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Review Article

Linagliptin in type 2 diabetes mellitus: glycemic control and beyond

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is a progressive metabolic disorder requiring comprehensive strategies to achieve sustained glycemic control and reduce complications. Linagliptin, a dipeptidyl peptidase-4 inhibitor (DPP-4i), provides effective glycemic control with a low risk of hypoglycaemia and weight neutrality. Its once-daily dosing without the need for renal or hepatic dose adjustment makes it suitable for patients with multiple comorbidities. Large clinical trials, including CARMELINA and CAROLINA, have established its cardiovascular and renal safety. Beyond monotherapy, combination therapy with dapagliflozin, a sodium-glucose co-transporter-2 inhibitor (SGLT2i), demonstrates synergistic benefits. This combination improves glycemic parameters, supports weight reduction, and enhances cardiorenal outcomes. Phase III trials show that fixed-dose combinations of dapagliflozin and linagliptin achieve superior HbA1c reduction and improved postprandial glucose control compared with monotherapy, with favourable safety and tolerability.

Keywords: Linagliptin, Type 2 diabetes mellitus, DPP-4 inhibitor, SGLT2 inhibitor, Glycemic control, Cardiovascular safety, Renal safety, Combination therapy

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a prevalent chronic condition globally, significantly impacting public health. It is characterized by insulin resistance and relative insulin deficiency, leading to various long-term complications, including cardiovascular (CV) disease, chronic kidney disease (CKD), neuropathy, and retinopathy. Hyperglycemia and its related metabolic dysfunctions affecting carbohydrates, fats, and proteins disrupt normal functioning of multiple organs. These effects worsen gradually due to hyperglycemia-induced damage to the microvasculature and macrovasculature , which are crucial for organ structure and function. The resulting vascular complications cause organ damage, dysfunction, and ultimately, organ failure, particularly affecting the eyes, kidneys, heart, and nerves.[1,2] According to the International Diabetes Federation (IDF), the global prevalence of diabetes among adults aged 20-79 was 10.5% in 2021, affecting approximately 537 million individuals. This figure is projected to rise to 12.2% by 2045, equating to around 783 million people.[3]

MANAGEMENT OF TYPE 2 DIABETES MELLITUS

Persistent hyperglycemia in T2DM can lead to target organ damage by increasing the risk of vascular diseases.[4] The global prevalence of T2DM has surged, driven by rapid urbanization, sedentary lifestyles, and the widespread adoption of calorie-dense diets. Alongside these genetic predispositions, environmental changes, particularly in

populations prone to insulin resistance, also contribute. This combination of lifestyle and genetics highlights the need for comprehensive management strategies. Most patients eventually require medication to achieve optimal blood sugar levels. Treatment goals have evolved beyond lowering blood sugar also to address complications like CV risks, kidney damage, and obesity.[5]

While lifestyle modifications, including dietary changes and increased physical activity, are effective in improving glycemic control, many individuals with T2DM will require pharmacological interventions over time. Currently, there are several classes of oral antidiabetic medications available for T2DM management: sulfonylureas, meglitinides, biguanides (e.g., metformin), thiazolidinediones (TZDs), alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors (DPP-4is), Sodium-glucose cotransporter-2 inhibitors (SGLT2is) and oral glucagon-like peptide-1 receptor agonists (GLP-1-RAs). Additionally, certain injectable medications are used in T2DM treatment, including GLP-1RAs, dual GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptor agonists.[4]

DPP-4 inhibitors in the management of type 2 diabetes and beyond

DPP-4 is, commonly referred to as gliptins, are a class of oral medications approved by the U.S. Food and Drug Administration (FDA) for the treatment of T2DM in adults. FDA-approved DPP-4 includes sitagliptin, saxagliptin, linagliptin, and alogliptin. However, while vildagliptin is approved by the European Medicines Agency (EMA), it has not received FDA approval. DPP-4s work by blocking the DPP-4 enzyme, which normally breaks down incretin hormones like GLP-1 and GIP. These hormones stimulate insulin secretion and inhibit glucagon release in response to food, helping regulate blood glucose levels.

By preventing the breakdown of incretins, DPP-4s prolong their action, enhancing insulin release when glucose is high and reducing liver glucose production, leading to better control of post-meal blood sugar levels.[6] Beyond their glucose-lowering effects, increased GLP-1 and GIP levels confer various metabolic and cardiovascular benefits. By activating GLP-1R1, these incretins trigger insulin release, lower blood sugar, and reduce Reactive Oxygen Species (ROS). They also improve myocardial function by increasing contractility and blood flow while reducing inflammation, apoptosis, and oxidative stress.

In addition to incretin actions, DPP-4 inhibition increases circulating levels of several cardioprotective peptides, such as brain natriuretic peptide (BNP), stromal cell-derived factor-1 (SDF-1), and substance P. BNP promotes natriuresis, vasodilation, and diuresis, and lowers renin and aldosterone levels. SDF-1 supports angiogenesis, and substance P reduces apoptosis and fibrosis. Together, these pathways highlight the wide-ranging protection that DPP-4 inhibitors offer for metabolism, renal, and cardiovascular health. These drugs can be prescribed as monotherapy or in combination with other antidiabetic agents, including metformin, sulfonylureas, thiazolidinediones, or insulin.[7] DPP-4is offer several advantages in managing T2DM. They are weight-neutral, which is beneficial for patients aiming to avoid weight gain during treatment. These agents have a low risk of hypoglycemia, making them suitable for older adults and those at risk of hypoglycemic events. DPP-4is effectively lower HbA1c levels and reduce both fasting (FPG) and postprandial glucose (PPG) levels, demonstrating efficacy in monotherapy and combination therapy. They are also considered safe for patients with hepatic or renal insufficiency, providing flexibility in treatment options. Additionally, DPP-4is have been explored for potential repurposing in conditions like COVID-19, highlighting their versatility in patient care.[8] This review aims to explore the efficacy, safety, and clinical benefits of linagliptin and its combinations in T2DM.

GLYCAEMIC EFFICACY AND CARDIORENAL OUTCOMES OF LINAGLIPTIN

Glycaemic efficacy

Linagliptin has been evaluated in various clinical trials to assess its efficacy in managing T2DM. In a 24-week placebo-controlled trial, linagliptin 5 mg daily showed significant HbA1c reductions of -0.57% to -0.69%, and up to -1.01% in patients with higher baseline HbA1c, along with improvements in fasting and postprandial glucose levels.[9] The table below summarizes key findings from several studies, highlighting changes in glycosylated haemoglobin (HbA1c), FPG and PPG levels (Table 1).

Cardiorenal Outcomes

The following table summarizes key trials that have assessed the CV and renal efficacy and safety of linagliptin in patients with T2DM (Table 2). Linagliptin demonstrated CV safety, being noninferior to placebo (CARMELINA) and to glimepiride (CAROLINA) for major adverse CV events, with no significant benefit on cardiac function markers. For renal outcomes, linagliptin reduced albuminuria progression and preserved eGFR in some studies, though it did not significantly affect hard renal endpoints (CARMELINA).

Combinations of Linagliptin

The complex nature of T2DM progression leads to a gradual deterioration of β-cell function as the disease advances. Consequently, single-drug treatments may not effectively control blood glucose levels in certain patients. The United Kingdom Prospective Diabetes Study (UKPDS) revealed a year-on-year decrease in the number of patients maintaining HbA1c levels below 7% with monotherapy during follow-up, indicating its potential ineffectiveness for long-term hyperglycemia management.

Combination drug therapy operates through various mechanisms, including synergistic and complementary effects, as well as resistance counteractions. The multifaceted nature of this strategy contributes to its therapeutic efficacy.[10] Combining medications is essential in T2DM management, as it allows for comprehensive blood glucose control without significantly increasing the risk of hypoglycemia or other adverse events. Initiating combination therapy early can help preserve β-cell function and delay the progression of glycemic deterioration. Utilizing drugs with complementary mechanisms addresses various pathophysiological aspects of T2DM. Linagliptin is available in combination with metformin, empagliflozin, and dapagliflozin, offering dual or triple therapy options.[10]

Table 1: Efficacy of linagliptin in type 2 diabetes mellitus: summary of clinical trials.

Study	Design and duration and intervention	Change in †hba1c from baseline	*fpg reduction	Key takeaway
Ito T et al 2021[15]	Randomized controlled trial 24 weeks Linagliptin (n=2,130)	– 0.49±1.33% (95% CI (-0.54,-0.44))	-15.27±59.96 mg/dl (95% CI: -19.54 to -11.00 mg/dl)	Reduction in †HbA1c were observed over the course of the 3-year period
Hoogwerf et al 2020[16]	Non-interventional retrospective cohort study 6 months Linagliptin (n=11,001)	- 0.51±1.46% (p≤ 0.001)	-	Linagliptin significantly lowered †HbA1c.
Han et al 2018 Guard extension study[17]	Randomized, placebo-controlled, double-blinded, phase 3b Study 40 weeks Linagliptin 5 mg (n = 52)	-0.65±0.22% (p= 0.003)	-4.08±12.09 mg/dl (p= 0.355)	Linagliptin effectively lowered †hba1c and *FPG
Parthan et al 2018[18]	Randomized, double-blind, placebo-controlled trial 6 months Linagliptin 5 mg (n=10)	0.2% (p=0.474)	4 mg/dl (p=0.308)	Linagliptin modestly improved glycemic profile
Prato et al 2011[9]	Randomized controlled trial 24 weeks Linagliptin 5 mg (n=336)	-0.69± 0.08% (p<0.0001)	-23.4±3.6 mg/dl (p<0.0001)	Linagliptin produced a significant and sustained improvement in †HbA1c levels
Lajara et al 2014[19]	Pooled data of randomized, double-blind, placebo-controlled, phase 3 trials 24 weeks Linagliptin 5 mg (n=122)	-0.66% (p<0.0001)	-15.5 mg/dl (p=0.0323)	Linagliptin significantly improved †HbA1c and *FPG levels
Barnett et al 2012[20]	Double-blind study 1-year Linagliptin 5 mg (n=151)	−0.60% (p<0.0001)	-20.5 mg/dl (p=0.0002)	Linagliptin significantly improved glycemic control
Kawamori et al 2012[21]	Randomized, Placebo-controlled, double-blind Study 12 weeks Linagliptin 5 mg (n=159) Linagliptin 10 mg (n=160)	5 mg: -0.24±0.06% (p< 0.0001) 10 mg: -0.25± 0.06% (p< 0.0001)	5 mg and 10 mg: -12.6±1.8 mg/dl(p<0.0001 for both)	Linagliptin 5 and 10 mg showed significant reductions in †HbA1c and *FPG levels
Forst et al 2010[22]	Multi-center, randomized, double-blind,	1 mg: 0.40% (p=0.005) 5 mg: 0.73%	1 mg: -19.8 mg/dl (p=0.002)5 mg:	All 3 doses of linagliptin showed significant

Continued.

Study	Design and duration and intervention	Change in †hba1c from baseline	*fpg reduction	Key takeaway
	Placebo-controlled, 5 parallel-group study12 weeks Linagliptin 1 linagliptin 5 linagliptin 10 mg	(p<0.001)10 mg: 0.67% (p<0.001)	-34.2 mg/dl (p<0.0001) 10 mg: -28.8 mg/dl (p< 0.0001)	improvements in †HbA1c and *FPG reductions.
Ross et al 2012[23]	Randomized, double-blind, placebo-controlled trial12 weeks Linagliptin 2.5 mg BD (n=223) Linagliptin 5 mg OD (n=224) Placebo (n=44)	2.5 mg: 0.74% 5 mg: 0.80%. (p<0.0001 vs. Placebo).	2.5 mg: 13.7 mg/dl (p=0.0029)5 mg: 17.8 mg/dl (p= 0.0001)	Linagliptin 2.5 mg and 5 mg doses significantly reduced †HbA1c and *FPG levels.

*FPG, fasting plasma glucose; †HbA1c, glycosylated haemoglobin.

Table 2: Cardiovascular outcome trials evaluating cardiorenal efficacy of linagliptin.

Study	Design	Inclusion criteria	Intervention	Results
Cardiovascular outcomes				
Carmelina 2019[24]	Randomized, placebo-controlled, noninferiority trial	Patients with ††T2DM and high ‡CV risk	Linagliptin 5 mg (n=3494) Placebo (n=3485)	Patients with 3P-MACE: Linagliptin: 434 of 3,494 (12.4%) Placebo: 420 of 3,485 (12.1%) ‖HR: 1.02 (0.89–1.17) P<0.001 for noninferiority
Carolina 2019[25]	Randomized, double-blind, active-controlled, noninferiority trial	Patients with early type 2 diabetes and elevated cardiovascular risk	Linagliptin 5mg (n=3023) Glimepiride 1-4 mg (n=3010)	Patients with 3P-MACE: Linagliptin: 356 of 3023 (11.8%) glimepiride: 362 of 3010 (12.0%) HR: 0.98 (0.84-1.14) P<0.001 for noninferiority
Dyda-2 trial 2021[26]	Multicenter, randomized, double-blind, placebo-controlled, parallel-group study	Individuals with ††T2DM and asymptomatic impaired left ventricular systolic Function	Linagliptin Placebo	Midwall fractional shortening (%): Linagliptin: Baseline: 13.29 final: 13.82 change: +4.1% Placebo: Baseline: 13.58 final: 13.84 change: +1.8% Between group difference: 2.3-fold higher increase in linagliptin group (non-significant) P=0.86
Release study 2016[27]	Randomized, double-blind, controlled trial	Individuals with ††T2DM and assessable **PWV at screening	Linagliptin 5 mg Placebo	PWV decreased by 0.91 m/s in linagliptin group (p=0.035)
Renal outcomes				
Carmelina[24]	Randomized, placebo-controlled, noninferiority trial	Patients with ††T2DM and high ‡CV risk	Linagliptin 5 mg (n=3494) Placebo (n=3485)	- linagliptin: 9.4% (327/3,494) patients experienced the primary renal outcome. - placebo: 8.8% (306/3,485) patients experienced the primary renal outcome. -‖HR: 1.04;95% confidence interval (CI): 0.89-1.22; p=0.62. -linagliptin was associated with a reduction in albuminuria progression compared to placebo.

Continued.

Study	Design	Inclusion criteria	Intervention	Results
Carmelina subgroup analysis 2020[28]	Randomized, placebo-controlled, noninferiority trial	Patients with ††T2DM and high ‡CV risk	Age <65 years: Linagliptin (n = 1467) Placebo (n= 1501) Age 65 to <75 years: Linagliptin (n= 1405) Placebo (n = 1395) Age ≥75 years Linagliptin (n = 622) Placebo (n = 589)	-no significant interaction between age and treatment effect (HR,1.02 [95% confidence interval (CI) 0.89, 1.17,p=0.0937) -linagliptin did not increase the risk of adverse kidney outcomes or hospitalization for HF across age groups.
Perkovic et al 2020 Carmelina secondary analysis[29]	Multicenter, randomized, double-blind clinical trial	Participants with CV disease and/or †CKD		
McGill et al 2013[30]	Randomized, double-blind, placebo-controlled, parallel-group study 52 weeks	Patients with ††T2DM and severe renal failure (CKD stage 4/5)	Linagliptin 5 mg/day (n=68) Placebo (n=65)	Renal function (§EGFR): Linagliptin group: median decrease of 0.8 ml/min/1.73 m². Placebo group: median decrease of 2.2 ml/min/1.73 m². These reductions were not clinically significant. Adverse events: Renal and urinary disorders: Linagliptin: 25.0%. Placebo: 21.5%. No renal failure cases were linked to linagliptin.
Yagoglu et al 2020[31]	Prospective randomized controlled study	Stage 3-4 †CKD patients	Group 1: linagliptin 5 mg Group 2: insulin	-linagliptin use is associated with a significantly reduced risk of progression -§EGFR significantly increased in linagliptin group (p=0.033)

*CI, confidence interval; †CKD, chronic kidney disease; ‡CV, cardiovascular; §eGFR, estimated glomerular filtration rate; ||HR, hazard ratio;3P-MACE, 3-point major adverse cardiovascular events; **PWV, pulse wave velocity; ††T2DM, type 2 diabetes mellitus.

SGLT2I + DPP-4I combination

Combining SGLT2is with DPP-4is offers a synergistic approach to managing T2DM (Figure 1). SGLT2is reduce glucose reabsorption in the kidneys, leading to glycosuria and modest weight loss. DPP-4is act by enhancing insulin secretion and suppressing glucagon release, thereby improving glycemic control. Together this combination has shown to significantly reduce HbA1c levels, fasting plasma glucose, and postprandial plasma glucose while lowering body weight and SBP. Beyond glycemic control, SGLT2is offer additional benefits, including reductions in systolic blood pressure (SBP) and body weight. A meta-analysis indicated that the CV and renal benefits of SGLT2is are consistent, regardless of concurrent DPP-4i therapy. Interestingly, the addition of a DPP-4i to an SGLT2i regimen has been associated with a reduced incidence of genital infections, a common side effect of SGLT2i.[11] Both SGLT2is and DPP4is improve time-in-range (TIR: percentage of a 24-hour period during which blood glucose levels remain between 70-180 mg/dL, complementing HbA1c as a marker of glycemic control) by reducing fasting and postprandial glucose, with DPP4i primarily targeting postprandial hyperglycemia. Both classes are linked to lower hypoglycemia risk. Reducing glycemic variability (GV) is crucial in preventing T2DM complications, and randomized controlled trials (RCTs)

have shown that SGLT2i and DPP4i lower GV. DPP4i use is also associated with reduced insulin requirements. Combining SGLT2i and DPP4i separately or as fixed-dose combinations (FDCs) targets multiple components of the "ominous octet." 12 FDCs of SGLT2is and DPP-4is have emerged as a promising therapeutic approach in the management of T2DM. These combinations leverage the complementary mechanisms of action of both drug classes, offering enhanced glycemic control, reduced risk of hypoglycemia, and additional benefits such as weight loss and blood pressure reduction. Several SGLT2i and DPP-4i combinations have already received regulatory approval. For example, empagliflozin plus linagliptin received US FDA approval in 2015 and DCGI approval in 2017. Dapagliflozin plus saxagliptin was approved by the USFDA in 2017 and by the DCGI in 2019. The USFDA also approved ertugliflozin plus sitagliptin in 2017, but it is not approved in India. In contrast, remogliflozin plus vildagliptin is approved only in India (2020) and has not been approved by the USFDA. Some combinations, like canagliflozin plus teneligliptin, are not yet approved by

both regulatory bodies.[12] More recently, the DCGI approved dapagliflozin plus linagliptin in 2024, even though it remains unapproved by the USFDA.[13] These regulatory milestones show the increasing use and importance of SGLT2i and DPP-4i fixed-dose combinations in managing T2DM.

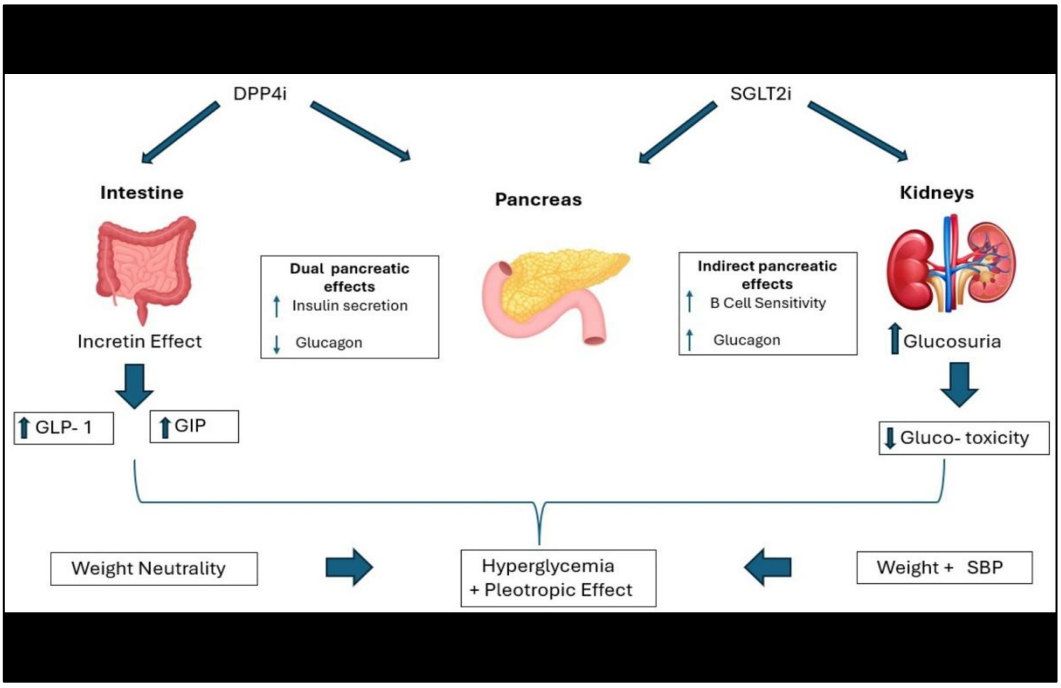

Figure 1: Mechanisms of DPP4i and SGLT2i combination.

Table 3: Clinical trials evaluating dapagliflozin and linagliptin combination therapy in type 2 diabetes management.

Study	Design	Inclusion criteria	Intervention	Results
Dharmalingam et al 2024[32]	Multicenter, randomized, double-blind, active-controlled, parallel-group, phase iii clinical study 18 weeks	-age ≥18 to ≤65 years-diagnosis of **T2DM -*BMI≥45.0 kg/m2	Treatment A: dapagliflozin 10 mg + linagliptin 5 mg Treatment B: dapagliflozin 10 mg + vildagliptin SR 100 mg	§HbA1c reduction: Dapagliflozin/linagliptin: -1.59% Dapagliflozin/vildagliptin: -1.25% (p<0.0001)
				||PPBG reduction: Dapagliflozin/linagliptin: -59.99 mg/dl Dapagliflozin/vildagliptin: -55.34 mg/dl
				‡FPG reduction: Dapagliflozin/linagliptin: -32.91 mg/dl Dapagliflozin/vildagliptin: -26.78 mg/dl
				Compared to dapagliflozin and vildagliptin combination therapy, dapagliflozin and linagliptin †FDC significantly improved glycemic control.
Hong et al 2024[33]	Multicenter, randomized, double-blind, Parallel-group, placebo-controlled phase iii study	7% ≤ §HbA1c ≤ 10.5%	Dapagliflozin +linagliptin 10/5 mg/day(n=117) Linagliptin 5 mg + placebo (n=118)	- §HbA1c reduction: Dapagliflozin +linagliptin: 7.93% ± 0.82% to 7.11% ± 0.61% Control: 7.80% ± 0.71% to 7.87% ± 0.94% Difference: -0.88% (95% CI: -1.07 to -0.68; p<0.0001)
				Patients achieving §HbA1c <7.0%: Dapagliflozin +linagliptin: 44.8% Control: 18.6% (p<0.001)
				Dapagliflozin and linagliptin †FDC showed potent glucose-lowering effects

Continued.

Study	Design	Inclusion criteria	Intervention	Results
Ahmad et al 2024[34]	Randomized double-blind study	**T2DM patients on stable dose of metformin	Group 1: dapagliflozin 10mg+linagliptin 5mg Group 2: linagliptin	-dapagliflozin+ linagliptin group experienced a mean decrease of 1.36% (±0.05%).
				-there was a reduction of 25.90 (±1.23) % in ‡FPG from baseline.
				-a decrease of 52.41 (±2.29)% in ‖PPG was observed.
				-a modest weight loss was noted, with least squares mean decrease of 1.34 kg (±0.07 kg).
				The dapagliflozin-linagliptin combination provided superior glycemic control with good tolerability
Kumthekar et al 2025[35]	Phase 3, prospective, randomized, double-blind, multicenter study	-patients with **T2DM - stable dose of metformin ≥1000 mg/day as monotherapy	Arm A: dapagliflozin 10 mg + linagliptin 5 mg Arm B: linagliptin 5 mg	§HbA1c reduction: −1.28% (combination) vs. −0.83% (linagliptin); p = 0.0003
				‡FPG reduction: −26.94 mg/dl (combination) vs. −21.59 mg/dl (linagliptin); p=0.0003
				‖PPG reduction: −49.16 mg/dl (combination) vs. −29.14 mg/dl (linagliptin); p=0.0022
				Body weight reduction: −1.06 kg (combination) vs. −0.54 kg (linagliptin); p=0.0253
				†FDC of dapagliflozin 10 mg + linagliptin 5 mg was Superior to linagliptin 5 mg in terms of efficacy

*BMI, body mass index; †FDC, fixed-dose combination; ‡FPG, fasting plasma glucose; §HBA1c, glycosylated hemoglobin; ‖PPG, postprandial glucose; SR, sustained release; **T2DM, type 2 diabetes mellitus.

Dapagliflozin + linagliptin combination

The combination of dapagliflozin and linagliptin offers a promising approach for managing T2DM due to their complementary mechanisms of action and distinct metabolic pathways, which minimize potential drug interactions. These benefits have been demonstrated in initial combination therapy and stepwise treatment approaches. Notably, a recent randomized, double-blind, parallel-group phase III trial investigated the efficacy and safety of an FDC of dapagliflozin and linagliptin in patients with inadequately controlled T2DM on metformin.[14] Clinical Evidence and Outcomes of Dapagliflozin and Linagliptin Combination (Table 3). Across multiple phase 3 trials, the FDC of dapagliflozin+ linagliptin consistently provided superior glycemic control and modest weight loss compared to linagliptin alone or dapagliflozin+vildagliptin.

Guideline recommendations

Various international and national guidelines provide recommendations regarding their use, either as monotherapy or in combination with other glucose-lowering agents. The following table summarizes key recommendations from major guidelines on DPP-4is in T2DM management (Table 4).

EMERGING EVIDENCE AND FUTURE PERSPECTIVES

Ongoing trials

Several ongoing studies are evaluating the effects of linagliptin in patients with T2DM (Table 5).

Table 4: Summary of recommendations for DPP4i use.

Guideline	Recommendations
American diabetes association (ADA) 2025[32]	-combination therapy can be considered in adults with ‡‡T2DM at treatment initiation to shorten the time to the attainment of individualized treatment goals. -glucose-lowering medications like metformin, †SGLT2IS, §DPP-4IS, dopamine agonists, bile acid sequestrants, and *AGIS are weight-neutral or offer modest weight loss, making

Continued.

Guideline	Recommendations
	them suitable as add-on therapies for individuals with ‡‡T2DM and obesity who need further glucose control or cannot use more effective treatments.
Expert consensus on dipeptidyl peptidase-4 inhibitor-based therapies in the modern era of type 2 diabetes mellitus management in India 2024[11]	- §DPP-4is are considered safe/neutral in terms of ‡CV outcomes, including HF, and can be a useful add-on to existing †AHAS, including insulin. - for patients with newly diagnosed ‡‡T2DM with mild hyperglycemia (††HbA1c <7.5%) and in whom metformin is not tolerated or contraindicated, lifestyle therapy plus antihyperglycemic monotherapy with a §DPP-4i may be initiated with a dose titrated based on the patient's clinical condition and baseline ‖EGFR. - ‡‡T2DM patients who present with an ††HbA1c ≥7.5% to <8.5% at diagnosis may be started on metformin + §DPP-4i FDC (single-pill) therapy.
American association of clinical endocrinology (AACE) 2023[33]	§DPP-4is are alternative options for patients with overweight/obesity, hypoglycemia risk, or cost concerns but are not preferred for severe hyperglycemia. They can be used in combination if additional glycemic control is needed.
Research society for the study of diabetes in India (RSSDI)-endocrine society of India (ESI) clinical practice guidelines 2022[34]	-§DPP-4is, †SGLT2is, *AGIS, or oral **GLP-1RAS can be initial options when metformin is not tolerated or contraindicated. -if glucose control targets are not achieved: add †SGLT2I, §DPP-4i, sulfonylurea, *TZDS, *AGI or oral **GLP1-RA. -if glucose targets are not achieved with 2 agents: start third oral agent-*AGI, §DPP4i, †,SGLT2I, *TZDS or oral **GLP1RA (depending on the second line agent used). -in elderly patients with increased risk of hypoglycemia, use a DPP-4i is as an alternative to sulfonylurea.
2022 expert opinion on optimum clinical approach to combination-use of †,SGLT2I + §DPP4i in the indian diabetes setting[12]	- initial combination therapy with a SGLT2I + §DPP-4i FDC may be considered in patients presenting with high ††HbA1c levels (1.5% above individualized target) - in patients with high ‡CV risk, second-line agents such as SGLT2is and **GLP-1RAS with proven ‡CV benefits should be prioritized; if additional glycemic control is needed, combining an †GLT2i with a §DPP-4i may be particularly relevant for those with ††HbA1c levels more than 1.5% above their individualized target.
2023 European society of cardiology guidelines[35]	- §DPP-4is (sitagliptin and linagliptin) have a neutral effect on the risk of HF hospitalization, and should be considered for glucose-lowering treatment in patients with ‡‡T2DM at risk of or with HF.

*AGI, alpha-glucosidase inhibitors; †AHA, antihyperglycemic agent; ‡CV, cardiovascular; §DPP4i, dipeptidyl peptidase 4 inhibitor; ‖,eGFR, estimated glomerular filtration rate; FDC, fixed-dose combination; **GLP-1RA, glucagon like peptide-1 receptor agonist; ††HbA1c, glycosylated hemoglobin; HF, heart failure; ‡‡T2DM, type 2 diabetes mellitus; *TZDs, thiazoolidinediones; †,SGLT2i, sodium glucose transporter-2 inhibitor.

Table 5: Summary of ongoing trials on linagliptin and combinations.

Study name/ CTRI no	Study design	Objective	Study population	Interventions
Light-MCI study[36]	Multi-center, randomized, parallel-controlled clinical trial with an extension phase	Assess the impact of liraglutide, empagliflozin, and linagliptin on the remission of mild cognitive impairment in §T2DM patients	§T2DM patients with mild cognitive impairment	Liraglutide, empagliflozin, and linagliptin
Bestmed study[37]	Observational study	Compare the effectiveness of second-line diabetes medications using electronic patient data	Patients with T2DM	*DPP-4is, ‡GLP-1RAS, ‖SGLT2is, sulfonylureas, and basal insulin
On target dm study[38]	Comparative study	Compare various §T2DM pharmacotherapy regimens	Patients with §T2DM	Linagliptin, exenatide, liraglutide, empagliflozin, glimepiride, and glipizide

Continued.

Study name/ CTRI no	Study design	Objective	Study population	Interventions
CTRI/2024/ 01/062128[39]	Interventional, multi-center clinical study	Evaluate the efficacy and safety of an †FDC of linagliptin, glimepiride, and metformin	§T2DM patients without complications	†FDC of linagliptin, glimepiride, and metformin
CTRI/2024/ 04/066007[40]	Interventional study	Assess the role of linagliptin and dapagliflozin versus vildagliptin and dapagliflozin in §T2DM	§T2DM patients without complications	Linagliptin + dapagliflozin vs. Vildagliptin + dapagliflozin
CTRI/2024/ 07/070821[41]	Real-world, interventional study	Compare different combination therapies using continuous glucose monitoring in §T2DM patients with kidney complications	§T2DM patients uncontrolled on metformin with kidney complications	Vildagliptin 50 mg + metformin, vildagliptin 100 mg + metformin, sitagliptin 100 mg + metformin, and linagliptin 5 mg + metformin

*DPP4is, peptidase-4 inhibitors; †FDC, fixed-dose combination; ‡GLP-1Ras, glucagon-like peptide-1 receptor agonist; §T2DM, type 2 diabetes mellitus; ||SGLT2is; sodium glucose transporter-2 inhibitors.

FUTURE PERSPECTIVES

The FDC of dapagliflozin and linagliptin offers a promising dual therapeutic approach for managing T2DM, particularly in patients requiring complementary mechanisms to address glycemic control, weight management, and blood pressure reduction. While clinical trials support its efficacy, dedicated long-term studies evaluating the combination's impact on cardiovascular and renal outcomes—including major adverse cardiovascular events, heart failure hospitalizations, and kidney function—are lacking. Future trials targeting these endpoints could establish its role in high-risk populations.

Additionally, real-world data on adherence, persistence, and cost-effectiveness, especially in resource-limited settings, would provide meaningful insights into the practical benefits of this FDC. Further research should explore the utility of Dapa/Lina in special populations such as the elderly, individuals with advanced kidney disease, or those with established cardiovascular conditions.

Given linagliptin's renal safety and dapagliflozin's expanding role in heart failure and chronic kidney disease, the combination may serve a broader population than currently indicated. There is also potential for earlier use in treatment algorithms, including as a second-line or initial therapy in patients with multiple metabolic comorbidities. Comparative trials versus other dual or triple therapies could help refine its optimal placement in routine diabetes care.

CONCLUSION

Linagliptin, a DPP-4i, is effective and safe in T2DM management. Trials show significant reductions in HbA1c, FPG, and PPG. Major studies confirm CV and renal safety. Combination with agents like metformin and SGLT2is enhances glycemic control, reduces weight, and lowers BP, offering a comprehensive T2DM approach. Future research should explore its role in specific subgroups and combination therapies. Real-world data will further define its place in clinical practice. Linagliptin provides effective glycemic control with low hypoglycemia risk and added CV and renal benefits, supporting its long-term use in T2DM.

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