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Survey to Specify SGLT2 Inhibitor Choice in T2DM Management

ABSTRACT

Objective: There are no major head-to-head comparative studies till date to compare the differences in glycemic efficacy, safety, or cardio-renal effects within SGLT2 inhibitors. This survey was conducted to understand the different parameters that clinicians identify while choosing an SGLT2 inhibitor in routine clinical practice.
Materials and methods: A cross-sectional questionnaire-based survey of healthcare professionals (HCP) was conducted across India. Data were analyzed and expressed as descriptive statistics.
Results: In clinical practice, the majority of HCPs identified a history of cardiovascular disease (CVD) as the most important factor for prescribing SGLT2 inhibitors in patients with T2DM. The majority of HCPs opined that among all the SGLT2 inhibitors, canagliflozin had the strongest effect on HbA1c reduction (56%), reduction in body weight (59%), and renal benefit (66%), whereas empagliflozin was associated with CV benefits (48%). In terms of heart failure, canagliflozin, empagliflozin, and dapagliflozin were similarly preferred.
Conclusions: This survey gives us an understanding of the current clinical practice prevalent among Indian physicians as far as the prescription pattern of SGLT2 inhibitors is concerned. (Clin Diabetol 2022; 11; 5: 326–332)

Keywords: SGLT2 inhibitors, canagliflozin, empagliflozin, survey, T2DM, CVD

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Introduction

Diabetes mellitus is a serious threat to global health that respects neither socioeconomic status nor national boundaries [1]. This major health issue has reached alarming proportions with nearly half a billion people living with diabetes worldwide [1]. As per the IDF 2019 report, about 77 million people in India aged 20–79 years suffer from diabetes, making it one of the top three countries in the world with the number of people living with diabetes [1]. Patients with diabetes are at a risk of morbidity and mortality related to micro- and macro-vascular complications with the number of deaths estimated to be 4.2 million per year [1]. Chronic kidney disease (CKD) and cardiovascular disease (CVD) account for approximately 30% each, of patients with type 2 diabetes mellitus (T2DM) [2]. While more than 65% of T2DM patients die of CVD [3], the total deaths attributable to CKD due to diabetes mellitus rose by more than 90% between 1990 and 2012 [4], and this is expected to increase further in the years to come.

Owing to the increasing realization of diabetes as a disease beyond the increase in blood glucose, its management should involve addressing cardiorenal risk in addition to managing blood glucose levels. This has led to an important change in the recent American Diabetes Association (ADA) as well as Research Society for the Study of Diabetes in India — Endocrine Society of India (RSSDI-ESI) clinical practice recommendations, in which the use of agents belonging to sodium-glucose co-transporter 2 inhibitors (SGLT2i) and glucagon-like peptide 1 receptor agonists (GLP-1RAs) have received preference over other antihyperglycemic drugs, specifically in patients with established CVD, CKD or heart failure (HF) [5, 6]. This change was seen over the last few years with evolving evidence, particularly with SGLT2i, from being used for glycemic control to its

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present positioning for cardio-renal protection as well. It started with evidence from the EMPA-REG Outcome trial with empagliflozin demonstrating major adverse cardiovascular events (MACE) and CV death risk reduction in patients with T2DM with established CVD [7]. Similar result (MACE risk reduction) was observed in CANVAS Program, with canagliflozin which was evaluated in a mixed population of T2DM patients (majority with established CVD and remaining with CV risk factors) [8]. Results from DECLARE TIMI 58 (dapagliflozin) and VERTIS-CV (ertugliflozin) demonstrated no benefits on MACE, although the former was associated with a significant reduction in co-primary endpoint composed of hospitalization for heart failure (hHF) or CV death [9, 10]. Another SGLT2i, currently approved only in India, remogliflozin, has not yet been evaluated for its effect on cardiovascular outcomes. Currently, there are four SGLT2 inhibitors approved in India (canagliflozin, dapagliflozin, empagliflozin, and remogliflozin).

Clinical rationale for the study

There are no large, head-to-head comparative outcome trials till date to observe differences in glycemic efficacy, safety, and cardio-renal effects within the SGLT2i class. All these factors make it challenging to choose a particular SGLT2i for T2DM patients. With this survey (Sodium GlucosE co-transporter 2 inhibitors in type 2 diabetes meLlitus-differEntiating in Clinical pracTice-SELECT), we aimed to understand the parameters that clinicians consider in routine clinical practice to differentiate and choose among various SGLT2 inhibitors.

Materials and methods

This cross-sectional, questionnaire-based study was conducted involving Indian healthcare professionals (HCPs) over a span of a month, from April 2020 to May 2020. The HCPs irrespective of gender and age, who predominantly manage T2DM patients and were willing to participate in the study, were included in this survey.

The HCPs involved in the survey were electronically provided the survey protocol along with the data-sharing consent form. A structured questionnaire was shared digitally (via email) only after the consent form was signed. This filled-up questionnaire was considered as the principal source of data for subsequent analysis.

The questionnaire was prepared after reviewing the existing literature on the pattern of SGLT2i usage in clinical practice. The questionnaire consisted of 20 questions, designed to assess parameters such as demographics, the prevalence of comorbid conditions (overweight/obesity, CVD, CKD, and HF) in T2DM, the difference in efficacy and safety within the class of SGLT2i, and preference of SGLT2i in various patient populations (T2DM along with having CV risk factors, being overweight/obese, established CVD, CKD, HF and CVD & CKD). Data analysis was performed using Microsoft® Excel® (Microsoft 365; Version 2105). All the variables were presented through counts and percentages. All rank data were calculated using a weighted linear combination method. Post-data-lock, approval, data analysis, and table-listing-graph (TLG) were prepared.

Results

Participant demographics

The survey was completed by 406 HCPs across 103 Indian cities/towns. All questions in the survey were mandatory and the online portal was designed in a way that HCPs could submit the survey questionnaire only after they had responded to all questions. As a result, there were no incomplete survey forms. Approximately two-thirds of the HCPs who participated in the survey had a post-graduate degree in medicine (MD; 67.57%), approximately one-fifth had graduate degree (MBBS; 19.31%), more than one-tenth had super-specialization degree (DM/DNB; 12.38%), or any other qualification (0.74%). More than half of them were involved in private practice (55.69%). Most HCPs (72.41%) belonged to the age group ranging between 30–50 years.

Prevalence of comorbidities and complications observed in T2DM patients

More than half of HCPs mentioned that up to 30% of T2DM patients were overweight or obese (i.e. body mass index ≥ 23 kg/m^2), while almost a quarter of HCPs mentioned the prevalence of overweight or obese T2DM patients was more than 40%. CKD [estimated glomerular filtration rate (eGFR) $\leq$ 60 mL/min/1.73 m^2 and urine albumin-to-creatinine ratio (UACR) $\geq$ 30 mg/g] was found in up to 30% of T2DM patients, according to almost all HCPs (91.13%), while up to 30% of T2DM patients had established CVD (history of stroke, myocardial infarction, peripheral revascularization, etc.), according to 80% of HCPs. Further, two out of three HCPs suggested that up to 20% of their T2DM patients had both CKD and CVD. Over one-third of doctors indicated that less than 10% of their T2DM patients had congestive heart failure (CHF) and for another one-third, the prevalence was between 10 to 20%.

SGLT2i in clinical practice: Preferred patient populations and expected benefits

When asked to rank patient-related clinical parameters (in order of decreasing importance) considered before prescribing an SGLT2i, HCPs chose the history

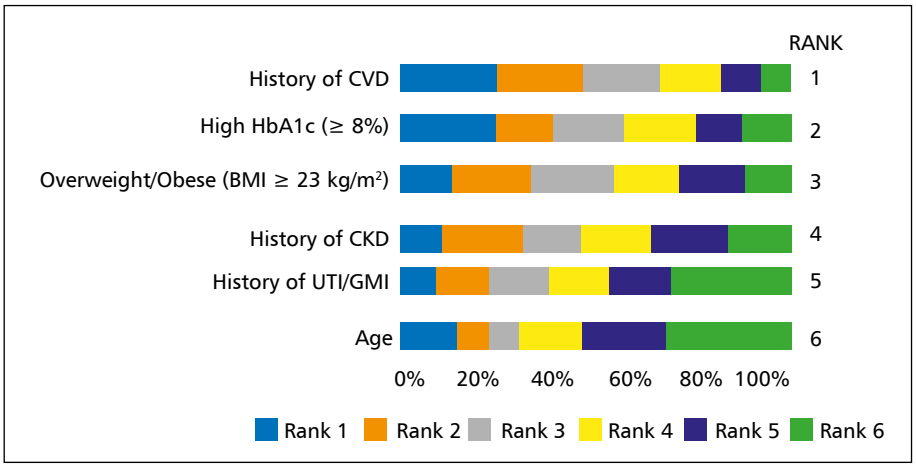

Figure 1. Preference of Patient Factors Considered Before Prescribing SGLT2i
BMI — body mass index; CKD — chronic kidney disease; CVD — cardiovascular disease; GMI — genital mycotic infection; HbA1c — glycated hemoglobin; SGLT2i — sodium-glucose co-transporter 2 inhibitors; UTI — urinary tract infection

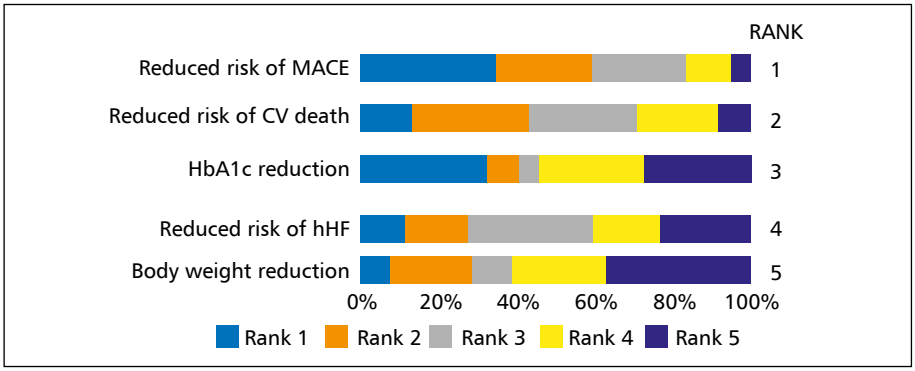

Figure 2. Preference of Benefits for Prescribing SGLT2i in T2DM Patients with Established Cardiovascular Disease
CV — cardiovascular, HbA1c — glycated hemoglobin; hHF — hospitalization for heart failure; MACE — major adverse cardiovascular events (composite of non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death); SGLT2i — sodium-glucose co-transporter 2 inhibitors; T2DM — type 2 diabetes mellitus

of CVD as the most important factor, followed by high HbA1c levels (> 8%), overweight, or obesity (BMI ≥ 23 kg/m^2), history of CKD, history of urinary tract infections (UTI)/genital mycotic infections (GMI) and finally age (Fig. 1). The most important benefit for which an SGLT2i was considered in T2DM patients with established CVD was "reduction of MACE", followed by "reduced risk of CV death", "HbA1c reduction", "reduced risk of hospitalization for heart failure" and "bodyweight reduction" (least important) (Fig. 2).

Comparison among SGLT2i for their effects

Respondents were asked to opine on which of the SGLT2i (canagliflozin, dapagliflozin, empagliflozin, and remogliflozin) provided the strongest effect on various included parameters (HbA1c reduction, weight reduction, CV benefits, renal benefits, heart failure benefits). More than half of HCPs suggested that canagliflozin was best suited for the reduction in HbA1c (56%), bodyweight (59%), and renal benefits (66%) (Fig. 3). For CV benefits, almost half of HCPs indicated that empagliflozin provided the strongest benefit (48%) followed by canagliflozin (31%). In terms of heart failure benefits, opinion was split among canagliflozin (35%), dapagliflozin (31%), and empagliflozin (28%). Interestingly, when asked to opine whether the cardio-renal benefits offered by SGLT2i are a class effect, almost equal proportion of HCPs agreed (47.54%) and disagreed (52.46%). In terms of safety, most of the HCPs (> 50%) mentioned that the incidence of UTI and GMI were similar among all SGLT2i. In terms of discontinuation (not only related to safety), HCPs observed the highest rate with empagliflozin, followed by canagliflozin, dapagliflozin, and remogliflozin.

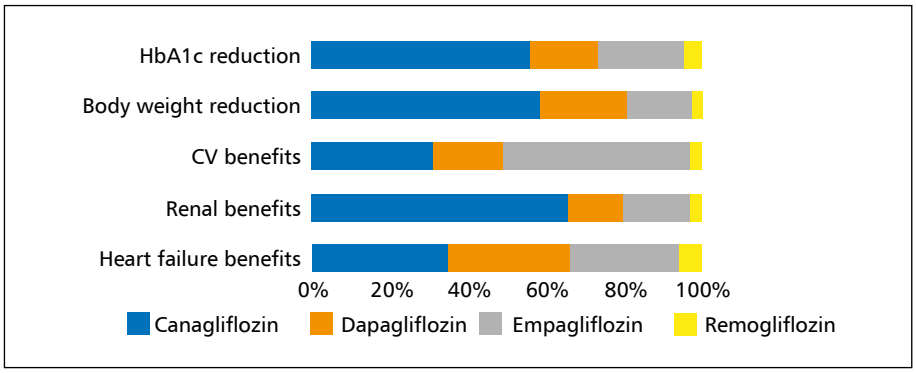

Figure 3. Effect of Different SGLT2i on Metabolic and Cardio-Renal Benefits
CV — cardiovascular; HbA1c — glycated hemoglobin; SGLT2i — sodium-glucose co-transporter 2 inhibitors

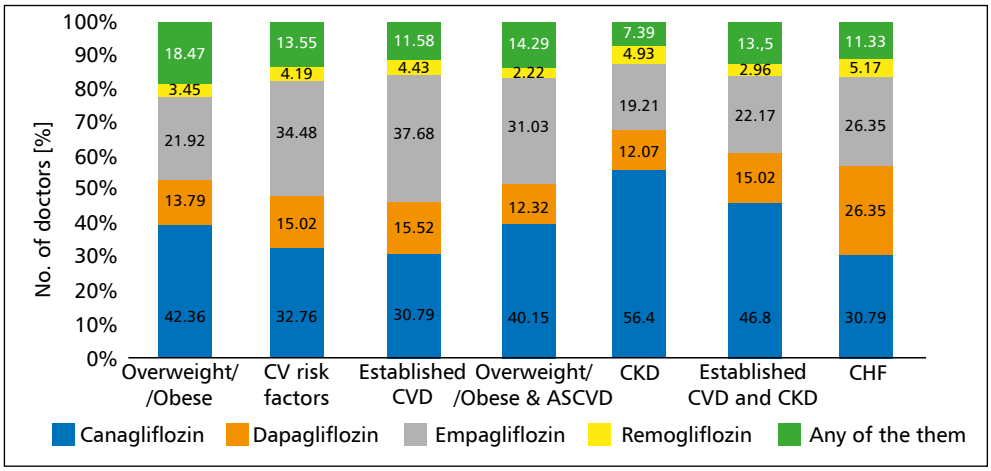

Figure 4. Preferred SGLT2i in Various T2DM Patient Populations
ASCVD — atherosclerotic cardiovascular disease; CHF — chronic heart failure; CKD — chronic kidney disease; CV — cardiovascular disease; SGLT2i — sodium-glucose co-transporter 2 inhibitors; T2DM — type 2 diabetes mellitus

Preference among SGLT2 inhibitors in various T2DM patients

In T2DM patients who are overweight or obese, most HCPs preferred canagliflozin (42.36%) as the SGLT2i of choice, followed by empagliflozin (21.92%) (Fig. 4). In patients with T2DM and CV risk factors, almost equal proportion of HCPs chose empagliflozin (34.48%) and canagliflozin (32.76%) as the most preferred SGLT2i. This trend was also observed in patients with T2DM and established CVD, with empagliflozin (37.68%) being preferred slightly more compared with canagliflozin (30.79%) (Fig. 4). However, in T2DM patients who were overweight or obese and had established CVD, the preference was tilted slightly towards canagliflozin (40.15%) over empagliflozin (31.03%). Canagliflozin was the preferred SGLT2i, to retard the progression of kidney disease in T2DM patients (55.67%) as well as in T2DM patients with established CKD (56.40%). In T2DM patients with documented CVD and CKD, the preference for canagliflozin vs other SGLT2i persisted. In patients with T2DM with a history of CHF, HCPs were split in their choice of SGLT2i (canagliflozin — 30.79%, dapagliflozin — 26.35%, and empagliflozin — 26.35%) (Fig. 4).

Discussion

We report results from the first-ever survey conducted in India, to the best of our knowledge, to assess the practice and perceptions of HCPs across the country on clinical factors determining their choice of drug among the class of SGLT2i for management of T2DM.

Previous studies from India have shown the prevalence of overweight and obesity across India ranges from 20 to 50% [11]. In our study, the prevalence of overweight and obesity was observed to be up to 30% for half of the HCPs and more than 40% for the

quarter of HCPs. A cross-sectional study estimated the prevalence of CKD (defined as eGFR < 60 mL/min/1.73 m^2 and/or UACR ≥ 30 mg/g) to be 48.4% in Indian patients with T2DM [12]. In our survey, the reported prevalence was lesser with HCPs mentioning that up to 30% of their T2DM patients had CKD. CVD is one of the major complications observed in T2DM patients [13]. The prevalence of coronary artery disease (CAD) in Indian patients with diabetes was reported to be 21.4% [14]. Our survey reflected a similar prevalence observed in clinical practice with up to 30% of T2DM patients diagnosed with CVD according to the majority of HCPs. Another complication that manifests either with CAD or independently is heart failure (HF). It shares its presence with many cardiac diseases, pulmonary diseases, obesity, CKD, and hypertension [15]. In fact, patients with diabetes mellitus have over twice the risk of developing HF than patients without diabetes [16]. HF is highly prevalent with about 25% of T2DM patients having concomitant CHF [17]. In our survey, two-thirds of HCPs said that up to 20% of T2DM patients have associated CHF.

Recent ADA and RSSDI-ESI clinical practice guidelines recommend a patient-centered approach to guide the choice of antihyperglycemic agents (AHA) [5, 6]. Among patients with T2DM with established atherosclerotic CVD, or those with established kidney disease or HF, an SGLT2i or a GLP1 RA with proven benefit is recommended as part of the therapy. In accordance with the guidelines, HCPs in our survey ranked the history of CVD as the most important patient-related parameter, even more important than elevated HbA1c levels, to initiate SGLT2i. Further, in T2DM patients with established CVD, HCPs preferred SGLT2i mostly for its impact on the reduction of MACE. Thus, there is a reasonable acceptance of the evidence and recommendations on positioning the use of SGLT2i for CV risk reduction in addition to lowering blood glucose levels.

Even though the evidence of benefits beyond glucose-lowering with SGLT2i has been increasing [7, 18, 19], there has been little evidence to help clinicians choose among various SGLT2i in T2DM patients. Individual cardiovascular and renal outcome trials with SGLT2i have distinct study designs and baseline characteristics making it difficult to compare the results [7–10, 18, 20]. In the absence of evidence from clinical trials, our survey attempted to understand the HCPs' perception of the choice of an SGLT2i for various clinical benefits. These findings give valuable insights into the mindset of an HCP while choosing these agents in clinical practice. In our survey, HCPs indicated canagliflozin to provide the strongest effect benefit in reducing HbA1c levels and body weight in their T2DM patients compared with other SGLT2 inhibitors (currently available in India). The renal benefits were also opined to be strongest with canagliflozin. This could have been due to the evidence from the CREDENCE Trial demonstrating the effects of canagliflozin in slowing decline in renal function in patients with T2DM with established nephropathy [18]. For CV benefits, empagliflozin was indicated to have the strongest effect — possibly due to strong reduction in CV death demonstrated by empagliflozin in the EMPA-REG Outcome [7]. Cardiovascular outcome trials (CVOT) with multiple SGLT2i have demonstrated consistent benefits on hHF [7–10]. In congruence with the evidence, we found a split among empagliflozin, canagliflozin, and dapagliflozin, in terms of benefits on hHF. In terms of safety, all SGLT2i are known to increase the risk of genital mycotic infections and urinary tract infections [21]. In our survey, the majority of HCPs opined that the incidence of infections observed with all SGLT2i is similar.

This survey also tried understanding the HCP preference of SGLT2 inhibitors in diverse T2DM patient profiles. Almost half of the HCPs preferred the use of canagliflozin in overweight or obese patients with T2DM versus other SGLT2 inhibitors. Real-world evidence has also shown potent weight loss benefit with the use of canagliflozin as was in a retrospective study done in obese or overweight patients with diabetes demonstrating a mean weight loss of 5 kg, reduction in waist circumference of about 7 cm at the end of 12 months with 42.7% of patients on canagliflozin achieving a weight loss of more than 5% [22]. In patients with diabetes and CV risk factors (history of hypertension, dyslipidemia, smoking, being overweight/obese, etc.), HCPs preferred the use of canagliflozin or empagliflozin but only a small proportion opted for dapagliflozin. Among canagliflozin, dapagliflozin, and empagliflozin, only the former two included patients with CV risk factors in their CVOT, while the latter included only patients with established CVD in its CVOT [7–9]. We observed a greater preference for empagliflozin (vs. others) in T2DM patients with established CVD. However, in T2DM patients with established CVD who were either overweight/obese or had CKD, canagliflozin was preferred over others — a preference arising, probably due to the benefits observed in various clinical trials [8, 23–25]. A similar trend was observed in patients with T2DM and CKD where the preference of use among the SGLT2i was with canagliflozin vs others. This was again reflected when HCPs were questioned on their SGLT2i of choice to slow CKD progression. When the results are taken together, they suggest that when CKD was one of the underlying comorbid condition in T2DM patients, the majority of HCPs preferred the

use of canagliflozin. The evidence from all three CV-OTs of canagliflozin, empagliflozin, and dapagliflozin showed a similar risk reduction in hHF endpoint [7–9]. This evidence was translated into practice as seen in our survey with HCPs preferring any of these agents in their T2DM patients with CHF.

The strength of the present survey was that it addressed the need gap of the patient factors/parameters used by the clinician as a deciding factor for use of a particular SGLT2i in clinical practice. Moreover, it gives a clear picture of the preference of an SGLT2i in a selected patient population. Furthermore, the survey included 103 cities/towns across India, which helps understand the clinical practice and HCP perceptions across a large country.

Our survey has certain limitations. The survey depicts Indian clinical practice and hence results cannot be extrapolated beyond borders. The results of the survey should be interpreted carefully as these are opinions/ /perceptions of HCPs as no data from the patient database or electronic medical records (EMR) were captured for this survey. While the three SGLT2 inhibitors (canagliflozin, dapagliflozin, and empagliflozin) were similarly priced at the time the survey was conducted, one of the SGLT2 inhibitor (remogliflozin) was more economical. However, we did not seek the perception of choice of SGLT2 inhibitor based on price. The questionnaire used for this survey was not validated. It was designed to gain insights into the current clinical practice while considering use of an SGLT2 inhibitor.

Conclusions

Treatment of T2DM encompasses several aspects from managing risk factors to reducing future adverse cardio-renal outcomes. Since its availability, SGLT2i has raised the bar of expectations from an antihyperglycemic agent. This drug class has demonstrated benefits in lowering blood glucose, blood pressure, weight and conferring cardio-renal protection. This survey provides insights into the selection of various SGLT2i in current clinical practice. The survey also gives an idea about the possible parameters used by HCPs to decide the type of SGLT2i to manage T2DM and its associated complications.

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Conflicts of interest

Dr. Samit Ghosal has not received any financial assistance from Cipla for this survey. Dr. Radhika Joshi, Rahul Iyer, Dr. Samir Adsule are employees of Cipla Ltd.

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