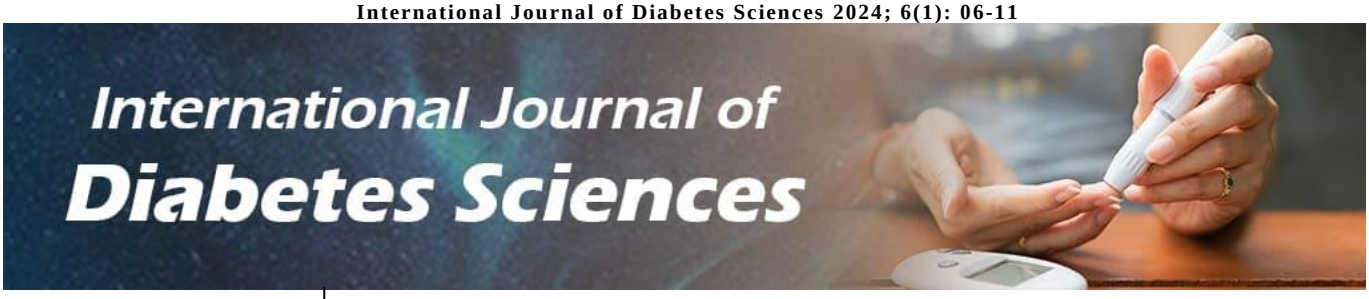

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Expert opinion on the use of sodium-glucose co-transporter-2 inhibitors, with a focus on dapagliflozin, for managing T2DM in Indian settings

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Abstract
Objective: The present survey-based study aims to gather the clinicians' perspective regarding the prescription patterns of sodium-glucose co-transporter-2 (SGLT2) inhibitors with a special focus on dapagliflozin for effective management of type 2 diabetes mellitus (T2DM) in Indian settings.
Methodology: The cross-sectional questionnaire-based survey consisted of 19 carefully crafted items designed to capture clinicians' perspectives on factors such as patient age distribution, awareness levels about diabetes, utilization of oral anti-diabetic drugs (OADs), recent advancements in OADs, co-morbidities, cardiovascular (CV) complications, SGLT2 inhibitors usage, prescribing patterns, and preferences for combination therapies.
Results: Majority (75%) of the clinicians recommended prescribing SGLT2 inhibitors to achieve both glycemic targets and leverage pleiotropic benefits. Nearly 59% noted a reduction in HbA1c levels by 1 to 1.5% after three months of treatment, while 54% reported reduced rates of CV death and hospitalization as the primary pleiotropic benefit. Most clinicians (58.1%) prescribed SGLT2 inhibitor + DPP4 inhibitor combination for patients with uncontrolled T2DM, and CV and renal comorbidities. Additionally, 49% of clinicians noted that 21-30% of their patients required SGLT2 inhibitor + DPP4 inhibitor therapy, with 52.51% initiating it when the entry level was HbA1c>8%. Majority (98%) of the clinicians favored dapagliflozin as the commonly prescribed SGLT2 inhibitor in their practice, with preferences split between metformin (41%) and DPP4 inhibitors (39%). Additionally, a significant proportion (74.3%) observed a reduction in systolic blood pressure of 5 to 10 mmHg with dapagliflozin. Additionally, a significant proportion (74.3%) observed a reduction in systolic blood pressure of 5 to 10 mmHg with dapagliflozin.
Conclusion: The survey underscored clinicians' preference for SGLT2 inhibitors to achieve glycemic control and leverage pleiotropic benefits. Combination therapy with SGLT2 inhibitor + DPP4 inhibitor is widely prescribed for uncontrolled T2DM and comorbidities, emphasizing its efficacy. Clinicians favored dapagliflozin as it demonstrates significant reductions in systolic blood pressure, reinforcing its therapeutic value in managing T2DM and associated complications.

Keywords: Type 2 diabetes mellitus, sodium-glucose co-transporter-2, comorbidities, dapagliflozin, vildagliptin

Introduction
The prevalence of type 2 diabetes mellitus (T2DM) has surged globally, becoming a significant healthcare concern [1]. The IDF Diabetes Atlas 10th edition emphasizes the rising global prevalence of diabetes as a significant health concern. Presently, 537 million adults aged 20-79 have diabetes, projected to increase to 643 million by 2030 and a staggering 783 million by 2045 [2]. Patients with T2DM exhibit a two- to three-fold elevated susceptibility to cardiovascular (CV) disease, a risk further compounded by concurrent chronic renal impairment. Individuals with T2DM face an increased risk of developing diabetic kidney disease and heart failure, alongside atherosclerotic CV disease [3-5]. The 2023 Indian Council of Medical Research-India Diabetes (ICMR INDIAB) study, involving 113,043 individuals, reported a diabetes prevalence of 11.4%, affecting 10,151 out of 107,119 participants [6]. According to WHO estimates, around 77 million Indian adults aged 18 and above suffer from T2DM, with nearly 25 million classified as prediabetic [7]. Sodium-glucose cotransporter-2 (SGLT2) inhibitors, the latest FDA-approved class of anti-hyperglycemic agents, have garnered attention for their distinct mechanism of action, independently

reducing glucose levels without insulin stimulation. Recent findings underscore their efficacy and benefits, establishing their role in diabetes treatment. By reducing renal tubular glucose reabsorption, SGLT2 inhibitors not only lower blood glucose but also offer additional advantages such as favorable effects on blood pressure and weight. Moreover, they enhance β-cell function by mitigating glucotoxicity, reducing insulin resistance, and enhancing insulin sensitivity [8, 9]. Antidiabetic drug combinations, tailored to individual patient needs, emphasize patient-centric, comprehensive management of cardiometabolic risks. Combining SGLT2 inhibitors with dipeptidyl peptidase 4 (DPP4) inhibitors provides numerous advantages, including decreased metabolic and vascular risks, enhanced glycemic control and weight management, safety, and improved long-term adherence [10].

Dapagliflozin, recognized as a potent and selective sodium-glucose cotransporter-2 (SGLT2) inhibitor, functions by selectively inhibiting SGLT2, which accounts for approximately 90% of renal glucose reabsorption in the early proximal tubule. This mechanism results in reduced serum glucose levels independently of insulin. Numerous clinical trials have evaluated the safety and efficacy of dapagliflozin, with recent randomized controlled trials (RCTs) specifically investigating its cardiorenal outcomes [11-13]. Given the persistent challenge of T2DM management, characterized by the risk of CV and renal complications, understanding the prescription patterns and use of SGLT2 inhibitors and dapagliflozin is crucial for optimizing patient care and enhancing treatment outcomes in the Indian context. The present survey-based study investigated the prescription patterns of SGLT2 inhibitors in Indian healthcare settings, particularly focusing on dapagliflozin, for the management of patients with T2DM.

Methods

We carried out a cross sectional, multiple-response questionnaire based survey among clinicians experienced in treating T2DM patients in the major Indian cities from June 2023 to December 2023.

Questionnaire

The questionnaire booklet titled CROWN-2 (Clinical Experience of Indian Clinicians on T2DM Management with Dapagliflozin) study was sent to the physicians who were interested to participate. The CROWN-2 study questionnaire consisted of 19 questions designed to capture clinicians' perspectives on factors such as patient age distribution, awareness levels about diabetes, utilization of oral anti-diabetic drugs (OADs), recent advancements in OADs, comorbidities, CV complications, SGLT2 inhibitors usage, and prescribing patterns and preferences for combination therapies. The study was conducted after receiving 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 leading clinicians in managing T2DM patients in the month of March 2023 for participation in this Indian survey. Clinicians were provided the option to skip any questions they did not wish to answer and were instructed to complete the questionnaire independently, without consulting their colleagues. Prior to the initiation of the study, written informed consent was obtained from all study participants.

Statistical analysis

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

Results

Majority (61%) of the respondents reported that 11-20% of individuals newly diagnosed with diabetes are <40 years of age. According to 51% of the clinicians, 25-50% are aware of diabetes as a medical condition and its consequences. Approximately 52% of clinicians stated that 40-60% of diabetic patients are on OADs. Nearly 41% of the clinicians noted that recent advancements in OADs, such as DPP4 and SGLT2 inhibitors, have contributed to reduced insulin utilization by 25-50%. About 61% of clinicians reported that 21-30% of patients have comorbid hypertension in their clinical practice. Additionally, CV complications are frequently reported among uncontrolled T2DM patients, according to 64% of clinicians.

Most clinicians (58%) noted that on a monthly average, 26-40% of patients require the addition of SGLT2 inhibitors to attain their glycemic targets. Additionally, the majority (75%) of the clinicians preferred SGLT2 inhibitors to achieve both glycemic targets and to leverage their pleiotropic benefits. Fifty-nine percent of clinicians noted a reduction in HbA1c levels by 1 to 1.5% after three months of treatment with SGLT2 inhibitors. Moreover, more than half (54%) of the clinicians reported that the main pleiotropic benefit SGLT2 inhibitors offer to patients beyond glycemic control is the reduced rate of CV death and hospitalization for heart failure.

Approximately 58% of the clinicians reported prescribing the SGLT2 inhibitors + DPP4 inhibitors combination for patients with uncontrolled T2DM, and CV and renal comorbidities (Figure 1). Majority (49%) of the clinicians reported that 21-30% of patients require a combination of SGLT2 inhibitors + DPP4 inhibitors in their clinical practice (Table 1). Nearly 53% of the clinicians opted to initiate treatment with a combination of SGLT2 inhibitors + DPP4 inhibitors when the entry-level HbA1c exceeded 8% (Figure 2).

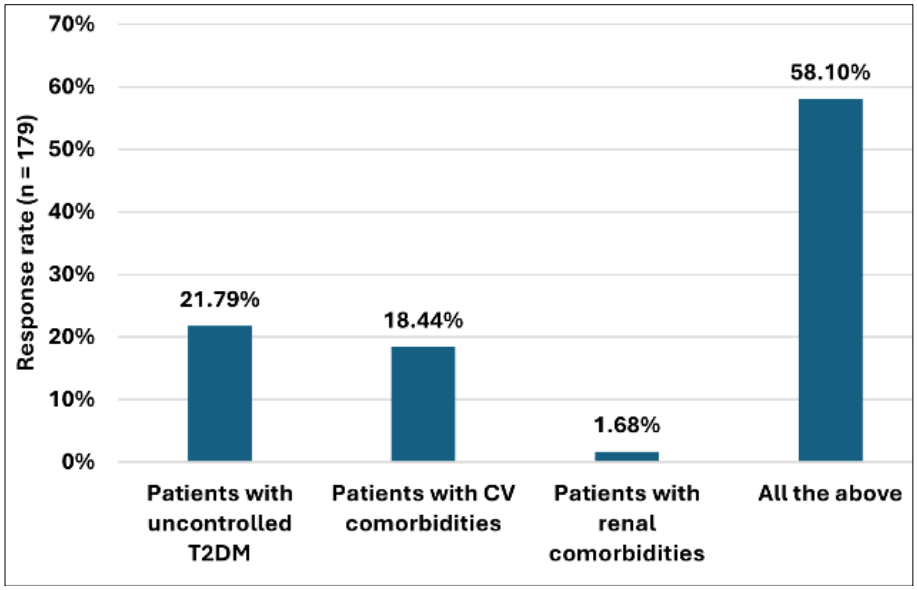

Fig 1: Distribution of response to patient profiles in which clinicians preferred prescribing a combination of SGLT2 inhibitor and DPP4 inhibitor in their clinical practice

Table 1: Distribution of response to initiation of treatment with combination SGLT2 inhibitors + DPP4 inhibitors based on entry HbA1c Level

Percentage	Response rate (n = 179)
<10%	7 (3.91%)
11-20%	45 (25.14%)
21-30%	88 (49.16%)
31-40%	38 (21.23%)
60	1 (0.56%)

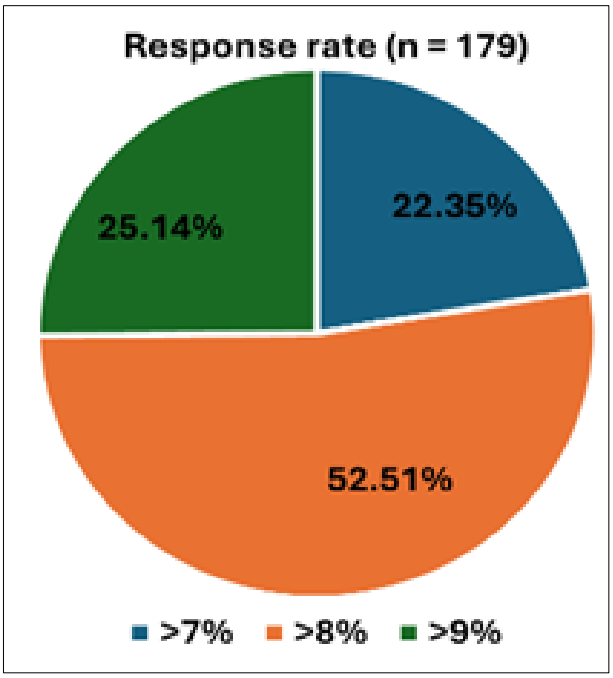

Fig 2: Distribution of response to initiation of treatment with combination SGLT2 inhibitors + DPP4 Inhibitors based on entry HbA1c Level

A significant proportion (98%) of clinicians reported dapagliflozin as the commonly prescribed SGLT2 inhibitor in their clinical practice (Figure 3). Approximately 41% of the respondents preferred dapagliflozin as an add-on to metformin, while 39% of clinicians preferred it as an add-on to DPP4 inhibitors (Table 2). Additionally, a significant proportion (74.3%) of clinicians observed a reduction in systolic blood pressure of 5 to 10 mmHg with dapagliflozin (Figure 4).

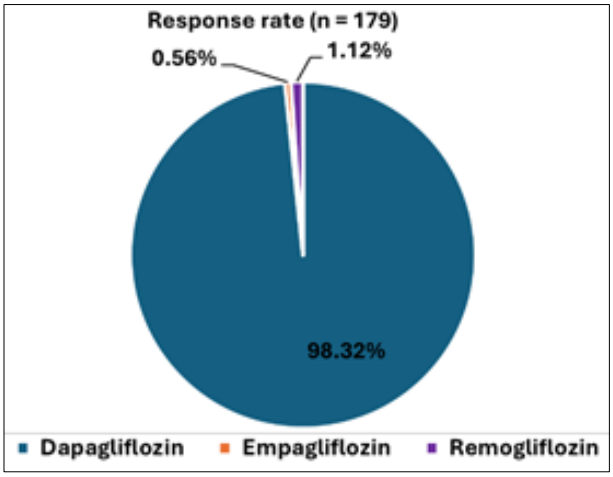

Fig 3: Distribution of response to commonly prescribed SGLT2 inhibitors in clinical practice

Table 2: Distribution of response to categories in which clinicians preferred prescribing dapagliflozin in their clinical practice

Category	Response rate (n = 179)
As an add-on to metformin	74 (41.34%)
As an add-on to sulphonylureas	30 (16.76%)
As an add-on to DPP4 inhibitors	70 (39.11%)
All of the above	5 (2.79%)

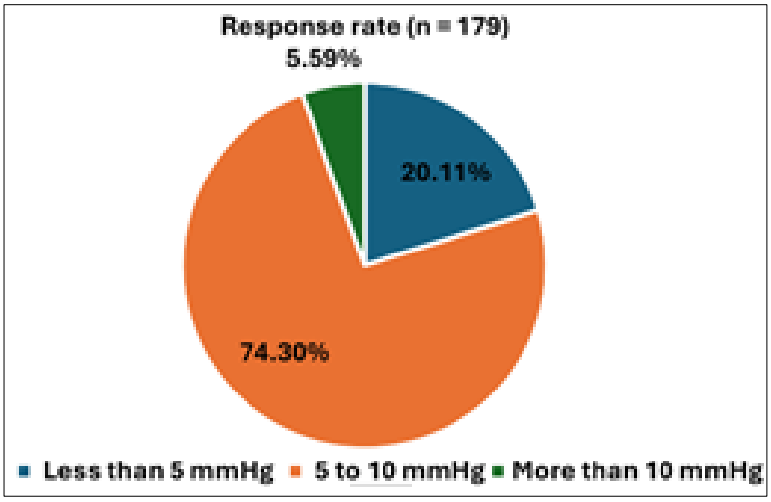

Fig 4: Distribution of response to systolic blood pressure reduction observed with dapagliflozin 10 mg

A significant proportion of clinicians (68%) reported prescribing dapagliflozin + vildagliptin as the most common combination in their routine practice (Table 3). Majority of the clinicians (54%) preferred the combination of dapagliflozin + vildagliptin in T2DM patients with CV comorbidities, while 46% of the clinicians preferred it for those with renal comorbidities (Table 4).

Table 3: Distribution of response to the most commonly prescribed SGLT2 inhibitor + DPP4 inhibitor combinations in routine clinical practice

SGLT2 Inhibitor + DPP4 Inhibitor	Response rate (n = 179)
Dapagliflozin + sitagliptin	55 (30.73%)
Dapagliflozin + vildagliptin	121 (67.6%)
Remogliflozin + vildagliptin	1 (0.56%)
Empagliflozin + linagliptin	1 (0.56%)
All of the above	1 (0.56%)

Table 4: Distribution of response to preferred SGLT2 inhibitor + DPP4 inhibitor combination in T2DM patients with cardiovascular and renal comorbidities

SGLT2 Inhibitor + DPP4 Inhibitor	Response rate (n = 179)	
	Cardiovascular	Renal
Dapagliflozin + sitagliptin	73 (40.78%)	56 (31.28%)
Dapagliflozin + vildagliptin	98 (54.75%)	82 (45.81%)
Remogliflozin + vildagliptin	0 (0%)	2 (1.12%)
Empagliflozin + linagliptin	8 (4.47%)	39 (21.79%)

Discussion

Most respondents in the current survey recommended SGLT2 inhibitors for achieving glycemic targets and leveraging their pleiotropic benefits, emphasizing reductions in HbA1c levels, and mitigating CV risks. A multicenter, retrospective trial conducted by Bashier *et al*. involving 307 patients with T2DM found that the utilization of SGLT2 inhibitors correlated with notable reductions in both HbA1c levels and weight. Furthermore, these inhibitors exhibited a significant decrease in total cholesterol and LDL levels [14]. SGLT2 inhibitors have received successive FDA approvals for reducing CV death and the risk of stroke and heart attack in adults diagnosed with T2DM and CVD, as well as for treating HF with reduced ejection fraction and preserved ejection fraction. Additionally, they are indicated for treating diabetic kidney disease and reducing the risk of hospitalization for heart failure in patients with T2DM and DKD [9].

A review by Mikhail *et al*. noted that SGLT2 inhibitors demonstrate a reduction in HbA1c levels by an average of 0.5% to 0.8% compared to placebo, whether used as monotherapy or add-on therapy. These drugs offer additional benefits such as modest weight loss of around 2 kg, minimal risk of hypoglycemia, and a decrease in blood pressure by approximately 4 mmHg systolic and 2 mmHg diastolic [15]. In Another review by Tentolouris *et al*., it was noted that SGLT2 inhibitors reduce glycated hemoglobin by 0.5%-1.0% and exhibit favorable effects on body weight, blood pressure, lipid profile, arterial stiffness, and endothelial function. Additionally, SGLT2 inhibitors have demonstrated notable cardioprotective and renoprotective effects [16]. In a meta-analysis of randomized controlled trials by Berhan *et al*., it was concluded that in patients with T2DM, all doses of SGLT2 inhibitors, whether used alone or in combination with other antidiabetic agents, consistently improved glycemic control. Additionally, these inhibitors were found to be associated with a significant reduction in body weight and blood pressure [17].

The present study findings highlighted a notable preference among clinicians for prescribing the SGLT2 inhibitor + DPP4 inhibitor combination therapy, particularly for patients with uncontrolled T2DM, and CV and renal comorbidities. Moreover, a substantial proportion of clinicians emphasized the importance of this combination for a significant portion of their patient population, particularly those with elevated entry-level HbA1c levels

exceeding 8%. In a systematic review conducted by Min *et al*., encompassing 7 randomized controlled trials with a total of 2,082 patients, significant improvements were observed in HbA1c levels, fasting plasma glucose, 2-hour postprandial plasma glucose, and body weight when compared to placebo plus DPP4 inhibitor. Notably, SGLT2 inhibitor/DPP4 inhibitor demonstrated superior glycemic control and greater weight reduction than placebo plus DPP4 inhibitor, all without increasing the risk of hypoglycemia or urinary tract infections in patients with inadequately controlled T2DM [18].

In the current study, dapagliflozin emerged as the preferred SGLT2 inhibitor, often chosen as an add-on therapy to metformin or DPP4 inhibitors. Clinicians also noted a significant reduction in systolic blood pressure with dapagliflozin use, indicating its favorable CV effects. A systematic review and meta-analysis comprising 6 RCTs revealed that dapagliflozin monotherapy was both well-tolerated and effective. It significantly reduced levels of HbA1c, fasting plasma glucose, and body weight in patients with T2DM, without increasing the risk of hypoglycemia [19]. Multiple randomized, double-blind, multicenter, phase 3 trials, investigating dapagliflozin as both monotherapy and combination therapy, have consistently shown its effectiveness in enhancing glycemic control, as well as reducing body weight and blood pressure. These trials encompass a diverse range of patients with T2DM, including those with initially high HbA1c levels (≥ 9%) and elderly individuals aged 65 years and above [20, 21].

In line with these findings, a meta-analysis conducted by Zheng *et al*., encompassing 6,738 patients with HF noted significant reductions in the incidence of hospitalization for HF, all-cause mortality, CV death, and major adverse cardiovascular events (MACE). Furthermore, patients receiving dapagliflozin demonstrated notable improvement in systolic blood pressure and body weight [22]. A meta-analysis examining CV events across 21 placebo-/active comparator-controlled phase 2b/3 clinical trials, each lasting up to 208 weeks, revealed no elevated CV risk with dapagliflozin treatment in patients with T2DM. Instead, there was an indication of potential CV benefits with treatment, as evidenced by hazard ratios (HRs) of less than 1 for CV outcomes [23]. DECLARE-TIMI 58 validated the CV safety profile of dapagliflozin in patients with T2DM who either had or were at risk of atherosclerotic cardiovascular disease (ASCVD). The study showed noninferiority between dapagliflozin and placebo for the primary composite safety outcome of MACE (p<0.001 for noninferiority) and demonstrated superiority for one of the two dual composite efficacy outcomes [24].

In the present survey, dapagliflozin + vildagliptin emerged as a preferred combination therapy among clinicians, particularly for T2DM patients with CV or renal comorbidities. In an opinion-based consensus study by Agrawala *et al*., involving 200 healthcare professionals (HCPs) T2DM in Indian patients, vildagliptin-dapagliflozin FDC was deemed an appealing option suitable for various Indian T2DM patient profiles, including those with ASCVD, a history of heart failure, as well as older and obese individuals [25]. The experts endorsed vildagliptin-dapagliflozin FDC as the primary treatment for obese and hypertensive T2DM patients, with a consensus level of C (Moderate). Additionally, it was recommended as a second-line treatment for obese and hypertensive T2DM patients uncontrolled on metformin, with a consensus level of B (Strong).

The survey findings provide valuable insights for clinicians, aiding in informed decision-making and enhancing patient outcomes. This survey offers guidance to clinicians and researchers on the use of SGLT2 inhibitors in the Indian context to improve patient care strategies and contribute to evidence-based guidelines for optimal treatment outcomes. While highlighting the significance of SGLT2 inhibitors in managing T2DM patients, the strength of the study lies in its meticulous questionnaire design and validation. However, acknowledging potential biases from individual perspectives and preferences, careful interpretation of results is warranted. Future research should focus on validating and expanding upon these findings to further advance clinical understanding and practice.

Conclusion

The current survey underscored the prominent role of SGLT2 inhibitors in managing T2DM, achieving glycemic control, and mitigating CV risks. Clinicians reported a clear preference for the SGLT2 inhibitor + DPP4 inhibitor combination therapy, especially in patients with uncontrolled T2DM and comorbidities. Dapagliflozin emerged as the favored SGLT2 inhibitor, often chosen alongside metformin or DPP4 inhibitors, with notable reductions in systolic blood pressure and favorable CV effects. The combination of dapagliflozin + vildagliptin garnered attention as an optimal therapeutic agent for patients with CV or renal comorbidities.

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