Dapagliflozin for prevention of macrovascular complication among Diabetic patients: A cost-utility analysis

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INTRODUCTION

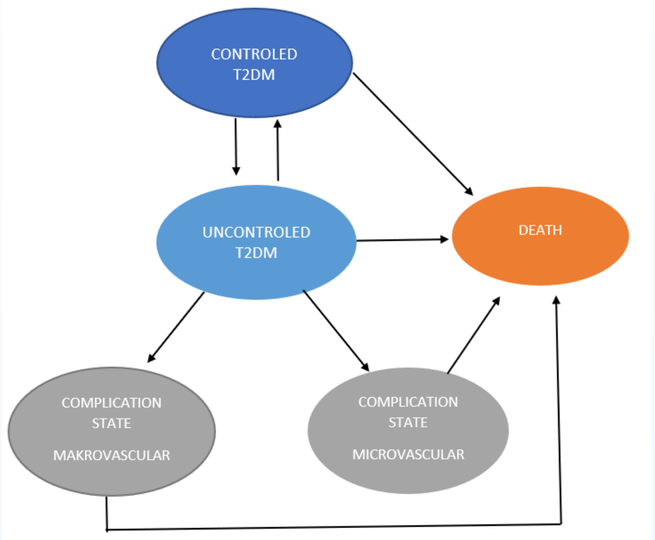
Diabetes mellitus type 2 (T2DM) is a degenerative disease whose prevalence continues to increase in the world, including in Indonesia. According to the International Diabetes Federation (IDF) organization in 2021, Indonesia is included in the top 10 countries with the most diabetes sufferers, namely 5th with 19.47 million sufferers[1]. In 2030, it is estimated that Indonesia's population over the age of 20 will be 194 million people with a projected diabetes prevalence of 41.9 million[2]. The cost of diabetes in Indonesia in 2021 was recorded at US$ 323.8 per person per year and is estimated to increase 14% to US$ 370.6 in 2030. The global cost of diabetes in 2007 was US$ 232 billion, rising to US$ 966 billion[3,4].

The increase in costs of T2DM is influenced by the incidence of macrovascular and microvascular complications as a result of uncontrolled hyperglycemia. The risk of complications can be correlated with hemoglobin A1c (HbA1c) levels, which indicate hyperglycemia during the previous 3 months. A 1% reduction in HbA1c levels can reduce the risk of death due to DM by 21%, myocardial infarction by 14%, and microvascular complications by 37%[1]. In research conducted by Zhaolan Liu (2010), the prevalence of DM in China with macrovascular complications was 33.4% while microvascular complications were 34.7%. Of the macrovascular complications that occurred, 30.1% were cardiovascular disorders, 6.8% cerebrovascular, 17.8% neuropathy, 10.7% nephropathy, 14.8% ocular lesions, and 0.8% foot problems2. In this study, the highest incidence of macrovascular complications was cardiovascular disorders[2]. Therefore, various studies have been conducted on antidiabetic drugs and their effects on macrovascular events.

Dapaglifozin is a new drug in the class of sodium-glucose co-transporter (SGLT2) inhibitors that has benefits in preventing and reducing complications because it can significantly reduce HbA1c. The results of research by Bailey (2010) show that dapagliflozin can reduce HbA1c by 0.67% at a dose of 2.5 mg, 0.70% at a dose of 5 mg, and 0.84% at a dose of 10 mg[3]. The use of dapagliflozin in Indonesia according to the 2021 PERKENI guidelines is an option for T2DM patients with a risk of atherosclerotic cardiovascular disease, heart failure, and chronic kidney disease; however, its use is still limited due to availability and price considerations[4]. In the phase three clinical study DECLARE-TIMI 58 (dapagliflozin effect on cardiovascular events-thrombolysis in myocardial infraction 58) dapagliflozin was found to reduce the risk of atrial fibrillation by 19% with a hazard ratio [HR], 0.81 [95% CI, 0.68- 0.95]; P=0.009) compared with placebo and reduced hospitalization for heart failure HR 0.73 (95%CI, 0.61-0.88)[5].

OBJECTIVE

This study aims to determine the cost-effectiveness of dapagliflozin in preventing macrovascular complications. The cost-utility analysis method is a suitable method for pharmacoeconomic research on new drugs. The course of diabetes is a degenerative disease with recurrent events over a long period of time, so the cost-utility analysis in this study was carried out using the Markov model[26].



METHOD

This research is a modeling-based pharmacoeconomic study using a Markov model for T2DM and is represented by a simulated cohort of 1,000 DM patients. The Markov model in T2DM describes conditions that occur randomly and repeatedly and is simulated in a cohort. This simulation combines outcomes in the form of utility and costs incurred in each state1. This model describes the condition of T2DM into 5 states, namely (1) controlled T2DM, (2) uncontrolled T2DM, (3) macrovascular complications, (4) microvascular complications, and (5) death. The cohort simulation starts at age 30 years; calculations are carried out for a 1-year cycle for 40 years (time horizon). With this model, we compared the therapy of T2DM patients who used metformin+dapagliflozin and metformin+glimepiride using cohort simulation.2 Each arrow depicts a transition from one state to another. In the first state there are 3 transitions, namely from controlled to uncontrolled T2DM, remaining in a controlled condition, and death. In the next stage the transition is indicated by the direction of the arrow.

Model inputs

The input parameters required in the Markov model T2DM are transition probability, cost, utility, Risk Ratio (RR) of dapagliflozin against macrovascular events, and discount rate. Transition probability values are obtained from primary data, secondary literature, or previous research, and from incidence rates or new occurrences of a condition within a certain time period. Primary data was obtained retrospectively from data on type 2 DM patients in outpatient care at Pelabuhan Cirebon Hospital in 2022. Meanwhile, data that was not available at the hospital was supplemented using secondary data obtained through literature searches via PubMed and Google Scholar. Inclusion criteria for data collection at the hospital were (1) patients diagnosed with T2DM with an age range of 30-70 years with or without complications, (2) patients who had suffered from T2DM for a long time or had at least 3 visits to the clinic outpatient and (3) received metformin + sulfonylurea therapy. Meanwhile, the exclusion criteria are patients who are not National Health Insurance participants.

Transition Probability

The transition probability value can be obtained from the literature or can be calculated from the incidence rate or number of new events in primary data within a certain time period using the following formula[26] .

$$p=1-\exp(-rt)$$

p = probability
r = instantaneous event rate
t = time
The rate value is obtained using the following formula:

$$r = -[\ln(1-p)/t]$$

Cost

Cost parameters are calculated based on a societal perspective consisting of direct medical costs, direct non-medical costs and indirect costs. Costs for controlled T2DM patients are calculated based on estimated costs at first level health facilities consisting of doctor fees, medication and blood glucose checks. In uncontrolled T2DM (metformin+glimepiride), direct medical costs are calculated based on retrospective data at the hospital consisting of medical administration costs, medical professional services and medical support. Non-medical direct costs are calculated based on the results of interviews with patients or the patient's family. Indirect costs are calculated using the Human Capital Approach method, namely by calculating the number of days lost due to illness with the income earned each day, with the following formula[26]

$$\text{Loss productivity} = \frac{\text{number of days absent work x income per month}}{365}$$

Utility

Measurement of the utility or quality of life of patients in the metformin+glimepiride group was obtained using the Indonesian version of the EQ-5D-5L questionnaire published by EuroQol Group EQ-5D in 20204. Measurements were carried out by interviewing subjects who were included in the sample. The utility value is calculated using the Indonesian value set based on the research results of Purba (2017) [5]. Utility in the metformin+dapagliflozin group was obtained from a synthesis of previously published literature.

Risk Ratio

The Declare-TIMI 58 study, which is a phase 3 study of dapagliflozin which aims to determine the effect on cardiovascular events[6]. Macrovascular complications in this study were defined as a reduced incidence of heart failure hospitalization, myocardial infarction, ischemic stroke, and amputation. Synthesis of data from the results of this study resulted in an RR value of 0.898 in the dapagliflozin group compared to placebo while continuing to use antidiabetic therapy that had been used before the study[5].

RESULT

Tabel 3. Transition Probabilities

Transition Probabilities [references]	Age (Years) 30-34	35-39	40-44	45-49	50-54	55-59	60	61- 64	65-69	70
From controlled T2DM to										
Controlled	0,981	0,980	0,979	0,977	0,836	0,832	0,824	0,894	0,874	0,859
Uncontrolled	0,014[7]	0,014[7]	0,014[7]	0,014[7]	0,150[9]	0,150[9]	0,150[9]	0,080[9]	0,080[9]	0,080[9]
Death[10]	0,005	0,006	0,007	0,009	0,014	0,018	0,026	0,026	0,046	0,061
Death other[10]	0,001	0,006	0,006	0,008	0,012	0,017	0,023	0,023	0,043	0,058
From Uncontrolled T2DM to										
Uncontrolled	0,73863	0,74063	0,75163	0,74763	0,74363	0,74163	0,69263	0,69263	0,69363	0,69863
Controlled [4]	0,10237	0,10237	0,10237	0,10237	0,10237	0,10237	0,10237	0,10237	0,10237	0,10237
Microvascular[11]	0,05100	0,05100	0,05100	0,05100	0,05100	0,05100	0,05100	0,05100	0,05100	0,05100
Macrovascular[10]	0,10600	0,10500	0,09300	0,09800	0,10200	0,10300	0,15200	0,15200	0,15000	0,13900
Death[10]	0,00200	0,00100	0,00200	0,00100	0,00100	0,00200	0,00200	0,00200	0,00300	0,00900
From Microvascular to										
Microvascular					0,97800					
Death[11]					0,02200					
From Macrovascular to										
Macrovascular	0,99000	0,99800	0,99900	0,99800	0,99700	0,99600	0,99600	0,99600	0,99300	0,98800
Death[10]	0,01000	0,00200	0,00100	0,00200	0,00300	0,00400	0,00400	0,00400	0,00700	0,01200

Reference: [2] ; d= primary data

Table 4. Costs and Utilities

Parameter	Value	Reference
Cost Therapy		
Controlled T2DM	1.699.400	2
Uncontrolled T2DM (metfotmin+dapagliflozin)	14.663.786	Pimary data
Uncontrolled T2DM (metformin+glimepiride)	5.807.786	2
Macrovascular Complication	119.814.792	3
Microvascular Complication	37.976.784	3
Utilities		
Controlled T2DM	0,880	12
Uncontrolled T2DM (metformin+dapagliflozin)	0,850	13
Uncontrolled T2DM (metformin+glimepiride)	0,800	2
Microvascular Complication	0,760	14
Macrovascular complication	0,710	14
Death	0,000	

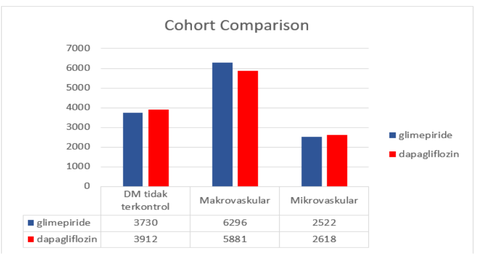
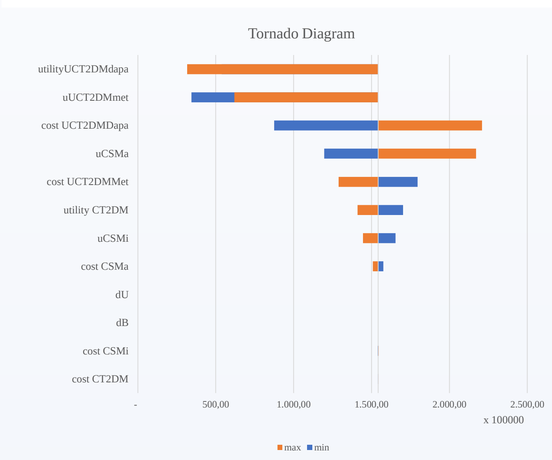


Figure 2 Comparison cohort value between Dapagliflozin and Glimepiride

Table 5 Base-case result

	Cost	QALYs	Incremental Cost	Incremental QALYs	ICER
Metformin+Glimepiride	65,040,366,722	18.200	-	-	-
Metformin+Dapagliflozin	81,911,332,926	18.310	16,869,552,709	109	154,215,757



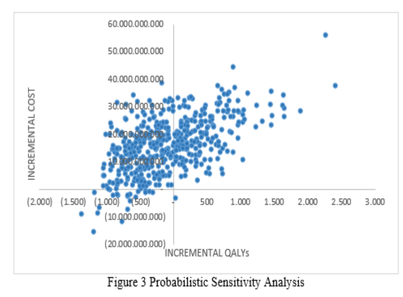


Figure 3 Probabilistic Sensitivity Analysis

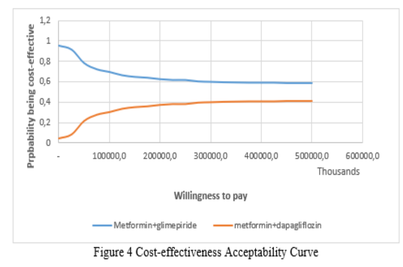


Figure 4 Cost-effectiveness Acceptability Curve

The estimated total cost and QALYs of the current treatment are IDR 64,563,608,920.00 and 18,200, respectively. While in the dapagliflozin cohort, the cost and the QALYs are IDR. 81,433,061,692.00 and 18,310, respectively. Furthermore, the ICER of Dapagliflozin is IDR. 154,215,757.00/QALYs and it is considerably cost-effective. The sensitivity analysis demonstrates that the probability of dapagliflozin to be cost-effective is 37.8%.

CONCLUSIONS

Dapagliflozin was deemed to be cost-effective compared to standard therapy T2DM for preventing macrovascular complications.

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