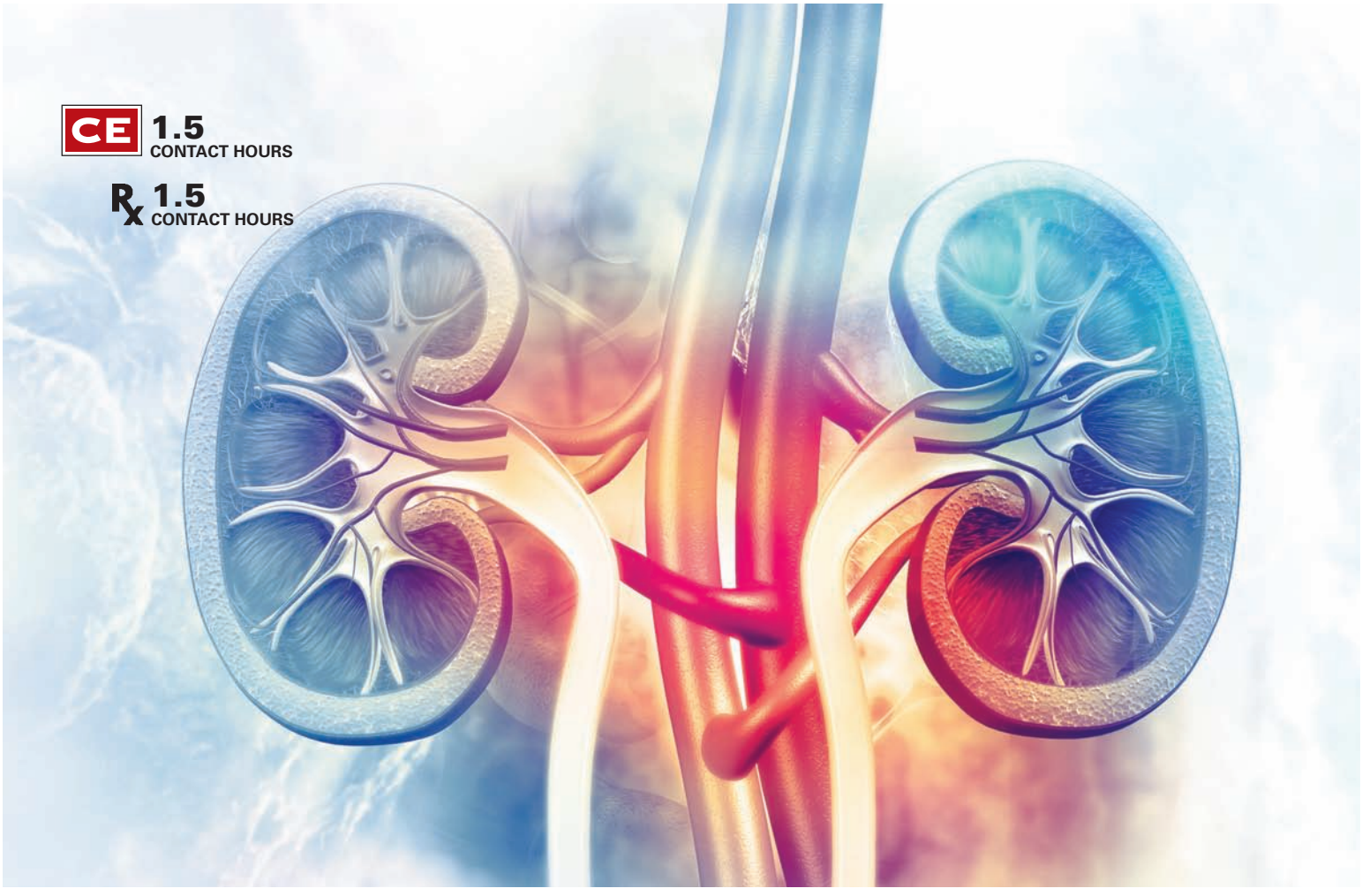
CE 1.5 CONTACT HOURS

Rx 1.5 CONTACT HOURS



Use of GLP-1 receptor agonists in patients with T2DM and chronic kidney disease

Abstract: Diabetes mellitus is the leading cause of chronic kidney disease (CKD) in the US. An increasing number of glucagon-like peptide-1 receptor agonists are available for diabetes management. Differences between medications in this class, as well as limited data on patients with CKD, underscore the importance of a patient-centered approach to care.

By Sarah Aldrich, PharmD, and Emily Ashjian, PharmD, BCPS, BCACP

Ms. L, a 68-year-old White female, presents to the clinic for follow-up management of type 2 diabetes mellitus (T2DM). Her medical history is significant for stage 3 chronic kidney disease (CKD), hypertension, hyperlipidemia, hypothyroidism, and clinical atherosclerotic cardiovascular disease (ASCVD). She is status post a two-vessel coronary artery bypass graft 2 years ago after an ST-elevation myocardial infarction (MI).

Her vital signs at her most recent clinic visit include: temperature, 98.1° F (36.7° C); HR, 72; respirations, 18; oxygen saturation 96% by pulse oximetry; and BP, 132/70 mm Hg; weight, 190 lb (86 kg); height, 5 ft 1 in; and BMI, 35.9. Her estimated glomerular filtration rate (eGFR) is currently 34 mL/min/1.73 m^2 based on a serum creatinine (SCr) level of 1.52 mg/dL using the Modification of Diet in Renal Disease equation. Her current hemoglobin A1C (A1C) of 8.4% is suboptimally

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Keywords: chronic kidney disease, diabetes, dialysis, dulaglutide, end-stage renal disease, exenatide, glucagon-like peptide-1 receptor agonist, liraglutide, lixisenatide, semaglutide, type 2 diabetes mellitus

controlled and increased from 7.7% 3 months ago. She has a normal urine microalbumin to creatinine ratio of 5 mg/g. All other labs are within normal limits.

Ms. L's current medications include metformin extended release 1,000 mg daily, insulin glargine 34 units daily, atorvastatin 40 mg daily, lisinopril 40 mg daily, metoprolol succinate 50 mg daily, and levothyroxine 50 mcg daily. She reports today that she does not want to start mealtime insulin and shares that despite her best efforts she has struggled to lose weight. Ms. L also reports that her sister recently started a glucagon-like peptide-1 (GLP-1) receptor agonist (RA), resulting in improvements in glycemic control and weight loss. Based on this information, the NP begins to consider adding a GLP-1 RA to this patient's regimen. However, based on this patient's history, the NP should first consider the use of this class of medications in patients with CKD.

Background

Diabetes mellitus and hypertension are the leading causes of CKD in the US.[1] Despite efforts to slow the rate of decline in renal function, over 650,000 individuals in the US have end-stage renal disease (ESRD); over 450,000 in this patient population receive dialysis.[1] Individuals age 60 and older have the highest prevalence of CKD, with 22.6% of those age 60 and older in the 2011-2014 National Health and Nutrition Examination Survey having an eGFR less than 60 mL/min/1.73 m^2.[2]

CKD is a general term used to describe a variety of disorders that affect the structure and function of the kidneys.[3,4] It is defined as an eGFR less than 60 mL/min/1.73 m^2 and/or markers of kidney damage that last for a minimum of 3 months. Markers of kidney damage include albuminuria, urine sediment abnormality, electrolyte abnormality caused by tubular disorders, structural abnormalities detected by imaging, histologic abnormalities, or a history of kidney transplant.[4] CKD is staged using eGFR and albuminuria classification. There are five stages of CKD, with stage 5 being the most severe.[3,4] (See *CKD staging and albuminuria.*)

Several factors are associated with a higher risk of CKD, including advanced age, low income or education level, reduced kidney mass, low birth weight, and family history of CKD. Racial and ethnic minorities are also more likely to be affected by CKD.[5-8] In the US, compared with White Americans, the prevalence of ESRD is approximately 3.7 times higher in Black Americans, 1.4 times higher in Native Americans, and 1.5 times higher in Asian Americans.[1,9] Hypertension can be both a cause and a result of CKD, and early treatment is necessary to slow progression.[9] Proteinuria is another progression factor that is directly related to cardiovascular morbidity and mortality.[10] Proteinuria also predicts kidney damage and CKD progression.[11] Smoking and obesity can also contribute to progression.[12-14]

Nephropathy affects an estimated 20% to 40% of those with diabetes.[15] Patients should be screened annually for diabetic nephropathy using measurements of eGFR and urine albumin. In patients who are diagnosed with diabetic nephropathy, an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) should be initiated to slow disease progression in conjunction with measures to improve overall glycemic control.[4,15]

In addition, nearly 50% of patients with CKD also have diabetes and/or cardiovascular disease (CVD).[1] Diabetes alone largely increases the risk of CVD, with the risk of future cardiovascular (CV) events the same as the risk in a patient with a previous MI.[16] It has also been shown that CKD or reduced eGFR is associated with increased risks of death, CV events, and hospitalization. A large multivariate analysis found an increased risk of death, CV events, and hospitalization in patients with an eGFR less than 60 mL/min/1.73 m^2 and a further increase in risk in patients with an eGFR less than 45 mL/min/1.73 m^2.[17] It has been speculated that this increased risk of CV events could be attributable to the many common metabolic abnormalities leading to atherosclerosis that exist between CKD and T2DM, which are often worsened by CKD. These risks contribute to the importance of not only targeting glycemic control but also reducing CV risk in patients with T2DM and CKD.[18]

There are many classes of medications available for treatment of T2DM; however, safety and efficacy data are limited in patients with CKD, particularly in advanced stages. The Cardiovascular Outcome Trial guidelines published in 2008 require new antihyperglycemic agents to undergo studies for CV safety due to the history of increased rates of MI and CV death shown with rosiglitazone.[19,20] This additional requirement has provided data resulting in new recommendations for the treatment of T2DM in patients with clinical ASCVD and CKD. After metformin and lifestyle changes, the 2019 American Diabetes Association (ADA) guidelines recommend the second-line agent be chosen based on the presence or absence of established ASCVD or CKD.[21] For patients with clinical ASCVD,

CKD staging and albuminuria

CKD is defined as abnormalities of kidney structure or function present for greater than 3 months with implications for health. CKD is classified based on cause, GFR category, and albuminuria category (CGA).

Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR and Albuminuria Categories KDIGO 2012				Persistent albuminuria categories (description and range)		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/1.73 m²) (description and range)	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); yellow: moderately increased risk; orange: high risk; red: very high risk.

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the 2019 ADA guidelines recommended initiating a GLP-1 RA with demonstrated CVD benefit with the strongest evidence supporting the use of liraglutide followed by semaglutide and exenatide extended release, respectively, or an SGLT-2 inhibitor with demonstrated CVD benefit if eGFR is adequate, with clinical trial evidence considered modestly stronger for empagliflozin as compared with canagliflozin.[21-26]

GLP-1 RAs

GLP-1 RAs work to bind and activate the GLP-1 receptor. Endogenous GLP-1 is an incretin hormone that works to increase insulin release from pancreatic beta cells, decrease glucagon secretion from alpha cells, increase muscular glucose uptake, decrease hepatic glucose production, and slow gastric emptying. Both endogenous GLP-1 and GLP-1 RAs work to reduce fasting and postprandial glucose levels. GLP-1 RAs have been demonstrated to result in decreases in weight and have a low risk of hypoglycemia when used as monotherapy.[27]

The most common adverse reaction of GLP-1 RAs is nausea and vomiting. Nausea may improve after a few weeks of therapy. It is recommended to start

semaglutide, liraglutide, and lixisenatide at lower doses to ensure tolerability before increasing to the therapeutically effective dose.[28-30] There is a warning for pancreatitis for this class. Semaglutide, liraglutide, dulaglutide, and exenatide ER also have a black box warning for thyroid c-cell tumors in animals and multiple endocrine neoplasia type 2.[28,29,31,32] Uniquely, there is a precaution for complications of diabetic retinopathy with use of semaglutide.[28] Note that there is a kidney impairment warning based on postmarketing reports of exenatide. The drug itself has not been found nephrotoxic but it has been suggested that adverse reactions such as nausea, vomiting, and diarrhea in the setting of reduced fluid intake may lead to hypovolemia and extracellular volume contraction. This change in volume may lead to kidney impairment, especially in patients who are also taking medications affecting the kidneys such as ACE inhibitors, ARBs, nonsteroidal anti-inflammatory drugs, and diuretics.[33]

Overall, GLP-1 RAs have been found to effectively reduce A1C and facilitate weight loss. Exenatide and lixisenatide have renal dosing recommendations; however, semaglutide, liraglutide, and dulaglutide do not have specific recommendations.[28-32,34] The LIRA-RENAL study demonstrated efficacy and safety of the use of liraglutide in patients with T2DM and stage 3 CKD.[35] Limited data exist regarding the use of GLP-1 RA in patients with stage 4 or 5 CKD. Studies investigating the efficacy, safety, and CV benefit in patients with clinical ASCVD have recently been published for semaglutide, liraglutide, lixisenatide, and exenatide ER.[22-24,36] These medications may have a relatively high cost and insurance plans may limit coverage to preferred GLP-1 RAs. Manufacturer copay assistance programs and cards are available for select GLP-1 RAs.

Exenatide/exenatide extended release

The first GLP-1 RA available was exenatide (Byetta), a short-acting formulation administered twice daily. The extended release (ER) formulations (Bydureon Pen, Bydureon Bcise) are administered once weekly and are available in two different pen devices; the newest device provides patients with an easier reconstitution process. Caution is recommended for exenatide and exenatide ER with a creatinine clearance (CrCl) less than 50 mL/min, with use not recommended when CrCl is less than 30 mL/min.[32,34] When added to metformin, sulfonylurea, thiazolidinedione, or a combination of two of these oral therapies, exenatide ER once weekly resulted in an A1C reduction of 1.6%, and short-acting exenatide (10 mcg twice daily) resulted in lowering A1C by 0.9% after 24 weeks.[32,34] As with the other GLP-1 RAs, nausea is one of the most common adverse reactions. The incidence of nausea was lower with exenatide ER (7% to 14%) than exenatide twice daily (35%).[37,38]

An analysis of 19 placebo-controlled and pooled-comparator-controlled clinical trials was conducted to determine the safety and tolerability of exenatide twice daily. Data were reviewed from controlled clinical trials of exenatide 5 or 10 mcg twice daily, compared with insulin and/or placebo, and included 5,594 intent-to-treat patients who were followed for 12 to 52 weeks. The study reviewed the incidence of adverse reactions between patients who received the drug and those who did not. Researchers found that nausea was the most frequent adverse reaction (36.9% in the exenatide group versus 8.3% in the control group) and that hypoglycemia was more common in patients with concomitant sulfonylurea use (26.5% in the exenatide group versus 20.7% in the control group) than in those who were not taking a sulfonylurea (3.1% in the exenatide group versus 2.7% in the control group). They found no difference in the incidence rates of renal impairment between the groups with 1.6 renal impairment-related adverse reactions occurring per 100 patient years in both groups.[39]

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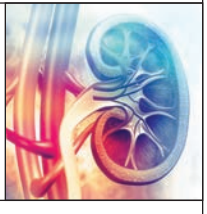
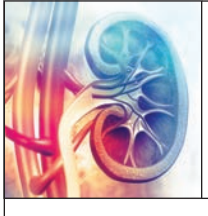


The CV effects of exenatide ER were evaluated in a double blind randomized controlled trial that included 14,752 patients with T2DM, randomized to receive once-weekly exenatide ER 2 mg or placebo. Patients with or without previous CVD were followed for a median of 3.2 years with a primary composite outcome of time to first occurrence of death from CV causes, nonfatal MI, or nonfatal stroke. Exenatide ER was found to be noninferior to placebo based on the primary composite outcome, which occurred in 11.4% of the exenatide group versus 12.2% in the placebo group (hazard ratio 0.91; 95% confidence

interval, 0.83 to 1.00). Exenatide was also determined noninferior to placebo in the intent-to-treat analysis regarding safety ($P < .001$ for noninferiority). There was no difference between the groups in the rates of death from CV causes, fatal or nonfatal MI, fatal or nonfatal stroke, hospitalization for heart failure, and hospitalization for acute coronary syndrome. Overall, there was no difference in CV event rate in patients with T2DM with or without previous CV disease.[24]

Liraglutide

Liraglutide (Victoza) was the second GLP-1 RA granted FDA approval. A once-daily injection, liraglutide is initiated at a dose of 0.6 mg daily for the first week of therapy to ensure tolerability. The 0.6 mg daily dose has not been demonstrated to improve glycemic control. If the patient tolerates the medication after the first week, it is recommended to increase the dose to 1.2 mg daily. If needed for further glycemic control and tolerated, liraglutide may be increased to 1.8 mg daily.[29] A 52-week trial including 746 patients evaluated monotherapy with liraglutide 1.2 mg daily, liraglutide 1.8 mg daily, and glimepiride 8 mg daily, and was completed prior to liraglutide approval. Patients had a mean A1C of 8.2% at baseline and mean weight of approximately 92 kg in the liraglutide groups. Liraglutide significantly reduced A1C over glimepiride, with an A1C lowering potential of 0.8% (1.2 mg) and 1.1% (1.8 mg) from baseline compared with 0.5% with glimepiride. In addition, body weight was reduced by 2.1 kg (liraglutide 1.2 mg) and 2.5 kg (liraglutide 1.8 mg) from baseline, whereas patients in the glimepiride group gained about 1.2 kg from baseline.[40]



Patients in the liraglutide group had lower rates of both renal and retinal microvascular outcomes compared with placebo.

Liraglutide is the only GLP-1 RA that has been studied for efficacy and safety in stage 3 CKD. A 26-week double-blind, placebo-controlled trial compared liraglutide 1.8 mg daily to placebo in 279 patients with T2DM and eGFR 30-59 mL/min/1.73 m^2. At baseline, patients had a mean A1C of 8%, an eGFR of 45 mL/min/1.73 m^2, and a mean duration of diabetes of 15.9 years in the liraglutide group versus 14.2 years in the placebo group. At the end of the study, A1C was reduced by 1.05% in the liraglutide group as compared with 0.38% in the placebo group (estimated treatment difference −0.66%; 95% CI −0.90 to −0.43, $P < .0001$). Patients in the liraglutide group also had significant lowering of fasting blood glucose (−22.0 mg/dL versus −10.3 mg/dL, 95% CI −22.5 to −0.76, $P = .036$). Weight loss was more pronounced with liraglutide versus placebo (−2.41 kg versus −1.09 kg, $P = .0052$). There was no difference in rates of hypoglycemia between the groups, although there was a significant difference in the incidence of gastrointestinal adverse reactions (35.7% with liraglutide versus 17.5% with placebo). Regarding renal outcomes, there was no significant change in eGFR or SCr relative to baseline between liraglutide and placebo. At 26 weeks, the urine albumin to creatinine ratio was 0.87 in the liraglutide group and 1.05 in the placebo group. This numerically favored liraglutide but was not statistically significant ($P = .19$). The authors concluded that liraglutide was safe and effective in patients with stage 3 CKD. However, a longer study duration may be needed to definitively confirm safety and efficacy over time in this population.[35]

In addition to the data in CKD, CV data are available for liraglutide. The LEADER Trial was a double-blind, randomized, controlled trial that compared liraglutide 1.8 mg daily to placebo in 9,340 patients with T2DM at high CV risk. The primary composite outcome included first occurrence of death from CV causes, nonfatal MI, or nonfatal stroke. Patients were followed for a median of 3.8 years with the primary composite outcome occurring in fewer patients treated with liraglutide compared with placebo (13% in the liraglutide group versus 14.9% in the placebo group; HR 0.87; 95% CI 0.78 to 0.97; $P < .001$ for noninferiority; $P = .01$ for superiority). Overall, fewer patients in the liraglutide group died from CV causes (4.7% in the liraglutide group versus 6.0% in the placebo group; HR 0.78; 95% CI 0.66 to 0.93; $P = .007$). A lower rate of death from any cause was seen in the liraglutide group (8.2% versus 9.6% in the placebo group; HR 0.85; 95% CI 0.74 to 0.97; $P = .02$). There were nonsignificant differences in the rates of nonfatal MI, nonfatal stroke, and hospitalizations in the liraglutide group. The mean difference in A1C between the liraglutide and placebo groups was 0.4%. The initial decrease in A1C with liraglutide was from about 8.7% to about 7.2% compared with about

8.7% to about 8.2% in the placebo group. However, the difference became less pronounced throughout the study as additional medications, with the exception of dipeptidyl peptidase-4 inhibitors, pramlintide, or a second GLP-1 RA, were permitted to target A1C lower than 7% in patients who remained above goal after randomization. Regarding weight loss as compared with placebo, patients in the liraglutide group lost 2.3 kg more. The most common adverse events were gastrointestinal in nature with significantly more nausea, vomiting, diarrhea, decreased appetite, and abdominal discomfort in the liraglutide group. Patients in the liraglutide group had lower rates of both renal and retinal microvascular outcomes compared with placebo (HR 0.84; 95% CI 0.73 to 0.97; $P = .02$). This reduction in microvascular outcomes was due to a significant reduction in rates of nephropathy events in the liraglutide group (1.5 versus 1.9 events per 100 patient years; HR 0.78; 95% CI 0.67 to 0.92; $P = .003$). Retinopathy events were nonsignificantly higher in the liraglutide group (0.6 versus 0.5 events per 100 patient years; HR 1.15; 95% CI 0.87 to 1.52; $P = .33$).[22] Overall, liraglutide was shown to reduce the first occurrence of CV death, nonfatal MI, and nonfatal stroke along with death from CV causes in patients with T2DM and high CV risk and also reduce rates of nephropathy events, a finding that resulted in incorporation of liraglutide in the 2019 ADA guidelines to be considered as a preferred agent for patients with T2DM and clinical ASCVD as well as an option for patients where CKD predominates who are not candidates for SGLT2 inhibitors.[21,22]

Lixisenatide

Lixisenatide (Adlyxin) is another GLP-1 RA used for the treatment of T2DM. It is initiated at 10 mcg daily before being titrated to 20 mcg daily after 14 days. A1C lowering with lixisenatide compared with placebo was found to be 0.65% after 12 weeks.[30] Among patients with CKD, a single randomized controlled trial found mild to moderate kidney impairment did not alter the pharmacokinetics of lixisenatide, but that severe kidney impairment may increase drug exposure.[41] A posthoc assessment of nine trials was completed in patients with normal kidney function or mild to moderate kidney impairment. There were no patients with severe kidney dysfunction included. When comparing patients with mild or moderate kidney impairment to those with normal kidney function, there was no difference in A1C, hypoglycemia, or blood glucose readings. As compared with those with normal kidney function, patients in the mild kidney impairment group receiving lixisenatide had a 10% higher incidence of nausea and vomiting and a 14% higher rate of gastrointestinal adverse reactions ($P = .003$). There were no significant differences in adverse events seen between those with mild and moderate impairment or moderate impairment and normal kidney function. However, only 4.3% of the study population who received lixisenatide had moderate kidney impairment.[42]

A CV study was completed comparing 6,068 patients with T2DM and a recent acute coronary syndrome event randomized to lixisenatide or placebo. The ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome) trial was a time-to-event analysis with a primary composite endpoint of CV death, MI, stroke, or hospitalization for unstable angina. The median follow-up period was 25 months. Patients were randomized to receive either lixisenatide with a starting dose of 10 mcg up to a maximum of 20 mcg daily or placebo. At baseline, the mean A1C and eGFR was 7.7% and 76.7 mL/min/1.73 m^2, respectively, in the lixisenatide group and 7.6% and 75.2 mL/min/1.73 m^2, respectively, in the placebo group. The study was powered for noninferiority and demonstrated a reduction in the primary composite outcome as compared with placebo (13.4% versus 13.2%; HR 1.02; CI 95% 0.89 to 1.17) that confirmed noninferiority of lixisenatide to placebo ($P < .001$) but not superiority ($P = .81$). The study also looked at the percent change in urine albumin to creatinine ratio from baseline to 108 weeks. Lixisenatide reduced the change in the albumin to creatinine ratio over placebo (24% versus 34%, $P = .004$) initially, but the difference became less pronounced during posthoc analysis after adjustment for baseline and 3-month A1C ($P = .07$).[36]

Dulaglutide

Dulaglutide (Trulicity) is a once-weekly GLP-1 RA. It is initiated as a 0.75 mg subcutaneous injection once weekly and may be increased to 1.5 mg subcutaneous injection once weekly for further A1C reduction.[31] During a 26-week monotherapy study in patients with T2DM, change in A1C was compared between dulaglutide and metformin. Dulaglutide demonstrated an A1C lowering potential of 0.7% for the 0.75 mg dose and 0.8% for the 1.5 mg dose. Metformin lowered A1C by 0.6%.[43] No randomized clinical trials have been completed evaluating the safety and efficacy in

patients with CKD or benefit in CV disease.[31] However, the REWIND (Researching Cardiovascular Events with a Weekly Incretin in Diabetes) Trial is currently in progress to evaluate the CV benefit of dulaglutide and includes a secondary renal outcome.[44]

One pharmacokinetic study was completed in healthy patients and those with renal impairment. The study compared the pharmacokinetics of dulaglutide 1.5 mg in patients with normal, mild, moderate, and severe kidney impairment using pharmacokinetic information from clinical trials including phase 2 and 3 studies in patients with T2DM. There were no patients in the severely impaired or ESRD categories for phase 2 or 3. In phase 1, only 4.2% of the patients had moderate kidney impairment. In phase 2 and 3, only 0.6% and 0.3% of patients, respectively, had moderate kidney impairment. They found no pharmacokinetic changes between patients with normal kidney function and those with kidney impairment. Therefore, there are no renal dose adjustments recommended for this agent.[45] However, because of the lack of patients in the phase 2 and 3 trials with stage 4 and 5 CKD, caution should be used in this population.

Semaglutide

Semaglutide (Ozempic) is another once-weekly GLP-1 RA. It is initiated as a 0.25 mg subcutaneous injection once weekly for 4 weeks to ensure tolerability and then increased to 0.5 mg subcutaneous injection once weekly for at least 4 weeks. Thereafter, it may be increased to 1 mg subcutaneous injection once weekly if further glycemic control is needed. A1C reduction was shown to be 1.2% with the 0.5 mg dose and 1.4% with the 1 mg dose from baseline when used as monotherapy as compared with placebo.[28,46]

There have not been any randomized clinical trials conducted to determine the safety and efficacy of semaglutide in CKD. However, a pharmacokinetic study was completed after one dose of semaglutide 0.5 mg and included patients with normal kidney function (n = 14), and mild (n = 11), moderate (n = 11), and severe (n = 10) kidney dysfunction as well as ESRD requiring hemodialysis (n = 10). The authors found no change in semaglutide pharmacokinetics between the groups after adjustment for differences in age, gender, and body weight. Therefore, no renal dose adjustments are recommended.[47]

SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes) was a CV study that compared semaglutide 0.5 mg or 1 mg once weekly with placebo. This randomized clinical trial included 3,297 patients and lasted for 104 weeks. At baseline, the mean A1C was 8.7% and the mean duration of T2DM was 13.9 years. Inclusion criteria were age 50 or older and a history of CVD or stage 3 or higher CKD, or age 60 or older and at least one CV risk factor. The authors determined the superiority of semaglutide compared with placebo for a primary composite outcome of first occurrence of CV death, nonfatal MI, or nonfatal stroke. Semaglutide had significantly less occurrence of the primary outcome as compared with placebo (6.6% in the semaglutide group versus 8.9% in the placebo group; HR 0.74; 95% CI 0.58 to 0.95; $P < .001$ for noninferiority, $P = .02$ for superiority). Semaglutide significantly reduced the risk of nonfatal stroke within the composite (1.6% versus 2.7%, HR 0.61; 95% CI 0.38 to 0.99; $P = 0.04$). Semaglutide significantly reduced A1C over placebo (−1.1% with the 0.5 mg dose, −1.4% with the 1 mg dose, and −0.4% with placebo). Also, more patients in the placebo group received additional antihyperglycemic agents, and insulin was initiated twice as frequently. Regarding microvascular outcomes, semaglutide had lower rates of new or worsening nephropathy (3.8% versus 6.1%, HR 0.64, 95% CI 0.46 to 0.88, $P = .005$) but increased rates of retinopathy complications (3% versus 1.8%, HR 1.76; 95% CI 1.11 to 2.78, $P = .02$). Retinopathy events were more likely to occur in patients who had higher A1C at baseline, a longer duration of diabetes, and those with a history of diabetic retinopathy complications as compared with the general population.[23]

Clinical application

Overall, the ADA guidelines recommend following a patient-specific approach when selecting therapy for treating patients with T2DM.[21] For patients with stage 3 CKD and T2DM, liraglutide is the GLP-1 RA with the strongest evidence for use.[35] Semaglutide and liraglutide were demonstrated to reduce new or worsening nephropathy in SUSTAIN-6 and LEADER, respectively; however, renal endpoints were secondary outcomes in both studies.[22,23]

When considering steps in pharmacotherapy after metformin, the 2019 ADA Standards of Medical Care recommend considering the presence or absence of established ASCVD or CKD.[21] In patients for whom

ASCVD predominates, a GLP-1 RA with demonstrated CVD benefit or SGLT2 inhibitor with demonstrated CVD benefit if eGFR is adequate is recommended. Among GLP-1 RAs, the strongest evidence supports the use of liraglutide, followed by semaglutide and exenatide ER.[22,23,24] Among SGLT2 inhibitors, available clinical trial evidence is considered modestly stronger for empagliflozin as compared with canagliflozin.[25,26]

Patient case example revisited. *Returning to Ms. L, the patient described above with stage 3 CKD (eGFR 34 mL/min/1.73 m^2), there are a few clinical pieces of information to consider when determining the best GLP-1 RA for initiation. First, as with all patients with T2DM, evaluation of her glycemic control is imperative. Ms. L is currently above her A1C goal and requires consideration of additional therapeutic options. Second, after electing to start a GLP-1 RA, review the evidence to determine a safe and effective option based on her past medical history including CKD and clinical ASCVD. The GLP-1 RA with the strongest data to support its use in this population is liraglutide. The LIRA-RENAL (Efficacy and Safety of Liraglutide Versus Placebo as Add-on to Glucose-Lowering Therapy in Patients with Type 2 Diabetes and Moderate Renal Impairment) study supports use in stage 3 CKD and the* LEADER *(Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) study supports its potential benefits in patients with a history of clinical ASCVD.[22,35] Therefore, liraglutide 0.6 mg subcutaneous injection once daily for 1 week and then 1.2 mg subcutaneous injection once daily thereafter could be considered for the patient with continued uptitration to 1.8 mg subcutaneous injection once daily as tolerated.*

Conclusion

CKD is a common complication and comorbidity in patients with T2DM. Patients being treated for T2DM with concomitant CKD create a complex clinical problem with the need for a balance between glycemic control, prevention of further decline in kidney function, optimization of additional CV risk factors, and safety. Improving glycemic control may help to slow the progression of CKD, but potential adverse reactions, especially with initiation of drug therapy, may also put patients at higher risk for further decline. Patient-centered decision-making prior to the initiation of a GLP-1 RA and additional studies to further delineate the potential benefits of the use of GLP-1 RA in patients with CKD are needed. NP

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