

# Standards of Medical Care for Patients With Diabetes Mellitus

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**D**iabetes is a chronic illness that requires continuing medical care and patient self-management education to prevent acute complications and to reduce the risk of long-term complications. Diabetes care is complex and requires that many issues, beyond glycemic control, be addressed. A large body of evidence exists that supports a range of interventions to improve diabetes outcomes.

These standards of care are intended to provide clinicians, patients, researchers, payers, and other interested persons with the components of diabetes care, treatment goals, and tools to evaluate the quality of care. While individual preferences, comorbidities, and other patient factors may require modification of goals, targets that are desirable for most patients with diabetes are provided. These standards are not intended to preclude more extensive evaluation and management of the patient by other specialists as needed. For more detailed information, refer to Skyler (Ed.): *Medical Management of Type 1 Diabetes* and Zimmerman (Ed.): *Medical Management of Type 2 Diabetes*.

The recommendations included are diagnostic and therapeutic actions that are known or believed to favorably affect health outcomes of patients with diabetes. A grading system (Table 1), developed by the Association and modeled after existing methods, was utilized to clarify and codify the evidence that forms the basis for the recommendations.

## CLASSIFICATION, DIAGNOSIS, AND SCREENING

### Classification

In 1997, the American Diabetes Association issued new diagnostic and classification criteria.

The classification of diabetes mellitus includes four clinical classes

- Type 1 diabetes ( $\beta$ -cell destruction, usually leading to absolute insulin deficiency)
- Type 2 diabetes (Results from a pro-

- gressive insulin secretory defect on the background of insulin resistance)
- Other specific types of diabetes (due to other causes, e.g., genetic defects in  $\beta$ -cell function, genetic defects in insulin action, diseases of the exocrine pancreas, drug or chemical induced)
- Gestational diabetes mellitus (GDM) (diagnosed during pregnancy)

### Diagnosis

Criteria for the diagnosis of diabetes in nonpregnant adults are shown in Table 2. Three ways to diagnose diabetes are

**Table 1. ADA evidence grading system for clinical practice recommendations**

Level of evidence	Description
A	Clear evidence from well-conducted, generalizable, randomized controlled trials that are adequately powered including: <ul style="list-style-type: none"> <li>• Evidence from a well-conducted multicenter trial</li> <li>• Evidence from a meta-analysis that incorporated quality ratings in the analysis</li> <li>• Compelling nonexperimental evidence, i.e., “all or none” rule developed by Center for Evidence Based Medicine at Oxford*</li> </ul> Supportive evidence from well-conducted randomized controlled trials that are adequately powered including: <ul style="list-style-type: none"> <li>• Evidence from a well-conducted trial at one or more institutions</li> <li>• Evidence from a meta-analysis that incorporated quality ratings in the analysis</li> </ul>
B	Supportive evidence from well-conducted cohort studies <ul style="list-style-type: none"> <li>• Evidence from a well-conducted prospective cohort study or registry</li> <li>• Evidence from a well-conducted prospective cohort study</li> <li>• Evidence from a well-conducted meta-analysis of cohort studies</li> </ul> Supportive evidence from well-conducted case-control study
C	Supportive evidence from poorly controlled or uncontrolled studies <ul style="list-style-type: none"> <li>• Evidence from randomized clinical trials with one or more major or three or more minor methodological flaws that could invalidate the results</li> <li>• Evidence from observational studies with high potential for bias (such as case series with comparison to historical controls)</li> <li>• Evidence from case series or case reports</li> </ul>
E	Conflicting evidence with the weight of evidence supporting the recommendation Expert consensus or clinical experience

\*Either all patients died prior to therapy and at least some survived with therapy, or some patients died without therapy and none died with therapy. Example: use of insulin in the treatment of DKA.

**Table 2. Criteria for the diagnosis of diabetes\***

1. Symptoms of diabetes and a casual plasma glucose  $\geq 200$  mg/dl (11.1 mmol/l). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.  
OR
2. FPG  $\geq 126$  mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.  
OR
3. 2-h PG  $\geq 200$  mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

\*In the absence of unequivocal hyperglycemia with acute metabolic decompensation, these criteria should be confirmed by repeat testing on a different day. The OGTT is not recommended for routine clinical use, but may be required in the evaluation of patients with IFG (see text) or when diabetes is still suspected despite a normal FPG.

available and each must be confirmed on a subsequent day. Because of ease of use, acceptability to patients and lower cost, the fasting plasma glucose (FPG) is the preferred test.

Hyperglycemia not sufficient to meet the diagnostic criteria for diabetes is categorized as either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), depending on whether it is identified through a FPG or an oral glucose tolerance test (OGTT):

- IFG = FPG  $\geq 110$  mg/dl (6.1 mmol/l) and  $< 126$  mg/dl (7.0 mmol/l)  
 Or FPG [110 mg/dl (6.1 mmol/l) to 125 mg/dl (6.9 mmol/l)]  
 IGT = 2-h PG  $\geq 140$  mg/dl (7.8 mmol/l) and  $< 200$  mg/dl (11.1 mmol/l)  
 Or 2-h PG [140 mg/dl (7.8 mmol/l) to 199 mg/dl (11.0 mmol/l)]

Both categories, IFG and IGT, are risk factors for future diabetes and cardiovascular disease. Recent studies have shown that lifestyle interventions can reduce the rate of progression to type 2 diabetes.

**Screening**

Generally, people with type 1 diabetes present with acute symptoms of diabetes and markedly elevated blood glucose levels. Type 2 diabetes is frequently not diagnosed until complications appear, and approximately one-third of all people with diabetes may be undiagnosed. Although the burden of diabetes is well

known, the natural history is well characterized, and there is good evidence for benefit from treating cases diagnosed through usual clinical care, there are no randomized trials demonstrating the benefits of early diagnosis through screening of asymptomatic individuals. Nevertheless, there is sufficient indirect evidence to justify opportunistic screening in a clinical setting of individuals at high risk. Criteria for testing for diabetes in asymptomatic, undiagnosed adults are listed in Table 3. The recommended screening test for nonpregnant adults is the FPG.

The incidence of type 2 diabetes in children and adolescents has been shown to be increasing. Consistent with screening recommendations for adults, only children and youth at increased risk for

the presence or the development of type 2 diabetes should be tested. See Table 4.

**Detection and diagnosis of GDM**

Risk assessment for GDM should be undertaken at the first prenatal visit. Women with clinical characteristics consistent with a high risk for GDM (those with marked obesity, personal history of GDM, glycosuria, or a strong family history of diabetes) should undergo glucose testing as soon as possible. A fasting plasma glucose  $\geq 126$  mg/dl or a casual plasma glucose  $\geq 200$  mg/dl meets the threshold for the diagnosis of diabetes, if confirmed on a subsequent day. High-risk women not found to have GDM at the initial screening and average-risk women should be tested between 24 and 28 weeks of gestation. Testing should follow one of two approaches:

- One-step approach: perform a diagnostic OGTT.
- Two-step approach: perform an initial screening by measuring the plasma or serum glucose concentration 1 h after a 50-g oral glucose load (glucose challenge test [GCT]) and perform a diagnostic OGTT on that subset of women exceeding the glucose threshold value on the GCT. When the two-step approach is employed, a glucose threshold value  $\geq 140$  mg/dl identifies ~80% of women with GDM, and the

**Table 3. Criteria for testing for diabetes in asymptomatic adult individuals**

1. Testing for diabetes should be considered in all individuals at age 45 years and above and, if normal, it should be repeated at 3-year intervals.
2. Testing should be considered at a younger age or be carried out more frequently in individuals who
  - are obese ( $\geq 120\%$  desirable body weight or a BMI  $\geq 27$  kg/m<sup>2</sup>)
  - have a first-degree relative with diabetes
  - are members of a high-risk ethnic population (e.g., African-American, Latino, Native American, Asian-American, Pacific Islander)
  - have delivered a baby weighing  $> 9$  lb or have been diagnosed with GDM
  - are hypertensive ( $\geq 140/90$  mmHg)
  - have HDL cholesterol level  $\leq 35$  mg/dl (0.90 mmol/l) and/or a triglyceride level  $\geq 250$  mg/dl (2.82 mmol/l)
  - on previous testing, had IGT or IFG
  - have other clinical conditions associated with insulin resistance (e.g., PCOS or acanthosis nigricans)

**Table 4. Testing for type 2 diabetes in children**

- Criteria\*
  - Overweight (BMI >85th percentile for age and sex, weight for height >85th percentile, or weight >120% of ideal for height)
  - Plus
  - Any two of the following risk factors:
    - Family history of type 2 diabetes in first- or second-degree relative
    - Race/ethnicity (Native American, African-American, Latino, Asian-American, Pacific Islander)
    - Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, or PCOS)
- Age of initiation: age 10 years or at onset of puberty, if puberty occurs at a younger age
- Frequency: every 2 years
- Test: FPG preferred

\*Clinical judgment should be used to test for diabetes in high-risk patients who do not meet these criteria.

yield is further increased to 90% by using a cutoff of  $\geq 130$  mg/dl.

Diagnostic criteria for the 100-g OGTT is as follows:  $\geq 95$  mg/dl fasting;  $\geq 180$  mg/dl at 1 h;  $\geq 155$  mg/dl at 2 h;  $\geq 140$  mg/dl at 3 h. Two or more of the plasma glucose values must be met or exceeded for a positive diagnosis. The test should be done in the morning after an overnight fast of 8–14 h. The diagnosis can be made using a 75-g glucose load, but that test is not as well validated for detection of at-risk infants or mothers as the 100-g OGTT.

Low risk status requires no glucose testing, but this category is limited to those women meeting all of the following characteristics:

- Age <25 years
- Weight normal before pregnancy
- Member of an ethnic group with a low prevalence of GDM
- No known diabetes in first-degree relatives
- No history of abnormal glucose tolerance
- No history of poor obstetric outcome

**Recommendations**

**A-Level evidence**

- In those with IFG/IGT, lifestyle modification should be considered.

**Expert consensus**

- The FPG is the preferred test to screen for and diagnose diabetes.
- Screen for diabetes in high-risk, asymptomatic, undiagnosed adults and children within the health care setting.
- Screen for diabetes in pregnancy using risk factor analysis and screening tests as noted.

**INITIAL EVALUATION**

**Glycemic control**

Glycemic control is fundamental to the management of diabetes. Prospective randomized clinical trials have shown that achieving glycemic control is associated with decreased rates of retinopathy, nephropathy, and neuropathy, and epidemiological studies support the potential of intensive glycemic control in the reduction of cardiovascular disease.

In the Diabetes Control and Complications Trial (DCCT), 1,441 patients with type 1 diabetes were randomized to either standard or intensive care. The standard care group received one to two daily insulin injections and routine follow-up with treatment aimed at minimizing symptoms. Patients in the intensive care group were treated with multiple daily injections or continuous insulin infusion, received intensive dia-

betes self-management education, and were followed closely by a health care team with active case management that included monthly visits and weekly phone contact. The intensive treatment group achieved a mean A1C test of ~7% while the standard care group maintained an approximate A1C test of 9%. With a mean of 6.5 years of follow-up, there were significant reductions in the incidence and rate of progression of retinopathy, albuminuria, and clinical neuropathy in the intensive group.

The U.K. Prospective Diabetes Study (UKPDS) enrolled newly diagnosed adults with type 2 diabetes. After 3 months of dietary treatment that reduced average A1C test results from ~9 to 7%, patients with FPG >6.0 mmol/l (107 mg/dl) were randomized to either intensive or standard treatment. In the intensive treatment group, patients were assigned to initial therapy with insulin, sulfonylurea, or metformin. In the standard care group, patients were maintained on lifestyle interventions until symptoms of marked hyperglycemia developed. Over time, both groups experienced deterioration in glycemic control. A 0.9% difference in A1C values between the intensive and standard treatments groups (7 vs. 7.9%) was associated with significant reductions in all microvascular end points.

A recent systematic review examined cardiovascular outcomes in type 1 diabetes and included data from six randomized controlled trials comparing intensive insulin therapy versus conventional treatment. This review noted moderate treatment effects of glycemic control on macrovascular events. In the UKPDS, the trend toward a reduction in cardiovascular events did not reach statistical significance. However, epidemiological analysis of the UKPDS cohort showed a statistically significant effect of A1C lowering with an approximate 14% reduction in all-cause mortality and myocardial infarction for every 1% reduction in A1C. All of the above stud-

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ies demonstrated an increased risk of hypoglycemia and weight gain associated with intensive glycemic control.

A major limitation to the available data is that they do not identify the optimum level of control for particular patients, as there are individual differences in the risks of hypoglycemia, weight gain, and other adverse effects. Furthermore, with multifactorial interventions, it is unclear how different components (e.g., educational interventions, glycemic targets, lifestyle changes, and pharmacological agents) contribute to the reduction of complications. There are no clinical trial data available for the effects of glycemic control in patients with advanced complications, the elderly (≥65 years of age), or young children (<13 years of age).

In summary, treatment regimens that reduced average A1C to ~7% (~1% above the upper limits of normal) were associated with fewer long-term, microvascular complications; however, intensive control has been found to increase risk of hypoglycemia and weight gain. Epidemiological analyses suggest that there is no threshold or lower limit of A1C above normal levels at which further lowering has no benefit. An average A1C >8% is associated with a higher risk of complications, at least in patients with reasonably long life expectancies. The relative benefit of achieving an A1C of 7% is documented in randomized controlled clinical trials with relative risk reductions of 15–30% per 1% absolute reduction in A1C.

Recommended glycemic goals for nonpregnant individuals are shown in Table 6. Less stringent treatment goals may be appropriate for patients with limited life expectancies, in the very young or older adults, and in individuals with comorbid conditions. Severe or frequent hypoglycemia is an indication for the modification of treatment regimens, including setting higher glycemic goals. Postprandial glucose monitoring and therapies targeting postprandial excursions may be necessary to reach A1C

**Table 6. Glycemic control for nonpregnant individuals with diabetes**

	Normal	Goal	Additional action suggested*
Plasma values‡			
Average preprandial glucose (mg/dl)	<110	90–130	<90/>150
Average bedtime glucose (mg/dl)	<120	110–150	<110/>180
Whole blood values‡			
Average preprandial glucose (mg/dl)	<100	80–120	<80/>140
Average bedtime glucose (mg/dl)	<110	100–140	<100/>160
A1C (%)	<6	<7	>8

The values shown in this table are by necessity generalized to the entire population of individuals with diabetes. Patients with comorbid diseases, the very young and older adults, and others with unusual conditions or circumstances may warrant different treatment goals. These values are for nonpregnant adults. \*Values above/below these levels are not “goals” nor are they “acceptable” in most patients. They are an indication for a significant change in the treatment plan. “Additional action suggested” depends on individual patient circumstances. Such actions may include enhanced diabetes self-management education, comanagement with a diabetes team, referral to an endocrinologist, change in pharmacological therapy, initiation of or increase in SMBG, or more frequent contact with the patient. A1C is referenced to a non-diabetic range of 4.0 – 6.0% (mean 5.0%, SD 0.5%). †Measurement of capillary blood glucose, ‡values calibrated to plasma glucose.

goals and/or to reduce the risk of hypoglycemia.

Elevated postchallenge (2-h OGTT) glucose values have been associated with increased cardiovascular risk independent of fasting plasma glucose in some epidemiological studies. Postprandial plasma glucose (PPG) levels >140 mg/dl are unusual in nondiabetic individuals, though large evening meals can be followed by plasma glucose values up to 180 mg/dl. There are now pharmacological agents that primarily modify PPG and thereby reduce A1C in parallel. Thus, in individuals who have premeal glucose values within targets but who are not meeting A1C targets, consideration of monitoring PPG 1–2 h after the start of the meal and treatment aimed at reducing average PPG values <180 mg/dl may lower A1C. However, it should be noted that this approach has not been validated to reduce complications in outcome studies in patients with either type 1 or type 2 diabetes.

For information on glycemic control for women with GDM, refer to the American Diabetes Association position statement on Gestational Diabetes Mellitus. For information on glycemic control during pregnancy in women with pre-existing diabetes, refer to *Medical Man-*

*agement of Pregnancy Complicated by Diabetes* (3rd ed.).

**Referral for diabetes management**

For a variety of reasons (e.g., intercurrent illness, diabetic ketoacidosis [DKA], recurrent hypoglycemia), it may not be possible to provide care that achieves the desired goals of treatment (Table 6). In such instances, additional actions suggested may include enhanced diabetes self-management education, comanagement with a diabetes team, or referral to an endocrinologist if the patient is currently being followed by a primary care provider.

**Recommendations**

**A-Level Evidence**

- Lowering A1C has been associated with a reduction of microvascular and neuropathic complications of diabetes.

**B-Level Evidence**

- Develop or adjust the management plan to achieve normal or near-normal glycemia with an A1C test goal of ≤7%.
- Self-monitoring of blood glucose is an integral component of therapy.

**Expert consensus**

- Less stringent treatment goals may be appropriate for patients with limited life expectancies, in the very young or older adults, and in individuals with comorbid conditions.

**Assessment of glycemic control**

Techniques are available for health providers and patients to assess the effectiveness of the management plan on glycemic control.

**Self-monitoring of blood glucose**

The American Diabetes Association's consensus statements on self-monitoring of blood glucose (SMBG) provide a comprehensive review of the subject. As stated earlier, major clinical trials assessing the impact of glycemic control on diabetes complications have included SMBG as part of multifactorial interventions, suggesting that SMBG is a component of effective therapy. SMBG allows patients to evaluate their individual response to therapy and assess if glycemic targets are being achieved. Results of SMBG are useful in preventing hypoglycemia and adjusting medications, MNT, and physical activity.

The frequency and timing of SMBG should be dictated by the particular needs and goals of the patients. Daily SMBG is especially important for patients treated with insulin to monitor for and prevent asymptomatic hypoglycemia. For most patients with type 1 diabetes and pregnant women taking insulin, SMBG is recommended three or more times daily. The optimal frequency and timing of SMBG for patients with type 2 diabetes is not known, but should be sufficient to facilitate reaching glucose goals. When adding to or modifying therapy, type 1 and type 2 diabetic patients should test more often than usual. The role of SMBG in stable diet-treated patients with type 2 diabetes is not known.

Because the accuracy of SMBG is instrument- and user-dependent, it is

important for health care providers to evaluate each patient's monitoring technique, both initially and at regular intervals thereafter. In addition, optimal use of SMBG requires proper interpretation of the data. Patients should be taught how to use the data to adjust food intake, exercise, or pharmacological therapy to achieve specific glycemic goals. Health professionals should evaluate at regular intervals the patient's ability to use SMBG data to guide treatment.

**Recommendations****Expert consensus**

- Include SMBG in the management plan.
- Instruct the patient in SMBG and routinely evaluate the patient's technique and ability to use data to adjust therapy.

**A1C**

By performing an A1C test, health providers can measure a patient's average glycemia over the preceding 2–3 months and, thus, assess treatment efficacy.

A1C testing should be performed routinely in all patients with diabetes, first to document the degree of glycemic control at initial assessment, then as part of continuing care. Since the A1C test reflects a mean glycemia over the preceding 2–3 months, measurement approximately every 3 months is required to determine whether a patient's metabolic control has reached and been maintained within the target range. Thus, regular performance of the A1C test permits detection of departures from the target range in a timely fashion. For any individual patient, the frequency of A1C testing should be dependent on the treatment regimen used and on the judgment of the clinician.

**Recommendations****Expert consensus**

- Perform the A1C test at least two times a year in patients who are

meeting treatment goals (and who have stable glycemic control) and quarterly in patients whose therapy has changed or who are not meeting glycemic goals.

**MNT****Recommendations****B-Level evidence**

- People with diabetes should receive individualized MNT as needed to achieve treatment goals, preferably provided by a registered dietitian familiar with the components of diabetes MNT.

**Physical Activity****Recommendations****B-Level evidence**

- A regular physical activity program, adapted to the presence of complications, is recommended for all patients with diabetes who are capable of participating.

**PREVENTION AND MANAGEMENT OF DIABETES COMPLICATIONS****Cardiovascular disease: management of risk factors and screening for CAD**

Cardiovascular disease (CVD) is the major cause of mortality for persons with diabetes. It is also a major contributor to morbidity and direct and indirect costs of diabetes. Type 2 diabetes is an independent risk factor for macrovascular disease and its common coexisting conditions (e.g., hypertension and dyslipidemia) are also risk factors.

Studies have shown the efficacy of reducing cardiovascular risk factors in preventing or slowing CVD. Evidence is summarized in the following sections and reviewed in detail in the American Diabetes Association technical reviews on hypertension, dyslipidemia, aspirin therapy, and smoking cessation and in the consensus statement on CHD in people with diabetes. Emphasis should be placed on reducing cardiovascular

risk factors, when possible, and clinicians should be alert for signs of atherosclerosis.

### Blood pressure control

Hypertension (blood pressure  $\geq 140/90$  mmHg) is a common comorbidity of diabetes, affecting 20–60% of people with diabetes, depending on age, obesity, and ethnicity. Hypertension is also a major risk factor for cardiovascular disease and microvascular complications such as retinopathy and nephropathy. In type 1 diabetes, hypertension is often the result of underlying nephropathy. In type 2 diabetes, hypertension is likely to be present as part of the metabolic syndrome (i.e., obesity, hyperglycemia, dyslipidemia) that is accompanied by high rates of CVD.

Randomized clinical trials have demonstrated the incontrovertible benefit of lowering blood pressure to approximately  $<140$  mmHg systolic and  $<80$  mmHg diastolic in persons with diabetes. Epidemiologic analyses show that blood pressures  $>120/80$  mmHg are associated with increased cardiovascular event rates and mortality in persons with diabetes. Therefore, a target blood pressure goal of  $<130/80$  mmHg is reasonable if it can be safely achieved.

Although there are no well-controlled studies of diet and exercise in the treatment of hypertension in persons with diabetes, reducing sodium intake, body weight (when indicated) and alcohol consumption and increasing activity levels have been shown to be effective in reducing blood pressure in nondiabetic individuals. These nonpharmacological strategies may also positively affect glycemia and lipid control.

Lowering of blood pressure with regimens based on antihypertensive drugs including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs),  $\beta$ -blockers, diuretics, and calcium channel blockers has been shown to be effective in lowering cardiovascular events and/or, in some studies, slowing progression of nephropathy and retinopathy. Other

classes of hypertensive drugs have not been studied in diabetic patients with respect to improving outcomes. There is no conclusive evidence favoring one class of drugs, although several studies suggest that ACE inhibitors may be superior to dihydropyridine calcium channel blockers (DCCBs) in reducing cardiovascular events. ACE inhibitors have been shown to decrease the risk of progression of nephropathy in patients with type 1 diabetes and to decrease cardiovascular events in type 2 diabetic patients with or without hypertension. ARBs have been shown to reduce the rate of progression of nephropathy in patients with type 2 diabetes. The  $\alpha$ -blocker arm of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was terminated after interim analysis showed that  $\alpha$ -blockers were substantially less effective in reducing congestive heart failure than diuretic therapy. Many patients will require three or more drugs to reach target goals.

Before beginning treatment, patients with elevated blood pressures should have their blood pressure re-examined within 1 month to confirm the presence of hypertension unless the diastolic blood pressure is  $>110$  mmHg. Patients with hypertension should be seen as often as needed until adequate blood pressure control is obtained and then seen as necessary; in these patients, other cardiovascular risk factors, including hyperlipidemia, smoking, urinary albumin excretion (assessed before initiation of treatment), and glycemic control, should be carefully assessed and treated.

### Recommendations Screening and Diagnosis Expert consensus

- Blood pressure should be measured at every routine diabetes visit. Patients found to have systolic blood pressure  $\geq 130$  or diastolic blood pressure  $\geq 80$  mmHg should have blood pressure confirmed on a separate day.

- Orthostatic measurement of blood pressure should be performed to assess for the presence of autonomic neuropathy.

### Treatment

#### A-Level evidence

- Patients with diabetes should be treated to a diastolic blood pressure  $<80$  mmHg.
- Patients with a systolic blood pressure of 130–139 mmHg or a diastolic blood pressure of 80–89 mmHg should be given lifestyle/behavioral therapy alone for a maximum of 3 months and then, if targets are not achieved, in addition, should be treated pharmacologically.
- Patients with hypertension (systolic blood pressure  $\geq 140$  or diastolic blood pressure  $\geq 90$  mmHg) should receive drug therapy in addition to lifestyle/behavioral therapy.
- Initial drug therapy may be with ACE inhibitors, ARBs,  $\beta$ -blockers, or diuretics. Additional drugs may be chosen from these classes or another drug class.
- In hypertensive patients with microalbuminuria or clinical albuminuria, an ACE inhibitor or an ARB should be strongly considered. If one class is not tolerated, the other should be substituted.
- In patients over age 55 years, with hypertension or without hypertension but with another cardiovascular risk factor (history of CVD, dyslipidemia, microalbuminuria, smoking), an ACE inhibitor (if not contraindicated) should be considered to reduce the risk of cardiovascular events.
- In patients with a recent myocardial infarction,  $\beta$ -blockers, in addition, should be considered to reduce mortality.

#### B-Level evidence

- Patients with diabetes should be treated to a systolic blood pressure  $<130$  mmHg.

**C-Level evidence**

- In patients with microalbuminuria or overt nephropathy, in whom ACE inhibitors or ARBs are not well tolerated, a non-DCCB should be considered.

**Expert consensus**

- If ACE inhibitors or ARBs are used, monitor renal function and serum potassium levels.
- In elderly hypertensive patients, blood pressure should be lowered gradually to avoid complications.
- Patients not achieving target blood pressure on three drugs including a diuretic and patients with severe renal disease, should be referred to a specialist experienced in the care of patients with hypertension.

**Lipid management**

Patients with type 2 diabetes have an increased prevalence of lipid abnormalities that contributes to higher rates of CVD. Lipid management aimed at lowering LDL cholesterol, raising HDL cholesterol, and lowering triglycerides has been shown to reduce macrovascular disease and mortality in patients with type 2 diabetes mellitus, particularly those who have had prior cardiovascular events.

In three secondary prevention studies using HMG CoA reductase inhibitors (statins), patients with diabetes achieved significant reductions in coronary and cerebrovascular events. A primary prevention study using statins showed a similar trend of reduced events in the small number of patients with diabetes. In two studies using the fibric acid derivative gemfibrozil, reductions in cardiovascular end points were also achieved. In the Helsinki Heart Study, a primary prevention trial, a trend toward significant reductions in CHD events was observed in the small group of subjects with diabetes mellitus. In the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT), a

secondary trial, a significant reduction in events occurred with improved HDL and triglycerides and no change in LDL cholesterol.

Target lipid levels are shown in Table 7. Nutrition assessment and intervention, increased physical activity, and weight loss should allow some patients to reach these lipid levels. Nutrition intervention should be tailored according to each patient's age, type of diabetes, pharmacological treatment, lipid levels and other medical conditions and should focus on the reduction of saturated fat and cholesterol intake. Glycemic control can also beneficially modify plasma lipid levels. In particular, triglycerides may be significantly reduced with optimal glucose lowering.

Pharmacological treatment is indicated if there is an inadequate response to lifestyle modifications and improved glucose control. The first priority of pharmacological therapy is to lower LDL cholesterol to a target goal of <100 mg/dl (2.60 mmol/l). For LDL lowering, statins are the drugs of choice. Statins raise HDL modestly, but a greater increase is usually achieved with fibrates.

In patients with LDL between 100 mg/dl (2.60 mmol/l) and 129 mg/dl (3.30 mmol/l), a variety of treatment strategies are available, including more aggressive nutrition intervention and pharmacological treatment with a statin. In addition, if the HDL is <40 mg/dl and the LDL is between 100 and 129 mg/dl, a fibric acid such as fenofibrate might be used.

Niacin is the best drug for raising HDL but may significantly increase blood glucose. However, glycemic con-

trol may be maintained with appropriate adjustment of diabetes therapy and moderate doses of nicotinic acid ( $\leq 3$  g/day).

Combination therapy, with a statin and a fibrate, may be efficacious for patients needing treatment for all three lipid fractions, but this combination is associated with an increased risk for myositis and/or rhabdomyolysis.

Following the recommendations of the National Cholesterol Education Program's Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents, LDL cholesterol should be lowered to  $\leq 110$  mg/dl (2.80 mmol/l) in children with cardiovascular risk factors in addition to diabetes.

**Recommendations**

**General recommendations**

**A-Level evidence**

- Lowering LDL cholesterol is associated with a reduction in cardiovascular events.

**B-Level evidence**

- Lowering triglycerides and increasing HDL cholesterol are associated with a reduction in cardiovascular events.

**Goals**

**B-Level evidence**

- Lower LDL cholesterol to  $\leq 100$  mg/dl (2.6 mmol/l) as the primary goal of therapy for adults.

**C-Level evidence**

- Lower triglycerides to <150 mg/dl (1.7 mmol/l) and raise HDL cholesterol to

**Table 7. Target lipid levels for adult patients with diabetes**

	Goal	Level of evidence
LDL cholesterol	<100 mg/dl (2.6 mmol/l)	B
HDL cholesterol	Men: >45 mg/dl (1.15 mmol/l) Women: >55 mg/dl (1.40 mmol/l)	C
Triglycerides	<150 mg/dl (1.7 mmol/l)	C

Note: the recent NCEP/ATP III guidelines suggest that in patients with triglycerides  $\geq 200$  mg/dl, the "non-HDL cholesterol" be calculated with a goal being <130.

>45 mg/dl (1.15 mmol/l) in men and >55 mg/dl (1.40 mmol/l) in women.

## Screening

### Expert consensus

- In adult patients, test for lipid disorders at least annually and more often if needed to achieve goals. In adults with low-risk lipid values (Table 6), repeat lipid assessments every 2 years.
- In children >2 years of age, perform a lipid profile after diagnosis of diabetes and when glucose control has been established. If values are considered low risk and there is no family history, assessments should be repeated every 5 years.

## Treatment

### A-Level evidence

- MNT focusing on the reduction of saturated fat and cholesterol intake, weight loss, and increased physical activity has been shown to improve the lipid profile in patients with diabetes.
- Patients who do not achieve lipid goals with lifestyle modifications require pharmacological therapy.
- Statins should be used as first-line pharmacologic therapy for LDL lowering.
- Therapy with fibrates in patients with low HDL has been shown to reduce CVD rates and progression of carotid intimal medial progression. When prescribing fibrates, in combination therapy with a statin, care is needed to minimize the risk of myositis.

### Aspirin therapy in diabetes

Aspirin blocks thromboxane synthesis by acetylating platelet cyclo-oxygenase and has been used as a primary and secondary therapy to prevent cardiovascular events in diabetic and nondiabetic individuals. One large meta-analysis and several clinical trials demonstrate the efficacy of using aspirin as a preventive measure for cardiovascular events including stroke and myocardial infarction. Many trials have shown an approx-

imate 30% decrease in myocardial infarction and a 20% decrease in stroke in a wide range of patients, including young and middle-aged patients, patients with and without a history of cardiovascular disease, males and females, and patients with hypertension.

Dosages used in most clinical trials ranged from 75–325 mg/day. There is no evidence to support any specific dose, but using the lowest possible dosage and enteric-coated preparations may help reduce side effects.

There is no evidence for a specific age at which to start aspirin, but at ages below 30 years, when the risk of CVD is low, there is no evidence of benefit of aspirin for primary prevention.

In a secondary analysis of some studies, aspirin therapy may have lessened the beneficial effects of ACE inhibitors in patients with established CVD (i.e., prior myocardial infarction, angina, and congestive heart failure). However, pending additional studies, therapy with ACE inhibitors does not preclude the use of aspirin. Clopidogrel has been demonstrated to reduce CVD rates in nondiabetic individuals. Adjunctive therapy in very high-risk patients or as alternative therapy in aspirin-intolerant patients should be considered.

## Recommendations

### A-Level evidence

- Use aspirin therapy (75–325 mg/day) in all adult patients with diabetes and macrovascular disease.
- Consider beginning aspirin therapy (75–325 mg/day) for primary prevention in patients  $\geq 40$  years of age with diabetes and one or more other cardiovascular risk factors.
- Do not use aspirin in patients <21 years of age because of the increased risk of Reye's syndrome.

### B-Level evidence

- Consider aspirin therapy for patients between 30 and 40 years of age with other cardiovascular risk factors.

## Smoking Cessation

## Recommendations

### A-Level evidence

- Advise all patients not to smoke.

### B-Level evidence

- Include smoking cessation counseling and other forms of treatment as a routine component of diabetes care.

## CHD screening and treatment

To identify the presence of CHD in diabetic patients without clear or suggestive symptoms of CAD, a risk factor–based approach to the initial diagnostic evaluation and subsequent follow-up is recommended. At least annually, cardiovascular risk factors should be assessed. These risk factors include dyslipidemia, hypertension, smoking, a positive family history of premature coronary disease, and the presence of micro- or macroalbuminuria. Candidates for screening exercise stress (ECG) testing include those with 1) typical or atypical cardiac symptoms; 2) an abnormal resting ECG; 3) a history of peripheral or carotid occlusive disease; 4) sedentary lifestyle, age >35 years, and plans to begin a vigorous exercise program; or 5) those with two or more risk factors noted above. There is, however, no current evidence that exercise testing in asymptomatic patients with risk factors improves prognosis. Patients with abnormal exercise ECG and patients unable to perform an exercise ECG require additional/alternative testing. Currently, stress nuclear perfusion and stress ECHO are valuable next-level diagnostic procedures. A consultation with a cardiologist is recommended regarding further work-up.

## Recommendations

### Expert consensus

- Perform exercise stress testing in asymptomatic diabetic patients



based on the criteria outlined above. Consider a risk factor–based strategy for the diagnosis of CAD that might include stress ECG and/or stress ECHO and/or perfusion imaging.

- Refer patients with signs and symptoms of CVD or with positive noninvasive test for CAD to a cardiologist for further evaluation.

## SCREENING AND MANAGEMENT OF OTHER COMPLICATIONS

### Nephropathy screening and treatment

#### General recommendations

##### A-Level evidence

- To reduce the risk and/or slow the progression of nephropathy, optimize glucose control.
- To reduce the risk and/or slow the progression of nephropathy, optimize blood pressure control.

#### Screening

##### Expert consensus

- Perform an annual test for the presence of microalbuminuria in 1) type 1 diabetic patients who have had diabetes >5 years and 2) all type 2 diabetic patients starting at diagnosis.

#### Treatment

##### A-Level evidence

- In the treatment of albuminuria/nephropathy, both ACE inhibitors and ARBs can be used:
  - in hypertensive and nonhypertensive type 1 diabetic patients with microalbuminuria or clinical albuminuria, ACE inhibitors are the initial agents of choice;
  - in hypertensive type 2 diabetic patients with microalbuminuria or clinical albuminuria, ARBs are the initial agents of choice.
- If one class is not tolerated, the other should be substituted.

##### B-Level evidence

- With the onset of overt nephropathy, initiate protein restriction to  $\leq 0.8 \text{ g} \cdot \text{kg}^{-1} \text{ body wt} \cdot \text{day}^{-1}$  (~10% of daily calories), the current adult recommended daily allowance for protein. Further restriction may be useful in slowing the decline of GFR in selected patients.
- Combination of ACE inhibitors and ARBs will decrease albuminuria more than with either agent alone.

##### Expert consensus

- If ACE inhibitors or ARBs are used, monitor serum potassium levels for the development of hyperkalemia.
- Consider referral to a physician experienced in the care of diabetic renal disease when the GFR has fallen to either  $<70 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ , serum creatinine has increased to  $>2.0 \text{ mg/dl}$  ( $>180 \text{ } \mu\text{mol/l}$ ), or difficulties occur in the management of hypertension or hyperkalemia.
- Consider the use of non-DCCBs in patients unable to tolerate ACE inhibitors or ARBs.

#### Foot care

#### Recommendations

##### A-Level evidence

- A multidisciplinary approach is recommended for persons with foot ulcers and high risk feet, especially those with a history of prior ulcer or amputation.

##### B-Level evidence

- The foot examination can be accomplished in a primary care setting and should include the use of a Semmes-Weinstein monofilament, tuning fork, palpation, and a visual examination.
- Educate all patients, especially those with risk factors or prior lower-extremity complications, about the risk and prevention of foot prob-

lems, and reinforce self-care behavior.

##### C-Level evidence

- Refer high-risk patients to foot care specialists for ongoing preventive care and life-long surveillance.
- Refer patients with claudication for further vascular assessment and consider exercise and surgical options.

##### Expert consensus

- Perform a comprehensive foot examination annually on patients with diabetes to identify risk factors predictive of ulcers and amputations. Perform a visual inspection of patients' feet at each routine visit.

#### Diabetic retinopathy screening and treatment

#### General Recommendations

##### A-Level evidence

- Optimal glycemic control can substantially reduce the risk and progression of diabetic retinopathy.
- Optimal blood pressure control can reduce the risk and progression of diabetic retinopathy.
- Aspirin therapy does not prevent retinopathy or increase the risks of hemorrhage.

#### Screening

##### B-Level evidence

- Patients with type 1 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist within 3–5 years after the onset of diabetes.
- Patients with type 2 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist shortly after the diagnosis of diabetes is made.
- Subsequent examinations for type 1 and type 2 diabetic patients should be

repeated annually by an ophthalmologist or optometrist who is knowledgeable and experienced in diagnosing the presence of diabetic retinopathy and is aware of its management. Examinations will be required more frequently if retinopathy is progressing.

- When planning pregnancy, women with pre-existing diabetes should have a comprehensive eye examination and should be counseled on the risk of development and/or progression of diabetic retinopathy. Women with diabetes who become pregnant should have a comprehensive eye examination in the first trimester and close follow-up throughout pregnancy and for 1 year postpartum. This guideline does not apply to women who develop GDM because such individuals are not at increased risk for diabetic retinopathy.

### **Treatment**

#### **A-Level evidence**

- Laser therapy can reduce the risk of vision loss in patients with high-risk characteristics.

- Promptly refer patients with any level of macular edema, severe NPDR, or any PDR to an ophthalmologist who is knowledgeable and experienced in the management and treatment of diabetic retinopathy.

### **PREVENTIVE CARE**

#### **Preconception Care**

##### **Recommendations**

###### **B-Level evidence**

- A1C levels should be normal or as close to normal as possible in an individual patient before conception is attempted.

###### **C-Level evidence**

- ACE inhibitors should be discontinued before pregnancy.

##### **Expert consensus**

- All women with diabetes and child-bearing potential should be educated about the need for good glucose control before pregnancy. They should participate in family planning.

- Women with diabetes who are contemplating pregnancy should be evaluated and, if indicated, treated for diabetic retinopathy, nephropathy, neuropathy, and CVD.
- Oral antidiabetic agents and ARBs should be discontinued before pregnancy.

#### **Immunization**

##### **Recommendations**

###### **C-Level evidence**

- Annually provide an influenza vaccine to all diabetic patients 6 months of age or older.
- Provide at least one lifetime pneumococcal vaccine for adults with diabetes. A one-time revaccination is recommended for individuals >64 years of age previously immunized when they were <65 years of age if the vaccine was administered more than 5 years ago. Other indications for repeat vaccination include nephrotic syndrome, chronic renal disease, and other immunocompromised states, such as postorgan transplantation.