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Original Article

COST-EFFECTIVENESS OF METFORMIN-GLIMEPIRIDE COMBINATION COMPARED TO SINGLE METFORMIN USE IN DECREASING 2 H POST PRANDIAL BLOOD GLUCOSE

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ABSTRACT

Objective: Complications related to diabetes could reduce the quality of life. In Indonesia, the costs incurred for diabetes mellitus annually will increase as complications of the disease increase. This study explored the cost-effectiveness therapy of metformin-glimepiride combination on post-prandial blood glucose.

Methods: Glimepiride is added to the first category for diabetes mellitus receiving metformin to improve blood sugar levels and reduce costs. An observational study was conducted retrospectively to analyze post-prandial blood sugar levels with the total direct medical costs at Universitas Andalas Hospital. The study involved 114 medical records of patients referred during 2021. The combination of Metformin HCL and Glimepiride was compared to Metformin alone in measuring cost and effect parameters. The categorical dependent-independent groups were statistically analyzed using Chi-square, while the cost and effect parameters were calculated to get the Incremental Cost-Effectiveness Ratio (ICER) value.

Results: There were no significant differences between groups on sociodemographic characteristics (p<0.05). An incremental cost value of IDR 43,291 was obtained for reducing post-prandial blood sugar by 21.92 mg/dl.

Conclusion: Increasing cost and effect parameters require further analysis to determine the trade-off point.

Keywords: Type 2 diabetes mellitus, Metformin, Glimepiride, 2 h postprandial

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INTRODUCTION

In managing diabetes mellitus, patients are significantly expected to add to the burden on society and the government because it requires a large amount of money, such as direct medical costs (drug therapy, visits to doctors and screening, and costs of treating disease complications) and indirect costs (loss of productivity) [1]. *The International Diabetes Federation (IDF)* estimates that the total cost of managing diabetes will reach USD 1.03 trillion in 2030 and USD 1.05 trillion in 2045 [2]. This condition would be a challenge in the health financing system because diabetes mellitus is a chronic disease that requires lifelong care, where the costs incurred will also become an economic burden that must be considered in the health care system [3]. So the treatment strategy must consider several aspects, including effectiveness, patient satisfaction, quality of life, and cost [4–6].

According to the Indonesian Society of Endocrinology (Perkeni), the basis for prescribing metformin and the metformin-glimepiride combination is that metformin is the first-line drug in treating type 2 diabetes mellitus [7]. Metformin was chosen as the first line because of its relatively good effectiveness, low side effects of hypoglycemia, does not cause weight gain, improves cardiovascular outcomes, and is inexpensive. Metformin works to reduce hepatic glucose production (gluconeogenesis) and increase sensitivity to insulin. Metformin can be given as monotherapy or in combination [8, 9]. If metformin cannot be provided, other available drugs are given according to the patient's condition. Metformin is commonly used with sulfonylurea, glibenclamide, glimepiride, and gliclazide). Previous research also showed that the metformin-glimepiride combination had better efficacy in controlling blood sugar levels than the metformin-glibenclamide combination. The metformin-glimepiride combination also produces a lower hypoglycemic effect than the metformin-glibenclamide combination in type 2 diabetes mellitus patients [9].

The duration of type 2 diabetes mellitus therapy is generally quite long, so the required medical costs are also quite large. The economic burden caused by the treatment of diabetes mellitus is quite high, and the available antidiabetic drugs have numerous benefits and costs. Based on this description, it is necessary to research the analysis of treatment costs, especially cost-effectiveness, which aims to help decide on more cost-effective treatment options by considering the benefits and costs. The research analyzed the cost-effectiveness of treating type 2 diabetes mellitus in outpatients at Andalas University Hospital by calculating postprandial blood glucose as an effect parameter.

MATERIALS AND METHODS

Materials

The data used in this study is medical record data of type 2 diabetes mellitus patients at Andalas University Hospital in 2021. This data is then cross-checked with billing data in the hospital management information system (SIM-RS).

Research design, target population, and location

This research is a descriptive study-based health economics evaluation through retrospective data collection. In this study, we refer to *the Consolidated Health Economic Evaluation Reporting Standards 2022* (CHEERS 2022) checklist available on the *Enhancing the QUality and Transparency Of health Research* (Equator) network [10]. The research was conducted at Universitas Andalas Hospital. This study compared metformin-glimepiride (intervention) with metformin alone (comparator). Sampling was conducted non-randomly using a purposive sampling technique, where samples that met the inclusion criteria were used as research samples.

Inclusion and exclusion criteria

The inclusion criteria in this study were outpatient type 2 diabetes mellitus patients undergoing therapy in 2021 who had insurance. Outpatient type 2 diabetes mellitus patients receive metformin therapy or the combination of metformin-glimepiride and routine control for at least three months. Outpatient type 2 diabetes mellitus patients aged 15-64 y (productive age). The treatment duration of 3 mo is intended to see the effect of therapy in patients referred back. Because the patient is referred back, they refill the drug at the hospital after the third month. We excluded type 2 diabetes mellitus patients with incomplete medical record data, pregnant patients,

and patients who died during treatment.

Perspective, time horizon, and index year

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

Currency and discount rate

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

Cost-effect variables

The data taken is then entered into the data collection sheet. The data collected included: First, patient sociodemographic data: gender, age, educational level, and occupation. Second, patient clinical data: type of antidiabetic given, disease diagnosis, and therapy outcomes (initial blood glucose, final blood glucose after three months of therapy, and decrease in blood glucose levels). Third, direct cost data: includes administrative costs, treatment costs, support costs, and medicines costs that categorize to total direct costs.

Data analyze

Patients who met the inclusion criteria were grouped according to the type of antidiabetic drug received and followed by comparing the basic conditions of the data obtained from patients with type 2 diabetes mellitus. After that, the therapeutic outcomes were calculated, such as initial postprandial blood glucose levels, postprandial blood glucose levels after three months of therapy, and the decrease in average blood glucose levels for each antidiabetic group. A compare means analysis was conducted for data on the average value between the two groups. The compare mean analysis can calculate the average and the univariate relationship between the dependent and independent variables. Meanwhile, group data will be tested statistically using Chi-square. After obtaining the base case data, a pharmacoeconomic analysis was carried out to get the Incremental Cost-Effectiveness Ratio (ICER) value.

Sensitivity analysis

Sensitivity analysis is a method that can be used to analyze uncertainty and analyze decisions (decision analysis). A Deterministic sensitivity analysis (DSA) is carried out to overcome this uncertainty, which explores the specified input model for several different point estimates. In this study, the total cost of the hospital (SIM-RS) is assumed to be the total direct medical cost.

Theory/calculation

The cost-effect analysis in economic evaluation assesses the ICER of new interventions and comparators. The ICER value was calculated using the formula:

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

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

$$\text{ICER} = \frac{\text{metformin–glimepiride cost} - \text{metformin cost}}{\text{metformin–glimepiride effect} - \text{metformin effect}}$$

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

RESULTS

After being selected according to the inclusion and exclusion criteria, 114 patient medical records met the inclusion criteria. The rest met the exclusion criteria that had been set in this study. The data obtained from the two interventions in this study were then analyzed for their cost effectiveness using the Cost Effectiveness Incremental Ratio (ICER) value to see which antidiabetic therapy is more cost-effective. This research is expected to be a source of information for the hospital in making decisions when compiling a hospital formulary. From the medical records that have been observed, the following results were obtained.

Study parameter

Sociodemographic characteristics

Sociodemographic characteristics seen in this study included gender, age, education level, and occupation of the patients. The sociodemographic description of T2DM patients can be seen in table 1.

Table 1: Sociodemographic characteristic T2DM patients receiving metformin and metformin-glimepiride

Characteristics		Number of patients (%)		*p-value**
		Metformin	Metformin+glimepiride	
Gender	Male	6 (26.09)	36 (39.56)	0.235
	Female	17 (73.91)	55 (60.44)	
Age (year)	<35	0 (0.0)	1 (1.10)	0.968
	35-44	1 (4.35)	4 (4.40)	
	45-54	10 (43.48)	38 (41.76)	
	>55	12 (52.18)	48 (52.75)	
Education	Elementary	2 (8.70)	10 (10.99)	0.828
	Junior high school	1 (4.35)	10 (10.99)	
	Senior high school	11 (47.83)	47 (51.65)	
	Undergraduate	1 (4.35)	3 (3.30)	
	Graduate	8 (34.78)	21 (23.08)	
Occupation	Civil servant	10 (43.48)	23 (25.27)	0.344
	Private sector	5 (21.74)	15 (16.49)	
	Retiree	2 (8.70)	10 (10.99)	
	Homemaker	6 (26.09)	32 (35.16)	
	Others	0	9 (9.89)	
	Refuse to answer	0	2 (2.20)	

*Chi-square test, As a result, in table 1 provided, there is no significant difference in the sociodemographic dependent variable. Nonetheless, women over 55 y of age have the highest number of T2DM sufferers, either in the metformin alone group or metformin in combination with glimepiride.

Effect parameter

The effectiveness of antidiabetic therapy observed in this study was the average reduction in blood glucose during the first visit and after three months of regular treatment. The blood glucose observed was fasting blood glucose and blood glucose 2 h postprandial. According to guidelines for managing type 2 diabetes mellitus in Indonesia, a person is said to have diabetes mellitus if the fasting blood glucose check is ≥126 mg/dl or if the blood glucose check 2 h postprandial is ≥200 mg/dl [7] In patients receiving single metformin therapy, the

average 2 h postprandial glucose reduction was 33.09 mg/dl with a standard deviation of 51.71, as seen in table 2.

Cost parameter

Based on a study at Andalas University Hospital, the total direct medical costs for patients using single antidiabetics were cheaper than the metformin-glimepiride combination, as seen in table 3.

Cost-effectiveness analysis

Antidiabetic cost-effectiveness analysis in this study was calculated as Cost Effectiveness Incremental Ratio (ICER). ICER is a ratio value obtained from the difference in costs and the difference in therapeutic outcomes of each intervention. ICER can assess whether an intervention has value for money and whether the cost difference between interventions is commensurate with the resulting therapeutic effects [1, 11].

Table 2: Decrease in 2-h postprandial blood sugar by group

Oral antidiabetes	Decrease of 2-h pp blood glucose	*p-value*	Incremental effect (mg/dl)
Metformin	33.09±51.71	0.90	21.92
Metformin-Glimepiride	55.01±55.77		

The *p*-value for the average 2 h postprandial reduction in blood glucose was 0.90 (>0.05), meaning that there was no significant difference in the average 2 h postprandial reduction in blood glucose between the two groups of antidiabetic types that patients received.

Table 3: The total direct medical costs in each group

Oral antidiabetes	Direct medical cost	*p-value*	Incremental cost
Metformin	IDR 682,173.91±100105.03	0.75	IDR 43,290.93
Metformin-Glimepiride	IDR 725,464.84±121,321.21		

Although the cost of metformin alone is cheaper than the combination of metformin-glimepiride, there was no significant difference in the direct medical cost between the two groups of antidiabetic types patients received.

The ICER value for type 2 diabetes mellitus patients by calculating the average 2 h postprandial reduction in blood glucose as a parameter of its effectiveness is 1,974.59 for every 1 mg/dl decrease in blood glucose. This means that each additional fee of IDR 1,974.59 for using the metformin-glimepiride combination will reduce 1 mg/dl blood glucose 2 h postprandial. This ICER value is in the northeast quadrant, as seen in fig. 1.

In this condition, a trade-off occurs where the metformin-glimepiride combination's effectiveness is better than metformin alone. Still, the costs required by using metformin alone are also more expensive.

Deterministic sensitivity analysis

The DSA is an input model analysis specified for several types of point estimates, and the variations are made manually according to assumptions. The DSA results are shown in the tornado diagram, as shown in fig. 2.

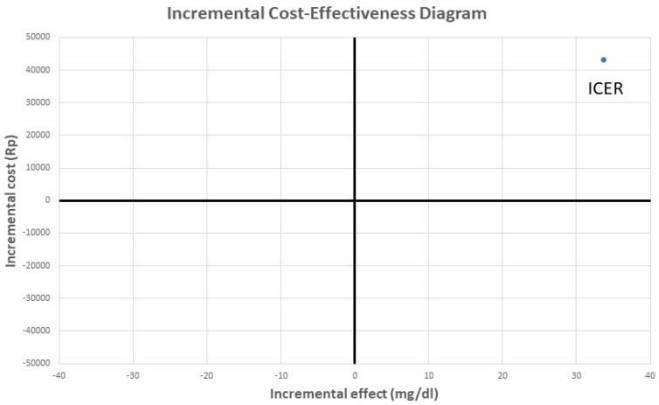

Fig. 1: Cost-effectiveness plane metformin-glimepiride combination on 2-h postprandial blood glucose

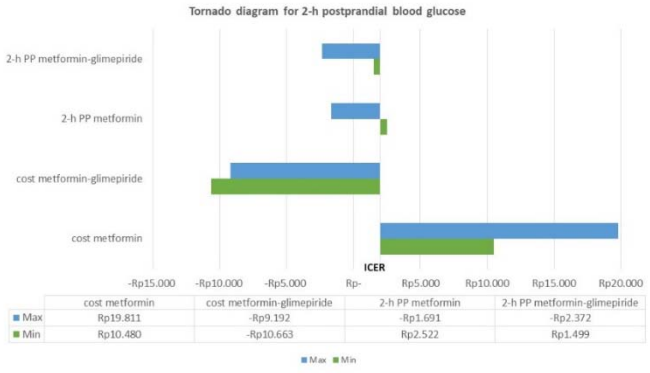

Fig. 2: Deterministic sensitivity analysis using tornado diagram

In the DSA, there was a decrease in blood glucose 2 h postprandial in the combination group. If the decrease in blood glucose 2 h postprandial was changed to a maximum and minimum value, the ICER values obtained were IDR-1,691.48 per 1 mg/dl and IDR 2,521.97 per 1 mg/dl, respectively. This variable can reduce the ICER value if changed to the maximum value and increase the ICER value if changed to the minimum value.

Meanwhile, if the average direct medical costs in the combination group were changed to the maximum and minimum values, the ICER values obtained were IDR 19,810.92 per 1 mg/dl and IDR 10,480.04 per 1 mg/dl. Then the variable average direct medical costs for the combined group is considered a variable that can significantly increase the ICER value.

DISCUSSION

Women and men are equally likely to suffer from diabetes mellitus. However, women have a greater risk of suffering from diabetes because, physically, the chances of increasing body mass index are greater for women. Some causes are monthly cycle syndrome (pre-menstrual syndrome) and post-menopause, which causes easy accumulation or accumulation of fat in the body due to these hormonal processes [12, 13].

Increasing age also causes the ability of pancreatic β cells to produce insulin to decrease [14, 15]. As well as causing a decrease in the sensitivity of pancreatic β cells to incretin hormones and triggering insulin resistance due to damage to pancreatic β cells resulting in diabetes mellitus [16, 17]. In statistical analysis, a *p*-value of 0.968 (>0.05) was obtained, meaning that there was no significant difference in the mean age of the patients between the two anti-diabetic groups received. There was no significant difference, telling the difference in the mean age of the patients between the two anti-diabetic groups received was not much different. So it can be seen that the patient's age has no effect on the type of antidiabetic received by the patient.

In this study, not all patients experienced a decrease in blood sugar levels, but there were also patients whose blood sugar levels increased. Several factors affect blood sugar levels: diet, physical activity, medication adherence, and knowledge. If properly controlled, blood sugar levels can stay stable. The impact is that there will be hypoglycemia shock due to blood sugar levels that are too low or hyperglycemia due to high blood sugar levels [18, 19].

The ICER value obtained was IDR 1,974.58 for every 1 mg/dl decrease in blood glucose. This means that IDR 1,974.58 is needed for every 1 mg/dl decrease in blood glucose 2 h post-prandial. This diagram shows that the ICER value of blood glucose 2 h post-prandial is also in the northeast (quadrant 1). Previous study by Fitria *et al.* that have compared the cost-effectiveness of single and combined metformin with insulin glargine also have similar results where the ICER is in the northeast quadrant (quadrant 1) [20]. This means that the combination intervention has better effectiveness than metformin alone, but the costs required by the new intervention are also more expensive than single-use metformin. This means that the increase of expenses is directly proportional to the rise in the effectiveness of therapy, in this case, the decrease in blood glucose 2 h postprandial. This condition is considered to have a "trade-off" (a trade-off between effectiveness and cost). So it is deemed necessary to conduct a further evaluation to prove whether the new intervention has "value for money," ie, whether the higher costs required by the recent intervention are proportional to the increased effectiveness to be produced [21].

The average direct medical cost of the combined group is the most influential factor on the ICER value of blood glucose 2 h post-prandial [22]. If the average direct medical cost for the combined group is changed to the maximum value, it will increase the ICER value. In the tornado chart, the bar with the longest span is the most influential variable [8, 16]. The two tornado diagrams obtained show that the variable that has the most influence on the ICER value is the average direct medical cost of the combined group. This can be seen from the bar with the longest span. Kwon *et al.* (2018) show that cost is included in the variables that affect the ICER value. The difference between this study and the study conducted by Kwon was that in Kwon's study, both the intervention and comparator groups were in the form of a combination of two drugs [23].

In this research, the Average Cost Effectiveness Ratio (ACER) was not utilized because relying solely on the ACER values of two interventions doesn't provide sufficient information to confirm that the intervention with a higher ACER is superior to the one with a lower ACER. As a result, the comparative costs and benefits of the interventions remain undisclosed. There is a potential scenario where the intervention with a lower ACER might still have favorable outcomes.

This study has advantages because it takes into account direct medical costs both based on packages and based on claims costs. At the same time, this study also has limitations, including confounding factors that can affect the assessment of the effectiveness of therapy, such as patient adherence to medication and patient lifestyle (diet and physical activity)—not recorded in the patient's medical record. In addition, the results of this study are also not representative of other healthcare providers because the study subjects were limited to type 2 diabetes mellitus patients at Universitas Andalas. It is hoped that further research will be carried out using a prospective cohort design by controlling for other confounding variables and conducted at several healthcare providers.

CONCLUSION

The metformin-glimepiride combination therapy group costs more and produces better effects than the single metformin group. Because it is in a trade-off position, conducting further cost-effectiveness analysis on the metformin-glimepiride combination compared to metformin alone is advisable, considering that the ICER values obtained are in the northeast quadrant on the cost-effectiveness diagram.

ETHICAL APPROVAL

This study received ethical approval from the Research Ethics Committee of the Faculty of Medicine, Andalas University No 618/UN.16.2/KEP-FK/2022.

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AUTHORS CONTRIBUTIONS

NF designed the study, MA and RR conducted the fieldwork, HN checked conceptual variables. NF wrote the manuscript, and all authors read and approved the final version.

CONFLICT OF INTERESTS

The author(s) declare no conflict of interest regarding this manuscript.

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