Trop J Nat Prod Res, February 2025; 9(2): 677 - 684 **ISSN 2616-0684 (Print)**
ISSN 2616-0692 (Electronic)

Tropical Journal of Natural Product Research

Available online at https://www.tjnpr.org

Original Research Article

Cost-Effectiveness Analysis of Antihypertensive Drugs in Hypertensive Patients with Diabetes Mellitus Comorbidity in Inpatient Patients of Bengkulu Province, Indonesia

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ARTICLE INFO

Article history:
Received 24 December 2024
Revised 31 December 2024
Accepted 15 January 2025
Published online 01 March 2025

ABSTRACT

In 2023, hypertensive inpatients with diabetes mellitus (DM) comorbidity were predominantly treated at Kaur Regional Hospital (KRH) and Harapan dan Doa Hospital (HDH) in Bengkulu Province, Indonesia. This study aimed to analyze the cost-effectiveness of inpatients o hypertension-DM therapy management strategies for social security administrators at KRH an HDH during 2022-2023. A cost-effectiveness analysis was conducted using retrospective medica records from January 2022 to December 2023. The drugs compared were amlodipine-captopri and bisoprolol-amlodipine. Additionally, KRH used candesartan-furosemide and HDH use amlodipine-candesartan as alternative treatments. The outcome parameter measured was a decreas in blood pressure. The analysis adopted the hospital perspective, focusing on direct cos components. The study included 112 and 118 patients from KRH and HDH, respectively, age between 25 and 59. The incremental cost-effectiveness ratio (ICER) at KRH in 2022 was IDI 5,159/mmHg for systolic blood pressure reduction and IDR 4,711/mmHg for diastolic bloo pressure reduction (comparing candesartan-furosemide with amlodipine-captopril). In 2023, th ICER was IDR 862,922/mmHg for systolic reduction and IDR 251,685/mmHg for diastoli reduction (comparing amlodipine-captopril with bisoprolol-amlodipine). At HDH in 2022, th ICER for systolic reduction was IDR 96,643/mmHg, and for diastolic reduction, it was IDI 2,967/mmHg (comparing amlodipine-captopril with bisoprolol-amlodipine). In 2023, the ICEI was IDR 339,000/mmHg for systolic reduction (comparing amlodipine-candesartan wit amlodipine-captopril) and IDR 37,474/mmHg for diastolic reduction (comparing amlodipine captopril with bisoprolol-amlodipine). In conclusion, amlodipine-captopril was more cost-effectiv than bisoprolol-amlodipine at KRH in 2022 and HDH in 2023. However, switching to amlodipine captopril required additional costs at KRH in 2023 and HDH in 2022.

Keywords: Pharmacoeconomic, Cost-effectiveness, Additional costs, Amlodipine-captopril.

Introduction

In 2018, the prevalence of hypertension in Bengkulu province was 28.1%, reflecting an increase compared to 2013.[1] According to 2023 data from the Health Office of Kaur District, hypertension cases at Kaur Regional Hospital (KRH) ranked first, while data from the Health Office of Bengkulu City ranked Harapan dan Doa Hospital (HDH) second. Among these cases, hypertension with diabetes mellitus (DM) comorbidity was the most common. The World Health Organization (WHO) identifies the primary risk factors for hypertension as tobacco use (37%), physical inactivity (23%), excessive salt intake (10%), and obesity (7%). WHO data from 2019 showed that hypertension caused 1,816,000 deaths.

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Citation: Tanjung R, Wardati Y, Widiyawati IE, Permana I, Ningsih CF, Julita EE, Saptarini MN. Cost-Effectiveness Analysis of Antihypertensive Drugs in Hypertensive Patients with Diabetes Mellitus Comorbidity in Inpatient Patients of Bengkulu Province, Indonesia. Trop J Nat Prod Res. 2025; 9(2): 677 – 684 https://doi.org/10.26538/tjnpr/v9i2.33

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These deaths were attributed to cardiovascular disease (38.4%), cardiovascular disease specifically linked to high systolic blood pressure (3.8%), and premature mortality from noncommunicable disease (1.4%).[2] Comorbidities, such as hypertension and DM, significantly impact patient outcomes by prolonging treatment times in general cases, increasing mortality rates, and decreasing recovery rates in critical patients. Hypertension and DM may be important factors affecting the clinical course and prognosis of both ordinary and critically ill patients.[3]

For patients aged 18 years and older with chronic kidney disease or DM, the treatment thresholds and blood pressure goals are the same as those for the general population under 60 years old. Specifically, the target blood pressure is a systolic threshold of 140 mmHg or a diastolic threshold of 90 mmHg. In the general population, including individuals with DM, the initial antihypertensive treatment should include a thiazide diuretic, calcium channel blocker, an angiotensin-converting enzyme inhibitor, or an angiotensin receptor blocker (ARB). Blood pressure should be monitored, and the treatment regimen adjusted until the target blood pressure is achieved.[4] The use of hypertension medications can be quite expensive, especially in cases where hypertension is accompanied by DM comorbidities. For patients covered by the Social Security Administrator for Health (Badan Penyelenggara Jaminan Sosial, BPJS), this often becomes a financial burden for both health service providers (hospitals) and the payers (BPJS). BPJS is a public agency that manages a health insurance program. The benefit of BPJS is that each participant is entitled to receive health insurance benefits in the form of individual health services including promotive, preventive, curative, and rehabilitative services. This also covers drug services and disposable medical

materials according to the medical needs required, irrespective of the amount of contributions paid to BPJS.[5]

To consider the cost aspect in particular, or the economy in general, and its effectiveness, it is necessary to conduct a pharmacoeconomic study.[6,7] The application of pharmacoeconomics involves the systematic evaluation of the costs and benefits associated with pharmaceutical interventions. This analysis is essential for understanding the long-term implications of these interventions for public health and the healthcare system.[8] Cost-effectiveness analysis (CEA) is an integral part of pharmacoeconomics. The relationship between the two lies in the shared goal of evaluating pharmaceutical interventions based on costs and health outcomes. Pharmacoeconomics provides the conceptual framework, while CEA provides the analytical tools for making evidence-based decisions in health systems.[6,9] Pharmacoeconomic studies have been conducted related to DM,[10] but studies regarding hypertension with DM comorbidity have never been done, especially in Bengkulu province, which has two hospitals, KRH and HDH. This study aimed to determine the cost-effectiveness analysis (CEA) as a strategy for managing therapy for BPJS inpatients with hypertension-DM comorbidity in KRH and HDH of Bengkulu Province during 2022-2023. The novelty of this study is that CEA is carried out on inpatients with hypertension-DM comorbidity, whereas generally, CEA is carried out on one disease only. Additionally, the study location in Bengkulu Province on Sumatra Island has not been widely explored, because most of the studies have been conducted on Java Island. This study helps hospitals achieve an optimal clinical balance, manage costs efficiently, and provide valuable insights for consideration when updating the hospital formulary.

Materials and Methods

Ethical clearance and the subject

This study was approved by the ethics commission of KRH (No. 445.01/282/RSUD-K/II/2024) and HDH (No. 224.01/161/RSHD/2024). This study was conducted according to an approved method. Medical records of inpatients with hypertension and DM comorbidities were collected from January 2022 to December 2023 at KRH and HDH in Bengkulu Province. The inclusion criteria were patients diagnosed with hypertension and DM comorbidity, aged from 25 to 60 years, who received amlodipine-captopril and bisoprolol-amlodipine, noting that candesartan-furosemide was used at KRH and amlodipine-candesartan at HDH. Patients with incomplete medical records were excluded.

Characteristics of the research subjects and outcome determination

The characteristics for selecting research subjects included age, gender, type of inpatient room, and length of stay (LOS). The outcome was determined by a decrease in systolic and diastolic blood pressure.

Determination of the perspective and cost components

The perspective used was healthcare, which included costs for hypertension and diabetes drugs, room, treatment, and laboratory and doctor's fees.

Pharmacoeconomic analysis

The cost of health interventions was measured in Indonesian rupiah (IDR) and the results of interventions in units or health indicators, both clinical and nonclinical (non-monetary). Data were used to calculate the cost-effectiveness ratio and make the cost-effectiveness table.[11]

Statistical analysis and sensitivity analysis

The results are presented as the mean ± SD. Data were analyzed statistically using SPSS statistics version 25.0 from IBM which reaseled in 2022,[12] and included the Kolmogorov–Smirnov test, followed by chi-square and one-way ANOVA.[13] Sensitivity analysis was conducted to determine the most influential factors on the ICER value by adjusting each cost and effectiveness parameter by ±25% (one-way sensitivity analysis). The results were illustrated in a tornado diagram.[14]

Results and Discussion

Table 1 shows that women were the most common in both KRH and HDH. Women experience more hypertension, which aligns with data from the Indonesian Central Statistics Agency and WHO.[1] This higher prevalence is attributed to hormonal factors, especially after menopause.[15] The length of stay (LOS) was mostly in the range of 1–5 days in both KRH and HDH, consistent with findings by Degefu et al.[16] These results were observed from the decrease in systolic or diastolic and the stabilization of blood pressure in patients.

In 2022, both KRH and HDH showed no differences in age, gender, and class type (in KRH), but there were differences in class type (in HDH) and LOS ($p < 0.05$). In 2023, both KRH and HDH showed no differences between age, gender (in HDH), and class type, but there were differences in gender (in KRH) and LOS ($p < 0.05$). These results showed that the most influential factor in this study was LOS. Since the study focused on adults, the drug options according to BPJS were consistent, with adjustments based on disease severity.

In this study, inpatients with hypertension and DM comorbidity were selected. The recommended first-line treatment included a combination of renin-angiotensin system inhibitors (ACEi) or angiotensin receptor blockers (ARB) combined with calcium channel blockers (CCB) or thiazide diuretics, as per the Indonesia Society of Hypertension (2019). Table 1 shows that drug 1 was a combination of ARB (candesartan) and diuretics (furosemide) in KRH, while in HDH, it was a combination of CCB (amlodipine) and ARB (candesartan). Drug 2 was a combination of CCB (amlodipine) and ACEi (captopril). Drug 3 was a combination of beta-1 adrenergic blockers (bisoprolol) and CCB (amlodipine). This third combination aligns with the management of hypertension in Indonesia.[17]

The drug combinations in both hospitals showed significant differences in cost-effectiveness (Table 2). This study aimed to determine the best drug selection with the most effective cost. Table 2 shows that all financial parameters showed significant differences ($p < 0.05$), except for laboratory costs at HDH and diastolic decrease at KRH. The decrease in systolic and diastolic blood pressure was influenced by the selection of hypertension and DM drugs. At KRH, there was no significant difference in 2022, but a significant difference was observed in 2023. At HDH, significant differences were observed in both 2022 and 2023.

The CEA study of inpatients with hypertension and DM comorbidities is highly urgent due to the increased risk of serious complications and significant health costs. This study yielded seven key results: First, reducing the risk of serious complications: patients with hypertension and DM have a high risk of cardiovascular complications (stroke, heart attack), kidney failure, retinopathy, and neuropathy. Cost-effective interventions can mitigate these risks. CEA helps determine the most effective and cost-effective treatment or multifactorial control strategy to reduce the disease burden on individuals and the health system, such as BPJS.[18,19] Second, reducing the high cost of care: treating these patients requires a combination of medications, intensive monitoring, and expensive complication management. CEA identifies interventions that provide maximum results at minimal cost, thereby reducing the financial burden on patients and the health system, including BPJS.[20,21] Third, simplifying clinical management complexity: managing these patients requires a multifactorial strategy, including controlling blood pressure, blood sugar, and lipids. An evidence-based approach is necessary to determine the best interventions. CEA ensures that clinical decision-making is based on cost-effectiveness, helping clinicians select the most appropriate therapy.[6] Fourth, prioritizing resource allocation: with limited health budgets, it is important to prioritize interventions that have the greatest impact on population health. CEA helps hospitals and health systems, such as BPJS, prioritize investments in the most cost-effective prevention, treatment, or technology programs.[22]

Fifth, improving patient quality of life: patients often experience decreased quality of life due to chronic complications. Cost-effective interventions can reduce morbidity and mortality. CEA is used to determine management programs that efficiently improve patient quality of life.[9] Sixth, supporting evidence-based policy: CEA provides valid data to support decisions in adopting health policies, such as the

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

Table 1: Characteristics of the Research Subjects

Characteristics	2022										2023									
	Drug 1		Drug 2		Drug 3		Total		p-value		Drug 1		Drug 2		Drug 3		Total		p-value	
	KRH	HDH	KRH	HDH	KRH	HDH	KRH	HDH	KRH	HDH	KRH	HDH	KRH	HDH	KRH	HDH	KRH	HDH	KRH	HDH
n	23	24	21	24	19	17	63	65			12	25	18	20	19	18	49	63		
Age																				
25–45	12 (52%)	19 (79%)	8 (38%)	10 (42%)	6 (32%)	13 (77%)	26 (41%)	42(65 %)	0.124	0.201	9 (75%)	13 (52%)	10 (56%)	10 (50%)	11 (58%)	9 (43%)	30 (61%)	32 (51%)	0.106	0.834
46–59	11 (48%)	5 (21%)	13 (62%)	14 (58%)	13 (68%)	4 (23%)	37 (59%)	23 (35%)			3 (25%)	12 (48%)	8 (44%)	10 (50%)	8 (42%)	9 (57%)	19 (39%)	31 (49%)		
Gender																				
Man	0 (0%)	13 (47%)	14 (67%)	11(53 %)	5 (26%)	6 (35%)	19 (30%)	30 (46%)	0.249	0.488	0 (0%)	9 (36%)	7 (39 %)	8 (40%)	7 (37 %)	8 (44%)	14 (29%)	25(40 %)	0.041	0.073
Woman	23 (100%)	11 (53%)	7 (33%)	13 (47%)	14 (74%)	11 (65%)	44 (70%)	35 (54%)			12 (100%)	16 (64%)	11 (61%)	12 (60%)	12 (63%)	10 (56%)	35 (71%)	38 (60%)		
Type of inpatient room																				
Class II	9 (39%)	12 (50%)	6 (29%)	6 (25 %)	7 (37%)	7 (35%)	22 (35%)	15 (31%)	0.007	0.175	5 (42%)	4 (16%)	5 (28%)	8 (40%)	8 (42%)	8 (35%)	18 (37%)	20 (32%)	0.099	0.103
Class III	14 (61%)	12 (50%)	15 (71 %)	18 (75%)	12 (63%)	10 (65%)	41 (65%)	48 (69%)			7 (58%)	21 (84%)	13 (72%)	12 (60%)	11 (58%)	10 (65%)	31 (63%)	43 (68%)		
LOS (days)																				
1–5	23 (100%)	19 (100%)	21 (100%)	21 (100%)	19 (100%)	17 (100%)	63 (100%)	57 (100%)	0.000	0.000	12 (100%)	25 (100%)	18 (100%)	20 (100%)	19 (100%)	18 (100%)	49 (100%)	63 (100%)	0.002	0.001
6–10	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)			0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)		

Drug 1: candesartan-furosemide (KRH), amlodipine-candesartan (HDH), drug 2: amlodipine-captopril, drug 3: bisoprolol-amlodipine

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

Table 2: Cost and Effectiveness Parameters

Parameter	Drug 1				Drug 2				Drug 3				p-value			
	KRH		HDH		KRH		HDH		KRH		HDH		KRH		HDH	
	2022	2023	2022	2023	2022	2023	2022	2023	2022	2023	2022	2023	2022	2023	2022	2023
No.	23	12	24	25	21	18	24	20	19	19	17	18				
Hypertensive drug	948,580	821,689	42,632	39,000	1,035,756	1,012,338	37,381	39,750	1,332,410	954,986	42,353	41,786	0.007	0.013	0.001	0.001
DM drug	84,406	76,444	34,737	37,000	77,206	72,296	36,429	36,750	77,474	99,930	37,647	33,929	0.002	0.011	0.001	0.001
Room	782,609	716,667	805,556	882,000	723,810	677,778	821,428	850,000	726,316	915,790	882,353	803,571	0.001	0.008	0.001	0.001
Physician	100,000	100,000	132,105	132,000	100,000	100,000	140,000	132,000	100,000	100,000	122,941	134,286	0.001	0.001	0.001	0.001
Nurse	476,609	436,450	141,316	126,000	440,800	412,767	127,143	126,000	442,326	557,716	114,118	126,429	0.002	0.008	0.001	0.001
Laboratory	85,000	85,000	103,947	118,400	85,000	85,000	121,905	116,000	85,000	85,000	103,824	109,643	0.001	0.001	0.179	0.179
Total	2,477,202	2,236,250	1,217,895	1,334,400	2,462,571	2,360,178	1,284,286	1,300,500	2,763,526	2,713,421	1,303,235	1,249,643	0.001	0.003	0.005	0.001
Systole decrease	25.2	22.5	23.68	24.8	22.38	22.22	23.33	24.5	20	22.63	23.53	25.71	0.010	0.002	0.004	0.005
Diastole decrease	7.39	5	12.11	13.6	4.29	3.33	7.14	13.5	3.16	4.74	13.53	12.14	0.184	0.059	0.001	0.004

Drug 1: candesartan-furosemide (KRH), amlodipine-candesartan (HDH), drug 2: amlodipine-captopril, drug 3: bisoprolol-amlodipine

use of new technologies or patient education programs.[9] Seventh, facing the chronic disease epidemic: CEA helps design long-term strategies to reduce the impact of this epidemic effectively and efficiently.[23] In conclusion, conducting CEA in patients with hypertension and DM comorbidity is crucial for ensuring efficient resource allocation, reducing care costs, improving clinical outcomes, and supporting evidence-based health policy-making. This approach aids in better managing populations at high risk of serious complications.

Table 3 shows that the diastolic average cost-effectiveness ratio (ACER) was higher than the systolic ACER in both hospitals. The ACER in KRH was higher than in HDH, and both systolic and diastolic decreased in 2022 and 2023. Replacing drug 2 (amlodipine-captopril) with drug 3 (bisoprolol-amlodipine) required additional costs in both KRH and HDH. This additional cost in KRH was mainly in 2023, while in HDH, it was observed in all outcomes (decrease in systolic and diastolic blood pressure), except in 2022, where it was only in diastolic. The most common side effects with amlodipine were flushing and leg edema. The combination of amlodipine and captopril was well tolerated, and no patients discontinued therapy. No significant treatment-related effects on biochemical and hematological parameters were noted.[24] The combination of bisoprolol and amlodipine was reasonable for lowering blood pressure, but given the concerns about the use of beta-blockers in hypertension, it should be used primarily in patients with coronary artery disease or heart failure with a reduced ejection fraction of 4.5 (or other comorbidities for which beta-blockers are beneficial), in patients younger than 60 years, and in patients who have problems with other classes of antihypertensive drugs. The availability of a fixed-dose combination is likely to improve patient compliance.[25]

ICER calculations provide significant benefits in decision-making. ICER is used to compare the incremental cost of a new intervention with its incremental effectiveness compared to the existing standard. It provides quantitative data that allows policymakers to evaluate the economic rationality of an intervention based on CEA results, determine whether the incremental cost of an intervention aligns with the willingness-to-pay threshold, and conduct sensitivity analysis to explore how results change with parameter variations, thereby understanding uncertainty in cost and effectiveness estimates.[6,9]

Table 4 showed that ICER at KRH in 2022 with systolic at IDR 5,159/mmHg and diastolic of IDR 4,711/mmHg (comparing candesartan-furosemide with amlodipine-captopril).

Table 3: ACER value

IDR		Drug 1				Drug 2				Drug 3			
		KRH		HDH		KRH		HDH		KRH		HDH	
		2022	2023	2022	2023	2022	2023	2022	2023	2022	2023	2022	2023
ACER	Systole	98,234	110,030	53,082	53,807	110,030	106,208	51,422	55,041	138,176	119,895	55,387	48,597
	Diastole	335,151	106,208	96,333	98,118	574,600	119,895	100,608	179,800	875,117	572,833	96,326	102,912

Drug 1: candesartan-furosemide (KRH), amlodipine-candesartan (HDH), drug 2: amlodipine-captopril, drug 3: bisoprolol-amlodipine

Table 4: ICER Value

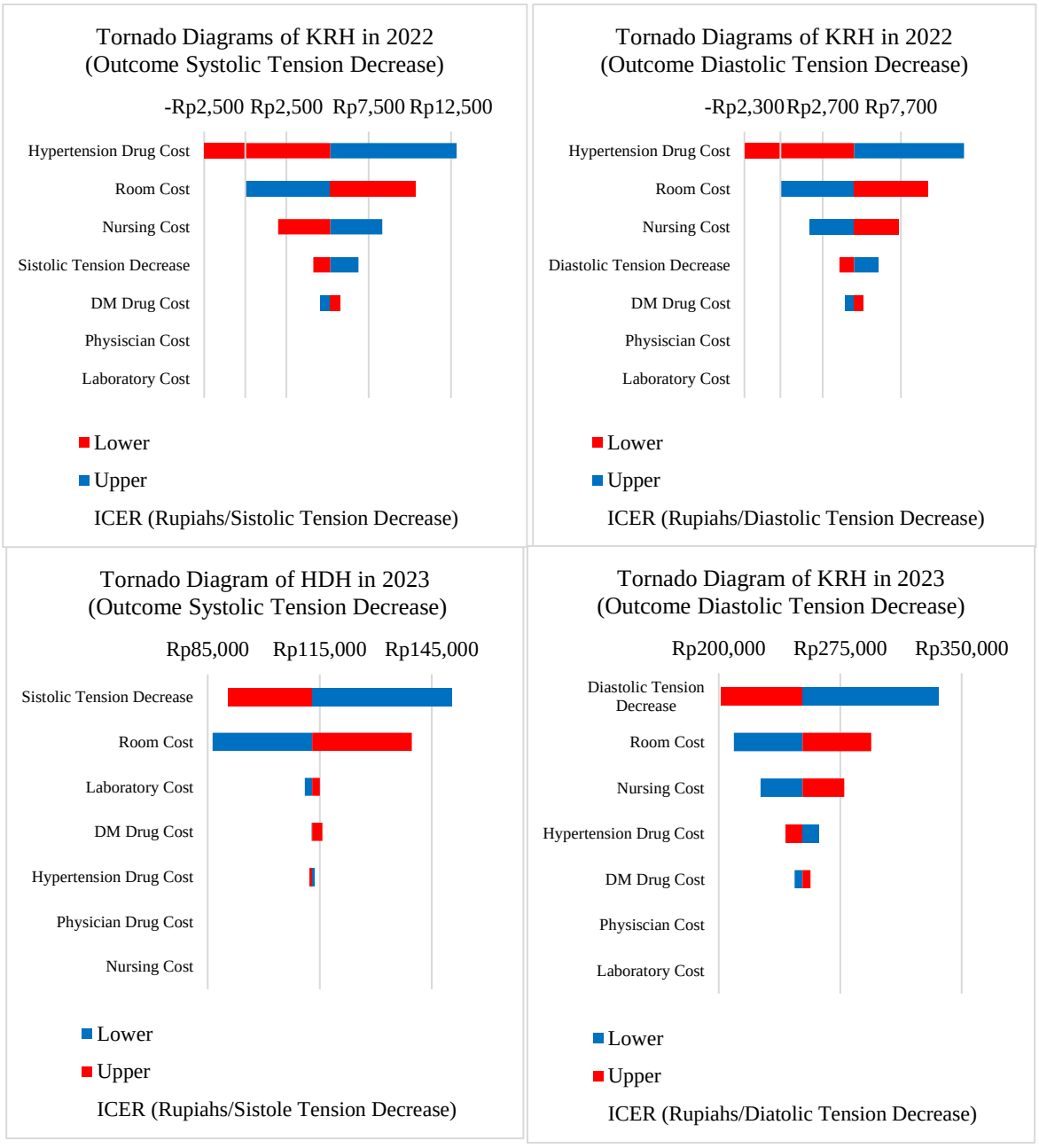
ICER value (IDR)	KRH				HDH			
	2022		2023		2022		2023	
	Drug name	ICER value	Drug name	ICER value	Drug name	ICER value	Drug name	ICER value
Systole	1–2	5,159	1–3	862,922	2–3	96,643	1–2	113,000
			2–3	3,626,500				
Diastole	1–2	4,711	2–3	251,685	2–3	2,967	1–2	339,000
					1–3	59,924	1–3	58,167
							2–3	37,474

Drug 1: candesartan-furosemide (KRH), amlodipine-candesartan (HDH), drug 2: amlodipine-captopril, drug 3: bisoprolol-amlodipine

In 2023, the ICER was systolic at IDR 862,922/mmHg and diastolic at IDR 251,685/mmHg (comparing amlodipine-captopril with bisoprolol-amlodipine). At HDH, the ICER in 2022 was systolic at IDR 96,643/mmHg and diastolic at IDR 2,967/mmHg (comparing amlodipine-captopril with bisoprolol-amlodipine). In 2023, the ICER was systolic at IDR 339,000/mmHg (amlodipine-candesartan with amlodipine-captopril) and diastolic at IDR 37,474/mmHg (amlodipine-captopril with bisoprolol-amlodipine). This indicates that replacing bisoprolol-amlodipine with amlodipine-captopril required additional costs in both KRH and HDH, with the most influential factor on ICER value being the outcome (decrease in systolic or diastolic blood pressure). Tornado diagrams are useful for identifying which parameters have the greatest impact on the results of an analysis. They visualize uncertainty by showing the range of results when parameters vary within predetermined limits, highlight areas that require more accurate data or greater attention in the decision-making process, and aid in the design of further studies by indicating where additional investment in data collection or research may provide the greatest benefits.[26] In Figure 1 of the tornado diagrams, in 2022, at KRH, the most influential factor was the cost of hypertension drugs, while at HDH, it was the cost of the room. In 2023, the influential factor was the outcome in both KRH and HDH. The tornado diagram was made only for those with the lowest ICER value. When comparing amlodipine-captopril with bisoprolol-amlodipine, the influential factor was similar in both KRH and HDH in 2023, specifically the outcome (decrease in diastolic blood pressure).

The policy implications of CEA results for inpatients of hypertension with DM comorbidity often focus on interventions that can reduce the

risk of long-term complications, reduce treatment costs, and improve the quality of life of patients. This study suggests six policies that hospitals can implement. First, use of cost-effective antihypertensive drugs: hospitals should prioritize the use of certain classes of drugs, such as ACEi or ARBs, which have been proven cost-effective for hypertensive patients with DM. These drugs can reduce the risk of cardiovascular complications and diabetic nephropathy. For example, ACEi is more cost-effective than calcium channel blockers (CCBs) in hypertensive patients with DM in preventing end-stage renal disease.[27,28] Second, multifactorial control to reduce the risk of complications: hospitals should control blood pressure, blood sugar, and lipid levels simultaneously. This strategy is more cost-effective than just focusing on one risk factor and can reduce the risk of microvascular and macrovascular complications.[18,19] Third, early detection and prevention of complications by conducting routine screening programs for complications such as nephropathy, retinopathy, and neuropathy in hypertensive-DM patients. Early detection is more cost-effective than treating advanced complications. For example, annual screening for diabetic nephropathy is more cost-effective than waiting for symptoms to appear.[20]



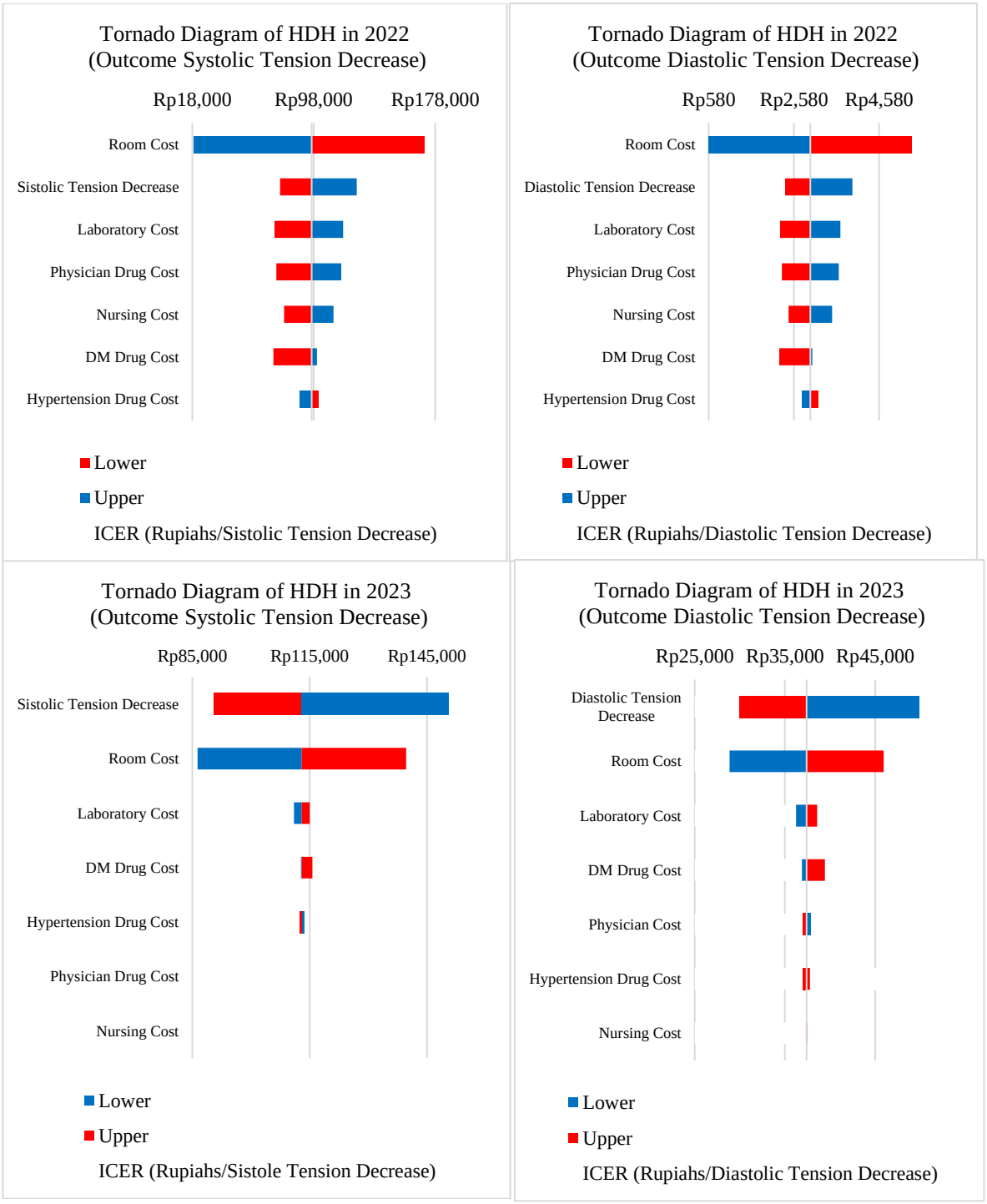


Figure 1: Tornado Diagrams

Fourth, a multidisciplinary team-based management program that includes doctors, diabetes educators, nutritionists, and pharmacists. This program has been shown to be more cost-effective than standard care, significantly decreasing in blood pressure and HbA1c.[21] Fifth, implementing an intensive lifestyle education program (low-sodium diet, regular physical activity, weight loss). These programs are more cost-effective in preventing cardiovascular complications than a single pharmacological treatment.[29] Sixth, the use of telemedicine technology for remote management to monitor blood pressure and blood sugar levels periodically. Telemedicine has been shown to be cost-effective in increasing patient compliance. Verhoeven et al. showed that telemedicine reduces outpatient and inpatient costs and improves blood pressure and blood sugar control.[30] The future prospects for CEA in patients with hypertension and DM comorbidity are very promising, especially with the development of health technology, personalized treatment, and integration of more complex models. CEA will become an increasingly important tool to inform efficient and evidence-based clinical decision-making and health policy.

Conclusion

In KRH in 2022 and HDH in 2023, amlodipine-captopril was found to be more cost-effective than bisoprolol-amlodipine. However, additional costs were required to switch to amlodipine-captopril in KRH in 2023 and in HDH in 2022. The future prospects of the CEA study are to inform efficient and evidence-based clinical decision-making and

health policy. Policies for patients with hypertension and DM comorbidity should prioritize a multifactorial approach, the use of cost-effective drugs, and lifestyle interventions.

Conflict of Interests

The authors declare no conflict of interests.

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