NARRATIVE REVIEW: COST-EFFECTIVENESS ANALYSIS OF BIGUANIDE AND SULFONYLUREA FOR HOSPITALIZED PATIENT WITH TYPE 2 DIABETES MELLITUS

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ABSTRACT

Diabetes mellitus requires management in the long term at a considerable cost. Therefore, a cost-effectiveness analysis was used to assess several health interventions in this study, the biguanide and sulfonylurea drugs, which gave the best results at the lowest cost. This study aimed to obtain a theoretical basis that supports the cost-effectiveness of a biguanide and sulfonylurea drugs. The method used in this study is the Narrative Review uses literature that discusses the cost-effectiveness of oral antidiabetic drug treatment of the biguanide class and sulfonylurea in type 2 diabetes mellitus patients. The results show that the age range for type 2 diabetes mellitus was 45-65 years, with the percentage of male patients larger than females and the most common complication was hypertension. Biguanide (metformin) drugs significantly decreased blood sugar levels at a reasonably low cost in this study. The Incremental Cost-Effectiveness Ratio (ICER) results show that combination drugs increase the additional cost, but their use is more effective in healing and improving patients' quality of life. In conclusion, biguanide and sulfonylurea class drugs are cost-effective compared to other antidiabetic drugs.

Keywords: Biguanide; Sulfonylureas; Cost-Effectiveness Analysis; Narrative review; Type 2 Diabetes Mellitus (T2DM)

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INTRODUCTION

Diabetes Mellitus is defined as a group of metabolic diseases with characteristic hyperglycemia caused due to abnormalities in insulin secretion, the work of Insulin or both. In the long term, hyperglycemia can cause damage and dysfunction in various organs, such as retinopathy, nephropathy, and ¹neuropathy[1]. About 8.8% of diabetes patients worldwide occur in people aged 20-79 years old. Type 2 Diabetes Mellitus (T2DM) accounts for 90% of all diabetes mellitus cases[2.] The prevalence of Diabetes Mellitus in Indonesia for those over-15 years old has increased from 5.7% in 2007 to 6.9% in 2013 and 10.9% in 2018[3,4.]

The pharmacological therapy used in Diabetes Mellitus type 2 is oral antidiabetics and Insulin. Diverse antidiabetics need to adjust aspects of therapy and costs because patients are entitled to therapy with good clinical outcomes and higher therapeutic cost-efficient. The Cost-Effectiveness Analysis (CEA) method can select some health interventions that provide the best results at the cheapest cost[5].

T2DM treatment aims to control blood sugar levels to improve the quality of life.

Therefore, it is necessary to prepare adequate costs. T2DM therapies have been available with their mechanisms of work and effectiveness. The cost of therapy incurred by the patient is one of the factors in drug selection. This study aimed to know the difference in cost-effectiveness in Type 2 Diabetes Mellitus patients who use the antidiabetic oral biguanide group and sulfonylurea group.

RESEARCH METHODS

Type of research

The type of research conducted in this study is *Narrative Review*. The literature used in this study is research on the cost-effectiveness analysis of antidiabetic drugs biguanide and sulfonylurea inpatients with T2DM

Research Time

The study was conducted from June to July 2020.

Inclusion and Exclusion Criteria

The literature used must meet the following criteria (1) using English and Indonesian writing, (2) published in 2010-2020, (3) accessible free full-text through PubMed, EBSCO, and Google Scholar electronic databases. (4) The literature discusses the analysis of the effect of the cost of treatment of patients diagnosed with Type 2 Diabetes Mellitus who use antidiabetic drugs biguanide and sulfonylurea groups, (5) contains a picture of the profile of patients such as gender, age, blood sugar levels, Body Mass Index (BMI), complications or accompanying diseases undergoing outpatient therapy.

Method

Creating *Narrative Review* is not mandatory; however, structured approaches such as PRISMA-P 2015 used in systematic *reviews* may be suggested in Narrative Review[6].

Literature search strategy

The literature search strategy used in this study is literature that meets the criteria using the PICO method. In addition, literature searches use keyword cost-effectiveness analysis, type 2 diabetes mellitus, cost-effectiveness analysis, type 2 diabetes mellitus, Glimepiride, and Metformin from 2010 to 2020. Furthermore, the literature documentation is carried out based on the title, the researcher's name, the literature's context, and the literature's variables.

Data extraction

Data extraction is done by reviewing aspects of population, intervention, outcomes and results that will be entered into a table compiled based on extraction form data that contains the following information: (1) author, (2) year of publication, (3) population criteria, (4) intervention, (5) comparator, (6) outcomes or results.

Data synthesis

The synthesis of data in narrative review is conducted narratively to analyze the effectiveness of the cost of antidiabetic drugs in patients with type 2 diabetes mellitus who use antidiabetic drugs biguanide and sulfonylurea as a single or combination drug. The collected literature is then analyzed to be discussed to conclude.

RESEARCH RESULTS

The results of this study are based on 1026 pieces of literature that have relevant potential filtered for eligibility, coming from PubMed, Cochrane, EBSCO, and Google Scholar. In the research process, 419 pieces of literature were found and then excluded based on free full-text screening, resulting in 648 potential literatures. Because the literature did not meet the inclusion criteria, 303 types of literature were excluded. After the screening, 109 types of literature were again excluded based on their titles and abstracts. Seven potential literature tested for eligibility are included in this narrative review.

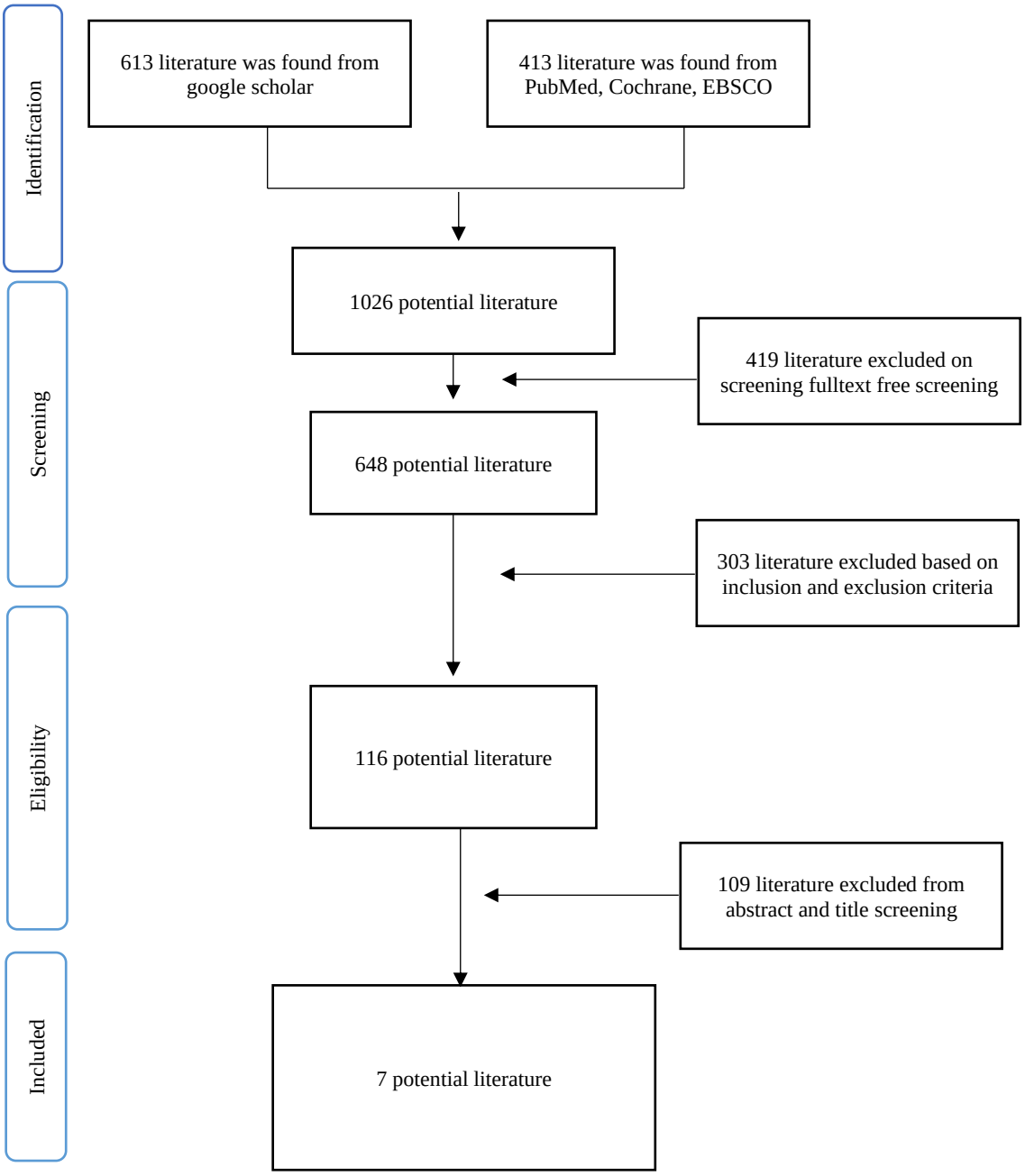

Chart 1. Flow of Literature Search Strategy

Table 1. Characteristics of The Literature Studied

No.	Country, Author, Year	Year of Data Retrieval	Characteristics of the Patient	Intervention & Comparator	Intervention & Comparator	Clinical Outcome / QALY	Cost	ICER
1.	India, Tandon *et al*., 2020	NA	Average age 47.64-48.75 years Average HbA1c 8.85-9.06% Average FDP 172.28-160.5 mg/dl Average PBG 271.21-256.75 mg/dl Average BMI 25.70-24.17$^{kg/m2}$ Number of patients: 39	• Metformin (500 mg) + Glimepiride (1 mg) • Metformin (500 mg)+ Teneligliptin (20 mg)	• Metformin (500 mg) + Glimepiride (1 mg) • Metformin (500 mg)+ Teneligliptin (20 mg)	• Metformin + Glimepiride Decrease in HbA1c 1.7% Decrease in FBG of 35.78 mg/dl Decrease in PBG 69.7 mg/dl Decrease in BMI of 0.14$^{kg/m2}$ • Metformin + Teneligliptin Decreased HbA1c 1.52% Decrease in FBG of 32.95 mg/dl Decrease in PBG 64.14 mg/dl • Decrease in BMI of 0.12 kg/m2	Cost of reduction per unit parameter • Metformin + Glimepiride HbA1c per 0.1%: INR 12,77 FPG per 1 mg/dl: INR 7.45 PPG per 1 mg/dl: INR 6.40 • Metformin + Teneligliptin HbA1c per 0.1%: INR 19.78 FPG per 1 mg/dl: INR 19,13 • PPG per 1 mg/dl: INR 8.72	• NA
2.	Nepal, Dhakal *et al*., 2019	2017	Newly diagnosed and followed up within three months Average age 50-60 years The male percentage was	• Metformin • Metformin + Sitagliptin • Metformin + Sulfonylurea	• Metformin • Metformin + Sitagliptin • Metformin + Sulfonylurea	Average FBG • Before Metformin: 155.34 mg/dl Metformin + Sitagliptin: 191.73 mg/dl	• Metformin: NRs 360 • Metformin + Sitagliptin: NRs 2,340	• NRs. 7.64 per mg/dl decrease in blood sugar levels

			58.7%, and female 41.3% Number of patients: 63			• Metformin + Sulfonylurea: 187.69 mg/dl • After Metformin: 130.33 mg/dl Metformin + Sitagliptin: 144.96 mg/dl • Metformin + Sulfonylurea : 137.34 mg/dl	• Metformin + Sulfonylurea : NRs 601.2	
3.	Thailand, Permsuwan *et al*., 2016	2014	Average age 72.8 years The average duration of diabetes is 10.5 years Average HbA1c 7.9% Time Horizon: Lifetime	• Saxagliptin (5 mg) • Sitagliptin (100 mg) • Vildagliptin (100 mg) • Metformin (2000 mg) • Sulfonylurea/glipizide (10 mg)	• Saxagliptin (5 mg) • Sitagliptin (100 mg) • Vildagliptin (100 mg) • Metformin (2000 mg) • Sulfonylurea/glipizide (10 mg)	QALY: • Saxagliptin: 5,965 years • Sitagliptin: 5,965 years • Vildagliptin: 5,965 years • Metformin: 5,986 years • Sulfonylurea/glipizide: 5,933 years •	Total Cost • Saxagliptin: THB 406,876 (US$ 12,344.54) • Sitagliptin: THB 434,982 (US$13,197.27) • Vildagliptin: THB 428,869 (US$13,011.80) • Metformin: THB 283,222 (US$8,592.90) • Sulfonylurea/ glipizide : THB 293,175 (US$ 8,894.87)	• Saxagliptin – Metformin: Dominated • Sitagliptin – Metformin: Dominated • Vildagliptin – Metformin: Dominated • Saxagliptin – Sulfonilurea: THB 3,632,604 (US$ 110,212.50) • Sitagliptin – Sulfonilurea: THB 4,530,556 (US$ 137,456.19) • Vildagliptin – Sulfonilurea : THB 4,335,273

								(US$ 131,531.34)
4.	China, Nian *et al*., 2020	NA	Time Horizon: Lifetime Number of patients: 33,830	• Metformin (1500 mg) vs placebo • Dapalyphzolin (10 mg) vs placebo	• Metformin (1500 mg) vs placebo • Dapalyphzolin (10 mg) vs placebo	• Metformin: 11.12 years • Dapalyphzolin : 11.03 years	Total Cost • Metformin: $15,262 • Dapaglifzolin - $17,450	• NA
5.	Indonesia, Laelasari *et al*., 2017	NA	Most patients are female with an age range of 50-59 Number of patients: 97	• Insulin • Sulfonylurea • Metformin + Sulfonylurea	• Insulin • Sulfonylurea • Metformin + Sulfonylurea	Average difference in HbA1c • Insulin:8.42% • Sulfonylureas: 8.17% • Metformin + Sulfonylurea: 7.48% Effectiveness • Insulin: 77.2% • Sulfonylureas: 79% • Metformin + Sulfonylurea : 86.9%	• Insulin: Rp 3,154,830 • Sulfonylurea: Rp 108,894 • Metformin + Sulfonylurea :Rp 227,761	• Metformin + Sulfonylurea – Sulfonylurea Rp 16,194
6	Indonesia, Wulandari *et al*., 2020	2018	The average age is 46-50 years and 50-55 years Number of patients: 176	• Metformin • Glimepiride	• Metformin • Glimepiride	• NA	Average cost • Metformin: Rp 1,209 • Glimepiride : Rp 1,228	• NA
7	Indonesia, Ramdhoni, 2018	2016	Percentage of Male Sex 46.43% Female 53.57% Age <65 years Number of patients 28 years old	• Metformin • Glimepiride	• Metformin • Glimepiride	Effectiveness • Metformin: 70% • Glimepiride: 62.5%	Total cost • Metformin: Rp 498,628 • Glimepiride : Rp 432,221	• Rp 20,771,829

NA: Not Available
HbA1C: Hemoglobin A1C
FDP: Fasting Blood Glucose
PBG: Postpandrial Blood Glucose

INR: Indian Rupee
THB: Thai Bath
Rp: Indonesian Rupiah
US$: US Dollar

In a study conducted by Tandon *et al.* (2020), a prospective observational, randomized comparative study was previously conducted for eight weeks.[7] The sample number of 39 patients with the criteria for inclusion of newly diagnosed patients with diabetes mellitus type 2 male and female with HbA1c ≥ 6.5% and FBG ≥ 126 mg/dl. The research subject will be given two types of oral antidiabetic combination drugs at random. A total of 20 patients were given a combination of metformin 500 mg and Glimepiride 1 mg, while 19 other patients were given Metformin 500 mg and Teneligliptin 20 mg. Outcomes assessed in the study were HbA1c levels, Fasting Blood Sugar, Post-Prandial Blood Sugar, and Body Mass Index. In addition, the cost-effectiveness analysis was conducted by calculating costs incurred at a 0.1% reduction in HbA1c and a 1 mg/dl reduction in fasting plasma glucose levels or postprandial blood sugar after eight weeks and compared for both groups. The same was also evaluated for differences in body mass index.

In the study, the results of the Metformin +Glimepiride group averaged HbA1c values changed from 8,581±1.48% to 6.96±1.57%, FBG from 172.28±31.52 mg/dl to 136.5±26.10 mg/dl, PBG 271.21±50.18 mg/dl to 201.51±40.23 mg/dl. While in the metformin+Teneligliptin group the change occurred at HbA1c 9.06±1.19% to 7.71±1.18%, Random Blood Glucose (RDS) 160.5±25.45 mg/dl to 127.55±22.27 mg/dl, PBG 256.75±34.52 mg/dl to 192.61±40.71 mg/dl. However, the two combination drugs did not significantly decrease body mass index. In the Metformin+Glimepiride group 25.70±2.01 kg/m^2 to 25.56±2.15 kg/m^2, and in the Metformin+Teneligliptin group 24.17±2.69 kg/m^2 to 24.04±2.87 kg/m^2. There was no significant difference between the reductions in both drug groups, but the metformin+glimepiride group showed less cost than the metformin+teneligliptin group. It can be concluded that the use of the combination drug Metformin 500 mg and Glimepiride 1 mg was assessed as more cost-*saving* in lowering the value of HbA1c, Fasting Blood Sugar, and postprandial blood sugar compared to the combination of Metformin 500 mg and Teneligliptin 20 mg. Both groups experienced significant reductions in HbA1c, FBG, and PBG levels.

Previously, prospective observation research in Nepal has been done, which aims to analyze patient demographics, prescribing patterns, and drug prices.[8] That study analyzed which antidiabetic drugs were the most *cost-effective* in treating type 2 diabetes mellitus in Nepal. The study was conducted for three months using patients with criteria: newly diagnosed type 2 diabetes mellitus, receiving single or combination antidiabetic drugs, male or female, aged 18-80 years, have a comorbid disease, responsible for the administration of the therapy, In outpatient medicine, patients can communicate using English and Nepalese in writing or orally. The study used 63 patients, and *the outcomes* used to look at the changes were HbA1C and Blood Sugar values.

Sixty-three prescription drugs were analyzed, and found as many as 53 drugs were antidiabetic. The most widely prescribed is Metformin (46.9%), followed by combination drugs metformin and sulfonylurea (17.2%) and combination drugs metformin and sitagliptin (9.4%). As a result, 57.1% of patients were found with controlled Fasting Blood Sugar, and 50.8% of patients with controlled HbA1c levels. A total of 53.3% of patients with metformin were found to have controlled blood sugar, and 54.5% of users of the combination drug metformin and sulfonylurea had controlled blood sugar. The average fasting blood sugar value before and after treatment was 158.52±5.3 mg/dL and 129.35±4.02 mg/dL, while the average HbA1c before and after treatment was 8.42%±0.19% and 7.02%±0.16%. Metformin+ Sulfonylurea, at the cost of NRs 601.2, was obtained on average fasting blood sugar before and after 187.69±14.99 mg/dL and 137.34±10.11 mg/dL also obtained average HbA1c levels before and after 9.5±0.66% and 7.4±0.55%. In administering metformin at the cost of Nepalese Rupee (NRs) 360, the average fasting blood glucose level before and after is 155.34±34.25 mg/dL and 130.33±32.69 mg/dL. The average HbA1c before and after was 8.16±0.97% and 6.9±0.95%. The drug combination of metformin and sitagliptin at the cost of NRs 2,340 obtained an average level of fasting blood glucose before and after 191.73±21.79 mg/dL and 144.96 ± 17.74 mg/dL, also obtained an average hbA1c level before and after 9.65±0.71% and 7.9±0.79%. Metformin + Sulfonylurea and Metformin administration shows significant changes in reducing HbA1C and Fasting Blood Sugar. The ICER value in this study amounted to NRs. 7.64 per mg/dL decreased blood sugar levels.

Previous research conducted by Permsuwan *et al.* (2016) using IMS CORE

Diabetes Model (CDM) that compares the treatment of a single drug Dipeptidyl Peptidase-4 (DPP-4) inhibitor: Saxagliptin (5 mg), sitagliptin (100 mg), and vildagliptin (100 mg) in elderly type 2 Diabetes Mellitus patients aged ≥65 years with a lifetime time horizon[9]. The drugs will be compared to single drug metformin (2000 mg) or sulfonylurea (10 mg) to see differences in cost and number of years of adjusted quality life (quality-adjusted life years, QALY). Cost-effectiveness analysis uses direct medical costs that include the cost of intervention, diabetes screening, management, and treatment of complications. The direct medical costs used in this study are a database of several hospitals in Thailand from previously published literature.

Based on the study results, all three single drug DPP-4 inhibitors cost reasonably high but produced low QALY values than metformin. Consecutive Saxagliptin, sitagliptin, and sitagliptin cost a total of THB 406,876 (US$12,344), THB 434,982 (US$13,197.27), and THB 428,869 (US$13,011.80), but only produced the same QALY value in the three types of DPP-4 inhibitor drugs of 5,965. On the other hand, with a total cost of THB 283,222 (US$8,592.90), metformin showed a QALY of 5,986 years. In other words, all DPP-4 inhibitors dominated, making the single drug metformin a more *cost-effective* treatment in the elderly with Type 2 Diabetes Mellitus in Thailand. Whereas when compared to sulfonylurea class drugs that have a total cost of THB 293,175 (US$ 8,894.87) and QALY of 5,933 years, all three DPP-4 inhibitors are more effective with an ICER value of 0.031 but more expensive than sulfonylureas. Among the three, Saxagliptin produced the lowest ICER value of THB 3,632,604/QALY (US$ 110,212.50/QALY), followed by vildagliptin with THB 4,335,273/QALY (US$ 131,531.34/QALY), and sitagliptin of THB 4,530,556/QALY (US$ 137,456.19/QALY). This study also conducted a sensitivity analysis used for health development and protection in Thailand and found a cost threshold of THB 160,000 / QALY (US $ 4,854.37/QALY), so DPP-4 inhibitors were declared not *cost-effective* compared to the sulfonylurea group.

Research Nian *et al.* (2020) uses the Chinese Outcomes Model for T2DM, an already validated policy analysis model, to track microvascular and macrovascular complications in each type 2 Diabetes Mellitus patient[10]. The study compared metformin (1500 mg) and dapagliflozin (10 mg) as a single drug therapy using HbA1c outcomes. In addition, the study developed a *meta-analysis network* that estimated average changes in levels of HbA1c, HDL, and systolic blood pressure. Compared to the single drug metformin, which has a total cost of $15,262 and QALY of 11.12 years, dapagliflozin is associated with a lower life expectancy and a reduced QALY at a total cost of $17,450 and QALY of 11.03 years, leading to a predominantly position with more expensive costs, and fewer benefits.

Research at Sitnala Hospital by Laelasari *et al.* (2017) is an analytical descriptive study with a *cross-sectional* research design that tested the effectiveness and cost difference in type 2 Diabetes Mellitus patients followed by 97 patients selected using *purposive sampling* techniques[11]. The sample was divided into three groups. The first group received insulin therapy for 29 patients, the second group received sulfonylurea for 29 patients, and the third group combined Sulfonylurea+Metformin for 39 patients. The Insulin used in this study was *rapid-acting, intermediate-acting, long-acting,* and *pre-mixed.* Sulfonylureas used in research times include glimepiride, gliclazide, gliquidone, and glibenclamide. The study was conducted over four months by looking at changes in HbA1c values. HbA1c measurements showed a high level of effectiveness in the group taking sulfonylurea and metformin combination drugs of 7.48±1.89, followed by the single drug sulfonylurea at 8.17±2.27 and those using Insulin at 8.42±1.73. The group that obtained the sulfonylurea+metformin combination was the most *cost-effective* choice with ICER of Rp 16,194/% decrease in HbA1c levels compared to other groups with Rp 227,760 and 86% effectiveness, followed by sulfonylurea with a cost of Rp 108,897 and effectiveness of 79.56%.

Research conducted by Wulandari *et al.* (2020) is a descriptive study of observational analytics with *cross-sectional* data taken retrospectively previously describes the cost of Metformin and Glimepiride, with a patient number of 176 people[12]. In this study, there was no significant difference between the cost of Metformin and Glimepiride. Metformin usage costs Rp 5,591,642 and Glimepiride Rp 4,961,315, with the average cost being Rp 1,209 and Rp 1,228, of Rp 1,228, for each other, and Rp 1,228, on average. [12]

A Research conducted by Romadhoni (2018), a descriptive retrospective previously, with a sample of 28 patients taken purposive sampling, the sample was divided into two groups that received metformin therapy as many as 20 Glimepiride as eight patients.[12] Analysis conducted in this study calculated Average Cost-Effectiveness ratio (ACER) and Incremental Cost-Effectiveness Ratio (ICER) by looking at changes in outcomes and achieving GDS targets. The group that got glimepiride was the most cost-effective option than the metformin group with a total cost of Rp 432,221 and 62.5% effectiveness, followed by Metformin for Rp 498,627.80 and 70% effectiveness. The result of ACER calculations found that the cost-effective value of ACER is Glimepiride which is Rp 691,553,600. In comparison, the ACER result of Metformin is Rp 712,325,429. ICER results between Glimepiride and Metformin that the most cost-effective antidiabetic drug is glimepiride with an ICER value of Rp 20,771,829.

DISCUSSION

Diabetes mellitus is one of the chronic diseases that require maintenance in the long term in order to maintain quality of life. Maintenance that can be done, among others, is maintaining a lifestyle and consuming drugs to control blood sugar levels to stay within safe limits. *Cost-effectiveness analysis* is one area in pharmacoeconomics that is considered to review treatment in the long term to achieve therapeutic targets more effectively without burdening the patient's finances. Therefore, various comparative studies are conducted to get the best results, one of which is comparing drugs between groups.

In cost-effectiveness analysis, the results are described as the cost-effectiveness ratio (C/E ratio), the ratio's numerator shows the total cost, and the ratio's denominator describes the variable outcome. The outcome in question must be clinically relevant and can be measured objectively by following standard measurement criteria to be accepted in the health care community. This study described the outcome values as GDS, FBG, PBG, HbA1c and QALY. There are two forms of cost-effectiveness ratio: ACER and ICER. ACER compares therapy and its *outcome*, while ICER shows the cost required to achieve one unit of outcome. In the study, Dhakal *et al.* (2019) compared the combination drug metformin+sulfonylurea and the single drug metformin required NRs. 7.64 per mg/dl decreased blood sugar levels[8]. Another study comparing class DPP-4 inhibitors with Metformin and Sulfonylurea compared Sulfonylurea with DPP-4 inhibitors found ICER of THB 3,632,604 (US$ 110,212.50) per QALY. [9] The previous study's equation found that a higher QALY value dominates metformin with a lower total cost.[9.10] From research conducted in Indonesia, ICER consecutively Rp 20,771,829 and Rp 16,194.[12.13]

Biguanide and sulfonylurea are drugs often used to control the blood sugar levels of patients with Type 2 Diabetes Mellitus. Metformin is one of the biguanide class drugs that suppress liver glucose production or gluconeogenesis. Sulfonylurea class drugs such as glimepiride, glipizide glibenclamide and gliquidone play an increased role in insulin secretion by beta cells. According to American Diabetes Association (ADA), biguanide and sulfonylurea drugs have a lower cost than other antidiabetic drugs[1]. Perkumpulan Endokrinologi Indonesia or Indonesian Society for Endocrinology (PERKENI) states that administering a single drug is one of the first steps in managing patients with type 2 diabetes mellitus. If the drug is given cannot meet the target or cannot help control blood sugar levels within three months, the therapy is increased to a combination of 2 types of drugs. If it still does not reach control is increased to a combination of 3 types of drugs. Monitoring the type 2 diabetes mellitus treatment results is done by examining BMI, GDS, FBG, systolic blood pressure, diastolic blood pressure, HbA1c, LDL cholesterol, HDL cholesterol, and triglycerides[14]. This narrative review analyzed and assessed the administration of Metformin and Sulfonylurea inpatients with Type 2 Diabetes Mellitus.

In the literature data taken, the incidence of Type 2 Diabetes Mellitus is found in the age range of patients, mostly 45-65 years, with a percentage of men more than women. The incidence of type 2 diabetes mellitus occurs mainly at >45 years, which is one of the risk factors for type 2 diabetes mellitus. Based on the Data and Information Center of the Ministry of Health, the proportion of type 2 diabetes mellitus sufferers is 55-64 years old and 64-67 years old.[3] The increase in the percentage of diabetes mellitus in old age could be due to decreased body function. Patients have suffered from Type 2 Diabetes Mellitus for many years and already have complications

Patients with type 2 diabetes mellitus found comorbid hypertension and dyslipidemia.

Hypertension usually occurs when blood pressure reaches more than 140 mmHg (systolic) and 85-90 mmHg (diastolic). If the condition of hypertension in a person is left without treatment, this condition can cause thickening of arterial blood vessels that causes the diameter of blood vessels to narrow. The hypertension condition will cause the glucose process in the blood to be disrupted. [15] Antihypertensive widely used in hypertension management is the ACE-Inhibitor, Calcium Channel Blocker (CCB) diuretic and Angiotensin-II Receptor Blocker (ARB). Drugs used in DM should not interfere with glucose tolerance, worsen lipid profile and have cardioprotective or empathic abilities. In previous studies, patients suffering from hypertension used amlodipine drugs from the CCB group to regulate hypertension, which has particular indications for patients at high risk of coronary disease and diabetes.[12] On the Dhakal *et al.* study. (2019) 58.7% of patients have comorbid disease, hypertension has 45.3% of the total patient sample. Furthermore, of the prescriptions given, 26.2% prescribed antihypertensive drugs. [8]

Another comorbid disease in Type 2 Diabetes Mellitus patients is dyslipidemia. According to PERKENI, dyslipidemia is defined as a lipid metabolic disorder characterized by elevated levels of total cholesterol (Ktotal), LDL cholesterol (K-LDL), triglycerides (TG), as well as a decrease in HDL (K-HDL) cholesterol. Type 2 Diabetes Mellitus dyslipidemia may increase risk factors for myocardial infarction disease because excess glucose in the blood (hyperglycemia) can damage the endothelial in the blood vessels and become atherosclerotic plaques. One of the drugs given for dyslipidemia is statins, which have the most significant effect in lowering cardiovascular risk in patients with type 2 diabetes mellitus. ADA in 2014 recommended that statins should be given immediately regardless of initial lipid levels of patients with Coronary Heart Disease (CHD) or patients over 40 years of age with one or more CHD risk factors such as family history, hypertension, smoking, dyslipidemia or albuminuria.[1] On the Dhakal *et al.* study. (2019) of the 58.7% of patients who had a comorbid disease, 11.3% had comorbid dyslipidemia. Furthermore, of the prescriptions given, 23.8% prescribed hypolipidemic drugs.[8]

Based on previous research, complications of Diabetes Mellitus Type 2 disease are divided into two, namely macrovascular and microvascular diseases. Macrovascular diseases include myocardial infarction, stroke, CHD, and other cardiovascular diseases like angina and atrial fibrillation. While microvascular diseases include cataracts, retinopathy, nephropathies such as kidney failure and diabetic ulcers.[9.10]

Tandon *et al.* (2020) conduct evaluations to assist policymakers in determining cost-effective therapeutic options in developing countries.[7] In his study, a comparison between two combination drugs, Metformin and Glimepiride, and metformin and teneligliptin. Combination therapy is believed to provide significant changes in reducing blood sugar levels. The results showed that both drug combinations significantly lowered blood sugar levels represented in fasting blood sugar, postprandial blood sugar, and HbA1c parameters. However, the study was only conducted for a short duration. Therefore, it could not be seen whether there were significant changes in weight changes between the two combinations. Compared to its cost-effectiveness, the combination of metformin and teneligliptin was less cost-effective than Metformin and Glimepiride.

In a previous study conducted by Dhakal *et al.* (2019), it was also found that the most commonly prescribed and most *cost-effective* antidiabetic drugs were Insulin, Metformin, and a combination of Metformin and Sulfonylurea. The study compared the types of prescription drugs using outcomes in fasting blood sugar and was of high effectiveness in Metformin and sulfonylureas.[8]

Permuswan *et al.* (2016) conducted a study on the cost-effectiveness of DPP-4 inhibitors using IMS CORE Diabetes Model (CDM) in elderly patients.[9] Elderly patients increase the risk of complications. DPP-4 inhibitors were cost-effective compared to the single drug metformin and the single drug sulfonylurea, which in this study used glipizide. However, DPP-4 inhibitors have low HbA1c reduction ability, high hypoglycemic risk, and higher prices than metformin.

Laelasari *et al.* (2017) conducted a study to compare Insulin, Sulfonylurea, and a combination of sulfonylureas and metformin with hbA1c outcomes.[11] In the results of the study found a more expensive cost on the combination drug sulfonylurea and metformin compared to a single sulfonylurea drug. However, the combination drug sulfonylurea and metformin provided higher effectiveness than the single drug sulfonylurea.[17] While previous studies found more use of

Metformin than Glimepiride. However, between the two, there was no significant difference in the average cost of the drug.[12]

Analysis economics is performed by Nian *et al.* (2020) against dapagliflozin and metformin, an analytical method using the Chinese *Outcomes Model for T2DM.* These drugs were tested with a placebo to see their ability to lower blood sugar levels. The results of ICER calculations showed the results of Dapaglizolin dominated. Following previous research, based on a meta-analysis conducted by Jia *et al.* (2019), metformin is still a first-line antidiabetic drug that effectively deals with type 2 diabetes mellitus. [18]

CONCLUSION

The patient profile found the age range of diabetes mellitus type 2 is 45-65 years, with a percentage of male patients more than women and complications that often occur is hypertension. While on the effectiveness of using biguanide class drugs (Metformin) and sulfonylurea proved to reduce blood sugar levels at a fairly cheap cost significantly. Among others, ICER found price comparisons that vary in the Dhakal *et al*. study, 2019, amounting to NRs. 7.64 per mg/dl decreased blood sugar levels, Permuswan *et al*, 2016 THB 3,632,604 (US$ 110,212.50), Laelasari *et al*, 2017 Rp 16,194, and Romadhoni, 2018 amounted to Rp 20,771,829.

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