



# 11. Microvascular Complications and Foot Care: *Standards of Medical Care in Diabetes—2019*

American Diabetes Association

*Diabetes Care* 2019;42(Suppl. 1):S124–S138 | <https://doi.org/10.2337/dc19-S011>

The American Diabetes Association (ADA) “Standards of Medical Care in Diabetes” includes 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, 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. Readers who wish to comment on the Standards of Care are invited to do so at [professional.diabetes.org/SOC](http://professional.diabetes.org/SOC).

For prevention and management of diabetes complications in children and adolescents, please refer to Section 13 “Children and Adolescents.”

## CHRONIC KIDNEY DISEASE

### Recommendations

#### Screening

**11.1** At least once a year, assess urinary albumin (e.g., spot urinary albumin-to-creatinine ratio) and estimated glomerular filtration rate in patients with type 1 diabetes with duration of  $\geq 5$  years, in all patients with type 2 diabetes, and in all patients with comorbid hypertension. **B**

#### Treatment

**11.2** Optimize glucose control to reduce the risk or slow the progression of chronic kidney disease. **A**

**11.3** For patients with type 2 diabetes and chronic kidney disease, consider use of a sodium–glucose cotransporter 2 inhibitor or glucagon-like peptide 1 receptor agonist shown to reduce risk of chronic kidney disease progression, cardiovascular events, or both (**Table 9.1**). **C**

**11.4** Optimize blood pressure control to reduce the risk or slow the progression of chronic kidney disease. **A**

**11.5** 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). For patients on dialysis, higher levels of dietary protein intake should be considered. **B**

**11.6** 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

*Suggested citation:* American Diabetes Association. 11. Microvascular complications and foot care: Standards of Medical Care in Diabetes—2019. *Diabetes Care* 2019;42(Suppl. 1):S124–S138

© 2018 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. More information is available at <http://www.diabetesjournals.org/content/license>.

ratio  $\geq 300$  mg/g creatinine and/or estimated glomerular filtration rate  $< 60$  mL/min/ $1.73$  m<sup>2</sup>. **A**

**11.7** 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**

**11.8** Continued monitoring of urinary albumin-to-creatinine ratio in patients with albuminuria treated with an ACE inhibitor or an angiotensin receptor blocker is reasonable to assess the response to treatment and progression of chronic kidney disease. **E**

**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. **B**

**11.10** When estimated glomerular filtration rate is  $< 60$  mL/min/ $1.73$  m<sup>2</sup>, evaluate and manage potential complications of chronic kidney disease. **E**

**11.11** Patients should be referred for evaluation for renal replacement treatment if they have an estimated glomerular filtration rate  $< 30$  mL/min/ $1.73$  m<sup>2</sup>. **A**

**11.12** 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. **B**

### 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 will be 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.

Normal UACR is generally defined as  $< 30$  mg/g Cr, and increased 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). Furthermore, because of biological variability 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 albuminuria. Exercise within 24 h, infection, fever, congestive heart failure, marked hyperglycemia, menstruation, and marked hypertension may elevate UACR independently of kidney damage.

eGFR should be calculated from serum Cr 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 Cr, and eGFR calculators are available from [www.nkdep.nih.gov](http://www.nkdep.nih.gov). An eGFR  $< 60$  mL/min/ $1.73$  m<sup>2</sup> is generally considered abnormal, though optimal thresholds for clinical diagnosis are debated (10).

Urinary albumin excretion and eGFR each vary within people over time, and abnormal results should be confirmed to stage CKD (1,2).

### 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 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. (3,4,11,12).

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) may suggest 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 (13).

### Staging of Chronic Kidney Disease

Stages 1–2 CKD have been defined by evidence of kidney damage (usually 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 (14) (Table 11.1). At any eGFR, the degree of albuminuria is associated with risk of CKD progression, cardiovascular disease (CVD), 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). Regardless of classification scheme, both eGFR and albuminuria should be quantified to guide treatment decisions: CKD complications (Table 11.2) correlate with eGFR, many drugs are limited to

**Table 11.1—CKD stages and corresponding focus of kidney-related care**

Stage	CKD stage†		Focus of kidney-related care			
	eGFR (mL/min/1.73 m <sup>2</sup> )	Evidence of kidney damage*	Diagnose cause of kidney injury	Evaluate and treat risk factors for CKD progression**	Evaluate and treat CKD complications***	Prepare for renal replacement therapy
No clinical evidence of CKD	≥60	—				
1	≥90	+	✓	✓		
2	60–89	+	✓	✓		
3	30–59	+/-	✓	✓	✓	
4	15–29	+/-		✓	✓	✓
5	<15	+/-			✓	✓

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate. †CKD stages 1 and 2 are defined by evidence of kidney damage (+), while CKD stages 3–5 are defined by reduced eGFR with or without evidence of kidney damage (+/-). At any stage of CKD, the degree of albuminuria, observed history of eGFR loss, and cause of kidney damage (including possible causes other than diabetes) may also be used to characterize CKD, gauge prognosis, and guide treatment decisions. \*Kidney damage is most often manifest as albuminuria (UACR ≥30 mg/g Cr) but can also include glomerular hematuria, other abnormalities of the urinary sediment, radiographic abnormalities, and other presentations. \*\*Risk factors for CKD progression include elevated blood pressure, hyperglycemia, and albuminuria. \*\*\*See **Table 11.2**.

acceptable eGFR ranges, and the degree of albuminuria may influence choice of antihypertensive (see Section 10 “Cardiovascular Disease and Risk Management”) 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 (15).

**Acute Kidney Injury**

Acute kidney injury (AKI) is usually diagnosed by a rapid increase in serum Cr, which is also reflected as a rapid decrease in eGFR, over a relatively short period of time. People with diabetes are at higher risk of AKI than those without diabetes (16). 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 is a 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, existing evidence from clinical trials and observational studies suggests that SGLT2 inhibitors do not significantly increase AKI (17–19). Timely identification and treatment of AKI are important because AKI is associated with increased risks of progressive CKD and other poor health outcomes (20).

**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 (21–23). 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 11.2**).

The need for annual quantitative assessment of albumin excretion after diagnosis of albuminuria, institution of ACE inhibitors or ARB therapy, and achieving 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

**Table 11.2—Selected complications of CKD**

Complication	Medical and laboratory evaluation
Elevated blood pressure	Blood pressure, weight
Volume overload	History, physical examination, weight
Electrolyte abnormalities	Serum electrolytes
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.

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 (24,25).

The prevalence of CKD complications correlates with eGFR (25a). When eGFR is  $< 60$  mL/min/1.73 m<sup>2</sup>, screening for complications of CKD is indicated (**Table 11.2**). 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” for further information on immunization).

## Interventions

### Nutrition

For people with nondialysis-dependent CKD, dietary protein intake should be approximately 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 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.

Restriction of dietary sodium (to  $< 2,300$  mg/day) may be useful to control blood pressure and reduce cardiovascular risk (26), and restriction of dietary potassium may be necessary to control serum potassium concentration (16,21–23). These interventions may be most important for patients with reduced eGFR, for whom urinary excretion of sodium and potassium may be impaired. 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 (27,28) and type 2 diabetes (1,29–34). 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 (35,36). 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 (33,37,38). Therefore, in some patients with prevalent CKD and substantial comorbidity, target A1C levels may be less intensive (1,39).

### 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 (18,40–43). Glucagon-like peptide 1 receptor agonists (GLP-1 RA) also have direct effects on the kidney and have been reported to improve renal outcomes compared with placebo (44–47). Renal effects should be considered when selecting antihyperglycemia agents (see Section 9 “Pharmacologic Approaches to Glycemic Treatment”).

### 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 (48,49). 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 (50), recommending use of eGFR instead of serum Cr 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  $< 45$  mL/min/1.73 m<sup>2</sup>, 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 RA 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 and GLP-1 RA are suggested because they appear to reduce risks of CKD progression, CVD events, and hypoglycemia.

**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) (42,44,47,51).**

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 Cr, ESRD, or death from ESRD) by 39% and the risk of doubling of serum Cr accompanied by  $eGFR \leq 45$  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 Cr, 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 Cr, 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 kidney disease (for example, the baseline prevalence of albuminuria in EMPA-REG OUTCOME was 53%), and some of the cardiovascular outcomes trials (CANVAS and LEADER) were enriched with patients with kidney disease through eligibility criteria based on albuminuria or reduced  $eGFR$ . 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 (19,46) and in CANVAS were similar for participants with or without atherosclerotic cardiovascular disease (ASCVD) at baseline (52). Smaller, shorter-term trials also demonstrate favorable renal effects of medications in these classes (53, 53a). Together, these consistent results suggest likely renal benefits of both drug classes.

Several large clinical trials of SGLT2 inhibitors focused on patients with CKD, and assessment of primary renal outcomes are completed or ongoing. Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDESCENCE), a placebo-controlled trial of canagliflozin among 4,401 adults with type 2 diabetes, UACR  $\geq 300$  mg/g, and  $eGFR$  30–90 mL/min/1.73 m<sup>2</sup>, has a primary composite end point of ESRD, doubling of serum Cr, or renal or cardiovascular death (54). It

was stopped early due to positive efficacy, with detailed results expected in 2019.

In addition to renal effects, some SGLT2 inhibitors and GLP-1 RA have demonstrated cardiovascular benefits. Namely, in EMPA-REG OUTCOME, CANVAS, and LEADER, empagliflozin, canagliflozin, and liraglutide, respectively, each reduced cardiovascular events, evaluated as primary outcomes, compared with placebo (see Section 10 “Cardiovascular Disease and Risk Management” for further discussion). The glucose-lowering effects of SGLT2 inhibitors are blunted with  $eGFR$  (18,51). However, the cardiovascular benefits of empagliflozin, canagliflozin, and liraglutide were similar among participants with and without kidney disease at baseline (42,44,51,55). Most participants with CKD in these trials also had diagnosed ASCVD at baseline, though approximately 28% of CANVAS participants with CKD did not have diagnosed ASCVD (19).

Important caveats limit the strength of evidence supporting the recommendation of SGLT2 inhibitors and GLP-1 RA in patients with type 2 diabetes and CKD. As noted above, published data address a limited group of CKD patients, mostly with coexisting ASCVD. Renal events have been examined primarily as 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. Therefore, additional clinical trials are needed to more rigorously assess the benefits and risks of these classes of drugs among people with CKD.

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. Empagliflozin and canagliflozin are only approved by the FDA for use with  $eGFR \geq 45$  mL/min/1.73 m<sup>2</sup> (though pivotal trials for each included participants with  $eGFR \geq 30$  mL/min/1.73 m<sup>2</sup> and demonstrated benefit in subgroups with low  $eGFR$ ) (18,19), and dapagliflozin is only approved for  $eGFR \geq 60$  mL/min/1.73 m<sup>2</sup>. Some GLP-1 RA may be used with lower  $eGFR$  and may have greater benefits for

reduction of ASCVD than for CKD progression or heart failure.

**Cardiovascular Disease and Blood Pressure**  
Hypertension is a strong risk factor for the development and progression of CKD (56). Antihypertensive therapy reduces the risk of albuminuria (57–60), and among patients with type 1 or 2 diabetes with established CKD ( $eGFR < 60$  mL/min/1.73 m<sup>2</sup> and UACR  $\geq 300$  mg/g Cr), ACE inhibitor or ARB therapy reduces the risk of progression to ESRD (61–63). Moreover, antihypertensive therapy reduces risks of cardiovascular events (57).

Blood pressure levels  $<140/90$  mmHg are generally recommended to reduce CVD mortality and slow CKD progression among people with diabetes (60). Lower blood pressure targets (e.g.,  $<130/80$  mmHg) may 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.

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  $\geq 300$  mg/g Cr because of their proven benefits for prevention of CKD progression (61–64). In general, ACE inhibitors and ARBs are considered to have similar benefits (65,66) 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 ( $\geq 300$  mg/g Cr) and cardiovascular events but not progression to ESRD (64,67). While ACE inhibitors or ARBs are often prescribed for albuminuria without hypertension, clinical trials have not been performed in this setting to determine whether this improves renal outcomes.

Absent kidney disease, ACE inhibitors or ARBs are useful to control blood pressure but may not be superior to alternative proven classes of antihypertensive therapy, including thiazide-like diuretics and dihydropyridine calcium channel blockers (68). 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 (69). 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 (70). *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) (71,72). *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 (73–75). 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, difficult management issues (anemia, secondary hyperparathyroidism, metabolic bone disease, resistant hypertension, or electrolyte disturbances), or advanced kidney disease (eGFR <30 mL/min/1.73 m<sup>2</sup>) requiring discussion of renal replacement therapy for ESRD. 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 (76). 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

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

### Screening

- 11.15** 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**
- 11.16** 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**
- 11.17** If there is no evidence of retinopathy for one or more annual eye exam and glycemia is well controlled, then exams 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**
- 11.18** Telemedicine programs that use validated retinal photography with remote reading by an ophthalmologist or optometrist and timely referral for a comprehensive eye examination when indicated can be an appropriate screening strategy for diabetic retinopathy. **B**
- 11.19** 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**
- 11.20** 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**

### Treatment

- 11.21** 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**
- 11.22** 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**
- 11.23** Intravitreal injections of anti-vascular endothelial growth factor ranibizumab 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**
- 11.24** 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**
- 11.25** The presence of retinopathy is not a contraindication to aspirin therapy for cardioprotection, as aspirin does not increase the risk of retinal hemorrhage. **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 (77). 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 (78), nephropathy (79), hypertension (80), and dyslipidemia (81). 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 (30,82–84).

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 (85,86). Laser photocoagulation surgery can minimize the risk of vision loss (86).

### Screening

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.

An ophthalmologist or optometrist who is knowledgeable and experienced in diagnosing diabetic retinopathy should perform the examinations. Youth with type 1 or type 2 diabetes are also at risk for complications and need to be screened for diabetic retinopathy (87). If diabetic retinopathy is present, 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 (88). Less frequent intervals have been found in simulated modeling to be potentially effective in screening for diabetic retinopathy in patients without diabetic retinopathy (89). 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 (82,83). 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 (90,91). 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. 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 (92).

### 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 (93,94). 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 (86). 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 (95).

### Treatment

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 (96) 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 (97). 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 (98) 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 laser (99–101). There are currently three anti-VEGF agents commonly used to treat eyes with central-involved diabetic macular edema—bevacizumab, ranibizumab, and aflibercept (77).

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 (102). 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 (83). ACE inhibitors and ARBs are both effective treatments in diabetic retinopathy (103). In patients with dyslipidemia, retinopathy progression may be slowed by the addition of fenofibrate, particularly with very mild nonproliferative diabetic retinopathy at baseline (81,104).

## NEUROPATHY

### Recommendations

#### Screening

**11.26** 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**

**11.27** 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**

**11.28** Symptoms and signs of autonomic neuropathy should be assessed in patients with microvascular complications. **E**

#### Treatment

**11.29** 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**

**11.30** 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**

**11.31** Pregabalin, duloxetine, or gabapentin are recommended as initial pharmacologic treatments for neuropathic pain in diabetes. **A**

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. Numerous treatment options exist for symptomatic diabetic neuropathy.
3. Up to 50% of diabetic peripheral neuropathy (DPN) may be asymptomatic. If not recognized and if preventive foot care is not implemented, patients are at risk for injuries to their insensate feet.
4. 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 DPN and cardiac autonomic neuropathy (CAN) in type 1 diabetes (105,106) and may modestly slow their progression in type 2 diabetes (32), but 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 (107) 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. 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 (108). See the American Diabetes Association (ADA) position statement “Diabetic Neuropathy” for more details (107).

#### **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 (109,110). 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 <sup>13</sup>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 (107). 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 (111). 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**

##### **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 (112–115). 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 (32,116). 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 (117).

##### **Neuropathic Pain**

Neuropathic pain can be severe and can impact quality of life, limit mobility, and contribute to depression and social dysfunction (118). 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 (119).

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 (120). 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 (121–123).

*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 (120,122,124–127). However, not all trials with pregabalin have been positive (120,122,128,129), especially when treating patients with advanced refractory DPN (126). Adverse effects may be more severe in older patients (130) 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 (131).

*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 (120,122,127,129). Duloxetine also appeared to improve neuropathy-related quality of life (132). In longer-term studies, a small increase in A1C was reported in people with diabetes treated with duloxetine compared with placebo (133). Adverse events may be more severe in older people but may be attenuated with lower doses and slower titrations 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 (134,135). 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 (120). 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 (107,120,122).

#### **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. 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 (136–138). In addition, foods with small particle size may improve key symptoms (139). Withdrawing drugs with adverse effects on gastrointestinal motility including opioids, anticholinergics, tricyclic antidepressants, GLP-1 RA, pramlintide, and possibly dipeptidyl peptidase 4 inhibitors

may also improve intestinal motility (136,140). 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 (140). Other treatment options include domperidone (available outside of the U.S.) and erythromycin, which is only effective for short-term use due to tachyphylaxis (141,142). 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 (143).

#### **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**

- 11.32** Perform a comprehensive foot evaluation at least annually to identify risk factors for ulcers and amputations. **B**
- 11.33** Patients with evidence of sensory loss or prior ulceration or amputation should have their feet inspected at every visit. **C**
- 11.34** 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**

- 11.35** 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**
- 11.36** 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**
- 11.37** 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**
- 11.38** 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**
- 11.39** Provide general preventive foot self-care education to all patients with diabetes. **B**
- 11.40** The use of specialized therapeutic footwear is recommended for high-risk patients with diabetes including those with severe neuropathy, foot deformities, 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)

Clinicians are encouraged to review ADA screening recommendations for further details and practical descriptions of how to perform components of the comprehensive foot examination (144).

### 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 (145). 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.

### 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 (146). 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 (145,147).

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 (148). 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 (148).

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 (149–151). In a relatively high-quality double-blind study of patients with chronic diabetic foot ulcers, hyperbaric oxygen as an adjunctive therapy resulted in significantly more complete healing of the index ulcer in patients treated with HBOT compared with placebo at 1 year of follow-up (152). However, multiple subsequently published studies have either failed to demonstrate a benefit of HBOT or have been relatively small with potential flaws in study design (150). 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 (153). 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 (150). HBOT also does not seem to have a significant effect on health-related quality

of life in patients with diabetic foot ulcers (154,155). 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 (156). Results from the recently published 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 (157). 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 (158). HBOT should be a topic of shared decision making before treatment is considered for selected patients with diabetic foot ulcers (158).

## References

- Tuttle KR, Bakris GL, Bilous RW, et al. Diabetic kidney disease: a report from an ADA Consensus Conference. *Diabetes Care* 2014;37:2864–2883
- National Kidney Foundation. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013;3:1–150
- Afkarian M, Zelnick LR, Hall YN, et al. Clinical manifestations of kidney disease among US adults with diabetes, 1988–2014. *JAMA* 2016;316:602–610
- de Boer IH, Rue TC, Hall YN, Heagerty PJ, Weiss NS, Himmelfarb J. Temporal trends in the prevalence of diabetic kidney disease in the United States. *JAMA* 2011;305:2532–2539
- de Boer IH; DCCT/EDIC Research Group. Kidney disease and related findings in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study. *Diabetes Care* 2014;37:24–30
- United States Renal Data System. *Annual Data Report: Epidemiology of Kidney Disease in the United States*. Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2016
- Fox CS, Matsushita K, Woodward M, et al.; Chronic Kidney Disease Prognosis Consortium. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. *Lancet* 2012;380:1662–1673
- Afkarian M, Sachs MC, Kestenbaum B, et al. Kidney disease and increased mortality risk in type 2 diabetes. *J Am Soc Nephrol* 2013;24:302–308
- Groop P-H, Thomas MC, Moran JL, et al.; FinnDiane Study Group. The presence and severity of chronic kidney disease predicts all-cause mortality in type 1 diabetes. *Diabetes* 2009;58:1651–1658
- Delanaye P, Glasscock RJ, Pottel H, Rule AD. An age-calibrated definition of chronic kidney disease: rationale and benefits. *Clin Biochem Rev* 2016;37:17–26
- Kramer HJ, Nguyen QD, Curhan G, Hsu C-Y. Renal insufficiency in the absence of albuminuria and retinopathy among adults with type 2 diabetes mellitus. *JAMA* 2003;289:3273–3277
- Molitch ME, Steffes M, Sun W, et al.; Epidemiology of Diabetes Interventions and Complications Study Group. Development and progression of renal insufficiency with and without albuminuria in adults with type 1 diabetes in the Diabetes Control and Complications Trial and the Epidemiology of Diabetes Interventions and Complications study. *Diabetes Care* 2010;33:1536–1543
- He F, Xia X, Wu XF, Yu XQ, Huang FX. Diabetic retinopathy in predicting diabetic nephropathy in patients with type 2 diabetes and renal disease: a meta-analysis. *Diabetologia* 2013;56:457–466
- Levey AS, Coresh J, Balk E, et al.; National Kidney Foundation. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med* 2003;139:137–147
- Coresh J, Turin TC, Matsushita K, et al. Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. *JAMA* 2014;311:2518–2531
- James MT, Grams ME, Woodward M, et al.; CKD Prognosis Consortium. A meta-analysis of the association of estimated GFR, albuminuria, diabetes mellitus, and hypertension with acute kidney injury. *Am J Kidney Dis* 2015;66:602–612
- Nadkarni GN, Ferrandino R, Chang A, et al. Acute kidney injury in patients on SGLT2 inhibitors: a propensity-matched analysis. *Diabetes Care* 2017;40:1479–1485
- Wanner C, Inzucchi SE, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med* 2016;375:323–334
- Neuen BL, Ohkuma T, Neal B, et al. Cardiovascular and renal outcomes with canagliflozin according to baseline kidney function: data from the CANVAS Program. *Circulation* 2018;138:1537–1550
- Thakar CV, Christianson A, Himmelfarb J, Leonard AC. Acute kidney injury episodes and chronic kidney disease risk in diabetes mellitus. *Clin J Am Soc Nephrol* 2011;6:2567–2572
- Hughes-Austin JM, Rifkin DE, Beben T, et al. The relation of serum potassium concentration with cardiovascular events and mortality in community-living individuals. *Clin J Am Soc Nephrol* 2017;12:245–252
- Bandak G, Sang Y, Gasparini A, et al. Hyperkalemia after initiating renin-angiotensin system blockade: the Stockholm Creatinine Measurements (SCREAM) Project. *J Am Heart Assoc* 2017;6:e005428
- Nilsson E, Gasparini A, Ärnlöv J, et al. Incidence and determinants of hyperkalemia and hypokalemia in a large healthcare system. *Int J Cardiol* 2017;245:277–284
- de Boer IH, Gao X, Cleary PA, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group. Albuminuria changes and cardiovascular and renal outcomes in type 1 diabetes: the DCCT/EDIC study. *Clin J Am Soc Nephrol* 2016;11:1969–1977
- Sumida K, Molnar MZ, Potukuchi PK, et al. Changes in albuminuria and subsequent risk of incident kidney disease. *Clin J Am Soc Nephrol* 2017;12:1941–1949
- Inker LA, Grams ME, Levey AS, et al.; CKD Prognosis Consortium. Relationship of estimated GFR and albuminuria to concurrent laboratory abnormalities: an individual participant data meta-analysis in a global consortium. *Am J Kidney Dis*. 19 October 2018 [Epub ahead of print]. DOI: 10.1053/j.ajkd.2018.08.013
- Mills KT, Chen J, Yang W, et al.; Chronic Renal Insufficiency Cohort (CRIC) Study Investigators. Sodium excretion and the risk of cardiovascular disease in patients with chronic kidney disease. *JAMA* 2016;315:2200–2210
- DCCT/EDIC Research Group. Effect of intensive diabetes treatment on albuminuria in type 1 diabetes: long-term follow-up of the Diabetes Control and Complications Trial and Epidemiology of Diabetes Interventions and Complications study. *Lancet Diabetes Endocrinol* 2014;2:793–800
- de Boer IH, Sun W, Cleary PA, et al.; DCCT/EDIC Research Group. Intensive diabetes therapy and glomerular filtration rate in type 1 diabetes. *N Engl J Med* 2011;365:2366–2376
- UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998;352:854–865
- UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837–853
- Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;358:2560–2572
- Ismail-Beigi F, Craven T, Banerji MA, et al.; ACCORD trial group. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. *Lancet* 2010;376:419–430
- Zoungas S, Chalmers J, Neal B, et al.; ADVANCE-ON Collaborative Group. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. *N Engl J Med* 2014;371:1392–1406
- Zoungas S, Arima H, Gerstein HC, et al.; Collaborators on Trials of Lowering Glucose (CONTROL) group. Effects of intensive glucose control on microvascular outcomes in patients with type 2 diabetes: a meta-analysis of individual participant data from randomised controlled trials. *Lancet Diabetes Endocrinol* 2017;5:431–437
- Miller ME, Bonds DE, Gerstein HC, et al.; ACCORD Investigators. The effects of baseline characteristics, glycaemia treatment approach, and glycated haemoglobin concentration on the risk of severe hypoglycaemia: post hoc epidemiological analysis of the ACCORD study. *BMJ* 2010;340:b5444
- Papademetriou V, Lovato L, Doumas M, et al.; ACCORD Study Group. Chronic kidney

- disease and intensive glycemic control increase cardiovascular risk in patients with type 2 diabetes. *Kidney Int* 2015;87:649–659
37. Perkovic V, Heerspink HL, Chalmers J, et al.; ADVANCE Collaborative Group. Intensive glucose control improves kidney outcomes in patients with type 2 diabetes. *Kidney Int* 2013;83:517–523
38. Wong MG, Perkovic V, Chalmers J, et al.; ADVANCE-ON Collaborative Group. Long-term benefits of intensive glucose control for preventing end-stage kidney disease: ADVANCE-ON. *Diabetes Care* 2016;39:694–700
39. National Kidney Foundation. KDOQI clinical practice guideline for diabetes and CKD: 2012 update. *Am J Kidney Dis* 2012;60:850–886
40. Cherney DZI, Perkins BA, Soleymanlou N, et al. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. *Circulation* 2014;129:587–597
41. Heerspink HJL, Desai M, Jardine M, Balis D, Meininger G, Perkovic V. Canagliflozin slows progression of renal function decline independently of glycemic effects. *J Am Soc Nephrol* 2017;28:368–375 PubMed
42. Neal B, Perkovic V, Mahaffey KW, et al.; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;377:644–657
43. Zelniker TA, Braunwald E. Cardiac and renal effects of sodium-glucose co-transporter 2 inhibitors in diabetes: JACC state-of-the-art review. *J Am Coll Cardiol* 2018;72:1845–1855
44. Marso SP, Daniels GH, Brown-Frandsen K, et al.; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016;375:311–322
45. Cooper ME, Perkovic V, McGill JB, et al. Kidney disease end points in a pooled analysis of individual patient-level data from a large clinical trials program of the dipeptidyl peptidase 4 inhibitor linagliptin in type 2 diabetes. *Am J Kidney Dis* 2015;66:441–449
46. Mann JFE, Ørsted DD, Brown-Frandsen K, et al.; LEADER Steering Committee and Investigators. Liraglutide and renal outcomes in type 2 diabetes. *N Engl J Med* 2017;377:839–848
47. Marso SP, Bain SC, Consoli A, et al.; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016;375:1834–1844
48. Karter AJ, Warton EM, Lipska KJ, et al. Development and validation of a tool to identify patients with type 2 diabetes at high risk of hypoglycemia-related emergency department or hospital use. *JAMA Intern Med* 2017;177:1461–1470
49. Moen MF, Zhan M, Hsu VD, et al. Frequency of hypoglycemia and its significance in chronic kidney disease. *Clin J Am Soc Nephrol* 2009;4:1121–1127
50. U.S. Food and Drug Administration. FDA drug safety communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function [Internet], 2016. Available from <http://www.fda.gov/Drugs/DrugSafety/ucm493244.htm>. Accessed 14 October 2016
51. Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;373:2117–2128
52. Mahaffey KW, Neal B, Perkovic V, et al.; CANVAS Program Collaborative Group. Canagliflozin for primary and secondary prevention of cardiovascular events: results from the CANVAS Program (Canagliflozin Cardiovascular Assessment Study). *Circulation* 2018;137:323–334
53. Tuttle KR, Lakshmanan MC, Rayner B, et al. Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial. *Lancet Diabetes Endocrinol* 2018;6:605–617
- 53a. Lambers-Heerspink HJ, Desai M, Jardine M, et al. Canagliflozin slows progression of renal function decline independent of glycemic effects. *J Am Soc Nephrol* 2017;28:368–375
54. Jardine MJ, Mahaffey KW, Neal B, et al.; CREDENCE study investigators. The Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) study rationale, design, and baseline characteristics. *Am J Nephrol* 2017;46:462–472
55. Wanner C, Lachin JM, Inzucchi SE, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin and clinical outcomes in patients with type 2 diabetes, established cardiovascular disease and chronic kidney disease. *Circulation* 2018;137:119–129
56. Leehey DJ, Zhang JH, Emanuele NV, et al.; VA NEPHRON-D Study Group. BP and renal outcomes in diabetic kidney disease: the Veterans Affairs Nephropathy in Diabetes Trial. *Clin J Am Soc Nephrol* 2015;10:2159–2169
57. Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2015;313:603–615
58. Cushman WC, Evans GW, Byington RP, et al.; ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010;362:1575–1585
59. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 1998;317:703–713
60. de Boer IH, Bangalore S, Benetos A, et al. Diabetes and hypertension: a position statement by the American Diabetes Association. *Diabetes Care* 2017;40:1273–1284
61. Brenner BM, Cooper ME, de Zeeuw D, et al.; RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;345:861–869
62. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD; The Collaborative Study Group. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *N Engl J Med* 1993;329:1456–1462
63. Lewis EJ, Hunsicker LG, Clarke WR, et al.; Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;345:851–860
64. Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000;355:253–259
65. Barnett AH, Bain SC, Bouter P, et al.; Diabetics Exposed to Telmisartan and Enalapril Study Group. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. *N Engl J Med* 2004;351:1952–1961
66. Wu H-Y, Peng C-L, Chen P-C, et al. Comparative effectiveness of angiotensin-converting enzyme inhibitors versus angiotensin II receptor blockers for major renal outcomes in patients with diabetes: a 15-year cohort study. *PLoS One* 2017;12:e0177654
67. Parving HH, Lehnert H, Bröchner-Mortensen J, Gomis R, Andersen S, Arner P; Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 2001;345:870–878
68. Bangalore S, Fakheri R, Toklu B, Messerli FH. Diabetes mellitus as a compelling indication for use of renin angiotensin system blockers: systematic review and meta-analysis of randomized trials. *BMJ* 2016;352:i438
69. Haller H, Ito S, Izzo JL Jr, et al.; ROADMAP Trial Investigators. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. *N Engl J Med* 2011;364:907–917
70. Mauer M, Zinman B, Gardiner R, et al. Renal and retinal effects of enalapril and losartan in type 1 diabetes. *N Engl J Med* 2009;361:40–51
71. Yusuf S, Teo KK, Pogue J, et al.; ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008;358:1547–1559
72. Fried LF, Emanuele N, Zhang JH, et al.; VA NEPHRON-D Investigators. Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med* 2013;369:1892–1903
73. Bakris GL, Agarwal R, Chan JC, et al.; Mineralocorticoid Receptor Antagonist Tolerability Study–Diabetic Nephropathy (ARTS-DN) Study Group. Effect of finerenone on albuminuria in patients with diabetic nephropathy: a randomized clinical trial. *JAMA* 2015;314:884–894
74. Williams B, MacDonald TM, Morant S, et al.; British Hypertension Society’s PATHWAY Studies Group. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. *Lancet* 2015;386:2059–2068
75. Filippatos G, Anker SD, Böhm M, et al. A randomized controlled study of finerenone vs. eplerenone in patients with worsening chronic heart failure and diabetes mellitus and/or chronic kidney disease. *Eur Heart J* 2016;37:2105–2114
76. Smart NA, Dieberg G, Ladhani M, Titus T. Early referral to specialist nephrology services for preventing the progression to end-stage kidney disease. *Cochrane Database Syst Rev* 2014;6:CD007333
77. Solomon SD, Chew E, Duh EJ, et al. Diabetic retinopathy: a position statement by the American Diabetes Association. *Diabetes Care* 2017;40:412–418
78. Klein R. Hyperglycemia and microvascular and macrovascular disease in diabetes. *Diabetes Care* 1995;18:258–268

79. Estacio RO, McFarling E, Biggerstaff S, Jeffers BW, Johnson D, Schrier RW. Overt albuminuria predicts diabetic retinopathy in Hispanics with NIDDM. *Am J Kidney Dis* 1998;31:947–953
80. Leske MC, Wu S-Y, Hennis A, et al.; Barbados Eye Study Group. Hyperglycemia, blood pressure, and the 9-year incidence of diabetic retinopathy: the Barbados Eye Studies. *Ophthalmology* 2005;112:799–805
81. Chew EY, Davis MD, Danis RP, et al.; Action to Control Cardiovascular Risk in Diabetes Eye Study Research Group. The effects of medical management on the progression of diabetic retinopathy in persons with type 2 diabetes: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study. *Ophthalmology* 2014;121:2443–2451
82. Nathan DM, Genuth S, Lachin J, et al.; Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977–986
83. Chew EY, Ambrosius WT, Davis MD, et al.; ACCORD Study Group; ACCORD Eye Study Group. Effects of medical therapies on retinopathy progression in type 2 diabetes. *N Engl J Med* 2010;363:233–244
84. Gubitosi-Klug RA, Sun W, Cleary PA, et al.; Writing Team for the DCCT/EDIC Research Group. Effects of prior intensive insulin therapy and risk factors on patient-reported visual function outcomes in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) cohort. *JAMA Ophthalmol* 2016;134:137–145
85. Fong DS, Aiello LP, Ferris FL 3rd, Klein R. Diabetic retinopathy. *Diabetes Care* 2004;27:2540–2553
86. Diabetes Control and Complications Trial Research Group. Effect of pregnancy on microvascular complications in the diabetes control and complications trial. *Diabetes Care* 2000;23:1084–1091
87. Dabelea D, Stafford JM, Mayer-Davis EJ, et al.; SEARCH for Diabetes in Youth Research Group. Association of type 1 diabetes vs type 2 diabetes diagnosed during childhood and adolescence with complications during teenage years and young adulthood. *JAMA* 2017;317:825–835
88. Agardh E, Tababat-Khani P. Adopting 3-year screening intervals for sight-threatening retinal vascular lesions in type 2 diabetic subjects without retinopathy. *Diabetes Care* 2011;34:1318–1319
89. Nathan DM, Bebu I, Hainsworth D, et al.; DCCT/EDIC Research Group. Frequency of evidence-based screening for retinopathy in type 1 diabetes. *N Engl J Med* 2017;376:1507–1516
90. Daskivich LP, Vasquez C, Martinez CJr, Tseng C-H, Mangione CM. Implementation and evaluation of a large-scale teleretinal diabetic retinopathy screening program in the Los Angeles County Department of Health Services. *JAMA Intern Med* 2017;177:642–649
91. Sim DA, Mitry D, Alexander P, et al. The evolution of teleophthalmology programs in the United Kingdom: beyond diabetic retinopathy screening. *J Diabetes Sci Technol* 2016;10:308–317
92. Hooper P, Boucher MC, Cruess A, et al. Canadian Ophthalmological Society evidence-based clinical practice guidelines for the management of diabetic retinopathy. *Can J Ophthalmol* 2012;47(Suppl. 1):S1–S30
93. Axer-Siegel R, Hod M, Fink-Cohen S, et al. Diabetic retinopathy during pregnancy. *Ophthalmology* 1996;103:1815–1819
94. Best RM, Chakravarthy U. Diabetic retinopathy in pregnancy. *Br J Ophthalmol* 1997;81:249–251
95. Gunderson EP, Lewis CE, Tsai A-L, et al. A 20-year prospective study of childbearing and incidence of diabetes in young women, controlling for glycemia before conception: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Diabetes* 2007;56:2990–2996
96. The Diabetic Retinopathy Study Research Group. Preliminary report on effects of photocoagulation therapy. *Am J Ophthalmol* 1976;81:383–396
97. Gross JG, Glassman AR, Jampol LM, et al.; Writing Committee for the Diabetic Retinopathy Clinical Research Network. Panretinal photocoagulation vs intravitreal ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. *JAMA* 2015;314:2137–2146
98. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. *Arch Ophthalmol* 1985;103:1796–1806
99. Elman MJ, Aiello LP, Beck RW, et al.; Diabetic Retinopathy Clinical Research Network. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology* 2010;117:1064–1077.e35
100. Mitchell P, Bandello F, Schmidt-Erfurth U, et al.; RESTORE study group. The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. *Ophthalmology* 2011;118:615–625
101. Elman MJ, Bressler NM, Qin H, et al.; Diabetic Retinopathy Clinical Research Network. Expanded 2-year follow-up of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology* 2011;118:609–614
102. Nguyen QD, Brown DM, Marcus DM, et al.; RISE and RIDE Research Group. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology* 2012;119:789–801
103. Shih C-J, Chen H-T, Kuo S-C, et al. Comparative effectiveness of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers in patients with type 2 diabetes and retinopathy. *CMAJ* 2016;188:E148–E157
104. Shi R, Zhao L, Wang F, et al. Effects of lipid-lowering agents on diabetic retinopathy: a meta-analysis and systematic review. *Int J Ophthalmol* 2018;11:287–295
105. Ang L, Jaiswal M, Martin C, Pop-Busui R. Glucose control and diabetic neuropathy: lessons from recent large clinical trials. *Curr Diab Rep* 2014;14:528
106. Martin CL, Albers JW, Pop-Busui R; DCCT/EDIC Research Group. Neuropathy and related findings in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study. *Diabetes Care* 2014;37:31–38
107. Pop-Busui R, Boulton AJM, Feldman EL, et al. Diabetic neuropathy: a position statement by the American Diabetes Association. *Diabetes Care* 2017;40:136–154
108. Freeman R. Not all neuropathy in diabetes is of diabetic etiology: differential diagnosis of diabetic neuropathy. *Curr Diab Rep* 2009;9:423–431
109. Pop-Busui R, Evans GW, Gerstein HC, et al.; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of cardiac autonomic dysfunction on mortality risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. *Diabetes Care* 2010;33:1578–1584
110. Pop-Busui R, Cleary PA, Braffett BH, et al.; DCCT/EDIC Research Group. Association between cardiovascular autonomic neuropathy and left ventricular dysfunction: DCCT/EDIC study (Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications). *J Am Coll Cardiol* 2013;61:447–454
111. Smith AG, Lessard M, Reyna S, Doudova M, Singleton JR. The diagnostic utility of Sudoscan for distal symmetric peripheral neuropathy. *J Diabetes Complications* 2014;28:511–516
112. Diabetes Control and Complications Trial (DCCT) Research Group. Effect of intensive diabetes treatment on nerve conduction in the Diabetes Control and Complications Trial. *Ann Neurol* 1995;38:869–880
113. CDC Study Group. The effect of intensive diabetes therapy on measures of autonomic nervous system function in the Diabetes Control and Complications Trial (DCCT). *Diabetologia* 1998;41:416–423
114. Albers JW, Herman WH, Pop-Busui R, et al.; Diabetes Control and Complications Trial /Epidemiology of Diabetes Interventions and Complications Research Group. Effect of prior intensive insulin treatment during the Diabetes Control and Complications Trial (DCCT) on peripheral neuropathy in type 1 diabetes during the Epidemiology of Diabetes Interventions and Complications (EDIC) study. *Diabetes Care* 2010;33:1090–1096
115. Pop-Busui R, Low PA, Waberski BH, et al.; DCCT/EDIC Research Group. Effects of prior intensive insulin therapy on cardiac autonomic nervous system function in type 1 diabetes mellitus: the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study (DCCT/EDIC). *Circulation* 2009;119:2886–2893
116. Callaghan BC, Little AA, Feldman EL, Hughes RAC. Enhanced glucose control for preventing and treating diabetic neuropathy. *Cochrane Database Syst Rev* 2012;6:CD007543
117. Pop-Busui R, Lu J, Brooks MM, et al.; BARI 2D Study Group. Impact of glycemic control strategies on the progression of diabetic peripheral neuropathy in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) cohort. *Diabetes Care* 2013;36:3208–3215
118. Sadosky A, Schaefer C, Mann R, et al. Burden of illness associated with painful diabetic peripheral neuropathy among adults seeking treatment in the US: results from a retrospective chart review and cross-sectional survey. *Diabetes Metab Syndr Obes* 2013;6:79–92
119. Waldfoegel JM, Nesbit SA, Dy SM, et al. Pharmacotherapy for diabetic peripheral neuropathy pain and quality of life: a systematic review. *Neurology* 2017;88:1958–1967
120. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults:

- a systematic review and meta-analysis. *Lancet Neurol* 2015;14:162–173
121. Bril V, England J, Franklin GM, et al.; American Academy of Neurology; American Association of Neuromuscular and Electrodiagnostic Medicine; American Academy of Physical Medicine and Rehabilitation. Evidence-based guideline: treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation [published correction appears in *Neurology* 2011;77:603]. *Neurology* 2011;76:1758–1765
  122. Griebeler ML, Morey-Vargas OL, Brito JP, et al. Pharmacologic interventions for painful diabetic neuropathy: an umbrella systematic review and comparative effectiveness network meta-analysis. *Ann Intern Med* 2014;161:639–649
  123. Ziegler D, Fonseca V. From guideline to patient: a review of recent recommendations for pharmacotherapy of painful diabetic neuropathy. *J Diabetes Complications* 2015;29:146–156
  124. Freeman R, Durso-Decruz E, Emir B. Efficacy, safety, and tolerability of pregabalin treatment for painful diabetic peripheral neuropathy: findings from seven randomized, controlled trials across a range of doses. *Diabetes Care* 2008;31:1448–1454
  125. Moore RA, Straube S, Wiffen PJ, Derry S, McQuay HJ. Pregabalin for acute and chronic pain in adults. *Cochrane Database Syst Rev* 2009;3:CD007076
  126. Raskin P, Huffman C, Toth C, et al. Pregabalin in patients with inadequately treated painful diabetic peripheral neuropathy: a randomized withdrawal trial. *Clin J Pain* 2014;30:379–390
  127. Tesfaye S, Wilhelm S, Lledo A, et al. Duloxetine and pregabalin: high-dose monotherapy or their combination? The “COMBO-DN study”—a multinational, randomized, double-blind, parallel-group study in patients with diabetic peripheral neuropathic pain. *Pain* 2013;154:2616–2625
  128. Ziegler D, Duan WR, An G, Thomas JW, Nothaft W. A randomized double-blind, placebo-, and active-controlled study of T-type calcium channel blocker ABT-639 in patients with diabetic peripheral neuropathic pain. *Pain* 2015;156:2013–2020
  129. Quilici S, Chancellor J, Löthgren M, et al. Meta-analysis of duloxetine vs. pregabalin and gabapentin in the treatment of diabetic peripheral neuropathic pain. *BMC Neurol* 2009;9:6
  130. Dworkin RH, Jensen MP, Gammaitoni AR, Olaleye DO, Galer BS. Symptom profiles differ in patients with neuropathic versus non-neuropathic pain. *J Pain* 2007;8:118–126
  131. Wiffen PJ, Derry S, Bell RF, et al. Gabapentin for chronic neuropathic pain in adults. *Cochrane Database Syst Rev* 2017;6:CD007938
  132. Wernicke JF, Pritchett YL, D’Souza DN, et al. A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain. *Neurology* 2006;67:1411–1420
  133. Hardy T, Sachson R, Shen S, Armbruster M, Boulton AJM. Does treatment with duloxetine for neuropathic pain impact glycemic control? *Diabetes Care* 2007;30:21–26
  134. Schwartz S, Etropolski M, Shapiro DY, et al. Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: results of a randomized-withdrawal, placebo-controlled trial. *Curr Med Res Opin* 2011;27:151–162
  135. Vinik AI, Shapiro DY, Rauschkolb C, et al. A randomized withdrawal, placebo-controlled study evaluating the efficacy and tolerability of tapentadol extended release in patients with chronic painful diabetic peripheral neuropathy. *Diabetes Care* 2014;37:2302–2309
  136. Camilleri M, Parkman HP, Shafi MA, Abell TL, Gerson L; American College of Gastroenterology. Clinical guideline: management of gastroparesis. *Am J Gastroenterol* 2013;108:18–37; quiz 38
  137. Parrish CR, Pastors JG. Nutritional management of gastroparesis in people with diabetes. *Diabetes Spectr* 2007;20:231–234
  138. Parkman HP, Yates KP, Hasler WL, et al.; NIDDK Gastroparesis Clinical Research Consortium. Dietary intake and nutritional deficiencies in patients with diabetic or idiopathic gastroparesis. *Gastroenterology* 2011;141:486–498, 498.e1–7
  139. Olausson EA, Störsrud S, Grundin H, Isaksson M, Attvall S, Simrén M. A small particle size diet reduces upper gastrointestinal symptoms in patients with diabetic gastroparesis: a randomized controlled trial. *Am J Gastroenterol* 2014;109:375–385
  140. Umpierrez GE, Ed. *Therapy for Diabetes Mellitus and Related Disorders*. 6th ed. Alexandria, VA, American Diabetes Association, 2014
  141. Sugumar A, Singh A, Pasricha PJ. A systematic review of the efficacy of domperidone for the treatment of diabetic gastroparesis. *Clin Gastroenterol Hepatol* 2008;6:726–733
  142. Maganti K, Onyemere K, Jones MP. Oral erythromycin and symptomatic relief of gastroparesis: a systematic review. *Am J Gastroenterol* 2003;98:259–263
  143. McCallum RW, Snape W, Brody F, Wo J, Parkman HP, Nowak T. Gastric electrical stimulation with Enterra therapy improves symptoms from diabetic gastroparesis in a prospective study. *Clin Gastroenterol Hepatol* 2010;8:947–954; quiz e116
  144. Boulton AJM, Armstrong DG, Albert SF, et al.; American Diabetes Association; American Association of Clinical Endocrinologists. Comprehensive foot examination and risk assessment: a report of the Task Force of the Foot Care Interest Group of the American Diabetes Association, with endorsement by the American Association of Clinical Endocrinologists. *Diabetes Care* 2008;31:1679–1685
  145. Hingorani A, LaMuraglia GM, Henke P, et al. The management of diabetic foot: a clinical practice guideline by the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine. *J Vasc Surg* 2016;63(Suppl.):35–215
  146. Bonner T, Foster M, Spears-Lanoix E. Type 2 diabetes-related foot care knowledge and foot self-care practice interventions in the United States: a systematic review of the literature. *Diabet Foot Ankle* 2016;7:29758
  147. Rizzo L, Tedeschi A, Fallani E, et al. Custom-made orthosis and shoes in a structured follow-up program reduces the incidence of neuropathic ulcers in high-risk diabetic foot patients. *Int J Low Extrem Wounds* 2012;11:59–64
  148. Lipsky BA, Berendt AR, Cornia PB, et al.; Infectious Diseases Society of America. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. *Clin Infect Dis* 2012;54:e132–e173
  149. Elraiyah T, Tsapas A, Prutsky G, et al. A systematic review and meta-analysis of adjunctive therapies in diabetic foot ulcers. *J Vasc Surg* 2016;63(2 Suppl.):46S–58S.e1–2
  150. Game FL, Apelqvist J, Attinger C, et al.; International Working Group on the Diabetic Foot. Effectiveness of interventions to enhance healing of chronic ulcers of the foot in diabetes: a systematic review. *Diabetes Metab Res Rev* 2016;32(Suppl. 1):154–168
  151. Kranke P, Bennett MH, Martyn-St James M, Schnabel A, Debus SE, Weibel S. Hyperbaric oxygen therapy for chronic wounds. *Cochrane Database Syst Rev* 2015;6:CD004123
  152. Löndahl M, Katzman P, Nilsson A, Hammarlund C. Hyperbaric oxygen therapy facilitates healing of chronic foot ulcers in patients with diabetes. *Diabetes Care* 2010;33:998–1003
  153. Fedorko L, Bowen JM, Jones W, et al. Hyperbaric oxygen therapy does not reduce indications for amputation in patients with diabetes with nonhealing ulcers of the lower limb: a prospective, double-blind, randomized controlled clinical trial. *Diabetes Care* 2016;39:392–399
  154. Li G, Hopkins RB, Levine MAH, et al. Relationship between hyperbaric oxygen therapy and quality of life in participants with chronic diabetic foot ulcers: data from a randomized controlled trial. *Acta Diabetol* 2017;54:823–831
  155. Boulton AJM. The Diabetic Foot [Internet], 2000. South Dartmouth, MA, MDText.com, Inc. Available from <http://www.ncbi.nlm.nih.gov/books/NBK409609/>. Accessed 5 October 2017
  156. Health Quality Ontario. Hyperbaric oxygen therapy for the treatment of diabetic foot ulcers: a health technology assessment. *Ont Health Technol Assess Ser* 2017;17:1–142
  157. Stoeckenbroek RM, Santema TB, Koelemay MJ, et al. Is additional hyperbaric oxygen therapy cost-effective for treating ischemic diabetic ulcers? Study protocol for the Dutch DAMOCLES multicenter randomized clinical trial? *J Diabetes* 2015;7:125–132
  158. Huang ET, Mansouri J, Murad MH, et al.; UHMS CPG Oversight Committee. A clinical practice guideline for the use of hyperbaric oxygen therapy in the treatment of diabetic foot ulcers. *Undersea Hyperb Med* 2015;42:205–247