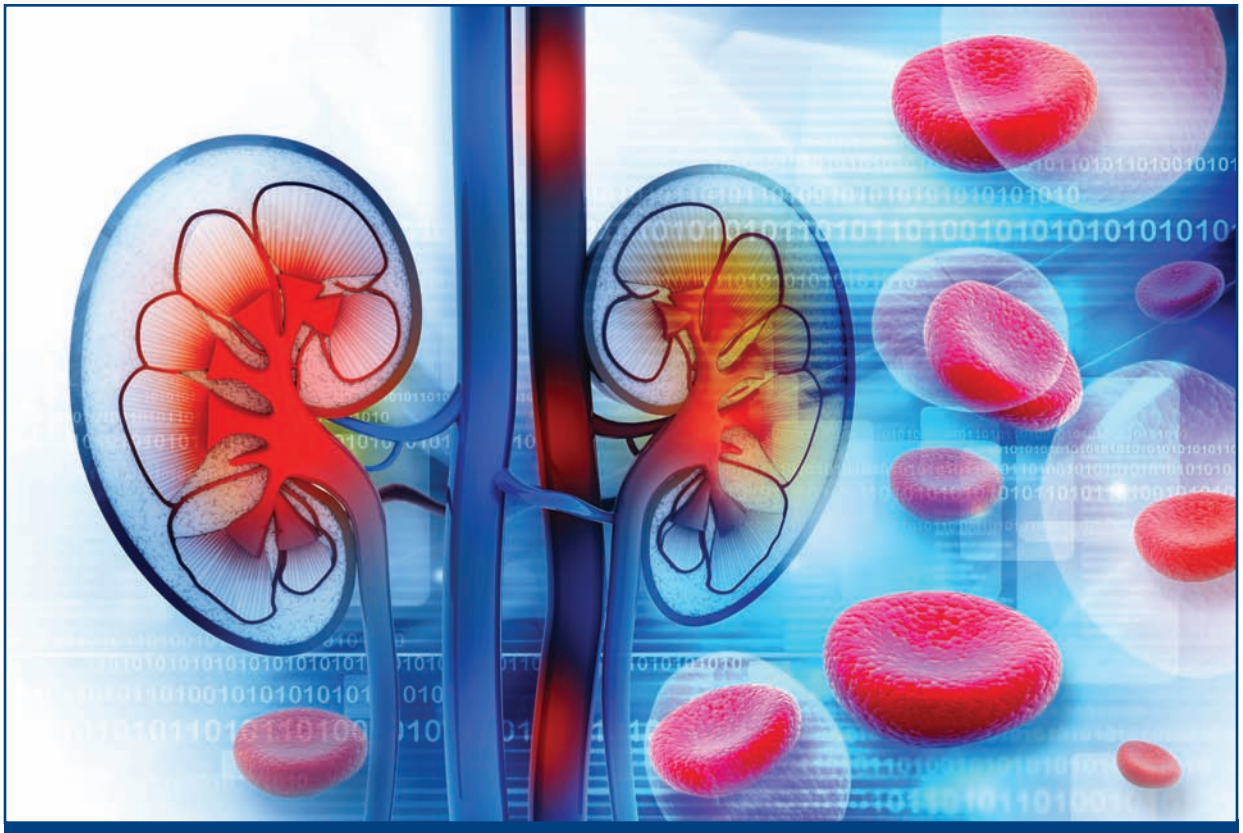

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# USE OF DIPEPTIDYL PEPTIDASE-4 INHIBITORS IN PATIENTS WITH type 2 diabetes & chronic kidney disease

OPEN

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***Abstract: There is a need for treatment options in patients with type 2 diabetes mellitus and kidney disease to achieve glucose targets without risk of hypoglycemia. This article describes management options for these patients using glucose-lowering therapies, in particular dipeptidyl peptidase-4 inhibitors.***

Chronic kidney disease (CKD) affects approximately 2 million individuals worldwide, and type 2 diabetes mellitus (T2DM) is its leading cause.[1] With the prevalence of T2DM increasing steadily, CKD will continue to rise.[1] Diabetic kidney disease (DKD) occurs in 20% to 40% of patients with diabetes mellitus and is defined as the presence of increased urinary albumin excretion ([UAE] a ratio of urinary albumin to creatinine 30 mg/g or more), decreased glomerular filtration rate ([GFR] less than 60 mL/min/1.73 $m^2$), or both.[2,3]

Persistent increased UAE (30 mg/g to 299 mg/g) is a well-established marker for the development of DKD and increased cardiovascular disease (CVD) risk in patients with T2DM and in the general population.[4] The incidence of end-stage renal disease (ESRD) in U.S. patients with diabetes

**Keywords: chronic kidney disease, CKD, diabetes mellitus, dipeptidyl peptidase-4 inhibitors, DPP-4, T2DM, type 2 diabetes mellitus**

mellitus increased to 30% between 1998 and 2012 reveals an urgent need for improved therapeutic options.[5]

A vital part of reducing the risk of DKD and preserving the kidney requires targeting glycated hemoglobin (HbA1C) levels to less than 7%.[6,7] Numerous studies show that intensive glucose lowering may delay the onset and progression of albuminuria in T2DM.[8,9] However, therapeutic choices for patients with T2DM and DKD can be limited because of the reduced renal clearance of some agents, which prolongs their half-life. Drug or metabolite accumulation may potentially increase the risk of adverse reactions.[10]

Therefore, some glucose-lowering agents are contraindicated in subjects with kidney insufficiency. Other agents require dosage adjustment and frequent monitoring to avoid adverse reactions (hypoglycemia, fluid retention and edema, weight gain, hepatic damage, or lactic acidosis), which may be more severe due to the underlying pathophysiology of DKD.[11]

Treatment strategies for patients with DKD should include reduction in BP, weight loss, diabetes and lipid management, protein restriction, smoking cessation, and lowering of urinary albumin levels. This article provides an overview of the management of DKD and appropriate glucose-lowering therapies for use in patients with T2DM.

## Glycemic control

Because the DKD patient population is often excluded from clinical studies, optimal glycemic targets in patients with DKD are poorly understood. Clinical trials have demonstrated that lowering HbA1C to less than 7% can prevent the progression of albuminuria and microvascular complications.[6,9,12,13]

A broader HbA1C range may be suitable for select patients. Specifically, less strict glycemic control (HbA1C, 7% to less than 8%) is recommended for patients with a history of severe hypoglycemia, over age 60, limited life expectancy, advanced kidney disease, microvascular or macrovascular complications, extensive comorbid conditions, or a long duration of T2DM. Additional health status considerations for adults age 65 and older are impairment in activities of daily living or mild to moderate cognitive impairment.[2,12]

## BP control

Hypertension is a common comorbidity in CKD and CVD.[13] The United Kingdom Prospective Diabetes Study indicated that BP control can reduce the development of DKD.[14] Patients randomized to tight BP control (mean achieved BP, 144/82 mm Hg) experienced a 32% reduction in diabetes-related mortality and a 44% reduction in stroke versus those assigned to less stringent BP control (mean achieved BP, 154/87 mm Hg).

In patients with T2DM and hypertension, treatment with either angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) can delay the onset of elevated albuminuria, a risk factor for CVD.[15] In addition, ARBs (irbesartan and losartan) reduced the progression of albuminuria and ESRD in patients with T2DM independent of their BP effects.[16,17] Data from the Heart Outcomes Prevention Evaluation (HOPE) and the Microalbuminuria, Cardiovascular, and Renal Outcomes (MICRO-HOPE) substudy demonstrated that the ACEI ramipril reduced the risk of overt nephropathy by 24% in patients with diabetes mellitus.[18]

Additionally, HOPE showed an improvement in cardiovascular outcomes. Ramipril treatment reduced the risk of the combined primary outcome of myocardial infarction (MI), stroke, and cardiovascular death by 25% after adjustment for changes in BP over a median follow-up of 4.5 years in patients with diabetes mellitus.[18]

For the treatment of patients with T2DM and hypertension, the American Diabetes Association (ADA) recommends either an ACEI or ARB (but not both).[2] Multiple-drug therapy with renin-angiotensin-aldosterone system (RAAS) inhibition and a thiazide diuretic will likely be required to reach BP targets of less than 140/90 mm Hg.[2,15] Lower systolic targets may be appropriate for certain individuals, such as younger patients, if they can be achieved without undue treatment burden.[12]

## Lowering albuminuria

Lowering albuminuria through BP reduction is associated with a decreased risk of progression to ESRD.[2,19] A post-hoc analysis of the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study concluded that a reduction in either albuminuria or BP is important for renal outcomes, and a reduction in both improved clinical outcomes.[19]

Several studies have demonstrated that multifactorial treatment with renin-angiotensin system blockade, aspirin, and lipid-lowering agents reduces the risk of albuminuria, declining kidney function, and adverse cardiovascular events.[20] The ADA has combined the previous two categories of microalbuminuria (30 mg/day to 299 mg/day) and macroalbuminuria (300 mg/day or more) into one grouping of albuminuria, now defined as a urine albumin to creatinine ratio (UACR) of 30 mg/g or more and has recently updated recommendations for regular screening and management of DKD in patients with T2DM (see *Screening and management suggestions in T2DM*).[2]

## Managing hyperglycemia

Metformin continues to be the drug of choice for patients with T2DM because of its demonstrated safety and low cost;

**Screening and management suggestions in T2DM[2,12]**

| Condition | Management | Treatment |
|---|---|---|
| Nephropathy | Annual measurement of creatinine, UACR, potassium for all patients:<br>• eGFR 45-60 mL/min/1.73 m²<br>– Monitor eGFR every 6 months<br>– Monitor electrolytes, bicarbonate, hemoglobin, calcium, phosphorus, parathyroid hormone at least annually<br>• eGFR 30-44 mL/min/1.73 m²<br>– Monitor eGFR every 3 months<br>– Monitor electrolytes, bicarbonate, hemoglobin, calcium, phosphorus, parathyroid hormone, albumin, weight every 3-6 months<br>• eGFR <30 mL/min/1.73 m²<br>– Refer to nephrologist<br>• Definitions of abnormalities in albumin excretions<br>– Normal: <30 mg/g creatinine<br>– Increased UAE*: ≥30 mg/g creatinine<br>*Historically, UAEs from 30 to 299 mg/g have been referred to as microalbuminuria, whereas those >300 have been referred to as macroalbuminuria, or clinical albuminuria<br>• Optimize BP control to reduce the risk or slow the progression of DKD<br>• Refer to a nephrologist when uncertain about the etiology of kidney disease, difficult management issues, or advanced kidney disease | • ACEIs/ARBs not recommended for the primary prevention of DKD in patients with normal BP, UACR (<30 mg/g), or normal eGFR<br>• ACEIs/ARBs suggested for the treatment of nonpregnant women with hypertension and modestly elevated UAE (30–299 mg/g) and strongly recommended for those with UAE ≥300 mg/g<br>• With ACEI/ARB, or diuretic use, monitor serum creatinine and potassium levels<br>• Continue monitoring of UACR in patients with albuminuria to assess progression of DKD<br>• When eGFR is <60 mL/min/1.73 m², evaluate and manage potential complications of CKD<br>• Refer to a nephrologist when uncertain about the etiology of kidney disease, difficult management issues, or advanced kidney disease |
| Hypertension | • Measure BP at every routine visit; reconfirm elevated BP on a separate day<br>• If BP >120/80 mm Hg, recommend lifestyle changes<br>• If BP >140/90 mm Hg, initiate pharmacotherapy<br>• Treat patients with diabetes mellitus and hypertension to a BP goal of <140 mm Hg (SBP) and <90 mm Hg (DBP)<br>– Lower systolic (130 mm Hg) and diastolic (80 mm Hg) targets may be appropriate for younger patients with albuminuria, and/or hypertension and ≥1 additional CVD risk factors, if they can be achieved without undue treatment burden<br>• In older adults, pharmacologic therapy to treatment goals of <130/70 mm Hg is not recommended | • If BP >120/80 mm Hg, recommend lifestyle changes<br>• If BP >140/90 mm Hg, initiate pharmacotherapy, either with an ACEI or an ARB<br>• In older adults, pharmacologic therapy to treatment goals of <130/70 mm Hg is not recommended<br>• Multiple-drug therapy is required to achieve BP targets, such as adding a thiazide diuretic and ACEI/ARB<br>• If ACEIs, ARBs, or diuretics are used, monitor serum creatinine/eGFR and serum potassium levels |
| Retinopathy | • Dilated and comprehensive eye exam by an ophthalmologist or optometrist shortly after diagnosis<br>– If there is no evidence of retinopathy for ≥1 eye exam, repeat eye exam every 2 years<br>– If there is retinopathy, repeat eye exam annually by an ophthalmologist or optometrist<br>– If retinopathy is progressing or sight-threatening, exams will be required more frequently<br>• Refer patients with macular edema, NPDR, or any PDR to an ophthalmologist | • Refer patients with macular edema, NPDR, or any PDR to an ophthalmologist<br>– Macular edema: Anti-VEGF therapy indicated<br>– High-risk PDR, severe macular edema, and severe NPDR: Laser photocoagulation<br>• Aspirin therapy for cardioprotection, not contraindicated |

## Screening and management suggestions in T2DM[2,12]

| Condition | Management | Treatment |
|---|---|---|
| Neuropathy | • Screen for diabetic peripheral neuropathy at diagnosis of T2DM; continue annually<br>• Screen for signs of cardiovascular autonomic neuropathy (orthostasis, resting tachycardia) with more advanced disease<br>• Optimize glucose control to slow the progression of neuropathy in patients with T2DM<br>• Assess and treat patients to reduce pain related to diabetic peripheral neuropathy and symptoms of autonomic neuropathy to improve quality of life | • Optimize glucose control to slow the progression of neuropathy in patients with T2DM<br>• Assess and treat patients to reduce pain related to diabetic peripheral neuropathy and symptoms of autonomic neuropathy to improve quality of life<br>• Either pregabalin or duloxetine is recommended as initial pharmacologic treatment for neuropathic pain in diabetes |
| Dyslipidemia | • Obtain a fasting lipid profile at diagnosis, then at least annually<br>• Lifestyle modification should focus on weight loss, calorie management, and exercise | • Statin therapy, unless otherwise contraindicated<br>– For patients of all ages with diabetes and atherosclerotic CVD, high-intensity statin therapy should be added to lifestyle therapy, unless otherwise contraindicated<br>– For patients with diabetes (age <40 years with additional atherosclerotic CVD risk factors) consider using moderate-intensity or high-intensity statin and lifestyle therapy<br>– For patients with diabetes (ages 40-75 years without additional atherosclerotic CVD risk factors) consider using moderate-intensity statin and lifestyle therapy<br>• Intensify lifestyle therapy and optimize glycemic control for patients with elevated triglyceride levels ≥150 mg/dL and/or low HDL cholesterol (<40 mg/dL for men, <50 mg/dL for women)<br>• For patients with fasting triglyceride levels ≥500 mg/dL, evaluate for secondary causes of hypertriglyceridemia and consider medical therapy to reduce the risk of pancreatitis |
| Foot care | • Perform annual comprehensive foot exam, including inspection and assessment of foot pulses<br>• Patients with a history of ulcers or amputations, foot deformities, insensate feet, and peripheral arterial disease should have their feet examined at every visit<br>• Refer patients with symptoms of claudication or decreased or absent pedal pulses for ankle-brachial index and further vascular assessment<br>• A multidisciplinary approach is recommended for patients with foot ulcers and high-risk feet (patients on dialysis and those with Charcot foot, prior ulcers, or amputation)<br>• Refer to a podiatrist or other appropriate specialist, patients who smoke or have loss of protective sensation, structural abnormalities, or those with a history of lower-extremity complications | • A multidisciplinary approach is recommended for patients with foot ulcers and high-risk feet (patients on dialysis and those with Charcot foot, prior ulcers, or amputation)<br>• Refer patients who smoke or have loss of protective sensation, structural abnormalities, or history of lower-extremity complications referred to a podiatrist or other appropriate specialist |

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BP = blood pressure; CKD = chronic kidney disease; CVD = cardiovascular disease; DBP = diastolic blood pressure; DKD = diabetic kidney disease; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; SBP = systolic blood pressure; T2DM = type 2 diabetes mellitus; UACR = urine albumin-to-creatinine ratio; UAE = urinary albumin excretion; VEGF = vascular endothelial growth factor

its mainly renal elimination pathway makes it unsuitable for patients with severe CKD because of the rare risk of lactic acidosis.[21] While the FDA has recently relaxed their labeling recommendations for metformin-containing products for use in patients with CKD, they are still contraindicated in patients with eGFR below 30 mL/min/1.73 $m^2$.[22]

If metformin is not tolerated or contraindicated, second-line agents are recommended. Sulfonylureas undergo significant renal clearance and increase the risk of hypoglycemia in patients with CKD. Glipizide is the preferred agent for patients with stage 3 to 5 CKD; glyburide should be avoided in these patients due to its long duration of action.[10] Thiazolidinediones, although not cleared via the kidney, are associated with fluid retention and edema, and should not be used in patients with heart failure and should be used with caution in those with CVD without heart failure. Initiation of thiazolidinediones in patients with established New York Heart Association Class III or IV heart failure is contraindicated, and thiazolidinedione use should be avoided in patients with symptomatic heart failure.[23]

Renal recommendations need to be considered for the glucagon-like peptide-1 (GLP-1) receptor agonists. Exenatide and exenatide extended release should not be used in patients with severe kidney impairment (creatinine clearance less than 30 mL/min) or ESRD, and should be used with caution in patients with moderate renal impairment or kidney transplantation.[24,25] In patients with moderate renal impairment, caution is advised when initiating or escalating doses of exenatide or liraglutide.[25,26] Lixisenatide should not be used in patients with ESRD.[27] No dose adjustment is needed for albiglutide, dulaglutide, liraglutide, or lixisenatide in patients with renal impairment, but renal function needs to be monitored if patients display severe gastrointestinal reactions.[26-29]

The glucose-lowering efficacy of sodium glucose cotransporter 2 (SGLT2) inhibitors is dependent on kidney function, and lower efficacy can be expected with decreased eGFR. The FDA has added warnings regarding urosepsis, urinary tract infections, and kidney injury in all SGLT2 inhibitors' prescribing labels. Canagliflozin and empagliflozin are not recommended for patients with eGFR less than 45 mL/min/1.73 $m^2$, and dapagliflozin should not be used when the eGFR is less than 60 mL/min/1.73 $m^2$.[30-32]

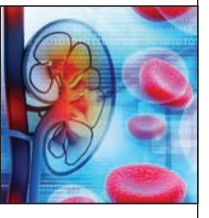
## Using DPP-4 inhibitors

Dipeptidyl peptidase-4 (DPP-4) inhibitors prevent the breakdown of GLP-1 and glucose-dependent insulinotropic peptide, two incretins pivotal for glucose regulation.

The four DPP-4 inhibitors currently approved for the treatment of T2DM in the United States include sitagliptin, saxagliptin, linagliptin, and alogliptin.[33-49] These agents are effective at lowering HbA1C in patients age 60 and older with a long duration of T2DM (more than 10 years) and with moderate-to-severe kidney insufficiency, including ESRD and dialysis, while displaying a low propensity for hypoglycemia and weight neutrality.[50,51]

A meta-analysis of 10 trials of 12 to 52 weeks with 1,951 patients who had moderate-to-severe CKD demonstrated that DPP-4 inhibitor monotherapy reduced HbA1C by –0.52% versus placebo or no treatment and was not associated with an increased risk of hypoglycemia or weight gain.[50] Compared with glipizide monotherapy, DPP-4 inhibitors showed no difference in HbA1C lowering but provided a lower incidence of hypoglycemia.[50] There were no reported increases in body weight, incidents of severe adverse events, or total mortality.

***In patients with moderate renal impairment, caution is advised when initiating or escalating doses of exenatide or liraglutide.***

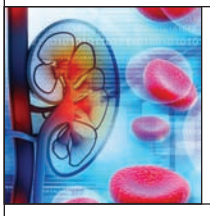


*Sitagliptin.* This drug reduced HbA1C by 0.7% to 0.8% from baseline in several randomized studies in patients with CKD and resulted in fewer cases of hypoglycemia than the active comparator.[37-39] Some trials also assessed changes in UAE or UACR and showed decreases with sitagliptin (mean change, –195 mg/g) versus placebo (457 mg/g).[37] In a 52-week study, sitagliptin added to sulfonylureas decreased UAE by more than 50% (76.2 mg/g to 33.0 mg/g).[52] One analysis showed that sitagliptin, as an add-on to metformin, was more likely to reduce UACR by more than 20% in patients with the highest baseline UACR levels (greater than 300 mg/g) than in those with lower baseline UACR levels (30 mg/g to 100 mg/g).[53] A retrospective claims-based cohort study showed that treatment with sitagliptin did not increase the risk of acute kidney failure status.[54]

The recently completed Trial to Evaluate Cardiovascular Outcomes after Treatment with Sitagliptin (TECOS) included patients with an eGFR of 30 mL/min/1.73 $m^2$ or greater and assessed secondary kidney function outcomes.[55] The mean baseline eGFR for all patients was 74.9 ± 21.1 mL/min/1.73 $m^2$. Of those, 9.4% on sitagliptin and 9.3% on placebo had an eGFR less than 50 mL/min/1.73 $m^2$. After 48 months, the mean change from baseline was greater in the sitagliptin group than in the placebo group (–4.0 ± 18.4 and –2.8 ± 18.3 mL/min/1.73 $m^2$, respectively). This slightly lower eGFR with sitagliptin remained consistent over all

visits .[55] Additionally, an ongoing phase 4 trial will evaluate the effects of sitagliptin plus an ACEI or ARB on reducing microalbuminuria in patients with T2DM.

*Saxagliptin.* In a 52-week study of patients with T2DM and CKD, use of saxagliptin resulted in a greater adjusted mean decrease in HbA1C than placebo (treatment difference, –0.73%, $P < 0.001$), with comparable rates of hypoglycemia (29% versus 28%). Reductions in adjusted mean HbA1C values were numerically greater with saxagliptin 2.5 mg once daily versus placebo in patients with moderate and severe CKD; however, reductions were similar in those with ESRD.[40]



***Lowering plasma glucose and HbA1C levels remains an important component of disease management.***

A prospective analysis of renal outcomes from the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction (SAVOR-TIMI) 53 trial was conducted in more than 16,000 patients with T2DM.[56] Patients receiving saxagliptin in addition to usual care were more likely to demonstrate improvements in UACR compared with those receiving placebo (11% versus 9%, $P < 0.01$), with the most noteworthy improvement occurring among those with albumin levels of 30 mg/g to 300 mg/g at baseline. After 1 year, 31.3% versus 25.7% of patients receiving saxagliptin compared with placebo reverted to normoalbuminuria ($P < 0.0001$).[56]

*Linagliptin.* Treatment with this drug resulted in mean placebo-corrected reductions in HbA1C from –0.53% to –1.08% in six randomized controlled studies comprising patients with mild-to-severe CKD, with an incidence of severe hypoglycemia comparable to or lower than placebo.[41-44,46,57] A recent retrospective analysis assessed data from two clinical trials in patients with T2DM and mild-to-severe CKD receiving linagliptin as an add-on to insulin.[46] Placebo-adjusted mean HbA1C changes from baseline were –0.59% and –0.69% after 24 weeks in patients with mild and moderate kidney impairment, respectively, and –0.43% after 12 weeks in patients with severe kidney impairment.

The frequencies of severe hypoglycemia with linagliptin (2% to 6%) were similar to those of placebo (1% to 6%) in patients with mild, moderate, or severe kidney impairment, respectively.[46] Data from this analysis show that the addition of linagliptin to insulin in patients with T2DM and CKD improved glycemic outcomes and was well tolerated. A pooled analysis of four studies involving 217 patients with T2DM and prevalent albuminuria (UACR, 30 mg/g to 3,000 mg/g creatinine) receiving linagliptin in addition to stable RAAS inhibitors found a significant reduction in albuminuria; this observation was independent of changes in glucose level or systolic BP.[42]

A meta-analysis of 13 phase 3 trials of linagliptin versus placebo in patients with T2DM evaluated renal outcomes using a composite primary endpoint of new-onset microalbuminuria, macroalbuminuria, CKD, acute kidney failure, and death by any cause.[58] This composite endpoint was reached in 12.8% of patients receiving linagliptin compared with 15.6% of those receiving placebo (hazard ratio = 0.84).

MARLINA-T2D (Efficacy, Safety & Modification of Albuminuria in Type 2 Diabetes Subjects With Renal Disease With LINAgliptin), a prospectively designed, 24-week trial assessing the effects of linagliptin on albuminuria in patients with T2DM and persistent albuminuria (UACR, 30 mg/g to 3,000 mg/g), demonstrated improved glycemic control without any significant changes to the UACR.[41]

*Alogliptin.* This drug has been assessed in patients with T2DM and CKD in a few small studies.[47,48] In a 48-week hemodialysis trial ($n = 30$), alogliptin significantly reduced HbA1C levels from a baseline of 7.1 ± 0.2% to 6.3 ± 0.2% ($P < 0.0001$) and was generally well tolerated.[48] In 16 patients undergoing hemodialysis, long-term administration of alogliptin once daily for 24 months decreased HbA1C levels significantly (7.1% to 5.8%) and was well tolerated, but required renal dosing considerations and safety monitoring.[47]

This class of agents may present a viable choice for patients with T2DM and renal impairment.[50,51] Whereas sitagliptin, saxagliptin, and alogliptin share renal elimination pathways and require dose adjustment in patients with moderate-to-severe renal impairment, linagliptin is primarily excreted via bile and gut and does not require dose adjustment for any level of kidney function. Warnings for DPP-4 inhibitors include the risk of acute pancreatitis, hypersensitivity reactions, severe and disabling arthralgia, and bullous pemphigoid. DPP-4 inhibitors should be discontinued if any of these conditions develop. Patients taking saxagliptin and alogliptin should be monitored for heart failure; if heart failure develops, treat the patient according to current standards of care and consider discontinuing the drug.[59]

## Clinical practice considerations

Patients with T2DM and DKD often have other comorbidities (hypertension, dyslipidemia) that require a multifactorial treatment approach. Patients should be counseled on proper nutrition, such as reducing sodium and moderating protein and potassium intake; emphasizing vegetables, low-fat or

nonfat dairy products, whole grains, nuts, legumes, fish, and poultry; and minimizing red meat.[2] Lifestyle changes should be applied to all high-risk patients, including smoking cessation, weight loss, and exercise.

Patients require regular visits to screen and monitor for micro- and macrovascular complications in a coordinated team approach addressing both T2DM and CKD in order to minimize the risk of adverse cardiovascular events. Lowering plasma glucose and HbA1C levels remains an important component of disease management and end-organ disease prevention.

NPs must balance the benefits of antidiabetic agents with potential adverse reactions, such as hypoglycemia and weight gain. The choice of glucose-lowering agents in patients with DKD is limited because renal function affects the safety profile of many agents. Metformin, the first choice for treatment of T2DM in the general population, had severe restrictions regarding its use in CKD; however, the FDA recently relaxed the labeling for metformin-containing products, making them a treatment option for patients with eGFR greater than 60 mL/min/1.73 $m^2$.[22] Among the sulfonylureas, glyburide cannot be used in CKD, but glipizide and glimepiride (if initiated at a low dose) can be appropriate choices with weight neutrality and the convenience of once-daily dosing.[60]

Thiazolidinediones should not be used in patients with heart failure and should be used with caution in those with CVD without heart failure due to the associated risks of fluid retention and edema.[23] Among the GLP-1 receptor agonists, exenatide should not be used in severe CKD and should be used with caution in kidney transplant patients.[24,25] SGLT2 inhibitors have a lower efficacy with a decreased eGFR and are generally not recommended for an eGFR less than 45 to 60 mL/min/1.73 $m^2$ because they rely on the ability of the kidneys to eliminate glucose.[30-32] Of note, the FDA includes warnings regarding urosepsis, urinary tract infections, and kidney injury in all SGLT2 labels.[2]

Evidence from clinical trials suggests that DPP-4 inhibitor therapy is also a viable option for patients with T2DM and CKD, affording a lower incidence of hypoglycemia, without weight gain, compared with other agents.[50] When combined with insulin secretagogues or insulin, dosage reduction is recommended to reduce the risk of hypoglycemia. Sitagliptin, saxagliptin, and alogliptin require dose adjustments in patients with moderate-to-severe renal impairment, whereas linagliptin is primarily excreted by bile and gut; therefore, no dose adjustment is required.[59] In addition, data suggest that linagliptin may reduce albuminuria, a well-established risk factor for CKD and CVD, therefore offering NPs therapeutic options for this complex patient population.[41,61]

Because patients with T2DM and CKD are a diverse, difficult-to-treat population, an individualized treatment strategy should be utilized. This treatment plan necessitates commitment of the patient in terms of self-monitoring, and a variety of healthcare practitioners for ongoing educational reinforcement and a multifactorial treatment approach that includes medications, proper nutrition with meal planning, and physical activity. This approach will ensure the best possible outcome, with the least potential adverse reactions, improving patient adherence, long-term benefits, and overall cardiovascular risk reduction. NP

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