Cost-Utility Analysis of Dapagliflozin Compared to Sulfonylureas for Type 2 Diabetes as Second-Line Treatment in Indian Healthcare Payer’s Perspective

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Background: Type 2 diabetes mellitus (T2DM) is a leading health issue, causing economic burden in India. Pharmacotherapy is a major cost driver in diabetic care usually funded through out of pocket expenditure; however, there has been a very limited economic evaluation evidence to guide the choice of diabetes pharmacotherapy in India. Therefore, this study aims to evaluate the long-term cost-effectiveness of dapagliflozin (sodium glucose transporter 2 inhibitor) compared to commonly used sulfonylureas as second-line drugs in Indian patients with T2DM.

Methods: Cost-utility analysis was employed to estimate the costs and health outcomes using a Markov model with 1-year cycle length during a lifetime horizon based on an Indian payer’s perspective. A treatment pathway with dapagliflozin as second-line therapy was compared to sulfonylureas after failure of initial metformin therapy. Clinical and cost data were collected from literature reviews and available secondary data sources. Both costs and outcomes were discounted at a 3% annual discount rate. The results were presented as the incremental cost-effectiveness ratio (ICER). One-way and probabilistic sensitivity analyses were performed to test parameter uncertainties.

Results: Compared to sulfonylurea, dapagliflozin was estimated to incur an additional cost of ₹182,632 (US$2,446) with an expected 3.49 life years (LY) or 1.72 quality adjusted life years (QALY) gained, resulting in an ICER of ₹52,270 (US$699) per LY gained, or ₹106,133 (US$1,421) per QALY gained. Uncertainty analyses showed that the ICER values were not sensitive to changes in most parameters.

Conclusion: Dapagliflozin would be cost-effective compared to sulfonylureas as the second line added to metformin for T2DM patients based on an Indian payer’s perspective.

Keywords: economic evolution, cost-effectiveness, sodium glucose transporter 2 inhibitor, type 2 diabetes, India, glibenclamide, gliclazide

Introduction
Diabetes is a leading public health burden in the world with approximately 431 million people1 and type 2 diabetes (T2DM) is the most common cause of diabetes (90%).2 Published literature indicate that nearly half (range 24.1–75.1%) of diabetes cases among adults were undiagnosed (about 174.8 million), and 72 million were found in India, resulting in 8.8% of global burden.3–5 T2DM is one of the leading causes of mortality and morbidity in India,6 as it is the second
that sodium-glucose transport inhibitors (SGLT2) and glycemic control in T2DM anywhere in the world, including India. 

Dapagliflozin is the first SGLT2 inhibitor approved for urinary glucose excretion and osmotic diuresis. Absorption in the proximal tubule of the kidney, leading to glycemic control according to standard guidelines. Based on the 2018 American Diabetes Association guidelines, sulfonylureas are commonly prescribed as second-line treatment with metformin when T2DM patients are not at risk for cardiovascular diseases due to the concerns regarding long-term cardiac safety and the risk of hypoglycemia. In addition, it is recommended that sodium-glucose transport inhibitors (SGLT2) and glucagon-like peptide 1 receptor agonists (GLP-1) are much better alternatives as second-line treatment, as these drugs have shown additional improvement in glucose control and reduction cardiovascular events in T2DM with atherosclerotic cardiovascular diseases.

Gliflozin class or SGLT2 can reduce glucose reabsorption in the proximal tubule of the kidney, leading to urinary glucose excretion and osmotic diuresis. Dapagliflozin is the first SGLT2 inhibitor approved for glycemic control in T2DM anywhere in the world, including India. Currently, the price of dapagliflozin is more expensive than sulfonylureas, and this can increase the cost of T2DM medications, of which 80% are mainly paid out-of-pocket by the patients and their families in India. Therefore, economic evaluation of dapagliflozin is required to confirm whether it is cost-effective to be used as second-line therapy for T2DM patients in India.

Based on our literature search, 13 economic evaluation studies were conducted in developed countries, but none were performed in low- and middle-income countries such as India. Therefore, our study aimed to investigate the cost-utility of dapagliflozin compared to sulfonylureas as second-line therapy in T2DM patients based on an Indian payer’s perspective. The results of our study could be used as evidence-based information for physicians as to whether dapagliflozin would be cost-effective to be prescribed as second-line therapy compared to sulfonylureas for T2DM patients in India.

**Methods**

A cost-utility analysis (CUA) using a Markov model was conducted to compare the costs and health outcomes of dapagliflozin (10 mg/day) with a usual treatment with sulfonylureas over a lifetime period. The study was performed based on an Indian payer’s perspective, as 80% of healthcare costs are paid by patients’ out of pocket in India. Target populations were newly diagnosed Indian T2DM patients aged 30 years, ie, the age at diabetic screening under the National Program for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke in India.

We compared two different treatment pathways. First, for a current practice in India, T2DM patients received metformin monotherapy, and, if it failed, sulfonylureas were added as second-line therapy, and finally insulin was added due to the second-line treatment failure. Second, for a new intervention, T2DM patients were prescribed with metformin monotherapy as first line treatment and received dual therapy, ie, metformin plus dapagliflozin due to first line treatment failure, finally received triple therapy, ie, metformin, dapagliflozin plus insulin when dual therapy failed. The treatment failure is defined as T2DM patients unable to maintain glycemic control (HbA1C <7%) according to the ADA guidelines. An annual discounting rate of 3% was applied to both costs and outcomes. The incremental cost-effectiveness ratio (ICER) was calculated by a difference in costs (Indian rupees, ₹) divided by a difference in life years (LY) or quality-adjusted life years (QALY) gained between two aforementioned alternatives. As there is no standard threshold in India, we referred to the recommendation from the World Health Organization (WHO), ie, less than one gross domestic product (GDP) per capita per QALY gained.
considered as highly cost-effective, 1–3 times GDP as cost-effective and more than 3 times GDP as not cost-effective. In India, one time GDP in the year 2019 equal to INR ₹1,56,798\textsuperscript{19} was applied as the willingness to pay (WTP) threshold.\textsuperscript{17} In addition, the incremental net benefit (INB) was calculated as the multiplication of the WTP threshold and incremental QALY minus incremental cost.

Model Overview

Figure 1 illustrates the Markov model simulating T2DM treatment pathways. The model consists of four health states, as follows: 1) metformin monotherapy, 2) dual therapy, ie, metformin plus second-line treatment of either sulfonylureas or dapagliflozin if first line treatment failed, 3) triple therapy, ie, metformin plus second line plus insulin as a third line drug, if second-line treatment failed, and 4) death. The arrows represent the transitional probabilities of moving from one health state to another. The model was applied to estimate costs and outcomes during a lifetime period with a 1-year cycle length using Microsoft Office Excel 2016 (Microsoft Corp., Redmond, WA).

The model started with T2DM patients initially treated with metformin monotherapy. If first line treatment failed, second-line therapy of either dapagliflozin or sulfonylureas was added to metformin for controlling the blood glucose level.\textsuperscript{12} T2DM patients who were on metformin monotherapy could remain in the same health state or move to dual therapy due to first line treatment failure. In the dual therapy state, T2DM patients could remain in the same state or move to triple therapy, where insulin was added, owing to second-line treatment failure. T2DM patients in any of the three health states could move to the death state. We considered the costs and outcomes related to complications such as hypoglycemia, myocardial infarction, heart failure, stroke and genital infection among T2DM patients receiving dual or triple therapy. These complications were selected based on the recent publication reporting the common complications among diabetics in India and the availability of relevant model input data.\textsuperscript{20} For hypoglycemia, we proportionated symptomatic hypoglycemia (symptomatic with no need of medical attention) and severe (requiring medical attention) for utility calculation. Only severe hypoglycemia costs were considered. It was assumed that the cohort did not have any baseline comorbidities.

Model Inputted Parameters

Clinical and Utility Data

Table 1 demonstrates all parameters used in the Markov model. The transitional probabilities of dual therapy for dapagliflozin and sulfonylureas were taken from a randomized controlled trial study which compared directly between dapagliflozin and sulfonylureas.\textsuperscript{20} Moreover, the probabilities of complications in each state were retrieved from published literature. Data on age standardized death rate were obtained from an open government data forum of India’s website (https://data.gov.in/catalog/estimated-age-specific-death-rates-sex). Due to a limited availability of head-to-head comparison between dapagliflozin and sulfonylureas in India, we obtained the efficacy data from a study by Nauck et al\textsuperscript{21} which compared dapagliflozin and glipizide. As a result, it was assumed that drug class effects across sulfonylureas were similar. Utility decrement values associated with complications were obtained from a systematic literature search. The initial utility value of diabetic patients during the first diagnosis was assumed to be equal to 1. The utility values calculated by the differences between initial utility and disutilities and all utility values are taken into account for all cycles.

Cost Data

The costs of commonly prescribed sulfonylureas, ie, glibenclamide and glimepiride tablets, were obtained from the prices of the National Pharmaceutical Pricing Authority with 12% of goods and service tax.\textsuperscript{22,23} The cost of sulfonylureas was the average cost of glibenclamide and glimepiride per tablet. The costs of dapagliflozin and human insulin (100 IU/mL) were retrieved from the market prices at the website of pharmacy chain stores in India.\textsuperscript{24} We assumed that a daily dose for insulin requirement was 30 IU/day\textsuperscript{25} for sulfonylureas and 20.5 IU/day\textsuperscript{26} for dapagliflozin. All costs were expressed in Indian rupees (₹), adjusted to the values in the year 2019 using the consumer price indexes (CPI), converted to the United State dollars (USD) with the exchange rate of ₹74.68 per USD.

Uncertainty Analysis

Both univariate and probabilistic sensitivity analyses (PSA) using the second order Monte Carlo simulation were performed to handle parameter uncertainties. For a univariate sensitivity analysis, each inputted parameter was varied by 25% for the upper and lower values. PSA was conducted to investigate the impact of parameter
uncertainties of all parameters. We assigned beta distribution for transitional probabilities and utility parameters and gamma distribution for cost parameters. Parameter values were randomly drawn from these distributions 1,000 times to estimate the mean costs, LYS, and QALYS. Univariate sensitivity analysis results were presented as a tornado diagram and PSA results were shown as the cost-effectiveness plane and cost-effectiveness acceptability curve (CEAC).

Results
Cost-Effectiveness Analysis
Table 2 presents the cost-effectiveness results. The total costs, LYS, and QALYS of second-line therapy were ₹292,416 ($3,915), 158.66 LYS, and 69.64 QALYS for sulfonylureas and ₹475,048 ($6,361), 162.16 LYS, and 71.36 QALYS for dapagliflozin. Compared to sulfonylureas, dapagliflozin therapy incurred an additional cost of ₹1,82,632 ($2,445), with an additional 3.49 LYS or 1.72 QALYS, resulting in an ICER of ₹52,270 ($699) per LYS gained, or ₹1,06,133 ($1,421) per QALYS gained. The corresponding INB calculated from PSA result was ₹2,69,895±47,217 ($3,614±632). Based on the cost-effectiveness plane (Figure 2), all ICER values were located on the upper-right hand quadrant of the plane, indicating the higher the incremental costs the higher QALYS of dapagliflozin compared to sulfonylureas. Figure 3 presents the cost-effectiveness acceptability curve demonstrating that at the current cost-effectiveness threshold or WTP per QALYS gained in India or one-time GDP per capita referred to the WHO recommendations. Based on the results from CEAC with different WTP level, our study revealed that at the WTP of one-time GDP per capita per QALYS gained, dapagliflozin had a 100% chance of being cost-effective compared to sulfonylureas. In addition, dapagliflozin and sulfonylureas as second-line therapy had a 50% chance of being cost-effective at the WTP per QALYS gained of approximately ₹69,000. Likewise, our study results were similar to previous studies comparing the costs and outcomes of dapagliflozin with sulfonylureas as well as dipeptidyl peptidase-4 inhibitors as second-line therapy for T2DM patients in the United Kingdom.27,28 Similar to the reports from the Nordic countries,28 the total costs and LYS of dapagliflozin were

Discussion
This is the first study to investigate the cost-utility of a treatment pathway with dapagliflozin as a second-line therapy compared to sulfonylureas for T2DM based on an Indian payer’s perspective during lifetime period using a Markov model. The results suggested that dapagliflozin as second-line therapy added to metformin monotherapy would be cost-effective at the WTP per QALYS gained in India or one-time GDP per capita referred to the WHO recommendations. Based on the results from CEAC with different WTP level, our study revealed that at the WTP of one-time GDP per capita per QALYS gained, dapagliflozin had a 100% chance of being cost-effective compared to sulfonylureas. In addition, dapagliflozin and sulfonylureas as second-line therapy had a 50% chance of being cost-effective at the WTP per QALYS gained of approximately ₹69,000. Likewise, our study results were similar to previous studies comparing the costs and outcomes of dapagliflozin with sulfonylureas as well as dipeptidyl peptidase-4 inhibitors as second-line therapy for T2DM patients in the United Kingdom.27,28 Similar to the reports from the Nordic countries,28 the total costs and LYS of dapagliflozin were
| Probabilities                                      | Mean (SE)  | Distribution | Source                  |
|---------------------------------------------------|------------|--------------|-------------------------|
| MET monotherapy failure                           | 0.043 (0.0053) | Beta         | Kahn et al 22           |
| MET+DAPA failure                                  | 0.102 (0.0179) | Beta         | Nauck et al 2014 21     |
| MET+SU failure                                    | 0.156 (0.0219) | Beta         | Nauck et al 2014 21     |
| Death from MET monotherapy                        | 0.019 (0.0004) | Beta         | Mohan et al 2006 33     |
| MET+DAPA treatment to death                       | 0.008 (0.0028) | Beta         | Toulis et al 2017 34    |
| MET+SU treatment to death                         | 0.012 (0.0012) | Beta         | Varvasi Rados et al 2016 35 |
| MET+SU+Ins treatment to death                     | 0.096 (0.0040) | Beta         | Anyanwagu et al 2016 16 |
| MET+DAPA+Ins treatment to death                   | 0.008 (0.0028) | Beta         | Toulis et al 2017 34    |

| Complications                                      |            |              |                         |
|---------------------------------------------------|------------|--------------|-------------------------|
| Hypoglycemia                                       |            |              |                         |
| With MET+SU                                        | 0.1362 (0.0051) | Beta         | Mishriky et al 2015 37  |
| With MET+SU requiring in-hospital treatment        | 0.0681 (0.0038) | Beta         | Goke et al 2010 38      |
| With MET+DAPA                                      | 0.0209 (0.0071) | Beta         | Nauck et al 21          |
| With Ins                                           | 0.0100 (0.0099) | Beta         | ORIGIN trial 39         |

| Myocardial infarction                              |            |              |                         |
|---------------------------------------------------|------------|--------------|-------------------------|
| With MET                                           | 0.0156 (0.0032) | Beta         | Kahn et al 2006 32      |
| With MET+DAPA                                      | 0.0049 (0.0069) | Beta         | Kosiborod et al 2018 40 |
| With MET+SU                                        | 0.0102 (0.0032) | Beta         | Roumie et al 2014 41    |
| With Ins                                           | 0.0093 (0.0096) | Beta         | ORIGIN trial 39         |

| Heart failure                                      |            |              |                         |
|---------------------------------------------------|------------|--------------|-------------------------|
| With MET                                           | 0.0033 (0.0032) | Beta         | Kahn et al 2006 32      |
| With MET + DAPA                                    | 0.0060 (0.0077) | Beta         | Kosiborod et al 2018 40 |
| With MET + SU                                      | 0.0196 (0.0112) | Beta         | Gitt et al 2013 42      |
| With Ins                                           | 0.0085 (0.0091) | Beta         | ORIGIN trial 39         |

| Stroke                                             |            |              |                         |
|---------------------------------------------------|------------|--------------|-------------------------|
| With MET                                           | 0.0032 (0.0015) | Beta         | Kahn et al 2006 32      |
| With MET+DAPA                                      | 0.0045 (0.0067) | Beta         | Kosiborod et al 2018 40 |
| With MET+SU                                        | 0.0119 (0.0034) | Beta         | Roumie et al 2014 41    |
| With Ins                                           | 0.0091 (0.0094) | Beta         | ORIGIN trial 38         |

| Other                                              |            |              |                         |
|---------------------------------------------------|------------|--------------|-------------------------|
| Genital infection with MET + DAPA                  | 0.0679 (0.0033) | Beta         | Puckrin et al 2018 43   |

| Health utility decrement                           |            |              |                         |
|---------------------------------------------------|------------|--------------|-------------------------|
| Myocardial infarction                              | −0.0550 (0.0061) | Beta         | Clarke et al 2004 46    |
| Heart failure                                      | −0.1080 (0.0311) | Beta         | Clarke et al 2004 46    |
| Stroke                                             | −0.1640 (0.0295) | Beta         | Clarke et al 2004 46    |
| Severe hypoglycemia                                | −0.0142 (0.0018) | Beta         | Currie et al 2006 46    |
| Symptomatic hypoglycemia                           | −0.0470 (0.0150) | Beta         | Currie et al 2006 46    |
| Genital infection                                  | −0.003 (0.0001)  | Beta         | Barry et al 1997 46     |
| Insulin injection                                  | −0.0200 (0.0050) | Beta         | Zhang et al 2012 47     |

| Costs per year                                     |            |              |                         |
|---------------------------------------------------|------------|--------------|-------------------------|
| Cost of MET monotherapy                            | ₹1211      | Gamma        | NPPO ceiling price 32   |
| Cost of MET+SU                                     | ₹6186      | Gamma        | NPPO ceiling price 32   |
higher than those of sulfonylureas. According to the one-way sensitivity analysis results, the main factors influencing the ICER values were the cost of triple therapy and transition probabilities of metformin monotherapy failure and dual therapy failure. It should be noted that these probabilities were obtained from international countries due to data scarcity in India. Therefore, future studies with clinical efficacy data for these newer anti-diabetic drugs should be generated from an Indian population.

It is significant to address study limitations. First, we assumed that T2DM patients entered the model at age 30 years old and their long-term outcomes were predicted using data obtained from short-term clinical trials in international countries due to data scarcity in India. Therefore, future studies with clinical efficacy data for these newer anti-diabetic drugs should be generated from an Indian population.

It should be noteworthy that the results might not reflect on the real situation in India, but our study might provide the best available cost-effectiveness information for physicians as decision-makers to select cost-effective second-line treatment for T2DM patients. Second, microvascular complications such as amputation, blindness, or end state renal disease were not considered, although patients receiving either dapagliflozin or sulfonylureas might have different costs and outcomes related to microvascular complications. Third, other adverse events associated with dapagliflozin, ie, diabetic ketoacidosis and acute kidney injury (AKI), were not included in the analysis, because the recent systematic review and meta-analysis of the effect of SGLT2 on renal adverse events demonstrated that SGLT2

### Table 1 (Continued).

| Probabilities                        | Mean (SE)   | Distribution | Source          |
|--------------------------------------|-------------|--------------|-----------------|
| Cost of MET+DAPA                     | ₹35,850     | Gamma        | Med-plus        |
| Cost of MET+SU+Ins                   | ₹94,334     | Gamma        | NPPO ceiling    |
| Cost of MET+DAPA+Ins                 | ₹96,951     | Gamma        | Med-plus        |
| Glybenclamide 4 mg (per tablet)      | ₹833        | Gamma        | NPPO ceiling    |
| Glimepiride 4 mg                     | ₹9116       | Gamma        | NPPO ceiling    |
| Dapagliflozin_10 mg                  | ₹34,638     | Gamma        | Med-plus        |
| Cost of insulin_per_20.5 unit per day| ₹58,363     | Gamma        | Medplus         |
| Cost of insulin_per_30 unit per day  | ₹85,410     | Gamma        | Medplus         |
| Insulin syringe                      | ₹2737       | Gamma        | Medplus         |

### Costs of Complications

|                  | Mean (SE) | Distribution | Source            |
|------------------|-----------|--------------|-------------------|
| Hypoglycaemia    | ₹10,903   | Gamma        | Kwon et al 2018   |
| Myocardial Infarction | ₹551,192 | Gamma        | Gu et al 2016     |
| Heart Failure    | ₹183,304  | Gamma        | Gu et al 2016     |
| Stroke           | ₹300,436  | Gamma        | Kwaatra et al 2013, Walker et al 2017 |
| Genital infection| ₹4112     | Gamma        | Charokopou et al 2015 |

Notes: Author’s compilation based on our reviews on published studies. All costs in Indian Rupee (₹) in 2017.

Abbreviations: MET, metformin; SU, sulfonylurea; DAPA, dapagliflozin; Ins, insulin.

### Table 2 Cost-Effectiveness Analysis Results

| Cost-Effectiveness Analysis Results | Sulfonylureas | Dapagliflozin |
|------------------------------------|---------------|---------------|
| Total costs                         | ₹292,416 ($3,915) | ₹475,048 ($6,361) |
| Total LYs                           | 158.66        | 162.16        |
| Total QALYs                         | 69.64         | 71.36         |
| Incremental costs (₹)               | ₹182,632 ($2,445) | ₹52,270 ($699) |
| Incremental LYs                     | 3.49          | 1.72          |
| Incremental QALYs                   | 1.72          | ₹106,133 ($1,421) |
| ICER per LY saved (₹ per LY)        | 71.36         | ₹106,133 ($1,421) |
| ICER per QALY (₹ per QALY)          | ₹106,133 ($1,421) |

Notes: Author’s compilation based on our cost-effectiveness analysis. Exchange rate = ₹74.68 per USD.

Abbreviations: LYs, Life years; QALYs, Quality adjusted life years.
Figure 2 One-way sensitivity analysis. Author’s compilation.

Figure 3 Cost-effectiveness plane. Author’s compilation based on probabilistic sensitivity analysis.
could significantly decrease the risk for serious adverse events due to AKI events. Fourth, owing to limited data of head to head comparison between dapagliflozin and sulfonylureas in India, the efficacy data were retrieved from the Nauck et al study comparing dapagliflozin and glipizide. Nevertheless, we did not consider the class effect for different drugs in sulfonylureas. Therefore, future studies should further investigate such drug class effects. Last, we did not consider patients’ direct non-medical costs, such as transportation and caregiver costs. Nevertheless, it is expected that dapagliflozin may be even more cost-effective if direct non-medical costs are incorporated into the analysis, since dapagliflozin can better control the blood glucose level and reduce cardiovascular events compared to sulfonylureas.

In spite of these limitations, our study suggested that dapagliflozin would be cost-effective to be prescribed as second-line therapy compared to sulfonylureas for treatment of T2DM based on an Indian healthcare payer’s perspective. This could provide the evidence-based information for physicians to make decisions on prescribing dapagliflozin as second-line therapy compared to sulfonylureas for T2DM patients in India. Besides, the results from this study can also be used as the useful information for decision-makers in low- and middle-income countries.

Ethics Approval and Consent to Participate
It was exempted, as the secondary data were obtained from publicly available data sources.

Declarations
There is nothing to declare.

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Author Contributions
All authors contributed to data analysis, drafting, or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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