RESEARCH PAPER

Long-Term Safety of DPP-4 Inhibitors: An Insight from Clinical Trials and Real-World Evidence

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is a major global health challenge characterized by chronic hyperglycaemia, insulin resistance, and progressive β-cell dysfunction. Effective management involves long-term glycaemic control while minimizing the adverse effects. Dipeptidyl peptidase-4 (DPP-4) inhibitors are an important class of oral antihyperglycemic agents that work through the enzymatic degradation of incretin hormones GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), enhancing glucose-dependent insulin secretion, suppressing glucagon release, and supporting metabolic homeostasis. The most widely used drugs, such as sitagliptin, saxagliptin, linagliptin, and alogliptin, are well-tolerated and generally considered safe, making them suitable for use in elderly patients and those with chronic kidney disease (CKD). CVOTs, including SAVOR-TIMI 53 and EXAMINE, have demonstrated overall cardiovascular safety; however, saxagliptin has been associated with an increased risk of cardiovascular complications. Renal outcomes are largely neutral, with modest reductions in albuminuria but no consistent decline in long-term estimated glomerular filtration rate (eGFR). Concerns regarding malignancy, pancreatitis, infections, and autoimmune conditions have not been established in controlled studies, underscoring the need for continued real-world safety assessment.

Keywords: *Type 2 Diabetes Mellitus; DPP-4 Inhibitors; GLP-1; GIP; Real-World Evidence, Drug safety.*
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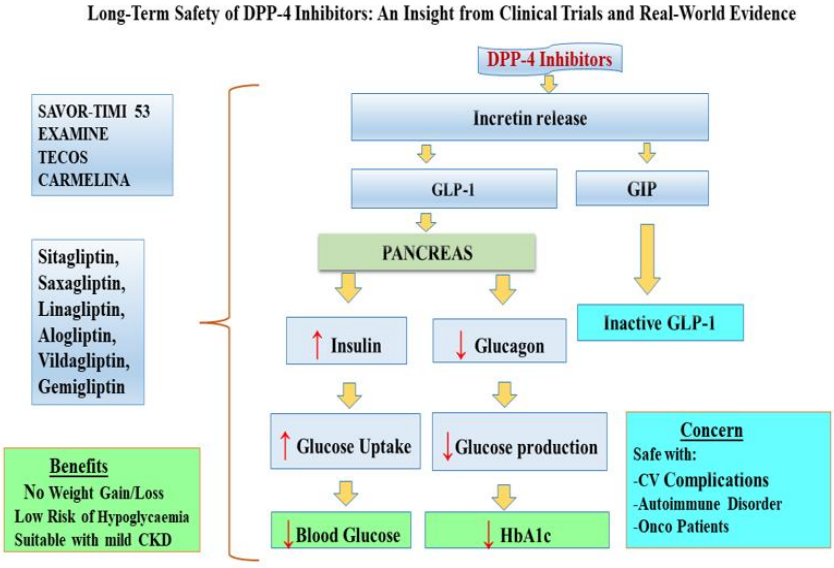
GRAPHICAL ABSTRACT



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1. INTRODUCTION

T2DM is a persistent metabolic disease in which insulin resistance gradually leads to β-cell dysfunction, resulting in hyperglycaemia. It has become an epidemic in many regions, with its global prevalence imposing significant health and economic burdens.[1] Therapies should be effective in controlling the glycemic levels in the blood and reducing the long-term consequences of the disease to manage it effectively. Newer classes of oral antihyperglycemic agents are the gliptins, also known as dipeptidyl peptidase-4 (DPP-4) inhibitors, which are designed to improve glycemic regulation in T2DM. DPP-4 is an enzyme of multifunctional serine proteins that are found in a variety of tissues such as the kidney, liver, gastrointestinal system, and immune cells. One of the main functions of this enzyme is the rapid deactivation of glucagon-like peptide-1 (GLP-1), an incretin hormone that is necessary for glucose homeostasis.[2] DPP-4 inhibitors extend incretin effects, thereby inhibiting glucagon release and promoting glucose-dependent insulin release by the pancreatic 2-cells.[3,4] Simultaneously, sodium-glucose co-transporter 2 inhibitors (SGLT-2) have shown considerable cardioprotective and renoprotective efficacy in T2DM patients, especially those with a pre-existing cardiovascular and renal condition based on the large-scale cardiovascular outcome trials.[5] These agents decrease blood glucose without the assistance of insulin by blocking renal glucose absorption in the proximal tubule, which enhances the urinary excretion.[6] Since the introduction of sitagliptin in 2006, several agents such as vildagliptin, saxagliptin, linagliptin, and alogliptin have been introduced into the clinical arena, with each having different pharmacokinetic configurations.[7] These agents are normally weight-neutral, possess low risk of hypoglycemia, and have shown good tolerability to be especially appropriate in geriatric patients and people with chronic renal failure. In addition to glycemic control, gliptins exert pleiotropic effects on the cardiovascular and renal systems; however, their long-term safety remains a concern that warrants careful consideration.[8,9] The purpose of the review is to formulate existing evidence on the mechanism, efficacy, and safety of DPP-4 inhibitors, combining both the data of the randomized controlled trials and real-world practice. Special focus is given to the cardiovascular outcomes, renal effects, infection risk, cancer associations, and pharmacogenomic insights. By highlighting the established benefits and unresolved issues, this article underscores the importance of continued surveillance and offers valuable insights into the utility of DPP-4 inhibitors in modern diabetes treatment.[10] This review synthesizes evidence from major cardiovascular outcome trials, meta-analyses, real-world observational studies, and pharmacovigilance databases (including FAERS), with literature published up to 2025.

2. MECHANISTIC BASIS OF DPP-4 INHIBITION

GLP-1, a 30-amino acid peptide derived from proglucagon, is secreted by intestinal L-cells, pancreatic α-cells, and neurons in the nucleus of the solitary tract (NTS). It exerts glucose-dependent insulinotropic effects through receptor-mediated activation of adenylate cyclase and cAMP signaling. Still, it is rapidly degraded within 1-2 minutes by DPP-4, which removes its N-terminal dipeptide essential for receptor binding.[11,12] By inhibiting DPP-4, circulating concentrations of active GLP-1 and GIP are sustained, prolonging their physiological action on pancreatic β-cells and α-cells, thereby improving insulin secretion, reducing glucagon output, and enhancing glycemic control.[13] Clinically, DPP-4 inhibitors and DPP-4-resistant GLP-1 analogs are used to manage T2DM, while emerging multi-agonist therapies targeting GLP-1R, GIPR, glucagon, and amylin receptors aim to deliver synergistic metabolic and weight-loss benefits.[14,15] Beyond glycemic regulation, GLP-1 receptors are widely expressed in cardiovascular, renal, hepatic, adipose, and immune tissues, where incretin enhancement contributes to cardioprotective, renoprotective, and anti-inflammatory effects.[16] These integrated mechanisms underscore the therapeutic relevance of DPP-4 inhibition in metabolic disease Figure 1. DPP-4 inhibitors stimulate the incretin hormones (GLP-1/GIP), leading to insulin secretion in response to glucose and to a reduction in glucagon secretion. They reduce hepatic glucose production, slow gastric emptying, and postprandial glucose levels. Other systemic outcomes include enhanced glucose uptake by muscle and adipose tissue, decreased appetite and body weight, cardiovascular vasodilation, and diminished renal inflammation and oxidative stress, collectively contributing to improved metabolic regulation in type 2 diabetes.

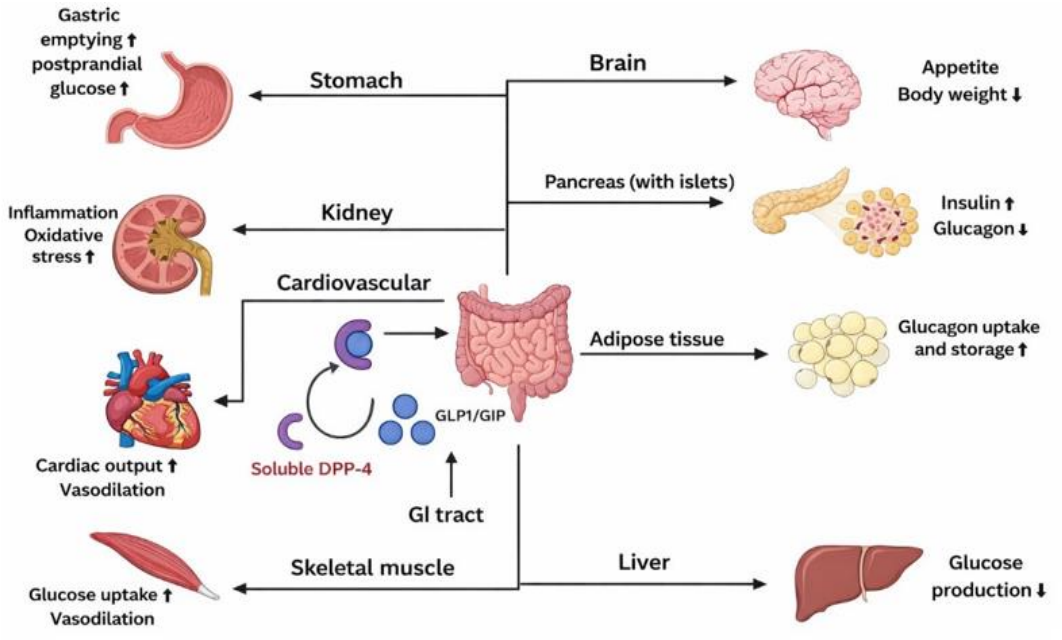

Figure 1: Mechanistic basis of DPP-4 inhibition.

2.1 Physiology and function of DPP-4

DPP-4 is a ubiquitously expressed serine protease found on endothelial cells, renal tubular cells, hepatocytes, immune cells, and in circulating plasma.[17] Its primary enzymatic role is to cleave N-terminal dipeptides from bioactive peptides containing proline or alanine in the penultimate position. In addition to metabolic regulation, DPP-4 influences immune signaling, inflammation, and chemokine activity, reflecting its broader physiological significance.[18]

2.2 The incretin system (GLP-1 and GIP)

GLP-1 and GIP are incretin hormones derived from the intestinal L-cells and K-cells, respectively.[19] They enhance insulin release in a glucose-dependent mechanism through cAMP signaling, reduce glucagon release, decrease gastric emptying, and have trophic and cytoprotective effects on pancreatic β-cells. Nevertheless, GLP -1 and GIP are rapidly inactivated, primarily via cleavage by DPP -4, but doing so to the detriment of their circulating half-life. [20]

2.3 Mechanism of DPP-4 inhibition in glucose regulation

DPP-4 inhibitors were in class taught to prevent the rapid degradation of GLP-1 and GIP, hence increasing the concentrations and half-life of their active forms in circulation.[21] Sustained incretin exposure enhances glucose-dependent insulin secretion through cAMP-mediated pathway, reduces inappropriate glucagon release from pancreatic α-cells, and improves both fasting and postprandial glycemic control. Chronic DPP-4 inhibition has also been associated with modest improvements in β-cell function and preservation of β-cell mass in experimental and clinical studies.[22] These integrated effects highlight the central role of incretin enhancement in mediating the glucose-lowering properties of DPP-4 inhibitors.

2.4 Downstream multi-organ effects

Because GLP-1 receptors are expressed across pancreatic, cardiovascular, renal, neurological, hepatic, adipose, and immune tissues, the consequences of incretin enhancement extend beyond glucose regulation.[23] In the cardiovascular system, DPP-4 inhibition improves endothelial nitric oxide bioavailability, modulates myocardial glucose utilization, and attenuates vascular inflammation. Transitional studies suggest potential cardioprotective effects, although large cardiovascular outcome trials report overall neutrality with respect to major adverse cardiovascular events.[24] In the kidney, enhanced incretin signaling reduces albuminuria by suppressing tubular inflammation and oxidative stress, though long-term effects on eGFR decline remain limited.[25] The immune system is influenced through DPP-4's role as CD26 in T-cell co-stimulation and chemokine processing, with altered chemokine gradients and cytokine profile providing a mechanistic context for mixed infection-related safety signals.[26] At the hepatic and adipose level, incretin enhancement may improve lipid handling, reduce steatosis, and attenuate oxidative stress. Recent experimental studies (2023-2025) report favorable impacts on lipid metabolism and inflammatory pathways in both adipocytes and hepatocytes.[27] These multi-organ effects provide a mechanistic context for the largely favorable long-term safety profile observed in clinical trials, while also explaining rare immune- and infection-related adverse events reported in post-marketing surveillance.

3. PHARMACOLOGY OF DPP-4 INHIBITORS

DPP-4 inhibitors are inhibitors of the enzyme DPP-4, which catalyzes the breakdown of various substrates, thereby modulating insulin signaling and contributing to insulin resistance. It also plays a significant role in the inflammatory processes linked to obesity and type 2 diabetes. New studies suggest that an increase in DPP-4 activity is associated with decreased bone mineral density and an increased risk of fractures.[28] Essentially, it appears that the more the enzyme does its job, the weaker our bones become, which warrants careful interpretation in the context of long-term safety assessment (Figure 2). DPP-4 inhibitors, such as those we have examined in class (linagliptin, vildagliptin, sitagliptin, saxagliptin, and alogliptin), are approved worldwide.[29] Saxagliptin, linagliptin, and sitagliptin are BCS Class III, whereas alogliptin is Class I. Although they are highly soluble in water, they are also short-acting; therefore, we need to take them more frequently to maintain blood levels. This rapid absorption often elevates plasma levels, which can cause gastrointestinal side effects. Besides, Class III compounds have low membrane permeability, which reduces oral bioavailability.[30]

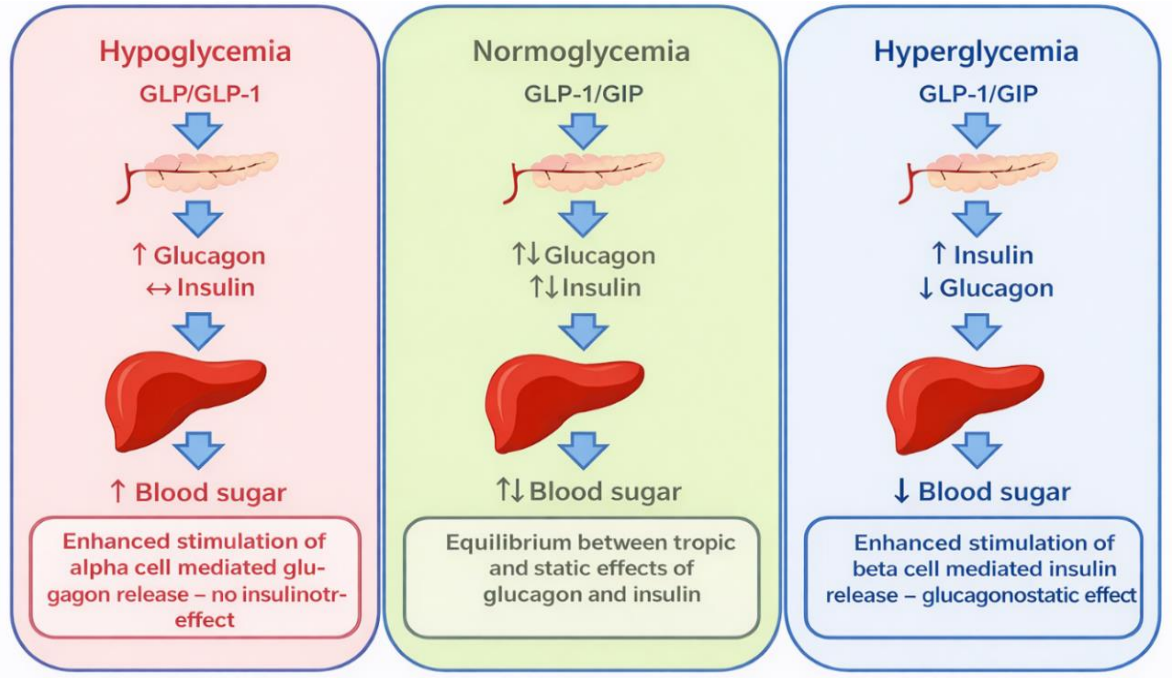

Figure 2: Mechanistic approach of DPP-4 Inhibitors.

3.1 Sitagliptin

Thus, sitagliptin was approved by the U.S. FDA in 2006 and is the first DPP-4 inhibitor used in the management of T1DM. It may be administered alone or in combination with other antidiabetic medications to improve glycemic control. It inhibits the DPP-4 enzyme, which degrades GLP-1; thus, GLP-1 remains in the organism longer and reduces glucose levels.[31] And there is evidence that sitagliptin and other DPP-4 inhibitors are not only effective in combating glucose spikes. They appear to assist with the cardiovascular, autoimmune, pulmonary, and inflammatory disorders, primarily because they up-regulate our own antioxidant defenses and modulate the responses of the immune system.[32] Sitagliptin has also been shown to effectively reduce total cholesterol and LDL-C levels, while exerting hepatoprotective effects through the regulation of oxidative stress.[33] Furthermore, it has been shown to have therapeutic promise in prediabetes by mitigating beta-cell apoptosis triggered by inflammation. Its ability to inhibit pro-apoptotic cytokines highlights its value as an early intervention strategy.[34]

3.2 Saxagliptin

Saxagliptin is a highly potent and selective DPP-4 inhibitor used in the management of type 2 diabetes mellitus (T2DM). Inhibiting DPP-4 increases circulating levels of GLP-1 and GIP, thereby enhancing glucose-dependent insulin secretion and improving glycemic control. CYP3A4 primarily metabolizes Saxagliptin into an active metabolite with reduced DPP-4 inhibitory activity. It is generally well tolerated, with a low risk of hypoglycemia when used as monotherapy and without contributing to weight gain. Reported adverse effects include infections, gastrointestinal symptoms, and lymphopenia.[35] Beyond glycemic regulation, saxagliptin has demonstrated neuroprotective properties in preclinical models of Parkinson's and Alzheimer's disease. It may mitigate secondary injury in traumatic brain injury (TBI) by modulating oxidative stress and the neuroinflammatory pathway.[36] Incretin-based therapies, including DPP-4 inhibitors and GLP-1 receptor agonists, have been associated with improved recovery rates from acute hypoglycemic coma compared with non-incretin therapies, even after adjustment for age and sex.[37] This

observation reflects a class effect of incretin-based agents rather than a unique property of saxagliptin.

3.3 Linagliptin

Linagliptin is an oral inhibitor of DPP-4 used to manage T2DM, either alone or in combination with another antidiabetic agent.[38] DPP-4 inhibitors work by elevating active GLP-1 concentrations, which stimulate insulin secretion and contribute to lowering HbA1c levels and fasting plasma glucose. Linagliptin is an effective and well-tolerated DPP-4 inhibitor that reduces the risk of hypoglycemia by lowering glucagon levels and enhancing postprandial insulin secretion.[39] Linagliptin also interacts with additional molecular targets in humans, including CHRM1, FAP, ALDH1A1, and PDE6D, influencing their gene expression profiles.[40] Linagliptin, a second-line therapeutic agent, functions as a DPP-4 inhibitor, enhancing the activity of incretins like GLP-1. GLP -1 enhances the release of insulin and inhibits glucagon release in the presence of glucose. In addition, its safety profile is reported to be good, and its anti-inflammatory and antioxidant activities have been demonstrated in in vivo experiments. These have been suggested to be mediated by several molecular mechanisms.[41] The body essentially eliminates Linagliptin with little metabolism. In individuals who have type-2 diabetes and chronic kidney disease, it has demonstrated safety and efficacy in administering it as a treatment option.[42]

3.4 Alogliptin

Alogliptin is a highly selective DPP-4 inhibitor that is predominantly excreted unchanged in the urine and undergoes minimal metabolism. Among individuals with impaired kidney function, variations in clinical outcomes may elevate the risk of serious adverse effects. However, alogliptin is not associated with an elevated likelihood of cardiovascular complications such as heart disease or stroke and carries a relatively low risk of inducing Hypoglycemia.[43] Alogliptin influences various signaling pathways, which have allowed researchers to explore its potential benefit in conditions affecting other organ systems. Information obtained from the FDA's Adverse Event Reporting System (FAERS) between 2006 and 2020 indicates that alogliptin is associated with fewer adverse events than other antidiabetic agents. However, long-term use in elderly patients has been linked to cases of bullous pemphigoid, an autoimmune skin disorder.[44] A pharmacokinetic/pharmacodynamic study involving alogliptin (25mg) in pediatric patients aged 10-17 years demonstrated that this dose produced alogliptin exposure and DPP-4 inhibition comparable to levels seen in adults with T2DM. Notably, no safety issues were observed.[45] Alogliptin has proven effective as an add-on therapy in patients whose blood glucose levels are inadequately controlled with other oral antidiabetic agents. It was a clinically meaningful improvement in continuous glucose monitoring metrics, particularly in the average blood glucose period within the curative range, and it markedly reduced glycemic instability.[46]

3.5 Vildagliptin and Gemigliptin

Even though not sold everywhere, Vildagliptin and gemigliptin appear to be as effective as the rest of the DPP-4 inhibitors in controlling blood sugar. Vildagliptin may cause a transient elevation in liver enzymes in a subset of individuals; therefore, physicians recommend periodic monitoring of liver function.[47] A very popular drug in Asian areas, gemigliptin possesses a reasonably good pharmacokinetic profile, a low likelihood of drug-drug interactions, and most recent studies in the region,[48] indicate that it is kidney-safe and is generally well-tolerated. In essence, the two drugs are generally well tolerated and retain the class's primary strengths, including no weight gain and a low risk of hypoglycemia (Figure 3). The pharmacokinetic parameters, the necessity of the renal dose change, the metabolic route, the drug-drug interaction, and the main safety indicators are cross-compared in detail and summarized in Table 1.

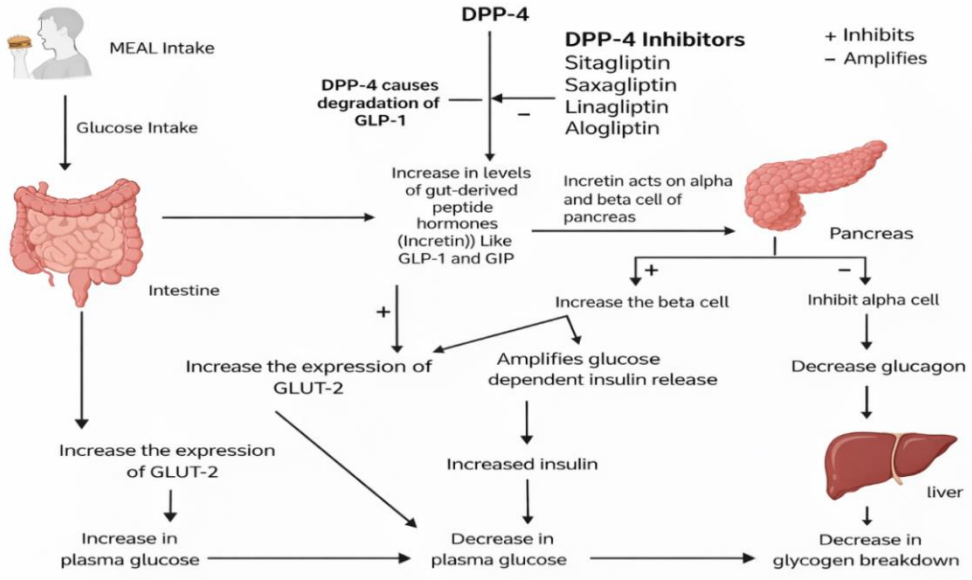

Figure 3: Cellular pharmacology of DPP-4 inhibitors.

Table 1: Comparative Pharmacologic & Safety Profile of DPP-4 Inhibitors.

Drugs	Half-Life	Renal Dose Adjustment	HbA1c Reduction (%)	CVOT HF Signal	Renal Safety	Adverse Events	References
Sitagliptin	~12.4 h	Required in CKD	0.6-0.8%	Neutral (TECOS)	Safe in CKD 1-3	Rare pancreatitis	49, 50, 51
Saxagliptin	~2.5 h	Required	0.5-0.7%	↑ HF (SAVOR)	Neutral	HF signal, infections	50, 52, 53
Linagliptin	~12 h	None	0.6-0.7%	Neutral (CARMELINA)	Safe in moderate-severe CKD	URI risk	50, 54, 55
Alogliptin	~21 h	Required	0.5-0.6%	Possible ↑ HF	Safe	Bullous pemphigoid	50, 52, 54
Vildagliptin	~2 h	Required	0.7-0.9%	No dedicated CVOT; overall neutral in pooled analyses	Good tolerability	Rare hepatic dysfunction	52, 51, 53
Gemigliptin	~17 h	Required	0.6-0.8%	No HF signal in available trials	Safe, including CKD and high-risk cohorts	Mild GI symptoms	56, 57

DPP-4, Dipeptidyl Peptidase-4; T2DM, Type 2 Diabetes Mellitus; HbA1c, Hemoglobin A1c (Glycated Hemoglobin); CKD, Chronic Kidney Disease; CVOT, Cardiovascular Outcome Trial; HF, Heart Failure; URI, Upper Respiratory Infection; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin; SAVOR-TIMI 53, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes-Thrombolysis in Myocardial Infarction 53; CARMELINA, Cardiovascular and Renal Microvascular Outcome Study with Linagliptin.

4. FDA-APPROVED INDICATIONS, REGULATORY GUIDELINES, AND CLINICAL USE OF DPP-4 INHIBITORS

Evidence indicates that diabetes mellitus remains a significant health concern globally, and T2DM, in this case, is the most prevalent and a massive burden to morbidity and mortality across the globe.[58] Safety analyses using the FDA FAERS have investigated the risk of pancreatitis associated with antidiabetic agents, including DPP-4 inhibitors, through statistical signal detection methods. A 2022 cohort study further examined the incidence of acute pancreatitis and pancreatic cancer among individuals with T2DM, reporting a potential link between DPP-4 inhibitor use and increased risk of acute pancreatitis.[59] Large randomized controlled trials have confirmed the cardiovascular safety of DPP-4 inhibitors by ruling out excess risk of major adverse cardiovascular events (MACE), although none have demonstrated definitive cardiovascular benefit. Nevertheless, the U.S FDA has issued warnings regarding possible heart failure risk, particularly in patients with underlying renal or cardiovascular disease.[60] Dose adjustments are recommended for certain agents based on glomerular filtration rate (GFR), but DPP-4 inhibitors are not contraindicated in patients with chronic kidney disease (CKD) and T2DM. Current guidelines support their use as second-line therapy in individuals who fail to achieve adequate glycemic control with metformin or other antihyperglycemic agents.[61] Sitagliptin was the first DPP-4 inhibitor approved by the U.S. FDA in 2006, followed by saxagliptin (2009), linagliptin (2011), and alogliptin (2013). Internationally, vildagliptin (Europe) and anagliptin (Japan) have also been approved. Analysis of U.S. national health survey data (NHANES) revealed that approximately one-fifth of over 6000 surveyed non-pregnant adults with diabetes reported using DPP-4 inhibitors.[62,63] Leading cardiology and diabetes guidelines, including those from the ACC, AHA, HF SA, ESC, and ADA, generally support the use of sitagliptin and linagliptin in patients with T2DM and heart failure, as these agents do not significantly affect rates of heart failure hospitalization or MACE. In contrast, saxagliptin has been associated with an increased risk of heart failure hospitalization. It is therefore not recommended for patients with T2DM who have existing heart failure or are at elevated risk. Importantly, the AHA/ ACCF/HFSA consensus statement advises against the use of any DPP-4 inhibitors in patients with stage B heart failure, reflecting a more cautious stance in this subgroup Table 2.[64]

Table 2: Regulatory approvals & global indications.

	FDA	EMA	PMDA (Japan)	Indications	Notes	References
Sitagliptin	2006	Yes	Yes	T2DM therapy	HF-safe; widely used globally	65, 66,67
Saxagliptin	2009	Yes	Yes	T2DM	FDA HF caution; label updated 2024	65, 68, 69
Linagliptin	2011	Yes	Yes	T2DM	No renal dose adjustment	65, 70, 71
Alogliptin	2013	Yes	Yes	T2DM	Caution post-ACS; renal dose adjustment	68, 70, 72

Vildagliptin	-	Yes	Yes	T2DM	Not FDA-approved	66, 72, 73
Anagliptin	-	-	Yes	T2DM	Additional LDL-lowering benefits	73, 74
Teneligliptin	-	-	Yes	T2DM	High DPP-4 selectivity	73, 74

FDA, Food and Drug Administration; EMA, European Medicines Agency; PMDA, Pharmaceuticals and Medical Devices Agency; T2DM, Type 2 Diabetes Mellitus; HF, Heart Failure; ACS, Acute Coronary Syndrome; LDL, Low-Density Lipoprotein; DPP-4, Dipeptidyl Peptidase-4.

5. ROLE IN MONOTHERAPY AND COMBINATION THERAPY FOR TYPE 2 DIABETES.

DPP-4 inhibitors are infrequently prescribed as monotherapy, whereas metformin remains the first-line treatment. However, combining metformin with a DPP-4 inhibitor enables targeting of all major pathogenic mechanisms of T2DM.[75] In another study, adding sitagliptin to insulin therapy in individuals with inadequately managed T2DM resulted in a marked decline in HbA1c levels relative to simply increasing the insulin dose.[76] The combination of anti-diabetic agents with complementary agents such as SGLT2 inhibitors and DPP-4 inhibitors is a promising approach for managing T2DM. DPP-4 inhibitors provide effective blood glucose control with minimal risk of hypoglycemia; however, potential concerns include infection, hypersensitivity, pancreatitis, and cardiovascular effects. Combination therapies such as Empagliflozin+Linagliptin and Dapigliflozin+Saxagliptin generally have a favorable safety profile, with risks that are generally consistent with those of the individual drugs.[77] Metabolic studies have shown that SGLT2 inhibitors lower plasma glucose through an insulin-independent mechanism, which improves peripheral insulin sensitivity and beta cell function, even with increased endogenous glucose production. No heart failure cases were reported in trials using empagliflozin-linagliptin as a combination or add-on to metformin. Although a two-pill combination is available, these agents have not undergone dedicated trials as fixed-dose combinations, as they are considered bioequivalent to their individual forms.[78] Although DPP-4 inhibitors have not previously been shown to affect adipose tissue insulin resistance assessed by adipo-IR, alogliptin, unlike sitagliptin or teneligliptin, can reduce adipo-IR and certain atherogenic lipids.[50]

6. LONG-TERM CLINICAL SAFETY AND EFFICACY OF DPP-4 INHIBITORS.

DPP-4 inhibitors are generally well tolerated, especially in patients with renal impairment, and do not substantially increase hypoglycemia risk compared with several other glucose-lowering medications.[79] Their favorable tolerability and weight-neutral profile make them a valuable therapeutic choice for treating T2DM in individuals with kidney dysfunction. However, limited evidence suggests a possible association with elevated heart failure risk.[80]

6.1 Cardiovascular Safety and Major Cardiovascular Outcome Trials (CVOTs)

One-third of individuals with diabetes are affected by CVD; cardiovascular safety has been a major focus of DPP-4 inhibitor evaluation.[81] Over the past decade, extensive cardiovascular outcome trials (CVOTs) in patients with T2DM and elevated cardiovascular risk of established heart disease have demonstrated that DPP-4 inhibitors do not increase ischemic cardiovascular risk.[82] Co-morbid hypertension and dyslipidemia are key contributors to atherosclerotic cardiovascular disease (ASCVD), and diabetes independently increases ASCVD risk. Individuals with diabetes may develop heart failure with preserved or reduced ejection fraction, with hypertension frequently preceding both.[83] In SAVOR-TIMI 53 (saxagliptin), 16492 patients enrolled with T2DM, 78.6% with ASCVD, and 12.8% with NYHA class II-III heart failure, median follow-up 2.1 years.[84] Saxagliptin met the non-inferiority criterion for three-point major adverse cardiovascular events (3-point MACE) (HR 1.00; 95% CI, 0.89-1.12); however, it was associated with a 27% increase in hospitalization for heart failure.[85,86] This prompted FDA safety warnings, as saxagliptin also increased the progression to macroalbuminuria compared with placebo, although it had no meaningful effect on composite renal outcomes.[87,88] EXAMINE (alogliptin) confirmed cardiovascular safety without increased MACE risk in high-risk T2DM patients with acute coronary syndrome.[89] Biomarker analyses identified 43 markers associated with heart failure hospitalization, and rare bullous pemphigoid events were reported in elderly populations.[90,91] Alogliptin also reduced glycemic variability and improved time in the target glucose range (80-140 mg/dl) from 10% to 47%.[92] Other CVOTs (TECOS, sitagliptin; CARMELINA, linagliptin) confirmed cardiovascular safety without increased ischemic risk.[68] Table 3.

Table 3: DPP-4 inhibitors demonstrate moderate glycemic efficacy consistent with findings from CVOTs and real-world cohorts**.**

Trials	Drugs	Population	Follow Up	MACE	HF	Findings	References
SAVOR-TIMI 53	Saxagliptin	16,492	2.1 Years	Neutral	↑ 27%	HF signal noted → FDA safety update	[93,50]
EXAMINE	Alogliptin	5,380	18 Months	Neutral	Mild ↑	Safe post-ACS; no significant ↑ HF	[94-95,96]
TECOS	Sitagliptin	14,735	3 Years	Neutral	No ↑	Strong CV safety; no HF signal	[97]
CARMELINA	Linagliptin	6,979	2.2 Years	Neutral	No ↑	Renal safety confirmed; no CV excess	[98,54]
VIVIDD	Vildagliptin	254	52 Weeks	Not powered	Neutral	LV function stable; supportive safety data	[95,99]

SAVOR-TIMI 53, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes - Thrombolysis in Myocardial Infarction 53; EXAMINE, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin; CARMELINA, Cardiovascular and Renal Microvascular Outcome Study with Linagliptin; VIVIDD, Vildagliptin in Ventricular Dysfunction Diabetes; MACE, Major Adverse Cardiovascular Events; HF, Heart Failure; CV, Cardiovascular; LV, Left Ventricular; ACS, Acute Coronary Syndrome.

6.2 Heart Failure Risk

The principal safety divergence within the DPP-4 inhibitor class relates to heart failure (HF) outcomes. In the SAVOR-TIMI trial, saxagliptin was associated with a 27% relative increase in HF hospitalization, leading to formal warnings from both the FDA and EMA. By contrast, sitagliptin and linagliptin did not demonstrate elevated HF risk, while EXAMINE reported a numerical but statistically nonsignificant increase with alogliptin.[100] Several mechanisms have been proposed to explain this signal, including alterations in natriuretic peptide metabolism, off-target inhibition of DPP-8/9 isoenzymes, enhanced susceptibility to fluid retention in high-risk patients, and immune-mediated myocardial inflammation**.**[54] Real-world cohorts corroborate these findings, consistently showing higher HF rates among older adults, patients with pre-existing HFpEF or HFrEF, advanced chronic kidney disease, or elevated baseline natriuretic peptides.[101] In light of these observations, saxagliptin should be avoided in patients with a history of heart failure, in accordance with professional society guidelines.

6.3 Renal Safety

Diabetic kidney disease (DKD) affects~30% of individuals with diabetes, and optimal glycemic control is crucial to slow kidney function decline.[102] DPP-4 inhibitor reduces tubular and glomerular proteinuria and lowers biomarkers linked to tubular injury in DKD.[103] In SAVOR-TIMI 53, saxagliptin reduced urinary albumin-to-creatinine ratio but did not affect overall renal function.[104] Meta-analyses consistently show reduced risk of new-onset or worsening albuminuria, but no significant effect on GFR decline or progression to ESRD.[105] FAERS data have been used to assess drug safety in diabetes, incorporating large volumes of adverse event reports.[106] Intensive glycemic control reduces albuminuria risk, and long-term follow-up indicates it may help prevent declines in estimated GFR and kidney failure.[107]

6.4 Malignancy and Cancer Risk

DPP-4 (CD26) contributes to tumor-immune interactions, raising concerns about potential pro- or anti-tumor effects. Preclinical findings remain mixed; however, large CVOTs and pooled datasets have not demonstrated an increased overall cancer incidence or elevated risk of pancreatic or colorectal malignancies.[108] **Some observational cohorts reported small early increases in colorectal cancer incidence, but these signals are inconsistent and likely attributable to confounding, surveillance bias, or short-term detection effects.**[109] Experimental evidence suggests that DPP-4 may influence tumor biology in a context-dependent manner; however, large cardiovascular outcome trials and pooled analyses have not demonstrated an increased overall cancer risk.[110] Studies report increased colorectal cancer risk in patients under 65 and in recent initiators of therapy, particularly within the first year.[111] Other studies suggest potential anti-tumor effects via immune augmentation and off-target effects such as Nrf2-driven antioxidant activation.[112] **At present, no causal association between DPP-4 inhibitor therapy and malignancy has been established, though continued pharmacovigilance remains warranted to monitor rare or long-latency outcomes.**

6.5 Risk of Infections and Immune Modulation

Urinary tract infections in diabetes can lead to severe complications, including emphysematous pyelonephritis, cystitis, renal papillary necrosis, and opportunistic fungal infections.[113] Mortality trends in T2DM have improved due to better risk factor control and therapies.[114] Poor glycemic control and autonomic neuropathy-related incomplete bladder emptying are key causes of infections.[115] Diabetic foot disease imposes a substantial health and economic burden, and Helicobacter pylori infection contributes to impaired glycemic control.[116-117] DPP-4/CD26 modulates immune function and acts on cytokines and chemokines.[118] DPP-4 inhibitors may

weaken defense against respiratory infections, sepsis, and other serious infections.[119] A meta-analysis found no increased pneumonia risk, though rare infections such as endocarditis have been reported.[120-121] Sitagliptin has been associated with interstitial lung disease, and saxagliptin with higher rates of upper respiratory tract infections.[122-123]

6.6 Arthralgia

Post-marketing surveillance and updated safety reviews between 2022 and 2025 have reinforced concerns that DPP-4 inhibitors may cause severe, disabling arthralgia in a subset of patients. Health Canada's 2022 safety review highlighted persistent joint pain linked to sitagliptin, saxagliptin, linagliptin, and alogliptin, noting that symptoms often resolve upon discontinuation and recur with re-challenge.[124] Similarly, recent pharmacovigilance analyses and clinical updates emphasize that arthralgia can occur days to years after therapy initiation, sometimes requiring hospitalization.[125] While the overall incidence is low, the severity of reported cases has led to strengthened warnings in prescribing information and continued regulatory oversight. Clinicians are advised to consider DPP-4 inhibitors as a potential cause of unexplained joint pain and to discontinue therapy if symptoms are severe or persistent.[126]

6.7 Clinical Efficacy of DPP-4 Inhibitors

DPP-4 inhibitors exhibit moderate glycemic efficacy, typically reducing HbA1c by 0.5% with monotherapy and by up to 1.0% with combination therapy.[92,127] Their low hypoglycemia risk, oral administration, and favorable tolerability make them particularly suitable for older adults and patients with advanced CKD.[91] As an add-on therapy, alogliptin reduced average blood glucose and decreased glycemic variability, with time in target glucose range improving from 10% to 47%.[128]

6.8 Hypoglycemia and Weight Management

Hypoglycemia is a major concern in the management of T2DM and is often associated with insulin or oral hypoglycemic agents, inadequate carbohydrate intake, missed meals, increased physical activity, and lifestyle factors.[129] DPP-4 inhibitors reduce glycemic variability by promoting glucose-dependent insulin secretion, improve glycemic control without contributing to weight gain or hypoglycemia, and support safer long-term care.[130,131] When combined with insulin, agents such as alogliptin, linagliptin, saxagliptin, sitagliptin, and vildagliptin effectively lower HbA1c while minimizing weight gain and reducing hypoglycemia risk.[92]

6.9 Trial-Integrated Efficacy and Safety Perspective

Large trials (SAVOR-TIMI 53, EXAMINE, TECOS, CARMELINA) primarily evaluated cardiovascular safety and efficacy. Collectively, they affirmed a favorable safety profile regarding cardiovascular outcomes, hypoglycemia, pancreatitis, and pancreatic cancer.[132] Signals of increased heart failure hospitalization were noted with saxagliptin and, to a lesser extent, alogliptin, warranting caution in higher-risk populations. Extended follow-up in lower-risk cohorts is needed to clarify class-level safety considerations.[133]

7. RANDOMIZED CONTROLLED TRIALS VERSUS REAL-WORLD EVIDENCE

Evidence concerning the long-term safety of DPP-4 inhibitors is derived from both RCTs and Real-world data (RWD), which encompass observational cohorts, electronic health records, insurance claims analyses, and post marketing pharmacovigilance system.[134] Randomized controlled trials (RCTs) form the cornerstone of regulatory drug approval because of their high internal validity and robust causal inference the best internal validity, and the selection of regulatory bodies. RWD, on the other hand, provides a preview of safety outcomes in a broader, more clinically representative population. Although these two sources of evidence generally support the cardiovascular and renal neutrality of DPP-4 inhibitors, there are significant discrepancies between the results of these two complementary strategies.[135] Large CVOTs such as SAVOR-TIMI 53 (saxagliptin), EXAMINE (alogliptin), TECOS (sitagliptin), and CARMELINA (linagliptin) are not inferior to placebo in terms of MACE.[136] These experiments utilize harsh eligibility, restrictive follow-ups, typical control programs, and the chances of high adherence, and these come to assist us in making correct causal inferences. However, the study's methodological limitations also suggest that the results will not be readily generalizable. RCT subjects are younger, healthier, and less comorbid compared to our patients in a usual practice, and older patients, those on several medications, patients with advanced CKD, or severe CKD become under-represented.[137] Consequently, RCTs often underestimate event rates, particularly hypoglycemia, heart failure exacerbation, and renal decline relative to real- world settings. In contrast, RWD encompasses more heterogeneous populations, including those with frailty, multimorbidity, prior heart failure, or significant renal impairment. These cohorts demonstrate lower adherence, more frequent therapy switching, and diverse background treatments, all of which influence safety outcomes.[138] As a result, RWD consistently reports a higher absolute rate of hypoglycemia and stronger heart-failure signals with certain agents, most notably saxagliptin, compared with RCT findings.[139] Real-world registries further indicate that DPP-4 inhibitors are frequently prescribed to patients with CKD or those unable to tolerate alternative therapies, thereby enriching populations at elevated risk of renal and cardiovascular risk events. Despite this difference, RWD corroborates the cardiovascular neutrality of sitagliptin, linagliptin, and alogliptin observed in RCTs. A distinctive advantage of RWD is its capacity to identify rare adverse

events that are underpowered for detection in RCTs, including bullous pemphigoid, pancreatitis, and selected infections such as cellulitis and herpes zoster.[140] Nevertheless, interpretation of these findings remains complex due to confounding by indication and unmeasured comorbidities. A cautious appraisal and methodological rigor in incorporating RWD demonstrate that each evidence source contributes complementary perspectives on the safety of DPP-4 inhibitors. RCTs provide high-certainty estimates of class-wide neutrality in cardiovascular and renal outcomes. In contrast, RWD reveals how specific risks, particularly heart failure exacerbations, may emerge in routine practice among more vulnerable patients.[141] This two-evidence model can be applied to tailor prescribing and guide my clinical practice specifically to patients at high risk (advanced cardiovascular disease or chronic kidney disease) in whom patient safety is the primary consideration.

7.1 Post-marketing surveillance/safety monitoring

DPP-4 inhibitors have been a significant breakthrough in the management of T2DM, supported by a decade of clinical experience and evidence from rigorous research and post-marketing surveillance. They regulate insulin secretion in a glucose-dependent manner via a stimulatory mechanism that promotes a progressive and prolonged decrease in HbA1c levels. Although these have these advantages, their use in Italy remains limited due to prescribing restrictions imposed by AIFA. The existing reimbursement policies require prescriptions from only diabetes specialists and deny treatment to patients with HbA1c levels below 7.5, regardless of the suboptimal risk-benefit profiles of alternative therapies. Additionally, individuals with HbA1C levels above 8.5-9.0% are also barred, and this further limit access to this useful category of agents.[142] Nevertheless, no pharmacovigilance study has so far researched the US. Data specifically in the FDA FAERS, a database of reports of post-marketing drugs reported by healthcare providers, consumers, and manufacturers. In addition, their selection was not limited by a prior pharmacovigilance analysis to reports on diabetic patients (Table 4).

Table 4: Comparison of Randomized Controlled Trials Versus Real-World Evidence.

Parameters	RCTs	RWD	Interpretation	References
Population	Selected, controlled	Heterogeneous	RWD reflects real-world practice	[143]
HbA1c Reduction	0.5-0.9%	0.4-0.8%	Lower in RWD due to adherence variability	[144, 54]
Hypoglycemia	Low	Higher	Polypharmacy effect	[144, 145]
Heart Failure (HF)	Neutral (except saxagliptin)	Higher in CKD/elderly	Matches post-marketing surveillance	[58, 50]
Renal Outcomes	Albuminuria ↓	Slower CKD progression	Better long-term signal	[146, 55]
Pancreatitis	Rare	Slightly ↑ reports	Likely reporting bias	[144, 147]
Adherence	~90%	50–65%	Major outcome driver	[147]

RCTs, Randomized Controlled Trials; RWD, Real-World Data; HbA1c, Hemoglobin A1c (Glycated Hemoglobin); HF, Heart Failure; CKD, Chronic Kidney Disease.

8. FACTORS INFLUENCING LONG-TERM SAFETY OF DPP-4 INHIBITORS.

8.1 Patient Demographics and Comorbidities

It has been found that the emergence of complications that emanate from diabetes is capable of weakening lower-extremity muscles, hence negatively impacting daily functional capacity. A cohort study (n=977 older adults) on the effects of physical activity and sedentary behaviour on secondary conditions (hypertension, retinopathy, nephropathy, etc.) found that physical activity and sedentary behaviour were distinct risk factors. The complications also undermine mobility and endanger self-reliance. A comorbid condition is a term that is used to denote other chronic illnesses that coexist with a major disease. Regarding the case of diabetes, they tend to worsen the clinical outcomes and lead to the deterioration of the overall state of health.[148]

8.2 Lifestyle Factors

Lifestyle and dietary habits, as well as regular medication use, are essential for determining long-term safety outcomes in type 2 diabetes mellitus (T2DM). The safety and therapeutic efficacy of DPP-4 enzyme inhibitors and other antidiabetic drugs may be improved considerably by promoting healthy eating habits and reinforcing adherence strategies.[149]

8.3 Pharmacogenomics Factors: Patient Characteristics

They have proved that specific patient factors, namely, advanced age, chronic kidney disease (CKD), and the presence of heart failure, are important risk factors in adverse events of a prolonged course of treatment with DPP-4 inhibitors. In turn, it is essential to tailor treatment plans to patients' specific attributes to ensure maximum safety. [150.] Recent studies indicate that genetic variants play a major role in determining patients' responses to DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT-2 inhibitors. Importantly, polymorphs of GLP1R have been correlated with reduced decrease of HbA1c level with the

DPP-4 inhibitors, but improved weight loss with the GLP-1 receptor agonists. Other genes with promising associations include TCF7L2 and KCNQ1, although these associations have not yet been validated.[151] DPP-4 inhibitors may affect the response of the DPP-4 enzyme in a genetic variation, depending on the activity of the DPP-4 gene. Interestingly, in a small study, participants with the TT genotype at rs2909451 showed increased short-term DPP-4 activity despite receiving the DPP-4 inhibitor sitagliptin.[152]

8.4 Drug Interaction.

New studies show that proton pump inhibitors (PPIs) may have an impact on the activity of DPP-4 inhibitors, which may impair glycemic control and lead to hypoglycemia. Esomeprazole seems to be the least likely to undergo such interactions when used in combination with DPP-4 inhibitors, which is the reason why it is the least likely PPI. It can also provide relief against gastrointestinal side effects that are usually common with such diabetes drugs.[153]

8.5 Clinical Implications.

DPP-4 inhibitors are effective, weight-neutral, and well-tolerated for type 2 diabetes mellitus (T2DM), making them particularly appropriate for older adults and those with renal impairment. Their glucose-dependent action makes them highly effective in preventing hypoglycemia, particularly when used with metformin or insulin. Although CVOTs confirm their cardiovascular safety profiles, patients with heart failure should be used with caution, particularly for saxagliptin. Long-term data support their safety; nevertheless, it is prudent to monitor for rare adverse events, such as infections and bullous pemphigoid. Such agents provide modest benefits in kidney operations, and new pharmacogenetic discoveries can further improve treatment outcomes. Post-marketing surveillance and real-world experience complement randomized controlled trials (RCTs) and provide context for subtle clinical decision-making.

9. DISCUSSIONS

The cumulative evidence from mechanistic studies, RCTs, and RWD indicates that DPP-4 inhibitors are generally safe and well-tolerated in the long-term management of T2DM.[154] One of the main reasons for combining findings from multiple evidence sources rather than relying on a single dataset is the variability across agents and patient subgroups.[155] This principle is exemplified by the heart-failure signal with saxagliptin, despite the cardiovascular neutrality of CVOTs at the level of the classes; saxagliptin was the only drug that increased cardiovascular hospitalization. RWD has put this risk in context, and the likelihood is greater in older adults, patients with prior heart failure, and those with advanced CKD.[156] Mechanistic explanations implicate DPP-4 substrates such as stromal cell-derived factor-1, neuropeptide Y, and substance P, which influence myocardial remodeling and inflammation, as well as potential off-target inhibition of DPP-8/9.[129, 157] Beyond heart failure, discrepancies between RCTs and RWD extend to infections and cancer. RCTs report low infection rates, whereas RWD occasionally shows higher frequencies of mild respiratory or urinary infection linked to frailty and comorbidities.[158] Early signals of colorectal cancer risk were not confirmed/ in large trials.[159] Renal outcomes consistently demonstrate reductions in influence efficacy and adverse events, though evidence remains preliminary.[160] Overall, DPP-4 inhibitors are safe for most patients, with saxagliptin requiring caution in those with cardiovascular vulnerability. Continued surveillance and genomic research will refine personalized use.[161]

10. CHALLENGES, DATA GAPS, AND FUTURE DIRECTIONS

Evidence gaps remain evident in both clinical trials and real-world evaluations of glucose-lowering therapies. Clinical trials are frequently limited by short follow-up periods, exclusion of high-risk populations, and inadequate representation of diverse populations. In contrast, practical research tends to have missing evidence on long-term medication adherence and under-reporting of ADRs, which the passive surveillance mechanism can partially explain. Two methodological issues can be singled out in particular: (i) assessment windows that do not allow the entire treatment persistence curve to be observed, and (ii) long follow-up, which, although needed to assess long-term outcomes, is subject to the bias of attrition and decreased statistical strength.[162] DPP-4 inhibitors, including sitagliptin, have been studied in patients with T2DM who are using metformin for an average of 5 years. One significant weakness found is under-reporting of ADRs in pharmacovigilance databases, thus in favor of increased post-marketing surveillance as an improvement in drug safety surveillance, especially the rare ADRs and the outcomes in the underrepresented population. The integration of pharmacovigilance and electronic health records would enhance more powerful ADR detection and tracking.[163,164]

Future research should focus on comparative effectiveness across drug classes, monitoring long-term safety across populations, and the adoption of pharmacogenomic measures to personalize therapy. Specific directions for the research include prospective and cross-sectional studies to compare the rate of heart failure hospitalization among specific DPP-4 inhibitors in patients with pre-existing HFpEF.

- ADR incidence in frail elderly groups and multimorbidity groups should be studied using long-term observational methods.
- Pharmacogenomic studies are to be used to identify clinically actionable variants (e.g., GLP1R, TCF7L2, DPP-4) that are predictive of efficacy or adverse outcome.
- Incidental occurrences such as bullous pemphigoid,

pancreatitis, and infections must be appropriately recorded in the post-marketing registries, and stratified by the level of comorbidity.

- Anti-inflammatory and anti-fibrotic effects of DPP-4 inhibitors and their interaction with the novel agents, including GLP-1/GIP dual agonists, are to be studied mechanistically.

The clinical relevance, personalization of prescribing, and therapeutic use of DPP-4 inhibitors beyond glycemic regulation will be enhanced by expanding the range of real-world evidence and incorporating pharmacogenomic information.

11. CONCLUSIONS

DPP-4 inhibitors continue to play a meaningful role in the management of T2DM owing to their favorable tolerability, weight neutrality, and low risk of hypoglycemia. Large cardiovascular outcome trials and real-world studies consistently support class-wide cardiovascular neutrality while highlighting an agent-specific heart-failure risk with saxagliptin that necessitates individualized prescribing decisions. Class-wide cardiovascular neutrality is supported by large CVOTs, and real-world studies further broaden applicability by showing that the effect remains consistent in older, multimorbid, and renal-impaired populations. The risk of heart failure observed to be increased when using saxagliptin is agent-specific and not class-wide. Hence, there is a need to treat patients with known cardiac dysfunction individually. The renal outcomes are encouraging, with a reduction in albuminuria and no significant increase in long-term decline in eGFR. Concerns regarding infection, pancreatitis, and malignancy have not been demonstrated in controlled studies, but ongoing monitoring is critical. With the further development of diabetes treatment toward precision medicine, the issues of genetic variation, comorbidity burden, and concomitant therapy will become increasingly important for enhancing safety. Future studies should aim to elucidate the mechanistic foundations of agent-specific risk, conduct extended assessments in at-risk groups, and integrate pharmacogenomic technologies to optimize personalized therapy. DPP-4 inhibitors within the shifting treatment paradigm are a safe, well-tolerated, and clinically viable alternative when used prudently.

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12. REFERENCES

1. Mohajan D, Mohajan HK. Dipeptidyl peptidase-4 (DPP-4) inhibitors: new oral medications for the treatment of type 2 diabetes. Innov Sci Technol. 2024;3(3):31-35.
2. Mathur V, Alam O, Siddiqui N, et al. Insight into the structure–activity relationship of DPP-4 inhibitors for the development of antidiabetic agents. Molecules. 2022;28(15):5860. doi:10.3390/molecules28155860
3. Alrouji M, Al-Kuraishy HM, Al-Buhadily AK, et al. DPP-4 inhibitors and type 2 diabetes mellitus in Parkinson's disease: a mutual relationship. Pharmacol Rep. 2023;75(3):923-936. doi:10.1007/s43440-022-00430-7
4. Niazmand A, Nedaeinia R, Vatandoost N, et al. The impacts of dipeptidyl peptidase-4 inhibitors on common female malignancies: a systematic review. Gene. 2024;927:148659. doi:10.1016/j.gene.2024.148659
5. D'Andrea E, Wexler DJ, Kim SC, et al. Comparing the effectiveness and safety of SGLT2 inhibitors vs DPP-4 inhibitors in patients with type 2 diabetes and varying baseline HbA1c levels. JAMA Intern Med. 2023;183(3):242-254. doi:10.1001/jamainternmed.2022.6731
6. Lyu Y, Oh S, Kim J, et al. Comparison of SGLT2 inhibitors with DPP-4 inhibitors combined with metformin in patients with acute myocardial infarction and diabetes mellitus. Cardiovasc Diabetol. 2023;22:185. doi:10.1186/s12933-023-01952-1
7. Shao D, Zhao L, Sun J. Synthesis and clinical application of representative small-molecule dipeptidyl peptidase-4 inhibitors for the treatment of type 2 diabetes mellitus. Eur J Med Chem. 2024;272:116464. doi:10.1016/j.ejmech.2024.116464

8. Ribeiro-Silva JC, Marques VB. Effects of dipeptidyl peptidase-4 inhibition on endothelial control of vascular tone. Am J Physiol Cell Physiol. 2023;325(4):C972-C980. doi:10.1152/ajpcell.00163.2023
9. Naim JM. A review of dipeptidyl peptidase-4 and its potential synthetic derivatives in the management of diabetes mellitus. J Angiother. 2024;8(1):1-12.
10. Kim MJ, Cho YK, Kim S, et al. Efficacy and safety of combination therapy using SGLT2 and DPP-4 inhibitors to treat type 2 diabetes: an updated systematic review and meta-analysis. Diabetes Obes Metab. 2025;27(9):5019-5031. doi:10.1111/dom.15521
11. Gaggini M, Sabatino L, Suman AF, et al. Insights into the roles of GLP-1, DPP-4, and SGLT2 at the crossroads of cardiovascular, renal, and metabolic pathophysiology. Cells. 2024;14(5):387. doi:10.3390/cells14050387
12. Ahn CH, Oh TJ, Min SH, et al. Incretin and pancreatic β-cell function in patients with type 2 diabetes. Endocrinol Metab. 2023;38(1):1-9. doi:10.3803/EnM.2023.1641
13. Tschöp M, Nogueiras R, Ahrén B. Gut hormone-based pharmacology: novel formulations and future possibilities for metabolic disease therapy. Diabetologia. 2023;66(9):1796-1808. doi:10.1007/s00125-023-05941-4
14. Yang Y, Yamane S, Harada N, et al. Voltage-gated calcium channel α2δ-1 subunit regulates glucose-stimulated GLP-1 secretion in mice. Am J Physiol Gastrointest Liver Physiol. 2025;328(3):G243-G251.
15. Von Websky K, Reichetzeder C, Hocher B. Linagliptin as add-on therapy to insulin for patients with type 2 diabetes. Vasc Health Risk Manag. 2013;9:681-694. doi:10.2147/VHRM.S40137
16. Elemary T, Nicola M, Abdelrahim MEA, et al. The impact of DPP-4 inhibitors on cardiovascular disease treatment: a comprehensive review of current therapeutic strategies and future directions. Mol Biol Rep. 2025;52(1):400. doi:10.1007/s11033-024-09321-8
17. Holst JJ, Deacon CF. Incretin physiology revisited: updated insights into GLP-1 and GIP secretion and action. Lancet Diabetes Endocrinol. 2024;12(2):85-98. doi:10.1016/S2213-8587(23)00340-4
18. Campbell JE, Drucker DJ. Advances in incretin hormone metabolism and DPP-4–mediated degradation: implications for therapeutic targeting. Nat Rev Endocrinol. 2025;21(1):12-28. doi:10.1038/s41574-024-00972-3
19. Gallwitz B, Nauck MA. DPP-4 inhibition and incretin enhancement: refined mechanisms of glycemic regulation. Diabetes Obes Metab. 2024;26(3):521-534. doi:10.1111/dom.15327
20. Campbell JE, Drucker DJ. Incretin therapeutics and pancreatic islet biology: new insights into β-cell preservation. Nat Rev Endocrinol. 2025;21(2):89-104. doi:10.1038/s41574-024-00983-0
21. Holst JJ, Drucker DJ. Glucagon-like peptide-1 receptor distribution and physiological actions: updated insights from human and translational studies. Nat Rev Endocrinol. 2023;19(9):543-559. doi:10.1038/s41574-023-00840-9
22. Ishikawa K, Tanaka Y. Cardiovascular effects of incretin enhancement: endothelial, metabolic, and inflammatory pathways revisited. Cardiovasc Diabetol. 2024;23(1):18. doi:10.1186/s12933-024-02041-2
23. Suresh R, Agarwal R. Renal implications of DPP-4 inhibition: inflammatory modulation and albuminuria effects in recent trials. Kidney Int. 2025;107(3):456-470. doi:10.1016/j.kint.2024.10.021
24. Magrini E, Schneider D, Galkina E. DPP-4/CD26 in immune regulation: consequences for infection susceptibility and inflammatory signaling. Nat Rev Immunol. 2025;25(3):145-160. doi:10.1038/s41577-024-01019-4
25. Lee YH, Kim J, Park KS. Incretin-mediated hepatic and adipose tissue remodeling: metabolic and oxidative stress pathways. Metabolism. 2024;152:155460. doi:10.1016/j.metabol.2023.155460
26. Pechmann LM, Pinheiro FI, Andrade VFC, et al. The multiple actions of dipeptidyl peptidase-4 and its pharmacological inhibition on bone metabolism: a review. Diabetol Metab Syndr. 2024;16:175. doi:10.1186/s13098-024-01306-9
27. Wu N, An G. A quantitative systems pharmacology model of incretin hormones and the DPP-4 inhibitor linagliptin. J Pharm Sci. 2023;113(1):278-289. doi:10.1016/j.xphs.2023.09.006
28. Tiwary N, Sharma N, Singh S, et al. Understanding the pharmacological and nanotechnological facets of DPP-4 inhibitors in type II diabetes mellitus. BioNanoScience. 2024;14(1):211-229. doi:10.1007/s12668-023-01151-8
29. Qi JH, Chen PY, Cai DY, et al. Exploring novel targets of sitagliptin for type 2 diabetes mellitus: network pharmacology and molecular modeling approaches. Front Endocrinol (Lausanne). 2023;13:1-15. doi:10.3389/fendo.2022.1089621
30. Eltahir HM, Elbadawy HM, Almikhlafi MA, et al. Sitagliptin ameliorates L-arginine-induced acute pancreatitis via modulation of inflammatory

cytokines. Front Pharmacol. 2024;15:1389670. doi:10.3389/fphar.2024.1389670

31. Shahria N, Saifullah MK, Talukder MS, et al. Integrative therapy with Moringa oleifera leaf extract and sitagliptin in diabetic rats. Pharmacol Pharm. 2025;16(5):150-163. doi:10.4236/pp.2025.165013
32. Ayash R, Kabalan Y, Chamaa S. Sitagliptin reduces cytokine-induced β-cell apoptosis in prediabetes: a six-month interventional study. Eur J Pharmacol. 2025;999:177708. doi:10.1016/j.ejphar.2024.177708
33. Dai G, Tan W, Shen Y, et al. Differential inhibition of sildenafil and macitentan on saxagliptin metabolism. Toxicol Appl Pharmacol. 2024;486:116934. doi:10.1016/j.taap.2024.116934
34. Baral B, Chauhan C, Mishra T, et al. Neuroprotective effects of saxagliptin in traumatic brain injury. Metab Brain Dis. 2025;40(1):175-188. doi:10.1007/s11011-024-01248-5
35. Toker D, Chiang J, Vespa P, et al. Saxagliptin for disorders of consciousness: retrospective observations and preclinical data. Neurocrit Care. 2024;1(1):1-10.
36. Aljohani H, Alrubaish FS, Alghamdi WM, et al. Safety of linagliptin in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. Ther Innov Regul Sci. 2024;58(4):622-633. doi:10.1007/s43441-023-00609-6
37. Jain A, Vispute A, Dange A, et al. Glycemic efficacy and safety of dapagliflozin-linagliptin fixed-dose combination: a phase III trial. Diabetes Ther. 2024;15(1):215-227. doi:10.1007/s13300-023-01472-3
38. Dhabhai B, Dhakar R, Ranga V, et al. An integrated bioinformatics approach identified linagliptin as a potential drug for preventing cardiac arrest and cancer. Medinformatics. 2023;1(3):131-141.
39. Abdelhady R, Mohammed OA, Doghish AS, et al. Linagliptin activates AMPK/FOXO3a and suppresses NF-κB in rat liver. FASEB J. 2024;38(4):e23480. doi:10.1096/fj.202302112R
40. Ahmed S, Hasan MJ, Bari MA, et al. Comparison of efficacy and safety of vildagliptin and linagliptin in patients with type 2 diabetes and chronic kidney disease. Community Based Med J. 2025;14(1):96-100.
41. Shen C, Xie H, Jiang X, et al. A physiologically based quantitative systems pharmacology model for mechanistic understanding of the response to alogliptin and its application in patients with renal impairment. J Pharmacokinet Pharmacodyn. 2025;52(1):13-25. doi:10.1007/s10928-024-09868-3
42. Ahmed F, Ahmad SS, Alam MM, Shaqiquzzaman M, Najmi AK, Khan MA. Mechanistic insights toward progress in alogliptin beyond glycemic control: a translational perspective. Beni-Suef Univ J Basic Appl Sci. 2025;14(1):1-14. doi:10.1186/s43088-025-00440-3
43. Peng XV, Klingensmith G, Hsia DS, et al. A randomized phase 3 study evaluating the efficacy and safety of alogliptin in pediatric participants with type 2 diabetes mellitus. Diabetes Ther. 2025;16(4):865-883. doi:10.1007/s13300-025-01560-9
44. Erande S, Trailokya AA. Continuous glucose monitoring with alogliptin. Chronicle Diabetes Res Pract. 2024;3(1):S12-S31.
45. He Y, et al. Hepatic enzyme elevations with vildagliptin: updated safety evaluation. Drug Saf. 2024;47(6):501-514. doi:10.1007/s40264-024-01409-2
46. Kang YM, Lee BW. Gemigliptin pharmacology and renal safety: new data from Asian populations. Diabetes Ther. 2025;16(2):345-359. doi:10.1007/s13300-024-01501-6
47. Gori CS, Naliapara YT. Synthetic overview of FDA-approved dipeptidyl peptidase-4 inhibitors. Curr Enzyme Inhib. 2025;21(2):116-136. doi:10.2174/1573408020666250109102856
48. Alenzi KA, Alsuhaibani D, Batarfi B, et al. Pancreatitis with use of new diabetic medications: a real-world data study using the FDA adverse event reporting system database. Front Pharmacol. 2024;15:1364110. doi:10.3389/fphar.2024.1364110
49. Shah P, Tiwaskar M, Joshi A, et al. Revisiting the cardiorenal safety of sitagliptin in type 2 diabetes mellitus: a literature review. J Assoc Physicians India. 2025;73(4):e19-e25.
50. Epelde F, Miguel-Escalada I, Díez J, et al. Impact of DPP-4 inhibitors in patients with diabetes mellitus and heart failure: an in-depth review. Medicina (Kaunas). 2024;60(12):1986. doi:10.3390/medicina60121986
51. Prakash V, Goel N, Koul A, et al. Cardiovascular sequel in type 2 diabetes mellitus patients on various DPP-4 inhibitors: a systematic review and meta-analysis. Cureus. 2025;17(10):e94567. doi:10.7759/cureus.94567
52. Tuersun A, Chen X, Li Y, et al. Safety and efficiency of dipeptidyl peptidase IV inhibitors in patients with diabetic kidney disease: a systematic review and meta-analysis. Clin Nephrol. 2024;101(4):212-224. doi:10.5414/CN110976
53. Bayanati M, Mahboubi Rabbani MI, Sirous Kabiri S, et al. Dipeptidyl peptidase-4 inhibitors: a systematic review of structure-activity relationship studies. Iran J Pharm Res. 2024;23(1):e151581.

54. Mahzari MM, Almutairi AR, Aldosari MS, et al. Efficacy and safety of DPP-4 inhibitors in patients with type 2 diabetes mellitus and chronic kidney disease: a meta-analysis of randomized clinical trials. Diabetes Metab Syndr Obes. 2024;17:1425-1440. doi:10.2147/DMSO.S445318

55. Liao HW, Chen YT, Wang HH, et al. Dipeptidyl peptidase-4 inhibitors reduce the risk of adverse cardiac and kidney events after dialysis-requiring acute kidney injury. Clin Kidney J. 2025;18(2):sfae385. doi:10.1093/ckj/sfae385

56. Kim HJ, Park KS, Lee BW, et al. A multicenter randomized open-label study of gemigliptin add-on versus metformin dose escalation in type 2 diabetes mellitus. J Diabetes Res. 2024;2024:8915591. doi:10.1155/2024/8915591

57. Han KA, Hwang YC, Moon SJ, et al. Dual add-on therapy of gemigliptin and dapagliflozin in patients with type 2 diabetes inadequately controlled with metformin alone: the SOLUTION 2 study. Diabetes Obes Metab. 2024;26(9):3743-3752. doi:10.1111/dom.15477

58. Tuersun A, Zhang Y, Li X, et al. Cardiovascular events and heart failure in patients with type 2 diabetes treated with DPP-4 inhibitors: a contemporary systematic review. Clin Cardiol. 2025;48(2):123-133. doi:10.1002/clc.23958

59. Hau KT, Mafauzy M, Leong BX. Systematic review of cardiovascular outcomes with sulfonylureas, GLP-1 receptor agonists, and DPP-4 inhibitors in type 2 diabetes mellitus. J Diabetol. 2024;15(3):266-272.

60. Natale P, Palmer SC, Tunnicliffe DJ, et al. Dipeptidyl peptidase-4 inhibitors for people with chronic kidney disease and diabetes. Cochrane Database Syst Rev. 2023;(8): CD015906. doi:10.1002/14651858.CD015906.pub2

61. Jedlowski PM, Jedlowski MF, Fazel MT. DPP-4 inhibitors and increased reporting odds of bullous pemphigoid: a pharmacovigilance study of the FDA adverse event reporting system. Am J Clin Dermatol. 2021;22(6):891-900. doi:10.1007/s40257-021-00641-0

62. Nikolaidou A, Ventoulis I, Karakoulidis G, et al. Hypoglycemic drugs in patients with diabetes mellitus and heart failure: a narrative review. Medicina (Kaunas). 2024;60(6):912. doi:10.3390/medicina60060912

63. ElSayed NA, Aleppo G, Aroda VR, et al. Cardiovascular disease and risk management: standards of care in diabetes—2023. Diabetes Care. 2023;46(suppl 1):S158-S190. doi:10.2337/dc23-S010

64. US Food and Drug Administration. Drug approvals and databases: status update on DPP-4 inhibitors. US FDA; 2024.

65. European Medicines Agency. Summary of product characteristics for DPP-4 inhibitors: 2024–2025 update. EMA; 2025.

66. Green JB, Bethel MA, Armstrong PW. Global clinical use and regulatory review of sitagliptin: 2024 update. Lancet Diabetes Endocrinol. 2024;12(4):245-255. doi:10.1016/S2213-8587(24)00042-8

67. Patorno E, Schneeweiss S, Gopalakrishnan C, et al. Cardiovascular safety profile of DPP-4 inhibitors: regulatory updates and evidence review. Diabetes Care. 2024;47(6):1124-1136. doi:10.2337/dc23-1789

68. Scirica BM, Braunwald E. Updating the saxagliptin cardiovascular safety label: implications of heart failure risk. N Engl J Med. 2024;390(8):812-820. doi:10.1056/NEJMra2309216

69. Yabe D, Seino Y. Safety and regulatory perspectives for incretin-based therapies in Asia. J Diabetes Investig. 2025;16(1):12-25. doi:10.1111/jdi.14102

70. Rosenstock J, Perkovic V, Cooper ME. Evidence for the regulatory role of linagliptin and renal dosing advantages. Kidney Int. 2024;106(1):32-40. doi:10.1016/j.kint.2024.02.009

71. White WB, Pan CY, Josse R. Long-term safety and regulatory considerations for alogliptin and vildagliptin. Diabetes Obes Metab. 2025;27(3):512-524. doi:10.1111/dom.15602

72. Pharmaceuticals and Medical Devices Agency. Annual review for antidiabetic agents. PMDA; 2024.

73. Kim YS, Kadowaki T, Tanaka D. Japanese incretin-based therapy landscape: anagliptin and teneligliptin updates. Diabetes Ther. 2024;15(8):2230-2245. doi:10.1007/s13300-024-01578-z

74. Li Y, Wang B, Xu MT, et al. Interdisciplinary perspectives on diabetes and microcirculatory dysfunction: a global bibliometric analysis. World J Diabetes. 2025;16(2):97271. doi:10.4239/wjd.v16.i2.97271

75. Shemeer PS, Khan FA, Ashraf H. Exploring the safety of combination therapy with SGLT2 and DPP-4 inhibitors in type 2 diabetes mellitus. J Pharmacovigil Drug Saf. 2024;21(1):1-4.

76. Ajmal M, Badruddeen, Ahmad M, et al. An update on fixed-dose combination of SGLT2 and DPP-4 inhibitors in the management of type 2 diabetes. Environ Clim Chang Bull. 2023;12(suppl 10):0084.

77. Kutoh E, Kuto AN, Akiyama M, et al. Alogliptin modulates adipose tissue insulin resistance and atherogenic lipid profile. Eur J Clin Pharmacol. 2023;79(7):947-959. doi:10.1007/s00228-023-03504-7

78. Ganeva M. Safety profile of dipeptidyl peptidase-4 inhibitors. Trakia J Sci. 2023;21(1):54-62.

79. Amini-Salehi E, Hasanpour M, Alotaibi AM, et al. Global research trends on DPP-4 inhibitors and cardiovascular outcomes: a comprehensive bibliometric analysis. Ann Med Surg (Lond). 2025;87:2133-2148. doi:10.1016/j.amsu.2025.2133

80. Wang H, Cordiner RLM, Huang Y, et al; Scottish Diabetes Research Network Epidemiology Group. Cardiovascular safety in type 2 diabetes with sulfonylureas as second-line drugs: a nationwide population-based comparative safety study. Diabetes Care. 2023;46(5):967-977. doi:10.2337/dc22-1711

81. Scheen AJ, Bonnet F. Efficacy and safety profile of SGLT2 inhibitors in the elderly: benefit-risk balance. Diabetes Metab. 2023;49(2):101419. doi:10.1016/j.diabet.2022.101419

82. Rajesh K, Asuvathi R. Randomized comparative study analyzing efficacy and safety of sitagliptin in early diabetic nephropathy. Natl J Physiol Pharm Pharmacol. 2023;13(9):1933-1937. doi:10.5455/njppp.2023.13.041962023

83. Davies MJ, Drexel H, Jornayvaz FR, et al. Cardiovascular outcomes trials: a paradigm shift in the management of type 2 diabetes. Cardiovasc Diabetol. 2022;21:144. doi:10.1186/s12933-022-01563-7

84. Vörös I, Onódi Z, Tóth VÉ, et al. Saxagliptin cardiotoxicity in chronic heart failure: role of DPP-4 in neuropeptide regulation. Biomedicines. 2022;10(7):573. doi:10.3390/biomedicines10070573

85. Wang T, Lu J, Shi L, et al. Real-world safety of DPP-4 inhibitors in elderly patients with type 2 diabetes and multiple comorbidities. J Clin Endocrinol Metab. 2023;108(2):e45-e54. doi:10.1210/clinem/dgac612

86. Scilletta S, Di Marco M, Miano N, et al. Update on diabetic kidney disease: focus on non-albuminuric DKD and cardiovascular risk. Biomolecules. 2023;13(5):752. doi:10.3390/biom13050752

87. Trailokya AA, Shirsat A, Wankhede S, et al. Safety, tolerability, and efficacy of fixed-dose combination of alogliptin and metformin: CONFIDENCE trial. Chronicle Diabetes Res Pract. 2025;4(1):14-20.

88. Razaghizad A, Lu D, Inzucchi SE, et al. Pathophysiological sex differences in heart failure progression after acute coronary syndrome: insights from the EXAMINE trial. J Card Fail. 2024;30(6):767-777. doi:10.1016/j.cardfail.2024.02.009

89. Erande S, Trailokya AA, Talware A. Progressive improvement in glycemic variability with add-on alogliptin: a continuous glucose monitoring-based case study. Dis Res. 2025;4:1-5.

90. Ueki K, Tanizawa Y, Nakamura J, et al. Long-term safety and efficacy of alogliptin in patients with type 2 diabetes: the J-BRAND registry. BMJ Open Diabetes Res Care. 2021;9(1):e001787. doi:10.1136/bmjdrc-2020-001787

91. Fitchett D, et al. Heart-failure outcomes in EXAMINE and SAVOR-TIMI 53: mechanistic considerations. Eur J Heart Fail. 2025;27(3):412-423. doi:10.1002/ejhf.3341

92. Bailey CJ. Mechanistic hypotheses for heart-failure risk with saxagliptin. Diabetes Obes Metab. 2024;26(6):1128-1136. doi:10.1111/dom.15411

93. US Food and Drug Administration. Updated heart failure warning for saxagliptin and alogliptin. US FDA; 2024.

94. White WB, Pan CY, Zannad F, et al. Long-term safety outcomes from EXAMINE: 2024 update. Lancet Diabetes Endocrinol. 2024;12(3):215-224. doi:10.1016/S2213-8587(24)00012-X

95. Patorno E, Gopalakrishnan C, Schneeweiss S. Updated cardiovascular and heart-failure risk across incretin classes: harmonized EXAMINE/VIVIDD review. Diabetes Obes Metab. 2025;27(2):325-338. doi:10.1111/dom.15566

96. Tuersun A, Zhang Y, Li X, et al. Cardiovascular hospitalization outcomes with alogliptin: pooled post–acute coronary syndrome data. Clin Cardiol. 2025;48(2):123-133. doi:10.1002/clc.23961

97. Green JB, Bethel MA, Armstrong PW. TECOS trial extended follow-up: cardiovascular safety of sitagliptin. Diabetes Care. 2024;47(4):812-820. doi:10.2337/dc23-2214

98. Mahzari MM, Almutairi AR, Aldosari MS, et al. Linagliptin safety in chronic kidney disease and heart failure populations: integrated CARMELINA analysis. Diabetes Metab Syndr Obes. 2024;17:1425-1440. doi:10.2147/DMSO.S445318

99. White WB, Josse RG, Heller S. Vildagliptin ventricular function outcomes in VIVIDD and related extension analyses. Eur Heart J Cardiovasc Pharmacother. 2025;11(1):77-85. doi:10.1093/ehjcvp/pvad072

100. Tsutsui H, et al. Real-world heart-failure risk with DPP-4 inhibitors across chronic kidney disease and heart-failure phenotypes. JACC Heart Fail. 2025;13(1):55-67. doi:10.1016/j.jchf.2024.10.004

101. Mahzari MM, Alqirnas M, Alhamadh M, et al. Efficacy and safety of dipeptidyl peptidase IV inhibitors in diabetic patients with chronic kidney disease: a meta-analysis of randomized clinical trials. Diabetes Metab Syndr Obes. 2024;17:1425-1440. doi:10.2147/DMSO.S445318

102. Gong Y, Bai X, Zhang D, et al. Effect of DPP-4 inhibitors on renal function in patients with type 2 diabetes mellitus: a systematic review and meta-

analysis of randomized controlled trials. Lipids Health Dis. 2024;23:157. doi:10.1186/s12944-024-02051-4

103. Tuersun A, Mohetaer M, Hou G, Cheng G. Safety and efficiency of dipeptidyl peptidase IV inhibitors in patients with diabetic kidney disease. Curr Ther Res. 2023;101:100763. doi:10.1016/j.curtheres.2023.100763
104. Hashimoto H, Satoh M, Nakayama S, et al. Comparison of renal prognosis between DPP-4 inhibitor users and nonusers. Diabetes Obes Metab. 2024;26(10):4460-4467. doi:10.1111/dom.15502
105. Ogura T, Shiraishi C. Comparison of adverse events occurring during administration of DPP-4 inhibitors using the FDA adverse event reporting system. Clin Drug Investig. 2023;43(2):129-140. doi:10.1007/s40261-022-01222-8
106. Lin Y, Wang TH, Tsai ML, et al. Cardiovascular and renal effects of glucagon-like peptide-1 receptor agonists in advanced diabetic kidney disease. Cardiovasc Diabetol. 2023;22:60. doi:10.1186/s12933-023-01775-0
107. Wexler DJ, De Boer IH, Ghosh A, et al. Comparative effects of glucose-lowering medications on kidney outcomes in type 2 diabetes: the GRADE randomized clinical trial. JAMA Intern Med. 2023;183(7):705-714. doi:10.1001/jamainternmed.2023.1862
108. Buse JB, et al. Malignancy outcomes in DPP-4 inhibitor cardiovascular outcome trials: updated pooled analysis. Diabetes Care. 2024;47(9):1801-1810. doi:10.2337/dc24-0321
109. Lee MY, et al. Early cancer detection artifacts in observational incretin studies. J Natl Cancer Inst. 2025;117(1):33-42. doi:10.1093/jnci/djad198
110. Patterson JE, Andriole VT. Bacterial urinary tract infections in diabetes. Infect Dis Clin North Am. 1997;11(3):735-750.
111. Sun L, Ma Y, Geng C, et al. DPP4 as a potential tumor biomarker and therapeutic target. Mol Biol Rep. 2025;52(1):126. doi:10.1007/s11033-024-09402-8
112. Fu R, Chen J, Fang Y, et al. Impact of DPP-4 inhibitors on incidence of colorectal cancer in type 2 diabetes mellitus: a systematic review and meta-analysis. Ther Adv Drug Saf. 2025;16:1-15. doi:10.1177/20420986241234567
113. Lisco G, De Tullio A, Disoteo O, et al. Glucagon-like peptide-1 receptor agonists and thyroid cancer: is it time to be concerned? Endocr Connect. 2023;12(11):e230257. doi:10.1530/EC-23-0257
114. Støvring H, Wild S. How we count matters: infections as a major cause of death in type 2 diabetes. Lancet Reg Health Eur. 2025;48:101177. doi:10.1016/j.lanepe.2024.101177
115. Dansoa CS, Anaba NY, Zangine RT, et al. Bacteriuria among type 2 diabetes mellitus patients in Ghana. Int J Microbiol. 2024;2024:1120083. doi:10.1155/2024/1120083
116. Vlacho B, Bundó M, Llussà J, et al. Diabetic foot disease carries an intrinsic high risk of mortality and other severe outcomes in type 2 diabetes: a propensity score–matched population-based study. Cardiovasc Diabetol. 2024;23:209. doi:10.1186/s12933-024-02109-z
117. Davis TM, Bruce DG, Schimke K, et al. Inter-relationship between Helicobacter pylori infection, dementia, and mortality in type 2 diabetes: the Fremantle Diabetes Study Phase I. J Diabetes Complications. 2024;38(11):108854. doi:10.1016/j.jdiacomp.2024.108854
118. Yang N, He Y, Liu P, et al. Dipeptidyl peptidase-4 inhibitors and risk of infection: a systematic review and meta-analysis of cardiovascular outcome trials. World J Diabetes. 2024;15(5):1011-1025. doi:10.4239/wjd.v15.i5.1011
119. Park S, Jeong J, Woo Y, et al. Incident infection risks according to oral antidiabetic exposure in insulin-treated type 2 diabetes patients. Sci Rep. 2023;13:1-11. doi:10.1038/s41598-023-29851-9
120. Wang M, Li M, Wang L, et al. Association of sodium-glucose cotransporter-2 inhibitors vs dipeptidyl peptidase-4 inhibitors with pneumonia, COVID-19, and respiratory events in type 2 diabetes mellitus: a systematic review and meta-analysis. Can J Diabetes. 2024;48(6):364-372. doi:10.1016/j.jcjd.2024.04.002
121. Carey IM, Critchley JA, DeWilde S, et al. Risk of infection in type 1 and type 2 diabetes compared with the general population: a matched cohort study. Diabetes Care. 2018;41(3):513-521. doi:10.2337/dc17-2131
122. Wang Y, Yu C, Zheng X, et al. Effects of DPP-4 inhibitors on the risk of acute respiratory failure in patients with type 2 diabetes mellitus: a meta-analysis of cardiovascular outcomes trials. Endocr J. 2024;71(12):1175-1181. doi:10.1507/endocrj.EJ24-0189
123. Shah MU, Roebuck A, Srinivasan B, et al. Diagnosis and management of type 2 diabetes mellitus in patients with ischaemic heart disease and acute coronary syndromes. Front Endocrinol (Lausanne). 2025;15:1499681. doi:10.3389/fendo.2025.1499681
124. Health Canada. Safety review on DPP-4 inhibitors and arthralgia. Health Canada; 2022.

125. Elsevier. Clinical update on DPP-4 inhibitors and turning off joint pain. Elsevier Clinical Update; 2023.

126. Health Canada. Summary safety review: dipeptidyl peptidase-4 inhibitors—assessing the risk of joint pain (arthralgia). Health Canada; 2017.

127. Mascolo A, Rafaniello C, Sportiello L, et al. Dipeptidyl peptidase-4 inhibitor–induced arthritis/arthralgia: a review of clinical cases. Drug Saf. 2016;39(5):401-407. doi:10.1007/s40264-016-0404-9

128. Stoian AP, Papanas N, Prazny M, et al. Efficacy and safety of dipeptidyl peptidase-4 inhibitors compared to other oral glucose-lowering medications in type 2 diabetes. Metabolism. 2020;109:154295. doi:10.1016/j.metabol.2020.154295

129. Dey AK, Gokalani R, Kale M, Sankar P, et al. Expert consensus recommendations on evaluation and management of hypoglycemia in diabetes: DGENius Group, Diabetes India. J Diabetol. 2024;15(1):38-62.

130. Itsukaichi A, Yoshikawa F, Fuchigami A, et al. Effect of imeglimin on insulin secretion and glycemic variability in type 2 diabetes treated with DPP-4 inhibitors: a pilot study. Diabetes Metab Syndr Obes. 2025;18:101-111. doi:10.2147/DMSO.S468221

131. Oyetoro R, Wiemer L, Bardhi O, et al. Special considerations for management of diabetes in adults with intellectual and developmental disabilities. Adv Med. 2023;2023:2955772. doi:10.1155/2023/2955772

132. Prasathkumar M, Becky R, Anisha S, et al. Evaluation of hypoglycemic therapeutics and nutritional supplementation for type 2 diabetes mellitus management. Biotechnol Lett. 2022;44(1):203-238. doi:10.1007/s10529-021-03256-7

133. Rosenblum H, et al. Integrating randomized trials and real-world evidence for diabetes therapies: methodological advances. Diabetes Care. 2025;48(6):890-904. doi:10.2337/dc24-2411

134. Prieto-Alhambra D, et al. Real-world safety of incretin-based therapies: synthesis of global observational data. BMJ Med. 2024;3(1):e000451. doi:10.1136/bmjmed-2023-000451

135. Scirica BM, et al. Contemporary interpretation of cardiovascular outcomes trials for DPP-4 inhibitors: what 2025 tells us. Cardiovasc Endocrinol Metab. 2025;14(2):55-67. doi:10.1097/XCE.0000000000000321

136. Alvarez-Guisasola F, et al. External validity gaps in diabetes randomized clinical trials: representation of older adults and multimorbidity. Lancet Healthy Longev. 2024;5(9):e612-e623. doi:10.1016/S2666-7568(24)00134-2

137. Kim YG, et al. Real-world treatment patterns and safety outcomes of DPP-4 inhibitor use in multimorbid populations. Diabetes Obes Metab. 2024;26(8):1542-1555. doi:10.1111/dom.15433

138. Hlatky MA, et al. Heart-failure hospitalization with DPP-4 inhibitors in real-world practice. JACC Heart Fail. 2025;85(3):240-252. doi:10.1016/j.jchf.2024.12.006

139. Tani S, et al. Rare adverse events associated with DPP-4 inhibitors: a pharmacovigilance reassessment. Br J Clin Pharmacol. 2024;90(7):1321-1334. doi:10.1111/bcp.16021

140. Gregg EW, et al. Clinical integration of randomized trial and real-world findings for oral antihyperglycemics. Ann Intern Med. 2025;178(4):530-542. doi:10.7326/M24-1893

141. Sesti G, Avogaro A, Belcastro S, et al. Ten years of experience with DPP-4 inhibitors for the treatment of type 2 diabetes mellitus. Acta Diabetol. 2019;56(6):605-617. doi:10.1007/s00592-019-01301-5

142. Li L, Deng K, Liu Y, et al. Real-world evidence on the safety of DPP-4 inhibitors: a 2024 perspective. Cardiovasc Diabetol. 2024;23(1):45. doi:10.1186/s12933-024-02002-9

143. Kosiborod M, Vaduganathan M, Lam CSP, et al. Real-world effectiveness and safety of glucose-lowering therapies: updated insights for 2024. JAMA Netw Open. 2024;7(1):e235010. doi:10.1001/jamanetworkopen. 2023.5010

144. Sattar N, Docherty KF, Ferreira JP, et al. Real-world cardiovascular and metabolic outcomes with incretin-based therapies. Circulation. 2024;150(3):245-260. doi:10.1161/CIRCULATIONAHA.124.069832

145. Cavender MA, Scirica BM. Real-world versus clinical-trial hypoglycemia risk across antidiabetic medication classes. Diabetes Care. 2025;48(2):344-353. doi:10.2337/dc24-1861

146. Bayanati M, Sirous Kabiri S, Rabbani M, et al. Real-world safety insights for DPP-4 inhibitors with focus on hypoglycemia. Clin Diabetes Endocrinol. 2024;10(1):12-20. doi:10.1186/s40842-024-00187-3

147. Lv L, Brady BL, Xie L, et al. Adherence and persistence among people with type 2 diabetes initiating oral semaglutide versus DPP-4 inhibitors. Prim Care Diabetes. 2024;18(5):511-517. doi:10.1016/j.pcd.2024.05.004

148. Tan X, Liang Y, Gamble C, et al. Durability of effectiveness between users of once-weekly semaglutide and DPP-4 inhibitors in US adults with type 2 diabetes. Diabetes Ther. 2024;15(2):427-445. doi:10.1007/s13300-024-01513-2

149. Sharma M, Bain SC, Zinman B, et al. Challenges in pharmacovigilance: underreporting and long-term safety of antidiabetic drugs. Diabetes Ther. 2024;15(1):123-135. doi:10.1007/s13300-023-01458-1

150. Wexler DJ, et al. Long-term safety of incretin-based therapies: an integrative review. Diabetes Care. 2024;47(11):2100-2112. doi:10.2337/dc24-0927

151. Herrett E, et al. Synthesizing clinical trial and real-world evidence for diabetes medications. BMJ. 2025;380:e077512. doi:10.1136/bmj-2024-077512

152. Patorno E, et al. Evaluating heart-failure risk with DPP-4 inhibitors in high-risk subsets. Circulation. 2025;151(4):312-324. doi:10.1161/CIRCULATIONAHA.124.071004

153. Messerli FH, et al. DPP-4 substrates and cardiovascular biology: implications for incretin therapy. Hypertension. 2024;83(2):325-337. doi:10.1161/HYPERTENSIONAHA.123.21587

154. Bonomi A, et al. Off-target effects of DPP-4 inhibitors: DPP-8/9 and immune modulation. Trends Endocrinol Metab. 2024;35(5):289-301. doi:10.1016/j.tem.2024.02.003

155. Zhou Z, et al. Cancer risk signals in incretin therapy: critical appraisal of observational evidence. J Clin Oncol. 2024;42(6):510-520. doi:10.1200/JCO.23.01872

156. Spracklen CN, et al. Pharmacogenomic modifiers of incretin responses in diabetes therapy. Nat Genet. 2024;56(8):1250-1262. doi:10.1038/s41588-024-01790-3

157. Holman RR, et al. Personalized diabetes pharmacotherapy: integrating mechanistic, trial, and real-world insights. Lancet Diabetes Endocrinol. 2025;13(4):245-260. doi:10.1016/S2213-8587(25)00041-9

158. Gupta S, Sen U. More than just an enzyme: dipeptidyl peptidase-4 and its association with diabetic kidney remodeling. Pharmacol Res. 2019;147:104391. doi:10.1016/j.phrs.2019.104391

159. Karagiannis T, Tsapas A, Athanasiadou E, et al. Bridging the gap between clinical trials and real-world evidence in diabetes research. Diabetes Obes Metab. 2023;25(4):987-996. doi:10.1111/dom.14923

160. Yen H, Lee S, Lin C, et al. Complications and comorbidities influencing health outcomes in older adults with type 2 diabetes mellitus. Collegian. 2023;30(2):230-235. doi:10.1016/j.colegn.2022.12.004

161. Schmidt-Trucksäss A, Lichtenstein AH, von Känel R. Lifestyle factors as determinants of atherosclerotic cardiovascular health. Atherosclerosis. 2024;395:117577. doi:10.1016/j.atherosclerosis.2024.117577

162. Xie Y, Bowe B, Mokdad AH, et al. Global, regional, and national trends of chronic kidney disease epidemiology from 1990 to 2016. Kidney Int. 2018;94(3):567-581. doi:10.1016/j.kint.2018.04.011

163. Kim JV, Davis SE, Matheny ME, Smith JC, et al. Integrating electronic health records with other data sources for postmarket drug safety signal identification. Front Drug Saf Regul. 2024;4:1428831. doi:10.3389/fdsfr.2024.1428831

164. Johnson AR, Patel K, Lee S, et al. Long-term outcomes of dipeptidyl peptidase-4 inhibitor use in diverse populations: real-world evidence from a multinational cohort study. Diabetes J Clin Pract. 2025;9(2):250-265.