International Journal of Endocrinology Sciences

ISSN Print: 2664-9284
ISSN Online: 2664-9292
IJES 2024; 6(1): 20-26
www.endocrinologyjournal.net
Received: 02-04-2024
Accepted: 01-05-2024

Manjula S
Sr. Vice President, Department of Medical Services, Micro Labs Limited, Bangalore, Karnataka, India

Krishna Kumar M
Sr. General Manager, Department of Medical Services, Micro Labs Limited, Bangalore, Karnataka, India

Corresponding Author:
Manjula S
Sr. Vice President, Department of Medical Services, Micro Labs Limited, Bangalore, Karnataka, India

Expert opinion on the use of SGLT2 inhibitors and its combination with a special focus on dapagliflozin in the management of type 2 diabetes in Indian settings

Manjula S and Krishna Kumar M

DOI: https://doi.org/10.33545/26649284.2024.v6.i1a.10

Abstract
Objective: The current survey-based study aims to gather expert opinion regarding the prescription practice of sodium-glucose cotransporter-2 inhibitors (SGLT2i) and its combination with a special focus on dapagliflozin treatment for managing uncontrolled type 2 diabetes mellitus (T2DM) in Indian settings.
Methodology: The cross-sectional survey utilized a 24-item, multiple-response questionnaire to gather expert opinions from specialists with expertise in managing diabetes. The survey encompassed questions about current prescription practices, clinical observations, preferences, and experiences related to the use of SGLT2i and combination in routine settings for diabetes management.
Result: According to 57% of clinicians, 26-40% of patients needed SGLT2 inhibitors as a monthly add-on to meet their glycemic target. Majority (92.37%) of the clinicians reported dapagliflozin as the commonly prescribed SGLT2i. Nearly 61% of the clinicians reported a reduction in HbA1c by 1 to 1.5% with SGLT2i treatment after three months. More than half (68.32%) of the clinicians reported prescribing a combination of SGLT2i + dipeptidyl peptidase 4 inhibitor (DPP4i) to patients with uncontrolled T2DM, and patients with cardiovascular (CV) and renal comorbidities. According to 52% of the clinicians, 21 to 30% of the patients required a combination of SGLT2i + DPP4i. Half (50%) of the clinicians reported that they preferred SGLT2i + DPP4 inhibitor in T2DM patients with CV comorbidities. About 46% of the clinicians opined empagliflozin + linagliptin as the preferred SGLT2i + DPP4i combination in T2DM patients with renal comorbidities.
Conclusion: The survey highlighted the widespread use of SGLT2 inhibitors, particularly dapagliflozin, and their efficacy in reducing HbA1c levels. Combination therapy with SGLT2 inhibitors and DPP4i is favored for uncontrolled T2DM, CV, and renal comorbidities.

Keywords: Dapagliflozin, type 2 diabetes mellitus, sodium-glucose cotransporter-2 inhibitors, dipeptidyl peptidase 4 inhibitors

Introduction
Managing type 2 diabetes mellitus (T2DM) presents persistent challenges due to its chronic nature and the intricate complexities involved in treatment and care. The global incidence of T2DM is estimated to reach 7079 cases per 100,000 individuals, reflecting a continuous upward trend across all regions [1]. Asia has 60% of global diabetes cases, with a substantial disease burden noted in China (139.9 million) and India (65 million). South Asians, particularly the Indian population, possess elevated T2DM risk compared to ethnic Europeans [2]. According to the latest edition of the International Diabetes Federation Diabetes Atlas, diabetes prevalence stood at 10.5%, 8.8%, and 9.6% globally, in Southeast Asia, and India respectively in 2021. By 2045, these figures are projected to rise to 12.5%, 11.5%, and 10.9% respectively [3]. In India, more than half of T2DM patients fail to achieve the recommended glycemic control target which is referred to as glycated hemoglobin (HbA1c) 7%, as per the American Diabetes Association while the American College of Endocrinologists set it at 6.5% [4]. Due to the progressive nature of T2DM, treatment adjustments are often necessary to sustain glycemic control. The association of various existing medications with adverse effects such as hypoglycemia and weight gain underscore the urgent need for innovative therapeutics that offer improved risk/benefit profiles [5].
Sodium-glucose cotransporter-2 inhibitors (SGLT2i), the newest FDA-approved class of anti-hyperglycemic agents, act by decreasing renal tubular glucose reabsorption, thereby

lowering blood glucose levels without triggering insulin release. Additionally, they offer favorable effects on blood pressure and weight [6]. These inhibitors are suggested as additional oral antidiabetic medications (OADs) for individuals diagnosed with T2DM who concurrently experience heart failure, atherosclerotic cardiovascular (CV) conditions, or chronic kidney disease [7]. Studies have shown that SGLT2i not only decreases the risk of hypoglycemia but also positively impacts body weight, blood pressure, dyslipidemia, and fatty liver disease. Promising findings regarding the CV and renal safety of these drugs have emerged from several clinical investigations [8, 9].

The FDA has approved three SGLT2 selective inhibitors-dapagliflozin, canagliflozin, and empagliflozin - for mono, dual, and triple therapy. However, it is observed that canagliflozin and sotagliflozin exhibit weak selectivity for SGLT2i [6, 10]. GLT2i are favored due to their minimal risk of hypoglycemia, especially when combined with other glucose-lowering agents. Combining SGLT2i with DPP-4i is particularly advantageous. DPP4i, known for its rare adverse effects like weight gain and hypoglycemia, complements SGLT2i well [11]. SGLT2i acts by increasing urinary glucose excretion independently of insulin, while DPP-4i improves glucose homeostasis by enhancing insulin secretion and reducing glucagon secretion in a glucose-dependent manner. This combination presents an effective and safe treatment for hyperglycemia in patients with sub-optimally controlled T2DM, leveraging the complementary mechanisms of action of both drugs [12].

Dapagliflozin, a commonly prescribed SGLT2i, improves blood glucose control by reducing both fasting and post-meal glucose levels. It is a valuable medication that can be used either alone in patients unable to tolerate metformin or in combination with other antidiabetic drugs. By inhibiting SGLT2, dapagliflozin decreases hyperglycemia, increases glucose excretion in the urine, and induces mild diuresis [13, 14]. It is effective as a standalone treatment and as an additional treatment for patients experiencing inadequate glycemic control [15]. According to a survey-based study, 98% of physicians agree that dapagliflozin is cost-effective, and has ideal characteristics of an ideal SGLT2i. They highlight its metabolic advantages, cardio protective properties, and nephron protection [16]. In another survey study, the clinical benefits of dapagliflozin and its fixed-dose combinations in patients with T2DM and CV or renal risks are highlighted. Early initiation and aggressive intensification with dapagliflozin fixed-dose combinations (FDCs) in T2DM patients are strongly recommended [17].

The present survey was intended to gather clinicians' perspectives regarding the prescription practice of the SGLT2i and its combination with a special focus on dapagliflozin for T2DM treatment in Indian settings.

Methodology

A cross sectional, multiple-response questionnaire based survey among physicians specialized in managing T2DM in the major Indian cities from June 2023 to December 2023.

Questionnaire

The questionnaire booklet titled CROWN-3 (Clinical Experience of Indian Clinicians on T2DM Management and Role of dapagliflozin with linagliptin) study was sent to the doctors who were interested to participate. The CROWN-3 study comprised 24 questions focused on current feedback, clinical observations, and experiences of specialists in managing diabetes with SGLT2i and its combinations. The study was performed after obtaining approval from Bangalore Ethics, an Independent Ethics Committee which was recognized by the Indian Regulatory Authority, Drug Controller General of India.

Participants

An invitation was sent to professionals across India based on their expertise and experience in treating T2DM in the month of March 2023 for participation in this Indian survey. About 262 clinicians from major cities of all Indian states representing the geographical distribution shared their willingness to participate and provide necessary data. Clinicians had the option to skip any questions they did not wish to answer and were instructed to complete the survey independently without consulting their colleagues. Written informed consent was obtained from all participants before the initiation of the study.

Statistical analysis

The data were analyzed using descriptive statistics. Categorical variables were presented as percentages to provide clear insight into their distribution. The frequency of occurrence and the corresponding percentage were used to represent the distribution of each variable. Graphs were created to visualize the distribution of the categorical variables, utilizing Microsoft Excel 2013 (version 16.0.13901.20400).

Results

The survey included 262 clinicians, with 51% of them reporting that 26 to 50% of the diabetic patients have other comorbidities. About 53% of the clinicians opined that 20 to 40% of the patients require two or more additional drugs along with metformin. Nearly 45% of the clinicians reported that 25 to 50% of the patients are aware of diabetes as a medical condition and its consequences. As reported by 42% of the clinicians, with the recent advancements in oral OADs like DPP4i and SGLT2i, insulin usage has been reduced by 25 to 50%. Nearly 45% of the respondents reported that 21to 30% of the patients have comorbid hypertension.

Table 1: Distribution of responses on the proportion of patients requiring addition of SGLT2i for achieving glycemic targets

Percentage of patients	Response rate (n=262)
<10%	4.96%
11-25%	25.95%
26-40%	57.25%
41-50%	11.83%

According to 57% of clinicians, 26% to 40% of patients need SGLT2i as an add-on on a monthly basis to meet their glycemic target (Table 1). Majority (92.37%) of the clinicians reported dapagliflozin as the commonly prescribed SGLT2i (Table 2).

Table 2: Distribution of responses on the commonly prescribed SGLT2i

SGLT2i	Response rate (n=262)
Dapagliflozin	92.37%
Empagliflozin	5.73%
Canagliflozin	1.15%
Remogliflozin	0.76%

More than half (55.34%) of the respondents preferred dapagliflozin as an add-on to DPP4i. According to 53% of the respondents, CV complications are the most commonly reported in uncontrolled T2DM patients.

According to 89% of clinicians, the prescription of SGLT2i is preferred due to the achievement of glycemic targets and pleiotropic benefits. Nearly 61% of clinicians reported observing a reduction in HbA1c by 1 to 1.5% after three months of treatment with SGLT2i (Fig. 1). As reported by 71% of clinicians, systolic blood pressure is reduced by 5 to 10 mm Hg with the use of dapagliflozin 10 mg.

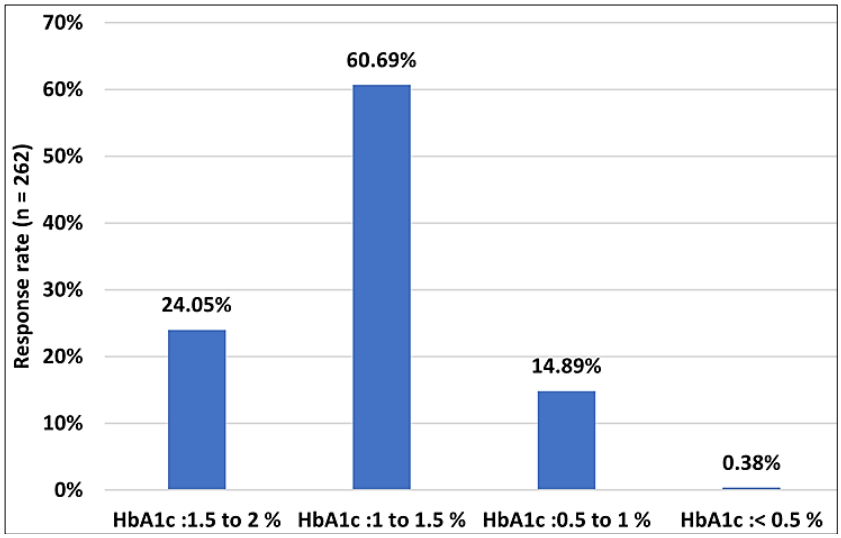

Fig 1: Distribution of response on the HbA1c reduction that you observed with SGLT2i after 3 months of treatment

Table 3: Distribution of response on the patient profiles for prescribing combination of SGLT2i + DPP4i

Patients profile	Response rate (n=262)
Patients with uncontrolled T2DM	18.7%
Patients with CV comorbidities	7.63%
Patients with renal comorbidities	5.34%
All the above	68.32%

About 40% of clinicians responded that the main pleiotropic benefits of SGLT2i offers to patients beyond glycemic control are the reduced rate of CV death and hospitalization for heart failure. More than half (68.32%) of clinicians reported prescribing a combination of SGLT2i + DPP4i in patients with uncontrolled T2DM, as well as in patients with CV and renal comorbidities (Table 3). As reported by 52% of clinicians, 21 to 30% of patients require a combination of SGLT2i+ DPP4i (Fig. 2).

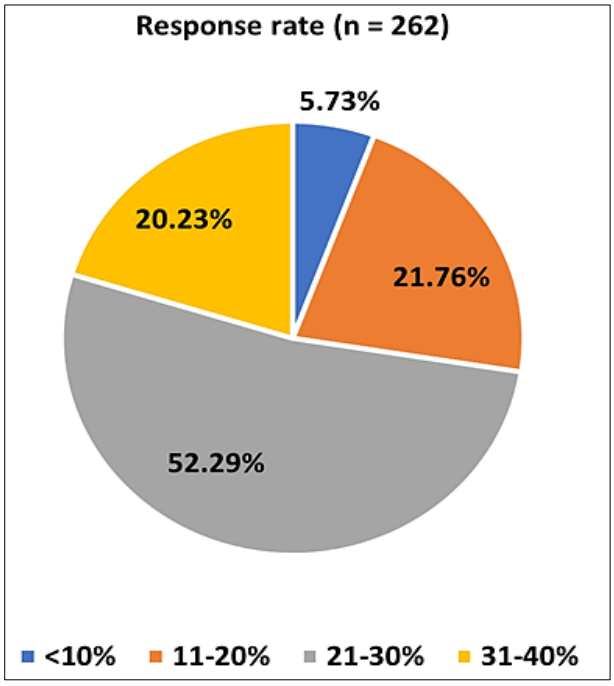

Fig. 2 Distribution of response on the initiation of combination treatment with SGLT2i + DPP4i based on entry HBa1c levels

According to 55% of the respondents, initiating the treatment with a combination of SGLT2i + DPP4i is preferred at an HbA1c level >8%. Half (50%) of the clinicians reported that they prefer SGLT2i + DPP4i the most among T2DM patients with CV comorbidities (Fig. 3). About 46% of the clinicians opined that the most preferred combination of SGLT2i + DPP4i in T2DM patients with renal comorbidities is empagliflozin + linagliptin (Fig. 4).

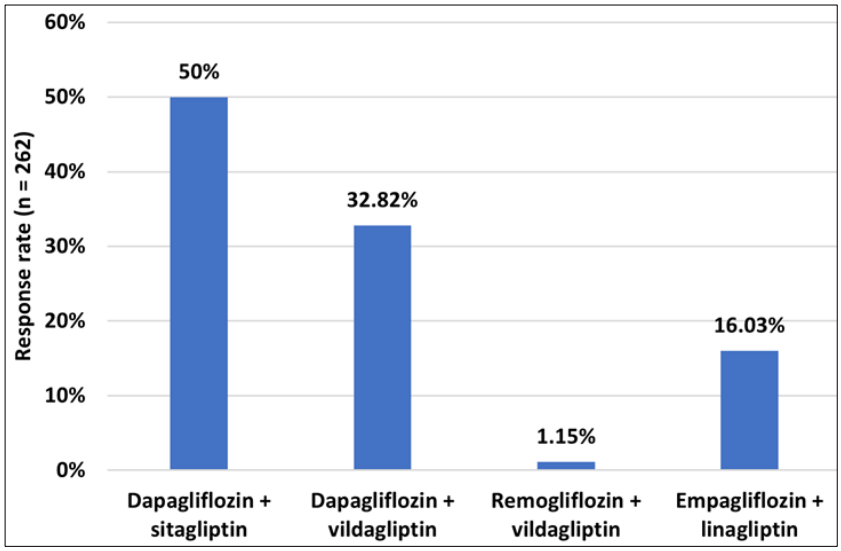

Fig 3: Distribution of responses on the preference of different combinations of SGLT2i +DPP4i in T2DM patients with CV co-morbidities

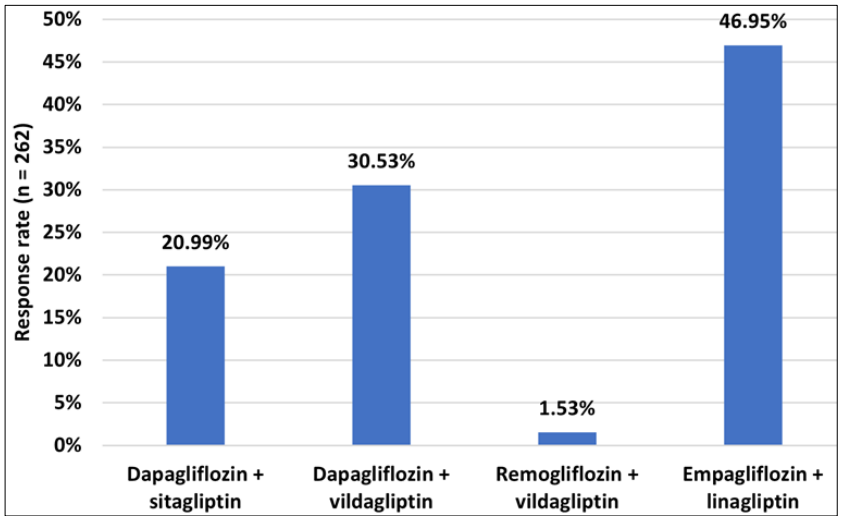

Fig 4: Distribution of responses on the preference of different combinations of SGLT2i +DPP4i in T2DM patients with renal comorbidities

Around 32% of clinicians reported using linagliptin for almost 2 to 3 years. According to 58% of clinicians, about 11 to 20% of diabetes mellitus patients are on linagliptin. Nearly 60% of clinicians opined that a definite improvement in estimated glomerular filtration rate (eGFR) was observed with linagliptin. According to 67% of clinicians, the most common reason for initiating combination therapy is the ease of achieving glycemic goals. Approximately 69% of clinicians preferred prescribing the combination of dapagliflozin + linagliptin fixed-dose combination for elderly diabetic patients as well as diabetics with obesity, cardiac, and renal complications. Nearly 31% reported better glycemic control as the key advantage of the fixed-dose combination, while 29% reported that the combination complements each other as the key advantage.

Discussion

The present study has emphasized the significant preference for SGLT2i and their combination with DPP4i in treating patients with T2DM. Effective management of glycemia plays a crucial role in averting diabetes-related complications, and SGLT2i significantly reduces HbA1c levels by enhancing renal glucose excretion. Dapagliflozin, as a widely utilized SGLT2i, is approved as monotherapy (in cases of metformin intolerance) and as an adjunct to combination therapy (alongside other antidiabetic agents, including insulin) for glycemic control in T2DM.[14]

The present survey has underscored the necessity for patients to include SGLT2i monthly in their treatment regimen to achieve their glycemic goals. Various studies have shown that SGLT2i can reduce HbA1c levels by 0.6 to 1.2% points when used alone, by 0.5 to 0.9% points when added to metformin therapy, and by 0.4 to 0.6 % points when added to insulin or other oral anti hyperglycemic agents, effectively reaching the patient's glycemic target.[18-20] DeFronzo *et al*. also indicated that SGLT2i improves glycemic control in diabetic patients and also helps in increasing glucose resorption by 30%.[21]

Current survey respondents reported dapagliflozin as the most frequently prescribed SGLT2i. This observation aligns

with findings from Fioretto *et al*., which reported that dapagliflozin is a highly selective and reversible inhibitor of SGLT2. It is approved for treating adult patients with T2DM either as monotherapy in patients' intolerance to metformin or as an adjunct to existing antidiabetic medications, including insulin, in patients with inadequate control [22]. Nicholson *et al*. indicated that dapagliflozin is the preferred SGLT2i for T2DM patients both as monotherapy and combination therapy for reducing glycemic levels.[23] Mehta *et al*. asserted within the SGLT2i class, dapagliflozin (91%) is the preferred option. Additionally, most participants favored dapagliflozin in both fixed-dose combinations and as an adjunct to DPP4i [17].

Among those diagnosed with T2DM, there is a notable inclination towards developing additional health conditions. CV problems emerge as a prominent factor contributing to both mortality and morbidity in patients with T2DM. Einarson *et al*. in a comprehensive systematic review involving a substantial cohort of 4.5 million individuals with T2DM, aimed to determine the prevalence of CV complications. Their findings highlighted the widespread occurrence of CV problems among patients with T2DM, with an estimated overall prevalence of 32%. Similarly, in the current study, the majority of clinicians identified CV complications as the most frequently reported issue in T2DM patients with poorly controlled blood sugar levels [24].

The current survey reported prescribing SGLT2i not only to achieve glycemic control but also to leverage their pleiotropic benefits. This is consistent with emerging evidence suggesting that SGLT2i offers CV and renal protective effects beyond their glucose-lowering capabilities. In a retrospective study, Shao et.al reported that SGLT2i resulted in better outcomes compared to other treatments. Patients using SGLT2i lost more weight, had lower blood pressure, and improved liver function. Additionally, they demonstrated a lesser decline in kidney function compared to those on other medications [25]. Klen *et al*. also reported similar results in their study regarding the pleiotropic protective effects of SGLT2i that extend beyond their glucose-lowering effects [26]. Kumar *et al*. found that SGLT2i not only improves glycemic control but also promotes weight loss, lowers blood pressure, and enhances lipid profiles, essential for metabolic health. Additionally, these inhibitors exhibit renal protective effects by reducing albuminuria and slowing the decline in eGFR, indicating a potential role in managing renal dysfunction [27].

Current respondents observed a reduction in HbA1c by 1 to 1.5% with SGLT2i treatment after three months. Mikhail et.al reported that all initial trials with SGLT2i were shown to be very effective in reducing glycated HbA1c, with an average reduction of HbA1c by 0.6-1.2 depending on the baseline level [28]. Sosale *et al*. demonstrated a decrease of 1.0% in mean HbA1c levels following 3 months of SGLT2i therapy [29]. Bashier *et al*. observed a significant decrease in HbA1c levels associated with the utilization of SGLT2i. Initially, the mean HbA1c was 8.9±1.7%, which decreased to 8±1.5% after 6 months (P = 0.0001) [30].

More than half (68.32%) of the current clinicians reported prescribing a combination of SGLT2i +DPP4i in patients with uncontrolled T2DM, patients with CV, and renal comorbidities. Min *et al*. concluded that SGLT2i and DPP4i combination therapy improves glycemic control and reduces body weight without increasing the risk of hypoglycemia and urinary tract infection (UTI) in patients with inadequately controlled T2DM [12]. Similarly, Chadha *et al*. demonstrated that the combination of DPP4i + SGLT2i effectively manages T2DM in Asian Indian patients, addressing multiple pathophysiological aspects without increasing hypoglycemia risk. It provides meaningful glycemic control, improves metabolic profiles, and is preferred for patients at higher CV and kidney disease risk. Overcoming clinical inertia and ensuring long-term adherence is essential for optimizing outcomes with this therapy [31]. Gupta *et al*. concluded that in T2DM patients with comorbidities, a combination of SGLT2i and DPP4i is safe, well-tolerated, and has been efficacy and cardio-renal safety [32].

Studies have shown that combining DPP4i and SGLT2i offered improved glycemic control in T2DM patients due to their complementary mechanisms. When adding an SGLT2i to existing DPP4i therapy, it enhances glucose control while minimizing adverse effects like hypoglycemia, weight gain, and heart failure risk. Conversely, when adding a DPP4i to ongoing SGLT2i therapy, it may decrease endogenous glucose production and enhance the glucose-lowering effect of SGLT2i. Hence, clinicians prefer this combination for uncontrolled T2DM patients to optimize treatment outcomes [33-35]. Similar preferences were also observed in the present survey.

Combining SGLT2i and DPP4i in T2DM patients with CV disease may offer synergistic benefits, including reduced hospitalization for heart failure, improved renal outcomes, and lowered risk of major adverse cardiac events (MACE) and CV death. Studies on SGLT2i have consistently shown these benefits, with some differences observed among individual agents like empagliflozin and canagliflozin. Additionally, the CREDENCE study has highlighted the significant improvement in renal outcomes with canagliflozin in advanced kidney disease. Combining these agents could provide a comprehensive approach to managing T2DM and its CV and renal complications [31, 36-38]. Similar results are also observed in the present study.

According to the current respondents, the preferred SGLT2i +DPP4i in T2DM patients with renal comorbidities is empagliflozin + linagliptin. In line with this finding, Hussain *et al*. found that both empagliflozin and dapagliflozin demonstrated excellent efficacy and safety profiles. These agents should be considered as add-on therapy in patients with T2DM taking conventional first line OADs [8]. Varshney *et al*. observed that by increasing the glucose excretion in the urine, dapagliflozin and empagliflozin enhance the glycemic control. Additionally, the diuretic actions of these medications lower blood pressure and body weight [32].

The present survey has highlighted the effectiveness of dapagliflozin + linagliptin FDC in elderly diabetic patients and those with obesity, cardiac, and renal complications. This combination offers superior glycemic control and mutually complements the mechanisms of action [40]. Shi *et al*. in their comparative analysis revealed that dapagliflozin at a dosage of 10 mg provided greater protection compared to empagliflozin and placebo. This superiority of dapagliflozin is attributed to the inclusion of a large number of patients with heart failure with preserved ejection fraction in empagliflozin studies, who often presented with multiple comorbidities such as obesity, hypertension, and atrial fibrillation [41].

The current survey offers valuable insights for clinicians aiming to optimize treatment strategies and patient care for T2DM. A significant strength lies in the utilization of a meticulously designed and validated questionnaire for data collection from clinicians. However, it is crucial to acknowledge certain limitations inherent in the survey methodology. The reliance on expert opinion may introduce bias, as varied perspectives and preferences among clinicians could potentially influence the reported results. Thus, it is imperative to exercise caution when interpreting these findings. It is important to note that the survey might not fully capture evolving trends or emerging evidence in diabetes management, particularly about the use of SGLT2i and its combination. It is essential to consider these limitations when interpreting the findings. Prospective trials or real-world observational studies are warranted to corroborate the survey results and provide a more comprehensive understanding of optimal treatment approaches.

Conclusion

The current survey corroborated the clinical use of SGLT2i, particularly dapagliflozin, in reducing HbA1c levels. The survey highlighted the benefits of combination therapy with SGLT2i and DPP4i for uncontrolled T2DM, CV, and renal comorbidities, showcasing their role in comprehensive diabetes management.

Acknowledgement

We would like to thank all the doctors who were participated in this study.

References

1. Khan MAB, Hashim MJ, King JK, Govender RD, Mustafa H, Al Kaabi J. Epidemiology of Type 2 Diabetes - Global Burden of Disease and Forecasted Trends. J Epidemiol Glob Health. 2020 Mar;10(1):107-11.
2. Yusufi FNK, Ahmed A, Ahmad J, Alexiou A, Ashraf GM, Yusufi ANK. Impact of Type 2 Diabetes Mellitus with a Focus on Asian Indians Living in India and Abroad: A Systematic Review. Endocr Metab Immune Disord Drug Targets. 2023;23(5):609-16.
3. Kumar A, Gangwar R, Zargar AA, Kumar R, Sharma A. Prevalence of Diabetes in India: A Review of IDF Diabetes Atlas 10th Edition. Curr Diabetes Rev. 2024;20(1): e130423215752.
4. Lloyd A, Sawyer W, Hopkinson P. Impact of long-term complications on quality of life in patients with type 2 diabetes not using insulin. Value Health. 2001;4(5):392-400.
5. Miller BR, Nguyen H, Hu CJH, Lin C, Nguyen QT. New and Emerging Drugs and Targets for Type 2 Diabetes: Reviewing the Evidence. Am Health Drug Benefits. 2014 Nov;7(8):452-63.
6. Hsia DS, Grove O, Cefalu WT. An Update on SGLT2 Inhibitors for the Treatment of Diabetes Mellitus. Current opinion in endocrinology, diabetes, and obesity. 2017 Feb;24(1):73.
7. Fatima Z, Atal S, Joshi R, Sadasivam B. Implications and Economic Impact of Applying International Guidelines and Recommendations to the Management of High-Risk Group of Type 2 Diabetes Mellitus Patients in India. Cureus. 2022;14(2):e22141.
8. Hussain M, Elahi A, Iqbal J, Bilal Ghafoor M, Rehman H, Akhtar S. Comparison of Efficacy and Safety Profile of Sodium-Glucose Cotransporter-2 Inhibitors as Add-On Therapy in Patients With Type 2 Diabetes. Cureus. 2021 Apr 3;13(4):e14268.
9. Pereira MJ, Eriksson JW. Emerging Role of SGLT-2 Inhibitors for the Treatment of Obesity. Drugs. 2019;79(3):219-30.
10. Chen JY, Pan HC, Shiao CC, Chuang MH, See CY, Yeh TH, *et al*. Impact of SGLT2 inhibitors on patient outcomes: a network meta-analysis. Cardiovascular Diabetology. 2023 Oct 27;22(1):290.
11. Ajmal M, Badruddeen, Ahmad M, Akhter M, Khushtar M, Akhtar J, *et al*. An Update On Fixed-Dose Combination Of Sglt-2 And Dpp-4 Inhibitors In The Management Of Type-2 Diabetes Section A-Research paper Eur. 2023 Aug 4;12:707-16.
12. Min SH, Yoon JH, Moon SJ, Hahn S, Cho YM. Combination of sodium-glucose cotransporter 2 inhibitor and dipeptidyl peptidase-4 inhibitor in type 2 diabetes: a systematic review with meta-analysis. Sci Rep. 2018 Mar 13;8(1):4466.
13. Filippatos TD, Liberopoulos EN, Elisaf MS. Dapagliflozin in patients with type 2 diabetes mellitus. Ther Adv Endocrinol Metab. 2015 Feb;6(1):29-41.
14. Dhillon S. Dapagliflozin: A Review in Type 2 Diabetes. Drugs. 2019;79(10):1135-46.
15. Yang L, Li H, Li H, Bui A, Chang M, Liu X, *et al*. Pharmacokinetic and Pharmacodynamic Properties of Single- and Multiple-Dose of Dapagliflozin, a Selective Inhibitor of SGLT2, in Healthy Chinese Subjects. Clinical Therapeutics. 2013 Aug 1;35(8):1211-1222.e2.
16. Sharma K, Chandorkar A, Kovil R, Venkataraman S, Subrahmanyam K, Mandal P, *et al*. Expert Opinion About the Pharmacoeconomic Edge of Low-Cost Dapagliflozin in Type 2 Diabetes Mellitus in Indian Clinical Settings. Cureus. 2021 Nov 1; 13(11):e19194.
17. Mehta A, Bafna A, Goel S, Trivedi AK, Mishra C, Naik P, *et al*. Diabetes treatment with dapagliflozin and its combinations: Insights from clinical practice. In: Endocrine Abstracts [Internet]. Bioscientifica; 2023 [cited 2024 Mar 18].
18. Stenlöf K, Cefalu WT, Kim KA, Alba M, Usiskin K, Tong C, *et al*. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. Diabetes Obes Metab. 2013 Apr;15(4):372-82.
19. Liang Y, Arakawa K, Ueta K, Matsushita Y, Kuriyama C, Martin T, *et al*. Effect of canagliflozin on renal threshold for glucose, glycemia, and body weight in normal and diabetic animal models. PLoS One. 2012;7(2):e30555.
20. Tsushima Y, Lansang MC, Makin V. The role of SGLT-2 inhibitors in managing type 2 diabetes. CCJM. 2021 Jan 1;88(1):47-58.
21. Characterization of Renal Glucose Reabsorption in Response to Dapagliflozin in Healthy Subjects and Subjects With Type 2 Diabetes | Diabetes Care | American Diabetes Association [Internet]. [cited 2024 Mar 18].
22. Fioretto P, Giaccari A, Sesti G. Efficacy and safety of dapagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, in diabetes mellitus. Cardiovascular Diabetology. 2015 Oct 17;14(1):142.

23. Nicholson MK, Ghazal Asswad R, Wilding JP. Dapagliflozin for the treatment of type 2 diabetes mellitus - an update. Expert Opinion on Pharmacotherapy. 2021 Nov 22;22(17):2303-10.
24. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007-2017. Cardiovascular Diabetology. 2018 Jun 8;17(1):83.
25. Shao SC, Chang KC, Lin SJ, Chien RN, Hung MJ, Chan YY, *et al*. Favorable pleiotropic effects of sodium glucose cotransporter 2 inhibitors: head-to-head comparisons with dipeptidyl peptidase-4 inhibitors in type 2 diabetes patients. Cardiovascular Diabetology. 2020 Feb 12;19(1):17.
26. Klen J, Dolžan V. SGLT2 Inhibitors in the Treatment of Diabetic Kidney Disease: More than Just Glucose Regulation. Pharmaceutics. 2023 Jul;15(7):1995.
27. Kumar KMP, Unnikrishnan AG, Jariwala P, Mehta A, Chaturvedi R, Panchal S, *et al*. SGLT2 Inhibitors: Paradigm Shift from Diabetes Care to Metabolic Care—An Indian Perspective. Indian Journal of Endocrinology and Metabolism. 2024 Feb;28(1):11.
28. Mikhail N. Place of sodium-glucose co-transporter type 2 inhibitors for treatment of type 2 diabetes. World J Diabetes. 2014 Dec 15;5(6):854-9.
29. Sosale B, Sosale A, Bhattacharyya A. Clinical Effectiveness and Impact on Insulin Therapy Cost After Addition of Dapagliflozin to Patients with Uncontrolled Type 2 Diabetes. Diabetes Ther. 2016 Dec;7(4):765-76.
30. Bashier A, Khalifa AA, Rashid F, Abdelgadir EI, Al Qaysi AA, Ali R, *et al*. Efficacy and Safety of SGLT2 Inhibitors in Reducing Glycated Hemoglobin and Weight in Emirati Patients With Type 2 Diabetes. J Clin Med Res. 2017 Jun;9(6):499-507.
31. Chadha M, Das AK, Deb P, Gangopadhyay KK, Joshi S, Kesavadev J, *et al*. Expert Opinion: Optimum Clinical Approach to Combination-Use of SGLT2i + DPP4i in the Indian Diabetes Setting. Diabetes Ther. 2022 May;13(5):1097-114.
32. Consensus on the use of DPP4 Inhibitors and SGLT2 Inhibitors in T2DM with Chronic Kidney Disease-from Indian Context. DOIJ. 2021;6(2):1-14.
33. Kalra S, Kesavadev J, Chadha M, Kumar GV. Sodium-glucose Cotransporter-2 Inhibitors in Combination with Other Glucose-lowering Agents for the Treatment of Type 2 Diabetes Mellitus. Indian Journal of Endocrinology and Metabolism. 2018 Dec;22(6):827.
34. Dual Add-on Therapy in Type 2 Diabetes Poorly Controlled With Metformin Monotherapy: A Randomized Double-Blind Trial of Saxagliptin Plus Dapagliflozin Addition Versus Single Addition of Saxagliptin or Dapagliflozin to Metformin | Diabetes Care | American Diabetes Association [Internet]. [cited 2024 Mar 18].
35. Scheen AJ. DPP-4 inhibitor plus SGLT-2 inhibitor as combination therapy for type 2 diabetes: from rationale to clinical aspects. Expert Opinion on Drug Metabolism & Toxicology. 2016 Dec 1;12(12):1407-17.
36. Seidu S, Kunutsor SK, Cos X, Gillani S, Khunti K, For and on behalf of Primary Care Diabetes Europe. SGLT2 inhibitors and renal outcomes in type 2 diabetes with or without renal impairment: A systematic review and meta-analysis. Prim Care Diabetes. 2018 Jun;12(3):265-83.
37. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, *et al*. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013 Oct 3;369(14):1317-26.
38. Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, *et al*. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2015 Jul 16;373(3):232-42.
39. Varshney A, Rawat R. Comparison of safety and efficacy of dapagliflozin and empagliflozin in type 2 diabetes mellitus patients in India. Rev Assoc Med Bras. 1992; 69(8):e20230090.
40. Jain A, Vispute A, Dange A, Naskar A, Mondal A, Vivekanand B, *et al*. A Randomized, Double-Blind, Parallel-Group Phase III Trial Investigating the Glycemic Efficacy and Safety Profile of Fixed-Dose Combination Dapagliflozin and Linagliptin Over Linagliptin Monotherapy in Patients with Inadequately Controlled Type 2 Diabetes with Metformin. Diabetes Ther. 2024 Jan 1;15(1):215-27.
41. Shi Z, Gao F, Liu W, He X. Comparative Efficacy of Dapagliflozin and Empagliflozin of a Fixed Dose in Heart Failure: A Network Meta-Analysis. Front Cardiovasc Med [Internet]. 2022 Apr 4 [cited 2024 Mar 18];9.

How to Cite This Article
Manjula S and Krishna KM. Expert opinion on the use of SGLT2 inhibitors and its combination with a special focus on dapagliflozin in the management of type 2 diabetes in Indian settings. International Journal of Endocrinology Sciences 2024; 6(1): 20-26.

Creative Commons (CC) License
This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International (CC BY-NC-SA 4.0) License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.