Identification & Prevention of Diabetes Complications

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Identification & Prevention of Diabetes Complications is supported by an educational grant from Novo Nordisk Inc. It has been accredited by the American Association of Diabetes Educators (AADE) for nurses, dietitians, and pharmacists.
The following program is a taped presentation by Barbara Kocurek.

Ms. Kocurek graduated from the University of Pittsburgh in 1987 with a Bachelor of Science in Pharmacy and she received her PharmD degree from the Medical College of Virginia in 1989. Since that time she has been involved in diabetes education in various health care settings. Currently she is the Diabetes Education Coordinator for the Baylor Health Care System Diabetes Education Services located in north Texas. She oversees the American Diabetes Association (ADA) recognition and data management for 11 outpatient diabetes education centers.

Ms. Kocurek served on the National Certification Board for Diabetes Educators (NCBDE) from 1998–2002 and was Chair for the 2000–2001 year. In 2002–2003 she served as a member of the AADE’s Nominating Committee and in 2004 served on the Professional Development, Education, and Resources Committee. She currently serves on AADE’s Professional Practice Committee and in 2010 became a Fellow of the American Association of Diabetes Educators.
The objectives for this program are:

- List the major macrovascular and microvascular complications of type 2 diabetes
- Discuss key findings from clinical outcome studies that have investigated the relationship between the control of glucose levels, blood pressure, blood lipids, and/or other major risk factors and the development of macrovascular and microvascular complications
- Describe practical therapeutic approaches for optimizing glucose control in patients with type 2 diabetes
- Describe practical therapeutic approaches in addition to glucose management that can help to prevent the complications of diabetes
Numerous complications affecting many different organ systems can develop as a result of diabetes. These complications are usually divided into 2 major categories—macrovascular and microvascular.

Macrovascular complications primarily affect large blood vessels and can lead to heart disease (coronary artery disease [CAD]), cerebrovascular disease (stroke), and peripheral arterial disease (PAD), which manifests as poor circulation in the lower extremities. Although this condition is often referred to as “peripheral vascular disease” (PVD), PAD is the more accurate term, since it is the arteries rather than the veins that are primarily affected.

Microvascular complications affect smaller blood vessels and can lead to damage to the kidneys (nephropathy), eyes (retinopathy), or nerves (neuropathy).

Less well-known complications include bone conditions (eg, osteoporosis in type 1 diabetes, fractures in type 2 diabetes), collagen disorders (eg, scleroderma), impaired wound healing, altered clotting factors, and periodontal disease. Many of these complications share cellular, metabolic, and pathophysiologic mechanisms with macrovascular and microvascular complications.
Data from the Centers for Disease Control and Prevention (CDC) and the National Institute of Diabetes and Digestive and Kidney Diseases show that many persons with diabetes have macrovascular and microvascular complications. According to recent estimates, approximately:

- 0.2 million people have end-stage renal disease (ESRD)
- 3.6 million are visually impaired
- 8.8 million are hospitalized for diabetic neuropathy
- 3.5 million have CAD
- 5.9 million have cardiovascular disease (CVD)
- 0.1 million are hospitalized for diabetes-related PAD
Impact of Diabetes-Related Macrovascular Complications

- CAD and Cerebrovascular disease
  - Account for ~65% of deaths
  - Death rate from CAD elevated ~2–4 times
  - Risk for stroke elevated ~2–4 times
  - ~50% of patients with CAD have undiagnosed impaired glucose tolerance or diabetes
- PAD
  - Risk factor for lower-limb amputation
  - More than 60% of nontraumatic lower-limb amputations occur in persons with diabetes

In terms of macrovascular complications:
- ~65% of deaths among people with diabetes are caused by myocardial infarctions (MIs) or strokes
- The death rate from CAD is ~2 to 4 times higher among men with diabetes than in those without diabetes and is even higher in women with diabetes
- The risk for stroke is also ~2 to 4 times higher in people with diabetes compared with those without diabetes
- Approximately half of patients already have CAD by the time they are diagnosed with impaired glucose tolerance or diabetes
- PAD is a risk factor for lower-limb amputation
- More than 60% of all nontraumatic lower-limb amputations occur in people with diabetes
Data from the CDC also show the enormous impact of diabetes and its complications on morbidity and mortality in the United States.

Diabetic nephropathy is the leading cause of ESRD, accounting for about 44% of new cases.

Diabetic retinopathy is the leading cause of new cases of blindness in adults.

Severe forms of diabetic neuropathy are a major cause of lower-extremity amputations.
Many modifiable risk factors for diabetes-related complications have been identified. They include overweight (defined as a body mass index [BMI] between 25.0 and 29.9 kg/m²), obesity (defined as a BMI of 30.0 kg/m² or greater), hypertension, high cholesterol, physical inactivity, and smoking.

Unfortunately, many people with diabetes report having these risk factors. For example, 82.3% of people with diabetes are also overweight, 62.5% have hypertension, 56% have high cholesterol, 49% are obese, 37.7% are inactive, and 16.1% smoke.
Many practices can reduce the risk for diabetes-related complications. Each 1% drop in A1C (e.g., from 8% to 7%) reduces the risk for microvascular complications by about 40%. Regulation of blood pressure can reduce the risks for CAD and CVD by approximately 33% to 50% and the risk for microvascular complications by about 33%. Lowering cholesterol levels can reduce the risk for CAD and CVD by approximately 20% to 50%. Eating a healthy diet, engaging in physical activity, and not smoking can further reduce the risk for complications.

Data from several observational studies suggest that weight loss can also reduce the risk for diabetes-related complications. Definitive information about the relationship between weight loss and macrovascular complications will eventually be provided by the Look AHEAD Study, a prospective, randomized controlled trial that includes more than 5000 overweight or obese individuals with type 2 diabetes. One-year results of this long-term trial showed that the average weight loss of 8.6% in the intensive lifestyle intervention group was associated with an improvement in CVD risk factors.
Several other prevention strategies can also significantly reduce the risk and severity of diabetes complications.

Detecting and treating early diabetic kidney disease by lowering blood pressure can reduce the decline in kidney function by 30% to 70%.

Detecting and treating diabetic eye disease can reduce the development of severe vision loss by approximately 50% to 60%.

Comprehensive foot care programs, which include daily examinations by the patient or caregiver and annual examinations by a health care provider, can reduce amputation rates by 45% to 85%.
Because microalbuminuria and macroalbuminuria are often used as end points in diabetes outcome studies, basic knowledge about these conditions is necessary for understanding the findings of key outcome trials. Albumin is a common water-soluble protein found in the body. Because the albumin concentration in the urine is a measure of renal health, it should be measured at the time of diagnosis and then annually in persons with type 2 diabetes. The urine spot collection technique is a convenient and accurate means of measuring albumin excretion.

As shown in the table, persons with normal kidney function have an albumin concentration of less than 30 μg/mg creatinine, whereas the concentration ranges from 30 to 299 μg/mg creatinine in persons with microalbuminuria and is at least 300 μg/mg creatinine in those with macroalbuminuria.

Microalbuminuria is important because it is a marker for the development of nephropathy in patients with type 2 diabetes and because it is a well-established marker of cardiovascular disease 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. We will discuss abnormalities of albumin excretion in greater detail in the section that deals with diabetic nephropathy.
The glomerular filtration rate (GFR) is considered the best overall index of kidney function. GFR is seldom measured directly; 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, including age, gender, and sometimes ethnicity. A normal eGFR is a value above 90 mL/min/1.73 m² of body surface area (BSA). Chronic kidney disease (CKD) is defined as an eGFR below 60 mL/min/1.73 m² BSA for at least 3 months.

Appreciating the significance of the glomerular filtration rate (GFR) is also important for understanding some of the major complications of diabetes. The 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, including age, gender, and sometimes ethnicity.

A normal eGFR is a value above 90 mL/min/1.73 m² of body surface area (BSA). Chronic kidney disease (CKD) is defined as an eGFR below 60 mL/min/1.73 m² BSA for at least 3 months.

We will discuss the significance of eGFR values in greater detail later in this activity.
Macrovascular complications of diabetes include __________.

a) coronary artery disease and altered clotting factors
b) peripheral arterial disease and retinopathy
c) cerebrovascular disease and peripheral arterial disease
d) myocardial infarction and osteoporosis
The correct answer is c.

Macrovascular complications of diabetes include cerebrovascular disease and peripheral arterial disease.
Several large outcome studies have demonstrated the capacity of intensive glycemic control to reduce the frequency of diabetic complications. The Diabetes Control and Complications Trial (DCCT) evaluated the effects of different treatment approaches on long-term complications in persons with type 1 diabetes. A total of 1441 participants were randomized to receive intensive or standard treatment. Patients in the intensive treatment group received insulin pump therapy or at least 3 daily insulin injections, in addition to frequent self-monitoring of blood glucose. Patients in the standard treatment group received 1 or 2 insulin injections per day.

At about 6.5 years of follow-up, patients who received intensive treatment had better glycemic control and a lower risk for complications than those who received standard treatment. Mean plasma glucose and A1C levels in patients who received standard treatment were 231 mg/dL and 9.0%, respectively, compared with 155 mg/dL and 7.2%, in those who received intensive treatment. These differences were statistically significant.

Percent risk reduction in retinopathy, microalbuminuria, macroalbuminuria, and neuropathy in patients who received intensive therapy was 76%, 34%, 44%, and 69%, respectively. These reductions were also significant compared with reductions in the standard treatment group. The relative youth of the patient population made detection of treatment-related differences in the rate of macrovascular disease unlikely. A 41% reduction in macrovascular risk was noted, but was not statistically significant.
The Epidemiology of Diabetes Interventions and Complications (EDIC) study followed patients after the DCCT for an additional 8 years to determine whether the effects of intensive therapy could be sustained.

After DCCT ended, the difference in A1C levels between the intensive and standard treatment groups diminished. Nevertheless, differences in outcomes between the 2 groups persisted. These differences included the risk for developing microvascular and macrovascular complications.

The EDIC study showed a:

- 59% reduction in the risk for new cases of microalbuminuria
- 84% reduction in the risk for new cases of macroalbuminuria
- 42% reduction in the risk for any macrovascular event
- 57% reduction in the risk for nonfatal myocardial infarction (MI), nonfatal stroke, and death from cardiovascular disease

All of these reductions were statistically significant.

The reduction in microvascular and macrovascular events observed in patients who initially received intensive treatment has been attributed to the metabolic memory of tight glucose control that persists over time. Therefore, the results of the EDIC study suggest that glycemic control can have long-term benefits at any point in the course of diabetes.
Unlike DCCT and the EDIC study, which evaluated the effects of intensive therapy in people with type 1 diabetes, the United Kingdom Prospective Diabetes Study (UKPDS) assessed the effects of intensive interventions in people with type 2 diabetes.

In UKPDS, 3867 patients with newly diagnosed diabetes were randomized to intensive therapy with a sulfonylurea or insulin or to standard therapy with dietary modification.

Over 10 years, participants who received intensive therapy maintained a median A1C of 7.0%, whereas those who received standard therapy had a mean A1C of 7.9%.

Intensive therapy was associated with clinically and statistically significant reductions in the risk for developing any diabetes-related complication (12%), microvascular complications (25%), retinopathy (21%), and albuminuria (34%). Intensive therapy was also associated with a 16% reduction in the risk for macrovascular events, but this reduction was not statistically significant.
The UKPDS showed that each 1% reduction in A1C resulted in a 21% reduction in the incidence of any clinical complication, a 21% reduction in diabetes-related deaths, a 14% reduction in MI, and a 37% reduction in microvascular complications, with no threshold for any end point.

In addition to evaluating the benefits of glycemic control, the UKPDS assessed the effects of lowering systolic blood pressure (SBP). For each 10-mm Hg reduction in SBP, there was a 12% reduction in the incidence of any clinical complication, a 15% reduction in deaths, an 11% reduction in MI, and a 13% reduction in microvascular complications.

All of these reductions were highly statistically significant.
Long-Term Risk Reduction in UKPDS Follow-up Study

Patient monitoring continued after the conclusion of the UKPDS, and 10-year follow-up data were published in 2008. Although differences in A1C levels between the conventional and intensive therapy groups were lost after the first year of follow-up, the investigators continued to observe significant differences in other end points after 10 years.

As shown in the graph on the left, compared with those who received conventional therapy, patients who received intensive therapy with a sulfonylurea and insulin had a significantly lower risk of experiencing any diabetes-related end point, MI, or microvascular disease.

As shown on the right, compared with conventionally treated patients, those receiving intensive metformin therapy had a significantly reduced risk for experiencing any diabetes-related end point or MI.

The investigators concluded that their results highlight the importance of glucose lowering in reducing the risk for macrovascular events. These findings emphasize the importance of achieving optimal glycemic control in patients with type 2 diabetes.
The Steno 2 study also compared the effects of intensive and standard therapy on the development of diabetes complications in patients with type 2 diabetes.

Eighty patients with type 2 diabetes and microalbuminuria were assigned to receive standard therapy according to national guidelines. Another 80 patients received intensive treatment, with stepwise implementation of behavior modification and pharmacologic therapy that targeted hyperglycemia, hypertension, dyslipidemia, and microalbuminuria, along with secondary prevention of cardiovascular disease with aspirin.

After approximately 8 years of follow-up, intensive multifactorial intervention reduced the risk of microvascular and cardiovascular events by about 50%.

This graph shows Kaplan-Meier estimates for the composite end point of death from cardiovascular causes, nonfatal MI, coronary artery bypass grafting, percutaneous coronary intervention, nonfatal stroke, amputation, or surgery for PVD in the 2 groups. Intensive multifactorial intervention was associated with a 20% reduction in the risk for cardiovascular events.
### Current Management Goals

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ADA</th>
<th>AACE</th>
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<tbody>
<tr>
<td>A1C (%)</td>
<td>&lt;7</td>
<td>≤6.5</td>
</tr>
<tr>
<td>Fasting/preprandial glucose (mg/dL)</td>
<td>70–130</td>
<td>&lt;110</td>
</tr>
<tr>
<td>Postprandial glucose (mg/dL)</td>
<td>&lt;180*</td>
<td>&lt;140 †</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>&lt;130/80</td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>&lt;100 (&lt;70 for existing CVD)</td>
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<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>&gt;40 for men, &gt;50 for women</td>
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</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>&lt;150</td>
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</table>

AACE = American Association of Clinical Endocrinologists; ADA = American Diabetes Association; LDL = low-density lipoprotein; HDL = high-density lipoprotein.

*Peak postprandial capillary plasma glucose.
†2-Hour postprandial glucose.

Current management goals for diabetes developed by the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) aim to reduce the risk of complications by improving glycemic control, reducing blood pressure, and treating dyslipidemia.

The glycemic goals recommended by the ADA and the AACE are based on data from major outcome trials, including those reviewed in earlier slides. These goals reflect the findings that sustained reductions in blood glucose levels decrease the risk of developing microvascular and macrovascular complications. Because there is no threshold below which the risk of complications is zero, these targets are intended to maintain glucose levels as near to normal as possible without an excessive risk of hypoglycemia.

Treating hypertension to reach the blood pressure target of <130/80 mm Hg has been shown to reduce macrovascular complications as well as microvascular complications—especially nephropathy.

Clinical evidence also suggests that attaining the recommended lipid goals decreases the risk of primary and secondary cardiovascular events as well as cardiovascular-related deaths.
Overall glycemic control is improving in the United States. A recent analysis of National Health and Nutrition Examination Survey (NHANES) data showed that the mean estimated A1C for the US population with diagnosed type 1 or type 2 diabetes improved significantly between 1988 and 2006, from about 7.7% to about 7.0%. Most of this improvement occurred between 2000 and 2002.

Probable reasons for this recent improvement in glycemic control include strengthened clinical guidelines, improved diabetes disease management programs, improved delivery of diabetes care services in the health system, enhanced public health education, and the introduction of new drugs for glycemic control.

Between 1988 and 2006 there were also significant improvements in mean SBP and diastolic blood pressure, total cholesterol, and high-density lipoprotein (HDL) cholesterol levels. The net result of these improvements is a projected 1-year increase in the life expectancy of persons with newly diagnosed diabetes.
Although overall glycemic control has improved in the United States in recent years, this improvement has been uneven across ethnic groups.

The graphs on this slide show analyses of NHANES A1C data by ethnic group for the 1999–2000, 2001–2002, and 2003–2004 waves. (Analyses of more recent data by ethnicity have not yet been published.)

These graphs show that much needs to be done to improve glycemic control, particularly among black non-Hispanic and Hispanic persons. In Hispanic participants, for example, the mean A1C rose between the beginning and the end of the study period, from 8.1% to 8.4%, and 63% had an A1C of at least 7% at the end of the study period.

The mean A1C dropped from 8.3% to 7.6% in black non-Hispanic persons by the end of the study period, but this level was still well above the ADA threshold value. Nearly half of the participants in this ethnic group had an A1C of at least 7% at the end of the period.

These differences provide evidence of persistent disparities in access to medical care and in the quality of medical care among different ethnic groups in the United States.
Baseline Data and Methods: ACCORD, ADVANCE, VADT

<table>
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<tr>
<th>Characteristic</th>
<th>ACCORD</th>
<th>ADVANCE</th>
<th>VADT</th>
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<tbody>
<tr>
<td>Patients</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>N</td>
<td>10,251</td>
<td>11,140</td>
<td>1791</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>62</td>
<td>66</td>
<td>60</td>
</tr>
<tr>
<td>Diabetes duration (years)</td>
<td>10</td>
<td>8</td>
<td>11.5</td>
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<tr>
<td>Median baseline A1C (%)</td>
<td>8.1</td>
<td>7.2</td>
<td>9.4</td>
</tr>
<tr>
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<tr>
<td>A1C study goal (%)</td>
<td>&lt;6.0 vs 7.0–7.9</td>
<td>≤6.5 vs “local guidelines”</td>
<td>&lt;6.0 (action if &gt;6.5) vs planned separation of 1.5</td>
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<tr>
<td>Glycemic control,</td>
<td>Multiple drugs</td>
<td>Multiple drugs</td>
<td>Multiple drugs</td>
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<tr>
<td>intensive vs standard</td>
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<tr>
<td>therapy</td>
<td>gliclizide</td>
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</tbody>
</table>


Although landmark outcome trials have shown a relationship between intensive glycemic control and a significant reduction in the risk for microvascular complications, confirming a relationship between glycemic control and a significant reduction in the risk for macrovascular complications has proven more difficult.

In the hope of clarifying the relationship between tight control and macrovascular complications in persons with type 2 diabetes, 3 large long-term outcome trials were launched in the past decade to compare the effects of intensive versus standard glycemic control on cardiovascular disease outcomes in relatively high-risk patients with established diabetes. These trials were:

- Action to Control Cardiovascular Risk in Diabetes (ACCORD)
- Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE), and
- Veterans Affairs Diabetes Trial (VADT)

The complete name of the ADVANCE trial includes the European brand names of 2 products. Preterax is the name of a fixed combination of perindopril, an angiotensin-converting enzyme (ACE) inhibitor, and indapamide, a diuretic. It is licensed in Europe for the treatment of hypertension in patients who require combination therapy. Diamicron is a European brand name for gliclizide, a sulfonylurea.
This slide summarizes the primary results of ACCORD, ADVANCE, and VADT. In each case, the primary outcome was a composite of fatal and nonfatal macrovascular events. In the ADVANCE trial, microvascular events were also included in the primary outcome.

In each of these studies, the primary results failed to show a significant reduction in macrovascular outcomes with intensive glycemic control in the populations studied.

In both ACCORD and VADT, the risk of death was greater in patients who received intensive glycemic therapy than in those who received standard therapy. The finding of a 1.22 hazard ratio for mortality in the intensive therapy group led to the early discontinuation of the glycemic control arm of ACCORD, although other arms of the study continued.
To gain greater insight into the relationship between intensive glycemic control and macrovascular outcomes, the Control Group conducted a prospectively planned meta-analysis. This analysis included more than 27,000 patients, including participants in ACCORD, ADVANCE, and VADT. Collectively, these patients had nearly 2400 major cardiovascular events following randomization.

The analysis showed that allocation to intensive glucose control reduced the risk of experiencing a major macrovascular event by 9%. This significant reduction was largely due to a 15% reduction in the risk for MI with intensive glucose control.

Cardiovascular outcomes were significantly better in intensively treated patients without established macrovascular disease than in those with a history of macrovascular disease.

In this analysis, intensive glucose control did not have a significant effect on mortality. Instead, the patients with the highest mortality were those randomized to intensive therapy who were unable to get to goal.

Interpretation of the data from these large and complex outcome studies is ongoing. Many additional primary and secondary publications will be appearing during the next few years.
Based on available evidence, the ADA has made several recommendations concerning glycemic control and macrovascular risk reduction.

The overall recommendation is that glycemic goals should be individualized. The general A1C goal of less than 7% appears reasonable for many adults.

For selected individual patients, health care providers might reasonably suggest even lower A1C goals than the general goal of less than 7% if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Such patients might include those with a short duration of diabetes, long life expectancy, and no significant CVD.

However, a less stringent A1C goal may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, or extensive comorbidities. A less stringent goal may also be appropriate for individuals with long-standing diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents, including insulin.
In major outcome studies of patients with diabetes, intensive glycemic control __________.

a) consistently reduced the risk for microvascular and macrovascular complications in all populations
b) consistently reduced the risk for microvascular complications and reduced the risk for macrovascular complications in many populations
c) consistently reduced the risk for macrovascular complications, but had a variable effect on microvascular complications
d) consistently reduced the risk for microvascular and macrovascular complications, but was usually associated with increased mortality rates

In major outcome studies of patients with diabetes, intensive glycemic control __________.

a) consistently reduced the risk for microvascular and macrovascular complications in all populations
b) consistently reduced the risk for microvascular complications and reduced the risk for macrovascular complications in many populations
c) consistently reduced the risk for macrovascular complications, but had a variable effect on microvascular complications
d) consistently reduced the risk for microvascular and macrovascular complications, but was usually associated with increased mortality rates
The correct answer is b.

In major outcome studies of patients with diabetes, intensive glycemic control consistently reduced the risk for microvascular complications and reduced the risk for macrovascular complications in many populations.
Cardiovascular Risk Factors

- Hypertension
- Obesity (BMI ≥ 30 kg/m²)
- Dyslipidemia
- Cigarette smoking
- Physical inactivity
- Microalbuminuria
- Diabetes mellitus
- GFR < 60 mL/min
- Age (>55 years for men, >65 years for women)
- Family history of premature CVD (<55 years for men, <65 years for women)


In addition to diabetes, numerous cardiovascular risk factors contribute to the development of macrovascular complications. These include modifiable risk factors, such as hypertension, obesity, dyslipidemia, smoking, physical inactivity, and microalbuminuria. Note that microalbuminuria can be modified by the administration of ACE inhibitors or angiotensin II receptor blockers, as well as by intensive management of diabetes.

Hypertension, obesity, and dyslipidemia commonly coexist with diabetes. Together, these conditions constitute the metabolic syndrome.

Nonmodifiable risk factors include diabetes itself, a GFR of < 60 mL/min/173 m² BSA, age, and family history.
## Macrovascular Complications

<table>
<thead>
<tr>
<th>CAD</th>
<th>Cerebrovascular disease</th>
</tr>
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<tbody>
<tr>
<td>Atherosclerosis</td>
<td>Transient ischemic attack</td>
</tr>
<tr>
<td>Angina</td>
<td>Ischemic stroke</td>
</tr>
<tr>
<td>MI</td>
<td>Cerebral thrombosis</td>
</tr>
<tr>
<td>PAD</td>
<td>Cerebral occlusion</td>
</tr>
<tr>
<td>Ischemia</td>
<td>Hemorrhagic stroke</td>
</tr>
<tr>
<td>Infarction</td>
<td>Aneurysm</td>
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<tr>
<td></td>
<td>Arteriovenous malformation</td>
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</table>

As previously mentioned, the macrovascular complications of diabetes include 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 the progression of atherosclerosis in persons with diabetes.

The blockage of the coronary arteries that occurs with CAD can lead to the development of the acute coronary syndrome (ACS), a constellation of clinical symptoms caused by myocardial ischemia. The components of ACS include:

- Angina (chest pain that occurs with exertion)
- Unstable angina (chest pain that occurs at rest), and
- MI resulting from coronary thrombosis or occlusion

When vessels supplying the brain become blocked, transient ischemic attack or stroke can occur. The 2 types of stroke are:

- Ischemic stroke, which results from cerebral thrombosis or occlusion, and
- Hemorrhagic stroke, which results from rupture of an aneurysm or arteriovenous malformation
Several studies have shown that women with diabetes and CAD have poorer outcomes than men. A meta-analysis of 37 studies, which investigated fatal CAD in persons with type 2 diabetes, found that the relative risk for CAD death was 50% greater in diabetic women than in diabetic men. This increased risk is due in part to a heavier risk factor burden in diabetic women than in nondiabetic women or diabetic men.

Women with CAD and diabetes are less likely than men to have their modifiable risk factors controlled or to receive lipid-lowering treatments, suggesting a treatment bias in favor of men.

Furthermore, some investigators have suggested that inflammation may interact with female sex hormones, decreasing their protective effect on body fat distribution and insulin action. In postmenopausal women with diabetes, the loss of the protective effect of estrogen increases the risk for CAD and fatal CAD.

In both women and men, atypical symptoms may contribute to poor outcomes. For example, patients may complain of a sore shoulder or toothache rather than chest pain.
Screening for Macrovascular Disease Risk

- Assess for CV risk factors at least annually
  - Dyslipidemia
  - Hypertension
  - Smoking
  - Family history of premature coronary disease
  - Presence of microalbuminuria or macroalbuminuria

- Stratify patients by 10-year risk and treat risk factors accordingly
  - Online risk calculators available

- Screen for PAD using ankle-brachial index (ABI)

All patients with diabetes should have a cardiovascular risk assessment at least annually. Patients should be stratified by their 10-year risk for a cardiovascular disease event, and risk factors should be treated accordingly. Several online risk calculators are available, including:

- Framingham risk calculator

- Mayo Clinic heart disease risk calculator
  (http://www.mayoclinic.com/health/heart-disease-risk/HB00047)

- Foundation for Informed Medical Decision Making cardiovascular risk calculator
  (http://cardiacriskcalculator.org/)

Patients should be told to report any pain above the waist, as it may be a symptom of MI.

The ankle-brachial index (ABI) is used to screen for PAD. The ABI is a ratio of SBP at the ankle and brachial artery. Screening is performed by placing the blood pressure cuff just above the ankle and inflating to just above the patient’s SBP while using a handheld Doppler device 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 are 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, moderate obstruction; and less than 0.4, severe obstruction.
Since diabetes itself, hypertension, and dyslipidemia are all contributing factors to macrovascular complications in persons with diabetes, each should be managed carefully, following consensus guidelines developed by the ADA and the American Heart Association. Maintaining glycemic control (A1C <7%), regulating blood pressure (goal <130/80 mm Hg), and controlling lipid levels are essential for the primary prevention of cardiovascular disease.

Lifestyle management considerations, such as medical nutrition therapy, physical activity, weight management, and smoking cessation, are also important.

Use of antiplatelet therapy is recommended as a primary prevention strategy for patients at increased cardiovascular risk.
Many lifestyle changes can help to reduce SBP.

Weight reduction generally has the greatest impact on SBP. Every 10 kg of weight loss can reduce SBP by 5 to 20 mm Hg.

The Dietary Approaches to Stop Hypertension (DASH) diet is also very effective in lowering SBP and can provide an 8– to 14–mm Hg reduction.

Other modifications that are effective in lowering blood pressure are reducing dietary sodium, which can result in a decrease of 2 to 8 mm Hg; increasing physical activity, which can lower SBP by 4 to 9 mm Hg; and moderating alcohol intake, which can reduce SBP by 2 to 4 mm Hg.
The ADA and Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) both recommend a blood pressure less than 130/80 mm Hg for people with diabetes. This target is lower than that for people without diabetes (<140/90 mm Hg), because a more aggressive approach to reducing cardiovascular and renal morbidity and mortality is needed in persons with diabetes.

JNC-7 guidelines also recommend that treatment and prevention of high blood pressure begin with lifestyle modifications, such as weight reduction, adoption of the DASH diet, and increased physical activity.

Combination treatment with 2 or more antihypertensive drugs from different classes is often needed to achieve blood pressure goals. Specific drugs are recommended for patients with compelling indications. Individuals with compelling indications are patients with hypertension who are at high risk for cardiovascular events as a direct consequence of hypertension or because of comorbid conditions such as diabetes and CAD.

Consultation with a cardiologist with expertise in the management of hypertension is recommended for patients who do not attain their blood pressure goals after optimal dosages and a trial of additional drugs.
The JNC-7 recommendations for specific antihypertensive drug use according to compelling indication are based on data from outcome studies. The compelling indication is managed in conjunction with blood pressure regulation. All drug classes except aldosterone antagonists (eg, spironolactone) are recommended for the management of hypertension in persons with diabetes.

The ADA recommends that drug therapy for patients with diabetes and hypertension include either an ACE inhibitor or an angiotensin receptor blocker (ARB). If one class is not tolerated, the other should be substituted.
One of the substudies of the ACCORD trial investigated whether intensive therapy to reach a target SBP less than 120 mm Hg was associated with a significantly lower risk for cardiovascular events than standard therapy to reach a target SBP less than 140 mm Hg.

After 1 year, mean SBP was 119.3 mm Hg in the intensive therapy group and 133.5 mm Hg in the standard therapy group. The incidence of any stroke and nonfatal stroke was significantly lower in the intensive therapy group than in the standard therapy group. Otherwise, the incidence of cardiovascular outcomes was similar in the 2 groups.

The incidence of serious adverse events attributed to antihypertensive treatment was significantly higher in the intensive therapy group (3.3%) than in the standard therapy group (1.3%).

The investigators noted that the event rate observed in the standard therapy group was almost 50% lower than the expected rate, and speculated that this may have been due to frequent use of statins in the trial and exclusion of very high-risk patients from this substudy. The investigators concluded that their findings do not support the use of intensive therapy to reach a target SBP less than 120 mm Hg in patients with type 2 diabetes. In light of these findings, the current ADA blood pressure goal of less than 130/80 mm Hg remains in force.
Lipid parameters recommended by the ADA are low-density lipoprotein (LDL) cholesterol less than 100 mg/dL for persons without overt CVD and less than 70 mg/dL for individuals with overt CVD. HDL-cholesterol goals are greater than 40 mg/dL for men and greater than 50 mg/dL for women. The triglyceride goal is less than 150 mg/dL.

Most patients should have their fasting lipid profile evaluated at least annually. Patients with low-risk lipid profiles can have repeat assessments every 2 years.

To improve the lipid profile, lifestyle modification should be recommended for all patients with diabetes. Goals of lifestyle modification should include the reduction of saturated fat, trans fat, and cholesterol intake; increase of n-3 fatty acids, viscous fiber, and plant stanols/sterols; weight loss (if indicated); and increased physical activity.

Statin therapy should be added to lifestyle therapy, regardless of baseline lipid levels, for patients with overt CVD and for those without overt CVD who are over the age of 40 years and have 1 or more other CVD risk factors. For lower-risk patients, statin therapy should be considered in addition to lifestyle therapy if LDL cholesterol remains above 100 mg/dL or if multiple CVD risk factors are present. If drug-treated patients do not reach LDL targets on maximal-tolerated statin therapy, a reduction in LDL cholesterol of approximately 30% to 40% from baseline is an alternative therapeutic goal.
A substudy of the ACCORD trial investigated whether combination therapy with a statin plus a fibrate, compared with statin monotherapy, would reduce the risk for CVD in patients with type 2 diabetes who were at high risk for CVD. Patients treated with open-label simvastatin were randomized to receive either masked fenofibrate or placebo. The primary outcome was the first occurrence of nonfatal MI, nonfatal stroke, or death from a cardiovascular cause. Secondary outcomes included a composite of the primary outcome plus revascularization or hospitalization for congestive heart failure, a major coronary disease event, nonfatal MI, death from any cause, or death from a cardiovascular cause.

After a mean follow-up period of 4.7 years, there were no significant differences between the 2 study groups for the primary outcome or any secondary outcome. Subgroup analysis indicated that men benefited from fenofibrate therapy, whereas women did not. Patients who had both a triglyceride level in the highest third and an HDL-cholesterol level in the lowest third appeared to benefit from fenofibrate, whereas other fenofibrate patients did not.

The investigators concluded that the findings of this study do not support the use of combination fibrate–statin therapy, rather than statin therapy alone, to reduce cardiovascular risk in the majority of patients with type 2 diabetes who are at high risk for cardiovascular disease.
ADA Recommendations for Antiplatelet Therapy

- Consider low-dose aspirin therapy (75–162 mg/day) as a primary prevention strategy in patients whose 10-year CV risk is >10%
- Aspirin should not be recommended for CVD prevention for adults with diabetes at low CVD risk, as the potential adverse effects from bleeding offset the potential benefits
- Low-dose aspirin therapy might be considered for persons with diabetes at intermediate CVD risk
- Aspirin therapy should be used as a secondary prevention strategy in patients with a history of CVD
- Clopidogrel (75 mg/day) should be used for patients with CVD and documented aspirin allergy

According to the ADA, low-dose aspirin therapy (75–162 mg/day) should be considered as a primary prevention strategy in patients whose 10-year cardiovascular risk exceeds 10%. This includes most men older than 50 years of age or women older than 60 years of age who have at least 1 additional major risk factor, including family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria.

Aspirin should not be recommended for CVD prevention for adults with diabetes at low CVD risk, because the potential adverse effects from bleeding offset the potential benefits.

Low-dose aspirin use for prevention might be considered for persons with diabetes at intermediate CVD risk until further research is available.

Aspirin therapy (75–162 mg/day) should be used as a secondary prevention strategy in patients with diabetes with a history of CVD.

Clopidogrel (75 mg/day) should be used for patients with CVD and documented aspirin allergy.

Use of combination therapy with aspirin (75–162 mg/day) and clopidogrel (75 mg/day) is reasonable for up to 1 year after an acute coronary event.
Current ADA guidelines include the recommendation for

a) A1C ≤7%

b) blood pressure <120/80 mm Hg

c) HDL cholesterol <50 mg/dL in women

d) triglycerides <150 mg/dL
The correct answer is d.

Current ADA guidelines include the recommendation for triglycerides <150 mg/dL.
Diabetic nephropathy occurs in 20% to 40% of patients with diabetes. According to the US Renal Data System (USRDS), more than 527,000 US residents were treated for ESRD in 2007. These included 111,000 patients who began ESRD therapy in that year. Diabetes was the cause of nearly half of the new cases of ESRD.

At the end of 2007, nearly 24,000 patients with diabetes were on the wait list for kidney and kidney/pancreas transplants.

Estimated direct medical costs in 2007 for diabetes-related ESRD were $15.5 billion.
Diabetic nephropathy has 5 stages:

- **Stage 1** is characterized by hyperfiltration and renal hypertrophy. Changes are usually seen when diabetes is diagnosed. Increased hyperfiltration is a consequence of hyperglycemia.

- During **Stage 2**, structural changes occur. These include glomerular basement membrane thickening, mesangial expansion (expansion of phagocytic cells of the mesangium), and diffuse intercapillary glomerulosclerosis (a degenerative process resulting in scarring of the renal glomeruli). The disease remains clinically silent at this stage.

- During **Stage 3**, also referred to as incipient diabetic nephropathy, microscopic amounts of albumin (microalbuminuria) inadvertently slip through sclerosed glomerular membranes, signifying a progressive deterioration in kidney filtration. Metabolic wastes start accumulating in the blood, since unaffected nephrons can no longer compensate and responsiveness to diuretic therapy decreases. Blood pressure may be normal or slightly elevated. This stage usually develops after 7 to 15 years of diabetes.

- **Stage 4**, also referred to as overt or clinical diabetic nephropathy, is characterized by detection of significantly large amounts of protein in the urine (macroalbuminuria). Notable amounts of metabolic waste, particularly urea and creatinine, begin to accumulate. Patients generally do not become symptomatic until this stage, when oliguria, edema, and hypertension can develop.

- **Stage 5**, renal failure or ESRD, results in aggressive treatment, deteriorating vasculature.

The ADA recommends that serum creatinine be measured at least annually in all adults with diabetes. As discussed earlier in this activity, the serum creatinine level is used to calculate the eGFR and stage the level of CKD, if present.
### Risk factors for diabetic nephropathy

Risk factors for diabetic nephropathy include duration of diabetes and hypertension. Screening for nephropathy should include:

- **Evaluation of blood pressure** at every office visit, with a blood pressure goal less than 130/80 mm Hg

- **Screening for abnormalities in albumin excretion**, usually by measuring the albumin-to-creatinine ratio in a random spot collection. This screening should be performed annually, beginning at diagnosis, for people with type 2 diabetes and annually, beginning 5 years after diagnosis, for people with type 1 diabetes. The reason for this difference in timing is that the onset of type 1 diabetes is usually clear cut, whereas people may have type 2 diabetes for many years prior to diagnosis.

- **Regardless of the degree of urine albumin excretion**, serum creatinine should be measured annually in all adults to calculate the eGFR. As discussed earlier, the eGFR is used to estimate the stage of diabetic nephropathy.

### Screening for Diabetic Nephropathy

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Timing</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure</td>
<td>At each office visit</td>
<td>Goal: &lt;130/80 mm Hg</td>
</tr>
<tr>
<td>Urine albumin excretion</td>
<td>Type 2: annually, beginning at diagnosis</td>
<td>Normal: &lt;30 μg albumin/mg creatinine Microalbuminuria: 30–299 μg albumin/mg creatinine Macroalbuminuria: ≥300 μg albumin/mg creatinine</td>
</tr>
<tr>
<td>(measurement of albumin-to-creatinine ratio in random spot collection)</td>
<td>Type 1: annually, beginning 5 years after diagnosis</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine (to determine eGFR)</td>
<td>Annually in all adults, regardless of degree of urine albumin excretion</td>
<td>Normal: 0.5 to 1.4 mg/dL</td>
</tr>
</tbody>
</table>

In the treatment of nonpregnant patients with micro- or macroalbuminuria, either ACE inhibitors or ARBs should be used.

- In patients with type 2 diabetes, hypertension, and microalbuminuria, both ACE inhibitors and ARBs have been shown to delay the progression to macroalbuminuria.
- In patients with type 2 diabetes, hypertension, macroalbuminuria, and renal insufficiency (serum creatinine $>1.5$ mg/dL), ARBs have been shown to delay the progression of nephropathy.
- In patients with type 1 diabetes, hypertension, and any degree of albuminuria, ACE inhibitors have been shown to delay the progression of nephropathy.

In patients with CKD, reduction of protein intake to the levels shown in the table may improve measures of renal function, including the urine albumin excretion rate and the GFR, and is therefore recommended.

When ACE inhibitors or ARBs are used, serum creatinine levels should be monitored for the development of acute kidney disease and potassium levels should be monitored for the development of hyperkalemia.
Management of ESRD

- Timing of renal replacement therapy
  - Planning should begin when serum creatinine level reaches 3 mg/dL (or sooner)
  - Therapy usually begins when serum creatinine is >6 mg/dL or creatinine clearance is <20 mL/min; should begin before development of severe uremic symptoms
  - Treatment options depend on patient characteristics and preferences and include no treatment, hemodialysis, peritoneal dialysis, kidney transplantation, and kidney–pancreas transplantation
  - Maintenance of glycemic control during dialysis is challenging, and best carried out with insulin therapy
  - Rates of mortality and morbidity, particularly due to CVD and infections, are high in persons with ESRD
  - All-cause mortality rates 6.7–8.5 times higher for dialysis patients than for their counterparts in the general population

USRDS data show that many patients and their families do not plan for ESRD treatment until they are severely symptomatic. Ideally, patients should have their initial contact with a nephrologist when their serum creatinine level reaches 2 mg/dL and should begin active planning when this level reaches 3 mg/dL. Initiation of renal replacement therapy typically begins when serum creatinine exceeds 6 mg/dL or creatinine clearance is less than 20 mL/min. The most important consideration, however, is that treatment begin before development of severe uremic symptoms, such as uremic pericarditis, treatment-refractory hypertension, or disabling lethargy, nausea, or vomiting.

Treatment options depend on the patient’s overall condition and preference, and include no treatment, hemodialysis, peritoneal dialysis, kidney transplantation, and kidney–pancreas transplantation. Maintenance of glycemic control in patients who are receiving dialysis is challenging, and is best achieved with insulin therapy.

Rates of mortality and morbidity, particularly due to CVD and infections, are high in patients with ESRD. All-cause mortality rates are 6.7 to 8.5 times higher for dialysis patients than for their counterparts in the general population.

Diabetic retinopathy is a highly specific vascular complication of type 1 and type 2 diabetes. During their first 2 decades with diabetes, nearly all persons with type 1 diabetes and more than 60% 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.

As shown on the lower right of the 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.
Clinical Features of Diabetic Retinopathy

<table>
<thead>
<tr>
<th>Progression*</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild NPDR</td>
<td>Increased vascular permeability, microaneurysms, intraretinal hemorrhages</td>
</tr>
<tr>
<td>Moderate NPDR</td>
<td>Venous caliber changes, intraretinal microvascular abnormalities, intraretinal hemorrhages</td>
</tr>
<tr>
<td>Severe NPDR</td>
<td>Retinal ischemia, intraretinal microvascular abnormalities, extensive hemorrhage, and microaneurysms</td>
</tr>
<tr>
<td>PDR</td>
<td>Ischemia-induced neovascularization, vitreous hemorrhage, retinal traction, tears, and detachment</td>
</tr>
</tbody>
</table>

NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy.  
*Diabetic macular edema (DME) can develop during any stage of retinopathy.

The rate of progression of diabetic retinopathy varies among patients. However, unless diabetic retinopathy is treated, it generally progresses through 4 stages, from mild nonproliferative diabetic retinopathy (NPDR) to proliferative diabetic retinopathy (PDR). Diabetic macular edema (DME), a contributor to blindness, can develop at any stage of retinopathy. Clinically significant macular edema occurs when edema threatens the center of vision or is within 500 μm of the central fovea of the retina.

Mild NPDR is characterized by increased vascular permeability, microaneurysms, and intraretinal hemorrhages. Moderate NPDR is identified by venous caliber changes, intraretinal microvascular abnormalities (IRMAs), and intraretinal hemorrhages. Severe NPDR is characterized by retinal ischemia, IRMAs, extensive hemorrhage, and microaneurysms.

PDR occurs when new blood vessels form as a result of retinal ischemia. This usually occurs at the optic disk. The new vessels are very weak and tend to break, causing vitreous hemorrhage. The new vessels can also cause retinal traction, tears, and detachment.

In addition to diabetic retinopathy, people with diabetes may also experience cataracts, glaucoma, dry eye, and iritis.
Earlier we described the ACCORD outcomes trial and its blood pressure control substudy. Another ACCORD substudy, The ACCORD Eye Study, investigated whether intensive glycemic control, combination therapy for dyslipidemia, and intensive blood pressure control would limit the progression of diabetic retinopathy in individuals with type 2 diabetes. A total of 2856 patients were enrolled in this substudy.

This slide shows the proportion of participants who experienced retinopathy progression at the 4-year follow-up. Compared with those who received standard glucose-lowering therapy to maintain their A1C level in the range of 7.0% to 7.9%, participants who received intensive therapy with the intent of keeping their A1C level below 6% had a significantly lower progression rate. Similarly, participants whose dyslipidemia regimen included fenofibrate as well as simvastatin had a significantly lower progression rate than those who received simvastatin alone.

However, the progression rate of participants who received intensive blood pressure control to maintain their SBP below 120 mm Hg was not significantly different from that of participants who received standard blood pressure control to keep their SBP below 140 mm Hg.

The ACCORD Eye Study confirms the importance of controlling blood glucose and lipid levels to prevent the complications of diabetes.
Screening for Diabetic Retinopathy

- Dilated and comprehensive examinations should be performed by an ophthalmologist or optometrist who is knowledgeable and experienced in diagnosing diabetic retinopathy and is familiar with its management.
- If necessary, follow-up examinations can be done with retinal photographs (with or without dilation of pupil) and read by experts.

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation About Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial examination</td>
<td></td>
</tr>
<tr>
<td>Adults and children &gt;10 years</td>
<td>Within 5 years after onset</td>
</tr>
<tr>
<td>old with type 1 diabetes</td>
<td></td>
</tr>
<tr>
<td>Patients with type 2 diabetes</td>
<td>Shortly after diagnosis</td>
</tr>
<tr>
<td>Follow-up examination</td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>Annually in most cases</td>
</tr>
</tbody>
</table>

Initial screening for diabetic retinopathy should consist of a dilated and comprehensive eye examination performed by an ophthalmologist or optometrist who is knowledgeable and experienced in diagnosing this disorder and is skilled in its management. In areas where qualified eye care professionals are not available, initial and follow-up examinations can be done with retinal (fundus) photographs (with or without dilation of the pupil) that are read by a qualified eye specialist.

Since retinopathy is estimated to take at least 5 years to develop after the onset of hyperglycemia, patients with type 1 diabetes should have an initial examination within 5 years after the onset of diabetes. Because patients with type 2 diabetes have generally had years of undiagnosed diabetes, they should have an initial examination soon after diagnosis.

Follow-up examinations for patients with type 1 and type 2 diabetes should generally be repeated annually. Less frequent exams (every 2—3 years) may be considered following one or more normal eye exams. Exams are required more frequently if retinopathy is progressing.
Procedures Used to Treat 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

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

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.

Several procedures are used to treat diabetic retinopathy and DME. Laser photocoagulation therapy is generally considered the “gold standard” 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, clear aqueous fluid can fill the eye.
Currently, no drug therapy is specifically approved by the US Food and Drug Administration (FDA) for the treatment of diabetic retinopathy or DME, but some drugs are used off label and other agents are under active investigation for these indications.

Intravitreal injection of a corticosteroid, such as triamcinolone, has been successfully used in the eyes of patients with persistent DME and loss of vision following the failure of laser photoacoagulation therapy. However, reinjections are commonly needed, and patients may experience infection, glaucoma, and cataract formation.

Intravitreal injection of the anti–vascular endothelial growth factor agents pegaptamib and ranibizumab is approved for the treatment of neovascular (wet) age-related macular degeneration, and these agents are currently under investigation for the treatment of DME.

Fenofibrate is a peroxisome proliferator-activated receptor-α agonist that is indicated for the treatment of hypertriglyceridemia and mixed dyslipidemia. However, it has also been shown to reduce the frequency of laser treatment for DME and PDR and to reduce the progression of existing retinopathy.

The ARBs, which are primarily used for the treatment of hypertension, have been shown to delay the progression of nephropathy in patients with type 2 diabetes. However, the blockade of the renin-angiotensin system (RAS) that follows treatment with an ARB may also reduce the progression of diabetic retinopathy, since the RAS is expressed in the eye and RAS activation appears to play an important role in the development of diabetic retinopathy.
Diabetic neuropathies are heterogeneous, affecting different parts of the nervous system and have 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 text, the most common presentations are chronic sensorimotor distal symmetric neuropathy (DPN), which often involves the feet, and diabetic autonomic neuropathy (DAN), which can involve any system in the body.

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 blood pressure, 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 long-term poor glycemic control.
According to the ADA, all patients should be screened for DPN at diagnosis and at least annually thereafter. Screening for signs and symptoms of cardiovascular autonomic neuropathy, an important subcomponent of DAN, should be instituted upon diagnosis of type 2 diabetes and 5 years after diagnosis of type 1 diabetes.

Early recognition and appropriate management of neuropathy in patients with diabetes is important for many reasons:

- Nondiabetic neuropathies may be present in patients with diabetes and may be treatable
- Many treatment options exist for symptomatic diabetic neuropathy
- Up to 50% of cases of DPN are asymptomatic, and patients are at risk of insensate injury to their feet
- Autonomic neuropathy may involve every system in the body
- Cardiovascular autonomic neuropathy causes substantial morbidity and mortality
Patients should be screened annually for DPN 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 tests 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 signs and symptoms of DAN should be elicited carefully during the history and physical examination. Major clinical manifestations include resting tachycardia, exercise intolerance, orthostatic hypotension, gastroparesis, constipation, erectile dysfunction, sudomotor dysfunction, impaired neurovascular function, “brittle diabetes,” and hypoglycemic autonomic failure.

Cardiovascular autonomic neuropathy, a risk factor for CVD, is the most clinically important form of DAN. Patients should be checked for resting tachycardia (heart rate >100 bpm) and orthostasis (fall in SBP >20 mm Hg upon standing, without appropriate heart rate response). Patients should also be asked about symptoms that might indicate the presence of disturbances in autonomic nervous system function involving the skin, pupils, or gastrointestinal and genitourinary systems.
Specific treatment for underlying nerve damage in patients with diabetic neuropathy is not currently available. The first step in the management of patients with DPN is to aim for stable and optimal glycemic control. Although evidence from controlled clinical trials is lacking, several observational studies have suggested that neuropathic symptoms diminish when glycemic control improves and extreme blood glucose fluctuations are avoided.

Patients with painful DPN may benefit from pharmacologic treatment of their symptoms. Both pregabalin, an anticonvulsant, and duloxetine, a 5-hydroxytryptamine and norepinephrine uptake inhibitor, are approved by the FDA for the treatment of painful diabetic neuropathy. Other anticonvulsants and tricyclic drugs may also be beneficial.

Metanx®, which includes the active forms of folate, vitamin B₆, and vitamin B₁₂, is a prescription medical food indicated for the dietary management of endothelial function in patients with DPN. This agent increases nitric oxide synthesis, increasing blood flow to the peripheral nerves. Metanx® differs from other available treatments in that it promotes repair and regeneration of the myelin sheath rather than merely treating the pain associated with DPN.

Capsaicin cream, a substance P inhibitor that is applied to the skin, is often effective in relieving symptoms.

### Table: Management of DPN

<table>
<thead>
<tr>
<th>Class of Drug</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral agents</td>
<td></td>
</tr>
<tr>
<td>Tricyclics</td>
<td>Amitriptyline, nortriptyline, imipramine</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Gabapentin, carbamazepine, pregabalin*</td>
</tr>
<tr>
<td>5-Hydroxytryptamine and norepinephrine uptake inhibitor</td>
<td>Duloxetine*</td>
</tr>
<tr>
<td>Prescription medical food</td>
<td>Folate + vitamin B₆ + vitamin B₁₂ (Metanx®)†</td>
</tr>
<tr>
<td>Topical agent</td>
<td>Capsaicin cream</td>
</tr>
</tbody>
</table>

*US Food and Drug Administration (FDA) indication for treatment of painful diabetic neuropathy.
†FDA indication for the dietary management of endothelial dysfunction in patients with DPN.
At least annually, all adults with diabetes should have a comprehensive foot examination to identify high-risk conditions. Clinicians should ask about history of 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).

Vascular assessment should include inspection and assessment of pedal pulses to screen for PAD. The ABI should be determined for patients with symptoms of PAD. Determination of the ABI is also advisable for patients over age 50 years and for younger patients who have other PAD risk factors, including smoking, hypertension, hyperlipidemia, or a duration of diabetes more than 10 years.

Patients with diabetes and high-risk foot conditions should be educated regarding their risk factors and appropriate management. They should understand the implications of LOPS, the importance of daily foot monitoring, proper care of the foot including nail and skin care, and the selection of appropriate footwear.
Cardiovascular autonomic dysfunction is the most studied and clinically important form of DAN because of its potentially life-threatening consequences. Clinical features include resting tachycardia (defined as heart rate > 100 bpm), exercise intolerance, and orthostatic hypotension (defined as a fall in SBP > 20 mm Hg upon standing, without appropriate heart rate response). Additional features are difficulties with thermoregulation and disturbances involving the skin, pupils, gastrointestinal system, and genitourinary systems.

Exercise intolerance can be managed with graded supervised exercise and administration of an ACE inhibitor or beta blocker.

Patients with orthostatic hypotension benefit from slow changes in position, elevating the head of their bed, measures that increase plasma volume, and treatment with pharmacologic agents such as clonidine, mitodrine, and octreotide.

Patients with thermoregulation problems should be advised to avoid exercise in extreme heat and cold and to be vigilant about adequate hydration.
Gastrointestinal neuropathy can affect the esophagus, stomach, and intestines, causing symptoms that vary with the area 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. The dopamine antagonist metoclopramide 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 to prevent nausea. A dietitian should be consulted when designing a meal plan for a patient with gastroparesis. Dopamine antagonists such as metoclopramide and domperidone can be used before meals to improve gastric emptying. Patients with gastroparesis and impaired absorption should be monitored for hypoglycemia.

Widespread neuropathy of the intestines can cause enteropathy, which can lead to constipation, diarrhea, and even fecal incontinence. Because diarrhea can have various causes, including bacterial overgrowth, poor intestinal motility, and celiac disease, the cause should be determined before treatment is initiated. Loperamide may be administered to treat intestinal motility disorders, and antibiotics can be used to correct bacterial overgrowth. Stool softeners and increased dietary fiber can be given to treat constipation.
Genitourinary autonomic neuropathy can lead to bladder dysfunction, erectile dysfunction, and other types of sexual dysfunction in men, and dyspareunia in women. Genitourinary neuropathy should be suspected in patients with recurrent urinary tract infections, pyelonephritis, urinary incontinence, a palpable bladder, or in men with erectile dysfunction.

Clinical features of bladder dysfunction may include urinary retention, urinary frequency or urgency, nocturia, or incontinence. Urinary retention, which results from visceral sensory denervation of the bladder, occurs in 40% to 50% of patients with type 1 diabetes and in about 25% of patients with type 2 diabetes. Urinary retention can be extremely challenging to treat, and may require surgery in severe cases.

Erectile dysfunction is a common manifestation of genitourinary autonomic neuropathy in men. It can be managed by administration of phosphodiesterase type 5 inhibitors or prostaglandin E1 injections or suppositories, or by the use of a vacuum assistance device or penile implant. Vaginal dryness is a common manifestation of genitourinary neuropathy in women, and can be managed by using a vaginal lubricant.
Diabetic autonomic neuropathy may also manifest as sudomotor or pupillomotor dysfunction.

Patients with sudomotor dysfunction exhibit sweat-related abnormalities, ranging from anhidrosis (no sweating) to hyperhidrosis (excessive sweating). Depending on the patient’s symptoms, management may include the use of emollients and skin lubricants to relieve dry skin; administration of scopolamine, glycopyrrolate, or botulinum toxin to reduce sweating; or vasodilators to improve heat tolerance.

Symptoms of pupillomotor dysfunction include blurred vision, impaired adaptation to ambient light, impaired visceral sensation, and heart rate variability. Patients should be especially careful when driving at night. Patients and health care professionals should be alert for unusual presentations of MI when pupillomotor dysfunction is present.
## Focal and Multifocal Neuropathies

<table>
<thead>
<tr>
<th>Type</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal limb or truncal</td>
<td>Sudden onset; usually involves ulnar, median, peroneal, or medial plantar nerve entrapment; may also involve demyelination or axonal degeneration</td>
</tr>
<tr>
<td>Cranial neuropathies</td>
<td>Extremely rare; often resolve spontaneously within months</td>
</tr>
<tr>
<td>Proximal motor (amyotrophy)</td>
<td>Usually occurs in older adults with type 2 diabetes; involves severe neuropathic pain, unilateral or bilateral muscle weakness, and atrophy of proximal thigh muscles; spinal stenosis must be ruled out</td>
</tr>
<tr>
<td>Coexisting chronic inflammatory demyelinating polyneuropathy (CIDP)</td>
<td>Marked by severe motor deficits and progressive polyneuropathy despite optimal glycemic control</td>
</tr>
</tbody>
</table>

Focal limb or truncal neuropathies have a sudden onset and usually involve the ulnar, median, peroneal, or medial plantar nerves. Most of these neuropathies result from nerve entrapment, but they can also be caused by demyelination or axonal degeneration. Cranial neuropathies are extremely rare (only 0.05% of cases) and usually involve cranial nerves III, IV, VI, or VII. They appear to be infarct related and usually resolve spontaneously within a few months.

Patients who develop severe neuropathic pain with unilateral or bilateral muscle weakness and atrophy of proximal thigh muscles should be evaluated for proximal motor neuropathy. Spinal stenosis must be ruled out, since the symptoms are often similar.

Coexisting chronic inflammatory demyelinating polyneuropathy (CIDP) is characterized by progressive, severe symmetric or asymmetric motor deficits and progressive sensory neuropathy even when glycemic control is optimal. Patients with CIDP have an unusually high level of protein in the cerebrospinal fluid.
Management of focal and multifocal neuropathies depends on the cause of the neuropathy and the severity of symptoms.

Some nerve entrapments can be managed conservatively with rest, splinting, use of diuretics to reduce edema, administration of nonsteroidal anti-inflammatory drugs, and injection of steroids and local anesthetics. Entrapments that do not respond to conservative management require surgery.

Neuropathic pain should be managed with tricyclics, anticonvulsants, or duloxetine.

CIDP is usually treated by administering a course of intravenous immunoglobulin therapy. Alternative treatments are plasmapheresis or immunosuppressive therapy with a corticosteroid or azathioprine.
Screening for microvascular complications is often recommended near the time of diagnosis in patients with type 2 diabetes and 5 years after diagnosis in patients with type 1 diabetes because __________.

a) patients with type 2 diabetes generally have a higher incidence of microvascular complications
b) patients with type 1 diabetes usually have less severe microvascular complications
c) microvascular complications typically develop more gradually in patients with type 1 diabetes
d) patients with type 2 diabetes have generally had diabetes for many years before their diagnosis
The correct answer is d.

Screening for microvascular complications is often recommended near the time of diagnosis in patients with type 2 diabetes and 5 years after diagnosis in patients with type 1 diabetes because patients with type 2 diabetes have generally had diabetes for many years before their diagnosis.
• Macrovascular complications of diabetes include coronary artery disease, cerebrovascular disease, and peripheral vascular disease. Microvascular complications include nephropathy, retinopathy, and neuropathy

• Outcome studies have shown that control of glucose levels, blood pressure, and lipid levels reduces the incidence of microvascular and macrovascular complications

• Patients with type 2 diabetes can optimize their glucose control by following the recommendations in consensus guidelines (such as those developed by the ADA) related to lifestyle modification, use of glucose-lowering medications, and medical screening and care

• Patients with type 2 diabetes can reduce their risk for complications by adhering to recommendations in consensus guidelines related to blood pressure regulation, control of lipid levels, and the management of other factors associated with macrovascular and microvascular complications