

Cost-effectiveness analysis of metformin-based combination therapy in type 2 diabetes mellitus inadequately controlled with metformin

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ABSTRACT

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This research aims to analyze the cost-effectiveness of type 2 diabetes mellitus (T2DM) therapy regimens based on metformin-dual therapy. This was a retrospective cohort study using medical records and billing data from T2DM patients. Study samples were chosen using consecutive sampling, including those aged 18 or older with type 2 diabetes with metformin combined with sulfonylurea, acarbose, or dipeptidyl peptidase-4 inhibitor (DPP4i); those with incomplete medical or financial records were excluded. The incremental cost-effective ratio (ICER) analysis showed that the metformin-sulfonylurea regimen was dominant, offering lower costs and greater effectiveness. Meanwhile, metformin-DPP4i demonstrated higher effectiveness than metformin-acarbose (ICER: IDR. 24,055,460 per unit increase in the proportion of controlled patients) and may serve as a therapeutic alternative.

Keywords: diabetes mellitus; metformin; cost-effectiveness analysis; pharmacoeconomics; oral-hypoglycemic

1. INTRODUCTION

Diabetes mellitus is a growing global health threat, affecting an estimated 529 million people in 2021, with a prevalence of 6.1% among adults (GBD 2021 Diabetes Collaborators, 2023). This condition represents a major

public health challenge due to its increasing incidence, chronic nature, and strong association with cardiovascular disease, kidney failure, blindness, and premature mortality. The World Health Organization (WHO) predicts a substantial rise in the number of individuals with type 2 diabetes mellitus (T2DM) in the coming decades, driven by

population aging, urbanization, lifestyles, and unhealthy dietary patterns. Indonesia is projected to experience a particularly sharp increase, with an estimated 21.3 million T2DM patients by 2030, placing the country sixth globally in terms of diabetes burden (Perkumpulan Endokrinologi Indonesia, 2021).

Pathophysiological, T2DM is characterized by a combination of pancreatic β -cell dysfunction and insulin resistance in peripheral tissues, leading to chronic hyperglycemia (Hardianto, 2021; Ke et al., 2022). Progressive β -cell failure reduces insulin secretion over time, while insulin resistance in muscle, liver, and adipose tissue impairs glucose uptake and utilization. These mechanisms not only complicate glycemic control but also contribute to the development of long-term microvascular and macrovascular complications, thereby increasing healthcare utilization and economic burden.

Metformin monotherapy is widely recommended as the first-line pharmacological treatment for type 2 diabetes mellitus due to its proven efficacy, safety profile, low risk of hypoglycemia, and affordability. However, as T2DM is a progressive disease, glycemic control often deteriorates over time, and a substantial proportion of patients fail to achieve target blood glucose levels with metformin monotherapy alone. In such cases, combination dual therapy with additional oral hypoglycemic agents (OHAs) is required to improve glycemic control through complementary mechanisms of action.

In Indonesia, the dual-combination of metformin with sulfonylureas, particularly glimepiride and glibenclamide, is among the most commonly prescribed second-line therapies and has demonstrated good effectiveness in controlling blood glucose levels in routine clinical practice (Wulandari et al., 2021). Sulfonylureas enhance insulin secretion from pancreatic β -cells, thereby providing a rapid and potent glucose-lowering effect when added to metformin. Another frequently used combination involves metformin and acarbose, especially in populations with high carbohydrate-based diets, as acarbose delays intestinal carbohydrate absorption and reduces postprandial glucose excursions. However, several studies have reported that metformin–acarbose combinations may be less effective in lowering glycated hemoglobin (HbA1c) levels compared to metformin–sulfonylurea regimens, although they are associated with a lower risk of hypoglycemia (Du et al., 2020; Ono et al., 2023).

Diabetes treatment incurs a substantial economic burden on healthcare systems, patients, and society, with medication costs constituting the largest proportion of direct medical expenditures. This high cost is primarily driven by the chronic nature of the disease, the need for lifelong pharmacotherapy, and the frequent presence of diabetes-related complications that require additional medical interventions. In Indonesia, the annual direct medical costs for patients with T2DM range from approximately US\$421 to US\$930, depending on the presence and severity of complications, highlighting the significant financial burden associated with disease progression (Hidayat et al., 2022).

Given these economic challenges, selecting cost-effective pharmacological regimens is crucial to optimize healthcare resource allocation, particularly in low- and middle-income countries. Several studies have demonstrated that metformin-based dual combination therapy with sulfonylureas, such as glimepiride, offers a

favorable balance between clinical effectiveness and treatment cost when compared to alternative regimens, including combinations with dipeptidyl peptidase-4 inhibitors (DPP4i) (Laelasari et al., 2017; Tandon et al., 2019). Sulfonylureas remain widely used due to their strong glucose-lowering efficacy, extensive clinical experience, and relatively low acquisition cost.

Specifically, the metformin–glimepiride combination has been reported to provide superior cost-effectiveness outcomes, with an incremental cost-effectiveness ratio (ICER) of Indonesian Rupiah (IDR) 19,883 per mg/dL reduction in blood glucose, indicating a lower cost per unit of therapeutic benefit compared to other treatment options (Yusmaniar et al., 2022). In light of the growing prevalence of T2DM and the increasing pressure on healthcare budgets, this research aims to determine the cost-effectiveness of metformin-based dual combination therapy regimens in patients with T2DM, thereby providing evidence to support rational drug selection and efficient resource utilization in clinical practice.

2. MATERIALS AND METHODS

2.1 Study design

This study employed a pharmacoeconomic evaluation using the cost-effectiveness analysis (CEA) method from a healthcare perspective. Data were collected retrospectively by reviewing medical records and patient billing data for individuals diagnosed with T2DM receiving metformin-based dual combination therapy. The study was conducted in four hospitals in Bali and Yogyakarta, Indonesia, which serve as an initial representation of the Indonesian setting.

The study population consisted of patients who were inadequately treated with metformin monotherapy. Due to the limited availability of clinical data in the hospitals, fasting blood glucose (FBG) was used as the primary outcome. Following HTA guidance documents which allow for the use of surrogate endpoints when final clinical outcomes are unavailable, FBG was selected as a validated proxy for glycemic control in this study. Also, the FBG has been reported to be significantly positively correlated with HbA1c (Ketema & Kibret, 2015; Hasanah & Ikawati, 2021; Sari et al., 2024). The inadequately metformin was determined through documented clinical actions and refers to patient who had previously used metformin and added a second OHA after failing to achieve therapy target (FBG at < 130 mg/dL) (Ministry of Health of the Republic of Indonesia, 2020; Perkumpulan Endokrinologi Indonesia, 2021).

The study utilized a 4-month period, aligning with the *Perkumpulan Endokrinologi Indonesia* guidelines, which recommend a minimum evaluation period of 12 weeks (3 months). The 4-month period followed the hospital's monthly clinical cycle. The first day was the date of the initial prescription, while the last day was the final clinical visit or laboratory test within the fourth month. This approach accounts for real-world scheduling variations while ensuring that the data accurately represents the completion of a 4-month therapy phase.

This economic evaluation was conducted and reported in accordance with the Consolidated Health Economics Evaluation Reporting Standards (CHEERS) 2022 guidelines. The completed CHEERS checklist is provided in the Supplementary file.

2.2 Study samples

Samples were selected using a consecutive sampling. The inclusion criteria were 1) patients aged ≥ 18 years diagnosed with T2DM (ICD-10 code E11); and 2) patients with inadequate glycemic control on metformin monotherapy, who received an additional second-line OHA. Patients were excluded if they had incomplete medical or financial records. These were defined as those lacking essential data, including patient demographics (name, gender, and age), complete clinical data (height, weight, drug name, dosage, and total quantity dispensed), and FBG measurements at baseline and after the 4-month follow-up period. All patients received therapy for 4 months. The interventions in this study included metformin+acarbose and metformin+DPP4i, which represent newer therapeutic regimens. These were compared against metformin+sulfonylurea, the established standard of care (usual therapy) in the study setting. The clinical outcome was defined as the proportion of patients achieving the glycemic target (FBG < 130 mg/dL) within a 4-month time horizon.

2.3 Data collection

Data collection began by screening medical records of patients diagnosed with T2DM (ICD-10 code E11). Samples were then selected based on predefined inclusion and exclusion criteria. Cost data were retrospectively extracted from the hospital's electronic billing system. The study used hospital billing charges as proxies for direct medical costs, as reflect the monetary value assigned to healthcare services and resources utilized, including physician consultations, antidiabetic medications, other medications, and laboratory fees during the 4-month therapy period. No cost-to-charge ratio adjustment was applied. To account for inflation, all costs were adjusted to 2023 values using the Indonesian consumer price index (CPI) for the health sector (Bank Indonesia, n.d.). The primary outcome was FBG levels at baseline and at 4 months.

2.4 Data analysis

Data were analyzed statistically using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA), with results considered significant if the p -value was less than 0.05. Bivariate analysis determined differences among the independent variables, dependent variables (effectiveness and cost), and the confounding variables. Variables with a p -value < 0.25 in the bivariate analysis were included in the subsequent logistic regression model. Direct medical costs across therapy regimens were compared using the Kruskal-Wallis test. If a p -value < 0.05 was observed, a post-hoc Mann-Whitney test was performed to examine the relationship between therapy regimens and components of direct medical cost. Confounding variables were also analyzed with the Mann-Whitney test.

Before calculating the ICER value, multivariate adjustments were performed for both cost and effectiveness to ensure a robust and unbiased cost-effectiveness analysis. By utilizing the estimated marginal means from our generalized linear model, significant baseline imbalances in age, BMI, and Charlson comorbidity index (CCI) were controlled. This dual adjustment ensured that the ICER reflected the true incremental value of the therapy regimens, independent of patient-level confounders.

ICER was calculated as the difference in estimate marginal means in cost divided by the difference of estimate marginal means for effectiveness between the two treatment regimens. Effectiveness was defined as patients achieving the glycemic target (FBG < 130 mg/dL) at the end of the 4-month follow-up period. Effectiveness was evaluated as a proportion; thus, the ICER represents the incremental cost required to achieve therapeutic success in one additional patient. A one-way sensitivity analysis (OSA) was conducted to assess the robustness of the results. Total direct costs and effectiveness were varied independently using the 95% of confident interval in each regimen.

2.5 Ethics

This study was reviewed and approved by the Ethics Committee of the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, under ethical clearance number KE/FK/1435/EC/2024. All procedures conducted in this study complied with the ethical standards of the institutional research committee and adhered to the principles of the Declaration of Helsinki. Patient confidentiality and data privacy were strictly maintained by anonymizing all personal identifiers during data collection and analysis.

3. RESULTS AND DISCUSSION

3.1 Patients characteristics

The study was conducted at four hospitals located in Bali and Yogyakarta, Indonesia. A total of 113 patients met the initial inclusion criteria and were included for baseline characteristic analysis. However, for the cost-effectiveness analysis, the sample was narrowed to 88 patients who had FBG data, which ensured a standardized evaluation of the primary clinical outcome (FBG < 130 mg/dL). As shown in Table 1, the majority of patients were female, aged over 60 years, had a body mass index (BMI) of less than 25 kg/m^2 , a CCI score greater than 2, and were receiving medications other than those for diabetes mellitus.

Diabetes mellitus poses not only a health threat but also a significant global economic burden. Therefore, a comprehensive approach to therapeutic management is essential to reduce this burden, particularly through rational drug use. The wide range of possible drug combinations has prompted researchers to evaluate the cost-effectiveness of metformin-based oral hypoglycemic agent (OHA) therapy in patients who have failed metformin monotherapy. In addition to assessing cost-effectiveness, this study also examines how patient characteristics affect therapeutic effectiveness and direct medical costs.

Regarding gender, men and women have an equal probability of developing T2DM. However, in this study, a higher proportion of female patients (56%) were diagnosed with T2D. This finding is supported by Ciarambino et al. (2022) and Kautzky-Willer et al. (2023), who reported that the prevalence of T2DM varies according to reproductive life stages, with an increased incidence in women post-menopause. This phase is associated with a decline in estrogen levels, contributing to the development of organs and tissues, while increasing glucose sensitivity in key diabetes-related organs.

Significant differences were observed in therapy regimen selection. Regardless of gender and age group, patients were

most frequently prescribed the metformin-sulfonylurea combination. This combination is the most commonly prescribed in Africa and Asia due to its favorable safety profile, efficacy, and affordability (Kalra et al., 2020; Hougen et al., 2021). Clinical characteristics and BMI also showed significant associations with therapy regimen selection. Similar to gender

and age, the preference for metformin-sulfonylurea remained dominant over other regimens. Several T2DM management guidelines recommend sulfonylureas over further titration of metformin beyond its half-maximal dose, citing better safety, glucose-lowering efficacy, and tolerability (Kalra et al., 2020; Mohan et al., 2022).

Table 1. Patients' characteristics

Characteristics	Therapy regimens			Total (%)	p-value
	Met+Sul	Met+Aca	Met+DPP4i		
Gender					
Male	34	11	16	61(46)	0.033*
Female	45	20	7	72(54)	
Age					
< 60	17	2	14	33(25)	0.000*
≥ 60	62	29	9	100(75)	
BMI					
< 25	51	12	16	79(59)	0.025*
≥ 25	28	19	7	54(41)	
CCI					
< 2	16	1	8	25(19)	0.012*
≥ 2	63	30	15	108(81)	
Other drugs used					
Yes	44	16	9	69(52)	0.375
No	35	15	14	64(48)	

Note: Met+Sul = metformin and sulfonylurea; Met+Aca = metformin and acarbose; Met+DPP4i = metformin and dipeptidyl peptidase-4 inhibitor; BMI = body mass index; CCI = Charlson comorbidity index; *indicates significant effect using chi-square test (p -value < 0.05)

3.2 Effectiveness

The effectiveness of therapy was assessed based on patients' FBG levels reaching < 130 mg/dL; patients meeting this criterion were considered to have achieved the therapeutic target. Based on Table 2, only the therapy regimen and BMI showed a statistically significant difference in therapeutic effectiveness (p -value < 0.05).

The combination of metformin and sulfonylurea demonstrated the highest target achievement rate at 57.89%, followed by metformin and DPP4i at 52.63%, and metformin and acarbose at 29.03%. The BMI variable indicated that patients with a BMI < 25 had a higher rate of achieving therapeutic targets compared to those with a BMI ≥ 25 kg/m² (58% and 31.58%, respectively).

Table 2. Therapy effectiveness

Variables	Effectiveness		p-value
	Achieved	Not achieved	
Therapy regimens			
Met+Sul	22	16	0.048*
Met+Aca	9	22	
Met+DPP4i	10	9	
Sex			
Male	21	21	0.669
Female	20	26	
Age			
< 60	13	8	0.135
≥ 60	28	39	
BMI			
< 25	29	21	0.018*
≥ 25	12	26	
CCI			
< 2	7	7	0.780
≥ 2	34	40	
Other drugs used			
Yes	23	28	0.830
No	18	19	

Note: *indicating significant effect using chi-square test (p -value < 0.05)

The American Diabetes Association does not prioritize any specific medication and recommends that physicians select treatment based on efficacy, risk of hypoglycemia, effects on body weight, side effects, and cost. In this study, based on therapeutic effectiveness, the combination of metformin and sulfonylurea showed the highest achievement in FBG target, followed by metformin–DPP4i and metformin–acarbose. Research by Moon et al. (2017) reported that metformin-based combination therapy was more effective in reducing HbA1c compared to metformin–DPP4i during the first three months of use; however, the risk of hypoglycemia and weight gain was lower in patients receiving the metformin–DPP4i combination. Meanwhile, the combination of metformin and acarbose showed lower effectiveness in reducing postprandial blood glucose (GDS) compared to metformin–sulfonylurea (Masiani et al., 2024).

Differences in BMI were found to significantly influence therapeutic target achievement. Patients with a BMI < 25 kg/m² were more likely to achieve the therapeutic target compared to those with a BMI ≥ 25 kg/m². Previous studies have demonstrated a correlation between elevated BMI and poor glycemic control, which is primarily attributed to increased visceral fat that contributes to insulin resistance (Mun-Vitcu et al., 2017; Bobby & Latha, 2018; Hara et al., 2024).

Further analysis was conducted using simple logistic regression (Table 3). The logistic regression results indicated BMI had a significant effect on therapeutic effectiveness. The obtained odds ratio was 0.334 (95% CI: 0.138–0.810). Higher BMI levels significantly reduced the probability of reaching therapy targets. Each unit increase in BMI correlated with a 66.6% reduction in the odds of treatment success. Concomitant medications did not significantly influence therapeutic effectiveness in this study. The variation of concomitants in T2DM treatment was a potential limitation that may have influenced the

study outcomes. As demonstrated by Boussageon et al. (2013) in their systematic review of type 2 diabetes trials, failure to account for differences in concomitant factors can lead to an overestimation or underestimation of the treatment effectiveness. In our study, while differences existed, we attempted to mitigate this by generalized linear regression for statistical adjustment.

Table 3. Simple logistic regression of BMI to effectiveness

Variable	sig.	Exp(B)	95% CI for Exp(B)	
			Lower	Upper
BMI	0.015	0.334	0.138	0.810
Constant	0.027	2.167		

Note: sig = signification; Exp(B) = Odd ratio; CI = confidence interval

3.3 Direct medical-cost analysis

The components of medical costs were categorized into physician consultation fees, laboratory costs, diabetes medication costs, and other medication costs (Table 4). The highest expenditure was observed in the category of other medications, amounting to IDR 46,166,250 (31%), with an average cost of IDR 347,114 ± 422,478. In contrast, the lowest expenditure was found in laboratory costs, totaling IDR 3,745,414 (14%), with an average cost of IDR 281,610 ± 369,817.

Based on the direct medical cost analysis, it was found that the variables therapy regimen, age, CCI, and BMI showed significant differences (*p*-value < 0.05) (Table 5). A post hoc Mann–Whitney test (Table 6) was conducted for the therapy regimen variable, revealing significant differences in total costs between the metformin–sulfonylurea group and both the metformin–acarbose and metformin–DPP4i. The metformin–sulfonylurea regimen had the lowest total cost, averaging IDR 866,410 ± 476,002.

Table 4. Components of direct-medical cost

Descriptive	Components (IDR)				
	Doctor consultation	Laboratory test	Diabetes medicines	Other medicines	Total
Mean	338,951	281,610	166,705	347,114	1,120,487
Median	145,220	173,840	114,272	235,139	927,872
Standard deviation	378,857	369,817	121,798	422,478	759,406
Minimum	59,360	20,140	19,376	-	270,497
Maximum	1,845,800	3,439,038	604,800	3,686,504	5,622,578
Total cost	45,080,598	3,745,414	22,171,862	46,166,250	149,024,791
Percentage	30%	14%	25%	31%	100%

Note: a: Kruskal-Wallis Test; b: Mann-Whitney Test; *indicating significant effect (p -value < 0.05)

Variables	Cost component (cost per person; IDR, mean±SD)									
	Doctor consultation	p-value	Laboratory test	p-value	Diabetes medicines	p-value	Other medicines	p-value	Total	p-value
Therapy regimens ^a										
Met+Sul	243,655±228,516	0.000*	278,157±277,403	0.361	100,204±54,263	0.000*	244,394±229,477	0.000*	866,410±476,002	0.000*
Met+Aca	347,556±407,178		297,668±605,741		212,652±90,697		597,644±715,876		1,455,522±1,135,437	
Met+DPP4i	654,678±559,500		271,824±216,567		333,196±139,705		362,266±242,532		1,541,615±568,728	
Sex ^b										
Male	359,600±452,992	0.599	307,556±461,521	0.821	172,469±123,886	0.488	429,281±552,960	0.174	1,259,683±947,077	0.232
Female	321,457±335,884		259,627±270,547		161,822±120,654		277,500±250,459		1,002,556±532,382	
Age ^b		0.002*		0.854		0.447		0.244		0.006*
< 60	489,010±473,549		333,436±356,767		196,418±157,215		323,570±363,697		1,330,143±727,521	
≥ 60	289,432±330,014		264,507±374,192		156,900±106,766		354,884±441,568		1,051,300±760,500	
CCI ^b		0.007*		0.019*		0.299		0.651		0.005*
< 2	488,548±463,742		436,630±393,800		163,888±149,247		359,160±370,330		1,423,013±743,588	
≥ 2	304,323±349,845		245,725±356,399		167,357±115,336		344,326±435,187		1,050,457±749,057	
BMI ^b		0.012*		0.464		0.488		0.178		0.038*
< 25	281,567±343,767		254,327±231,662		161,515±122,919		324,946±458,501		1,019,447±650,711	
≥ 25	422,903±414,087		321,523±508,828		174,299±120,880		379,545±365,166		1,268,303±880,721	
Other drugs ^b										
Yes	344,139±415,588	0.919	290,300±458,985	0.456	153,043±100,720	0.300	378,597±518,021	0.966	1,147,453±914,122	0.313
No	333,358±338,013		272,240±242,888		181,435±140,384		313,172±286,488		1,091,414±552,020	

Table 6. Post-hoc analysis of direct medical costs across therapy regimens

Regimens	<i>p-value</i>		
	Met+Sul	Met+Aca	Met+DPP4i
Met+Sul		a: 0.355 b: 0.000* c: 0.000* d: 0.001*	a: 0.000* b: 0.000* c: 0.011* d: 0.000*
Met+Aca			a: 0.002* b: 0.003* c: 0.457 d: 0.051
Met+DPP4i			

Note: a: doctor fee; b: diabetes medicine; c: other medicines; d: total direct medical cost; *indicating significant effect using Mann-Whitney test ($p\text{-value} < 0.05$)

The largest component of direct medical costs was related to medication, particularly other medication costs (31%). This finding is consistent with the study by Kristina et al. (2020), where medication costs represented the largest burden, followed by physician fees. The high proportion of medication costs in the overall direct costs may be a consequence of patients' adherence to treatment as well as diabetes-related complications, which significantly influence medication costs (Hidayat et al., 2022).

The relationship between patient characteristic differences and direct medical costs was tested, with therapy regimen, age, CCI, and BMI showing significant differences in total direct medical costs ($p\text{-value} < 0.05$). The metformin-sulfonylurea combination exhibited the lowest total direct medical costs and antidiabetic medication costs compared to metformin-acarbose and metformin-DPP4 inhibitors. This may be due to the fact that DPP4 inhibitors are a newer class of antidiabetic

drugs, which tend to be more expensive. According to Perkumpulan Endokrinologi Indonesia (2021), DPP4 inhibitors are classified as high-cost medications, acarbose as a medium-cost medication, and both sulfonylureas and metformin as low-cost medications. Previous studies have also shown that DPP4 inhibitors are more expensive than sulfonylurea drugs (Permsuwan et al., 2017).

3.4 Incremental cost-effectiveness ratio (ICER)

The analysis was continued by determining the ICER (incremental cost-effectiveness ratio) of the implemented interventions (Table 7). When compared with the metformin-sulfonylurea regimen, this regimen remained dominant, as it incurred lower costs and demonstrated higher therapeutic effectiveness than the comparator. In contrast, when comparing metformin-DPP4i and metformin-acarbose, the metformin-DPP4i regimen could be considered a trade-off or substitute for metformin-acarbose, as it showed higher therapeutic effectiveness.

Table 7. ICER value for each regimen

Intervention Vs. Comparator	Mean direct medical cost (IDR)	Adjustment of mean direct medical cost [95%CI]	Patients achieving target (n/N)	Therapy achievement (Proportion)	Adjustment of therapy achievement [95%CI]	ICER (IDR per one-unit increase in the proportion of controlled patients)
Met+Aca vs Met+Sul						
Met+Sul	866,410	692,147 [587,409;815,560]	22/38	0.5789	0.58 [0.42;0.73]	Dominated by Met+Sul
Met+Aca	1,455,522	1,488,819 [1,233,131; 1,797,522]	9/31	0.2903	0.35 [0.18;0.56]	
Met+DPP4i vs Met+Sul						
Met+DPP4i	1,541,615	2,691,592 [2,095,926;3,456,548]	10/19	0.5263	0.40 [0.18;0.68]	Dominated by Met+Sul
Met+Sul	866,410	692,147 [587,409;815,560]	22/38	0.5789	0.58 [0.42;0.73]	
Met+DPP4i vs Met+Aca						
Met+DPP4i	1,541,615	2,691,592 [2,095,926;3,456,548]	10/19	0.5263	0.40 [0.18;0.68]	24,055,460
Met+Aca	1,455,522	1,488,819 [1,233,131; 1,797,522]	9/31	0.2903	0.35 [0.18;0.56]	

Note: Therapy achieved mean FBG < 130 mg/dL; Adjustment of mean direct medical cost and adjustment of therapy achievement were performed with generalized linier regression

This study differs from two previous studies, which concluded that the metformin–DPP4i combination was more cost-effective than metformin–sulfonylurea. Kwon et al. (2018) compared metformin–DPP4i with metformin–sulfonylurea and concluded that DPP4i as a second-line therapy was more cost-effective than sulfonylurea using a Markov model simulation approach. A review by Kusumawati and Andayani (2024) also reaffirmed that the metformin–DPP4i combination was more cost-effective than metformin–sulfonylurea, using the same Markov simulation model. Meanwhile, a study by Tandon et al. (2019), based on a randomized controlled trial with an 8-week observation period, found that the metformin–glimepiride therapy was more cost-effective than metformin–teneligliptin in terms of reducing HbA1c and FBS. The differences in research methods can lead to variations in cost-effectiveness analysis results, as the Markov model estimates were conducted over a lifetime, while this study (a retrospective cohort study) was conducted over a 4-month observation period.

In the metformin–acarbose therapy group, the metformin–DPP4i therapy had an ICER of IDR 24,055,460/one-unit

increase in the proportion of controlled patients. This value is below the national willingness-to-pay threshold of 1 to 3 times the GDP per capita in Indonesia (approximately IDR 78,600,000 – IDR 235,800,000), suggesting that the metformin–DPP4i regimen offers favorable value for money within the Indonesian healthcare context (Badan Pusat Statistik, 2025).

OSA was conducted by varying range values in the base-case to determine potential impacts on the results. The percentage changes in ICER from base-case are presented in the tornado graph (Figure 1). Effectiveness emerged as the most influential parameter across all comparisons. In the metformin+acarbose versus metformin+sulfonylurea analysis, the ICER remained consistently negative, confirming that metformin+acarbose is a dominant strategy. For metformin+DPP4i versus metformin+acarbose, although the ICER was sensitive to clinical effectiveness, the values stayed well within the acceptable WTP threshold. This indicates that the base-case conclusion identifying metformin+DPP4i as a cost-effective alternative to metformin+acarbose is statistically robust.

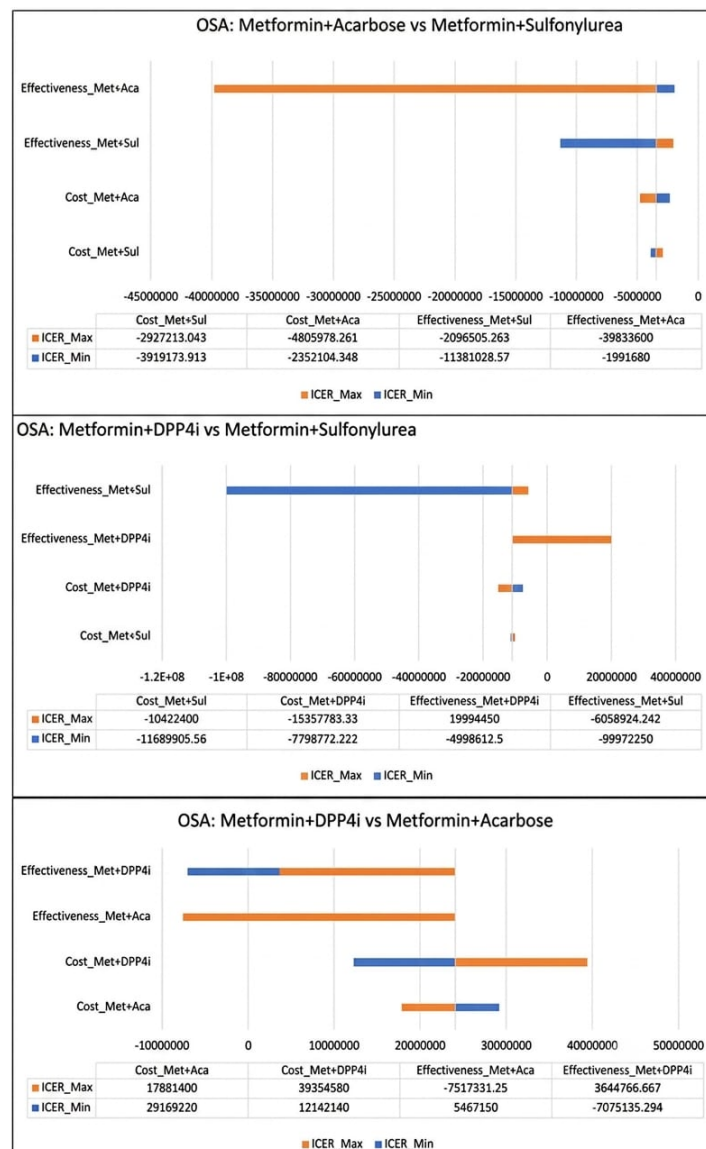


Figure 1. One-way sensitivity analysis in each scenario

Our CEA results demonstrate that metformin+sulfonylurea remains the most cost-effective strategy in the Indonesian clinical setting as it dominates other combinations even after rigorous statistical adjustment for confounders. This supports the current national healthcare policy that prioritizes these agents in primary care. The findings also have significant implications for clinical practice in Indonesia, such as BMI, must be strictly monitored.

Several limitations should be acknowledged. The retrospective cohort design limits the ability to establish causal relationships between therapy regimens and outcomes, and the study is dependent on the completeness and accuracy of medical record data. This study utilized FBG as a surrogate endpoint to evaluate CEA. While HTA guidelines generally prioritize final clinical outcomes, such as quality-adjusted life years (QALYs) or the incidence of long-term complications, FBG remains a highly relevant clinical indicator in real-world settings. However, it is important to note that the 4-month time horizon of this study captures short-term efficacy, and further modelling might be required to extrapolate these findings into long-term health economics benefits. The relatively short observation period of four months may not adequately reflect long-term glycemic control, diabetes-related complications, or lifetime costs. Furthermore, indirect costs such as productivity loss, transportation, and caregiver burden were not included, potentially underestimating the total economic burden of T2DM. Last, the study was conducted in a specific healthcare setting, which may limit the generalizability of the findings to other regions or health systems with different drug pricing structures and reimbursement policies.

4. CONCLUSION

This study evaluated the cost-effectiveness of metformin-based therapies in patients who failed metformin monotherapy, focusing on the ICER of different drug combinations. The metformin+sulfonylurea combination was found to be cost savings, with the lowest direct medical costs and higher therapeutic effectiveness compared to metformin+acarbose and metformin+DPP4i. In contrast to previous studies that favored metformin+DPP4i, our findings showed that metformin-sulfonylurea dominated in terms of cost-effectiveness. ICER analysis revealed that metformin+DPP4i had an ICER of IDR 24,055,460/one-unit increase in the proportion of controlled patients, due to its higher costs and greater therapeutic effectiveness. These results highlight the importance of considering both treatment efficacy and cost when making therapeutic decisions, especially in resource-limited settings.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

AUTHOR CONTRIBUTIONS

D.E. conceived and designed the study, managed the overall project, and supervised the research. I.K.S. led the data collection, performed the data analysis, and drafted the manuscript. T.P. contributed to the study design, verified the analytical methods, and helped interpret the results. D.E. and I.K.S. wrote the final manuscript with input from T.P. All authors reviewed, discussed the results, and approved the final manuscript.

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