Management of Diabetes Mellitus in Patients With CKD: Core Curriculum 2022

Allison J. Hahr and Mark E. Molitch

The most common cause of kidney failure in the United States and across the world is diabetes mellitus (DM). Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in persons with diabetes, and chronic kidney disease (CKD) further increases overall CVD risk. It is important to individualize glycemic targets for patients to maintain glucose levels that will reduce the development and progression of complications while avoiding hypoglycemia. CKD alters the relationship of glucose levels to measures of long-term control, such as hemoglobin A_{1c}. Medications used to treat DM may need dose adjustments as CKD progresses. Some medications have particular characteristics in patients with CKD. Insulin and sulfonylureas increase the risk of hypoglycemia, some glucagon-like peptide 1 receptor agonists reduce the risk of CVD outcomes, and most sodium/glucose cotransporter 2 inhibitors reduce the risk of CKD and CVD outcomes. Therefore, for the individual patient, changes in medication types and doses may need constant attention as CKD progresses.

Complete author and article information provided at end of article.

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Introduction

The number of people affected by diabetes mellitus (DM) increases each year, and about 34 million children and adults in the United States now have diabetes. The most common cause of kidney failure in the United States and across the world is DM. It is important to understand the safe use of antihyperglycemic medications in individuals with chronic kidney disease (CKD) to maintain necessary glycemic control, reduce hypoglycemia, and optimize cardiac and kidney disease. An understanding of how to treat type 1 versus type 2 diabetes is important, as is knowledge of the glycemic target for an individual patient.

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in persons with DM, and CKD further increases overall CVD risk. It is important to not only focus on glycemic control but control other cardiovascular risk factors. Other factors such as weight, diet/nutrition, and exercise should also be assessed regularly. This installment of *AJKD*'s Core Curriculum in Nephrology discusses glycemic control targets, the use of diabetes medications, and management strategies for patients with type 1 and type 2 diabetes with CKD. Close communication between primary care clinicians, nephrologists, diabetologists, cardiologists, diabetes and kidney disease educators, and others is very important in making decisions about how and when to use the various medications discussed here.

Glycemic Control Targets

Case 1: *A 65-year-old man with a 9-year history of type 2 diabetes has a hemoglobin A_{1c} (HbA_{1c}) of 8.7%. He has been referred by his primary care physician to discuss management of his diabetes. He is taking glyburide at 10 mg daily and metformin at 1,000 mg twice daily along with candesartan and atorvastatin. On examination his body mass index (BMI) is 29 kg/m^2, his blood pressure (BP) is 138/78 mm Hg, and he has evidence of peripheral neuropathy. He has an estimated glomerular filtration rate (eGFR) of 33 mL/min/1.73 m^2 and a urinary albumin-creatinine ratio (UACR) of 317 mg/g. The first thing you discuss with him is his HbA_{1c} goal.*

Question 1: Which one of the following HbA_{1c} goals is appropriate for this patient?

a) <6.0%
b) <7.0%
c) <8.0%
d) <9.0%

Question 2: Which of the following is correct regarding HbA_{1c} measurements in this patient?

a) HbA_{1c} becomes inaccurate for assessing glycemia when the eGFR is <60 mL/min/1.73 m^2.
b) Glycated albumin is preferable to HbA_{1c} when assessing glycemia for the past 3 months.
c) When the eGFR is <30 mL/min/1.73 m^2, the HbA_{1c} measures 0.5% to 1.0% lower than it should.
d) Patients with nephrotic-range proteinuria and low albumin have inaccurate measures of both glycated albumin and HbA_{1c}.

For the answers to the questions, see the following text.

The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

Glycemic control has been shown to slow the development of CVD and CKD. The recommended target HbA_{1c} in nonpregnant adults by the American Diabetes Association (ADA) is ≤7%. The ADA supports higher targets (<8%) for select patients, such as those with shorter life expectancies, a history of severe hypoglycemia, extensive comorbidities, and advanced complications. An HbA_{1c} goal of <6.5% may be appropriate for certain populations. A goal HbA_{1c} of ≤6.5% in healthy patients who are at low risk for hypoglycemia has been recommended by the American Association of Clinical Endocrinologists (AACE), but they also acknowledge that these goals need to be individualized.

These recommendations are based on several studies. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study showed that intensive therapy (HbA_{1c} 7.2% vs 9.1%) decreased the development of moderately increased albuminuria, the progression to severely increased albuminuria, and the proportion of patients developing stage 3 CKD (eGFR < 60 mL/min/1.73 m^2) in type 1 diabetes. In patients with type 2 diabetes, the Kumamoto Study, the United Kingdom Prospective Diabetes Study (UKPDS), Veterans Affairs Diabetes Trial (VADT), the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial, and the Action to Control Cardiovascular Disease in Diabetes (ACCORD) trial showed decreases of new-onset CKD as well as progression of nephropathy with intensive glycemic control. The last 3 of these studies showed no reduction in CVD with even more intensive glycemic control (HbA_{1c} of 6.4% vs 7.5% in ACCORD, 6.3% vs 7.3% in ADVANCE, and 6.9% vs 8.4% in VADT). In light of these 3 more recent studies, the target HbA_{1c} is typically recommended to be less than 7.0% rather than 6.5%. Of note, however, such reductions in HbA_{1c} are associated with improved kidney and other microvascular outcomes but also with increased hypoglycemia. Overall, a target HbA_{1c} of ~7.0% appears to offer an optimal risk to benefit ratio compared with a lower target. Whether a lower target would show a better overall benefit-risk ratio if only medications that do not cause hypoglycemia were used is unknown.

How the above recommendations apply to patients with CKD is uncertain. The 2007 Kidney Disease Outcomes Quality Initiative (KDOQI) guideline on diabetes and CKD endorsed an HbA_{1c} of <7.0%; however, their updated 2012 guideline recommended an HbA_{1c} of ~7.0%. The Controversies Conference on diabetic kidney disease (DKD) held by KDIGO (Kidney Disease: Improving Global Outcomes) noted that there are insufficient data from clinical trials regarding the ideal glycemic control target in patients with CKD stage 3 or worse. They noted that patients with diabetes and kidney failure treated by kidney replacement therapy benefit most from maintaining their HbA_{1c} levels in the 7% to 8% range, as HbA_{1c} levels above 8% or below 7% carry increased risks of all-cause and CVD mortality. Thus, for question 1, the best answer is (c), an HbA_{1c} goal < 8%. However, if the patient is not taking any medications that may cause hypoglycemia, an HbA_{1c} < 7% could be considered. Many other aspects of care may influence glycemic goals (Fig 1).

HbA_{1c} levels should be measured every 6 months in individuals with stable glycemic control that is at goal; however, HbA_{1c} levels should be checked every 3 months if the glycemic goal is not being met or if changes have occurred in treatment. The risk for hypoglycemia increases as GFR declines, primarily in those taking insulin, sulfonylureas, or glinides. Renal gluconeogenesis is impaired owing to lower kidney mass, and the clearance of insulin and oral diabetes medications decreases as CKD progresses. Anorexia and weight loss related to uremia can also increase hypoglycemia risk.

HbA_{1c} measurement can be inaccurate in some patients with CKD when the eGFR approaches 30 mL/min/1.73 m^2 and below (stages 4-5 CKD). Anemia from reduced red blood cell life span, hemolysis, and iron deficiency can all falsely lower the HbA_{1c}; in contrast, an increased HbA_{1c} can be seen resulting from carbamylation of hemoglobin and the presence of acidosis. Glycated

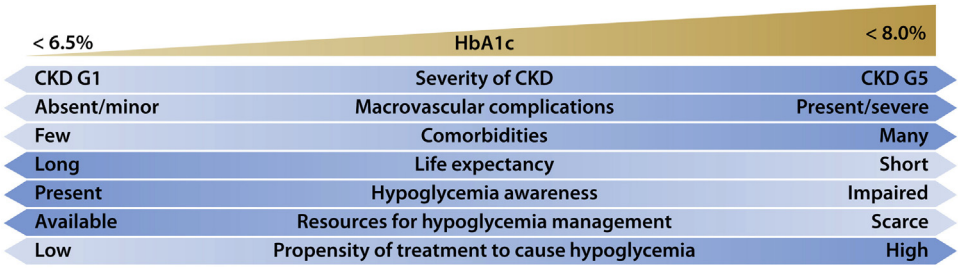

Figure 1. Factors guiding decisions on individual HbA_{1c} targets. Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; G1, eGFR ≥ 90 mL/min/1.73 m^2; G5, eGFR <15 mL/min/1.73 m^2; HbA_{1c}, glycated hemoglobin. Image ©2020 International Society of Nephrology; reproduced from the KDIGO 2020 clinical practice guideline for diabetes management in CKD (https://doi.org/10.1016/j.kint.2020.06.019) with permission of the copyright holder.

albumin provides an estimate of glycemic control over the previous 2 weeks. Some studies have shown that glycated albumin is better than HbA_{1c} in dialysis patients because HbA_{1c} tends to underestimate glycemic control as assessed by continuous glucose monitoring (CGM) in maintenance dialysis patients. However, for assessing long-term control, HbA_{1c} remains the measurement of choice because questions remain for glycated albumin related to its accuracy and interlaboratory variability as well as when serum albumin levels are particularly low when patients have nephrotic syndrome. Furthermore, the HbA_{1c} reflects 3 months of glycemic control versus only 2 weeks for glycated albumin.

When the eGFR is < 30 mL/min/1.73 m^2, the HbA_{1c} measures 0.5% to 1.0% lower than it should; a rule-of-thumb estimate could be to add this amount to the measured HbA_{1c} to get an idea of the "true" HbA_{1c}. Thus, for question 2, because the patient is now near stage 4 CKD, because glycated albumin only measures glycemic control for the prior 2 weeks and not 3 months, and because nephrotic-range albuminuria does not affect HbA_{1c}, the best answer is (c), a reduction of 0.5%-1.0% occurs in those with eGFR < 30 mL/min/1.73 m^2. Multiple daily blood glucose measurements are critical in such patients when insulin is used to assess glycemic control and avoid hypoglycemia.

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Management of Diabetes in Patients With CKD

Case 2: *A 65-year-old woman with a 12-year history of type 2 diabetes is referred for further management. She is taking metformin at 1,000 mg twice daily, atorvastatin at 40 mg daily, and valsartan at 320 mg daily. Her examination is significant for a BMI of 32 kg/m^2, a BP of 142/86 mm Hg, decreased vibratory sensation in her feet with absent Achilles reflexes, and absent pedal pulses. She has no lower extremity edema. Laboratory testing shows an HbA_{1c} of 8.5%, a serum creatinine of 1.8 mg/dL (eGFR 28 mL/min/1.73 m^2), a UACR of 162 mg/g, and an low-density lipoprotein cholesterol of 93 mg/dL. Because the eGFR was <30 mL/min/1.73 m^2, metformin was discontinued.*

Question 3: Which of the following can you tell her has been shown with liraglutide treatment?

a) Decreased risk of cardiovascular death
b) Average body weight loss of 20%
c) Increased risk of pancreatic cancer
d) Worsening of nephropathy

Question 4: Which medication should be avoided given her GFR?

a) Glyburide
b) Insulin glargine
c) Pioglitazone
d) Linagliptin

For the answers to the questions, see the following text.

The DM medication regimen needs to be individualized and calibrated as kidney function declines. Those with type 1 diabetes require insulin, and multiple insulin regimens can be devised. For those with type 2 diabetes, there are many therapeutic options and combinations. Because

patients with CKD have decreased clearances of insulin and other medications, they are at higher risk of hypoglycemia. As kidney function decreases, diabetes medications may need frequent adjustment. Notably, some medications can reduce the progression of kidney disease.

Injectable Medications

Insulin

About 30% to 80% of insulin clearance is carried out by the kidney. A reduction in GFR results in prolongation of the insulin half-life and a need to reduce insulin doses to avoid hypoglycemia. All insulin preparations can be used in CKD, but modifications of insulin type and dose may be necessary to reduce the risk of hypoglycemia while still achieving glycemic goals. Careful home glucose monitoring is required to adjust insulin doses safely. The increased risk of hypoglycemia with insulin use in patients with CKD is especially concerning in the older, potentially frail person and those with osteodystrophy, as hypoglycemia-induced falls can easily result in major fractures.

The long-acting insulin analogs U-100 (100 units/mL) glargine, U-300 glargine, detemir, U-100 degludec, and U-200 degludec are used as basal insulins. Insulin glargine has its onset of action 2-4 hours after injection, does not have a clear peak after injection, and has a duration of 20-24 hours; therefore, it is usually dosed once daily. Doses lower than 15 U may have a modest peak and a shorter half-life; with doses greater than 50-60 U, splitting the dose is helpful to improve absorption. Insulin detemir has an onset of action at 1-3 hours, peaks at 6-8 hours, and duration of action of 18-22 hours. In patients with type 1 diabetes, insulin detemir is dosed twice daily, but in those with type 2 diabetes once daily dosing usually suffices. Because U-300 insulin glargine and insulin degludec (both U-100 and U-200) have prolonged half-lives, once-daily injection suffices. These longer durations of action of U-300 glargine and degludec are because of a delayed absorption from the subcutaneous injection sites and are not due to lower clearance. No changes in pharmacokinetics occur as the GFR decreases for degludec, but such information for U-300 glargine has not been published. For all of these basal insulins, no specific dose changes are needed as the GFR falls other than the general dose reduction needed to avoid hypoglycemia.

The only intermediate-acting insulin is isophane NPH (neutral protamine Hagedorn) insulin. NPH has an onset of action at 2-4 hours, has a pronounced but irregular peak at 4-10 hours, and lasts for up to 10-18 hours; when given as a twice daily injection it can be used as a basal insulin. It has highly variable absorption, resulting in considerable day-to-day and dose-to-dose variability, making the long-acting insulins preferable as basal insulins. However, compared with insulin analogs, the cost of NPH is much lower.

Regular crystalline insulin is the only short-acting insulin available and has an onset of action at 30-60 minutes, peaks at 2-3 hours, and lasts for 5-8 hours. Ideally, regular insulin should be given 30 minutes before a meal. It is also much less costly compared with insulin analogs. When used intravenously, regular insulin has a rapid onset of action and a much shorter duration of action—on the order of minutes rather than hours.

The insulin analogs aspart, lispro, and glulisine have a more rapid onset of action compared with regular insulin and a shorter duration of action. They are ideal as prandial insulins, with an onset of action of about 15 minutes, peak action of about 60 minutes, and a duration of up to 4 hours. They are injected up to 15 minutes before meals and are used in "basal-bolus therapy," also known as multiple daily injections. A fast-acting insulin aspart (Fiasp in the United States) and a fast-acting insulin lispro (Lyumjev in the United States) have even faster onsets and offsets, so they can be given immediately before eating and can even be dosed up to 20 minutes after beginning to eat. Although rapid-acting insulins are usually injected before eating, some patients with stage 4-5 CKD and on dialysis may have delayed gastric emptying, so giving these rapid-acting insulins after the meal may help to match the insulin peak with the time of the postprandial blood glucose peak. In patients with very poor appetites, injecting the rapid-acting insulin after eating may allow for adjusting the insulin dose in proportion to the amount of carbohydrate eaten. Regular insulin and all these rapid-acting insulin preparations can be used in insulin pumps except for aspart, which cannot be used in pumps from Tandem Diabetes Care because of an increased risk of occlusion.

Premixed insulin preparations contain fixed percentages of NPH and a rapid- or short-acting insulin. Therefore, they have 2 separate peaks and 2 durations of actions; one example is insulin "70/30," which consists of 70% NPH and 30% short- or rapid-acting insulin. Although the premixed preparations offer the convenience of twice daily dosing, they limit flexibility of dosing, require injection at fixed times, and require consistent food intake.

Most insulin is U-100 unless stated otherwise. U-500 is only available as regular insulin. This very high concentration alters its pharmacokinetics; its onset of action is similar to that of regular insulin, around 30 minutes, but its peak is at 4-8 hours, and its duration is 14-15 hours. U-500 regular is usually given up to 30 minutes before meals and is typically given 2 to 3 times daily with meals, without the need of a separate basal insulin. U-500 is usually used in patients with severe insulin resistance who require very high insulin doses, and it can be given as subcutaneous injections or in a pump. As noted previously, there are also U-300 glargine, U-200 degludec, and U-200 lispro, which can be useful in similar patients because an equal amount of insulin can be provided in a smaller volume.

Inhaled insulin is rapid-acting and can be used as a prandial insulin. Its onset of action is about 12-15 minutes, with a peak at 50 minutes, and duration of 2.5-3.0 hours. Inhaled insulin carries a risk of pulmonary complications and is not used in individuals with pulmonary disease. Although it has not been studied specifically in individuals with reduced kidney function, dosing should be adjusted just as with any insulin use in patients with CKD.

An insulin pump that delivers a continuous subcutaneous infusion of insulin (CSII) provides the closest approximation of physiologic insulin secretion and potentially can be used in all stages of CKD. Rapid-acting insulin analogs infused via the pump serve as the basal, bolus, and correction insulin. The correct use of insulin pumps requires considerable vigilance on the part of the patient; their use should be overseen by experienced endocrinologists and certified diabetes educators. A critical aspect of the appropriate use of pumps and multiple daily injections is the necessary adjustment of insulin doses based upon pre- and post-meal capillary glucose measurements, requiring either multiple finger-sticks or the newer CGM devices. "Closed loop" insulin delivery systems combine the use of an insulin pump and a CGM sensor; the pump and sensor are in communication to automatically decrease, increase, or temporarily stop the delivery of insulin in response to the glucose levels. Boluses via the pump, however, are still needed to cover the amounts of carbohydrate consumed. Currently, there are 2 systems available, one from Medtronic and one from Tandem Diabetes Care.

Glucagon-like Peptide 1 Receptor Agonists

The glucagon-like peptide 1 (GLP-1) receptor agonists are injectable subcutaneous medications that stimulate glucose-dependent insulin release, decrease glucagon secretion, delay gastric emptying, and suppress appetite; the last may result in significant weight loss. They are fairly potent, generally causing a decrease in HbA_{1c} of 0.5% to 1.5%. Although cases have been reported of pancreatitis with their use, epidemiologic studies have not shown a higher risk of pancreatitis in comparison with other agents. Nausea is a common side effect. Although GLP-1 receptor agonists have been associated with the development of thyroid C-cell tumors in animal studies, no such cases have been reported in humans; nonetheless, no GLP-1 receptor agonists should be given to patients with or at risk for medullary thyroid cancer. These drugs do not cause hypoglycemia by themselves, but because they lower glucose levels hypoglycemia can be increased if they are given with insulin or sulfonylurea medications. Exenatide (Byetta) is given twice daily, and liraglutide (Victoza) and lixisenatide (Adlyxin) are given once daily; exenatide extended-release (Bydureon), semaglutide (Ozempic), and dulaglutide (Trulicity) are dosed once weekly. Fixed dose combinations with insulin are also available, such as degludec/liraglutide (Xultophy) and insulin glargine/lixisenatide (Soliqua). Semaglutide is also now available as an oral preparation (Rybelsus). The LEADER, SUSTAIN-6, and REWIND studies showed significant reductions in CVD mortality with liraglutide, semaglutide, and dulaglutide, respectively, along with reductions in the development of severe albuminuria but no effects on GFR. However, the REWIND study with dulaglutide showed a benefit on eGFR as a secondary outcome. Neither CVD nor CKD benefits were seen with extended-release exenatide or lixisenatide.

With declines in GFR, exenatide clearance decreases. Cases of acute kidney injury (AKI) associated with exenatide use have been reported, so caution is warranted in patients with GFR of 30-50 mL/min/1.73 m^2; exenatide should be discontinued for GFR < 30 mL/min/1.73 m^2. No dose adjustment is needed for liraglutide in CKD, including kidney failure, although data are limited. However, due to some reports of AKI, caution is warranted when GFR is <30 mL/min/1.73 m^2. No dosage restrictions are required with decreasing GFR for dulaglutide or semaglutide. Due to lack of data, lixisenatide should not be used if the GFR < 15 mL/min/1.73 m^2, and close monitoring is needed in patients with eGFR < 60 mL/min/1.73 m^2. Thus, for question 3, the best answer is (a), liraglutide has been shown to reduce cardiovascular deaths. Weight loss can be significant but does not approach 20%. Liraglutide has not been shown to cause pancreatic cancer or worsening of kidney function.

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Oral Medications

Metformin

Metformin improves insulin sensitivity and decreases hepatic glucose production; it does not cause hypoglycemia and reduces HbA_{1c} by 1.0%-1.5%. The most common adverse effects are diarrhea, bloating, and abdominal cramping, which limit use in about 15% of patients. Long-term use can lead to vitamin B_{12} deficiency. Because metformin levels may increase when the GFR is decreased, patients can be at increased risk for lactic acidosis. However, the incidence of lactic acidosis with metformin use is only increased when the GFR is < 30 mL/min/1.73 m^2. As summarized by Inzucchi et al (2014), the risk of lactic acidosis in metformin users increases from 7.6 (95% CI, 0.9-27.5) per 100,000 patient-years among patients with a normal eGFR to 39 (95% CI, 4.72-140.89) per 100,000 patient-years among those with an eGFR < 30 mL/min/1.73 m^2.

The revised US Food and Drug Administration (FDA) guidelines state that metformin should not be used in patients with an eGFR < 30 mL/min/1.73 m^2 and suggest that metformin should not be started for eGFR of 30-45 mL/min/1.73 m^2. Furthermore, if the eGFR drops below 45 mL/min/1.73 m^2 in the course of treatment, the risks and benefits of continuing metformin should be reviewed because of the increasing probability of further decrease. It has been recommended also that the maximum metformin dose should be reduced to no more than 1,000 mg/d with an eGFR < 45 mL/min/1.73 m^2. It is important to hold metformin when a patient is unstable such as being in a hypoxic, hypotensive, or septic state or after iodinated contrast administration until it is clear that there is no long-term decrease in GFR.

Sulfonylureas and Glinides

Sulfonylureas increase insulin secretion. The currently used sulfonylureas are glipizide, glimepiride, glyburide, and gliclazide (the latter is not available in the United States). The sulfonylureas lower HbA_{1c} on average by 1.0%-2.0% and can cause hypoglycemia, particularly glyburide and chlorpropamide (a first-generation agent sometimes still used). As the GFR declines, there is a decrease in clearance of sulfonylureas and their metabolites, resulting in an increased risk of hypoglycemia. With an eGFR < 60 mL/min/1.73 m^2, the risk of hypoglycemia is greatly increased with glyburide and is moderately increased with glimepiride. Glyburide should not be used with an eGFR < 60 mL/min/1.73 m^2. Thus, for question 4, the best answer is (a), glyburide should be avoided. Glimepiride should be used with caution if the eGFR is < 60 mL/min/1.73 m^2 and should be discontinued if eGFR is < 30 mL/min/1.73 m^2. Glipizide and gliclazide do not have active metabolites that are cleared by the kidney, so dose adjustments are not needed; however, caution is still needed and it has been recommended that gliclazide not be used when the eGFR is <40 mL/min/1.73 m^2.

Nateglinide and repaglinide ("glinides") also increase insulin secretion and can cause hypoglycemia but generally are much less potent than sulfonylureas. Glucose must be present for them to work, and they themselves have a short half-life and cause a quick insulin release of short duration; therefore, they should be given before each meal. Nateglinide has an active metabolite that accumulates in CKD and should not be used with an eGFR < 60 mL/min/1.73 m^2. Because this active metabolite is cleared by hemodialysis, however, it is possible to use nateglinide in patients on dialysis. Repaglinide is not cleared by the kidney and appears to be safe to use in CKD. However, with an eGFR < 30 mL/min/1.73 m^2, the lowest dose (0.5 mg) with slow titration up should be carried out to avoid hypoglycemia.

Thiazolidinediones

The thiazolidinediones (pioglitazone and rosiglitazone) increase insulin sensitivity, do not cause hypoglycemia, and lower HbA_{1c} levels by 0.5%-1.4%. Fluid retention can be a major side effect, so they should not be used in advanced heart failure. Because they have been associated with increased fracture rates and bone loss, their use in patients with renal osteodystrophy requires further study. Thiazolidinediones are not cleared by the kidney, and they can be used in CKD, so no dose adjustment is needed. An earlier restriction of use of rosiglitazone by the FDA based on studies linking it to increased ischemic heart disease was removed in 2014 because subsequent analyses did not support these findings. Also, although some studies reported an association between pioglitazone and bladder cancer, subsequent analyses failed to support this. Interestingly, some retrospective cohort studies showed both cardiovascular and kidney outcome benefits with use of thiazolidinediones in patients with CKD.

α-Glucosidase Inhibitors

The α-glucosidase inhibitors acarbose and miglitol slow the digestion of carbohydrates, delaying absorption of glucose after food intake and resulting postprandial glucose reduction. Bloating, flatulence, and abdominal cramping are the most common adverse effects. These drugs usually lower HbA_{1c} by 0.5%-0.8%. With reduced GFR, serum levels of acarbose and metabolites are significantly elevated; its use with a GFR <26 mL/min/1.73 m^2 is not recommended. Miglitol has >95% kidney excretion, and its use should be avoided with a low GFR.

Dipeptidyl Peptidase 4 Inhibitors

The dipeptidyl peptidase 4 (DPP-4) inhibitors reduce the breakdown of incretin hormones such as GLP-1 and glucose-insulinotropic peptide (GIP). They are weight neutral, do not cause hypoglycemia, and decrease HbA_{1c} by 0.5%-0.8%. All DDP-4 inhibitors can be used in CKD, but all require dose adjustments except for linagliptin (see Table 1 for details). They have all been studied in cardiovascular outcome trials and have not been shown to have CVD or CKD benefits or risks compared with placebo.

Sodium/Glucose Cotransporter 2 Inhibitors

The sodium/glucose cotransporter 2 (SGLT2) inhibitors reduce glucose absorption in the proximal tubule of the kidney, resulting in an increase in glycosuria and a reduction in HbA_{1c} of about 0.5%-1.0%. Weight loss up to 5 kg in 1 year is common, and they do not cause hypoglycemia. Genital yeast infections occur in about 10% of women and 1%-2% of uncircumcised men. Although an increase in urinary tract infections has been observed in some studies, the large CVD outcome trials did not show this. Some older patients may experience orthostatic hypotension with drug initiation, especially if they are also taking diuretics; diuretic doses should be reduced when starting these drugs.

An unusual but significant adverse effect is a 2- to 3-fold increased risk for the development of "euglycemic" diabetic ketoacidosis (DKA), primarily when used off-label in patients with type 1 diabetes but also rarely in patients with type 2 diabetes. In part, this DKA may be related to elevated glucagon levels, reduction in insulin doses, and volume depletion. Education is needed so that patients can monitor for signs and symptoms of DKA, including nausea or vomiting; if such symptoms occur (even if blood glucose levels are normal), they should be checked for ketones in the urine or serum (such as using a home ketone meter). The STICH protocol was developed as an early protocol to initiate when patients detect elevated ketones: once ketones are detected, the patient should STop the SGLT2 inhibitor, Inject insulin, Consume 30 g of carbohydrates, and Hydrate. Ketones should still be monitored, and the patient should seek medical care if ketosis persists or symptoms of DKA develop.

Significant reduction of cardiovascular outcomes (especially heart failure), slower kidney disease progression, and fewer renal events (such as kidney replacement therapy initiation) with empagliflozin use were shown in the EMPA-REG

Table 1. Dose Adjustment for Medications for Diabetes in CKD

Medication Class	CKD Stages 3-5[a]
Insulins	No advised dose adjustment[b]
Sulfonylureas	
Glipizide	No dose adjustment
Glimepiride	Start conservatively at 1 mg daily
Glyburide	Avoid use
Gliclazide	Avoid use when eGFR <40 mL/min/1.73 m^2
Glinides	
Repaglinide	No dose adjustment
Nateglinide	Start with 60 mg with meals; do not use if eGFR < 60 mL/min/1.73 m^2 (can be used if on dialysis)
Biguanides	
Metformin	eGFR < 45 mL/min/1.73 m^2, maximum dose is 1,000 mg/d; discontinue for eGFR < 30 mL/min/1.73 m^2
Thiazolidinediones	
Pioglitazone	No dose adjustment
Rosiglitazone	No dose adjustment
α-Glucosidase inhibitors	
Acarbose	Avoid if GFR < 26 mL/min/1.73 m^2
Miglitol	Avoid use
DPP-4 inhibitor	
Sitagliptin	GFR >50 mL/min/1.73 m^2: 100 mg daily GFR 30-50 mL/min/1.73 m^2: 50 mg daily GFR <30 mL/min/1.73 m^2: 25 mg daily
Saxagliptin	GFR >50 mL/min/1.73 m^2: 5 mg daily GFR ≤50 mL/min/1.73 m^2: 2.5 mg daily
Alogliptin	GFR >50 mL/min/1.73 m^2: 25 mg daily GFR 30-50 mL/min/1.73 m^2: 12.5 mg daily GFR <30 mL/min/1.73 m^2: 6.25 mg daily
Linagliptin	No restrictions
GLP-1 agonists	
Exenatide	GFR <30 mL/min/1.73 m^2: not recommended
Liraglutide	No dose adjustment
Semaglutide	No dose adjustment
Dulaglutide	No dose adjustment
Lixisenatide	eGFR <15 mL/min/1.73 m^2: not recommended
SGLT2 inhibitors[c]	
Canagliflozin	eGFR 30-<60 mL/min/1.73 m^2: max dose 100 mg once daily eGFR <30 mL/min/1.73 m^2: initiation not recommended
Dapagliflozin	eGFR <25 mL/min/1.73 m^2: initiation not recommended
Empagliflozin	eGFR <30 mL/min/1.73 m^2: not recommended
Ertugliflozin	eGFR <45 mL/min/1.73 m^2: not recommended

Select dosing recommendations shown; for full information consult drug labels at Drugs@FDA. Abbreviations: CKD, chronic kidney disease; DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; GLP-1, glucagon-like peptide 1; NPH, neutral protamine Hagedorn; SGLT2, sodium/glucose cotransporter 2.

[a]Not including those receiving dialysis, unless otherwise noted.

[b]Adjust dose based on patient response.

[c]These recommendations are based on glycemic lowering. Canagliflozin and dapagliflozin may be used below these eGFR levels to decrease the risks of kidney failure, cardiovascular death, and hospitalization for heart failure. For empagliflozin, while use for glycemic control is not recommended below the given threshold, data are insufficient with regard to dosing recommendations for patients with CKD, cardiovascular disease, and hospitalization for heart failure. None of these drugs should be used in patients on dialysis.

study, with canagliflozin in the CANVAS study, and dapagliflozin in the DECLARE-TIMI study. Although the VERTIS-CV study showed a significant reduction heart failure with ertugliflozin, the other CVD and CKD benefits were not statistically significant. The CREDENCE study showed that canagliflozin use resulted in cardiovascular and kidney benefits that were quite significant in patients with an eGFR down to 30 mL/min/1.73 m^2. Similar results were seen with dapagliflozin in the DAPA-CKD trial. Reduced risks of death and hospitalization for heart failure in those newly started on empagliflozin, canagliflozin, or dapagliflozin compared with other diabetes medications were shown in the CVD-REAL study. In the EASEL study, patients treated with SGLT2 inhibitors compared with other diabetes medications had reduced risks of major adverse cardiovascular events (hazard ratio [HR], 0.67 [95% CI, 0.60-0.75]) and all-cause mortality and hospitalization for heart failure (HR 0.57 [95% CI, 0.50-0.60]). There was also a higher risk of below-the-knee amputations (HR 1.99 [95% CI, 1.12-3.51]), mostly in those receiving canagliflozin. An increased risk of amputations was also seen with canagliflozin in the CANVAS study but not in the CREDENCE study, and no such increase was seen with empagliflozin in the EMPA-REG study, dapagliflozin in the DECLARE-TIMI study, or the DAPA-CKD trial, or ertugliflozin in the VERTIS-CV trial. Fournier gangrene, a necrotizing fasciitis of the perineum, has been reported with the use of SGLT2 inhibitors, leading to an FDA warning in 2018.

The efficacy of SGLT2 inhibitors in glucose lowering decreases substantially as the GFR declines below 60 mL/min/1.73 m^2. Because of the marked benefits in reducing cardiovascular outcomes and slowing kidney disease progression, canagliflozin, empagliflozin, and dapagliflozin are very much indicated in patients down to an eGFR of 30 mL/min/1.73 m^2, based on the studies cited previously, although the package inserts state that dapagliflozin and empagliflozin should not be used with an eGFR < 45 mL/min/1.73 m^2. The dose of canagliflozin should be reduced to 100 mg daily in patients with an eGFR < 60 mL/min/1.73 m^2. The mechanisms by which SGLT2 inhibitors cause CVD and CKD benefits are not clear but likely involve diuretic effects, increased sodium sensitivity, reduced arterial stiffness, and direct vascular effects. Because of these benefits on CVD and CKD outcomes, it is now recommended that SGLT2 inhibitors with proven CKD benefits be used in all patients with type 2 diabetes who have evidence of CKD.

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Summary of Management of Type 2 Diabetes With CKD

We now have many therapeutic options for patients with type 2 diabetes. Lifestyle changes are always part of treatment. Lifestyle/nutritional recommendations are complex and are fully discussed in the recent KDIGO guideline. In newly diagnosed patients, if the diabetes is mild and lifestyle changes are unable to achieve adequate glycemic control, a single oral medication is started and

generally metformin is chosen because of efficacy and possible CVD benefit. It is now recommended that SGLT2 inhibitors be added as the second oral agent because of their proven CVD and CKD benefits, especially if there is evidence of CKD. The GLP-1 receptor agonists can be used, but because of similar modes of action they should not be used concurrently with DPP-4 inhibitors. In patients with known CVD, liraglutide, semaglutide, and dulaglutide are now recommended as a second agent because of their proven CVD benefits. Although the need for weekly injections are a downside, the potential for glycemic improvement and the rather substantial weight loss are additional benefits. Semaglutide is now available as an oral agent and CVD outcome studies are pending. The GLP-1 receptor agonists can also be used as single agents. Unfortunately, SGLT2 inhibitors and GLP-1 receptor agonists are underutilized in practice, in part related to high cost, concern about potential adverse effects, and insurance barriers. The DPP-4 inhibitors can be safely used in CKD, but all but linagliptin require dose adjustment. They do not cause hypoglycemia and are well tolerated, but the reduction in HbA_{1c} is generally modest.

Thiazolidinediones reduce HbA_{1c} moderately but can cause fluid retention and weight gain. The second-generation sulfonylureas are inexpensive and effective, but they can cause hypoglycemia. In CKD, glipizide and gliclazide are preferable; glyburide must be avoided. Thus, for case 2, glyburide is the medication that should be discontinued because of its high risk for hypoglycemia. The other medications can all be used. It is not unusual for patients to be treated with multiple agents at the same time, but insulin may need to be added as diabetes progresses.

Insulin may be required in patients with very high glucose levels, significant insulin resistance, or β-cell failure, and an inability to achieve glycemic control with other medications. Insulin can often be started by giving a long-acting insulin such as glargine, detemir, or degludec as a basal insulin once daily, with a starting dose of 10-15 units. The insulin dose can be increased by 1-2 units every few days until the fasting goal is reached while avoiding hypoglycemia. Many patients can achieve glycemic control with the combination of basal insulin and oral agents or GLP-1 receptor agonists. If such control cannot be achieved with basal insulin, a rapid-acting insulin before meals can be started, especially if hyperglycemia occurs during the day but fasting blood glucose levels meet the target. The rapid-acting insulin is often added initially before the largest meal of the day; however, prandial insulin may be required for each meal. The doses of prandial insulin are guided by the premeal glucose level and the carbohydrate content of the meal. Uncommonly, when fasting glucose levels are not very high but hyperglycemia is present during the day, prandial rapid-acting insulin may suffice.

Repaglinide, pioglitazone, linagliptin, liraglutide, dulaglutide, and semaglutide can be used safely in patients on dialysis, particularly if the diabetes is fairly mild. Most patients on dialysis, however, will require insulin. Patients who experience delayed gastric emptying may find it helpful to take their rapid-acting insulin after meals. Glycemic responses during hemodialysis can be quite variable and unpredictable, so frequent dose adjustment may be needed. In those on peritoneal dialysis (PD), large amounts of glucose in the dialysate may result in marked hyperglycemia. In patients receiving continuous PD, a standard basal/bolus insulin regimen is best. In those receiving overnight cycled PD, a fixed mixture insulin combination, such as 70/30 or 75/25 insulin given at the start of PD, often provides better coverage of the increased glucose load. So that insulin doses can be adjusted appropriately, the patient's endocrinologist must be informed of changes in the glucose concentration of the dialysate because of the need for more or less fluid removal.

Table 1 provides CKD-associated dosing adjustments for diabetes medications.

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Article Information

Authors' Full Names and Academic Degrees: Allison J. Hahr, MD, and Mark E. Molitch, MD.

Authors' Affiliation: Division of Endocrinology, Metabolism, and Molecular Medicine, Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois.

Address for Correspondence: Mark Molitch, MD, 645 N Michigan Ave, Suite 530, Chicago, IL 60611. Email: molitch@northwestern.edu

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