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Mortality Benefits of DPP-4 Inhibitors Compared to Other Oral Hypoglycemic Agents or Placebo in Type 2 Diabetes Mellitus: A Systematic Review of Randomized Controlled Trials

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Abstract

Background

Type 2 diabetes mellitus (T2DM) is one of the most consequential drivers of premature death globally, largely through its acceleration of cardiovascular and renal disease. Dipeptidyl peptidase-4 (DPP-4) inhibitors have become a major cornerstone of second-line glucose-lowering therapy, valued for their glycemic efficacy, weight neutrality, and low hypoglycemia risk. Whether these attributes translate into a tangible mortality advantage over comparators, however, has not yet been consistently demonstrated across the trial literature.

Objectives

To evaluate the mortality benefits of DPP-4 inhibitors compared with placebo or other oral hypoglycemic agents (OHAs) in adults with T2DM, using only evidence from randomized controlled trials published between 2015 and 2025.

Methods

A pre-registered systematic review was conducted in line with PRISMA 2020 reporting standards (PROSPERO: CRD420251108505). PubMed and Embase were searched from January 2015 to January 2025 for RCTs enrolling adult T2DM patients randomized to a DPP-4 inhibitor versus placebo or an alternative OHA, with mortality as a reported endpoint. Two independent reviewers performed screening, data extraction, and risk-of-bias assessment (Cochrane RoB 2.0). Certainty of evidence was graded using the GRADE framework. Given substantive clinical heterogeneity, data were synthesized descriptively rather than pooled in a formal meta-analysis.

Results

Sixty-six records were retrieved across both databases. After removing 11 duplicates, 55 records were screened; 33 were excluded at title and abstract review. Twenty-two full texts were assessed, of which 8 were excluded for methodological or eligibility reasons, leaving 14 studies in the qualitative synthesis. These included the four major cardiovascular outcome trials (CVOTs): SAVOR-TIMI 53 (saxagliptin), EXAMINE (alogliptin), TECOS (sitagliptin), and CARMELINA (linagliptin vs. placebo), alongside CAROLINA (linagliptin vs. glimepiride) and additional RCTs and RCT-level meta-analyses. Across all CVOTs, all-cause mortality hazard ratios ranged from 0.97 to 1.11, none reaching statistical significance. Cardiovascular mortality was similarly neutral across trials. A notable outlier was the hospitalization-for-heart-failure signal in SAVOR-TIMI 53, which was not replicated in subsequent trials. Risk of bias was rated low in CVOTs and some concerns to high in smaller trials. Overall certainty of evidence for mortality outcomes was rated moderate by GRADE.

Conclusion

DPP-4 inhibitors are cardio-vascularly safe, but they do not appear to confer a statistically significant reduction in all-cause or cardiovascular mortality compared with placebo or active OHAs. Their clinical value lies in tolerability, hypoglycemia sparing, and suitability for complex patient populations rather than in mortality superiority. Larger, longer-term trials inclusive of low-income country populations, where sulphonyl-ureas remain the dominant comparator, are needed to resolve remaining uncertainty.

PROSPERO Registration: CRD420251108505

Clinical trial number: not applicable.

1. Introduction

1.1 The Mortality Burden of Type 2 Diabetes Mellitus

Type 2 diabetes mellitus sits at the intersection of virtually every major cause of premature death. It accelerates atherosclerosis, impairs cardiac function, drives renal failure, and suppresses immune competence, each pathway capable of shortening life independently, and collectively compounding risk in ways that standard risk calculators frequently underestimate [28]. The International Diabetes Federation estimated in 2021 that 537 million adults were living with diabetes worldwide, a number expected to surpass 780 million by 2045, with the steepest growth concentrated in sub-Saharan Africa and South-East Asia.[1] Cardiovascular disease accounts for the largest share of diabetes-related mortality, yet deaths from infection, liver disease, and cancer also occur at elevated rates [27], a reminder that T2DM is both a systemic condition and a vascular one.

Against this backdrop, the choice of glucose-lowering therapy can no longer be evaluated on glycemic efficacy alone. Over the past decade, cardiovascular and renal outcome data have become as decisive as HbA1c reduction in shaping prescribing decisions and clinical guidelines. [2] The question of which agents, if any, meaningfully reduce mortality in T2DM patients, beyond what is achieved through background cardiovascular risk management, remains central to evidence-based prescribing.

1.2 DPP-4 Inhibitors: Mechanism and Clinical Profile

Dipeptidyl peptidase-4 is a ubiquitous serine protease whose primary metabolic function is the rapid inactivation of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). [3] By blocking this degradation, DPP-4 inhibitors, collectively termed as gliptins, prolong incretin-mediated insulin secretion and glucagon suppression in a glucose-dependent manner, thereby lowering post-prandial glucose excursions without significant risk of hypoglycemia in the fasting state. [4]

Five agents are widely approved: sitagliptin, saxagliptin, alogliptin, linagliptin, and vildagliptin. Teneligliptin and trelagliptin hold approval in selected Asian markets. [4] As a class, the gliptins reduce HbA1c by approximately 0.5–0.9 percentage points, are weight neutral, and are generally well tolerated[4]. Linagliptin is unique within the class for its predominantly biliary excretion, meaning no dose adjustment is required in the case of chronic kidney disease, an important practical consideration given that 20–40% of T2DM patients have concomitant nephropathy[28]. [5] Early preclinical data suggested pleiotropic cardiovascular

benefits including improved endothelial function, reduced oxidative stress, and mild anti-inflammatory effects, generating optimism that DPP-4 inhibitors might deliver mortality advantages that their glycemic profile alone could not explain. [6]

1.3 The Cardiovascular Outcome Trial Era

A turning point in antidiabetic pharmacology came in 2008, when the FDA mandated cardiovascular outcome trials (CVOTs) for all new glucose-lowering agents following concerns raised by meta-analyses of rosiglitazone data[26]. This regulatory requirement catalyzed a series of large, rigorously conducted trials powered primarily to exclude cardiovascular harm, which have secondarily enabled evaluation of potential benefit. [7] Four CVOTs cover the DPP-4 inhibitor class: SAVOR-TIMI 53 for saxagliptin, EXAMINE for alogliptin, TECOS for sitagliptin, and CARMELINA for linagliptin. A fifth trial, CAROLINA, compared linagliptin head-to-head with glimepiride, providing the only CVOT-grade active comparator mortality data within the class. Collectively, these trials enrolled more than 47,000 participants and have follow-up periods ranging from 1.5 to 6.2 years. [8]

1.4 Rationale and Research Gap

Despite this substantial evidence base, a pre-registered systematic review specifically focused on mortality outcomes, comparing DPP-4 inhibitors against placebo and active OHAs, within the 2015–2025 literature window, and applying contemporary methods (PRISMA 2020, Cochrane RoB 2.0, GRADE), has not been published. Existing meta-analyses vary in their inclusion criteria, outcome definitions, and risk-of-bias handling[11, 18, 19, 22]. This review addresses that gap directly, with the specific goal of characterizing what the available RCT evidence says, and does not say, about whether DPP-4 inhibitors reduce mortality in T2DM.

1.5 Objectives

Primary objective

To evaluate the mortality benefits of DPP-4 inhibitors compared with placebo or other OHAs in adults with T2DM, based on RCT evidence published between January 2015 and January 2025.

Secondary objective

To characterize the pattern of mortality outcomes across trials stratified by agent, comparator, patient risk profile, and follow-up duration.

2. Methods

This systematic review was prospectively registered with PROSPERO (CRD420251108505, 21 July 2025) and is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement. [9]

2.1 Eligibility Criteria

2.1.1 Population

Adult patients (aged ≥ 18 years) with an established clinical or biochemical diagnosis of type 2 diabetes mellitus were eligible. Studies enrolling patients with type 1 diabetes, gestational diabetes, monogenic diabetes, or diabetes secondary to pancreatitis or other identifiable causes were excluded. Studies enrolling mixed T1DM/T2DM populations were included only if T2DM-specific data could be extracted separately.

2.1.2 Intervention

Any approved DPP-4 inhibitor (sitagliptin, saxagliptin, alogliptin, linagliptin, vildagliptin, teneligliptin, or trelagliptin) administered at a licensed dose, as monotherapy or added to any permitted background antidiabetic regimen.

2.1.3 Comparator

Placebo (with or without background OHA) or any alternative active oral hypoglycemic agent, including metformin, sulphonyl-ureas, thiazolidinediones, SGLT2 inhibitors, alpha-glucosidase inhibitors, and meglitinides.

2.1.4 Outcomes

Primary outcome: All-cause mortality. Secondary outcomes: cardiovascular mortality, three-point major adverse cardiovascular events (3P-MACE: cardiovascular death, non-fatal myocardial infarction, non-fatal stroke), hospitalization for heart failure, and any other mortality endpoints reported.

2.1.5 Study Design and Language

Only randomized controlled trials were eligible, with no minimum trial duration. Non-randomized studies, observational cohorts, case-control studies, registry analyses, case reports, editorials, and conference abstracts without full data were excluded. Only English-language publications were included.

2.1.6 Search Date Restriction

Database searches were restricted to studies published from 1 January 2015 through 1 January 2025. This window captures the contemporary regulatory and clinical era for this drug class while excluding earlier pharmacokinetic dose-finding trials not designed to detect mortality differences.

2.2 Information Sources and Search Strategy

Structured searches were executed in PubMed (including MEDLINE) and Embase via Ovid. Search terms combined controlled vocabulary (MeSH headings for PubMed; Emtree for Embase) with free-text synonyms. The core concept blocks were: ("dipeptidyl peptidase-4 inhibitors" OR "DPP-4 inhibitors" OR "gliptin*" OR "sitagliptin" OR "saxagliptin" OR "alogliptin" OR "linagliptin" OR "vildagliptin") AND ("type 2 diabetes mellitus" OR "T2DM") AND ("mortality" OR "death" OR "all-cause mortality" OR "cardiovascular mortality") AND ("randomized controlled trial" OR "clinical trial[pt]"). The full search strategy is available in

the PROSPERO record. Reference lists of all included studies and relevant systematic reviews were hand-searched for any additional eligible trials not captured by the database searches. [10, 11]

2.3 Study Selection

Records retrieved from both databases were exported and deduplicated using Rayyan QCRI. Two reviewers (IA and JN) independently screened titles and abstracts. Full texts were retrieved for all records that passed or were considered ambiguous. Full-text eligibility was assessed independently by two additional reviewers (JM and AM); disagreements at either stage was resolved through discussion and, where necessary, arbitration by a third reviewer (CD). Decisions at each stage were documented to support construction of the PRISMA 2020 flow diagram. [9]

2.4 Data Extraction

Structured data extraction was conducted independently by paired reviewers using a pre-piloted form. Fields extracted included: trial identifier, study design, sample size, participant characteristics (mean age, sex, baseline HbA1c, cardiovascular risk profile, eGFR), DPP-4 inhibitor name and dose, comparator type and dose, permitted background therapy, follow-up duration, and outcome data for all-cause mortality, cardiovascular mortality, 3P-MACE, and hospitalization for heart failure. Where a trial published multiple outcome reports, the primary publication and longest available follow-up report were used.

2.5 Risk of Bias Assessment

Individual trial risk of bias was assessed using the Cochrane Risk of Bias tool version 2 (RoB 2), which evaluates five domains: randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of reported results. Each domain was rated as low risk, some concerns, or high risk; an overall risk judgment was assigned accordingly. [10] Assessments were performed in independent pairs (IA/JN and JM/CD) with consensus resolution.

2.6 Certainty of Evidence

The certainty of evidence for each outcome was appraised using the GRADE approach. Evidence from RCTs begins at high certainty and may be downgraded for risk of bias, inconsistency, indirectness, imprecision, or publication bias. A Summary of Findings table was developed for the primary outcome. [9]

2.7 Data Synthesis

Given the substantive heterogeneity across included studies, in comparator type (placebo vs. active OHA), patient cardiovascular risk profiles, DPP-4 inhibitor molecules, and follow-up durations, pooling data in a meta-analysis was judged inappropriate. A descriptive and thematic synthesis was therefore employed, organizing findings by comparator type and then by DPP-4 inhibitor molecule. Event rates, hazard ratios, and 95% confidence intervals are presented in structured tables with accompanying narrative commentary. [11]

3. Results

3.1 Search Results and Study Selection

The combined database search yielded 66 records (PubMed: 52; Embase: 14). After removing 11 duplicates, 55 unique records were screened at the title-and-abstract stage, of which 33 were excluded, primarily for being observational studies, narrative reviews, or trials not reporting a mortality endpoint. Twenty-two full-text articles were retrieved for eligibility assessment. Eight were excluded: four were narrative reviews without original trial data, two were non-randomized studies, one did not report any mortality outcome, and one enrolled a mixed T1DM/T2DM population without stratified data. Fourteen studies met all eligibility criteria and were included in the qualitative synthesis. The full PRISMA 2020 flow diagram is provided as a supplementary document accompanying this paper. (Fig. 1) (Table 1)

Table 1
PRISMA 2020 Selection Summary

Stage	Records (n)
Records identified — PubMed	52
Records identified — Embase	14
Total records retrieved	66
Duplicates removed	11
Records screened (title/abstract)	55
Excluded at title/abstract stage	33
Full texts retrieved	22
Full texts excluded — narrative review / no RCT data	4
Full texts excluded — non-randomized design	2
Full texts excluded — no mortality outcome	1
Full texts excluded — mixed T1DM/T2DM without stratified data	1
Studies included in qualitative synthesis	14

3.2 Characteristics of Included Studies

The 14 included studies comprised: the five major cardiovascular outcome trials (SAVOR-TIMI 53, [12] EXAMINE, [13] TECOS, [14] CAROLINA, [15] and CARMELINA [16]); four smaller head-to-head RCTs comparing DPP-4 inhibitors with sulphonyl-ureas or thiazolidinediones; and five RCT-level systematic reviews and meta-analyses that pooled mortality data across multiple trials. [17, 18, 19, 20, 21] Sample sizes ranged from 380 to 16,492 participants. Mean participant age was 65.5 years (range 57–71 years), and male participants comprised 54–71% across trials. Baseline HbA1c ranged from 7.0% to 9.2%. The five CVOTs enrolled predominantly patients with established cardiovascular disease or at high cardiovascular risk; the remaining trials included lower-risk or unselected T2DM populations. Median follow-up ranged from 1.5 to 6.2 years. (Table 2)

Table 2
Characteristics of Included Studies

Trial / Study	DPP-4 Inhibitor	Comparator	N	Follow-up	Primary Outcome
SAVOR-TIMI 53 [12]	Saxagliptin 5 mg	Placebo	16,492	2.1 yr	3P-MACE
EXAMINE [13]	Alogliptin 25 mg	Placebo	5,380	1.5–3.0 yr	3P-MACE
TECOS [14]	Sitagliptin 100 mg	Placebo	14,671	3.0 yr	4P-MACE
CAROLINA [15]	Linagliptin 5 mg	Glimepiride 1–4 mg	6,033	6.2 yr	3P-MACE
CARMELINA [16]	Linagliptin 5 mg	Placebo	6,979	2.2 yr	3P-MACE
Sesti et al., 2019 [17]	Multiple gliptins	SU / TZD	~ 2,400	1.0–2.0 yr	HbA1c, safety
Mannucci & Monami, 2016 [18]	Incretin agents	Various OHA	~ 14,000	0.5–4.0 yr	MACE
Liu et al., 2019 [19]	DPP-4 inh. (all)	Non-DPP-4	~ 47,000	Variable	CV outcomes
Cai et al., 2015 [20]	DPP-4 inh. (all)	Placebo / OHA	~ 15,000	0.5–2.0 yr	HbA1c, β-cell
Pantea Stoian et al., 2020 [21]	DPP-4 inh. (all)	OHA / placebo	~ 30,000	Variable	Safety/efficacy
Hemmingsen et al., 2017 [22]	DPP-4 / GLP-1	Placebo	~ 12,000	0.5–3.0 yr	Mortality/CV
Chan et al., 2016 [23]	DPP-4 inh.	Other OHA	~ 4,800	2.5 yr	CV outcomes
Rodrigues & Ndayishimye, 2018 [24]	DPP-4 inh. (all)	Placebo / OHA	~ 20,000	Variable	Clinical outcomes
Kunutsor et al., 2024 [25]	Antidiabetic agents	Various	~ 80,000	Variable	Glycaemic + CV

3.3 Primary Outcome: All-Cause Mortality

3.3.1 DPP-4 Inhibitors Versus Placebo

In SAVOR-TIMI 53, saxagliptin versus placebo was evaluated in 16,492 patients with T2DM and established cardiovascular disease or multiple risk factors, over a median of 2.1 years. All-cause mortality occurred in 5.1% of saxagliptin-treated patients and 4.6% with placebo (HR 1.11; 95% CI 0.96–1.27; p = 0.15). [12] The direction of the point estimate attracted scrutiny, particularly given the concurrent heart failure hospitalization finding, but the difference did not reach statistical significance.

EXAMINE enrolled 5,380 patients who had experienced an acute coronary syndrome within 90 days of randomization. All-cause mortality at a median follow-up of approximately 18 months was 7.6% with alogliptin versus 8.0% with placebo (HR 0.98; 95% CI 0.82–1.16). [13] The result was consistent with cardiovascular neutrality, with the confidence interval comfortably excluding substantial excess harm.

TECOS, the largest of the DPP-4 CVOTs with 14,671 participants, compared sitagliptin against placebo over three years in patients with established cardiovascular disease. All-cause mortality was 7.5% in the sitagliptin arm and 7.3% in the placebo arm (HR 1.01; 95% CI 0.90–1.14). [14] No mortality signal, in either direction, was detected.

CARMELINA enrolled 6,979 patients, including 60% with established cardiovascular disease and 74% with diabetic nephropathy, making it the trial with the highest cardiorenal burden. All-cause mortality was 11.0% with linagliptin and 11.8% with placebo over a median of 2.2 years (HR 0.98; 95% CI 0.84–1.13). [16] As in the other CVOTs, the result confirmed safety without any mortality benefit.

3.3.2 DPP-4 Inhibitor Versus Active Comparator - CAROLINA

CAROLINA is the only CVOT to have used an active OHA, glimepiride, as the comparator, providing six years of follow-up data in 6,033 patients with relatively early T2DM. All-cause mortality was 9.0% in the linagliptin arm and 9.3% in the glimepiride arm (HR 0.97; 95% CI 0.81–1.16). [15] The trial confirmed equivalent cardiovascular and mortality outcomes for the two agents while demonstrating a markedly lower hypoglycemia rate with linagliptin (2.1% vs. 11.1%; $p < 0.001$) - a finding with direct practical relevance in populations where hypoglycemia carries high consequence.

3.3.3 Pooled Analyses and Smaller RCTs

Across the remaining included studies, RCT-level systematic reviews and smaller head-to-head trials, mortality was infrequently powered as a primary endpoint. Hemmingsen et al.'s Cochrane review of DPP-4 inhibitors and GLP-1 analogues for prevention of cardiovascular events reported no statistically significant difference in all-cause mortality versus placebo or active comparators across 55 RCTs (OR 0.96; 95% CI 0.80–1.16). [22] Liu et al.'s 2019 meta-analysis similarly found no significant difference in all-cause mortality between DPP-4 inhibitor users and non-users (HR 1.00; 95% CI 0.93–1.07). [19] Pantea Stoian et al.'s 2020 systematic review reinforced mortality neutrality while highlighting tolerability advantages, particularly in patients with moderate CKD and the elderly.[21] (Table 3)

Table 3
All-Cause and Cardiovascular Mortality Across CVOTs

Trial	DPP-4 Inhibitor	Comparator	All-Cause Mortality HR (95% CI)	CV Mortality HR (95% CI)	HF Hospitalisation HR (95% CI)
SAVOR-TIMI 53 [12]	Saxagliptin	Placebo	1.11 (0.96–1.27)	1.03 (0.87–1.22)	1.27 (1.07–1.51)*
EXAMINE [13]	Alogliptin	Placebo	0.98 (0.82–1.16)	0.85 (0.66–1.10)	1.19 (0.90–1.58)
TECOS [14]	Sitagliptin	Placebo	1.01 (0.90–1.14)	1.03 (0.89–1.19)	1.00 (0.83–1.20)
CAROLINA [15]	Linagliptin	Glimepiride	0.97 (0.81–1.16)	0.96 (0.79–1.16)	0.90 (0.74–1.08)
CARMELINA [16]	Linagliptin	Placebo	0.98 (0.84–1.13)	0.96 (0.81–1.14)	0.90 (0.74–1.08)

* Statistically significant (p = 0.007); HR = hazard ratio; CI = confidence interval; CV = cardiovascular; HF = heart failure.

3.4 Secondary Outcomes

3.4.1 Cardiovascular Mortality

Cardiovascular mortality mirrored all-cause mortality across all five CVOTs, with hazard ratios ranging from 0.85 to 1.03, none statistically significant. The EXAMINE trial's point estimate of 0.85 (0.66–1.10) for cardiovascular death was the most favorable numerically, though the wide confidence interval precludes a firm conclusion given the shorter follow-up and smaller sample size in a post-ACS population. [13]

3.4.2 Hospitalization for Heart Failure

The most clinically disruptive finding across DPP-4 CVOTs was the statistically significant 27% relative increase in hospitalization for heart failure in the saxagliptin arm of SAVOR-TIMI 53 (HR 1.27; 95% CI 1.07–1.51; p = 0.007). [12] This signal was not replicated in EXAMINE (HR 1.19; 0.90–1.58), TECOS (HR 1.00; 0.83–1.20), CARMELINA (HR 0.90; 0.74–1.08), or CAROLINA (HR 0.90; 0.74–1.08). The inconsistency across agents has been attributed to molecule-specific effects, possibly involving saxagliptin's prolongation of substrates such as stromal cell-derived factor-1α beyond the GLP-1/GIP axis, as well as population-level differences in baseline heart failure prevalence between trials. [3, 6] Regulatory bodies in both the US and Europe subsequently required updated labelling for saxagliptin and alogliptin.

3.4.3 3P-MACE

Across all five CVOTs, DPP-4 inhibitors were non-inferior to placebo for 3P-MACE, with hazard ratios of 1.00 (SAVOR-TIMI 53), 0.96 (EXAMINE), 0.98 (TECOS), 0.98 (CAROLINA), and 0.98 (CARMELINA). [12, 13, 14, 15, 16] No trial demonstrated statistically significant superiority for the MACE composite. Non-fatal myocardial infarction and non-fatal stroke rates were similarly equivalent across trial arms.

3.5 Risk of Bias Assessment

All five CVOTs were rated as low overall risk of bias under Cochrane RoB 2.0, with pre-registered protocols, blinded endpoint adjudication by independent committees, intention-to-treat analysis, and low differential dropout rates. [10] Among the smaller included RCTs, two were rated 'some concerns' due to open-label designs (despite blinded endpoint adjudication, PROBE design), and two were rated high risk owing to small sample sizes, high loss-to-follow-up rates, and absence of pre-registration. (Table 4)

Table 4
Risk of Bias Summary (Cochrane RoB 2.0)

Study	Randomization	Deviations	Missing Data	Outcome Measurement	Reporting	Overall
SAVOR-TIMI 53 [12]	Low	Low	Low	Low	Low	Low
EXAMINE [13]	Low	Low	Low	Low	Low	Low
TECOS [14]	Low	Low	Low	Low	Low	Low
CAROLINA [15]	Low	Low	Low	Low	Low	Low
CARMELINA [16]	Low	Low	Low	Low	Low	Low
Hemmingsen et al. [22]	Low	Some concerns	Low	Low	Some concerns	Some concerns
Liu et al. [19]	Low	Some concerns	Low	Low	Some concerns	Some concerns
Smaller RCTs (n = 2)	Some concerns	Some concerns	High	Low	High	High

3.6 Certainty of Evidence (GRADE) (Table 5)

Table 5
GRADE Summary of Findings - All-Cause Mortality (DPP-4 Inhibitors vs. Comparators)

Outcome	No. Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Certainty
All-cause mortality (vs. placebo)	5 CVOTs	Not serious	Not serious	Serious[1]	Not serious	⊕⊕⊕◯ Moderate
All-cause mortality (vs. active OHA)	1 CVOT (CAROLINA)	Not serious	N/A	Serious[1]	Serious[2]	⊕⊕◯◯ Moderate
Cardiovascular mortality	5 CVOTs	Not serious	Not serious	Serious[1]	Not serious	⊕⊕⊕◯ Moderate
Hospitalisation for HF	5 CVOTs	Not serious	Serious[3]	Serious[1]	Not serious	⊕⊕◯◯ Low
3P-MACE	5 CVOTs	Not serious	Not serious	Serious[1]	Not serious	⊕⊕⊕◯ Moderate

[1] Downgraded: populations had established or high cardiovascular risk, limiting applicability to lower-risk or primary-prevention T2DM patients.

[2] Downgraded: single trial; wide confidence interval does not exclude clinically meaningful benefit or harm.

[3] Downgraded: significant between-trial inconsistency for HF hospitalization (SAVOR-TIMI 53 vs. all others).

4. Discussion

4.1 Principal Findings

This review synthesized 14 randomized controlled trials, anchored by five CVOTs enrolling more than 47,000 participants, and arrived at a consistent, reproducible finding: DPP-4 inhibitors do not reduce all-cause or cardiovascular mortality compared with placebo or active OHAs in adults with T2DM, but they equally do not increase it. The evidence for mortality neutrality is rated moderate certainty by GRADE, downgraded primarily for indirectness, as the overwhelming majority of CVOT data comes from patients with established cardiovascular disease, a population that differs meaningfully from the broader T2DM population in whom these drugs are frequently used. [12, 13, 14, 15, 16]

This finding sits in sharp contrast to the positive mortality and cardiovascular outcome signals demonstrated by SGLT2 inhibitors (empagliflozin in EMPA-REG OUTCOME[29]; canagliflozin in CANVAS [30]) and GLP-1 receptor agonists (liraglutide in LEADER[31]; semaglutide in SUSTAIN-6[32]), which have redefined treatment hierarchies in the most recent ESC and ADA/EASD guidelines. [1, 2] The DPP-4 inhibitors' cardiovascular neutrality is not, in itself, a clinical failure, these trials were powered for non-inferiority, not superiority, but it does mean that mortality reduction cannot be cited as a reason to choose a gliptin over other available options when those alternatives carry demonstrated outcome benefits.

4.2 Interpreting the Heart Failure Signal

The 27% relative increase in HF hospitalization with saxagliptin in SAVOR-TIMI 53 remains the most consequential and unresolved finding across the DPP-4 CVOT literature. [12] Its non-replication in EXAMINE, TECOS, CARMELINA, and CAROLINA has prompted debate about whether the result reflects a molecule-specific pharmacological effect unique to saxagliptin, a chance finding inflated by multiple-testing in a large trial, or a population-specific interaction in patients with particularly high baseline HF rates. Mechanistically, saxagliptin's inhibition of DPP-4 may prolong stromal cell-derived factor-1α (SDF-1α) beyond levels achieved by other gliptins, potentially mobilizing cardiac progenitor cells in ways that worsen, rather than improve, ventricular remodeling.[3] What the evidence clearly does not support is a class-wide signal for HF harm. For saxagliptin and alogliptin specifically, however, caution in patients with pre-existing heart failure or a reduced ejection fraction is warranted and reflected in current prescribing labels[34].

4.3 Why Mortality Neutrality Makes Mechanistic Sense

Several mechanistic observations help explain why DPP-4 inhibitors have not translated their theoretical pleiotropic benefits into measurable mortality reduction. First, DPP-4 cleaves many substrates beyond GLP-1 and GIP, including neuropeptide Y, peptide YY, SDF-1α, and brain natriuretic peptide, creating a pharmacological landscape where beneficial incretin augmentation co-exists with potentially adverse effects on other pathways. [4, 6] Second, the CVOTs were conducted against an intensive background of optimized cardiovascular care: statin use exceeded 80%, renin-angiotensin-aldosterone system blockade was present in over 70% of participants, and anti-platelet therapy was near-universal[12, 13, 14, 15, 16]. This high floor of background risk reduction makes it statistically unlikely that any single add-on agent would demonstrate additional mortality benefit within a 2–6 year window, regardless of mechanism. Third, patient populations in CVOTs were predominantly white, male, and from high-income countries[12, 13, 14, 15, 16], limiting the generalizability of null findings to populations where the drug's practical advantages (no renal dose adjustment; low hypoglycemia risk; low cost relative to newer agents) may matter most.

4.4 CAROLINA - What Active Comparator Data Tells Us

CAROLINA's six-year head-to-head comparison of linagliptin against glimepiride is the most practically instructive trial in this review for clinicians working in settings where sulphonyl-ureas remain dominant. [15] Equivalent cardiovascular and mortality outcomes across a longer follow-up than any other DPP-4 CVOT, combined with a dramatically lower hypoglycemia burden (2.1% vs. 11.1%), means that in a patient where the choice genuinely is between a gliptin and a sulphonyl-urea, the gliptin achieves at least as good an outcome with meaningfully less harm from low blood sugar. This matters mostly in populations engaged in manual labor, in elderly patients with impaired hypoglycemia awareness, and in settings without reliable access to glucose supplementation, all characteristics prevalent across sub-Saharan Africa and other low-resource contexts[33]. [2, 15]

4.5 Implications for Clinical Practice

The evidence reviewed here supports DPP-4 inhibitors as effective, safe, and well-tolerated second- or third-line agents in T2DM, particularly in patients where hypoglycemia avoidance is a priority, in those with

moderate CKD (especially linagliptin), and in settings where SGLT2 inhibitors and GLP-1 receptor agonists are inaccessible or unaffordable. [4, 5, 17] What the evidence does not support is their use as preferred agents specifically for mortality reduction in patients with established cardiovascular disease, a space now occupied by SGLT2 inhibitors and GLP-1 receptor agonists with moderate-to-high certainty evidence per current guideline recommendations[1].

4.6 Implications for Research

Significant evidence gaps persist. No adequately powered RCT has evaluated DPP-4 inhibitor mortality effects in a low-income country population, where T2DM phenotypes differ (leaner body habitus, earlier onset, higher rates of concurrent infection, less established cardiovascular risk management)[33] and sulphonyl-ureas remain first-line therapy by necessity. The CAROLINA trial provides the nearest analogue but drew its population predominantly from Europe, North America, and East Asia. [15] Platform trials that allow serial evaluation of sequential glucose-lowering regimens, or trials with longer follow-up extending beyond the current 6-year maximum, may be needed to detect deferred mortality signals, if they exist, that are undetectable within current CVOT windows. Pharmacogenomic analyses of DPP-4 polymorphisms in diverse populations may also clarify whether subgroups exist that are particularly likely or unlikely to benefit from this drug class.

4.7 Limitations

This review has several limitations. Restriction to English-language publications may have excluded relevant data, though all major CVOTs were reported in English. The search window of 2015–2025, while capturing the entire era of contemporary DPP-4 CVOT evidence, excludes earlier pharmacokinetic and safety trials from the pre-approval period; this was a deliberate protocol decision rather than an oversight. The descriptive synthesis, while appropriate given heterogeneity, does not yield the quantitative precision of a pooled meta-analysis. Finally, between-trial variability in outcome definitions, particularly the distinction between 3P- and 4P-MACE, required careful attention during data extraction and limits direct numerical comparisons across trials.[9, 10]

5. Conclusion

Based on a systematic review of 14 RCTs, including five major cardiovascular outcome trials enrolling more than 47,000 adults with T2DM, this review concludes that DPP-4 inhibitors are cardio-vascularly safe but do not demonstrate a statistically significant reduction in all-cause or cardiovascular mortality compared with placebo or active OHAs. The certainty of this conclusion is rated moderate. Their clinical value rests on glycemic efficacy, tolerability, hypoglycemia sparing, and practical suitability in complex patient populations rather than mortality superiority. Future trials in lower-risk and lower-resource settings, where sulphonyl-ureas are the dominant alternative, will be important for determining whether the mortality-neutral conclusion generalizes to the global T2DM population [1, 2, 15]

Abbreviations

T2DM: Type 2 diabetes mellitus; DPP-4: Dipeptidyl peptidase-4; OHA: Oral hypoglycaemic agent; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO: International Prospective Register of Systematic Reviews; RCT: Randomised controlled trial; CVOT: Cardiovascular outcome trial; HbA1c: Glycated haemoglobin; GLP-1: Glucagon-like peptide-1; GIP: Glucose-dependent insulinotropic polypeptide; FDA: Food and Drug Administration; HR: Hazard ratio; CI: Confidence interval; GRADE: Grading of Recommendations, Assessment, Development and Evaluations; RoB 2: Cochrane Risk of Bias tool version 2; 3P-MACE: Three-point major adverse cardiovascular events; 4P-MACE: Four-point major adverse cardiovascular events; CV: Cardiovascular; HF: Heart failure; CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate; SGLT2: Sodium-glucose cotransporter-2; SDF-1α: Stromal cell-derived factor-1 alpha; RAAS: Renin-angiotensin-aldosterone system; ACS: Acute coronary syndrome; MACE: Major adverse cardiovascular events; SSA: Sub-Saharan Africa; IDF: International Diabetes Federation; T1DM: Type 1 diabetes mellitus; MeSH: Medical Subject Headings; QCRI: Qatar Computing Research Institute; ADA: American Diabetes Association; EASD: European Association for the Study of Diabetes; ESC: European Society of Cardiology; OR: Odds ratio; PROBE: Prospective, Randomised, Open-label, Blinded-Endpoint; TZD: Thiazolidinedione; SU: Sulphonylurea; NP-Y: Neuropeptide Y; PYY: Peptide YY; BNP: Brain natriuretic peptide

Declarations

Funding: This review received no external funding and was conducted by the review team in their own time.

Competing Interest: No author declares any conflict of interest relevant to this review.

Ethics Approval: This review analyzed only previously published, publicly available data and did not require ethical approval.

Consent for publication: Not applicable.

Availability of data and materials: All data generated and analyzed during this study are included in this article and its supplementary information files.

Authors Contribution: IA conceived and designed the study, developed the search strategy, and led the title, abstract, and full-text screening process. CD, CN, and LM contributed to the execution of the search strategy and participated in the screening of records for eligibility. JM conducted the data extraction, performed the quality assessment of included studies, carried out the formal analysis and synthesis of evidence, and drafted the manuscript. JN, AM, and MF reviewed and critically appraised the manuscript for important intellectual content. All authors read and approved the final manuscript.

The initials map as: IA = Issack Alio, CD = Calvin David, CN = Chepkirui Naomi, LM = Lilian Mumbi, JM = Joel Mumo, AM = Annette Maina, MF = Mwenda Faith, JN=Jimmy Njoroge.

Clinical trial number: Not applicable.

PROSPERO Registration: CRD420251108505.

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Figures

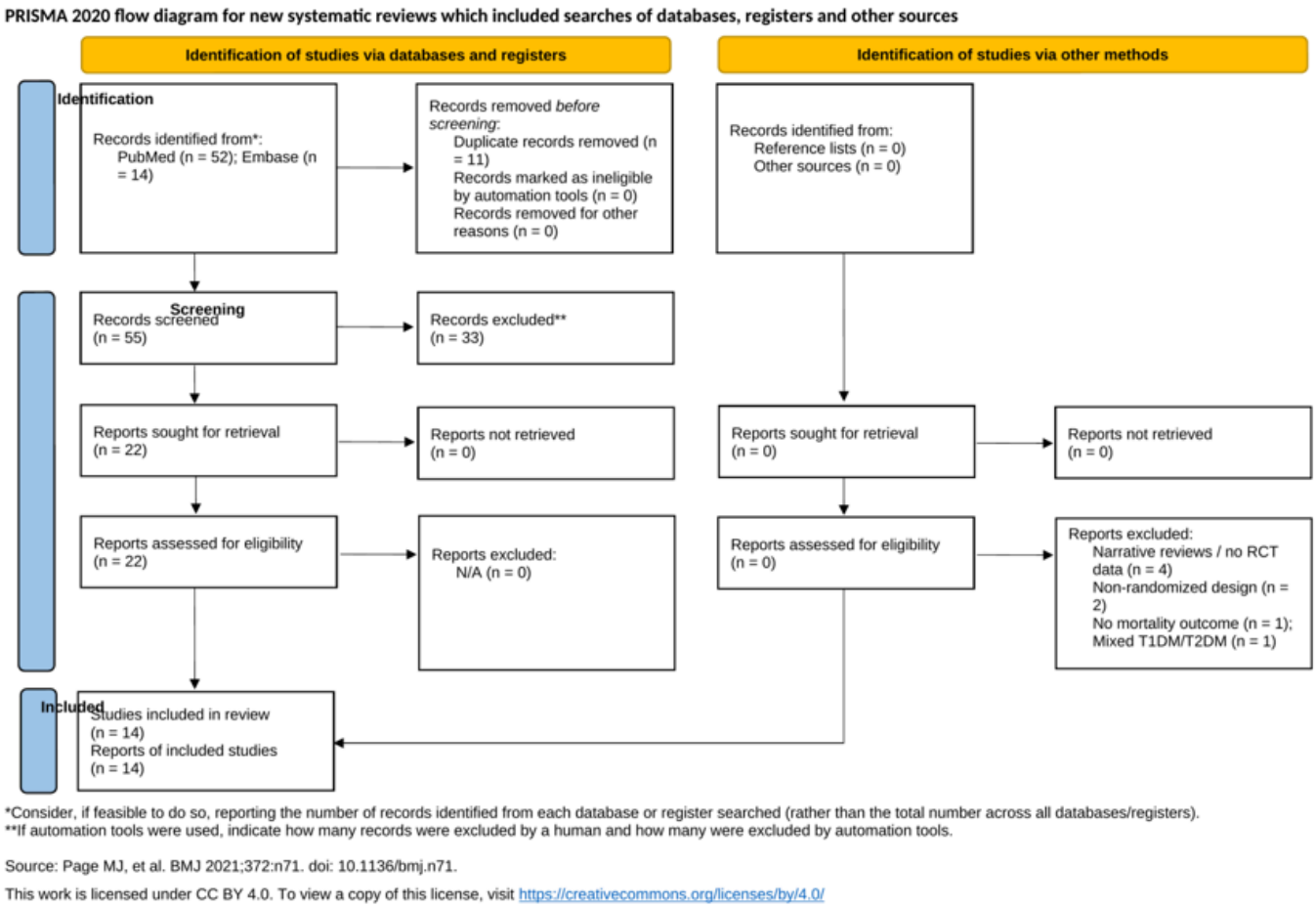


Figure 1

PRISMA 2020 flow diagram illustrating the study selection process for the systematic review of DPP-4 inhibitor mortality outcomes in T2DM (search period: January 2015–January 2025).

Supplementary Files

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