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Review Article



Saxagliptin and Dapagliflozin for type 2 Diabetes mellitus: A Review

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ABSTRACT

Qtern® is a fixed dose combination tablet of Saxagliptin and Dapagliflozin which is indicated for the advancement of glycaemic control in adults with type 2 diabetes mellitus (T2DM). It can be done either when medication with metformin and/or a sulfonylurea with a monocomponent of either Saxagliptin or Dapagliflozin render poor glycaemic control, or when the subject is treated with the free combination of Saxagliptin and Dapagliflozin. This review compiles pathophysiology of type 2 diabetes mellitus (T2DM) along with pharmacological properties, mechanism of action, and side effects of both the drugs. Furthermore, the method of determination of combination is described in this review. The agents have corresponding mechanisms of action, which further adds to the benefit of using this combination. The mixture is associated with reduced body weight and a low risk of hypoglycaemia. It is the first dipeptidyl peptidase-4 (DPP-4) inhibitor and sodium-glucose cotransporter (SGLT2) inhibitor fixed-dose combination available in the EU therefore can act as potent option for glycaemic control in patients with T2DM.

Keywords: Qtern, Saxagliptin, Dapagliflozin, Type 2 diabetes mellitus, Pharmacokinetics, Pharmacodynamics.

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1. Introduction

Diabetes mellitus is one of the most widespread chronic diseases in almost all countries and continues to rise in numbers and significance, as economic development and urbanisation lead to changing lifestyles characterised by reduced physical activity, and increased obesity. Estimates of the ongoing and future burden of diabetes are significant to allocate community and health resources, to emphasise the role of lifestyle, and encourage measures to counteract trends for increasing prevalence (1-4). According to a research conducted by International Diabetes Federation (IDF), it is predicted that by 2030 up to 79.4 million individuals in India may be afflicted diabetes mellitus, while China (42.3 million) and the United States (30.3 million) will also see significant increases in those affected by the disease (5,6).

It is a group of metabolic disorders during which blood sugar levels increase over a prolonged period. Symptoms of raised blood sugar include recurrent urination, increased thirst, and increased hunger. If left untreated, it can cause several complications. Acute complexities

include diabetic ketoacidosis, hyperosmolar hyperglycemic state, or death. Severe chronic complications include cardiovascular disease, stroke, chronic kidney disease, foot ulcers, and damage to the eyes.

According to WHO, there are two main types of diabetes:

Type 1 diabetes (T1DM) – It usually develops in childhood and adolescence, and patients require lifelong insulin injections for survival.

Type 2 diabetes (T2DM) - It develops in adulthood and is associated with obesity, the absence of physical activity, and unhealthy diets. It is the more prevalent type of diabetes (representing 90% of the cases worldwide), and treatment may include lifestyle modifications and weight loss alone, or oral medications or even insulin injections.

Other categories of diabetes include gestational diabetes (a state of hyperglycemia which develops during pregnancy) and "other" rarer causes (genetic syndromes, acquired processes such as pancreatitis, diseases such as cystic fibrosis, exposure to specific drugs, viruses, and

miscellaneous causes). As well, intermediate states of hyperglycemia (reduced fasting glucose or undermined glucose tolerance) have been described. These states are notable in that they can advance to diabetes, but with weight loss and lifestyle modifications, this progression can be prevented or delayed (7).

Pathophysiology of Diabetes Mellitus

Insulin insensitivity characterises type 2 DM as a result of insulin resistance, declining insulin production, and eventual pancreatic beta-cell failure (8,9). It leads to a reduction in glucose transport into the liver, muscle cells, and fat cells. There is an increase in the division of fat with hyperglycemia. The involvement of impaired alpha-cell function has recently been recognised in the pathophysiology of type 2 DM (10). As a consequence of this dysfunction, glucagon and hepatic glucose levels that increase during fasting are not contained with a meal. Given inadequate levels of insulin and elevated insulin resistance results in hyperglycemia. The incretins are essential to gut mediators of insulin release and glucagon suppression in the case of GLP-1. Although GLP activity is undermined in those with type 2 DM, GLP-1 insulinotropic effects are preserved, and thus GLP-1 represents a potentially beneficial therapeutic option. However, like GLP; DPP-IV rapidly inactivates GLP-1 in vivo.

To achieve and maintain glycemic control, patients with type 2 diabetes often require multiple antidiabetic agents due to the escalating nature of the disease (11,12). Most patients undergo traditional stepped-up therapy with metformin as the primary therapy, followed by the sequential addition of single oral antidiabetic drugs (OADs) as glycemic control worsens (11). Several guidelines suggest the use of dual or triple therapy depending on glycated hemoglobin (HbA1c) levels, but clinical trial evidence determining the optimal use of available pharmacologic options, particularly in dual or triple combinations, depending on the degree of glycemic control is limited (13-15).

As a progressive disease, patients often need multiple antihyperglycemic agents for adequate control. Drugs using the different mode of action are recommended, whenever combination therapy is required (16). The addition of a dipeptidyl peptidase-4 (DPP4) inhibitor and/or a sodium-glucose co transporter type 2 (SGLT2) inhibitor is supported by the latest guidelines from AACE/ACE and ADA/EASD citing higher level evidence

(17,18). Although SGLT2 inhibitors can enhance insulin sensitivity; endogenous glucose production is raised through enhanced glucagon (19). On the contrary, DPP4 inhibitors additionally raise insulin sensitivity but suppresses glucagon leading to a synergistic action of the combination (20). Single-pill combination of Dapagliflozin 10 mg /Saxagliptin 5 mg has been created to capitalize on this advantage (21). Single-tablet combination (STC) pills are being used in many chronic ailments such as cardiovascular diseases, AIDS, and diabetes (22). By simplifying medication plan, combination pills are shown to enhance adherence and quality of life (23, 24).

Dapagliflozin/Saxagliptin is the first SGLT2 and DPP4 inhibitor combination medicine approved in Europe as a potent agent for the management of T2DM (25). As of February 2017, this combination has also been certified for use by the U.S. Food and Drug Administration (FDA) as a supplement to lifestyle modification for the control of diabetes mellitus 2 (26). This article will review the efficacy and safety of Dapagliflozin and Saxagliptin for use as individual and combination therapy.

2. SGLT2 Inhibitors: A New Class of Diabetes Medications

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a new category of diabetic medications indicated just for the treatment of type 2 diabetes. Along with exercise and a healthy diet, they can improve glycaemic control. They have been studied alone and with other medications including metformin, sulfonylureas, pioglitazone, and insulin.

SGLT2 is a protein that promotes glucose reabsorption in the kidney. SGLT2 inhibitors prevent the reabsorption of glucose in the kidney, enhance glucose excretion, and lower blood glucose levels (27,28).

Mechanism of action

SGLT2 is a low-affinity, high capability glucose transporter found within the proximal tubule in the kidneys. It is accountable for 90% of glucose reabsorption. Inhibition of SGLT2 ends up in the decrease in the blood glucose due to the rise in renal glucose excretion. The mechanism of action of this new category of medications also provides further glucose control by allowing high insulin sensitivity and uptake of glucose in the muscle cells, reduced gluconeogenesis and advanced first phase insulin secretion from the beta cells.

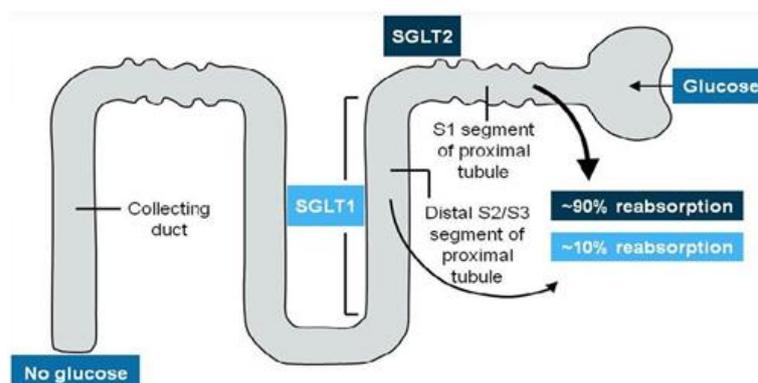


Figure 1. Mechanism of Action of SGLT-2 inhibitors

Table 1 List of FDA approved SGLT-2 Inhibitors

Trade Name	Active
Forxiga	Dapagliflozin
Invokana	Canagliflozin
Jardiance	Empagliflozin

Sodium-glucose co-transporter 2 inhibitors work by inhibiting SGLT2 in the Proximal convoluted tubule, to prevent reabsorption of glucose and facilitate its excretion in urine. As glucose is excreted, its plasma levels fall leading to an improvement in all glycaemic parameters.

This mechanism of action is reliant on blood glucose levels and unlike the works of thiazolidinedione (mediated through GLUTs), is not dependent on the effects of insulin. Thus, there is minimal potential for hypoglycaemia and no risk of overstimulation or fatigue of the beta cells. Because their mechanism of action relies upon normal renal glomerular-tubular function, SGLT2i efficacy is reduced in persons with the renal impairment (27,28).

Benefits of taking an SGLT2 inhibitor

- It can reduce heart complications - SGLT-2 inhibitors likely minimize arterial stiffness via a multifactorial mechanism which incorporates weight loss, decreased fasting insulin levels, vascular smooth muscle relaxation, and multiple beneficial anti-inflammatory effects.
- It can reduce systolic blood pressure - SGLT2 inhibitors considerably reduced Systolic Blood Pressure after one month and Diastolic Blood Pressure after six months in obese patients with type 2 diabetes. The primary mechanism of the BP-lowering effect may be plasma volume reduction by osmotic diuresis at two weeks and after SGLT2 inhibitor administration.
- It can cause weight loss -Weight loss during SGLT2 therapy is much lower than anticipated, given the amount of energy lost through glycosuria. Patients with T2DM might experience more weight loss during SGLT2 inhibitor therapy if they followed stricter dietary recommendations to decrease appetite and overeating
- It lowers blood glucose levels- SGLT-2 works with an insulin-independent mechanism of action it reduces blood glucose level by increasing the excretion of blood glucose through urine.

Dapagliflozin

Dapagliflozin is a novel inhibitor of renal sodium-glucose cotransporter 2, which allows an insulin independent approach to improve type 2 diabetes hyperglycaemia. It is a C-aryl glucoside derivative and is chemically known as (1s)-1, 5-anhydro-1-C-[4chloro-3-(4-ethoxyphenyl) methyl] phenyl]-D- glucitol (29-31).

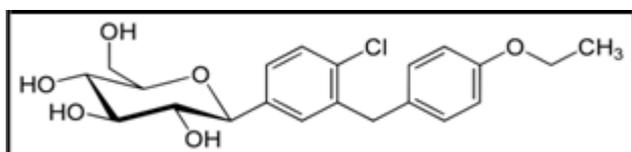


Figure 2. Structure of Dapagliflozin

Pharmacokinetics

Dapagliflozin is rapidly and well absorbed after oral administration. Maximum Dapagliflozin plasma concentrations occur within 2 hours of consumption (in the fasted state). Bioavailability is 78% with the 10 mg once daily (OD) dosing. It can be consumed with or without food. It is 91% protein-bound, and this is not affected by the hepatic or renal disease. Dapagliflozin is metabolised to its inactive metabolite – Dapagliflozin 3-O-glucuronide - in the liver and kidney by the enzyme uridine diphosphate-glucuronosyltransferase 1A9. The mean plasma terminal half-life for Dapagliflozin is 13 hours (10 mg dosing). Dapagliflozin and its metabolites are excreted mainly via the urine, and the excretion is impaired in the presence of renal disease; 15% is excreted unaltered via the faeces, and 2% excreted unchanged via the urine (32).

Pharmacodynamics

Dapagliflozin is associated with dose-dependent glycosuria and increased diuresis averaging 375 mL/day. There is a temporary rise in urinary sodium excretion, but that does not seem to influence serum sodium. There is also a momentary increase in urinary uric acid excretion, but a sustained decrease in serum uric acid levels. The mechanism of decreased serum uric acid levels is not clear but was recently proposed to be due to glycosuria-induced uric acid secretion via GLUT9 isoform 2 in the proximal tubule or inhibition of uric acid uptake at the collecting duct of the renal tubule. Additionally, this could be due to the weight loss linked with Dapagliflozin (33,34).

Side effects of Dapagliflozin may include

- **Hypoglycaemia-** This adverse event is observed with some glucose-lowering therapies and is seldom a limiting factor in achieving good glycaemic control. Hypoglycaemia is correlated with negative effects such as unwanted symptoms like weight gain (through increased appetite), poor adherence to therapy, uncontrolled glycaemia because of the fear of new hypoglycemic episodes, reduced quality of life and, in some patients, mishaps such as falls and cognitive disorders, essentially in elderly and frail patients. A link between severe hypoglycaemia and increased cardiovascular risk and total mortality has recently been described.
- **Genital infections-** According to their nature, the most common primary safety concern of SGLT-2 inhibition is that they cause glucose levels to increase in urine, which may lead to urinary tract and genital infections, enhanced the urinary frequency and electrolyte imbalances. An increase in urinary glucose elimination caused by SGLT-2 treatment also has the potential to increase fungal growth in the perineum and genitourinary tract. Non-sexually transmitted perineal and genitourinary tract mycotic infections are regarded as adverse events of particular interest.
- **Urinary tract infections-** Urinary tract infections (UTIs) are common in patients with

T2DM. The tendency to urinary tract infections (UTIs) in diabetes mellitus occurs from various factors. Susceptibility increases with extended duration and greater severity of diabetes.

- **Blood pressure**-Chronic osmotic diuresis caused by glycosuria would be anticipated to reduce blood pressure, and dose-related increases in 24-h urinary volumes of between 100ml and 470ml have been reported. Reductions in systolic blood pressure (SBP) of up to 5mmHg have been described in trials of Dapagliflozin, whether used as an add-on therapy or on its own. It is well known that SGLT-2-i have diuretic-like effects, lowering SBP by 3-5 mmHg, which could benefit most of the patients with T2DM. The exact mechanism behind the BP-lowering action of SGLT-2-i, however, is still unclear and does not appear to be based on natriuretic effects. Indeed, although these agents have mildly natriuretic effects, they are nothing like diuretics. Part of their BP-lowering result is presumed to be due to osmotic diuresis. However, they might also reduce BP too much in some patients, with consequences including hypotension (mainly postural), dizziness and dehydration.
- **Renal effects**- Chronic kidney disease (CKD) is a significant health problem in patients with T2DM. Stage 3-5 CKD (GFR < 60ml/min) affects around 25% of such patients and represents an under-recognized problem in clinical practice. Most OADs have limitations in cases of renal impairment because they require dose adjustments or are contraindicated for safety reasons. In fact, the activity of SGLT-2 depends on the number of nephrons, which means that the first consequence of renal impairment on the SGLT-2 action is reduced efficacy. For this reason, the use of SGLT-2 is neither

recommended nor allowed in those with an estimated GFR (eGFR) < 40ml/min because of the lack of effectiveness rather than risks.

3. Dipeptidyl-Peptidase IV Inhibitors

Dipeptidyl-Peptidase IV (DPP-4) inhibitors are not considered as initial therapy for the majority of patients with type 2 diabetes. Initial therapy in most patients with type 2 diabetes should begin with diet, weight reduction, exercise, and metformin (in the absence of contraindications). DPP-4 inhibitors can be considered as monotherapy in patients who are intolerant of or have contraindications to metformin, sulfonylureas, or thiazolidinediones, such as patients with chronic kidney disease or who are at particularly high risk for hypoglycemia. DPP-4 inhibitors can be considered as add-on drug therapy for patients who are inadequately controlled on metformin, a thiazolidinedione, or a sulfonylurea. However, their modest glycemia-lowering effectiveness and expense temper our enthusiasm for these drugs.

Dipeptidyl-peptidase (DPP) IV inhibitors inhibit dipeptidyl peptidase-4 (DPP-4), a universal enzyme that immediately inactivates both GLP-1 and GIP, increase active levels of those hormones and, in doing so, enhances islet function and glycemic control in type 2 DM. DPP-4 inhibitors are a new category of anti-diabetogenic drugs that provide relative efficacy to current treatments. They are efficient as monotherapy in patients inadequately controlled with diet and exercise and as add-on therapy in combination with insulin, metformin, and thiazolidinediones. The DPP-4 inhibitors are well tolerated, carry a low risk of producing hypoglycemia and are weight neutral. However, they are relatively expensive. The long-term durability of effect on glycemic control and beta-cell morphology and function remain to be established (35,36).

Table 2 List of FDA approved DPP-4 Inhibitors

Brand name	Active Ingredient(s)
Januvia	Sitagliptin
Janumet	Sitagliptin & Metformin
Janumet XR	Sitagliptin & Metformin extended release
Onglyza	Saxagliptin
Kombiglyze XR	Saxagliptin & Metformin extended release
Tradjenta	Linagliptin
Glyxambi	Linagliptin & Empagliflozin
Jentadueto	Linagliptin & Metformin
Nesina	Alogliptin
Kazano	Alogliptin & Metformin
Oseni	Alogliptin & Pioglitazone

Saxagliptin

Saxagliptin (37) is an oral hypoglycemic (anti-diabetic drug) of the class dipeptidyl peptidase-4 (DPP-4) inhibitors. It is sold under the brand name Onglyza. It is chemically known as (1S, 3S, 5S)-2-[(2S)-2-amino-2-(3-hydroxy-1-adamantyl) acetyl]-2-azabicyclo [3.1.0] hexane-3-carbonitrile.

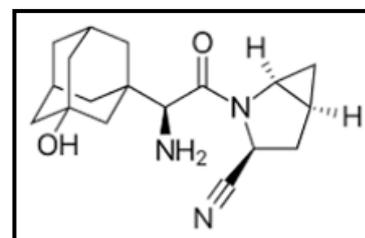


Figure 3. Structure of Saxagliptin (37)

Mechanism of Action

Saxagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor for the treatment of type 2 diabetes. DPP-4 inhibitors are a category of compounds that work by altering the action of natural hormones in the body called incretins. Incretins lower blood sugar by enhancing consumption of sugar by the body, principally through increasing insulin production in the pancreas, and by decreasing production of sugar by the liver. DPP-4 is a membrane-associated peptidase which is seen in many tissues, lymphocytes and plasma. DPP-4 has two primary

modes of action, an enzymatic function and another mode where DPP-4 binds adenosine deaminase, which carries intracellular signals via dimerisation when activated. Saxagliptin forms a reversible, histidine-assisted covalent bond between its nitrile group and the S630 hydroxyl oxygen on DPP-4. The inhibition of DPP-4 raises levels active of glucagon-like peptide 1 (GLP-1), which hinders glucagon production from pancreatic alpha cells and enhances production of insulin from pancreatic beta cells.

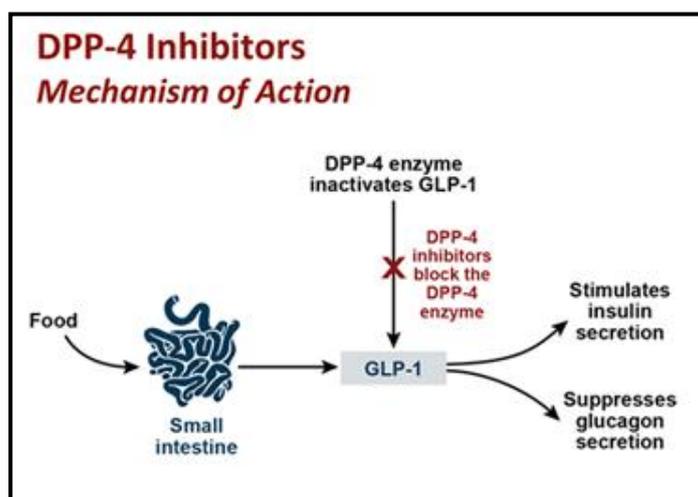


Figure 4. Mechanism of Action of Saxagliptin

Pharmacokinetics

Saxagliptin is quickly and well absorbed after oral administration. Saxagliptin did not accumulate following repeated doses. The bioavailability is 67% for 2.5 - 50 mg dose. The protein binding (in vitro) of Saxagliptin and its active metabolite in human serum is negligible (<10%). The metabolism of Saxagliptin is primarily mediated by cytochrome P450 3A4/5 (CYP3A4/5). Half of the dose i.e. 50% of the absorbed dose will undergo hepatic metabolism. The major metabolite of Saxagliptin, 5-hydroxy Saxagliptin, is also a DPP4 inhibitor, which is one-half as potent as Saxagliptin. The mean plasma terminal half-life for Saxagliptin is 2.5 hours, and its metabolite 5-hydroxy Saxagliptin is 3.1 hours.

Both renal and hepatic pathways can be used to excrete out Saxagliptin. Following a single 50 mg dose of 14C-Saxagliptin, 24%, 36%, and 75% of the dose was eliminated in the urine as Saxagliptin, its active metabolite, and total radioactivity, respectively. A total of 22% of the administered radioactivity was recovered in faeces representing the fraction of the Saxagliptin dose excreted in bile and/or unabsorbed drug from the gastrointestinal tract.

Pharmacodynamics

After administration of Saxagliptin, GLP-1 and GIP levels increase up to 2- to 3- fold. Because of its selectivity of DPP-4 inhibition, there are lesser systemic side effects. Saxagliptin inhibits DPP-4 enzyme activity for a period of 24-hours. It also decreases glucagon concentrations and increases glucose-dependent insulin secretion from pancreatic beta cells. The half maximal

inhibitory concentration (IC₅₀) is 0.5 nmol/L. Saxagliptin did not prolong the QTc interval to a clinically significant degree.

Side Effects

Saxagliptin is an orally-active DPP4 enzyme inhibitor used either separately or with alternative medications, and with a correct diet and exercise program, to regulate high blood sugar. It is used in people with type 2 (non-insulin-dependent) diabetes. Common side effects include the runny or stuffy nose, sore throat, cough, headache, or stomach pain.

Saxagliptin by itself sometimes usually does not induce low blood sugar (hypoglycaemia), but low blood sugar could occur if this drug is prescribed with alternative anti-diabetic medications. Symptoms of low blood sugar include sudden sweating, shaking, quick heartbeat, hunger, blurred vision, dizziness, or stinging hands/feet. Some very serious side effects of Saxagliptin include indications of disease of the pancreas (such as severe stomach or abdominal pain which may expand to the back, or constant nausea or vomiting).

The suggested dose of Onglyza is 2.5 mg or 5 mg once daily taken regardless of meals. It may cause low blood sugar if prescribed with other anti-diabetes medications. During pregnancy, it should strictly be used only when prescribed. Pregnancy may cause or worsen diabetes.

4. Method of determination

Combination of Active substance by UV Spectroscopy

Qtern (10 mg dapagliflozin and 5 mg saxagliptin) was developed and assessed by UV- spectrophotometric

method. ICH guidelines were followed to validate the developed method. The drug showed two different wavelengths of maximum absorption, at 203nm and 237nm. This method can be successfully applied for the estimation of combination in bulk for routine analysis with UV detection at 237nm. A Lab India UV-Visible spectrophotometer with 1cm matched quartz cells and ethanol solvent were employed in this method (36). The developed method followed Beer's-Lambert's law in the concentration range of 0.5-0.9µg/ml, having the correlation coefficient of 0.994. Various validation parameters like precision studies (intra-day and inter-day), limit of detection (LOD), and limit of quantitation (LOQ), ruggedness and robustness were studied and were found to be within limits.

Combination of Active substance by RP-HPLC

Combination developed and validated by RP-HPLC method. The methods were validated as per ICH guidelines. The linearity was found to be 25-150µg/ml and 1-5µg/ml for RP-HPLC. The RP-HPLC method was validated for accuracy, linearity, precision, LOD, LOQ, system suitability and robustness (38).

All the results were found to be within limits as per ICH guidelines, and hence the proposed two methods can be successfully employed for the determination of Combination in its API for regular and routine analysis.

5. Conclusion

The addition of Dapagliflozin/Saxagliptin takes advantage of complementary mechanisms of action and provides augmented glycemic control. The increased incidence of genital infection seen with Dapagliflozin single add-on therapy is attenuated in combined add-on therapy, suggestive of a possible protective effect. It is otherwise well tolerated with a safety profile similar to single add-on therapy, and the risk of hypoglycemia remains low. Therefore, for patients in need of dual add-on therapy or with poorly controlled diabetes despite add-on with either monocomponent, initiation of Dapagliflozin/Saxagliptin combination is a safe and rational option.

Participants tolerate combination therapy with comparable rates of adverse events to individual therapies. Of interest, there appear to be fewer reported genital infections in patients taking the combination of Saxagliptin and Dapagliflozin compared to those taking Dapagliflozin alone. The rate of hypoglycemia associated with combination therapy is low (< 1%).

Patient characteristics and preferences should be considered to help guide treatment of T2DM after metformin. Qtern (Dapagliflozin & Saxagliptin combination) is a safe and effective combination agent for patients with T2DM. The combination of these two agents produces antihyperglycemic effects leading to beneficial outcomes regarding reduction in blood sugar and HBA1C.

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Conflict of interest

The authors declare that there are no conflicts of interest.

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