VALUE IN HEALTH REGIONAL ISSUES 18 (2019) 65–73

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/vhri

Economic Evaluation

Long-Term Clinical Benefits of Canagliflozin 100 mg Versus Sulfonylurea in Patients With Type 2 Diabetes Mellitus Inadequately Controlled With Metformin in India

Vishal Gupta, MD[1], *Michael Willis, PhD*[2], *Pierre Johansen, MSc*[2], *Andreas Nilsson, MSc*[2], *Manan Shah, MBBS, MHA*[3], *Amey Mane, MD*[3], *Cheryl Neslusan, PhD*[4*]

[1]"VG-ADVANTAGE" Diabetes, Thyroid and Endocrine Center and Breach Candy Hospital, Mumbai, Maharashtra, India; [2]The Swedish Institute for Health Economics, Lund, Sweden; [3]Janssen India Medical Affairs, Mumbai, Maharashtra, India; [4]Janssen Global Services, LLC, Raritan, NJ, USA

ABSTRACT

Objectives: To simulate the long-term health outcomes of canagliflozin 100 mg versus glimepiride over 20 years in patients with type 2 diabetes mellitus (T2DM) inadequately controlled on metformin from the perspective of the Indian health care system. **Methods:** Health outcomes were simulated using the validated Economic and Health Outcomes Model of T2DM. Patient demographic characteristics, biomarker values, and treatment effects were sourced from a subgroup of Indian patients enrolled in a 52-week, head-to-head study of canagliflozin versus glimepiride (mean maximum dose of 5.6 mg/d) in patients with T2DM inadequately controlled with metformin. Outcomes were discounted at 5%. Sensitivity analyses were conducted using alternative values for key model inputs. **Results:** Relative to glimepiride, treatment with canagliflozin 100 mg was associated with approximately 14 more patients surviving at year 20 per 1,000 patients treated and 0.43 quality-adjusted life-years gained, largely because of improved body weight and reduced risk of macrovascular and microvascular morbidity over 20 years. Risk reductions were the largest for microvascular complications (e.g., chronic kidney disease and albuminuria). Improved health outcomes were driven by better glycated hemoglobin control associated with canagliflozin versus glimepiride, which also delayed the need for rescue therapy. Key components of quality-adjusted life-year gains included the avoidance of hypoglycemic episodes, chronic kidney disease, and weight gain, as well as increased survival with canagliflozin compared with glimepiride. **Conclusions:** Simulation results suggest that canagliflozin 100 mg may provide better long-term health outcomes compared with glimepiride in Indian patients with T2DM inadequately controlled with metformin.

Keywords: health outcomes, modeling, SGLT2 inhibitors, type 2 diabetes.

Introduction

India is home to the second largest population of people with diabetes in the world (~70 million), of which approximately 90% have type 2 diabetes mellitus (T2DM) [1]. Steady urbanization, lifestyle changes, and increasing obesity and age have contributed to the rise in diabetes prevalence in India [2,3]. Public health care funding in India is limited, so health care expenditure is primarily administered in the private sector [4]. Thus, patients typically assume responsibility for diabetes management costs [5].

T2DM is associated with chronic hyperglycemia [6,7], which can lead to multiple comorbidities, complications, and premature death [8]. Historically, glycemic control has been the primary goal of T2DM management to minimize these risks [9–11]. The Research Society for the Study of Diabetes in India recommends a glycated hemoglobin (HbA_{1c}) target of less than 7.0% and consideration of patient characteristics to individualize T2DM treatment

Canagliflozin has been developed by Janssen Research & Development, LLC, in collaboration with Mitsubishi Tanabe Pharma Corp.

Conflicts of interest: M. Willis and A. Nilsson are full-time employees of The Swedish Institute for Health Economics, which has provided consulting services for Janssen Global Services, LLC. P. Johansen was a full-time employee of The Swedish Institute for Health Economics at the time of the analysis and is currently a full-time employee of Novo Nordisk A/S. M. Shah and A. Mane are full-time employees of Janssen India. C. Neslusan is a full-time employee of Janssen Global Services, LLC. V. Gupta has no relevant disclosures.

* *Address correspondence to:* Cheryl Neslusan, PhD, Janssen Global Services, LLC, 920 Route 202 South, Raritan, NJ 08869.
Email: cneslusa@its.jnj.com.

2212-1099/$36.00 – see front matter
https://doi.org/10.1016/j.vhri.2018.06.002

[12], which is consistent with the recommendations of the American Diabetes Association and the European Association for the Study of Diabetes [13]. Globally, guidelines also emphasize multifactorial management of cardiovascular risk factors, such as weight, blood pressure (BP), and lipids, and encourage smoking cessation when applicable [10,13].

More than half the patients with T2DM in India are unable to reach the HbA_{1c} target of <7.0% with available antihyperglycemic agents (AHAs), and many patients eventually need multiple insulin injections daily [14]. Some treatments (e.g., sulfonylureas and insulin) have poor durability as the disease progresses and are associated with hypoglycemia and weight gain [10,15]. Despite these limitations, sulfonylureas remain widely used in India partly because of their low acquisition costs [16].

Unlike other AHAs, agents that inhibit sodium glucose cotransporter 2 (SGLT2) lower blood glucose via a renal mechanism that works independently of insulin and, thus, is complementary to other AHAs (including insulin) [17]. SGLT2 inhibitors reduce the renal threshold for glucose reabsorption and lead to increased urinary glucose excretion, thereby reducing blood glucose, body weight, and BP, with a low inherent risk of hypoglycemia [17]. Evidence from the CANagliflozin cardioVascular Assessment Study (CANVAS) Program and the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) showed cardiovascular and renal benefits with these SGLT2 inhibitors in patients with T2DM and increased cardiovascular risk [18,19]. Therefore, SGLT2 inhibitors may beneficially manage multiple factors that could have an impact on long-term health outcomes in patients with T2DM.

Canagliflozin 100 mg was the first SGLT2 inhibitor approved for the treatment of adults with T2DM in India, with the 300-mg dose recently becoming available. In phase 3 studies, canagliflozin was associated with reductions in HbA_{1c}, body weight, and BP, and was generally well tolerated in a broad range of patients with T2DM [20], including patients from India [21]. In an active-controlled, phase 3 study, canagliflozin 100 and 300 mg and maximally tolerated glimepiride (a sulfonylurea) were administered once daily to patients inadequately controlled on metformin during a 52-week core period, followed by a 52-week extension period [22,23]. In the overall population, canagliflozin 100 mg demonstrated noninferiority and canagliflozin 300 mg demonstrated superiority in HbA_{1c} lowering at 52 weeks compared with glimepiride (mean maximum dose of 5.6 mg/d) [22]. Both canagliflozin doses also provided significant reductions in body weight and modest reductions in systolic blood pressure (SBP) with significantly fewer hypoglycemic episodes at 52 weeks. Notably, more patients had reductions in both HbA_{1c} and body weight with canagliflozin versus glimepiride over 52 weeks [24]. The safety profile of canagliflozin was consistent with other phase 3 studies, including higher incidences of adverse events (AEs) related to the SGLT2 mechanism of action (e.g., genital mycotic infections and osmotic diuresis–related AEs) [25,26]. Findings at 104 weeks were generally consistent with results at 52 weeks, but with both canagliflozin doses showing a larger relative treatment effect versus glimepiride in a mixed model for repeated-measures analysis [23].

Economic simulation modeling techniques are widely used and accepted tools to bridge the gap between shorter term clinical data and longer term health outcomes, survival, health-related quality of life (HRQOL), and costs of alternative competing interventions for T2DM, which can be important for health care decision making, especially in a self-pay environment [27]. To date, there has been only one study investigating long-term health and economic outcomes of T2DM interventions using Indian data. The study found that total costs were lower among Indian patients who were on oral AHAs versus insulin aspart over short (1-year) and long (30-year) time horizons [28]. Because of the lack of reliable costing data in India, cost has not been not modeled in the present analysis; instead, we focused on predicting disease progression and health outcomes associated with the use of canagliflozin 100 mg, the most widely used dose in India, and maximally tolerated glimepiride as add-on to metformin over 20 years from an Indian health care perspective.

Methods

Model Overview

Simulations were performed using the Economic and Health Outcomes Model of T2DM (ECHO-T2DM) version 2.3.0, which is a stochastic, microsimulation (patient-level), multiapplication model for estimating the cost effectiveness of T2DM treatments [29]. An overview of the model is shown in Appendix Figure A1 in Supplemental Materials found at 10.1016/j.vhri.2018.06.002 [30] and a description is presented in Appendix B in Supplemental Materials found at 10.1016/j.vhri.2018.06.002. The ECHO-T2DM model has been subject to regular internal and external validation, which has been the subject of two publications [30, 31]. In addition, the Assessment of the Validation Status of Health-Economic decision models [32] was completed for the latest ECHO-T2DM validation [30] and is included in Appendix C in Supplemental Materials found at 10.1016/j.vhri.2018.06.002.

Microvascular and Macrovascular Risk Functions

In ECHO-T2DM, hypothetical patients are assigned risks for microvascular and macrovascular complications and mortality that are individualized to patient characteristics using risk functions. Transition probabilities for microvascular health states (e.g., retinopathy, chronic kidney disease [CKD], and neuropathy) were sourced from previous studies and reflect differences in HbA_{1c} levels, SBP, and/or T2DM duration [33–36]. Event risks for macrovascular complications (myocardial infarction, ischemic heart disease, congestive heart failure, and stroke) and mortality were modeled using risk equations from the UK Prospective Diabetes Study (UKPDS 82) [37], which is less likely to overpredict risks than the previous version (UKPDS 68) [38]. The risk equations in these simulations were tailored to the Indian population via the UKPDS 82 covariate for "Asian Indians," which was the assumed ethnicity of all hypothetical patients in these simulations.

Simulation Parameters and Patient Profile

Key model assumptions are presented in Table 1. Baseline demographic and disease characteristics reflecting the distribution of the Indian subgroup population were sourced from the 52-week, head-to-head study of canagliflozin versus glimepiride as add-on to metformin (see Appendix Table A1 in Supplemental Materials found at 10.1016/j.vhri.2018.06.002). In the base case, 1,000 cohorts of 2,000 hypothetical patients (i.e., 2,000,000 unique patients) were generated and their health histories were simulated over 20 years.

Treatment Effects and Algorithm

Hypothetical patients with T2DM inadequately controlled with metformin were assigned to canagliflozin 100 mg or glimepiride. In India, glimepiride is usually administered at doses of 2 to 4 mg/d. Because these simulations were based on a clinical trial designed to compare the efficacy of canagliflozin versus maximally-tolerated glimepiride, the dose could be up to 6 or 8 mg based on local guidelines. Treatment effects and AEs for canagliflozin 100 mg and glimepiride were applied for each patient in the first year of simulation and were obtained from a post hoc analysis of the

Table 1 – Key simulation assumptions.

Parameter	Assumption
Perspective	Indian health care system
Time horizon	20 y
Cycle length	1 y
Discount rate	5%
Treatment intensification thresholds	
HbA_{1c}	>8.0%
SBP	>130 mm Hg
LDL-C	>100 mg/dl
HDL-C	<45 mg/dl
Triglycerides	>150 mg/dl
Annual biomarker drift	
HbA_{1c}	
Canagliflozin 100 mg	0.14% [15],*
Glimepiride	0.24% [15],†
Pioglitazone	0.07% [15],‡
Insulin	0.15% [38]
SBP	0.3 mm Hg [38]
Lipids (LDL-C, HDL-C, total cholesterol, and triglycerides)	0.03 mg/dl [38]
BMI	0.0381 kg/m^2§
Rescue therapy treatment pathway	
First rescue	Basal insulin (NPH) 10 IU/d, titrated up to 60 IU/d
Second rescue	Prandial insulin (Humulin-R) 5 IU/d, titrated up to 200 IU/d
Mean delay to rescue therapy	
Pioglitazone	9.95 y
Basal insulin	8.66 y
Antihypertension treatment algorithm	
First treatment	ACE inhibitor (enalapril 2.5 mg)
Second treatment	+ARB (telmisartan 40 mg)
Third treatment	+ARB (telmisartan 40 mg) + diuretic (hydrochlorothiazide 12.5 mg)
Fourth treatment	+Calcium channel blocker (amlodipine 2.5 mg)
Lipid-lowering treatment	Atorvastatin 10 mg → 80 mg
Macrovascular and mortality risk equations	UKPDS 82 [37]
Microvascular risk equations	CDC model of CKD, WESDR, and REP [35,36,69,70]

ACE, angiotensin-converting enzyme; ADOPT, A Diabetes Outcome Progression Trial; ARB, angiotensin receptor blocker; BMI, body mass index; CDC, Centers for Disease Control and Prevention; CKD, chronic kidney disease; HbA_{1c}, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NPH, neutral protamine Hagedorn; REP, Rochester Epidemiology Project; SBP, systolic blood pressure; UKPDS, United Kingdom Prospective Diabetes Study; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

* Canagliflozin 100 mg was assumed to have the same drift as the metformin arm from the 5-y ADOPT study [15].

† Glimepiride was assumed to have the same drift as the sulfonylurea arm from the ADOPT study [15].

‡ Pioglitazone was assumed to have the same drift as the rosiglitazone arm from the ADOPT study [15].

§ BMI calculated using average Indian heights (162 cm) [71].

subgroup of Indian patients enrolled in the head-to-head study of canagliflozin versus glimepiride (see Appendix Table A2 in Supplemental Materials found at 10.1016/j.vhri.2018.06.002) [22]. Biomarkers were assumed to deteriorate each year at published rates [11,39].

In the base case, estimated glomerular filtration rate (eGFR) was assumed to remain stable with canagliflozin [40]; the Centers for Disease Control and Prevention (CDC) model of CKD drift in eGFR was applied for patients who discontinued canagliflozin (and initiated rescue therapy) and for patients assigned to glimepiride [35]. Treatment effects for canagliflozin 100 mg were adjusted to account for the declining eGFR on the basis of a pooled analysis of patients with moderate renal impairment (eGFR ≥45 and <60 ml/min/1.73 m^2) [41,42]. As per the Indian product label, canagliflozin 100 mg was discontinued at an eGFR of less than 45 ml/min/1.73 m^2 [43]. In the first year, discontinuation due to AEs was modeled according to rates from the Indian subgroup of the trial.

In the simulations, rescue therapy was added to maintain HbA_{1c} at less than 8.0%, which may be more reflective of the Indian setting. When HbA_{1c} first exceeded 8.0% (or because of drug discontinuation as explained earlier), basal insulin (neutral protamine Hagedorn) was added, starting at 10 IU/d and titrated to maintain HbA_{1c} at 8.0% or lower, up to 60 IU/d (sulfonylurea treatment discontinued upon initiation of basal insulin). After maximizing the basal insulin dose, prandial insulin (aspart) was added as needed to maintain glycemic control, starting at 5 IU/d and titrated up to 200 IU/d. Published treatment effects and hypoglycemia rates with insulin were used [44–46]. Clinical inertia (i.e., lack of treatment intensification when additional glycemic control is needed) has been well documented in patients with T2DM [47,48]. Because of the lack of data specific to the Indian setting, clinical inertia associated with insulin was modeled according to findings from the United Kingdom (basal insulin initiation delayed by mean 8.66 years [47] after HbA_{1c} reached 8.0%). Antihypertensive and lipid-lowering treatments were added when SBP or lipid levels exceeded Indian-specific thresholds presented in Table 1; treatment effects were sourced from the literature [49,50].

Severe hypoglycemic events (i.e., episodes requiring assistance or resulting in seizure or loss of consciousness) and nonsevere symptomatic hypoglycemic events (i.e., episodes in which symptoms were accompanied by a glucose reading of less than or equal to 3.9 mmol/l [70 mg/dl] and did not meet the criteria for a severe

episode) were modeled. AEs associated with the mechanism of SGLT2 inhibition (e.g., urinary tract infections [51], genital mycotic infections [e.g., yeast infections] [52], and osmotic diuresis–related AEs [53]) were also included [25,26].

Quality of Life

Improvements in HRQOL have been shown to be associated with increased performance of self-care behaviors and thus potentially better outcomes in patients with T2DM [54–56]. HRQOL is captured in the model using life-years (LYs) and quality-adjusted life-year (QALY) disutility weights, which reflect decrements in quality of life associated with the negative impact of each health state. QALYs reflect parameters that might affect the value of an LY (e.g., sociodemographic characteristics and health conditions). Published QALY disutility weights were used [57,58] and were derived from studies in patients with T2DM, whenever possible (see Appendix Table A3 in Supplemental Materials found at 10.1016/j.vhri.2018.06.002) [34,53,59,60]. To our knowledge, Indian-specific disutility weights are not available. A discount rate of 5% was applied to deflate QALYs to their net present value [61].

Outcomes

Biomarker evolution curves, cumulative incidences and relative risk reductions (RRRs) in macrovascular and microvascular events, years without selected complications, AEs, survival, LYs, and QALYs are reported.

Sensitivity Analyses

One-way sensitivity analyses were used to explore how the simulation results change by varying model parameters. In this analysis, sensitivity analyses included the following:

1. *Time horizon*: 30 years (SA1);
2. *Clinical inertia:* no delay in initiation of rescue therapy (SA2);
3. *Rescue therapy:* initiate pioglitazone as first rescue therapy (SA3);
4. *eGFR drift:* assume no eGFR drift for glimepiride (SA4), assume eGFR drift for canagliflozin to be 50% of eGFR drift from the CDC model of CKD (SA5), apply eGFR drift from the CDC model of CKD for canagliflozin (SA6); and
5. *Rescue therapy and eGFR drift:* initiate pioglitazone as initial rescue therapy as in SA3 and apply eGFR drift from the CDC model of CKD for canagliflozin as in SA6 (SA7).

Results

Base Case

In the base case, canagliflozin 100 mg was associated with better survival and improved health outcomes compared with glimepiride over 20 years (Table 2). Overall, 67.8% and 66.5% of patients in the canagliflozin and glimepiride groups, respectively, were still alive at the end of the simulation (difference of ~1.4 percentage points). In other words, approximately 14 more simulated patients in the canagliflozin group compared with the glimepiride group survived by year 20 per 1,000 patients treated. Discounted LYs were moderately higher for canagliflozin-treated patients (0.02) and discounted QALYs were substantially greater (0.43 years of perfect health).

The better simulated HbA_{1c}, body mass index, and SBP timepaths with canagliflozin 100 mg compared with glimepiride are illustrated over 20 years in Appendix Figure A2 in Supplemental Materials found at 10.1016/j.vhri.2018.06.002. The greater HbA_{1c} lowering and better durability in the canagliflozin arm over time reduced the need for rescue therapy (Fig. 1). HbA_{1c} levels were higher with glimepiride at the end of the simulation, consistent with the poorer known durability of sulfonylureas (i.e., upward drift of HbA_{1c} while on treatment) [62] and the clinical inertia associated with initiating rescue therapy. Less insulin rescue therapy in the canagliflozin arm also led to less weight gain and fewer hypoglycemic events.

Overall, biomarker improvements with canagliflozin were associated with decreased incidence of macrovascular and microvascular complications versus glimepiride (Table 2). The largest RRRs were seen for CKD where, for example, 0.4% of patients in the canagliflozin 100 mg group were modeled to have stage 3A CKD after 20 years versus 20.9% of patients in the glimepiride group (RRR of 98.2%). Similarly, canagliflozin 100 mg reduced the risk of stages 3B, 4, and 5 CKD and end-stage renal disease, as well as microalbuminuria and macroalbuminuria, versus glimepiride, which is consistent with the modeled differences in eGFR deterioration between canagliflozin and glimepiride.

The largest macrovascular benefits with canagliflozin 100 mg versus glimepiride were seen for congestive heart failure, stroke, and ischemic heart disease (RRRs of 14.3%, 6.8%, and 6.7%, respectively). As expected, canagliflozin 100 mg had higher rates of female genital mycotic infections, lower urinary tract infections, and osmotic diuresis–related AEs compared with glimepiride. Simulated rates of nonsevere symptomatic and severe hypoglycemic episodes were higher with glimepiride versus canagliflozin 100 mg, not only because of the inherent excess risk that sulfonylurea use conveys but also the greater and earlier use of insulin rescue therapy in the glimepiride arm.

QALY gains were mainly driven by the avoidance of hypoglycemic episodes, CKD, and weight gain, as well as increased survival with canagliflozin versus glimepiride (see Appendix Table A4 in Supplemental Materials found at 10.1016/j.vhri.2018.06.002). These improvements were attributable to larger and more durable reductions in HbA_{1c}, leading to less need for rescue therapy, lack of eGFR deterioration, and weight loss, respectively, in the canagliflozin arm. There were also small QALY gains for other complications. As expected, canagliflozin led to a small increase in disutility (i.e., lower utility or less benefit) for AEs related to the SGLT2 inhibitor mechanism.

Sensitivity Analyses

Representative results of the sensitivity analyses are shown in Figure 2, with full results presented in Appendix Table A5 in Supplemental Materials found at 10.1016/j.vhri.2018.06.002. In SA1, the time horizon was increased to 30 years, which may better capture the long-term benefits with canagliflozin versus glimepiride. Over 30 years, life expectancy and QALYs increased with canagliflozin versus glimepiride. Cumulative incidences of complications were generally higher in both groups and QALY gains with canagliflozin versus glimepiride because of increased longevity, with similar trends in RRRs as in the base case. Hypoglycemic event rates remained lower with canagliflozin versus glimepiride, but were higher in both groups compared with the base case because patients spent more time on insulin.

In SA2, the conservative assumption of no clinical inertia for insulin rescue therapy resulted in smaller between-group differences in HbA_{1c} over time and smaller reductions in RRRs for some complications. Consistent with the earlier insulin initiation, hypoglycemic event rates were higher in both groups. Similar results as in the base case were also seen when rescue therapy was first initiated with pioglitazone rather than insulin (SA3);

Table 2 – Base-case results.

Outcome Parameter	Canagliflozin 100 mg	Glimepiride	Difference
Health outcomes (discounted)			
LYs	11.29	11.27	0.02
QALYs	8.89	8.46	0.43
Survival (%)	67.8	66.5	1.4
Years without a complication			
Amputation	12.56	12.52	0.04
ESRD	12.77	12.74	0.04
Blindness	12.69	12.63	0.06
CHD (MI or IHD)	11.55	11.46	0.10
CVD (MI, IHD, or stroke)	11.43	11.33	0.10
Cumulative incidence of outcomes (%)			**RRR**
Macrovascular			
MI	13.9	14.7	5.8%
IHD	12.1	13.0	6.7%
CHF	4.1	4.8	14.3%
Stroke	4.0	4.2	6.8%
CHD (MI and IHD)	23.8	25.3	5.7%
CVD (MI, IHD, and stroke)	26.8	28.4	5.6%
PVD	35.1	36.2	2.9%
Microvascular			
Background diabetic retinopathy	42.8	53.9	20.6%
Proliferative diabetic retinopathy	0.5	0.8	39.0%
Macular edema	17.4	23.7	26.6%
Blindness			
One eye	0.3	0.5	35.7%
Both eyes	0.3	0.5	33.5%
Symptomatic neuropathy	24.1	26.0	7.5%
Diabetic foot ulcer	18.9	20.0	5.3%
Lower extremity amputation	10.1	10.8	6.7%
Microalbuminuria	3.3	5.4	39.6%
Macroalbuminuria	0.1	1.3	93.4%
CKD			
Stage 3A	0.4	20.9	98.2%
Stage 3B	0.2	11.3	98.3%
Stage 4	0.1	5.4	98.2%
Stage 5	0.0	1.6	98.2%
ESRD	0.0	1.1	98.2%
Other AEs, event rate/100 patient-years			**HR**
Osmotic diuresis–related AEs	0.1	0.1	1.0
Lower UTI	12.9	3.9	3.3
Upper UTI	0.1	0.1	1.0
Male genital mycotic infection	0.1	0.1	1.0
Female genital mycotic infection	3.2	0.0	81.7
Hypoglycemic events, event rate/100 patient-years			
Nonsevere symptomatic	153.4	707.9	0.2
Severe	1.7	7.4	0.2

AE, adverse event; CHD, coronary heart disease; CHF, congestive heart failure; CKD, chronic kidney disease; CVD, cardiovascular disease; ESRD, end-stage renal disease; HR, hazard ratio; IHD, ischemic heart disease; LY, life-year; MI, myocardial infarction; PVD, peripheral vascular disease; QALY, quality-adjusted life-year; RRR, relative risk reduction; UTI, urinary tract infection.

nevertheless, hypoglycemic event rates were lower than in the base case because of the delay in insulin initiation.

Sensitivity analyses were conducted that varied assumptions related to eGFR drift with both canagliflozin and glimepiride. When eGFR was assumed to be stable with glimepiride as well as canagliflozin (SA4), differences in QALYs and survival were smaller compared with the base case. Because eGFR did not deteriorate with glimepiride in SA4, absolute rates of CKD were lower with glimepiride, which led to slightly smaller RRRs for canagliflozin versus glimepiride compared with the base case. In SA5, RRRs were slightly smaller for renal-related complications compared with the base case when eGFR for canagliflozin drifted at half the rate used for glimepiride. This was consistent with more patients in the canagliflozin group developing CKD over time; nevertheless, there was minimal impact on overall LYs, QALYs, and survival. In SA6 and SA7, when eGFR drift from the CDC model of CKD was used for canagliflozin, the benefits seen for CKD were eliminated and improvements in LYs, QALYs, and survival were smaller compared with the base case.

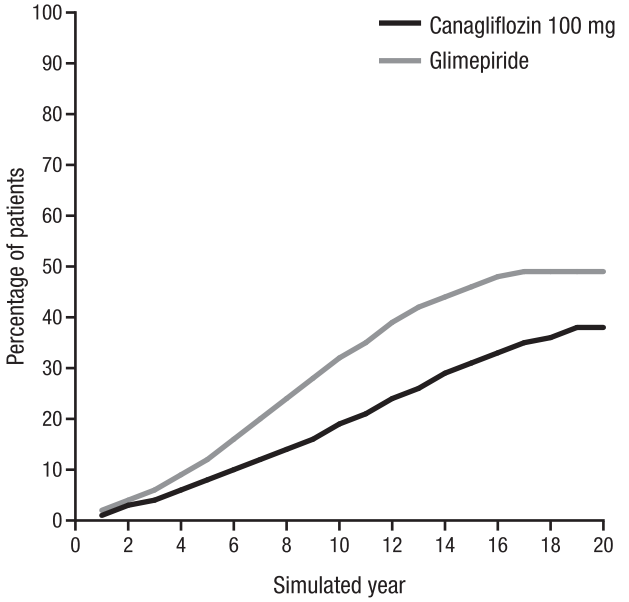

Fig. 1 – Percentage of patients taking insulin over 20 y in the base case.

Conclusions

Economic simulation modeling suggests that better initial HbA_{1c} lowering, SBP lowering, weight loss instead of weight gain, better HbA_{1c} durability, and beneficial renal effects associated with canagliflozin 100 mg can improve health outcomes compared with glimepiride over 20 years in Indian patients with T2DM inadequately controlled with metformin. Importantly, canagliflozin delayed the onset of complications and was associated with RRRs in macrovascular and microvascular complications, with the largest benefits seen for CKD. Together with avoidance of hypoglycemic events, an improved weight profile, and increased survival, these outcomes translated into QALY gains. It is not surprising that avoidance of hypoglycemia was a driver of QALY gains in this analysis, because canagliflozin demonstrated better HbA_{1c} lowering, thus reducing the need for insulin rescue therapy in the cohort of Indian patients simulated in this analysis. In contrast, glimepiride is associated with hypoglycemia, and its poor glycemic durability over time leads to more insulin use, which also increases the risk of hypoglycemia. There was also a small loss of QALYs with canagliflozin versus glimepiride that was attributable to AEs related to the mechanism of SGLT2 inhibition (e.g., female genital mycotic infections). Base-case findings were generally robust to a longer time horizon (30 years) and variations in assumptions surrounding rescue therapy (including the conservative assumption of no clinical inertia) and eGFR deterioration.

Assuming that eGFR remains stable with canagliflozin in these simulations was a key driver of the overall benefits. This assumption was justified on the basis of clinical data with canagliflozin and other SGLT2 inhibitors, which typically show a transient initial reduction in eGFR after initiating treatment that attenuates and stabilizes over time; therefore, long-term renal damage is not anticipated [63]. In the study used as the basis for this analysis, eGFR remained stable with canagliflozin, whereas a small decline was seen with glimepiride over 2 years [23]. The stability of eGFR has also been seen with empagliflozin over 4 years in EMPA-REG

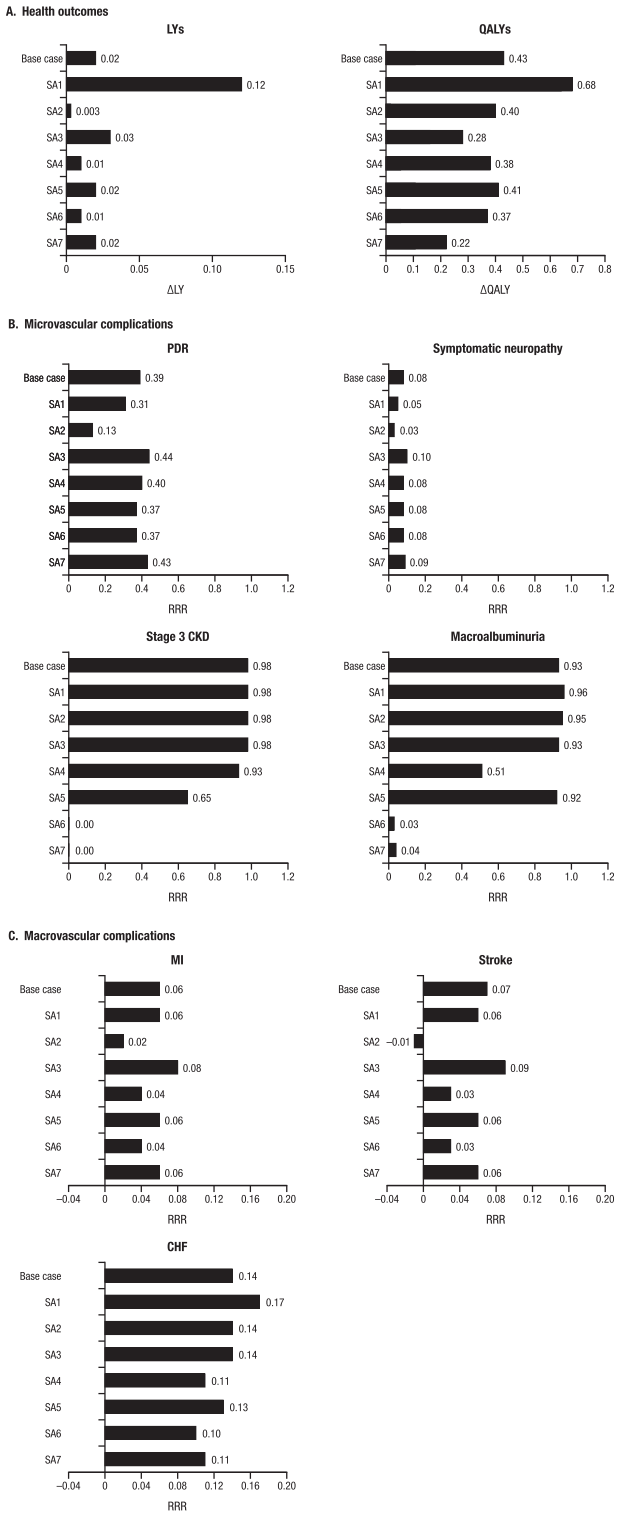

Fig. 2 – Base-case and sensitivity analysis results for (A) health outcomes and (B) RRRs in selected microvascular complications, and (C) RRRs in selected macrovascular complications. Data are differences with canagliflozin 100 mg vs. glimepiride. CHF, congestive heart failure; CKD, chronic kidney disease; LY, life-year; MI, myocardial infarction; PDR, proliferative diabetic retinopathy; QALY, quality-adjusted life-year; RRR, relative risk reduction.

OUTCOME [64]. It has been hypothesized that SGLT2 inhibitors may confer renoprotection in patients with T2DM [63], consistent with the reduced risk of CKD with canagliflozin versus glimepiride in the base case. This hypothesis is supported by data from the CANVAS Program and EMPA-REG OUTCOME, which showed favorable effects on renal outcomes with canagliflozin and empagliflozin, respectively [19,64]. In this analysis, there was a modest decline in the renal benefit when eGFR was modeled to deteriorate at half the rate of glimepiride (SA5) and it was completely eliminated when eGFR drift was the same for canagliflozin and glimepiride. Therefore, in addition to its glycemic, weight loss, and BP-lowering benefits, the potential renoprotective effects of canagliflozin may be an important driver of long-term health benefits. Data from the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE; ClinicalTrials.gov identifier NCT02065791) will explicitly evaluate the long-term impact of canagliflozin on renal outcomes, including the incidence of end-stage renal disease, doubling of serum creatinine, and renal or cardiovascular death, in patients with T2DM and established diabetic kidney disease.

Of note, there is recent data on the cardiovascular safety of canagliflozin in patients with T2DM and a history or high risk of cardiovascular disease [19]. In the CANVAS Program, there was a reduced risk of the primary composite end point of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke with canagliflozin versus placebo (hazard ratio [95% confidence interval] 0.86 [0.75–0.97]) [19]. These results were consistent with previous results from EMPA-REG OUTCOME with empagliflozin [18] and with real-world data from the Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors (CVD-REAL) study [65]. Taken together, these data suggest a likely classwide benefit on cardiovascular outcomes for SGLT2 inhibitors that may have important implications in future modeling exercises. The present analysis did not account for the potential cardioprotective effects of canagliflozin compared with glimepiride, which may have led to an underestimation of the long-term QALY gains and differences in macrovascular event rates.

In addition, inclusion of recently reported safety data from the CANVAS Program is warranted in future modeling exercises to more accurately predict relative benefits and risks in certain populations. Lower extremity amputation, mainly of the toe or metatarsal, was identified as a new safety signal on the basis of data from the CANVAS Program, which enrolled a higher-risk patient population. There was an increased risk of lower extremity amputations with canagliflozin compared with placebo, although events were relatively infrequent (6.3 and 3.4 per 1,000 patient-years, respectively) [19]. The mechanism is unknown, but is under investigation [66]. Preliminary analyses revealed that patients with a history of amputation, peripheral vascular disease, and neuropathy were at the highest risk [19]. The European summary of product characteristics includes recommendations for monitoring amputation risk in the absence of a specific drug-related mechanism [67]. The European Medicines Agency also now requires studies of all SGLT2 inhibitors to systematically collect data on lower extremity amputations [68]. Therefore, clinicians should carefully monitor high-risk patients and provide education on routine preventative foot care and maintaining adequate hydration. Clinicians may also consider terminating canagliflozin treatment in patients who develop known amputation-preceding events (e.g., lower extremity skin ulcer, infection, osteomyelitis, and gangrene) [67].

Additional long-term economic simulation modeling is needed to evaluate the cost effectiveness of T2DM treatments, including canagliflozin, from the Indian health care system perspective. Although ECHO-T2DM supports cost-effectiveness simulations, these data were not generated in the present analysis because of the lack of reliable health economic data for patients with T2DM in India. Most studies report data on direct and indirect costs borne by patients, with limited evidence of the cost burden borne by the health care system [4]. Similarly, this analysis would have benefited from using India-specific disutility values. Nevertheless, in the absence of such data, well-known disutility values from broad populations of patients with T2DM were used. Finally, the assumption that the delay in insulin initiation in India mirrors that in the United Kingdom may not sufficiently approximate current clinical practice in India. We are, however, unaware of similar studies in Indian patients. Although ECHO-T2DM has been validated extensively in broad populations, it has not been evaluated with Indian trial data. This analysis was strengthened by the use of the Indian covariate for the UKPDS 82 risk equation and the patient characteristics and treatment effects derived from Indian patients enrolled in a clinical trial of canagliflozin, thus making the simulations more relevant to this population.

T2DM management remains an important challenge in India because inadequate disease control can lead to debilitating complications. Therefore, treatments that address the multifactorial nature of T2DM will be beneficial to attenuate the potential consequences of poor T2DM management. Findings from this analysis suggest that the glycemic efficacy, weight loss, and BP reduction, as well as low hypoglycemia risk, potential renoprotective effects, and generally favorable tolerability profile seen with canagliflozin 100 mg, are likely to provide improved long-term health outcomes compared with glimepiride in Indian patients with T2DM inadequately controlled on metformin.

Acknowledgment

We thank Alaina Mitsch, PhD, of MedErgy for providing medical writing support.

Source of financial support: This study was funded by Janssen Global Services, LLC (Raritan, NJ).

Supplemental Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at http://dx.doi.org/10.1016/j.vhri.2018.06.002 or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

REFERENCES

[1] International Diabetes Federation. IDF Diabetes Atlas (7th ed.). Brussels, Belgium: International Diabetes Federation, 2015.
[2] Kaveeshwar SA, Cornwall J. The current state of diabetes mellitus in India. Australas Med J 2014;7:45–8.
[3] Anjana RM, Deepa M, Pradeepa R, et al. Prevalence of diabetes and pre-diabetes in 15 states of India: results from the ICMR-INDIAB population-based cross-sectional study. Lancet Diabetes Endocrinol 2017;5:585–96.
[4] Yesudian CA, Grepstad M, Visintin E, Ferrario A. The economic burden of diabetes in India: a review of the literature. Global Health 2014;10:80.
[5] Singh J. Economic burden of diabetes. In: Muruganathan A, ed. Medicine Update—2013. Mumbai, India: The Association of Physicians of India, 2013:205–8.
[6] Defronzo RA. Pathogenesis of type 2 diabetes mellitus. Med Clin North Am 2004;88:787–835. ix.
[7] Kahn SE, Cooper ME, Del Prato S. Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. Lancet 2014;383:1068–83.
[8] American Diabetes Association. Standards of medical care in diabetes—2016. Diabetes Care 2016;39(Suppl. 1):S1–108.

[9] Stratton IM, Adler AI, Neil HAW, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405–12.
[10] Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015;38:140–9.
[11] UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–53.
[12] Madhu SV, Saboo B, Makkar BM, et al. RSSDI clinical practice recommendations for management of type 2 diabetes mellitus, 2015. Int J Diabetes Dev Ctries 2015;35(Suppl. 1):1–71.
[13] American Diabetes Association. Standards of medical care in diabetes—2017. Diabetes Care 2017;40(Suppl. 1):S1–135.
[14] Venkataraman K, Kannan AT, Mohan V. Challenges in diabetes management with particular reference to India. Int J Diabetes Dev Ctries 2009;29:103–9.
[15] Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006;355:2427–43.
[16] Kalra S, Aamir AH, Raza A, et al. Place of sulfonylureas in the management of type 2 diabetes mellitus in South Asia: a consensus statement. Indian J Endocrinol Metab 2015;19:577–96.
[17] Mudaliar S, Polidori D, Zambrowicz B, Henry RR. Sodium-glucose cotransporter inhibitors: effects on renal and intestinal glucose transport: from bench to bedside. Diabetes Care 2015;38:2344–53.
[18] Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–28.
[19] Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644–57.
[20] Rosenthal N, Meininger G, Ways K, et al. Canagliflozin: a sodium glucose co-transporter 2 inhibitor for the treatment of type 2 diabetes mellitus. Ann NY Acad Sci 2015;1358:28–43.
[21] Prasanna Kumar KM, Mohan V, Sethi B, et al. Efficacy and safety of canagliflozin in patients with type 2 diabetes mellitus from India. Indian J Endocrinol Metab 2016;20:372–80.
[22] Cefalu WT, Leiter LA, Yoon KH, et al. Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial. Lancet 2013;382:941–50.
[23] Leiter LA, Yoon KH, Arias P, et al. Canagliflozin provides durable glycemic improvements and body weight reduction over 104 weeks versus glimepiride in patients with type 2 diabetes on metformin: a randomized, double-blind, phase 3 study. Diabetes Care 2015;38:355–64.
[24] Leiter LA, Langslet G, Vijapurkar U, et al. Simultaneous reduction in both HbA1c and body weight with canagliflozin versus glimepiride in patients with type 2 diabetes on metformin. Diabetes Ther 2016;7:269–78.
[25] Usiskin K, Kline I, Fung A, et al. Safety and tolerability of canagliflozin in patients with type 2 diabetes: pooled analysis of phase 3 study results. Postgrad Med 2014;126:16–34.
[26] Qiu R, Balis D, Xie J, et al. Longer-term safety and tolerability of canagliflozin in patients with type 2 diabetes: a pooled analysis. Curr Med Res Opin 2017;33:553–62.
[27] Eddy DM, Hollingworth W, Caro JJ, et al. Model transparency and validation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force 7. Value Health 2012;15:843–50.
[28] Shafie AA, Gupta V, Baabbad R, et al. An analysis of the short- and long-term cost-effectiveness of starting biphasic insulin aspart 30 in insulin-naive people with poorly controlled type 2 diabetes. Diabetes Res Clin Pract 2014;106:319–27.
[29] Mt Hood Diabetes Challenge Network. ECHO-T2DM. Available from: https://www.mthooddiabeteschallenge.com/copy-of-ecoh2. [Accessed April 4, 2018].
[30] Willis M, Johansen P, Nilsson A, Asseburg C. Validation of the Economic and Health Outcomes Model of Type 2 Diabetes Mellitus (ECHO-T2DM). Pharmacoeconomics 2017;35:375–96.
[31] Willis M, Asseburg C, He J. Validation of economic and health outcomes simulation model of type 2 diabetes mellitus (ECHO-T2DM). J Med Econ 2013;16:1007–21.
[32] Vemer P, Corro Ramos I, van Voorn GA, et al. AdViSHE: a validation-assessment tool of health-economic models for decision makers and model users. Pharmacoeconomics 2016;34:349–61.
[33] Eastman RC, Javitt JC, Herman WH, et al. Model of complications of NIDDM: II. A analysis of the health benefits and cost-effectiveness of treating NIDDM with the goal of normoglycemia. Diabetes Care 1997;20:735–44.
[34] Bagust A, Beale S. Modelling EuroQol health-related utility values for diabetic complications from CODE-2 data. Health Econ 2005;14:217–30.
[35] Hoerger TJ, Wittenborn JS, Segel JE, et al. A health policy model of CKD: 1. Model construction, assumptions, and validation of health consequences. Am J Kidney Dis 2010;55:452–62.
[36] Hoerger TJ, Wittenborn JS, Segel JE, et al. A health policy model of CKD: 2. The cost-effectiveness of microalbuminuria screening. Am J Kidney Dis 2010;55:463–73.
[37] Hayes AJ, Leal J, Gray AM, et al. UKPDS outcomes model 2: a new version of a model to simulate lifetime health outcomes of patients with type 2 diabetes mellitus using data from the 30 year United Kingdom Prospective Diabetes Study: UKPDS 82. Diabetologia 2013;56:1925–33.
[38] Clarke PM, Gray AM, Briggs A, et al. A model to estimate the lifetime health outcomes of patients with type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS no. 68). Diabetologia 2004;47:1747–59.
[39] Chaudhry ZW, Gannon MC, Nuttall FQ. Stability of body weight in type 2 diabetes. Diabetes Care 2006;29:493–7.
[40] Heerspink HJ, Desai M, Jardine M, et al. Canagliflozin slows progression of renal function decline independent of glycemic effects. J Am Soc Nephrol 2017;28:368–75.
[41] Janssen Research & Development, LLC. Canagliflozin as an adjunctive treatment to diet and exercise alone or co-administered with other antihyperglycemic agents to improve glycemic control in adults with type 2 diabetes mellitus. 2012.
[42] Yamout HM, Perkovic V, Davies M, et al. Efficacy and safety of canagliflozin in patients with type 2 diabetes and stage 3 nephropathy. Am J Nephrol 2014;40:64–74.
[43] Johnson & Johnson Pvt. Ltd. INVOKANA® (canagliflozin tablets) [package insert]. Mumbai, India: Johnson & Johnson Pvt. Ltd., 2015.
[44] Rosenstock J, Davies M, Home PD, et al. A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes. Diabetologia 2008;51:408–16.
[45] Riddle MC, Vlajnic A, Zhou R, Rosenstock J. Baseline HbA1c predicts attainment of 7.0% HbA1c target with structured titration of insulin glargine in type 2 diabetes: a patient-level analysis of 12 studies. Diabetes Obes Metab 2013;15:819–25.
[46] Fonseca V, Gill J, Zhou R, Leahy J. An analysis of early insulin glargine added to metformin with or without sulfonylurea: impact on glycaemic control and hypoglycaemia. Diabetes Obes Metab 2011;13:814–22.
[47] Khunti K, Wolden ML, Thorsted BL, et al. Clinical inertia in people with type 2 diabetes: a retrospective cohort study of more than 80,000 people. Diabetes Care 2013;36:3411–7.
[48] O'Connor PJ, Sperl-Hillen JAM, Johnson PE, et al. Clinical inertia and outpatient medical errors. In: Henriksen K, Battles JB, Marks ES, Lewin DI, eds. Advances in Patient Safety: From Research to Implementation (Vol. 2: Concepts and Methodology). Rockville, MD: Agency for Healthcare Research and Quality, 2005.
[49] Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ 2009;338:b1665.
[50] Adams SP, Tsang M, Wright JM. Lipid lowering efficacy of atorvastatin. Cochrane Database Syst Rev 2012;12:CD008226.
[51] Nicolle LE, Capuano G, Fung A, Usiskin K. Urinary tract infection in randomized phase III studies of canagliflozin, a sodium glucose co-transporter 2 inhibitor. Postgrad Med 2014;126:7–17.
[52] Nyirjesy P, Sobel JD, Fung A, et al. Genital mycotic infections with canagliflozin, a sodium glucose co-transporter 2 inhibitor, in patients with type 2 diabetes mellitus: a pooled analysis of clinical studies. Curr Med Res Opin 2014;30:1109–19.
[53] Coyne KS, Sexton CC, Irwin DE, et al. The impact of overactive bladder, incontinence and other lower urinary tract symptoms on quality of life, work productivity, sexuality and emotional well-being in men and women: results from the EPIC study. BJU Int 2008;101:1388–95.
[54] Pi-Sunyer FX. The impact of weight gain on motivation, compliance, and metabolic control in patients with type 2 diabetes mellitus. Postgrad Med 2009;121:94–107.
[55] Traina S, Weiser J, Katz EG, Palak A. Satisfaction with health and motivation to follow a diabetes diet and exercise vary by weight status among people with type 2 diabetes mellitus (T2DM). Presented at: 71st Scientific Sessions of the American Diabetes Association (ADA), San Diego, CA, June 24–28, 2011.
[56] Traina S, Johnson P, Bancroft T, et al. Motivation to perform diabetes self-care activities and satisfaction with health vary by weight status among people living with type 2 diabetes mellitus (T2DM). Presented at: 72nd Scientific Session of the American Diabetes Association (ADA), Philadelphia, PA, June 8–12, 2012.
[57] Neslusan C, Teschemaker A, Johansen P, et al. Cost-effectiveness of canagliflozin versus sitagliptin as add-on to metformin in patients with type 2 diabetes mellitus in Mexico. Value Health Reg Issues 2015;8:8–19.

[58] Sabapathy S, Neslusan C, Yoong K, et al. Cost-effectiveness of canagliflozin versus sitagliptin when added to metformin and sulfonylurea in type 2 diabetes in Canada. J Popul Ther Clin Pharmacol 2016;23:e151–68.
[59] Evans M, Khunti K, Mamdani M, et al. Health-related quality of life associated with daytime and nocturnal hypoglycaemic events: a time trade-off survey in five countries. Health Qual Life Outcomes 2013;11:90.
[60] Shingler S, Fordham B, Evans M, et al. Utilities for treatment-related adverse events in type 2 diabetes. J Med Econ 2015;18. 45–4.
[61] Siegel JE, Weinstein MC, Russell LB, Gold MR. Recommendations for reporting cost-effectiveness analyses. Panel on Cost-Effectiveness in Health and Medicine. JAMA 1996;276:1339–41.
[62] Defronzo RA. Lilly lecture 1987. The triumvirate: beta-cell, muscle, liver. A collusion responsible for NIDDM. Diabetes 1988;37:667–87.
[63] Perkovic V, Jardine M, Vijapurkar U, Meininger G. Renal effects of canagliflozin in type 2 diabetes mellitus. Curr Med Res Opin 2015;31:2219–31.
[64] Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med 2016;375:323–34.
[65] Kosiborod M, Cavender MA, Fu AZ, et al. Lower risk of heart failure and death in patients initiated on SGLT-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL study. Circulation 2017;136:249–59.
[66] European Medicines Agency. SGLT2 inhibitors: information on potential risk of toe amputation to be included in prescribing information. Available from http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2017/02/WC500222191.pdf. [Accessed May 26, 2017].
[67] Janssen-Cilag International NV. INVOKANA (300 mg film-coated tablets) [package insert]. Beerse, Belgium: Janssen-Cilag International NV, 2017.
[68] European Medicines Agency. PRAC assessment report. 2017. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/SGLT2_inhibitors_Canagliflozin_20/European_Commission_final_decision/WC500227102.pdf. [Accessed June 16, 2017].
[69] Eastman RC, Javitt JC, Herman WH, et al. Model of complications of NIDDM: I. Model construction and assumptions. Diabetes Care 1997;20:725–34.
[70] Bagust A, Hopkinson PK, Maier W, Currie CJ. An economic model of the long-term health care burden of type II diabetes. Diabetologia 2001;44:2140–55.
[71] Mohan V, Shah SN, Joshi SR, et al. Current status of management, control, complications and psychosocial aspects of patients with diabetes in India: results from the DiabCare India 2011 Study. Indian J Endocrinol Metab 2014;18:370–8.