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Evidence-Based Consensus on Positioning of SGLT2i in Type 2 Diabetes Mellitus in Indians

Awadhesh Kumar Singh · Ambika G. Unnikrishnan · Abdul H. Zargar ·

Ajay Kumar · Ashok K. Das · Banshi Saboo · Binayak Sinha ·

Kalyan Kumar Gangopadhyay · Pradeep G. Talwalkar ·

Samit Ghosal · Sanjay Kalra · Shashank Joshi · Surendra Kumar Sharma ·

Usha Sriram · Viswanathan Mohan

ABSTRACT

The current diabetes management strategies not only aim at controlling glycaemic parameters but also necessitate continuous medical care along with multifactorial risk reduction through a comprehensive management concept. The sodium-glucose cotransporter 2 inhibitors (SGLT2i) are a group of evolving antidiabetic agents that have the potential to play a pivotal role in the comprehensive management of patients with diabetes due to their diverse beneficial effects. SGLT2i provide moderate glycaemic control, considerable body weight and blood pressure reduction, and thus have the ability to lower the risk of macrovascular and microvascular complications. Some of the unique characteristics associated with SGLT2i, such as reduction in body weight (more visceral fat mass loss than subcutaneous fat loss), reduction in insulin resistance and improvement in β-cell function, as measured by homeostatic model assessment-β (HOMA-β) could be potentially beneficial and help in overcoming some of the challenges faced by Indian patients with diabetes. In addition, a patient-centric approach with individualised

A. K. Singh (✉)
GD Hospital and Diabetes Institute, Kolkata, West Bengal, India
e-mail: singhawadheshkumar2018@gmail.com

A. G. Unnikrishnan
Chellaram Diabetes Institute, Pune, Maharashtra, India

A. H. Zargar
Advanced Centre for Diabetes and Endocrine Care, Srinagar, Jammu and Kashmir, India

A. Kumar
Diabetes Care and Research Centre, Patna, Bihar, India

A. K. Das
Pondicherry Institute of Medical Sciences, Pondicherry, India

B. Saboo
Diacare-Diabetes Care & Hormone Clinic, Ahmedabad, Gujarat, India

B. Sinha
AMRI Hospitals, Kolkata, West Bengal, India

K. K. Gangopadhyay
Fortis and Peerless Hospitals, Kolkata, West Bengal, India

P. G. Talwalkar
Talwalkar Diabetes Clinic, Mumbai, Maharashtra, India

S. Ghosal
Nightingale Hospital, Kolkata, West Bengal, India

S. Kalra
Bharti Hospital & B.R.I.D.E, Karnal, Haryana, India

△ Adis

treatment during SGLT2i therapy is inevitable in order to reduce diabetic complications and improve quality of life. Despite their broad benefits profile, the risk of genital tract infections, volume depletion, amputations and diabetic ketoacidosis associated with SGLT2i should be carefully monitored. In this compendium, we systematically reviewed the literature from Medline, Cochrane Library, and other relevant databases and attempted to provide evidence-based recommendations for the positioning of SGLT2i in the management of diabetes in the Indian population.

Keywords: Dapagliflozin; Glycaemic efficacy; Indian population; SGLT2i; Type 2 diabetes

EXECUTIVE SUMMARY

A. SGLT2i

    A1. SGLT2i decrease blood glucose concentration by reducing glucose reabsorption from proximal convoluted tubules and by increasing urinary glucose excretion (Grade A, Evidence Level [EL] 1)

    A2. SGLT2i are associated with durable glycaemic efficacy, body weight and blood pressure (BP) reduction with cardiovascular benefits and renoprotective action without a higher risk of hypoglycaemia (Grade A, EL 2)

    A3. Treatment with SGLT2i is associated with side-effects such as genital tract

S. Joshi
Lilavati Hospital and Research Centre, Mumbai, Maharashtra, India

S. K. Sharma
Galaxy Speciality Centre, Jaipur, Rajasthan, India

U. Sriram
Clinical Endocrinology Education and Research (ACEER), Chennai, Tamil Nadu, India

V. Mohan
Dr Mohan's Diabetes Specialities Centre and Madras Diabetes Research Foundation, Chennai, Tamil Nadu, India

infections (GTIs) and volume depletion-related adverse events; however, these can be minimised with proper education and counselling with close patient monitoring (Grade A, EL 2)

    A4. Body weight, A1C and systolic BP are important parameters that can be used to identify non-responders to SGLT2i therapy (Grade B, EL2)

    A5. Treatment with SGLT2i results in persistent calorie loss, which leads to weight loss. There is also some evidence of a reduction in β-cell stress and hyperinsulinaemia, and an increase in insulin sensitivity and the rate of insulin secretion (Grade C, EL 4).

B. SGLT2i: Monotherapy

    B1. SGLT2i as monotherapy reduce HbA1c, fasting plasma glucose (FPG), body weight and BP in patients with type 2 diabetes mellitus (T2DM); however, the risk of GTIs, especially in women, should be carefully monitored (Grade A, EL 1)

    B2. SGLT2i can be used as monotherapy if metformin is contradicted or not tolerated (Grade A, EL 1)

    B3. SGLT2i are associated with superior A1C reduction compared to DPP4 inhibitors (DPP4i), especially in marked hyperglycaemia, but have a similar effect as metformin and sulphonylureas. However, body weight and BP reduction abilities of SGLT2i are superior to metformin, sulphonylureas and DPP4i (Grade A, EL1).

C. SGLT2i: Dual Therapy

    C1. In T2DM patients with unmet needs of glycaemic control with metformin monotherapy, SGLT2i are a preferred option as a second-line agent (Grade A, EL 1)

    C2. SGLT2i as monotherapy and as an add-on to metformin effectively reduce A1C, FPG, body weight and BP in patients with T2DM (Grade A, EL 1)

    C3. In patients with T2DM, SGLT2i provide long-term glycaemic efficacy that

is superior to DPP4i and sulfonylureas (Grade A, EL 1)

C4. Compared to sulfonylureas, SGLT2i as a second-line agent are associated with non-inferior glycaemic control with a significant reduction in body weight, BP and rates of hypoglycaemia (Grade A, EL 1)

C5. When used as a second-line agent after metformin, SGLT2i are more effective in terms of glycaemic control, body weight, and BP reduction compared to DPP4i (Grade A, EL 1)

C6. SGLT2i significantly reduce the risk of cardiovascular morbidity and mortality (Grade A, EL 1)

C7. SGLT2i are associated with renoprotective effects such as slower progression to kidney disease and progression of albuminuria, and reduction of estimated glomerular filtration rate (eGFR) in patients with T2DM (Grade A, EL 1).

D. SGLT2i: Miscellaneous Effects

D1. SGLT2i improve insulin sensitivity and β-cell function and reduce insulin resistance and are therefore recommended in insulin-resistant T2DM patients (Grade A, EL 2)

D2. When combined with insulin, SGLT2i may decrease the cost of insulin treatment by reducing daily insulin dose requirements (Grade B, EL 3)

D3. Treatment with SGLT2i may reduce the level of uric acid and decrease albuminuria; thus, they might decrease diabetic complications in patients with T2DM (Grade B, EL 3).

E. SGLT2i: Safety, Tolerability and Contraindications

E1. The risk of hypoglycaemia in patients with T2DM is lower with SGLT2i than with insulin secretagogues and insulin. Patients taking a combination of SGLT2i and insulin or insulin secretagogues should be closely monitored (Grade A, EL1)

E2. SGLT2i are associated with a higher rate of GTIs than other antidiabetic drugs; however, differences in the incidence of urinary tract infections (UTIs) between SGLT2i and other antidiabetic drugs are inconsistently reported (Grade A, EL1).

E3. SGLT2i may be associated with volume depletion or osmotic diuresis-related adverse events compared to other antidiabetic drugs (Grade A, EL1)

E4. There is insufficient evidence to suggest causality between SGLT2i and an increased risk of bone fracture and osteoporosis in patients with T2DM. Treatment should be individualised in high-risk patients (older patients, with a prior history/risk of cardiovascular disease) (Grade A, EL1)

E5. SGLT2i (canagliflozin; CANA) are associated with an increased risk of peripheral vascular disease/amputation (Grade A, EL1)

E6. SGLT2i are contraindicated in patients with an eGFR of < 45 mL/min/1.73 m^2, extreme insulinopaenia or type 1 diabetes, on a fluid/carbohydrate restricted diet, or with decompensated medical/surgical illness, pregnancy, lactation and in children (Grade A, EL1).

F. SGLT2i: Indian Phenotype

F1. SGLT2i are emerging agents that can provide multiple benefits in Indian diabetes patients (Grade B, EL 3)

F2. The weight reduction associated with SGLT2i is due to loss of fat mass primarily from the abdomen rather than lean mass (Grade A, EL 2)

F3. The benefits associated with SGLT2i such as improvement of β-cell function and reduction of insulin resistance may be more useful in Indian patients with diabetes (Grade A, EL 2).

INTRODUCTION

Diabetes mellitus (DM) is a complex and chronic disorder that necessitates continuous medical care along with multifactorial risk reduction strategies beyond glycaemic control

[1]. The endemic nature of the disease is continuously increasing the global disease burden and affecting the patient's quality of life (QoL). According to the recent International Diabetes Federation (IDF) 2017 estimates, the global prevalence of diabetes in patients aged 20–79 years is 8.8% (425 million), which may rise to 9.9% (629 million) by 2045 [2]. Astonishingly, India has the second largest population with diabetes in the world with an estimated 69.2 million in 2017 and may overtake China (currently positioned first place) by 2045 with an estimated population with diabetes of 134.3 million [3]. Moreover, large-scale surveys such as the District Level Household and Facility Survey (DLHS) 2012–2013, and the Annual Health Survey (AHS) 2014 reported that around 7% of Indian adults are suffering from diabetes and the prevalence is higher in urban areas (9.8%) than in rural areas (5.7%) [4].

The World Health Organization (WHO) has reported that overweight and obesity are the strongest risk factors for diabetes, and people from high- and middle-income countries have a two-fold higher prevalence of overweight and obesity than low-income countries [5]. In addition, the STEPwise approach to Surveillance of non-communicable diseases (STEPS) survey from India reports that hypertension, obesity and family history of diabetes are significant risk factors associated with DM [6]. Several studies reported that approximately 30–70% of patients fail to achieve target glycaemic control in spite of treatment [7, 8]. Furthermore, a recent study from India estimated that only 9% of type 2 DM (T2DM) patients are achieving A1C, blood pressure (BP), and cholesterol (ABC) goals [9]. Uncontrolled DM leads to several microvascular and macrovascular complications and among these, cardiovascular (CV) complications are the most common causes of death and disability [10]. Moreover, the risk of stroke or coronary artery disease (CAD) also doubles in diabetes patients who are overweight [11].

Therefore, a comprehensive management concept comprising of (a) the achievement of glycaemic targets, (b) the reduction of the risk of diabetes-associated macrovascular and microvascular complications, (c) approaches for reduction of weight and obesity, (d) the reduction of blood pressure (BP) and lipid levels, and (e) improvement of patient compliance, is highly obligatory in the management of T2DM [5]. Sodium-glucose cotransporter 2 inhibitors (SGLT2i), pertaining to their relative glycaemic efficacy, weight and BP reduction, lipid level regulation, and lowering the risk of macrovascular and microvascular complications, could be a better drug of choice in the current era of diabetes management. The scope of this consensus is to review and provide evidence-based recommendations for the positioning of SGLT2i in the management of diabetes in the Indian population.

METHODOLOGY

The recommendations in the current consensus document were developed in accordance with the American Association of Clinical Endocrinologists (AACE) protocol for the standardised production of clinical practice guidelines after reviewing the recent evidence on SGLT2i [12]. A thorough review of the literature was initiated in Medline, Cochrane Library, and other related databases to impart the highest possible evidence base for the use of SGLT2i in the management of T2DM. Existing guidelines, meta-analyses, systematic reviews, randomised controlled trials (RCTs), non-RCTs, and key articles related to T2DM management were reviewed and recommendations were framed. The recommendations for each section of the consensus statement were discussed by expert panels and where there was a little or no evidence, the panel relied on logical empiricism and consensus to make the recommendations. The recommendations are based on clinical importance (Grade A: strong, B: intermediate, C: weak, and D: no evidence available), which were coupled with four intuitive levels of evidence (1 = at least one RCT or meta-analysis of RCTs, 2 = at least one non-randomised or non-controlled, prospective epidemiological study, 3 = cross-sectional or observational or surveillance or pilot study and 4 = existing guideline or consensus expert opinion on extensive patient experience or review) (Table 1).

Table 1 Evidence and recommendation grading [12]

Evidence level	Semantic descriptor (reference methodology)	Grades	Recommendation
1	Meta-analysis of randomised controlled trials, Randomised controlled trials	A	Strong
2	Meta-analysis of non-randomised prospective or case–controlled trials, non-randomised controlled trial, prospective cohort study, retrospective case–control study	B	Intermediate
3	Cross-sectional study, surveillance study (registries, surveys, epidemiologic study, retrospective chart review, mathematical modelling of database), consecutive case series, single case reports	C	Weak
4	No evidence (theory, opinion, consensus, review, or preclinical study)	D	No evidence

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

SGLT2I AND DIABETES

SGLT2I

SGLT2i are a promising novel class of glucose-lowering agents that interrupt the metabolic pathway without impairing β-cell function and insulin resistance [13]. Phlorizin, the first SGLT2i, was a naturally occurring substance obtained from apple tree bark. However, since it was non-selective and has poor oral bioavailability, work on its development could not continue [14]. Subsequently, selective drugs that inhibit SGLT2 receptor have now been developed.

Dapagliflozin (DAPA), canagliflozin (CANA), empagliflozin (EMPA), and recently ertugliflozin, are the four SGLT2i that have been approved by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) either as monotherapy or as an add-on to other antidiabetic agents [15]. Ipragliflozin, luseogliflozin, and tofogliflozin are approved only in Japan [16]; sotagliflozin and remogliflozin are in the clinical development stage [15]. Hence, the word 'SGLT2i' used in the entire consensus document will represent only DAPA, CANA, and EMPA. Details regarding approval, pharmacokinetic/pharmacodynamic profiles, contradictions, and dose adjustment required for different SGLT2i are described in Table 2 [13, 17–22].

Mechanism of Action

SGLT2i act on glucose metabolism and homeostasis through regulating the kidney function. The kidneys play a vital role in glucose homeostasis via three processes such as renal gluconeogenesis, glomerular filtration, and glucose reabsorption in the proximal convoluted tubule (PCT) [23]. In a healthy individual, the kidney can filter around 180 g of glucose daily; all of this glucose is reabsorbed in the PCT ($\sim$ 90% reabsorption occurs from the S1 segment while $\sim$ 10% reabsorption occurs from the S2/S3 segments of PCT). This reabsorption process in the PCT is generally mediated by the SGLT receptor family (6 members, SGLT 1–6). Details of the SGLT family members are given in Table 3 [13, 15]. Among the SGLT receptor family, SGLT2 receptor is found in the S1 segment and SGLT1 receptor is found in the S2/S3 segment of the PCT. All of the reabsorbed glucose is then transported back into circulation by a passive transport mechanism through facilitative glucose transporters; as a result, the glucose concentration in the plasma increases [13, 24]. The mechanisms of action of SGLT2i and their effect on various physiological parameters are depicted in Fig. 1 [13, 25].

Table 2 Details regarding approvals, pharmacokinetic/pharmacodynamic profiles, contradictions, and dose adjustment required for different SGLT2i [13, 17–22]

	Canagliflozin	Dapagliflozin	Empagliflozin
US-FDA approval	March, 2013	January, 2014	August, 2014
DCGI approval	November 2014	February 2015	August 2015
Dosage (range)	100–300 mg daily	5–10 mg daily	10–25 mg daily
Absorption	Time to peak in plasma: 1 to 2 h	Time to peak in plasma: 2 h	Time to peak in plasma: 1.5 h
V_d (L)	83.5	118	73.8
Protein binding (%)	99 mainly to albumin	91	86.2
Metabolism	O-glucuronidation by UGT1A9 and UGT2B4	O-glucuronidation by UGT1A9; CYP-mediated metabolism (minor)	O-glucuronidation by UGT2B7, UGT1A3, UGT1A8, and UGT1A9
Excretion	Faeces > urine	Urine > faeces	Urine > faeces
Bioavailability (%)	65	78	78
Half-life (h)	10.6–13.1	12.9 (10 mg dose)	12.4
Onset of action (h)	Within 24 h (dose-dependent)		
Duration of action (h)	24		
Drug–drug interaction	↑Efficacy: alpha lipoic acid, heparin guanethidine, MAO inhibitors, salicylates	↑Efficacy: alpha lipoic acid, MAO inhibitors, salicylates, quinolone antibiotics, SSRIs	↑Efficacy: alpha lipoic acid, MAO inhibitors, salicylates, quinolone antibiotics, SSRIs
	↓ Efficacy: carbamazepine, efavirenz, phenytoin, rifampicin, ritonavir	↓ Efficacy: rifampicin, diuretics, NSAIDs	↓ Efficacy: rifampicin, diuretics, NSAIDs
Contraindications	History of serious hypersensitivity, severe renal impairment (eGFR < 30 mL/min/1.73 m^2), ESRD		
Dose adjustment in hepatic impairment	Mild-to-moderate (Child–Pugh class A, B): no dosage adjustment	No dosage adjustment necessary; use caution if initiating in severe impairment	No dosage adjustment
	Severe (Child–Pugh class C): use not recommended		

Table 2 continued

	Canagliflozin	Dapagliflozin	Empagliflozin
Dose adjustment in renal impairment	eGFR $\geq$ 60 mL/min/1.73 m^2: no dosage adjustment	eGFR $\geq$ 45 mL/min/1.73 m^2: no dosage adjustment	eGFR $\geq$ 45 mL/min/1.73 m^2: no dosage adjustment
	eGFR 45–60 mL/min/1.73 m^2: 100 mg once daily (maximum)	eGFR < 45 mL/min/1.73 m^2: not recommended	eGFR < 45 mL/min/1.73 m^2: not recommended

USFDA United Stated Food and Drug Administration, *DCGI* Drugs Controller General of India, *mg* milligram, *h* hours, *Vd* Volume of distribution, *UGT* Uridine 5'-diphospho-glucuronosyltransferase, *CYP* Cytochrome P450, *MAO* Monoamine oxydase, *SSRI* Selective serotonin reuptake inhibitor, *NSAIDs* Non-steroidal anti-inflammataory drugs, *eGFR* estimated glomerular filtration rate, *ESRD* end stage renal disease

Table 3 Characteristics of SGLT family [13, 15]

| SGLT family	Gene	Substrate	Distribution in tissue	Function	Expression
SGLT1	*SLC5A1*	Glucose, galactose	Small intestine, kidney (S3 segment of PCT), trachea, heart, brain, testis, prostate	Transportation of glucose/galactose	Intestine > kidney
SGLT2	*SLC5A2*	Glucose	Kidney (S1 and S2 segment of PCT), brain, liver, thyroid, muscle, heart	Transportation of glucose and sodium	Mainly found in kidney
SGLT3	*SLC5A4*	Glucose	Intestine, testis, uterus, lung, brain, thyroid	Glucose sensor	–
SGLT4	*SLC5A9*	Glucose, mannose	Intestine, kidney, liver, brain, lung, trachea, uterus, pancreas	Transportation of glucose and mannose	–
SGLT5	*SLC5A10*	Glucose, galactose	Kidney	Unknown	–
SGLT6	*SLC5A11*	D-chiro-inositol	Spinal cord, kidney, brain	Absorption of glucose	–

SGLT sodium-glucose cotransporter, *SLC* Sodium carrier family, *PCT* proximal convoluted tubule

The SGLT2i selectively inhibit the SGLT2 receptors and reduce glucose reabsorption in the PCT, and thereby lower hyperglycaemia by increasing urinary glucose excretion (UGE). Furthermore, SGLT2i therapy results in persistent calorie loss that leads to weight loss, β-cell stress reduction and hyperinsulinaemia, increased insulin sensitivity and rate of insulin secretion. Consecutively, all these mechanisms continuously regulate blood glucose despite insulin resistance or β-cell dysfunction [13, 26–30]. In addition, SGLT2i may also be effective in the advanced stages of T2DM (when pancreatic β-cell reserves are permanently lost) due to their insulin-independent mechanism of action [31].

Place in Therapy

SGLT2i are the most recent addition to the T2DM management armamentarium. They have some adjunct advantages such as weight
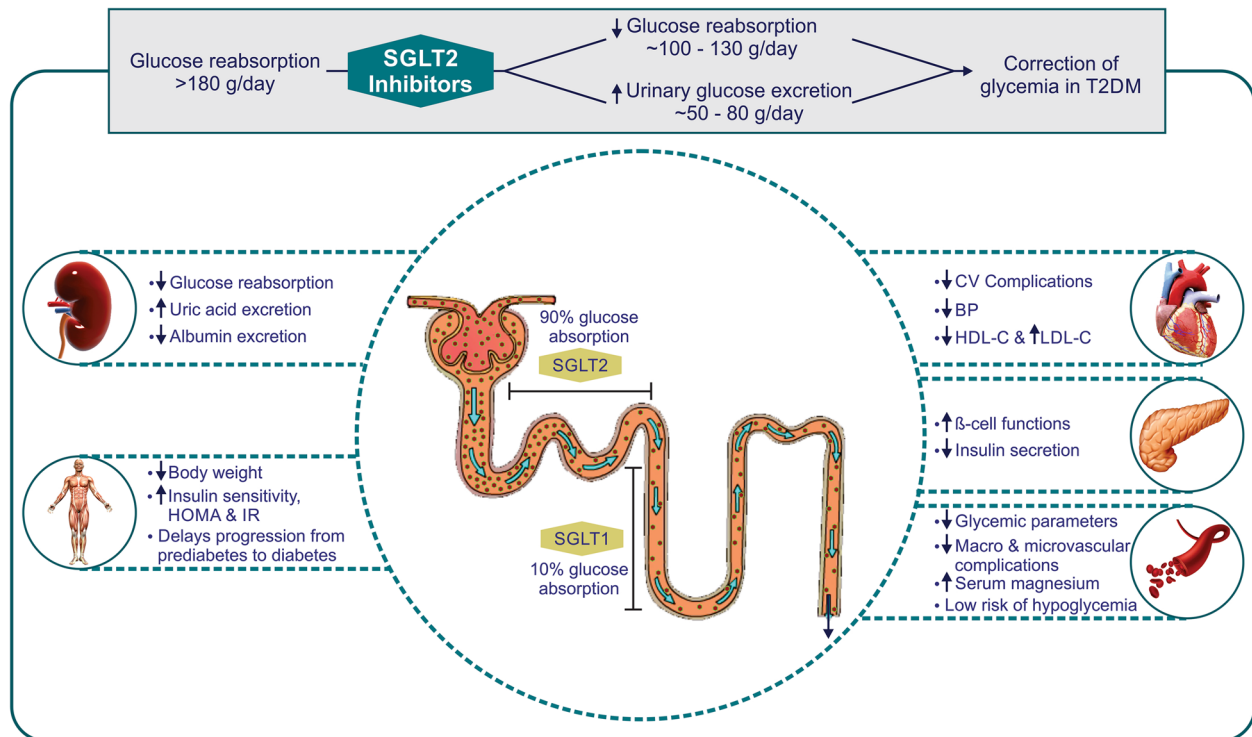
Fig. 1 Mechanisms of action of SGLT2i and their effect on the physiological system in the human body [13, 25]. *BP* blood pressure, *CV* cardiovascular, *HDL-C* high-density lipoprotein cholesterol, *HOMA* homeostatic model assessment, *LDL-C* low-density lipoprotein cholesterol, *IR* insulin resistance, *IS* insulin sensitivity, *SGLT* sodium glucose co-transporter, *T2DM* type 2 diabetes mellitus, ↑ increase, ↓ decrease. Reproduced with permission from Kalra. S, Ghosh. S, Aamir. A.H, et al. Safe and pragmatic use of sodium-glucose co-transporter 2 inhibitors in type 2 diabetes mellitus: South Asian Federation of Endocrine Societies consensus statement. Indian J Endocrinol Metab. 2017; 21:210–230

and BP reduction, low risk of hypoglycaemia, and reduction in macrovascular and microvascular events [32]. Moreover, these drugs may also rectify some core defects like improvement in β-cell function and insulin sensitivity in T2DM patients. However, they also have several adverse effects, especially genital tract infections (GTIs), volume depletion, toe amputation and diabetic ketoacidosis [32]. Pertaining to their potential advantages, several guidelines have placed SGLT2i in both monotherapy and combination therapy in the management of T2DM (Table 4) [1, 33–39].

Responders to SGLT2i

Body weight, A1C, and systolic BP are the various parameters used to determine the responders/non-responders to SGLT2i treatment in various studies [40–43]. In a post hoc analysis of two double-blind RCTs, patients in the SGLT2i treatment arm who had a 12-week A1C or systolic BP change lower than the median were considered as an A1C or systolic BP responder; a non-responder was defined as a 12-week A1C or systolic BP change on or above the median [40]. Similarly, in a retrospective study, SGLT2i-treated patients who had $\geq 5\%$ body weight reduction were classified as responders and those with $< 5\%$ body weight reduction were classified as non-responders [43]. Moreover, baseline fasting C-peptide level was the important factor influencing change in body weight; it was found to be higher in the responder group than in the non-responder group (3.25 ± 1.07 vs 2.62 ± 1.02 ng/mL, $P = 0.023$) [43].

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Recommendation: SGLT2i

- SGLT2i decrease blood glucose concentration by reducing glucose reabsorption from the PCT and by increasing UGE (Grade A, EL 1)

- SGLT2i are associated with durable glycaemic efficacy, body weight and BP reduction with CV benefits and renoprotective action without a higher risk of hypoglycaemia (Grade A, EL 2)

- Treatment with SGLT2i is associated with side-effects such as GTIs and volume depletion-related adverse events; however, these can be minimised with proper education and counselling with close patient monitoring (Grade A, EL 2)

- Body weight, A1C and systolic BP are important parameters that can be used to identify non-responders to SGLT2i therapy (Grade B, EL2)

- Treatment with SGLT2i results in persistent calorie loss, which leads to weight loss. There is also some evidence of a reduction in β-cell stress and hyperinsulinaemia, and an increase in insulin sensitivity and the rate of insulin secretion (Grade C, EL 4)

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Clinical Efficacy

Evidence from numerous clinical trials, systematic reviews, and meta-analyses suggests that SGLT2i as monotherapy are effective and safe in controlling glycaemic parameters in patients with T2DM.

A systematic review and network meta-analysis (NMA) including 38 RCTs (23,997 participants with a duration of ≥ 24 weeks) investigated the efficacy of SGLT2i in patients with T2DM. Compared to placebo, all SGLT2i reduced A1C (− 0.6% to − 0.9%), fasting plasma glucose (FPG) (− 1.1 to − 1.9 mmol/l), body weight (− 1.6 to − 2.5 kg), and BP (systolic − 4.9 to − 2.8 mmHg; diastolic − 2.0 to − 1.5 mmHg) [44]. However, more hypoglycaemic episodes were reported with CANA than DAPA. Moreover, GTI episodes (odds ratios [OR] 4–6) are reported to be higher with SGLT2i compared to placebo [44]. Recently, a systematic review and NMA by Johnston et al. reported that SGLT2i as

monotherapy significantly improved glycaemic parameters, induced weight loss, and reduced BP [45]. All RCTs included in this study were of ≥ 24 weeks. Compared to placebo or active comparator, SGLT2i reduced A1C ($P < 0.001$), body weight ($P < 0.001$), lipid level ($P < 0.01$), and BP ($P < 0.001$) in patients with T2DM [45]. All RCTs reported a 4–9% increase in urinary tract infections (UTIs) and GTIs with SGLT2i treatment mainly in women. In line with the evidence, another systematic review and meta-analysis including 39 RCTs (25,468 patients) reported that SGLT2i were associated with better glycaemic control (A1C reduction − 1.01% to − 0.51%), weight loss (− 2.66 to − 1.80 kg), and BP reduction (systolic − 4.77 to − 2.66 mmHg; diastolic − 1.99 to − 1.76 mmHg) compared to placebo [46]. Similarly, a meta-analysis including placebo-controlled trials reported that SGLT2i were associated with an A1C reduction of 0.5%, 0.6% and 0.6% at 12, 24 and 52 weeks, respectively [47]. Furthermore, several

Table 4 Place of SGLT2i in therapy by various guidelines

American College of Physicians (ACP) 2017 [33]	Recommends addition of either SU/TZD/SGLT2i/DPP4i to metformin to improve glycaemic control when a second oral therapy is considered
	Combinations of metformin and SGLT2i reduce weight more than metformin monotherapy
	SGLT2i, as monotherapy or with metformin, reduce SBP more than metformin monotherapy
National Institute for Health and Care Excellence (NICE) 2017 [34]	As a first line agent, SGLT-2i instead of DPP4i should be preferred if an SU/TZD is not appropriate
	If A1C > 7.5%, DPP4i/SU/TZD/SGLT2i can be used as a second-line or third-line agent
International Diabetes Federation (IDF) 2017 [35]	The preferred combinations may be metformin + SU, DPP4i or SGLT2i
	Recently SGLT2i have been considered as an option to add to metformin + SU or metformin + DPP4i combination
American Diabetes Association (ADA) 2018 [1]	If A1C > 9%, consider dual therapy
	If A1C target not achieved in 3 months, proceed to triple therapy
	SGLT2i along with other antidiabetic drugs can be used as dual or triple therapy
AACE 2017 [36]	If entryA1C < 7.5%, consider monotherapy
	If entry A1C ≥ 7.5%, consider dual and triple therapies
	SGLT2i placed before DPP4i, SU, and TZD in mono, dual, and triple therapies
Diabetes Canada Clinical Practice Guidelines 2018 [37]	If A1C > 1.5% above target, incretins and/or SGLT2i should be considered if lower risk of hypoglycaemia and/or weight gain are priorities
	In adults with T2DM, on insulin, with inadequate glycaemic control, SGLT2i should be considered as an add-on therapy to improve glycaemic control with weight loss and lower hypoglycaemic risk compared to additional insulin
Stable coronary artery disease (SCAD) management protocols in India 2016 [38]	All SCAD patients with diabetes should be treated with oral antidiabetics which have shown CV safety/benefits such as metformin, gliclazide, gliptins, SGLT2i
Research Society for the Study of Diabetes in India (RSSDI) 2017 [39]	SGLT2i can be considered as a second-line agent when glucose targets are not being achieved
	SGLT2i can be considered as a third-line agent along with AGIs, DPP4i, or TZD

SU sulphonylureas, *TZD* thiazolidinediones, *SGLT2i* sodium-glucose cotransporter 2 inhibitors, *DPP4i* dipeptidyl peptidase 4 inhibitors, *A1C* Hemoglobin A1C, *AACE* American Association of Clinical Endocrinologists

systematic reviews and meta-analyses of RCTs reported that SGLT2i as monotherapy were efficacious, reduced body weight and BP, and were well tolerated by T2DM patients [48–52]. In addition, several RCTs also reported that SGLT2i

– 4.43 mmHg, respectively) [46]. Details of the studies comparing SGLT2i with placebo are given in Table 5 [54, 55, 57–60].

> **Recommendation: Monotherapy**
>
> - SGLT2i as monotherapy reduce A1C, FPG, body weight and BP in patients with T2DM; however, the risk of GTIs in women should be carefully monitored (Grade A, EL 1)
>
> - SGLT2i can be used as monotherapy if metformin is contradicted or not tolerated (Grade A, EL 1)
>
> - SGLT2i are associated with superior A1C reduction compared to DPP4i, especially in marked hyperglycaemia, but have a similar effect as metformin and sulphonylureas. However, body weight and BP reduction abilities of SGLT2i are superior to metformin, sulphonylureas and DPP4i (Grade A, EL1)

were associated with clinically meaningful improvements in glycaemic parameters, and a reduction in body weight and BP in patients with baseline A1C $\geq$ 9% or $\geq$ 10% [53–55].

Monotherapy with SGLT2i has been found to be effective and safe compared to other antidiabetic agents. A systematic review and meta-analysis including 25 RCTs reported that SGLT2i were associated with a significantly higher reduction in A1C (weighted mean difference [WMD] 0.13%, $P = 0.005$) and FPG (WMD 0.80 mmol/L, $P < 0.00001$) than DPP4 inhibitors (DPP4i) [56]. However, there was no significant difference of hypoglycaemic risk between the treatments (RR 0.99; $P = 0.92$). Another systematic review and meta-analysis including 39 RCTs (25,468 patients) reported that SGLT2i were similar to metformin and sulphonylureas, but superior to DPP4i (– 0.15%) regarding A1C reduction, and were better than metformin, sulphonylureas, and DPP4i in lowering body weight (– 1.04 kg, – 4.76 kg and – 2.45 kg) and systolic BP reduction (– 5.86 mmHg, – 5.44 mmHg, and

POSITIONING OF SGLT2I IN TREATMENT CONTINUUM—FOCUS ON AFTER METFORMIN

Glycaemic Efficacy

SGLT2i vs Placebo

In unmet needs of glycaemic control with metformin monotherapy, the addition of SGLT2i has been found to be more effective in reducing A1C in patients with T2DM. A meta-analysis of 9 RCTs (each lasting < 1 year) compared metformin alone with metformin plus SGLT2i. The study reported that a combination therapy was associated with a greater reduction in A1C compared to metformin monotherapy (pooled between-group difference 0.61%; 95% CI 0.52–0.71) [61]. Moreover, a systematic review and NMA investigated the efficacy of SGLT2i in patients with T2DM inadequately controlled with metformin monotherapy. The mean difference (MD) of A1C between dual therapies compared to placebo (metformin)

Table 5 A summary of studies investigating the efficacy and safety of SGLT2i as monotherapy in patients with T2DM

Author et al.	Study	Patients (n)	Intervention	Glycaemic efficacy	Change in Weight	Change in BP	Adverse effects (AE)	Outcome/conclusion
Canagliflozin								
Inagaki et al. [57]	RCT	272	A: CANA 100 mg or 200 mg B: Placebo 24 weeks	Change in A1C (A vs B): − 0.74 or − 0.76 vs +0.29% Change in FPG: − 31.6 or − 31.9 vs +3.7 mg/dl Change in PPG: − 84.9 or − 79.0 vs − 0.5 mg/dl (all, $P < 0.05$)	% Change: − 3.76 or − 4.02 vs − 0.76 ($P < 0.05$)	% Change: − 7.88 or − 6.24 vs − 2.72 mmHg ($P < 0.05$)	% Genital infections: 6.5 or 6.3 vs 0 % Symptomatic hypoglycaemia: 2.2 or 1.1 vs 1.1	CANA significantly improved glycaemic control and was well tolerated
Stenlöf et al. [55]	RCT	584	A: CANA 100 or 300 mg vs B: Placebo 26-weeks	Change in A1C (A vs B): (− 0.77 or − 1.03 vs 0.14% ($P < 0.001$) LS mean changes in FPG vs placebo: − 2.0 or − 2.4 mmol/l (all, $P < 0.001$) LS mean changes in PPG vs placebo: − 2.7 and − 3.6 mmol/l (all, $P < 0.001$)	LS mean changes vs placebo: − 2.2% (− 1.9 kg) and − 3.3% (− 2.9 kg) ($P < 0.001$)	LS mean changes vs placebo: − 3.7 and − 5.4 mmHg ($P < 0.001$)	Incidences of GTI, UTI and osmotic diuresis-related AEs were higher with CANA	CANA treatment improved glycaemic control, reduced body weight and was generally well tolerated

Table 5 continued

Author et al.	Study	Patients (n)	Intervention	Glycaemic efficacy	Change in Weight	Change in BP	Adverse effects (AE)	Outcome/conclusion
Dapagliflozin								
Kaku et al. [58]	RCT	261	A: DAPA (5 or 10 mg) OD B: Placebo 24 weeks	Change in A1C (A vs B): − 0.41% or − 0.45% vs − 0.06% Change in FPG (A vs B): − 8.6 mg/dl or − 13.7 mg/dl vs +5.8 mg/dl	− 2.13 kg or − 2.22 kg vs − 0.84 kg		Two patients on DAPA 10 mg had hypoglycaemia; Events suggestive of GTI or UTI are each reported in four patients	DAPA as monotherapy was well tolerated and effective in reducing A1C, FPG and BW over 24 weeks
Ji et al. [59]	RCT	393	A: DAPA (5 or 10 mg) OD B: Placebo 24 weeks	Change in A1C (A vs B): − 1.04% or − 1.11% vs − 0.29% ($P < 0.0001$, both) Change in FPG (A vs B): − 25.1 mg/dl or − 31.6 mg/dl vs +2.5 mg/dl Change in PPG (A vs B): − 46.8 mg/dl or − 54.9 mg/dl vs +1.1 mg/dl	− 1.64 or − 2.25 kg vs − 0.27 kg		Hypoglycaemia was uncommon; GTI: 3.1% or 4.5% vs 0.8%; UTI: 3.9% or 5.3% vs 3.0%	DAPA as monotherapy in drug-naive Asian patients was well tolerated, significantly improving glycaemic control with the additional benefit of weight loss

Table 5 continued

Author et al.	Study	Patients (n)	Intervention	Glycaemic efficacy	Change in Weight	Change in BP	Adverse effects (AE)	Outcome/conclusion
Empagliflozin								
Gupta et al. [60]	RCT	108	A: EMPA10 mg (E10) or 25 mg (E25); B: Placebo; 76 weeks	Adjusted mean change in A1C vs placebo: E10 (− 0.81%, $P = 0.0029$); E25 (− 1.11%, $P < 0.0001$); A1C < 7% vs placebo: E10 (20.8%, $P < 0.0001$); E25 (28.0%, $P < 0.0001$); Adjusted mean change in FPG vs placebo: E10 (− 35.7, $P < 0.0001$); E25 (− 32.9, $P < 0.0001$)	Adjusted mean change vs placebo: E10 (− 1.41, $p = 0.0125$); E25 (− 1.50, $P = 0.0051$)	Non-significant	AEs were similar except for GTI (E10, 20.8%); (E25, 3.4%); (placebo, 3.6%)	Treatment with EMPA was well tolerated and resulted in sustained glycaemic efficacy over long-term (76 weeks) in drug-naive Indian T2DM patients
Roden et al. [54]	RCT	899	A: EMPA10 mg (E10); B: EMPA 25 mg (E25); C: SITA 100 mg (S100); D: Placebo; 24 weeks	Adjusted mean change in A1C from baseline vs placebo: E10 (− 0.74%, $P < 0.0001$); E25 (− 0.85, $P < 0.0001$); S100 (− 0.73, $P < 0.0001$)			Reported AEs: A vs B vs C vs D: 55% vs 60% vs 53% vs 61%	EMPA provides a tolerable and efficacious strategy to reduce A1C in patients with T2DM who had not previously received drug treatment

RCT randomised controlled trial, *A1C* Hemoglobin A1C, *FPG* Fasting plasma glucose, *PPG* Postprandial glucose, *GTI* genital tract infection, *UTI* urinary tract infection, *AE* adverse events

ranged from − 0.54 to − 0.77%, and relatively more patients achieved A1C < 7.0% with dual therapy compared to placebo (risk ratio [RR], 1.46–2.16) [62]. Similarly, another NMA reported that the addition of SGLT2i was associated with an A1C reduction of 0.48–0.72% compared to metformin monotherapy [63]. Several RCTs have also reported a meaningful A1C reduction with dual therapy of metformin and SGLT2i compared to metformin monotherapy in patients with T2DM. The glycaemic efficacy of SGLT2i as a second-line agent investigated in various RCTs is elaborated in Table 6 [64–72].

SGLT2i vs Active Comparator

A meta-analysis including 6 RCTs compared the efficacy and safety of SGLT2i with non-SGLT2i combinations as an add-on to metformin [73]. The study reported that SGLT2i reduced A1C significantly more than non-SGLT2i (glimepiride/linagliptin/sitagliptin/glipizide) combinations after 52 weeks ($P = 0.002$) and after 104 weeks ($P < 0.00001$). Furthermore, FPG was also significantly reduced ($P < 0.00001$) with SGLT2i compared to non-SGLT2i combinations at 52 and 104 weeks [73]. In a meta-analysis of several RCTs, Bolen et al. reported that in terms of A1C reduction, metformin + SGLT2i was more favoured than metformin + sulfonylureas (pooled between-group difference 0.17%; 95% CI 0.14–0.20%), and metformin + DPP4i (pooled between-group difference 0.17%; 95% CI 0.08–0.26%) [61]. A systematic literature review and Bayesian NMA of RCTs investigated the efficacy of antidiabetic treatments added to metformin. The A1C reduction after 1 year of treatment with SGLT2i was − 0.08% (95% CI, − 0.25 to 0.10) relative to DPP4i, − 0.02% (95% CI, − 0.24 to 0.21) relative to thiazolidinediones, and 0.0% (95% CI, − 0.16 to 0.16)] relative to sulphonylureas [74]. Numerous RCTs also favour metformin and SGLT2i combinations over metformin and other antidiabetic agent combinations for efficacy in controlling glycaemic parameters. A list of RCTs comparing the efficacy of metformin and SGLT2i combination versus metformin and other antidiabetic agent combinations is shown in Table 7 [64, 75–79].

Evidence suggests that SGLT2i produce a long-term glycaemic response compared to other antidiabetic agents. In a meta-analysis, SGLT2i, as an add-on to metformin, were associated with a greater reduction in A1C at ≥ 52 weeks (MD − 0.11; − 0.20 to − 0.03) compared to DPP4i [80]. Similarly, an NMA also reported that A1C reduction with SGLT2i as a second-line agent was high when compared to DPP4i, and that the A1C reduction was at least as large as glucagon-like peptide receptor agonists (GLP-1 RA) at 104 weeks [81]. An extension of an earlier double-blind phase III RCT compared the durability of SGLT2i versus sulfonylureas. At 208 weeks, SGLT2i produced sustained reductions in A1C (MD − 0.30%, − 0.51 to − 0.09) compared to sulfonylureas; and the A1C coefficient of failure was significantly lower for SGLT2i than for sulfonylureas (0.19 vs 0.61, difference − 0.42; $P = 0.0001$) [76]. This confirms the durability of SGLT2i in the reduction of A1C in patients with T2DM compared to other antidiabetic agents.

Emerging evidence also suggests that SGLT2i might be more efficacious in lowering plasma glucose when the A1C value is > 8–8.5% while DPP4 inhibitors work better when the A1C value is < 8.0% [82, 83].

In short-term real-world settings, SGLT2i have produced consistent efficacy and safety effects in an Indian population with T2DM. In a post hoc analysis of 4 double-blind RCTs, SGLT2i were associated with an A1C reduction of − 0.74% to − 0.88%, and FPG reduction of − 1.0 mmol/L to − 1.8 mmol/L [84]. Similarly, a prospective analysis by Sosale et al. reported an A1C reduction of − 1.02 ± 0.24%, and a retrospective study by Baruah et al. reported a significant A1C reduction from baseline (9.0% at baseline to 6.8% at follow-up, $P < 0.005$) with SGLT2i [85, 86].

Extra-Glycaemic Benefits

In addition to glycaemic benefits, SGLT2i have several extra-glycaemic benefits such as body weight reduction, BP reduction, lipid level regulation, CV risk reduction, renoprotective effect, and lowering hypoglycaemic risk. Extra-

Table 6 A summary of RCTs investigating the efficacy of SGLT2i as an add-on to metformin in patients with T2DM

Author et al.	Patients (N)	Intervention	Comparator	Glycaemic efficacy
Lavalle-González et al. [64]	918	A: CANA 100 mg or 300 mg daily	B: Placebo 26 weeks	A1C: ↓from baseline (A vs B): − 0.79 or − 0.94% vs − 0.17% ($P < 0.001$)
				FPG: ↓from baseline (A vs B): − 1.5 or − 2.1 mmol/l vs +0.1 mmol/l ($P < 0.001$)
				PPG: ↓from baseline (A vs B): − 2.7 or −3.2 mmol/l vs − 0.6 mmol/l ($P < 0.001$)
				Achievement of target A1C < 7% (A vs B): 45.5 or 57.8% vs 29.8% ($P = 0.000$)
Qiu et al. [65]	279	A: CANA 50 mg or 150 mg BID	B: Placebo 18 weeks	A1C: ↓from baseline (A vs B): − 0.45 or − 0.61% vs − 0.01% ($P < 0.001$)
				FPG: ↓from baseline (A vs B): − 0.7 or − 1.2 mmol/l vs + 0.3 mmol/l
				Achievement of target A1C < 7% (A vs B): 47.8 or 57.1% vs 31.5% ($P < 0.05$ or $P < 0.001$ vs placebo)
Ji et al. [66]	676	A: CANA 100 mg or 300 mg daily	B: Placebo 18 weeks	A1C: ↓from baseline (A vs B): − 0.97 or − 1.06% vs − 0.47% ($P < 0.001$)
				FPG: ↓from baseline (A relative to B): − 1.0 or − 1.4 mmol/l
Schumm-Draeger et al. [67]	400	A: DAPA 2.5 mg or 5 mg BID	B: Placebo 16 weeks	A1C: ↓from baseline (A vs B): − 0.52 or − 0.65% vs − 0.30% ($P = 0.0106$ or $P < 0.0001$)
				FPG: Significantly greater improvements for DAPA vs placebo
				Achievement of target A1C < 7%: Significantly greater improvements for DAPA vs placebo
Bailey et al. [68]	546	A: DAPA 2.5 mg or 5 mg or 10 mg daily	B: Placebo 102 weeks	A1C: ↓from baseline (A vs B): − 0.48% ($P = 0.0008$) or − 0.58% ($P < 0.0001$), or − 0.78% ($P < 0.0001$) vs + 0.02%
				FPG: ↓from baseline (A vs B): − 1.07 or − 1.47 ($P = 0.0003$), or − 1.36 mmol/l ($P = 0.0012$) vs − 0.58 mmol/l
				Achievement of target A1C < 7% (A vs B): 20.7 or 26.4 (($P = 0.0202$) or 31.5% ($P = 0.0014$) vs 15.4%

Table 6 continued

Author et al.	Patients (N)	Intervention	Comparator	Glycaemic efficacy
Henry et al. [69]	–	A: DAPA 5 mg or 10 mg daily	B: Placebo 24 weeks	A1C: ↓from baseline (A vs B): − 2.05 vs − 1.35% ($P < 0.0001$); or − 1.98% vs − 1.44% ($P < 0.0001$)
				FPG: Combination therapy statistically superior to monotherapy ($P < 0.0001$)
Häring et al. [70]	637	A: EMPA 10 mg or 25 mg daily	B: Placebo 24 weeks	A1C:↓from baseline (A vs B): − 0.70 or − 0.77% vs − 0.13% ($P < 0.001$)
				FPG: ↓from baseline (A vs B): − 1.11 or − 1.24 mmol/l vs + 0.35 mmol/l ($P < 0.001$)
				PPG: ↓from baseline (A vs B): − 2.55 or − 2.47 mmol/l vs + 0.33 mmol/l ($P < 0.001$)
				Achievement of target A1C < 7% (A vs B): 37.7 or 38.7% vs 12.5% ($P < 0.001$)
Ross et al. [71]	983	A: EMPA 12.5 BID or 25 mg OD or 5 mg BID or 10 mg OD	B: Placebo 16 weeks	A1C:↓from baseline (E12.5 mg BID vs 25 mg daily), − 0.11%; and (E5 mg BID vs 10 mg daily), − 0.02%
Merker et al. [72]	463	A: EMPA 10 mg or 25 mg daily	B: Placebo 76 weeks	A1C: ↓from baseline (vs B): − 0.6 or − 0.7% ($P < 0.001$)

A1C Hemoglobin A1C, *FPG* Fasting plasma glucose, *PPG* Postprandial glucose, *CANA* canagliflozin, *DAPA* dapagliflozin, *EMPA* empagliflozin

glycaemic benefits associated with SGLT2i are depicted in Fig. 2 [13, 87].

Body Weight Reduction

Reduction of body weight decreases diabetes-related complications and improves the patient's QoL and wellbeing. Details regarding the benefits associated with body weight reduction in patients with T2DM are depicted in Fig. 3 [1, 88–91]. A systematic review and meta-analysis of RCTs concluded that a weight loss of > 5% had beneficial effects on A1C, lipids, and BP in patients with T2DM [91]. A post hoc analysis of the Look AHEAD trial reported that patients with T2DM who lost at least 10% of body weight during a 1-year period have a 21% lower risk of fatal and non-fatal CV events (adjusted hazard ratio [AHR] 0.79, $P = 0.034$) and a 24% reduced risk of other CV events (AHR 0.76,

$P = 0.003$) compared with individuals with stable weight or weight gain [92]. Evidence from the Look AHEAD trial also reported that body weight reduction reduced several microvascular complications in T2DM patients [90, 93]. In addition, a reduction of body weight improved glycaemic control, insulin sensitivity, insulin resistance, HOMA IR, and β-cell function in patients with T2DM [88, 89, 94]. Therefore, weight reduction is inevitable in T2DM patients to reduce mortality and morbidity.

SGLT2i have a significant effect on body weight reduction, which occurs primarily (about two-thirds) due to fat mass loss from the abdomen rather than lean mass [95]. Tosaki et al. investigated 132 T2DM patients and reported that 6 months of treatment with SGLT2i was associated with a significant reduction of the visceral fat area ($P < 0.001$) and waist

Table 7 A summary of RCTs investigating the efficacy of SGLT2i compared to non-SGLT2i as an add-on to metformin in patients with T2DM

Author et al.	Patients (N)	Intervention	Comparator	Glycaemic efficacy
Leiter et al. [75]	1450	A: CANA 100 mg or 300 mg daily	B: GLIM titrated up to 6 or 8 mg/daily	A1C: ↓from baseline (A vs B): − 0.65 or − 0.74% vs − 0.55%
			104 weeks	FPG: ↓from baseline (A vs B): − 1.1 or − 1.3 mmol/l vs − 0.6 mmol/l
				Achievement of target A1C < 7% (A vs B): 42.5 or 50.2% vs 43.9%
Del Prato et al. [76]	814	A: DAPA 2.5, 5 or 10 mg	B: GLIP 5, 10 or 20 mg	A1C: ↓from baseline (A vs B): − 0.10 vs + 0.20%
			208 weeks	FPG: ↓from baseline (A vs B): − 0.7 vs − 0.2 mmol/l
				A1C coefficient of failure (A vs B): 0.19 vs 0.61 ($P = 0.0001$)
Ridderstråle et al. [77]	1549	A: EMPA 25 mg OD	B: GLIM 1-4 mg OD	A1C: ↓from baseline (A vs B): − 0.66 vs − 0.55% ($P < 0.0001$ for non-inferiority)
			104 weeks	FPG: ↓from baseline (A relative to B): − 0.85 or − 0.17 mmol/l ($P < 0.0001$)
Lavalle-González et al. [64]	1284	A: CANA 100 mg or 300 mg daily	B: SITA 100 mg daily	A1C: ↓from baseline (A vs B): − 0.73 or − 0.88% vs − 0.73%
			52 weeks	FPG: ↓from baseline (A vs B): − 1.5 or − 2.0 vs − 1.0 mmol/l ($P < 0.001$)
				Achievement of target A1C < 7%(A vs B): 41.4 or 54.7% vs 50.6%
Rosenstock et al. [78]	355	A: DAPA 10 mg daily	B: SAXA 5 mg daily	A1C: ↓from baseline (A vs B): − 1.20% vs − 0.88%
			102 weeks	FPG: ↓from baseline (A vs B): − 32 mg/dl vs − 14 mg/dl
				PPG: ↓from baseline (A vs B): − 70 mg/dl vs − 36 mg/dl
				Achievement of target A1C < 7% (A vs B): 22% vs 18%

Table 7 continued

Author et al.	Patients (N)	Intervention	Comparator	Glycaemic efficacy
DeFronzo et al. [79]	413	A: EMPA 10 mg or 25 mg daily	B: LINA 5 mg daily 52 weeks	A1C: ↓from baseline (A vs B): − 0.66 or − 0.62% vs − 0.70% FPG: ↓from baseline (A vs B): − 18.8 mg/dl or − 20.8 vs − 13.1 mg/dl Achievement of target A1C < 7% (A vs B): 32.6 or 28.0% vs 36.1%

CANA canagliflozin, *GLIM* glimepiride, *A1C* Hemoglobin A1C, *FPG* Fasting plasma glucose, *PPG* Postprandial glucose, *DAPA* dapagliflozin, *GLIP* glipizide, *EMPA* empagliflozin, *SITA* sitagliptin, *SAXA* saxagliptin, *LINA* linagliptin
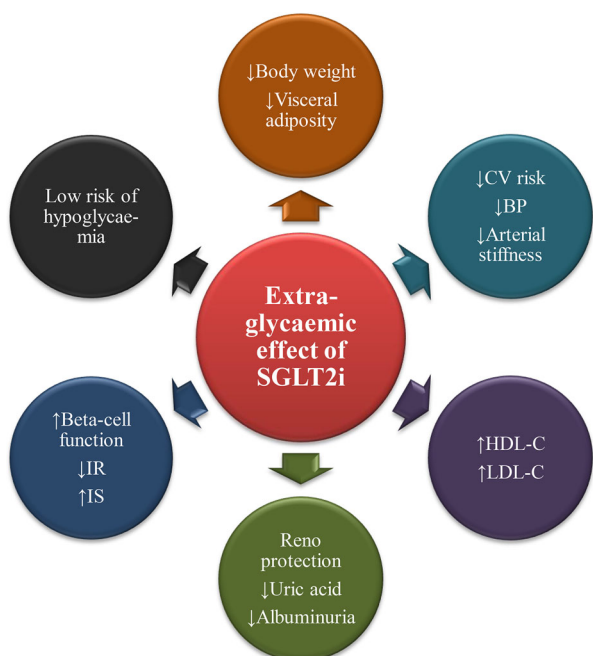
Fig. 2 Extra-glycaemic effects of SGLT2i [13, 87]. *BP* blood pressure, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *IR* insulin resistance, *IS* insulin sensitivity, ↓ decrease/reduction, ↑ increase

circumference (WC) ($P < 0.001$) compared to baseline [96]. Similarly, Bolinder et al., in a double-blind RCT, reported that the addition of SGLT2i in patients uncontrolled with metformin reduced body weight by − 4.54 kg, WC by − 5.0 cm and fat mass by − 2.80 kg over 102 weeks [97].

A meta-analysis including 6 RCTs ($\leq$ 26 weeks) reported that a combination of SGLT2i and metformin was associated with greater body weight reduction compared to metformin monotherapy (pooled between-group difference − 2.0 kg; 95% CI − 2.5 to − 1.5 kg) [61]. Similarly, a systematic review and NMA stated that the addition of SGLT2i contributed a greater weight loss (range from − 1.63 to − 2.5 kg) compared to metformin monotherapy in T2DM patients [62].

Similarly, SGLT2i have been shown to produce a significant weight loss compared to some active comparators when used as a second-line agent. In a systematic review and meta-analysis of RCTs, Li et al. reported that SGLT2i compared to non-SGLT2i (glimepiride/linagliptin/sitagliptin/glipizide), both an add-on to metformin, significantly ($P < 0.00001$) reduced body weight after 52 weeks (MD − 3.87; − 4.94 to − 2.80) and after 104 weeks (MD − 3.53; − 4.86 to − 2.21) [73]. Moreover, this reduction in body weight was associated with a significant reduction in fat mass (both subcutaneous adipose tissue and visceral adipose tissue) as well as lean mass [73]. Similarly, a meta-analysis of several RCTs found that a combination of metformin and SGLT2i were strongly favoured over metformin and sulfonylurea combination (pooled MD − 4.7 kg), and significantly favoured over metformin and DPP4i combination (range in MD 1.8–3.6 kg) in terms of body weight reduction [61]. In addition, low- and high-dose SGLT2i + metformin therapy contributed
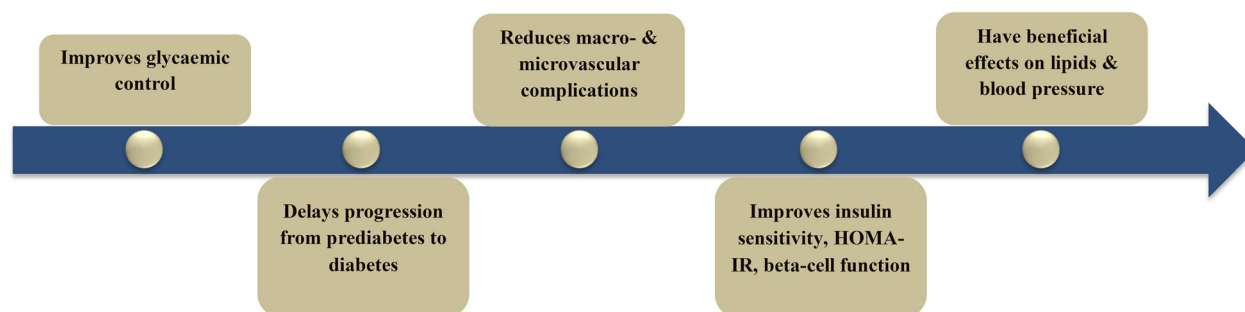
Fig. 3 Possible benefits of weight loss in patients with T2DM [1, 88–91]

1.8 kg (WMD = − 2.2 kg, p = 0.0000), and 2.1 kg (WMD = − 2.5 kg, p = 0.0000) weight loss, respectively, while DPP4i + metformin resulted in a weight gain of < 0.5 kg [98]. A recent meta-analysis of 97 RCTs (≥ 12 weeks) reported that SGLT2i were associated with a significant change in body weight from baseline (− 2.04 kg, $P < 0.001$), and GLP-1 RAs were associated with a comparable change in body weight from baseline (− 1.70 kg, $P < 0.001$), when used as an add-on therapy [99]. Numerous RCTs also reported a significant weight loss with SGLT2i as a second-line agent (for details see Table 8).

THE INDIAN PHENOTYPE

Indians have distinct clinical and biochemical deformities, which make them the so-called 'Asian Indian Phenotype'. These abnormalities include higher insulin resistance, elevated abdominal adiposity (i.e., higher visceral fat in spite of lower body mass index [BMI]), lower level of adiponectin and higher level of high sensitive C-reactive protein [100–103]. Moreover, Asian Indians have an increased metabolic risk compared to their counterparts; because of

- the existence of high leptin levels [104]; leptin concentration is a significant indicator of body fat ($P < 0.0001$), hip circumference, and fasting insulin [105];
- greater insulin resistance [102, 106, 107];
- higher insulin sensitivity index and lower acute insulin response to glucose [108];
- early loss of β-cell function [102];
- 'thin-fat Indian concept' or 'sarcopenic obesity' (Asian Indians have thinner limbs

[smaller muscle mass] with central obesity, with a higher waist-to-hip ratio and higher subscapular-to-triceps skin fold ratio than their British counterparts, which leads to higher insulin resistance) [109];
- more people suffer from diabetes at a relatively lower BMI compared with those of European descent [110];
- elevated mean A1C level (9.0%), which is 2.0% higher than the target suggested by international bodies [109].

SGLT2i could produce multiple benefits in Indian diabetes patients. Table 9 [100–103, 111] shows the list of challenges faced by Indian patients and describes how SGLT2i could overcome the complications.

Evidence advocates that SGLT2i cause weight loss in the Indian population as in the global population. In a post hoc analysis of 4 double-blind RCTs, SGLT2i were associated with body weight reduction in the Indian population (mean reduction of − 2.5% and − 3.2% for CANA 100 mg and 300 mg, respectively) [84]. Similarly, a prospective analysis by Sosale et al. reported a weight reduction of 2.64 ± 1.27 kg ($P < 0.05$), and a retrospective study by Baruah et al. reported a mean change of weight from baseline (− 2.1 kg; − 3.8 to − 0.32, $P < 0.05$) with SGLT2i therapy [85, 86].

Blood Pressure Reduction

It is postulated that certain properties of SGLT2i such as osmotic diuresis, mild natriuresis, changes in nitric oxide release, and reductions in arterial stiffness may contribute to BP reduction [61]. A recent systematic review and meta-analysis of RCTs evaluated the efficacy of

Table 8 A summary of RCTs investigating the extra-glycaemic effect of SGLT2i as an add-on to metformin in patients with T2DM

Author et al.	Patients (*n*)	Intervention	Comparator	Change in BW	Change in SBP
Lavalle-González et al. [64]	918	A: CANA 100 mg or 300 mg daily	B: Placebo 26 weeks	− 3.3 or − 3.6 kg vs − 1.1 kg (both $P < 0.001$)	− 3.8 or − 5.1 mmHg vs + 1.5 mmHg (both $P < 0.001$)
Bailey et al. [68]	546	A: DAPA 2.5 mg or 5 mg or 10 mg daily	B: Placebo 102 weeks	− 1.10 or − 1.70 or − 1.74 vs + 1.36 kg (all $P < 0.0001$)	+ 0.7 or − 1.1 or − 0.3 vs + 1.5 mmHg
Haring et al. [70]	637	A: EMPA 10 mg or 25 mg daily	B: Placebo 24 weeks	− 2.08 or − 2.46 kg vs − 0.45 kg (both $P < 0.001$)	− 4.5 or − 5.2 mmHg vs − 0.4 mmHg (both $P < 0.001$)
Leiter et al. [75]	1450	A: CANA 100 mg or 300 mg daily	B: GLIM titrated up to 6–8 mg/daily 104 weeks	− 3.6 or − 3.6 kg vs + 0.8 kg	− 2.0 or − 3.1 mmHg vs − 1.7 mmHg
Del Prato et al. [76]	814	A: DAPA 2.5, 5 or 10 mg	B: GLIP 5, 10 or 20 mg 208 weeks	− 3.65 kg vs + 0.73 kg	− 3.69 mmHg vs − 0.02 mmHg
Ridderstråle et al. [77]	1449	A: EMPA 25 mg daily	B: GLIM 1–4 mg daily 104 weeks	Difference − 4.5 kg ($P < 0.0001$)	− 3.1 mmHg vs + 2.5 mmHg ($P < 0.0001$)
Lavalle-González et al. [64]	1284	A: CANA 100 mg or 300 mg daily	B: SITA 100 mg daily 52 weeks	− 3.3 or − 3.7 kg vs − 1.2 kg (both $P < 0.001$)	− 3.5 or − 4.7 mmHg vs − 0.7 mmHg (both $P < 0.001$)
Rosenstock et al. [78]	355	A: DAPA 10 mg daily	B: SAXA 5 mg daily 102 weeks	− 2.4 kg vs 0.0 kg	− 3.5 mmHg vs 0.0 mmHg
DeFronzo et al. [79]	413	A: EMPA 10 mg or 25 mg daily	B: LINA 5 mg daily 52 weeks	− 2.9 or − 2.8 kg vs − 0.3 kg	− 3.5 or − 2.8 mmHg vs + 0.3 mmHg

BW body weight, *SBP* systoli BP, *CANA* canagliflozin, *DAPA* dapagliflozin, *EMPA* empagliflozin, *GLIM* glimepiride, *GLIP* glipizide, *SITA* sitagliptin, *SAXA* saxagliptin, *LINA* linagliptin

SGLT2i in 24-h ambulatory BP [113]. SGLT2i significantly reduced 24-h ambulatory systolic and diastolic BP by − 3.76 mmHg (95% CI − 4.23 to − 2.34; $I^2 = 0.99$) and − 1.83 mmHg (95% CI − 2.35 to − 1.31; $I^2 = 0.76$), respectively [113]. Similarly, several meta-analyses have also advocated that the addition of SGLT2i to metformin was associated with a significant reduction in BP when compared to metformin monotherapy [61–63].

Compared to other antidiabetic drugs, SGLT2i also provide a significant reduction in

Table 9 Evolving role of SGLT2i in Indian phenotype with T2DM [100–103, 111]

Challenges with Indian patients	Relevant SGLT2i features
Higher abdominal adiposity and visceral fat at any given body mass index	↓ Body weight (more visceral fat mass loss than subcutaneous fat loss)
Higher waist circumference and waist to hip ratio	↓ Waist circumference
Low level of adipokine and high plasma leptin increases concentrations of triglycerides	↓ Both triglycerides and leptin
Low rate of glucose disposal	↑ Rate of glucose disposal
Impaired insulin secretion and increased insulin resistance	Improve β-cell function and ↓ insulin resistance

BP when used as a second-line agent. In an NMA, SGLT2i significantly reduced systolic BP compared to sulfonylurea (range 4.4–5.64 mmHg), and DPP4i (range 2.26–5.79 mmHg) [63]. In another meta-analysis, the combination of metformin and SGLT2i were favoured in terms of BP reduction compared to metformin and sulfonylurea combination (pooled between-group difference 5.1 mmHg; 95% CI 4.2–6.0 mmHg), and metformin and DPP4i combination (pooled between-group difference 4.1 mmHg; 95% CI 3.6–4.6 mmHg) [61]. In addition, the durability of BP reduction with SGLT2i is similar to that of its other properties, such as glycaemic control and body weight reduction [76], which may boost its use in patients with T2DM. Moreover, evidence advocates that, unlike GLP1 RAs, SGLT2i do not trigger an increase in heart rate, despite reductions in BP [13]. Numerous RCTs also reported a significant systolic BP reduction with SGLT2i as a second-line agent (for details see Table 8).

Regulation of Lipid Levels

SGLT2i have been associated with a small increase in high-density lipoprotein cholesterol (HDL-C) as well as low-density lipoprotein cholesterol (LDL-C) and a reduction in triglyceride levels [13, 87]. Meta-analyses of several RCTs reported that treatment with SGLT2i was associated with a small increase in HDL-C level in T2DM patients with no clinically significant changes in LDL-C and triglyceride level [47, 114]. In a double-blind RCT, SGLT2i treatment in T2DM patients who were uncontrolled with metformin reported an increase in HDL-C and a reduction in triglycerides compared with placebo [115]. Furthermore, SGLT2i compared to DPP4i caused a significant increase in HDL-C and LDL-C levels after 24 weeks [116].

Cardiovascular Risk Reduction

Cardiovascular disease (CVD) remains the prominent cause of mortality and morbidity in developing countries [117]. The literature advocates that hypertension and diabetes are more important risk factors in younger Indian women than in men; women have a higher prevalence of hypertension and diabetes compared to men [118]. Moreover, abnormalities in lipid metabolism play a vital role in the development of CAD in young Indians [118]. Evidence suggests that SGLT2i provide CV benefits in patients with T2DM [119, 120]. Various possible routes that might influence the CV benefits of SGLT2i are depicted in Fig. 4 [87]. A systematic review and meta-analysis including several RCTs reported that SGLT2i reduced the risk of major adverse CV events (MACE) (RR 0.84; $P = 0.006$), CV death (RR 0.63; $P < 0.0001$), heart failure (RR 0.65; $P = 0.002$), and death from any cause (RR 0.71; $P < 0.0001$), compared to a control group. However, an adverse effect on non-fatal stroke (RR 1.30; $P = 0.049$) was observed. Moreover, these CV benefits of SGLT2i are a class effect rather than an individual effect [120].

Similarly, an NMA compared the effectiveness of SGLT2i against other oral antidiabetic drugs (OADs) (metformin, sulfonylureas, thiazolidinedione, and DPP4i) in preventing CV
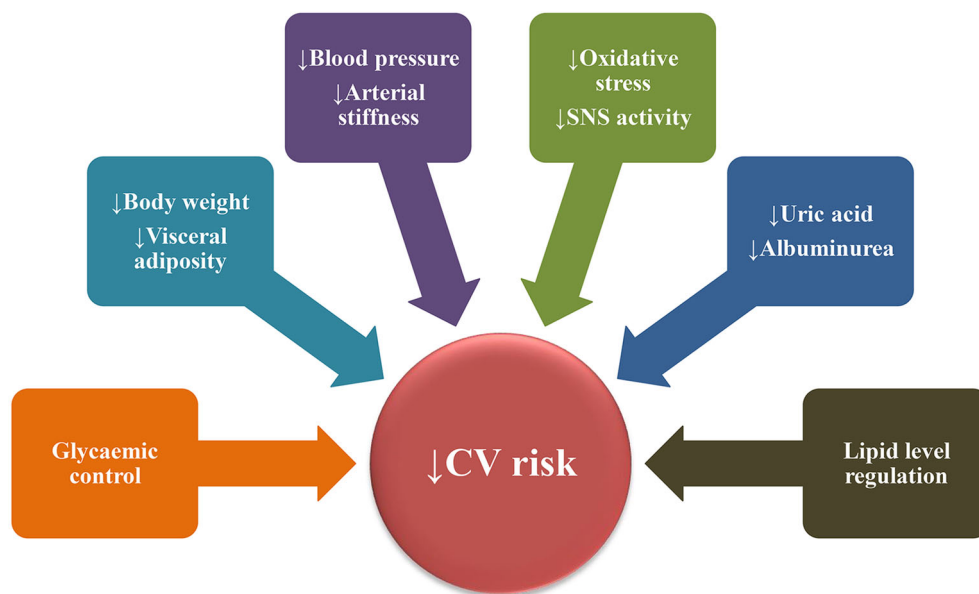
Fig. 4 Possible pathways that may impact CV benefits of SGLT2i [87]. *CV* cardiovascular, *SNS* somatic nervous system, ↓ decrease/reduction. Reproduced with permission from Inzucchi, Zinman, Wanner, et al. SGLT-2 inhibitors and cardiovascular risk: Proposed pathways and review of ongoing outcome trials. Diabetes and Vascular Disease Research. 2015; 12:90–100

mortality and morbidity [119]. The relative risk for all-cause mortality, CV mortality, acute coronary syndrome, and myocardial infarction (MI) (only against DPP4i and placebo) were reported to be low for SGLT2i compared to all other OADs [119]. Moreover, another meta-analysis reported that SGLT2i along with their multifactorial benefits were associated with no increased risk for MACE in various subgroup populations (e.g., degree of CV risk, any other risk, and hypoglycaemia) [121]. In line with the evidence, several pooled analyses of RCTs [122, 123], CANVAS trial [124], and EMPA-REG OUTCOME trial [125] advocate that SGLT2i are associated with a lower incidence of CV mortality and morbidity compared to placebo in high-risk CV patients. Moreover, the results of the major ongoing Dapagliflozin Effect on CardiovascuLAR Events (DECLARE-TIMI 58) trial will shed light on the long-term CV effectiveness of SGLT2i in T2DM patients [126]. Thus, SGLT2i may have a better impact on women with CVD as more women are prone to heart disease in India.

In addition, several instances of real-world evidence including the CVD-REAL study [127],

UK THIN database study [128], and Swedish national registries [129] have also reported that treatment with SGLT2i was associated with a lower risk of CV event, mortality and morbidity compared with other glucose-lowering agents in T2DM patients. The CVD-REAL study included 309,056 patients from six countries (US, Norway, Denmark, Sweden, Germany and the UK) who were newly initiated on either SGLT2i or other antidiabetic drugs. Compared to other antidiabetic drugs, SGLT2i were associated with lower rates of heart failure hospitalization (HHF) (hazard ratio [HR] 0.61; 95% CI 0.51–0.73; $P < 0.001$); death (HR 0.49; 95% CI 0.41–0.57; $P < 0.001$), and HHF or death (HR 0.54; 95% CI 0.48–0.60, $P < 0.001$) with no significant heterogeneity by country [127].

Reno-Protective Effect

Like other benefits, SGLT2i also contribute a renoprotective effect in patients with T2DM. SGLT2i acutely reduced estimated glomerular filtration rate (eGFR), followed by progressive recovery and stabilisation of renal function [130]. In recently published RCTs (CANVAS,

EMPA-REG OUTCOME), SGLT2i were associated with slower progression of kidney disease, reduced progression of albuminuria, and reduction of eGFR with lower rates of clinically relevant renal adverse events in high-risk patients [124, 131]. Moreover, a pooled analysis of 12 RCTs reported that SGLT2i were not associated with an increased risk of acute renal toxicity or deterioration of renal function in T2DM patients with normal or mildly impaired renal function [132]. Furthermore, compared to glimepiride, SGLT2i reduced the progression of renal disease over 104 weeks, and may confer renoprotective effects independently of their glycaemic effects in patients with T2DM [133].

MISCELLANEOUS EFFECTS

Improved Insulin Sensitivity and B-Cell Function

Evidence suggests that SGLT2i improve insulin sensitivity and β-cell function in the setting of A1C and weight reduction in patients with T2DM [112, 134, 135]. SGLT2i may be beneficial in insulin-resistant patients due to their proven benefits in both improving insulin sensitivity and weight reduction. In a placebo-controlled RCT, SGLT2i significantly ($P = 0.0059$)

Recommendation: Dual Therapy

- In T2DM patients with unmet needs of glycaemic control with metformin monotherapy, SGLT2i are a preferred option as a second-line agent (Grade A, EL 1)

- SGLT2i as monotherapy and as an add-on to metformin effectively reduce A1C, FPG, body weight and BP in patients with T2DM (Grade A, EL 1)

- In patients with T2DM, SGLT2i provide superior long-term glycaemic efficacy compared to DPP4i and sulfonylureas (Grade A, EL 1)

- Compared to sulfonylureas, SGLT2i as a second-line agent, are associated with non-inferior glycaemic control with a significant reduction in body weight, BP and rates of hypoglycaemia (Grade A, EL 1)

- When used as a second-line agent after metformin, SGLT2i are more effective in terms of glycaemic control, body weight, and BP reduction than DP44 inhibitors (Grade A, EL 1)

- SGLT2i significantly reduce the risk of CV morbidity and mortality (Grade A, EL 1)

- SGLT2i are associated with renoprotective effects such as slower progression to kidney disease and slower progression of albuminuria, and a reduction of eGFR in patients with T2DM (Grade A, EL 1)

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improved insulin sensitivity versus placebo [134] and in another RCT [136] they significantly reduced insulin resistance ($p < 0.001$) in T2DM patients.

Improves Serum Magnesium

A post hoc analysis of 4 RCTs reported that SGLT2i control the level of serum magnesium in hypomagnesaemia patients with T2DM, which may subsequently improve the cardio-metabolic outcome [142].

Recommendation: Miscellaneous Effects

- SGLT2i improve insulin sensitivity and β-cell function and reduce insulin resistance; therefore, they are recommended in insulin-resistant T2DM patients (Grade A, EL 2)

- When combined with insulin, SGLT2i may decrease the cost of insulin treatment by reducing the daily insulin dose requirements (Grade B, EL 3)

- Treatment with SGLT2i may reduce the level of uric acid and decrease albuminuria; thus, they might decrease diabetes complications in patients with T2DM (Grade B, EL 3)

Reduction of Daily Insulin Dose and Cost of Treatment

In patients with unmet needs of glycaemic control with maximum doses of OADs and insulin, the addition of SGLT2i reduces daily insulin dose requirement and therefore the cost of insulin therapy [137]. Moreover, a UK healthcare system perspective analysis confirmed that SGLT2i + metformin are more cost-effective than DPP4i + metformin [138].

Reduction of Uric Acid Level

Many patients with T2DM have high serum uric acid levels that might damage the kidney and cause several microvascular complications [139]. Evidence suggests that SGLT2i significantly reduced the levels of uric acid in the plasma [140, 141]. They may also inhibit reabsorption of sodium coupled-uric acid in the PCT, resulting in increased uric acid elimination [13].

SAFETY AND TOLERABILITY

Hypoglycaemia

Hypoglycaemia is a major cause of concern with some antidiabetic agents; however, pertaining to their insulin-independent mechanism of action, SGLT2i produce less hypoglycaemia than other antidiabetic agents [13, 25]. Nonetheless, when SGLT2i are used concomitantly with insulin or insulin secretagogues, the risk of hypoglycaemia increases, and close monitoring of the patient is required [143]. Li et al., in a meta-analysis, found that SGLT2i compared to non-SGLT2i were associated with a significantly lower incidence of hypoglycaemic events when used as an add-on to metformin (OR 0.27; $P = 0.02$) [73]. SGLT2i were associated with a lower incidence of mild or moderate hypoglycaemia compared to sulfonylureas when used after metformin monotherapy (5% vs 34%) [144]; and a similar incidence of hypoglycaemia was documented when compared to DPP4i (4.2% vs 4.7%) [64].

UTI and GTI

Increased urinary glucose levels due to the use of SGLT2i results in glycosuria. This subsequently increases the risk of GTIs (balanitis and balanoposthitis in men and vulvovaginitis in women) and to a relatively lesser extent UTIs [13]. In a meta-analysis of RCTs, the incidence of suspected or confirmed GTIs was reported to be significantly ($P < 0.00001$) higher with SGLT2i (OR 6.41 [95% CI 3.58, 11.45] for men and 5.12 [95% CI 3.48, 7.54] for women) compared to non-SGLT2i agents, both used as an add-on to metformin [73]. However, a meta-analysis of several RCTs found inconsistent results regarding the incidence of UTI between SGLT2i and DPP4i, and between SGLT2i and sulfonylureas, when all added to metformin [13]. Similar results were also reported in a post hoc analysis conducted in Indian T2DM patients [9]. Nevertheless, the incidence of GTIs and UTIs is more common in females than in males, and can be corrected through standard treatment. The South Asian Federation of Endocrine Societies (SAFES) consensus statement advocates that perineal hygiene should be maintained to prevent GTIs and, after 3 months of GTI-free status, patients with T2DM can be prescribed with SGLT2i along with prophylactic antifungal coverage. However, SGLT2i should be avoided in the case of a previous history of upper UTIs, complicated GTIs, or refractory or resistant GTIs [13].

Volume Depletion

Glycosuria caused by SGLT2i triggers volume depletion by eliminating more fluid from the body through the process of osmotic diuresis [13, 145]. The adverse events associated with volume depletion are BP reduction, dehydration, postural dizziness, orthostatic hypotension, orthostatic intolerance, syncope, and reduction in urine output. A meta-analysis of several RCTs stated that the difference in volume depletion between SGLT2i + metformin and DPP4i + metformin was unclear. However, the study found a small difference between sulfonylureas + metformin and SGLT2i + metformin (pooled OR 1.0; 95% CI 0.6–1.7) [61]. Moreover, volume depletion-related events were reported to be higher with SGLT2i in

different RCTs when compared to sulfonylureas (3% vs < 1%) [144], and DPP4i (3.0% vs 0.5%) [64]. In addition, a post hoc analysis of phase III RCTs also reported a similar incidence of volume depletion-related adverse events with SGLT2i in an Indian population vis-à-vis the overall population [84]. Hence, before prescribing SGLT2i, analysis of volume status and thorough monitoring of volume depletion-related adverse events is highly obligatory in T2DM patients.

Bone Fractures and Osteoporosis

The risk of bone fracture is increased in people with diabetes compared to their non-diabetic counterparts [146]. Patients with type 1 DM are at a higher risk of osteoporosis, and the risk of hip fracture is generally increased in patients with T2DM [1]. SGLT2i should be used with caution in patients with T2DM who have a high fracture risk [1]. Due to their osmotic diuresis effect, SGLT2i cause volume depletion which subsequently disturbs the electrolyte (serum calcium and phosphate) concentration in the body, and may show a harmful effect on bone health [147]. Moreover, SGLT2i elevate serum phosphate and subsequently enhance the secretion of a parathyroid hormone that may increase bone resorption and the risk of bone fractures [148]. In addition, hyponatraemia caused by SGLT2i might increase osteoporosis and fracture risk [147]. A pooled analysis of 9 RCTs (including the CANVAS trial; $n = 4{,}327$) reported that only patients from the CANVAS trial who were continuing CANA had shown a higher risk of fracture when compared to non-CANA patients (4% vs 2.6%) [149]. Moreover, EMPA also revealed few fracture incidents in CKD patients with T2DM in a double-bind RCT [150]. However, an international multi-centre, parallel-group, double-blind RCT reported that DAPA had no effect on markers of bone formation and resorption or bone mineral density in T2DM patients [151]. Similarly, a recent meta-analysis of 20 RCTs ($n = 8{,}286$) revealed that there was no increased risk of bone fracture with SGLT2i treatment compared to placebo in patients with T2DM (SGLT2i vs placebo; pooled risk ratio 0.67, 95% CI 0.42–1.07) [152]. Nonetheless, SGLT2i should be used cautiously in older patients, and in those

with a prior history/risk of CVD, with lower baseline eGFR and taking more diuretics at baseline [149].

Peripheral Vascular Disease/Toe Amputation

The literature suggests that SGLT2i are associated with improvement in CV prognosis in high CV-risk patients with T2DM [153]. However, recent evidence reported that SGLT2i (CANA) was associated with an unexpectedly increased risk of amputation in patients with T2DM [124]. Moreover, the underlying mechanisms that lead to amputation and whether the risk of amputation is particular to SGLT2i remain unclear [153]. The risk of amputation nearly doubled in patients on CANA compared to placebo in participants in the CANVAS trial (6.3 vs 3.4 participants per 1,000 patient-years, corresponding to an HR of 1.97; 95% CI 1.41–2.75) with T2DM and a high CV risk; 71% of amputations were primarily at the level of the toe or metatarsal [124]. However, a pooled analysis from 15 RCTs (phase I–III) including the EMPA-REG OUTCOME trial reported no difference in the incidence of amputation in EMPA and placebo-treated T2DM patients (both 1.1%) [154]. Data regarding DAPA on peripheral vascular disease are limited.

Recommendation: Safety

- Hypoglycaemia risk in patients with T2DM is less with SGLT2i when compared to insulin secretagogues and insulin. Patients taking a combination of SGLT2i and insulin or insulin secretagogues should be closely monitored (Grade A, EL1)

- SGLT2i are associated with a higher rate of GTIs than other antidiabetic drugs; however, differences in the incidence of UTIs between SGLT2i and other antidiabetic drugs are inconsistently reported (Grade A, EL1)

- Compared to other antidiabetic drugs, SGLT2i are associated with volume depletion- or osmotic diuresis-related adverse events (Grade A, EL1)

- There is insufficient evidence to suggest causality between SGLT2i and an increased risk of bone fracture and osteoporosis in patients with T2DM. Treatment should be individualised in high-risk patients (older patients, with a prior history/risk of CVD) (Grade A, EL1)

- SGLT2i (CANA) are associated with a higher risk of peripheral vascular disease/amputation (Grade A, EL1)

CONTRAINDICATIONS/WHEN NOT TO USE

The labelling for SGLT2i includes some warnings or precautions. These include genital mycotic infections, hypoglycaemia (when used with insulin or insulin secretagogues), hyperkalaemia, hypersensitivity reactions, hypotension, impaired renal function, increased LDL-C, UTIs, etc. [143]. SGLT2i are contraindicated in patients with eGFR < 45 mL/min/1.73 m^2, extreme insulinopenic or type 1 diabetes, patients on a fluid/carbohydrate restricted diet, or patients with decompensated medical/surgical illness, pregnant and lactating women and in children [13].

management of T2DM. SGLT2i improve all glycaemic parameters (A1C, FPG, and PPG), and have additional benefits like body weight and BP reduction, and lipid level regulation. Apart from this, they are also associated with a reduction in CV and renal risk. However, GTIs, DKA and to a lesser extent UTIs are some of the concerns with SGLT2i which can be managed with appropriate patient counselling and treatment individualisation. Taken together, SGLT2i are an attractive option for the management of T2DM patients in the Indian scenario after initial metformin monotherapy failure. Moreover, they can be specifically preferred if body weight and BP reduction and improving insulin sensi-

> **Recommendation: Contradictions/When NOT to use**
>
> - SGLT2i are contraindicated in patients with eGFR < 45 mL/min/1.73 m^2, extreme insulinopenic or type 1 diabetes, on a fluid/carbohydrate restricted diet, or with decompensated medical/surgical illness, pregnancy, lactation and in children (Grade A, EL1)

CONCLUSION

SGLT2i appear to be generally well tolerated and can be safely used as monotherapy or in combination with other OADs and insulin in the

tivity are the part of the primary treatment concern.

> **Recommendation: Indian Phenotype**
>
> - SGLT2i are emerging agents that can provide multiple benefits in Indian diabetes patients (Grade B, EL 3)
> - The weight reduction associated with SGLT2i is due to loss of fat mass mainly from the abdomen rather than lean mass (Grade A, EL 2)
> - The benefits associated with SGLT2i such as improvement of β-cell function and reduction of insulin resistance may be more useful in Indian diabetes patients (Grade A, EL 2)

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