table 7.** Cost-effectiveness relationship of hypertension monotherapy in hypertensive patients with Type 2 DM

| | **Lower Costs** | **Same Cost** | **Higher Cost** |
|---|---|---|---|
| **Lower Effectiveness** | A (ICER calculation required) **Candesartan** | B (Dominatedi) | C (Dominated) **Furosemide** |
| **Same Effectiveness** | D (dominant) | E Balanced Position | F (Dominated) |
| **Higher Effectiveness** | G (Dominant) | H (Dominant) | I (ICER calculation required) |

**Description:** Amlodipine as comparison

Based on this study, amlodipine monotherapy is the most cost-effective treatment option for hypertensive patients with type 2 DM. Furosemide is not considered as an alternative therapy because it has lower effectiveness with higher costs than amlodipine in column C (dominated). while candesartan has lower effectiveness and lower costs than amlodipine in column A (ICER calculation required). The ICER value can be determined by calculating the difference in cost and effectiveness between alternative therapy and amlodipine.

$$\textbf{ICER} = \frac{(\text{total average } DML \text{ dominated options}) - (\text{total average } DML \ dominant \text{ options})}{(\text{the effectiveness of dominated options}) - (\text{effectiveness of the dominant option})}$$

Through this formula, the ICER value can be determined to determine the amount of additional costs required for every 1 mmHg reduction compared to amlodipine, which is the most dominant therapy. The results of calculating the ICER value from kandesartan monotherapy showed that the difference in the average direct medical costs was -Rp. 276,958, while the difference in the average effectiveness was -5.92 mmHg. Kandesartan can be an alternative therapy if you want to use hypertension monotherapy at a lower cost than amlodipine or if amlodipine therapy is not available (the dominant option).

Table 8. ACER calculation results of Combination Therapy in hypertensive patients with Type 2 DM

| Drug Code | Name of Drug | Direct Medical Cost (Rp) | Average Decrease in Systolic diastolic (mmHg) | ACER Value (Rp) | Number of Patient |
|---|---|---|---|---|---|
| 1 | Amlodipine + Candesartan | Rp2.309.914 ± Rp1.126.035 | 8,80 ± 1,00 | Rp262.626 | 2 |
| 2 | Amlodipine + Furosemide | Rp5 .276.708 ±Rp2.423.649 | 10,79 ± 6,09 | Rp488.832 | 9 |
| 3 | Candesartan + Furosemide | Rp3.023.481 ± Rp1.119.518 | 7,17 ± 4,02 | Rp483.437 | 3 |
| 4 | Furosemide + Spironolactone | Rp6.257.683 ± Rp6.285.810 | 12,52 ± 6,39 | Rp499.846 | 2 |
| 5 | Amlodipine + Candesartan + Furosemide | Rp8.509.447 ± 0,00 | 6,35 ± 0,00 | Rp1.340.529 | 1 |
| 6 | Amlodipine + Candesartan + Nicardipine | Rp4.476.460 ± 0,00 | 10,92 ± 0,00 | Rp410.057 | 1 |
| 7 | Amlodipine + Furosemide + Spironolactone | Rp14.176.391±0, 00 | 19,05 ± 0,00 | Rp744.028 | 1 |
| 8 | Amlodipine + Furosemide + Lisinopril | Rp6.953.825 ± 0,00 | 20,23 ± 0,00 | Rp343.738 | 1 |
| 9 | Amlodipine + Candesartan + Uresix + Klondin | Rp3.478.534 ± 0,00 | 12,89 ± 0,00 | Rp269.886 | 1 |
| 10 | Amlodipine + Klondin + Furosemide + Valsartan | Rp7.486.058 ± 0,00 | 17,76 ± 0,00 | Rp421.512 | 1 |
| 11 | Adalat Oros + Bisoprolol + Candesartan + Klondin + Furosemide | Rp13.586.634 ± 0,00 | 22,38± 0,00 | Rp607.088 | 1 |
| 12 | Amlodipine + Candesartan + Uretic + Nicardipine + Bisoprolol + Clonidine + Spironolactone | Rp7.311.809 ± 0,00 | 21,59 ± 0,00 | Rp338.608 | 1 |
| 13 | Furosemide + Amlodipine + Nicardipine + Lisinopril + Spironolactone | Rp29.668.230 ± 0,00 | 20,85 ± 0,00 | Rp1.422.936 | 1 |

Description: Compare to combination of amlodipine + candesartan hypertension therapy

: Highest direct medical cost

: Lowest direct medical cost

The results of the ACER values obtained were then analyzed for the cost-effectiveness relationship to facilitate decision making in determining alternative treatments that can be used in hypertensive patients with type 2 DM. All combinations of hypertension therapy used in hypertensive patients with type 2 DM were compared with candesartan + amlodipine which is combination therapy (dominant option). The results of the cost-effectiveness relationship are presented as the following table:

Table 9. Cost-effectiveness relationship of combination hypertension therapy in hypertensive patients with Type 2 DM

| | Lower Costs | Same Cost | Higher Cost |
|---|---|---|---|
| **Lower Effectiveness** | A (ICER calculation required) | B (Dominatedi) | C (Dominated) **3,5** |
| **Same Effectiveness** | D (dominant) | E Balanced Position | F (Dominated) |
| **Higher Effectiveness** | G (Dominant) | H (Dominant) | I (ICER calculation required) **2,4,6,7,8,9,10,11,12,13** |

Description: Code 1 (amlodipine + candesartan as a comparison); code 2 (amlodipine + Furosemide); code 3 (Candesartan + Furosemide); code 4 (Furosemide + Spironolactone); code 5 (Amlodipine + Candesartan + Furosemide); code 6 (Amlodipine+Candesartan + Nicardipinee); code 7 (Amlodipine + Furosemide + Spironolactone); code 8 (Amlopine + Furosemide + Lisinopril); code 9 (Amlodipine + Candesartan + Uresix + Injection + clonidine); code 10 (Amlodipine + Clondine + Furosemide + Valsartan); code 11 (Adalat Oros + Bisoprolol+ Candesartan, Klondin, Furosemide); code 12 (Amlodipine + Candesartan + Uretic + Nicardipinee + Spironolactone + Bisoprolol + Clondine); code 13 (Furosemide + Amlodipine + Spironolactone + Nicardipine + Lisinopril)

Combination therapy with codes 3 and 5 is not worth considering because of lower effectiveness and higher costs. Combination therapy with codes 2, 4, 6, 7, 8, 9, 10, 11, 12, and 13 has higher effectiveness, but the costs are also higher. These drugs can be considered as an alternative to obtain higher effectiveness even though it requires higher costs. Drugs that are included in group I require an ICER calculation to determine the amount of additional costs for each unit of additional benefit (average reduction in blood pressure of 1 mmHg). The ICER value is calculated by the difference in therapy costs and therapy effectiveness between the dominant drug (combination of amlodipine + candesartan) and the other drugs that are dominated.

Tabel 10. ICER Calculation result of combination therapy for Hypertension Patients with Type 2 DM

| Drug Code | Name of Drug | Direct Medical Cost (Rp) | Average Decrease in Systolic diastolic (mmHg) | ACER Value (Rp) |
|---|---|---|---|---|
| 9 | Amlodipine + Candesartan + Uresix + Clonidine | Rp1.168.620 | 4,09 | Rp285.486 |
| 12 | Amlodipine + Candesartan + Uretic + Nicardipine + Spironolactone + Bisoprolol + Clonidine | Rp5.001.895 | 12,8 | Rp390.825 |
| 8 | Amlodipine + Furosemide + Lisinopril | Rp4.643.911 | 11,43 | Rp406.308 |
| 9 | Amlodipine + Clonidine + Furosemide + Valsartan | Rp5.176.144 | 8,96 | Rp577.402 |

| | | | | |
|---|---|---|---|---|
| 11 | Adalat Oros + Bisoprolol + Candesartan + Clondine + Furosemide | Rp11.276.720 | 13,58 | Rp830.264 |
| 6 | Amlodipine + Candesartan + Nicardipine | Rp2.166.546 | 2,12 | Rp1.021.372 |
| 4 | Furosemide + Spironolactone | Rp3.947.769 | 3,72 | Rp1.060.152 |
| 7 | Amlodipine + Furosemide + Spironolactone | Rp11.866.477 | 10,26 | Rp1.156.789 |
| 2 | Amlodipine + Furosemide | Rp2.966.794 | 2 | Rp1.484.091 |
| 13 | Furosemide + Amlodipine + Spironolactone + Nicardipine + Lisinopril | Rp27.358.316 | 12,05 | Rp2.269.953 |

**Description:** Compare to combination of amlodipine + candesartan hypertension therapy
: Highest direct medical cost
: Lowest direct medical cost

Based on table 5.19, it can be seen that the lowest ICER value compared to amlodipine + candesartan is in the combination therapy for hypertension using amlodipine + candesartan + uresix + clondin (Rp. 285,486) while the highest is the use of furosemide + amlodipine + spironolactone + nicardipine + lisinopril (Rp. 2,269,953). A positive ICER value can be interpreted as the amount of costs required to replace the same outcome value, namely for every 1 mmHg decrease in mean blood pressure. The smaller the ICER value, the more potential it has to be used as an alternative therapy. Combination therapy with the lowest ICER value can be used as an alternative hypertension therapy in hypertensive patients with type 2 DM. This therapy has higher effectiveness even though it is accompanied by increased costs.

## CONCLUSION

The use profile of hypertension therapy in hospitalized hypertensive patients with type 2 diabetes mellitus at RSUD dr. Soehadi Prijonegoro Sragen indicates that combination therapy was employed more frequently (80.65%) than monotherapy (19.35%). The widely used monotherapy is furosemide (66.67%), while the most prevalent combination therapy is furosemide and amlodipine (36%). The most effective monotherapy was amlodipine with an effectiveness value of 12.42 mmHg, while combination therapy used Adalat oros® + candesartan + bisoprolol + furosemide + clonidine demonstrating an efficacy value of 22.38 mmHg. The most cost-effective monotherapy is amlodipine with an Acer value (Rp. 283,962) while the combination therapy of amlodipine + candesartan costs Rp262,626.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest

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