Long-Term Efficacy and Safety of Empagliflozin Monotherapy in Drug-Naïve Patients with Type 2 Diabetes in Indian Subgroup: Results from a 76-week Extension Trial of Phase III, Double-Blind, Randomized Study

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Abstract

Background and Objectives: Empagliflozin, a sodium glucose cotransporter-2 inhibitor, was recently evaluated in a randomized, controlled trial (RCT) in drug-naïve Type 2 diabetes mellitus (T2DM) patients managed on diet and exercise therapy. Efficacy and safety of empagliflozin in Indian subgroup of patients from a 76-week extension study of the initial multicentric RCT are reported in this article. **Materials and Methods:** In this study, patients were randomized to empagliflozin 10 mg (E10, $n = 24$), empagliflozin 25 mg (E25, $n = 29$), placebo ($n = 28$) and sitagliptin 100 mg (S100, $n = 27$). Exploratory efficacy endpoints were changed from baseline to week 76 in glycosylated hemoglobin (HbA1c, %) and fasting blood glucose (mg/dL) along with body weight (kg) and blood pressure (BP) (mmHg) reduction. Safety analysis included clinically relevant adverse events (AEs). **Results:** In 108 randomized patients, adjusted mean reduction in HbA1c compared to placebo was significant with E10 (-0.81, 95% confidence interval (CI) -1.33, -0.28; $P = 0.0029$) and E25 (-1.11, 95% CI -1.60, -0.61; $P < 0.0001$). HbA1c below 7% at week 76 was achieved in significantly higher number of patients with E10 (20.8%, $P < 0.0001$) and E25 (28.0%, $P < 0.0001$). There was significant reduction in adjusted mean weight as compared to placebo with E10 (-1.41, 95% CI -2.51, -0.31; $P = 0.0125$) and E25 (-1.50, 95% CI -2.54, -0.46; $P = 0.0051$) but nonsignificant with S100 (-0.75 95% CI -1.86, -0.36; $P = 0.1842$). BP reduction was numerically higher with empagliflozin compared to placebo. AEs were similar in all treatment groups except for genital infections which were more common in E10 (20.8%) but not in E25 (3.4%) as compared to placebo (3.6%). All treatments were well tolerated with no severe AEs. **Conclusion:** Treatment with empagliflozin was well tolerated and resulted in sustained glycemic efficacy over long-term (76 weeks) in drug-naïve Indian T2DM patients.

Keywords: Drug naïve, empagliflozin, Indian subgroup, type 2 diabetes

INTRODUCTION

Type 2 diabetes mellitus (T2DM) poses a significant burden in terms of morbidity and mortality in India. Coupled with high rates of complications and cost of therapy, socioeconomic impact on individuals and families can be huge.[1,2] Largely, the treatment of T2DM in India is based on metformin, sulfonylureas, and insulin. However, newer therapies such as dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium-glucose cotrasporter-2 (SGLT-2) inhibitors in the armamentarium of T2DM management promise a substantial benefit in treatment of naïve, as well as uncontrolled diabetes patients.[3,4] Inhibition of SGLT-2 in kidneys is now a novel noninsulin dependent established path for T2DM management which offers potential add-on benefits of weight loss and blood pressure (BP) reduction with a low risk of hypoglycemia.[5] Empagliflozin is a potent and selective SGLT-2 inhibitor and has shown to be effective as monotherapy and as an add-on

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treatment for T2DM.[6-9] Further, significant add-on benefit of body weight and systolic BP (SBP) reduction has been noted with empagliflozin.[8,10-12]

Empagliflozin was evaluated in drug-naïve T2DM patients in a phase III, randomized, placebo-controlled trial (EMPA-REG MONO™) wherein sitagliptin 100 mg once a day was active comparator used with two doses of empagliflozin (10 and 25 mg, once a day) being evaluated. In this 24-week study, empagliflozin shown significant reductions from baseline in glycosylated hemoglobin (HbA1c) (−0.74% and −0.85% with 10 and 25 mg, respectively) compared to placebo. No significant difference was found for HbA1c reduction with empagliflozin (both doses) compared to sitagliptin. Empagliflozin was well tolerated.[13]

Extension of the above clinical trial, EMPA-REG EXTEND™ MONO was done with objective of assessing the long-term efficacy, safety, and tolerability of empagliflozin. This article presents Indian subgroup data from 76-week randomized, double-blind, placebo-controlled trial.

MATERIALS AND METHODS

Study design and participants

These data represent the Indian subgroup of larger, phase III, multicenter, randomized, controlled, EMPA-REG MONO clinical trial. Detailed methodology has been published elsewhere.[13,14] Briefly, this study was a 24-week randomized, controlled study conducted across 124 centers worldwide. Initial randomization continued till 24 weeks. Patients who did not contravene the exclusion criteria at 24 weeks were allowed to enter ≥52-week double-blind extension trial stretching to a long-term period of 76-week. Observations were compared from baseline to week 76.

T2DM patients previously untreated (no oral or injected antidiabetes treatment for 12 weeks before randomization) were recruited with inclusion criteria of age 18–65 years (for India), body mass index ≤45 kg/m², and inadequate glycemic control despite a diet and exercise regimen (HbA1c 7·0%–10·0%). Patients with uncontrolled hyperglycemia (glucose concentration >13·3 mmol/L), estimated glomerular filtration rate (eGFR, estimated with the modification of diet in renal disease [MDRD] equation) <50 mL/min per 1·73 m², contraindications to sitagliptin, treatment with antiobesity drugs within 3 months, with systemic steroids at the time of informed consent, change in dose of thyroid hormones within 6 weeks, or any other uncontrolled endocrine disorder were excluded from the study.

Ethical statement

The trial was done in compliance with the protocol and the principles of the Declaration of Helsinki and the International Conference on Harmonization Tripartite Guideline for Good Clinical Practice. All patients provided signed and dated informed consent before enrolment; the study was approved by institutional review boards, independent ethics committees, and competent authorities according to national and international regulations. Throughout this trial, independent data monitoring committee monitored the safety of the patients (every 3 months).

Randomization procedure

Patients who passed the screening were randomized in a triple-dummy manner to empagliflozin 10 mg (E10), empagliflozin 25 mg (E25), sitagliptin 100 mg (S100), or placebo. All treatments were given once-a-day. Randomization sequence was computer generated, and allocation was performed using interactive voice and internet-bases response systems. Blinding of patients, investigators, and data analysis team was ensured. Access to the randomization code was strictly limited. In case of emergency, code break was available to the investigator through the interactive voice and internet-based response system. Unexpected Suspected Serious Adverse Reactions were according to regulatory requirements for drug safety analyses.

During extension phase, lifestyle advice to the patients was continued as per local recommendations. Rescue medications administered during initial 24-week randomization period were continued during extension phase if patients were still receiving those treatments. During this phase, rescue drug was allowed if patients had confirmed plasma glucose level after an overnight fast was >10 mmol/L or HbA1c was >8% and the choice was as per the discretion of investigator. DPP-4 inhibitors and glucagon-like peptide-1 analogs were not allowed as rescue medications as sitagliptin was one of the study arms. If control of any hypo- or hyper-glycemia was not achieved in any patient, such patients were discontinued from the trial.

Efficacy endpoints

During the initial 24-week randomized trial, the primary efficacy endpoint was change from baseline in HbA1c level. No primary efficacy endpoints were defined for extension phase study, but exploratory efficacy endpoints during this phase were change from baseline in HbA1c, fasting plasma glucose (FPG) body weight, SBP, and diastolic BP (DBP) at week 76. Other exploratory endpoints included the percentage of patients with HbA1c <7% and the need of rescue therapy. Baseline was defined as the last observed measurement before the first administration of study drug in the initial trial.

Safety assessments

Reported adverse events (AEs) were assessed for safety. AE of special interest was confirmed hypoglycemia event (plasma glucose ≤3.9 mmol/L and/or requiring assistance). Other AEs such as urinary tract infection (UTI), genital infection, and volume depletion and clinical laboratory values were assessed as change from baseline to week-76.

Statistical analysis

There was no estimation of sample size as any eligible patient was allowed to enter the extension phase. Hence, the formal calculations for sample size were not done. Changes from baseline in HbA1c, FPG, weight, SBP, and DBP at 76 were

analyzed using an analysis of covariance (ANCOVA) model in the full analysis set (patients who received ≥1 dose of study drug and had a baseline HbA1c measurement in the initial study) with baseline HbA1c and the baseline value of the endpoint in question as linear covariates, and baseline eGFR (MDRD), region (Asia, etc.,) and treatment as fixed effects. Data after rescue therapy were set as missing and all missing data were imputed considering last observation carried forward (LOCF) approach. Percentage of patients achieving HbA1c <7% at week 76 was assessed with a logistic regression model. Treatment, baseline eGFR, region, and baseline HbA1c were parameters considered for logistic regression. Patients who did not complete 76-week were considered failures for this assessment.

Changes in HbA1c, FPG, weight, SBP, and DBP were analyzed with sensitivity analyses. Restricted maximum likelihood-based mixed model repeated measures approach considering baseline HbA1c and the baseline value of the endpoint in question as linear covariates, and baseline eGFR, region, treatment, visit, and visit by treatment interaction as fixed effects were used for the same. Rescue therapy use was assessed with logistic regression carried with treatment as a factor and baseline HbA1c as a covariate.

Safety was assessed in the patients who received ≥1 dose of study drug. Descriptive analyses were done except for lipid parameters (assessed using ANCOVA) considering linear covariates as baseline values and baseline HbA1c, and fixed effects as baseline eGFR and treatment.

RESULTS

From India, 108 patients in total were randomized. Baseline population characteristics have been summarized in Table 1.

Compared to placebo, adjusted mean reduction in HbA1c was significant for both empagliflozin 10 mg (−0.81, 95% confidence interval [CI] −1.33, −0.28; $P = 0.0029$) and 25 mg (−1.11, 95% CI − 1.60, −0.61; $P < 0.0001$) and for sitagliptin 100 mg (−0.81 95% CI − 1.34, −0.28; $P = 0.0031$) [Table 2]. No significant difference was observed adjusted mean reduction in HbA1c with empagliflozin as compared to sitagliptin. Although study was not powered to detect significant difference in efficacy in comparison to sitagliptin, numerically higher reduction in HbA1c was achieved with empagliflozin 25 mg as compared to sitagliptin. Among patients with baseline HbA1c ≥7%, significantly higher number of patients achieved HbA1c <7% with empagliflozin 10 mg (20.8%, odds ratio [OR] >99.99, 95% CI > 99.99, >99.99; $P < 0.0001$) and 25 mg (28.0%, OR > 99.99, 95% CI > 99.99, >99.99; $P < 0.0001$) as compared to placebo. However, compared to sitagliptin (7.4%), no significant difference was found either with empagliflozin 10 mg (OR 2.77, 95% CI 0.43, 17.61; $P = 0.279$) or empagliflozin 20 mg (OR 3.83, 95% CI 0.65, 22.37; $P = 0.136$) [Figure 1].

As compared to placebo, adjusted mean FPG (mg/dL) reduction was significant for empagliflozin 10 mg (−35.7, 95% CI − 50.7, −20.6; $P < 0.0001$) and 25 mg (−32.9, 95% CI − 47.1, −18.6; $P < 0.0001$) but was nonsignificant for sitagliptin 100 mg (−14.7, 95% CI − 30.0, 0.5; $P = 0.0578$). When compared to sitagliptin, a significant reduction in FPG was observed for treatment with empagliflozin 10 mg ($P = 0.0076$) as well as 25 mg ($P = 0.0147$) [Table 2].

Compared to placebo, patients in empagliflozin 10 mg (−1.41, 95% CI − 2.51, −0.31; $P = 0.0125$) and 25 mg arms (−1.50, 95% CI − 2.54, −0.46; $P = 0.0051$) experienced significant reduction in adjusted mean weight but was nonsignificant

Table 1: Baseline characteristics of study population

Characteristic	Placebo (*n*=28)	E10 (*n*=24)	E25 (*n*=29)	S100 (*n*=27)	Total (*n*=108)
Sex (%)					
Male	12 (42.9)	13 (54.2)	19 (65.5)	15 (55.6)	59 (54.6)
Female	16 (57.1)	11 (45.8)	10 (34.5)	12 (44.4)	49 (45.4)
Age (mean±SD)	48.7±8.7	47.4±8.1	47.1±8.6	49.5±9.4	48.2±8.6
History of hypertension (%)	10 (35.7)	8 (33.3)	10 (34.5)	7 (25.9)	35 (32.4)
Duration of diabetes (years)					
≤1	14 (50.0)	14 (58.3)	14 (48.3)	11 (40.7)	53 (49.1)
>1-5	11 (39.3)	8 (33.3)	14 (48.3)	13 (48.1)	46 (42.6)
>5-10	2 (7.1)	1 (4.2)	1 (3.4)	3 (11.1)	7 (6.5)
>10	1 (3.6)	1 (4.2)	0	0	2 (1.9)
Weight (kg)	67.25±12.35	68.82±11.81	68.03±12.46	68.48±14.98	68.11±12.81
BMI (kg/m²)	26.85±4.49	26.09±3.37	26.49±4.07	26.47±3.61	26.49±3.89
Waist circumference (cm)	96.4±11.6	96.8±11.7	93.1±8.3	95.1±7.2	95.3±9.8
SBP	126.5±17.6	127.6±21.5	122.3±14.7	125.6±12.7	125.4±16.7
DBP	79.6±10.5	78.4±12.0	76.5±11.4	77.2±6.6	77.9±10.2
HbA1c% (mean±SD)	7.92±0.70	8.35±0.98	8.09±1.11	8.31±0.68	8.16±0.89
FBS (mg/dL)	148.1±35.8	149.3±30.7	145.8±40.8	139.3±29.2	145.5±34.4
Baseline eGFR (ml/min/1.73 m²)	86.54±20.12	88.85±21.71	95.94±21.17	97.98±22.75	92.38±21.66

Data are *n* (%) or mean (SD). eGFR: Estimated glomerular filtration rate, SD: Standard deviation, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BMI: Body mass index, HbA1c: Glycosylated hemoglobin, FBS: Fasting blood glucose

with sitagliptin 100 mg (−0.75 95% CI − 1.86, −0.36; *P* = 0.1842). Compared to sitagliptin 100 mg, reduction in body weight was numerically higher for empagliflozin 10 mg and 25 mg [Table 3]. Adjusted average reduction in SBP and DBP was 3.3 mmHg and 1.0 mmHg for 10 mg, and 3.8 mmHg and 1.6 mmHg for 25 mg of empagliflozin, respectively, but

the systolic and diastolic reduction did not reach statistical significance for both groups as compared to placebo [Table 3]. On logistic regression analysis, requirement of rescue therapy during 76-week treatment was found to be significantly lower with empagliflozin 10 mg (OR 0.112, 95% CI 0.020, 0.611; *P* = 0.0115) and 25 mg (OR 0.148, 95% CI 0.034, 0.652; *P* = 0.0115) as compared to placebo. There were no significant differences in either empagliflozin 10 mg (OR 0.27, 95% CI 0.04, 1.51; *P* = 0.137) and 25 mg (OR 0.35, 95% CI 0.08, 1.60; *P* = 0.179) when compared to sitagliptin [Figure 2].

Overall, the number of any AEs including investigator defined drug-related AEs was comparable in all treatment groups [Table 4]. Events fatal in nature and requiring hospitalization were infrequent with either empagliflozin groups. AEs of major clinical concern are described in Table 4. The events consistent with UTIs were slightly higher in empagliflozin 25 mg (27.6%) compared to 10 mg (20.9%) but was similar to placebo (28.5%). The events consistent with UTIs were more in females in empagliflozin groups as compared to placebo group. Majority of the events consistent
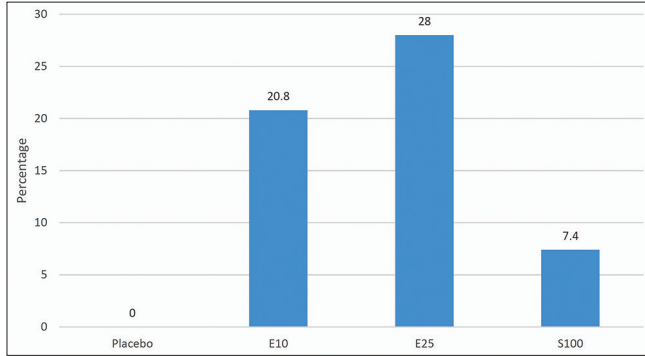

Figure 1: Percentage of patients achieving glycosylated hemoglobin below 7% at week 76

Table 2: Change in efficacy parameters from baseline to week 76

Characteristic	Placebo (*n*=28)	E10 (*n*=24)	*P*	E25 (*n*=29)	*P*	S100 (*n*=27)	*P*
HbA1c%							
Baseline	7.92	8.35		8.09		8.31	
Change from baseline	0.58	−0.35		−0.56		−0.31	
Comparison versus placebo		−0.81 (−1.33-−0.28)	0.0029	−1.11 (−1.60-−0.61)	<0.0001	−0.81 (−1.34-−0.28)	0.0031
Comparison versus sitagliptin		0.00 (−0.53-0.53)	0.997	−0.30 (−0.80-0.20)	0.241		
FPG (mg/dL)							
Baseline	148.1	149.3		145.8		139.3	
Change from baseline	8.9	−21.9		−18.0		9.8	
Comparison versus placebo		−35.7 (−50.7-−20.6)	<0.0001	−32.9 (−47.1-−18.6)	<0.0001	−14.7 (−30.0-0.5)	0.0578
Comparison versus sitagliptin		−20.9 (−36.2-−5.7)	0.0076	−18.1 (−32.6-−3.6)	0.0147		

Data are mean (95% CI) or adjusted mean (95% CI) for changes from baseline in randomized groups. HbA1c: Glycosylated hemoglobin, FPG: Fasting plasma glucose, CI: Confidence interval

## Table 3: Change in body weight and blood pressure from baseline to week 76

Characteristic	Placebo (*n*=28)	E10 (*n*=24)	*P*	E25 (*n*=29)	*P*	S100 (*n*=27)	*P*
Body weight (kg)							
Baseline	67.25	68.82		68.03		68.48	
Change from baseline	0.39	−1.01		−1.16		−0.43	
Comparison versus placebo		−1.41 (−2.51-−0.31)	0.0125	−1.50 (−2.54-−0.46)	0.0051	−0.75 (−1.86-−0.36)	0.1842
Comparison versus sitagliptin		−0.66 (−1.77-0.44)	0.2372	−0.75 (−1.81-0.30)	0.1578		
SBP (mmHg)							
Baseline	126.5	127.6		122.3		125.6	
Change from baseline	−2.5	−5.6		−3.0		−0.4	
Comparison versus placebo		−3.3 (−9.8-3.2)	0.3161	−3.8 (−9.9-2.4)	0.2313	−0.1 (−6.4-6.7)	0.9685
Comparison versus sitagliptin		−3.4 (−10.0-3.1)	0.3028	−3.9 (−10.1-2.3)	0.2179		
DBP (mmHg)							
Baseline	79.6	78.4		76.5		77.2	
Change from baseline	−1.3	−1.3		−1.0		−0.4	
Comparison versus placebo		−1.0 (−4.9-2.9)	0.4115	−1.6 (−5.3-2.0)	0.3780	−1.4 (−5.4-2.5)	0.4676
Comparison versus sitagliptin		0.4 (−3.5-4.3)	0.8276	−0.2 (−3.9-3.5)	0.9115		

Data are mean (95% CI) or adjusted mean (95% CI) for changes from baseline in randomized groups. SBP: Systolic blood pressure, DBP: Diastolic blood pressure, CI: Confidence interval

Table 4: Adverse events among the randomized treatments during 76-week				
AEs	Placebo (*n*=28)	E10 (*n*=24)	E25 (*n*=29)	S100 (*n*=27)
Any AE (%)	24 (85.7)	20 (83.3)	26 (89.7)	22 (81.5)
Severe AE (%)	0	0	0	1 (3.7)
Investigator defined drug-related AEs (%)	4 (14.3)	5 (20.8)	7 (24.1)	5 (18.5)
AEs leading to drug discontinuation (%)	1 (3.6)	0	0	0
Serious AEs				
Fatal (%)	1 (3.6)	2 (8.3)	0	2 (7.4)
Immediate life-threatening (%)	0	0	0	0
Requiring hospitalization (%)	0	1 (4.2)	0	1 (3.7)
Other (%)	1 (3.6)	1 (4.2)	0	1 (3.7)
Primary system organ class AEs				
Infections and infestations (%)	11 (39.3)	10 (41.7)	12 (41.4)	9 (33.3)
Urinary tract infections (%)	8 (28.5)	5 (20.9)	8 (27.6)	7 (25.9)
Male (%)	4/12 (33.3)	2/13 (15.4)	3/19 (15.8)	2/15 (13.3)
Female (%)	4/16 (25.0)	3/11 (27.3)	5/10 (50.0)	4/12 (33.3)
Genital infections (%)	1 (3.6)	5 (20.8)	1 (3.4)	0
Male (%)	0	3/13 (23.1)	1/19 (5.3)	0
Female (%)	1/16 (6.3)	2/11 (18.2)	0	0
Hyperglycemia (%)	11 (39.3)	3 (12.5)	3 (10.3)	7 (25.9)
Hypoglycemia (%)	2 (7.1)	1 (4.2)	0	0
Dyslipidemia (%)	7 (25.0)	8 (33.3)	5 (17.2)	5 (18.5)
Diarrhea (%)	0	2 (8.3)	0	0
Arthralgia (%)	3 (10.7)	4 (16.7)	2 (6.9)	0
Neoplasm (%)	0	0	0	1 (3.7)
Reduced creatinine clearance (%)	2 (7.1)	1 (4.2)	1 (3.4)	3 (11.1)

AEs: Adverse events
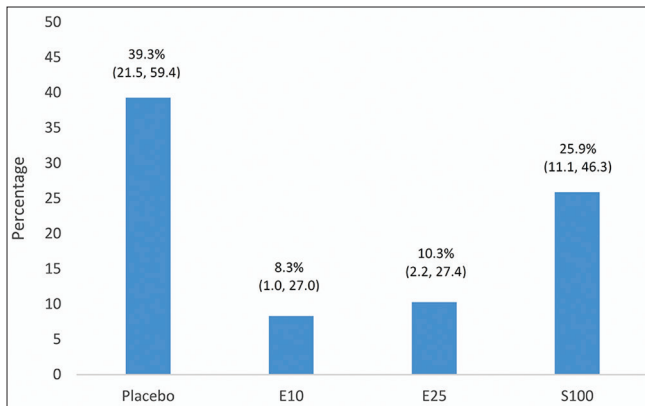
Figure 2: Rescue therapy need during 76-week treatment

with UTIs were mild in intensity except for one patient in empagliflozin 25 mg arm and sitagliptin 100 mg arm each, who experienced UTI of moderate intensity. None of the UTI events required or prolonged hospitalization nor lead to treatment discontinuations in any treatment groups. Events consistent with genital infections were more frequent in empagliflozin 10 mg (20.8%) as compared to placebo (3.6%) or empagliflozin 25 mg (3.4%). No specific differences in frequency of genital infections in males and females were observed. Overall, genital infections occurred after 3 months of active treatment. Only one event in empagliflozin 10 mg treatment group was of moderate intensity while the remaining events of genital infections were mild in nature. Possibly, this was the only event that led to discontinuation of the study drug among all treatments arms. The AE of hyperglycemia was most frequent in placebo (39.3%) followed by sitagliptin 100 mg (25.9%) group. The frequency of hypoglycemic events was comparable in all treatments. Symptomatic hypoglycemia or that requiring treatment was seen in one patient receiving placebo treatment. No severe hypoglycemia was observed in any of the treatment arms. Dyslipidemia was frequent in empagliflozin 10 mg (33.3%) as compared to placebo (25.0%) and sitagliptin (18.5%) in empagliflozin 25 mg (17.2%) group.

DISCUSSION

This extension study proved that in Indian patients, treatment with empagliflozin (10 and 25 mg) over long-term is efficacious and safe when compared to placebo. Significant reductions in HbA1c compared to placebo and in FPG compared placebo as well as sitagliptin suggest sustained glycemic control with both 10 and 25 mg doses of empagliflozin. These results are consistent with the initial 24-week randomized study.[13] This is also well supported by a finding that a significant number of patients achieved glycemic target of HbA1c <7% at week 76 compared to placebo and though nonsignificantly but numerically higher compared to sitagliptin. Among nonglycemic benefits, weight loss observed with empagliflozin was sustained and was significantly more when compared to placebo but not that of sitagliptin though weight loss was

numerically higher. This finding is essential in the context of weight gain being a common side effect with major antidiabetic drugs and maintaining clinically meaningful weight is a challenge in most patients.[15,16] Further, weight loss has potential benefits of improvement in insulin sensitivity and cardiovascular (CV) risk profile.[17] Weight loss due to empagliflozin is due to reduction in fat mass from visceral as well as abdominal subcutaneous adipose fat stores.[18] In T2DM, obese patients with multiple insulin injections per day, empagliflozin 10 and 25 mg for 52 weeks, resulted in significant glycemic lowering and reduction in weight and had significant reductions in daily insulin requirement as compared to placebo.[19] Empagliflozin is thus a useful agent for obese, inadequately controlled T2DM receiving multiple daily doses of insulin. This finding is essential to note as Indian diabetics are obese, overweight, and have a high degree of insulin resistance.[20,21] Empagliflozin thus seem as a suitable antidiabetic agent in Indian diabetics.

BP reduction, especially SBP has been reported with empagliflozin as compared to placebo.[22,23] In this Indian subgroup, we found no significant reduction in SBP and DBP with either dose of empagliflozin compared to placebo or sitagliptin. Although nonsignificant, the reduction in SBP reached to a magnitude of nearly 4 mmHg with empagliflozin 25 mg in comparison to placebo and sitagliptin which is similar to that observed in other long-term studies with empagliflozin.[14,18] Consistent effects on glycemic parameters, body weight, and BP possibly confer benefits in CV outcomes. This was evident in a recent EMPA-REG OUTCOME® trial.[24] In T2DM patients with high CV risk, addition of empagliflozin to standard treatment significantly reduced primary composite outcome (CV death nonfatal myocardial infarction or nonfatal stroke), CV death, heart failure hospitalizations, and overall mortality as compared to placebo.[24] Although the exact mechanisms by which it conferred CV outcome benefits are not clear, it is argued that effect on glycemia, BP, and weight along with reduction in plasma volume leads to observed effects.[25] Further, reduction vascular in arterial stiffness and vascular resistance may have contributed to the beneficial outcome.[23]

Tolerability of empagliflozin in both 10 and 25 mg doses was equivalent to that of sitagliptin and placebo. Because of unique mechanism of action reducing glycemic load with no dependence on insulin,[26] hypoglycemia is likely to be minimal with empagliflozin. Results in Indian subgroup are consistent with previous reports where empagliflozin monotherapy displayed a lack of hypoglycemia.[12,22] Significantly less number of patients required rescue therapy in both doses of empagliflozin compared to placebo supports the fact that no severe hypoglycemia were encountered. Proportion of patients with UTI was similar in placebo, sitagliptin, and empagliflozin treatment groups. This is consistent with previous reports of empagliflozin highlighting no increased risk of UTI with empagliflozin.[12-14,18] Higher frequency in females suggests ascending infection because of short urethra in females. Proportion of genital infections was higher in empagliflozin

groups compared to placebo and sitagliptin. This is in-line with previous reports suggesting higher genital infections with SGLT-2 inhibitors.[27,28] A higher frequency of genital infections with empagliflozin has been described previously in a long-term trial.[14] Importantly, no single AE was responsible for discontinuation of treatment either with empagliflozin or sitagliptin suggesting treatments being well tolerated.

Strengths of this extension study include continuation of randomized, double-blind treatments over long term, and inclusion of sitagliptin as an active comparator group. Limitation is that the endpoints though prespecified were exploratory and not primary endpoints and data imputation using LOCF approach.

Conclusion

Empagliflozin 10 and 25 mg are safe and effective treatments for glycemic control in Indian patients with T2DM. Nonglycemic benefits of weight loss and BP reduction can significantly contribute to the improvement of insulin resistance which is a common phenotype in Indian diabetic patients. Sustained glycemic and weight benefits over 76 weeks promise a definite long-term well-tolerated therapy with empagliflozin in Indian T2DM.

Conflicts of interest

Dr. Sunil Gupta and Dr. Shehla Sheikh have nothing to declare. Dr. Pooja Joshi, Dr. Shraddha Bhure, and Dr. Viraj Suvarna are the employees of Boehringer Ingelheim India Ltd.

References

1. 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.
2. Kaveeshwar SA, Cornwall J. The current state of diabetes mellitus in India. Australas Med J 2014;7:45-8.
3. George RE, Joseph S. A review of newer treatment approaches for type-2 diabetes: Focusing safety and efficacy of incretin based therapy. Saudi Pharm J 2014;22:403-10.
4. Dutta D, Kalra S. Sodium glucose transporter 2 (SGLT2) inhibitors: Current status in clinical practice. J Pak Med Assoc 2014;64:1203-6.
5. DeFronzo RA, Davidson JA, Del Prato S. The role of the kidneys in glucose homeostasis: A new path towards normalizing glycaemia. Diabetes Obes Metab 2012;14:5-14.
6. Meyer C, Gerich JE. Role of the human kidney in glucose homeostasis. Curr Opin Endocrinol Diabetes Obes 2000;7:19-24.
7. Kovacs CS, Seshiah V, Merker L, Christiansen AV, Roux F, Salsali A,

et al. Empagliflozin as add-on therapy to pioglitazone with or without metformin in patients with type 2 diabetes mellitus. Clin Ther 2015;37:1773-88.e1.

8. Ferrannini E, Berk A, Hantel S, Pinnetti S, Hach T, Woerle HJ, *et al.* Long-term safety and efficacy of empagliflozin, sitagliptin, and metformin: An active-controlled, parallel-group, randomized, 78-week open-label extension study in patients with type 2 diabetes. Diabetes Care 2013;36:4015-21.

9. Grempler R, Thomas L, Eckhardt M, Himmelsbach F, Sauer A, Sharp DE, *et al*. Empagliflozin, a novel selective sodium glucose cotransporter-2 (SGLT-2) inhibitor: Characterisation and comparison with other SGLT-2 inhibitors. Diabetes Obes Metab 2012;14:83-90.

10. Kovacs CS, Seshiah V, Swallow R, Jones R, Rattunde H, Woerle HJ, *et al.* Empagliflozin improves glycaemic and weight control as add-on therapy to pioglitazone or pioglitazone plus metformin in patients with type 2 diabetes: A 24-week, randomized, placebo-controlled trial. Diabetes Obes Metab 2014;16:147-58.

11. Barnett AH, Mithal A, Manassie J, Jones R, Rattunde H, Woerle HJ, *et al.* Efficacy and safety of empagliflozin added to existing antidiabetes treatment in patients with type 2 diabetes and chronic kidney disease: A randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol 2014;2:369-84.

12. Nishimura R, Tanaka Y, Koiwai K, Inoue K, Hach T, Salsali A, *et al.* Effect of empagliflozin monotherapy on postprandial glucose and 24-hour glucose variability in Japanese patients with type 2 diabetes mellitus: A randomized, double-blind, placebo-controlled, 4-week study. Cardiovasc Diabetol 2015;14:11.

13. Roden M, Weng J, Eilbracht J, Delafont B, Kim G, Woerle HJ, *et al.* Empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Diabetes Endocrinol 2013;1:208-19.

14. Roden M, Merker L, Christiansen AV, Roux F, Salsali A, Kim G, *et al.* Safety, tolerability and effects on cardiometabolic risk factors of empagliflozin monotherapy in drug-naïve patients with type 2 diabetes: A double-blind extension of a phase III randomized controlled trial. Cardiovasc Diabetol 2015;14:154.

15. Provilus A, Abdallah M, McFarlane SI. Weight gain associated with antidiabetic medications. Therapy 2011;8:113-20.

16. McFarlane SI. Antidiabetic medications and weight gain: Implications for the practicing physician. Curr Diab Rep 2009;9:249-54.

17. Bonora E. Antidiabetic medications in overweight/obese patients with type 2 diabetes: Drawbacks of current drugs and potential advantages of incretin-based treatment on body weight. Int J Clin Pract Suppl 2007; 61:19-28.

18. Ridderstråle M, Andersen KR, Zeller C, Kim G, Woerle HJ, Broedl UC; EMPA-REG HH-SU Trial Investigators. Comparison of empagliflozin and glimepiride as add-on to metformin in patients with type 2 diabetes: A 104-week randomised, active-controlled, double-blind, phase 3 trial. Lancet Diabetes Endocrinol 2014;2:691-700.

19. Rosenstock J, Jelaska A, Frappin G, Salsali A, Kim G, Woerle HJ, *et al.* Improved glucose control with weight loss, lower insulin doses, and no increased hypoglycemia with empagliflozin added to titrated multiple daily injections of insulin in obese inadequately controlled type 2 diabetes. Diabetes Care 2014;37:1815-23.

20. Mohan V, Sandeep S, Deepa R, Shah B, Varghese C. Epidemiology of type 2 diabetes: Indian scenario. Indian J Med Res 2007;125:217-30.

21. Kumar A, Tewari P, Sahoo SS, Srivastava AK. Prevalence of insulin resistance in first degree relatives of type-2 diabetes mellitus patients: A prospective study in north Indian population. Indian J Clin Biochem 2005;20:10-7.

22. Tikkanen I, Narko K, Zeller C, Green A, Salsali A, Broedl UC, *et al.* Empagliflozin reduces blood pressure in patients with type 2 diabetes and hypertension. Diabetes Care 2015;38:420-8.

23. Chilton R, Tikkanen I, Cannon CP, Crowe S, Woerle HJ, Broedl UC, *et al.* Effects of empagliflozin on blood pressure and markers of arterial stiffness and vascular resistance in patients with type 2 diabetes. Diabetes Obes Metab 2015;17:1180-93.

24. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, *et al.* Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-28.

25. Cherney DZ, Perkins BA, Soleymanlou N, Maione M, Lai V, Lee A, *et al.* Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. Circulation 2014;129:587-97.

26. Hattersley AT, Thorens B. Type 2 diabetes, SGLT2 Inhibitors, and glucose secretion. N Engl J Med 2015;373:974-6.

27. Johnsson KM, Ptaszynska A, Schmitz B, Sugg J, Parikh SJ, List JF. Urinary tract infections in patients with diabetes treated with dapagliflozin. J Diabetes Complications 2013;27:473-8.

28. Haas B, Eckstein N, Pfeifer V, Mayer P, Hass MD. Efficacy, safety and regulatory status of SGLT2 inhibitors: Focus on canagliflozin. Nutr Diabetes 2014;4:e143.