Current Approaches to Preventing Chronic Diabetes Complications

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Current Approaches to Preventing Chronic Diabetes Complications is supported by an educational grant from Novo Nordisk Inc. It has been accredited by the American Association of Diabetes Educators (AADE) for nurses, dietitians, and pharmacists.
The following program is a recorded presentation by Linda Haas.

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Ms. Haas is a past president of the American Association of Diabetes Educators (AADE) and past President, Health Care and Education of the American Diabetes Association (ADA). She received AADE’s Distinguished Service Award in 1994, ADA’s Outstanding Educator of the Year Award in 1995 and ADEs Living Legend Award in 2013. In 1999, she received the Veteran’s Health Administration’s National Award for Excellence in Nursing (Expanded Role). Ms. Haas has lectured throughout the country on diabetes management including medication management.

We'll now join Ms. Haas.
The objectives for this knowledge-based program are:

• Describe the major chronic complications of diabetes

• Review the epidemiology and impact of major chronic complications of diabetes in the United States

• Describe current approaches for preventing the development of major chronic complications of diabetes in adults with type 2 diabetes

Although this program focuses on the prevention of chronic complications in adults with type 2 diabetes, many of the preventive approaches discussed here also apply to adults with type 1 diabetes.
Section One

OVERVIEW OF MAJOR CHRONIC DIABETES COMPLICATIONS
According to the Centers for Disease Control and Prevention (CDC), 29.1 million US residents, or 9.3% of the entire US population, have diabetes. Approximately 72% of affected individuals have diagnosed diabetes, and the others have undiagnosed diabetes. Type 2 diabetes accounts for about 90% to 95% of all US cases of diabetes.

This graph shows the age-adjusted percentage of US adults aged 20 years or older with diagnosed diabetes by major ethnic group. Note the wide variation in diabetes prevalence in these groups. For example, the prevalence of diabetes in American Indians/Alaska Natives is more than twice that among non-Hispanic whites. Diabetes rates also vary substantially within ethnic groups. Among Asian-Americans, for example, estimated diabetes rates are 4.4% for Chinese adults and 13.0% for Asian-Indian adults.

Diabetes is associated with many serious acute and chronic complications. Major acute complications are hypoglycemia, diabetic ketoacidosis (DKA), and hyperosmolar hyperglycemic state (HHS).

The major chronic complications of diabetes are caused primarily by damage to the endothelial cells lining the blood vessels. Chronic complications are classified as macrovascular or microvascular, based on the size of the damaged vessels.

Macrovascular complications result from damage to large blood vessels and include coronary artery disease (CAD), which is also called coronary heart disease (CHD); cerebrovascular disease (CBVD), causing strokes; and peripheral arterial disease (PAD).

Microvascular complications are caused by damage to smaller blood vessels and include diabetic kidney disease (DKD), which is also called nephropathy; retinopathy; and neuropathy.

This activity begins with an overview of the major chronic complications of diabetes, including clinical presentation, epidemiology and impact, and patient management. We then focus on the main topic of the activity—the primary prevention of major chronic complications in adults with type 2 diabetes.

This graph shows prevalence data for major chronic diabetes complications in US adults with diabetes. Regarding macrovascular complications, 21.9% of adults with diabetes have CAD, 16.0% have another type of heart disease, and 9.1% have a history of stroke. With respect to microvascular complications, 40.1% of adults with diabetes have chronic kidney disease (CKD), and most of these individuals have DKD, a subtype of CKD. Also among adults with diabetes, more than 60% have neuropathy and 28.5% have retinopathy.

Because many patients with type 2 diabetes have had diabetes for several years before their diagnosis, a substantial proportion have already developed chronic macrovascular and microvascular complications by the time they are diagnosed. Many people often have more than one chronic complication.


Current US data show that the personal and societal impact of chronic diabetic complications in the United States is massive.

Diabetes is the seventh-leading cause of death.

Compared to adults without diagnosed diabetes, the rate of cardiovascular disease (CVD) death is 1.7 times higher, the rate of hospitalization due to myocardial infarction (MI) is 1.8 times higher, and the rate of hospitalization due to stroke is 1.5 times higher in adults with diabetes.

Diabetes is the primary cause of kidney failure in 44% of all new cases.

Among adults with diabetes aged ≥40 years, 4.4% have advanced retinopathy.


In 2013, the American Diabetes Association (ADA) published a new analysis of the economic costs of diabetes in the US. It included data for type 1 and type 2 diabetes and infrequently occurring types of diabetes, but not gestational diabetes. The study estimated that the total cost of diagnosed diabetes in 2012 was $245 billion, including $176 billion in direct medical costs and $69 billion in reduced productivity. It also showed that people with diabetes, on average, have medical expenditures that are about 2.3 times higher than those of people without diabetes.

In another important economic study, Zhuo and colleagues studied the average lifetime direct medical costs of treating type 2 diabetes and major chronic diabetes complications in US adults. Treatment costs for CAD, stroke, DKD, retinopathy, and neuropathy were calculated. This graph shows that the cost of complications was related to the age at which type 2 diabetes was diagnosed. Average lifetime direct costs of complications in men ranged from $62,900 for individuals diagnosed between age 25 and 44 years to $35,000 for those diagnosed at age 65 years or older. For women, costs were $63,200 for those aged 25 to 44 years when diagnosed and $31,300 for those diagnosed at age 65 or older. For both men and women, chronic complications represented a greater percentage of the direct medical costs of diabetes as the age at diagnosis increased. Costs of complications were 50% of total direct medical costs for men diagnosed between 26 and 44 years and 64% of total costs for men diagnosed at age 65 years or older. Corresponding percentages for women were 48% and 55%.


Zhuo X, Zhang P, Hoerger TJ. Lifetime direct medical costs of treating type 2 diabetes and diabetic
The accurate statement is: __________.

a. about 9% of the US population has diabetes
b. retinopathy is the most prevalent chronic complication of diabetes
c. the risk of cardiovascular death is about 4 times higher in people with diabetes compared to those without diabetes
d. the cost of major chronic diabetes complications represents about one quarter of the total lifetime direct medical cost of type 2 diabetes
The correct answer is a.

About 9% of the US population has diabetes.
Section Two

OVERVIEW OF SPECIFIC COMPLICATIONS
As mentioned previously, macrovascular complications of diabetes include CAD, cerebrovascular disease, and PAD. Patients with diabetes and CAD may experience angina, MI, congestive heart failure (CHF), or sudden cardiac death. Compared to people without diabetes, individuals with diabetes often have more diffuse CAD involving more of the smaller coronary vessels. CAD generally begins at an earlier age in people with diabetes. Some individuals with diabetes and CAD do not experience typical angina symptoms because they also have cardiac autonomic neuropathy.

Patients with cerebrovascular disease may present with a transient ischemic attack (TIA) or cerebrovascular accident (stroke). In people with diabetes, most TIAs are of thrombotic rather than embolic origin. As in the general population, the majority of people with diabetes experience ischemic instead of hemorrhagic stroke. Many individuals with diabetes do not summon emergency assistance at the first sign of TIA or stroke because they believe they are experiencing a hypoglycemic episode. As part of their diabetes self-management education (DSME), patients must be taught about the early-warning symptoms of TIA and stroke, instructed to check their blood glucose (BG) whenever they experience unexplained symptoms, and counseled to call 9-1-1 immediately if they are not hypoglycemic and have possible TIA or stroke symptoms.

PAD is characterized by lower-extremity ischemia. Because of neuropathy, people with diabetes and PAD may not experience the classic symptom of claudication pain in the thigh and calf that is relieved by rest. They may not present for treatment until they develop a neurogenic or ischemic ulcer or gangrene.


The burden of macrovascular complications is great, both in terms of the number of people affected and the direct medical costs of treatment.

The graph on the left shows that, among US adults aged 35 years or older with diabetes, 5 million have CAD, 3.7 million have another type of heart disease, and 1.5 million have a history of stroke.

The graph on the right shows that the average lifetime direct medical cost of CAD and stroke in US adults with type 2 diabetes ranges from $22,300 for a woman diagnosed with diabetes at age 65 or older to $35,000 for a man diagnosed between the ages of 45 and 54 years.

Macrovascular complications account for a large proportion of lifetime diabetes-related direct medical costs. On average, the cost of macrovascular complications represents 19% of total costs for a woman diagnosed with diabetes between the ages of 25 and 44 years and 52% of costs for a man diagnosed at age 65 years or older.


This slide shows risk factors for macrovascular complications in people with diabetes. Except for age, race, sex, and family history, these risk factors are modifiable to a greater or lesser extent. We will discuss the use of CV risk calculators in Section 5 of this activity. Some major risk factors are discussed here.

Hypertension in patients with diabetes often has atypical features. Supine hypertension with orthostatic hypotension may occur due to autonomic neuropathy. In addition, many people with diabetes do not have the usual nocturnal drop in blood pressure (BP).

The pattern of dyslipidemia most commonly seen in individuals with diabetes includes elevated total cholesterol; decreased high-density lipoprotein cholesterol (HDL-C) levels; increased small, dense low-density lipoprotein cholesterol (LDL-C) levels; and elevated triglyceride levels.

The hypercoagulability observed in people with diabetes has multiple causes, including increased levels of plasminogen activator inhibitor (PAI), von Willebrand factor, factor VII, fibrinogen, and C-reactive protein.

Both chronic hyperglycemia and insulin resistance affect vascular function by producing vasoconstrictive substances and advanced glycation end products that disturb endothelial function and affect vessel walls by causing increased stiffness.


This slide summarizes key ADA treatment recommendations for patients with known macrovascular disease.

Angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy should be considered for patients with hypertension.

Providers should prescribe aspirin therapy at a dose of 75–162 mg/day. If aspirin is contraindicated, clopidogrel (75 mg/day) should be substituted. Dual antiplatelet therapy with aspirin and clopidogrel can be considered for at least 1 year after acute coronary syndrome.

Statin therapy should be initiated or continued unless contraindicated. (Later in this activity, recent American College of Cardiology–American Heart Association and ADA guidelines about statin use will be discussed in detail.)

Beta-blocker therapy should be continued for at least 2 years after MI.

Thiazolidinedione (TZD) treatment should be avoided in patients with symptomatic heart failure because of the risk of exacerbating the condition.

Metformin can be continued for patients with stable CHF and normal renal function but should not be used in unstable or hospitalized patients.

As previously mentioned, DKD is a subtype of CKD. DKD typically begins as mild albuminuria and, unless managed effectively, can progress to severe albuminuria, hypertension, severely impaired renal function, and the need for renal replacement therapies (dialysis or transplantation).

According to the 2012 Clinical Practice Guideline developed by the Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, the diagnostic criterion for CKD is the presence of abnormalities of kidney structure or function for more than 3 months. The Work Group recommends that CKD be staged using the glomerular filtration rate (GFR) and albuminuria categories shown on the slide. A GFR less than 60 mL/min/1.73 m², an albumin excretion rate (AER) ≥30 mg/24 h, and/or an albumin-to-creatinine ratio (ACR) ≥30 mg/g that persists for 3 months indicates that CKD is present.

The ADA recommends that, beginning at diagnosis, people with type 2 diabetes be screened for increased urinary albumin excretion by measurement of the ACR in a random spot collection. Because of variability in urinary albumin excretion, 2 of 3 specimens collected within a 3- to 6-month period should be abnormal before considering a patient to have developed increased urinary albumin excretion or to have had a progression in albuminuria. In addition, serum creatinine with estimated GFR should be assessed at least annually in all adults with diabetes, regardless of the degree of urine albumin excretion. Note that the ADA no longer uses the term “microalbuminuria” for an AER of 30 to 299 mg/24 h or the term “macroalbuminuria” to refer to levels ≥300 mg/24 h. This decision was made to emphasize the continuous nature of albuminuria as a risk factor for end-stage renal disease (ESRD) and macrovascular complications.


DKD is a devastating complication that contributes substantially to diabetes-related mortality.

The graph on the left shows that the likelihood of developing CKD has decreased substantially among US adults with diabetes in recent years. The odds ratio for CKD was 4.1 from 1988‒1994 and 3.4 from 2005‒2010. Experts attribute this reduction to advances in diabetes care. Despite this favorable trend, US adults with diabetes are still more than 3 times as likely to develop CKD as their counterparts without diabetes.

The graph on the right shows that the average lifetime direct medical cost of DKD in US adults with type 2 diabetes ranges from $1,600 for a man diagnosed with diabetes at age 65 years or older to $16,200 for a woman diagnosed between the ages of 25 and 44 years. Women had greater lifetime medical costs for DKD than men because, on average, they live longer.


This slide shows major risk factors for DKD and DKD progression.

The presence of DKD in a first-degree relative is a major non-modifiable risk factor. Other non-modifiable factors are advanced age (especially being 75 years of age or older), increased diabetes duration, and being of African-American, Hispanic, or Native American ancestry.

Having an elevated A1C value, hypertension, smoking, and obesity are major modifiable risk factors.

DKD is itself a risk factor for cardiovascular events and cardiovascular mortality. DKD promotes the development of macrovascular disease through multiple mechanisms, including exacerbation of hypertension, systemic inflammation, oxidative stress, endothelial dysfunction, anemia, the accumulation of small-molecule toxins, and disordered mineral metabolism.


This and the next slide summarize current ADA treatment recommendations for patients with DKD. They are contained in “Standards of Medical Care in Diabetes—2015,” and the 2014 report of an ADA consensus conference on DKD authored by Tuttle and colleagues.

Health care providers should help their patients with DKD make necessary lifestyle modifications. It is important for patients to maintain a healthy diet, which in most cases includes what the ADA calls a “usual” dietary protein intake. Patients should be referred to a dietitian specializing in kidney disease so they can receive help in moderating their intake of dietary sodium, phosphorus, and potassium. Unless contraindicated, physical activity goals are ≥150 minutes per week of moderate-intensity aerobic physical activity and resistance training ≥2 times per week. Facilitation of smoking cessation and weight reduction is also important.

Because intensive glucose control has been shown to limit DKD progression, providers should strive to help patients optimize their glycemic control, using individualized targets. Adopting strategies that minimize the risk of hypoglycemia is imperative, since patients with DKD have an increased hypoglycemia risk. Providers must prescribe appropriate doses of glucose-lowering drugs that are safe for use in patients with renal impairment. In the absence of other contraindications, agents that can be used without dose adjustment in patients with DKD include glipizide, pioglitazone, albiglutide, and linagliptin. Because insulin requirements often decrease in patients with DKD, regular self-monitoring of blood glucose (SMBG) is especially important for this population.


Effective BP control is another essential intervention for limiting DKD progression. Either an ACE inhibitor or an ARB is suggested for the treatment of the non-pregnant patient with modestly elevated urinary albumin excretion (30–299 mg/day), and is recommended for those with urinary albumin excretion >300 mg/day. Diuretics, calcium channel blockers, and beta-blockers can be used for additional or alternative therapy. When ACE inhibitors, ARBs, or diuretics are used, serum creatinine and potassium levels should be monitored for the development of increased creatinine or changes in potassium levels.

Statin and antiplatelet therapy should be initiated if warranted.

It is important to evaluate and manage potential DKD complications when the estimated GFR (eGFR) falls below 60 mL/min/1.73 m².

Providers should consider referring a patient to a physician experienced in the care of kidney disease when there is uncertainty about the etiology of the patient's kidney disease, difficult management issues arise, or the patient has advanced disease.

Patients should be educated about the progressive nature of DKD, the renal preservation benefits of managing BG and BP optimally, the importance of a low-sodium diet, and the potential need for renal replacement therapy in the future.


Neuropathy is a major contributor to mortality, morbidity, and reduced quality of life (QoL) in people with diabetes. The neuropathy that occurs in individuals with diabetes is actually a heterogeneous group of syndromes that affects different parts of the nervous system and has diverse clinical manifestations. The most common neuropathies are chronic sensorimotor distal symmetric polyneuropathy (DPN) and autonomic neuropathy.

DPN is the most frequently occurring neuropathy in diabetes, eventually affecting at least 50% of patients. It is characterized by the progressive loss of sensory nerve fibers. The most distal portions of the longest nerves are affected first, so that patients typically experience symptoms in a “stocking” pattern, and later in a “stocking-glove” pattern. Symptoms of DPN depend on the type of nerve fiber damage:
- Small: pain, dysesthesias, numbness
- Large: numbness, unsteady gait, loss of balance

Most patients have a mixture of small- and large-fiber involvement. However, up to 50% of patients with DPN are asymptomatic.

The ADA recommends that all patients with type 2 diabetes be screened for DPN at diagnosis and then at least annually, using simple clinical tests.


Autonomic neuropathy usually involves the cardiovascular, gastrointestinal (GI), urogenital, or sudomotor system. It is often extremely debilitating and difficult to treat.

Cardiovascular autonomic neuropathy (CAN) is the most clinically important form of autonomic neuropathy because it is independently associated with increased risk of mortality independent of other CV risk factors. Impaired heart rate variability is the earliest sign of CAN and may be asymptomatic. As CAN progresses, patients may experience exercise intolerance, resting tachycardia, abnormal BP regulation, and orthostatic hypotension.

Clinical features of GI neuropathy include gastroparesis, esophageal dysfunction, severe and persistent diarrhea, and constipation. Urogenital neuropathy results in bladder dysfunction and male and female sexual dysfunction. Patients with sudomotor neuropathy may experience anhidrosis, heat intolerance, dry skin, or hyperhidrosis.

The ADA recommends that screening for the signs and symptoms of CAN begin upon diagnosis of type 2 diabetes. Standard cardiovascular reflex testing is the screening method of choice, since it is noninvasive, easily performed, reliable, and reproducible.
The lifetime prevalence of neuropathy in diabetes is extremely high. More than 60% of patients have some type of neuropathy, more than 50% have DPN, about 20% have CAN, and at least 25% have another type of autonomic neuropathy. At the time they are diagnosed with type 2 diabetes, about 20% of patients already have DPN.

The graph on the right shows that the average lifetime direct medical cost of neuropathy in US adults with type 2 diabetes ranges from $2,000 for a man diagnosed with diabetes at age 65 years or older to $13,400 for a woman diagnosed between the ages of 25 and 44 years. Cost estimates are based on the direct costs of managing DPN, treating a diabetes-related foot ulcer, and lower-extremity amputation.


Most of the studies that have investigated risk factors for neuropathy in diabetes have focused on DPN and CAN. Modifiable risk factors for these conditions are hyperglycemia, hypertension, dyslipidemia (especially elevated triglycerides), obesity, and smoking. Non-modifiable risk factors are advanced age (especially age greater than 70 years) and long diabetes duration.

Tall stature is a non-modifiable established risk factor for DPN. Although the basis for this finding is currently unknown, experts speculate that height is a surrogate for nerve length and that longer nerves may be especially susceptible to metabolic derangement.

Several possible risk factors for DPN and CAN are under investigation. Possible modifiable factors are fluctuating BG levels and alcohol consumption. Genetics is a possible non-modifiable factor.


According to the ADA, early recognition of neuropathy is important because some patients have treatable types of nondiabetic neuropathy, such as neuropathy caused by neurotoxic medications or substances, alcohol abuse, hypothyroidism, and vitamin B12 deficiency. Extended treatment with metformin is a risk factor for vitamin B12 deficiency. Early diagnosis is also important because up to 50% of patients with DPN are asymptomatic and therefore at risk for insensate foot injury.

In patients with type 2 diabetes and diabetes-related neuropathy, tightening glucose control may modestly slow the progression of neuropathy. Depending on the severity of the damage that has already occurred, improved glucose control may or may not reverse existing neuronal loss.

The Steno-2 Study showed that an intensive multifactorial CV risk intervention targeting glucose, blood pressure (BP), lipids, smoking, and other lifestyle factors can reduce the progression and development of CAN in patients with type 2 diabetes.

Despite the current lack of a specific treatment for nerve damage, symptomatic treatment is important because it can improve patients’ QoL and reduce neuropathic pain.


This slide shows some symptomatic treatments for DPN and autonomic neuropathy. As of December 2014, the FDA had approved duloxetine, pregabalin, and tapentadol for neuropathic pain associated with DPN. Other antidepressants, antiepileptic drugs, and opioids are used on an off-label basis.

Metanx® is a medical food that has been approved by the FDA for the dietary management of endothelial dysfunction. It contains the active forms of folate, vitamin B6, and vitamin B12. Metanx® increases nitric oxide synthesis, increasing blood flow to the peripheral nerves. Some evidence suggests that it promotes repair and regeneration of the myelin sheath in patients with DPN, as long as the damage is not too extensive.

Note that both pharmacologic and nonpharmacologic interventions may reduce the symptoms of autonomic neuropathy. In patients with CAN, for example, ACE inhibitors, beta-blockers, and graded supervised exercise may lessen resting tachycardia. Symptoms of orthostatic hypotension may be reduced by drug therapy or mechanical measures, such as elevating the head of the bed by 30 degrees at night or increasing venous pressure with supportive elastic stockings.

Thanks to extensive patient and professional education about the importance of foot care, hospitalization rates for foot ulcers and lower-extremity amputations have decreased substantially among people with diabetes in recent years. Nevertheless, about 60% of non-traumatic lower-limb amputations in adults 20 years of age or older occur in people with diagnosed diabetes, and nearly 75,000 non-traumatic lower-limb amputations are performed each year in this population.

To improve foot health in people with diabetes, the ADA recommends that all patients have an annual comprehensive foot exam to identify risk factors predictive of ulcers and amputations. Furthermore, all patients should receive general foot self-care education. It is important for them to understand the importance of daily foot monitoring; proper foot care, including nail and skin care; and the selection of appropriate footwear. Patients with loss of protective sensation (LOPS) should learn to use hand palpation and visual inspection to identify early foot problems.

Patients who smoke, have LOPS and structural abnormalities, or a history of prior lower-extremity complications should be referred to foot care specialists for ongoing preventive care and lifelong surveillance.


People with diabetes are at an elevated risk of developing many age-related eye disorders, such as cataracts and glaucoma. However, the most severe diabetes-related eye disease is diabetic retinopathy, a highly specific vascular complication. Recall that the retina is a layer of nerve tissue at the back of the eye that converts light into electrical signals interpreted by the brain. It is often compared to the film in a traditional camera. Diabetic retinopathy occurs when the small blood vessels that nourish the retina are damaged as a result of hyperglycemia and hypertension, permitting leakage of blood components through vessel walls.

This slide shows the International Clinical Disease Severity Scale (ICDSS) staging of diabetic retinopathy. The major categories are nonproliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). Early NPDR abnormalities include microaneurysms (pouches along weakened vascular walls), flame- or dot-shaped intraretinal hemorrhages, and cotton-wool spots. Increased vascular leakage leads to retinal thickening (edema) and fluid deposits that become hard exudates. As the disorder progresses, retinal blood vessels gradually close, leading to decreased perfusion and ischemia. Signs of ischemia are vascular abnormalities characterized by beads and loops, dilated capillaries clustered around ischemic areas, and additional retinal hemorrhages and exudates.

PDR, the more advanced and vision-threatening stage, is marked by the growth of new blood vessels along the retinal surface (neovascularization) and hemorrhages into the vitreous or other preretalin structures. The new vessels may extend to the vitreous cavity using the posterior vitreous surface as a scaffold. These vessels are fragile and rupture easily, resulting in vitreous hemorrhages. Hemorrhages may cause vitreo-retinal traction bands, retinal tears, and retinal detachments.

Diabetic macular edema (DME) may accompany any stage of NPDR or PDR. Recall that the macula is the specialized portion of the retina responsible for central vision. Macular edema is the leakage of fluid and exudate from the blood vessels into the macula. This is a serious complication because it affects the primary area of focus. The slide shows the ICDSS staging system for DME. The term “posterior pole” refers to the back of the eye.

DME may also be classified as clinically significant or not clinically significant, based on criteria developed by the Early Treatment Diabetic Retinopathy Study (ETDRS) Group. Using the ICDSS staging system shown in the table, patients with clinically significant DME have either moderate or severe DME.

Vision loss in patients with clinically significant DME ranges from mild blurring to visual acuity of 20/200 (the criterion for legal blindness) or less.


In the US today, 9.3% of adults in the general population and 19.1% of adults with diagnosed diabetes have some degree of visual impairment. Diabetes is the leading cause of blindness among adults aged 20–74 years. Up to 23,000 new cases of diabetes-related legal blindness present annually.

The graph on the right shows that the average lifetime direct medical cost of retinopathy in US adults with type 2 diabetes ranges from $2700 for a man diagnosed with diabetes at age 65 years or older to $10,300 for a woman diagnosed between the ages of 45 and 54 years. Costs are based on the estimated direct medical costs associated with photocoagulation and blindness.


This slide shows the major risk factors for retinopathy and retinopathy progression. Diabetes duration and DKD are non-modifiable risk factors. In addition, patients undergoing cataract surgery may experience worsening retinopathy. Retinopathy can also progress during pregnancy, particularly in the first trimester. Women with preexisting diabetes who are contemplating pregnancy or have become pregnant should have a comprehensive eye exam and be counseled on the risk of development or progression of diabetic retinopathy. Eye examination should occur in the first trimester, with close follow-up during pregnancy and for 1 year postpartum.

The most important modifiable risk factor is hyperglycemia, followed by hypertension. Other modifiable factors are dyslipidemia, smoking, anemia, and abdominal obesity. Sudden improvement in diabetes control, which often occurs when an intensive insulin regimen is initiated, can sometimes lead to a transient worsening of retinopathy. It is advisable for patients contemplating a major change in their glucose-lowering regimen to have a dilated retinal examination shortly before and shortly after the change is made to monitor the change in retinal status.

The ACCORD investigators have recently reported that retinopathy is associated with cognitive decline in people with type 2 diabetes, although the nature of this association has yet to be determined.


### Management of Retinopathy

- Adults with type 2 diabetes should have an initial dilated and comprehensive eye examination shortly after the diagnosis of diabetes.
  - Clinical findings should determine follow-up exam frequency.
  - Retinal photography may serve as a screening tool.
- Patients with any level of DME, severe NPDR, or any PDR should be referred to an experienced ophthalmologist.
- Laser photocoagulation therapy: indicated for treatment of high-risk PDR, clinically significant DME, some cases of severe NPDR.
- Approved for DME: ranibizumab* and aflibercept (anti-VEGF agents), dexamethasone and fluocinolone acetonide (corticosteroid) intravitreal implants.

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Early recognition of diabetic retinopathy is essential for preventing vision loss. Therefore, patients with type 2 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist shortly after their diabetes diagnosis. Clinical findings should determine the frequency of follow-up examinations. High-quality fundus photography may serve as a screening tool for retinopathy. However, it is not a substitute for a comprehensive eye exam, which should be performed initially and then at recommended intervals.

Patients with any level of DME, severe NPDR, or any PDR should be referred to an ophthalmologist experienced in the management of diabetic retinopathy. Laser photocoagulation therapy is recommended to reduce the risk of vision loss in patients with high-risk PDR, clinically significant DME, and some cases of severe NPDR. Anti-vascular endothelial growth factor (VEGF) therapy with ranibizumab or aflibercept is indicated for the treatment of DME, and ranibizumab is also indicated for the treatment of diabetic retinopathy in patients with DME. Long-term corticosteroid therapy with a dexamethasone or fluocinolone acetonide intravitreal implant has also received FDA approval for the treatment of DME.

**Note:** Full citations are given in the reference list for this activity.


As we have discussed in this section, the major chronic complications of diabetes, including macrovascular disease, DKD, neuropathy, and retinopathy, are highly prevalent in people with type 2 diabetes and are associated with a massive personal and economic burden.

Once they have developed, chronic complications are rarely reversible. There are numerous management options for these complications, but nearly all of them are suboptimal. In many cases they reduce symptoms without addressing underlying pathologic processes.

The major reversible risk factors for chronic diabetes complications are hyperglycemia, hypertension, and dyslipidemia. To prevent or delay the development of these complications, mitigating these risk factors is essential.

The rest of this activity will deal with the evidence-based management of these risk factors.
The accurate statement is: ____________.

a. concurrent treatment with an ACE inhibitor and an ARB is beneficial for many patients with macrovascular disease or DKD
b. CAN is the most prevalent type of neuropathy in patients with diabetes
c. the highest percentage of non-traumatic lower-limb amputations in adults occurs in people with diagnosed diabetes
d. patients usually experience marked improvement in retinopathy symptoms after starting an intensive insulin regimen
The correct answer is c.

The highest percentage of non-traumatic lower-limb amputations in adults occurs in people with diagnosed diabetes.
Section Three

ACHIEVING AND MAINTAINING GLYCEMIC CONTROL
Since diabetes is characterized by hyperglycemia, glycemic control is fundamental to diabetes management.

Large outcome studies in patients with type 2 diabetes, such as UKPDS, ACCORD, ADVANCE, and VADT, have explored the relationship between glycemic control and chronic complications. These studies have shown that lowering the A1C to below or around 7% reduces the incidence and progression of

- DKD, neuropathy, and retinopathy
- Macrovascular disease, if implemented soon after diabetes diagnosis

Reducing the A1C to near-normal levels is also associated with long-term reduction in macrovascular disease, as long as interventions to lower the A1C are implemented soon after the diagnosis of type 2 diabetes. The results of ACCORD, ADVANCE, and VADT suggest that intensive glycemic control does not significantly improve preexisting macrovascular complications in patients with advanced type 2 diabetes.
This is a timeline of major recent clinical practice guidelines on glycemic control in type 2 diabetes. Overall, these guidelines reflect a shift in emphasis from algorithm-based to individualized glycemic control and an openness to earlier use of insulin.

The 2012 ADA–EASD guideline of Inzucchi et al. is a ground-breaking document because it emphasizes the need for individualized therapy. Instead of an algorithm for glucose-lowering drugs, it includes general treatment recommendations, which are shown later in this activity. Insulin is recommended as a possible treatment for any patient with an inadequate response or contraindication to metformin.

The 2013 AACE guideline of Garber et al. includes a series of algorithms, one of which deals with glycemic control. Like the 2009 AACE–ACE guideline, it tracks patients based on their initial A1C. The 2013 algorithm has 3 sequential steps—monotherapy, dual therapy, and triple therapy. Basal insulin is considered a possible component of dual- and triple-therapy regimens. The guideline’s text emphasizes an individualized approach to all aspects of patient management, including the choice of glucose-lowering drugs.

The 2015 update to the 2012 ADA–EASD guideline of Inzucchi et al. includes recommendations based on evidence that was not available in 2012, such as data supporting the safety and efficacy of the sodium–glucose cotransporter 2 (SGLT2) inhibitors.

*Note:* Full citations are given in the Reference List for this activity.


The central message of the 2012 ADA–EASD position statement and the 2015 update to that statement is that glycemic targets and glucose-lowering therapy must be individualized.

Other key points are that diet, exercise, and self-management remain the foundation of any type 2 diabetes education program.

Ultimately, many patients will require insulin therapy alone or in combination with other agents.

All treatment decisions, when possible, should be made in conjunction with the patient, focusing on his/her preferences, needs, and values.

Comprehensive CV risk reduction should also be a major focus of therapy.


The key points of the 2013 AACE consensus statement are similar to those of the 2012/2015 ADA–EASD position statement. Treatment decisions must consider the whole patient, the patient’s spectrum of risks and complications, and evidence-based treatment approaches.

Lifestyle optimization is essential for all patients.

Determining the precise glucose target and A1C goal for each patient requires a nuanced approach that balances

- Patient age
- Comorbidities
- The ease of achieving a glucose level as close to normal as possible while avoiding hypoglycemia

Although both the ADA and the AACE emphasize that glycemic targets must be individualized, these organizations recommend specific targets for many people with diabetes. These targets are based on the results of major outcome studies.

The ADA recommends an A1C of less than 7%, preprandial capillary plasma glucose in the range of 80 to 130 mg/dL, and peak postprandial capillary plasma glucose of less than 180 mg/dL. Postprandial glucose measurements should be made 1 to 2 hours after the beginning of the meal, since they are generally peak levels in patients with diabetes. Note that the preprandial capillary plasma glucose range of 80 to 130 mg/dL recommended in the ADA’s Standards of Medical Care for 2015 differs slightly from the previously recommended range of 70 to 130 mg/dL.

The AACE recommends an A1C target of ≤6.5% for most patients. Additional recommendations are a fasting plasma glucose value of <110 mg/dL and a 2-hour postprandial plasma glucose value of less than 140 mg/dL.


As we have seen, both the 2012/2015 ADA–EASD Position Statement and the 2013 AACE Consensus Statement emphasize that individual patient characteristics must be the basis for setting glycemic targets. This diagram, taken from the 2015 ADA–EASD statement, summarizes factors that should determine appropriate glycemic targets for a specific patient. This guidance is similar to that presented in the AACE statement.

Note that the diagram depicts a scaled approach to A1C targets—more stringent (on the left) or less stringent (on the right). Characteristics suggesting that an A1C target below 7% (or even below 6.5%) should be considered are a low level of risk associated with hypoglycemia and other potential adverse effects of glucose-lowering therapy; a recent diabetes diagnosis; long life expectancy; absence of important comorbidities and established vascular complications; high level of motivation and treatment adherence; robust self-care capacity; ready availability of personal, medical, and economic resources; and a strong support system.

Other characteristics suggest that an A1C target of 7% or even higher is appropriate. These are high level of risk associated with hypoglycemia and other adverse effects of glucose-lowering therapy, long-standing diabetes diagnosis, short life expectancy, presence of important comorbidities and established vascular complications, low level of motivation and treatment adherence, limited self-care capacity; limited availability of resources, and weak support system. Regardless of these characteristics, decisions about the intensity of glucose-lowering therapy should reflect the patient’s desires and values, since attaining glycemic control requires the patient’s participation and commitment.

The soundness of this overall approach has recently been confirmed by a large data analysis. The authors found that while improved glycemic control can provide substantial benefits for younger patients, additional glycemic treatment offers no more than modest benefits for most metformin-treated patients over age 50 with an A1C of less than 9%. Furthermore, even mild adverse effects can be problematic for many older patients.


The 2012 ADA-EASD position statement and its 2015 update do not contain an algorithm for the use of glucose-lowering drugs, but they do contain some general recommendations about glucose-lowering therapy in type 2 diabetes. This diagram summarizes the 2015 recommendations.

There are four tiers of therapy. The first is for metformin monotherapy, since metformin is the initial glucose-lowering agent for most patients without contraindications. The second tier is for 2-drug combinations of glucose-lowering agents, the third is for 3-drug combinations, and the fourth is for metformin plus combination injectable therapy. Note that in tiers 2 and 3, the order of the treatment options is determined by year of introduction and route of administration and does not denote any specific preference for one agent over another. The usual transition to a new therapy is vertical, from top to bottom, but horizontal movement within therapy stages is also possible, depending on the situation.

The figure depicts drugs commonly used both in the US and Europe. However, meglitinides may be used in place of sulfonylureas. Other drugs not shown, including the α-glucosidase inhibitors, colesevelam, bromocriptine, and pramlintide, may be used in selected patients but have modest efficacy and/or problematic side effects.

This is the glycemic control algorithm from the 2013 AACE Consensus Statement. An important difference from the 2012/2015 ADA–EASD Position Statement is that glucose-lowering drugs are listed in a suggested hierarchy of use. Furthermore, agents are divided into 2 major categories: those that have few adverse effects or provide possible benefits, such as weight loss, and those that should be used with caution because of possible safety issues. The more clearly beneficial agents are marked with a plus sign, while potentially problematic agents are denoted with a minus sign.

The algorithm gives precedence to metformin, the GLP-1 agonists, and the DPP-4 inhibitors. Although the SGLT2 inhibitors are included, the recommendation for the use of these newer agents is based on phase 3 clinical trial data rather than on real-world experience. The “use with caution” symbol reflects the agents’ association with genitourinary infections and increased LDL-C concentrations.

The sulfonylureas and glinides occupy the last position in the hierarchy of use, primarily because they pose the highest hypoglycemia risk of any non-insulin agents.

Today, given our knowledge of the effects of eating patterns and physical activity on BG levels and the availability of many complementary classes of glucose-lowering drugs, it is theoretically possible for nearly all patients with type 2 diabetes to achieve and maintain their individualized glycemic targets. However, as with other chronic diseases that may have few early symptoms, rates of adherence to type 2 diabetes drug treatments are often less than 50%. Here are some proven approaches that health care providers can take to optimize patients’ adherence.

Patients are most likely to be adherent when they understand that type 2 diabetes has serious consequences unless BG values are effectively managed over the long term. Therefore, without resorting to threats, it is important to give patients a realistic sense of the potential for developing complications, as well as the role that glucose-lowering drug therapy can play in maintaining glucose control and preventing or delaying complications. Because a sense of self-efficacy increases adherence, providers should ensure that their patients receive adequate DSME and that their treatment regimen is as simple as possible. Similarly, it is important for providers to ensure that patients receive adequate, ongoing support from a nurse specialist or diabetes educator, since this support increases adherence. When insulin therapy is considered beneficial, providers should start their patients on an insulin pen whenever it is financially feasible, since using insulin pens increases adherence. Providers can also boost adherence by doing everything in their power to reduce the financial burden of diabetes for their patients. One effective approach is helping patients switch from a traditional formulary insurance plan to a value-based plan.


Providers can take many steps to implement clinical practice guidelines for glycemic control in their practice settings. It is important to remain familiar with the content of major guidelines, such as those promulgated by the ADA and the AACE. The provider should collaborate with the patient to determine his/her individual glycemic goals and the most appropriate approaches for attaining and maintaining them.

Providers and administrators of health care facilities should work cooperatively to introduce patient-management software or “low-tech” alternatives to alert medical staff that patients are due for screenings, such as A1C tests, or other diabetes-related services, such as regular foot care. Similarly, providers and administrators should adopt effective electronic or other approaches to communicate with patients about pending appointments, test results, and ongoing BG management issues. Both automated Internet-based and telephone-based services can improve the quality of patient–provider communications and have a positive impact on glycemic management.


The accurate statement is: __________.

a. recent outcome trials have shown that lowering the A1C to below or around 7% reduces CVD incidence in all patient populations

b. both the 2012/2015 ADA–EASD Position Statement and the 2013 AACE Consensus Statement emphasize the importance of individualizing glycemic goals

c. according to the 2012/2015 ADA–EASD Position Statement, stringent glycemic goals would be appropriate for most patients with important comorbidities

d. providers should not discuss the potential for diabetes-related complications because it discourages patients from adhering to their treatment regimen
The correct answer is b.

Both the 2012/2015 ADA–EASD Position Statement and the 2013 AACE Consensus Statement emphasize the importance of individualizing glycemic goals.
Section Four

PREVENTING COMPLICATIONS
BY REGULATING BP
Today, 66% of all adults with diabetes and 40% of adults with newly diagnosed type 2 diabetes have hypertension. These rates are alarming because, as we have seen, hypertension is a major risk factor for macrovascular and microvascular complications.

Blood pressure reduction is a key preventive strategy for adults with type 2 diabetes, since it is associated with reduced rates of overall CV mortality, stroke, CAD events, and DKD.

Effective BP management includes lifestyle changes, including weight loss, adoption of the Dietary Approaches to Stop Hypertension (DASH) diet or similar eating pattern, reduction of alcohol consumption to no more than moderate levels, and increased physical activity. Most adults with type 2 diabetes and hypertension also require antihypertensive medication to achieve their BP goals.


The report of the Eighth Joint National Committee (JNC 8 Report) was published in February 2014 and sponsored by the National Heart, Lung, and Blood Institute (NHLBI). This is a comprehensive, evidence-based guideline for the management of hypertension in adults aged 18 years or older.

The JNC 8 Report includes 9 recommendations addressing thresholds and goals for BP treatment and the selection of antihypertensive drugs.

JNC 8 BP goals for the general population of adults younger than age 60 are systolic blood pressure (SBP) less than 140 mmHg and diastolic blood pressure (DBP) less than 90 mmHg. Goals for the general population of patients aged 60 years of age or older are SBP less than 150 mmHg and DBP less than 90 mmHg.

This table summarizes evidence-based JNC 8, ADA, and AACE BP recommendations for adults with diabetes. The BP targets advocated by both the JNC 8 Report and the ADA’s Standards of Medical Care in Diabetes—2015 are <140 mmHg for SBP and <90 mmHg for DBP. Note that the ADA’s 2015 DBP target is more lenient than the <80 mmHg target recommended in the 2014 Standards.

The ADA Standards include the suggestion that lower targets, such as SBP <130 mmHg and DBP <80 mmHg, may be appropriate for certain individuals, including younger patients, if they can be achieved without undue treatment burden.

The 2013 AACE Consensus Statement recommends an SBP target of about 130 mmHg and a DBP target of about 80 mmHg.
When implementing BP guidelines in clinical practice, it is important for providers to involve their patients in shared decision-making about the BP goals to be adopted, the lifestyle modifications to be initiated, and the antihypertensive agent or agents to be used (if warranted).

Patients receiving drug therapy for hypertension should be routinely assessed for medication adherence barriers, such as difficulty in paying for their medications or problematic side effects. It is important for any identified barriers to be addressed promptly.

Providers should consider an evaluation for secondary forms of hypertension if a patient’s BP remains uncontrolled despite confirmed adherence to adequate regimen.
Section Five

PREVENTING COMPLICATIONS THROUGH LIPID MANAGEMENT
Effective lipid management is essential for preventing the chronic complications of diabetes. Patients with type 2 diabetes have a high prevalence of lipid abnormalities, which contributes to their high risk for macrovascular complications. As we have seen, dyslipidemia is also a risk factor for microvascular complications.

For most patients with diabetes, as for the general population, lowering LDL-C levels with statin therapy is the most effective way to prevent atherosclerotic CVD (ASCVD) events.

It is also important to treat hypertriglyceridemia when it occurs because it a major risk factor for DPN and CAN. Elevated triglyceride levels can often be managed effectively by making lifestyle changes. In more severe cases, treatment with a fibric acid derivative, niacin, or fish oil is also warranted. Because hypertriglyceridemia can be caused by poor glycemic control, tightening glycemic control may reduce triglyceride levels.
The definitive statement on the treatment of elevated LDL-C levels is the “2013 ACC [American College of Cardiology]/AHA [American Heart Association] Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults.” This document was released in November 2012 and published in final form in 2014. The guideline differs from earlier lipid guidelines because the treatment goal is the intensity of statin treatment, not LDL-C or non-high-density lipoprotein cholesterol (HDL-C) targets.

The ACC/AHA guideline defines 4 groups in whom the potential of an ASCVD risk reduction benefit clearly exceeds the potential for AEs from statin therapy. For convenience, we have assigned a number to each group. Group 1 consists of individuals with clinical ASCVD, including some people with diabetes. Group 2 consists of individuals with primary LDL-C elevations ≥190 mg/dL. Some members of this group have diabetes. Group 3 consists of individuals 40 to 75 years of age with diabetes but without clinical ASCVD and with LDL-C levels from 70 to 189 mg/dL. Note that everyone in this group has diabetes. Group 4 consists of individuals without clinical ASCVD or diabetes who are 40 to 75 years of age, with LDL-C from 70 to 189 mg/dL and an estimated 10-year ASCVD risk of 7.5% or higher. Ten-year ASCVD risk can be determined using the AHA/ACC 2013 Prevention Guidelines Tools: CV Risk Calculator, which is available online and discussed on the next slide.


Risk calculators use mathematical models to predict the probability (expressed as a percentage) that an individual will develop CVD or have a CV event over the next 10 years or a lifetime.

Using a validated risk calculator is beneficial because it increases patients’ knowledge of their health status and their willingness to make lifestyle changes and adhere to their medication regimen. Using a risk calculator also reduces providers’ clinical inertia, making them more likely to address risk factors, recommend lifestyle changes, and prescribe appropriate medications.

For many years the Framingham Risk Calculator was the most widely used. However, it has largely been replaced by the ACC/AHA Risk Calculator, which can be used easily by both patients and providers and is available online at the web address shown below.

The ACC/AHA Risk Calculator predicts 10-year risk for adults aged 20 to 79 years and lifetime risk for adults aged 20 to 59 years. The degree of risk is determined after the patient or provider enters the following data: sex, age, race (African American or white/other), total cholesterol, HDL-C, SBP, treatment for high BP (yes/no), diabetes (yes/no), and smoking (yes/no).


The 2013 ACC/AHA Guideline makes specific recommendations for the intensity of statin therapy that various risk groups should receive. These recommendations have been incorporated into the ADA’s 2015 recommendations for statin treatment in people with diabetes. These recommendations are summarized in the table.

Note that the ADA categorizes patients in each of three age cohorts according to their risk status: CVD risk factors absent, CVD risk factors present, and overt CVD present. CVD risk factors include LDL-C ≥100 mg/dL, hypertension, smoking, and overweight and obesity. Overt CVD is manifested by a history of CV events or acute coronary syndromes.

Regarding lipid panel monitoring, the ADA recommends use of a screening lipid panel (total cholesterol, LDL-C, HDL-C, and triglycerides) at the time of first diagnosis of diabetes, at the initial medical evaluation, and/or at age 40 and then every 1 to 2 years thereafter. Once a patient is receiving a statin, testing for LDL-C may be considered on an individual basis to monitor adherence and efficacy. When patients are adherent but the LDL-C level is not responding to treatment, clinical judgment is recommended to determine the need for and timing of lipid panels.

This table shows options for moderate- or high-intensity statin therapy as defined in the 2013 ACC/AHA guideline.

Daily dosing with high-intensity statin therapy achieves an approximate average LDL-C reduction of at least 50%. High-intensity therapy consists of atorvastatin, 40 to 80 mg/day, and rosuvastatin, 20 to 40 mg/day.

Daily dosing with moderate-intensity statin therapy achieves an average LDL-C reduction of approximately 30% to less than 50%. Moderate-intensity therapy consists of atorvastatin, 5 to 10 mg/day; rosuvastatin, 5 to 10 mg/day; simvastatin, 20 to 40 mg/day; pravastatin, 40 to 80 mg/day; lovastatin, 40 mg/day; fluvastatin XL, 80 mg/day; fluvastatin, 40 mg/day; and pitavastatin, 2 to 4 mg/day.

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It is important for providers to remind their patients that intensive lifestyle management remains the cornerstone of lipid control. It is also important to involve patients in shared decision-making about the lipid management strategy to be adopted.

In addition to assessing patients’ adherence to lifestyle modification and medication and their therapeutic response to statin therapy, providers should regularly assess patients for safety issues. It is especially important to monitor statin-treated patients for muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or fatigue. Providers should also monitor their patients for development of a confusional state or memory impairment while on statin therapy.

If unacceptable side effects arise, clinicians should attempt to find a dose or alternative statin that is tolerable. There is evidence for significant LDL-C lowering even from extremely low, less than daily, statin doses.


The accurate statement is: __________

a. the JNC 8 Report advocates the same BP goals for all patients, regardless of their age and diabetes status
b. the ADA’s Standards of Medical Care in Diabetes—2015 recommend a SBP target of <140 mmHg and a DBP target of <80 mmHg
c. for most patients with diabetes, lowering LDL-C levels with statin therapy is the most effective way to prevent ASCVD events
d. the ADA currently recommends high-intensity statin therapy for all patients with diabetes who are 40 to 75 years old
Answer to Check Point 4

The correct answer is c.

For most patients with diabetes, lowering LDL-C levels with statin therapy is the most effective way to prevent ASCVD events.

The correct answer is c.

For most patients with diabetes, lowering LDL-C levels with statin therapy is the most effective way to prevent ASCVD events.
The major chronic complications of diabetes are macrovascular disease, DKD, neuropathy, and retinopathy.

Chronic diabetes complications are highly prevalent and impose a massive burden on individuals and society.

In patients with type 2 diabetes, major chronic complications can often be prevented by effectively managing hyperglycemia, hypertension, dyslipidemia, and other risk factors, such as obesity and smoking.

Patients with diabetes can reduce their risk for chronic complications and lessen the severity of complications that do develop by adhering to recommendations in evidence-based consensus guidelines dealing with BG control, BP regulation, and lipid management.