



American Diabetes Association

# 11. Microvascular Complications and Foot Care: *Standards of Medical Care in Diabetes—2021*

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The American Diabetes Association (ADA) “Standards of Medical Care in Diabetes” includes the ADA’s current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee (<https://doi.org/10.2337/dc21-SPPC>), are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA’s clinical practice recommendations, please refer to the Standards of Care Introduction (<https://doi.org/10.2337/dc21-SINT>). Readers who wish to comment on the Standards of Care are invited to do so at [professional.diabetes.org/SOC](https://professional.diabetes.org/SOC).

For prevention and management of diabetes complications in children and adolescents, please refer to Section 13 “Children and Adolescents” (<https://doi.org/10.2337/dc21-S013>).

## CHRONIC KIDNEY DISEASE

### Screening

#### Recommendations

- 11.1a** At least annually, urinary albumin (e.g., spot urinary albumin-to-creatinine ratio) and estimated glomerular filtration rate should be assessed in patients with type 1 diabetes with duration of  $\geq 5$  years and in all patients with type 2 diabetes regardless of treatment. **B**
- 11.1b** Patients with diabetes and urinary albumin  $>300$  mg/g creatinine and/or an estimated glomerular filtration rate  $30\text{--}60$  mL/min/1.73 m<sup>2</sup> should be monitored twice annually to guide therapy. **B**

### Treatment

#### Recommendations

- 11.2** Optimize glucose control to reduce the risk or slow the progression of chronic kidney disease. **A**
- 11.3a** For patients with type 2 diabetes and diabetic kidney disease, consider use of a sodium–glucose cotransporter 2 inhibitor in patients with an estimated glomerular filtration rate  $\geq 30$  mL/min/1.73 m<sup>2</sup> and urinary albumin  $>300$  mg/g creatinine. **A**

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- 11.3b** In patients with type 2 diabetes and diabetic kidney disease, consider use of sodium–glucose cotransporter 2 inhibitors additionally for cardiovascular risk reduction when estimated glomerular filtration rate and urinary albumin creatinine are  $\geq 30$  mL/min/1.73 m<sup>2</sup> or  $>300$  mg/g, respectively. **A**
- 11.3c** In patients with chronic kidney disease who are at increased risk for cardiovascular events, use of a glucagon-like peptide 1 receptor agonist reduces renal end point, primarily albuminuria, progression of albuminuria, and cardiovascular events (**Table 9.1**). **A**
- 11.4** Optimize blood pressure control to reduce the risk or slow the progression of chronic kidney disease. **A**
- 11.5** Do not discontinue renin-angiotensin system blockade for minor increases in serum creatinine ( $<30\%$ ) in the absence of volume depletion. **A**
- 11.6** For people with nondialysis-dependent chronic kidney disease, dietary protein intake should be approximately 0.8 g/kg body weight per day (the recommended daily allowance). **A** For patients on dialysis, higher levels of dietary protein intake should be considered, since malnutrition is a major problem in some dialysis patients. **B**
- 11.7** In nonpregnant patients with diabetes and hypertension, either an ACE inhibitor or an angiotensin receptor blocker is recommended for those with modestly elevated urinary albumin-to-creatinine ratio (30–299 mg/g creatinine) **B** and is strongly recommended for those with urinary albumin-to-creatinine ratio  $\geq 300$  mg/g creatinine and/or estimated glomerular filtration rate  $<60$  mL/min/1.73 m<sup>2</sup>. **A**
- 11.8** Periodically monitor serum creatinine and potassium levels for the development of increased creatinine or changes in potassium when ACE inhibitors, angiotensin receptor blockers, or diuretics are used. **B**

- 11.9** An ACE inhibitor or an angiotensin receptor blocker is not recommended for the primary prevention of chronic kidney disease in patients with diabetes who have normal blood pressure, normal urinary albumin-to-creatinine ratio ( $<30$  mg/g creatinine), and normal estimated glomerular filtration rate. **A**
- 11.10** Patients should be referred for evaluation by a nephrologist if they have an estimated glomerular filtration rate  $<30$  mL/min/1.73 m<sup>2</sup>. **A**
- 11.11** Promptly refer to a physician experienced in the care of kidney disease for uncertainty about the etiology of kidney disease, difficult management issues, and rapidly progressing kidney disease. **A**

### Epidemiology of Diabetes and Chronic Kidney Disease

Chronic kidney disease (CKD) is diagnosed by the persistent presence of elevated urinary albumin excretion (albuminuria), low estimated glomerular filtration rate (eGFR), or other manifestations of kidney damage (1,2). In this section, the focus is on CKD attributed to diabetes (diabetic kidney disease), which occurs in 20–40% of patients with diabetes (1,3–5). CKD typically develops after diabetes duration of 10 years in type 1 diabetes but may be present at diagnosis of type 2 diabetes. CKD can progress to end-stage renal disease (ESRD) requiring dialysis or kidney transplantation and is the leading cause of ESRD in the U.S. (6). In addition, among people with type 1 or 2 diabetes, the presence of CKD markedly increases cardiovascular risk and health care costs (7).

### Assessment of Albuminuria and Estimated Glomerular Filtration Rate

Screening for albuminuria can be most easily performed by urinary albumin-to-creatinine ratio (UACR) in a random spot urine collection (1,2). Timed or 24-h collections are more burdensome and add little to prediction or accuracy. Measurement of a spot urine sample for albumin alone (whether by immunoassay or by using a sensitive dipstick test specific for albuminuria) without simultaneously measuring urine creatinine (Cr) is less expensive but susceptible to false-negative and

false-positive determinations as a result of variation in urine concentration due to hydration (8).

Normal UACR is defined as  $<30$  mg/g Cr, and high urinary albumin excretion is defined as  $\geq 30$  mg/g Cr. However, UACR is a continuous measurement, and differences within the normal and abnormal ranges are associated with renal and cardiovascular outcomes (7,9,10). Furthermore, because of high biological variability of  $>20\%$  between measurements in urinary albumin excretion, two of three specimens of UACR collected within a 3- to 6-month period should be abnormal before considering a patient to have high or very high albuminuria (1,2,11,12). Exercise within 24 h, infection, fever, congestive heart failure, marked hyperglycemia, menstruation, and marked hypertension may elevate UACR independently of kidney damage (13).

eGFR should be calculated from serum creatinine using a validated formula. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation is generally preferred (2). eGFR is routinely reported by laboratories with serum creatinine, and eGFR calculators are available online at [nkdep.nih.gov](http://nkdep.nih.gov). An eGFR persistently  $<60$  mL/min/1.73 m<sup>2</sup> is considered abnormal, though optimal thresholds for clinical diagnosis are debated in older adults (2,14).

### Diagnosis of Diabetic Kidney Disease

Diabetic kidney disease is usually a clinical diagnosis made based on the presence of albuminuria and/or reduced eGFR in the absence of signs or symptoms of other primary causes of kidney damage. The typical presentation of diabetic kidney disease is considered to include a long-standing duration of diabetes, retinopathy, albuminuria without gross hematuria, and gradually progressive loss of eGFR. However, signs of CKD may be present at diagnosis or without retinopathy in type 2 diabetes, and reduced eGFR without albuminuria has been frequently reported in type 1 and type 2 diabetes and is becoming more common over time as the prevalence of diabetes increases in the U.S. (3,4,15,16).

An active urinary sediment (containing red or white blood cells or cellular casts), rapidly increasing albuminuria or nephrotic syndrome, rapidly decreasing eGFR, or the absence of retinopathy (in type 1 diabetes) suggests alternative or additional causes of kidney disease.

For patients with these features, referral to a nephrologist for further diagnosis, including the possibility of kidney biopsy, should be considered. It is rare for patients with type 1 diabetes to develop kidney disease without retinopathy. In type 2 diabetes, retinopathy is only moderately sensitive and specific for CKD caused by diabetes, as confirmed by kidney biopsy (17).

### Staging of Chronic Kidney Disease

Stages 1–2 CKD have been defined by evidence of high albuminuria with eGFR  $\geq 60$  mL/min/1.73 m<sup>2</sup>, while stages 3–5 CKD have been defined by progressively lower ranges of eGFR (18) (Fig. 11.1). At any eGFR, the degree of albuminuria is associated with risk of cardiovascular disease (CVD), CKD progression, and mortality (7). Therefore, Kidney Disease: Improving Global Outcomes (KDIGO) recommends a more comprehensive CKD staging that incorporates albuminuria at all stages of eGFR; this system is more closely associated with risk but is also more complex and does not translate directly to treatment decisions (2). Thus, based on the current classification system, both eGFR and albuminuria must be quantified to guide treatment decisions. This is also important since eGFR levels are essential to modify drug dosage or restrictions of use (Fig. 11.1) (19,20). The degree of albuminuria may influence choice of antihypertensive (see Section 10 “Cardiovascular Disease and Risk Management,” <https://doi.org/10.2337/dc21-S010>) or glucose-lowering medications (see below). Observed history of eGFR loss (which is also associated with risk of CKD progression and other adverse health outcomes) and cause of kidney damage (including possible causes other than diabetes) may also affect these decisions (21).

### Acute Kidney Injury

Acute kidney injury (AKI) is diagnosed by a 50% or greater sustained increase in serum creatinine over a short period of time, which is also reflected as a rapid decrease in eGFR (23,24). People with diabetes are at higher risk of AKI than those without diabetes (25). Other risk factors for AKI include preexisting CKD, the use of medications that cause kidney injury (e.g., nonsteroidal anti-inflammatory drugs), and the use of medications that alter renal blood flow and intrarenal

hemodynamics. In particular, many antihypertensive medications (e.g., diuretics, ACE inhibitors, and angiotensin receptor blockers [ARBs]) can reduce intravascular volume, renal blood flow, and/or glomerular filtration. There was concern that sodium–glucose cotransporter 2 (SGLT2) inhibitors may promote AKI through volume depletion, particularly when combined with diuretics or other medications that reduce glomerular filtration; however, this has not been found to be true in randomized clinical outcome trials of advanced kidney disease (26) or high cardiovascular disease risk with normal kidney function (27–29). Timely identification and treatment of AKI is important because AKI is associated with increased risks of progressive CKD and other poor health outcomes (30).

Small elevations in serum creatinine (up to 30% from baseline) with renin-angiotensin system blockers (such as ACE inhibitors and ARBs) must not be confused with AKI (31). An analysis of the Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD BP) trial demonstrates that those randomized to intensive blood pressure lowering with up to a 30% increase in serum creatinine did not have any increase in mortality or progressive kidney disease (32–36). Moreover, a measure of markers for AKI showed no significant increase of any markers with increased creatinine (34). Accordingly, ACE inhibitors and ARBs should not be discontinued for minor increases in serum creatinine (<30%), in the absence of volume depletion.

### Surveillance

Albuminuria and eGFR should be monitored regularly to enable timely diagnosis of CKD, monitor progression of CKD, detect superimposed kidney diseases including AKI, assess risk of CKD complications, dose drugs appropriately, and determine whether nephrology referral is needed. Among people with existing kidney disease, albuminuria and eGFR may change due to progression of CKD, development of a separate superimposed cause of kidney disease, AKI, or other effects of medications, as noted above. Serum potassium should also be monitored for patients treated with ACE inhibitors, ARBs, and diuretics because these medications can cause hyperkalemia or hypokalemia, which are associated with cardiovascular risk

and mortality (37–39). For patients with eGFR <60 mL/min/1.73 m<sup>2</sup>, appropriate medication dosing should be verified, exposure to nephrotoxins (e.g., nonsteroidal anti-inflammatory drugs and iodinated contrast) should be minimized, and potential CKD complications should be evaluated (Table 11.1).

The need for annual quantitative assessment of albumin excretion after diagnosis of albuminuria, institution of ACE inhibitors or ARB therapy, and achievement of blood pressure control is a subject of debate. Continued surveillance can assess both response to therapy and disease progression and may aid in assessing adherence to ACE inhibitor or ARB therapy. In addition, in clinical trials of ACE inhibitors or ARB therapy in type 2 diabetes, reducing albuminuria from levels  $\geq 300$  mg/g Cr has been associated with improved renal and cardiovascular outcomes, leading some to suggest that medications should be titrated to minimize UACR. However, this approach has not been formally evaluated in prospective trials. In type 1 diabetes, remission of albuminuria may occur spontaneously, and cohort studies evaluating associations of change in albuminuria with clinical outcomes have reported inconsistent results (40,41).

The prevalence of CKD complications correlates with eGFR (42). When eGFR is <60 mL/min/1.73 m<sup>2</sup>, screening for complications of CKD is indicated (Table 11.1). Early vaccination against hepatitis B virus is indicated in patients likely to progress to ESRD (see Section 4 “Comprehensive Medical Evaluation and Assessment of Comorbidities,” <https://doi.org/10.2337/dc21-S004>, for further information on immunization).

### Interventions

#### Nutrition

For people with nondialysis-dependent CKD, dietary protein intake should be  $\sim 0.8$  g/kg body weight per day (the recommended daily allowance) (1). Compared with higher levels of dietary protein intake, this level slowed GFR decline with evidence of a greater effect over time. Higher levels of dietary protein intake (>20% of daily calories from protein or >1.3 g/kg/day) have been associated with increased albuminuria, more rapid kidney function loss, and CVD mortality and therefore should be avoided. Reducing the amount of dietary protein

CKD is classified based on: • Cause (C) • GFR (G) • Albuminuria (A)				Albuminuria categories		
				Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (mL/min/1.73m <sup>2</sup> ) Description and range	G1	Normal to high	≥90	1 if CKD	Treat 1	Refer* 2
	G2	Mildly decreased	60-89	1 if CKD	Treat 1	Refer* 2
	G3a	Mildly to moderately decreased	45-59	Treat 1	Treat 2	Refer 3
	G3b	Moderately to severely decreased	30-44	Treat 2	Treat 3	Refer 3
	G4	Severely decreased	15-29	Refer* 3	Refer* 3	Refer 4+
	G5	Kidney failure	<15	Refer 4+	Refer 4+	Refer 4+

**Figure 11.1**—Risk of chronic kidney disease (CKD) progression, frequency of visits, and referral to nephrology according to glomerular filtration rate (GFR) and albuminuria. The GFR and albuminuria grid depicts the risk of progression, morbidity, and mortality by color, from best to worst (green, yellow, orange, red, dark red). The numbers in the boxes are a guide to the frequency of visits (number of times per year). Green can reflect CKD with normal eGFR and albumin-to-creatinine ratio only in the presence of other markers of kidney damage, such as imaging showing polycystic kidney disease or kidney biopsy abnormalities, with follow-up measurements annually; yellow requires caution and measurements at least once per year; orange requires measurements twice per year; red requires measurements three times per year; and dark red requires measurements four times per year. These are general parameters only, based on expert opinion, and underlying comorbid conditions and disease state as well as the likelihood of impacting a change in management for any individual patient must be taken into account. “Refer” indicates that nephrology services are recommended. \*Referring clinicians may wish to discuss with their nephrology service, depending on local arrangements regarding treating or referring. Reprinted with permission from Vassalotti et al. (22).

below the recommended daily allowance of 0.8 g/kg/day is not recommended because it does not alter glycemic measures, cardiovascular risk measures, or the course of GFR decline (43).

Restriction of dietary sodium (to <2,300 mg/day) may be useful to control blood pressure and reduce cardiovascular risk (44,45), and restriction of dietary potassium may be necessary to control serum potassium concentration (25,37–39). These interventions may be most important for patients with reduced eGFR, for whom urinary excretion of sodium and potassium may be impaired. For patients on dialysis, higher levels of dietary protein intake should be considered, since malnutrition is a major problem in some dialysis patients (46). Recommendations for dietary sodium and potassium intake should be individualized on the basis of comorbid conditions, medication use, blood pressure, and laboratory data.

**Glycemic Targets**

Intensive glycemic control with the goal of achieving near-normoglycemia has been shown in large prospective randomized studies to delay the onset

and progression of albuminuria and reduced eGFR in patients with type 1 diabetes (47,48) and type 2 diabetes (1,49–55). Insulin alone was used to lower blood glucose in the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study of type 1 diabetes, while a variety of agents were used in clinical trials of type 2 diabetes, supporting the conclusion that glycemic control itself helps prevent CKD and its progression. The effects of glucose-lowering therapies on CKD have helped define A1C targets (see **Table 6.2**).

The presence of CKD affects the risks and benefits of intensive glycemic control and a number of specific glucose-lowering medications. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial of type 2 diabetes, adverse effects of intensive glycemic control (hypoglycemia and mortality) were increased among patients with kidney disease at baseline (56,57). Moreover, there is a lag time of at least 2 years in type 2 diabetes to over 10 years in type 1 diabetes for the effects of intensive

glucose control to manifest as improved eGFR outcomes (53,58,59). Therefore, in some patients with prevalent CKD and substantial comorbidity, target A1C levels may be less intensive (1,60).

**Direct Renal Effects of Glucose-Lowering Medications**

Some glucose-lowering medications also have effects on the kidney that are direct, i.e., not mediated through glycemia. For example, SGLT2 inhibitors reduce renal tubular glucose reabsorption, weight, systemic blood pressure, intraglomerular pressure, and albuminuria and slow GFR loss through mechanisms that appear independent of glycemia (28,61–64). Moreover, recent data support the notion that SGLT2 inhibitors reduce oxidative stress in the kidney by >50% and blunt increases in angiotensinogen as well as reduce NLRP3 inflammasome activity (65–67). Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) also have direct effects on the kidney and have been reported to improve renal outcomes compared with placebo (68–71). Renal effects should be considered when selecting antihyperglycemia agents (see Section 9 “Pharmacologic Approaches to



**Table 11.1—Selected complications of chronic kidney disease**

Complication	Medical and laboratory evaluation
Elevated blood pressure >140/90 mmHg	Blood pressure, weight
Volume overload	History, physical examination, weight
Electrolyte abnormalities	Serum electrolyte
Metabolic acidosis	Serum electrolytes
Anemia	Hemoglobin; iron testing if indicated
Metabolic bone disease	Serum calcium, phosphate, PTH, vitamin 25(OH)D

Complications of chronic kidney disease (CKD) generally become prevalent when estimated glomerular filtration rate falls below 60 mL/min/1.73 m<sup>2</sup> (stage 3 CKD or greater) and become more common and severe as CKD progresses. Evaluation of elevated blood pressure and volume overload should occur at every clinical contact possible; laboratory evaluations are generally indicated every 6–12 months for stage 3 CKD, every 3–5 months for stage 4 CKD, and every 1–3 months for stage 5 CKD, or as indicated to evaluate symptoms or changes in therapy. PTH, parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D.

Glycemic Treatment,” <https://doi.org/10.2337/dc21-S009>).

#### **Selection of Glucose-Lowering Medications for Patients With Chronic Kidney Disease**

For patients with type 2 diabetes and established CKD, special considerations for the selection of glucose-lowering medications include limitations to available medications when eGFR is diminished and a desire to mitigate high risks of CKD progression, CVD, and hypoglycemia (72,73). Drug dosing may require modification with eGFR <60 mL/min/1.73 m<sup>2</sup> (1).

The U.S. Food and Drug Administration (FDA) revised its guidance for the use of metformin in CKD in 2016 (74), recommending use of eGFR instead of serum creatinine to guide treatment and expanding the pool of patients with kidney disease for whom metformin treatment should be considered. The revised FDA guidance states that metformin is contraindicated in patients with an eGFR <30 mL/min/1.73 m<sup>2</sup>; eGFR should be monitored while taking metformin; the benefits and risks of continuing treatment should be reassessed when eGFR falls to <45 mL/min/1.73 m<sup>2</sup> (75,76); metformin should not be initiated for patients with an eGFR <45 mL/min/1.73 m<sup>2</sup>; and metformin should be temporarily discontinued at the time of or before iodinated contrast imaging procedures in patients with eGFR 30–60 mL/min/1.73 m<sup>2</sup>. Within these constraints, metformin should be considered the first-line treatment for all patients with type 2 diabetes, including those with CKD.

SGLT2 inhibitors and GLP-1 RAs should be considered for patients with type 2 diabetes and CKD who require another drug added to metformin to attain target

A1C or cannot use or tolerate metformin. SGLT2 inhibitors reduce risks of CKD progression, CVD events, and hypoglycemia. GLP-1 RAs are suggested because they reduce risks of CVD events and hypoglycemia and appear to possibly slow CKD progression (77).

A number of large cardiovascular outcomes trials in patients with type 2 diabetes at high risk for CVD or with existing CVD examined kidney effects as secondary outcomes. These trials include EMPA-REG OUTCOME [BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients], CANVAS (Canagliflozin Cardiovascular Assessment Study), LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results), and SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes) (63,68,71,78). Specifically, compared with placebo, empagliflozin reduced the risk of incident or worsening nephropathy (a composite of progression to UACR >300 mg/g Cr, doubling of serum creatinine, ESRD, or death from ESRD) by 39% and the risk of doubling of serum creatinine accompanied by eGFR ≤45 mL/min/1.73 m<sup>2</sup> by 44%; canagliflozin reduced the risk of progression of albuminuria by 27% and the risk of reduction in eGFR, ESRD, or death from ESRD by 40%; liraglutide reduced the risk of new or worsening nephropathy (a composite of persistent macroalbuminuria, doubling of serum creatinine, ESRD, or death from ESRD) by 22%; and semaglutide reduced the risk of new or worsening nephropathy (a composite of persistent UACR >300 mg/g Cr, doubling of serum creatinine, or ESRD) by 36% (each *P* < 0.01).

These analyses were limited by evaluation of study populations not selected primarily for CKD and examination of renal effects as secondary outcomes. However, all of these trials included large numbers of people with stage 3a (eGFR 45–59 mL/min/1.73 m<sup>2</sup>) kidney disease. In addition, subgroup analyses of CANVAS and LEADER suggested that the renal benefits of canagliflozin and liraglutide were as great or greater for participants with CKD at baseline (29,70) and in CANVAS were similar for participants with or without atherosclerotic cardiovascular disease (ASCVD) at baseline (79).

Several large clinical trials of SGLT2 inhibitors focused on patients with advanced CKD, and assessment of primary renal outcomes are completed or ongoing. Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE), a placebo-controlled trial of canagliflozin among 4,401 adults with type 2 diabetes, UACR ≥300 mg/g Cr, and mean eGFR 56 mL/min/1.73 m<sup>2</sup> with a mean albuminuria level of over 900 mg/day, had a primary composite end point of ESRD, doubling of serum creatinine, or renal or cardiovascular death (26,80). It was stopped early due to positive efficacy and showed a 32% risk reduction for development of ESRD over control (26). Additionally, the development of the primary end point, which included chronic dialysis for ≥30 days, kidney transplantation or eGFR <15 mL/min/1.73 m<sup>2</sup> sustained for ≥30 days by central laboratory assessment, doubling from the baseline serum creatinine average sustained for ≥30 days by central laboratory assessment, or renal death or cardiovascular death, was reduced by 30%. This benefit was on background ACE inhibitor or ARB therapy in >99% of the patients (26). Moreover, in this advanced CKD group, there were clear benefits on cardiovascular outcomes demonstrating a 31% reduction in cardiovascular death or heart failure hospitalization and a 20% reduction in cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (26,81,82).

In addition to renal effects, some SGLT2 inhibitors and GLP-1 RAs have demonstrated cardiovascular benefits. Namely, in EMPA-REG OUTCOME, CANVAS, LEADER, and SUSTAIN-6, empagliflozin, canagliflozin, liraglutide, and semaglutide, respectively, each reduced cardiovascular

events, evaluated as primary outcomes, compared with placebo (see Section 10 “Cardiovascular Disease and Risk Management,” <https://doi.org/10.2337/dc21-S010> for further discussion). While the glucose-lowering effects of SGLT2 inhibitors are blunted with eGFR <45 mL/min/1.73 m<sup>2</sup>, the renal and cardiovascular benefits were still seen down to eGFR levels of 30 mL/min/1.73 m<sup>2</sup> with no significant change in glucose (26,28,47, 49,56,60,71,78). Most participants with CKD in these trials also had diagnosed ASCVD at baseline, though ~28% of CANVAS participants with CKD did not have diagnosed ASCVD (29).

Based on evidence from the CREDESCENCE trial and secondary analyses of cardiovascular outcomes trials with SGLT2 inhibitors, cardiovascular and renal events are reduced with SGLT2 inhibitor use in patients down to an eGFR of 30 mL/min/1.73 m<sup>2</sup>, independent of glucose-lowering effects (81,82).

While there is clear cardiovascular risk reduction associated with GLP-1 RA use in patients with type 2 diabetes and CKD, the proof of benefit on renal outcome will come with the results of the ongoing FLOW (A Research Study to See How Semaglutide Works Compared with Placebo in People With Type 2 Diabetes and Chronic Kidney Disease) trial with injectable semaglutide (83). As noted above, published data address a limited group of CKD patients, mostly with coexisting ASCVD. Renal events have been examined, however, as both primary and secondary outcomes in published large trials. Also, adverse event profiles of these agents must be considered. Please refer to **Table 9.1** for drug-specific factors, including adverse event information, for these agents. Additional clinical trials focusing on CKD and cardiovascular outcomes in CKD patients are ongoing and will be reported in the next few years.

For patients with type 2 diabetes and CKD, the selection of specific agents may depend on comorbidity and CKD stage. SGLT2 inhibitors may be more useful for patients at high risk of CKD progression (i.e., with albuminuria or a history of documented eGFR loss) (**Fig. 9.1**) because they appear to have large beneficial effects on CKD incidence. The SGLT2 inhibitors empagliflozin and dapagliflozin are approved by the FDA for use with eGFR ≥45 mL/min/1.73 m<sup>2</sup> (though pivotal trials for each included participants

with eGFR ≥30 mL/min/1.73 m<sup>2</sup> and demonstrated benefit in subgroups with low eGFR) (28,29,84). Canagliflozin was recently approved to be started down to eGFR levels of 30 mL/min/1.73 m<sup>2</sup>. Some GLP-1 RAs may be used with lower eGFR, but most require dose adjustment.

**Cardiovascular Disease and Blood Pressure**  
Hypertension is a strong risk factor for the development and progression of CKD (85). Antihypertensive therapy reduces the risk of albuminuria (86–89), and among patients with type 1 or 2 diabetes with established CKD (eGFR <60 mL/min/1.73 m<sup>2</sup> and UACR ≥300 mg/g Cr), ACE inhibitor or ARB therapy reduces the risk of progression to ESRD (90–92). Moreover, antihypertensive therapy reduces risks of cardiovascular events (86).

Blood pressure levels <140/90 mmHg are generally recommended to reduce CVD mortality and slow CKD progression among all people with diabetes (89). Lower blood pressure targets (e.g., <130/80 mmHg) should be considered for patients based on individual anticipated benefits and risks. Patients with CKD are at increased risk of CKD progression (particularly those with albuminuria) and CVD and therefore may be suitable in some cases for lower blood pressure targets, especially in those with ≥300 mg/g Cr albuminuria.

ACE inhibitors or ARBs are the preferred first-line agent for blood pressure treatment among patients with diabetes, hypertension, eGFR <60 mL/min/1.73 m<sup>2</sup>, and UACR ≥300 mg/g Cr because of their proven benefits for prevention of CKD progression (90–93). In general, ACE inhibitors and ARBs are considered to have similar benefits (94,95) and risks. In the setting of lower levels of albuminuria (30–299 mg/g Cr), ACE inhibitor or ARB therapy has been demonstrated to reduce progression to more advanced albuminuria (≥300 mg/g Cr) and cardiovascular events but not progression to ESRD (93,96). While ACE inhibitors or ARBs are often prescribed for high albuminuria without hypertension, outcome trials have not been performed in this setting to determine whether this improves renal outcomes. Moreover, two long-term, double-blind studies demonstrate no renoprotective effect of either ACE inhibitors or ARBs in type 1 and type 2 diabetes among those who were

normotensive with or without high albuminuria (formerly microalbuminuria) (97,98).

Absent kidney disease, ACE inhibitors or ARBs are useful to control blood pressure but have not proven superior to alternative classes of antihypertensive therapy, including thiazide-like diuretics and dihydropyridine calcium channel blockers (99). In a trial of people with type 2 diabetes and normal urine albumin excretion, an ARB reduced or suppressed the development of albuminuria but increased the rate of cardiovascular events (100). In a trial of people with type 1 diabetes exhibiting neither albuminuria nor hypertension, ACE inhibitors or ARBs did not prevent the development of diabetic glomerulopathy assessed by kidney biopsy (97). This was further supported by a similar trial in patients with type 2 diabetes (98). *Therefore, ACE inhibitors or ARBs are not recommended for patients without hypertension to prevent the development of CKD.*

Two clinical trials studied the combinations of ACE inhibitors and ARBs and found no benefits on CVD or CKD, and the drug combination had higher adverse event rates (hyperkalemia and/or AKI) (101,102). *Therefore, the combined use of ACE inhibitors and ARBs should be avoided.*

Mineralocorticoid receptor antagonists (spironolactone, eplerenone, and finerenone) in combination with ACE inhibitors or ARBs remain an area of great interest. Mineralocorticoid receptor antagonists are effective for management of resistant hypertension, have been shown to reduce albuminuria in short-term studies of CKD, and may have additional cardiovascular benefits (103–105). There has been, however, an increase in hyperkalemic episodes in those on dual therapy, and larger, longer trials with clinical outcomes are needed before recommending such therapy.

#### **Referral to a Nephrologist**

Consider referral to a physician experienced in the care of kidney disease when there is uncertainty about the etiology of kidney disease, for difficult management issues (anemia, secondary hyperparathyroidism, metabolic bone disease, resistant hypertension, or electrolyte disturbances), or when there is advanced kidney disease (eGFR <30 mL/min/1.73 m<sup>2</sup>) requiring discussion of renal

replacement therapy for ESRD (2). The threshold for referral may vary depending on the frequency with which a provider encounters patients with diabetes and kidney disease. Consultation with a nephrologist when stage 4 CKD develops (eGFR <30 mL/min/1.73 m<sup>2</sup>) has been found to reduce cost, improve quality of care, and delay dialysis (106). However, other specialists and providers should also educate their patients about the progressive nature of CKD, the kidney preservation benefits of proactive treatment of blood pressure and blood glucose, and the potential need for renal replacement therapy.

## DIABETIC RETINOPATHY

### Recommendations

- 11.12** Optimize glycemic control to reduce the risk or slow the progression of diabetic retinopathy. **A**
- 11.13** Optimize blood pressure and serum lipid control to reduce the risk or slow the progression of diabetic retinopathy. **A**

Diabetic retinopathy is a highly specific vascular complication of both type 1 and type 2 diabetes, with prevalence strongly related to both the duration of diabetes and the level of glycemic control (107). Diabetic retinopathy is the most frequent cause of new cases of blindness among adults aged 20–74 years in developed countries. Glaucoma, cataracts, and other disorders of the eye occur earlier and more frequently in people with diabetes.

In addition to diabetes duration, factors that increase the risk of, or are associated with, retinopathy include chronic hyperglycemia (108), nephropathy (109), hypertension (110), and dyslipidemia (111). Intensive diabetes management with the goal of achieving near-normoglycemia has been shown in large prospective randomized studies to prevent and/or delay the onset and progression of diabetic retinopathy and potentially improve patient reported visual function (50,112–114).

Several case series and a controlled prospective study suggest that pregnancy in patients with type 1 diabetes may aggravate retinopathy and threaten vision, especially when glycemic control is poor at the time of conception (115,116).

Laser photocoagulation surgery can minimize the risk of vision loss (116). However, intervention is not appropriate during pregnancy. This problem often resolves after pregnancy and so does not require treatment.

## Screening

### Recommendations

- 11.14** Adults with type 1 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist within 5 years after the onset of diabetes. **B**
- 11.15** Patients with type 2 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist at the time of the diabetes diagnosis. **B**
- 11.16** If there is no evidence of retinopathy for one or more annual eye exams and glycemia is well controlled, then screening every 1–2 years may be considered. If any level of diabetic retinopathy is present, subsequent dilated retinal examinations should be repeated at least annually by an ophthalmologist or optometrist. If retinopathy is progressing or sight-threatening, then examinations will be required more frequently. **B**
- 11.17** Programs that use retinal photography (with remote reading or use of a validated assessment tool) to improve access to diabetic retinopathy screening can be appropriate screening strategies for diabetic retinopathy. Such programs need to provide pathways for timely referral for a comprehensive eye examination when indicated. **B**
- 11.18** Women with preexisting type 1 or type 2 diabetes who are planning pregnancy or who are pregnant should be counseled on the risk of development and/or progression of diabetic retinopathy. **B**
- 11.19** Eye examinations should occur before pregnancy or in the first trimester in patients with preexisting type 1 or type 2 diabetes, and then patients

should be monitored every trimester and for 1 year postpartum as indicated by the degree of retinopathy. **B**

The preventive effects of therapy and the fact that patients with proliferative diabetic retinopathy (PDR) or macular edema may be asymptomatic provide strong support for screening to detect diabetic retinopathy.

Diabetic retinopathy screening should be performed using validated approaches and methodologies. Youth with type 1 or type 2 diabetes are also at risk for complications and need to be screened for diabetic retinopathy (117). If diabetic retinopathy is evident on screening, prompt referral to an ophthalmologist is recommended. Subsequent examinations for patients with type 1 or type 2 diabetes are generally repeated annually for patients with minimal to no retinopathy. Exams every 1–2 years may be cost-effective after one or more normal eye exams, and in a population with well controlled type 2 diabetes, there was essentially no risk of development of significant retinopathy with a 3-year interval after a normal examination (118). Less frequent intervals have been found in simulated modeling to be potentially effective in screening for diabetic retinopathy in patients without diabetic retinopathy (119). More frequent examinations by the ophthalmologist will be required if retinopathy is progressing.

Retinal photography with remote reading by experts has great potential to provide screening services in areas where qualified eye care professionals are not readily available (112,113). High-quality fundus photographs can detect most clinically significant diabetic retinopathy. Interpretation of the images should be performed by a trained eye care provider. Retinal photography may also enhance efficiency and reduce costs when the expertise of ophthalmologists can be used for more complex examinations and for therapy (120,121). In-person exams are still necessary when the retinal photos are of unacceptable quality and for follow-up if abnormalities are detected. Retinal photos are not a substitute for comprehensive eye exams, which should be performed at least initially and at intervals thereafter as recommended by an eye care professional. Artificial intelligence systems that detect more than



mild diabetic retinopathy and diabetic macular edema authorized for use by the FDA represent an alternative to traditional screening approaches (122). However, the benefits and optimal utilization of this type of screening have yet to be fully determined. Artificial intelligence systems should not be used for patients with known retinopathy, prior retinopathy treatment, or symptoms of vision impairment. Results of eye examinations should be documented and transmitted to the referring health care professional.

#### Type 1 Diabetes

Because retinopathy is estimated to take at least 5 years to develop after the onset of hyperglycemia, patients with type 1 diabetes should have an initial dilated and comprehensive eye examination within 5 years after the diagnosis of diabetes (123).

#### Type 2 Diabetes

Patients with type 2 diabetes who may have had years of undiagnosed diabetes and have a significant risk of prevalent diabetic retinopathy at the time of diagnosis should have an initial dilated and comprehensive eye examination at the time of diagnosis.

#### Pregnancy

Pregnancy is associated with a rapid progression of diabetic retinopathy (124,125). Women with preexisting type 1 or type 2 diabetes who are planning pregnancy or who have become pregnant should be counseled on the risk of development and/or progression of diabetic retinopathy. In addition, rapid implementation of intensive glycemic management in the setting of retinopathy is associated with early worsening of retinopathy (116). Women who develop gestational diabetes mellitus do not require eye examinations during pregnancy and do not appear to be at increased risk of developing diabetic retinopathy during pregnancy (126).

#### Treatment

##### Recommendations

**11.20** Promptly refer patients with any level of macular edema, severe nonproliferative diabetic retinopathy (a precursor of proliferative diabetic retinopathy), or any proliferative diabetic retinopathy to an ophthalmologist who is knowledgeable and

experienced in the management of diabetic retinopathy. **A**

**11.21** The traditional standard treatment, panretinal laser photocoagulation therapy, is indicated to reduce the risk of vision loss in patients with high-risk proliferative diabetic retinopathy and, in some cases, severe nonproliferative diabetic retinopathy. **A**

**11.22** Intravitreal injections of anti-vascular endothelial growth factor are not inferior to traditional panretinal laser photocoagulation and are also indicated to reduce the risk of vision loss in patients with proliferative diabetic retinopathy. **A**

**11.23** Intravitreal injections of anti-vascular endothelial growth factor are indicated for central involved diabetic macular edema, which occurs beneath the foveal center and may threaten reading vision. **A**

**11.24** The presence of retinopathy is not a contraindication to aspirin therapy for cardioprotection, as aspirin does not increase the risk of retinal hemorrhage. **A**

Two of the main motivations for screening for diabetic retinopathy are to prevent loss of vision and to intervene with treatment when vision loss can be prevented or reversed.

#### Photocoagulation Surgery

Two large trials, the Diabetic Retinopathy Study (DRS) in patients with PDR and the Early Treatment Diabetic Retinopathy Study (ETDRS) in patients with macular edema, provide the strongest support for the therapeutic benefits of photocoagulation surgery. The DRS (127) showed in 1978 that panretinal photocoagulation surgery reduced the risk of severe vision loss from PDR from 15.9% in untreated eyes to 6.4% in treated eyes with the greatest benefit ratio in those with more advanced baseline disease (disc neovascularization or vitreous hemorrhage). In 1985, the ETDRS also verified the benefits of panretinal photocoagulation for high-risk PDR and in older-onset patients with severe nonproliferative diabetic retinopathy or less-than-high-risk PDR. Panretinal laser photocoagulation is still commonly used to

manage complications of diabetic retinopathy that involve retinal neovascularization and its complications.

#### Anti-Vascular Endothelial Growth Factor Treatment

Recent data from the Diabetic Retinopathy Clinical Research Network and others demonstrate that intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) agent, specifically ranibizumab, resulted in visual acuity outcomes that were not inferior to those observed in patients treated with panretinal laser at 2 years of follow-up (128). In addition, it was observed that patients treated with ranibizumab tended to have less peripheral visual field loss, fewer vitrectomy surgeries for secondary complications from their proliferative disease, and a lower risk of developing diabetic macular edema. However, a potential drawback in using anti-VEGF therapy to manage proliferative disease is that patients were required to have a greater number of visits and received a greater number of treatments than is typically required for management with panretinal laser, which may not be optimal for some patients. Other emerging therapies for retinopathy that may use sustained intravitreal delivery of pharmacologic agents are currently under investigation. The FDA approved ranibizumab for the treatment of diabetic retinopathy in 2017.

While the ETDRS (129) established the benefit of focal laser photocoagulation surgery in eyes with clinically significant macular edema (defined as retinal edema located at or within 500  $\mu\text{m}$  of the center of the macula), current data from well-designed clinical trials demonstrate that intravitreal anti-VEGF agents provide a more effective treatment regimen for central-involved diabetic macular edema than monotherapy or even combination therapy with a laser (130,131). There are currently three anti-VEGF agents commonly used to treat eyes with central-involved diabetic macular edema—bevacizumab, ranibizumab, and aflibercept (107).

In both the DRS and the ETDRS, laser photocoagulation surgery was beneficial in reducing the risk of further visual loss in affected patients but generally not beneficial in reversing already diminished acuity. Anti-VEGF therapy improves vision and has replaced the need for laser photocoagulation in the vast majority of patients



with diabetic macular edema (132). Most patients require near-monthly administration of intravitreal therapy with anti-VEGF agents during the first 12 months of treatment, with fewer injections needed in subsequent years to maintain remission from central-involved diabetic macular edema.

#### Adjunctive Therapy

Lowering blood pressure has been shown to decrease retinopathy progression, although tight targets (systolic blood pressure <120 mmHg) do not impart additional benefit (113). ACE inhibitors and ARBs are both effective treatments in diabetic retinopathy (133). In patients with dyslipidemia, retinopathy progression may be slowed by the addition of fenofibrate, particularly with very mild nonproliferative diabetic retinopathy at baseline (111,134).

## NEUROPATHY

### Screening

#### Recommendations

- 11.25** All patients should be assessed for diabetic peripheral neuropathy starting at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes and at least annually thereafter. **B**
- 11.26** Assessment for distal symmetric polyneuropathy should include a careful history and assessment of either temperature or pinprick sensation (small fiber function) and vibration sensation using a 128-Hz tuning fork (for large-fiber function). All patients should have annual 10-g monofilament testing to identify feet at risk for ulceration and amputation. **B**
- 11.27** Symptoms and signs of autonomic neuropathy should be assessed in patients with microvascular complications. **E**

The diabetic neuropathies are a heterogeneous group of disorders with diverse clinical manifestations. The early recognition and appropriate management of neuropathy in the patient with diabetes is important.

1. Diabetic neuropathy is a diagnosis of exclusion. Nondiabetic neuropathies may be present in patients with diabetes and may be treatable.

2. Up to 50% of diabetic peripheral neuropathy may be a symptomatic. If not recognized and if preventive foot care is not implemented, patients are at risk for injuries to their insensate feet.
3. Recognition and treatment of autonomic neuropathy may improve symptoms, reduce sequelae, and improve quality of life.

Specific treatment for the underlying nerve damage, other than improved glycemic control, is currently not available. Glycemic control can effectively prevent diabetic peripheral neuropathy (DPN) and cardiac autonomic neuropathy (CAN) in type 1 diabetes (135,136) and may modestly slow their progression in type 2 diabetes (52), but it does not reverse neuronal loss. Therapeutic strategies (pharmacologic and nonpharmacologic) for the relief of painful DPN and symptoms of autonomic neuropathy can potentially reduce pain (137) and improve quality of life.

### Diagnosis

#### Diabetic Peripheral Neuropathy

Patients with type 1 diabetes for 5 or more years and all patients with type 2 diabetes should be assessed annually for DPN using the medical history and simple clinical tests (137). Symptoms vary according to the class of sensory fibers involved. The most common early symptoms are induced by the involvement of small fibers and include pain and dysesthesia (unpleasant sensations of burning and tingling). The involvement of large fibers may cause numbness and loss of protective sensation (LOPS). LOPS indicates the presence of distal sensorimotor polyneuropathy and is a risk factor for diabetic foot ulceration. The following clinical tests may be used to assess small- and large-fiber function and protective sensation:

1. Small-fiber function: pinprick and temperature sensation
2. Large-fiber function: vibration perception and 10-g monofilament
3. Protective sensation: 10-g monofilament

These tests not only screen for the presence of dysfunction but also predict future risk of complications. Electrophysiological testing or referral to a neurologist is rarely needed, except in situations

where the clinical features are atypical or the diagnosis is unclear.

In all patients with diabetes and DPN, causes of neuropathy other than diabetes should be considered, including toxins (e.g., alcohol), neurotoxic medications (e.g., chemotherapy), vitamin B12 deficiency, hypothyroidism, renal disease, malignancies (e.g., multiple myeloma, bronchogenic carcinoma), infections (e.g., HIV), chronic inflammatory demyelinating neuropathy, inherited neuropathies, and vasculitis (138). See the American Diabetes Association (ADA) position statement "Diabetic Neuropathy" for more details (137).

#### Diabetic Autonomic Neuropathy

The symptoms and signs of autonomic neuropathy should be elicited carefully during the history and physical examination. Major clinical manifestations of diabetic autonomic neuropathy include hypoglycemia unawareness, resting tachycardia, orthostatic hypotension, gastroparesis, constipation, diarrhea, fecal incontinence, erectile dysfunction, neurogenic bladder, and sudomotor dysfunction with either increased or decreased sweating.

**Cardiac Autonomic Neuropathy.** CAN is associated with mortality independently of other cardiovascular risk factors (139,140). In its early stages, CAN may be completely asymptomatic and detected only by decreased heart rate variability with deep breathing. Advanced disease may be associated with resting tachycardia (>100 bpm) and orthostatic hypotension (a fall in systolic or diastolic blood pressure by >20 mmHg or >10 mmHg, respectively, upon standing without an appropriate increase in heart rate). CAN treatment is generally focused on alleviating symptoms.

**Gastrointestinal Neuropathies.** Gastrointestinal neuropathies may involve any portion of the gastrointestinal tract with manifestations including esophageal dysmotility, gastroparesis, constipation, diarrhea, and fecal incontinence. Gastroparesis should be suspected in individuals with erratic glycemic control or with upper gastrointestinal symptoms without another identified cause. Exclusion of organic causes of gastric outlet obstruction or peptic ulcer disease (with esophagogastroduodenoscopy or a barium study of the stomach) is needed before considering a diagnosis of or specialized testing for gastroparesis. The diagnostic

gold standard for gastroparesis is the measurement of gastric emptying with scintigraphy of digestible solids at 15-min intervals for 4 h after food intake. The use of  $^{13}\text{C}$  octanoic acid breath test is emerging as a viable alternative.

**Genitourinary Disturbances.** Diabetic autonomic neuropathy may also cause genitourinary disturbances, including sexual dysfunction and bladder dysfunction. In men, diabetic autonomic neuropathy may cause erectile dysfunction and/or retrograde ejaculation (137). Female sexual dysfunction occurs more frequently in those with diabetes and presents as decreased sexual desire, increased pain during intercourse, decreased sexual arousal, and inadequate lubrication (141). Lower urinary tract symptoms manifest as urinary incontinence and bladder dysfunction (nocturia, frequent urination, urination urgency, and weak urinary stream). Evaluation of bladder function should be performed for individuals with diabetes who have recurrent urinary tract infections, pyelonephritis, incontinence, or a palpable bladder.

## Treatment

### Recommendations

- 11.28** Optimize glucose control to prevent or delay the development of neuropathy in patients with type 1 diabetes **A** and to slow the progression of neuropathy in patients with type 2 diabetes. **B**
- 11.29** Assess and treat patients to reduce pain related to diabetic peripheral neuropathy **B** and symptoms of autonomic neuropathy and to improve quality of life. **E**
- 11.30** Pregabalin, duloxetine, or gabapentin are recommended as initial pharmacologic treatments for neuropathic pain in diabetes. **A**

### Glycemic Control

Near-normal glycemic control, implemented early in the course of diabetes, has been shown to effectively delay or prevent the development of DPN and CAN in patients with type 1 diabetes (142–145). Although the evidence for the benefit of near-normal glycemic control is not as strong for type 2 diabetes, some studies have demonstrated a modest slowing of progression without reversal of neuronal loss (52,146). Specific glucose-lowering strategies may have

different effects. In a post hoc analysis, participants, particularly men, in the Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D) trial treated with insulin sensitizers had a lower incidence of distal symmetric polyneuropathy over 4 years than those treated with insulin/sulfonylurea (147).

### Neuropathic Pain

Neuropathic pain can be severe and can impact quality of life, limit mobility, and contribute to depression and social dysfunction (148). No compelling evidence exists in support of glycemic control or lifestyle management as therapies for neuropathic pain in diabetes or prediabetes, which leaves only pharmaceutical interventions (149).

Pregabalin and duloxetine have received regulatory approval by the FDA, Health Canada, and the European Medicines Agency for the treatment of neuropathic pain in diabetes. The opioid tapentadol has regulatory approval in the U.S. and Canada, but the evidence of its use is weaker (150). Comparative effectiveness studies and trials that include quality-of-life outcomes are rare, so treatment decisions must consider each patient's presentation and comorbidities and often follow a trial-and-error approach. Given the range of partially effective treatment options, a tailored and stepwise pharmacologic strategy with careful attention to relative symptom improvement, medication adherence, and medication side effects is recommended to achieve pain reduction and improve quality of life (151–153).

*Pregabalin*, a calcium channel  $\alpha 2\text{-}\delta$  subunit ligand, is the most extensively studied drug for DPN. The majority of studies testing pregabalin have reported favorable effects on the proportion of participants with at least 30–50% improvement in pain (150,152,154–157). However, not all trials with pregabalin have been positive (150,152,158,159), especially when treating patients with advanced refractory DPN (156). Adverse effects may be more severe in older patients (160) and may be attenuated by lower starting doses and more gradual titration. The related drug, *gabapentin*, has also shown efficacy for pain control in diabetic neuropathy and may be less expensive, although it is not FDA approved for this indication (161).

*Duloxetine* is a selective norepinephrine and serotonin reuptake inhibitor. Doses of 60 and 120 mg/day showed efficacy in the treatment of pain associated with DPN in multicenter randomized trials, although some of these had high drop-out rates (150,152,157,159). Duloxetine also appeared to improve neuropathy-related quality of life (162). In longer-term studies, a small increase in A1C was reported in people with diabetes treated with duloxetine compared with placebo (163). Adverse events may be more severe in older people but may be attenuated with lower doses and slower titration of duloxetine.

*Tapentadol* is a centrally acting opioid analgesic that exerts its analgesic effects through both  $\mu$ -opioid receptor agonism and noradrenaline reuptake inhibition. Extended-release tapentadol was approved by the FDA for the treatment of neuropathic pain associated with diabetes based on data from two multicenter clinical trials in which participants titrated to an optimal dose of tapentadol were randomly assigned to continue that dose or switch to placebo (164,165). However, both used a design enriched for patients who responded to tapentadol and therefore their results are not generalizable. A recent systematic review and meta-analysis by the Special Interest Group on Neuropathic Pain of the International Association for the Study of Pain found the evidence supporting the effectiveness of tapentadol in reducing neuropathic pain to be inconclusive (150). Therefore, given the high risk for addiction and safety concerns compared with the relatively modest pain reduction, the use of extended-release tapentadol is not generally recommended as a first- or second-line therapy. The use of any opioids for management of chronic neuropathic pain carries the risk of addiction and should be avoided.

Tricyclic antidepressants, venlafaxine, carbamazepine, and topical capsaicin, although not approved for the treatment of painful DPN, may be effective and considered for the treatment of painful DPN (137,150,152).

### Orthostatic Hypotension

Treating orthostatic hypotension is challenging. The therapeutic goal is to minimize postural symptoms rather than to restore normotension. Most patients require both nonpharmacologic measures

(e.g., ensuring adequate salt intake, avoiding medications that aggravate hypotension, or using compressive garments over the legs and abdomen) and pharmacologic measures. Physical activity and exercise should be encouraged to avoid deconditioning, which is known to exacerbate orthostatic intolerance, and volume repletion with fluids and salt is critical. There have been clinical studies that assessed the impact of an approach incorporating the aforementioned nonpharmacologic measures. Additionally, supine blood pressure tends to be much higher in these patients, often requiring treatment of blood pressure at bedtime with shorter-acting drugs that also affect baroreceptor activity such as guanfacine or clonidine, shorter-acting calcium blockers (e.g., isradipine), or shorter-acting  $\beta$ -blockers such as atenolol or metoprolol tartrate. Alternatives can include enalapril if patients are unable to tolerate preferred agents (166–168). Midodrine and droxidopa are approved by the FDA for the treatment of orthostatic hypotension.

#### Gastroparesis

Treatment for diabetic gastroparesis may be very challenging. A low-fiber, low-fat eating plan provided in small frequent meals with a greater proportion of liquid calories may be useful (169–171). In addition, foods with small particle size may improve key symptoms (172). Withdrawing drugs with adverse effects on gastrointestinal motility, including opioids, anticholinergics, tricyclic antidepressants, GLP-1 RAs, pramlintide, and possibly dipeptidyl peptidase 4 inhibitors, may also improve intestinal motility (169,173). In cases of severe gastroparesis, pharmacologic interventions are needed. Only metoclopramide, a prokinetic agent, is approved by the FDA for the treatment of gastroparesis. However, the level of evidence regarding the benefits of metoclopramide for the management of gastroparesis is weak, and given the risk for serious adverse effects (extrapyramidal signs such as acute dystonic reactions, drug-induced parkinsonism, akathisia, and tardive dyskinesia), its use in the treatment of gastroparesis beyond 12 weeks is no longer recommended by the FDA or the European Medicines Agency. It should be reserved for severe cases that are unresponsive to other therapies (173). Other treatment options include

domperidone (available outside of the U.S.) and erythromycin, which is only effective for short-term use due to tachyphylaxis (174,175). Gastric electrical stimulation using a surgically implantable device has received approval from the FDA, although its efficacy is variable and use is limited to patients with severe symptoms that are refractory to other treatments (176).

#### Erectile Dysfunction

In addition to treatment of hypogonadism if present, treatments for erectile dysfunction may include phosphodiesterase type 5 inhibitors, intracorporeal or intraurethral prostaglandins, vacuum devices, or penile prostheses. As with DPN treatments, these interventions do not change the underlying pathology and natural history of the disease process but may improve the patient's quality of life.

### FOOT CARE

#### Recommendations

- 11.31** Perform a comprehensive foot evaluation at least annually to identify risk factors for ulcers and amputations. **B**
- 11.32** Patients with evidence of sensory loss or prior ulceration or amputation should have their feet inspected at every visit. **B**
- 11.33** Obtain a prior history of ulceration, amputation, Charcot foot, angioplasty or vascular surgery, cigarette smoking, retinopathy, and renal disease and assess current symptoms of neuropathy (pain, burning, numbness) and vascular disease (leg fatigue, claudication). **B**
- 11.34** The examination should include inspection of the skin, assessment of foot deformities, neurological assessment (10-g monofilament testing with at least one other assessment: pinprick, temperature, vibration), and vascular assessment including pulses in the legs and feet. **B**
- 11.35** Patients with symptoms of claudication or decreased or absent pedal pulses should be referred for ankle-brachial index and for further vascular assessment as appropriate. **C**
- 11.36** A multidisciplinary approach is recommended for individuals

with foot ulcers and high-risk feet (e.g., dialysis patients and those with Charcot foot or prior ulcers or amputation). **B**

- 11.37** Refer patients who smoke or who have histories of prior lower-extremity complications, loss of protective sensation, structural abnormalities, or peripheral arterial disease to foot care specialists for ongoing preventive care and lifelong surveillance. **C**

- 11.38** Provide general preventive foot self-care education to all patients with diabetes. **B**

- 11.39** The use of specialized therapeutic footwear is recommended for high-risk patients with diabetes including those with severe neuropathy, foot deformities, ulcers, callous formation, poor peripheral circulation, or history of amputation. **B**

Foot ulcers and amputation, which are consequences of diabetic neuropathy and/or peripheral arterial disease (PAD), are common and represent major causes of morbidity and mortality in people with diabetes.

Early recognition and treatment of patients with diabetes and feet at risk for ulcers and amputations can delay or prevent adverse outcomes.

The risk of ulcers or amputations is increased in people who have the following risk factors:

- Poor glycemic control
- Peripheral neuropathy with LOPS
- Cigarette smoking
- Foot deformities
- Preulcerative callus or corn
- PAD
- History of foot ulcer
- Amputation
- Visual impairment
- CKD (especially patients on dialysis)

Moreover, there is good-quality evidence to support use of appropriate therapeutic footwear with demonstrated pressure relief that is worn by the patient to prevent plantar foot ulcer recurrence or worsening. However, there is very little evidence for the use of interventions to prevent a first foot ulcer or heal ischemic, infected, nonplantar, or proximal foot



ulcers (177). Studies on specific types of footwear demonstrated that shape and barefoot plantar pressure–based orthoses were more effective in reducing submetatarsal head plantar ulcer recurrence than current standard-of-care orthoses (178).

Clinicians are encouraged to review ADA screening recommendations for further details and practical descriptions of how to perform components of the comprehensive foot examination (179).

### Evaluation for Loss of Protective Sensation

All adults with diabetes should undergo a comprehensive foot evaluation at least annually. Detailed foot assessments may occur more frequently in patients with histories of ulcers or amputations, foot deformities, insensate feet, and PAD (180,181). To assess risk, clinicians should ask about history of foot ulcers or amputation, neuropathic and peripheral vascular symptoms, impaired vision, renal disease, tobacco use, and foot care practices. A general inspection of skin integrity and musculoskeletal deformities should be performed. Vascular assessment should include inspection and palpation of pedal pulses.

The neurological exam performed as part of the foot examination is designed to identify LOPS rather than early neuropathy. The 10-g monofilament is the most useful test to diagnose LOPS. Ideally, the 10-g monofilament test should be performed with at least one other assessment (pinprick, temperature or vibration sensation using a 128-Hz tuning fork, or ankle reflexes). Absent monofilament sensation suggests LOPS, while at least two normal tests (and no abnormal test) rules out LOPS.

### Evaluation for Peripheral Arterial Disease

Initial screening for PAD should include a history of decreased walking speed, leg fatigue, claudication, and an assessment of the pedal pulses. Ankle-brachial index testing should be performed in patients with symptoms or signs of PAD. Additionally, at least one of the following tests in a patient with a diabetic foot ulcer and PAD should be performed: skin perfusion pressure ( $\geq 40$  mmHg), toe pressure ( $\geq 30$  mmHg), or transcutaneous oxygen pressure (TcPO<sub>2</sub>  $\geq 25$  mmHg). Urgent vascular imaging and revascularization

should be considered in a patient with a diabetic foot ulcer and an ankle pressure (ankle-brachial index)  $< 50$  mmHg, toe pressure  $< 30$  mmHg, or a TcPO<sub>2</sub>  $< 25$  mmHg (137,182).

### Patient Education

All patients with diabetes and particularly those with high-risk foot conditions (history of ulcer or amputation, deformity, LOPS, or PAD) and their families should be provided general education about risk factors and appropriate management (183). Patients at risk should understand the implications of foot deformities, LOPS, and PAD; the proper care of the foot, including nail and skin care; and the importance of foot monitoring on a daily basis. Patients with LOPS should be educated on ways to substitute other sensory modalities (palpation or visual inspection using an unbreakable mirror) for surveillance of early foot problems.

The selection of appropriate footwear and footwear behaviors at home should also be discussed. Patients' understanding of these issues and their physical ability to conduct proper foot surveillance and care should be assessed. Patients with visual difficulties, physical constraints preventing movement, or cognitive problems that impair their ability to assess the condition of the foot and to institute appropriate responses will need other people, such as family members, to assist with their care.

### Treatment

People with neuropathy or evidence of increased plantar pressures (e.g., erythema, warmth, or calluses) may be adequately managed with well-fitted walking shoes or athletic shoes that cushion the feet and redistribute pressure. People with bony deformities (e.g., hammertoes, prominent metatarsal heads, bunions) may need extra wide or deep shoes. People with bony deformities, including Charcot foot, who cannot be accommodated with commercial therapeutic footwear, will require custom-molded shoes. Special consideration and a thorough workup should be performed when patients with neuropathy present with the acute onset of a red, hot, swollen foot or ankle, and Charcot neuroarthropathy should be excluded. Early diagnosis and treatment of Charcot neuroarthropathy is the best way to prevent deformities that increase the risk

of ulceration and amputation. The routine prescription of therapeutic footwear is not generally recommended. However, patients should be provided adequate information to aid in selection of appropriate footwear. General footwear recommendations include a broad and square toe box, laces with three or four eyes per side, padded tongue, quality lightweight materials, and sufficient size to accommodate a cushioned insole. Use of custom therapeutic footwear can help reduce the risk of future foot ulcers in high-risk patients (180,183).

Most diabetic foot infections are polymicrobial, with aerobic gram-positive cocci. Staphylococci and streptococci are the most common causative organisms. Wounds without evidence of soft tissue or bone infection do not require antibiotic therapy. Empiric antibiotic therapy can be narrowly targeted at gram-positive cocci in many patients with acute infections, but those at risk for infection with antibiotic-resistant organisms or with chronic, previously treated, or severe infections require broader-spectrum regimens and should be referred to specialized care centers (184). Foot ulcers and wound care may require care by a podiatrist, orthopedic or vascular surgeon, or rehabilitation specialist experienced in the management of individuals with diabetes (184).

Hyperbaric oxygen therapy (HBOT) in patients with diabetic foot ulcers has mixed evidence supporting its use as an adjunctive treatment to enhance wound healing and prevent amputation (185–188). A well-conducted randomized controlled study performed in 103 patients found that HBOT did not reduce the indication for amputation or facilitate wound healing compared with comprehensive wound care in patients with chronic diabetic foot ulcers (189). Moreover, a systematic review by the International Working Group on the Diabetic Foot of interventions to improve the healing of chronic diabetic foot ulcers concluded that analysis of the evidence continues to present methodological challenges as randomized controlled studies remain few, with a majority being of poor quality (186). Thus, HBOT does not have a significant effect on health-related quality of life in patients with diabetic foot ulcers (190,191). A recent review concluded that the evidence to date remains inconclusive regarding the clinical and cost-effectiveness of HBOT as an adjunctive



treatment to standard wound care for diabetic foot ulcers (192). Results from the Dutch DAMOCLES (Does Applying More Oxygen Cure Lower Extremity Sores?) trial demonstrated that HBOT in patients with diabetes and ischemic wounds did not significantly improve complete wound healing and limb salvage (193). While the Centers for Medicare & Medicaid Services currently covers HBOT for diabetic foot ulcers that have failed a standard course of wound therapy when there are no measurable signs of healing for at least 30 consecutive days (194), given the data not supporting an effect, such an approach is not currently warranted. HBOT should be a topic of shared decision-making before treatment is considered for selected patients with diabetic foot ulcers (194).

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