Media Farmasi: Jurnal Ilmu Farmasi (Journal of Pharmaceutical Science) e-ISSN 2503-5223
Vol. 19, No. 2, September 2022, pp. 103-111
http://journal.uad.ac.id/index.php/Media-Farmasi/index

Cost-effectiveness analysis of metformin and metformin-glimepiride in patients with type 2 diabetes at Nene Mallomo General Hospital, Sidenrang Rappang

Shabran Hadiq, Woro Supadmi, Dyah Aryani Perwitasari*

Faculty of Pharmacy, Universitas Ahmad Dahlan, Yogyakarta, Indonesia
*corresponding author: e-mail: dyah.perwitasari@pharm.uad.ac.id

ARTICLE INFO

Article history
Received: 28-08-2021
Revised : 18-04-2022
Accepted: 09-08-2022

Keywords
Cost-Effectiveness Analysis
Diabetes Mellitus
Glimepiride
Metformin

ABSTRACT

Metformin and metformin-glimepiride are cost-effective therapy options and are most commonly prescribed to treat type 2 diabetes mellitus (DM). This study aims to determine the cost-effectiveness of using metformin and metformin-glimepiride in patients with type 2 DM at Nene Mallomo General Hospital, Sidenreng Rappang. This analytical descriptive observational research employed a retrospective cohort design. The data of type 2 DM patients, new and old patients, were obtained from the medical record unit. The target population was data of outpatients for the period January-December 2019. The parameter of the therapeutic effectiveness is the random blood sugar levels of the patients after receiving treatment. The data on cost from the hospital perspective were obtained from the administration and finance unit. Cost-effectiveness analysis employed calculations of the average cost-effectiveness ratio (ACER) and the incremental cost-effectiveness ratio (ICER). Meanwhile, the risk ratio (RR) employed the analytical Chi-squared method to determine the relationship between the two types of therapies and their effectiveness. This study has revealed that 30 patients met the inclusion criteria; 14 patients received metformin therapy and 16 patients received metformin-glimepiride therapy. Metformin therapy is more effective (64.29%) and more costly (IDR120,736). The metformin's ACER value is 1877.99, and its ICER value is -3107.26. The cost-effectiveness analysis has revealed that metformin therapy is more cost-effective than metformin-glimepiride therapy. Meanwhile, the Chi-squared analysis has discovered no relationship between the two therapies and their effectiveness. The RR value of 1.080 concludes that metformin has 1.080 as much therapeutic effectiveness as the metformin-glimepiride.

1. Introduction

Diabetes mellitus (DM) is a chronic disease with metabolic disorders characterized by increased blood sugar levels as well as carbohydrate, protein disorders, and fat metabolism disorders due to insulin secretion, insulin sensitivity, or both (Dipiro et al., 2015). DM is a degenerative disease that can cause other diseases or complications (Wulandari & Martini, 2013), affect the sufferers' quality of life, and require a lot of medical expenses (Dinaryanti et al., 2012).

In 2015, 415 million adults suffered from diabetes; this number is four times higher than 108 million sufferers in the 1980s. It is estimated that the number of sufferers will increase to 642 million by 2040 (Cho et al., 2018). The Basic Health Research (Riskesdas) reports that in 2013, the number of DM patients aged 15 years was twice as many as the number in 2007 (Kemenkes, 2014). Moreover, Riskesdas reports that in 2018, the number of DM patients aged 15 years and over increased by 2% from the results of Riskesdas in 2013 (Kemenkes, 2018). The data of Riskesdas in 2007 and 2013

show that DM cases in South Sulawesi have increased from 0.8% to 3.4%. Sidenreng Rappang Regency has a higher number of DM cases than the national DM cases (Marewa, 2015). In 2018 the Riskesdas of South Sulawesi reports that the prevalence of DM in sufferers aged 15 years based on the doctor's diagnosis in Sidenreng Rappang Regency is 1.02% (Kemenkes, 2019).

Pathophysiology classifies DM disease into two types: DM type 1 and DM type 2 (Dipiro et al., 2015). Type 2 DM is also called non-insulin-dependent DM caused by a lack of insulin production (Kemenkes, 2014), which is marked by increased blood sugar due to impaired insulin functions and/or decreased insulin secretion by pancreatic beta cells (Fatimah, 2015). Such conditions can make blood sugar levels uncontrollable. One of the aims of therapy for patients with type 2 DM is to improve their quality of life so that blood glucose levels are necessarily controlled. However, the process of this aim requires a long period (Kemenkes, 2019).

In general, metformin is the first-line therapy considered logical in almost all guidelines and recommendations for type 2 DM. The effectiveness and tolerability of metformin are well tested, safe, and inexpensive (Ferrannini, 2014), and its use in children has been approved by the Food and Drug Administration (FDA) (Diani & Pulungan, 2010). Combination therapy is intended to optimize the target if a single therapy is not achieved. The sulfonylurea group is the best choice to lower glucose levels in the blood. A study shows that the combination between metformin and glimepiride significantly decreases glucose levels (Ilahi, 2014).

Selecting an appropriate therapy for patients, a single or combined therapy, is expected to provide therapeutic effectiveness that can control blood sugar levels (Fatimah, 2015). However, each sufferer has a different economic background that will affect his choice of appropriate therapy. Therefore, many parties should understand pharmacoeconomic concepts and help pharmacists compare inputs (costs for pharmaceutical products and services) with outputs (treatment results) (Khoiriyah & Lestari, 2018). The cost of treatment refers to the concept of the cost of providing goods, services, or service resources (Refasi et al., 2018). In pharmacoeconomic studies, the cost is always an important consideration because the number of resources, especially funds, is limited (Kemenkes, 2013).

Cost-effectiveness analysis (CEA) is an economic analysis technique for comparing the cost with simple therapeutic effectiveness; thus, this analysis is widely used in pharmacoeconomic research to compare two or more health interventions that provide different levels of effects (Rascati, 2009). The CEA technique enables users to determine the most efficient and most affordable type of therapy for Type 2 DM patients to gain the desired therapeutic results (Kemenkes, 2013).

Data from the medical record of Nene Mallomo General Hospital, Sidenreng Rappang show that the number of patients with type 2 DM continuously increases. Metformin and metformin-glimepiride therapies are the most commonly prescribed therapy options at Nene MallomoGeneral Hospital, Sidenreng Rappang. Previous research suggests that metformin therapy in outpatients with type 2 DM is more effective than another antidiabetic therapy (Dinaryanti et al., 2012). Another study has revealed that, unlike metformin-teneligliptin therapy, metformin-glimepiride therapy is more cost-effective and significantly lowers HbA1c and GDP in patients with Type 2 DM (Tandon et al., 2019).

The findings of previous research arise two problems. The first problem deals with the cost-effectiveness of using metformin and metformin-glimepiride therapies in outpatients diagnosed with type 2 DM at Nene Mallomo General Hospital. The second problem deals with the relationship between metformin and metformin-glimepiride therapies and their therapeutic effectiveness. Therefore, it is necessary to investigate these two problems at Nene Mallomo General Hospital, Sidenreng Rappang in 2019.

2. Materials and Methods

This study employed a retrospective cohort design. Data were collected prospectively from the patients' medical records. The profile data of the therapeutic effectiveness and therapies were gained from the medical record unit of type 2 DM patients at Nene MallomoGeneral Hospital, Sidenreng Rappang in 2019. Meanwhile, the data on costs were obtained from the finance department unit by considering the hospital's perspectives. These data were then analyzed using the cost-effectiveness analysis. This study design was conducted to determine any differences or therapeutic effectiveness of administering metformin and metformin-glimepiride therapies.

2.1. Tools and Materials

The tool used in this research was a form to collect data. Meanwhile, the research materials used in this research were the patients' medical records and data collection sheets. The subjects of this study were patients with DM who visited Nene Mallomo General Hospital,Sidenreng Rappang from January 2019 to December 2020.

2.2 Research Stages

The data on the study population were collected by considering the inclusion and exclusion criteria determined during the research. The inclusion criteria of this study were 1) new patients diagnosed with type 2 DM and without comorbid diseases or complications; 2) patients aged > 15 years; 3) patients suffering from type 2 DM for at least 1 month since the diagnosis. Meanwhile, the exclusion criteria were 1) patients receiving an additional insulin therapy or another oral antidiabetic therapy in addition to metformin and metformin-glimepiride; 2) patients with cancer diseases; 3) patients infected by human immunodeficiency virus (HIV); 4) pregnant and lactating patients (for female patients); and 5) incomplete, missing, or unreadable data. The data from patient medical records and hospital management information systems were noted, and the data of direct medical costs from the financial unit were collected.

3. Data analysis

A cost-effectiveness analysis was conducted to calculate the cost-effectiveness values using the cost-effectiveness ratio (ACER) and the incremental cost-effectiveness ratio (ICER). In addition, the Chi-squared test was employed to determine the RR of the cohort design. The cost-effectiveness analysis was conducted by comparing the total direct medical costs spent with the effectiveness of outcome therapy obtained. The outcome parameter of DM therapy was the patients' random blood sugar levels after receiving the treatment. The therapy is considered effective if the random blood sugar levels reach the target of <200 mg/dL after the therapies; in contrast, the therapy is considered ineffective if the random blood sugar levels do not reach the target (Soelistijo et al., 2019). Meanwhile, data of cost represent direct medical costs in the form of drug costs, doctor examination and consultation costs, administrative costs, and laboratory costs (random blood sugar tests).

After obtaining and processing the data, they were then analyzed. The data on medical costs were classified according to the therapy received. Afterward, the data were calculated using the ACER method to determine the average direct treatment costs of each drug therapy. The cost was divided by the effectiveness of the therapy by involving an objective examination to gain blood sugar data. To determine the increase in therapy cost, this study employed the ICER method by replacing or adding a treatment that possibly increased the therapy cost; however, this increasing therapy cost will result in significant drug effects and more benefits for the patients.

Furthermore, this study conducted a statistical analysis of the Chi-squared testa cross table-based statistical measurement that tabulates (arranged in a tabular form) a variable in a category and tests a hypothesis for no difference between the observation frequency (observational data) and the expected frequency (theoretical frequency). The chi-squared test was conducted to determine a significant/insignificant difference or a meaningful/meaningless relationship between metformin and metformin-glimepiride therapies and their effectiveness to treat patients with type 2 DM.

4. Results and discussion

The target population of this study was all outpatients primarily diagnosed with DM in the period January-December 2019. This research has been approved by the Research Ethics Committee of Universitas Ahmad Dahlan (KEP UAD) with No. 012011080. The data of 501 DM patients were obtained from medical records at Nene MallomoGeneral Hospital, Sidenreng Rappang.

The obtained data were then selected by considering the inclusion and exclusion criteria. This selection resulted in 30 patients (14 patients with a single therapy o metformin and 16 patients with combination therapy of metformin-glimepiride). Meanwhile, the data on direct medical costs were obtained from the financial unit, including drug costs, examination costs, doctor consultation costs, administrative costs, and laboratory costs. Data of the therapy outcomes are in the form of laboratory

results of random blood sugar levels used as a parameter to determine the therapeutic effectiveness of the drug therapies.

4.1. Demographics of Research Subjects

The demographic data of the research subjects included gender, age, comorbid diseases, and complication diseases. In this study, comorbid diseases are defined as comorbid diseases not related to the diagnosis of the main disease; meanwhile, complication diseases are defined as comorbid diseases related to the diagnosis of the main disease (Liza & Mentari, 2020). The demographics of the research subjects are presented in Table I. The table shows that the number of female patients is higher than male patients at 76.67%. This finding denotes that type 2 DM more frequently occurs in women than in men. Women are more at risk of diabetes because they physically have a greater chance of increasing body mass index (Fatimah, 2015).

The data on age characteristics show that more patients are ≤ 45 years old (70%) than > 45 years old (30%).This research has discovered that DM most frequently occurs in people aged > 45 years because aging decreases insulin sensitivity and body functions for glucose metabolism (Evi & Yanita, 2016). Meanwhile, the characteristics of patients with other comorbid diseases indicate that the number of type 2 DM patients with comorbid diseases is higher than those without comorbid diseases. Comorbid diseases of osteoarthritis and bronchopneumonia have a higher percentage of 20%.

Table. 1.Characteristics ofpatients with type 2 DM at Nene Mallomo General Hospital, Sidenreng Rappang

Characteristics	Total (n=30)	Percentage
Gender		
Male	7	23.33 %
Female	23	76.67%
Age Group		
≤ 45 years old	9	30.00%
> 45 years old	21	70.00%
Comorbid Diseases		
Without comorbid diseases	14	46.67%
With comorbid diseases	16	53.33%
Osteoarthritis	6	20.00%
Tuberculosis	2	6.67%
Bronchopneumonia	6	20.00%
Vertigo	1	3.33%
Gastroesophageal Reflux Disease	1	3.33%
Complication Diseases		
Without complication diseases	18	60.00%
With complication diseases	12	40.00%
Coronary Artery Disease	1	3.33%
Heart Failure	6	20.00%
Dyslipidemia	5	16.67%

Chronic hyperglycemia in DM is suspected to increase inflammation in the joints and degeneration in cartilage; as a result, joint inflammation and the risk of osteoarthritis increase. Previous research conducted at Dr. Soetomo Regional Public Hospital Surabaya in 2018 has discovered that osteoarthritis patients with severe intensity more frequently occur in DM patients (Puspasari & Hidayati, 2020). A meta-analysis study explains that ten studies have reported that type 2 DM has a significant relationship with osteoarthritis, even after body mass index and body weight are controlled (Williams et al., 2016).

Patients with DM tend to increasingly suffer from infections, such as pneumonia (Polat et al., 2017), a disease caused by an infection in the lungs (Dipiro et al., 2015). Moreover, it is reported that a patient diagnosed with a hyperosmolar hyperglycemic state (HHS) is caused by bronchopneumonia infection; this disease is an acute hyperglycemic condition in type 2 DM (Zamri et al., 2020). Another

study has discovered a relationship between DM and mortality of pneumonia patients at Dr. Kariadi Government General Hospital, Semarang (Pitaloka & Wibisono, 2015).

The data on characteristics of DM patients with complications signify that the percentage of patients without complications (60%) is higher than that of patients with complications. This finding is supported by (Laelasari et al., 2017) who conducted research at Sitanala Hospital Tangerang and have discovered that there are more type 2 DM patients without complicated diseases than those with complications. Heart failure is the highest disease suffered by patients with type 2 DM (20%). A previous study has discovered that DM type 2 and heart failure have a significant relationship with morbidity and mortality (Wilkinson et al., 2019). Changes in systemic and cardiac glucose metabolism of patients with various diseases, such as impaired glucose control and DM, result in structural and functional abnormalities of the heart and cardiac dysfunctions (Rosano et al., 2017).

4.2. Cost Effectiveness Analysis

Direct medical costs are the most commonly measured costs and an input, which is used directly to provide therapy (Andayani, 2013). In this study, direct medical costs include drugs, doctor examination and consultation costs, administrative costs, and laboratory test costs. The data on direct medical costs were obtained from the finance unit by calculating and averaging the total direct medical costs. Table 2 shows that the total direct medical costs of metformin and metformin-glimepiride therapies at Nene MallomoGeneral Hospital, Sidenreng Rappang are IDR120,736 and IDR126,298, respectively.These results conclude that the direct medical cost of metformin therapy is less expensive than that of metformin-glimepiride therapy.

Table 2. Direct medical costs of metformin and metformin-glimepiride therapies

Cost Components (IDR)	Type of Therapy	
	Metformin n = 14	Metformin-Glimepiride n = 16
Cost of Medicine		
Total	108,300	212,764
Average	7736	13,298
Cost of Doctor Examination and Consultation		
Total	210,000	240,000
Average	15,000	15,000
Administrative Costs		
Total	238,000	272.000
Average	17,000	17,000
Cost of Random Blood Sugar Test		
Total	1,134,000	1,296,000
Average	81,000	81,000
Average Total of Direct Medical Costs	120,736	126,298

Table 3. Therapeutic effectiveness ofmetformin and metformin-glimepiride therapies

Type of Therapy	Therapeutic Effectiveness (Random Blood Glucose)	
	Effective n (%)	Ineffective n (%)
Metformin (n = 14)	9 (64.29)	5 (35.71)
Metformin-Glimepiride (n = 16)	10 (62.50)	6 (37.50)

In this study, the therapeutic effectiveness is determined by a decreasing random blood glucose level from the first laboratory results to post-therapy-laboratory results, which reach the target of random blood glucose levels. The PERKENI consensus (2015) suggests that therapy is considered effective if random blood glucose levels reach the target of <200 mg/dL after the therapy (Soelistijo et al., 2019). Table 3describes that the administration of metformin therapy is more effective (64.29%) than the administration of metformin-glimepiride therapy (62.50%).

The cost-effectiveness analysis was conducted using the ACER method to compare the total cost of a program or alternative treatment divided by clinical outputs; this analysis produces a comparison

that represents the cost of each specific and independent clinical outcome from the comparators (Kemenkes, 2019). The results of the ACER calculation are summarized in Table 4. The table shows that the administration of metformin therapy has a value of 1877.99 per % therapeutic effectiveness of the therapy. Meanwhile, the administration of metformin-glimepiride therapy has a value of 2020.77 per % therapeutic effectiveness. These results conclude that the administration of single metformin therapy is more cost-effective than the administration of combination metformin-glimepiride therapy. The lower the value of ACER is, the higher the value cost-effective of a group will be (Priharsi et al., 2015).

Table 4. Results of cost-effectiveness analysis from ACER calculations

Type of Therapy	Average Total of Direct Medical Costs (IDR)	Therapeutic Effectiveness (%)	ACER (IDR)
Metformin	120,736	64.29	1877.99
Metformin-Glimepiride	126,298	62.50	2020.77

Note: ACER (Average Cost Effectiveness Ratio)

The cost-effectiveness analysis method with ICER is defined as ratios between the cost differences of two interventions and their different effectiveness. The ICER enables this research to discover the number of additional costs for each change for one unit of cost-effectiveness (Kemenkes, 2013). ICER thresholds are usually expressed by λ, which indicates people's maximum limit of willingness to pay additional health and medical benefits (Bang & Zhao, 2012). The calculation of ICER is presented in **Table V**. The result of ΔC was obtained from differences between the average medical cost of metformin therapy and the average medical cost of metformin-glimepiride therapy. Meanwhile, the ΔE was obtained from differences between the therapeutic effectiveness of metformin therapy and the therapeutic effectiveness of metformin-glimepiride therapy (Priharsi et al., 2015). The ICER calculation has obtained a score of -3107.26 which means that to achieve a 1% increase in the therapeutic effectiveness, the additional cost of -3107. 26 is required. A therapy with negative values of ICER analysis is considered more effective and inexpensive (Andayani, 2013).

Table 5. Results of cost-effectiveness analysis from ICER calculations

Type of Therapy	C	E	ΔC	ΔE	ICER (IDR/% Effectiveness)
Metformin	120,736	64.29	-5562	1.79	-3107.26
Metformin-Glimepiride	126,298	62.50			

Ket: C (Cost); E (Effectiveness); ICER (Incremental Cost Effectiveness Ratio)

4.3. Chi-Squared Analysis

The Chi-squared analysis is one of the statistical tests frequently used to measure the relationship between two categories of variables (Ugoni & Walker, 1995). This study employed the Chi-squared test to determine a significant/insignificant difference or a meaningful/meaningless relationship between metformin and metformin-glimepiride therapies and their effectiveness. The results of the Chi-squared test are presented in Table 6.

Table 6. Analysis results of relationship between "type of therapy and therapeutic effectiveness"

Type of Therapy	Therapeutic Effectiveness		Total	p-Value	RR value
	Effective	Ineffective			
Metformin	9 (64.3%)	5 (35.7%)	14 (100%)		
Metformin-Glimepiride	10 (62.5%)	6 (37.5%)	16 (100%)	1.000	1.080
Total	19 (63.3%)	11 (36.7%)	30 (100%)		

Note: RR(Risk Ratio)

The test results of the Chi-square test show the p-value is 1.000. If the p-value is < 0.05, H0 is rejected and Ha is accepted; vice versa. H0 indicates no relationship between the two variables, and Ha indicates a relationship between the two variables. Therefore, the p-value of 1.000 > 0.05 signifies no relationship between metformin and metformin-glimepiride therapies and their effectiveness for

patients with type 2 DM at Nene Mallomo General Hospital, Sidenreng Rappang. Lulu and Imaniar (2019) conducted a study at three public health centers in Yogyakarta and have discovered no relationship between the accuracy of the therapy and its outcome although a combination therapy in the three public health centers is more widely used (Hauri & Faridah, 2019).

The parameter of relationship strength used in this study is the risk ratio (RR), which has obtained an RR value of 1.080 and a conventional interval of 95% of 0.243-4.791. These results conclude that metformin therapy has 1,080 times as effective therapeutic effectiveness as metformin-glimepiride therapy.

5. Conclusion

ACER and ICER values show that the single metformin therapy is more cost-effective than the combination metformin-glimepiride therapy. The single metformin therapy's ACER value is 1877.99, and its ICER value is -3107.26. The Chi-squared test has revealed no relationship between the types of therapies and their therapeutic effectiveness with a p-value = 1000 and an RR value = 1080. These findings indicate that the administration of metformin therapy has 1,080 times as effective therapeutic effectiveness as the administration of metformin-glimepiride therapy. The retrospective method causes less maximal effectiveness data; thus, it is necessary to conduct a study using a prospective method.

Author Contributions: Shabran Hadiq conducted and designed the study. Shabran Hadiqcollected and analyzed the data. Shabran Hadiq, Woro Supadmi and Dyah Aryani Perwitasari interpreted the results and revised the journal. Shabran Hadiq wrote the manuscript. All of the authorsread and approved the final manuscript.

Funding

This research was funded by the Directorate of Research and Community Services of the Directorate General of Research Development, Research Strengthening, and Higher Education or the National Research and Innovation Agencywith the contract number: PTM-011/SKPP.TT/LPPM UAD/VI/2020 dated June 08, 2020.

Competing Interests

The authors declare no conflict of interest.

Acknowledgment

The authors would like to thank the Directorate of Research and Community Services of the Directorate General of Research Development, Research Strengthening, and Higher Education or the National Research and Innovation Agency for funding this research. Moreover, the authors would like to thank Nene Mallomo General Hospital, Sidenreng Rappang and Universitas Ahmad Dahlan Yogyakarta for providing support and facilities so that this research could be completed.

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