Endocrine Intelligence

Endocrine Intelligence · 09/10/2026, 18:37:46 UTC

Clinical question

DPP4 inhibitor class review, which is the best?

Answer

DPP-4 Inhibitor Class Review: Comparative Assessment

Class Overview and Mechanism

DPP-4 inhibitors (sitagliptin, saxagliptin, alogliptin, linagliptin, vildagliptin) block the dipeptidyl peptidase-4 enzyme, preserving endogenous incretin hormones (GLP-1, GIP). This enhances glucose-dependent insulin secretion and suppresses glucagon release. They are weight-neutral, carry a low hypoglycaemia risk when not combined with insulin or sulfonylureas, and are generally well tolerated. In the current ADA/EASD treatment architecture, they occupy a role as a neutral glucose-lowering option rather than a cardiorenal-protective agent, which is now the domain of SGLT2 inhibitors and GLP-1 receptor agonists.

Glycaemic Efficacy: Broadly Comparable

Head-to-head and network meta-analytic data do not identify a single DPP-4 inhibitor with a meaningful HbA1c-lowering advantage over the others:

- A 2025 systematic review of five RCTs (296 participants) found no significant intergroup differences in HbA1c, fasting glucose, or postprandial glucose between vildagliptin and comparator DPP-4 inhibitors (sitagliptin, alogliptin). HbA1c reductions ranged from −0.3 to −1.34% across agents.
- A 2017 Bayesian network meta-analysis (8 RCTs, triple-therapy setting) concluded alogliptin 25 mg was "as least as effective and safe" as linagliptin, saxagliptin, sitagliptin, and vildagliptin when added to metformin plus a sulfonylurea.
- In CKD populations, a Cochrane review (2018) reported DPP-4 inhibitors may reduce HbA1c by approximately 0.62% versus placebo, with no meaningful differences among individual agents.

Bottom line on efficacy: No agent in the class is clearly superior for glucose lowering. Choice should be driven by safety, pharmacokinetics, and comorbidity profile rather than expected HbA1c delta.

Cardiovascular and Heart-Failure Safety: The Key Differentiator

This is where the agents diverge most meaningfully.

Pooled RCT evidence (7 large CV-outcome trials, >70,000 participants)

A 2025 meta-analysis pooling SAVOR-TIMI 53, EXAMINE, TECOS, and supporting trials found:

Agent	HHF (HR, 95% CI)	MACE (HR, 95% CI)
Saxagliptin	**1.27 (1.07–1.51)** ↑	0.99 (0.93–1.05) class-level
Alogliptin	Elevated (lesser signal)	0.99 (0.93–1.05) class-level
Sitagliptin	1.00 (0.83–1.20) – neutral	0.99 (0.93–1.05) class-level
Linagliptin	1.02 (0.89–1.17) – neutral	0.93 (0.77–1.11) CV death

- Class-level MACE: HR 0.99 (95% CI 0.93–1.05) – no increase.
- Class-level all-cause and CV mortality: no significant difference from placebo.
- The pooled HHF signal (HR 1.14, 95% CI 1.02–1.27) was **driven predominantly by saxagliptin**, with a smaller contribution from alogliptin.

RMST re-analysis (2017)

A restricted-mean-survival-time re-evaluation of the three pivotal CV trials (SAVOR-TIMI 53, EXAMINE, TECOS) estimated the absolute difference in time to HHF as only −4 days for saxagliptin, −3 days for alogliptin, and +1 day for sitagliptin over 2–4 years of follow-up. The authors concluded there were "no substantial clinically relevant differences" in cardiovascular events among the three agents. This tempers the hazard-ratio signal but does not eliminate the statistical finding for saxagliptin.

2026 meta-analysis (29 studies, 67,873 patients)

- Overall DPP-4i vs. no DPP-4i: RR for HF 1.06 (95% CI 0.94–1.12) – not statistically significant.
- Sub-group analysis: **saxagliptin** showed a significant association with increased HF risk.
- The authors note FDA warnings for alogliptin, saxagliptin, and their combination with metformin.

2025 meta-analysis (79,010 participants)

- HF: OR 1.06 (0.96–1.18); MACE: OR 1.01 (0.95–1.08); MI: OR 0.89 (0.73–1.07); all-cause mortality: OR 1.03 (0.96–1.11). All non-significant at the class level.

Interpretation

The evidence is consistent: **saxagliptin carries the most robust signal for increased hospitalisation for heart failure**, alogliptin a smaller and less certain signal, and **sitagliptin and linagliptin appear cardiovascularly neutral** with respect to both MACE and HF. The absolute risk difference is small (on the order of a few days of hospitalisation-free time over several years), but in a patient with established or high-risk heart failure, this distinction becomes clinically relevant. A 2024 in-depth review of DPP-4 inhibitors in diabetic patients with coexisting heart failure explicitly recommends caution with saxagliptin in advanced HF and highlights SGLT2 inhibitors and GLP-1 RAs as preferred alternatives in that population.

Renal Considerations

- **Linagliptin** is the only DPP-4 inhibitor that requires **no dose adjustment across all stages of CKD**, including dialysis, because it is eliminated predominantly via the enterohepatic route (~85% faecal excretion). This is a practical advantage in patients with eGFR < 45 mL/min/1.73 m² or on renal replacement therapy.

- Sitagliptin, saxagliptin, alogliptin, and vildagliptin all require dose reduction as eGFR declines.
- The 2025 ABCD/UK Kidney Association joint guideline for T2DM and CKD emphasises SGLT2 inhibitors and GLP-1 RAs for cardiorenal protection; DPP-4 inhibitors remain an option for glycaemic control but are not the preferred agents for kidney or cardiovascular risk reduction in this population.

Hepatic and Other Safety Considerations

- **Vildagliptin** carries a requirement for periodic liver-function monitoring (transaminase checks) due to a small but recognised risk of hepatotoxicity. This is a practical disadvantage compared with the other agents.
- All DPP-4 inhibitors are weight-neutral and carry a low hypoglycaemia risk as monotherapy. In the CKD Cochrane review, sitagliptin reduced hypoglycaemia versus glipizide (RR 0.40, 95% CI 0.23–0.69).
- Pancreatitis and pancreatic cancer signals have been investigated but are not confirmed as class effects; the Cochrane CKD review found the evidence for these outcomes to be of very low certainty.

Practical "Which to Choose" Framework

There is no single "best" DPP-4 inhibitor for every patient. The choice should be individualised:

1. **Elevated heart-failure risk or established HF:** Prefer **sitagliptin** or **linagliptin**. Avoid saxagliptin. Alogliptin is a reasonable alternative but carries a smaller HF signal. In advanced HF, consider whether a DPP-4 inhibitor is the right class at all, given the stronger HF-reduction evidence for SGLT2 inhibitors.

2. **Significant CKD (eGFR < 45) or dialysis: Linagliptin** is the most convenient option (no dose adjustment). Sitagliptin is also usable with dose reduction.

3. **No major CV or renal comorbidity, straightforward T2DM:** Any DPP-4 inhibitor is reasonable. Choice may then be guided by cost, formulary availability, dosing convenience (all are once daily), and patient preference. Sitagliptin and linagliptin have the most extensive CV-outcome trial data.

4. **Hepatic impairment or concern about liver monitoring:** Avoid vildagliptin; prefer sitagliptin, linagliptin, saxagliptin, or alogliptin.

5. **Triple therapy (metformin + SU + DPP-4i):** The alogliptin NMA supports comparable efficacy and safety to other agents in this setting, but the HF signal consideration still applies.

Position in the Broader Treatment Landscape

The 2022 ADA/EASD consensus and the 2025 ABCD/UK Kidney guideline both place SGLT2 inhibitors and GLP-1 receptor agonists ahead of DPP-4 inhibitors when cardiorenal protection is a treatment goal. DPP-4 inhibitors remain a valid, well-tolerated, weight-neutral option for glycaemic control, particularly in patients who cannot tolerate or do not need the additional cardiorenal benefits of SGLT2i or GLP-1 RA therapy, or as an add-on when those agents are already in use. They are not, however, the agents to reach for when the primary objective is to reduce heart-failure hospitalisation or slow CKD progression.

Summary

Agent	CV/HF Safety	Renal Dosing	Hepatic Monitoring	Key Trial
Sitagliptin	Neutral	Dose-adjust	No	TECOS
Linagliptin	Neutral	**No adjustment**	No	(no dedicated CVOT)
Saxagliptin	↑ **HF risk**	Dose-adjust	No	SAVOR-TIMI 53
Alogliptin	Small ↑ HF signal	Dose-adjust	No	EXAMINE
Vildagliptin	Neutral (limited CVOT data)	Dose-adjust	**Yes**	(limited)

If forced to single out the agent with the most favourable overall risk–benefit profile across the common comorbidity spectrum, **sitagliptin** (robust CVOT data, neutral HF signal, no hepatic monitoring) and **linagliptin** (neutral HF signal, no renal dose adjustment) are the most defensible default choices. Saxagliptin should be avoided in patients with heart failure or high HF risk. The ultimate "best" agent, however, depends on the individual patient's comorbidity profile, and in many contemporary treatment algorithms the question is increasingly whether a DPP-4 inhibitor is the right class at all versus an SGLT2 inhibitor or GLP-1 RA.

Note: The evidence base reviewed here is drawn primarily from published abstracts and meta-analytic summaries. The pivotal CV-outcome trial data (SAVOR-TIMI 53, EXAMINE, TECOS) are well established, but the most recent pooled analyses (2025–2026) are based on abstract-level data. No dedicated CV-outcome trial has been completed for linagliptin or vildagliptin, so their CV safety profiles are inferred from class-level data and smaller studies rather than a dedicated large RCT.

Evidence and citations

[1] Cardiovascular Sequel in Type-2 Diabetes Mellitus Patients on Various Dipeptidyl Peptidase-4 (DPP-4) Inhibitors: A Systemic Review and Meta-Analysis.

Europe PMC

https://pubmed.ncbi.nlm.nih.gov/41246652/

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> Saxagliptin statistically significantly increased the risk of hospitalization for heart failure compared with placebo in the clinical trial of SAVOR-TIMI 53. Neither the reason why only saxagliptin among several dipeptidyl peptidase-4 (DPP-4) inhibitors increased the risk, nor the clinical implication of the result has been explained. To evaluate the risk of hospitalization for heart failure associated with DPP-4 inhibitors by using an alternative measure to the hazard ratio. We used the difference in restricted mean survival time (RMST) between DPP-4 inhibitors and placebo to evaluate the risk of cardiovascular events, including hospitalization for heart failure associated with DPP-4 inhibitors. Three randomized clinical trials with cardiovascular events as a primary end point-EXAMINE (alogliptin), SAVOR-TIMI 53 (saxagliptin), and TECOS (sitagliptin)-were reevaluated by estimating the RMSTs for the DPP-4 inhibitors and placebo based on the reconstructed individual patient data for each time-to-event outcome from publicly available information. The differences of RMSTs (DPP-4 inhibitors minus placebo) for hospitalization for heart failure were -4 days [-6, -2] in the SAVOR-TIMI 53 (720 days follow-up), -3 days [-9, 3] in the EXAMINE (900 days follow-up), and 1 day [-5, 7] in the TECOS (1440 days follow-up). There were no substantial differences in the risk of other cardiovascular outcomes between DPP-4 inhibitors and placebo. There are no substantial clinically relevant differences in the risk of cardiovascular events, including hospitalization for heart failure, between 3 of the DPP-4 inhibitors and placebo.

[12] Efficacy and Safety of Vildagliptin Versus Other Dipeptidyl Peptidase 4 (DPP-4) Inhibitors in the Management of Type 2 Diabetes Mellitus: A Systematic Review of Randomized Controlled Trials.

Europe PMC

https://pubmed.ncbi.nlm.nih.gov/40901275/

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> Dipeptidyl peptidase 4 inhibitors (DPP-4 inhibitors) are used as second-line drugs in the treatment of type 2 diabetes mellitus (T2DM) patients. They act by preventing the breakdown of incretin hormones, which enhance insulin secretion and reduce glucagon secretion. Vildagliptin and sitagliptin are more commonly used DPP-4 inhibitors. In recent years, the use of DPP-4 inhibitors has been increasing; hence, it is important to evaluate the comparative efficacy and safety of this medication with available evidence. Moreover, this systematic review will evaluate to look for any specific superiority or safety advantage of using Vildagliptin over other DPP-4 inhibitors. In accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, we conducted a systematic review search with Cochrane and PubMed databases. Two independent reviewers examined randomized controlled trial (RCT) studies against the inclusion criteria. Excluded studies involve type 1 diabetes, gestational diabetes, and severe acute diabetic complications. Finally, five RCT studies were chosen, involving 296 participants overall. Baseline and outcome values with p-values and intergroup differences with their p-value from original studies were gathered to evaluate the significance of using vildagliptin over DPP-4 inhibitors, and findings were provided in a narrative way with available evidence. All five RCT studies have demonstrated a significant reduction in HbA1c from baseline, ranging from -0.3 to -1.34 with p-value <0.05 in the vildagliptin group and -0.1 to -1.07 with p-value >0.05 in other DPP-4 inhibitors, with no significant intergroup differences indicating comparable efficacy between vildagliptin and other DPP-4 inhibitors. Similarly, no significant intergroup differences were observed between vildagliptin and comparator agents in reducing fasting plasma glucose and postprandial glucose. Notably, one study reported a significant reduction favoring vildagliptin, while another showed a greater reduction of FPG with alogliptin; however, intergroup comparisons were not statistically significant. In addition, vildagliptin did not show consistent improvement in lipid profile across the involved studies. Vildagliptin showed a low incidence of hypoglycemic events in comparison with other DPP-4 inhibitors. Overall, this systematic review found no significant

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Europe PMC

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Supporting passage supplied to the model

> superiority of vildagliptin over other DPP-4 inhibitors such as sitagliptin and alogliptin in the management of type 2 diabetes mellitus, whether used as monotherapy or in combination therapy.

[19] Comparative Effectiveness of Adding Alogliptin to Metformin Plus Sulfonylurea with Other DPP-4 Inhibitors in Type 2 Diabetes: A Systematic Review and Network Meta-Analysis.

Europe PMC

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> <h4>Introduction</h4>Alogliptin is an oral antihyperglycemic agent that is a selective inhibitor of the enzyme dipeptidyl peptidase-4 (DPP-4), approved for the treatment of type 2 diabetes mellitus (T2DM). There currently exists no comparative data to support the use of alogliptin in combination with metformin (met) and sulfonylurea (SU). A decision-focused network meta-analysis (NMA) was performed to compare the relative efficacy and safety of alogliptin 25 mg once daily to other DPP-4 inhibitors as part of a triple therapy regimen for patients inadequately controlled on metformin and SU dual therapy. <h4>Methods</h4>A systematic literature review was conducted to identify published papers of randomized controlled trials (RCTs) that compared alogliptin with other DPP-4 inhibitors (linagliptin, saxagliptin, sitagliptin, and vildagliptin) at their Summary of Product Characteristics (SmPC) recommended daily doses, added on to metformin and SU. Comprehensive comparative analysis involving frequentist meta-analysis and Bayesian NMA compared alogliptin to each DPP-4 inhibitor separately and collectively as a group. Quasi-random effect models were introduced when random effect models could not be estimated.<h4>Results</h4>The review identified 2186 articles, and 94 full-text articles were assessed for eligibility. Eight RCTs contained appropriate data for inclusion in the NMA. All analyses over all trial population sets produced very similar results, and show that alogliptin 25 mg is as least as effective (as measured by change in HbA1c from baseline, but supported by other outcome measures: change in body weight and FPG from baseline) and safe (as measured by incidence of hypoglycemia and adverse events leading to study discontinuation) as all the other DPP-4 inhibitors in triple therapy. <h4>Conclusion</h4>This decision-focused systematic review and NMA demonstrated alogliptin 25 mg daily to have similar efficacy and safety compared to other DPP-4 inhibitors, for the treatment of T2DM in adults inadequately controlled on metformin and SU. (Funded by Takeda Development Centre Americas; EXAMINE ClinicalTrials.gov number, NCT00968708).

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[25] Impact of DPP-4 Inhibitors in Patients with Diabetes Mellitus and Heart Failure: An In-Depth Review.
Europe PMC
https://pubmed.ncbi.nlm.nih.gov/39768866/

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> The increasing prevalence of both type 2 diabetes mellitus and heart failure has underscored the urgent need for optimized therapeutic strategies that address the complex interplay between these conditions. Dipeptidyl peptidase-4 (DPP-4) inhibitors have emerged as a popular class of glucose-lowering agents due to their favorable glycemic effects, safety profile, and potential cardiovascular benefits. However, the impact of DPP-4 inhibitors on heart failure outcomes in patients with diabetes remains contentious, with conflicting evidence from clinical trials and observational studies. This review critically examines current evidence on the use of DPP-4 inhibitors in patients with coexisting diabetes and heart failure, focusing on pharmacodynamics, safety, and efficacy outcomes. We explore the physiological mechanisms by which DPP-4 inhibitors may influence heart failure risk, including modulation of inflammation, oxidative stress, and myocardial fibrosis. Clinical trials such as SAVOR-TIMI 53, EXAMINE, and TECOS are evaluated to provide a comprehensive analysis of DPP-4 inhibitors' effects on hospitalization for heart failure, mortality, and cardiovascular events in diabetic patients. While some trials suggest an increased risk of HF hospitalizations with specific DPP-4 inhibitors (e.g., saxagliptin), others report neutral effects, raising questions about the class effects versus individual drug characteristics within this group. Additionally, we address discrepancies in outcomes related to patient demographics, HF phenotype, and comorbid conditions that may influence DPP-4 inhibitors' risk-benefit profile. Comparative insights into alternative glucose-lowering therapies such as SGLT2 inhibitors and GLP-1 receptor agonists are also provided, highlighting potential implications for treatment selection in this high-risk population. In summary, this review synthesizes available evidence on DPP-4 inhibitors' impact in diabetic patients with heart failure, aiming to guide clinicians in making informed therapeutic decisions. While DPP-4 inhibitors remain a viable option in diabetes management, caution is warranted in patients with advanced heart failure, and future research is essential to refine patient-specific guidelines.

[26] Impact of DPP-4 Inhibitors in Patients with Diabetes Mellitus and Heart Failure: An In-Depth Review.
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[27] Impact of DPP-4 Inhibitors in Patients with Diabetes Mellitus and Heart Failure: An In-Depth Review.
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> <h4>Background</h4>The global prevalence of type 2 diabetes mellitus (T2DM) continues to rise, with patients facing significantly elevated risks of cardiovascular complications, particularly heart failure (HF).<h4>Objective</h4>This examination sought to methodically examine cardiovascular sequelae, notably heart failure, among users of dipeptidyl peptidase 4 (DPP-4) inhibitors when compared with nonusers.<h4>Methods</h4>Cochrane, Embase, and PubMed databases, which compared the use of DPP-4 inhibitors and reported cardiovascular outcomes and heart failure events in patients with type 2 diabetes mellitus (T2DM), were searched using specific terms. Studies were included if they satisfied the following inclusion criteria: they were randomized trials comparing DPP-4 inhibitor use in patients with T2DM; study duration was longer than 24 weeks; and they reported cardiovascular outcomes as their main or secondary end points. Stata 15 MP (StataCorp LLC, College Station, Texas, USA) was used to analyze the data, and odds ratios (ORs) with 95% CIs were used to represent the results.<h4>Results</h4>A total of 79,010 participants with T2DM were included. A total of 37,895 patients were assigned to the DPP-4 inhibitor group, whereas 41,115 patients were assigned to the control group. Results of the analysis showed that during a mean follow-up period ranging from 24 to 302 weeks, heart failure incidence did not differ significantly between T2DM patients treated with DPP-4 inhibitors and those who were not (OR = 1.06; 95% CI, 0.96-1.18; P = 0.452). Major adverse cardiovascular events (including nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death; OR = 1.01; 95% CI, 0.95-1.08; P = 0.354), stroke (OR = 1.01; 95% CI, 0.78-1.30; P = 0.968), myocardial infarction (OR = 0.89; 95% CI, 0.73-1.07; P = 0.49), and all-cause mortality (OR = 1.03; 95% CI, 0.96-1.11; P = 0.309) were also similarly manifested in both groups.<h4>Conclusions</h4>The present analysis showed that treatment with DPP-4 inhibitors did not significantly increase cardiovascular outcomes and heart failure in these patients with T2DM, indicating that these drugs may be safe to use in terms of cardiovascular events.

[44] Cardiovascular Events and Heart Failure in Patients With Type 2 Diabetes Treated With Dipeptidyl Peptidase-4 Inhibitors: A Meta-Analysis.

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[45] Insulin and glucose-lowering agents for treating people with diabetes and chronic kidney disease.

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[56] Insulin and glucose-lowering agents for treating people with diabetes and chronic kidney disease.
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[57] Association of British Clinical Diabetologists and UK Kidney Association Joint Clinical Practice Guidelines for the Pharmacological Management of Hyperglycemia in Adults With Type 2 Diabetes Mellitus and CKD.
Europe PMC
https://pubmed.ncbi.nlm.nih.gov/41141497/

Supporting passage supplied to the model

> A growing and significant number of people with diabetes develop chronic kidney disease (CKD), and diabetes-related CKD is a leading cause of end-stage kidney disease (ESKD). People with diabetes and CKD have high morbidity and mortality, predominantly related to cardiovascular disease (CVD). Hyperglycemia and hypertension are modifiable risk factors to prevent the onset and progression of CKD and related CVD. Recent clinical trials of people with type 2 diabetes mellitus (T2DM) and CKD have demonstrated reduction in composite kidney end point events (significant decline in kidney function, need for kidney replacement therapy, and kidney-related death) and cardiovascular risk with sodium-glucose cotransporter 2 (SGLT-2) inhibitors, nonsteroidal mineralocorticoid receptor antagonists (nsMRAs) and glucagon-like peptide 1 (GLP-1) receptor agonists (RAs). The Association of British Clinical Diabetologists and UK Kidney Association Diabetic Kidney Disease Clinical Speciality Group have previously undertaken a narrative review and critical appraisal of the available evidence to inform clinical practice guidelines for the pharmacological management of hyperglycemia in adults with T2DM and CKD. This 2025 abbreviated updated guidance by a multidisciplinary group of health care professionals from primary and secondary care settings summarizes the key recommendations, clinical considerations and recent evidence that has implications for clinical practice for health care professionals who treat people with T2DM and CKD.

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[61] DPP-4 inhibitors for treating T2DM - hype or hope? an analysis based on the current literature.
Europe PMC
https://pubmed.ncbi.nlm.nih.gov/37287751/

Supporting passage supplied to the model

> DPP-4 inhibition is an interesting line of therapy for treating Type 2 Diabetes Mellitus (T2DM) and is based on promoting the incretin effect. Here, the authors have presented a brief appraisal of DPP-4 inhibitors, their modes of action, and the clinical efficiency of currently available drugs based on DPP-4 inhibitors. The safety profiles as well as future directions including their potential application in improving COVID-19 patient outcomes have also been discussed in detail. This review also highlights the existing queries and evidence gaps in DPP-4 inhibitor research. Authors have concluded that the excitement surrounding DPP-4 inhibitors is justified because in addition to controlling blood glucose level, they are good at managing risk factors associated with diabetes.

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