



12. Retinopathy, Neuropathy, and Foot Care: Standards of Care in Diabetes—2023

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Nuha A. ElSayed, Grazia Aleppo, Vanita R. Aroda, Raveendhara R. Bannuru, Florence M. Brown, Dennis Bruemmer, Billy S. Collins, Christopher H. Gibbons, John M. Giurini, Marisa E. Hilliard, Diana Isaacs, Eric L. Johnson, Scott Kahan, Kamlesh Khunti, Jose Leon, Sarah K. Lyons, Mary Lou Perry, Priya Prahalad, Richard E. Pratley, Jane Jeffrie Seley, Robert C. Stanton, Jennifer K. Sun, and Robert A. Gabbay, on behalf of the American Diabetes Association

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For prevention and management of diabetes complications in children and adolescents, please refer to Section 14, “Children and Adolescents.”

DIABETIC RETINOPATHY

Recommendations

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

Diabetic retinopathy is a highly specific vascular complication of both type 1 and type 2 diabetes, with prevalence strongly related to both the duration of diabetes and the level of glycemic control (1). 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 eye disorders 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 (2,3), nephropathy (4), hypertension (5), and dyslipidemia (6). 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, reduce the need for future ocular surgical procedures, and potentially improve patient-reported visual function (2,7–10). A meta-analysis of data from cardiovascular outcomes studies showed no association between glucagon-like peptide 1 receptor agonist (GLP-1 RA) treatment and retinopathy per se, except through the association between retinopathy and average A1C reduction at the 3-month and 1-year follow-up. Long-term impact of improved glycemic control on retinopathy was not studied

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in these trials. Retinopathy status should be assessed when intensifying glucose-lowering therapies such as those using GLP-1 RAs, since rapid reductions in A1C can be associated with initial worsening of retinopathy (11).

Screening

Recommendations

- 12.3** 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**
- 12.4** People 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**
- 12.5** If there is no evidence of retinopathy for one or more annual eye exams and glycemia is well controlled, then screening every 1–2 years may be considered. If any level of diabetic retinopathy is present, subsequent dilated retinal examinations should be repeated at least annually by an ophthalmologist or optometrist. If retinopathy is progressing or sight-threatening, then examinations will be required more frequently. **B**
- 12.6** Programs that use retinal photography (with remote reading or use of a validated assessment tool) to improve access to diabetic retinopathy screening can be appropriate screening strategies for diabetic retinopathy. Such programs need to provide pathways for timely referral for a comprehensive eye examination when indicated. **B**
- 12.7** Individuals of childbearing potential 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**
- 12.8** Individuals with preexisting type 1 or type 2 diabetes should receive an eye exam before pregnancy and in the first

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

The preventive effects of therapy and the fact that individuals with proliferative diabetic retinopathy (PDR) or macular edema may be asymptomatic provide strong support for screening to detect diabetic retinopathy. Prompt diagnosis allows triage of patients and timely intervention that may prevent vision loss in individuals who are asymptomatic despite advanced diabetic eye disease.

Diabetic retinopathy screening should be performed using validated approaches and methodologies. Youth with type 1 or type 2 diabetes are also at risk for complications and need to be screened for diabetic retinopathy (12) (see Section 14, “Children and Adolescents”). If diabetic retinopathy is evident on screening, prompt referral to an ophthalmologist is recommended. Subsequent examinations for individuals with type 1 or type 2 diabetes are generally repeated annually for individuals with minimal to no retinopathy. Exams every 1–2 years may be cost-effective after one or more normal eye exams. In a population with well-controlled type 2 diabetes, there was little risk of development of significant retinopathy within a 3-year interval after a normal examination (13), and less frequent intervals have been found in simulated modeling to be potentially effective in screening for diabetic retinopathy in individuals without diabetic retinopathy (14). However, it is important to adjust screening intervals based on the presence of specific risk factors for retinopathy onset and worsening retinopathy. More frequent examinations by the ophthalmologist will be required if retinopathy is progressing or risk factors such as uncontrolled hyperglycemia, advanced baseline retinopathy, or diabetic macular edema are present.

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 (15–17). High-quality fundus photographs can detect most clinically significant diabetic retinopathy. Interpretation of the images should be performed by a trained eye care professional. Retinal

photography may also enhance efficiency and reduce costs when the expertise of ophthalmologists can be used for more complex examinations and for therapy (15,18,19). 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 dilated comprehensive eye exams, which should be performed at least initially and at yearly intervals thereafter or more frequently as recommended by an eye care professional. Artificial intelligence systems that detect more than mild diabetic retinopathy and diabetic macular edema, authorized for use by the U.S. Food and Drug Administration (FDA), represent an alternative to traditional screening approaches (20). However, the benefits and optimal utilization of this type of screening have yet to be fully determined. Results of all screening 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, people with type 1 diabetes should have an initial dilated and comprehensive eye examination within 5 years after the diagnosis of diabetes (21).

Type 2 Diabetes

People 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

Individuals who develop gestational diabetes mellitus do not require eye examinations during pregnancy since they do not appear to be at increased risk of developing diabetic retinopathy during pregnancy (22). However, individuals of childbearing potential with preexisting type 1 or type 2 diabetes who are planning pregnancy or who have become pregnant should be counseled on the baseline prevalence and risk of development and/or progression of diabetic retinopathy. In a systematic review and meta-analysis of 18 observational studies of pregnant individuals with preexisting

type 1 or type 2 diabetes, the prevalence of any diabetic retinopathy and PDR in early pregnancy was 52.3% and 6.1%, respectively. The pooled progression rate per 100 pregnancies for new diabetic retinopathy development was 15.0 (95% CI 9.9–20.8), worsened nonproliferative diabetic retinopathy was 31.0 (95% CI 23.2–39.2), pooled sight-threatening progression rate from nonproliferative diabetic retinopathy to PDR was 6.3 (95% CI 3.3–10.0), and worsened PDR was 37.0 (95% CI 21.2–54.0), demonstrating that close follow-up should be maintained during pregnancy to prevent vision loss (23). In addition, rapid implementation of intensive glycemic management in the setting of retinopathy is associated with early worsening of retinopathy (24).

A systematic review and meta-analysis and a controlled prospective study demonstrate that pregnancy in individuals with type 1 diabetes may aggravate retinopathy and threaten vision, especially when glycemic control is poor or retinopathy severity is advanced at the time of conception (23,24). Laser photocoagulation surgery can minimize the risk of vision loss during pregnancy for individuals with high-risk PDR or center-involved diabetic macular edema (24). Anti-vascular endothelial growth factor (anti-VEGF) medications should not be used in pregnant individuals with diabetes because of the theoretical risks to the vasculature of the developing fetus.

Treatment

Recommendations

- 12.9** Promptly refer individuals with any level of diabetic macular edema, moderate or worse 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**
- 12.10** Panretinal laser photocoagulation therapy is indicated to reduce the risk of vision loss in individuals with high-risk proliferative diabetic retinopathy and, in some cases, severe nonproliferative diabetic retinopathy. **A**

12.11 Intravitreal injections of anti-vascular endothelial growth factor are a reasonable alternative to traditional panretinal laser photocoagulation for some individuals with proliferative diabetic retinopathy and also reduce the risk of vision loss in these individuals. **A**

12.12 Intravitreal injections of anti-vascular endothelial growth factor are indicated as first-line treatment for most eyes with diabetic macular edema that involves the foveal center and impairs vision acuity. **A**

12.13 Macular focal/grid photocoagulation and intravitreal injections of corticosteroid are reasonable treatments in eyes with persistent diabetic macular edema despite previous anti-vascular endothelial growth factor therapy or eyes that are not candidates for this first-line approach. **A**

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

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

Photocoagulation Surgery

Two large trials, the Diabetic Retinopathy Study (DRS) in individuals with PDR and the Early Treatment Diabetic Retinopathy Study (ETDRS) in individuals with macular edema, provide the strongest support for the therapeutic benefits of photocoagulation surgery. The DRS (25) 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 individuals 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. A more gentle, macular focal/grid laser photocoagulation technique was shown in the ETDRS to be effective in treating eyes with clinically significant macular edema from diabetes (26), but this is now largely considered to be second-line treatment for diabetic macular edema.

Anti-Vascular Endothelial Growth Factor Treatment

Data from the DRCR Retina Network (formerly the Diabetic Retinopathy Clinical Research Network) and others demonstrate that intravitreal injections of anti-VEGF agents are effective at regressing proliferative disease and lead to noninferior or superior visual acuity outcomes compared with panretinal laser over 2 years of follow-up (27,28). In addition, it was observed that individuals 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 individuals. The FDA has approved aflibercept and ranibizumab for the treatment of eyes with diabetic retinopathy. Other emerging therapies for retinopathy that may use sustained intravitreal delivery of pharmacologic agents are currently under investigation. Anti-VEGF treatment of eyes with nonproliferative diabetic retinopathy has been demonstrated to reduce subsequent development of retinal neovascularization and diabetic macular edema but has not been shown to improve visual outcomes over 2 years of therapy and therefore is not routinely recommended for this indication (29).

While the ETDRS (26) established the benefit of focal laser photocoagulation surgery in eyes with clinically significant macular edema (defined as retinal edema

located at or threatening the macular center), current data from well-designed clinical trials demonstrate that intravitreal anti-VEGF agents provide a more effective treatment plan for center-involved diabetic macular edema than monotherapy with laser (30,31). 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. There are currently three anti-VEGF agents commonly used to treat eyes with central-involved diabetic macular edema—bevacizumab, ranibizumab, and aflibercept (1)—and a comparative effectiveness study demonstrated that aflibercept provides vision outcomes superior to those of bevacizumab when eyes have moderate visual impairment (vision of 20/50 or worse) from diabetic macular edema (32). For eyes that have good vision (20/25 or better) despite diabetic macular edema, close monitoring with initiation of anti-VEGF therapy if vision worsens provides similar 2-year vision outcomes compared with immediate initiation of anti-VEGF therapy (33).

Eyes that have persistent diabetic macular edema despite anti-VEGF treatment may benefit from macular laser photocoagulation or intravitreal therapy with corticosteroids. Both of these therapies are also reasonable first-line approaches for individuals who are not candidates for anti-VEGF treatment due to systemic considerations such as pregnancy.

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 (8). In individuals with dyslipidemia, retinopathy progression may be slowed by the addition of fenofibrate, particularly with very mild nonproliferative diabetic retinopathy at baseline (34,35).

NEUROPATHY

Screening

Recommendations

12.15 All people with diabetes 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**

12.16 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 people with diabetes should have annual 10-g monofilament testing to identify feet at risk for ulceration and amputation. **B**

12.17 Symptoms and signs of autonomic neuropathy should be assessed in people with diabetes starting at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes and at least annually thereafter and with evidence of other microvascular complications, particularly kidney disease and diabetic peripheral neuropathy. Screening can include asking about orthostatic dizziness, syncope, or dry cracked skin in the extremities. Signs of autonomic neuropathy include orthostatic hypotension, a resting tachycardia, or evidence of peripheral dryness or cracking of skin. **E**

Diabetic neuropathies are a heterogeneous group of disorders with diverse clinical manifestations. The early recognition and appropriate management of neuropathy in people with diabetes is important. Points to be aware of include the following:

1. Diabetic neuropathy is a diagnosis of exclusion. Nondiabetic neuropathies may be present in people with diabetes and may be treatable.
2. Up to 50% of diabetic peripheral neuropathy may be asymptomatic. If not recognized and if preventive foot care is not implemented, people with diabetes are at risk for injuries as well as diabetic foot ulcers and amputations.
3. Recognition and treatment of autonomic neuropathy may improve

symptoms, reduce sequelae, and improve quality of life.

Specific treatment to reverse the underlying nerve damage is currently not available. Glycemic control can effectively prevent diabetic peripheral neuropathy (DPN) and cardiac autonomic neuropathy (CAN) in type 1 diabetes (36,37) and may modestly slow their progression in type 2 diabetes (38), but it does not reverse neuronal loss. Treatments of other modifiable risk factors (including lipids and blood pressure) can aid in prevention of DPN progression in type 2 diabetes and may reduce disease progression in type 1 diabetes (39–41). Therapeutic strategies (pharmacologic and nonpharmacologic) for the relief of painful DPN and symptoms of autonomic neuropathy can potentially reduce pain (42) and improve quality of life.

Diagnosis

Diabetic Peripheral Neuropathy

Individuals with a type 1 diabetes duration ≥ 5 years and all individuals with type 2 diabetes should be assessed annually for DPN using the medical history and simple clinical tests (42). 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: lower-extremity reflexes, 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 people 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 (43). See the American Diabetes Association position statement “Diabetic Neuropathy” for more details (42).

Diabetic Autonomic Neuropathy

Individuals who have had type 1 diabetes for ≥ 5 years and all individuals with type 2 diabetes should be assessed annually for autonomic neuropathy (42). 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 resting tachycardia, orthostatic hypotension, gastroparesis, constipation, diarrhea, fecal incontinence, erectile dysfunction, neurogenic bladder, and sudomotor dysfunction with either increased or decreased sweating. Screening for symptoms of autonomic neuropathy includes asking about symptoms of orthostatic intolerance (dizziness, lightheadedness, or weakness with standing), syncope, exercise intolerance, constipation, diarrhea, urinary retention, urinary incontinence, or changes in sweat function. Further testing can be considered if symptoms are present and will depend on the end organ involved but might include cardiovascular autonomic testing, sweat testing, urodynamic studies, gastric emptying, or endoscopy/colonoscopy. Impaired counterregulatory responses to hypoglycemia in type 1 and type 2 diabetes can lead to hypoglycemia unawareness but are not directly linked to autonomic neuropathy.

Cardiovascular Autonomic Neuropathy. CAN is associated with mortality independently of other cardiovascular risk factors (44,45). 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 reversible/iatrogenic causes such as medications or organic causes of gastric outlet obstruction or peptic ulcer disease (with esophagogastroduodenoscopy or a barium study of the stomach) is needed before considering a diagnosis of or specialized testing for gastroparesis. The diagnostic gold standard for gastroparesis is the measurement of gastric emptying with scintigraphy of digestible solids at 15-min intervals for 4 h after food intake. The use of ^{13}C octanoic acid breath test is an approved 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 (42). 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 (46). Lower urinary tract symptoms manifest as urinary incontinence and bladder dysfunction (nocturia, frequent urination, urination urgency, and weak urinary stream). Evaluation of bladder function should be performed for individuals with diabetes who have recurrent urinary tract infections, pyelonephritis, incontinence, or a palpable bladder.

Treatment

Recommendations

12.18 Optimize glucose control to prevent or delay the development of neuropathy in people with type 1 diabetes **A** and to slow the progression of

neuropathy in people with type 2 diabetes. **C** Optimize blood pressure and serum lipid control to reduce the risk or slow the progression of diabetic neuropathy. **B**

12.19 Assess and treat pain related to diabetic peripheral neuropathy **B** and symptoms of autonomic neuropathy to improve quality of life. **E**

12.20 Gabapentinoids, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, and sodium channel blockers are recommended as initial pharmacologic treatments for neuropathic pain in diabetes. **A** Refer to neurologist or pain specialist when pain control is not achieved within the scope of practice of the treating physician. **E**

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 people with type 1 diabetes (47–50). Although the evidence for the benefit of near-normal glycemic control is not as strong that for type 2 diabetes, some studies have demonstrated a modest slowing of progression without reversal of neuronal loss (38,51). 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 (52). Additionally, recent evidence from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial showed clear benefit of intensive glucose and blood pressure control on the prevention of CAN in type 2 diabetes (53).

Lipid Control

Dyslipidemia is a key factor in the development of neuropathy in people with type 2 diabetes and may contribute to neuropathy risk in people with type 1 diabetes (54,55). Although the evidence for a relationship between lipids

and neuropathy development has become increasingly clear in type 2 diabetes, the optimal therapeutic intervention has not been identified. Positive effects of physical activity, weight loss, and bariatric surgery have been reported in individuals with DPN, but use of conventional lipid-lowering pharmacotherapy (such as statins or fenofibrates) does not appear to be effective in treating or preventing DPN development (56).

Blood Pressure Control

There are multiple reasons for blood pressure control in people with diabetes, but neuropathy progression (especially in type 2 diabetes) has now been added to this list. Although data from many studies have supported the role of hypertension in risk of neuropathy development, a recent meta-analysis of data from 14 countries in the International Prevalence and Treatment of Diabetes and Depression (INTERPRET-DD) study revealed hypertension as an independent risk of DPN development with an odds ratio of 1.58 (57). In the ACCORD trial, intensive blood pressure intervention decreased CAN risk by 25% (53).

Neuropathic Pain

Neuropathic pain can be severe and can impact quality of life, limit mobility, and contribute to depression and social dysfunction (58). 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 (59). A recent guideline by the American Academy of Neurology recommends that the initial treatment of pain should also focus on the concurrent treatment of both sleep and mood disorders because of increased frequency of these problems in individuals with DPN (60).

A number of pharmacologic therapies exist for treatment of pain in diabetes. The American Academy of Neurology update suggested that gabapentinoids, serotonin-norepinephrine reuptake inhibitors (SNRIs), sodium channel blockers, tricyclic antidepressants (TCAs), and SNRI/opioid dual-mechanism agents could all be considered in the treatment of pain in DPN (60). These American Academy of Neurology recommendations offer a supplement to a recent American Diabetes Association pain monograph, although

some areas of disagreement exist, particularly around SNRI/opioid dual-mechanism agents (61). A recent head-to-head trial suggested therapeutic equivalency for TCAs, SNRIs, and gabapentinoids in the treatment of pain in DPN (62). The trial also supported the role of combination therapy over monotherapy for the treatment of pain in DPN.

Gabapentinoids. Gabapentinoids include several calcium channel α 2- δ subunit ligands. Eight high-quality studies and seven medium-quality studies support the role of pregabalin in treatment of pain in DPN. One high-quality study and many small studies support the role of gabapentin in the treatment of pain in DPN. Two medium-quality studies suggest that microgabalin has a small effect on pain in DPN (60). Adverse effects may be more severe in older individuals (63) and may be attenuated by lower starting doses and more gradual titration.

SNRIs. SNRIs include duloxetine, venlafaxine, and desvenlafaxine, all selective SNRIs. Two high-quality studies and five medium-quality studies support the role of duloxetine in the treatment of pain in DPN. A high-quality study supports the role of venlafaxine in the treatment of pain in DPN. Only one medium-quality study supports a possible role for desvenlafaxine for treatment of pain in DPN (60). Adverse events may be more severe in older people but may be attenuated with lower doses and slower titration of duloxetine.

Tapentadol and Tramadol. Tapentadol and tramadol are centrally acting opioid analgesics that exert their analgesic effects through both μ -opioid receptor agonism and norepinephrine and serotonin reuptake inhibition. SNRI/opioid agents are probably effective in the treatment of pain in DPN. However, the use of any opioids for management of chronic neuropathic pain carries the risk of addiction and should be avoided.

Tricyclic Antidepressants. Tricyclic antidepressants have been studied for treatment of pain, and most of the relevant data was acquired from trials of amitriptyline and include two high-quality studies and two medium-quality studies supporting the treatment of pain in DPN (60,62). Anticholinergic side effects may be dose limiting and restrict use in individuals \geq 65 years of age.

Sodium Channel Blockers. Sodium channel blockers include lamotrigine, lacosamide, oxcarbazepine, and valproic acid. Five medium-quality studies support the role

of sodium channel blockers in treating pain in DPN (60).

Capsaicin. Capsaicin has received FDA approval for treatment of pain in DPN using an 8% patch, with one high-quality study reported. One medium-quality study of 0.075% capsaicin cream has been reported. In patients with contraindications to oral pharmacotherapy or who prefer topical treatments, the use of topical capsaicin can be considered.

Carbamazepine and α -Lipoic Acid. Carbamazepine and α -lipoic acid, although not approved for the treatment of painful DPN, may be effective and considered for the treatment of painful DPN (41,54,56).

Orthostatic Hypotension

Treating orthostatic hypotension is challenging. The therapeutic goal is to minimize postural symptoms rather than to restore normotension. Most patients require both nonpharmacologic measures (e.g., ensuring adequate salt intake, avoiding medications that aggravate hypotension, or using compressive garments over the legs and abdomen) and pharmacologic measures. Physical activity and exercise should be encouraged to avoid deconditioning, which is known to exacerbate orthostatic intolerance, and volume repletion with fluids and salt is critical. There have been clinical studies that assessed the impact of an approach incorporating the aforementioned nonpharmacologic measures. Additionally, supine blood pressure tends to be much higher in these individuals, often requiring treatment of blood pressure at bedtime with shorter-acting drugs that also affect baroreceptor activity such as guanfacine or clonidine, shorter-acting calcium blockers (e.g., isradipine), or shorter-acting β -blockers such as atenolol or metoprolol tartrate. Alternatives can include enalapril if an individual is unable to tolerate preferred agents (64–66). 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 (67–69). In addition, foods with small particle size may improve key symptoms (70). Withdrawing drugs with adverse effects on

gastrointestinal motility, including opioids, anticholinergics, tricyclic antidepressants, GLP-1 RAs, and pramlintide, may also improve intestinal motility (67,71). However, the risk of removal of GLP-1 RAs should be balanced against their potential benefits. 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. It should be reserved for severe cases that are unresponsive to other therapies (71). Other treatment options include domperidone (available outside the U.S.) and erythromycin, which is only effective for short-term use due to tachyphylaxis (72,73). Gastric electrical stimulation using a surgically implantable device has received approval from the FDA, although its efficacy is variable and use is limited to individuals with severe symptoms that are refractory to other treatments (74).

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 a person's quality of life.

FOOT CARE

Recommendations

- 12.21** Perform a comprehensive foot evaluation at least annually to identify risk factors for ulcers and amputations. **A**
- 12.22** 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**

- 12.23** Individuals with evidence of sensory loss or prior ulceration or amputation should have their feet inspected at every visit. **A**

- 12.24** 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**

- 12.25** Initial screening for peripheral arterial disease should include assessment of lower-extremity pulses, capillary refill time, rubor on dependency, pallor on elevation, and venous filling time. Individuals with a history of leg fatigue, claudication, and rest pain relieved with dependency or decreased or absent pedal pulses should be referred for ankle-brachial index and for further vascular assessment as appropriate. **B**

- 12.26** A multidisciplinary approach is recommended for individuals with foot ulcers and high-risk feet (e.g., those on dialysis, those with Charcot foot, those with a history of prior ulcers or amputation, and those with peripheral arterial disease). **B**

- 12.27** Refer individuals who smoke and have a history 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. **B**

- 12.28** Provide general preventive foot self-care education to all people with diabetes, including those with loss of protective sensation, on appropriate ways to examine their feet (palpation or visual inspection with an unbreakable mirror) for daily surveillance of early foot problems. **B**

- 12.29** The use of specialized therapeutic footwear is recommended for people with diabetes at high risk for ulceration, including those with loss of protective sensation, foot deformities, ulcers, callous formation, poor peripheral circulation, or history of amputation. **B**

- 12.30** For chronic diabetic foot ulcers that have failed to heal with optimal standard care alone, adjunctive treatment with randomized controlled trial-proven advanced agents should be considered. Considerations might include negative-pressure wound therapy, placental membranes, bioengineered skin substitutes, several acellular matrices, autologous fibrin and leukocyte platelet patches, and topical oxygen therapy. **A**

Foot ulcerations and amputations are common complications associated with diabetes. These may be the consequences of several factors, including peripheral neuropathy, peripheral arterial disease (PAD), and foot deformities. They represent major causes of morbidity and mortality in people with diabetes. Early recognition of at-risk feet, preulcerative lesions, and prompt treatment of ulcerations and other lower-extremity complications can delay or prevent adverse outcomes.

Early recognition requires an understanding of those factors that put people with diabetes at increased risk for ulcerations and amputations. Factors that are associated with the at-risk foot include the following:

- Poor glycemic control
- Peripheral neuropathy/LOPS
- PAD
- Foot deformities (bunions, hammer-toes, Charcot joint, etc.)
- Preulcerative corns or calluses
- Prior ulceration
- Prior amputation
- Smoking
- Retinopathy
- Nephropathy (particularly individuals on dialysis or posttransplant)

Identifying the at-risk foot begins with a detailed history documenting diabetes control, smoking history, exercise tolerance, history of claudication or rest pain, and prior ulcerations or amputations. A thorough examination of the feet should be performed annually in all people with diabetes and more frequently in at-risk individuals (75). The examination should include assessment of skin integrity, assessment for LOPS using the 10-g monofilament along with at least one other neurological assessment tool, pulse examination of the dorsalis pedis and posterior tibial arteries, and assessment for foot deformities such as bunions, hammertoes, and prominent metatarsals, which increase plantar foot pressures and increase risk for ulcerations. At-risk individuals should be assessed at each visit and should be referred to foot care specialists for ongoing preventive care and surveillance. The physical examination can stratify patients into different categories and determine the frequency of these visits (76) (Table 12.1).

Evaluation for Loss of Protective Sensation

The presence of peripheral sensory neuropathy is the single most common component cause for foot ulceration. In a multicenter trial, peripheral neuropathy was found to be a component cause in 78% of people with diabetes with ulcerations and that the triad of peripheral sensory neuropathy, minor trauma, and foot deformity was present in >63% of participants (77). All people with diabetes should undergo a comprehensive foot examination at least annually, or

more frequently for those in higher-risk categories (75,76).

LOPS is vital to risk assessment. One of the most useful tests to determine LOPS is the 10-g monofilament test. Studies have shown that clinical examination and the 10-g monofilament test are the two most sensitive tests in identifying the foot at risk for ulceration (78). The monofilament test should be performed with at least one other neurologic assessment tool (e.g., pinprick, temperature perception, ankle reflexes, or vibratory perception with a 128-Hz tuning fork or similar device). Absent monofilament sensation and one other abnormal test confirms the presence of LOPS. Further neurological testing, such as nerve conduction, electromyography, nerve biopsy, or intraepidermal nerve fiber density biopsies, are rarely indicated for the diagnosis of peripheral sensory neuropathy (42).

Evaluation for Peripheral Arterial Disease

Initial screening for PAD should include a history of leg fatigue, claudication, and rest pain relieved with dependency. Physical examination for PAD should include assessment of lower-extremity pulses, capillary refill time, rubor on dependency, pallor on elevation, and venous filling time (75,79). Any patient exhibiting signs and symptoms of PAD should be referred for noninvasive arterial studies in the form of Doppler ultrasound with pulse volume recordings. While ankle-brachial indices will be calculated, they should be interpreted carefully, as they are known to be inaccurate in people with diabetes due to

noncompressible vessels. Toe systolic blood pressure tends to be more accurate. Toe systolic blood pressures <30 mmHg are suggestive of PAD and an inability to heal foot ulcerations (80). Individuals with abnormal pulse volume recording tracings and toe pressures <30 mmHg with foot ulcers should be referred for immediate vascular evaluation. Due to the high prevalence of PAD in people with diabetes, it has been recommended by the Society for Vascular Surgery and the American Podiatric Medical Association in their 2016 guidelines that all people with diabetes >50 years of age should undergo screening via noninvasive arterial studies (79,81). If normal, these should be repeated every 5 years (79).

Patient Education

All people with diabetes (and their families), particularly those with the aforementioned high-risk conditions, should receive general foot care education, including appropriate management strategies (82–84). This education should be provided to all newly diagnosed people with diabetes as part of an annual comprehensive examination and to individuals with high-risk conditions at every visit. Recent studies have shown that while education improves knowledge of diabetic foot problems and self-care of the foot, it does not improve behaviors associated with active participation in their overall diabetes care and to achieve personal health goals (85). Evidence also suggests that while patient and family education are important, the knowledge is quickly forgotten and needs to be reinforced regularly (86).

Table 12.1—International Working Group on the Diabetic Foot risk stratification system and corresponding foot screening frequency

Category	Ulcer risk	Characteristics	Examination frequency*
0	Very low	No LOPS and No PAD	Annually
1	Low	LOPS or PAD	Every 6–12 months
2	Moderate	LOPS + PAD, or LOPS + foot deformity, or PAD + foot deformity	Every 3–6 months
3	High	LOPS or PAD and one or more of the following: <ul style="list-style-type: none"> ● History of foot ulcer ● Amputation (minor or major) ● End-stage renal disease 	Every 1–3 months

Adapted with permission from Schaper et al. (76). LOPS, loss of protective sensation; PAD, peripheral artery disease. *Examination frequency suggestions are based on expert opinion and patient-centered requirements.

Individuals considered 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 inspections on a daily basis. Individuals with LOPS should be educated on appropriate ways to examine their feet (palpation or visual inspection with an unbreakable mirror) for daily surveillance of early foot problems. Patients should also be educated on the importance of referrals to foot care specialists. A recent study showed that people with diabetes and foot disease lacked awareness of their risk status and why they were being referred to a multidisciplinary team of foot care specialists. Further, they exhibited a variable degree of interest in learning further about foot complications (87).

Patients' understanding of these issues and their physical ability to conduct proper foot surveillance and care should be assessed. Those 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.

The selection of appropriate footwear and footwear behaviors at home should also be discussed (e.g., no walking barefoot, avoiding open-toed shoes). Therapeutic footwear with custom-made orthotic devices have been shown to reduce peak plantar pressures (84). Most studies use reduction in peak plantar pressures as an outcome as opposed to ulcer prevention. Certain design features of the orthoses, such as rocker soles and metatarsal accommodations, can reduce peak plantar pressures more significantly than insoles alone. A systematic review, however, showed there was no significant reduction in ulcer incidence after 18 months compared with standard insoles and extra-depth shoes. Further, it was also noted that evidence to prevent first ulcerations was non-existent (88).

Treatment

Treatment recommendations for people with diabetes will be determined by their risk category. No-risk or low-risk individuals can often be managed with

education and self-care. People in the moderate- to high-risk category should be referred to foot care specialists for further evaluation and regular surveillance as outlined in **Table 12.1**. This includes individuals with LOPS, PAD, and/or structural foot deformities, such as Charcot foot, bunions, or hammertoes. Individuals with any open ulceration or unexplained swelling, erythema, or increased skin temperature should be referred urgently to a foot care specialist or multidisciplinary team.

Initial treatment recommendations should include daily foot inspection, use of moisturizers for dry, scaly skin, and avoidance of self-care of ingrown nails and calluses. Well-fitted athletic or walking shoes with customized pressure-relieving orthoses should be part of initial recommendations for people with increased plantar pressures (as demonstrated by plantar calluses). Individuals with deformities such as bunions or hammertoes may require specialized footwear such as extra-depth shoes. Those with even more significant deformities, as in Charcot joint disease, may require custom-made footwear.

Special consideration should be given to individuals with neuropathy who present with a warm, swollen, red foot with or without a history of trauma and without an open ulceration. These individuals require a thorough workup for possible Charcot neuroarthropathy (89). Early diagnosis and treatment of this condition is of paramount importance in preventing deformities and instability that can lead to ulceration and amputation. These individuals require total non-weight-bearing and urgent referral to a foot care specialist for further management. Foot and ankle X-rays should be performed in all individuals presenting with the above clinical findings.

There have been a number of developments in the treatment of ulcerations over the years (90). These include negative-pressure therapy, growth factors, bioengineered tissue, acellular matrix tissue, stem cell therapy, hyperbaric oxygen therapy, and, most recently, topical oxygen therapy (91–93). While there is literature to support many modalities currently used to treat diabetic foot wounds, robust randomized controlled trials (RCTs) are often lacking. However, it is agreed that the initial treatment and evaluation of ulcerations

include the following five basic principles of ulcer treatment:

- Offloading of plantar ulcerations
- Debridement of necrotic, nonviable tissue
- Revascularization of ischemic wounds when necessary
- Management of infection: soft tissue or bone
- Use of physiologic, topical dressings

However, despite following the above principles, some ulcerations will become chronic and fail to heal. In those situations, advanced wound therapy can play a role. When to employ advanced wound therapy has been the subject of much discussion, as the therapy is often quite expensive. It has been determined that if a wound fails to show a reduction of 50% or more after 4 weeks of appropriate wound management (i.e., the five basic principles above), consideration should be given to the use of advanced wound therapy (94). Treatment of these chronic wounds is best managed in a multidisciplinary setting.

Evidence to support advanced wound therapy is challenging to produce and to assess. Randomization of trial participants is difficult, as there are many variables that can affect wound healing. In addition, many RCTs exclude certain cohorts of people, e.g., individuals with chronic renal disease or those on dialysis. Finally, blinding of participants and clinicians is not always possible. Meta-analyses and systematic reviews of observational studies are used to determine the clinical effectiveness of these modalities. Such studies can augment formal RCTs by including a greater variety of participants in various clinical settings who are typically excluded from the more rigidly structured clinical trials.

Advanced wound therapy can be categorized into nine broad categories (90) (**Table 12.2**). Topical growth factors, acellular matrix tissues, and bioengineered cellular therapies are commonly employed in offices and wound care centers to expedite healing of chronic, more superficial ulcerations. Numerous clinical reports and retrospective studies have demonstrated the clinical effectiveness of each of these modalities. Over the years, there has been increased evidence to support the use of these modalities.

Table 12.2—Categories of advanced wound therapies

Negative-pressure wound therapy
Standard electrically powered
Mechanically powered
Oxygen therapies
Hyperbaric oxygen therapy
Topical oxygen therapy
Oxygen-releasing sprays, dressings
Biophysical
Electrical stimulation, diathermy
Pulsed electromagnetic fields, pulsed radiofrequency energy
Low-frequency noncontact ultrasound
Extracorporeal shock wave therapy
Growth factors
Becaplermin: platelet-derived growth factor
Fibroblast growth factor
Epidermal growth factor
Autologous blood products
Platelet-rich plasma
Leukocyte, platelet, fibrin multilayered patches
Whole blood clot
Acellular matrix tissues
Xenograft dermis
Bovine dermis
Xenograft acellular matrices
Small intestine submucosa
Porcine urinary bladder matrix
Ovine forestomach
Equine pericardium
Bovine collagen
Bilayered dermal regeneration matrix
Human dermis products
Human pericardium
Placental tissues
Amniotic tissues/amniotic fluid
Umbilical cord
Bioengineered allogeneic cellular therapies
Bilayered skin equivalent (human keratinocytes and fibroblasts)
Dermal replacement therapy (human fibroblasts)
Stem cell therapies
Autogenous: bone marrow–derived stem cells
Allogeneic: amniotic matrix with mesenchymal stem cells
Miscellaneous active dressings
Hyaluronic acid, honey dressings, etc.
Sucrose octasulfate dressing
Adapted with permission from Frykberg and Banks (90).

Nonetheless, use of those products or agents with robust RCTs or systematic reviews should generally be preferred over those without level 1 evidence (Table 12.2).

Negative-pressure wound therapy was first introduced in the early to mid-1990s. It has become especially useful in wound preparation for skin grafts and flaps and assists in the closure of deep, large wounds (95,96). A variety of types exist in the marketplace and range from electrically powered to mechanically

powered in different sizes depending upon the specific wound requirements.

Electrical stimulation, pulsed radiofrequency energy, and extracorporeal shockwave therapy are biophysical modalities that are believed to upregulate growth factors or cytokines to stimulate wound healing, while low-frequency noncontact ultrasound is used to debride wounds. However, most of the studies advocating the use of these modalities have been retrospective observational or poor-quality RCTs.

Hyperbaric oxygen therapy is the delivery of oxygen through a chamber, either individual or multiperson, with the intention of increasing tissue oxygenation to increase tissue perfusion and neovascularization, combat resistant bacteria, and stimulate wound healing. While there had been great interest in this modality being able to expedite healing of chronic diabetic foot ulcers (DFUs), there has only been one positive RCT published in the last decade that reported increased healing rates at 9 and 12 months compared with control subjects (97). More recent studies with significant design deficiencies and participant dropouts have failed to provide corroborating evidence that hyperbaric oxygen therapy should be widely used for managing nonhealing DFUs (98,99). While there may be some benefit in prevention of amputation in selected chronic neuroischemic ulcers, recent studies have shown no benefit in healing DFUs in the absence of ischemia and/or infection (93,100).

Topical oxygen therapy has been studied rather vigorously in recent years, with several high-quality RCTs and at least five systematic reviews and meta-analyses all supporting its efficacy in healing chronic DFUs at 12 weeks (19,20,30–34,91,92,101–105). Three types of topical oxygen devices are available, including continuous-delivery, low-constant-pressure, and cyclical-pressure modalities. Importantly, topical oxygen therapy devices provide for home-based therapy rather than the need for daily visits to specialized centers. Very high participation with very few reported adverse events combined with improved healing rates makes this therapy another attractive option for advanced wound care.

If DFUs fail to heal despite appropriate wound care, adjunctive advanced therapies should be instituted and are best managed in a multidisciplinary manner. Once healed, all individuals should be enrolled in a formal comprehensive prevention program focused on reducing the incidence of recurrent ulcerations and subsequent amputations (75,106,107).

References

1. Solomon SD, Chew E, Duh EJ, et al. Diabetic retinopathy: a position statement by the American Diabetes Association. *Diabetes Care* 2017;40:412–418

2. Diabetes Control and Complications Trial Research Group; Nathan DM, Genuth S, Lachin J, et al. 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
3. Stratton IM, Kohner EM, Aldington SJ, et al. UKPDS 50: risk factors for incidence and progression of retinopathy in type II diabetes over 6 years from diagnosis. *Diabetologia* 2001;44:156–163
4. 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
5. Yau JWY, Rogers SL, Kawasaki R, et al.; Meta-Analysis for Eye Disease (META-EYE) Study Group. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care* 2012;35:556–564
6. Eid S, Sas KM, Abcouwer SF, et al. New insights into the mechanisms of diabetic complications: role of lipids and lipid metabolism. *Diabetologia* 2019;62:1539–1549
7. 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
8. 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
9. Writing Team for the DCCT/EDIC Research Group; Gubitosi-Klug RA, Sun W, Cleary PA, et al. 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
10. Aiello LP, Sun W, Das A, et al.; DCCT/EDIC Research Group. Intensive diabetes therapy and ocular surgery in type 1 diabetes. *N Engl J Med* 2015;372:1722–1733
11. Bethel MA, Diaz R, Castellana N, Bhattacharya I, Gerstein HC, Lakshmanan MC. HbA_{1c} change and diabetic retinopathy during GLP-1 receptor agonist cardiovascular outcome trials: a meta-analysis and meta-regression. *Diabetes Care* 2021;44:290–296
12. Dabelea D, Stafford JM, Mayer-Davis EJ, D'Agostino R, Dolan L, Imperatore G, et al. 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
13. 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
14. 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
15. Silva PS, Horton MB, Clary D, et al. Identification of diabetic retinopathy and ungradable image rate with ultrawide field imaging in a national teleophthalmology program. *Ophthalmology* 2016;123:1360–1367
16. Bragge P, Gruen RL, Chau M, Forbes A, Taylor HR. Screening for presence or absence of diabetic retinopathy: a meta-analysis. *Arch Ophthalmol* 2011;129:435–444
17. Walton OB 4th, Garoon RB, Weng CY, et al. Evaluation of automated teleretinal screening program for diabetic retinopathy. *JAMA Ophthalmol* 2016;134:204–209
18. Daskivich LP, Vasquez C, Martinez C Jr, Tseng CH, 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
19. Sim DA, Mity 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
20. Abramoff MD, Lavin PT, Birch M, Shah N, Folk JC. Pivotal trial of an autonomous AI-based diagnostic system for detection of diabetic retinopathy in primary care offices. *NPJ Digit Med* 2018;1:1–8
21. Hooper P, Boucher MC, Cruess A, Dawson KG, Delpero W, Greve M, et al. Canadian Ophthalmological Society evidence-based clinical practice guidelines for the management of diabetic retinopathy. *Can J Ophthalmol* 2012;47(2 Suppl):S1–S54
22. Gunderson EP, Lewis CE, Tsai AL, 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
23. Widyaputri F, Rogers SL, Kandasamy R, Shub A, Symons RCA, Lim LL. Global estimates of diabetic retinopathy prevalence and progression in pregnant women with preexisting diabetes: a systematic review and meta-analysis. *JAMA Ophthalmol* 2022;140:486–494
24. 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
25. The Diabetic Retinopathy Study Research Group. Preliminary report on effects of photocoagulation therapy. *Am J Ophthalmol* 1976;81:383–396
26. 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
27. 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
28. Sivaprasad S, Prevost AT, Vasconcelos JC, et al.; CLARITY Study Group. Clinical efficacy of intravitreal aflibercept versus panretinal photocoagulation for best corrected visual acuity in patients with proliferative diabetic retinopathy at 52 weeks (CLARITY): a multicentre, single-blinded, randomised, controlled, phase 2b, non-inferiority trial. *Lancet* 2017;389:2193–2203
29. Maturi RK, Glassman AR, Josic K, et al.; DRCR Retina Network. Effect of intravitreal anti-vascular endothelial growth factor vs sham treatment for prevention of vision-threatening complications of diabetic retinopathy: the Protocol W randomized clinical trial. *JAMA Ophthalmol* 2021;139:701–712
30. 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
31. 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
32. Wells JA, Glassman AR, Ayala AR, et al.; Diabetic Retinopathy Clinical Research Network. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *N Engl J Med* 2015;372:1193–1203
33. Baker CW, Glassman AR, Beaulieu WT, et al.; DRCR Retina Network. Effect of initial management with aflibercept vs laser photocoagulation vs observation on vision loss among patients with diabetic macular edema involving the center of the macula and good visual acuity: a randomized clinical trial. *JAMA* 2019;321:1880–1894
34. 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
35. 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
36. 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
37. Martin CL, Albers JW; 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
38. 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
39. Bashir M, Elhadd T, Dabbous Z, et al. Optimal glycaemic and blood pressure but not lipid targets are related to a lower prevalence of diabetic microvascular complications. *Diabetes Metab Syndr* 2021;15:102241
40. Look AHEAD Research Group. Effects of a long-term lifestyle modification programme on peripheral neuropathy in overweight or obese adults with type 2 diabetes: the Look AHEAD study. *Diabetologia* 2017;60:980–988
41. Callaghan BC, Reynolds EL, Banerjee M, et al. Dietary weight loss in people with severe obesity stabilizes neuropathy and improves symptomatology. *Obesity (Silver Spring)* 2021;29:2108–2118
42. 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

43. Freeman R. Not all neuropathy in diabetes is of diabetic etiology: differential diagnosis of diabetic neuropathy. *Curr Diab Rep* 2009;9:423–431
44. 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
45. 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
46. 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
47. 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
48. 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
49. 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
50. 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
51. Callaghan BC, Little AA, Feldman EL, Hughes RAC. Enhanced glucose control for preventing and treating diabetic neuropathy. *Cochrane Database Syst Rev* 2012;6:CD007543
52. 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
53. Tang Y, Shah H, Bueno Junior CR, et al. Intensive risk factor management and cardiovascular autonomic neuropathy in type 2 diabetes: the ACCORD trial. *Diabetes Care* 2021;44:164–173
54. Callaghan BC, Xia R, Banerjee M, et al.; Health ABC Study. Metabolic syndrome components are associated with symptomatic polyneuropathy independent of glycemic status. *Diabetes Care* 2016;39:801–807
55. Andersen ST, Witte DR, Dalsgaard EM, et al. Risk factors for incident diabetic polyneuropathy in a cohort with screen-detected type 2 diabetes followed for 13 years: ADDITION-Denmark. *Diabetes Care* 2018;41:1068–1075
56. Afshinnia F, Reynolds EL, Rajendiran TM, et al. Serum lipidomic determinants of human diabetic neuropathy in type 2 diabetes. *Ann Clin Transl Neurol* 2022;9:1392–1404
57. Lu Y, Xing P, Cai X, et al. Prevalence and risk factors for diabetic peripheral neuropathy in type 2 diabetic patients from 14 countries: estimates of the INTERPRET-DD study. *Front Public Health* 2020;8:534372
58. 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
59. Waldfogel 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
60. Price R, Smith D, Franklin G, et al. Oral and topical treatment of painful diabetic polyneuropathy: practice guideline update summary: report of the AAN Guideline Subcommittee. *Neurology* 2022;98:31–43
61. Pop-Busui R, Ang L, Boulton AJM, et al. *Diagnosis and Treatment of Painful Diabetic Peripheral Neuropathy*. Arlington, VA, American Diabetes Association, 2022
62. Tesfaye S, Sloan G, Petrie J, et al.; OPTION-DM trial group. Comparison of amitriptyline supplemented with pregabalin, pregabalin supplemented with amitriptyline, and duloxetine supplemented with pregabalin for the treatment of diabetic peripheral neuropathic pain (OPTION-DM): a multicentre, double-blind, randomised crossover trial. *Lancet* 2022;400:680–690
63. 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
64. Briasoulis A, Silver A, Yano Y, Bakris GL. Orthostatic hypotension associated with baroreceptor dysfunction: treatment approaches. *J Clin Hypertens (Greenwich)* 2014;16:141–148
65. Figueroa JJ, Basford JR, Low PA. Preventing and treating orthostatic hypotension: as easy as A, B, C. *Cleve Clin J Med* 2010;77:298–306
66. Jordan J, Fanciulli A, Tank J, et al. Management of supine hypertension in patients with neurogenic orthostatic hypotension: scientific statement of the American Autonomic Society, European Federation of Autonomic Societies, and the European Society of Hypertension. *J Hypertens* 2019;37:1541–1546
67. Camilleri M, Parkman HP, Shafi MA, Abell TL; American College of Gastroenterology. Clinical guideline: management of gastroparesis. *Am J Gastroenterol* 2013;108:18–37
68. Parrish CR, Pastors JG. Nutritional management of gastroparesis in people with diabetes. *Diabetes Spectr* 2007;20:231–234
69. 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.e1–498.e7
70. 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
71. Umptier GE (Ed.) *Therapy for Diabetes Mellitus and Related Disorders*. 6th ed. Arlington, VA, American Diabetes Association; 2014
72. 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
73. Maganti K, Onyemere K, Jones MP. Oral erythromycin and symptomatic relief of gastroparesis: a systematic review. *Am J Gastroenterol* 2003;98:259–263
74. 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
75. 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
76. Schaper NC, van Netten JJ, Apelqvist J, Bus SA, Hinchliffe RJ; IWGDF Editorial Board. Practical guidelines on the prevention and management of diabetic foot disease (IWGDF 2019 update). *Diabetes Metab Res Rev* 2020;36(Suppl. 1):e3266
77. Reiber GE, Vileikyte L, Boyko EJ, et al. Causal pathways for incident lower-extremity ulcers in patients with diabetes from two settings. *Diabetes Care* 1999;22:157–162
78. Pham H, Armstrong DG, Harvey C, Harkless LB, Giurini JM, Veves A. Screening techniques to identify people at high risk for diabetic foot ulceration: a prospective multicenter trial. *Diabetes Care* 2000;23:606–611
79. 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
80. Conte MS, Bradbury AW, Kolh P, White JV, Dick F, Fitridge R, et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. *Eur J Vasc Endovasc Surg* 2019;58(1S):S1–S109.e33
81. American Diabetes Association. Peripheral arterial disease in people with diabetes. *Diabetes Care* 2003;26:3333–3341
82. Reaney M, Gladwin T, Churchill S. Information about foot care provided to people with diabetes with or without their partners: Impact on recommended foot care behavior. *Appl Psychol Health Well-Being* 2022;14:465–482
83. Heng ML, Kwan YH, Ilya N, et al. A collaborative approach in patient education for diabetes foot and wound care: A pragmatic randomised controlled trial. *Int Wound J* 2020;17:1678–1686
84. Bus SA, Lavery LA, Monteiro-Soares M, et al.; International Working Group on the Diabetic Foot. Guidelines on the prevention of foot ulcers in persons with diabetes (IWGDF 2019 update). *Diabetes Metab Res Rev* 2020;36(Suppl. 1):e3269

85. Goodall RJ, Ellauzi J, Tan MKH, Onida S, Davies AH, Shalhoub J. A systematic review of the impact of foot care education on self efficacy and self care in patients with diabetes. *Eur J Vasc Endovasc Surg* 2020;60:282–292
86. Yuncken J, Williams CM, Stolwyk RJ, Haines TP. People with diabetes do not learn and recall their diabetes foot education: a cohort study. *Endocrine* 2018;62:250–258
87. Walton DV, Edmonds ME, Bates M, Vas PRJ, Petrova NL, Manu CA. People living with diabetes are unaware of their foot risk status or why they are referred to a multidisciplinary foot team. *J Wound Care* 2021;30:598–603
88. Bus SA, van Deursen RW, Armstrong DG, Lewis JE, Caravaggi CF; International Working Group on the Diabetic Foot. Footwear and offloading interventions to prevent and heal foot ulcers and reduce plantar pressure in patients with diabetes: a systematic review. *Diabetes Metab Res Rev* 2016;32(Suppl. 1):99–118
89. Rogers LC, Frykberg RG, Armstrong DG, et al. The Charcot foot in diabetes. *Diabetes Care* 2011;34:2123–2129
90. Frykberg RG, Banks J. Challenges in the treatment of chronic wounds. *Adv Wound Care (New Rochelle)* 2015;4:560–582
91. Carter MJ, Frykberg RG, Oropallo A, Sen CK, Armstrong DG, Nair HKR, et al. Efficacy of topical wound oxygen therapy in healing chronic diabetic foot ulcers: systematic review and meta-analysis. *Adv Wound Care (New Rochelle)*. 21 June 2022 [Epub ahead of print]. DOI: 10.1089/wound.2022.0041
92. Frykberg RG, Franks PJ, Edmonds M, et al.; TWO2 Study Group. A multinational, multicenter, randomized, double-blinded, placebo-controlled trial to evaluate the efficacy of cyclical topical wound oxygen (TWO2) therapy in the treatment of chronic diabetic foot ulcers: the TWO2 study. *Diabetes Care* 2020;43:616–624
93. Boulton AJM, Armstrong DG, Löndahl M, et al. *New Evidence-Based Therapies for Complex Diabetic Foot Wounds*. Arlington, VA, American Diabetes Association, 2022
94. Sheehan P, Jones P, Caselli A, Giurini JM, Veves A. Percent change in wound area of diabetic foot ulcers over a 4-week period is a robust predictor of complete healing in a 12-week prospective trial. *Diabetes Care* 2003;26:1879–1882
95. Blume PA, Walters J, Payne W, Ayala J, Lantis J. Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers: a multicenter randomized controlled trial. *Diabetes Care* 2008;31:631–636
96. Argenta LC, Morykwas MJ, Marks MW, DeFranzo AJ, Molnar JA, David LR. Vacuum-assisted closure: state of clinic art. *Plast Reconstr Surg* 2006;117(Suppl.):127S–142S
97. 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
98. Santema KTB, Stoekenbroek RM, Koelemay MJW, et al.; DAMO2CLES Study Group. Hyperbaric oxygen therapy in the treatment of ischemic lower- extremity ulcers in patients with diabetes: results of the DAMO2CLES multicenter randomized clinical trial. *Diabetes Care* 2018;41:112–119
99. 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
100. Lalieu RC, Brouwer RJ, Ubbink DT, Hoencamp R, Bol Raap R, van Hulst RA. Hyperbaric oxygen therapy for nonischemic diabetic ulcers: a systematic review. *Wound Repair Regen* 2020;28:266–275
101. Niederauer MQ, Michalek JE, Liu Q, Papas KK, Lavery LA, Armstrong DG. Continuous diffusion of oxygen improves diabetic foot ulcer healing when compared with a placebo control: a randomised, double-blind, multicentre study. *J Wound Care* 2018;27(Suppl. 9):S30–S45
102. Serena TE, Bullock NM, Cole W, Lantis J, Li L, Moore S, et al. Topical oxygen therapy in the treatment of diabetic foot ulcers: a multicentre, open, randomised controlled clinical trial. *J Wound Care* 2021;30(Suppl. 5):S7–S14
103. Sun XK, Li R, Yang XL, Yuan L. Efficacy and safety of topical oxygen therapy for diabetic foot ulcers: an updated systematic review and meta-analysis. *Int Wound J*. 5 May 2022 [Epub ahead of print]. DOI: 10.1111/iwj.13830
104. Frykberg RG. Topical wound oxygen therapy in the treatment of chronic diabetic foot ulcers. *Medicina (Kaunas)* 2021;57:917
105. Sethi A, Khambhayta Y, Vas P. Topical oxygen therapy for healing diabetic foot ulcers: a systematic review and meta-analysis of randomised control trials. *Health Sci Rep* 2022;3:100028
106. van Netten JJ, Price PE, Lavery LA, et al.; International Working Group on the Diabetic Foot. Prevention of foot ulcers in the at-risk patient with diabetes: a systematic review. *Diabetes Metab Res Rev* 2016;32(Suppl. 1):84–98
107. Frykberg RG, Vileikyte L, Boulton AJM, Armstrong DG. The at-risk diabetic foot: time to focus on prevention. *Diabetes Care* 2022;45:e144–e145