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Cost-Effectiveness Analysis of the Combination of Metformin-Insulin Glargine and Metformin-Glimepiride in Type 2 Diabetes Mellitus Patients in Rupit Hospital

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Abstract
Type 2 diabetes mellitus (T2DM) is a chronic disease requiring lifelong care and much money. A combination of antidiabetic drugs aims to increase effectiveness in lowering blood sugar levels. The combination of two drugs consists of a first-line drug class plus another class of drugs with a different mechanism of action. This study aimed to determine the cost-effectiveness of the combination therapy of metformin-insulin glargine and metformin-glimepiride, expressed by the value of the Cost Effectiveness Incremental Ratio (ICER). **Method**: This research was a descriptive study, and data collection was carried out retrospectively using patient medical record data. This study used a healthcare provider perspective. Of the 406 population, only 102 samples met the inclusion criteria. **Result:** Fifty-seven records (55.88%) used the metformin-glimepiride combination, and the other forty-five (44.12%) used metformin-insulin glargine. The ICER value of random blood sugar during (RBG) was IDR 21,748.89 for every 1 mg/dL decrease in RBG. The ICER value of fasting blood sugar (FBG) was IDR 38,824.46 for every 1 mg/dL decrease in FBG. Meanwhile, the ICER of HbA1c value was IDR 43,257.46 for every 1% decrease in HbA1c. **Conclusion:** The three ICER values were in the northeast quadrant (quadrant I), where the metformin-insulin glargine therapy group had the better blood sugar value. Still, the costs required were also higher than the metformin-glimepiride group.

Keywords: *Cervical cancer, cost-utility analysis, human papillomavirus, Indonesia, vaccination.*

Introduction

The prevalence of Diabetes Mellitus Type 2 (T2DM) has increased drastically in industrialized and developing countries, including Indonesia. The International Diabetes Federation (IDF) organization estimates that the number of diabetes mellitus sufferers in Indonesia will increase from 19.5 million in 2021 to 28.6 million in 2045. Currently, Indonesia is the fifth country with the highest number of diabetes mellitus patients globally after China, India, Pakistan, and the United States of America (USA) [1]

The results of the Basic Health Research survey in 2018 showed that the prevalence of people with diabetes mellitus diagnosed by a doctor reached 1.5% of the total population of Indonesia. As much as 0.9% of the population of South Sumatra suffers from diabetes. Meanwhile, in North Musi Rawas Regency, 0.63% of the population suffers from diabetes [2]. Based on a survey by the Musi Rawas Utara District Health Office in 2021, diabetes mellitus ranks 3rd out of the ten most common diseases, with 3769 sufferers.

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) [3]. *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 (IDF, 2021). 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 [4]. So the treatment strategy must consider several aspects, including effectiveness, patient satisfaction, and cost [5].

Managing type 2 diabetes mellitus begins with adopting a healthy lifestyle and pharmacological interventions, namely oral antihyperglycemic drugs and/or injections. Antihyperglycemic oral medicines can be given as a combination therapy [6]. Administration of a combination of antidiabetic drugs aims to increase the effectiveness of the drug in lowering the patient's blood sugar levels [7]. The combination of 2 drugs consists of a first-line drug class combined with another type of drug with a different action mechanism [8]. Metformin is the recommended first-line therapy in managing T2DM [9]. At the same time, the choice of combination therapy is not determined. In a previous study, a cost-effectiveness analysis was carried out on the

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metformin-insulin and metformin-sulfonylureas combinations. It was found that the metformin-sulfonylureas combination therapy was more cost-effective than the metformin-insulin combination [10]. The combination of metformin-sulfonylureas with a different mechanism of action is known to improve glycemic control effectively. This combination resulted in a better reduction in HbA1c of 0.5% compared to its monotherapy use [11]. However, safety concerns continue to increase, including the risk of hypoglycemia and weight gain [12]. In type 2 diabetes mellitus, the function of β cells will be significantly reduced, reaching 50-80%, so insulin therapy will be needed [13]. The metformin-insulin combination improves β-cell function better than the metformin-sulfonylurea combination [13]. It also showed a better decrease in HbA1c and smaller weight gain compared to the other combinations [14].

Based on the results of a preliminary study at the Rupit Hospital in North Musi Rawas Regency, the most common prescribing pattern in type 2 diabetes mellitus outpatients was the combination of metformin-glimepiride and metformin-insulin glargine. The general price for metformin is IDR 231.00/tablet, glimepiride IDR 4,719.00/tablet, and insulin glargine IDR 109,135.00/pen [15]. Meanwhile, the claim price from the Social Security Agency of Health (BPJS) for metformin is IDR 99.00/tablet, glimepiride IDR. 157.00/tablet and insulin glargine IDR 112,140.00/pen [15]. Seeing the price difference, the researchers are interested in analyzing the direct medical costs and costs of BPJS claims for using the metformin-insulin glargine and metformin-glimepiride combinations. Variations in type 2 diabetes mellitus combination therapy can result in differences in average costs and therapeutic outcomes. Considering that diabetes mellitus requires long-term care with a large burden of therapeutic costs both for the patient himself and for the government, a pharmacoeconomic analysis was carried out to determine the cost-effectiveness of combination therapy of metformin-insulin glargine and metformin-glimepiride in outpatient type 2 diabetes mellitus patients in Rupit Hospital, Musi Rawas Utara Regency.

Methods

Research design, target population

The research was conducted at Rupit Hospital, North Musi Rawas Regency. The research was conducted in December 2022 – February 2023. This study used a descriptive approach. The data collection technique was carried out retrospectively on medical records of type 2 diabetes mellitus outpatients. This study compared metformin-insulin glargine (intervention) with metformin glimepiride (control).

Inclusion and exclusion criteria

The inclusion criteria in this study were patients participating in BPJS with a diagnosis of type 2 diabetes mellitus, both men and women aged > 18 years, patients receiving antidiabetic therapy with the combination of metformin-glimepiride or metformin-insulin glargine and routine control for at least 3 months with this therapy, and type 2 diabetes mellitus patients with or without comorbidities. Meanwhile patients with type 2 diabetes mellitus with incomplete medical record data, hospital rates data and financial data (billing system), patients who died or dropped out of treatment, pregnant women, and patients who received high-dose steroid therapy were excluded from this study.

Perspective, time horizon, and index year

The cost perspective in this study is the hospital perspective (healthcare perspective), where the cost used was the direct cost paid to the hospital. And the perspective of the patient payer / guarantor (payer perspective) is the costs incurred by the guarantor, in this case the BPJS, in the form of reimbursement of costs to health service institutions (hospitals) in accordance with the regional INA-CBG tariff standards 2 Type D Government Hospitals in outpatient units and non-INA-CBG rates in the form of chronic disease drug costs. The sample of this study is a portion of the population of BPJS patients diagnosed with type 2 diabetes mellitus in January - December 2022 who meet the inclusion and exclusion criteria. The time horizon is determined in 3 months of treatment, with 2022 as the index year.

Currency and discount rate

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

Cost-Effect variables

The variable cost used here is direct medical costs in medicines, doctor visits, screening, and treating complications. The general price for metformin is IDR 231.00/tablet, glimepiride IDR 4,719.00/tablet, and insulin glargine IDR 109,135.00/pen [15]. Meanwhile, the BPJS claim price for metformin is IDR 99.00/tablet, glimepiride IDR. 157.00/tablet and insulin glargine IDR 112,140.00/pen [15]. Whereas the variable effects

comprise of fasting blood glucose value (FBG), random blood glucose (RBG), and HbA1c.

Data Analysis

Data analysis began by calculating the effectiveness based on the outcome of therapy, which were initial blood sugar levels and blood sugar levels after three months of therapy, then calculating the average decrease in blood sugar levels for each group of metformin-insulin glargine and metformin-glimepiride combinations in percentage form. Furthermore, a cost analysis was carried out, consisting of direct medical costs and BPJS claim costs for the combination of metformin-insulin glargine and metformin-glimepiride at Rupit Hospital, Musi Rawas Utara Regency. The ICER value is determined based on the value of each effect parameter (FBG, RBG, and HbA1c). For each dependent variable, a normality test was carried out first. Parametric data with two dependent variables would be tested using the T-Test, while non-parametric was tested using the Mann-Whitney test. The categorical variables will be tested with chi square. The *p* value < 0.05 was declared as a result that has a significant effect.

Results

Study Parameter

a. Sociodemographic characteristic

Table 1 Sociodemographic Characteristics

Sociodemographic characteristics	Metformin-Insulin glargine (N=45)		Metformin-Glimepiride (N=57)		*p*-value
	N	%	N	%	
Age, year (Mean±SD)	53.56 (10.70)		53.84 (9.12)		0.884[a]
Gender					
Male	20	44.44	24	42.11	0.843[b]
Female	25	55.56	33	57.89	
Education level					
No school	1	2.22	1	1.75	0.162[b]
Elementary	7	15.56	9	15.79	
Junior high school	13	28.89	7	12.28	
Senior high school	19	42.22	27	47.37	
Undergraduate	4	8.89	13	22.81	
Post =graduate	1	2.22	0	0	

Table 1 shows the sociodemographic picture of T2DM sufferers at Rupit Hospital. The level of education of patients with type 2 diabetes mellitus at the Rupit Hospital in Musi Rawas Utara Regency was divided into six categories: Not Schooling, Elementary School, Junior High School, Senior High School, Graduate, and Postgraduate. The highest number of type 2 diabetes mellitus patients in this study was the high school education level of 45.10%. Meanwhile, the level of junior high school education was 37.25%. And the percentage of patients with education levels of Graduate and Postgraduate is less, namely 17.65%, in line with research conducted by Fitria et al. (2022), where the level of high school education has the greatest prevalence of type 2 diabetes mellitus, namely as much as 50.88% [5]. In the sociodemographic picture, it was found that there was no significant difference between the recipients of the metformin-glimepiride and metformin-insulin glargine combinations. It can be assumed that there is no relationship between sociodemographic characteristics and the type of antidiabetic received. Table 1 shows that the value close to p <0.05 is the education level variable. The level of education is considered to affect the incidence of type 2 diabetes mellitus. High education is associated with a broad level of knowledge, including in the health sector. So that people with a high level of education are believed to be able to prevent and control symptoms that arise with proper treatment. A person's knowledge can increase awareness of the importance of health [16].

b. Effect parameter

The effectiveness of antidiabetic therapy observed in this study was the outcome of the therapy in the form of a decrease in the patient's blood sugar levels during the first visit and after taking the drug regularly for three months. The blood sugar observed was GDS, GDP, and HbA1c (Table 2.). According to the guidelines for the management of type 2 diabetes mellitus in Indonesia, a person is said to have diabetes mellitus if the plasma blood sugar test results are ≥ 200 mg/dL along with classic complaints or hyperglycemia crises, fasting blood sugar test results ≥ 126 mg/dL, and HbA1c test results ≥ 6.5% [17].

Table 2 Parameters of the outcome of the use of antidiabetic therapy

Therapeutic outcomes	Antidiabetic combination		*p-value*
	Metformin-Insulin Glargine	Metformin-Glimepiride	
% Decreasing of RBG over time (Mean ± SD)	21.87 ± 16.48	24.96 ± 19.10	0.529 [1]
% Decreasing of FBG over time (Mean ± SD)	31.92 ± 27.75	33.68 ± 19.89	0.956 [2]
% Decreasing of HbA1c over time (Mean ± SD)	15.09 ± 2.16	12.36 ± 12.97	0.554 [2]

[1] : *independent-sample T test*; [2]: *Mann Whitney*

The results showed that the average decrease in GDS, GDP, and HbA1c in patients receiving metformin-insulin glargine combination therapy was not much

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different from the metformin-glimepiride combination. In the compare mean analysis, the p-values for patients' average reduction in GDS, GDP, and HbA1c were obtained for this anti-diabetic combination, respectively, 0.529, 0.956, and 0.554 (> 0.05). This value shows no significant difference in the therapeutic outcome of the two antidiabetic combinations received by the patients. In line with the research conducted by Fitriyani et al. (2021), the average difference in the reduction in HbA1c between the metformin-insulin and metformin-sulfonylurea combinations was 0.123%. The results of the compare mean analysis showed a p-value of 0.608, which also meant that there was no significant difference in effectiveness—the significant difference between the two combination therapies [10]. However, the results of this study contrast with previous studies, which stated that the metformin-insulin combination therapy had a lower HbA1c value when compared to the metformin-sulfonylurea combination (mean difference = 0.20%; p = 0.1) [18–20]. The non-significant difference in therapeutic outcomes between metformin-insulin glargine and metformin-glimepiride combination therapy can be related to patient adherence to the drug. Previous studies found that patients using combination therapy with oral antihyperglycemic and insulin could have poor blood sugar control five times greater than patients with oral therapy alone. This phenomenon was due to non-adherence and health literacy in using the drug [21–23].

Cost analysis

In this study, a cost analysis was carried out for the types of antidiabetics to see the difference in costs for using the two antidiabetic combinations, both direct medical costs and BPJS claim costs. Direct medical costs include administrative costs, medical services, medical support, and medicines. Meanwhile, BPJS claim costs include the cost of the INA-CBG tariff package and the non-INA-CBG tariff (chronic disease claim fee).

Table 3 Analysis of direct medical costs and costs of BPJS claims

Cost analysis	Antidiabetes combination (Mean + SD)		*p-value*
	Metformin-Insulin Glargine	Metformin-Glimepiride	
Direct medical cost	602.145,09 ± 139.679,544	555.167,49 ± 131.046,628	0,084[1]
BPJS claim	335.802,09 ± 61.681,256	204.183,00 ± 16.664,012	0,000[1]

[1] : *independent-sample T test*

In this study, an analysis of direct medical costs and costs of BPJS claims was carried out on the use of metformin-insulin glargine and metformin-glimepiride combination therapy. Based on the study's results, the average direct medical cost for the metformin-insulin glargine combination therapy was IDR 602,145.09. For the metformin-glimepiride combination therapy, it was IDR 555,167.49. The results of the compare mean analysis obtained a p-value of 0.084, meaning there is no significant difference in the average direct medical costs of the two combination therapies. This value contrasts with the results of a study by Fitriyani et al. (2021), which stated that the direct medical costs of the metformin-insulin combination (IDR 1,593,427) were greater than those of metformin-sulfonylurea (IDR 922,611). [10]. Based on the analysis of the cost components in this study, the most dominant cost is the cost of antidiabetic drugs. In this study, the sample used a combination of metformin with various brands of insulin or types of sulfonylureas, causing the total direct medical costs of the insulin and sulfonylurea groups to differ greatly. In this study, the sample was determined only to use a combination of metformin with insulin glargine or glimepiride, based on hospital rates for drug prices plus a 30% margin and 11% VAT.

The average BPJS claim fee for using the metformin-insulin glargine combination is IDR 335,802.09 and IDR 204,183.00 for metformin-glimepiride combination therapy. The compare mean analysis obtained a p-value of 0.000; there was a significant difference in the average cost of BPJS claims for the two therapy combinations. In T2DM outpatients, two cost components are included in the BPJS claim costs: the INA-CBG rate and the non-INA-CBG rate, which have been set based on the Minister of Health Regulation No. 52 of 2016. The INA-CBG rate for T2DM two outpatient care at Rupit Hospital in North Musi Rawas Regency is included in the Regional-2 rate standard for Government Hospital type D in outpatient units, with the INA-CBG code Q-5-44-0, namely other minor chronic diseases of IDR 177,800.00 [24]. This rate includes the cost of medicine for seven days. Meanwhile, non-INA-CBG rates are obtained through claims for chronic disease drugs, which are given separately outside the INA-CBG package, namely for the needs of 23 days. Chronic disease drugs must be listed in the National Formulary and administered through a pharmaceutical installation.

Incremental Cost-Effect Ratio (ICER)

Antidiabetic cost-effectiveness analysis in this study was calculated using the Incremental Cost-Effectiveness Ratio (ICER) value. The average blood sugar reduction and direct medical costs are plugged

ISSN 3025-5198

Table 4 ICER values for effect parameters

Antidiabetic	Random Blod Glucose (RBG)			Fasting blood glucose (FBG)			HbA1c		
	Total cost (IDR)	reduction	ICER	Total cost (IDR)	reduction	ICER	Total cost (IDR)	reduction	ICER
Metformin-Insulin Glargine	602.145,09	73,13 mg/dL	21.748,89 per decreasing 1 mg/dL	602.145,09	81,81 mg/dL	38.824,46 per decreasing 1 mg/dL	602.145,09	2,40%	43.257,46 per decreasing 1%
Metformin-Glimepiride	555.167,49	70,97 mg/dL		555.167,49	80,60 mg/dL		555.167,49	1,31%	

into the RIEB formula. Three ICER values were obtained because the antidiabetic effectiveness assessed in this study consisted of three types and showed a decrease in GDS, GDP, and HbA1c.

The effectiveness of the antidiabetic combination assessed in this study consisted of three types: a decrease in RBG, FBG, and HbA1c. Thus three ICER values will be obtained, namely the ICER value. The ICER value for RBG in patients with type 2 diabetes mellitus is 21,748.89 for every 1 mg/dL decrease in RBG. This result means that each additional fee of IDR 21,748.89 for using the metformin-insulin glargine combination will reduce the patient's RBG by 1 mg/dL. The ICER value for the FBG of type 2 diabetes mellitus patients is 38,824.46 for every 1 mg/dL decrease in FBG. This number means that each additional fee of IDR 38,824.46 for using the metformin-insulin glargine combination will reduce 1 mg/dL of FBG. And the ICER value for HbA1c in patients with type 2 diabetes mellitus is 43,257.46 for every 1 mg/dL decrease. This ICER means that each additional fee of IDR 43,257.46 for using the metformin-insulin glargine combination will reduce HbA1c by 1%.

The cost-effectiveness diagram for HbA1c also occurs in the same way as GDS, GDP, and HbA1c, as seen in Figure 1. The incremental value of the effect will be inputted as the x-axis. Meanwhile, the difference in the average direct medical costs between the metformin-insulin glargine and metformin-glimepiride groups remained the same, which was IDR 46,977.60, and this was inputted as the y-axis. This value means that the cost of the new therapy group is greater than that of the old therapy group. And the effectiveness produced by the metformin-insulin garglin group is greater than the effectiveness of the metformin-glimepiride therapy group. The ICER value of the three effect parameters is in the northeast quadrant (quadrant 1). The increase in cost is directly proportional to the rise in the effectiveness of therapy, in this case, the average decrease in HbA1c. The three cost-effectiveness diagrams are both in the northeast quadrant (quadrant I) and are considered to have a "trade-off" (a trade-off between effectiveness and cost). So it is considered necessary to carry out a further evaluation to prove whether the new therapy group has "value for money," i.e., whether the higher cost of the new therapy group is proportional to the increased effectiveness it will produce [25].

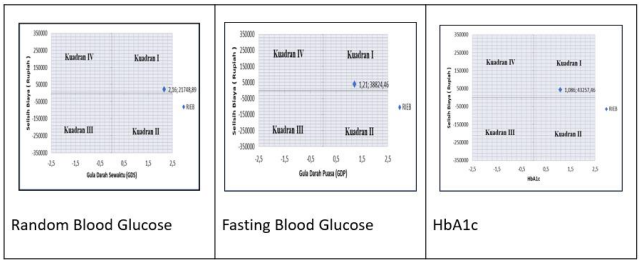

Figure 1 Cost-effectiveness curve

Strength and limitation

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 Rupit Hospital, Musi Rawas Utara District. 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 different healthcare providers.

Conclusion

The Cost-Effective Incremental Ratio (ICER) value for random blood sugar is IDR 21,748.89 for every 1 mg/dL decrease in RBG. The ICER value of fasting blood sugar is IDR 38,824.46 for every 1 mg/dL decrease in FBG. And the RIEB HbA1c value is IDR 43,257.46 for every 1% decrease in HbA1c. The three RIEB values were in the northeast quadrant, where the metformin-insulin glargine group had better effectiveness than the metformin-glimepiride group, but the costs required were also higher.

ISSN 3025-5198

Ethical approval

This research was conducted at Rupit Hospital, North Musi Rawas Regency, from December 2022 to January 2023, and received approval from the Ethics Commission of the Faculty of Pharmacy, Andalas University, with number 01/UN.16.10.D.KEPK-FF/2023.

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Authors' Contributions

NF designed the study, LFA conducted the fieldwork, and YOS checked conceptual variables; NF wrote the manuscript; and all authors read and approved the final version of the manuscript.

Competing Interests

The authors declare no conflict of interest regarding this manuscript. No funding was provided for this study.

Abbreviations

BPJS: *Badan Penyelenggara Jaminan Sosial*/ Social Security Agency of Health
DMT2: Diabetes Mellitus Type 2
ICER: Incremental Cost Effectiveness Incremental Ratio
HbA1c: Hemoglobin A1c
IDF: The International Diabetes Federation
IDR: Indonesian Rupiah
Ina-CBGs: Indonesia Case Based Groups
FBG: Fasting Blood Glucose
RBG: Random Blood Glucose
T2DM: Type 2 diabetes mellitus
USA: United States of America

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