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Review

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Dapagliflozin-Saxagliptin Combination - The Quest for Optimal Glycemic Control With Cardio-Renal Protection in Type 2 Diabetes Mellitus: An Expert Consensus in Indian Settings

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Abstract

The combination of dapagliflozin (DAPA; a sodium-glucose cotransporter-2 inhibitor (SGLT2i)) and saxagliptin (SAXA; a dipeptidyl peptidase-4 inhibitor (DPP4i)) added on to metformin targets multiple pathophysiological pathways and provides a synergistic effect on glycemic control. Notably, both DAPA and SAXA have demonstrated cardiovascular safety and shown to slow the progression of declining renal function in patients with type 2 diabetes mellitus (T2DM) having comorbid cardiovascular or renal diseases. Together, DAPA + SAXA has an acceptable tolerability profile, comparable with the individual agents and with a low propensity for hypoglycemia. The addition of DAPA + SAXA to metformin has been associated with low frequency of urinary tract and genital infections, attributed to the complementary effects of combining an SGLT2i and a DPP4i. This review compiles insights from a group of leading experts from India, summarizing concise clinical practice recommendations for the use of a fixed-dose combination of DAPA (10 mg) + SAXA (5 mg) in Indian patients with T2DM. The review encompasses available evidence and clinical experiences, highlighting the benefits of this combination for comprehensive glycemic control and enhanced cardio-renal protection in the management of T2DM.

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Introduction

Type 2 diabetes mellitus (T2DM) is a global health problem, with Southeast Asia at the epicenter. India is often regarded as the diabetic capital of the world and is central to the burden of T2DM in the Southeast Asian region as well as globally. Per the 2021 International Diabetes Federation (IDF) estimates, there are 537 million adults living with T2DM globally, with 74.2 million residing in India [1]. In the 2023, the Indian Council of Medical Research-India Diabetes (ICMR-INDIAB) cross-sectional study, conducted among 113,043 individuals from urban and rural India, reported the overall weighted prevalence of diabetes as 11.4% and prediabetes as 15.3%. The study highlighted the escalating prevalence of metabolic noncommunicable diseases, including hypertension, obesity, and dyslipidemia, emphasizing the need for optimal management of T2DM with comprehensive effects [2].

India faces several challenges around the management of T2DM, which includes the economic transition, rampant urbanization, and declining nutritional value, coupled with a general lack of awareness and literacy about T2DM, its management, complications, and long-term impact. Additionally, distinct Asian-Indian phenotypic features such as young age of onset, high visceral fat, waist circumference, waist-hip ratio, high levels of insulin resistance and early β-cell dysfunction despite low body mass index (BMI) heighten the clinical risk of T2DM in Indians [3, 4]. In the Investigation of Glycosylated Hemoglobin on Therapy in Indian Diabetics (TIGHT) study, nearly 77% of patients with T2DM receiving oral hypoglycemic agents with or without insulin had poor glycemic control (uncontrolled glycated hemoglobin (HbA1c) ≥ 7%) [5]. Other issues that confound the management of T2DM in India include delayed diagnosis, longer duration of disease and poor glycemia management, which are also associated with greater

odds of developing severe microvascular and macrovascular complications in this population [6-9].

The Asian-Indian phenotype in T2DM is also predisposed to an increased risk of developing cardiovascular and renal diseases [9]. In an observational study from India, a large majority of the 5,080 patients with newly diagnosed T2DM were grouped in the high-risk category for developing cardiovascular diseases (2,007 patients (39.5%) classified as "high-risk" and 3,073 (60.5%) classified as "very high-risk") [10]. Previous studies have also demonstrated high prevalence of cardiovascular disorders in patients with T2DM [11, 12]. A high prevalence of renal disorders also co-exists in Indian patients with T2DM. The SEEK study, a large cross-sectional study (n = 5,588) screening patients for early signs of renal diseases across India, reported that 31.6% patients with chronic kidney disease (CKD) have T2DM [13]. A similar study reporting the prevalence of renal dysfunction in normoalbuminuric Indian patients with T2DM (n = 3,534) concluded that more than one-third of the patients assessed developed CKD [14].

Adequate glycemic control is fundamental to achieving the larger goals of T2DM management, which include prevention of chronic complications, managing cardiovascular risk factors, improving the patient's quality of life, and avoiding hypoglycemia. Compelling evidence supports the use of combination of oral antihyperglycemic agents with different mechanisms of action and wide-ranging clinical effects to achieve superior glycemic control and delay progressive cardiometabolic deteriorations [15, 16]. Optimized fixed-dose combinations (FDCs) of oral antihyperglycemic agents have shown to achieve the desired glycemic targets with acceptable safety and tolerability and additional benefits of improved adherence and reduced cost [17].

The FDC of once daily dapagliflozin (DAPA, 10 mg), a sodium-glucose cotransporter-2 inhibitor (SGLT2i) and saxagliptin (SAXA, 5 mg), a dipeptidyl peptidase-4 inhibitor (DPP4i) was approved for the treatment of T2DM in adults by the US Food and Drug Administration in 2017 [18, 19]. Following this, it was approved for T2DM in adults by the Drug Controller General of India (DCGI, Central Drugs Standard Control Organization (CDSCO)) in September 2019 [17, 20]. The FDC of DAPA and SAXA has demonstrated optimal bioequivalence to the combination therapy administered as two separate medications. Thus, although no phase 3 studies investigating the efficacy of the FDC have been conducted, several clinical studies have demonstrated potent and durable efficacy of the combination in lowering HbA1c and fasting plasma glucose (FPG) [21-24]. The FDC of DAPA + SAXA added to background metformin (MET) therapy might be particularly useful in Indian patients for achieving clinically meaningful glycemic control and improving associated metabolic disruptions (cardio-renal benefits) specific to patients with T2DM of the Asian-Indian phenotype [17].

Although several international diabetes guidelines advocate the use of optimum combination therapies, there are no specific clinical recommendations elucidating the use of DAPA + SAXA and their cardio-renal benefits in the Indian population. The present review provides clinical practice recommendations for the use of the DAPA + SAXA FDC in Indian patients with T2DM, focusing on their complementary mechanism of action, combined physiologic effects and available clinical evidence supporting their clinical benefits.

Methodology

A group of 10 experts from India convened a consensus meeting on May 12, 2023, which was held virtually to discuss the use of the FDC of DAPA + SAXA in Indian patients with T2DM. Discussions during this meeting were facilitated by a questionnaire intended to gather more structured information on the current clinical practice related to the use of the FDC in Indian patients with T2DM. Reported here are the statements recorded during the consensus meeting that were based on the clinical experiences of the expert panel along with supporting evidence from the literature. A comprehensive literature search was performed on PubMed and Google Scholar databases, using relevant search terms such as "diabetes", "type 2 diabetes mellitus", "fixed-dose combination", "DPP4-inhibitor", "SGLT2-inhibitor", "dapagliflozin", "saxagliptin" and "India". The search was strengthened by using a combination of free text and Medical Subject Headings (MeSH) terms and Boolean operators to combine keywords. Primarily, clinical trials, systematic reviews and real-world evidence (RWE) studies served as primary data source.

Combination Therapy in the Management of T2DM

Over the years, the treatment standards for T2DM have evolved with a greater emphasis now on early detection, treatment initiation and intensification to dampen the progressive decline in β-cell function and the persistent increase in blood glucose levels. Early initiation of combination therapy is therefore recommended to improve prognosis in patients with T2DM. International guidelines for the management of diabetes mellitus from the American Diabetes Association (ADA) and American Association of Clinical Endocrinologists-American College of Endocrinology (AACE) advocate a stepwise intensification approach for glycemic control (Table 1) [15, 25, 26]. The AACE provides a broader choice of initial treatments and advocates a more individualized approach based on HbA1c levels. Both groups encourage early initiation of treatment with combination of complementary pharmacotherapies to delay onset of diabetic complications and treatment failure. Aligned with these guidelines, the Research Society for the Study of Diabetes in India (RSSDI) also advocates initiation of combination therapy if the HbA1c is 1.5 above the target (< 7%) in adult Indian patients with T2DM (Table 1) [27].

In general, all treatment guidelines provide recommendations that focus on cardiovascular and renal safety, prevention of hypoglycemia, weight gain, as well as offer convenience of administration (oral agents, single-pill choices or once-a-day therapy) for improved adherence and long-term management [28, 29]. Thus, optimal treatment may require drugs with complementary mechanisms of action, which can target multiple pathophysiological defects [29, 30].

FDCs have been shown to be associated with improved

Table 1. Summary of Recommendation of T2DM Management Pertaining to Pharmacologic Agents by ADA, AACE and RSSDI

ADA [25]	AACE [26]	RSSDI [27]
• Metformin should be continued upon initiation of insulin therapy (unless contraindicated or not tolerated) for ongoing glycemic and metabolic benefits. • Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals. Consider effects on cardiovascular and renal comorbidities, efficacy, hypoglycemia risk, impact on weight, cost and access, risk for side effects, and individual preferences. • Early combination therapy can be considered in some individuals at treatment initiation to extend the time to treatment failure. • Among individuals with T2DM who have established atherosclerotic cardiovascular disease or indicators of high cardiovascular risk, established kidney disease, or heart failure, SGLT2i and/or GLP-1 RA with demonstrated cardiovascular disease benefit is recommended as part of the glucose-lowering regimen and comprehensive cardiovascular risk reduction, independent of A1c and in consideration of person-specific factors.	• Metformin should be initiated if there is no contraindication. • Clinicians should consider multiple factors when selecting the second agent, including presence of overweight or obesity, hypoglycemia risk, access/cost, and presence of severe hyperglycemia. • In drug naive persons with newly diagnosed T2DM, prospective studies support the initiation of combination therapy to achieve glycemic targets more quickly as compared with a stepwise approach. • For overweight/obese patients GLP-1RA or SGLT2i is preferred, alternately DPP4i can be used. • For patients at risk of hypoglycemia, GLP-1RA or SGLT2i is preferred, alternately, DPP4i can be used. • In those patients with overweight or obesity and the additional goal of weight loss, dual GIP/GLP-1 RA, GLP-1 RA, or SGLT2i class are preferred options. Persons with a history of hypoglycemia, at high risk of hypoglycemia. and/or at risk for severe complications from hypoglycemia should preferentially be initiated with an agent associated with low risk for hypoglycemia, including GLP-1 RA, SGLT2i, dual GIP/GLP-1 RA, TZD, or DPP4i.	• Metformin can be initiated in combination with lifestyle interventions at the time of diagnosis. • Other options: sulfonylureas (or glinides), TZD, DPP4i, SGLT2i, AGi or oral GLP1-RA can be used initially for cases where metformin is contraindicated or not tolerated. • Consider cardiovascular/heart failure risk, renal/hepatic (NASH) risk and other comorbidities while deciding therapy. • Consider initiating combination therapy if the HbA1c > 1.5 above the target. • If glucose control targets are not achieved: Add SGLT2i, or DPP4i or sulfonylurea or TZD or AGi or oral GLP1-RA. • For patients with established or having high-risk for atherosclerotic cardiovascular disease, heart failure, diabetic kidney disease or in need of weight reduction consider using SGLT2i or oral GLP-1RA. • If glucose targets are not achieved with two agents: start third oral agent-AGI, DPP4i, SGLT2i, or TZD or oral GLP-1 RA (depending on the second-line agent used).

ADA: American Diabetes Association; AACE: American Association of Clinical Endocrinology; AGi: alpha-glucosidase inhibitors; DPP4i: dipeptidyl peptidase-4 inhibitor; GLP-1 RA: glucagon-like peptide-1 receptor agonist; GIP: gastric inhibitory polypeptide; GLP-1: glucagon-like peptide-1; HbA1c: glycated hemoglobin; NASH: nonalcoholic steatohepatitis; RSSDI: Research Society for the Study of Diabetes in India; SGLT2i: sodium-glucose cotransporter-2 inhibitor; T2DM: type 2 diabetes mellitus; TZD: thiazolidinediones.

medication adherence compared with free-drug combination regimen [30, 31]. In T2DM, studies have shown improved outcomes with combination therapy as opposed to monotherapy [32-35].

Do you perceive any challenge while prescribing FDCs?

Concurring with the available evidence, the majority of experts on the panel only recognized the lack of flexibility in dose adjustments and alterations as one of the challenges with prescribing FDCs [36-38]. A recent real-world study in patients with T2DM reported a significant ($P < 0.001$) improvement in adherence with the use of FDC versus the same drugs taken individually, with a safety profile comparable to that of the monotherapy [38] (Fig. 1).

Rationale for Combining DAPA and SAXA

Eight major metabolic processes involving multiple organs that

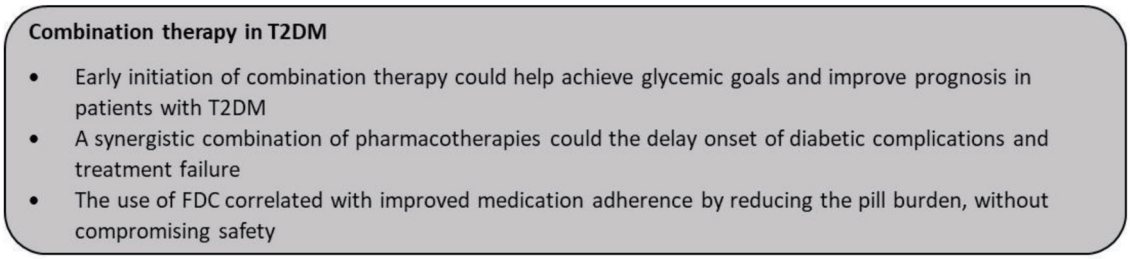

Figure 1. Combination therapy in T2DM. T2DM: type 2 diabetes mellitus.

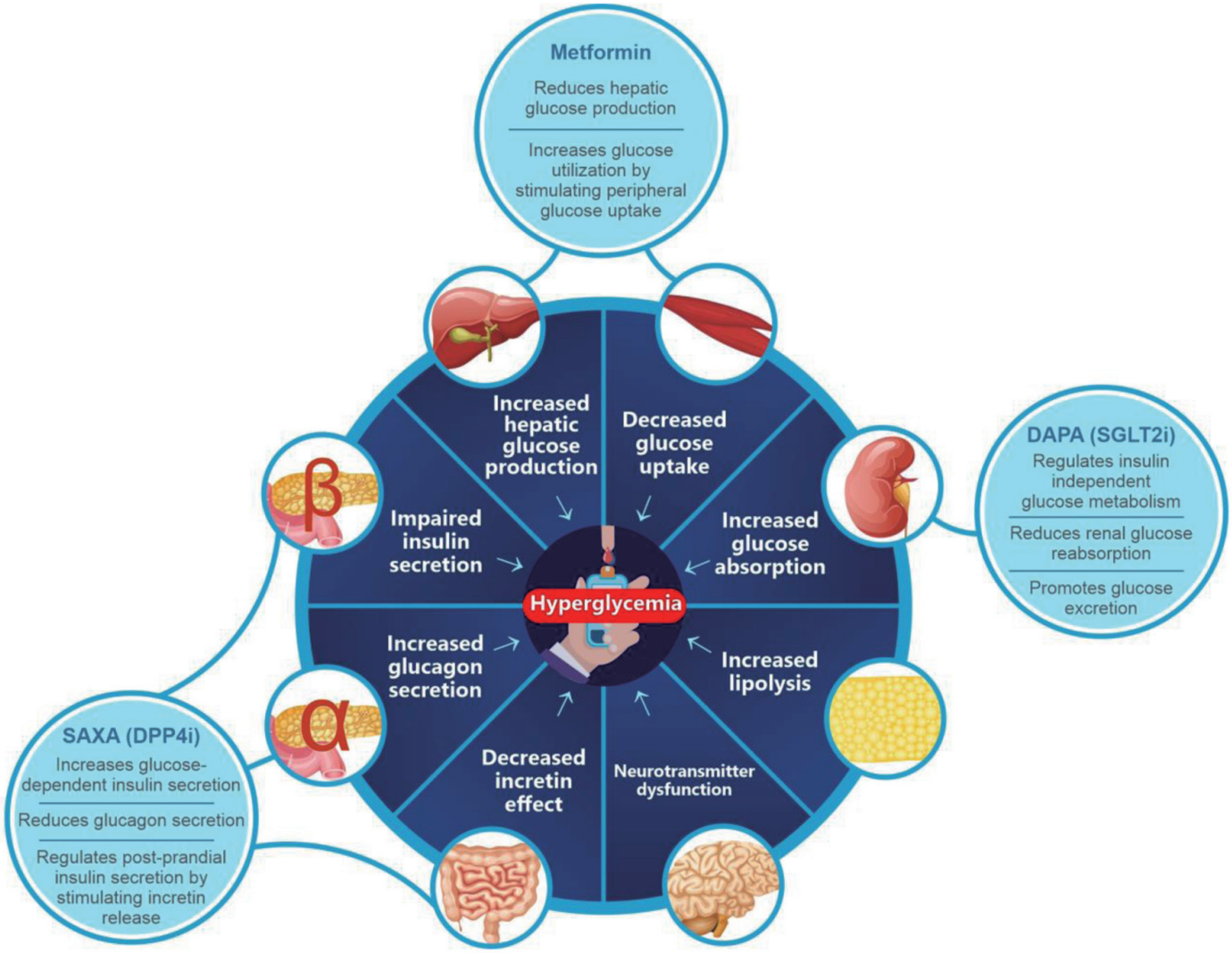

Figure 2. The ominous octet. DPP4i: dipeptidyl peptidase-4 inhibitor; SGLT2i: sodium-glucose cotransporter-2 inhibitor.

impact glucose metabolism have been identified as key players in the pathophysiology of T2DM. Together, these are called the ominous octet and comprise decreased insulin secretion, decreased incretin effect, increased lipolysis, increased glucagon secretion, increased glucose absorption, increased hepatic glucose production, neurotransmitter dysfunction and decreased glucose uptake (Fig. 2) [29, 39, 40]. The ominous octet reflects the multifactorial characteristic of T2DM, thus corroborating the use of therapeutics with effects at multiple physiological levels and early initiation of such therapies to prevent or slow the progressive damage of β cells and other detrimental downstream effects [29].

DAPA, an SGLT2i, reduces renal glucose reabsorption and promotes glucose excretion, thus targeting the kidney-mediated regulation of insulin-independent, glucose metabolism in the ominous octet [28, 41]. A large body of evidence from clinical trials and RWE studies have demonstrated clinically relevant outcomes with DAPA in lowering HbA1c, FPG and postprandial plasma glucose (PPG), and minimizing the occurrence of hypoglycemia, cardiovascular events and all-cause mortality [42-46]. FOREFRONT, an RWE study conducted in India, reported that treatment with DAPA significantly ($P < 0.001$) reduced the HbA1c level by 1% at 3 months and by 1.49% at 6 months. Meaningful reductions in body weight (mean (standard deviation (SD)) change from baseline: -1.86 kg (3.04), $P < 0.001$) and improvement in the systolic blood pressure (SBP) and diastolic blood pressure (mean (SD) change from baseline: -3.77 (12.22) and -1.46 (8.30) mm Hg, respectively) were also observed in the study [47]. Other studies of DAPA in Indian patients with T2DM have reported adequate glycemic control and favorable metabolic effects (Table 2) [21, 22, 24, 43, 44, 47-65].

DDP4is such as SAXA are involved in glucose-dependent insulin secretion, glucose-dependent decrease in glucagon secretion, improving β-cell sensitivity/function and inhibiting the degradation of incretin hormones, collectively resulting in the lowering of HbA1c and FPG levels [28]. Thus, SAXA's insulin-dependent mode of action targets the gut, pancreas and liver to achieve glucose lowering effect [28]. In a multicenter, randomized, double-blind, placebo-controlled, parallel-group

Table 2. Summary of the Studies Investigating the Outcomes of DAPA, DAPA + SAXA, and SAXA in Patients With T2DM

Author and trial name	Type of trial	Country	Patients and intervention	Key outcomes
Wiviott et al, 2019 [62] (DECLARE TIMI 58)	RCT	Multinational	Patients with T2DM (n = 17,160; n = 10,186 without atherosclerotic CVD) treated with DAPA 10 mg vs. PBO	• MACE: 8.8%, DAPA; 9.4%, PBO; HR: 0.93; 95% CI: 0.84 to 1.03; P = 0.17 • CVD death or hHF: 4.9% DAPA; 5.8% PBO; HR: -0.83; 95% CI: 0.73 to 0.95; P = 0.005 • Risk of hHF: HR: 0.73; 95% CI: 0.61 to 0.88 • Renal composite outcome: 4.3%, DAPA; 5.6%, PBO; HR: 0.76; 95% CI: 0.67 to 0.87 • Genital infections: 0.9%, DAPA; 0.1%, PBO, P < 0.01
McGurnaghan et al, 2019 [44]	RWE	Scotland, UK	Patients with T2DM (n = 8,566) treated with DAPA as per recommended dose	• HbA1c: -1.19% • SBP: -4.32 mm Hg, 95% CI: -4.84, -3.79 • BMI: -0.82 kg/m^2, 95% CI: -0.87, -0.77 • Body weight: -2.20 kg, 95% CI: -2.34, -2.06 • CVD in 111, DKA in 13 and LLA in 28 • CVD significantly low in ever-users vs. never-users (HR: 0.71, P = 0.02)
Viswanathan et al, 2019 [47] (FOREFRONT)	RWE	India	Patients with T2DM (n = 1,941, treated with DAPA) as per recommended dose	• HbA1c: -1.00% at 3 months; 1.49% at 6 months (P < 0.001) • Body weight reduction: 1.14 ± 2.21 kg, 3 months; 1.86 ± 3.04 kg, 6 months, P< 0.001 • Vulvovaginitis: 9 (0.5%); fungal infection and UTI: 4 (0.2%) each
McMurray et al, 2019 [59] (DAPA-HF)	RCT	United Kingdom (UK)	Patients with T2DM and NYHA class II, III, or IV HF and an ejection fraction of 40%, treated with DAPA 10 mg (n = 2,373) vs. PBO (n = 2,371)	• First worsening HF event: 237 (10.0%), DAPA; 326 (13.7%), PBO; HR: 0.70; 95% CI: 0.59 to 0.83 • Death from CV: 227 (9.6%), DAPA; 273 (11.5%), PBO; HR: 0.82; 95% CI: 0.69 to 0.98 • Death from any cause: 276 (11.6%), DAPA; 329 (13.9%), PBO; HR: 0.83; 95% CI: 0.71 to 0.97
Fuchigami et al, 2020 [63] (DIVERSITY-CVR)	RCT	Japan	Patients with T2DM treated with DAPA 5 - 10 mg (n = 170) vs. SITA 50 - 100 mg (n = 170)	• Achievement ratio of composite endpoint: (HbA1c ≤ 7.0%, maintenance of sensor glucose > 54 mg/dL, body weight loss ≥ 3.0%) higher in DAPA vs. SITA: 24.4% vs. 13.8% (P < 0.05) • Higher in DAPA vs. SITA: 24.4% vs. 13.8% (P < 0.05) • Hypoglycemia: 88.7 vs. 92.3%, DAPA vs. SITA • Body weight: ≥ -3.0%, DAPA (P < 0.001)
Brown et al, 2020 [54] (DAPA-LVH)	RCT	Scotland, UK	Patients with T2DM and LVH, treated with DAPA 10 mg (n = 66)	• LVM reduction: -2.82 g (95% CI: -5.13 to -0.51, P = 0.018), DAPA vs. SITA • Reduction in 24 h SBP (P = 0.012), nocturnal SBP (P = 0.017), body weight (P < 0.001), VAT (P < 0.001), SCAT (P = 0.001), HOMA-IR (P = 0.017), DAPA vs. SITA
Khunti et al, 2021 [57] (CVD REAL)	RWE	Multinational	T2DM patients who were new users of SGLT2i (n = 440,599); DAPA contributed 60% of total exposure time	• Lower risk of all-cause death: ITT-unadjusted pooled HR: 0.52, 95% CI: 0.45 - 0.60; P < 0.001 • hHF or all-cause death: 6932 and 10,275 events of in SGLT-2i and oGLD • Lower risk of composite of hHF or all-cause death: ITT-unadjusted pooled HR: 0.60, 95% CI: 0.53 - 0.68; P < 0.001 • MI events: 2,203 and 2,677 in the SGLT2i and oGLD group • Lower risk of MI: ITT-unadjusted pooled HR: 0.85, 95% CI: 0.78 - 0.92; P< 0.001
Hassoun et al, 2022 [43] (REWARD)	RWE	UAE and Kuwait	Patients with T2DM treated with DAPA 10 mg (n = 511)	• HbA1c: -0.9±0.3% (P < 0.001) • SBP: -1.9 mm Hg (P = 0.003) • BMI: 29.9 to EOS 29.7 (P < 0.001) • Reduction in cholesterol (P = 0.005); LDL (P = 0.001), and HDL (P = 0.005) • Hypoglycemic episodes: n = 90, 0 severe • UTIs: 1.96%
Morales et al, 2022 [64] (DAPA-RWE)	RWE	Spain	Patients with T2DM treated with DAPA (n = 594) and SITA (n = 452)	• HbA1c: -1.63% • body weight: -2.88 kg • SBP/DBP: -4.82/-2.70 mm Hg, P < 0.05 • UACR: -17.38 mg/g (P < 0.05), LDL cholesterol: -4.1 mg/dL (P < 0.05), uric acid: -0.30 mg/dL (P < 0.05) • No hypoglycemia, DKA, Fournier gangrene, fractures or amputations reported

Table 2. Summary of the Studies Investigating the Outcomes of DAPA, DAPA + SAXA, and SAXA in Patients With T2DM - *(continued)*

Author and trial name	Type of trial	Country	Patients and intervention	Key outcomes
Sethi et al, 2022 [48]	RWE	India	Patients with T2DM treated with DAPA as an add-on to other antihyperglycemic agents with or without INS (n = 1,935)	• HbA1c: -1.1% (P < 0.001) • FPG: -30.5 mg/dL (P < 0.001) • PPG: -57.5 mg/dL (P < 0.001) • SBP: -12.1 mm Hg (P < 0.001), DBP: -5.8 mm Hg (P < 0.001) • Cholesterol: -20.9 mg/dL (P < 0.001) • BMI: -1.1 kg/m^2 (P < 0.001)
Solomon et al, 2022 [61] (DELIVER)	RCT	Multinational	Patients with T2DM with HF and LVEF of more than 40% treated with DAPA 10 mg (n = 3,131) and PBO (n = 3,132)	• Worsening HF: 368 (11.8%) vs. 455 (14.5%); HR: 0.79; 95% CI: 0.69 to 0.91, DAPA vs. PBO • SAE including death: 43.5% vs. 45.5%, DAPA vs. PBO • CV deaths: 7.4% vs. 8.3%; HR: 0.88; 95% CI: 0.74 to 1.05, DAPA vs. PBO
Rosenstock et al, 2015 [53]	RCT	Multinational	Patients with T2DM treated with DAPA (10 mg) + SAXA (5 mg) + MET (n = 179) vs. SAXA + MET or PBO (n = 176) vs. DAPA + MET or PBO (n = 179)	• HbA1c: -1.5%, DAPA + SAXA + MET vs. -0.9%, SAXA + MET vs. -1.2%, DAPA + MET • FPG: -38 ± 2.8 mg/dL, SAXA + DAPA + MET vs. -14 ± 2.9 mg/dL, SAXA + MET group vs. -32 ± 2.8 mg/dL, DAPA + MET • Body weight: -2.1 kg, SAXA + DAPA + MET vs. -2.4 kg, DAPA + MET vs. no change, SAXA + MET • Genital infections: 0, SAXA + DAPA + MET; 6%, DAPA + MET; 0.6%, SAXA + MET • SBP: -1.9 mm Hg, SAXA + DAPA + MET; -3.5 mm Hg, DAPA + MET; 0, SAXA + MET • DBP: -1.0 mm Hg, SAXA + DAPA + MET; -0.4, SAXA + MET; -1.4 mm Hg, DAPA + MET
Mathieu et al, 2016 [21]	RCT	Multinational	Patients with T2DM treated with PBO + SAXA + MET (n = 158) vs. DAPA 10 mg + SAXA + MET (n = 158)	• HbA1c: -0.74% vs. 0.07%, DAPA + SAXA + MET vs. PBO + SAXA + MET • FPG: -27 vs. 10 mg/dL, DAPA + SAXA + MET vs. PBO + SAXA + MET • Body weight: -2.1 vs. -0.4 kg, DAPA + SAXA + MET vs. PBO + SAXA + MET • AE events: 66% vs. 71% DAPA + SAXA + MET vs. PBO + SAXA + MET • Genital infections: 6% vs. 1% for DAPA + SAXA + MET vs. PBO + SAXA + MET
Matthaei et al, 2016 [58]	RCT	Multinational	Patients with T2DM treated with DAPA 10 mg + MET + SAXA 5 mg (n = 153) vs. DAPA 10 mg + MET + PBO (n = 162)	• HbA1c: -0.38% vs. -0.05%; difference (95% CI): -0.42% (-0.64, -0.20), DAPA + MET + SAXA vs. DAPA + MET + PBO • Genital infections: 3.3% vs. 6.2%, DAPA + MET + SAXA vs. DAPA + MET + PBO
Muller et al, 2018 [51]	RCT, DapaZu study	Germany, Czech Republic, Hungary, Poland and Slovakia	Patients with T2DM treated with MET + DAPA 10 mg (n = 314) vs. MET + DAPA 10 mg + SAXA 5 mg (n = 312) vs. MET + GLIM 1 to 6 mg (titrated) (n = 313)	• HbA1c: -1.20% vs. 0.82% vs. 0.99%, DAPA + SAXA vs. DAPA vs. GLIM • Body weight: -3.2 kg vs. -3.5 kg vs. +1.8 kg, DAPA + SAXA vs. DAPA vs. GLIM • SBP: -6.4 mm Hg vs. -5.6 mm Hg vs. -1.6 mm Hg in DAPA + SAXA vs. DAPA vs. GLIM • PPG: -37.8 mg/dL vs. -27 mg/dL vs. -28.8 mg/dL, DAPA + SAXA vs. GLIM vs. DAPA
Vilsboll et al, 2020 [24]	RCT	Multinational	Patients with T2DM treated with DAPA 10 mg + SAXA 5 mg (n = 306) vs. INS 100 U/mL (n = 294)	• HbA1c: -1.5% vs. -1.3% in DAPA + SAXA vs. INS • Body weight: -1.8 kg (95% CI: -2.4, -1.3), DAPA + SAXA vs. +2.8 kg (95% CI: 2.2, 3.3) • Hypoglycemia: < 7.0% vs. 9.1%, DAPA + SAXA vs. INS • UTI infections: 6.2% in DAPA + SAXA vs. 5% in INS • Genital infections: 4.9% in DAPA + SAXA vs. 0.6% in INS
Frias et al, 2020 [22]	RCT	Multinational	Patients with T2DM treated with DAPA 10 mg + SAXA 5 mg (n = 227) vs. GLIM 1 - 6 mg (titrated; n = 217)	• HbA1c: -1.35%, DAPA + SAXA vs. -0.98%, GLIM (P < 0.001) • Body weight: -3.1 kg, DAPA + SAXA vs. 1.0 kg (P < 0.001), GLIM • SBP: -2.6 mm Hg, DAPA + SAXA; +1.0 mm Hg (P = 0.007), GLIM • UTI: 6.2%, DAPA + SAXA vs. 4.2% in GLIM • Genital infections: 5.3%, DAPA + SAXA vs. and 1.9%, GLIM • Renal impairment: 4% vs. 1.4%, DAPA + SAXA vs. GLIM

Table 2. Summary of the Studies Investigating the Outcomes of DAPA, DAPA + SAXA, and SAXA in Patients With T2DM - *(continued)*

Author and trial name	Type of trial	Country	Patients and intervention	Key outcomes
Johansson et al, 2020 [56]	RCT	Multinational	Patients with T2DM treated with DAPA 10 mg + SAXA 5 mg + MET (n = 46) vs. GLIM + MET (n = 36)	• > 30% reduction in liver fat (P = 0.007) and > 10% reduction in adipose tissue volumes (P < 0.01) with DAPA + SAXA + MET vs. GLIM + MET
Nowicki et al, 2011 [52]	RCT	Multinational	Patients with T2DM and renal impairment (moderate, severe or ESRD on hemodialysis) treated with SAXA 2.5 mg (n = 85) vs. PBO (n = 85)	• HbA1c: -1.35% (95% CI: 1.69 - 1.00) vs. -0.53% (95% CI: -0.83 to -0.23), P < 0.001, SAXA vs. PBO • FPG: -14.76 mg/dL vs. -2.7 mg/dL, SAXA vs. PBO • HbA1c w.r.t to renal impairment: SAXA vs. PBO moderate (-0.94% vs. 0.19%), severe (-0.81% vs. -0.49%), ESRD (-1.13% vs. -0.99%)
Kumar et al, 2014 [50]	RCT	India	Treatment-naive pts with T2DM treated with SAXA (n = 107) vs. PBO (n = 106)	• HbA1c: -0.51% vs. -0.05%, SAXA vs. PBO, P = 0.0011 • FPG: -10.44 ± 3.78 vs. -0.00 ± 3.78 mg/dL; P = 0.06, SAXA vs. PBO • Body weight change: +0.75 kg vs. -0.27 kg, SAXA vs. PBO • TEAEs: 5.6% vs. 7.5%, SAXA vs. PBO
Scirica et al, 2014 [60] (SAVOR-TIMI)	RCT	Multinational	Patients with T2DM and a history of, or at risk of, cardiovascular events treated with SAXA 5 mg or 2.5 mg (n = 8,280) vs. PBO (n = 8,212)	• hHF: 3.5% vs. 2.8%; HR: 1.27; 95% CI: 1.07 - 1.51; P = 0.007, SAXA vs. PBO • Body weight: 87.6 ± 18.4 vs. 87.9 ± 19.4 kg; P = 0.87, SAXA vs. PBO
Mosenzon et al 2016 [65] (SAVOR-TIMI)	RCT	Multinational	Patients with T2DM and history of established CVD or multiple risk factors for CVD (n = 16,492) treated with SAXA 5 mg or 2.5 mg vs. PBO	• SAXA improves/reduces deterioration in ACR categories, P = 0.021, P < 0.001, and P = 0.049 in pts with baseline normoalbuminuria, microalbuminuria, and macroalbuminuria • ACR change in SAXA vs. PBO: -19.3 mg/g (P = 0.033) for eGFR > 50 mL/min/BSA/1.73 m^2, -105 mg/g (P = 0.011) for 50 ≥ eGFR ≥ 30 mL/min/BSA, and -245.2 mg/g (P = 0.086) for eGFR < 30 mL/min/BSA
Ha et al, 2018 [55]	RWE	Korea	Patients with T2DM who are newly prescribed DPP4i, SITA (n = 167,157), VILD (n = 67,412), SAXA (n = 29,479), LINA (n = 220,672), or GEMI (n = 49,607)	• CVD risk: HR (95% CI); VILD, 0.97 (0.94 - 1.01), P = 0.163; SAXA, 0.76 (0.71 - 0.81), P < 0.001; LINA, 0.95 (0.92 - 0.98), P < 0.001; GEMI, 0.84 (0.80 - 0.88), P < 0.001
Kalra et al, 2019 [49] (ONTARGET-INDIA)	RWE	India	Patients with T2DM inadequately controlled on MET treated with SAXA 5 mg (n = 1,109)	• HbA1c: -0.86% ± 1.76 (P < 0.0001) • UTI and genital tract infection: 13.35% and 5.23% each

ACR: albumin to creatinine ratio; AE: adverse event, BSA: body surface area; BW: body weight; BMI: body mass index; CI: confidence interval; CVD: cardiovascular disease; DAPA: dapagliflozin; DBP: diastolic blood pressure; DPP4i: dipeptidyl peptidase-4 inhibitor; DKA: diabetic ketoacidosis; ESRD: end-stage renal disease; FPG: fasting plasma glucose; GLIM: glimepiride; HF: heart failure; hHF: hospitalization for heart failure; HR: hazard ratio; HOMA-IR: homeostatic model assessment of insulin resistance; eGFR: estimated glomerular filtration rate; MET: metformin; NYHA: New York heart association; LINA: linagliptin; PPG: post-prandial plasma glucose; INS: insulin; ITT: intent to treat; MI: myocardial infraction; oGLD: other glucose lowering drugs; UTI: urinary tract infection; LDL: low-density lipoprotein; MACE: major adverse cardiovascular event; RWE: real-world evidence; RCT: randomized controlled trial; SGLT2i: sodium-glucose cotransporter-2 inhibitor; PBO: placebo; SAXA: saxagliptin; SBP: systolic blood pressure; SITA: sitagliptin; VILD: vildagliptin; SU: sulfonylurea; SCAT: subcutaneous adipose tissue; TEAE: treatment emergent adverse events; UTI: urinary tract infection; VAT: visceral adipose tissue.

study in Indian patients with T2DM, SAXA showed clinically meaningful reductions in HbA1c with no new safety concerns, aside the known adverse event profile of SAXA [50]. In the ONTARGET-INDIA study conducted in 1,109 patients with T2DM inadequately controlled on MET alone, SAXA in combination with MET as a first add-on significantly reduced HbA1c levels, with an acceptable tolerability profile and no new risks being identified [49]. Additionally, significantly elevated (P < 0.001) circulating plasma DPP4 levels have been observed in non-obese Asian Indian patients with T2DM (receiving treatment with MET) vs. non-obese, non-diabetic patients. The elevated level of DPP4 was associated with metabolic markers of obesity such as increasing waist-to-hip ratio, total intra-abdominal adipose volume, and excess liver span [66]. Thus, treatment with DPP4is, such as SAXA, can produce improvements in metabolic derailments beyond glycemic control.

Taken together, these complementary mechanisms of action of DAPA + SAXA, when administered with MET (reduces hepatic glucose production and increases glucose utilization, thereby reducing plasma glucose levels) [67], can efficiently target six of the eight pathophysiological defects of T2DM, making it a potentially potent and effective combination [28, 39, 68]. The mean half-lives of oral DAPA and SAXA necessitate once daily administration and have an overall acceptable

Table 3. Comparison of Key Outcomes for SGLT2i + DPP4i Fixed-Dose Combinations Approved in India

Outcomes	DAPA + SAXA [22, 24, 53, 80]	Empagliflozin + linagliptin [75, 76, 78]	Remogliflozin + vildagliptin [74, 79, 81]	DAPA + sitagliptin [77]
Mean reduction in HbA1c, %	-1.37 to -1.5	-0.93 to -1.19	-1.2 to -1.8	0.0 to -0.4
Mean reduction in FPG, mg/dL	-35.8 to -38	-35.3 to -47.11	-32.5 to -47.37	-23.2 to -25.7
Mean reduction in body weight, kg	-1.9 to -3.1	-1.53 to -3.0	NA	-1.4 to -2.5
Genital infections, %	0 to 5.30	1.1 to 8.6	NA	9.8
Urinary tract infections, %	0.6 to 6.5	0 to 10.2	NA	6.7
Hypoglycemia, %	1 to 6.2	0 to 3.6	None	5.3
CVOT trials	SAVOR-TIMI [65], DECLARE-TIMI [62], DAPA-HF [59], DAPA-LVH [54], CVD REAL [57, 84], DELIVER [61]	EMPA-REG [88], CARMELINA [87], CAROLINA [89], EMPEROR-Preserved [82], EMPEROR-Reduced [86]	VIVIDD [85]	TECOS [83]
FDC US/EU approval status				
US FDA approval	Yes	Yes	No	No
EMA approval	Yes	Yes	No	No

CARMELINA: Cardiovascular and Renal Microvascular Outcome Study With Linagliptin; CARLINA: Cardiovascular Outcome Study of Linagliptin; CVOT: Cardiovascular Outcome Trial; CVD REAL: Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors; DAPA: dapagliflozin; DAPA-HF: Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; DAPA-LVH: Dapagliflozin on Left Ventricular Hypertrophy; DECLARE-TIMI: Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction; DELIVER: Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure; EMA: European Medicines Agency; EMPA-REG: Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose; FDA: Food and Drug Administration; FDC: fixed-dose combination; NA: not available; SAXA: saxagliptin; SAVOR-TIMI: Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus-Thrombolysis in Myocardial Infarction; TECOS: Trial Evaluating Cardiovascular Outcomes With Sitagliptin; VIVIDD: Vildagliptin in Ventricular Dysfunction Diabetes.

pharmacokinetic profile, no clinically meaningful drug interactions [69, 70]. Pharmacodynamic studies have further confirmed the complementary mode of action of the two agents [71]. The combination of DAPA + SAXA was shown to improve β-cell function, as evaluated by the homeostasis model assessment (HOMA-2) method [72]. The pharmacokinetic and pharmacodynamic attributes of DPP4i and SGLT2i make their combination feasible and clinically viable. However, combining SGLT2i with glucagon-like peptide 1 (GLP-1) receptor agonists, another class of antihyperglycemic drugs with complementary mechanism of action, may prove challenging due to differences in route of administration (majority of GLP-1 agonists are subcutaneous) and the absence of a convenient FDC [73]. These findings suggest that DAPA + SAXA is an optimal combination with a synergistic mechanism of action that produces clinically meaningful pharmacodynamic effects in patients with T2DM. Furthermore, among the various combinations of SGLT2i and DPP4i currently available in India, the DAPA + SAXA combination has extensive data evaluating the cardiovascular and renal safety and benefits of the individual agents (Table 3) [22, 24, 53, 54, 57, 59, 61, 62, 65, 74-89].

Clinical Evidence for Improved Glycemic Control With the Combination Therapy of DAPA and SAXA

Early initiation of triple therapy (add-on dual therapy to MET) as opposed to a stepwise accentuation strategy could be considered in patients failing to achieve glycemic goals. Studies of empagliflozin/linagliptin single-pill combination, SAXA add-on to DAPA and MET, and DAPA add-on to SAXA and MET have shown sustained glycemic control for up to 52 weeks with added benefits of weight control and improvements in blood pressure (Fig. 3) [28].

Concurrent dual addition of DAPA + SAXA to ongoing MET therapy was associated with greater glycemic control (1.5%) as compared with treatment with DAPA + MET (difference -0.27%, $P < 0.02$) and SAXA + MET (difference -0.59%, $P < 0.0001$) in patients with uncontrolled T2DM. This improvement in HbA1c levels was associated with meaningful reductions in SBP and body weight in patients with advanced disease and considerable β-cell dysfunction, representative of inadequately controlled T2DM [53].

These findings were further substantiated in a longer 52-week, double-blind, randomized trial wherein triple therapy with a combination of low-dose DAPA (5 mg) + SAXA (5 mg) added on to MET significantly reduced FPG (-27.0 mg/dL vs. -19.8 mg/dL (DAPA + MET; $P = 0.0135$) vs. -12.6 mg/dL (SAXA + MET; $P < 0.0001$)) and body weight (-2.0 kg vs. -0.4 kg (SAXA + MET; $P < 0.0001$)) when compared with dual therapy of SAXA or DAPA added-on to MET in patients with uncontrolled T2DM [90].

The combination of DAPA (10 mg) + SAXA (5 mg) and MET has also demonstrated improved glycemic control compared with glimepiride plus MET. The mean HbA1c change from baseline was -1.20% with DAPA + SAXA and -0.82% with

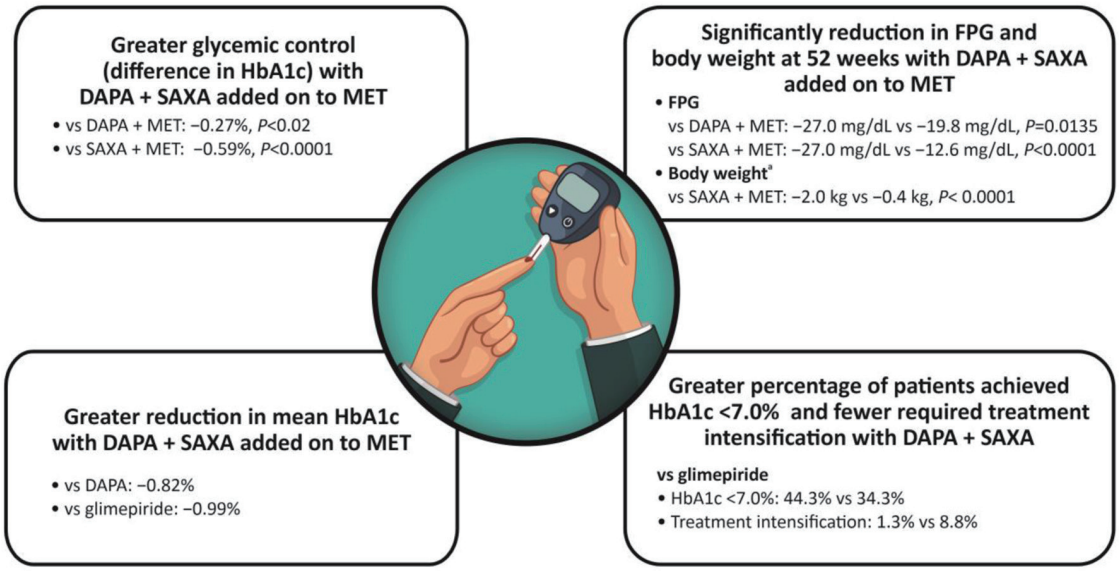

Figure 3. Clinical evidence for improved glycemic control with DAPA + SAXA. [a]Differences in the change in total body weight between DAPA + SAXA + MET and DAPA + MET were not available. DAPA: dapagliflozin; FPG: fasting plasma glucose; HbA1c: glycated hemoglobin; MET: metformin; SAXA: saxagliptin.

DAPA, vs. -0.99% with glimepiride. There were also significant reductions in the FPG and PPG in the DAPA + SAXA group compared with glimepiride [51]. In another long-term, 52-week, multicenter, double-blind, active-controlled study, efficacy and safety of DAPA (10 mg) + SAXA (5 mg) was compared with glimepiride (1 - 6 mg) in patients with T2DM. More patients achieved HbA1c < 7.0% (44.3% vs. 34.3%; P = 0.044), and fewer patients required treatment intensification (1.3% vs. 8.8%; P = 0.002) with DAPA + SAXA than with glimepiride. The combination of DAPA and SAXA also improved body weight and other metabolic parameters in patients inadequately controlled on MET [22]. These findings supported the use of DAPA + SAXA as an oral alternative in insulin-naive patients with T2DM.

Is the glycemic efficacy of the FDC (DAPA + SAXA) equal to insulin, with benefits in terms of weight and SBP reduction?

Based on their clinical experience in Indian patients with T2DM, 50% of the experts noted that the combination of DAPA + SAXA can potentially produce effects that are comparable with insulin along with additional benefits of improved weight and blood pressure management. The oral combination of DAPA + SAXA versus insulin resulted in non-inferior reductions in HbA1c (adjusted mean ± SE change, -1.7±0.1% vs. -1.5±0.1%; P = 0.118), along with beneficial reductions in body weight (between-group difference, -3.64 kg (95% confidence interval (CI): -4.20 to -3.09); P < 0.001) and a lower frequency of hypoglycemia (20.9% vs. 13.1%, P = 0.008) versus insulin [23, 24]. Thus, in line with clinical recommendations, the DAPA + SAXA FDC can be initiated instead of progressing directly to insulin therapy, in case of inadequate glycemic control with ongoing therapy [91] (Fig. 4).

Safety of DAPA and SAXA in Patients With T2DM

The safety of DAPA and SAXA as monotherapies has been well-established and the DAPA + SAXA FDC has a safety profile comparable to its mono components, including their propensity for reducing the risk of hypoglycemia [42-45]. Among the DPP4is, SAXA has shown to be well tolerated in patients with renal impairment [52, 92]. DAPA has also shown to be generally well-tolerated in broader patient populations and associated with non-serious incidences of genital and urinary tract infections [93].

In a year-long study of DAPA + SAXA versus glimepiride, no episodes of severe hypoglycemia were observed in the DAPA

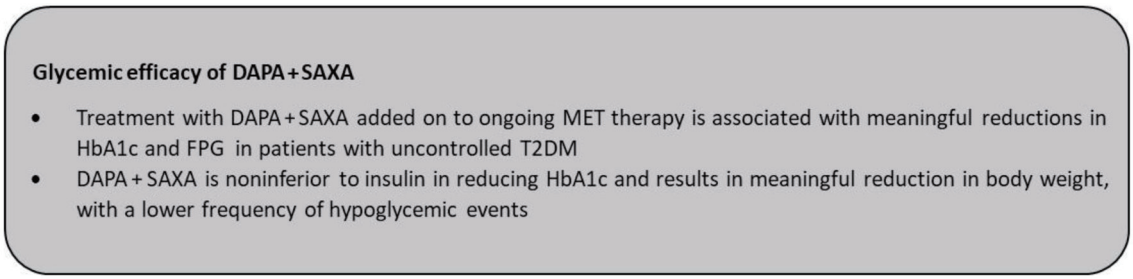

Figure 4. Glycemic efficacy of DAPA + SAXA. DAPA: dapagliflozin; SAXA: saxagliptin.

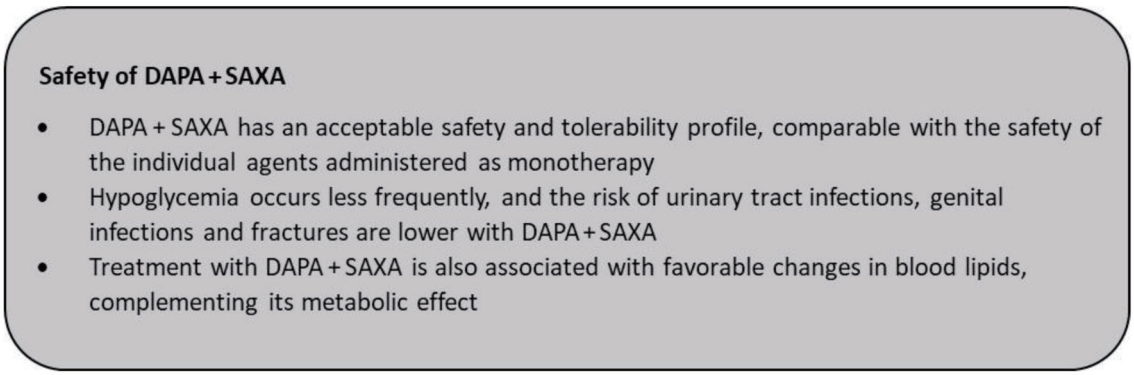

Figure 5. Safety of DAPA + SAXA. DAPA: dapagliflozin; SAXA: saxagliptin.

+ SAXA group and no patients discontinued the treatment due to hypoglycemia [22]. Triple therapy with DAPA + SAXA added on to MET was well tolerated during 52 weeks of treatment; the incidence of adverse events in patients receiving triple therapy was similar to the sitagliptin add-on group [94]. In a study of DAPA versus placebo as add-on to SAXA plus MET, adverse events were similar in DAPA (66%) and placebo (71%) groups. Genital infections occurred more often with DAPA (6%) than with placebo (1%); frequency of urinary tract infections was similar between the two groups (9% vs. 10%) [21].

No new safety signals were observed in patients with T2DM who were administered SAXA as an add-on to DAPA and MET. Hypoglycemia was infrequent in both groups (≤ 2.5%), with no major episodes. The rate of urinary tract infections was similar in the SAXA and placebo add-on groups (7.8% vs. 7.4%). The incidence of genital infections was lower (3.3%) with SAXA added on to DAPA and MET, as compared with the placebo add-on group (6.2%) [58]. Notably, urinary tract and genital infections have been reported to occur less frequently with triple therapy of DAPA + SAXA added on to MET, and this has been attributed to the complementary effects of the combination of an SGLT2i and a DPP4i [21, 58]. Also the small risk of fractures and amputations, which are reported with SGLT2is, has not been observed with the combination of DAPA + SAXA [95].

Rosenstock et al have shown that treatment with a triple combination of DAPA + SAXA + MET leads to significant increase in high-density lipoprotein (HDL) cholesterol (4.4% (95% CI: 1.1-7.8%), P = 0.009) versus SAXA + MET and reductions in triglycerides (-8.5% (95% CI: -15.9% to -0.4%), P = 0.04) when compared with DAPA + MET [53]. Combination of DAPA + SAXA significantly decreased liver fat (P < 0.007) and adipose tissue volume (P < 0.01) versus glimepiride, and reduced serum liver enzyme levels, suggestive of a favorable metabolic profile in patients with T2DM inadequately controlled on MET therapy [56].

Does the FDC have an acceptable safety and tolerability including hypoglycemia risk?

Supported by their clinical experience, all experts agreed that the FDC has an acceptable safety and tolerability and achieves adequate glycemic control with fewer incidences of hypoglycemia in Indian patients with T2DM. This concurs with several studies that report lower incidences of hypoglycemia in patients treated with a combination of DAPA + SAXA when compared with other oral antihyperglycemics [23, 24, 51] (Fig. 5).

Cardiovascular Safety of SAXA

Findings from several studies reveal the protective effects of most DPP4is against cardiovascular diseases driven by various effects including reduced inflammation, lipid levels, adiposity, decreased plaque development and endothelium-mediated vasodilatation [96-100]. In a pooled analysis of eight clinical studies, cardiovascular events, including death, myocardial infarction, and stroke were observed in 1.1% of patients treated with SAXA and 1.8% treated with a comparator (placebo, MET, or up-titrated glyburide) (relative risk (RR): 0.44, 95% CI: 0.24 - 0.82) [101]. Another retrospective analysis of 20 phase 2/3 studies of SAXA evaluating the incidence of major adverse cardiovascular event (MACE), reported a 25% reduction in the risk of MACE with SAXA versus the control treatments [102].

The SAXA Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) study enrolled 16,492 patients with T2DM at a risk or a history of cardiovascular disease to evaluate the cardiovascular outcomes for SAXA vs. placebo added on to usual care [103]. The 2-year all-cause mortality rates were similar between SAXA and placebo-treated patients (4.9% and 4.2%, respectively; hazard ratio (HR): 1.11, 95% CI: 0.96 - 1.27; P = 0.15) [103]. As with other DPP4is, treatment with SAXA met the primary composite endpoint of cardiovascular safety (MACE) by demonstrating no increased risk of cardiovascular death, nonfatal myocardial infarction and nonfatal ischemic stroke (HR: 1.00, 95% CI: 0.89 - 1.12) [103]. The incidence of cardiovascular death was also comparable between the SAXA and placebo arms (HR: 1.03, 95% CI: 0.87 - 1.22) [103]. SAXA was reported to be neutral even in the composite secondary endpoint. However, an increase (27%, P = 0.007) in the rate of hospitalization for heart failure (hHF) was noted, which was one of the six components of the composite of the secondary endpoint. Notably, the risk of heart failure was highest in patients with CKD (estimated glomerular filtration rate (eGFR) ≤ 60 mL/min/1.73 m^2), elevated N-

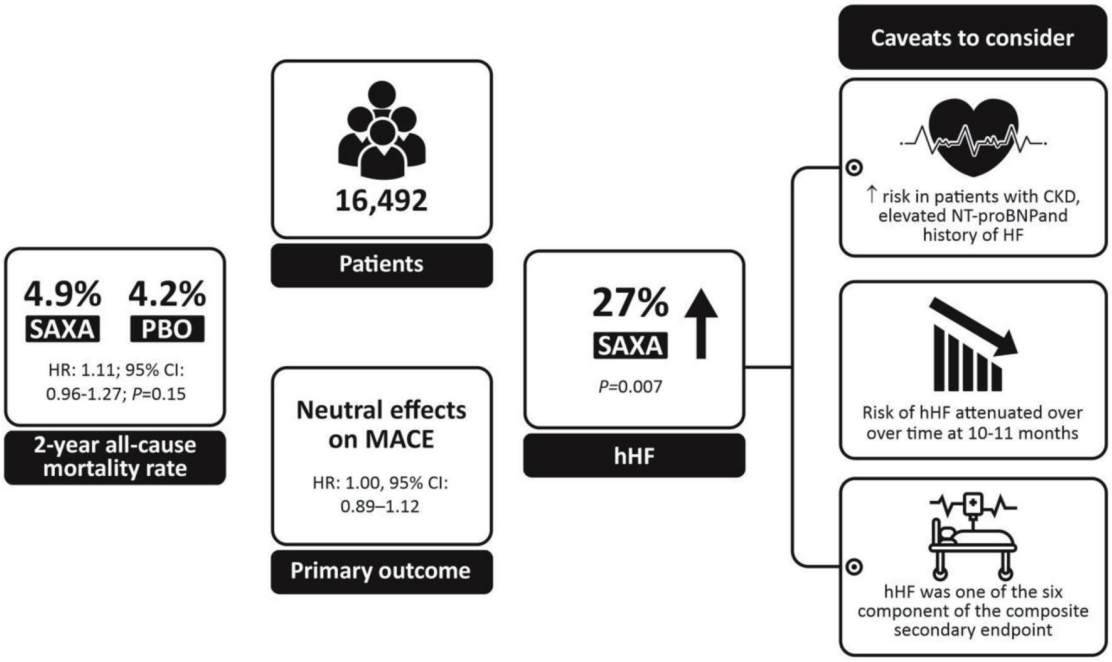

Figure 6. Summary of results from SAVOR-TIMI 53. CKD: chronic kidney disease; hHF: hospitalization for heart failure; MACE: major adverse cardiovascular event; NT-proBNP: N-terminal pro-B-type natriuretic peptides; PBO: placebo; SAXA: saxagliptin.

terminal pro-B-type natriuretic peptides (NT-proBNP) levels and those with a history of previous heart failure, suggesting an interplay of several clinical factors (Fig. 6) [60]. The risk of hHF was similar for SAXA and placebo at 6 months (2.4% vs. 2.1%, HR: 1.11 (95% CI: 0.91 - 1.36), P = 0.31) and 12 months (1.7% vs. 1.5%, HR: 1.09 (95% CI: 0.85 - 1.39), P = 0.51). A time-varying coefficients model was developed to further evaluate the attenuating effects of SAXA on the risk of hospitalization as a result of heart failure over time. The analysis revealed that the risk of hospitalization with SAXA attenuated over time at 10 to 11 months (at around 314 days, log HR surpasses 0) after randomization, indicating a possible absence of an underlying molecular pathogenesis for this effect [60]. Additionally, the observation of increased heart failure risk should be interpreted with caution as this is mainly derived from one study designed to assess MACE, with hHF being one component of the composite secondary endpoint. Findings may also be impacted by the heterogeneous definition of the event (heart failure requiring hospitalization) [60, 104]. Contrasting these findings from the SAVOR-TIMI 53 study, the pooled analysis of 20 SAXA studies also reported a lower incidence of heart failure (HR: 0.55 (95% CI: 0.27 - 1.12)) in patients receiving SAXA vs. the control groups [102]. Furthermore, a meta-analysis of studies, including the SAVOR-TIMI 53 trial, revealed that SAXA did not increase the rate of heart failure as compared to either sulfonylurea or placebo (RR: 0.99, 95% CI: 0.89 - 1.10) [105]. The recent Mechanistic Evaluation of Glucose-lowering Strategies in Patients With Heart Failure (MEASURE-HF) study was conducted to further investigate findings from the SAVOR-TIMI 53 study [106, 107]. It was designed to determine the effects of SAXA (vs. sitagliptin and placebo) on left ventricular structure, function and NT-proBNP levels in patients with T2DM and established symptomatic heart failure. Overall, there were no significant differences in left ventricular end systolic volume index, ejection fraction and mass, and NT-proBNP levels between SAXA and the placebo arm and consistent changes between SAXA and the sitagliptin arm [106, 107]. Thus, SAXA treatment did not correlate with any unfavorable physiological changes in the heart that are typically suggestive of heart failure. Taken together these findings underscore a neutral effect of SAXA on the risk of adverse cardiovascular outcomes [104] (Fig. 7).

Large RWE studies evaluating the risk for hHF also showed lack of association between the use of SAXA and an increased risk of hHF when evaluated against other select antihyperglycemic agents [108-110]. A population-based study of SAXA users (n = 78,553) reported that the risk of hHF was not higher with SAXA when compared with other antihyperglycemic agents (pioglitazone, second-generation sulfonylureas, or long-acting insulin formulations) [108]. A large Korean RWE study of 534,327 participants who were newly prescribed SAXA (n = 29,479), sitagliptin (n = 167,157), vildagliptin (n = 67,412), linagliptin (n = 220,672), or gemigliptin (n = 49,607), showed that SAXA was associated with lower risk of cardiovascular events as compared with other DPP4is [55]. In the French DIAPAZON epidemiological RWE study, 2.4% of the 1,033 patients with T2DM suffered a cardiovascular event but none was considered to be related with the use of SAXA [111].

Is the use of the FDC associated with lower risk of cardiovascular and renal adverse events?

The experts highlighted that use of DAPA + SAXA in Indian

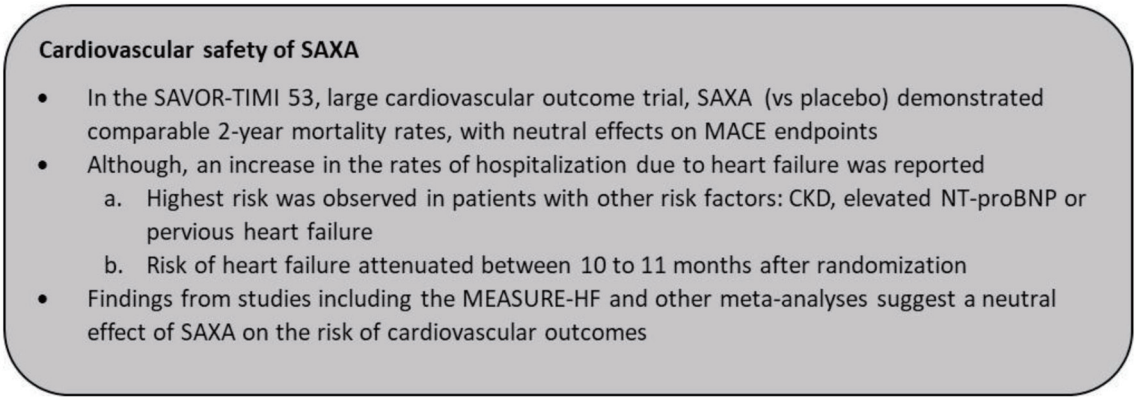

Figure 7. Cardiovascular safety of SAXA. SAXA: saxagliptin.

patients with T2DM was not associated with any major cardiovascular and renal adverse events. The combination of DAPA + SAXA is generally well tolerated, and no unexpected adverse events have been observed during routine clinical practice in Indian patients.

Is the use of the FDC associated with lower rates of treatment discontinuations due to cardiovascular and renal adverse events?

A majority of experts suggested that in their clinical practice, fewer patients discontinued the FDC treatment following cardiovascular or renal adverse events. Overall, these observations corroborate with findings from large clinical studies of DAPA + SAXA that report a low frequency of discontinuations due to adverse events [112].

Cardio-Renal Risk Reduction With DAPA + SAXA Combination

Individually, treatment with DAPA and SAXA has shown promising results in improving cardiovascular and renal outcomes in several large landmark studies [59, 62, 65, 92, 103, 113].

Cardiovascular risk reduction

In the Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial of 17,160 patients with T2DM who had or were at risk for atherosclerotic cardiovascular disease were randomized to receive either DAPA or placebo. There was a significant risk reduction in hHF (4.9% vs. 5.8%; HR: 0.83; 95% CI: 0.73 - 0.95; P = 0.005) and cardiovascular death with DAPA (HR: 0.98; 95% CI: 0.82 - 1.17) [62]. DAPA has also shown to dampen renal disease progression in patients with T2DM with relatively good baseline renal function [62, 113]. In the DAPA in Patients With Heart Failure and Reduced Ejection Fraction (DAPA-HF) trial (n = 4,744), DAPA significantly reduced the composite endpoint of worsening heart failure (hospitalization or urgent visit resulting in intravenous therapy for heart failure) or death from cardiovascular causes by 26% (P < 0.001) as compared with placebo [59]. In the DAPA on Left Ventricular Hypertrophy (DAPA-LVH) trial, patients with T2DM, and left ventricular hypertrophy were randomized to receive DAPA 10 mg once daily or placebo for 12 months; DAPA significantly reduced left ventricular mass compared with placebo with an absolute mean change of -2.82 g (95% CI: -5.13 to -0.51, P = 0.018). This was also accompanied by reductions in SBP, body weight, visceral and subcutaneous adipose tissue and insulin resistance, suggesting reverse remodelling in the left ventricular structure that may partly contribute to the cardio-protective effects of DAPA [54].

The phase 3 DAPA Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) study is the largest (n = 6,262) trial designed to evaluate the effects of DAPA on cardiovascular death, and hHF in patients with chronic heart failure and a left ventricular ejection fraction of more than 40%. At 2.3 years, treatment with DAPA was associated with reduced risk of worsening heart failure (HR: 0.79; 95% CI: 0.69 - 0.91) and cardiovascular deaths (HR: 0.88; 95% CI: 0.74 - 1.05) as compared with placebo, with lower incidences of heart failure events and symptoms [61].

In the Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors in the Real-world Setting (CVD-REAL), a large RWE study conducted across 13 countries, the initiation of SGLT2is (including DAPA, empagliflozin and canagliflozin) was associated with a significantly lower risk of hospitalization due to heart failure (HR: 0.66, 95% CI: 0.58 - 0.75; P < 0.001), all-cause death (ACD (HR: 0.52, 95% CI: 0.45 - 0.60; P < 0.001)), myocardial infraction (HR: 0.85, 95% CI: 0.78 - 0.92; P < 0.001), and stroke (HR: 0.78; 95% CI: 0.72 - 0.85; P < 0.001) when compared with other glucose lowering agents over a period of 1 year [57]. These outcomes were consistent across all patient subgroups of age, sex, comorbidities, geographic region and ethnicities. Notably, among the SGLT2is, DAPA contributed to 60% of total exposure time in patients [57]. An electronic medical records database-based RWE study in Taiwan also demonstrated better outcome of DAPA in terms of

reduction of heart failure compared with empagliflozin [114]. Similar outcomes have also been reported in other extensions of the CVD-REAL studies conducted across several countries [57, 115, 116]. Lower risk of hospitalization due to heart failure, ACD and myocardial infarction have also been associated with SGLT2is in the CVD-REAL 2 study (DAPA being 75% of total exposure, and 235,064 new SGLT2i users) [84]. In their recent evaluation, real-world data from the Maccabi database in Israel (n = 5,307 for SGLT2is and n = 5,307 for other glucose lowering agents), initiation of SGLT2is versus other glucose lowering agents was associated with lower risk of hospitalization due to heart failure or death overall (HR: 0.57, 95% CI: 0.46 - 0.70; P < 0.001) and in patients with both reduced ejection fraction (HR: 0.61, 95% CI: 0.40 - 0.93) and preserved ejection fraction (HR: 0.55, 95% CI: 0.43 - 0.70) [117].

In the large SAVOR-TIMI 53 study, SAXA met the primary composite endpoint, demonstrating no heightened risk of MACE, including cardiovascular death, nonfatal myocardial infarction, and nonfatal ischemic stroke (HR: 1.00, 95% CI: 0.89 - 1.12) [103]. Retrospective analyses of SAXA studies have revealed a notable 25% reduction in the risk of MACE and a lower incidence (or absence of increased risk) of heart failure in patients receiving SAXA when compared with the control treatments (HR: 0.55; 95% CI: 0.27 - 1.12) [102, 105]. Several RWE studies evaluating the risk of hHF have also found no association between SAXA use or an increased risk of hHF when compared with other antihyperglycemic agents [108-110].

Renal risk reduction

Effect of DAPA on renal outcomes

Studies assessing cardiovascular safety of SGLT2is have suggested that these agents lower albuminuria and impede the progressive deterioration of kidney function over time [118]. Declining eGFR and worsening albuminuria are deemed as independent markers of adverse renal outcomes and cardiovascular death in patients with T2DM [119]. In a post-authorization safety study for DAPA, real-world data from three databases - one in the UK (Clinical Practice Research Datalink (CPRD)) and two in the USA (the HealthCore Integrated Research Database (HIRD)) and the Medicare database - were derived to compare hospitalization for acute kidney injury (hAKI) among DAPA initiators and other glucose lowering drugs. Results demonstrated a lower risk of hAKI in patients treated with DAPA compared with other glucose lowering drugs [120]. The long-term renoprotective effects of DAPA were further substantiated in the DAPA and Prevention of Adverse Outcomes in CKD (DAPA-CKD) study. At 2.4 years, treatment with DAPA in patients with CKD was associated with a significantly lower risk (P < 0.001) of a composite of a sustained decline in the eGFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes as compared with the placebo group, regardless of the presence or absence of T2DM [121].

Effect of SAXA on renal outcomes

Incretin modifying therapies, specifically DPP4is, have shown to ameliorate albuminuria and exert renal cell protection by reducing oxidative stress [65, 122-125]. Studies of SAXA added on to ongoing therapy in patients with T2DM and moderate or severe CKD or end-stage renal disease have demonstrated meaningful reductions in HbA1c and FPG with good tolerability [52, 92, 126]. The SAVOR-TIMI 53 study included patients with varying degrees of renal function and at the end of 2.1 years, the use of SAXA was associated with reduced urinary albumin/creatinine ratio (UACR) levels (vs. placebo), a predictor of declining renal and cardiovascular function. This reduction in UACR was observed in patients with normo-, micro-, and macroalbuminuria, without affecting eGFR. Patients treated with SAXA were less likely to have worsening UACR levels than patients on placebo [65]. There was no deterioration in renal safety outcomes such as doubling of serum creatinine, initiation of chronic dialysis, renal transplant and the composite endpoint of death. Notably, the majority of patients in SAVOR-TIMI 53 were treated with angiotensin-converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs) and the addition of SAXA further improved UACR levels without any other adverse renal effects [65]. In patients with diabetic nephropathy receiving renin-angiotensin-aldosterone system blockade therapy, SAXA significantly lowered albuminuria at week 12 (-57.9%, P < 0.001) vs. standard antidiabetic agents [127]. SAXA showed superior efficacy to vildagliptin in transitioning patients to a lower albuminuria category, despite achieving similar reductions in UACR [127]. Thus, SAXA has shown clinically important advantages with regard to renal outcomes that could potentially mitigate progressive deterioration of renal function associated with chronic T2DM.

A combination of an SGLT2i and DPP4i is therefore purported to have beneficial effects on the kidney function. The DELIGHT study was the first prospective study to evaluate the efficacy of DAPA + SAXA in patients with T2DM and moderate-to-severe CKD, receiving ACEi or ARB therapy. The results showed significant lowering in albuminuria (38%, P < 0.0001) and HbA1c (0.58%, P < 0.0001) after 24 weeks of treatment compared with placebo [95]. The substantial magnitude of reduction in UACR suggests that the combination could potentially dampen the deterioration of kidney function and provide long-term renoprotection in T2DM patients with moderate-to-severe CKD [95]. Furthermore, the reduction in eGFR at week 1 and reversal of this effect at week 3 following discontinuation of the study medication, alludes to the activation of tubuloglomerular feedback, a mechanism suggested to curtail renal damage. The DAPA + SAXA combination had a manageable safety profile and was well tolerated in patients with eGFR as low as 25 mL/min/1.73 m^2 [95].

Is the use of the DAPA + SAXA FDC associated with better cardiovascular and renal outcomes?

In view of the complementary cardiovascular and renal benefits of DAPA and SAXA, the panel members recommended the use of the combination in Indian patients with T2DM and early stages

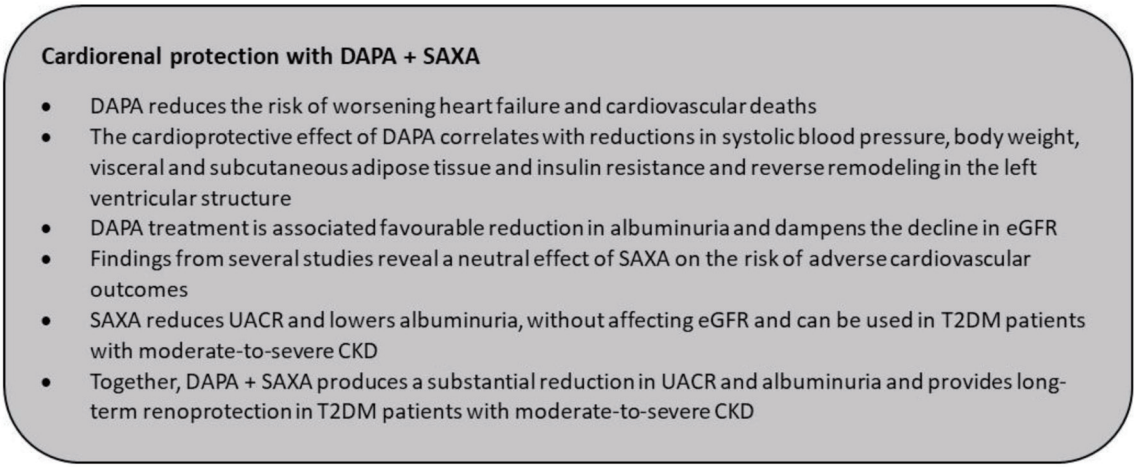

Figure 8. Cardiorenal protection with DAPA + SAXA. DAPA: dapagliflozin; SAXA: saxagliptin.

of heart failure. Results from the DAPA-HF, MEASURE-HF and DELIGHT studies and the more pragmatic real-world studies elucidate the clinical benefits of DAPA and SAXA in T2DM patients with CKD or heart failure that could guide clinicians to optimize treatment for these patients [59, 92, 95, 106, 107, 128] (Fig. 8).

Use of DAPA + SAXA in Indian Patients With T2DM

Landmark clinical trials and several real-world studies have illustrated the cardio and renal benefits conferred by the DAPA + SAXA combination while achieving durable glycemic control. Clinic and population-based data provide overwhelming evidence for the higher risk of chronic renal and cardiovascular diseases in South Asian patients with T2DM as compared with other ethnicities [6]. The large real-world TIGHT study revealed a high burden of CKD and heart failure in Indian patients with long-standing T2DM [5]. Collectively, these data indicate the need for more intensive multimodal treatment in Indian patients with T2DM. Understanding the prescribing practices of newer agents and combinations in the population will help maximize the benefits of these therapies. The following statements provide clinical experience-based recommendations for the use of DAPA + SAXA, which could potentially support individualization of treatment goals according to the specific needs of the Indian population (Fig. 9).

When do you recommend initiating treatment with DAPA-SAXA FDC?

The experts recommended the initiation of FDC based on the individual treatment goal and patient centric factors. The FDC can be introduced as part of treatment intensification for patients not meeting treatment goals (inadequately controlled on MET or other anti-hyperglycemic agents), regardless of the presence of cardio-renal comorbidities [26]. The FDC can also be used earlier at treatment initiation and in patients with cardiovascular and renal comorbidities to attain desirable glycemic control and arrest the progression of cardiovascular and renal complications [25-27, 129].

At what duration of diabetes, do your patients receive the FDC?

Aligned with the treatment initiation strategy, the experts recommended treatment with the FDC in patients who have been diagnosed with T2DM for < 1 to 5 years of T2DM, as an approach to achieve adequate glycemic control and mitigate cardiovascular and renal complications.

At what HbA1c levels do your patients receive the FDC?

The experts recommended prescribing FDC to patients with T2DM when their HbA1c levels are between 7.6% and 9.0%. This concurs with the RSSDI recommendation of initiating combination therapy in patients with HbA1c > 1.5 above the recommended goal of 7% [27].

What are the comorbidities in your patients receiving FDC?

Currently Indian patients with T2DM who are being prescribed the FDC in primary care have comorbid CKD and cardiovascular diseases. Supported by cardiovascular outcome trials and studies in CKD, the combination of DAPA + SAXA is expected to provide comprehensive vascular risk control and metabolic benefits that can potentially reduce the risk of advancing these comorbid conditions to renal or heart failure.

Conclusions

The statements provided in this paper can be used by Indian diabetologists and endocrinologists to aid treatment decisions

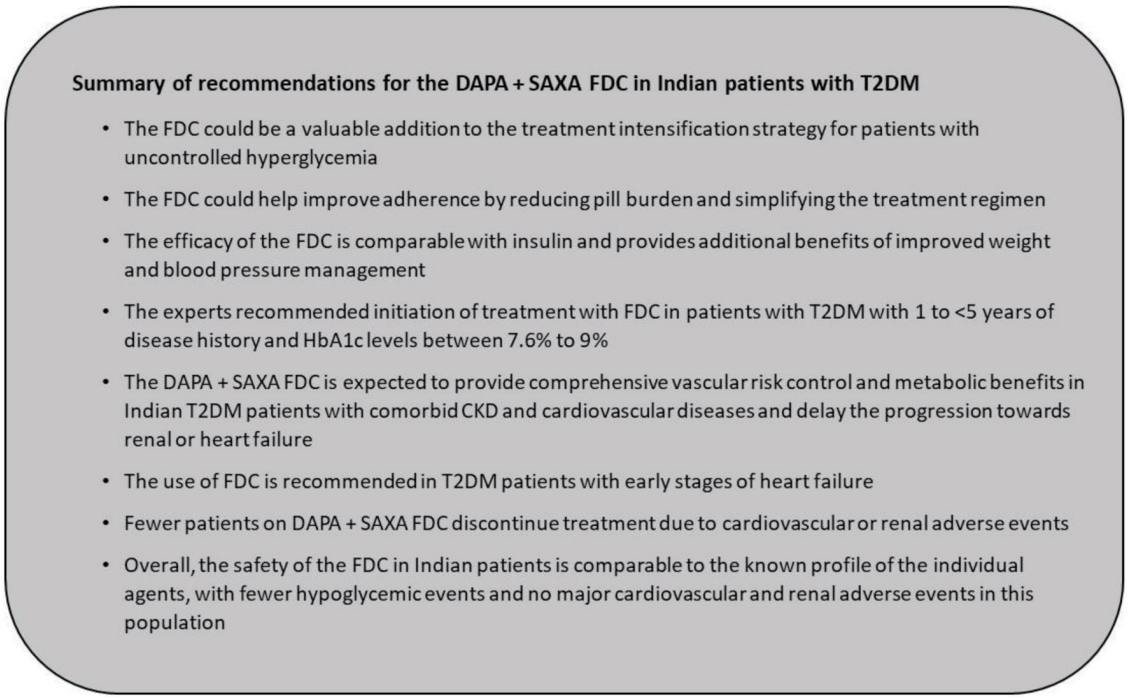

Figure 9. Summary of recommendations for the DAPA + SAXA FDC in Indian patients with T2DM. DAPA: dapagliflozin; FDC: fixed-dose combination; SAXA: saxagliptin; T2DM: type 2 diabetes mellitus.

that reflect the experience and opinion of experts in the field. Overall, available clinical evidence suggests that the inclusion of DAPA + SAXA FDC in the management of T2DM is associated with greater improvements in glycemic control, with benefits in weight management, lower risk of hypoglycemia and an acceptable safety profile. Together, these antihyperglycemic agents represent a synergistic combination, which is associated with improved cardiovascular outcomes and renoprotection. Together, these antihyperglycemic agents form a synergistic combination, contributing to improved cardiovascular outcomes and renoprotection, with DAPA exhibiting favorable effects on body weight, blood pressure, reduced risk of hHF, and clinically meaningful alterations in markers of declining renal function, complemented by SAXA's effects on ischemic events and improvements in UACR. The FDC of DAPA + SAXA addresses patient preference for oral antihyperglycemic agents and could enhance patient adherence enabling improved long-term management of T2DM. The FDC of DAPA + SAXA may be a suitable therapy for the metabolically deranged Indian patients for improving the long-term cardiovascular and renal outcomes. The strategies and approaches presented in this paper should be implemented in accordance with the existing clinical practice guidelines and as determined appropriate by the treatment physician, considering the condition of the individual patient.

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Conflict of Interest

Authors Sujoy Ghosh, Subhash K. Wangnoo, Sachin Chittawar, Suresh Damodharan, Yogesh Kadam, Pramila Kalra, K.P. Suresh Kumar, I. Periyandavar, and S.K. Sharma have nothing to disclose. Abdul Hamid Zargar has received honoraria from Novo Nordisk, Eli Lilly, Johnson & Johnson, AstraZeneca, BI and Sanofi.

Author Contributions

All authors contributed to the study conception, scope, and design, and participated in the consensus meeting. All authors critically reviewed the manuscript and approved the final version.

Data Availability

The authors declare that data supporting the findings of this

study are available within the article.

Abbreviations

AACE: American Association of Clinical Endocrinologists-American College of Endocrinology; ACD: all-cause death; ACEi: angiotensin-converting enzyme inhibitor; ADA: American Diabetes Association; ARB: angiotensin receptor blocker; BMI: body mass index; CDSCO: Central Drugs Standard Control Organization; CKD: chronic kidney disease; CVD-REAL: Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors in the Real-world Setting; CPRD: Clinical Practice Research Datalink; DAPA: dapagliflozin; DAPA-CKD: DAPA and Prevention of Adverse Outcomes in CKD; DAPA-HF: DAPA in Patients With Heart Failure and Reduced Ejection Fraction; DAPA-LVH: DAPA on Left Ventricular Hypertrophy; DCGI: Drug Controller General of India; DECLARE-TIMI 58: Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58; DELIVER: DAPA Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure; DPP4: dipeptidyl peptidase-4; DPP4i: dipeptidyl peptidase 4 inhibitor; eGFR: estimated glomerular filtration rate; FDC: fixed-dose combination; FPG: fasting plasma glucose; HbA1c: glycated hemoglobin; HOMA-2: homeostasis model assessment; hHF: hospitalization for heart failure; HR: hazard ratio; ICMR-INDIAB: Indian Council of Medical Research-India Diabetes; IDF: International Diabetes Federation; MACE: major adverse cardiovascular event; MEASURE-HF: Mechanistic Evaluation of Glucose-lowering Strategies in Patients With Heart Failure; MET: metformin; NT-proBNP: N-terminal pro-B-type natriuretic peptides; PPG: postprandial plasma glucose; RSSDI: Research Society for the Study of Diabetes in India; SAXA: saxagliptin; SAVOR-TIMI 53: SAXA Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53; SGLT2: sodium-glucose cotransporter-2; SGLT2i: sodium-glucose cotransporter-2 inhibitor; T2DM: type 2 diabetes mellitus; TIGHT: The Investigation of Glycosylated Hemoglobin on Therapy in Indian Diabetics; UACR: urinary albumin/creatinine

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