Learning Objectives
Upon completion of this activity, participants should be better able to:

- Appropriately screen patients with type 2 diabetes mellitus (T2DM) for their risk of diabetic kidney disease (DKD)
- Implement guideline-based strategies to slow progression of DKD in patients with T2DM through individualized, comprehensive management and patient education
- Apply criteria for the selection of optimal diabetes therapy in patients with DKD based on the available evidence

Introduction
Most of the 29 million Americans with diagnosed diabetes have type 2 diabetes mellitus (T2DM), an acquired and progressive disease associated with substantial morbidity due to complications that damage the vasculature, eyes, nerves, and kidneys.1-4 Diabetes care costs the nation an estimated $245 billion annually, including almost 1 in 3 dollars spent on neurologic, cardiovascular (CV), peripheral vascular, and renal care.2 Although improvements in care have reduced the rate of these complications since 1990—including a 28% reduction in the risk of end-stage renal disease (ESRD)—patients with T2DM remain at substantially higher risk than nondiabetic individuals for both microvascular and macrovascular complications.5

DKD is a common, but often overlooked, consequence of T2DM that negatively impacts patients’ long-term health and increases mortality.

Diabetes is the leading cause of chronic kidney disease (CKD), with other risk factors including hypertension, older age, certain ethnic groups (eg, African American, Hispanic, American Indian), and a family history of CKD.
Chronic Kidney Disease in T2DM

Concomitant CKD almost triples mortality risk in T2DM. A recent study using National Health and Nutrition Examination Survey (NHANES) III data found that 10-year all-cause mortality for patients with T2DM was 11.5%, whereas for those with T2DM plus CKD it was 31.1%. However, it is important to note that patients with T2DM can be given a diagnosis of CKD independent of diabetic kidney disease (DKD). CKD in such patients may also be due to renal artery stenosis, characterized generally by the presence of refractory hypertension during treatment with renin-angiotensin system (RAS) inhibitors, or immunoglobulin A (IgA) nephropathy accompanied by heavy proteinuria. CKD also may be a result of systemic diseases such as systemic lupus erythematosus.

If the etiology of CKD cannot be determined clinically, patients should be referred to a nephrologist for a more extensive workup. Other findings that should prompt a nephrology referral for comanagement include severe kidney impairment (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m²) or resistant hypertension and difficult management issues, such as the inability to carry out the recommended treatment evaluation, requiring assistance in creating the patient’s clinical action plan, or difficulties in implementing the recommended treatment plan.

Diabetic Kidney Disease

DKD is a very specific and progressive form of CKD caused by the microvascular damage to the kidneys that often accompanies diabetes. DKD affects up to 40% of patients with diabetes. In the most advanced cases, ESRD and kidney failure are present. The relationship between diabetes and kidney disease cannot be overemphasized. Diabetes is the leading cause of kidney failure, implicated in 44% of all new cases of kidney failure annually. In 2008, almost a quarter million patients with T2DM had begun treatment for ESRD, were living on long-term dialysis, or had undergone a kidney transplant.

As would be expected, the prevalence of DKD increases with time, given the progressive nature of T2DM (Figure 1). The cost of treating patients with DKD also is substantially higher than that of nondiabetic patients with CKD. Schernthaner and Schernthaner reported that expenditures for DKD before and after the onset of ESRD were 69% and 79% higher,

### Figure 1. Prevalence of DKD increases with time since T2DM diagnosis

- Prevalence of Persistent Albuminuria or More Severe Nephropathy UKPDS 64
- Prevalence (%)
- Years Since Diagnosis

<table>
<thead>
<tr>
<th>Years Since Diagnosis</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>7.3</td>
</tr>
<tr>
<td>5</td>
<td>17.3</td>
</tr>
<tr>
<td>10</td>
<td>24.9</td>
</tr>
<tr>
<td>15</td>
<td>28.0</td>
</tr>
</tbody>
</table>

DKD Pathogenesis Is Multifactorial, With Multiple Independent Risk Factors

*aPersistent albuminuria ≥30 mg/d.

UKPDS = United Kingdom Prospective Diabetes Study.
respectively, than those of their nondiabetic counterparts.\textsuperscript{9} In addition, DKD is the cause of 55\% of US deaths due to renal disease.\textsuperscript{2}

Although most patients with T2DM and CKD meet criteria for DKD, the latter diagnosis does not include coincidental CKD (eg, renal artery stenosis) present in a patient with diabetes. The clinical diagnosis of DKD is based on the presence of persistent albuminuria (\(\geq 30 \text{ mg/d}\)), a decline in eGFR, and hypertension in the setting of diabetes.\textsuperscript{4,7} Absence of signs and symptoms of another kidney disease also is a factor in assigning a DKD diagnosis.\textsuperscript{12} In the patient with T2DM, DKD is less likely to be diagnosed if kidney disease is characterized by active urine sediment, a rapid decline in eGFR, or the absence of retinopathy (suggesting minimal microvascular damage).

### Comprehensive Assessment of Patients With DKD

The 2014 American Diabetes Association (ADA) Standards include recommendations for CKD screening in patients with T2DM, shown in Table 1.\textsuperscript{7} These new recommendations combine the previous categories of microalbuminuria (30-299 mg/d) and macroalbuminuria (\(\geq 300 \text{ mg/d}\)) into a single category of persistent albuminuria, defined as \(\geq 30 \text{ mg/d}\).\textsuperscript{7} The ADA recommends using the spot test to determine the serum albumin:creatinine ratio, although it is subject to false-positive and false-negative results. The accuracy of the spot test also may be influenced by the presence of infection or fever, recent exercise, or marked hyperglycemia or hypertension. Therefore, the test should be repeated at least 3 times over a 3- to 6-month period. Abnormal results on 2 of 3 tests indicate abnormal urinary albumin excretion, defined as \(\geq 30 \mu \text{g/mg creatinine} \) on the spot test.\textsuperscript{7} Importantly, persistent albuminuria alone is not sufficient to make the diagnosis of DKD.

The eGFR is used to assess kidney function and to stage kidney disease (Table 2). In general, eGFR <90 mL/min/1.73 m\(^2\) indicates some degree of kidney damage, with lower levels indicating more advanced decline.\textsuperscript{7,8} One can assess eGFR using validated calculation tools that factor in patients’ serum creatinine level, age, and race—serum creatinine alone cannot be used to estimate kidney function because patients with identical creatinine clearance can have very different levels of kidney function.\textsuperscript{7,8} Two recommended eGFR calculators include the CKD Epidemiology Collaboration and the Modification of Diet in Renal Disease equations.\textsuperscript{8}

### Table 1. Recommendations for CKD Screening in Patients With T2DM\textsuperscript{7}

<table>
<thead>
<tr>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Measure urine albumin excretion at diagnosis and annually\textsuperscript{a}</td>
</tr>
<tr>
<td>- Persistent albuminuria ((\geq 30 \text{ mg/d})) may represent early kidney injury, endothelial dysfunction, and generalized vascular injury</td>
</tr>
<tr>
<td>• Urine albumin alone should not be used to screen for DKD, as decreased GFR in absence of persistent albuminuria is common</td>
</tr>
<tr>
<td>• Measure serum creatinine level at least annually\textsuperscript{a}: serum creatinine level should be used to estimate GFR and to determine stage of CKD</td>
</tr>
</tbody>
</table>

\textsuperscript{a}May be more frequent depending on evidence of disease.
Early Diabetic Kidney Disease in Patients With Type 2 Diabetes

Assessment of eGFR often is included in a basic metabolic panel, but there also are tools and an app available from the National Kidney Disease Education Program that help make the calculation (http://nkdep.nih.gov/identify-manage.shtml).

The likelihood of DKD and risk of adverse outcomes increases with lower eGFRs and higher levels of albuminuria. For example, patients with eGFR of 30 to 60 mL/min/1.73 m² and albuminuria <30 mg/d are unlikely to have DKD, despite stage 3 CKD. In contrast, those with the same eGFR but albuminuria >300 mg/d will be given a diagnosis of DKD. Because treatment with an RAS inhibitor (angiotensin-converting enzyme [ACE] inhibitor or angiotensin receptor blocker [ARB]) can improve albuminuria, clinicians should use values taken before the initiation of therapy, if possible. Screening for kidney dysfunction should be done at diagnosis and at least annually thereafter using urinary albumin excretion and eGFR. Both measures are needed to ensure an accurate picture of patients’ renal function.7,8

DKD is one of the most powerful predictors of adverse CV events among patients with T2DM.

Appropriate screening is crucial because prevention of DKD-related complications requires first recognizing the presence of impaired kidney function. DKD is common but often overlooked, resulting in missed opportunities for prevention or to halt progression.4 In a large, retrospective study of outpatient medical records, 35.2% of patients with T2DM had eGFR evidence of DKD, ranging from moderate renal disease to ESRD. However, only 20% of these patients had a chart-documented diagnosis of renal impairment. In this study, the mean time from first eGFR evidence of moderate kidney disease to a chart-documented diagnosis was 253 days.13

**DKD and Other T2DM Complications**
The development of kidney impairment in T2DM is related to the progressive microvascular damage that accompanies uncontrolled hyperglycemia. Multifactorial risk factor management,
including smoking cessation, weight loss, glycemic control, and blood pressure reduction slows the progression of DKD.\textsuperscript{12}

DKD is one of the most powerful predictors of adverse CV events among patients with T2DM.\textsuperscript{4} In a study of CV disease (CVD) among patients with or without T2DM, the presence of any degree of CKD was associated with a substantially increased risk of CVD (Figure 2).\textsuperscript{14} CKD and CVD share multiple overlapping risk factors, including diabetes; hypertension, which is present in 67\% of patients with T2DM; persistent albuminuria, which increases CVD risk by 2- to 4-fold; and obesity, which is independently associated with increased risk for both CVD and DKD.\textsuperscript{3,4,12,15} The importance of taking a comprehensive, multifactorial approach to the care of patients with DKD is underscored by recent data showing that fewer than 1 in 7 patients have achieved collective goals for glycated hemoglobin (A1C), blood pressure, low-density lipoprotein cholesterol (LDL-C) targets, and nonsmoking status.\textsuperscript{16}

Data from the United Kingdom Prospective Diabetes Study (UKPDS) showed that patients treated for hypertension had a slower progression of DKD. At initial follow-up, patients with well-controlled blood pressure had significantly lower risks for diabetes-related death ($P = .019$), stroke ($P = .013$), and albuminuria of 30 to 299 mg/dl ($P = .009$), as well as lower rates of all-cause mortality and myocardial infarction.\textsuperscript{17} Within a few years, blood pressure in the tight control group increased, and the differences in outcome were no longer significant at 10 years’ follow-up. These findings emphasize the importance of ongoing risk factor management and avoiding clinical inertia to minimize patients’ risk for long-term complications.\textsuperscript{18}

In contrast, early aggressive glycemic control confers long-term benefits that persist even if glucose levels later rise.\textsuperscript{18} In other data from the UKPDS, early aggressive glycemic control in patients with newly diagnosed T2DM led to a 25\% reduction in risk for any microvascular end point compared with conventional therapy ($P = .0099$).\textsuperscript{19} This benefit persisted through 10 years of follow-up, with a statistically significant 24\% reduction in microvascular disease ($P = .001$), 9\% reduction in any diabetes-related end point ($P = .04$), and 17\% reduction in diabetes-related mortality ($P = .01$). Additionally, patients who maintained glycemic control through the 10-year period had a 15\% reduction in risk of myocardial infarction ($P = .01$).\textsuperscript{20}

![Prevalence of CVD (% of patients) According to CKD Stages and Diabetes Statistics](chart.png)

**Figure 2.** Diabetes + any stage of CKD increases CVD risk.\textsuperscript{14}

Similar long-term benefits with early, intensive glycemic control have been observed in the Kumamoto Study of patients with T2DM and in the Diabetes Control and Complications Trial of patients with type 1 diabetes mellitus. However, it should be noted that the relationship between intensive glycemic control and survival is not as clear-cut among patients with DKD.

Intensive management of both glycemic and CV end points provides additional long-term benefit. In the Steno-2 study, at-risk patients with T2DM who received aggressive treatment—RAS blockers, aspirin, and lipid-lowering agents—in an effort to achieve optimal A1C (<6.5%) and CV goals (blood pressure <130/80 mm Hg, total cholesterol <175 mg/dL, triglycerides <150 mg/dL) were significantly more likely than those receiving conventional treatment to demonstrate sustained benefits with respect to vascular complications and CV and all-cause mortality at the 7.8-year follow-up (Figure 3). Intensive risk factor management also resulted in significantly lower risk of developing nephropathy at both 7.8-year and 13.3-year follow-up.

However, several studies have suggested that although intensive glycemic control may improve long-term renal function, for certain patients it also may contribute to excess morbidity or mortality. One large study (Action to Control Cardiovascular Risk in Diabetes) showed an increase in all-cause mortality among high-risk patients and an increase in serious adverse events—including severe hypoglycemia—in the populations studied. These results may reflect the general poor health or level of comorbid illness in these patient cohorts, suggesting that aggressive A1C goals best serve individuals with a shorter duration of T2DM, low hypoglycemia risk, and without established atherosclerosis.

**Figure 3.** Steno-2: interventions to adequately control multiple clinical end points can improve kidney function outcomes.

RR = relative risk.

Importance of Individualizing Treatment Goals

ADA guidelines emphasize the importance of individualizing T2DM treatment goals based on each patient’s particular combination of disease duration, comorbid conditions, vascular complications, and hypoglycemia risk, as well as personal factors such as motivation and social support (Table 3).4,7,31,32 The guidelines recommend healthy lifestyle changes for all patients and suggest metformin as an initial agent for most individuals with adequate renal function. Two- and eventually 3-drug combinations are used when A1C targets are not achieved, and many patients eventually will require addition of basal insulin. Key factors to consider in choosing therapy are a treatment’s expected A1C-lowering potential, effects on hypoglycemia risk and weight, adverse effects, and costs.7 Over the long term, combining treatments from different classes is the most effective way to achieve glycemic control, making an understanding of the mechanism of action and other characteristics of each treatment type crucial to optimal treatment selection and overall patient management (Table 4).23,31,33

Treatment Choice in the Setting of DKD

Metformin and the thiazolidinediones (TZDs) carry contraindications or warnings for use in patients with renal or hepatic impairment, the TZDs due to their association with fluid retention and potential congestive heart failure.4,23 The sodium-glucose cotransporter 2 (SGLT2) inhibitors are generally ineffective when renal impairment is moderate or worse.23 The sulfonylureas glipizide and glipizide extended release,34 the TZD pioglitazone,35 the dipeptidyl peptidase-4 (DPP-4) inhibitor linagliptin,35,36 and the glucagon-like peptide-1 receptor agonist (GLP-1 RA) albiglutide37 do not need dosage adjustment or special precaution in patients with renal insufficiency, although it is recommended that clinicians monitor patients taking albiglutide who may be experiencing a serious gastrointestinal (GI) reaction. Tables 5 and 6 list dosing recommendations and other information specific to use of diabetes medications in patients with renal impairment.4,33,37-39

Metformin is the most commonly prescribed and recommended oral agent for treatment of T2DM, but this agent is eliminated by the kidney and is expected to accumulate in patients with renal impairment. It is specifically contraindicated for male patients whose serum creatinine level

### Table 3. Glycemic, BP, and Lipid Goals: Recommendations for Most Patients

<table>
<thead>
<tr>
<th>Guideline</th>
<th>A1C</th>
<th>BP</th>
<th>LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA 20147</td>
<td>&lt;7.0%</td>
<td>&lt;140/&lt;80 mm Hg</td>
<td>&lt;100 mg/dL</td>
</tr>
<tr>
<td>NKF 2007/20124,32</td>
<td>~7.0%</td>
<td>&lt;130/&lt;80 mm Hg</td>
<td>&lt;100 mg/dL</td>
</tr>
<tr>
<td>AACE 201331</td>
<td>&lt;6.5% without comorbidities</td>
<td>~130/~80 mm Hg</td>
<td>&lt;100 mg/dL</td>
</tr>
</tbody>
</table>

Individualize based on patient factors, including age, disease duration, comorbidities, hypoglycemia risk, and patient motivation.
Early Diabetic Kidney Disease in Patients With Type 2 Diabetes

is ≥1.5 mg/dL and for female patients whose serum creatinine level is ≥1.4 mg/dL.⁴⁰ Although
the current ADA/European Association for the Study of Diabetes position statement,
*Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach*, questions whether
serum creatinine levels are too restrictive, no updated guidance has been published and following
this restriction is a safe course of action.³⁵ There is evidence that metformin is used inappropri-
ately for patients with DKD. A retrospective study of healthcare data found that after patients
had received an eGFR result indicating renal impairment, only 0.1% received the correct dose
of metformin.¹³ Another retrospective study found that only 25% of patients had their serum
creatinine measured or GFR assessed prior to initiating metformin treatment.⁴¹

| Table 4. No Single Class of Agents Targets All Key T2DM Pathophysiologies: MOA²³,³¹,³³ |
|----------------------------------|----------|-----------------|------------------|
| Class/Agent | ROA | MOA | Mitigation Strategy in DKD |
| Biguanides (ie, metformin) | Oral | Inhibit glucose output from the liver | CrCl may contraindicate |
| TZDs | Oral | Enhance insulin sensitivity | Safe, but may cause fluid retention |
| AGIs | Oral | Slow carbohydrate absorption in GI tract | Avoid in kidney failure |
| SUs | Oral | Insulin secretagogues; increase insulin secretion | Use with caution, hypoglycemia risk |
| Glinides | Oral | Insulin secretagogues; increase insulin secretion | Safer than SUs, hypoglycemia risk |
| Colesevelam | Oral | Not known; may inhibit hepatic glucose production | No data |
| Bromocriptine QR | Oral | Increases insulin sensitivity | No data |
| DPP-4 inhibitors | Oral | Increase endogenous incretin levels, increase insulin production, and inhibit glucagon release in glucose-dependent manner | Dose adjustment (except linagliptin) |
| SGLT2 inhibitors | Oral | Increase glucosuria (excess glucose excreted in urine) | Cannot be used in kidney failure |
| GLP-1 RAs | Injected | Increase insulin production, inhibit glucagon release in glucose-dependent manner, slow gastric emptying, increase satiety | Avoid due to GI adverse effects, risk for AKI |
| Insulin | Injected | Replaces endogenous insulin | Dose adjustment due to hypoglycemia risk |

AGIs = alpha-glucosidase inhibitors; AKI = acute kidney injury; CrCl = creatinine clearance; GI = gastrointestinal; MOA = mechanism of action; QR = quick release; ROA = route of administration; SUs = sulfonylureas.
Table 5. Use of Oral Agents in Patients With RI

<table>
<thead>
<tr>
<th>Class/Agent</th>
<th>Use in Patients With RI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin/metformin XR</td>
<td>Contraindicated with serum creatinine levels ≥1.5 mg/dL (men) and ≥1.4 mg/dL (women), due to potential for lactic acidosis; consider discontinuation if eGFR &lt;30 mL/min/1.73 m²</td>
</tr>
<tr>
<td>SU: glipizide, glipizide XL</td>
<td>No dosage adjustment is required</td>
</tr>
<tr>
<td>SU: glimepiride</td>
<td>Start conservatively (1 mg/d)</td>
</tr>
<tr>
<td>TZD: pioglitazone</td>
<td>No dosage adjustment is required</td>
</tr>
<tr>
<td>Glinide: nateglinide</td>
<td>eGFR &lt;30 mL/min/1.73 m²: start conservatively (60 mg with meals)</td>
</tr>
<tr>
<td>Glinide: repaglinide</td>
<td>eGFR &lt;30 mL/min/1.73 m²: start conservatively (0.5 mg with meals)</td>
</tr>
<tr>
<td>AGI: acarbose</td>
<td>eGFR &lt;30 mL/min/1.73 m²: not recommended</td>
</tr>
<tr>
<td>DPP-4 inhibitor: alogliptin</td>
<td>½ maximum dose in patients with moderate RI (CrCl ≥30–&lt;60 mL/min); ¼ maximum dose in patients with severe RI (CrCl &lt;30 mL/min)</td>
</tr>
</tbody>
</table>
| DPP-4 inhibitor: sitagliptin | eGFR 30-50 mL/min/1.73 m²: ½ maximum dose  
                  | eGFR <30 mL/min/1.73 m²: ¼ maximum dose in patients                                                                                                                    |
| DPP-4 inhibitor: saxagliptin | eGFR ≤50 mL/min/1.73 m²: ½ maximum dose  
                  | eGFR >50 mL/min/1.73 m²: no dosage adjustment                                                                                                                     |
| DPP-4 inhibitor: linagliptin | No dosage adjustment recommended for patients with RI                                                                                                           |
| Colesevelam          | No overall differences in safety and effectiveness were observed between patients with CrCl <50 mL/min and ≥50 mL/min                                                                                       |
| Bromocriptine QR     | Not studied in patients with reduced GFR; use with caution in these patients                                                                                                                                              |

*There have been postmarketing reports of worsening renal function in patients with renal insufficiency, some of whom received inappropriate doses of sitagliptin.
RI = renal impairment; XL/XR = extended release.
Patients with DKD and T2DM are at increased risk for developing hypoglycemia due to impaired renal gluconeogenesis (because of reduced kidney mass) and the delayed elimination of renally excreted drugs, including many antidiabetes agents. Studies have shown that 25% of fasting gluconeogenesis can be ascribed to the kidney. The hypoglycemia potential of these agents is affected by diminished renal function. A delay in renal excretion of select antidiabetes agents may promote an “accumulation” of their glucose-lowering effects and, therefore, lead to the development of hypoglycemia. These effects are present in oral insulin secretagogues; first-generation sulfonylureas, particularly glyburide, should be avoided in patients with DKD. Glipizide is the recommended choice if a sulfonylurea is necessary. Almost all antidiabetic agents require dose adjustment, if not complete avoidance, in the presence of renal impairment.

The optimal management of patients with DKD includes a comprehensive approach to address multiple end points. All patients should receive diabetes self-management education (DSME) and support, as well as nutrition counseling, which includes whether protein intake limitations are necessary and ways to reduce sodium and increase potassium intake. Smoking cessation counseling is a must. Patients require regular surveillance for microvascular and macrovascular complications, with the caveat that radiocontrast agents should be used with caution. Bone density testing is recommended. Patients should avoid certain common nondiabetes medications such as nonsteroidal anti-inflammatory drugs. Finally, coordination of care through a team approach that addresses both T2DM and CKD is important to ensuring healthy outcomes.
CASE: A 52-Year-Old African American Woman With a Previous Diagnosis of Hypertension and Hyperlipidemia

History and Presentation
Sandra is a teacher, and she recently switched primary care providers. She is married with 3 teenaged boys, enjoys an occasional glass of wine, and stopped smoking 5 years ago. Both her parents are deceased; her father had T2DM for 20 years before his death.

Physical Examination
Height: 5 ft 4 in
Weight: 175 lb
Body mass index: 30 kg/m²

Glycemic Measures
- A1C at presentation: 7.6%
- Fasting plasma glucose (FPG): 135 mg/dL

Other Relevant Findings (all others within normal range)
- Blood pressure (treated): 143/86 mm Hg
- Lipids (treated) (mg/dL): total cholesterol, 235; LDL-C, 125; high-density lipoprotein cholesterol, 45
- Serum creatinine: 0.93 mg/dL
- eGFR: 77 mL/min/1.73 m²

Current Medications
- Hydrochlorothiazide (HCTZ) 25 mg/d
- Simvastatin 40 mg/day

Based on Sandra’s A1C and FPG values, T2DM is diagnosed. Along with prescribing metformin, you provide lifestyle counseling and help her enroll in a DSME program. You recommend that she start metformin at 500 mg twice daily and then adjust the dose to 1000 mg twice daily, though keeping in mind potential GI side effects with an escalating dose.
Early Diabetic Kidney Disease in Patients With Type 2 Diabetes

Clinical Decision Point
Which of the following is true regarding Sandra’s kidney status?
A. It is normal because her serum creatinine is within normal limits
B. She has stage 2 CKD
C. She has DKD
D. Additional testing is needed

Comment
Serum creatinine is only one aspect of renal function; Sandra’s eGFR suggests some degree of kidney disease. Correct answer: D

Case (cont’d)
To get a better picture, you perform 3 spot tests to determine Sandra’s albumin:creatinine ratio over a 3-month period and find that she is positive for persistent albuminuria (range, 45-65 mg/d) and her eGFR is 77 mL/min/1.73 m². These findings, plus an ophthalmologist’s diagnosis of retinopathy, suggest microvascular damage from T2DM. Sandra is given the diagnosis of stage 2 CKD, likely due to DKD. Recognition of diabetes-related CV damage is crucial for the health of patients with DKD, as the major cause of death among these patients is CVD.

Clinical Decision Point
Thinking about Sandra’s presentation, what should you do to ensure the best possible outcome for her?
A. Ensure that she attends nutritional counseling
B. Intensify her blood pressure control
C. Switch her from metformin to a DPP-4 inhibitor
D. Intensify LDL-C control

Comment
As was shown in the Steno-2\textsuperscript{24,25} and UKPDS\textsuperscript{18} studies, multifactorial risk factor management improves long-term outcomes for patients with T2DM. Sandra’s blood pressure is above recommended targets with HCTZ. The ADA recommends that ACE inhibitors or ARBs be included in hypertension management of patients with T2DM due to their positive effects on renal health.\textsuperscript{7,12} Additionally, Sandra’s lipid levels are somewhat high; the recommended LDL-C target in T2DM is <100 mg/dL and <70 mg/dL for patients with established CVD.\textsuperscript{7} Both her blood pressure and lipid medications should be adjusted to intensify control. You recommend a combination of the HCTZ and an ARB and that she switch from simvastatin to atorvastatin at a starting dose of 20 mg/day. Atorvastatin can be titrated upward if needed, and no dose adjustments are necessary for renal impairment. Correct answers: B and D

Case (cont’d)
Sandra began to have regular follow-up examinations and to date is doing very well. At a 4-year follow-up examination, her lipids and blood pressure are within target levels and her A1C is well controlled with metformin. However, laboratory tests reveal that her serum creatinine level has crept up to 1.4 mg/dL, though her eGFR remains essentially unchanged. Given that serum
creatinine level, you decide it is time to adjust Sandra’s T2DM medication, despite her good response. Metformin will be discontinued. Research shows that metformin is contraindicated for patients whose serum creatinine levels are ≥1.5 mg/dL in men and ≥1.4 mg/dL in women.35

Clinical Decision Point
Which of these is a suitable replacement for metformin in Sandra’s case?
A. Alogliptin  
B. Basal insulin  
C. Linagliptin  
D. Liraglutide

Comment
Among these choices, linagliptin is the only agent that does not require dose adjustment for renal impairment. As a once-daily oral treatment, linagliptin is a good option for Sandra, unless added to a sulfonylurea or insulin, which may induce a degree of hypoglycemia. It should be noted, however, that this agent is not associated with an increased incidence of severe hypoglycemia risk or weight gain when added to a sulfonylurea.43 Alogliptin and other DPP-4 inhibitors can be used with dose adjustments based on the degree of renal impairment, and saxagliptin is well studied in this setting.44

However, if over time linagliptin does not provide an adequate level of glycemic control, basal insulin can be added at a later date. All DPP-4 inhibitors are approved for use with basal insulin and in clinical use do not result in an increase in severe hypoglycemia risk. Careful titration of the insulin dose should minimize any hypoglycemia due to renal impairment.23,43

GLP-1 RAs (liraglutide) must be used with caution, if at all, in patients with renal insufficiency due to their mechanism of action and adverse events of nausea and vomiting, which could worsen renal condition due to volume depletion.23 Correct answer: C

Click here to access the self-assessment and evaluation form.

References
8. National Kidney Foundation. Frequently
asked questions about GFR estimates. 


