Diabetes Ther (2016) 7:765–776
DOI 10.1007/s13300-016-0204-9

ORIGINAL RESEARCH

Clinical Effectiveness and Impact on Insulin Therapy Cost After Addition of Dapagliflozin to Patients with Uncontrolled Type 2 Diabetes

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Received: August 23, 2016 / Published online: October 19, 2016
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ABSTRACT

Introduction: Dapagliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor, is a promising drug approved for the treatment of type 2 diabetes mellitus (T2DM). However, its cost is an obstacle for use in developing countries like India. Thus, we aimed to analyse the impact on the cost of insulin therapy after adding dapagliflozin for patients using insulin in real-world clinical practice.

Methods: This retrospective chart review study included patients with uncontrolled T2DM previously on maximum doses of OADs and insulin therapy, initiated on dapagliflozin. Parameters measured were: HbA1c, changes in weight and insulin dosage, frequency and cost, at baseline and after 3 months of adding dapagliflozin 10 mg. Hospital records of patients attending the diabetes outpatient departments at the study centres were scrutinised to identify eligible patients. A treat-to-target approach was used to make changes in the insulin dosages and regimen. The cost of insulin was calculated based on the total daily dose, cost per unit based on the formulation and insulin delivery device. Statistical analysis included descriptive and inferential methods.

Results: Overall, 70 patients meeting the inclusion criteria were included in the study. The mean age of patients and duration of T2DM were 52.6 ± 10 and 12 ± 5 years respectively. The mean reduction in HbA1c and weight was $2.1 \pm 1\%$ ($p < 0.01$) and 2.4 ± 1 kg ($p < 0.01$) respectively. Genital mycotic infections were reported in two (2.8%) patients. The mean reduction in the total daily dose of insulin was 9.5 ± 6 units. A significant reduction in the daily insulin requirement (19.87%, $p < 0.01$) was observed. The cost of insulin decreased by 22.3% or 17.8 ± 15 INR per day ($\$0.27 \pm 0.22$ per day) and the frequency of insulin shots administered per day decreased significantly ($p < 0.01$). In 12.8% and 2.8% of patients the frequency of administration of insulin

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decreased by one and two injections per day respectively.

Conclusions: Reduction in HbA1c and body weight along with minimal side effects was observed. Addition of dapagliflozin reduced the insulin daily dose requirement and cost of insulin therapy in these patients.

Funding: Diacon Hospital, Bangalore, India.

Keywords: Dapagliflozin; Dosage; HbA1c; Health economics; Insulin cost; SGLT2 inhibitors; Sodium glucose co-transporter 2 inhibitors; Type 2 diabetes; Weight reduction

INTRODUCTION

The prevalence of diabetes and especially type 2 diabetes mellitus (T2DM) is on the rise with a prevalence of 415 million cases globally and 69.1 million cases of diabetes in India in 2015 [1]. With the increasing incidence, cost of health care, lack of education, lack of lifestyle modifications, side effects of medications and physician inertia to up-titrate medications are factors amongst many that contribute to hyperglycaemia. In addition to its impact on micro- and macro-vascular outcomes, morbidity and mortality, the cost involved in the treatment of diabetes to the health care system is enormous [2, 3]. The individual expenditure to have access to standard care is 2.4 times higher for a patient with T2DM than for those without diabetes [4–10].

Patients with T2DM need constant up-titration of their medications because of the progressive beta cell failure [11]. Up-titration of oral and injectable antidiabetic drugs increases the short-term cost of medication. This is essential to improve the glycaemic control and to reduce the long-term costs incurred from the treatment of diabetes-related complications. Diabetes patients who do not achieve glycaemic control on monotherapy can benefit by either intensifying the dose or combination therapy with oral anti-diabetic drugs (OADs) and insulin [12–16]. However, insulin therapy is associated with weight gain and increased risk of hypoglycaemia. [16].

Sodium glucose transporter receptor 2 (SGLT2) inhibitors (with their insulin-independent mechanism of action) improve glycaemic control by increasing the renal excretion of glucose. [17, 18]. The glycaemic and extra-glycaemic benefits such as weight loss, reduction in blood pressure, decrease in uric acid levels, improvement in cardiovascular (CV) outcomes and renal outcomes are known with this class of agents [19–26]. Dapagliflozin, an SGLT2 inhibitor, can be used as monotherapy or as an adjunctive therapy in patients inadequately controlled with existing antidiabetic medications, including insulin [27]. However, the cost of dapagliflozin (43.2 INR, $0.64) remains a major challenge in clinical practice in developing countries like India.

Thus, the current study was conducted in a real-world clinical practice setting to evaluate the clinical effectiveness and impact on the cost of insulin therapy when dapagliflozin was added to uncontrolled T2DM patients on insulin and OADs.

METHODS

Study Design

This retrospective chart review planned to include patients with uncontrolled T2DM who were previously on maximum doses of OADs and insulin therapy. The study planned to evaluate the clinical effectiveness of

dapagliflozin when added to insulin therapy in T2DM patients. In addition, the present study attempted to evaluate the cost of insulin therapy when it was added to dapagliflozin in these patients.

Inclusion and Exclusion Criteria

The patients included in the study had uncontrolled T2DM for more than 3 months, HbA1c >8%, and were on insulin and maximum doses of OADs, without a clinical contraindication to receive an SGLT2 inhibitor. They were started on dapagliflozin 10 mg once a day. Baseline OADs prescribed by the treating physician remained unchanged and included sulfonylureas (glimiperide and gliclazide), metformin, DPP4 inhibitors, pioglitazone and alpha glucosidase inhibitors.

Patients with type 1 diabetes mellitus, pregnancy, recurrent urinary tract infections, genital mycotic infections and glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 were excluded from participating in this study.

Data Collection

Patients were evaluated for effectiveness and safety based on the following parameters: fasting plasma glucose (FPG), postprandial plasma glucose (PPG), glycated haemoglobin (HbA1c), lipid profile, renal function tests and urine analysis. The treat-to-target approach was used to adjust insulin doses as per standard of care. The insulin regimens included basal insulin once a day, premixed insulin twice a day, premixed insulin before breakfast and neutral protamine Hagedorn (NPH)/basal insulin at night, basal plus or basal bolus regimen. Patients were advised to do self-monitoring of blood glucose (SMBG) and adjust their insulin dose accordingly at home. The initial insulin regimen was unchanged at the time of initiation of dapagliflozin; however, patients who had recurring hypoglycaemia (more than three episodes in spite of reducing insulin dose based on the SMBG monitoring at home) were reviewed. In this subset of patients, the insulin regimen was changed and the frequency of insulin administration was reduced by the treating physician.

Data Abstraction

Patients from the study centres were evaluated for the inclusion and exclusion criteria. Overall, the present study planned to include those patients who had T2DM taking a combination of OADs and insulin, in whom dapagliflozin was initiated for the treatment of T2DM. Hospital records of patients attending the diabetes outpatient departments at two study centres, namely Diacon Hospital, a university-recognised specialised private 25-bed hospital for diabetes care, research and post-graduate studies, and Shivajyoti, a specialised private paediatric and adult endocrine outpatient practice hospital, were critically examined. The patient records between August 2015 and December 2015 were examined for inclusion of patients in the study.

Study Outcomes

The clinical effectiveness parameters measured were HbA1c and weight reduction. The study also assessed reduction in the total daily dose and frequency of insulin administration. The cost of insulin therapy at baseline and 3 months after adding dapagliflozin was evaluated. The cost of insulin included the total daily dose, cost per unit of insulin based on the formulation and the insulin delivery device.

Safety and tolerability were assessed by evaluating renal function tests, urinary

ketones and urine analysis recorded before and 3 months after the addition of dapagliflozin 10 mg. Mild hypoglycaemic episodes that occurred during the study period were not recorded. Patients were asked to report severe hypoglycaemic episodes, which were defined as an event of hypoglycaemia leading to a plasma glucose of <50 mg/dl, resulting in loss of consciousness or requiring intravenous administration of dextrose or hospitalisation.

Statistical Analysis

Microsoft Excel was used for the statistical analysis. Continuous variables are presented as mean ± standard deviation (SD) and categorical variables are presented in percentages (%). Continuous outcomes were tested using paired t test and Wilcoxon signed rank test for ordinal outcomes. *P* values <0.05 and 95% confidence intervals (CI) were considered to be statistically significant. A linear regression model was used to study the relationships between continuous outcomes and explanatory variables.

Compliance with Ethics Guidelines

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

RESULTS

Patient Characteristics

Overall, 5592 T2DM patient records were available from the outpatient department. A total of 264 patients had been initiated on dapagliflozin. One hundred ten patients out of these were the patients in whom dapagliflozin had been initiated over background insulin therapy and OADs. Of the 110 patients, 70 were included because their complete medical record was available; however, the remaining 40 patients were excluded from the entire analysis as they were lost to follow-up after the first hospital visit (Fig. 1).

The mean age and percentage of male patients were 52.6 ± 10 years and 44.3% respectively. Overall, an amount of less than 50 INR ($0.75) and an amount of more than 100 INR ($1.49) were being spent per day on insulin by 21 (30%) patients, and 28 (40%) patients were spending an amount of between 50 INR ($0.75) and 100 INR ($1.49) on insulin per day. The majority of the patients used insulin pens and cartridges ($n = 60$, 85.8%) as the insulin delivery device and a smaller proportion used syringes and vials ($n = 10$, 14.2%). The detailed demographics and baseline clinical parameters are presented in Table 1. The patients were taking insulin NPH, glargine, degludec, regular insulin, aspart and lispro in different insulin regimens at baseline. Details of the different insulin regimens being received by patients at baseline are presented in Table 2.

Effectiveness of Dapagliflozin on Addition to Insulin Therapy and Reduction in Insulin Dose

Reduction of HbA1c Levels and Changes in Body Weight

The mean change in HbA1c from baseline to 3 months after the addition of dapagliflozin was 2.1 ± 1% [10.3 ± 2% vs. 8.2 ± 1%, ($p < 0.01$)] and weight reduction was 2.4 ± 1 kg [75.3 ± 13 and 72.9 ± 12, ($p < 0.01$)] (Table 3).

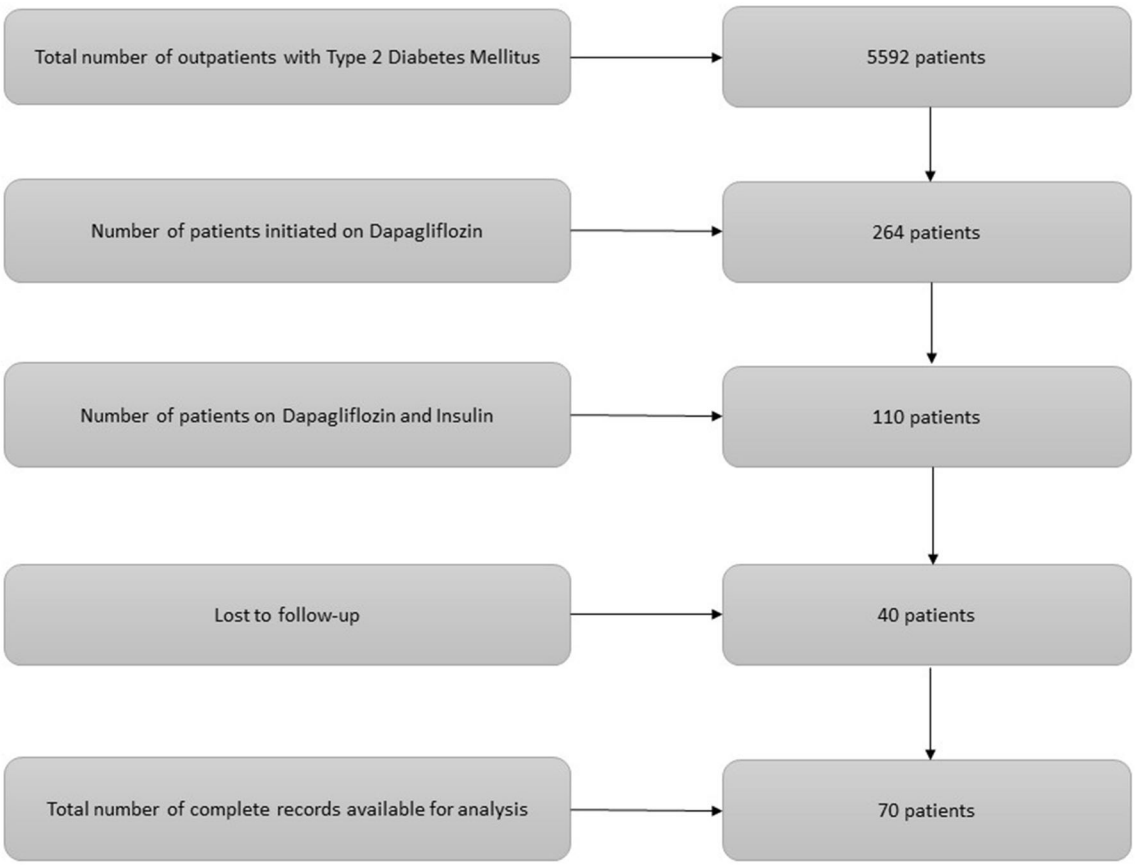

Fig. 1 Patient disposition

Reduction in Insulin Dose, Cost and Frequency

Insulin cost and dose at baseline and follow-up are shown in Table 3. A clinically and statistically significant ($p < 0.01$) reduction in total daily dose of insulin (9.5 ± 6 units) was observed from baseline to the 3-month follow-up period. There was a significant reduction in daily cost on insulin therapy by 17.8 ± 15 INR per day ($\$0.27 \pm 0.22$, $p < 0.01$). The relationship between insulin dose reduction and cost reduction was analysed. For reduction in insulin cost, the β value of the dosage reduction was estimated to be 1.85 units [1.66–2.03, ($p < 0.01$)] and did not change when adjusted for confounders such as age, gender and duration of diabetes. One-unit reduction in insulin dose translated to a cost reduction of 1.85 INR ($0.03, Fig. 2).

There was a statistically significant reduction ($p < 0.01$) in cost after the addition of dapagliflozin in all groups viz. patients spending less than 50 INR ($0.75); patients spending between 50–100 INR ($0.75–1.49); and patients spending more than 100 INR ($1.49). Specifically, in patients (30%) whose daily insulin expenditure exceeded 100 INR per day ($1.49 per day), the decrease in insulin cost was observed to be 45 INR [$0.67, baseline: 151.8 ± 33 ($\$2.25 \pm 0.49$); 3-month follow-up: 106.8 ± 29 ($\$1.59 \pm 0.43$), $p < 0.01$, Table 3].

There was a significant reduction in the frequency of insulin administration after the

Table 1 Demographics and baseline clinical parameters

Parameters	Uncontrolled T2DM ($N = 70$)
Mean age (±SD), years	52.6 ± 10
Males (%)	44.3
Mean duration of disease (±SD), years	12 ± 5
Mean HbA1C (±SD), %	10.3 ± 2
Mean weight (±SD), kg	75.3 ± 13
Insulin total daily dose, units	47.8 ± 30
Mean insulin cost per day, INR ($)	79.5 ± 53 (1.19 ± 0.79)
Cost of insulin per day, (INR ($)	
<50 INR per day (<$0.75 per day)	21 (30%)
50–100 INR per day ($0.75–1.49 per day)	28 (40%)
>100 INR per day ($1.49 per day)	21 (30%)
Insulin delivery devices	
Syringes and vials	10 (14.2%)
Insulin pens and cartridges	60 (85.8%)

Table 2 Different insulin regimens patients received at baseline

Insulin regimen	*n* (%)
Glargine OD	22 (31.4)
Premixed insulin OD	2 (2.8)
30% aspart with 70% Degludec	
Premixed insulin BID	11 (15.7)
30% soluble aspart with 70% NPH	
Premixed insulin BID	4 (5.7)
25% lispro with 75% NPH	
Premixed 30% aspart with 70% NPH before breakfast + degludec at bedtime	2 (2.8)
Premixed insulin BID	4 (5.7)
30% regular with 70% NPH	
Lispro before breakfast + glargine at bedtime	2 (2.8)
Premixed insulin 30% aspart with 70% NPH before breakfast + glargine at bedtime	8 (11.4)
Aspart before breakfast + aspart before lunch + premixed insulin 30% aspart with 70% NPH before dinner	7 (10)
Regular insulin before breakfast + regular insulin before lunch + premixed insulin 30% regular with 70% NPH before dinner	2 (2.8)
Basal bolus	6 (8.5)
Glargine at bedtime with aspart thrice a day before meals	

addition of dapagliflozin ($p < 0.01$). There was a reduction in insulin injections by one and two injections per day in 12.8% and 2.8% of patients respectively (Table 3).

Safety and Tolerability

Although the frequency of mild hypoglycaemic episodes was not recorded during the study period, none of the patients reported severe hypoglycaemic episodes. Patients who experienced hypoglycaemia were advised to reduce the dose of insulin as per the standard of care. In addition, patients experienced only mild hypoglycaemic episodes that did not require intravenous dextrose or hospitalisation. Mild hypoglycaemic episodes were self-managed at home by the patients with oral glucose consumption (15–20 gm), which did not add to the treatment cost as the cost of oral glucose was minimal. Genital mycotic infections were observed in two (2.8%) patients and treated successfully with topical fluconazole-based creams with no further recurrence. The cost of treatment was a single time additional cost of 43 INR ($0.64) per

Table 3 Changes in study outcomes from baseline to 3-month follow-up period

Parameter	Baseline	3-month follow-up after addition of dapagliflozin
HbA1c %*	10.3 ± 2	8.2 ± 1
Weight in kg*	75.3 ± 13	72.9 ± 12
Insulin cost INR ($)*	79.5 ± 53 (1.19 ± 0.79)	61.7 ± 38 (0.92 ± 0.57)
Insulin dose units*	47.8 ± 30	38.3 ± 24
Cost of insulin in those spending >100 INR/day (>$1.49/day)*	151.8 ± 33 (2.26 ± 0.49)	106.8 ± 29 (1.59 ± 0.43)
Number of insulin shots per day*		
Four	5 (7.1)	4 (5.7)
Three	9 (12.8)	8 (11.4)
Two	30 (42.8)	26 (37.1)
One	26 (37.1)	28 (40)
Zero	0	4 (5.7)

Data are presented as mean ± SD for continuous variables and as *n* (%) for categorical variables. Paired *t* test was used to calculate *p* values for continuous variables and Wilcoxon signed rank test for ordinal variables

* $p < 0.01$ at 5% level of significance

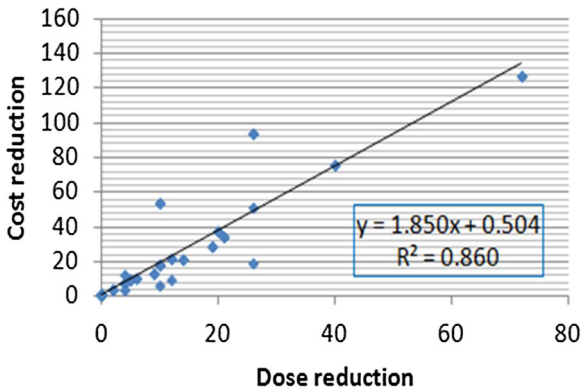

Fig. 2 Correlation between cost reduction and reduction in total daily dose of insulin

patient. No other side effects were reported, including ketonuria.

DISCUSSION

In this retrospective study the addition of dapagliflozin 10 mg resulted in a significant improvement in glycaemic control and body weight and a reduction in the dose, frequency and cost of insulin therapy. Dapagliflozin, an SGLT2 inhibitor, reduces HbA1c levels and provides extra benefits beyond glycaemic control. Although the efficacy of dapagliflozin is evident from randomised control trials, its performance outside a controlled environment may be variable. The safety profile and cost also present challenges to the use of medications in real-world scenarios [11, 15–20, 28–31]. The results of this study provide valuable evidence on the clinical effectiveness, safety and implications for the cost of treatment.

There was a 19.87% reduction in the total daily dose of insulin from baseline in this study. Wilding et al. evaluated the effect of adding dapagliflozin to insulin in T2DM patients. The study showed that the dose of insulin progressively increased by +18.3 IU/day over a

period of 104 weeks in patients who were receiving placebo along with insulin; however, the dose of insulin requirement remained stable over the 104-week study period in patients receiving dapagliflozin along with insulin [33].

The cost of diabetes therapy in India is borne by the patients and not by the health care system [34]. Efficacy, effectiveness and safety are insufficient if the therapeutic option is financially not viable. Our study has shown an overall reduction in insulin cost by 17.8 ± 15 INR per day ($0.27 ± 0.22 per day) in patients at the end of the 3-month follow-up period. The maximum benefit was seen in individuals spending more than 100 INR per day ($1.49 per day) on insulin, the savings offsetting the cost of dapagliflozin, which costs approximately 43 INR ($0.64) per dose. Similar results were observed in another study wherein addition of dapagliflozin to insulin was found to be a cost-effective treatment option for T2DM patients [27, 32].

Improved glycaemic control also warranted a change in the insulin regimen and reduction in the frequency of insulin administration in 15% of the patients in this study. Such changes can directly impact the health economics by reducing the cost of medication and monitoring. Decreased frequency of dosing reduces pain and is also a fundamental determinant of patient compliance and preference [35]. Intangible psychological benefits increase the productivity and quality of life (QoL) [36]. Previous studies have reported a decrease in the total daily dose of insulin with the use of SGLT2 inhibitors with no difference in the number of insulin shots per day [37–40].

Insulin use complicates diabetes care and adds to weight gain and fear of injectables, thus reducing adherence to treatment. Many studies have demonstrated improved glycaemic control and weight loss and a slight increase in hypoglycaemia when patients were treated on SGLT2 inhibitors and insulin [6, 7, 33, 38, 39, 41]. Although the present study did not evaluate the frequency of hypoglycaemic episodes experienced by the patients, none of them were observed to experience severe hypoglycaemia during the entire study period. Although the evidence evaluating the overall efficacy and safety of dapagliflozin as an add-on therapy to high-dose insulin in T2DM patients is limited, most of the available studies suggest that addition of dapagliflozin reduces the HbA1c levels without increasing the risk of hypoglycaemic events. In addition, a small proportion of patients reported genital mycotic infections during the study period. It is important to mention that such patients were successfully treated with topical anti-fungal agents, which was a one-time cost and did not exceed 43 INR ($0.64) per patient. Patients with T2DM often experience genital infections caused by several factors such as glucosuria, adherence of bacteria to the uroepithelium and immune dysfunction. Patients taking SGLT2 inhibitors viz. dapagliflozin are more prone to genital infections because these agents are known to induce glucosuria pharmacologically. However, these genital infections are generally not serious and easily managed with anti-fungal agents [42].

Some of the limitations of the study are the short duration and small sample size. The impact on the glycaemic variability, number of hypoglycaemic episodes and cost of treating hypoglycaemia was not analysed. Additionally, it is important to mention that glycaemic variability was not measured in this study as it was a real-world retrospective study and assessment of this parameter with a continuous glucose monitoring device was not

a part of routine care, so these data were not available. The impact on the monitoring frequency and SMBG costs were not analysed as most patients were unable to produce records of the same.

While it is easier to estimate the direct reduction in daily health care-related costs, the indirect health economic benefits of improved glycaemic control, weight loss and cardiovascular risk reduction are invaluable and difficult to quantify monetarily. Direct costs such as the cost of medication, investigations and hospitalisation are easy to quantify, but the indirect economic burden, such as absenteeism from work, low self-esteem, depression and caregiver burden, are difficult to assess and were not assessed in this study.

Improved glycaemic control and weight reduction are accompanied by a better QoL. Long-term studies must be carried out to evaluate the effect of this therapy on long-term cardiovascular, micro- and macrovascular complications in patients with T2DM. The lack of integration among the health care system, insurance providers and the health care regulators and out of pocket expenses for diabetes care have resulted in a scarcity of information on pricing and cost analysis studies on a national level. The results of this study should be a premise for further larger studies evaluating the cost of treatment with a better integrated health care system to ensure adequate cost management in the future in a country like India. If the above findings can be replicated in larger long-term studies, SGLT2 inhibitors may have the potential to occupy a higher place in the treatment algorithm for T2DM for health care providers, policy makers and health insurers. A greater understanding of health economic benefits is necessary, especially in developing countries like India, to ensure that the medications we prescribe are indeed 'value for money'.

CONCLUSION

The present study has demonstrated that the addition of dapagliflozin to existing insulin and OADs in uncontrolled T2DM patients reduces HbA1C and weight, along with reducing the insulin dose, frequency and cost.

ACKNOWLEDGMENTS

Medical writing assistance and article processing charges for this paper were funded by AstraZeneca Pharma India, Ltd., Bangalore, India. The authors acknowledge Turacoz Healthcare Solutions for editing support. All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole and have given final approval for the version to be published.

Disclosures. Bhavana Sosale, Aravind Sosale and Arpandev Bhattacharyya have nothing to disclose.

Compliance with Ethics Guidelines. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

Data availability. The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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