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Literature Review

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Linagliptin for Type 2 Diabetes Mellitus: A Systematic Review of Efficacy, Safety, Combination Therapy, and Use in High Risk Populations

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Abstract

Background: Type 2 diabetes mellitus requires glucose-lowering therapy that balances efficacy and safety, particularly in patients with renal or cardiovascular comorbidities. Linagliptin is a dipeptidyl peptidase-4 inhibitor with predominantly nonrenal elimination. **Objectives:** To evaluate the efficacy, safety, combination therapy, and clinical use of linagliptin in selected high-risk populations. **Methods:** PubMed and Google Scholar were searched for primary clinical studies published from 2015 through 19 August 2026. Eleven eligible studies were synthesized according to PRISMA 2020 principles. Risk of bias was assessed using RoB 2, and clinically heterogeneous outcomes were summarized narratively. **Results:** Linagliptin reduced HbA1c compared with placebo and demonstrated cardiovascular noninferiority in CARMELINA. Compared with glimepiride, glycemic control was broadly comparable, with less hypoglycemia and weight gain. Empagliflozin produced greater glycemic and metabolic improvements than linagliptin when added to premixed insulin, whereas linagliptin reduced HbA1c more effectively than voglibose in hemodialysis patients. Combination benefits and adverse effects varied according to the partner drug. **Conclusions:** Linagliptin provides modest glucose lowering with a generally low risk of hypoglycemia, although comparative benefits depend on population, comparator, and clinical outcome.

Keywords: Type 2 Diabetes Mellitus; Linagliptin; Systematic Review; Efficacy; Safety

Introduction

According to the International Diabetes Federation (IDF), 588.7 million people worldwide were living with diabetes in 2024, including 20.4 million people in Indonesia[1]. Diabetes mellitus is a chronic disease caused by metabolic disturbances characterized by elevated blood glucose levels resulting from impaired insulin function in maintaining glucose homeostasis. Over time, diabetes can damage the heart, blood vessels, eyes, kidneys, and nerves[2]. Diabetes mellitus is broadly classified into type 1 and type 2 diabetes, with type 2 diabetes accounting for approximately 90% of cases[3].

Type 2 diabetes mellitus is a metabolic disorder driven by three major factors: impaired insulin secretion by pancreatic beta cells, reduced responsiveness of insulin sensitive tissues to insulin, and an inadequate compensatory insulin secretory response to overcome insulin resistance[3]. Insulin is a hormone produced by pancreatic beta cells that maintains blood glucose within the normal range by facilitating glucose uptake into insulin target tissues such as skeletal muscle and adipose tissue and by suppressing hepatic glucose output[2]. Based on methods standardized by the National Glycohemoglobin Standardization Program (NGSP) and the

Diabetes Control and Complications Trial (DCCT) assay, diabetes mellitus can be diagnosed when HbA1c is ≥6.5%[4].

During the treatment of type 2 diabetes, blood glucose may fall to a level that produces clinical signs and symptoms known as hypoglycemia. Medications are the most common exogenous cause of hypoglycemia. Among these, glucose lowering drugs, particularly agents that increase circulating insulin concentrations, are the most frequent causes[3].

Dipeptidyl peptidase 4 (DPP 4) inhibitors are oral antihyperglycemic agents used in adults with type 2 diabetes mellitus. They inhibit the DPP 4 enzyme, prolong endogenous incretin activity, increase glucose dependent insulin secretion, and reduce glucagon secretion. Linagliptin is an approved DPP 4 inhibitor[5].

Unlike several other DPP 4 inhibitors, linagliptin has predominantly nonrenal elimination, with only a small proportion recovered in urine after oral administration[6]. This pharmacokinetic feature is clinically relevant when renal function is impaired. Pharmacotherapy should nevertheless be considered within comprehensive diabetes management that also includes lifestyle, education, and long term adherence. This review aimed to evaluate linagliptin neutrally as monotherapy, combination therapy, and treatment in selected renal and cardiovascular risk populations, with separate consideration of glycemic efficacy, hypoglycemia, body weight, cardiovascular outcomes, renal outcomes, and treatment burden.

Materials and Methods

This study was designed as a systematic review of primary clinical research evaluating linagliptin for type 2 diabetes mellitus, either as monotherapy or in combination with other antidiabetic agents, in patients with or without comorbidities. The research question was structured using the existing PICO framework in Table 1. Reporting was revised in accordance with PRISMA 2020 principles[7].

The prespecified primary outcome was change in HbA1c. Secondary outcomes included hypoglycemia, body weight, cardiovascular events, renal outcomes, albuminuria, adverse events, and treatment related quality of life when reported. Eligible studies were primary clinical studies published from 1 January 2015 through 19 August 2026 in English or Indonesian that evaluated linagliptin in adults with type 2 diabetes mellitus. Reviews, editorials, nonclinical studies, duplicate publications, and reports without extractable linagliptin outcomes were excluded.

Table 1. PICO Framework

Population	Patients with T2DM with or without comorbidities
Intervention	Linagliptin administered as monotherapy or combination therapy
Comparison	Other antidiabetic agents
Outcome	Efficacy of linagliptin assessed primarily by HbA1c and other relevant clinical parameters

Study characteristics and outcomes were extracted into a structured evidence table covering design, sample, intervention, comparator, duration, HbA1c, safety, renal and cardiovascular outcomes, and quality of life where available. Risk of bias for randomized evidence was evaluated using the RoB 2 framework[8]. Because the trials differed in comparators, treatment backgrounds, follow up periods, and outcome definitions, statistical pooling was not considered appropriate. The review therefore used a structured narrative synthesis and retained effect estimates and 95% confidence intervals when they were reported by the primary study. The bibliometric component was separated from the clinical

review because the archived manuscript did not preserve a reproducible mapping dataset or complete VOSviewer settings.

PubMed and Google Scholar were the review databases. The PubMed search used the reproducible string: linagliptin AND (type 2 diabetes mellitus OR T2DM) AND (monotherapy OR combination OR efficacy OR safety OR renal OR cardiovascular OR hemodialysis). The Google Scholar search used the same concept terms in free text. The last verification search was performed on 19 August 2026. Zotero was used to identify duplicate records. Titles and abstracts were screened first, followed by full text assessment against the eligibility criteria. For the original archived search, 265 records were identified, 74 duplicates were removed, 191 records were screened, 91 reports underwent full text assessment, and 10 studies were included. The 2026 verification identified one additional eligible randomized trial published in 2025, producing 11 studies in the updated synthesis.

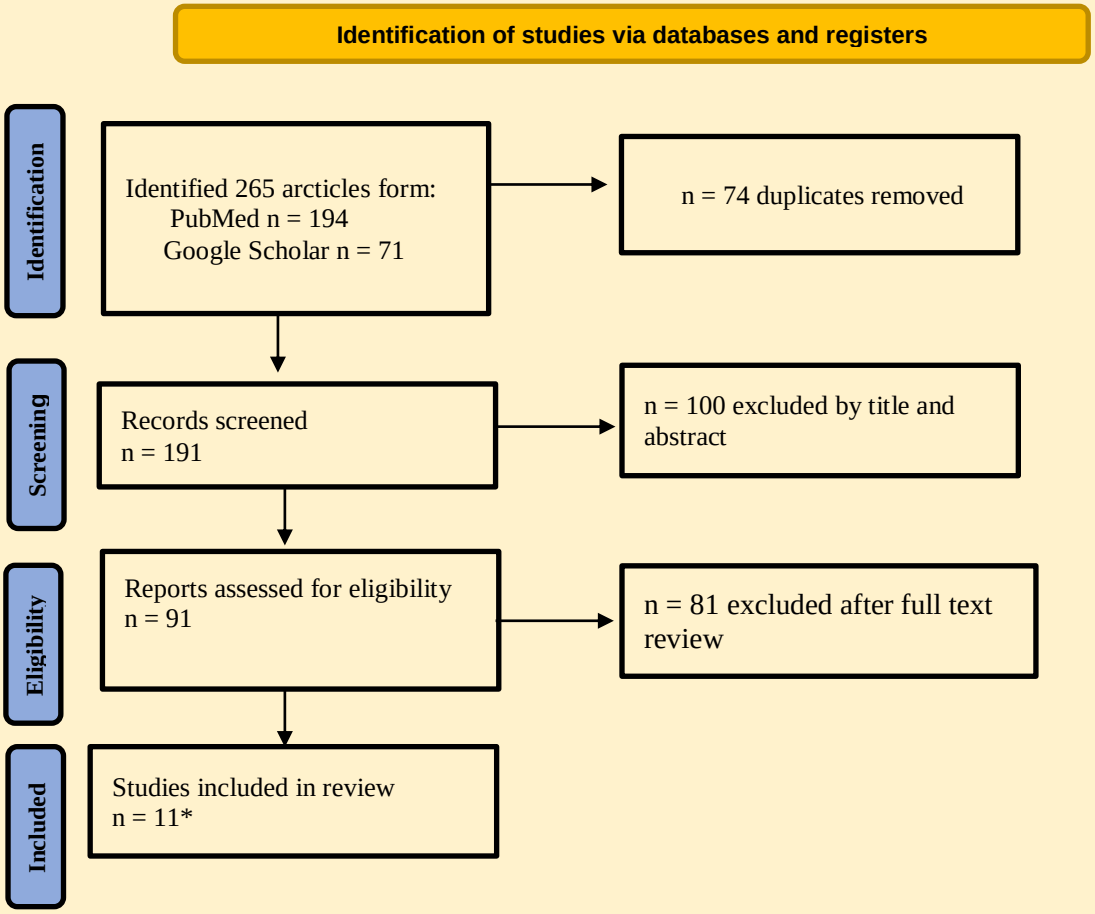

Figure 1. Article Selection Flow Diagram

Figure 1 documents the numerical flow of the original search and the later update. The identification, duplicate removal, screening, and full text counts are retained from the archived search. The included box is marked n = 11* to show the 10 studies from the original search plus one eligible randomized trial identified during the 2026 verification. The archived screening log did not retain article specific reasons for every full text exclusion beyond lack of relevance, ineligible publication type, or failure to meet the date and language criteria, which remains a reporting limitation.

Results

Table 2. Characteristics and Findings of the Included Studies

Title and Authors	Method	Therapy	Findings
Linagliptin and its effects on hyperglycemia and albuminuria in patients with type 2 diabetes and renal dysfunction: the MARLINA T2D trial[9].	Randomized, double blind, placebo controlled clinical trial for 24 weeks in 360 patients with type 2 diabetes and renal dysfunction.	Linagliptin 5 mg once daily vs placebo.	HbA1c decreased by about 0.60 percentage points relative to placebo. The prespecified albuminuria outcome was not significantly improved and eGFR was not materially changed.
Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk: The CARMELINA Randomized Clinical Trial[10].	Randomized, double blind, placebo controlled cardiovascular outcome trial in 6,979 treated participants; median follow up 2.2 years.	Linagliptin 5 mg once daily vs placebo plus usual care.	Cardiovascular outcome HR 1.02 (95% CI 0.89 to 1.17), meeting noninferiority. Major kidney composite HR 1.04 (95% CI 0.89 to 1.22). Acute pancreatitis occurred in 0.3% vs 0.1%.
Safety and efficacy of initial combination of linagliptin and metformin in patients with type 2 diabetes: a subgroup analysis of Indian patients[11].	Randomized, double blind, placebo controlled subgroup analysis for 24 weeks.	Linagliptin 2.5 mg plus metformin 1000 mg twice daily and component comparators.	The combination produced larger HbA1c reductions than placebo and component monotherapies; hypoglycemia was uncommon.
Initial Combination of Empagliflozin and Linagliptin in Subjects With Type 2 Diabetes[12].	Randomized, double blind, active controlled trial for 52 weeks in 677 participants.	Empagliflozin 25 or 10 mg plus linagliptin 5 mg vs component monotherapies.	At week 24, HbA1c changed by about −1.08% and −1.24% in the combination groups versus −0.67% with linagliptin alone. The 25 mg combination was not significantly better than empagliflozin 25 mg alone.
Linagliptin and pioglitazone combination therapy versus monotherapy with linagliptin or pioglitazone[13].	Randomized, double blind, active controlled phase 3 trial for 84 weeks in 896 patients.	Linagliptin 5 mg plus pioglitazone 15, 30, or 45 mg once daily vs component monotherapies.	Combination therapy improved HbA1c more than monotherapy at the higher pioglitazone doses. Weight gain and edema remained relevant pioglitazone related adverse effects.
Combination of the dipeptidyl peptidase 4 inhibitor linagliptin with insulin based regimens in type 2 diabetes and chronic kidney disease[14].	Analysis of two randomized, double blind, placebo controlled phase 3 trials lasting up to 52 weeks.	Linagliptin 5 mg added to basal, basal bolus, or premixed insulin.	Placebo adjusted HbA1c reductions were approximately 0.59%, 0.69%, and 0.43% across reported renal impairment strata. Severe hypoglycemia remained uncommon.
Effect of Linagliptin vs Glimepiride on Major Adverse Cardiovascular Outcomes in Patients With Type 2 Diabetes: The CAROLINA Randomized Clinical Trial[15].	Randomized, double blind, active controlled noninferiority trial; median follow up about 6.3 years.	Linagliptin 5 mg vs glimepiride 1 to 4 mg once daily.	Cardiovascular outcomes and glycemic control were broadly comparable. Linagliptin caused substantially less hypoglycemia and less weight gain.
Efficacy and safety of empagliflozin vs linagliptin added to premixed insulin in patients with	Randomized, open label, parallel group trial for 24 weeks with follow up at week 36 in 106 participants.	Empagliflozin 25 mg or linagliptin 5 mg once daily plus premixed insulin.	Empagliflozin produced greater HbA1c reduction (1.01% vs 0.06%), weight loss, systolic blood pressure reduction, and insulin dose reduction; hypoglycemia difference was not significant.

Title and Authors	Method	Therapy	Findings
uncontrolled type 2 diabetes[16].			
Liraglutide relieves cardiac dilated function than DPP 4 inhibitors[17].	Randomized, open label, parallel group single center trial for 48 months in 98 patients.	Liraglutide 0.9 mg vs sitagliptin 50 mg vs linagliptin 5 mg once daily.	HbA1c reductions were broadly similar, while liraglutide showed additional benefits for blood pressure, albuminuria, and cardiac diastolic function.
Linagliptin monotherapy compared with voglibose monotherapy in patients with type 2 diabetes undergoing hemodialysis[18].	Multicenter, randomized, open label, active controlled trial for 12 weeks.	Linagliptin 5 mg once daily vs voglibose 0.2 mg three times daily.	Linagliptin produced greater HbA1c improvement, adjusted difference −0.40% (95% CI −0.74 to −0.06; P=0.022), with no severe hypoglycemia reported.
Efficacy and safety of a fixed dose combination of dapagliflozin and linagliptin in patients with type 2 diabetes mellitus[19].	Multicenter, randomized, double blind, parallel group, placebo controlled phase 3 study in 235 patients; 24 week main period with extension to 52 weeks.	Dapagliflozin 10 mg plus linagliptin 5 mg fixed dose combination vs linagliptin 5 mg plus placebo, on background metformin.	At week 24, the adjusted HbA1c difference was −0.88% (95% CI −1.07 to −0.68; P<0.0001) in favor of dapagliflozin plus linagliptin. Adverse event incidence was similar and no symptomatic hypoglycemia was reported.

The updated synthesis included 11 clinical studies. Using RoB 2 as a structured quality framework, large blinded randomized trials generally showed low risk of bias, whereas open-label trials, subgroup analyses, and secondary analyses raised some concerns related to deviations from blinding, selective subgroup reporting, or analytical limitations. No overall GRADE certainty rating was assigned. Therefore, findings from large blinded randomized trials were interpreted more confidently than smaller or secondary analyses.

Discussion

Bibliometric Analysis of "Linagliptin"

The bibliometric mapping was not retained as an analytic component in the revised review. The archived manuscript did not document which record set was used for VOSviewer, the analyzed fields, term thresholds, counting method, or software settings. Removing the mapping avoids mixing an incompletely documented bibliometric dataset with the clinical systematic review. Accordingly, no bibliometric findings are reported or interpreted as part of the evidence synthesis in the revised manuscript. This subsection is retained only to document that decision, while the clinical evidence synthesis remains the focus of the article.

Linagliptin as a DPP 4 Inhibitor

DPP 4 is widely expressed in tissues including the intestinal brush border, kidneys, vascular endothelium, liver, pancreas, glandular epithelium, and immune cells[20]. DPP 4 degrades incretin hormones, particularly glucagon like peptide 1 and glucose dependent insulinotropic polypeptide. Inhibiting this enzyme increases endogenous incretin activity, enhances glucose dependent insulin secretion, and suppresses glucagon secretion, thereby reducing fasting and postprandial hyperglycemia[5].

Efficacy and Safety

The 11 included studies evaluated linagliptin as monotherapy, in combinations with metformin, empagliflozin or dapagliflozin, pioglitazone, and insulin, and in direct comparisons with glimepiride, empagliflozin, liraglutide, sitagliptin, and voglibose. The evidence

therefore represents different clinical questions rather than a single uniform treatment contrast.

Across placebo controlled studies, linagliptin produced modest HbA1c reductions. Comparative trials showed that its relative performance depended on the comparator and endpoint: glycemic efficacy was broadly comparable with glimepiride, empagliflozin was superior on several metabolic endpoints when added to premixed insulin, and linagliptin was superior to voglibose for HbA1c in hemodialysis patients. Combination treatment could enhance glycemic lowering, but partner specific adverse effects such as edema and weight gain with pioglitazone remained relevant. These differences precluded a single claim of overall superiority.

Table 3. Summary of Comparative Glycemic and Safety Findings with Linagliptin

Therapy	Intervention	HbA1c Finding	Other Effects and Interpretation
Monotherapy	Linagliptin vs placebo in MARLINA T2D	About −0.60% relative to placebo	MARLINA T2D showed glycemic benefit but no significant prespecified albuminuria benefit.
		About −0.36% to −0.51% at reported time points	Cardiovascular noninferiority; no superiority for the major kidney composite.
Combination	Linagliptin plus metformin	Adjusted reduction about −1.83% vs placebo subgroup reference	Greater glucose lowering than component monotherapies in the studied subgroup; hypoglycemia uncommon.
	Empagliflozin plus linagliptin	About −1.08% to −1.24% at week 24	Combination benefit depended on empagliflozin dose and comparator; weight reduction reflected SGLT 2 therapy.
	Linagliptin plus pioglitazone	Up to about −1.09%	Greater glycemic lowering than monotherapy at higher pioglitazone doses, with weight gain and edema tradeoffs.
	Linagliptin plus insulin	About −0.43% to −0.69% placebo adjusted across renal strata	Useful glucose lowering in CKD; severe hypoglycemia remained uncommon but monitoring remains necessary.
Comparison	Linagliptin vs empagliflozin plus premixed insulin	−0.06% vs −1.01%	Empagliflozin favored for HbA1c, weight, blood pressure, and insulin dose in this trial.
	Linagliptin vs glimepiride	Broadly comparable long term glycemic control	Linagliptin caused substantially less hypoglycemia and less weight gain.
	Liraglutide vs sitagliptin vs linagliptin	Broadly similar modest HbA1c reductions	Liraglutide showed additional blood pressure, albuminuria, and cardiac functional effects.
	Linagliptin vs voglibose	Adjusted difference −0.40%	Linagliptin favored for HbA1c at 12 weeks in hemodialysis patients.
	Dapagliflozin plus linagliptin	Adjusted difference −0.88% vs linagliptin plus placebo	Updated 2025 trial supports additional glucose lowering from adding dapagliflozin on background metformin and linagliptin.

Monotherapy

According to the 2021 Indonesian Society of Endocrinology guideline[4], DPP 4 inhibitors can be used within individualized glucose lowering therapy. In the MARLINA T2D trial, linagliptin reduced HbA1c by about 0.60 percentage points relative to placebo in patients with type 2 diabetes and renal dysfunction[9]. The study did not demonstrate a significant improvement in the prespecified albuminuria endpoint, so renal findings should not be interpreted as proof of renal protection.

Microvascular complications remain clinically important consequences of chronic hyperglycemia[21], and urine albumin measurement is useful for kidney risk assessment[22].

In CARMELINA, 6,979 treated participants with high cardiovascular and renal risk were followed for a median of 2.2 years. The primary cardiovascular outcome occurred with a hazard ratio of 1.02 (95% CI 0.89 to 1.17), meeting the trial criterion for noninferiority versus placebo. The kidney composite had a hazard ratio of 1.04 (95% CI 0.89 to 1.22), indicating no superiority for the major renal outcome[10]. Thus, CARMELINA supports cardiovascular and renal safety in the studied high risk population rather than cardiovascular or renal benefit.

The importance of this population is reinforced by the close interaction of diabetes, chronic kidney disease, and cardiovascular disease. Cardiorenal metabolic mechanisms include neurohormonal activation, sodium and water retention, inflammation, and progressive vascular and renal injury[23].

CARMELINA also showed sustained glucose lowering, but the magnitude was modest and should be interpreted separately from the cardiovascular safety endpoint. The trial therefore supports use of linagliptin when cardiovascular neutrality and renal dosing practicality are relevant, not a claim of superior cardiorenal efficacy[10].

A pancreatitis signal warrants cautious interpretation. Acute pancreatitis occurred in 0.3% of linagliptin recipients and 0.1% of placebo recipients in CARMELINA[10]. Observational evidence on pancreatitis with DPP 4 inhibitors has been inconsistent[24]. These data support continued adverse event monitoring rather than a definitive causal conclusion.

Combination Therapy

Combination therapy should be interpreted according to the partner drug, background therapy, baseline HbA1c, and patient comorbidity. The included trials were clinically heterogeneous, so the review does not treat all linagliptin combinations as equivalent.

Metformin (Biguanide)

In the Indian subgroup analysis, initial linagliptin plus metformin produced a larger HbA1c reduction than placebo and the component monotherapies over 24 weeks, while hypoglycemia remained uncommon[11]. These results support glycemic efficacy of the combination in the studied subgroup but do not establish superiority over all contemporary alternatives.

Adverse events with linagliptin plus metformin were broadly comparable with the study comparators, and gastrointestinal events were not clearly increased by adding linagliptin[11].

Empagliflozin (SGLT 2 Inhibitor)

Lewin et al. evaluated initial empagliflozin and linagliptin combination therapy. At week 24, adjusted HbA1c changes were about −1.08% with empagliflozin 25 mg plus linagliptin 5 mg and −1.24% with empagliflozin 10 mg plus linagliptin 5 mg, compared with −0.67% for linagliptin alone[12]. The 10 mg empagliflozin combination was significantly more effective than each component, whereas the 25 mg combination was not significantly better than empagliflozin 25 mg alone. Empagliflozin belongs to the sodium glucose transport 2 inhibitor class, which lowers glucose partly by increasing urinary glucose excretion[25].

Weight reduction in the empagliflozin containing groups was driven primarily by the SGLT 2 component, while treatment convenience and other patient reported outcomes varied across treatment groups[12]. A

newer randomized trial published in 2025 found that dapagliflozin added as a fixed dose combination with linagliptin in patients inadequately controlled on metformin and linagliptin produced an adjusted HbA1c benefit of −0.88% (95% CI −1.07 to −0.68) versus linagliptin plus placebo at 24 weeks[19]. This updated evidence supports additional glucose lowering from adding an SGLT 2 inhibitor rather than superiority attributable to linagliptin itself.

Pioglitazone (TZD)

The linagliptin and pioglitazone combination produced greater HbA1c reductions than either monotherapy in the randomized trial, particularly with pioglitazone doses of 30 mg and 45 mg[13]. Pioglitazone improves insulin sensitivity, whereas linagliptin acts through DPP 4 inhibition[26].

Fewer participants required rescue therapy with combination treatment than with linagliptin monotherapy, although the magnitude varied by pioglitazone dose[13].

The combination did not eliminate the established thiazolidinedione tradeoffs. Weight gain and edema occurred more often with pioglitazone containing regimens, while hypoglycemia remained uncommon[13]. Therefore, the improved glycemic effect must be balanced against partner drug adverse effects.

Combination with Insulin

Insulin lowers blood glucose directly through insulin receptor mediated effects and remains necessary for many patients with advanced type 2 diabetes[27]. Linagliptin has been studied as an add on to basal, basal bolus, and premixed insulin regimens.

In the analysis by McGill et al., adding linagliptin to insulin based regimens in patients with chronic kidney disease produced placebo adjusted HbA1c reductions of approximately 0.59% in mild renal impairment, 0.69% in moderate renal impairment, and 0.43% in severe renal impairment at the reported time points[14]. Severe hypoglycemia remained uncommon, but overall hypoglycemia was numerically higher in some linagliptin groups. These findings support glucose lowering efficacy in CKD while requiring the same individualized monitoring used for insulin therapy.

Linagliptin Compared with Other Antidiabetic Agents

Direct comparisons demonstrate that linagliptin is not uniformly superior to other glucose lowering agents. Its relative strengths are most apparent for low hypoglycemia burden and renal dosing convenience, whereas some comparators produce larger effects on HbA1c, body weight, blood pressure, or albuminuria.

Linagliptin vs Empagliflozin as Add on Therapy to Premixed Insulin

In the randomized open label comparison by Liu et al., empagliflozin added to premixed insulin produced a larger HbA1c reduction than linagliptin, together with greater reductions in body weight, systolic blood pressure, and daily insulin dose[16]. Premixed insulin regimens can differ from basal bolus regimens in glycemic patterns and hypoglycemia considerations[28].

At 24 weeks, HbA1c decreased by 1.01% with empagliflozin and by 0.06% with linagliptin. Body weight changed by −1.5 kg and +0.2 kg, respectively. Hypoglycemia occurred in 30.2% versus 22.6%, but the difference was not statistically significant[16]. This trial therefore favored empagliflozin for glycemic and several metabolic endpoints in the studied insulin treated population.

Linagliptin vs Glimepiride (Sulfonylurea)

The CAROLINA trial compared linagliptin with glimepiride over a median follow up of

about 6.3 years in adults with relatively early type 2 diabetes and elevated cardiovascular risk[15]. Glimepiride is a sulfonylurea that lowers glucose through insulin secretory effects[29].

Linagliptin was noninferior to glimepiride for major cardiovascular outcomes, while glycemic control was broadly similar. Linagliptin caused substantially fewer hypoglycemic events and less weight gain[15]. These findings support a safety tradeoff in favor of linagliptin rather than superior glucose lowering.

Linagliptin vs Liraglutide (GLP 1) vs Sitagliptin (DPP 4 Inhibitor)

In the long duration open label comparison, HbA1c reductions were broadly similar across liraglutide, sitagliptin, and linagliptin, but liraglutide showed additional improvements in blood pressure, albuminuria, and cardiac diastolic function[17]. Liraglutide is a glucagon like peptide 1 receptor agonist with distinct metabolic effects[30]. Interpretation is limited by the small sample and open label design. Longitudinal monitoring of renal biomarkers remains important in diabetic kidney disease[31].

Linagliptin vs Voglibose (Alpha Glucosidase Inhibitor)

In patients with type 2 diabetes undergoing hemodialysis, Mori et al. found a greater HbA1c improvement with linagliptin than with voglibose at 12 weeks, with an adjusted treatment difference of −0.40% (95% CI −0.74 to −0.06; P=0.022)[18]. Alpha glucosidase inhibitors reduce intestinal carbohydrate digestion and absorption[32].

Hemodialysis can produce marked glucose fluctuations and increases the complexity of glucose lowering treatment[33]. Linagliptin has practical relevance in this setting because predominantly nonrenal elimination reduces the need for renal dose adjustment, although this pharmacokinetic convenience should not be interpreted as proof of superiority on all clinical outcomes[6].

The same hemodialysis comparison reported no severe hypoglycemia attributable to linagliptin and supported short term glycemic efficacy relative to voglibose[18].

A related quality of life analysis found greater improvement with linagliptin than voglibose in total treatment related quality of life and in social and daily activity burden[34]. In Indonesian practice, diabetes related kidney disease is an important high risk context[35], while medication adherence and health professional education remain relevant to long term treatment implementation[36]. Pharmacotherapy should also be integrated with nonpharmacological self management such as exercise and lifestyle modification[37].

Conclusion

This systematic review found that linagliptin provides modest HbA1c lowering as monotherapy and can contribute additional glucose lowering in selected combination regimens. Large cardiovascular outcome trials support cardiovascular safety in the studied populations, while renal outcome data do not establish superiority for major kidney endpoints. Compared with glimepiride, linagliptin offers a lower hypoglycemia burden and less weight gain with broadly comparable glycemic control. Empagliflozin produced larger glycemic and metabolic improvements than linagliptin when added to premixed insulin, whereas linagliptin produced greater short term HbA1c improvement than voglibose in patients undergoing hemodialysis. The evidence therefore supports individualized use based on renal function, hypoglycemia risk, treatment burden, comparator efficacy, and comorbidity rather than a universal claim that linagliptin is superior. Interpretation should remain cautious because several included reports were open label, subgroup, or

secondary analyses and the heterogeneous outcomes were not pooled quantitatively.

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