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Dapagliflozin in Clinical Practice - Benefits beyond Glycaemic Control An Expert Review from India

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is a major lifestyle disorder with a steep rise in the prevalence rates all over the world. India is epicentre of diabetes mellitus and most patients fail to achieve their glycaemic targets resulting in long term micro and macro vascular complications. Considering the complex pathophysiology, T2DM may not be managed efficiently through a glucocentric approach. Several new pharmacological options have been explored for better management of T2DM. Sodium-glucose co-transporter-2 inhibitors (SGLT2i) is one category, which acts by inhibiting SGLT2 co-transporter and prevents the reabsorption of urinary glucose thereby facilitating its excretion in urine. In India, SGLT2i are recommended in management of T2DM either as monotherapy or as combination therapy. Dapagliflozin, an SGLT2i, apart from glycaemic control is associated with non-glycaemic benefits such as cardioprotective, nephro-protective effects, delay progression of prediabetes to diabetes, and reduction in body weight, blood pressure. Safety and benefit/risk profile of dapagliflozin is predictable and favourable. This is a comprehensive review article of dapagliflozin summarizing the available evidence, not limited to glycaemia but extending to benefits beyond glycaemic control.

Keywords: Dapagliflozin, Oral hypoglycaemic agents, SGLT2 inhibitors, Type 2 diabetes mellitus

Abbreviations

ADA: American Diabetes Association; AEs: Adverse Events; ASCVD: Atherosclerotic cardiovascular disease; BP: Blood Pressure; CAD: Coronary Artery Disease; CANVAS: Canagliflozin Cardiovascular Assessment Study; CAP: Controlled Attenuation Parameter; CKD: Chronic Kidney Disease; CVD: Cardiovascular Disease; DAPA-HF: Dapagliflozin and Prevention of Adverse- Outcomes in Heart Failure; DBP: Diastolic blood pressure; DECLARE-TIMI58: Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58; DELIVER: Dapagliflozin Evaluation to Improve the LIVEs of Patients With Preserved Ejection Fraction Heart Failure; DEPICT 1: Dapagliflozin Evaluation in Patients With Inadequately Controlled Type 1 Diabetes; DKA: Diabetic Ketoacidosis; DKD: Diabetic Kidney Disease; DPP-4: Dipeptidyl Peptidase-4;EAT: Epicardial Adipose Tissue; EMPA-REG: Empagliflozin Cardiovascular Outcome Event Trial in T2DM Patients-Removing Excess Glucose; FDA: Food and drug administration; FPG: Fasting plasma glucose; ESRD: End-Stage Renal Disease; GLP-1: Glucagon-Like Peptide 1; GFR: Glomerular Filtration Rate; HFrEF: Heart Failure And Reduced Ejection Fraction; HFpEF: Heart Failure And Preserved Ejection Fraction; HR: Hazard Ration; Hb1Ac: Glycosylated haemoglobin; HDL: High-density lipoprotein; HF: Heart Failure; HHF: Hospitalization for Heart; IHD: Ischemic Heart Disease; KDIGO: Kidney Disease Improving Global Outcomes; KCCQ: Kansas City Cardiomyopathy Questionnaire; LDL: Low Density Lipoprotein; LSM: liver stiffness measurement; MACE: Major Adverse Cardiovascular Events; MI: Myocardial Infarction; NAFLD: Non-Alcoholic Fatty Liver Disease; OHA: Oral Hypoglycaemic Agents; OR: Odds ratio; OSAHS: Obstructive Sleep Apnea-Hypopnea Syndrome; PCT: Proximal Convoluted Tubule; PPG: Post-Prandial Plasma Glucose; SBP: Systolic Blood Pressure; SGLT2i: Sodium-Glucose Co-Transporter-2 Inhibitors; T2DM: Type 2 Diabetes Mellitus; UTIs: Urinary Tract Infections; VAT: Visceral Adipose Tissue.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic condition with a worldwide prevalence of around 463 million in 2019 [1]. In India, around 77 million patients are suffering from diabetes [2]. India is epicentre of diabetes mellitus and has the world's second-largest population of diabetes in 2017 which will double by 2045 [3]. Asian-Indian phenotype is characterized by obesity, hyperinsulinemia, insulin resistance, and atherogenic dyslipidaemia, which predispose Indians to T2DM and premature cardiovascular disease (CVD) [4]. Indian epidemiological evidence reported a substantial burden of vascular complications in diabetes. Neuropathy (24.6%) was the most common complication, followed by cardiovascular (23.6%), renal (21.1%), and ocular (16.6%) complications as perA1chieve study [6]. Heart failure (HF) risk was increased by 2.5 to 5-fold in T2DM. CVD was responsible for two-thirds of deaths in T2DM patients [5]. Several studies had exhibited around a 2-fold increased risk of myocardial infarction (MI), stroke, or ischemic heart disease (IHD) and a 2.35-fold higher risk of coronary artery disease (CAD) in patients with diabetes than non-diabetes [7,8]. In the 'Joint Asia Diabetes Evaluation' registry, people with diabetes from India ranked highest in the prevalence of chronic kidney disease (CKD) and second highest in the prevalence of albuminuria among 7 Asian countries [9].

The majority of diabetic patients on anti-diabetic drug therapy suffer from poor glycaemic control, dyslipidaemia, and diabetic vascular complications [10]. Combination therapy (54%) is most prescribed followed by monotherapy (46%) [11]. Most widely prescribed class of drug is sulfonylureas while metformin is a commonly prescribed individual drug among oral hypoglycaemic agents (OHA). Also, insulin and a fixed-dose combination of biguanide and sulfonylurea are prescribed and used frequently [10].

BACKGROUND

T2DM is a multi-organ disease arising from the combination of insulin resistance and a beta-cell secretory defect. Since the complications related to T2DM impact multiple organ systems and daily life significantly, reducing glycosylated haemoglobin (HbA1c) levels to the normal range is extremely crucial [12]. The uncontrolled glycaemia in T2DM aggravates the other pathophysiological processes in CVD or CKD which may lead to developing progressive vascular complication(s) (diabetic kidney disease (DKD) or diabetic cardiomyopathy) and may give rise to hypertension or dyslipidaemia [2, 13]. In India, around 70% of patients with diabetes in India have HbA1c ≥7; thus, fail to achieve the optimal glycaemic control as recommended by most guidelines [14].

The T2DM management strategy should achieve glycaemic control and decrease micro-and macrovascular outcomes. The approach of earlier T2DM management was glucocentric which contemplated hyperglycaemia as the primary target. Whereas several new classes of pharmacological agents focus on treating the under lying disease process and not only reacting to the blood glucose levels [12]. Since the advent of sulfonylureas in 1950, they have been a mainstay in T2DM treatment with metformin. However, recent evidence showed a lowering of glycaemic control after 6 months after the addition of sulfonylurea to metformin. The novel classes of drugs have shown glucose-lowering efficacy, higher safety, and long-term outcomes when added in patients having inadequate glycaemic control with metformin. Some are superior to sulfonylureas in lowering the risk of cardiovascular complications [15]. Sodium-glucose co-transporter-2 inhibitors (SGLT2i) is one such category, which is found effective in T2DM patients with insulin resistance and cardiovascular complications [16].

Gliflozins

Gliflozin drugs are the SGLT2i. SGLT2i are the recent class of OHA used in treating T2DM [17]. They act by inhibiting the SGLT2 in the proximal convoluted tubule (PCT); prevent the absorption of glucose and expedite its excretion in urine. This lowers blood glucose levels and improves glycaemic parameters [18].

Recently, EMPA-REG OUTCOME, DECLARE-TIMI and CANVAS trials demonstrated that SGLT2i reduce CVDs in T2DM patients. The evidence suggested that SGLT2i have a regulatory role in cellular stress, biochemical equilibrium, and inflammation in addition to lowering glycated haemoglobin and fasting blood glucose levels [17]. SGLT2i are related to improvements in a variety of cardiovascular risk factors such as a reduction in body weight, blood pressure (BP), waist circumference, and triglycerides, and an increase in high-density lipoprotein (HDL) cholesterol [19].

The pleiotropic effect in terms of cardiovascular benefits with SGLT2i is due to an improvement in ventricular loading caused by a reduction in cardiac load. The inhibition of glucose and sodium reabsorption in the PCT by SGLT2i causes an increase innatriuresis and glucosuria, followed by an increase in osmotic diuresis and reductions in preload. These effects result in reductions in BP and changes in vascular function. Apart from these most known mechanisms, complex cellular effects such as optimization of energy balance, oxidative stress down regulation, and pro-inflammatory signalling pathway modulation are associated with favourable outcomes observed in clinical trials [18, 20-21]. In addition, SGLT2i can change metabolism from glucose to oxidation of fatty acids and increase ketone plasma concentrations [22]. This fuel selection allows for more effective oxygen utilization and improved mitochondrial efficiency, which restores myocardial function in diabetics [23].

SGLT2i cause a substantial decrease in the risk of kidney disease progression relative to placebo in cardiovascular outcome trials in T2DM patients [18]. Increased natriuresis leads to higher sodium levels at the macula densa and triggerstubuloglomerular feedback which reduced renal blood flow and glomerular hyperfiltration [19,20]. Glial hyperfiltration is correlated to rapid function loss and glomerular filtration rate (GFR) decline in DKD and SGLT2i directly minimize it [20]. The position of SGLT2i in various guidelines is described in **(Table 1).**

Table 1: SGLT2i and recommendation by international guidelines.

Guidelines	Recommendation
RSSDI-ESI 2020 guidelines [16]	For patients with established atherosclerotic cardiovascular disease (ASCVD), HF, DKD or in need of weight reduction consider using SGLT2i Patient-centric approach: Dual or triple therapy with SGLT2i
American Diabetes Association (ADA) [24]	SGLT2i with demonstrated cardiovascular benefit are recommended as part of glycaemic control for patients with T2DM who have developed ASCVD and also in HF or CKD Compelling need for reducing hypoglycaemia and/or weight loss
Kidney Disease Improving Global Outcome (KDIGO) [25]	Recommends treatment of patients with T2D, CKD, and an estimated glomerular filtration rate (eGFR) ≥30 ml/min/1.73m^2 with an SGLT2i
The American Association of Clinical Endocrinologists (AACE) [26]	Initiating therapy with metformin, a glucagon-like peptide 1 (GLP-1 agonist), a dipeptidyl Peptidase-4 (DPP-4) inhibitor, an SGLT2i, or an α-glucosidase inhibitor for patients with an entry A1C <7.5%

DAPAGLIFLOZIN PHARMACOLOGY

Dapagliflozin is a reversible and highly potent SGLT2i (inhibitory constant=0.55 nmol/L). It is >1400 times more selective to SGLT2 than SGLT1 [27]. Dapagliflozin improves glycaemic control and lowers bodyweight and BP in a wide variety of patients with T2DM, including those with elevated baseline HbA1c (9%) [28] and elderly (≥65 years) [29]. Dapagliflozin is administered orally with or without food and absorbed rapidly. The maximum peak plasma concentrations are reached within 2 hours (fasted state) [7]. The absolute oral bioavailability of dapagliflozin is 78% and mean plasma terminal elimination half-life of dapagliflozin is 12.9 hour at 10 mg dose. It is 91% protein-bound with a mean steady-state volume of distribution 118 l. It is metabolized by uridine diphosphate-glucuronosyltransferase 1A9 to its major inactive metabolite3-O-glucuronide in the liver and kidneys. The excretion of dapagliflozin and its metabolites occurs mainly via urine [27,30].

Dapagliflozin in T2DM management

Glycaemic efficacy trials Monotherapy

There have been several clinical trials reporting the efficacy of dapagliflozin when given as monotherapy (Table 2) [31-34]. Bailey et al. [31] conducted a 24-week randomized, double-blind, placebo-controlled, parallel group trial including 274 patients with baseline HbA1c (8.0%). They were randomized to receive placebo or dapagliflozin monotherapy 2.5 mg, 5 mg, or 10 mg once daily in the morning. After 24 weeks, low-dose metformin 500 mg/day was added to the placebo group therapy. The mean changes in HbA1c in the dapagliflozin 2.5, 5 and 10mg and placebo groups at 24 weeks were -0.58%, -0.77%, -0.89% and-0.23% (p values vs placebo: 0.0005, < 0.0001, and < 0.0001 respectively). These mean reductions in HbA1c and fasting plasma glucose (FPG) levels were maintained up to 102 weeks in the dapagliflozin 5mg (p=0.018 and 0.044) and 10mg (p=0.048 and 0.001 respectively) groups.

A pooled analysis of efficacy data from eight Phase IIb/III trials included 1453 Asian patients with T2DM, treated with placebo, dapagliflozin 5 mg, or dapagliflozin 10 mg over 24 weeks. It demonstrated that dapagliflozin was efficacious and well-tolerated in Asian patients with T2DM and showed similar results observed in diverse ethnicities. Greater reductions in HbA1c were seen with dapagliflozin 5 and 10 mg versus placebo at 24 weeks. At 24 weeks, placebo-corrected adjusted mean changes from baseline in HbA1c were -0.52%, and -0.58% for dapagliflozin 5 mg and 10 mg respectively [34] **(Table2)**.

Add-on Therapy

Dapagliflozin has been studied as adjunctive therapy to several oral agents **(Table 3)** [35-40]. Yang et al. [35] reported that dapagliflozin+metformin had brought significant reductions in both Hb1Ac and FPG at week 24 compared to placebo **(Table 2)**. A 24-week, randomized study conducted by Matthaei and colleagues [36] demonstrated superiority of dapagliflozin 10 mg/day with

Table 2: Efficacy of dapagliflozin monotherapy in patients with T2DM.

Study	Intervention	N	Mean baseline HbA1c (%)	Mean change in HbA1c from baseline (%) to end of treatment	Mean change in fasting plasma glucose levels (FPG) from baseline to end of treatment (mmol/l)	Adjusted mean change in total body weight from baseline to end of treatment (kg)
Bailey et al. [31]	Placebo	75	7.84	-0.17	-0.38	-1.34
	Dapagliflozin 2.5 mg	65	7.92	-0.30	-0.54	-0.58
	Dapagliflozin 5 mg	64	7.86	-0.70	-1.08	-1.59
	Dapagliflozin 10 mg	70	8.01	-0.61	-1.50	-3.94
Ferrannini et al. [32]	Placebo	75	7.84	-0.23±0.10	-4.1 ± 3.9	-2.2 ± 0.4
	Dapagliflozin 2.5 mg (morning)	65	7.92	-0.58 ± 0.11	-15.2 ± 4.2	-3.3 ± 0.5
	Dapagliflozin 5 mg (morning)	64	7.86	-0.77± 0.11	-24.1± 4.3	-2.8± 0.5
	Dapagliflozin 10 mg (morning)	70	8.01	-0.89 ±0.11	-28.8 ± 4.0	-3.2± 0.5
	Dapagliflozin 2.5 mg (evening)	67	7.99	-0.83 ±0.11	-25.6± 4.1	-3.8 ± 0.5
	Dapagliflozin 5 mg (evening)	68	7.82	-0.79 ±0.11	-27.3 ± 4.2	-3.6± 0.5
	Dapagliflozin 10 mg (evening)	76	7.99	-0.79 ±0.10	-29.6± 4.0	-3.1 ± 0.4
	Dapagliflozin 5 mg in higher A1c (≥ 10.1%)	34	10.82	-2.88 ±1.41	-77.1± 53.4	-2.1 ± 3.4
	Dapagliflozin 10 mg in higher A1c (≥ 10.1%)	39	10.73	-2.66 ±1.26	-84.3 ±61.0	-1.9± 3.5
Kaku et al. [33]	Placebo	87	7.50	-0.06	5.8	-0.84
	Dapagliflozin 5 mg	86	7.50	-0.41	-8.6	-2.13
	Dapagliflozin 10 mg	88	7.46	-0.45	-13.7	-2.22
Yang et al. [34]	Placebo	497	8.18	-0.35	-0.43	-0.6
	Dapagliflozin 5 mg	491	8.10	-0.87	-1.50	-1.9
	Dapagliflozin 10 mg	465	8.08	-0.93	-1.89	-2.4

metformin and sulfonylurea in patients with inadequate glycaemic control on metformin and sulfonylurea. A significant reduction in HbA1c and FPG was reported at the end of 24 weeks from baseline (p=0.0001 for both groups). A large number of patients receiving dapagliflozin 10 mg/day were able to achieve a therapeutic glycaemic response (p=0.0001) than patients in the placebo group.

Jabbour et al [38] conducted a randomized, 24-week long study in 432 patients. The mean change in HbA1c from

baseline was statistically significant in the dapagliflozin group ((10mg/day+sitagliptin) (100mg/day) ±metformin)) compared with placebo (sitagliptin (100mg/day) ±metformin) at week 24 (p=0.0001). The reduction in HbA1c in the dapagliflozin group was significant versus placebo when added to sitagliptin alone (p=0.0001) or to sitagliptin plus metformin (p=0.0001).

Rosenstock et al. [39] studied the effects of dapagliflozin when added with pioglitazone in a randomized, 24-week study (n=972). The discontinuation due to lack of glycaemic control took place mostly in placebo (34%) compared to dapagliflozin (11-18%). The reduction in HbA1c, FPG, and post-prandial plasma glucose (PPG) were significant in dapagliflozin 5and 10mg+pioglitazone compared with placebo+pioglitazone at week 24 and were maintained through week 48. The HbA1c decreased significantly in dapagliflozin+pioglitazone than the placebo+pioglitazone at week 24 (p=0.0007and p=0.0001 for dapagliflozin 5 and 10mg groups, respectively) and was maintained and found dose-dependent at 48 weeks. The fall in FPG was rapid and significant at week 24. At week 48, the mean change from baseline in PPG was greater with dapagliflozin+pioglitazone(-60.4 to -80.9 mg/dL [−3.35 to −4.49 mmol/L] than with placebo+pioglitazone (-25.4 mg/dL [1.41 mmol/L]).

In a placebo-controlled, double-blind study by wilding et al [40] randomly assigned 808 patients with T2DM inadequately controlled with insulin ≥30 IU/day with or without up to two OHAs, to receive placebo or 2.5, 5 or 10 mg/day of dapagliflozin. Mean change in HbA1c from baseline at 104 weeks was -0.4% (p = 0.0002) and -0.4% (p = 0.0007) in the dapagliflozin 5/10 mg and 10 mg groups, respectively. Long-term reductions in HbA1c were evident at all dapagliflozin dosages. In patients receiving insulin and 1-2 OHAs, difference between the dapagliflozin 10-mg and placebo groups in HbA1c adjusted mean change from baseline was ((-0.4% (p=0.0050)) compared to patients on insulin alone ((0.3% (p=0.0563)). The mean reduction in placebo-adjusted mean changes in FPG from baseline at 104 weeks was −0.89 mmol/l (p=0.0031) and −0.31 mmol/l (p=0.3065) in the dapagliflozin 5/10-mg and 10-mg groups. There was an increase in insulin requirement in the placebo group (+18.3 IU/day), whereas it was stable throughout in the dapagliflozin groups. The difference in mean change in insulin daily-dose from baseline at 104 weeks from placebo were-16.8 IU (p<0.0001) and -19.2 IU (p<0.0001) in the dapagliflozin 5/10-mg and 10-mg groups, respectively.

Declare-TIMI 58 trial

The Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE–TIMI 58) trial was conducted to assess the effects of dapagliflozin on CV and renal outcomes in patients aged ≥40 years with T2DM(HbA1c≥6.5 to <12%) and creatinine clearance ≥60 mL/min and established atherosclerotic cardiovascular disease (ASCVD)(40%) or multiple risk factors for ASCVD(60%). The primary efficacy outcomes were major adverse cardiovascular events (MACE) and the composite of cardiovascular death and hospitalization for heart (HHF). The two pre-specified secondary endpoints were renal composite outcome and death from any cause [41,42]. Dapagliflozin met the pre-specified criterion for non-inferiority with respect to MACE (P<0.001 for non-inferiority). Dapagliflozin resulted in a lower rate of cardiovascular death or hospitalization for HF than placebo (4.9% vs. 5.8%; hazard ratio (HR=0.83; P=0.005). This outcome was mainly driven by fewer hospitalization for HF in the dapagliflozin group(HR=0.73). Dapagliflozin didn't cause a reduction in the rate of MACE than placebo (8.8% and 9.4%; HR=0.93; P=0.17). Moreover, the incidence of renal composite was lower in dapagliflozin group vs placebo ((estimated GFR (eGFR) by ≥40% to <60 mL/min/1.73 m^2 (HR=0.54; p<0·0001), end-stage renal disease (ESRD) (HR=0.31; p=0.013), renal death or ESRD (HR=0.41; p=0.012)) and reduced the progression of renal disease. The HbA1c values were lower in dapagliflozin than placebo recipients throughout the study (LS mean treatment difference=0.42%) [41,43] **(Table 3).**

Subgroup Analysis

The different subgroup analyses of DECLARE-TIMI 58 are described in **(Table 4).**

Dapagliflozin - benefits beyond glycaemic control

Cardio protection

The Dapagliflozin and Prevention of Adverse- Outcomes in Heart Failure (DAPA-HF) trial showed that dapagliflozin in addition to standard of care reduced the risk of mortality and HF hospitalization. Trial enrolled 4,744 patients who had HFrEF (left ventricular EF≤40%). At baseline, 45% had T2DM.The combination improved symptoms in patients with HF and reduced ejection fraction (HFrEF). The patients were distributed according to the age groups i.e.<55, 55-64, 65-74, ≥75. There was significant reduction in the rate of cardiovascular death or HF hospitalization/urgent HF visit in the patients >55 years old (P<0.005; p for interaction in various age groups=0.75). The effect of dapagliflozin compared with placebo on cardiovascular death, HF hospitalization/urgent HF visit, all-cause death, and cardiovascular death/HF hospitalization recurrent events examined was consistent across all the categories of age (p-value for interaction=0.97). The patients treated with dapagliflozin showed greater improvement in Kansas City Cardiomyopathy Questionnaire (KCCQ-TSS) from baseline to 8 months; it was consistent across age categories (p-value for interaction=0.65). This result was important in elder people (≥75 years of age) as improvement or prevention of

Table 3: Efficacy of dapagliflozin in adjunct with other oral agents in patients with T2DM.

Study	Intervention	N	Mean baseline HbA1c (%)	Mean change in HbA1c from baseline (%) to end of treatment	Mean change in fasting plasma glucose levels (FPG) from baseline to end of treatment (mmol/l)	Adjusted mean change in total body weight from baseline to end of treatment (kg)
Yang et al. [35]	Placebo+metformin	145	8.13	-0.23	0.03	-0.7
	Dapagliflozin (5mg) + metformin	147	8.09	-0.82	-1.20	-1.8
	Dapagliflozin (10mg) + metformin	152	8.17	-0.85	-1.48	-2.6
Matthaei et al. [36]	Placebo+ metformin and sulfonylurea	108	8.24	-0.17	-0.8	-0.6
	Dapagliflozin 10 mg+ metformin and sulfonylurea	108	8.08	-0.86	-34.2	-2.7
Strojeck et al. [37]	Placebo+Glimepiride	145	8.15	-0.13	-	-0.72
	Dapagliflozin 2.5 mg+Glimepiride	154	8.11	-0.58	-	-.1.18
	Dapagliflozin 5 mg+Glimepiride	142	8.12	-0.63	-	-1.56
	Dapagliflozin 10 mg+Glimepiride	151	8.07	-0.82	-	-2.26
Jabbour et al. [38]	Placebo + Sitagliptin+metformin	224	7.9	0	3.8	-0.3
	Dapagliflozin + 10 mg Sitagliptin+ metformin	223	7.8	-0.5	-24.1	-2.1
Rosenstock et al. [39] Pioglitazone use at baseline	Placebo	139	8.34	-0.54 ± 0.08	-0.73±0.20	2.99±0.41
	Dapagliflozin 5 mg	141	8.40	-0.95 ± 0.08	-1.27±0.18	1.35±0.38
	Dapagliflozin 10 mg	140	8.37	-1.21 ± 0.07	-1.84±0.17	0.69±0.36
Wilding et al. [40]	Placebo+ Insulin	193	8.47	–0.43	-1	1.83
	Dapagliflozin 2.5 mg + Insulin	202	8.46	-0.64	-1.14	-0.99
	Dapagliflozin 5 mg + Insulin	211	8.62	-0.82	-1.89	-1.03
	Dapagliflozin 10 mg + Insulin	194	8.57	-0.78	-1.30	-1.50

Table 4: A summary of efficacy results of subgroup analysis of DECLARE-TIMI 58.

Study	Subgroups	Efficacy results	P for interaction
Wiviott et al. [41]	Patients with T2DM and 1.Established ASCVD 2.Multiple risk factors	Efficacy of dapagliflozin with respect to rate of CV deaths or HHF was similar (dapagliflozin vs placebo) In patients with established ASCVD (7.8% vs 9.3%; HR= 0.83) and In patients with multiple risk factors (2.8% vs 3.4%; HR: 0.84)	0.99
		No significant reduction in rate of major adverse cardiovascular events (MACE) In patients with ASCVD (HR= 0.90) or In patients with multiple risk factors (HR=1.01)	Non-significant
		Reduction in rate of progression of renal disease with dapagliflozin seen among patients with or without established ASCVD, HF, or CKD at baseline	Non-significant
Furtado et al. [44]	Patient with T2DM and 1. MI 2. Prior MI or 3. No prior MI but with established ASCVD	The 16% reduction in MACE In patients with prior MI on dapagliflozin (HR: 0.84; p=0.04), mainly due to lower rate of recurrent MI (HR=0.78) No significant reduction In patients with no prior MI (HR=1.00) or In patients with no prior MI but with established ASCVD (HR=0.98).	NA
		The absolute risk reduction (ARR) for MACE In patients with prior MI was 2.6%. (The treatment benefit with dapagliflozin was greater in patients closer to a recent MI (>12 to 24 months))	0.007
		A treatment benefit (HR<1) for cardiovascular death/HHF was seen with dapagliflozin relative to placebo in all subgroups In patients with prior MI (HR=0.81; p=0.046), In patients without prior MI (HR=0.85) and In patients with no prior MI but with ASCVD (HR:0.87)	NA
Kato et al. [45]	Patients with T2DM and 1. HF with reduced ejection fraction (HFrEF; ejection fraction (EF) < 45%) 2. Without HFrEF (included patients with HF without known reduced EF and patients without HF)	Decline in CV death/HHF events More in patients with HFrEF (HR=0.62) than in those without HFrEF (HR=0.88)	0.046
		Reduction in CV death In patients with HFrEF (HR=0.55, p=0.02).	NA
		Significant reduction in all cause death with dapagliflozin compared to placebo In patients with HFrEF (HR 0.59; p = 0.01), but not In those without known HFrEF (HR=0.97)	0.016
		HHF was reduced with dapagliflozin regardless of baseline EF, with similar reductions in patients both with HFrEF and without known HFrEF	0.045
Cahn et al. [46]	Patients with T2DM and Age<65 years ≥65 to <75 Age ≥ 75 years	Reduction in the composite of CV death or hospitalization for heart failure consistently in age-groups <65 (HR=0.88), ≥65 to <75 (HR=0.77), and ≥75 years (HR=0.94)	0.5277
		Dapagliflozin did not significantly decrease the rates of major adverse cardiovascular events in age-groups <65 (HR=0.93), ≥65 to <75 (HR=0.97), and ≥75 years (HR=0.84)	0.7352
		Relative risk reduction for the secondary pre-specified cardio-renal composite outcome varied from 18-28% in the different age-groups with no heterogeneity	NA

deterioration, in symptoms could be crucial as extending life. Also, these patients received slightly less conventional treatment, which further amplified the advantage of dapagliflozin in this study [47].

The cardio protective effects of dapagliflozin were further reinforced by CVD-REAL Nordic study (real-world data; n=40,908). Dapagliflozin caused significant reduction in the risk of MACE (non-fatal MI and stroke or CV mortality; HHF, and all-cause death (HR=0.79, 0.62, and 0.59 respectively) versus DPP-4 inhibitors after a mean follow-up of 0.95 years [48]. Berg et al [49] in patients with chronic HFrEF (n = 4744) evaluated the timing taken to the onset of clinical benefit with dapagliflozin. The reduction in the risk of cardiovascular death or worsening HF was rapid. Dapagliflozin reduced the relative risk of the primary outcome by 16% (HR=0.84), 27% (HR=0.73), and 36% (HR=0.64) in patients with a prior HF hospitalization never, >12 months ago, and 12 or fewer months ago, respectively (P=0.07 for trend). Accordingly, the absolute risk reduction was greater in patients with a more recent HF hospitalization at 2 years: 2.1%, 4.1%, and 9.9% respectively (P=0.05 for trend).

Nephro-protection

Reno-protective effects of SGLT2i have been studied and evident in patients with T2DM and CKD in the CREDENCE trial. DAPA-CKD trial enrolled 4304 CKD patients (estimated GFR: 25-75 ml/minute/1.73m^2 of body-surface area; urinary albumin to creatinine ratio of 200-5000 mg/g) and 67.5% of them had T2DM at baseline. Primary renal composite outcome of a sustained decline in the estimated GFR (of at least 50%), end-stage kidney disease, or death from renal or cardiovascular causes were lower in the dapagliflozin group than the placebo group (HR= 0.61, P<0.001), when added to standard of care. Change in eGFR in dapagliflozin and placebo groups were -1.67±0.11 and -3.59±0.11 ml/minute/1.73 m^2 respectively, for a between-group difference of 1.92 ml/minute/1.73m^2/year. DAPA-CKD showed that dapagliflozin reduced the risk of worsening kidney function or death from cardiovascular or kidney disease in CKD patients with or without T2DM [50,51].

Other beneficial effects

Bodyweight

Several randomized trials in dapagliflozin as mono- and add-on therapy have shown a reduction in bodyweight as one of their outcomes **(Table 1 and 2)**. Dapagliflozin is responsible for reducing body weight and is linked to a decrease in insulin requirement. The decline in weight is greater in patients with long diabetes history and higher baseline weight [16,52]. Analysis of 104-week data comparing dapagliflozin+insulin and placebo+insulin demonstrated that the total bodyweight increased progressively in the placebo group while it decreased in the dapagliflozin groups by 48 weeks. It was consistent over 104 weeks. The mean change in total bodyweight against placebo from baseline at 104 weeks were −2.86 kg (p<0.0001) and −3.33 kg (p<0.0001) in the dapagliflozin 5/10- mg and 10-mg groups, respectively [37]. Another analysis in patients receiving the add-on dapagliflozin 10 mg once daily showed a significant decrease in weight (p<0.0001), smaller waist circumference (p=0.0143), and less fat mass (p=0.0001) compared to add-on placebo at week 24. This study supported the findings that weight loss and reduction in fat mass with dapagliflozin were majorly due to caloric loss achieved from glucosuria [16,53]. A series of meta-analyses claimed that there was around 1-2 kg weight reduction with dapagliflozin and around 5 kg with metformin when compared against sulfonylurea [54-56].

Systolic blood pressure

Dapagliflozin caused reductions in 24-hour ambulatory BP monitoring, resulting in significantly lower systolic and diastolic BP (SBP and DBP) measurements [57]. A pooled analysis in asian populations showed reduction in seated SBP and DBP with dapagliflozin 5 and 10 mg versus placebo at 24 weeks. Placebo-corrected adjusted reductions were −2.5 and −3.1 mmHg in SBP, and −1.4 and −1.3 mmHg in DBP at 24 weeks with dapagliflozin 5 and 10 mg, respectively [34].

Obstructive sleep apnea

The prevalence of obstructive sleep apnea-hypopnea syndrome (OSAHS) in T2DM patients with obesity is 86%. The symptoms of OSAHS are apnea or reduced breathing during sleep. Tang et al [58] reported a significant reduction in apnea-hypopnea index, an increase in minimum oxygen saturation, and a decrease in Epworth somnolence scale score (p<0.05) in dapagliflozin and metformin group (n=18) but not in glimepiride and metformin group (n=18) over 24 weeks. Dapagliflozin and metformin aided in decreasing the patient's weight, ameliorating the blood glucose, BP, and blood lipid levels. Dapagliflozin improved patient's ventilation and daytime sleepiness, thus providing symptomatic relief inpatients [58, 59].

Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver disease with an estimated prevalence of 25% worldwide; it affects more than 50% of patients with T2DM [60]. Arandomized trial of 57 patients with T2DM and NAFLD received dapagliflozin (5 mg/day) or standard treatment with no SGLT2i for 24 weeks. At week 24, visceral adipose tissue (VAT), controlled attenuation parameter (CAP), liver enzymes, and bodyweight reduced significantly in dapagliflozin group, but, not in the control group. The CAP was significantly decreased from baseline in dapagliflozin group than the standard group (92.4±18.7 vs. 102.2±13.2%, p=0.0429). The change in liver stiffness

measurement (LSM) was non-significant in the dapagliflozin group (9.49 ±6.05 kPa to 8.01±5.78 kPa; p=0.0539). In 14 patients from this group, LSM decreased significantly (p=0.0158). Furthermore, the reduction in serum alanine aminotransferase and γ-glutamyltranspeptidase levels was found in dapagliflozin group, but not in the control group, accompanied with significant reduction in visceral fat mass in dapagliflozin group. This finding suggested an improvement in liver steatosis in patients with T2DM and NAFLD [61].

Epicardial adipose tissue

Epicardial adipose tissue (EAT) is a modifiable risk factor for T2DM related cardiovascular complications and an emerging therapeutic target. In 40 T2DM patients with CAD, EAT volume was compared prospectively between the dapagliflozin and conventional treatment groups during a 6-month period. At baseline, the EAT volumes in the dapagliflozin and conventional treatment groups were comparable with each other while it decreased significantly at follow-up; there duction was significantly greater in dapagliflozin group than the conventional treatment group (-16.4±8.3 vs. 4.7±8.8 cm^3, p=0.01). In addition, the TNF-α level decreased significantly in the dapagliflozin group (p=0.04); this change was significantly greater in dapagliflozin group than the conventional treatment group (-0.5±0.7 vs. 0.03±0.3 pg/ml, p=0.03). The correlation between the changes in the EAT volume and body weight (correlation co-efficient (r) =0.71, p=0.01) and also between the EAT volume and TNF-α level (r=0.51, p=0.04) was significant. Thus, dapagliflozin managed to establish glycaemic control and improve the levels of systemic inflammation markers and reduce the risk of cardiovascular events [62].

Dapagliflozin in type 1 diabetes mellitus

Dapagliflozin Evaluation in Patients with Inadequately Controlled Type 1 Diabetes (DEPICT-1) was the first report of the long-term use of a selective SGLT2i as an adjunct to insulin for the treatment of type 1 diabetes. Patients were randomized into dapagliflozin 5 mg, 10 mg, and placebo groups. Dapagliflozin 5 mg and 10 mg reduced HbA1c (difference vs. placebo 20.33% and 20.36% respectively) and body weight (difference vs. placebo 22.95% and 24.54% respectively) significantly at 52 weeks. Although hypoglycaemia events were comparable across treatment groups, more patients in the dapagliflozin groups had events such as definite diabetic ketoacidosis (DKA) (4.0%, 3.4%, and 1.9% in dapagliflozin 5 mg, 10 mg, and placebo groups, respectively) [63].

Dapagliflozin in diabetes prevention

The subgroup of 2,605 patients with HFrEF of DAPA-HF trial with no prior history of diabetes, and an HbA1c<6.5% at baseline was randomized to dapagliflozin 10 mg daily or placebo. Dapagliflozin decreased the incidence of T2D by 32%; predominantly in individuals with prediabetes at baseline. In patients with prediabetes, mean HbA1c levels decreased by -0.08% with dapagliflozin and by -0.04% with placebo at 8 months. The additional benefits of SGLT2i include improved insulin sensitivity, reduction in hyperinsulinemia, and enhancement of pancreatic β-cell function. These mechanisms could be efficacious in lowering the risk of developing T2DM in prediabetes [64].

PRE-D trial randomized the patients with BMI≥25 kg/m^2 (age=30-70 years) and prediabetesto dapagliflozin (10 mg once daily), metformin (1700 mg daily), interval-based exercise, or control. A small reduction in the mean amplitude of glycaemic excursions (MAGE) was found in the dapagliflozin group (17.1%, p=0.042) and exercise group (15.3%, p=0.067) compared to the control. There was a decline in MAGE by 17.2% (p=0.041) in the dapagliflozin group and 15.4% (p=0.065) in the exercise group compared to metformin after 13 weeks [65].

Dapagliflozin safety

Safety profile

A pooled analysis of safety data from 13 placebo-controlled trials reported a favourable and predictable tolerability profile of dapagliflozin over 24 weeks **(Figure 1)**.The overall incidence of hypoglycaemia was 13.7% and 12.4% with dapagliflozin and placebo, predominant in patients receiving insulin as background therapy. Food and drug administration (FDA) had issued the warning in educating and increasing awareness abouteuglycaemic ketoacidosis among patients receiving SGLT2i as ketoacidosis episodes after use of SGLT2i were observed. Overall, adverse events (AEs) related to renal function were seen in3.2% and 1.8% of patients receiving dapagliflozin and placebo. Events of reduction in renal creatinine clearance or renal impairment were more with Dapagliflozin; however, most events were transient, of mild/moderate intensity. Genital infections were more frequent in dapagliflozin than placebo group. Fewer lower-limb amputations were observed in the patients in the dapagliflozin and control groups [66]. Small but similar proportion of patients in the dapagliflozin and all control groups reported fractures during study periods (1.2% in each group). A pooled data from 21 clinical studies comprising patients with a history of CVD reported that dapagliflozin wasn't related to increased cardiovascular risk in patients with T2DM [67].

Risk vs benefit

Several meta-analyses on dapagliflozin have reported that dapagliflozin improves HbA1c by 0.50%, FPG by 1.1 mmol/L, reduces weight by 2 kg body mass index by 1.1%, and SBP/DBP by 4/2 mmHg. However, an increased risk of genitourinary (odds ratio (OR) 3.50) and urinary tract (OR=1.40) infections (UTIs) were observed [30, 55, 56, 68, 69]. Though certain AEs such as DKA and genital mycotic infections episodes were higher with SGLT2i, the absolute

hike in these complications is lesser than the absolute risk reductions produced by SGLT2i [70]. The genital infections can be managed by standard treatments [71]. Overall, data from major outcome trials clearly suggested that SGLT2 inhibitors are not associated with an increased risk of UTIs [72]. Looking at the overall safety and efficacy profile, dapagliflozin has shown astonishing potential as an OHA and can also offer pleiotropic effects which not only resolve

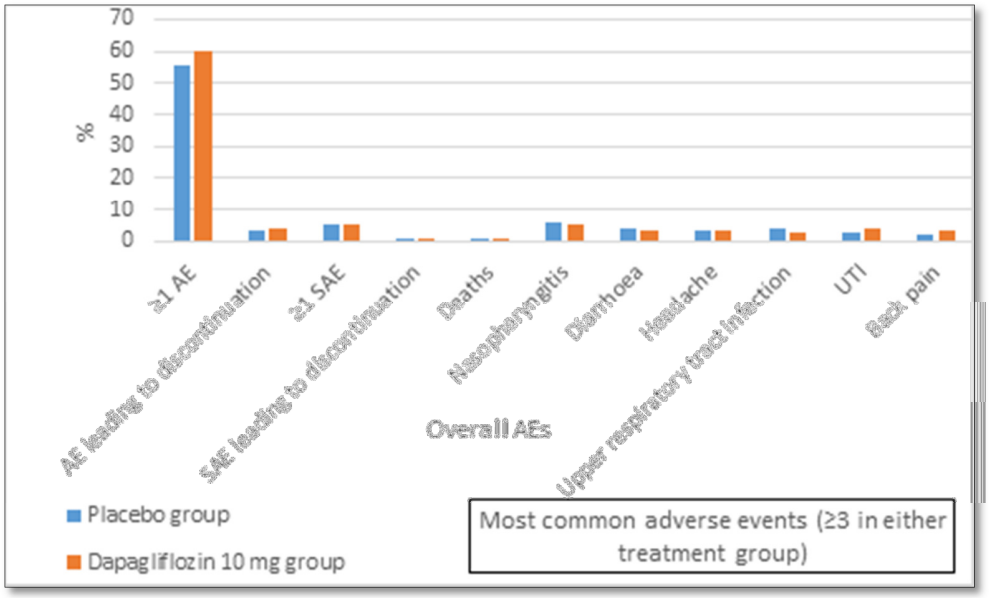

Figure 1: Summary of overall AEs (13-study pool safety data).

glycaemic disorders but also beneficial in treating other co-morbidities often present or developed with diabetes [73]. Dapagliflozin has shown favourable benefit/risk profile in all age categories [47].

When to avoid

There is no major evidence of SGLT2i exhibiting any clinically relevant drug-drug interactions with other OHAs. They can be concomitantly added or combined with metformin, sulfonylurea, pioglitazone, sitagliptin, and voglibose. However, ingestion of both loop diuretics and SGLT2i should be avoided in order to avoid hypotension and dehydration as they potentiate the risk of volume depletion [30]. The use of dapagliflozin isn't recommended in breastfeeding women and the paediatric population as respective data are unavailable. Due to profound polyuria along with renal glycosuria observed with SGLT2i, they won't be beneficial in pregnant women [74]. The co-administration of dapagliflozin with rifampicin led to a 22% decrease in dapagliflozin systemic exposure, but with no clinically meaningful effect on 24-hour urinary glucose excretion; thus, requiring no dose adjustment [75]. The use of dapagliflozin should be avoided in patients with higher DKA risk as it presents a risk of DKA episodes and volume depletion. There have been a number of case reports of euglycaemic ketoacidosis in the perioperative setting and hence, AACE has recommended not to ingestSGLT2i prior to surgery [76].

Place of dapagliflozin in clinical practice in the Indian context

A real-world evidence study in an Indian setting (FOREFRONT) [77] included 1978 Indian patients with T2DM to assess the efficacy and safety of dapagliflozin. A statistically significant reduction in HbA1c levels was observed from baseline to 3 and 6 months ($P<0.001$) irrespective of the HbA1c stratum (<8%, 8–10%, >10%). The effect was consistent in all Hb1Ac categories. Apart from the glycaemic effect, non-glycaemic effects such as weight loss (1.14 and 1.86 kg) and reduction in SBP (3.24 and 3.77 mmHg) were observed at the end of 3 and 6 months respectively. The RSSDI expert panel suggested that in Indian settings, SGLT2i are often recommended when metformin is not tolerated or contraindicated or when dual therapy is recommended (as a single agent is unable to achieve the glucose target), or when postprandial hypoglycaemia is a concern. The SGLT2i are recommended for benefits other than glycaemic control such as treating patients with comorbidities (established ASCVD, HF, DKD, or in need of weight reduction) [16]. Current ADA recommendations suggest SGLT2i and GLP-1 agonists as preferred add-on agents in addition to lifestyle interventions and metformin for diabetes patients with compelling indications for weight loss [24].

The use of dapagliflozin is not restricted solely to diabetes and its use has been approved for HFrEF and CKD in India [78-80]. Dapagliflozin is proven efficacious in T1DM as shown in DEPICT1 trial. A meta-analysis of DAPA-HF and

EMPEROR trials observed the reduction in all-cause and cardiovascular death and the combined risk of cardiovascular death or worsening HF, as well as in the composite renal endpoint (HR=0.62) irrespective of the presence of diabetes or baseline eGFR [81]. The DIAMOND trial had shown SGLT2i's effect on patients with CKD and without T2DM. An acute and reversible decline in measured GFR and a reduction in body weight were observed [82]. Looking at varied benefits of drugs of this class, cardiologists, nephrologists, endocrinologists, and primary care physicians should use these drugs while managing the cardio-renal disorders of their patients. As SGLT2i is newer class of drug, relying on multidisciplinary approach and gaining more experience can help lowering the barriers present in use of this therapy [83].

Lifelong treatment is needed in T2DM. Cost of treatment plays a major role while choosing the drugs in India as a large populace are devoid of medical insurance [16]. A Swedish study reported a lower hospital cost of US$321 per patient over 12 months associated with dapagliflozin, due to less cardiovascular risks, HF, and other T2D-related complications [84]. There have been ongoing trials which will fully evaluate therapeutic potential of SGLT2i in patients with or without T2DM. One such trial is DELIVER study; checking the impact of dapagliflozin on the rate of HHF and cardiovascular death in patients with heart failure preserved ejection fraction (HFpEF) and also, if those results will be able to complement DAPA-HF study [85]. Long-term clinical trials are being carried to find if SGLT2i can be efficient in major clinical kidney disorders in patients with CKD with and without diabetes [82].

CONCLUSION

In addition to glycaemic effects, presence of non-glycaemic effects (low risk of hypoglycaemia, concomitant weight loss, and the potential of lowering of BP) of dapagliflozin due to pleiotropic action make this molecule an attractive option in the treatment of T2DM. Apart from its use in diabetes with or without HF, CKD and ASCVD, the molecule has potential to change the management of CKD and HFrEF in patients without diabetes. The safety profile of dapagliflozin is favourable. Thus, dapagliflozin can be prescribed amongst broader range of T2DM patients with cardiac and renal disorders.

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