



The Effect of Dipeptidyl Peptidase-4 Inhibitors on Macrovascular and Microvascular Complications of Diabetes Mellitus: A Systematic Review

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ABSTRACT

Background: The World Health Organization estimates that diabetes is the seventh leading cause of death. Uncontrolled diabetes may cause severe consequences such as cardiovascular (CV) events (myocardial infarction, stroke, or CV mortality), lower-extremity amputations, and end-stage renal disease. Microvascular complications include retinopathy, autonomic and peripheral neuropathy, nephropathy, and diabetic ulcers. Major CV outcomes trials that were by the Food and Drug Administration for all new antihyperglycemic medications for patients at high risk for CV events were recently completed for all 4 US-marketed dipeptidyl peptidase-4 (DPP-4) inhibitors.

Objective: To present a comprehensive review of the clinical trials that evaluate macrovascular and microvascular complications reported with DPP-4 inhibitors in patients with type 2 diabetes mellitus.

Methods: In this review, we analyzed published articles in PubMed and Ovid databases between January 2008 and September 2019 that evaluated the effect of DPP-4 inhibitors on macrovascular and microvascular complications in patients with type 2 diabetes mellitus.

Results: A total of 18 studies, which included randomized controlled trials and meta-analyses were assessed. Current evidence demonstrates that the addition of DPP-4 inhibitors to standard antihyperglycemic and CV risk reduction treatment has not shown CV benefit relative to placebo in contrast to recently published studies for other medications within the glucagon-like peptide 1 agonist and sodium-glucose co-transporter 2 inhibitor classes. Notably, the potential risk for heart failure hospitalizations may exist for saxagliptin, and this effect is not extrapolated as a class effect. Based on our review, DPP-4 inhibitors may not influence microvascular complications in patients with diabetes. However, some studies have shown that saxagliptin and linagliptin may slow down the progression of albuminuria in patients with type 2 diabetes mellitus. The overall quality of the studies included in this review was high due to the inclusion of randomized controlled trials and meta-analyses.

Conclusions: DPP-4 inhibitors were found to have a neutral effect on macrovascular and microvascular complications, with the exception of saxagliptin, which may increase the risk for heart failure hospitalizations.

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Introduction

Recent American Diabetes Association guidelines recommend that the selection of antihyperglycemic therapy includes consideration of the patient's complications of type 2 diabetes mellitus (T2DM) comorbidities, cardiovascular (CV) and renal risk factors.¹

Major CV outcomes trials that were mandated by the Food and Drug Administration (FDA) for all new antihyperglycemic medications in patients at high risk for CV events were recently completed for all 4 US-marketed dipeptidyl peptidase-4 (DPP-4) inhibitors.² Medications within drug classes such as sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists have shown to improve the incidence of CV death, nonfatal myocardial infarction (MI), or nonfatal stroke (3-point major adverse CV events [MACE]) and/or risk of chronic kidney disease (CKD) progression.^{3–8} There are also case reports of

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antihyperglycemia drugs causing microvascular complications that led to changes to FDA labeling to include risk of amputations for canagliflozin.⁹

DPP-4 inhibitors are a class of oral glucose-lowering drugs that dependently increase insulin secretion and lower glucagon secretion. In the United States, there are 4 FDA-approved DPP-4 inhibitors: sitagliptin, saxagliptin, linagliptin, and alogliptin. This class of medications has a favorable profile of being weight-neutral with minimal hypoglycemia risk. Publications about sitagliptin, saxagliptin, and alogliptin have evaluated the CV safety in previous prospective randomized controlled trials (RCTs). Recently, results of 2 new trials were published evaluating the CV safety of linagliptin.^{15,16}

The purpose of this article is to present a comprehensive review of the clinical trials that evaluate macrovascular and microvascular complications reported with DPP-4 inhibitors in patients with T2DM.

Methods

Study design

This systematic review was performed according to the recommendations from the Preferred Reporting Items for Systematic Review and Meta-analysis statement.¹⁰ The study was registered with PROSPERO, the prospective international register of systematic reviews.

Eligibility criteria

Studies were considered relevant if they were RCTs or meta-analyses, and 1 treatment arm had received a DPP-4 inhibitor and if outcomes evaluated the effect of DPP-4 inhibitors on macrovascular or microvascular complications of T2DM. Studies were excluded if outcomes studied secondary biomarkers of diseases with the exception of nephropathy, in vitro studies, Phase I and II clinical trials, meta-analyses that included other classes of antihyperglycemic medications, systematic reviews, combined systematic reviews and meta-analyses, and post hoc analysis of baseline characteristics and outcomes (see Table 1).

Outcome measures

The primary outcome was to determine the effect of DPP-4 inhibitors on macrovascular and microvascular complications of T2DM. Macrovascular complications were identified as a composite of CV outcomes (3-point and 4-point MACE) and hospitalization for heart failure (HF). Three-point MACE is defined as a composite of nonfatal stroke, nonfatal MI, and CV death. Four-point MACE is defined as a composite of nonfatal stroke, nonfatal MI, CV death, and hospitalization for unstable angina. Microvascular complications and related conditions were identified as retinopathy, nephropathy, the presence of albuminuria, neuropathy, diabetic ulcers, and amputations. Other outcomes include evaluating the effect of DPP-4 inhibitors on biomarkers of nephropathy, such as changes in estimated glomerular filtration rate (eGFR) and urinary albumin creatinine ratio (UACR) from baseline, and on composite renal outcomes.

Study selection

Four investigators (CL, OT, Danyang Zhou, Carrie Respondek) performed a literature search of PubMed and Ovid between January 2008 to September 2019 using the terms *DPP-4 inhibitors* or *Dipeptidyl Peptidase-4 Inhibitors* or *sitagliptin* or *saxagliptin* or *alogliptin* or *linagliptin* combined with *cardiovascular outcomes* or

microvascular complications or *retinopathy* or *nephropathy* or *albuminuria* or *neuropathy* or *diabetic ulcer* or *amputation*. Articles were further limited to the English language, human studies, meta-analyses, and Phase III and IV RCTs. Any disagreements on study eligibility were resolved by the 2 primary investigators (CL and OT) (see the Figure 1).

Data collection

Due to the different outcomes assessed in each trial and the heterogeneity of the population, a formal meta-analysis of the included studies was not performed. A descriptive analysis of the data was provided in the form of a systematic qualitative review. The following data points were extracted: study design, study size, study duration, treatment arms, and primary and secondary outcomes. The risk of bias was assessed using the Cochrane risk-of-bias tool for randomized controlled trials (see Table 2).¹¹

Results

A total of 627 titles and abstracts were screened, and a total of 35 studies were identified for a full review. Eighteen studies met the inclusion criteria (see the Figure 1). Common reasons for exclusion were qualitative systematic reviews, a combination of meta-analyses and systematic reviews, Phase I and II clinical trials, post hoc analysis of baseline characteristics and/or outcomes, and studies with outcomes evaluating biomarkers for progression of the disease except for nephropathy. Common treatment arms in RCTs were DPP-4 inhibitors versus placebo, DPP-4 inhibitors versus sulfonylurea, and DPP-4 inhibitors versus glucagon-like peptide-1 agonists. The outcomes of interest explored the effect of DPP-4 inhibitors on macrovascular or microvascular complications of T2DM. An excellent interobserver agreement was observed in the final selection of included studies.

Cardiovascular outcomes

A total of 54 titles and abstracts were screened for CV complications and 13 studies were identified for a full review. Eleven

Table 1
Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Prospective randomized controlled trials	Narrative reviews, post-hoc analyses, subgroup analyses
Meta analyses of DPP-4 inhibitors (quantitative systematic reviews)	Qualitative systematic reviews, combination qualitative systematic reviews and meta-analysis, meta-analysis that include other classes of antihyperglycemic medications
Phase III, IV clinical trials	Phase I, II or in-vitro studies
RCT looking at these outcomes: cardiovascular (3- and 4-point MACE) nephropathy, neuropathy, retinopathy, diabetic foot ulcer, amputation	Outcomes of glycemic efficacy, other outcomes not listed under inclusion criteria
• Definition of clinical nephropathy includes change of eGFR, change in urinary albumin, and/or percentage of patients progressing to ESRD	
• Definition of clinical diabetic foot ulcer and amputation includes markers of wound healing	
Treatment arm containing any of US marketed DPP-4 inhibitors	Biomarkers of disease (secondary markers of disease)

DPP-4 = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; MACE = major adverse cardiovascular events; RCT = randomized controlled trials.

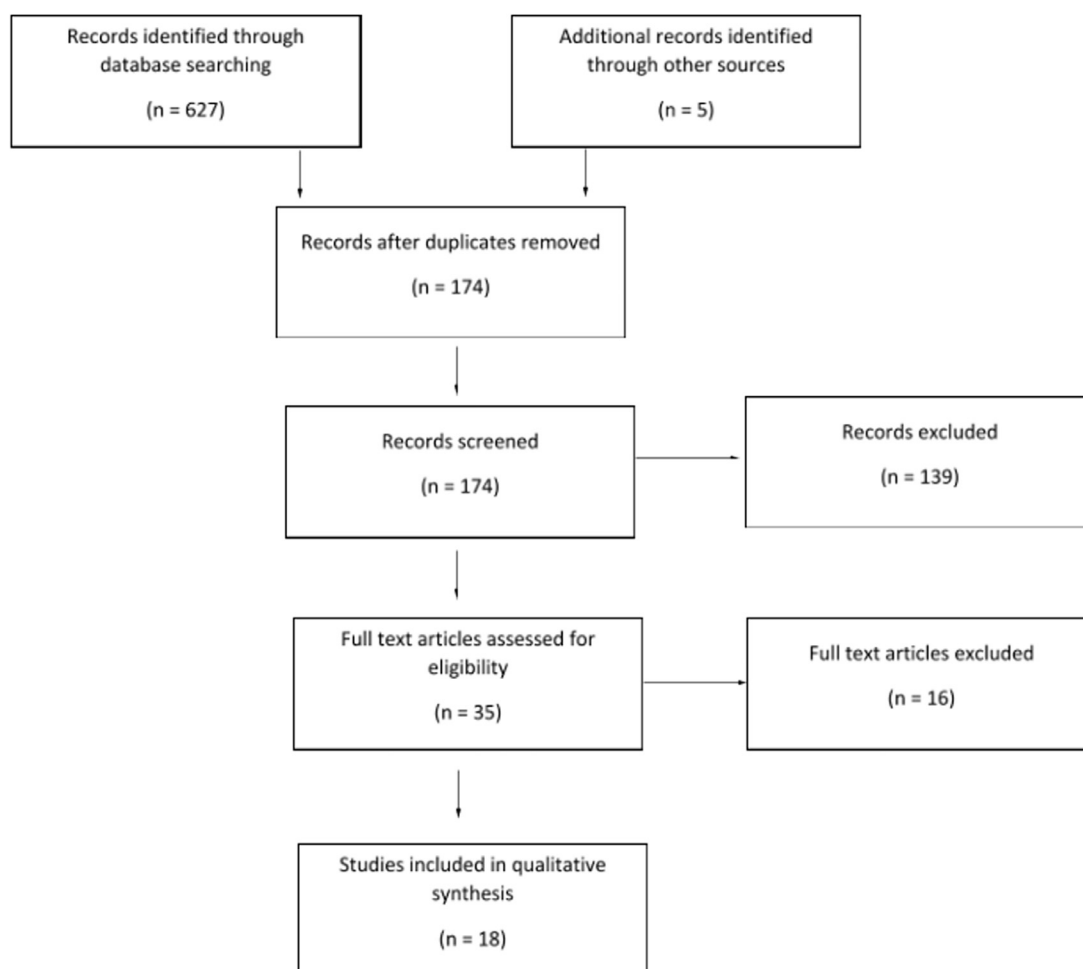


Figure 1. Study screening and selection.

studies met the inclusion criteria. Therefore, 6 meta-analyses, and 5 prospective RCTs have described the CV safety and efficacy of DPP-4 inhibitors (Table 3).

Prospective RCTs

All 4 of the US-marketed DPP-4 inhibitors have completed randomized MACE trials mandated by the FDA to assess CV safety with respect to placebo.

Alogliptin. A prospective, double-blind, noninferiority, randomized, placebo-controlled, Phase IV trial, Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes (EXAMINE), evaluated the rates of major adverse CV events in patients with T2DM at very high CV risk who had a recent acute coronary syndrome. Patients were randomized to receive alogliptin 6.25 to 25 mg based on renal function versus placebo in addition to standard of care for CV risk factors and treatment for T2DM. Baseline characteristics were similar between the 2 groups; the mean duration of T2DM was 7.3 years in the placebo and 7.1 years in the treatment group, respectively. Recent acute coronary syndromes were defined as MI or unstable angina requiring hospitalization within 15 to 90 days before randomization. This trial demonstrates similar rates of major CV events with alogliptin to that of placebo for the primary end point of 3-point MACE (11.3% vs 11.8%, respectively; $P < 0.0001$ for noninferiority). The principal secondary end point for alogliptin was the primary composite end point with the addition of urgent revascularization due to unstable angina within 24 hours after hospitalization (12.7% vs 13.4%, respectively; hazard ratio [HR], 0.95;

the upper boundary of repeated 1-sided CI, 1.14). This trial demonstrates that in patients at very high risk of CV disease, rates of major adverse CV events were neither significantly increased or decreased with alogliptin compared with placebo. Rates of hospitalizations for HF were not evaluated in the a priori analysis of the trial, and thus not included in this systematic review.¹²

Saxagliptin. A multicenter, randomized, double-blind, placebo-controlled, Phase IV trial, Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus (SAVOR-TIMI 53), evaluated the safety and efficacy of DPP-4 inhibition with saxagliptin versus placebo on MACE in patients with T2DM who had a history of or were at risk for CV events. Patients were randomized to saxagliptin 2.5 to 5 mg renally adjusted based on eGFR versus placebo in a 1:1 ratio in addition to background therapy for the treatment of T2DM and CV risk factors. Baseline characteristics were similar between the 2 groups, with 78.4% of patients in the placebo and 78.7% of patients in the saxagliptin group having had established CV disease. Patients at risk of CV events included men aged 55 years or older or women aged 60 years or older with at least 1 of the following: dyslipidemia, hypertension, or active smoking. The study demonstrated that for the primary outcome of 3-point MACE the addition of saxagliptin compared with placebo to standard of care treatment for T2DM and CV disease neither reduced nor increased the risk of the primary composite end point of CV death, nonfatal MI, or nonfatal ischemic stroke (7.3% vs 7.2%, respectively; HR, 1.00; CI, 0.89–1.12; $P < 0.001$ for noninferiority). The major secondary end point for saxagliptin versus placebo for a

Table 2
Cochrane Collaboration tool for assessment of risk of bias in randomized controlled trials.¹¹

Trial	Statistical analysis		Selection bias		Performance bias		Detection bias blinding		Attribution bias		Reporting bias		Other bias	
	Modified ITT	ITT for secondary and to corroborate PP	Random sequence generator	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Anything else, ideally prespecified					
EXAMINE ¹²	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
SAVOR-TIMI 53 ¹³	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
TECOS ¹⁴	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	Unclear risk
CAROLINA ¹⁵	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
CARMELINA ¹⁶	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Ferreira JCA, et al. ²³	Low risk	Low risk	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Mori H, et al. ²⁴	Unclear risk	Unclear risk	Unclear risk	Unclear risk	High risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Tonnejck L, et al. ²⁵	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
MARLINA-T2D ²⁶	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Han SY, et al. ²⁷	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
McGill JB, et al. ²⁸	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Ott C, et al. ²⁹	Low risk	Low risk	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk

ITT = intention to treat; PP = per protocol.

composite CV death, MI, stroke, hospitalization for unstable angina, coronary revascularization, or HF was 12.8% versus 12.4%, respectively ($P=0.66$). Notably, a statistically significant finding demonstrated that more patients in the saxagliptin group than in the placebo group were hospitalized for HF (3.5% vs 2.8%, respectively; HR, 1.27; 95% CI, 1.07–1.51).¹³

Sitagliptin. A randomized, double-blind, placebo-controlled, event driven trial, Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes (TECOS), evaluated the safety and efficacy of DPP-4 inhibition with sitagliptin versus placebo in patients with T2DM and established CV disease. Patients were randomized to sitagliptin 50 to 100 mg based on renal function versus placebo in a 1:1 ratio in addition to background therapy for T2DM and CV disease. Baseline characteristics were similar between the 2 groups, 73.6% of patients in the sitagliptin versus 74.5% of patients in the placebo group had established CV disease. For the primary outcome of 4-point MACE, the study demonstrated that the addition of sitagliptin compared with placebo to usual care did not affect rates of major atherosclerotic CV disease events (11.4% vs 11.6%, respectively; HR, 0.98; CI 0.89–1.09). The secondary outcome of 3-point MACE occurred in 10.2% and 10.2% of patients receiving sitagliptin and placebo, respectively. Additionally, sitagliptin therapy compared with placebo was not associated with changes in rates of hospitalizations for HF (3.1% vs 3.1%, respectively; HR, 1.00; CI, 0.83–1.20).¹⁴

Linagliptin. A randomized, double-blind, active-controlled, noninferiority trial, Effect of Linagliptin vs Glimepiride on Major Adverse Cardiovascular Outcomes in Patients with Type 2 Diabetes: the CAROLINA Randomized Controlled Trial, evaluated the safety of DPP-4 inhibition with linagliptin versus glimepiride in patients with T2DM and elevated CV risk. Elevated CV risk was defined as documented atherosclerotic CV disease, presence of multiple CV risk factors, aged at least 70 years, and evidence of microvascular complications. Baseline characteristics were similar between the 2 groups, with 42% of enrolled participants diagnosed with CV disease, and <5% of patients in both groups having had a prior history of HF. The study demonstrated that the addition of linagliptin to standard therapy compared with glimepiride to standard of care resulted in rates of primary outcome of 3-point MACE that were noninferior (11.8% vs 12%, respectively; HR 0.98, CI 0.84–1.14). The secondary outcome of 4-point MACE occurred in 13.2% versus 13.3% of patients receiving linagliptin, respectively (HR, 0.99; CI, 0.86–1.14). The rates for HF hospitalizations were 3.7% and 3.1% for linagliptin and glimepiride, respectively (HR, 1.21; CI, 0.92–1.59).¹⁵

A randomized, double-blind, placebo-controlled trial, 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, evaluated the safety and efficacy of linagliptin versus placebo in patients with T2DM and elevated CV and renal risk. High CV risk was defined as a history of coronary artery disease, stroke, or peripheral vascular disease and microalbuminuria or macroalbuminuria, defined as UACR higher than 30 mg/g or equivalent. High renal risk was defined as eGFR 45 to 75 mL/min/1.73 m² and UACR higher than 200 mg/g or equivalent or eGFR 15 to 45 mL/min/1.73 m² regardless of UACR. Patients were randomized to linagliptin 5 mg/d versus placebo in addition to antihyperglycemic medications and treatment for CV risk factors. Baseline characteristics were similar between the 2 groups: 57% of patients had CV disease, 75% had kidney disease, and 33% had both CV disease and kidney disease. The study demonstrated that the addition of linagliptin to patients with CV disease and kidney disease was noninferior to placebo for occurrence of 3-point MACE when added to standard of care on effects of CV risk (12.4% vs 12.1%, respectively; HR, 1.02; CI, 0.89–1.17).¹⁶

Table 3
Cardiovascular outcomes in randomized controlled trials.

DPP-4 inhibitor	Study (y)	Duration (median y)	Arms (n)	Primary outcome	Primary outcome result (intervention vs control)	Secondary outcome	Secondary outcome result (intervention vs control)	Hospitalization for HF (intervention vs control)
Alogliptin	EXAMINE (2013) ¹²	1.5	Alogliptin (2701) Placebo (2679)	Composite of CV death, nonfatal MI, or nonfatal stroke (3-point MACE)	11.3% vs 11.8% HR, 0.96; upper boundary of 1-sided repeated CI ≤ 1.16	Composite of CV death, nonfatal MI or nonfatal stroke, urgent revascularization due to unstable angina within 24 h after hospital admission (4-point MACE)	12.7% vs 13.4% HR, 0.95; upper boundary of 1-sided CI ≤ 1.14	N/A
Saxagliptin	SAVOR-TIMI 53 (2013) ¹³	2.1	Saxagliptin (8280) Placebo (8212)	Composite of CV death, nonfatal MI, or nonfatal stroke (3-point MACE)	7.3% vs 7.2% HR, 1.00; CI 0.89–1.12	Composite of CV death, myocardial infarction, stroke, hospitalization for unstable angina, coronary revascularization, or HF	12.8% and 12.5% HR, 1.01, CI, 0.94–1.11	3.5% vs 2.8% HR, 1.27; CI, 1.07–1.51; $P=0.007$
Sitagliptin	TECOS (2015) ¹⁴	3.0	Sitagliptin (7332) Placebo (7339)	Composite of CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina (4-point MACE)	11.4% vs 11.6% HR, 0.98; CI, 0.89–1.08	Composite of CV death, nonfatal MI, or nonfatal stroke (3-point MACE)	10% vs 10.2% HR, 0.99; CI 0.89–1.10	3.1% vs 3.1% HR, 1.0; CI, 0.83–1.20
Linagliptin	CAROLINA (2019) ¹⁵	6.3	Linagliptin (3023) Glimepride (3010)	Composite of CV death, nonfatal MI, or nonfatal stroke (3-point MACE)	11.8% vs 12% HR, 0.98; CI, 0.84–1.14	Composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina pectoris	13.2% vs 13.3% HR, 0.99; CI, 0.86–1.14	3.7% vs 3.1% HR, 1.21; CI, 0.92–1.59
	CARMELINA (2019) ¹⁶	2.2	Linagliptin (3494) Placebo (3485)	Composite of CV death, nonfatal MI, or nonfatal stroke (3-point MACE)	12.4% vs 12.1% HR, 1.02; CI, 0.89–1.17	N/A	N/A	N/A

CV = cardiovascular; DPP-4 = dipeptidyl peptidase-4; HF = heart failure; HR = hazard ratio; MACE = major adverse cardiovascular events; MI, myocardial infarction; N/A, not available.

Meta-analyses

A total of 6 meta-analyses met the inclusion criteria after screening. Older studies indicated that DPP-4 inhibitors are either safe or reduce the risk of MACE, particularly MI and all-cause mortality in patients with T2DM.^{17,18} A subsequent meta-analysis that included the data from the SAVOR-TIMI 53 and Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes (EXAMINE) trials did not observe any significant differences in the pooled odds of 3-point MACE with the DPP-4 inhibitors.²⁰ However, a meta-analysis exploring the class effect on the risk of HF, determined that treatment with DPP-4 inhibitors was associated with a statistically increased risk of acute HF (odds ratio, 1.19; CI, 1.03–1.37).²⁰ Further exploring the effect on HF, a meta-analysis sought to analyze whether a differential effect for each DPP-4 inhibitor was present. Use of saxagliptin significantly increased the risk of HF by 21%, especially among patients with high CV risk, whereas no signals of such an effect were detected with the other agents in the DPP-4 inhibitor class.²¹ Finally, a meta-analysis found that the risk of mortality, CV mortality, MI, or ischemic stroke was similar between treatment with DPP-4 inhibitors and placebo. As a class, this study found that there is only weak evidence for an increased risk of heart failure.²² Despite mixed results reported with prior meta-analysis, the most recent evidence points to a neutral effect on MACE with the addition of DPP-4 inhibition to standard therapy.

Nephropathy. Ten articles were selected to evaluate the effect of DPP-4 inhibitors on nephropathy. Table 4 summarizes each trial's clinical renal outcome and end points. There was 1 prospective trial that looked at the effect of alogliptin, 1 for saxagliptin, 4 for sitagliptin, and 4 for linagliptin.

Alogliptin. The EXAMINE trial evaluated the mean change in eGFR from baseline and rates of initiation of renal replacement therapy in patients on alogliptin compared with glimepiride. Baseline characteristics were similar between the 2 groups; mean (SD) eGFR was 71.2 mL/min/1.73 m² and 71.1 mL/min/1.73 m² in the treatment group, respectively. Also, the percentage of patients on a renin-angiotensin-aldosterone blocking agent in the treatment group were similar to the placebo group (82.5% vs 81.5%, respectively). Changes in eGFR from baseline were similar regardless of baseline and rates of initiation of dialysis were similar in the treatment group compared with the placebo group (0.8% vs 0.9%, respectively; $P=0.88$). This study showed that alogliptin did not influence renal function indices with any statistical differences but was not powered to detect a difference for these end points.¹²

Saxagliptin. The SAVOR-TIMI 53 trial evaluated the mean change in eGFR, change from baseline in UACR, and the composite renal clinical outcome (doubling of creatinine level, initiation of dialysis, renal transplantation, or creatinine >6 mg/dL). Both the saxagliptin and placebo arms were balanced with regard to baseline mean (SD) eGFR (72.5 mL/min/1.73 m² [22.6] vs 72.7 mL/min/1.73 m² [22.6], respectively) and median UACR (1.8 mg/g vs 1.9 mg/g, respectively), and the number of patients on angiotensin-converting enzyme inhibitor (28.2% vs 27.6%, respectively; $P=0.09$) or angiotensin receptor blocker (28.2% vs 27.6%, respectively; $P=0.38$). At the 1-year mark after study initiation, the treatment arm had a higher incidence of improved UACR compared with the treatment arm (11.8% vs 9.6%, respectively), and saxagliptin continued to reduce the development and progression of microalbuminuria by the end of study (10.7% vs 8.7%, respectively). There were no statistical differences in doubling of serum creatinine, initiation of chronic dialysis, renal transplant, or serum creatinine >6 mg/dL, and the composite end point of death between the saxagliptin and placebo. This study shows that saxagliptin may reduce or prevent

the progression of microalbuminuria but has no influence on renal outcomes of doubling creatinine level, initiating dialysis, renal transplantation, or creatinine >6 mg/dL.¹³

Sitagliptin. The Efficacy and Safety of Sitagliptin Versus Glipizide in Patients with Type 2 Diabetes and Moderate-to-Severe Chronic Renal Insufficiency was a multinational, randomized, double-blinded, parallel-group trial. Study participants had moderate to severe chronic renal insufficiency (eGFR <50 mL/min/1.73 m²). Patients were randomized to receive sitagliptin 25 to 50 mg/d based on eGFR versus glipizide 2.5 to 20 mg/d. Baseline characteristics were similar between both groups; the mean duration of T2DM was 10.7 years in the treatment group. Majority of the patients in the treatment and placebo arms had moderate CKD (72.6% vs 74.6%, respectively) compared with patients with severe CKD at baseline (sitagliptin 27.4% vs glipizide 25.4%). There were no differences between the treatment arm versus the placebo arm in the change of eGFR from baseline (−3.9 mL/min/1.73 m² vs −3.3 mL/min/1.73 m², respectively), change from baseline in UACR (+6.8 mg/g vs +12.4 mg/g, respectively), and rates of patients developing severe renal insufficiency. More patients in the sitagliptin arm had moderate CKD at baseline that progressed to severe renal insufficiency compared with the placebo arm (18.8% vs 11%, respectively). This study did not show any meaningful differences in changes from baseline in eGFR and UACR between arms. This study had some limitations, such as a short treatment duration of 54 weeks, and did not evaluate other renal outcomes.²³

An open-label, prospective, randomized study conducted by Mori and colleagues²⁴ evaluated the effect of sitagliptin on microalbuminuria in patients with T2DM. The primary outcome of this study was the change in log UACR at 6 months. Patients were randomized to receive either sitagliptin 50 mg/d or other oral glucose agents such as metformin, glinide, or alpha-glucosidase inhibitor. Baseline characteristics were similar between both arms; the mean (SD) eGFR for the sitagliptin arm was 77.1 (18.9) mL/min/1.73 m² as compared with the placebo arms of 75.5 (28.1) mL/min/1.73 m². At 6 months, the treatment group had a significant change in log UACR compared with the placebo group (−23.3% [37.3%] vs +0.8% [192%], respectively; $P=0.001$). The treatment arm was further divided into 2 subgroups according to the baseline UACR, patients with a baseline log UACR ≥ 30 mg/g compared with those with a baseline UACR <30 mg/g. The decrease in log UACR was significant in both groups, but there were no significant differences between the 2 subgroups in the percentage change in log UACR. There was no statistically significant difference between the percentage change in eGFR from baseline between the treatment arm versus placebo arm (−3.7% [8.2] vs −4.8% [1.8], respectively). This study demonstrated that sitagliptin could reduce UACR excretion in patients with T2DM without CKD.²⁴

The TECOS trial also looked at changes from baseline eGFR and UACR. At baseline, the eGFR (74.9 [21.3] mL/min/1.73 m² vs 74.9 [20.9] mL/min/1.73 m², respectively) and median UACR (10.3 mg/g vs 11.4 mg/g, respectively) were similar between the treatment arm versus the placebo arm. Only 9.5% of patients in the treatment arm had CKD, eGFR <50 mL/min/1.73 m², compared with 9.4% of patients in the placebo arm. Also, the percentages of patients on renin-angiotensin-aldosterone system blocking agents were similar between the treatment arm compared with the placebo arm (78.3% vs 79.2%, respectively). In the trial, change in eGFR from baseline was greater in the sitagliptin group compared with the placebo group (−4 [18.4] mL/min/1.73 m² vs −2.8 [18.3] mL/min/1.73 m², respectively). Unfortunately, Only 26% of patients had UACR data. Among those with UACR data, the median difference in UACR was slightly lower for the sitagliptin group (−0.18 mg/g; 95% CI, −0.35 to −0.02; $P=0.031$), but the clinical relevance is questionable. The incidence of microalbuminuria (7.8% vs 7.9%, respectively) and renal

Table 4
Renal markers and outcomes.

DPP-4 inhibitor	Study	Duration	Arms (n)	Renal status	Baseline eGFR (mL/min/1.73 m ²)	Change in eGFR (mL/min/1.73 m ²) (P value)	Baseline UACR mg/g	Change in UACR (P value) (mg/g)	Renal dialysis	Composite renal outcomes (HR)
Sitagliptin	Tonneijck L, et al. ²⁵	12 wk	Sitagliptin (19) Liraglutide (19) Placebo (17)	No CKD	Sitagliptin 87 (15)* Placebo 83 (19)*	Sitagliptin -6 (95% CI, -14 to 3) P=0.169	Sitagliptin 124.4 (54.3-463.8) [†]	-32 (95% CI, -69 to 46)	-	-
	Mori H, et al. ²⁴	26 wk	Sitagliptin (41) OGA (44)	No CKD	Sitagliptin 77.1 (18.9)* OGA 75.5 (28.1)*	Sitagliptin -3.7 (8.2)* OGA -4.8 (39.6)* P=NS	Sitagliptin 68.9 (133.4)* OGA 61.4 (154.3)*	Sitagliptin -36.3 (43.3)* OGA +1125 (255)* P < 0.001	-	-
	Ferreira JCA, et al. ²³	54 wk	Sitagliptin (211) Glipizide (212)	eGFR <50 mL/min/1.73 m ²	35.6 (10.9)*	Sitagliptin -3.9 Glipizide -3.3 P=NS	Sitagliptin 107.7 (170)*	Sitagliptin +6.8 Glipizide 12.4 P=NS	-	-
	TECOS ¹⁴	3.1 y	Sitagliptin (7257) Placebo (7266)	No CKD	Sitagliptin 74.9 (21.3)* Placebo 74.9 (20.9)*	Sitagliptin -1.34 (95% CI -1.76 to -0.91) P < 0.0001	Sitagliptin 10.3 (3.5 to 34.6) [†] Placebo 11.4 (3.6 to 36.2) [†]	Sitagliptin -0.18 (-0.35 to -0.02) [†] P=0.031	-	Renal failure 0.9
Saxagliptin	SAVOR-TIMI 53 ¹³	2.1 y	Saxagliptin (8280) Placebo (8212)	Included CKD	Saxagliptin 72.5 (22.6)* Placebo 72.7 (22.6)*	Saxagliptin -0.13 (P = .5794)	Saxagliptin 1.8 (0.7 to 7.5) [†] Placebo 1.9 (0.7 to 7.9) [†]	<u>Worsened</u> Saxagliptin: 833 patients (13.3%) Placebo: 969 patients (15.9%) <u>No change</u> Sitagliptin: 4762 (76%) Placebo: 4594 patients (75.4%) <u>Improved</u> Sitagliptin: 670 patients (10.7%) Placebo: 532 patients (8.7%) P < 0.001	0.9 (0.61 to 1.32) [†]	Doubling of creatinine level, initiation of dialysis, renal transplantation, or creatinine >6.0 mg/dL 1.08 (95% CI, 0.88 to 1.32) P=0.46
Lingliptin	MARLINA-T2D ²⁶	24 wk	Linagliptin (182) Placebo (178)	eGFR ≥30 mL/min/1.73 m ² UACR 30 to 3000	Linagliptin 75.4 (23.9)* Placebo 72.4 (24.4)*	None reported	Linagliptin 120.8 (152.9)* Placebo 131.9 (166.6)*	Linagliptin: -5.1% (95% CI, -11.4 to 1.6) Placebo: -6% (95% CI, -15 to 3) P=0.1954	-	-
	Han SY, et al. ²⁷	40 wk	Linagliptin (52) Gemigliptin (48)	eGFR 15 to 59 mL/min/1.73 m ²	Linagliptin 32.2 (10)* Gemigliptin 36.1 (15.2)*	Linagliptin -1.85 (5.09)* Gemigliptin -3.86 (6.24)* P=0.078	Linagliptin 290 (5.60 to 6718.3) [†] Gemigliptin 473.3 (4.60 to 7354.4) [†]	Linagliptin +31.6 (-1538.8 to +1727.1) [†] Gemigliptin +9.9 (-1447.3 to +4138.8) [†] P=0.499	-	-
	McGill JB, et al. ²⁸	52 wk	Linagliptin (68) Placebo (65)	eGFR <30 mL/min/1.73 m ²	Linagliptin 22.1 (6.3)* Placebo 25.1 (6.9)*	Linagliptin -0.8 Placebo -2.2	-	-	-	-
	CARMELINA ¹⁶	1.9 y	Linagliptin (2494) Placebo (3485)	Moderate to severe CKD	Linagliptin 54.7 Placebo 54.5	None reported	Linagliptin 162 (43 to 700) [†] Placebo 162 (44 to 750) [†]	-	1.8% vs 1.8%	Sustained ESRD, death due to kidney function, or sustained decrease of ≥40% in eGFR from baseline 1.04 (95% CI, 0.89 to 1.22) P=0.62

CKD = chronic kidney disease; DPP-4 = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; NS = not significant; OGA = Oral glucose-lowering agents; UACR = urinary albumin-to-creatinine ratio .

* Values are presented as mean (SD).

† Values are presented as median (interquartile range).

failure (1.4% vs 1.5%, respectively) were similar between the treatment compared with the placebo arm. This study showed that the addition of sitagliptin in patients with CV disease had a neutral influence on eGFR.¹⁴

A Phase IV, randomized, double-blinded, placebo-controlled, double-dummy, parallel-group, single-center trial evaluated the renal effects of sitagliptin 100 mg/d compared with liraglutide 1.8 mg/d, or placebo in obese patients during a 12-week treatment period. The primary end point was a change in GFR from baseline. Baseline characteristics were similar among the 3 arms; the mean (SD) GFR for the placebo arm was 83 mL/min/1.73 m² (19), the median GFR for the sitagliptin arm was 87 mL/min/1.73 m² (15), and the mean (SD) GFR for liraglutide was 79 mL/min/1.73 m² (14). The median duration of T2DM among all 3 groups was 6 years (range, 4–12 years). Neither sitagliptin or liraglutide arms (−6 mL/min/1.73 m²; 95% CI, −14 to 3; $P=0.169$ vs +3 mL/min/1.73 m²; 95% CI, −5 to 11; $P=0.464$) had significant changes in GFR compared with placebo. The mean difference between sitagliptin and placebo was not statistically significant (0.68 mg/mmol; range, 0.31–1.46 mg/mmol). This study concluded that neither sitagliptin nor liraglutide sustained changes in renal damages or alterations.²⁵

Linagliptin. The Efficacy, Safety, Modification of Albuminuria in Type 2 Diabetes Subjects with Renal Disease with Linagliptin was a randomized, placebo-controlled, multicenter, Phase IIIb clinical trial. Study participants had T2DM, glycated hemoglobin levels between 6.5 and 10%, eGFR ≥ 30 mL/min/1.73 m², body-mass index ≤ 40 kg/m², and evidence of renal dysfunction. The definition of renal dysfunction was albumin/urine range of 30 to 3000 mg/g, despite being on a renin-angiotensin-aldosterone system inhibitor. The renal efficacy end point was a time-weighted average of percentage change from baseline in UACR over 24 weeks of treatment, and the renal safety end point was the change from baseline in eGFR. Patients were randomized to receive either linagliptin or placebo. Baseline clinical characteristics were similar between both arms. Most patients in both arms had microalbuminuria and preserved kidney function of eGFR ≥ 60 mL/min/1.73 m². The mean (SD) UACR in the treatment arm was slightly higher than the placebo arm (120.8 mg/g [152.9] vs 131.9 mg/g [166.6], respectively). The renal efficacy end point showed a trend toward linagliptin reducing the time-weighted average of percentage change from baseline in UACR over 24 weeks compared with placebo (−11% vs −5.1%, respectively). The treatment difference in the time-weighted percentage change from baseline in UACR was not statistically significant (−6%; 95% CI, −15% to 3%; $P=0.1954$). In a post hoc analysis, there was no difference between participants receiving either a renin-angiotensin-aldosterone system inhibitor as therapy. There was no difference in mean change in eGFR between the 2 groups at weeks 6, 12, 18, and 24. Also, there were no new cases of end-stage kidney disease occurring during the study. This study suggested that linagliptin does not influence kidney function in patients with T2DM within 24 weeks of treatment.²⁶

The CARMELINA study evaluated renal outcomes, defined as time to the first occurrence of a composite of adjudication-confirmed end-stage renal disease (ESRD), death due to renal failure, or a sustained decrease of at least 40% in eGFR from baseline, among the secondary outcomes. Also, the exploratory renal end points included the composite of renal death or ESRD, microvascular composite outcome that includes albuminuria, sustained ESRD, sustained decrease of at least 50% in eGFR, death due to renal failure, and progression in albuminuria (change from normoalbuminuria to microalbuminuria/macrolalbuminuria or change from microalbuminuria to macrolalbuminuria). Baseline characteristics were similar amongst both arms. The difference in secondary renal composite outcome was not statistically significant between the

treatment arm compared with the placebo arm (9.4% vs 8.8%, respectively; HR, 1.04; 95% CI, 0.89–1.22; $P=0.62$). The exploratory composite renal outcomes, sustained ESRD, death due to renal failure, or sustained decrease of $>50\%$ in eGFR from baseline, also showed no difference between the linagliptin group compared with placebo (6.6% vs 6.5%, respectively; HR, 0.98; 95% CI, 0.82–1.18; $P=0.87$). There was also no difference between groups in rates of death due to renal failure or sustained ESRD (HR, 0.87; 95% CI, 0.69–1.10; $P=0.24$). The treatment arm showed that the progression of albuminuria category was less often than the placebo arm (35.5% vs 38.5%, respectively; HR, 0.86; 95% CI, 0.78–0.95; $P=0.003$). This study concluded that linagliptin, when added to usual care in adults with T2DM and high CV and renal risk, has a neutral effect on the renal outcomes over a median of 2.2 years.¹⁶

A randomized, placebo-controlled, double-blinded, Phase IIIb study, Comparative Efficacy and Safety of Gemigliptin versus Linagliptin in Type 2 Diabetes Patient with Renal Impairment: A 40-week extension of the GUARD randomized study, evaluated the long-term safety and efficacy of DPP-4 inhibition with linagliptin versus gemigliptin in patients with T2DM and moderate or severe renal impairment. Baseline characteristics were similar; 56% of the patients in the gemigliptin arm had moderate renal impairment, and 62% of patients in the linagliptin arm had moderate renal impairment. The median baseline UACR was slightly higher in the gemigliptin arm compared to the linagliptin arm (473.3 mg/g vs 290 mg/g, respectively). Also, 42% of patients in the gemigliptin arm were on renin-angiotensin-aldosterone system inhibitors compared with 39% of patients in the linagliptin arm. This study evaluated the following renal end points: changes in eGFR and UACR. Between groups, there was no difference in the percentage change in UACR in patients with macroalbuminuria. There was no difference in the change in eGFR (3.86 mL/min/1.73 m² vs 1.85 mL/min/1.73 m², respectively; $P=0.078$) or change in UACR (31.6 mg/g vs 9.9 mg/g; $P=0.499$) in both the linagliptin and gemigliptin arms. This study concluded that linagliptin has a neutral effect on eGFR and UACR in patients with T2DM and renal impairment.²⁷

A randomized, placebo-controlled, double-blinded, Long-Term Efficacy and Safety of Linagliptin in Patients with Type 2 Diabetes and Severe Renal Impairment, evaluated the efficacy and safety of DPP-4 inhibition with linagliptin versus placebo in patients with T2DM and severe renal impairment. Baseline characteristics were similar between both arms; the mean (SD) eGFR in the linagliptin arm was 22.1 (6.3) mL/min/1.73 m², and 25.1 (6.9) mL/min/1.73 m² in the placebo arm. The mean (SD) difference in baseline eGFR to the end of treatment therapy was statistically not significant between linagliptin compared with placebo (−0.8 mL/min/1.73 m² vs −2.2 mL/min/1.73 m²). Also, there were no new cases of drug-related renal failure. This study demonstrated that linagliptin has a neutral effect on eGFR in patients with T2DM and severe renal impairment.³⁰

Diabetic retinopathy. The effect of sitagliptin on diabetic retinopathy was evaluated in the TECOS trial. In the sitagliptin arm, 3.1% of patients developed diabetic eye disease and 2.5% in the placebo group. Among patients who developed diabetic eye disease, 2.8% of patients in the sitagliptin arm compared with 2.2% of patients in the placebo arm developed retinopathy. The incidence of blindness due to diabetes was much smaller in both the sitagliptin and placebo arm (0.3% vs 0.3%, respectively).¹⁴

Only 1 randomized controlled trial was conducted to evaluate the effect of saxagliptin on retinal microvascular changes. This was a randomized, double-blind, placebo-controlled, crossover study conducted for a mean duration of 4 years. Fifty patients were randomized to receive placebo or saxagliptin 5 mg/d for a total treatment duration of 12 weeks. By the end of the study, only 43 pa-

tients were evaluated. The primary objective was to evaluate the effect of saxagliptin on early vascular remodeling and the retinal capillary flow. Patients in the saxagliptin arm benefited from having a greater reduction in retinal capillary flow from baseline to 6 weeks of saxagliptin compared with placebo (288 arbitrary unit [13.2] vs placebo 331 arbitrary unit [13.6], respectively; $P=0.033$).²⁹

In the CARMELINA trial, investigators looked at various microvascular outcomes. Among them was the composite ocular end point, defined as time to first use of retinal laser-coagulation therapy or treatment with intravitreal injection(s) of an antivascular endothelial growth factor therapy for diabetic retinopathy or vitreous hemorrhage or diabetes-related blindness. There were no differences between the linagliptin compared with the placebo arm (1% vs 1.4%, respectively; HR, 0.73; 95% CI, 0.47–1.12; $P=0.15$).¹⁶

Neuropathy. There are limited clinical RCTs that evaluated diabetic neuropathy in patients taking DPP-4 inhibitors compared with placebo. The TECOS trial looked at diabetic neuropathy as additional clinical events of interest. In the sitagliptin arm, 4.1% of patients developed diabetic neuropathy compared with the 3.8% in the placebo arm. This study showed that saxagliptin may have a neutral impact on the incidence of diabetic neuropathy.¹⁴

Diabetic foot ulcer/amputation. There is very limited clinical evidence to show the beneficial effects of DPP-4 inhibitors on diabetic foot ulcers or amputation in T2DM. No studies met the inclusion criteria for this systematic review.

Discussion

The selection of antihyperglycemic agents for the treatment of T2DM is based on variables such as efficacy, tolerability, side effects, risk of hypoglycemia, comorbidities, and clinical outcomes. The potential of antihyperglycemic complications associated with T2DM has become an important topic of discussion based on positive results from several trials.^{3–7}

MACE outcome trials were completed as recently as 2019 for all 4 US-marketed DPP-4 inhibitors. To date, all randomized controlled MACE trials for this medication class determined that the addition of DPP-4 inhibition resulted in rates of major CV outcomes that were noninferior to placebo or control with HR <1.3, a margin set by the FDA concluding noninferiority. The addition of DPP-4 inhibitors to standard antihyperglycemic and CV risk reduction treatment has not shown CV benefit relative to placebo in contrast to recently published studies for other medication classes, glucagon-like peptide-1 agonists and sodium-glucose cotransporter 2 inhibitors. DPP-4 inhibitors are recommended by American Diabetes Association guidelines as among the first-line options for patients without established atherosclerotic CV disease, CKD, HF, and without indicators of high risk for these comorbidities.

As many as 50% of patients with T2DM may develop HF.¹ RCTs that evaluated the rates of hospitalizations for HF for this class of medications have shown mixed results. Saxagliptin was found to be associated with a statistically significant increase in rates of hospitalizations for HF. However, RCTs for sitagliptin and linagliptin did not find a significant increase in HF hospitalizations. This outcome was not evaluated in the a priori analysis for alogliptin; a post hoc analysis demonstrated no significantly increased risk.³⁰ The American Diabetes Association guidelines state that potential risk for HF may exist with saxagliptin, but do not extrapolate this risk as a class effect.¹

Earlier meta-analyses indicated that DPP-4 inhibitors are either safe from the CV standpoint or reduce risk of CV events.^{17,18} However, as more published data became available, a subsequent meta-analysis no longer observed a benefit but maintained that no sig-

nificant differences were found on CV outcomes.¹⁹ A meta-analysis specifically exploring the effect of DPP-4 inhibitors on HF found that the addition of DPP-4 inhibition was associated with a statistically significant risk of acute HF.²⁰ Furthermore, a meta-analysis exploring the differential effect on HF for individual DPP-4 inhibitors found that use of saxagliptin among the class resulted in an increased risk of HF.²¹ The most recent meta-analysis included in this review determined that risk of CV outcomes was similar between treatment with DPP-4 inhibitors and placebo, with weak evidence for increased risk of HF.²² These divergent results can likely be attributed to the heterogeneity of patient populations included in these meta-analyses as more published data becomes available for the pooled analyses. Additional meta-analyses that would include the most recently published data from CAROLINA and CARMELINA trials are desirable to add to the current body of evidence.

This systematic review found that specific DPP-4 inhibitors may have some beneficial effects on renal outcomes, mainly by reducing albuminuria compared with placebo or other antidiabetic drugs. Among the largest and longest studies was the SAVOR-TIMI 53 trial, which demonstrated beneficial renal effects of saxagliptin by reducing the development and progression of microalbuminuria.¹³ A further exploratory study showed that saxagliptin was associated with improving and/or preventing albuminuria in patients with normoalbuminuria, microalbuminuria, and macroalbuminuria.³¹ This study was excluded from our systematic review due to the nature of the study, but is noteworthy for further discussion. The CARMELINA trial also showed that linagliptin might slow down the progression of patients with microalbuminuria to clinical proteinuria or slow down the change from normoalbuminuria to either microalbuminuria or clinical proteinuria. The limitation of these studies was that they only looked at surrogate end points such as change in eGFR and UACR. It is difficult to assess if DPP-4 inhibitors have a positive impact on renal outcome. Also, most of these studies, except the SAVOR-TIMI 53 trial, did not evaluate composite renal outcomes (initiation of dialysis or death due to renal disease) in their statistical analysis. Compared with the renal benefits reported with liraglutide, dulaglutide, empagliflozin, and canagliflozin, DPP-4 inhibitors should not be selected to improve diabetic nephropathy.^{3–6}

As of right now, there are promising preclinical animal results regarding DPP-4 inhibitors having a benefit on the diabetic microvascular disease but limited clinical human trials. No trials evaluated in this review showed statistically significant prevention or delay in the progression of diabetic retinopathy, or neuropathy in patients with T2DM. We are unable to comment on the effect of DPP-4 inhibitors on diabetic foot wound healing. Based on these trials, we can conclude that DPP-4 inhibitors have a neutral effect on microvascular complications in patients with T2DM.

Our analysis has several limitations. This review is limited by inconsistent reporting of outcomes, specifically in trials evaluating retinopathy and nephropathy. A strength of this systematic review was the utilization of 4 independent reviewers and the development of a protocol that included objective inclusion and exclusion criteria. This, to our knowledge, is the first systematic review that evaluates the influence of all DPP-4 inhibitors on macrovascular and microvascular complications related to T2DM.

Conclusions

Our systematic review demonstrated that DPP-4 inhibitors have no cardioprotective effect, but saxagliptin has a potential risk for HF hospitalizations. This class of drugs has no renoprotective effect; however, saxagliptin and linagliptin may reduce the risk of progression of albuminuria. Additionally, there is suggestion that DPP-4 inhibitors may decrease the risk of retinopathy, neuropathy,

diabetic foot ulcers, and/or amputations. DPP-4 inhibitors are an attractive option for patients with no cardiovascular disease with a low influence on microvascular complications of T2DM.

Declaration of Competing Interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

References

- Standards of medical care in diabetes – 2020. *Diabetes Care*. 2020;43(Supplement1):S1–S212.
- Guidance for Industry Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes [Internet]. 2008 [cited 2020 Jan 22]. Available from: <https://www.fda.gov/media/71297/download>.
- Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med*. 2015;373(22):2117–2128.
- Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med*. 2017;377(7):644–657.
- Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2016;375(4):311–322.
- Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jodar E, Leiter LA, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med*. 2016;375(19):1834–1844.
- Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes: a double-blind, randomised placebo-controlled trial. *Lancet*. 2019;394(10193):121–130.
- Hernandez AF, Green JB, Janmohamed S, et al. Albiglutide and cardiovascular outcomes inpatients with type 2 diabetes and cardiovascular disease: a double-blind, randomised placebo-controlled trial. *Lancet*. 2018;392(10157):1519–1529.
- Invokana (canagliflozin). [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals; January 2020.
- Moher D, Liberati A, Tetzlaff J, Altman DGPRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009 Jul 21;339:b2535.
- Higgins JPT, Altman DG. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S, eds. *Cochrane handbook for systematic reviews of interventions* version 5.0.0 [updated February 2008]. The Cochrane Collaboration, 2008. Available: <http://www.cochranehandbook.org/>. Accessed 26 May 2019.
- White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med*. 2013;369(14):1327–1335.
- Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med*. 2013;369(14):1317–1326.
- Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, et al. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2015;373(3):232–242.
- Rosenstock J, Kahn SE, Johansen OE, Zinman B, Espeland MA, Woerle HJ, et al. Effect of Linagliptin vs Glimepiride on Major Adverse Cardiovascular Outcomes in Patients With Type 2 Diabetes: The CAROLINA Randomized Clinical Trial. *JAMA*. 2019. Epub 2019/09/20PubMed PMID:31536101PubMed Central PMCID: PMC6763993. doi:10.1001/jama.2019.13772.
- Rosenstock J, Perkovic V, Johansen OE, Cooper ME, Kahn SE, Marx N, et al. 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. *Jama*. 2019;321(1):69–79.
- Patil HR, Al Badarin FJ, Al Shami HA, Bhatti SK, Lavie CJ, Bell DS, et al. Meta-analysis of effect of dipeptidyl peptidase-4 inhibitors on cardiovascular risk in type 2 diabetes mellitus. *Am J Cardiol*. 2012;110(6):826–833.
- Monami M, Ahrn B, Dicembrini I, Mannucci E. Dipeptidyl peptidase-4 inhibitors and cardiovascular risk: a meta-analysis of randomized controlled trials. *Diabetes Obes Metab*. 2013;15:112–120.
- Agarwal S, Parashar A, Menon V. Meta-analysis of the cardiovascular outcomes with dipeptidyl peptidase 4 inhibitors: validation of the current FDA mandate. *Am J Cardiovasc Drugs*. 2014;14(3):191–207.
- Monami M, Dicembrini I, Mannucci E. Dipeptidyl peptidase-4 inhibitors and heart failure: a meta-analysis of randomized clinical trials. *Nutr Metab Cardiovasc Dis*. 2014;24(7):689–697.
- Kongwattcharapong J, Dilokthornsakul P, Nathisuwan S, Phrommintikul A, Chaiyakunapruk N. Effect of dipeptidyl peptidase-4 inhibitors on heart failure: A meta-analysis of randomized clinical trials. *Int J Cardiol*. 2016;211:88–95.
- Elgendy IY, Mahmoud AN, Barakat AF, Elgendy AY, Saad M, Abuzaid A, et al. Cardiovascular Safety of Dipeptidyl-Peptidase IV Inhibitors: A Meta-Analysis of Placebo-Controlled Randomized Trials. *Am J Cardiovasc Drugs*. 2017;17(2):143–155.
- Arjona Ferreira JC, Marre M, Barzilay N, Guo H, Golm GT, Sisk CM, et al. Efficacy and safety of sitagliptin versus glipizide in patients with type 2 diabetes and moderate-to-severe chronic renal insufficiency. *Diabetes Care*. 2013;36(5):1067–1073.
- Mori H, Okada Y, Arai T, Tanaka Y. Sitagliptin improves albuminuria in patients with type 2 diabetes mellitus. *J Diabetes Investig*. 2014;5(3):313–319.
- Tonnejck L, Smits MM, Muskiet MH, Hoekstra T, Kramer MH, Danser AH, et al. Renal Effects of DPP-4 Inhibitor Sitagliptin or GLP-1 Receptor Agonist Liraglutide in Overweight Patients With Type 2 Diabetes: A 12-Week, Randomized, Double-Blind, Placebo-Controlled Trial. *Diabetes Care*. 2016;39(11):2042–2050.
- Groop PH, Cooper ME, Perkovic V, Hocher B, Kanasaki K, Haneda M, et al. Linagliptin and its effects on hyperglycaemia and albuminuria in patients with type 2 diabetes and renal dysfunction: the randomized MARLINA-T2D trial. *Diabetes Obes Metab*. 2017;19(11):1610–1619.
- Han SY, Yoon SA, Han BG, Kim SG, Jo YI, Jeong KH, et al. Comparative efficacy and safety of gemigliptin versus linagliptin in type 2 diabetes patients with renal impairment: A 40-week extension of the GUARD randomized study. *Diabetes Obes Metab*. 2018;20(2):292–300.
- McGill JB, Sloan L, Newman J, Patel S, Sauce C, von Eynatten M, et al. Long-term efficacy and safety of linagliptin in patients with type 2 diabetes and severe renal impairment: a 1-year, randomized, double-blind, placebo-controlled study. *Diabetes Care*. 2013;36(2):237–244.
- Ott C, Raff U, Schmidt S, Kistner I, Friedrich S, Bramlage P, et al. Effects of saxagliptin on early microvascular changes in patients with type 2 diabetes. *Cardiovasc Diabetol*. 2014;13:19.
- Zannad F, Cannon CP, Cushman WC, Bakris GL, Menon V, Perez AT, et al. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial. *Lancet*. 2015;385(9982):2067–2076.
- Mosenzon O, Leibowitz G, Bhatt DL, Cahn A, Hirshberg B, Wei C, et al. Effect of Saxagliptin on Renal Outcomes in the SAVOR-TIMI 53 Trial. *Diabetes Care*. 2017;40(1):69–76.