REVIEW ARTICLE

Dapagliflozin in the Landscape of Type 2 Diabetes Management

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ABSTRACT

As per current statistics, India accounts for more than 74 million individuals living with diabetes. Many of these individuals have associated cardiovascular disease (CVD) and chronic kidney disease (CKD) comorbidities. Optimal glycemic management is important because uncontrolled glycemia may accelerate the macrovascular and microvascular complications, further aggravating the comorbid conditions. Metformin is used as the first-line therapy in most persons. However, there are some who do not tolerate metformin, are unable to achieve required glycemic targets or require greater efforts for cardiovascular (CV) risk reduction. These patients require an alternative hypoglycemic agent to be used as either monotherapy or as combination treatment with metformin, respectively. Sodium-glucose cotransporter-2 (SGLT2) inhibitors are one such novel class of drugs that can be used as either monotherapy or as part of two drug (dual) or three drug (triple) combinations with other oral hypoglycemic agents or insulin. Dapagliflozin is a promising option for managing type 2 diabetes with CV and renal benefits, weight and blood pressure reducing properties. A low risk of hypoglycemia and drug-drug interactions are the added advantages. In this article, the authors have reviewed the existing clinical evidences on dapagliflozin and highlighted its place in the diabetes management landscape.

Keywords: Type 2 diabetes mellitus, CVD, dapagliflozin

THE CURRENT LANDSCAPE OF DIABETES MANAGEMENT

Globally, 1 in 10 adults are living with diabetes, out of which half are undiagnosed. While worldwide, 537 million people live with diabetes, India accounts for a staggering 74 million plus adults living with diabetes. A significant proportion of those with diabetes have associated microvascular and macrovascular complications.[1]

Conventionally, treatment has focused on controlling hyperglycemia and preventing the devastating consequences of uncontrolled blood glucose on the body. Early and effective intervention to optimize blood glucose levels is a fundamental principle of diabetes. The current armamentarium of diabetes treatment includes several oral hypoglycemic agents including biguanides, sulfonylureas, meglitinides, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, thiazolidinediones and alpha-glucosidase inhibitors.[2]

The management of diabetes is flexible, individualized, and all treatment strategies are underlined by lifestyle modification, especially diet and exercise through diabetes education and self-management.[2] However, many patients do not achieve the targeted glycemic goal or manage blood glucose effectively, thereby requiring the need for multiple therapies and even insulin. Despite improved risk factor control with the currently available therapies, improved glycemic control is not always associated with robust macrovascular benefits. In these cases, antihyperglycemic agents which can solve the dual purpose of glycemic control and risk management are needed.[3]

Various factors must be considered when first-line therapy is personalized in individuals with type 2 diabetes mellitus (T2DM). Some of these factors are age, weight, pregnancy, renal or hepatic dysfunction, ease of use, polypharmacy, occupation, costs and side effects.

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Tolerability and side effects play an important role in noncompliance and therapy failure in individuals with T2DM. Besides, treatment for T2DM is a progressive therapy which frequently requires insulin replacement therapy. Obesity seen in most type 2 diabetes patients is associated with insulin resistance and it is important to target it in diabetes management.[4]

In this article, we have reviewed and integrated clinical trial data and the management approach of T2DM to demonstrate the place of SGLT2 inhibitors, particularly dapagliflozin, in the therapy of diabetes.

SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS

The current guidelines recommend metformin as the preferred initial pharmacological therapy for T2DM. However, for patients who do not tolerate metformin, SGLT2 inhibitors may be given as monotherapy. Additionally, patients who do not achieve adequate glycemic targets may require addition of a second oral hypoglycemic agent for achieving better glycemic control. SGLT2 inhibitors are a novel class of drugs approved for the management of T2DM, with a unique mechanism of action which is also insulin independent.[5] They can also be used to reduce the risk of cardiovascular (CV) and renal disease progression.

SGLT2 inhibitors have a glucose-lowering effect through a specific renal action. They lower the threshold for renal glucose reabsorption by competitively inhibiting the SGLT2-mediated glucose reabsorption, which in persons with diabetes, is observed to get enhanced as a maladaptive response. By removing glucose, SGLT2 inhibitors facilitate weight loss (caloric loss), and a related mild osmotic diuresis due to sodium co-excretion, which leads to volume depletion and therefore reduction in blood pressure.[2]

It has been seen that in persistent hyperglycemic conditions like diabetes, the renal threshold for renal reabsorption increases because of the upregulated SGLT2 inhibitors and thereby its enhanced activity, bringing about increased reabsorption of both glucose and salt, worsening hyperglycemia. SGLT2 inhibitors have demonstrated effectiveness in lowering glucose levels and also safety in preventing hypoglycemia as their glucose-lowering effect is dependent on ambient glycemia.[3]

Currently, there are seven identified SGLT2 inhibitors, including canagliflozin, dapagliflozin, empagliflozin, ipragliflozin, luseogliflozin, tofogliflozin and remogliflozin.[6] Out of the seven identified SGLT2 inhibitors, empagliflozin has the greatest selectivity for SGLT2 receptor compared to SGLT1, while canagliflozin is the least selective. Empagliflozin and dapagliflozin have shown efficacy in lowering combined risk of CV death or hospitalization for heart failure and favorable influence on renal functions in patients with diabetes.[7,8]

Dapagliflozin

Dapagliflozin is a selective inhibitor of SGLT2 and improves glycemic control.[9] It is rapidly absorbed following oral administration and reaches peak plasma concentration in 2 hours. Dapagliflozin exhibits oral bioavailability of 78% and gets metabolized by the uridine diphosphate-glucuronosyltransferase enzyme in liver and kidneys. Studies have shown that dapagliflozin is extensively metabolized, with 73.7% recovered in excretions (72.0% in urine and 1.65% in feces). The predominant metabolite in humans is dapagliflozin 3-O-glucuronide, that accounts for 60.7% of the dose being completely recovered in urine. The metabolite is formed in both kidney and the liver. It is suggested that both the liver and the kidney are involved in the metabolic clearance of dapagliflozin.[10]

Dapagliflozin has proven efficacy in managing uncontrolled T2DM. It is known to improve glycemic control and stabilize insulin dosing, with additional property of weight reduction and without any increment in hypoglycemic episodes in people with T2DM.[9,11] Studies have also demonstrated the long-term benefits of dapagliflozin when used with insulin.[11]

While SGLT2 inhibitors are widely accepted as second-line agents after metformin in the management of T2DM, there have been some inconsistent findings about their association with urinary tract infection (UTI) and genital mycotic infections. This also prompted Food and Drug Administration (FDA) to issue a warning in 2015 regarding the link between SGLT2 inhibitors and UTIs. However, most recent systemic review and meta-analytical data does not report any link between SGLT2 inhibitors and UTIs. The results from a real-world study in 2019 have shown that there is no associated increased risk of UTI, while there may be an associated increased risk of genital mycotic infections within 30 days in older women and men.[12]

In pediatric patients with T2DM, there are limited treatment options. It has been proven clinically that a single oral dose of dapagliflozin shows similar results in adults and pediatric patients.[13] However, its use is not approved in this patient population.

Place of dapagliflozin in T2DM management

Dapagliflozin is the first novel SGLT2 inhibitor with proven efficacy in improving glycemic parameters when used alone or in combination with metformin or other oral hypoglycemic agents.[6] It is also a reliable option as add on with insulin therapy in suboptimally controlled T2DM.[14] It effectively reduces glycemic levels and body weight in treatment-naïve patients including early type 2 diabetes patients.[15,16]

As monotherapy

Clinical studies in Asian population have evidenced the efficacy of dapagliflozin in controlling hyperglycemia in patients with T2DM who have experienced metformin failure. Dapagliflozin was proven to be efficacious and well-tolerated in these patients.[17,18] In a real-world, prospective study in Indian patients (n = 1,941), dapagliflozin significantly reduced glycated hemoglobin (HbA1c) and body weight in T2DM patients. It was well-tolerated, and no safety signals were detected in Indian population.[19]

Combination therapy of dapagliflozin with other agents

As dual therapy

Dapagliflozin has been studied with various oral hypoglycemic agents including metformin,[20] glimepiride,[21] pioglitazone,[22] sitagliptin[23] and exenatide.[24-26] The highest reduction in HbA1c was observed with metformin, while the weight benefit is greater when used with sulfonylureas. So far, no studies of dual therapy of dapagliflozin with GLP-1 analog therapy have been conducted.[4]

As triple therapy

Dapagliflozin has been used with metformin and sitagliptin, metformin and saxagliptin, and metformin and a sulfonylurea in triple combinations. In these studies, improved glycemic reduction and body weight reductions have been seen.[4]

Combination therapy showed benefits in patients with type 2 diabetes who could not be managed with metformin alone. In studies where saxagliptin and dapagliflozin have been added to background metformin therapy, an improved glycemic control without any significant occurrence of hypoglycemia was seen. Triple therapy with dapagliflozin, saxagliptin and metformin was effective over long-term and was well-tolerated.[27-31] When compared against glimepiride and metformin, the triple therapy showed comparable efficacy in glycemic control but reduced body weight and systolic blood pressure with reduced occurrence of hypoglycemic incidence.[32,33]

It has been observed that early intensification to triple therapy with dapagliflozin and saxagliptin led to better, more durable glycemic management compared with addition of sitagliptin only (dual therapy) in patients with high HbA1c level not managed with metformin monotherapy.[34] Many studies have been conducted to assess the benefits of triple therapy with metformin, saxagliptin and dapagliflozin and all showed better glucose-lowering compared to dual therapy when either agent was added to metformin background therapy in patients with uncontrolled type 2 diabetes.[35] Several other studies have demonstrated benefits of the triple therapy in glycemic control, decreasing HbA1c and lower risk of hypoglycemia, and clinically relevant body weight difference. These results were similar in insulin naïve patients and in those on insulin therapy.[36-38]

Table 1 shows the effect of dapagliflozin in combination with other oral hypoglycemic agents.

Table 1. Effect of Dapagliflozin Combined with Other Oral Hypoglycemic Agents in Individuals with T2DM

Dapagliflozin in combination with	Effect on glycemic control	HbA1c	Weight reduction	Hypoglycemia	Other effects	Tolerability
Dual combination						
Metformin[20]	Decrease glycemic levels in poorly managed patients	-	-	-	-	Well-tolerated
Pioglitazone[22]	-	Further lowering of HbA1c	Alleviated side effects of weight gain	Rare occurrence of hypoglycemia	Reduced edema, Rare occurrence of CHF and fracture	Well-tolerated
Glimepiride[21]	-	Significant reduction in HbA1c	Reduced weight	-	-	Well-tolerated

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Dapagliflozin in combination with	Effect on glycemic control	HbA1c	Weight reduction	Hypoglycemia	Other effects	Tolerability
Dual combination						
Sitagliptin[23]	-	Reduction in HbA1c	Reduced weight	-	Additional clinical benefit	Well-tolerated
Exenatide[24-26]	Improved glycemic parameter		Weight reduction		Improved CV safety profile Reduction in systolic blood pressure	Well-tolerated
Triple combination						
Saxagliptin + Metformin[27,28,30-34]	Improved glycemic control	Significant reduction	Reduced body weight	Rare occurrence of hypoglycemia	Reduced systolic blood pressure	Well-tolerated
Metformin + Sulfonylurea[39]	Sustained glycemic control	HbA1c reduced	Reduced body weight	-	Reduction in systolic blood pressure	Well-tolerated

In combination with insulin

With insulin, dapagliflozin increases insulin-mediated tissue glucose disposal and causes an endogenous glucose production.[6] Studies have shown that dapagliflozin can improve the sensitivity to insulin, thereby improving glycemic management.[40] It is also known that individuals with T2DM may not have adequately controlled blood glucose, thus requiring increase in insulin dose. Increased insulin dosage may result in troubling or dangerous side effects. In such patients, dapagliflozin given along with insulin inhibits the renal absorption of glucose and thus improves glycemic control. In fact, the use of dapagliflozin, in patients who are on insulin therapy, helps in stabilizing insulin to be given in lower dose thus alleviating the side effects due to high insulin dose.[9,41] The DAISY (Dapagliflozin Added to patients under InSulin therapY) trial has further strengthened the evidence suggesting that adding dapagliflozin to insulin has several clinical benefits, and is well-tolerated in patients with T2DM.[42] Long-term studies (3-4 years) have demonstrated a positive long-term benefit in glycemic control and reductions in body weight and systolic blood pressure with general well-tolerance.[43,44]

Pleiotropic Benefits of Dapagliflozin: Benefits Beyond Glucose Control

Weight reduction

Compared to metformin, dapagliflozin has a significant effect in reducing weight, either as monotherapy or given in combination.[39] When used in combination with metformin, dapagliflozin has a better positive and synergistic effect on body weight, waist circumference, glycemic, CV and metabolic parameters versus exclusive metformin therapy in overweight or obese at-risk women population with a recent history of gestational diabetes mellitus.[45] Studies have clearly suggested that a combination therapy of dapagliflozin and saxagliptin had a favorable metabolic profile and can reduce liver fat and adipose tissue.[46] These results make dapagliflozin a good choice in patients with high body mass index (BMI) or those who are obese or overweight.

Lipid-lowering

A study has shown that there is a modest but statistically significant increase in both high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol with no effect on triglycerides or the LDL/HDL ratio.[47] Dapagliflozin is also known to suppress potent atherogenic small dense LDL cholesterol (sdLDL-C) and increase HDL_2-C, a favorable cardiometabolic marker.[48]

Lowering of blood pressure

Dapagliflozin has a beneficial effect of lowering systolic blood pressure. It acts synergistically with drugs like β-blockers and calcium channel blockers to effectively lower blood pressure.[49] Studies have demonstrated dapagliflozin to be an important adjunct to insulin in managing hyperglycemia, reducing weight and blood pressure in Asian population.[50]

Benefits in CVD

Dapagliflozin is effective when added to usual regimen in patients with T2DM and pre-existing cardiovascular disease (CVD), a history of hypertension or chronic kidney disease (CKD). It significantly improved HbA1c

reduction, reduced systolic blood pressure, body weight without adversely affecting CV safety. Similar results were observed in elderly patients also.[51,52] The CVD-REAL 2 study conducted in patients from the Asia Pacific, the Middle East, and the North America, favored SGLT2 inhibitors over other glucose-lowering drugs for lower risk of death, hospitalization for heart failure, myocardial infarction and stroke.[53] These results suggested that the results of CVD-REAL 2 study can be juxtaposed in the high CVD risk Indian population who require more aggressive treatment for diabetes than other patient groups.

Benefits in heart failure

DECLARE-TIMI 58 trial showed that dapagliflozin lowered the incidence of CV death or hospitalization for heart failure in high-risk atherosclerotic cardiovascular disease (ASCVD). The results were equally pronounced irrespective of the patient's age and clear-cut benefits were shown in elderly patients as well.[54,55] In DECLARE-TIMI 58 study, dapagliflozin also reduced the risk of major CV events in patients with prior myocardial infarction.[56] The DIVERSITY-CVR study has highlighted dapagliflozin to be a better choice compared to DPP-4 inhibitors (sitagliptin) in alleviating cardiometabolic risk factors in patients with early-stage but insufficiently controlled T2DM.[57]

Currently, DAPA-MI trial is underway to assess the effect of dapagliflozin when given in addition to standard of care therapies for patients with myocardial infarction to prevent hospitalization for heart failure or CV death.[58] DAPA-AF trial is also ongoing to estimate the effectiveness of dapagliflozin in reducing the burden of atrial fibrillation (AF) in patients undergoing catheter ablation of symptomatic AF.[59]

Benefits in chronic kidney disease

Various landmark trials have enumerated the benefits of personalizing dapagliflozin in treatment of patients with diabetic kidney disease, CVD or at-risk of CVD or CKD. The results of DERIVE study evidenced the positive benefit of dapagliflozin in treating T2DM patients with concomitant CKD.[60]

The more recent DAPA-HF and DAPA-CKD trials have been much talked about in terms of dapagliflozin's benefit in T2DM patients with underlying CVD or CKD or those at high-risk. DAPA-HF trial has demonstrated that dapagliflozin consistently reduced the risk of death and worsening heart failure and improved symptoms in patients of all age groups.[61,62] The results were irrespective of whether the patients were given sacubitril/valsartan/mineralocorticoid receptor antagonist or not, but when used together, the combination further reduced the morbidity and mortality in patients with heart failure with reduced ejection fraction (HFrEF).[63,64] DAPA-HF trial has also shown that dapagliflozin reduced the risk of worsening heart failure and death, improved results with similar efficacy, safety and tolerability in ischemic and nonischemic patients.[65] DAPA-CKD trial has shown that dapagliflozin reduced the risk of sustained decline in the estimated glomerular filtration rate (eGFR) of at least 50%,[66] reduced the risk of main adverse kidney and CV events and all-cause mortality, end in patients with diabetic and nondiabetic kidney disease.[67]

Sleep apnea

Dapagliflozin has significant effect in reducing apnea-hypopnea index, and improved hypoxemia during sleep and excessive daytime sleepiness. Clinical studies have proven its benefits in T2DM patients with obstructive sleep apnea hypopnea syndrome.[68]

Liver disease

Dapagliflozin has significant benefits on liver diseases. Studies have shown that it improves liver steatosis in patients with T2DM and nonalcoholic fatty liver disease (NAFLD), and attenuates liver fibrosis, particularly in patients with significant liver fibrosis.[69,70]

Table 2 enumerates indications for dapagliflozin use in individuals with type 2 diabetes.

Table 2. Indications for Dapagliflozin use in Individuals with Type 2 Diabetes

Glycemic control	Extraglycemic benefits	Safety and tolerability
As monotherapy if metformin is contraindicated or not tolerated	To reduce risk of ASCVD in persons with established/ high-risk factors for ASCVD	To minimize risk of hypoglycemia
Dual therapy if monotherapy is not sufficient	To reduce risk of hospitalization for heart failure	To minimize risk of weight gain/promote weight loss
Triple therapy if dual therapy is insufficicent	To reduce rate of progression of CKD	To minimize risk of drug-drug interactions
With insulin, to reduce the dose of insulin		

TYPE 2 DIABETES MANAGEMENT GUIDELINES AND DAPAGLIFLOZIN

Research Society for the Study of Diabetes in India (RSSDI) Guidelines on the Pharmacotherapy of Type 2 Diabetes

SGLT2 inhibitors, such as dapagliflozin, are advised to be used in individuals where metformin is contraindicated or not tolerated. Dual therapy is recommended to be prescribed initially if it is thought that initial monotherapy may not achieve required glycemic targets.[71]

Dual therapy with metformin and SGLT2 inhibitors (dapagliflozin) is recommended if monotherapy fails. If dual therapy fails, triple therapy with dapagliflozin may be initiated. Dapagliflozin is favored as the second-line agent of choice in T2DM patients with a history of CVD.[71]

ADA Guidelines on the Pharmacotherapy of Type 2 Diabetes

American Diabetes Association (ADA) guidelines on type 2 diabetes pharmacotherapy recommendations are:[72]

- *Other medications including SGLT2 inhibitors, with or without metformin based on glycemic requirements are appropriate initial therapy for individuals with T2DM with or at high risk for ASCVD, heart failure and/or CKD.*
- *Among individuals with T2DM who have established ASCVD or indicators of high CV risk, established CKD or heart failure, and SGLT2-inhibitor and/or GLP-1 receptor agonist with demonstrated CVD benefit is recommended as part of the glucose-lowering regimen and comprehensive CV risk reduction, independent of A1c and in consideration of patient-specific factors.*
- *In patients with T2DM and established ASCVD, multiple ASCVD risk factors or diabetic kidney disease, and SGLT2-inhibitor with demonstrated CV benefit is recommended to reduce the risk of major adverse cardiovascular events (MACE) and/or heart failure hospitalization.*
- *In patients with type 2 diabetes and established ASCVD or multiple risk factors for ASCVD, combined therapy with an SGLT2 inhibitors with demonstrated CV benefit and a GLP-1 receptor agonist with demonstrated CV benefit may be considered for additive reduction in the risk of adverse CV and kidney events.*
- *In patients with T2DM and established HFrEF, SGLT2 inhibitor with proven benefit in this patient population is recommended to reduce risk of worsening heart failure and CV death.*
- *SGLT2 inhibitors should be given to all patients with stage 3 CKD or higher and type 2 diabetes, irrespective of glycemic control.*
- *In patients with T2DM and diabetic kidney disease, use of an SGLT2 inhibitor in patients with an eGFR ≥25 mL/min/1.73 m^2 and urinary albumin ≥300 mg/g creatinine is recommended to reduce CKD progression and CV events.*
- *In patients with CKD who are at increased risk for CV events or CKD progression or are unable to use an SGLT2 inhibitor, a nonsteroidal mineralocorticoid receptor antagonist (MRA) is recommended to reduce CKD progression and CV events.*

DAPAGLIFLOZIN IN TYPE 1 DIABETES MELLITUS

When compared with patients with T2DM, diabetic ketoacidosis is relatively frequent in patients with type 1 diabetes mellitus (T1DM) who are unable to produce sufficient insulin. In the DEPICT-1 and DEPICT-2 studies, frequent events of diabetic ketoacidosis were reported with dapagliflozin. The factors attributing to the increased frequency were missed insulin doses or failure of insulin pump. Though dapagliflozin safety and tolerability has been proven in T1DM with insulin, it is still important to judiciously select patients, given the risk of the occurrence diabetic ketoacidosis events.[73] Hence, it is not recommended for T1DM patients, however, in advanced conditions, it may be considered as beneficial, based upon the supportive evidence.

CONCLUSION

In T2DM patients, dapagliflozin can be effectively given as monotherapy, and in those who are already on metformin therapy but do not have adequate blood glucose control, dapagliflozin can be given safely as an adjunct to metformin therapy. In patients requiring aggressive therapy to manage blood glucose levels, dapagliflozin is a crucial component of combination therapy with other oral hypoglycemic agents (both two drug combinations and three drug combinations) and even insulin, as it reduces the chances of hypoglycemic events and lowers body weight. Dapagliflozin has a significant benefit in optimizing insulin doses to a lower value so that the side effects due to high insulin dose can be avoided. Based upon the evidence, dapagliflozin may be a worthwhile consideration for prescription even in T1DM cases in near future. It has various pleiotropic benefits including lowering of weight, small dense lipids, and systolic blood pressure, benefitting

patients with CVD and CKD. In conclusion, review of all the studies indicates that dapagliflozin is safe, effective, well-tolerated in all patient subgroups and offers multiple benefits making it particularly useful in elderly diabetics, obese diabetics, pregnant women with a recent history of gestational diabetes, lean patients with uncontrolled blood glucose, CVD or CKD comorbid patients or those at high risk of CVD or CKD.

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