Reducing Chronic Complications of Diabetes

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Reducing Chronic Complications of Diabetes 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.

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The following program is a recorded presentation by Jerry Meece.

Jerry Meece is owner and Director of Clinical Services of Plaza Pharmacy and Wellness Center in Gainesville, Texas, one of the first freestanding pharmacies in the country to achieve Provider Education Recognition from the American Diabetes Association.

In addition to serving on numerous consultant and advisory boards for health care and pharmaceutical companies, he has served on the Board of Directors for the American Association of Diabetes Educators and was elected to their Executive Board in the position of Vice President.

Mr. Meece speaks both nationally and internationally on the subject of diabetes, and clinician/patient behavior in the health care setting. He has also written many articles on diabetes care and insulin use in the patient with diabetes.

Mr. Meece has won many awards including the Innovative Practice Award by the Texas Pharmacy Association, the Legislative Leadership Award by the American Association of Diabetes Educators, and the Individual Educational Excellence Award by the Texas Pharmacy Association.

We will now join Mr. Meece.

PROGRAM OBJECTIVES

- Describe key findings of clinical outcome studies that have investigated the relationship between the control of blood glucose levels, blood pressure, serum lipids, and/or other major risk factors and the development of microvascular and macrovascular complications of diabetes
- Discuss the epidemiology and impact of major macrovascular and microvascular complications of diabetes
- State current recommendations for screening patients for and managing patients with major macrovascular and microvascular complications of diabetes

The objectives for this knowledge-based program are:

- Describe key findings of clinical outcome studies that have investigated the relationship between the control of blood glucose levels, blood pressure, serum lipids, and/or other major risk factors and the development of microvascular and macrovascular complications of diabetes
- Discuss the epidemiology and impact of major macrovascular and microvascular complications of diabetes
- State current recommendations for screening patients for and managing patients with major macrovascular and microvascular complications of diabetes

MAJOR CHRONIC COMPLICATIONS

- Macrovascular
  - Coronary artery disease (CAD)*
  - Cerebrovascular disease
  - Peripheral arterial disease (PAD)†
- Microvascular
  - Diabetic kidney disease (DKD)‡
  - Retinopathy
  - Neuropathy

*Also called coronary heart disease (CHD). †Also called peripheral vascular disease (PVD). ‡Also called nephropathy.

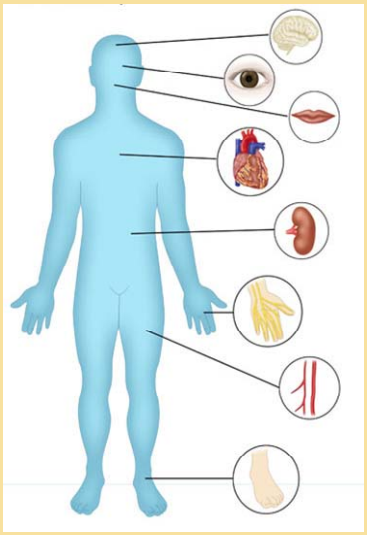


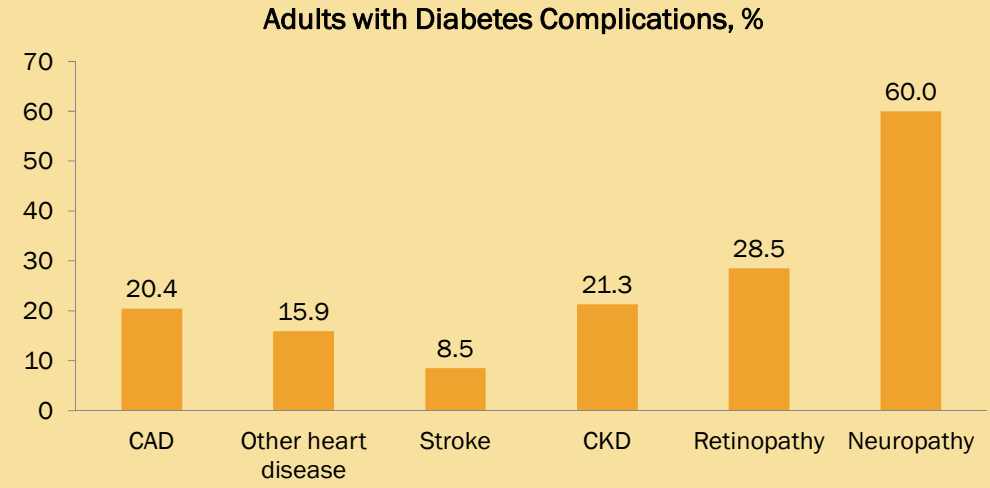
Figure: Diabetes Teaching Center, University of California San Francisco. Used with permission. Abbate. *The Art and Science of Diabetes Self-Management Education Desk Reference*. 2011.

The major chronic complications of diabetes are caused by damage to the endothelial cells lining the blood vessels. Chronic complications are divided into macrovascular and microvascular complications, 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; cerebrovascular disease; and peripheral arterial disease (PAD). Individuals with PAD have poor circulation in the lower extremities. Although this condition is sometimes called “peripheral vascular disease” (PVD), PAD is the more accurate term, since the arteries rather than the veins are primarily affected.

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

PREVALENCE OF COMPLICATIONS



CKD = chronic kidney disease.

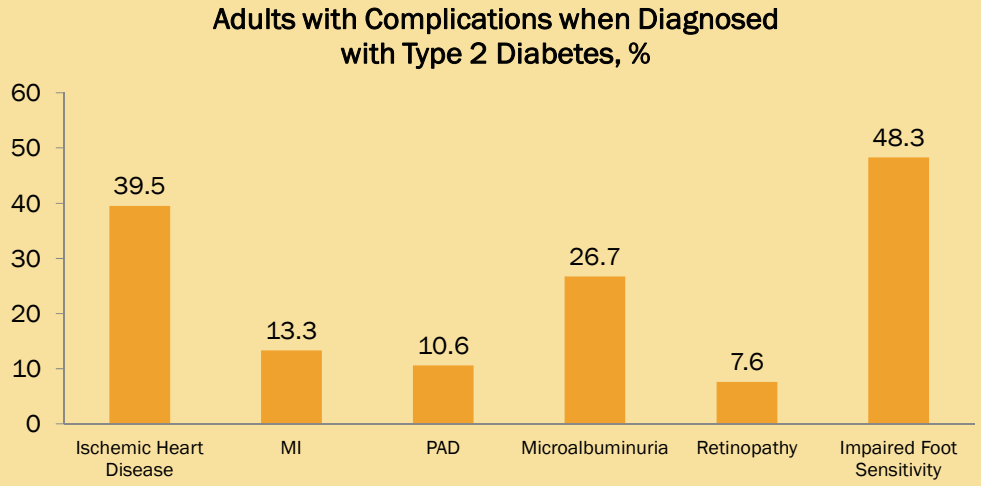
CDC. Diabetes Data & Trends. 2012.
CDC. *National Diabetes Fact Sheet, 2011*. 2011.
US Renal Data System. *Annual Data Report*. 2011.

This graph presents data compiled by the Centers for Disease Control and Prevention (CDC) and the US Renal Data System (USRDS) on the prevalence of macrovascular and microvascular complications in US adults with diabetes.

With regard to macrovascular complications, 20.4% of adults with diabetes have CAD, 15.9% have another type of heart disease, and 8.5% have a history of stroke.

With respect to microvascular complications, 21.3% of adults with diabetes have chronic kidney disease (CKD), one of the manifestations of DKD; 28.5% have retinopathy; and 60% have neuropathy.

COMPLICATIONS AT DIAGNOSIS



MI = myocardial infarction.

Spijkerman. *Diabetes Care*. 2003. Spijkerman. *J Intern Med*. 2004.

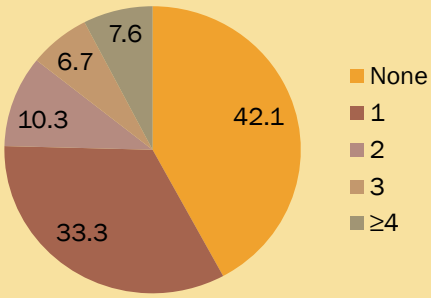
Because many patients with type 2 diabetes have diabetes for many years before their diagnosis, a substantial proportion have already developed chronic macrovascular and microvascular complications by the time they are diagnosed.

In the Hoorn Screening Study, which was conducted in the Netherlands, 39.5% of participants already had ischemic heart disease, 13.3% had a history of myocardial infarction (MI), and 10.6% had PAD at diagnosis. With regard to microvascular complications, 26.7% had microalbuminuria, an early manifestation of DKD, 7.6% had retinopathy, and 48.3% had impaired foot sensitivity, an early manifestation of neuropathy.

Since type 1 diabetes generally has a readily recognizable onset and is usually diagnosed promptly, chronic complications typically begin to emerge about 5 years after diagnosis. As we will discuss later, this disparity in the development of complications is reflected in some differences in American Diabetes Association (ADA) screening recommendations for people with type 1 and type 2 diabetes.

MULTIPLE COMPLICATIONS

Survey Respondents With Type 2 Diabetes by Number of Complications, %



- 57.9% of US adults with type 2 diabetes have ≥1 complication; 24.6% have ≥2 complications
- Complications surveyed were MI, stroke, CAD, congestive heart failure, chest pain, CKD, eye damage, and foot problems

American Association of Clinical Endocrinologists. *State of Diabetes Complications in America*. 2007.

The *State of Diabetes Complications in America,* an overview of major diabetes complications in US residents with type 2 diabetes, synthesized data from 2 large national surveys. Complications surveyed were MI, stroke, CAD, congestive heart failure, chest pain, CKD, eye damage, and foot problems that can lead to amputation.

Nearly 60% of respondents had at least 1 complication, and nearly 25% had 2 or more complications.

IMPACT OF MACROVASCULAR COMPLICATIONS

- Heart disease
  - Noted on 68% of diabetes-related death certificates among people ≥65 years old
  - ~2- to 4-fold increase in heart disease death with diabetes
- Stroke
  - Noted on 16% of diabetes-related death certificates among people ≥65 years old
  - 2- to 4-fold increase in risk for stroke with diabetes
- PAD
  - Risk factor for lower-limb amputation
  - >60% of nontraumatic lower-limb amputations are performed in people with diabetes

CDC. *National Diabetes Fact Sheet, 2011*. 2011.

Data compiled by the CDC show that macrovascular complications are major contributors to morbidity and mortality in US residents with diabetes. Heart disease is noted on 68% of diabetes-related death certificates among people aged 65 years or older. Furthermore, adults with diabetes have heart disease death rates that are about 2 to 4 times higher than those of adults without diabetes.

Stroke is noted on 16% of diabetes-related death certificates among people who are at least 65 years old. Compared to those without diabetes, adults with diabetes have a 2- to 4-fold increase in the risk for stroke.

PAD is a risk factor for lower-limb amputation, and more than 60% of nontraumatic lower-limb amputations are performed in people with diabetes.

IMPACT OF MICROVASCULAR COMPLICATIONS

- DKD
  - Leading cause of kidney failure (43.8% of new cases)
- Retinopathy
  - Chief cause of new cases of blindness in adults aged 20–74 years
- Neuropathy
  - Causes impaired sensation in feet or hands, slowed digestion of food in stomach, carpal tunnel syndrome, and many other conditions
  - Severe forms are a major cause of lower-extremity amputations

US Renal Data System. *Annual Data Report*. 2011.
CDC. *National Diabetes Fact Sheet, 2011*. 2011.
CDC. Diabetes Data & Trends. 2012.

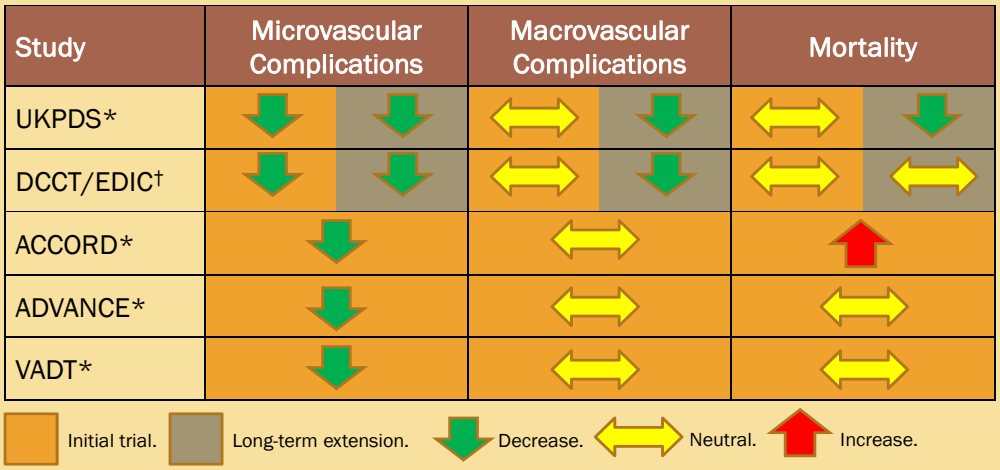
Data from the CDC and the USRDS also show the detrimental impact of microvascular complications on the health of US adults with diabetes.

DKD is the leading cause of kidney failure, accounting for about 44% of new cases.

Diabetic retinopathy is the chief cause of new cases of blindness in people aged 20 to 74 years.

Diabetic neuropathy causes impaired sensation in the feet or hands, slowed digestion of food in the stomach, carpal tunnel syndrome, and many other conditions. Severe forms are a major cause of lower-extremity amputations. In 2009, approximately 68,000 lower-extremity amputations were performed in people with diabetes.

EFFECTS OF INTENSIVE GLUCOSE-LOWERING THERAPY



*In type 2 diabetes. †In type 1 diabetes.
ACCORD = Action to Control Cardiovascular Risk in Diabetes; ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; DCCT/EDIC = Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications; UKPDS = UK Prospective Diabetes Study; VADT = Veterans Affairs Diabetes Trial.

Inzucchi. *Diabetes Care*. 2012. Adapted from Slide 10.

This table is taken from the slide set that accompanies the 2012 position statement of the ADA and the European Association for the Study of Diabetes (EASD) on the management of hyperglycemia in type 2 diabetes. It summarizes the effects of bringing the A1C to near-normal levels using intensive glucose-lowering therapy on rates of microvascular complications, macrovascular complications, and death in 5 large diabetes outcome trials. All of the trials were conducted in patients with type 2 diabetes except for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (DCCT/EDIC), which enrolled patients with type 1 diabetes.

The studies consistently showed that intensive glycemic control reduces the frequency of microvascular complications. The picture was less clear for cardiovascular disease (CVD). In the overall study populations, intensive control had a neutral effect during the initial phase of the trials and a beneficial effect during the long-term extensions of both studies that had them. Some subgroup analyses suggested that intensive control improved cardiovascular outcomes in participants who were recently diagnosed with diabetes and had relatively few complications, but not in participants with a greater disease burden. Intensive therapy also had mixed effects on overall mortality. In the overall study populations, intensive treatment significantly decreased mortality only in the long-term extension of the UK Prospective Diabetes Study (UKPDS) and significantly increased mortality only in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. As with cardiovascular outcomes, however, some subgroup analyses revealed a mortality advantage in patients with more recently diagnosed diabetes and a lower disease burden.

LESSONS FROM MAJOR OUTCOME TRIALS

- Glycemic targets and glucose-lowering therapies must be individualized
- All treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs, and values
- Comprehensive cardiovascular risk reduction must be a major focus of therapy

Inzucchi. *Diabetes Care*. 2012.

Based on their review of evidence from major outcome trials, the members of the ADA/EASD task force concluded that glycemic targets and glucose-lowering therapies must be individualized for patients with type 2 diabetes.

Furthermore, all treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs, and values. In a shared decision-making approach, the clinician and patient act as partners, mutually exchanging information and deliberating on options, in order to reach consensus on the therapeutic course of action.

Because CVD is the main cause of morbidity and mortality in individuals with diabetes, comprehensive cardiovascular risk reduction must be a major focus of therapy.

Note that these recommendations apply specifically to patients with type 2 diabetes. However, the emphasis on the individualization of treatment and the importance of addressing cardiovascular risk factors is consistent with the guidelines contained in the 2012 ADA Standards of Medical Care in Diabetes, which apply to patients with type 1, type 2, and other kinds of diabetes.

INDIVIDUALIZING GLYCEMIC TARGETS

- ADA targets for many people with diabetes
  - A1C: <7.0% (mean PG ~150–160 mg/dL)
  - Preprandial PG: 70–130 mg/dL
  - Postprandial PG: <180 mg/dL
- Individualization stressed by ADA/EASD position statement
  - Tighter targets (6.0% to 6.5%) – younger, healthier patients
  - Looser targets (7.5% to 8.0%+) – older patients, with comorbidities, prone to hypoglycemia
  - Avoidance of hypoglycemia is critical

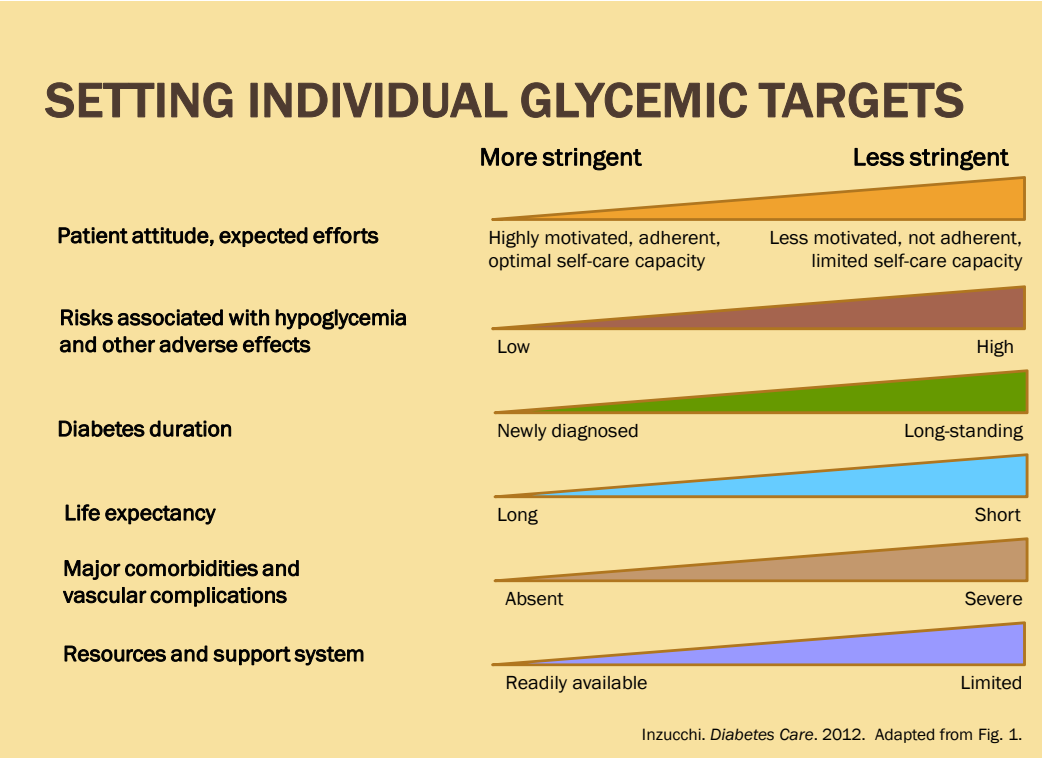
PG = plasma glucose.

ADA. *Diabetes Care*. 2012.
Inzucchi. *Diabetes Care*. 2012.

Currently, the ADA recommends that many people with diabetes try to achieve and maintain an A1C of less than 7%. This translates to a mean plasma glucose (PG) value of approximately 150 to 160 mg/dL. The ADA also recommends that most individuals strive for preprandial PG values in the range of 70 to 130 mg/dL and peak postprandial PG values of less than 180 mg/dL.

As just mentioned, the 2012 ADA/EASD position statement emphasizes the importance of individualizing glycemic targets. Tighter A1C targets, such as from 6.0% to 6.5%, might be appropriate for many younger, healthier patients. However, looser targets, such as from 7.5% to 8.0% or even higher, might be appropriate for older patients with comorbidities and for individuals who are prone to hypoglycemia.

The statement stresses the importance of avoiding hypoglycemia, since it is associated with confusion, falls and other accidents, work disability, reluctance to live independently, infection, dysrhythmias, and death.



The ADA/EASD task force identified several factors that can guide clinicians in deciding whether an individual patient should be encouraged to strive for the general A1C target of <7%, an even more stringent value, or a more relaxed value. Factors that should guide treatment goals include the patient's attitude toward diabetes and expected efforts, individual risks associated with hypoglycemia and other adverse effects, diabetes duration, life expectancy, the presence of major comorbidities and vascular complications, and the patient's resources and support system.

Patient characteristics associated with tighter glycemic targets are: high motivation, consistent adherence, and optimal self-care capacity; low risks associated with hypoglycemia and other adverse events; newly diagnosed diabetes; a long life expectancy; the absence of major comorbidities and vascular complications; readily available resources; and a strong support system. Conversely, characteristics associated with more relaxed targets are: lower motivation, lack of adherence, and limited self-care capacity; high risks associated with hypoglycemia and other adverse events; long-standing diabetes; a short life expectancy; the presence of major comorbidities and vascular complications; limited resources; and a limited support system.

CHECK POINT 1

The correct statement is: _____.

a. about 10% of patients have a chronic complication of diabetes by the time they are diagnosed with type 2 diabetes
b. compared to people without diabetes, people with diabetes have at least a 2-fold increase in the risk of heart disease death
c. major clinical trials have consistently shown that intensive glucose-lowering therapy reduces the risk of macrovascular complications in people with diabetes
d. the 2012 ADA/EASD position statement on hyperglycemia management emphasizes that all patients with type 2 diabetes should strive for an A1C target of <7%

The correct statement is: _____.

a. about 10% of patients have a chronic complication of diabetes by the time they are diagnosed with type 2 diabetes

b. compared to people without diabetes, people with diabetes have at least a 2-fold increase in the risk of heart disease death

c. major clinical trials have consistently shown that intensive glucose-lowering therapy reduces the risk of macrovascular complications in people with diabetes

d. the 2012 ADA/EASD position statement on hyperglycemia management emphasizes that all patients with type 2 diabetes should strive for an A1C target of <7%

ANSWER TO CHECK POINT 1

The correct answer is b.

Compared to people without diabetes, people with diabetes have at least a 2-fold increase in the risk of heart disease death.

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MACROVASCULAR COMPLICATIONS

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- CAD
  - Atherosclerosis
  - Angina
  - MI
- PAD
  - Ischemia
  - Infarction
- Cerebrovascular disease
  - Transient ischemic attack
  - Ischemic stroke
    - Cerebral thrombosis
    - Cerebral occlusion
  - Hemorrhagic stroke
    - Aneurysm
    - Arteriovenous malformation

Shen. *Type 2 Diabetes: Principles and Practice*. 2008.

As previously mentioned, the macrovascular complications of diabetes are CAD, cerebrovascular disease, and PAD. Extensive atherosclerosis is common in individuals with diabetes. In addition to conventional risk factors such as hypertension and hypercholesterolemia, endothelial dysfunction, increased platelet activation and aggregation, coagulation abnormalities, and abnormal plaque composition contribute to atherosclerosis progression. The coronary artery blockage that occurs in CAD can lead to the acute coronary syndrome (ACS), a constellation of symptoms caused by myocardial ischemia. The components of ACS are angina, consisting of chest pain that occurs with exertion, unstable angina, consisting of chest pain that occurs during periods of rest, and MI, which results from coronary thrombosis or occlusion.

When vessels supplying the brain become blocked, transient ischemic attack (TIA) or ischemic stroke can occur. The more severe event is ischemic stroke, which results from cerebral thrombosis or occlusion. The other major type of stroke is hemorrhagic stroke, which is caused by rupture of an aneurysm or arteriovenous malformation.

In individuals with PAD, blockage of vessels supplying the lower extremities can cause ischemia and infarction. The classic symptom of PAD is intermittent claudication, which manifests as pain, cramping, or aching in the calves, thighs, or buttocks that recurs with walking and is relieved by rest. Patients with severe PAD may experience ischemic pain at rest, tissue loss, or gangrene.

CVD SCREENING

- Assess for CV risk factors at least annually
  - Dyslipidemia
  - Hypertension
  - Smoking
  - Family history of premature coronary disease
  - Presence of microalbuminuria or macroalbuminuria
- CAD screening
  - Not recommended for asymptomatic patients
  - Individuals with typical/atypical cardiac symptoms or an abnormal resting ECG are candidates for cardiac testing

CV = cardiovascular; ECG = electrocardiogram.

ADA. *Diabetes Care.* 2012.

All patients with diabetes should have a cardiovascular risk assessment at least annually. Risk factors include dyslipidemia, hypertension, smoking, a positive family history of premature coronary disease, and the presence of microalbuminuria or macroalbuminuria. Modifiable risk factors should be treated according to current standards of care.

The ADA advises against the routine screening of asymptomatic patients for CAD. The rationale for this recommendation is that CAD screening does not improve outcomes as long as CVD risk factors are treated. Although newer noninvasive CAD screening methods, such as computed tomography (CT) and CT angiography, have become increasingly popular, their routine use leads to radiation exposure and may result in unnecessary invasive testing such as coronary angiography and revascularization procedures. Candidates for cardiac testing include individuals with typical or atypical cardiac symptoms and an abnormal resting electrocardiogram (ECG.)

PAD SCREENING

- Take claudication history and assess pedal pulses during initial screening
- Screening ABI
  - Perform in all patients with diabetes who are >50 years old; if normal, repeat every 5 years
  - Perform in patients ≤50 years old with PAD risk factors (smoking, hypertension, hyperlipidemia, diabetes for >10 years)
- Perform diagnostic ABI in patients with PAD symptoms
- Refer patients with significant claudication or positive ABI for further vascular assessment
- Consider exercise, drug therapy, and/or surgical options based on assessment findings

ABI = ankle brachial index.

ADA. *Diabetes Care*. 2012.
ADA. *Diabetes Care*. 2003.

The ADA recommends that the initial screening for PAD include a claudication history and an assessment of the pedal pulses. Since many people with PAD are asymptomatic, a screening ankle brachial index (ABI) should be performed in patients above the age of 50. A screening ABI should also be performed in younger patients with PAD risk factors, including smoking, hypertension, hyperlipidemia, and a greater than 10-year history of diabetes. A diagnostic ABI should be performed in patients with symptoms of PAD.

The ABI is a ratio of systolic blood pressure (SBP) at the ankle and brachial artery. The ABI is determined by placing the blood pressure (BP) cuff just above the ankle and inflating to above the patient's SBP. A handheld Doppler device is used to detect the systolic pulse in the dorsalis pedis and posterior tibial arteries as the cuff is deflated. Pressures are obtained in both ankles and divided by the brachial (arm) systolic pressure. An ABI of 0.91 to 1.30 is normal; 0.7 to 0.9 indicates mild obstruction; 0.4 to 0.7 indicates moderate obstruction, and less than 0.4 indicates severe obstruction. Patients with significant claudication or a positive ABI should be referred for further vascular assessment. Treatment options for PAD include exercise, drug therapy, and surgery. A 2003 ADA consensus statement provides detailed information about the diagnosis and management of PAD in people with diabetes.

IMPACT OF HYPERTENSION

- Hypertension criteria (mmHg)
  - ≥130/80 in people with diabetes
  - ≥140/90 in those without diabetes
- >75% of adults with diabetes have BP levels ≥130/80 mmHg or are using antihypertensive medication
- In type 1 diabetes, hypertension often results from underlying nephropathy
- In type 2 diabetes, hypertension usually coexists with other cardiometabolic risk factors and is present at diagnosis

BP = blood pressure.

ADA. *Diabetes Care*. 2012.
Bakris. *J Clin Hypertens (Greenwich)*. 2008.

Because of the clear synergistic risks of hypertension and diabetes, the diagnostic cutoff for a diagnosis of hypertension is lower in people with diabetes (BP ≥130/80 mmHg) than in those without diabetes (BP ≥140/90 mmHg).

More than 75% of adults with diabetes have BP levels of at least 130/80 mmHg or are using antihypertensive medication. In type 1 diabetes, hypertension often results from underlying nephropathy. In type 2 diabetes, hypertension usually coexists with other cardiometabolic risk factors and is present at the time of diagnosis.

IMPORTANCE OF BP CONTROL

- Dangers of uncontrolled hypertension
  - Major risk factor for CVD and microvascular complications
  - Hypertension increases mortality >7-fold
- Benefits of BP control
  - 33–50% reduction in CVD and stroke risk
  - 33% reduction in risk for microvascular complications
  - For every 10 mmHg SBP reduction, the risk for any diabetes-related complication decreases by 12%
  - Reducing DBP from 90 to 80 mmHg reduces the risk of major cardiovascular events by 50%

CVD = cardiovascular disease;
DBP = diastolic blood pressure;
SBP = systolic blood pressure.

ADA. *Diabetes Care*. 2012.
Bakris. *J Clin Hypertens (Greenwich)*. 2008.
CDC. *National Diabetes Fact Sheet, 2011*. 2011.

Hypertension is a major risk factor for both CVD and microvascular complications. There is a greater than 7-fold increase in mortality when hypertension is present in adults with diabetes.

According to the CDC, controlling BP has important benefits for people with diabetes. Effective BP regulation reduces the risk for CVD and stroke by 33% to 50% and reduces the risk for microvascular complications by 33%. In general, for every 10 mmHg reduction in SBP, the risk for any complication related to diabetes is reduced by 12%. Reducing diastolic BP (DBP) from 90 mmHg to 80 mmHg in people with diabetes reduces the risk of major cardiovascular events by 50%.

ADA BP TARGETS

- SBP
  - Target of <130 mmHg is appropriate for most patients
  - More or less stringent targets may be appropriate for some individuals
  - ACCORD 1-year data do not support routine use of intensive management to a target of <120 mmHg
- DBP
  - Patients should be treated to <80 mmHg

ADA. *Diabetes Care*. 2012.
ACCORD Study Group. *N Engl J Med*. 2010.

BP reduction efforts typically emphasize control of SBP rather than DBP because controlling SBP is often more difficult. Furthermore, elevated SBP is a more important CVD risk factor for most patients.

According to the ADA, a SBP goal of less than 130 mmHg is appropriate for most patients with diabetes. Targets more or less stringent than <130 mmHg may be appropriate for some patients based on their response to therapy, medication tolerance, and individual characteristics. However, most analyses have suggested that outcomes are worse if the SBP exceeds 140 mmHg. One-year data from the ACCORD trial do not support the routine use of intensive management to a SBP target of less than 120 mmHg.

The ADA recommends that patients with diabetes be treated to a DBP target of less than 80 mmHg.

MANAGING HYPERTENSION: LIFESTYLE CHANGES

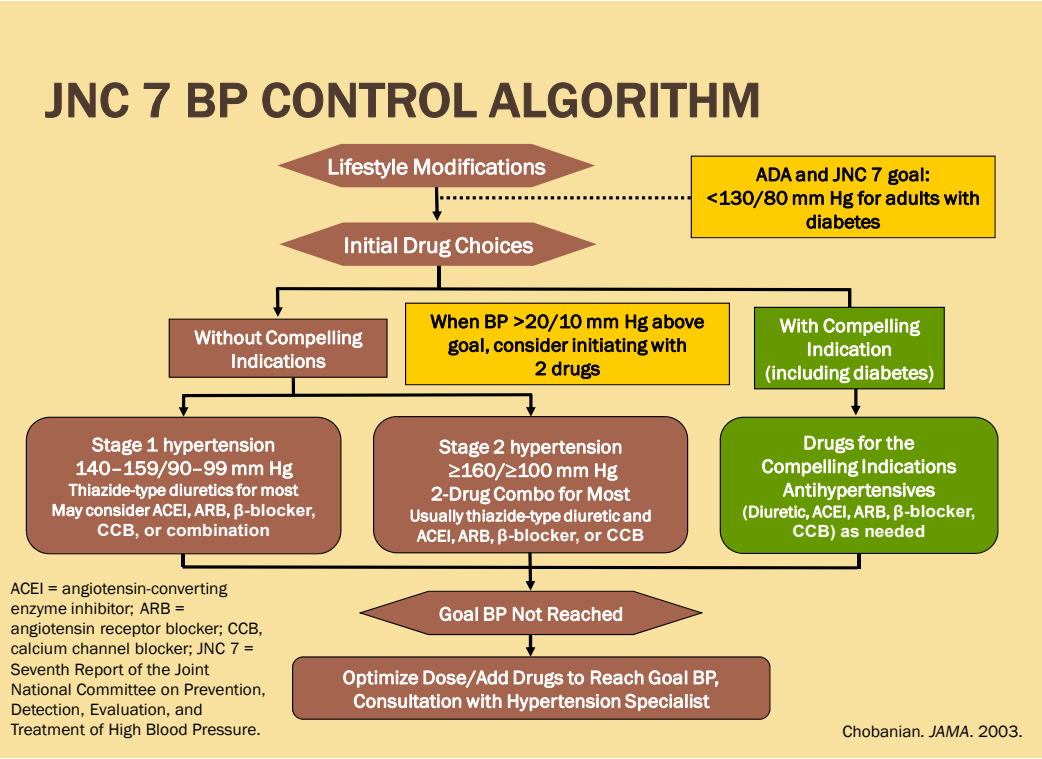
Change	Recommendation	Approximate SBP ↓, mmHg
Lose weight	Maintain normal body weight (BMI, 18.5–24.9 kg/m^2)	5–20 per 10-kg weight loss
Adopt DASH eating plan	Consume diet rich in fruits, vegetables, and low-fat dairy products with reduced saturated and total fat content	8–14
Reduce dietary sodium	Lower dietary sodium intake to ≤100 mEq/L (2.4 g sodium or 6 g sodium chloride)	2–8
Become physically active	Engage in regular aerobic physical activity (≥30 min/day, most days of week)	4–9
Moderate alcohol consumption	Limit intake to ≤2 drinks/day in most men and ≤1 drink/day in women and lighter-weight persons	2–4

BMI = body mass index;
DASH = Dietary Approaches to Stop Hypertension.

Chobanian. *JAMA*. 2003.

For more than 30 years, the National Heart, Lung, and Blood Institute (NHLBI) has administered the National High Blood Pressure Education Program Coordinating Committee, a coalition of professional, public, and voluntary organizations, as well as federal agencies. One of the committee's responsibilities is to periodically issue a Joint National Committee report on the prevention, detection, evaluation, and treatment of high blood pressure. The seventh of these reports, called "JNC 7," was issued in 2003. "JNC 8" was being finalized when this activity on the complications of diabetes was completed in the summer of 2012.

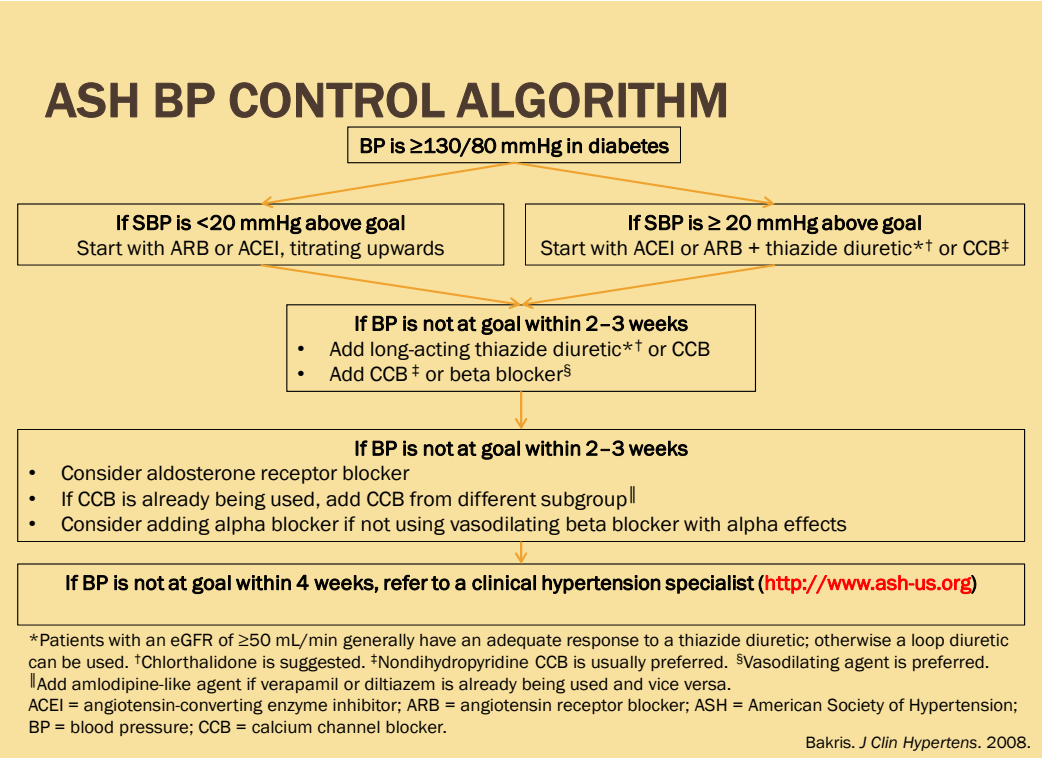
According to the JNC, adoption of healthy lifestyles is an indispensable part of the management of people with hypertension, including individuals with diabetes. As the slide shows, major lifestyle modifications proven to lower BP include: weight reduction in individuals who are overweight or obese; adoption of the Dietary Approaches to Stop Hypertension (DASH) eating plan, which is rich in potassium and calcium; dietary sodium reduction; physical activity; and moderation of alcohol consumption. These lifestyle modifications decrease BP, enhance antihypertensive drug efficacy, and decrease cardiovascular risk. For example, following a DASH eating plan that contains 1600 mg of sodium per day has effects similar to those of single-drug therapy. Combinations of 2 or more lifestyle modifications can achieve more robust results.



This slide shows the JNC 7 algorithm for controlling BP. Note especially the cells shaded in green, which pertain to high-risk conditions with compelling indications for antihypertensive drugs. Patients with diabetes, heart failure, a history of MI, high coronary disease risk, CKD, or a history of stroke are considered to have compelling indications.

According to JNC 7, drug therapy options for the management of hypertension in diabetes include diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta blockers, and calcium channel blockers.

Consultation with a cardiologist with expertise in the management of hypertension is recommended for patients who do not attain their BP goals after receiving optimal doses of at least 2 antihypertensive agents.



This slide shows the American Society of Hypertension (ASH) treatment algorithm for individuals with diabetes whose BP exceeds the goal of less than 130/80 mmHg. The algorithm emphasizes the use of ACE inhibitors, ARBs, and calcium channel blockers because these agents have beneficial or neutral effects on insulin sensitivity and glycemic control.

Other underlying considerations are that proteinuria is associated with increased cardiovascular event rates and that proteinuria reduction of more than 30% within the first 6 to 12 months of antihypertensive therapy reduces the incidence of cardiovascular events and heart failure and delays the progression of kidney disease. Therefore, antihypertensive therapy for persons with diabetes should focus both on achieving the BP goal and on reducing proteinuria, if present. To achieve these ends, the algorithm emphasizes the use of ACE inhibitors or ARBs, either alone or combined with a nondihydropyridine calcium channel blocker (verapamil or diltiazem). Whether an ACE inhibitor or an ARB is chosen for initial therapy, the dosage should be titrated to the highest tolerated level needed to reach the BP goal. If an ACE inhibitor is started and the adverse event of cough appears, ARB therapy should be substituted.

Because both ACE inhibitors and ARBs are in Pregnancy Category C during the first trimester and in Pregnancy Category D during the second and third trimesters of pregnancy, they should not be used by pregnant women or women who may become pregnant. (Recall that Category C includes drugs whose benefits may outweigh their risks despite adverse fetal effects in animals and a lack of adequate, well-controlled studies in humans OR a lack of animal studies or adequate, well-controlled human studies. Category D includes drugs whose benefits may outweigh their risks despite evidence of fetal risk based on human studies and/or adverse reaction reports that document fetal risk. In contrast, Category X includes drugs whose risks outweigh their benefits and are therefore contraindicated during pregnancy.)

The health care provider should refer a patient who has an inadequate response to the recommended agents within the specified timeframe to a clinical hypertension specialist. ASH maintains a specialist directory at its website (http://www.ash-us.org).

ADA ANTIHYPERTENSIVE THERAPY GUIDELINES

- Regimen should include either an ACE inhibitor or an ARB
- Multiple drug therapy (≥2 agents at maximal doses) is generally required to achieve BP targets
- Administer ≥1 antihypertensive medication at bedtime
- Monitor kidney function and serum potassium levels if ACE inhibitor, ARB, or diuretic is used

ADA. *Diabetes Care*. 2012.

The ADA recommends that the antihypertensive drug regimen for a patient with diabetes and hypertension include a renin-angiotensin system (RAS) inhibitor—either an ACE inhibitor or an ARB. In a clinical trial of high-risk individuals, including a large subset with diabetes, an ACE inhibitor reduced CVD outcomes. In patients with congestive heart failure (CHF), including subgroups of patients with diabetes, ARBs have reduced major CVD outcomes.

Multiple drug therapy, consisting of 2 or more agents at maximal doses, is generally required to achieve BP targets. The calcium channel blocker amlodipine or a thiazide diuretic (hydrochlorothiazide or chlorthalidone) can be added if needed to achieve BP targets. Patients whose estimated glomerular filtration rate (eGFR) is less than 30 $mL/min/m^2$ should receive a loop diuretic rather than a thiazide diuretic. Titration of and/or addition of further BP medications should be made in a timely fashion to overcome clinical inertia in achieving BP targets.

One or more antihypertensive medications should be administered at bedtime. The basis for this recommendation is 5-year data from a randomized clinical trial showing that administration of at least one BP-lowering agent at bedtime reduced cardiovascular events and mortality in patients with type 2 diabetes and hypertension.

Kidney function and serum potassium levels should be monitored if ACE inhibitors, ARBs, or diuretics are administered.

IMPACT OF DYSLIPIDEMIA

- Occurs in >95% of people with diabetes
- High triglyceride and low HDL-C concentrations is the most common pattern in diabetes
- LDL-C concentrations are similar in people with and without diabetes, but people with diabetes have a higher proportion of smaller, denser, more atherogenic particles, making elevated LDL-C more dangerous

HDL-C = high-density lipoprotein cholesterol;
LDL-C = low-density lipoprotein cholesterol.

Lorber. *The Art and Science of Diabetes Self-Management Education Desk Reference*. 2011.

Dyslipidemia occurs in more than 95% of people with diabetes. The most common pattern of dyslipidemia in diabetes is the combination of high triglyceride and low HDL cholesterol (HDL-C) concentrations.

LDL cholesterol (LDL-C) concentrations are similar in people with and without diabetes, but people with diabetes have a higher proportion of smaller, denser, more atherogenic particles, making elevated LDL-C levels more dangerous for them.

IMPORTANCE OF LIPID CONTROL

- Dangers of dyslipidemia
  - Each major lipoprotein abnormality of diabetes is a CVD risk factor
- Benefits of lipid control
  - Treatments that lower LDL-C and triglycerides or raise HDL-C reduce macrovascular events and mortality in the overall at-risk population and in people with diabetes
  - Benefits of LDL-C reduction have been most thoroughly studied
    - Improved LDL-C control can reduce cardiovascular complications by 20% to 50%

Lorber. *The Art and Science of Diabetes Self-Management Education Desk Reference*. 2011. ADA. *Diabetes Care*. 2012. CDC. *National Diabetes Fact Sheet, 2011*. 2011. Jellinger. *Endocr Pract*. 2012.

Achieving and maintaining lipid control is important for preventing macrovascular complications. Each of the major lipoprotein abnormalities of diabetes—high LDL-C and triglyceride concentrations and low HDL-C concentrations—are risk factors for CVD.

Treatments that lower LDL-C and triglyceride concentrations or raise HDL-C concentrations can reduce macrovascular events and mortality in the overall at-risk population and in people with diabetes. Currently, the benefits of LDL-C reduction have been more thoroughly studied and quantified than the benefits of controlling the levels of other lipids. According to data gathered by the CDC, increased LDL-C control can reduce cardiovascular complications by 20% to 50%.

ADA LIPID TARGETS

Parameter	Target, mg/dL
LDL-C	
Without overt CVD	<100
With overt CVD	<70
HDL-C	
Men	>40
Women	>50
Triglycerides	<150

- Most adults with diabetes should have their fasting lipid profile measured at least annually.
- Lipid assessments may be repeated every 2 years for adults with low-risk profiles (LDL-C <100 mg/dL, HDL-C >50 mg/dL, and triglycerides <150 mg/dL).

ADA. *Diabetes Care*. 2012.

The ADA recommends LDL-C targets of less than 100 mg/dL for people without overt CVD and less than 70 mg/dL for people with overt CVD. HDL-C targets are greater than 40 mg/dL for men and greater than 50 mg/dL for women. The triglyceride target is less than 150 mg/dL. Most adults with diabetes should have their fasting lipid profile measured at least annually. Lipid assessments may be repeated every 2 years for adults with low-risk profiles (LDL-C <100 mg/dL, HDL-C >50 mg/dL, and triglycerides <150 mg/dL).

When this activity on the complications of diabetes was completed in the summer of 2012, another major set of guidelines on dyslipidemia management was being finalized. These guidelines will be presented in the Fourth Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel IV), which is commonly referred to as ATP IV. When it is issued, ATP IV will replace the ATP III guidelines that were released in 2001.

LIFESTYLE MODIFICATION FOR LIPID CONTROL

- Individualized MNT
  - Reduction of saturated fat, cholesterol, and *trans* unsaturated fat intake
  - Increases in n-3 fatty acids, viscous fiber, and plant stanols/sterols
- Increased physical activity
- Weight loss
- Smoking cessation
- More stringent glycemic control (especially for patients with elevated triglycerides and high A1C levels)

MNT = medical nutrition therapy.

ADA. *Diabetes Care*. 2012.

Lifestyle modification alone may enable some patients with diabetes to reach their lipid targets. Medical nutrition therapy should be individualized based on the patient's age, type of diabetes, drug therapy, lipid levels, and other medical conditions. It should focus on the reduction of saturated fat, cholesterol, and *trans* unsaturated fat intake. It should also emphasize increases in n-3 fatty acids, viscous fiber (such as found in oats and legumes), and plant stanols and sterols. (Recall that plant stanols and sterols are substances that limit cholesterol absorption. They occur naturally in some nuts and seeds and are also found in some commercial margarines, such as Benecol® and Take Control®.)

Other beneficial lifestyle interventions are increased physical activity, weight loss for patients who are overweight or obese, and smoking cessation. More stringent glycemic control can also improve plasma sterol levels, particularly in patients with elevated triglyceride concentrations and high A1C levels.

DRUG THERAPY FOR LIPID CONTROL

- Add statin therapy to lifestyle modification, regardless of baseline lipid levels, for patients
  - With overt CVD
  - Without overt CVD who are over age 40 and have ≥1 other CVD risk factor(s)
- Consider statin therapy in addition to lifestyle modification for patients without overt CVD and under age 40 who have
  - An LDL-C concentration that remains >100 mg/dL
  - Multiple CVD risk factors
- Use LDL-C reduction of ~30–40% from baseline as an alternate goal for patients who do not reach lipid targets on maximal tolerated statin doses

ADA. *Diabetes Care*. 2012.

The ADA recommends that statin therapy be added to lifestyle modification, regardless of baseline lipid levels, for patients with overt CVD or for those without overt CVD who are over the age of 40 years and have at least one other CVD risk factor.

Health care providers should consider initiating statin therapy in addition to lifestyle modification for patients who do not have overt CVD and are under the age of 40 if they have an LDL-C concentration that remains above 100 mg/dL despite lifestyle modification. Statin therapy should also be considered for patients with multiple risk factors for CVD.

If patients do not reach ADA lipid targets while receiving the maximal tolerated dose of a statin, the health care provider can consider using an LDL-C reduction of approximately 30% to 40% from baseline as an alternate therapeutic goal.

ANTIPLATELET THERAPY FOR CVD PREVENTION

- Consider low-dose aspirin (75–162 mg/day) as a primary prevention strategy for patients whose 10-year CVD risk is >10%
- Do not recommend aspirin for adults with <5% 10-year CVD risk, as potential adverse effects from bleeding offset potential benefits
- Use clinical judgment when recommending aspirin for intermediate-risk adults (5–10% 10-year CVD risk)
- Use aspirin therapy as a secondary prevention strategy for patients with CVD history
- Prescribe clopidogrel (75 mg/day) for patients with CVD and documented aspirin allergy

10-Year Online CVD Risk Assessment Calculators:
National Cholesterol Education Program: http://hp2010.nhlbihin.net/atpIII/calculator.asp.
Mayo Clinic: http://www.mayoclinic.com/health/heart-disease-risk/HB00047.

Pignone. *Diabetes Care.* 2010.
ADA. *Diabetes Care.* 2012.

According to the ADA, low-dose aspirin therapy (75–162 mg/day) should be considered as a primary prevention strategy for patients whose 10-year CVD risk exceeds 10%. This includes most men older than 50 or women older than 60 years of age who have at least one additional major risk factor, including a family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria. Web addresses of 2 online 10-year CVD risk assessment calculators are shown on the slide.

Preventive aspirin therapy should not be recommended for adults whose 10-year CVD risk is less than 5%, because the potential adverse effects from bleeding offset the potential benefits. Until more data are available, clinical judgment should guide the preventive use of low-dose aspirin for people whose 10-year CVD risk is 5 to 10%. This intermediate-risk group includes younger patients with one or more risk factors or older patients with no risk factors.

Aspirin therapy (75–162 mg/day) should be used as a secondary prevention strategy in patients with diabetes with a history of CVD. The ADA recommends that clopidogrel (75 mg/day) be prescribed for patients with CVD and documented aspirin allergy.

DIABETIC KIDNEY DISEASE

IMPACT OF DKD

- Spectrum of kidney changes that occur in people with diabetes and cannot be ascribed to other causes
- Ranges in severity from microalbuminuria to stage 5 CKD
- Up to 40% of people with diabetes have DKD; 21.3% have CKD
- CKD leads to
  - RRT (hemodialysis, peritoneal dialysis, renal transplantation)
  - Premature death from CVD
- Optimizing glucose and BP control reduces the risk and slows the progression of DKD
- Detecting and treating early DKD by lowering BP can reduce kidney function decline by 30–70%

Byham-Gray. *The Art and Science of Diabetes Self-Management Education Desk Reference*. 2011.
ADA. *Diabetes Care*. 2012. US Renal Data System. *2011 Annual Data Report*. 2011.
CDC. *National Diabetes Fact Sheet, 2011*. 2011.

RRT = renal replacement therapy.

The term “DKD” describes the spectrum of kidney changes that occur in people with diabetes and that cannot be ascribed to other causes. DKD ranges in severity from microalbuminuria to stage 5 CKD, which is also known as end-stage renal disease (ESRD) or kidney failure. Up to 40% of people with diabetes have DKD, and 21.3% have CKD. Progressive CKD leads to the need for renal replacement therapy (RRT), including hemodialysis, peritoneal dialysis, and renal transplantation. In addition, it often results in premature death from CVD.

Optimizing glucose and BP control reduces the risk and slows the progression of DKD. The CDC reports that detecting and treating early DKD by lowering BP can reduce the decline in kidney function by 30% to 70%.

ALBUMIN EXCRETION ABNORMALITIES

- Albumin concentration in urine is an indicator of renal health
- Microalbuminuria is the earliest stage of DKD in type 1 diabetes and a marker for DKD development in type 2 diabetes, as well as a marker of CVD risk
- Patients who develop macroalbuminuria are likely to progress to ESRD

Definitions of Abnormalities in Albumin Excretion

Category	Spot Collection (µg albumin/ mg creatinine)
Normal	<30
Microalbuminuria	30–299
Macroalbuminuria	≥300

ESRD = end-stage renal disease.

ADA. *Diabetes Care.* 2012.

Albumin is a common water-soluble protein found in the body. The albumin concentration in the urine is an indicator of renal health, and can be conveniently and accurately measured using the urine spot collection technique. The results of this test are reported as the micrograms of albumin per milligram of creatinine.

As shown in the table, people with normal kidney function have an albumin concentration of less than 30 µg, those with microalbuminuria have concentrations ranging from 30 to 299 µg, and those with macroalbuminuria have concentrations that are greater than or equal to 300 µg of albumin per milligram of creatinine.

According to the ADA, persistent microalbuminuria is clinically significant because it is the earliest sign of DKA in type 1 diabetes and a marker for the development of DKD in type 2 diabetes. Microalbuminuria is also a well-established marker of increased CVD risk. Patients with microalbuminuria who develop macroalbuminuria are likely to progress to ESRD.

Achievement of near-normoglycemia through intensive diabetes management can delay the onset of microalbuminuria and the progression from microalbuminuria to macroalbuminuria. However, once macroalbuminuria has developed, tight glycemic control cannot prevent the development of renal insufficiency.

GLOMERULAR FILTRATION RATE

- Best overall index of kidney function
- Seldom measured directly; instead, eGFR is determined, usually by measuring creatinine concentration in serum
- eGFR is calculated using equations that account for patient variables (eg, age, gender)
- Normal eGFR is >90 mL/min/1.73 m^2 BSA
- CKD is eGFR <60 mL/min/1.73 m^2 BSA for ≥3 months

BSA = body surface area;
eGFR = estimated glomerular filtration rate;
GFR = glomerular filtration rate.

Cirillo. *J Nephrol.* 2010.
Thomas. *Dtsch Arztebl Int.* 2009.

The glomerular filtration rate (GFR) is considered the best overall index of kidney function. Within the kidney, urine production begins at the glomeruli, those clusters of capillaries in which plasma undergoes ultrafiltration. The GFR is the rate of glomerular ultrafiltration, and higher GFRs are associated with better kidney function.

The GFR is seldom measured directly because it requires invasive, expensive, and time-consuming procedures. Instead, the estimated GFR (eGFR) is determined, usually by measuring the creatinine concentration in serum. The eGFR is calculated using equations that take into account patient variables such as age, gender, and sometimes ethnicity.

A normal eGFR is a value above 90 mL/min per 1.73 m^2 of body surface area (BSA). CKD is defined as an eGFR below 60 mL/min per 1.73 m^2 BSA for at least 3 months.

STAGES OF CKD AND POSSIBLE RELATIONSHIP WITH ALBUMINURIA

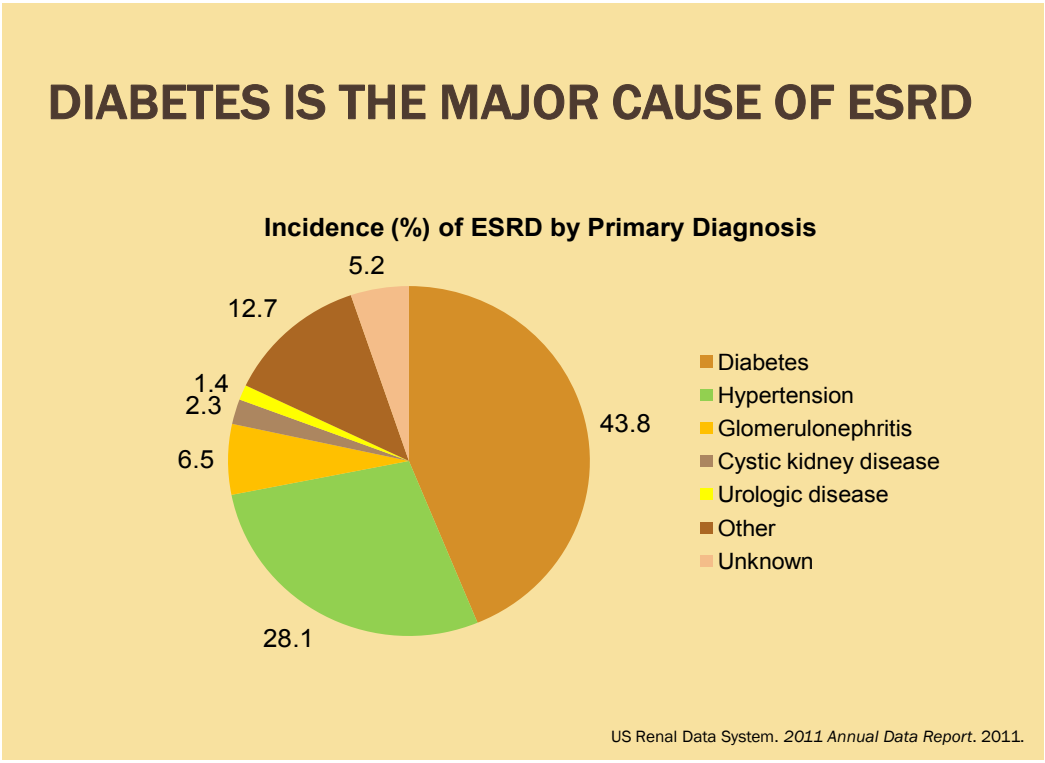
Stage*	Description	GFR, mL/min per 1.73 m^2 BSA	Albuminuria†
1	Kidney damage‡ with normal or increased GFR	≥90	Normal- or microalbuminuria
2	Kidney damage‡ with mildly decreased GFR	60–89	Microalbuminuria or possibly macroalbuminuria
3	Moderately decreased GFR	30–59	Macroalbuminuria
4	Severely decreased GFR	15–29	Macroalbuminuria
5	Kidney failure§	<15 or dialysis	Not applicable

*Stages of CKD as developed by National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI).
†Relationship to albuminuria as described by Wheeler, 2012.
‡As defined by structural or functional abnormalities of the kidney (with or without increased GFR) as manifested by either pathological abnormalities or markers of kidney damage (proteinuria, hematuria, pyuria, or abnormal imaging studies).
§Also called ESRD.

KDOQI. Clinical practice guidelines for chronic kidney disease. 2002.
Wheeler. *American Diabetes Association Guide to Nutrition Therapy for Diabetes*. 2012.

This table shows the 5 stages of CKD as defined in 2002 by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI). In these guidelines, the GFR is the index of kidney function.

The column shaded in green shows the possible relationship between the stages of CKD and albuminuria, as described in 2012 by Wheeler. Note that the relationships between glomerular structural lesions and the presence of microalbuminuria in CKD are not straightforward, particularly because a substantial proportion of patients with type 1 and type 2 diabetes and microalbuminuria can spontaneously revert to normoalbuminuria.



This chart shows that diabetes is, by far, the major cause of ESRD among U.S. residents. According to the *2011 Annual Data Report* of the USRDS, 43.8% of patients who developed ESRD in 2009 had diabetes as their primary diagnosis, as opposed to 28.1% with hypertension and 6.5% with glomerulonephritis. In terms of numbers, about 51,000 people with diabetes began treatment for ESRD in 2009.

The incidence of diabetes-related ESRD in 2009 was 187 per million in men and 128 per million in women. By age group, the incidence of diabetes-related ESRD per million people was 44 in adults aged 20 to 44 years, 314 in adults aged 45 to 64 years, 692 in adults aged 65 to 74 years, and 592 in adults 75 years or older.

There are marked ethnic disparities in the incidence of diabetes-related ESRD, and these differences are consistent with ethnic disparities in the incidence of diabetes. Per 1 million people, ESRD rates were 1363 for Native Hawiians/Pacific Islanders, 837 for Native Americans or Alaska Natives, 447 for blacks or African Americans, 149 for Asians, and 114 for whites.

DKD SCREENING

Assessment	Timing	Comments
UAE: to measure albumin-to-creatinine ratio by random spot collection	Type 1: annually, beginning 5 years after diagnosis Type 2: annually, beginning at diagnosis	2 of 3 specimens collected within 3- to 6-month period should be abnormal before diagnosing microalbuminuria or macroalbuminuria*
Serum creatinine: to determine eGFR	Annually in all adults, regardless of degree of UAE	Serum creatinine should be used to estimate GFR and determine CKD stage, if present

*Factors that can temporarily elevate UAE values are exercise within 24 h, infection, fever, congestive heart failure, marked hyperglycemia, and marked hypertension.

UAE = urinary albumin excretion.

ADA. *Diabetes Care.* 2012.

The ADA recommends that a urinary albumin excretion (UAE) test be performed to measure the albumin-to-creatinine ratio using the random spot collection approach. Compared to random spot collection, 24-hour or timed collections are more burdensome and add little accuracy or predictive power. Because of natural variations in UAE, 2 of 3 specimens collected within a 3- to 6-month period should be abnormal before a patient is considered to have developed microalbuminuria or macroalbuminuria. Exercise within 24 hours, infection, fever, congestive heart failure, marked hyperglycemia, and marked hypertension can all temporarily elevate UAE over baseline values. In patients with type 1 diabetes, UAE testing should begin 5 years after disease onset and then be performed annually. In patients with type 2 diabetes, testing should begin at diagnosis and then be repeated every year. As mentioned earlier, the reason for this difference is that type 1 diabetes generally has a readily identifiable onset, whereas people with type 2 diabetes often have the disease for many years prior to diagnosis.

The ADA also recommends that serum creatinine be measured at least annually in all adults with diabetes regardless of their UAE level. The serum creatinine value should be used to estimate the GFR and determine the stage of CKD, if present. The rationale for testing all patients at least annually is that many patients have a decreased GFR even when the UAE value is not elevated.

PREVENTION AND TREATMENT OF DKD

Approach	Benefits
Intensive diabetes management to achieve near-normoglycemia	Delays onset of microalbuminuria and progression from micro- to macroalbuminuria
BP control using a RAS inhibitor (ACE inhibitor or ARB)*	Delays onset of microalbuminuria, prevents or delays progression from micro- to macroalbuminuria; prevents or delays decline in GFR in patients with macroalbuminuria, reduces rates of major CVD events (MI, stroke, death)
Other antihypertensive therapy in combination with* or instead of RAS inhibitor therapy	Further lowers BP in patients already treated with a RAS inhibitor, alternate therapy for pregnant women, women contemplating pregnancy in the near future, or rare individuals unable to tolerate a RAS inhibitor

*In nonpregnant patients and women who are not likely to become pregnant in the near future.

RAS = renin-angiotensin system.

ADA. *Diabetes Care.* 2012.

The ADA recommends several approaches for preventing and treating DKD. Intensive diabetes treatment to achieve near-normoglycemia delays the onset of microalbuminuria and progression from micro- to macroalbuminuria.

Randomized clinical trials in different subpopulations of patients with diabetes have shown that BP control using a RAS inhibitor—either an ACE inhibitor or an ARB—offers many benefits. RAS inhibition can delay the onset of microalbuminuria, prevent or delay the progression from micro- to macroalbuminuria, prevent or delay the decline in the GFR in patients with macroalbuminuria, and reduce the rate of major CVD events, including MI, stroke, and CVD-related death. As mentioned earlier, RAS inhibitor therapy should be limited to nonpregnant patients and women who are not likely to become pregnant in the near future, since both ACE inhibitors and ARBs are in Pregnancy Category C for women in the first trimester and in Category D for women in the second and third trimesters of pregnancy.

Other antihypertensive drugs, such as diuretics, calcium channel blockers, and beta blockers, can be used as additional therapy to further lower BP in patients already receiving a RAS inhibitor. They should be used as alternative therapy for pregnant women, women who are likely to become pregnant in the near future, or the rare individuals who are unable to tolerate RAS inhibitor therapy.

NUTRITION THERAPY FOR DKD

- Protein need not be restricted in individuals with microalbuminuria
- Lowering protein intake to <1 g/kg/day in individuals with macroalbuminuria
  - May modestly improve albuminuria
  - Does not appear to reduce the rate of kidney function decline (GFR)
  - May cause malnutrition
- Salt (sodium) reduction can reduce BP significantly, particularly in individuals with microalbuminuria
- Individual prescriptions for restrictions or increases of micronutrients (potassium, phosphorus, and calcium) should be based on laboratory values and prescribed medications, as well as the CKD Evidence Analysis Library nondiabetic evidence base of the Academy of Nutrition and Dietetics

Wheeler. *American Diabetes Association Guide to Nutrition Therapy for Diabetes*. 2012

Because individuals with DKD excrete protein, restriction of dietary protein "to reduce kidney load" has been widely advocated for many years. However, the results of a recent systematic review of the medical literature indicate that protein need not be restricted in individuals with microalbuminuria.

Lowering protein intake to less than 1 g/kg/day in individuals with macroalbuminuria may modestly improve albuminuria but does not appear to reduce the rate of kidney function decline, as measured by the GFR. Furthermore, protein restriction may cause malnutrition, and adherence to prescribed low-protein diets is very limited.

Salt (sodium) reduction can reduce BP significantly, particularly in individuals with microalbuminuria.

There is currently no evidence base for restrictions or increases in the micronutrients potassium, phosphorus, or calcium in DKD. Therefore, individual prescriptions should be based on laboratory values and prescribed medications, as well as the CKD Evidence Analysis Library nondiabetic evidence base maintained by the Academy of Nutrition and Dietetics. (Until recently, the name of this organization was the American Dietetic Association.)

MANAGEMENT OF CKD IN DIABETES

GFR*	ADA Recommendation
Any	• Measure serum creatinine, UAE, and potassium annually • Administer HBV vaccination to patients likely to progress to ESRD
45–60	• Refer to nephrologist if possibility for non-DKD exists • Consider need to adjust medications • Monitor eGFR every 6 months • Monitor electrolytes, bicarbonate, hemoglobin, calcium, phosphorus, and parathyroid hormone at least annually • Assure that vitamin D intake is sufficient • Consider bone density testing • Refer for dietary counseling
30–44	• Monitor eGFR every 3 months • Consider need to adjust medications • Monitor electrolytes, bicarbonate, hemoglobin, calcium, phosphorus, parathyroid hormone, UAE, and weight every 3 to 6 months
<30	• Refer to nephrologist

*mL/min per 1.73 m^2 BSA. HBV = hepatitis B virus.

ADA. *Diabetes Care*. 2012.

The ADA recommends that individuals with diabetes and CKD of any stage have their serum creatinine, UAE, and potassium levels measured yearly. Early vaccination against the hepatitis B virus (HBV) is indicated in people who are likely to progress to ESRD, since HBV outbreaks occur frequently among unvaccinated patients treated at hemodialysis centers. Furthermore, primary HBV infections are more likely to become chronic in immunosuppressed individuals, such as hemodialysis patients, than in people whose immune system is intact.

The health care provider should consider the need to adjust the medication of patients with CKD, because some drugs are contraindicated, must be used with caution, or need to be given at reduced doses in patients with renal impairment.

Generally similar laboratory tests are recommended for patients whose GFR is between 45 and 60 and for those whose GFR is between 30 and 44 mL/min per 1.73 m^2 BSA, but patients at the lower GFR range should be monitored every 3 to 6 months rather than annually.

A patient should be referred to a nephrologist when there is uncertainty about the etiology of the patient's kidney disease, difficult management issues arise, or the GFR falls below 30 mL/min per 1.73 m^2 BSA. Additional details about triggers for referral to a nephrologist are given on the next slide.

TRIGGERS FOR REFERRAL TO A SPECIALIST

Trigger	Explanation
Uncertainty about the etiology of kidney disease	Heavy proteinuria, active urine sediment, absence of retinopathy, rapid decline in GFR, and resistant hypertension suggest that a patient may have another type of kidney disease instead of or addition to DKD
Difficult management issues	To optimize outcomes, many patients with anemia, secondary hyperthyroidism, metabolic bone disease, or an electrolyte disturbance should be treated by a specialist
GFR <30 mL/min per 1.73 m^2 BSA	When a patient develops Stage 4 CKD, referral to a nephrologist* reduces costs, improves quality of care, and delays the need for dialysis Earlier referral may be preferable when the health care provider has limited experience with significant kidney disease

*Following referral to a nephrologist, selected patients will be referred to a transplant surgeon to explore the feasibility of kidney transplantation. Kidney-pancreas transplantation is an option for some patients with type 1 diabetes).

ADA. *Diabetes Care*. 2012. Byham-Gray. *The Art and Science of Diabetes Self-Management Education Desk Reference*. 2011.

As just mentioned, the ADA has identified several triggers for referring an individual with CKD to a nephrologist or another physician who specializes in the treatment of kidney disease. One trigger for referral is uncertainty about the etiology of the patient's kidney disease. Heavy proteinuria, active urine sediment, absence of retinopathy, rapid decline in the GFR, and resistant hypertension suggest that a patient may have another type of kidney disease instead of or in addition to DKD.

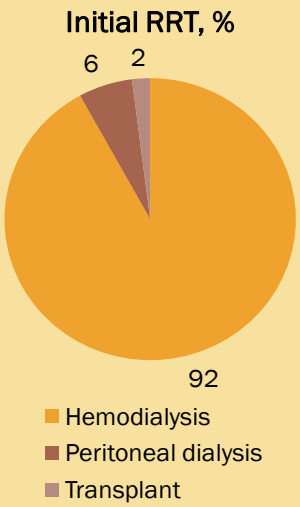
Difficult management issues is another referral trigger. To optimize outcomes, many patients with anemia, secondary hyperthyroidism, metabolic bone disease, or an electrolyte disturbance need to be treated by a specialist.

A third trigger is a decline in the GFR to less than 30 mL/min per 1.73 m^2 BSA—the threshold for Stage 4 CKD. Referral to a nephrologist at this stage reduces costs, improves quality of care, and delays the need for dialysis. Referral before Stage 4 may be preferable when the health care provider has limited experience with significant kidney disease. Following referral to a nephrologist, selected patients are referred to a transplant surgeon to explore the feasibility of kidney transplantation. Some patients with type 1 diabetes are candidates for kidney-pancreas transplantation.

Regardless of the timing of referral to a nephrologist, providers who are not renal specialists should not delay in educating their patients about the progressive nature of DKD, the renal preservation benefits of aggressive treatment of BP and blood glucose, and the potential need for RRT.

ESRD MANAGEMENT BY THE NEPHROLOGY TEAM

- Maintaining glycemic control is challenging in patients receiving RRT
- Among Medicare recipients, mortality of dialysis patients is more than 6 times higher than that of the general population
- CVD and infections are major causes of death in dialysis recipients



US Renal Data System. *2011 Annual Data Report*. 2011.
Byham-Gray. *The Art and Science of Diabetes Self-Management Education Desk Reference*. 2011.

Patients with ESRD should be closely managed by a nephrology team that includes a nephrologist, nurse, dietitian, and social worker. To optimize outcomes, the patient and family members must remain involved in treatment decisions.

Options for RRT depend on the patient's overall condition and preference, and include no treatment, hemodialysis, peritoneal dialysis, and kidney transplantation. As previously mentioned, kidney-pancreas transplantation is also an option for selected patients with type 1 diabetes. Maintenance of glycemic control in patients who are receiving RRT is challenging, and best achieved with insulin therapy.

As the chart shows, the overwhelming majority of individuals with ESRD receive hemodialysis as their initial RRT, and most patients remain on hemodialysis for the rest of their lives. Although the average lifespan of dialysis recipients has been gradually increasing, mortality rates remain high. Among Medicare recipients in 2009, for example, the death rate of dialysis patients was more than 6 times higher than that of the general population. CVD and infections associated with the use of vascular access devices are major causes of death in dialysis recipients.

Eventually, about 30% of patients with renal failure undergo kidney or kidney-pancreas transplantation. Patient outcomes continue to improve following transplantation, and the USRDS reports that more than 96% of patients who receive a deceased donor kidney transplant and nearly 99% of those who receive a kidney from a living donor survive the first year with a functioning graft.

CHECK POINT 2

The correct statement is: _____.

a. a systolic blood pressure target of <130 mmHg is appropriate for most people with diabetes
b. the decision to initiate statin therapy in a person with diabetes should always be governed by baseline lipid levels
c. urinary albumin excretion testing should begin as soon as an individual is diagnosed with type 1 diabetes
d. protein restriction is a valuable therapeutic approach for patients with diabetes and microalbuminuria

The correct statement is: _____.

a. a systolic blood pressure target of <130 mmHg is appropriate for most people with diabetes
b. the decision to initiate statin therapy in a person with diabetes should always be governed by baseline lipid levels
c. urinary albumin excretion testing should begin as soon as an individual is diagnosed with type 1 diabetes
d. protein restriction is a valuable therapeutic approach for patients with diabetes and microalbuminuria

ANSWER TO CHECK POINT 2

The correct answer is a.

A systolic blood pressure target of <130 mmHg is appropriate for most people with diabetes.

The correct answer is a.

A systolic blood pressure target of <130 mmHg is appropriate for most people with diabetes.

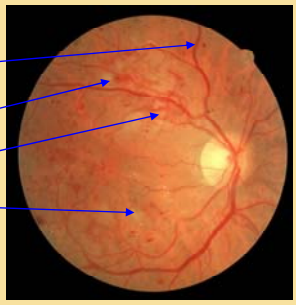
RETINOPATHY

DIABETIC RETINOPATHY

- Highly specific vascular complication of diabetes
- During their first 2 decades with diabetes, nearly all people with type 1 diabetes and >60% with type 2 diabetes will develop retinopathy
- Vision loss can be prevented or minimized with regular ophthalmologic assessments and appropriate treatment

Normal eye

Eye affected by diabetic retinopathy



Figures courtesy of ADA. Used with permission. Fong. *Diabetes Care*. 2004. Kiss. *The Art and Science of Diabetes Self-Management Education Desk Reference*. 2011.

People with diabetes are at higher risk than people without diabetes of developing many age-related eye disorders, including cataracts and glaucoma. However, the most severe eye disease experienced by people with diabetes is diabetic retinopathy. Diabetic retinopathy is a highly specific vascular complication of type 1 and type 2 diabetes. During their first 2 decades with diabetes, nearly all people with type 1 diabetes and more than 60% of those with type 2 diabetes will develop retinopathy. As mentioned earlier, diabetic retinopathy is the leading cause of blindness among adults aged 20 to 70 years of age, although not all forms of retinopathy lead to blindness.

Recall that the retina is a layer of nerve tissue at the back of the eye that converts light into the electrical signals interpreted by the brain. It is often compared to the film in a camera. Diabetic retinopathy occurs when the small blood vessels that nourish the retina are damaged as a result of elevated BG levels and hypertension. This damage permits leakage of blood components through the vessel walls. As shown on the lower right of this slide, frequent findings in eyes affected by diabetic retinopathy are dot hemorrhages, flame hemorrhages, neovascularization, and hard exudates.

Prompt identification of retinopathy is essential, because vision loss can be prevented or minimized with regular ophthalmic assessments and appropriate treatment.

DIABETIC RETINOPATHY: ICDSS STAGING

Stage	Abnormalities
No apparent retinopathy	None
Mild NPDR	Microaneurysms only
Moderate NPDR	More than just microaneurysms, but less than severe NPDR
Severe NPDR	Any of the following: • >20 Intraretinal hemorrhages in each of 4 quadrants • Definite venous beading in ≥2 quadrants • Prominent intraretinal microvascular abnormalities in ≥1 quadrant • No signs of PDR
PDR	One or both: • Neovascularization • Vitreous or preretinal hemorrhage

ICDSS = International Clinical Disease Severity Scale;
NPDR = nonproliferative diabetic retinopathy;
PDR = proliferative diabetic retinopathy.

Kiss. *The Art and Science of Diabetes Self-Management Education Desk Reference*. 2011.

This table shows the staging of diabetic retinopathy according to the International Clinical Disease Severity Scale (ICDSS). Diabetic retinopathy is divided into 2 major categories: nonproliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). Early abnormalities associated with NPDR include microaneurysms (visualized as pouches along weakened vascular walls), flame- or dot-shaped intraretinal hemorrhages, and cotton-wool spots. Increased vascular leakage leads to retinal thickening (edema), and deposits of fluid that become hard exudates.

As diabetic retinopathy progresses, retinal blood vessels gradually close, resulting in 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 preretinal structures. The new blood 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 into the vitreous may cause vitreo-retinal traction bands, retinal tears, and retinal detachments.

DIABETIC MACULAR EDEMA: ICDSS STAGING

Stage	Abnormalities
DME apparently absent	No apparent retinal thickening or hard exudates in posterior pole
DME apparently present	Some retinal thickening or hard exudates in posterior pole
Mild DME	Some retinal thickening or hard exudates in posterior pole, but distant from center of macula
Moderate DME	Retinal thickening or hard exudates approaching, but not involving, center of macula
Severe DME	Retinal thickening or hard exudates involving the center of macula

DME = diabetic macular edema.

Kiss. *The Art and Science of Diabetes Self-Management Education Desk Reference*. 2011.

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 table on the slide shows the ICDSS staging system for DME. The term “posterior pole” refers to the back of the eye.

Clinically significant macular edema is defined as retinal thickening within 2 disc diameters (~3 mm) of the center of the macula. Focal edema is associated with hard exudate rings caused by leakage from microaneurysms. Diffuse edema is caused by the breakdown of the blood-retinal barrier, with leakage from microaneurysms, renal capillaries, and arterioles.

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

DIABETIC RETINOPATHY RISK FACTORS

- Long duration of diabetes
- Suboptimal glycemic control
- Sudden improvement in glycemic control
- Hypertension
- Hypercholesterolemia
- Proteinuria and renal disease
- Anemia
- Abdominal obesity
- Cataract surgery
- Puberty
- Pregnancy

Cavallerano. *Joslin's Diabetes Deskbook*. 2010.

Many factors increase the risk that a person with diabetes will develop retinopathy. The longer a person has diabetes, the more likely he or she will be to develop retinopathy. Suboptimal control of glucose levels, BP, and cholesterol levels increase the risk of developing retinopathy. Ironically, a sudden improvement in glycemic control, often seen at the initiation of intensive insulin therapy, can sometimes lead to worsening of retinopathy.

Other risk factors for retinopathy are proteinuria and renal disease, anemia, abdominal obesity, cataract surgery, puberty, and pregnancy. A woman with preexisting diabetes who is contemplating pregnancy should have a dilated eye examination, and her retinal status should be stabilized before pregnancy.

ADA SCHEDULE FOR EYE EXAMINATIONS

Patient Characteristics	Recommended Schedule
Initial screening	
Adults and children aged ≥10 y with type 1 diabetes	Within 5 y after onset
People with type 2 diabetes	At diagnosis
Woman contemplating pregnancy	Before conception
Pregnant woman without preconception screening	During first trimester
Follow-up examinations	
Most patients	Annually
Patients with ≥1 normal eye exam	Every 2–3 years*
Progressive retinopathy	More than once per year*
Pregnancy	Close follow-up throughout pregnancy and for 1 year postpartum

*Based on clinical judgment.

ADA. *Diabetes Care*. 2012.

The ADA recommends that adults and children aged 10 years or older with type 1 diabetes have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist within 5 years after the onset of diabetes. The age of 10 years is used for the initiation of screening because diabetic retinopathy is rare in prepubertal patients with type 1 diabetes. Patients with type 2 diabetes should have an initial eye examination shortly after the diagnosis of diabetes. As previously mentioned, a woman with preexisting diabetes should have an eye examination before conception. A pregnant woman who has not had a preconception exam should be screened for diabetic retinopathy during her first trimester.

Most patients with type 1 and type 2 diabetes should have annual follow-up examinations. Based on clinical judgment, less frequent exams (every 2 to 3 years) may be considered following one or more normal eye exams. Exams will be required more often than once a year if retinopathy is progressing. Pregnant women should have close follow-up throughout pregnancy and for 1 year postpartum.

COMPONENTS OF THE INITIAL EYE EXAM

- Best corrected visual acuity
- Intraocular pressure
- Ocular motility
- Gonioscopy
- Slitlamp biomicroscopy
- Dilated funduscopy, including stereoscopic examination of posterior pole
- Examination of peripheral retina and vitreous
- Diagnostic imaging (when warranted)

Kiss. *The Art and Science of Diabetes Self-Management Education Desk Reference*. 2011.

This slide shows the recommended components of the initial eye examination for a patient with diabetes. Gonioscopy is a test to visualize the anterior chamber angle and to help classify glaucoma, when indicated. Slitlamp biomicroscopy is the examination of the lens and other structures at the front of the eye.

According to the ADA, the use of retinal photography with remote reading by experts has great potential in areas where qualified eye care professionals are not available. In-person exams are still necessary when the photographs are unacceptable and for follow-up of detected abnormalities. Photographs are not a substitute for a comprehensive eye exam, which should be performed initially and at recommended intervals thereafter by an eye care professional. Results of eye examinations should be documented and transmitted to the referring health care professional.

TREATMENT OF DIABETIC RETINOPATHY

- Laser photocoagulation therapy is indicated to reduce the risk of vision loss in patients with high-risk PDR, clinically significant DME, and in some cases of severe NPDR; other procedures may also be used. (See table.)
- Ranibizumab, an anti-VEGF agent, was approved for treatment of DME in August 2012; other anti-VEGF compounds are currently being investigated.

Procedure	Description
Panretinal laser photocoagulation	Laser places hundreds of microburns in peripheral retina, reducing new blood vessel growth. Existing neovascular growth dries up. Procedure decreases peripheral vision, but preserves central vision.
Focal laser photocoagulation	Limited area of microburns is placed in the area of leakage around macula, usually drying up clinically significant DME
Vitrectomy	Vitreous material is removed to treat hemorrhage

VEGF = vascular endothelial growth factor.

Kiss. *The Art and Science of Diabetes Self-Management Education Desk Reference*. 2011. ADA. *Diabetes Care*. 2012. Phelps. *Complete Nurse's Guide to Diabetes Care*. 2009. Lucentis® (ranibizumab injection). Prescribing information. 2012.

According to the ADA, patients with any level of DME, severe NPDR, or any PDR should be referred to an ophthalmologist who is knowledgeable and experienced in the management and treatment of diabetic retinopathy. Laser photocoagulation therapy is generally considered the "gold standard" of treatment for patients with advanced retinopathy. This intervention is indicated to reduce the risk of vision loss in patients with high-risk PDR, clinically significant DME, and in some cases of severe NPDR.

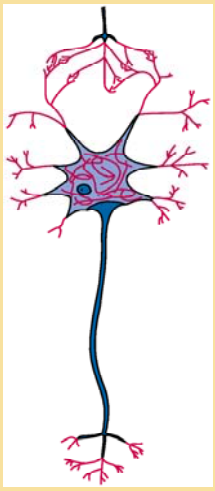
In the Diabetic Retinopathy Study, panretinal laser photocoagulation reduced the risk of severe vision loss from PDR from 15.9% in untreated eyes to 6.4% in treated eyes. The benefit was greatest in patients with high-risk characteristics, especially disc neovascularization or vitreous hemorrhage. The Early Treatment Diabetic Retinopathy Study established the benefit of focal laser photocoagulation in eyes with DME. It also confirmed the benefits of panretinal laser photocoagulation for high-risk PDR. Vitrectomy may be performed in eyes affected by PDR when fragile new blood vessels break and bleed into the vitreous material. Once the damaged vitreous material is removed, the eye can be filled with clear aqueous fluid.

Ranibizumab, an anti-vascular endothelial growth factor (VEGF) agent, was approved by the FDA for the treatment of DME in August 2012. Ranibizumab is administered by intravitreal injection once a month, and can be used in conjunction with laser photocoagulation therapy. During clinical trials, treatment with ranibizumab resulted in sustained improvement in visual acuity over a 3-year period. Other anti-VEGF agents, such as bevacizumab, are currently under investigation for the treatment of DME.

NEUROPATHY

DIABETIC NEUROPATHIES

- Can be diffuse or focal, with diverse clinical manifestations
- Generalized symmetric polyneuropathies
  - Acute sensory neuropathy
  - **Chronic sensorimotor distal symmetric polyneuropathy (DPN)***
  - **Diabetic autonomic neuropathy (DAN)***
    - Cardiovascular autonomic neuropathy (CAN)
- Focal and multifocal neuropathies
  - Cranial
  - Truncal
  - Focal limb
  - Proximal motor (amyotrophy)
  - Coexisting chronic inflammatory demyelinating polyneuropathy (CIDP)
- Optimizing glycemic control may modestly slow progression



*Most common presentations.

Boulton. *Diabetes Care*. 2005.
ADA. *Diabetes Care*. 2012.

Diabetic neuropathies are heterogeneous, affecting different parts of the nervous system and having diverse clinical manifestations.

Diabetic neuropathy is classified in many different ways. The classification on this slide is the one used by the ADA. As indicated by the **bold red text**, the most common presentations are chronic sensorimotor distal symmetric polyneuropathy (DPN), which often involves the feet, and diabetic autonomic neuropathy (DAN), which can involve any system in the body. The most important subtype of DAN is cardiovascular autonomic neuropathy (CAN).

DPN is very common, and at least 20% of adults with diabetes have 1 or more manifestations of DPN. Risk factors include marked hyperglycemia, dyslipidemia, elevated BP, long diabetes duration, and greater height.

Reported prevalence rates for DAN range from 1.6% to 90%, depending on the tests used, the populations examined, and the type and stage of diabetes. Risk factors include long diabetes duration, older age, and a history of high A1C values.

Optimizing glycemic control may modestly slow the progression of diabetic neuropathy, although it does not reverse neuronal loss.

DIABETIC NEUROPATHY SCREENING SCHEDULE

- Early diagnosis is important
  - Many treatment options exist for neuropathy symptoms
  - Up to 50% of DPN cases are asymptomatic, and patients are at risk for foot injury
  - DAN (especially CAN) is associated with substantial morbidity and mortality
  - Patient may have treatable nondiabetic neuropathy
- All patients should be screened for DPN and DAN
  - Starting at diagnosis of type 2 diabetes
  - Starting 5 years after diagnosis of type 1 diabetes
  - Screening should be repeated at least annually

ADA. *Diabetes Care.* 2012.

Early recognition and appropriate management of diabetic neuropathy are important for several reasons. Many effective treatments are available for relieving neuropathy symptoms. Up to 50% of patients with DPN have no symptoms, and these individuals are at risk for insensate injury to their feet. DAN, and especially CAN, is associated with substantial morbidity and even mortality. In addition, some patients may have treatable nondiabetic neuropathies.

The ADA recommends that all patients be screened on a regular basis for DPN and DAN. Screening should begin at diagnosis for patients with type 2 diabetes and 5 years after diagnosis for patients with type 1 diabetes. After the initial screening, all patients should be rescreened at least annually.

DIABETIC NEUROPATHY SCREENING PROCEDURE

- Electrophysiological and other specialized testing rarely needed
- DPN
  - Pinprick sensation
  - Vibration perception (using 128-Hz tuning fork)
  - 10-g monofilament pressure sensation at distal plantar aspect of both great toes and metatarsal joints
  - Ankle reflex assessment
- DAN
  - Inquire about relevant symptoms (eg, unexplained upper GI problems, constipation, urinary incontinence, erectile dysfunction)
  - Screen for CAN by checking for resting tachycardia (HR >100 bpm) and orthostatic hypotension (>20 mmHg fall in SBP upon standing without appropriate HR response)

Bpm = beats per minute; GI = gastrointestinal; HR = heart rate.

ADA. *Diabetes Care.* 2012.

According to the ADA, electrophysiological or other specialized testing is rarely needed when screening a patient for diabetic neuropathy. Instead, patients should be screened using tests such as pinprick sensation, vibration perception (using a 128-Hz tuning fork), 10-g monofilament pressure sensation at the distal plantar aspect of both great toes and metatarsal joints, and assessment of ankle reflexes. Combinations of more than one test have more than 87% sensitivity in detecting DPN. Loss of 10-g monofilament perception and reduced vibration perception predict the development of foot ulcers.

The symptoms of DAN should be elicited carefully during the history and physical examination. Common symptoms include upper gastrointestinal (GI) problems without another identified cause, constipation, urinary incontinence, and erectile dysfunction.

The health care provider should screen the patient for CAN by checking for resting tachycardia, defined as a heart rate greater than 100 bpm. The clinician should also check for orthostatic hypotension, defined as a greater than 20 mmHg fall in SBP upon standing, without an appropriate heart rate response.

TREATMENT OF PAINFUL DIABETIC NEUROPATHY

LoE	Agent	Dose
A	Pregabalin	300–600 mg/d
B	Gabapentin	900–3600 mg/d
	Sodium valproate	500–1200 mg/d
	Venlafaxine	75–225 mg/d
	Duloxetine	60–120 mg/d
	Amitriptyline	25–100 mg/d
	Dextromethorphan	400 mg/d
	Morphine sulfate	Titrated to 120 mg/d
	Tramadol	210 mg/d
	Oxycodone	Mean, 37 mg/d; max, 120 mg/d
	Capsaicin 0.075%	QID
	Isosorbide dinitrate spray	NA
	Electrical or percutaneous nerve stimulation	For 3 to 4 weeks
Not rated	Folate + vitamin B6 + vitamin B12 (Metanx®)	1 tablet BID

LoE = level of evidence.

Bril. *Neurology*. 2011.

Painful diabetic neuropathy (PDN), which affects 16% of people with diabetes, is often unreported and undertreated. This slide summarizes evidence-based recommendations for the treatment of PDN that were developed by an expert panel representing the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. These recommendations were published in 2011. Pregabalin was the only treatment rated as having an "A" level of evidence, meaning that it is clearly effective and should be offered for relief of PDN. Twelve other treatments were judged to have a "B" level of evidence, meaning that they are probably effective and should be considered for the treatment of PDN. Oxcarbazepine, lamotrigine, lacosamide, clonidine, pentoxifylline, mexiletine, magnetic field treatment, low-intensity laser therapy, and Reiki therapy were not recommended, either because they have a less robust evidence base or the evidence is negative.

Metanx®, which includes the active forms of folate, vitamin B_6, and vitamin B_{12}, was not included in the expert panel's assessment since it is a medical food rather than a drug or medical device. However, Metanx® is approved by the US Food and Drug Administration for the dietary management of endothelial dysfunction in patients with DPN. This agent increases nitric oxide synthesis, increasing blood flow to the peripheral nerves. Metanx® differs from other available treatments because it promotes repair and regeneration of the myelin sheath rather than merely treating the pain associated with DPN.

COMPREHENSIVE FOOT EXAMINATION

- Dermatologic inspection
  - Skin color, thickness, dryness, cracking
  - Sweating
  - Infection, including fungal infection between toes
  - Calluses, blistering, ulceration
- Musculoskeletal inspection
  - Deformity (eg, claw toes, Charcot joint)
  - Muscle wasting
- Neurologic assessment for loss of protective sensation
  - 10-g monofilament
  - Vibration (using 128-Hz tuning fork), pinprick sensation, ankle reflexes, OR vibration perception threshold
- Vascular assessment for PAD

Boulton. *Diabetes Care.* 2008.
ADA. *Diabetes Care.* 2012.

At least annually, all adults with diabetes should have a comprehensive foot examination that includes a dermatologic and musculoskeletal inspection, as well as a neurologic and vascular assessment. Clinicians should ask about previous foot ulceration or amputation, neuropathic or peripheral vascular symptoms, impaired vision, tobacco use, and foot-care practices. A general inspection of skin integrity and musculoskeletal deformities should be done in a well-lit room. The neurologic assessment should focus on the identification of loss of protective sensation (LOPS). As mentioned earlier in this activity, it is also important to screen patients for PAD by taking a claudication history and assessing pedal pulses, as well as by determining the ankle-brachial index (ABI) in selected patients.

Patients with high-risk foot conditions should be educated about appropriate management of these conditions. They must understand the implications of LOPS; the importance of daily foot monitoring; proper care of the foot, including nail and skin care; how to select appropriate footwear; and the need to seek immediate attention for foot injuries. Medicare beneficiaries should be reminded that Medicare routinely covers one foot exam every 6 months by a podiatrist or other foot care specialist. Medicare may cover more frequent visits for patients who have a history of nontraumatic amputation of all or part of a foot or whose feet have recently changed in appearance.

CARDIOVASCULAR AUTONOMIC NEUROPATHY

Clinical Feature	Management
Resting tachycardia, exercise intolerance	Graded supervised exercise, drug therapy with ACE inhibitor or beta blocker
Orthostatic hypotension	Make slow posture changes; elevate head of bed; wear supportive garments; drug therapy with clonidine, midodrine, octreotide, erythropoietin, or fludrocortisone acetate
Thermoregulation problems	Avoid exercise in temperature extremes, maintain adequate hydration

Boulton. *Diabetes Care*. 2005.
Freeman. *Joslin's Diabetes Deskbook*. 2010.
Vinik. *The Art and Science of Diabetes Self-Management Education Desk Reference*. 2011.

CAN is the most studied and clinically important form of DAN because of its potentially life-threatening consequences, including silent MI and respiratory failure. Estimates of CAN-related mortality range from 27% to 56% over a 5- to 10-year period.

Major clinical features of CAN include resting tachycardia, exercise intolerance, orthostatic hypotension, and thermoregulation disturbances. Patients with resting tachycardia and exercise intolerance benefit from a graded supervised exercise program and drug therapy with an ACE inhibitor or a beta blocker.

Management of orthostatic hypotension includes changing position slowly, elevating the head of the bed by 30 degrees at night, wearing supportive stockings or other garments, and drug therapy with clonidine, midodrine, octreotide, erythropoietin, or fludrocortisone acetate.

Patients with thermoregulation problems should be advised to avoid exercise in extreme heat and cold and to maintain adequate hydration.

GASTROINTESTINAL AUTONOMIC NEUROPATHY

Manifestation	Clinical Features	Management
Esophageal dysfunction	Difficulty in swallowing, heartburn	Drug therapy with metoclopramide
Gastroparesis	Anorexia, nausea, vomiting, early satiety	Eat small, frequent meals; drug therapy with metoclopramide, domperidone, or erythromycin
Diabetic enteropathy	Constipation, diarrhea	Constipation: follow high-fiber diet; use bulking agents, osmotic laxatives, lubricating agents Diarrhea: consume soluble dietary fiber; restrict gluten and lactose intake; drug therapy with anticholinergic agents, cholestyramine, antibiotics, somatostatin, pancreatic enzyme supplements

Boulton. *Diabetes Care*. 2005.
Vinik. *The Art and Science of Diabetes Self-Management Education Desk Reference*. 2011.

Gastrointestinal neuropathy can affect the esophagus, stomach, and intestines, causing symptoms that vary with the part of the digestive tract that is affected.

Esophageal autonomic complications include altered peristalsis and impaired sphincter control, which could cause difficulty in swallowing and heartburn. Metoclopramide, a prokinetic agent, may provide some relief.

Gastroparesis can cause anorexia, nausea, vomiting, early satiety, and postprandial fullness. It is treated by encouraging the patient to eat smaller, more frequent meals. A dietitian should help to design a meal plan for a patient with gastroparesis. Prokinetic agents such as metoclopramide, domperidone, or erythromycin can be used before meals to improve gastric emptying. Patients with gastroparesis and impaired absorption should be monitored for hypoglycemia.

Widespread intestinal neuropathy can cause enteropathy, resulting in constipation or diarrhea. Constipation can be managed by following a high-fiber diet and using bulking agents, osmotic laxatives, or lubricating agents. Because diarrhea can have various causes, including bacterial overgrowth, poor intestinal motility, and celiac disease, the cause should be determined before treatment is initiated. Depending on the cause, diarrhea can be managed by consuming more soluble dietary fiber, restricting gluten and lactose intake, and/or drug therapy with anticholinergic agents, cholestyramine, antibiotics, somatostatin, or pancreatic enzyme supplements.

GENITOURINARY AUTONOMIC NEUROPATHY

Manifestation	Clinical Features	Management
Bladder dysfunction	Urinary retention, frequency, urgency, nocturia, incontinence	Scheduled voiding, drug therapy with bethanechol, intermittent catheterization, surgery (in severe cases)
Sexual dysfunction in men	Erectile dysfunction, problems with excitement or ejaculation, pain	Drug therapy with phosphodiesterase type 5 inhibitor or prostaglandin E1; use vacuum assistance device or penile implant
Dyspareunia in women	Pain during intercourse, vaginal dryness	Use vaginal lubricant

Boulton. *Diabetes Care.* 2005.
Frimodt-Møller. *Therapy for Diabetes Mellitus and Related Disorders.* 2009.
Snow. *Therapy for Diabetes Mellitus and Related Disorders.* 2009.
Vinik. *The Art and Science of Diabetes Self-Management Education Desk Reference.* 2011.

Genitourinary autonomic neuropathy can lead to bladder dysfunction, erectile dysfunction, and other types of sexual dysfunction in men, and bladder dysfunction and dyspareunia in women. Features of bladder dysfunction may include urinary retention, urinary frequency or urgency, nocturia, or incontinence. Urinary retention, which results from bladder denervation, occurs in 40% to 50% of patients with type 1 diabetes and in about 25% of patients with type 2 diabetes. Management of bladder dysfunction includes scheduled voiding, drug therapy with the parasympathetic nervous system stimulant bethanechol, and intermittent catheterization. Urinary retention is often difficult to treat, and sometimes requires surgery.

Erectile dysfunction is a common manifestation of genitourinary autonomic neuropathy in men. Management includes drug therapy with a phosphodiesterase type 5 inhibitor or prostaglandin E1 injections, suppositories, or devices. A vacuum assistance device or penile implant can also be used. Vaginal dryness is a common sign of genitourinary neuropathy in women, and can be relieved by using a vaginal lubricant.

CHECK POINT 3

The correct statement is: _____.

a. a characteristic feature of nonproliferative diabetic retinopathy is neovascularization
b. the “gold standard” of treatment for patients with advanced retinopathy is vitrectomy
c. the most common presentations of diabetic neuropathy are chronic sensorimotor distal symmetric polyneuropathy and focal limb neuropathy
d. pinprick sensation and vibration perception tests are effective screening tools for DPN

The correct statement is: _____.

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ANSWER TO CHECK POINT 3

The correct answer is d.

Pinprick sensation and vibration perception tests are effective screening tools for DPN.

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Pinprick sensation and vibration perception tests are effective screening tools for DPN.

SUMMARY

- Clinical outcome studies have shown that control of blood glucose levels, BP, and serum lipids can prevent or delay the development of microvascular and macrovascular complications and reduce the severity of these complications
- To optimize patient outcomes, glycemic targets and glucose-lowering therapies must be individualized, based on the patient's overall condition and his or her preferences, needs, and values
- 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 (such as those developed by the ADA) related to BP regulation, control of lipid levels and other risk factors, and screening for chronic complications

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