DPP-4 inhibitors side-by-side comparison

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Introduction

Currently there are 4 dipeptidyl peptidase-4 (DPP-4) inhibitors approved by the US Food and Drug Administration: alogliptin (Nesina), linagliptin (Tradjenta), saxagliptin (Onglyza), and sitagliptin (Januvia). All DPP-4 inhibitors are approved as adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus (T2DM). None are approved for use in treatment of type 1 diabetes mellitus (T1DM) or diabetic ketoacidosis. All are dosed once daily and can be taken with or without meals. DPP-4 inhibitors slow the inactivation of incretin hormones, such as glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP), which are inactivated within minutes by the DPP-4 enzyme. Incretin hormones are secreted, via the small intestine, at low basal levels throughout the day and levels rise immediately after a meal. In the presence of normal and elevated blood glucose levels, GLP-1 and GIP increase insulin production and secretion from pancreatic beta cells. DPP-4 inhibitors delay inactivation of incretin hormones by binding to the DPP-4 enzyme, increasing bloodstream concentrations and reducing fasting and postprandial glucose concentrations.[a-d] Sitagliptin was the first to market in 2006; followed by saxagliptin in 2009, then linagliptin in 2011 and alogliptin in 2013. Alogliptin is the only DPP-4 inhibitor with an authorized generic, or when the brand name medication is marketed by the same manufacturer without the brand name on the label. True generic availability, or availability from other manufacturers, of alogliptin is expected in 2028, whereas loss of exclusivity of the other agents is expected in the next 1 to 5 years.[e] DPP-4 inhibitors are approved for use as monotherapy or add-on therapy to insulin or other oral antidiabetic agents. Other agents or classes include metformin, GLP-1 receptor agonists, sodium-glucose cotransporter 2 (SGLT2) inhibitors, sulfonylureas, and thiazolidinediones. Combination of DPP-4 inhibitors with GLP-1 receptor agonists does not have an additive effect on glucose lowering; therefore, concomitant use of DPP-4 inhibitors and GLP-1 receptor agonists is not recommended.[g]

Guidelines

The available guidelines do not recommend monotherapy with DPP-4 inhibitors as a first-line option, but rather fourth line as add-on therapy or if metformin, SGLT2 inhibitors, and GLP-1 receptor agonists are not tolerated or appropriate for use based on patient specific factors. Patient specific factors to consider include patient preference, comorbidities, renal function, minimization of hypoglycemia risk, minimization of weight gain, and cost and access considerations. The American Association of Clinical Endocrinologists 2020 guidelines recommend DPP-4 inhibitors as fourth-line agents.[f] The American Diabetes Association 2022 guidelines state DPP-4 inhibitors may be considered for patients with T2DM to minimize hypoglycemia and to minimize weight gain if GLP-1 receptor agonists are not tolerated or indicated.[g] The Kidney Disease Improving Global Outcomes 2020 guidelines state DPP-4 inhibitors may be utilized as an add-on to first-line therapy with metformin and a SGLT2 inhibitor in patients with T2DM and CKD; however, GLP-1 receptor agonists are preferred.[h]

Clinical efficacy

A multitude of studies are available which evaluate DPP-4 inhibitors compared with standard of care or placebo; however, head-to-head trials evaluating DPP-4 inhibitors are limited. The only trial available evaluated saxagliptin vs. sitagliptin as add-on therapy to stable doses of metformin. The primary outcome was change from baseline hemoglobin A1c (HbA1c) at week 18. Saxagliptin demonstrated noninferiority to sitagliptin in HbA1c reduction. Similar rates of minor hypoglycemic events and minimal weight reduction were observed in both treatment groups.[i]

Multiple meta-analyses have been conducted to evaluate DPP-4 inhibitors as monotherapy or in combination with other oral antidiabetic agents.[j-o] In a meta-analysis, as monotherapy or as add-on to other antidiabetic therapies, DPP-4 inhibitors were compared with placebo or standard of care. No differences, with one exception, were observed between the DPP-4 inhibitors for mean change in HbA1c from baseline, proportion of patients achieving HbA1c < 7%, mean change from baseline in body weight, and number of patients who experienced hypoglycemic events. The exception being, patients administered alogliptin plus metformin achieved HbA1c < 7% more frequently than those treated with saxagliptin and metformin (OR: 6.41 vs. 2.17).[j] In a meta-analysis evaluating cardiovascular outcomes, specifically the composite outcome of cardiovascular death, myocardial infarction, and stroke, no differences were observed between the DPP-4 inhibitors and the control group. Additionally, no difference was observed between groups for all-cause mortality, hospitalization for cardiovascular complications, or hospitalizations for heart failure.[k] A meta-analysis comparing DPP-4 inhibitors with sulfonylureas demonstrated less adverse events and cardiovascular events with DPP-4 inhibitors in combination with metformin vs. sulfonylureas. Higher rates of hypoglycemia and severe hypoglycemia were reported with sulfonylureas

regardless of whether administered as monotherapy or in combination with metformin. Additionally, the mean difference in weight gain favored DPP-4 inhibitors.[l] In a network meta-analysis, SGLT2 inhibitors demonstrated greater reduction in major adverse cardiovascular events as compared to DPP-4 inhibitors.[m,n] Lastly, a meta-analysis evaluating DPP-4 inhibitor use, as an add-on therapy compared with standard of care or placebo in patients ≥ 65 years of age, demonstrated no difference in all-cause mortality, incidence of hypoglycemia or overall adverse events.[o] The available meta-analyses demonstrate DPP-4 inhibitors are efficacious as mono-, dual, or triple therapy for the treatment of T2DM in adult patients.

Cardiovascular outcomes were evaluated in the EXAMINE[p], SAVOR-TIMI 53[q], TECOS[r], and CARMELINA[s] trials. The available trials demonstrate DPP-4 inhibitors are noninferior to placebo or glimepiride for cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. Similar rates of hypoglycemia and adjudication-confirmed cases of pancreatitis were seen between the DPP-4 inhibitors and the control groups. Increased hospitalizations for heart failure observed in EXAMINE[p], evaluating alogliptin, and SAVOR-TIMI 53[q], evaluating saxagliptin, have led to inclusion of a warning in the drug labels for all DPP-4 inhibitors.

Convenience factors

Drug interactions

Saxagliptin is metabolized primarily via CYP3A4/5 pathway. Strong CYP3A4/5 inhibitors can significantly increase saxagliptin exposure. The dose of saxagliptin should be limited to 2.5 mg when administered with a strong CYP3A4/5 inhibitor. Use of an alternative agent to linagliptin is recommended when a strong P-gp inducer or CYP3A4 inducer is coadministered as linagliptin exposure can be decreased. Coadministration of DPP-4 inhibitors with an insulin secretagogue (eg, sulfonylurea) or insulin may increase the risk of hypoglycemia. Lower doses of the insulin secretagogue or insulin may be required.[a-d]

Renal dosing

Linagliptin undergoes enterohepatic elimination and does not require dose adjustments for renal impairment. Alogliptin, saxagliptin, and sitagliptin require dose adjustments for renal impairment. Alogliptin can be administered regardless of hemodialysis timing but has not been evaluated in peritoneal dialysis. Saxagliptin should be administered after hemodialysis and has not been evaluated in patients undergoing peritoneal dialysis. Sitagliptin can be administered regardless of timing of both hemodialysis and peritoneal dialysis.[a-d]

Conclusions

The DPP-4 inhibitor class provides a 0.5% to 1% reduction in HbA1c.[a-d,ee] Although lacking the cardiorenal outcomes associated with the GLP-1 receptor agonists and SGLT2 inhibitors, the DPP-4 inhibitors provide an additional option for glycemic control with a favorable adverse effect profile. The DPP-4 inhibitors are weight neutral, have a low risk of hypoglycemia as compared to other antidiabetic agents, and are available for use in patients with renal impairment. The DPP-4 inhibitors are best suited for those at risk of hypoglycemia and patients with renal impairment, such as elderly patients, whose diabetes is not well-controlled, and those unable to tolerate the available first-line options for treatment of T2DM. Choice of DPP-4 inhibitor is dependent on patient specific considerations (eg, chronic kidney disease, heart failure, drug interactions) and payer preference.

Looking forward

Additional DPP-4 inhibitor therapy options in the pipeline include teneligliptin and trelagliptin. Teneligliptin (Tenelia, Mitsubishi Tanabe/Daiichi Sankyo) is a once daily oral DPP-4 inhibitor in phase 3 trials. Trelagliptin (SYR-472, Takeda) is a once-weekly oral DPP-4 inhibitor in phase 2 trials.[e]

DPP-4 inhibitors side-by-side comparison

	Generic name (brand name)			
	Alogliptin (Nesina)[a]	**Linagliptin (Tradjenta)[b]**	**Saxagliptin (Onglyza)[c]**	**Sitagliptin (Januvia)[d]**
Manufacturer	Takeda Pharmaceuticals	Boehringer Ingelheim Pharmaceuticals	AstraZeneca	Merck
Approval date	2013	2011	2009	2006
FDA-approved indications				
Indication	Adjunct to diet and exercise to improve glycemic control in adults with T2DM.			
Limitations of use	Not indicated for the treatment of T1DM or diabetic ketoacidosis.	• Not indicated for the treatment of T1DM or diabetic ketoacidosis. • Not studied in patients with a history of pancreatitis.	Not indicated for the treatment of T1DM or diabetic ketoacidosis.	• Not indicated for the treatment of T1DM or diabetic ketoacidosis. • Not studied in patients with a history of pancreatitis.
Pharmacology				
Mechanism of action	• DPP-4 inhibitors slow the inactivation of incretin hormones (GLP-1 and GIP) by binding to the DPP-4 enzyme, increasing their bloodstream concentrations and reducing fasting and postprandial glucose concentrations. • Incretin hormones are secreted, via the small intestine, at low basal level throughout the day and levels rise immediately after a meal. In the presence of normal and elevated blood glucose levels, GLP-1 and GIP increase insulin production and secretion from pancreatic beta cells.			
Pharmacokinetics				
Absorption	• Oral bioavailability ~ 100% • Tmax ~ 1 to 2 h • High-fat meals have a negligible effect; administer with or without food	• Oral bioavailability ~ 30% • Tmax ~ 1.5 h • High-fat meals have a negligible effect; administer with or without food	• Oral bioavailability not reported • Tmax ~ 2 h (4 h for active metabolite) • High-fat meals have a negligible effect; administer with or without food	• Oral bioavailability ~ 87% • Tmax ~ 1 to 4 h • High-fat meals have a negligible effect; administer with or without food
Distribution	Protein binding ~ 20%	Protein binding ~ 70% to 80%	Protein binding negligible	Protein binding ~ 38%
Metabolism	• CYP2D6 and CYP3A4 contribute to limited metabolism • 60% to 70% excreted unchanged in urine	• Not significantly metabolized • ~ 90% excreted unchanged	• Metabolism primarily mediated by CYP3A4 and CYP3A5	• CYP3A4 and CYP2C8 contribute to limited metabolism • ~ 16% excreted as metabolites of sitagliptin

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	Alogliptin (Nesina)[a]	**Linagliptin (Tradjenta)[b]**	**Saxagliptin (Onglyza)[c]**	**Sitagliptin (Januvia)[d]**
Excretion	• 13% recovered in feces as alogliptin • 76% excreted in urine	• 80% eliminated via the enterohepatic system • 5% excreted in urine	• 22% excreted in feces as saxagliptin • 24% excreted in urine and 36% excreted as active metabolite	• 13% excreted in feces as sitagliptin • 87% excreted in urine
Terminal half-life	21 h	200 h (accumulation half-life 11 h)	2.5 h (3.1 h for active metabolite)	12.4 h
HbA1c reduction	DPP-4 inhibitors have demonstrated a 0.5% to 1% reduction HbA1c in available clinical trials.			
Dosage and administration				
Prior to initiation	• Assess renal function • Assess risks and benefits in patients with heart failure	Assess risks and benefits in patients with heart failure	• Assess renal function • Assess risks and benefits in patients with heart failure	• Assess renal function • Assess risks and benefits in patients with heart failure
Dosage	25 mg	5 mg	2.5 mg or 5 mg	100 mg
Frequency	Once daily	Once daily	Once daily	Once daily
Route	Oral	Oral	Oral	Oral
Comments	Administer with or without food	Administer with or without food	Administer with or without food	Administer with or without food
Special populations				
Pregnancy / lactation	• Insufficient data for determination of a drug-associated risk for major birth defects or miscarriage. Animal reproductive studies demonstrated no adverse effect on embryo-fetal development when rats and rabbits were exposed to concentrations higher than the clinical dose during the organogenesis period. • No lactation data in humans are available. Studies have found DPP-4 inhibitors in rat milk.			
Pediatric	No data are available for use in pediatric patients.	No data are available for use in pediatric patients.	No data are available for use in pediatric patients.	The safety and effectiveness of sitagliptin has not been established in pediatric patients.
Geriatric	• Patients ≥ 65 y have similar safety and efficacy outcomes as younger patients in clinical studies; however, greater sensitivity of some older individuals cannot be ruled out. • For DPP-4 inhibitors renally excreted, renal function should be assessed more frequently.			
Renal impairment	• No dose adjustment needed for patients with CrCl ≥ 60 mL/min.	No dose adjustment needed for patients with renal impairment.	• No dose adjustment needed for patients with eGFR ≥ 45 mL/min/1.73 m^2. • The recommended dosage is 2.5 mg once daily for patients	• No dose adjustment needed for patients with eGFR ≥ 45 mL/min/1.73 m^2. • The recommended dosage is 50 mg once daily for patients

	Generic name (brand name)			
	Alogliptin (Nesina)[a]	**Linagliptin (Tradjenta)[b]**	**Saxagliptin (Onglyza)[c]**	**Sitagliptin (Januvia)[d]**
	• The recommended dosage is 12.5 mg once daily for patients with CrCl ≥ 30 to < 60 mL/min. • The recommended dosage is 6.25 mg once daily for patients CrCl ≥ 15 to < 30 mL/min or ESRD (CrCl < 15 mL/min or requiring hemodialysis). • Administer regardless of timing of hemodialysis. Alogliptin has not been studied in patients undergoing peritoneal dialysis.		with eGFR < 45 mL/min/1.73 m^2 (including ESRD requiring hemodialysis). • Administer after hemodialysis. Saxagliptin has not been studied in patients undergoing peritoneal dialysis.	with eGFR ≥ 30 to < 45 mL/min/1.73 m^2. • The recommended dosage is 25 mg once daily for patients with eGFR < 30 mL/min/1.73 m^2 (including ESRD requiring hemodialysis or peritoneal dialysis). • Administer regardless of dialysis timing.
Hepatic impairment	No dosage adjustment is needed in mild-moderate hepatic impairment (Child-Pugh Class A or B). No data are available for use in severe hepatic impairment (Child-Pugh Grade C).	No dosage adjustment is needed for patients with hepatic impairment.	No dosage adjustment is needed for patients with hepatic impairment.	No dosage adjustment is needed in moderate hepatic impairment (Child-Pugh Class B). No data are available for use in severe hepatic impairment (Child-Pugh Grade C).
Safety				
Boxed warning	DPP-4 inhibitors supplied alone do not carry a boxed warning. Combination products with metformin carry a boxed warning for lactic acidosis and for congestive heart failure with pioglitazone.			
Contraindications	Hypersensitivity to alogliptin or any other components.	Hypersensitivity to linagliptin or any other components.	Hypersensitivity to saxagliptin or any other components.	Hypersensitivity to sitagliptin or any other components.
Precautions	• Pancreatitis has been reported in postmarketing and randomized controlled trials. It is unknown if a history of pancreatitis increases risk. • Heart failure associated with the DPP-4 class has been observed in select studies, consider the risk and benefits prior to initiating in those at risk for heart failure. • Hypoglycemia when administered with an insulin secretagogue (eg, sulfonylurea) or insulin has been observed. Lower doses may be required when used in combination to reduce the risk of hypoglycemia. • Serious hypersensitivity reactions, including anaphylaxis, angioedema, or severe cutaneous reaction, have been observed in postmarketing reports. • Severe and disabling arthralgia has been reported in patients taking DPP-4 inhibitors. • Bullous pemphigoid requiring hospitalization was reported in postmarketing cases.			

	Generic name (brand name)			
	Alogliptin (Nesina)[a]	**Linagliptin (Tradjenta)[b]**	**Saxagliptin (Onglyza)[c]**	**Sitagliptin (Januvia)[d]**
	• Hepatic failure, fatal and nonfatal, has been reported in postmarketing reports. Serum ALT elevations greater than 3 times the ULN were observed in 1.3% of patients in glycemic control trials and 2.4% in the EXAMINE trial. • No clinical studies have established macrovascular risk reduction with alogliptin.	--	No clinical studies have established macrovascular risk reduction with saxagliptin.	Acute renal failure, requiring dialysis, has been reported in postmarketing reports.
Adverse reactions	The most common (incidence ≥ 4%) adverse reactions are nasopharyngitis, headache, and upper respiratory tract infection.	The most common (incidence ≥ 5%) adverse reaction is nasopharyngitis.	The most common (incidence ≥ 5%) adverse reactions are respiratory tract infection, urinary tract infection, and headache. Peripheral edema is more common in patients when a thiazolidinedione is administered with saxagliptin than placebo.	The most common (incidence ≥ 5%) adverse reactions are upper respiratory tract infection, nasopharyngitis, and headache. Hypoglycemia was more commonly reported than placebo.
Drug-drug interactions	• CYP450 metabolism negligible. • No significant interactions observed with CYP-substrates or inhibitors, or renally excreted drugs. • Coadministration with an insulin secretagogue or insulin may increase the risk of hypoglycemia. Lower doses of the insulin secretagogue or insulin may be required.	• Reduced efficacy when administered in combination with a strong P-gp or CYP3A4 inducer. • Coadministration with an insulin secretagogue or insulin may increase the risk of hypoglycemia. Lower doses of the insulin secretagogue or insulin may be required.	• CYP3A4/5 inhibitors increase plasma concentrations of saxagliptin. • When coadministered with strong CYP3A4/5 inhibitors the recommended dosage is 2.5 mg once daily. • Coadministration with an insulin secretagogue or insulin may increase the risk of hypoglycemia. Lower doses of the insulin secretagogue or insulin may be required.	Coadministration with an insulin secretagogue or insulin may increase the risk of hypoglycemia. Lower doses of the insulin secretagogue or insulin may be required.
How supplied				
Strength(s)	6.25, 12.5, and 25 mg	5 mg	2.5 and 5 mg	25, 50, and 100 mg
Dosage form	Tablet	Tablet	Tablet	Tablet
Generic available	Yes (authorized generic)	No	No	No

	Generic name (brand name)			
	Alogliptin (Nesina)[a]	**Linagliptin (Tradjenta)[b]**	**Saxagliptin (Onglyza)[c]**	**Sitagliptin (Januvia)[d]**
Estimated LOE[e]	2028	2025	2023	2027
Combinations available[t-dd]	• Alogliptin and metformin (Kazano) • Alogliptin and pioglitazone (Oseni)	• Linagliptin and empagliflozin (Glyxambi) • Linagliptin and metformin (Jentadueto and Jentadueto XR) • Linagliptin, empagliflozin, and metformin (Trijardy XR)	• Saxagliptin and dapagliflozin (Qtern) • Saxagliptin and metformin (Kombiglyze XR)	• Sitagliptin and ertugliflozin (Steglujan) • Sitagliptin and metformin (Janumet and Janumet XR)
Storage	• Store at 25˚C • Excursions permitted to 15 to 30˚C	• Store at 20 to 25˚C • Excursions permitted to 15 to 30˚C	• Store at 20 to 25˚C • Excursions permitted to 15 to 30˚C	• Store at 20 to 25˚C • Excursions permitted to 15 to 30˚C
Cost (WAC)	• Brand, $14 per 25 mg tablet • Authorized generic, $6.50 per 25 mg tablet	$17 per 5 mg tablet	• $16 per 2.5 mg tablet • $16 per 5 mg tablet	$17 per 100 mg tablet
Brand manufacturer participates in 340B Drug Pricing Program	Yes	Yes	Yes	Yes
Vizient contract	No	Yes	Yes	Yes
Insurance considerations[ff-ij]				
Coverage	Generally, non-formulary or non-preferred agent.	• Generally, a non-formulary agent for insurances. • Few preferred and non-preferred with prior authorization required.	• Generally, a non-formulary agent for insurances. • Few preferred and non-preferred with prior authorization required.	• Generally, a preferred agent for insurances. • Few are requiring prior authorization.
Copay card	No	Yes	Yes	Yes
Patient assistance program	Yes	Yes	Yes	Yes
Total US prescriptions in 2021[kk]				
DPP-4 inhibitor alone, n (% market share)	614,235 (5%)	2,340,752 (20%)	241,194 (2%)	8,413,533 (73%)

	Generic name (brand name)			
	Alogliptin (Nesina)[a]	Linagliptin (Tradjenta)[b]	Saxagliptin (Onglyza)[c]	Sitagliptin (Januvia)[d]
Combination products, n (% market share)	133,516 (4%)	592,539 (16%)	112,259 (3%)	2,950,221 (78%)
Total, n (% market share)	747,751 (5%)	2,933,291 (19%)	353,543 (3%)	11,363,754 (74%)

DPP-4 inhibitors evidence summary

A structured search of PubMed (1966-February 2022) was conducted to identify DPP-4 inhibitor literature. All searches were limited to reports in the English language and indexed as randomized controlled-trials, guidelines, systematic reviews, or meta-analyses. All search strategies were generated based on a PICO framework: population (T2DM), intervention (DPP-4 inhibitor), comparator (placebo, no treatment, standard of care, other oral antidiabetic agents), and outcomes (HbA1c, adverse events, cardiovascular outcomes, mortality). The search strategy included a combination of indexing terms (MeSH and supplementary terms) and free-text terms. To supplement the database search, reference lists of all relevant systemic reviews and meta-analysis were manually checked.

Head-to-head clinical trials

- ***Diabetes Metab Res Rev*. 2010;26(7):540-549.**[i] In a multicenter, randomized-controlled, double-blind trial, adults with T2DM (n = 801) and HbA1c 6.5% to 10% on a stable dose of metformin were administered 5 mg saxagliptin or 100 mg sitagliptin as add-on therapy. The primary outcome was change from baseline HbA1c at wk 18. Noninferiority of saxagliptin was confirmed if the upper boundary of the two-sided 95% CI was ≤ 0.3%. At 18 wks, the mean change in HbA1c was -0.52% (95% CI, -0.60 to -0.45) in the saxagliptin-treated group and -0.62% (95% CI, -0.69 to -0.54) in the sitagliptin-treated group (treatment difference: 0.09%; 95% CI, -0.01 to 0.20). Minor hypoglycemic events, defined as plasma glucose < 63 mg/dL with no symptoms or at least one symptom with no assistance needed, were observed in 3% of patients in both groups. The mean body weight decreased by 0.4 kg in both groups.

Meta-analyses

- ***Diabetes Ther*. 2014;5(1):1-41.**[j] In a meta-analysis of 83 randomized-controlled trials, adults with T2DM with insufficient glycemic controls were administered a DPP-4 inhibitor, including alogliptin, linagliptin, saxagliptin, sitagliptin, or vildagliptin, as mono-, dual, or triple therapy compared with placebo or standard of care. Five of the trials were open-label and the baseline HbA1c ranged from 6% to 12% amongst the trials, where higher HbA1c at baseline may have contributed to larger reductions. No differences, with one exception, were observed between the DPP-4 inhibitors and mean change in HbA1c from baseline, proportion of patients achieving HbA1c < 7%, mean change from baseline in body weight, and number of patients with hypoglycemic events. The exception being, patients administered alogliptin plus metformin achieved HbA1c < 7% more frequently than those treated with saxagliptin and metformin (OR: 6.41 vs. 2.17). The analysis included vildagliptin which is not available in the US.
- ***BMC Pharmacol Toxicol*. 2019;20(1):15.**[k] In a meta-analysis of 7 trials, 4 randomized-controlled trials and 3 observational cohorts, adults with T2DM were administered a DPP-4 inhibitor, including alogliptin, omarigliptin, saxagliptin, or sitagliptin, compared with a non-DPP-4 inhibitor control group. The primary outcome was a composite of cardiovascular death, non-fatal MI, and non-fatal stroke. No difference was observed in the primary outcome between the DPP-4 inhibitor-treated group vs. the control group (OR: 0.95; 95% CI, 0.86-1.04; *P* = .26). Additionally, no difference was noted between the 2 groups and rates of all-cause mortality (OR: 0.84; 95% CI, 0.59-1.15; *P* = .31), hospitalization for cardiovascular complications (OR: 1.02, 95% CI, 0.96-1.09; *P* = .45), and

hospitalization for heart failure (OR: 1.05; 95% CI, 0.90-1.23; *P* = .55). The duration of the studies ranged from 52 to 152 wks with varying durations of follow up. These differences may have affected the occurrence of outcomes. The analysis included omarigliptin which is not available in the US.

- ***Diabetes Res Clin Pract*. 2019;149:47-63.[l]** In a meta-analysis, 36 randomized,controlled trials that enrolled adults with T2DM who were randomized to receive a DPP-4 inhibitor or a sulfonylurea were included. Of the identified trials, 13 compared DPP-4 inhibitors with sulfonylureas given as monotherapy and 26 compared the 2 therapeutic classes in combination with metformin. Fewer adverse events and cardiovascular events were observed in combination with metformin in the DPP-4 inhibitor-treated group compared with the sulfonylurea-treated group (RR: 0.90; 95% CI, 0.86-0.94; I^2 = 83% and RR: 0.54; 95% CI, 0.37-0.79; I^2 = 0%, respectively). Additionally, less hypoglycemia and severe hypoglycemia were observed in combination with metformin in the DPP-4 inhibitor-treated group compared with the sulfonylurea-treated group (RR: 0.17; 95% CI, 0.13-0.22; I^2 = 76% and RR: 0.10; 95% CI, 0.05-0.19; I^2 = 0%). The mean difference in weight gain was 1.92 kg, in favor of DPP-4 treated patients. The observed rates of hypoglycemia, severe hypoglycemia, and weight gain favored DPP-4 inhibitors in the monotherapy evaluation also. Heterogeneity in the data for some outcomes is a limiting factor for the applicability of the meta-analysis. The analysis included both DPP-4 inhibitors and sulfonylureas not available in the US.
- ***Prim Care Diabetes*. 2021;15(2):227-233.[m,n]** In a network meta-analysis of 15 randomized,controlled trials, adults with T2DM (n = 125,796) were administered a DPP-4 inhibitor or an SGLT2 inhibitor compared with a control group of standard of care or placebo. Indirect comparison demonstrated SGLT2 inhibitors are more effective than DPP-4 inhibitors at reducing the incidence of MACE (OR: 0.86; 95% CI, 0.78-0.92). Compared with DPP-4 inhibitors, SGLT2 inhibitors demonstrated reductions in cardiovascular death (OR: 0.85; 95% CI, 0.71-1.01), nonfatal MI (OR: 0.84; 95% CI, 0.74-0.95), and all-cause mortality (OR: 0.78; 95% CI, 0.69-0.89). There was not a statistically significant difference in reduction of nonfatal stroke.
- ***Ther Adv Drug Saf*. 2022;13.[o]** In a meta-analysis of 16 randomized, controlled trials, patients ≥ 65 y with T2DM were administered a DPP-4 inhibitor, including alogliptin, linagliptin, saxagliptin, sitagliptin, teneligliptin, or vildagliptin, as an add-on therapy compared with standard of care, no treatment, or placebo. Studies were included if ≥ 80% of the study population was ≥ 65 y or reported subgroup analyses of patients ≥ 65 y. The baseline HbA1c ranged from 7.1% to 10%. No statistically significant differences in all-cause mortality (RR: 1.04; 95% CI, 0.89-1.21) or incidence of hypoglycemia (RR: 1.08; 95% CI, 1.01-1.16) were observed. Additionally, no difference in overall adverse events was observed between the groups. The analysis included teneligliptin and vildagliptin which are not available in the US.

Cardiovascular outcome trials

- ***N Engl J Med*. 2013;369(14):1327-35.[p]** EXAMINE was a multicenter, randomized, double-blind trial, in which adult patients with T2DM (n = 5,380) were administered alogliptin or placebo. Inclusion criteria consisted of adults with T2DM, HbA1c of 6.5% to 11.0%, or 7% to 11.0% if receiving insulin, and had an acute coronary syndrome within 15 to 90 d before randomization. The primary outcome was a composite of cardiovascular death, nonfatal MI, or nonfatal stroke. Noninferiority of linagliptin was confirmed if the upper boundary of the HR was < 1.3. At a median follow-up of 1.5 y, the primary outcome occurred in 11.3% of the alogliptin-treated group vs. 11.8% in the placebo group (HR: 0.96; *P* < .001). More patients in the alogliptin-treated group experienced at least 1 hospitalization for heart failure (3.9% vs. 3.3% for placebo). The mean difference in HbA1c was -0.36% in favor of alogliptin (*P* < .001). There were no statistically significant differences in incidence of hypoglycemia, cancer, pancreatitis, and initiation of dialysis between the 2 groups.
- ***N Engl J Med*. 2013;369(14):1317-26.[q]** SAVOR-TIMI 53 was a multicenter, randomized, double-blind trial, in which adult patients with T2DM (n = 16,492) were administered saxagliptin or placebo. Inclusion criteria consisted of adults with T2DM, HbA1c of 6.5% to 12.0%, and either established multiple risk factors (≥ 55 y for men, ≥ 60 y for women, dyslipidemia, hypertension, or smoking) or for cardiovascular disease (≥ 40 y, history of atherosclerosis involving the coronary, cerebrovascular, or peripheral vasculature). The primary outcome was a composite of cardiovascular death, MI, or ischemic stroke. At a median follow-up of 2.1 y, the primary outcome occurred in 7.3% of the saxagliptin-treated group vs. 7.2% in the placebo group (HR: 1.0; 95% CI, 0.89-1.12). Saxagliptin

demonstrated noninferiority to placebo. The secondary outcome of cardiovascular death, MI, stroke, hospitalization for unstable angina, coronary revascularization, or heart failure occurred in 12.8% of the saxagliptin-treated group vs. 12.4% of the placebo group (HR: 1.02; 95% CI, 0.94 to 1.11). More patients in the saxagliptin-treated group were hospitalized for heart failure than the placebo group (3.5% vs. 2.8%, respectively; HR: 1.27; 95% CI, 1.07-1.51). Adjudication-confirmed acute pancreatitis was recorded in 0.3% of the saxagliptin-treated group vs. 0.2% in the placebo group. Adjudication-confirmed chronic pancreatitis occurred in < 0.1% of the saxagliptin-treated group vs. 0.1% of the placebo group.

- ***Lancet.* 2015;385(9982):2067-76.**[ll] In a post-hoc analysis of EXAMINE, the investigators sought to determine the incidence of hospital admission for heart failure. Cardiovascular death and hospital admission for heart failure were assessed by history of heart failure and BNP concentration at baseline. No effect was observed on cardiovascular death and hospital admission for heart failure in the post-hoc analysis (HR: 1.00; 95% CI, 0.82-1.21).
- ***N Engl J Med*. 2015;373(3):232-42.**[s] TECOS was a multicenter, randomized, double-blind trial, in which adults with T2DM (n = 14,671) were administered sitagliptin or placebo in addition to their existing therapy. Inclusion criteria consisted of adults > 50 y with T2DM, HbA1c 6.5% to 8% at baseline when treated with 1 or 2 stable doses of oral antidiabetic agents (metformin, pioglitazone, or sulfonylurea) or insulin, and established cardiovascular disease. The primary outcome was a composite of cardiovascular death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina. Noninferiority of sitagliptin was confirmed if the upper boundary of the HR was < 1.3. At a median follow-up of 3 y, the primary outcome occurred in 11.4% of the sitagliptin-treated group vs. 11.6% in the placebo group (HR: 0.98; 95% CI, 0.88-1.09). The mean difference in HbA1c was -0.29% in favor of sitagliptin (P < .001). There was no statistical difference in rates of hospitalization for heart failure, or in the rates of acute pancreatitis and pancreatic cancer.
- ***JAMA*. 2019;321(1):69-79.**[t] CARMELINA was a multicenter, randomized, double-blind trial, in which adults with T2DM (n = 6,979) were administered linagliptin or glimepiride in addition to existing therapy. Inclusion criteria consisted of adults with T2DM, HbA1c 6.5% to 10% at baseline, and high cardiovascular and renal risk. The primary outcome was a composite of cardiovascular death, nonfatal MI, or nonfatal stroke. Noninferiority of linagliptin was confirmed if the upper boundary of the HR was < 1.3. At a median follow-up of 2.2 y, the primary outcome occurred in 12.4% of the linagliptin-treated group vs. 12.1% in the glimepiride group (HR: 1.02; 95% CI, 0.89-1.17). One or more episodes of hypoglycemia was observed in 29.7% of the linagliptin-treated group vs. 29.4% in the glimepiride group. Adjudication-confirmed pancreatitis was recorded in 0.3% of the linagliptin-treated group vs. 0.1% in the glimepiride group.

Abbreviations: ALT = alanine transaminase; BNP = brain natriuretic peptide; CI = confidence interval; CrCl = creatinine clearance; CYP = cytochrome enzyme; DPP-4 = dipeptidyl peptidase-4; eGFR = estimate glomerular filtration rate; ESRD = end-stage renal disease; GIP = gastric inhibitory peptide; GLP-1 = glucagon-like peptide-1; HR = hazard ratio; HbA1c = hemoglobin A1c; MACE = major adverse cardiovascular events; MI = myocardial infarction; OR = odds ratio; RR = relative risk; SGLT2 = sodium-glucose cotransporter 2; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; ULN = upper limit of normal; WAC = wholesale acquisition cost

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Vizient, Inc.
290 E. John Carpenter Freeway
Irving, TX 75062-5146
(800) 842-5146

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