ORIGINAL ARTICLE

TREATMENT PATTERN AND COST-EFFECTIVENESS ANALYSIS OF ORAL HYPOGLYCEMICS FOR TYPE 2 DIABETES MELLITUS OUTPATIENTS AT REGIONAL GENERAL HOSPITAL, INDONESIA

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ABSTRACT

Type 2 diabetes mellitus (DM) has become a major problem, with most cases appearing as a degenerative disease that is almost uncontrollable using single or combined oral therapy. Therefore, this study aims to examine the sociodemographics, treatment pattern, and cost-effectiveness analysis of oral hypoglycemics for type 2 DM outpatients at Cempaka Putih Regional General Hospital, Central Jakarta, Indonesia. This descriptive study was conducted within six months using a cross sectional design. The inclusion criteria were 18 years old type 2 DM patients receiving outpatient treatment, patients with a primary diagnosis of type 2 DM without complications, health insurance (BPJS), good medical records, and the pharmacoeconomic values approach with the Cost-Effectiveness Analysis (CEA) method, which is a review from hospital and healthcare perspective. A total of 79 patients participated and the analysis was carried out using ACER and ICER calculations of cost-effective therapy in each group. The results showed that the most cost-effective therapy for the oral group is a biguanide with metformin 500 mg and an ACER value of IDR19,196, 2 combination therapies namely Glibenclamide and metformin with ACER of IDR39,160, and the 3 combinations of metformin + glimepiride + acarbose IDR156,761. The lowest calculation of ICER value was between monotherapy metformin IDR16,896 and oral combination of metformin + glibenclamide IDR19,883. This indicated that pharmacoeconomic data allow users to make more rational decisions in selecting therapy, treatment, as well as clinical and administrative decision-makers, including physicians, pharmacists, formulary committee members, and administrators for insurance companies.

Keywords: Oral Hypoglycemics, Type 2 Diabetes, Cost-Effectiveness Analysis, OutPatient

INTRODUCTION

Type 2 Diabetes mellitus (DM) is a group of chronic metabolic disorders due to abnormalities in carbohydrate, fat, and protein metabolism characterized by hyperglycemia, which leads to micro and macrovascular, as well as neuropathic complications[1]. This disease is caused by multi-factorial originating from genetic factors with impaired insulin secretion, resistance, and environmental factors such as obesity, lack of exercise, all types of stress, and aging. The common symptoms include frequent urination, intense thirst and hunger, weight gain, unusual weight loss, fatigue, slow-healing sores and bruises, male sexual dysfunction, numbness, and tingling in the hands and feet[2]. The World Health Organization (WHO) predicts that the number of type 2 DM patients in Indonesia will increase from 8.4 million in 2000 to approximately 21.3 million in 2030. The International Diabetes Federation (IDF) also explained that between 2013 and 2017, DM patients increased from 20.3 million to 16.7 million[3]. Based on the 2018 Basic Health Research reports from the Indonesian Ministry of Health, the prevalence of the disease to 8.5%[4]. Meanwhile, DKI Jakarta Province experienced an increase of 2.5% to 3.4% between 2013 and 2018[4].

Oral antidiabetic treatment given to type 2 DM patients is carried out in the long term, but the cost increases annually, thereby creating an economic burden. For outpatients, the treatment is in form of single or combination therapy. Combination treatment is needed when type 2 DM therapy with monotherapy can not control the desired clinical HbA1C value[5].

A previous report stated that the cost of ADO used for inpatients in hospitals shows a significant value for combination and monotherapy with 55.65% and 44.34%, respectively[6]. Meanwhile, Gupta et al. (2021) stated that the results of drug combination therapy were 72.00% compared to Monotherapy at 28.00%[7]. Based on the American Diabetic Association estimation, the total annual economic cost of DM in America will reach 174 million dollars by 2021. Furthermore, the total medical expenditures are 116 billion dollars, consisting of 27, 58, and 31 billion dollars for diabetes care, chronic diabetes associated with several complications, and general medical costs, respectively[8].

Drug usage cost analysis shows funds effectiveness related to the use of direct and indirect medical costs based on the average class of treatment. It is also a method to select and assess the best program or drug when there are several options

with the same goal. The cost of health investigations, particularly the increasing cost of drugs, is influenced by the pattern of disease, changes in treatment, the use of highly sophisticated technology, and the elevated demand for health [9]. This indicated that an effective single and combination type 2 DM therapy is needed with a pharmacoeconomic approach using cost-effectiveness analysis. Therefore, this study aims to analyze the cost of using effective Oral Hypoglycemics for type 2 DM outpatients at the regional general hospital.

METHODS

Study Design/Setting

This descriptive study was conducted using a crossectional and retrospective design with data on outpatient treatment costs for type 2 DM. The use of the databases of the Social Health Insurance Administration Body (BPJS) was established to provide a health insurance program for Indonesian and the BPJS Registry of outpatients from January to December 2021.

Study Population and Sampling procedures

This study used the pharmacoeconomic values approach with the Cost-Effectiveness Analysis (CEA) method, which is a review from the hospital's perspective. The non-probability sampling, specifically the purposive technique was used based on consideration of inclusion and exclusion criteria. The inclusion criteria were 18 years old type 2 DM patients receiving outpatient treatment at the Cempaka Putih Hospital, patients with a primary diagnosis of type 2 DM without complications, single oral hypoglycemics or in combination, outpatients with health insurance (BPJS), good medical records and complete costs, including administration of patient identity consisting of name, gender, age, drug name, number of drugs, as well as the HBA1C laboratory data before and after 6 months of treatment. Meanwhile, the exclusion criteria were characteristics of population members who can not be selected as samples, namely loss treatment, type 2 DM patients on insulin, or died while receiving treatment from January to December 2021. The data obtained were medical record number, initial name, gender, and patient's age. The patients' clinical data consisted of the primary diagnosis of diabetes, the HbA1C value at the first initial examination and after 6 months of treatment, as well as the cost of diabetes drugs used during the outpatient treatment for six months until the time of the last control. The total direct medical cost analysis method was used, which includes all costs incurred for the type 2 DM outpatient treatment in 2020 at Cempaka Putih Hospital, Central Jakarta, specifically BPJS patients. The percentage value of effectiveness was calculated using the Health Organization guide to cost-effectiveness analysis (CEA).

Cost-effectiveness Analysis

The data were evaluated using descriptive analysis and the cost was calculated to obtain the most cost-effective antidiabetic therapy model for patients' treatment. The Cost-Effectiveness Analysis (CEA) calculated using the Cost-Effectiveness Ratio (ACER) formula was based on the total cost of antidiabetic use on its effectiveness to determine the most cost-effective therapy. ACER was calculated based on the equation from the World Health Organization guide to cost-effectiveness analysis (CEA). Subsequently, differences between DM and other diabetes treatments were analyzed using the Incremental Cost-Effectiveness Ratio (ICER) to determine the cost of each change in one unit of cost-effectiveness. The ICER was estimated using the ICER equation from the World Health Organization guide to cost-effectiveness analysis (CEA)[10].

Ethical Consideration: Ethical approval for this study was granted by the ethics committee of Health Polytechnic, Health Ministry Jakarta II, Indonesia, with ethical number LB.02.01/KE/39/212/2021.

RESULTS

This study was conducted at Cempaka Putih Regional General Hospital with a total sample of 79 patients, consisting of 49 females or 62.03% and 30 males or 37.97% who received treatment for type 2 DM with monotherapy and oral combination. The demographic characteristics of the patients are shown in Table 1.

The majority of patients namely 27 or 69.23% were in the productive age group ranging from 15-64 years. This is in line with Ghadah (2021) who stated that type 2 DM patients aged between 41-58 years are more susceptible to decreased physical activity, leading to abnormalities of glucose metabolism. This will affect glucose induction on insulin secretion and resistance. A total of 32 patients or 40.51% had long-term treatment for more than 2 years, while 21 patients or 26.58% received a combination of 2 drugs, 25 or 15.19% received 3, and 21 or 26.58% received only one. Furthermore, 57 patients who experienced HbA1C examinations had HbA1C values ranging from 7-9%, while 37 or 46.84% during the 6 months of treatment had HbA1C levels in the category of < 7%. This is in line with Johny et al. (2017) who reported that among the 22 respondents with type 2 DM, 17 or 77.3% had uncontrolled HbA1c levels namely above 7%[11], which can cause complications. Therefore, the ADA (American Diabetes Association) recommended that HbA1c levels < 7% or > 7% be declared controlled and uncontrolled in diabetes patients, respectively.[9]

Table 1: Demographic Characteristics Data and Clinical outcome of Type 2 DM Patients

Sociodemographic Characteristics	Total Patients N=79	Percentage (%)
Gender		
Female	49	62.03
Male	30	37.97
Age		
Productive (15-64 years)	50	69.23
Non-Productive <15 and ≥65 years	29	30.77
Long-term		
Less than 1 year	19	24.05
1-2 Years	28	35.44
> 2 Years	32	40.51
Treatment pattern		
Single ADO	21	26.58
Combination of Two	33	58.23
More Two Treatment	25	15.19
Initial Clinical Outcome		
HbA1C < 7 %	7	8.86
HbA1C 7-9 %	57	72.15
HbA1C > 9%	15	18.99
Final result Clinical Outcome		
- HbA1C < 7 %	37	46.84
- HbA1C 7-9 %	35	44.30
- HbA1C > 9%	2	8.86

Characteristics of Treatment Pattern

Data on the use of oral antidiabetic drugs for 6 consecutive months showed a total prescription of 480 R/(monotherapy and combination therapy pattern). The highest number and percentage of drugs prescribed was a combination of two ADOs with 204 R/, namely 43.50%. The data on the pattern of diabetes therapy are shown in Table 2.

Table 2: Treatment Pattern of Type 2 DM Patients

Therapy Pattern	Types of Medicine	Total R/	Percentage (%)
Monotherapy		**126**	**26.25**
B	Metformin	90	18.75
S	Gliquidone	18	3.75
S	Glimepiride	6	1.26
α	Acarbose	12	2.49
Two combination therapy		**204**	**42.50**
B+S	Metformin +Glimepiride	102	21.26
	Metformin +Gliquidone	24	4.99
	Metformin + Glibenklamida	6	1.25
α+S	Acarbose +Gliquidone	30	6.25
	Acarbose +Glimepiride	30	6.26
B+α	Metformin +Acarbose	12	2.49
Three combination		**150**	**31.25**
	Glimepiride +Metformin +Acarbose	114	23.75
S+B+α	Glibenklamida +Metformin + Acarbose	18	3.75
	Gliquidone +Metformin + Acarbose	18	3.75

B:Biguanide; S:Sulphonylurea;a: alfa glucosidase

According to Table 2, the use of oral antidiabetic drugs for 6 consecutive months showed a total prescription of 480 R/(monotherapy and combination therapy pattern). The highest number and percentage of drugs prescribed was a combination of two ADOs with 204 R/ namely 43.50%. The data on the pattern of diabetes therapy are shown in Table 2.

Among the total number of prescriptions, Monotherapy had 126 R/, while Metformin was prescribed with Monotherapy ADO for 90 R/ or 18,75%. The most prescribed drug regimen was a combination of two ADOs up to 204 R/ or 43.50%, while the combination of metformin + glimepiride was prescribed up to 102 R/ or 21.26%. Moreover, the group of three combinations of ADO most frequently prescribed was Glimepiride + Metformin + Acarbose for 114 R/ or 23.75%.

Cost-Effectiveness Analysis

Pharmacoeconomic studies can provide a cost-effectiveness measure that shows the success of antidiabetic drugs in achieving targeted blood sugar levels. DM diagnosis has an HbA1c value of 6.5% using the National Glycohaemoglobin Standardization Program (NGSP) method. Meanwhile, the cost-effectiveness in type 2 DM patients is shown in Table 3.

Table 3: Cost-effectiveness of single and combination of antidiabetic therapy in outpatients

Therapy Pattern	Number of Patients	Overall Price of Medicines (IDR)/month	Overall Price of Medicines (IDR)/peryear	Average value of HbA1C before	Average value of HbA1C after six months	Average difference (%)
Monotherapy						
Metformin	15	268.650	3.223.800	8.49	7.14	1.06
Glikuidone	3	116.190	1.394.280	8.33	7.00	1.33
Acarbose	2	86.400	1.036.800	8.20	7.60	0.60
Glimepiride	1	63.900	766.800	7.70	6.80	0.90
Two combination						
- Metformin +Glimepiride	17	485.520	5.826.240	9.27	7.83	1.44
- Acarbose + Glikuidone	4	327.720	3.932.640	9.38	8.58	0.80
- Metformin +Glikuidone	4	321.780	3.861.360	8.22	7.05	1.17
- Acarbose + Glimepiride	5	269.000	3.228.000	7.86	6.92	0.94
- Acarbose + Metformin	2	122.220	1.466.640	7.95	6.70	1.25
- Metformin +Glibenclamide	2	78.320	939.840	7.90	6.80	0.70
Three combination						
- Metformin+ Glimepiride + Acarbose	19	1.876.440	22.517.280	8.60	7.78	0.82
- Metformin+Glibenklamida + Acarbose	3	272.580	3.270.960	7.16	6.43	0.73
- Metformin +Glikuidone+ Acarbose	3	415.710	4.988.520	8.70	8.00	0.70

The most effective type of single oral antidiabetic treatment was metformin used by 15 patients with an average difference in HbA1C level of 1.06%. Meanwhile, 17 patients took a combination of metformin + glimepiride, with an average difference in HbA1C achievement of 1.44%.

Characteristics of Cost-effectiveness Based on ACER (*Average Cost-Effectiveness Ratio*) and ICER (*Incremental cost-effectiveness ratio*)

The cost-effectiveness analysis was carried out using the ACER and ICER methods. ACER is the cost required to increase the effectiveness of each treatment[12]. Both analyses of single and combined oral antidiabetic therapy are shown in Table 4a. The most cost-effective Monotherapy group had the lowest ACER value, namely the biguanide group with the drug metformin at an ACER value of IDR19,196 per outcome and a percentage difference of 1.06% HbA1C. However, in the combination of 2 classes of drugs, the most cost-effective with the lowest ACER value were Glimepirid and glibenclamide with an ACER value of IDR39,160 per 0.7% decrease in HbA1C outcomes as well as Metformin + glimepiride with an ACER value of IDR30,344 per 1.44% decrease.

Table 4a: ACER analysis of single and combined oral antidiabetic therapy at Regional General Hospital

Therapy Pattern	Total cost of treatment (per/month)	Total patient	Outcome therapy HbA1C	Effectiveness (%)	ACER (IDR/$^{mg}/_{dL}$)
Monotherapy					
- Metformin	17.910	15	14	93.30	19.196
- Glimepiride	22.650	1	1	100	22.650
- Glikuidone	38.730	3	2	66.70	58.065
- Acarbose	43.200	2	1	50.00	86.400
Two Combination Therapy					
- Metformin +Glibenklamide	39.160	2	2	100	39.160
- Metformin+Glimepirid	28.560	5	4	94.12	30.344
- Metformin +Acarbose	61.110	2	2	100	61.110
- Acarbose +Glimepiride	53.800	5	4	80	67.250
- Metformin +Glikuidone	80.445	4	3	75	107.273
- Acarbose+Glikuidone	81.930	4	3	60	136.550
Three Combination					
- Metformin + Glimepiride +Acarbose	98.760	19	12	63.16	156.761
- Metformin + Glibenklamide + Acarbose	90.860	3	1	33.33	275.333
- Metformin + Glikuidon Acarbose	138.570	3	1	33.33	419.909

The combination of the 3 types of oral antidiabetic therapy with the most cost-effective value is Metformin + Glimepiride + Acarbose with an ACER value of IDR156,761 per outcome reduction of 0.80% in HbA1C. One of the main requirements in the cost-effectiveness analysis of drugs is to calculate the ICER value, which is financing issued to optimize the effectiveness of the value of one therapy to another. Therefore, the calculation value of ACER and ICER has the same advantages and benefits, the results are shown in Table 4b.

Table 4b: ICER analysis of oral single and combination antidiabetic therapy at Regional General Hospital

Therapy Pattern	Total cost per/month	ΔE (mg/dL)	ΔC	ICER (IDR/$^{mg}/_{dL}$)
Monotherapy				
- Metformin	17.910	1.06	17.910	16.896
- Glimepiride	22.650	0.90	22.650	25.160
Combination Therapy				
- Metformin + Glimepiride	28.560	1.44	28.560	19.883
- Metformin +Acarbose	32.550	1.25	61.110	26.040
- Metformin +Glikuidone	80.445	1.17	19.335	16.525
- Metformin+Glimepiride+Acarbos	98.760	0.82	90.860	90.860

The ICER results from the ADO Monotherapy group showed that metformin cost IDR16,896. This indicated that metformin from the biguanide group had the most cost-effectiveness value compared to the sulfonylurea group with an additional cost of IDR25,160 for every increase in the outcome. Meanwhile, the 2 most cost-effective ADO combinations with the lowest ICER value were metformin and glimepiride with a value of IDR19,883 per mg/dl.

DISCUSSION

The majority of type 2 DM patients namely 27 or 69.23% were in the productive age group between 15-64 years. This is in line with Ghadah who stated that type 2 DM patients aged 41-58 years are more susceptible to a decrease in physical activity, leading to abnormalities of glucose metabolism. This will affect glucose induction on insulin secretion and insulin resistance[8]. A total of 57 patients had initial HbA1C values ranging from 7-

9%, but the clinical value during the 6 months of treatment was < 7% for 37 patients or 46.84%. Johny also reported that among the 22 respondents with type 2 DM, 17 or 77.3% had uncontrolled HbA1c levels, which were above 7%[11] and can cause complications. Therefore, the ADA (American Diabetes Association) recommended that HbA1c levels < 7% and > 7% be declared controlled and uncontrolled, respectively, in diabetes patients[9].

Saroj et al. (2019) stated that the most frequently prescribed combinations of oral antidiabetic drug groups were the combination of biguanides and sulfonylureas with up to 68 prescription sheets (54.50%)[13]. This combination has a complementary mechanism of action and a synergistic effect on insulin receptor sensitivity. Sulfonylureas will stimulate insulin secretion by pancreatic beta cells, thereby potentiating the effect of biguanide compounds to work effectively and improve insulin sensitivity by enhancing glucose uptake in muscles[14]. The selection of the proper oral antidiabetic drug will determine the success of diabetes therapy. This showed that there is a need to consider the severity of DM and patients' general health condition, including other diseases and complications[15].

Several studies reported that the fixed-dose combination of glimepiride+metformin is as effective as glibenclamide+metformin in reducing HbA1c, however, more patients achieve HbA1c<7% at 12 months of treatment with glimepiride/metformin[16]. The therapeutic outcomes produced by the 2 combinations had the same large ratio of % HbA1C reduction, namely glimepiride + metformin by 1.44% and glibenclamide + metformin by 1.17%. Furthermore, the most cost-effective combination of these drugs is the sulfonylurea and the biguanide group. The risk of hypoglycemia and weight gain can be minimized by using modern sulfonylureas such as glimepiride and gliquidone with fewer side effects and better efficacy, which contributes to their wider use. Combination therapy also shows a more significant blood-glucose-lowering effect than single-use as shown in various investigations, leading to the marketing of fixed-dose combinations (FDC) preparations[17]. Patients in the metformin group had better HbA1C levels than other antidiabetics because they had a higher target HbA1C value than the other groups[11, 18]. The metformin therapy group's quality of life scores were also the best compared to other antidiabetics. Efficacy parameters indicate that metformin therapy is more effective than other diabetes treatments[19].

The management of pharmacotherapy in patients with type 2 DM showed that metformin is one of the oral glucose-lowering drugs as the first line of choice. The treatment is the optimal initial therapy for DM monotherapy patients and is also used in combination with other glucose-lowering drugs because of high tolerance and minimal side effects[20]. Furthermore, the average cost of treatment in the metformin group was minimal compared to other diabetic therapy. This is because the specific type used was generic metformin, which has a low unit price per tablet. Metformin-sulfonylurea combination therapy has efficacy in controlling fasting blood glucose levels and long-term drug administration, without considering patients' food intake[21]. This combination therapy can also cause hypoglycemia and complaints related to the digestive tract[14]. The administration of sulfonylureas caused hypoglycemia in patients due to the drug's mechanism of action, which increases insulin secretion, thereby significantly reducing patients' sugar levels (hypoglycemia). High doses of metformin can cause side effects such as gastrointestinal bleeding, but there is no evidence of death from the combined use of metformin and sulfonylurea[22].

The lowest ICER value in the combination of the 3 drug classes was IDR90,860, which include biguanides (metformin), sulfonylureas (glibenclamide), and alpha-glucosidase (Acarbose). However, studies on the therapy of the 3 types of oral antidiabetic drug combinations are still limited. According to Tri Murti, the combination of ADO therapy with the addition of a third drug had a limiting value in reducing HbA1C levels (< 1.5-2%), hence, insulin is a more suitable choice for DM patients to control blood levels. Patients' blood sugar was lower as demonstrated by HbA 1c >9.5 % with 2 ADO combination therapy. The combination of 3 types of oral antidiabetics, specifically the sulfonylurea-metformin-thiazolidinediones, improved glycemic control in one placebo-controlled study. However, it was not approved by the FDA because of side effects that were discovered in other studies, where metformin affected the GI tract, acarbose caused digestive problems, and glibenclamide caused very rapid hypoglycemia[23].

The limitations of this study are that it did not identify insulin administration because the site was in a type C hospital. After receiving insulin preparation therapy, patients are referred to a regional general hospital with a complete dosage form. The addition of insulin in uncontrolled type 2 DM patients using a combination of 2 ADOs is more effective than 3 ADOs. Insulin can also be administered as monotherapy without the addition of ADO. This therapy is less expensive than the combination of ADO and insulin, but it has a more significant effect on weight gain and frequent episodes of hypoglycemia[24]. The tremendous economic burden of diabetes makes the disease an important clinical and public health problem. This makes it necessary to track future economic trends as healthcare policy, morbidity, and mortality evolve to formulate an effective response. Therefore, it is recommended

that further studies focus on refining methods to estimate costs, improve the interpretation of results, involve a large population, at different locations, and facilitate comparisons between studies.

CONCLUSIONS

The most cost-effective therapy for the oral group is a biguanide with metformin 500 mg with an ACER value of IDR19,196 and ICER of IDR16,896 (Rp/mg/dL). The cost-effectiveness analysis of oral antidiabetic therapy can provide benefits for choosing alternative treatments with lower costs for each clinic outcome (HbA1C) obtained. Meanwhile, the most cost-effective alternative is not always the cheapest for achieving a specific therapeutic goal. The patient's use of multiple medications also contributes to multiple drug interactions, which can sometimes be severe. This is possibly prevented by close monitoring of drug therapy and avoiding the use of some medications for less severe indications. When appropriately used, pharmacoeconomic data allows users to make more rational decisions in selecting therapy, treatment, as well as clinical and administrative decision-makers, including physicians, pharmacists, formulary committee members, and administrators (insurance companies).

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Conflict of Interest
All authors declare there is no conflict of interest with this study.

Contribution of Authors
This study was conducted by the authors named in this article, who contributed equally, and all liabilities for content-related claims are borne by them.

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