

Standards of Medical Care in Diabetes — 2009

American Diabetes Association

Diabetes 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, payors, and other interested individuals 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 references (American Diabetes Association, 2003; 2008a; 2008b).

The recommendations included are screening, 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 American Diabetes Association (ADA) and modeled after existing methods, was utilized to clarify and codify the evidence that forms the basis for the recommendations. The level of evidence

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that supports each recommendation is listed after each recommendation using the letters A, B, C, or E.

1.1. Classification and Diagnosis

1.1.1. Classification

In 1997, ADA issued new diagnostic and classification criteria (Expert Committee on Diagnosis and Classification of Diabetes Mellitus, 1997); in 2003, modifications were made regarding the diagnosis of impaired fasting glucose (Expert Committee on Diagnosis and Classification of Diabetes Mellitus, 2003). The classification of diabetes includes four clinical classes:

- type 1 diabetes (results from β -cell destruction, usually leading to absolute insulin deficiency)
- type 2 diabetes (results from a progressive insulin secretory defect on the background of insulin resistance)
- other specific types of diabetes due to other causes, e.g. genetic defects in β -cell function, genetic defects in insulin action, diseases of the exocrine pancreas (such as cystic fibrosis), and drug or chemical-induced (such as in the treatment of AIDS or after organ transplantation)
- gestational diabetes mellitus (GDM) (diabetes diagnosed during pregnancy)

Table 1 ADA Evidence Grading System for Clinical Practice Recommendations

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

Some patients cannot be clearly classified as type 1 or type 2 diabetes. Clinical presentation and disease progression vary considerably in both types of diabetes. Occasionally, patients who otherwise have type 2 diabetes may present with ketoacidosis. Similarly, patients with type 1 may have a late onset and slow (but relentless) progression of disease despite having features of autoimmune disease. Such difficulties in diagnosis may occur in children, adolescents, and adults. The true diagnosis may become more obvious over time.

1.1.2. Diagnosis of Diabetes

Current criteria for the diagnosis of diabetes in nonpregnant adults are shown in Table 2. Three ways to diagnose diabetes are recommended at the time of this statement, and each must be confirmed on a subsequent day unless unequivocal symptoms of hyperglycemia are present. Although the 75-g oral glucose tolerance test (OGTT) is more sensitive and modestly more specific than the fasting plasma glucose (FPG)

Table 2 Criteria for the Diagnosis of Diabetes

1. FPG ≥ 126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.*
- OR
2. Symptoms of hyperglycemia and a casual (random) plasma glucose ≥ 200 mg/dl (11.1 mmol/l). Casual (random) is defined as any time of day without regard to time since last meal. The classic symptoms of hyperglycemia include polyuria, polydipsia, and unexplained weight loss.
- OR
3. 2-h plasma glucose ≥ 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, these criteria should be confirmed by repeat testing on a different day (5).

to diagnose diabetes, it is poorly reproducible and difficult to perform in practice. Because of ease of use, acceptability to patients, and lower cost, the FPG has been the preferred diagnostic test. Though FPG is less sensitive than the OGTT, the vast majority of people who do not meet diagnostic criteria for diabetes by FPG but would by OGTT will have an A1C value well under 7.0% (Davidson *et al.*, 1999).

Though the OGTT is not recommended for routine clinical use, it may be useful for further evaluation of patients in whom diabetes is still strongly suspected but who have normal FPG or IFG (impaired fasting glucose) (see Section 1.1.3).

The use of the A1C for the diagnosis of diabetes has previously not been recommended due to lack of global standardization and uncertainty about diagnostic thresholds. However, with a worldwide move toward a standardized assay and with increasing observational evidence about the prognostic significance of A1C, an Expert Committee on the Diagnosis of Diabetes was convened in 2008. This joint committee of ADA, the European Association for the Study of Diabetes, and the International Diabetes Federation will likely recommend that the A1C become the preferred diagnostic test for diabetes. Diagnostic cut-points are being discussed at the time of publication of this statement. Updated recommendations will be published in *Diabetes Care* and will be available at diabetes.org.

1.1.3. Diagnosis of Prediabetes

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 the FPG or the OGTT:

- IFG = FPG 100 mg/dl (5.6 mmol/l) to 125 mg/dl (6.9 mmol/l)
- IGT = 2-h plasma glucose 140 mg/dl (7.8 mmol/l) to 199 mg/dl (11.0 mmol/l)

IFG and IGT have been officially termed “prediabetes.” Both categories of prediabetes are risk factors for future diabetes and for cardiovascular disease (CVD) (Nathan *et al.*, 2007).

1.2. Testing for Prediabetes and Diabetes in Asymptomatic Patients

Recommendations

- Testing to detect prediabetes and type 2 diabetes in asymptomatic people should be considered in adults of any age who are overweight or obese (BMI ≥ 25 kg/m²) and who have one or more additional risk factors for diabetes (Table 3). In those without these risk factors, testing should begin at age 45 years. (B)
- If tests are normal, repeat testing should be carried out at least at 3-year intervals. (E)
- To test for pre-diabetes or diabetes, an FPG test or 2-h OGTT (75-g glucose load) or both are appropriate. (B)
- An OGTT may be considered in patients with IFG to better define the risk of diabetes. (E)
- In those identified with prediabetes, identify and, if appropriate, treat other CVD risk factors. (B)

For many illnesses, there is a major distinction between screening and diagnostic testing. However, for diabetes, the same tests would be used for “screening” as for diagnosis. Type 2 diabetes has a long asymptomatic phase and significant clinical risk markers. Diabetes may be identified anywhere along a spectrum of clinical scenarios, ranging from a seemingly low-risk individual who happens to have glucose testing, to a higher-risk individual whom the provider tests because of high suspicion of diabetes, to the symptomatic patient. The discussion herein is primarily framed as testing for diabetes in those without symptoms. Testing for diabetes will also detect individuals with prediabetes.

Table 3 Criteria for Testing for Prediabetes and Diabetes in Asymptomatic Adult Individuals

1. Testing should be considered in all adults who are overweight (BMI ≥ 25 kg/m²*) and have additional risk factors:
 - physical inactivity
 - first-degree relative with diabetes
 - members of a high-risk ethnic population (e.g. African American, Latino, Native American, Asian American, Pacific Islander)
 - women who delivered a baby weighing > 9 lb or were diagnosed with GDM
 - hypertension ($\geq 140/90$ mm Hg or on therapy for hypertension)
 - HDL cholesterol level < 35 mg/dl (0.90 mmol/l) and/or a triglyceride level > 250 mg/dl (2.82 mmol/l)
 - women with polycystic ovarian syndrome (PCOS)
 - IGT or IFG on previous testing
 - other clinical conditions associated with insulin resistance (e.g. severe obesity, acanthosis nigricans)
 - history of CVD
2. In the absence of the above criteria, testing for prediabetes and diabetes should begin at age 45 years
3. If results are normal, testing should be repeated at least at 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.

*At-risk BMI may be lower in some ethnic groups.

1.2.1. Testing for Prediabetes and Type 2 Diabetes in Adults

Type 2 diabetes is frequently not diagnosed until complications appear, and approximately one-third of all people with diabetes may be undiagnosed. Although the effectiveness of early identification of prediabetes and diabetes through mass testing of asymptomatic individuals has not been definitively proven (and rigorous trials to provide such proof are unlikely to occur), prediabetes and diabetes meet established criteria for conditions in which early detection is appropriate. Both conditions are common, increasing in prevalence, and impose significant public health burdens. There is a long presymptomatic phase before the diagnosis of type 2 diabetes is

usually made. Relatively simple tests are available to detect preclinical disease (Engelgau *et al.*, 2007). Additionally, the duration of glycemic burden is a strong predictor of adverse outcomes, and effective interventions exist to prevent progression of prediabetes to diabetes (see Section 1.4) and to reduce the risk of complications of diabetes (see Section 1.6).

Recommendations for testing for prediabetes and diabetes in asymptomatic, undiagnosed adults are listed in Table 3. Testing should be considered in adults of any age with BMI ≥ 25 kg/m² and one or more risk factors for diabetes. Because age is a major risk factor for diabetes, testing of those without other risk factors should begin no later than age 45 years.

Either FPG testing or the 2-h OGTT is appropriate for testing. The 2-h OGTT identifies people with either IFG or IGT, and thus, more prediabetic people at increased risk for the development of diabetes and CVD. It should be noted that the two tests do not necessarily detect the same prediabetic individuals (Gabir *et al.*, 2000). The efficacy of interventions for primary prevention of type 2 diabetes (Knowler *et al.*, 2002; Tuomilehto *et al.*, 2001; Pan *et al.*, 1997; Buchanan *et al.*, 2002; Chiasson *et al.*, 2002; Gerstein, 2006; Ramachandran *et al.*, 2006) has primarily been demonstrated among individuals with IGT, not individuals with IFG (who do not also have IGT). As noted in the diagnosis section (Section 1.1.2), the FPG test is more convenient, more reproducible, less costly, and easier to administer than the 2-h OGTT (Expert Committee on Diagnosis and Classification of Diabetes Mellitus, 1997, 2003). An OGTT may be useful in patients with IFG to better define the risk of diabetes.

The appropriate interval between tests is not known (Johnson *et al.*, 2005). The rationale for the three-year interval is that false-negatives will be repeated before substantial time elapses, and there is little likelihood that an individual will develop significant complications of diabetes within three years of a negative test result.

Because of the need for follow-up and discussion of abnormal results, testing should be carried out

within the health care setting. Community screening outside a health care setting is not recommended because people with positive tests may not seek, or have access to, appropriate follow-up testing and care. Conversely, there may be failure to ensure appropriate repeat testing for individuals who test negative. Community screening may also be poorly targeted, i.e. it may fail to reach the groups most at risk and inappropriately test those at low risk (the worried well) or even those already diagnosed (Harris *et al.*, 2003; USPSTF, 2003).

1.2.2. Testing for Type 2 Diabetes in Children

The incidence of type 2 diabetes in adolescents has increased dramatically in the last decade, especially in minority populations (Dabelea *et al.*, 2007), although the disease remains rare in the general adolescent population (Liese *et al.*, 2006). Consistent with recommendations for adults, children and youth at increased risk for the presence or the development of type 2 diabetes, testing should be carried out within the health care setting (American Diabetes Association, 2000). The recommendations of the ADA consensus statement on type 2 diabetes in children and youth, with some modifications, are summarized in Table 4.

1.2.3. Screening for Type 1 Diabetes

Generally, people with type 1 diabetes present with acute symptoms of diabetes and markedly elevated blood glucose levels, and most cases are diagnosed soon after the onset of hyperglycemia. However, evidence from type 1 prevention studies suggests that measurement of islet autoantibodies identifies individuals who are at risk for developing type 1 diabetes. Such testing may be appropriate in high-risk individuals, such as those with prior transient hyperglycemia or those who have relatives with type 1 diabetes, in the context of clinical research studies (see, for example,

Table 4 Testing for Type 2 Diabetes in Asymptomatic 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, PCOS, or small-for-gestational-age birthweight)
- Maternal history of diabetes or GDM during the child's gestation

Age of initiation: age 10 years or at onset of puberty, if puberty occurs at a younger age

Frequency: every 3 years

Test: FPG preferred

<http://www2.diabetestrialnet.org>). Widespread clinical testing of asymptomatic low-risk individuals cannot currently be recommended, as it would identify very few individuals in the general population who are at risk. Individuals who screen positive should be counseled about their risk of developing diabetes. Clinical studies are being conducted to test various methods of preventing type 1 diabetes, or reversing early type 1 diabetes, in those with evidence of autoimmunity.

1.3. Detection and Diagnosis of GDM

Recommendations

- Screen for GDM using risk factor analysis and, if appropriate, use of an OGTT. (C)
- Women with GDM should be screened for diabetes 6–12 weeks postpartum and should be

followed up with subsequent screening for the development of diabetes or prediabetes. (E)

GDM is defined as any degree of glucose intolerance with onset or first recognition during pregnancy (Expert Committee on Diagnosis and Classification of Diabetes Mellitus, 1997). Although most cases resolve with delivery, the definition applies whether or not the condition persists after pregnancy and does not exclude the possibility that unrecognized glucose intolerance may have antedated or begun concomitantly

with the pregnancy. Approximately 7% of all pregnancies (ranging from 1 to 14% depending on the population studied and the diagnostic tests employed) are complicated by GDM, resulting in more than 200,000 cases annually.

Because of the risks of GDM to the mother and neonate, screening and diagnosis are warranted. The screening and diagnostic strategies, based on the 2004 ADA position statement on gestational diabetes mellitus (American Diabetes Association, 2004), are outlined in Table 5.

Table 5 Screening for and Diagnosis of GDM

Carry out GDM risk assessment at the first prenatal visit.

Women at very high risk for GDM should be screened for diabetes as soon as possible after the confirmation of pregnancy. Criteria for very high risk are:

- severe obesity
- prior history of GDM or delivery of large-for-gestational-age infant
- presence of glycosuria
- diagnosis of PCOS
- strong family history of type 2 diabetes

Screening/diagnosis at this stage of pregnancy should use standard diagnostic testing (Table 2).

All women of greater than low risk of GDM, including those above not found to have diabetes early in pregnancy, should undergo GDM testing at 24–28 weeks of gestation. Low risk status, which does not require GDM screening, is defined as women with ALL of the following characteristics:

- age < 25 years
- weight normal before pregnancy
- member of an ethnic group with a low prevalence of diabetes
- no known diabetes in first-degree relatives
- no history of abnormal glucose tolerance
- no history of poor obstetrical outcome

Two approaches may be followed for GDM screening at 24–28 weeks:

1. Two-step approach:

- Perform initial screening by measuring plasma or serum glucose 1 h after a 50-g oral glucose load. A glucose threshold after 50-g load of ≥ 140 mg/dl identifies $\sim 80\%$ of women with GDM, while the sensitivity is further increased to $\sim 90\%$ by a threshold of ≥ 130 mg/dl.
- Perform a diagnostic 100-g OGTT on a separate day in women who exceed the chosen threshold on 50-g screening.

2. One-step approach (may be preferred in clinics with high prevalence of GDM): Perform a diagnostic 100-g OGTT in all women to be tested at 24–28 weeks.

The 100-g OGTT should be performed in the morning after an overnight fast of at least 8 h.

To make a diagnosis of GDM, at least two of the following plasma glucose values must be found:

- Fasting: ≥ 95 mg/dl
 - 1 h: ≥ 180 mg/dl
 - 2 h: ≥ 155 mg/dl
 - 3 h: ≥ 140 mg/dl
-

Results of the Hyperglycemia and Adverse Pregnancy Outcomes study (Metzger *et al.*, 2008), a large-scale (including ~25,000 pregnant women) multinational epidemiologic study, demonstrated that risk of adverse maternal, fetal, and neonatal outcomes increased continuously as a function of maternal glycemia at 24–28 weeks, even within ranges previously considered normal for pregnancy. For most complications, there was no threshold for risk.

These results have led to careful reconsideration of the diagnostic criteria for GDM. An international group representing multiple obstetrical and diabetes organizations, including ADA, is currently working on consensus toward 1) a worldwide standard for which diagnostic test to use for GDM; and 2) rational diagnostic cut points.

Because women with a history of GDM have a greatly increased subsequent risk for diabetes (Kim *et al.*, 2002), they should be screened for diabetes 6–12 weeks postpartum, using nonpregnant OGTT criteria, and should be followed up with subsequent screening for the development of diabetes or prediabetes, as outlined in Section 1.2. For information on the National Diabetes Education Program (NDEP) campaign to prevent type 2 diabetes in women with GDM, go to www.ndep.nih.gov/diabetes/pubs/NeverTooEarly_Tipsheet.pdf.

1.4. Prevention/Delay of Type 2 Diabetes

Recommendations

- Patients with IGT (A) or IFG (E) should be referred to an effective ongoing support program for weight loss of 5–10% of body weight and for increasing physical activity to at least 150 min per week of moderate activity such as walking.
- Follow-up counseling appears to be important for success. (B)
- Based on potential cost savings of diabetes prevention, such counseling should be covered by third-party payors. (E)
- In addition to lifestyle counseling, metformin may be considered in those who are at very high risk for developing diabetes (combined IFG and IGT plus other risk factors such as A1C > 6%, hypertension, low HDL cholesterol, elevated triglycerides, or family history of diabetes in a first-degree relative) and who are obese and under 60 years of age. (E)
- Monitoring for the development of diabetes in those with prediabetes should be performed every year. (E)

Randomized controlled trials have shown that individuals at high risk for developing diabetes (those with IFG, IGT, or both) can be given interventions that significantly decrease the rate of onset of diabetes (Knowler *et al.*, 2002; Tuomilehto *et al.*, 2001; Pan *et al.*, 1997; Buchanan *et al.*, 2002; Chiasson *et al.*, 2002; Gerstein *et al.*, 2006; Ramachandran *et al.*, 2006). These interventions include intensive lifestyle modification programs that have been shown to be very effective ($\geq 58\%$ reduction after three years) and use of the pharmacologic agents metformin, acarbose, orlistat, and thiazolidinediones (TZDs), each of which has been shown to decrease the incident of diabetes by various degrees. A summary of major diabetes prevention trials is shown in Table 6.

Two studies of lifestyle intervention have shown persistent reduction in the rate of conversion to type 2 diabetes with 3 (Lindstrom *et al.*, 2006) to 14 years (Li *et al.*, 2008) of postintervention follow-up.

Based on the results of clinical trials and the known risks of progression of prediabetes to diabetes, an ADA Consensus Development Panel (Nathan *et al.*, 2007) concluded that persons with prediabetes (IGT and/or IFG) should be counseled on lifestyle changes with goals similar to those of the Diabetes Prevention Program (DPP) (5–10% weight loss and moderate physical activity of ~30 min per day). Regarding the more difficult issue of drug therapy for diabetes prevention, the consensus panel felt that metformin should be the only drug considered for use in diabetes prevention. For other drugs, the issues of cost, side effects, and lack of persistence of effect in some studies

Table 6 Therapies Proven Effective in Diabetes Prevention Trials

Study (ref.)	<i>n</i>	Population	Mean Age (years)	Duration (years)	Intervention (daily dose)	Conversion in Control Subjects (%/year)	Relative Risk
<i>Lifestyle</i>							
Finnish DPS (11)	522	IGT, BMI ≥ 25 kg/m ²	55	3.2	Individual diet/exercise	6	0.42 (0.30–0.70)
DPP (10)	2161*	IGT, BMI ≥ 24 kg/m ² , FPG > 5.3 mmol/l	51	3	Individual diet/exercise	10	0.42 (0.34–0.52)
Da Qing (12)	259*	IGT (randomized groups)	45	6	Group diet/exercise	16	0.62 (0.44–0.86)
Toranomon study (28)	458	IGT (men), BMI = 24 kg/m ²	55	4	Individual diet/exercise	2	0.33 (0.10–1.0) [†]
Indian DPP (16)	269*	IGT	46	2.5	Individual diet/exercise	22	0.71 (0.63–0.79)
<i>Medications</i>							
DPP (10)	2155*	IGT, BMI > 24 kg/m ² , FPG > 5.3 mmol/l	51	2.8	Metformin (1700 mg)	10	0.69 (0.57–0.83)
Indian DPP (16)	269*	IGT	46	2.5	Metformin (500 mg)	22	0.74 (0.65–0.81)
STOP NIDDM (14)	1419	IGT, FPG > 5.6 mmol/l	54	3.2	Acarbose (300 mg)	13	0.75 (0.63–0.90)
XENDOS (29)	3277	BMI > 30 kg/m ²	43	4	Orlistat (360 mg)	2	0.63 (0.46–0.86)
DREAM (15)	5269	IGT or IFG	55	3.0	Rosiglitazone (8 mg)	9	0.40 (0.35–0.46)

*Number of participants in the indicated comparisons, not necessarily in the entire study.

[†]Calculated from information in the article. DPP, Diabetes Prevention Program; DREAM, Diabetes REduction Assessment with ramipril and rosiglitazone Medication; DPS, Diabetes Prevention Study; STOP NIDDM, Study to Prevent Non-Insulin Dependent Diabetes; XENDOS, Xenical in the prevention of Diabetes in Obese Subjects. This table has been reprinted with permission (30) with some modification.

led the panel to not recommend their use for diabetes prevention. Metformin use was recommended only for very-high-risk individuals (those with combined IGT and IFG who are obese and under 60 years of age with at least one other risk factor for diabetes). In addition, the panel highlighted the evidence that in the DPP, metformin was most effective compared to lifestyle in those with BMI of at least 35 kg/m² and those under age 60 years.

1.5. Diabetes Care

1.5.1. Initial Evaluation

A complete medical evaluation should be performed to classify the diabetes, detect the presence of diabetes complications, review previous treatment and glycemic control in patients with established diabetes, assist in formulating a management plan, and provide a basis for continuing care. Laboratory tests appropriate to the evaluation of each patient's medical condition should be performed. A focus on the components of comprehensive care (Table 7) will assist the health care team to ensure optimal management of the patient with diabetes.

1.5.2. Management

People with diabetes should receive medical care from a physician-coordinated team. Such teams may include, but are not limited to, physicians, nurse practitioners, physician's assistants, nurses, dietitians, pharmacists, and mental health professionals with expertise and a special interest in diabetes. It is essential in this collaborative and integrated team approach that individuals with diabetes assume an active role in their care.

The management plan should be formulated as an individualized therapeutic alliance among the patient and family, the physician, and other members of the

health care team. A variety of strategies and techniques should be used to provide adequate education and development of problem-solving skills in the various aspects of diabetes management. Implementation of the management plan requires that each aspect is understood and agreed on by the patient and the care providers and that the goals and treatment plan are reasonable. Any plan should recognize diabetes self-management education (DSME) as an integral component of care. In developing the plan, consideration should be given to the patient's age, school or work schedule and conditions, physical activity, eating patterns, social situation and personality, cultural factors, and presence of complications of diabetes or other medical conditions.

1.5.3. Glycemic Control

1.5.3.1. Assessment of glycemic control

Two primary techniques are available for health providers and patients to assess the effectiveness of the management plan on glycemic control: Patient self-monitoring of blood glucose (SMBG) or of interstitial glucose and measurement of A1C.

a. Glucose monitoring

Recommendations

- SMBG should be carried out three or more times daily for patients using multiple insulin injections or insulin pump therapy. (A)
- For patients using less frequent insulin injections, noninsulin therapies, or medical nutrition therapy (MNT) and physical activity alone, SMBG may be useful as a guide to the success of therapy. (E)
- To achieve postprandial glucose targets, postprandial SMBG may be appropriate. (E)
- When prescribing SMBG, ensure that patients receive initial instruction in, and routine follow-up evaluation of, SMBG technique and their ability to use data to adjust therapy. (E)
- Continuous glucose monitoring (CGM) in conjunction with intensive insulin regimens can be a

Table 7 Components of the Comprehensive Diabetes Evaluation

<p>Medical history</p> <ul style="list-style-type: none"> • age and characteristics of onset of diabetes (e.g. DKA, asymptomatic laboratory finding) • eating patterns, physical activity habits, nutritional status, and weight history; growth and development in children and adolescents • diabetes education history • review of previous treatment regimens and response to therapy (A1C records) • current treatment of diabetes, including medications, meal plan, physical activity patterns, and results of glucose monitoring and patient's use of data • DKA frequency, severity, and cause • hypoglycemic episodes <ul style="list-style-type: none"> ○ hypoglycemia awareness ○ any severe hypoglycemia: frequency and cause • history of diabetes-related complications <ul style="list-style-type: none"> ○ microvascular: retinopathy, nephropathy, neuropathy (sensory, including history of foot lesions; autonomic, including sexual dysfunction and gastroparesis) ○ macrovascular: CHD, cerebrovascular disease, PAD ○ other: psychosocial problems,* dental disease* <p>Physical examination</p> <ul style="list-style-type: none"> • height, weight, BMI • blood pressure determination, including orthostatic measurements when indicated • fundoscopic examination* 	<ul style="list-style-type: none"> • thyroid palpation • skin examination (for acanthosis nigricans and insulin injection sites) • comprehensive foot examination: <ul style="list-style-type: none"> ○ inspection ○ palpation of dorsalis pedis and posterior tibial pulses ○ presence/absence of patellar and Achilles reflexes ○ determination of proprioception, vibration, and monofilament sensation <p>Laboratory evaluation</p> <ul style="list-style-type: none"> • A1C, if results not available within past 2–3 months <p>If not performed/available within past year:</p> <ul style="list-style-type: none"> • fasting lipid profile, including total, LDL- and HDL-cholesterol and triglycerides • liver function tests • test for urine albumin excretion with spot urine albumin/creatinine ratio • serum creatinine and calculated GFR • thyroid-stimulating hormone in type 1 diabetes, dyslipidemia or women over age 50 <p>Referrals</p> <ul style="list-style-type: none"> • annual dilated eye exam • family planning for women of reproductive age • registered dietitian for MNT • diabetes self-management education • dental examination • mental Health professional, if needed
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*See appropriate referrals for these categories.

useful tool to lower A1C in selected adults (age \geq 25 years) with type 1 diabetes. (A)

- Although the evidence for A1C lowering is less strong in children, teens, and younger adults, CGM may be helpful in these groups. Success correlates with adherence to ongoing use of the device. (C)
- CGM may be a supplemental tool to SMBG in those with hypoglycemia unawareness and/or frequent hypoglycaemic episodes. (E)

The ADA's consensus and position statements on SMBG provide a comprehensive review of the subject

(American Diabetes Association, 1987; 1994). Major clinical trials of insulin-treated patients that demonstrated the benefits of intensive 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 whether glycemic targets are being achieved. Results of SMBG can be useful in preventing hypoglycemia and adjusting medications (particularly prandial insulin doses), MNT, and physical activity.

The frequency and timing of SMBG should be dictated by the particular needs and goals of the patients. SMBG is especially important for patients treated with insulin to monitor for and prevent asymptomatic hypoglycemia and hyperglycemia. For most patients with type 1 diabetes and pregnant women taking insulin, SMBG is recommended three or more times daily. For this population, significantly more frequent testing may be required to reach A1C targets safely without hypoglycemia. The optimal frequency and timing of SMBG for patients with type 2 diabetes on noninsulin therapy is unclear. A meta-analysis of SMBG in noninsulin-treated patients with type 2 diabetes concluded that some regimen of SMBG was associated with a reduction in A1C of $\geq 0.4\%$. However, many of the studies in this analysis also included patient education with diet and exercise counseling and, in some cases, pharmacologic intervention, making it difficult to assess the contribution of SMBG alone to improved control (Welschen *et al.*, 2005). Several recent trials have called into question the clinical utility and cost-effectiveness of routine SMBG in noninsulin-treated patients (Farmer *et al.*, 2007; O’Kane *et al.*, 2007; Simon *et al.*, 2008).

Because the accuracy of SMBG is instrument- and user-dependent (Sacks *et al.*, 2002), it is important 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, and these skills should be reevaluated periodically.

CGM through the measurement of interstitial glucose (which correlates well with plasma glucose) is available. These sensors require calibration with SMBG, and the latter is still recommended for making acute treatment decisions. CGM devices also have alarms for hypo- and hyperglycemic excursions. Small studies in selected patients with type 1 diabetes have suggested that CGM use reduces the time spent in hypo- and hyperglycaemic ranges and may modestly improve glycemic control. A larger 26-week

randomized trial of 322 type 1 patients showed that adults age 25 years and above using intensive insulin therapy and CGM experienced a 0.5% reduction in A1C (from ~ 7.6 to 7.1%) as compared with usual intensive insulin therapy with SMBG (The Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, 2008). Sensor use in children, teens, and adults to age 24 years did not result in significant A1C lowering, and there was no significant difference in hypoglycemia in any group. Importantly, the greatest predictor of A1C lowering in this study for all age groups was frequency of sensor use, which was lower in younger age-groups. Although CGM is an evolving technology, emerging data suggest that, in appropriately selected patients who are motivated to wear it most of the time, it may offer benefit. CGM may be particularly useful in those with hypoglycemia unawareness and/or frequent episodes of hypoglycemia, and studies in this area are ongoing.

b. A1C

Recommendations

- Perform the A1C test at least twice a year in patients who are meeting treatment goals (and who have stable glycemic control). (E)
- Perform the A1C test quarterly in patients whose therapy has changed or who are not meeting glycemic goals. (E)
- Use of point-of-care testing for A1C allows for timely decisions on therapy changes, when needed. (E)

Because A1C is thought to reflect average glycemia over several months (Sacks *et al.*, 2002), and has strong predictive value for diabetes complications (Knowler *et al.*, 2002; Stratton *et al.*, 2000), A1C testing should be performed routinely in all patients with diabetes at initial assessment and then as part of continuing care. Measurement approximately every three months determines whether a patient’s glycemic targets have been reached and maintained. For any individual patient, the frequency of A1C testing

should be dependent on the clinical situation, the treatment regimen used, and the judgment of the clinician. Some patients with stable glycemia well within target may do well with testing only twice a year, while unstable or highly intensively managed patients (e.g. pregnant type 1 women) may be tested more frequently than every three months. The availability of the A1C result at the time that the patient is seen (point-of-care testing) has been reported to result in increased intensification of therapy and improvement in glycemic control (Cagliero *et al.*, 1999; Miller *et al.*, 2003).

The A1C test is subject to certain limitations. Conditions that affect erythrocyte turnover (hemolysis, blood loss) and hemoglobin variants must be considered, particularly when the A1C result does not correlate with the patient's clinical situation (Sacks *et al.*, 2002). In addition, A1C does not provide a measure of glycemic variability or hypoglycemia. For patients prone to glycemic variability (especially type 1 patients, or type 2 patients with severe insulin deficiency), glycemic control is best judged by the combination of results of SMBG testing and the A1C. The A1C may also serve as a check on the accuracy of the patient's meter (or the patient's reported SMBG results) and the adequacy of the SMBG testing schedule.

Table 8 contains the correlation between A1C levels and mean plasma glucose levels based on data from the international A1C-Derived Average Glucose (ADAG) trial utilizing frequent SMBG and continuous glucose monitoring in 507 adults (83% Caucasian) with type 1, type 2, and no diabetes (UKPDS, 1998). The ADA and American Association of Clinical Chemists have determined that the correlation ($r = 0.92$) is strong enough to justify reporting both an A1C result and an estimated average glucose (eAG) result when a clinician orders the A1C test. The table in the previous versions of the Standards of Medical Care in Diabetes describing the correlation between A1C and mean glucose was derived from relatively sparse data (one seven-point profile over one day per A1C reading) in the primarily Caucasian type 1 participants in the Diabetes Control and Complications

Table 8 Correlation of A1C with Average Glucose

A1C (%)	Mean Plasma Glucose	
	mg/dl	mmol/l
6	126	7.0
7	154	8.6
8	183	10.2
9	212	11.8
10	240	13.4
11	269	14.9
12	298	16.5

Estimates based on ADAG data of ~2700 glucose measurements over three months per A1C measurement in 507 adults with type 1, type 2, and no diabetes. Correlation between A1C and average glucose: 0.92 (42). A calculator for converting A1C results into eAG, in either mg/dl or mmol/l, is available at <http://professional.diabetes.org/eAG>.

Trial (DCCT) (Rohlfing *et al.*, 2002). Clinicians should note that the numbers in the table are now different, as they are based on ~2800 readings per A1C in the ADAG trial. In the ADAG study, there were no significant differences among racial and ethnic groups in the regression lines between A1C and mean glucose, although there was a trend towards a difference between African/African-American and Caucasian participants' regression lines that might have been significant had more African/African-American participants been studied. A recent study comparing A1C to CGM data in 48 type 1 children found a highly statistically significant correlation between A1C and mean blood glucose, although the correlation ($r = 0.7$) was significantly lower than in the ADAG trial (Wilson *et al.*, 2008). Whether there are significant differences in how A1C relates to average glucose in children or in African-American patients is an area for further study. For the time being, the question has not led to different recommendations about testing A1C or to different interpretations of the clinical meaning of given levels of A1C in those populations.

For patients in whom A1C/eAG and measured blood glucose appear discrepant, clinicians should consider the possibilities of hemoglobinopathy or altered red cell turnover and the options of more

frequent and/or different timing of SMBG or use of CGM. Other measures of chronic glycemia such as fructosamine are available, but their linkage to average glucose and their prognostic significance are not as clear as is the case for A1C.

1.5.3.2. Glycemic goals in adults

- Lowering A1C to below or around 7% has been shown to reduce microvascular and neuropathic complications of type 1 and type 2 diabetes. Therefore, for microvascular disease prevention, the A1C goal for nonpregnant adults in general is < 7%. (A)
- In type 1 and type 2 diabetes, randomized controlled trials of intensive versus standard glycemic control have not shown a significant reduction in CVD outcomes during the randomized portion of the trials. Long-term follow-up of the DCCT and UK Prospective Diabetes Study (UKPDS) cohorts suggests that treatment to A1C targets below or around 7% in the years soon after the diagnosis of diabetes is associated with long-term reduction in risk of macrovascular disease. Until more evidence becomes available, the general goal of < 7% appears reasonable for many adults for macrovascular risk reduction. (B)
- Subgroup analyses of clinical trials such as the DCCT and UKPDS and the microvascular evidence from the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial suggest a small but incremental benefit in microvascular outcomes with A1C values closer to normal. Therefore, for selected individual patients, providers might reasonably suggest even lower A1C goals than the general goal of < 7%, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Such patients might include those with short duration of diabetes, long life expectancy, and no significant CVD. (B)
- Conversely, less stringent A1C goals than the general goal of < 7% may be appropriate for patients with a history of severe hypoglycemia, limited life

expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain despite DSME, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin. (C)

Glycemic control is fundamental to the management of diabetes. The DCCT, a prospective, randomized, controlled trial of intensive versus standard glycemic control in patients with relatively recently diagnosed type 1 diabetes, showed definitively that improved glycemic control is associated with significantly decreased rates of microvascular (retinopathy and nephropathy) as well as neuropathic complications (DCCT, 1993). Follow-up of the DCCT cohorts in the Epidemiology of Diabetes Interventions and Complications (EDIC) study has shown persistence of this effect in previously intensively treated subjects, even though their glycemic control has been equivalent to that of previous standard arm subjects during follow-up (DCCT, 2000; Martin *et al.*, 2006).

In type 2 diabetes, the Kumamoto study (Ohkubo *et al.*, 1995) and the UKPDS (UKPDS, 1998a; UKPDS, 1998b) demonstrated significant reductions in microvascular and neuropathic complications with intensive therapy. Similar to the DCCT-EDIC findings, long-term follow-up of the UKPDS cohort has recently demonstrated a “legacy effect” of early intensive glycemic control on long-term rates of microvascular complications, even with loss of glycemic separation between the intensive and standard cohorts after the end of the randomized controlled (Holman *et al.*, 2008).

In each of these large randomized prospective clinical trials, treatment regimens that reduced average A1C to $\geq 7\%$ ($\geq 1\%$ above the upper limits of normal) were associated with fewer long-term microvascular complications; however, intensive control was found to increase the risk of severe hypoglycemia, most notably in the DCCT, and led to weight gain (Stratton *et al.*, 2000; Lawson *et al.*, 1999).

Epidemiological analyses of the DCCT and UKPDS (Stratton *et al.*, 2000; DCCT, 1993) demonstrate a curvilinear relationship between A1C and microvascular complications. Such analyses suggest that, on a population level, the greatest number of complications will be averted if patients are taken from very poor control to fair or good control. These analyses also suggest that further lowering of A1C from 7 to 6% is associated with further reduction in the risk of microvascular complications, albeit the absolute risk reductions become much smaller. Given the substantially increased risk of hypoglycemia (particularly in those with type 1 diabetes) and the relatively much greater effort required to achieve near normoglycemia, the risks of lower targets may outweigh the potential benefits on microvascular complications on a population level. However, selected individual patients, especially those with little comorbidity and long life expectancy (who may reap the benefits of further lowering of glycemia below 7%) may, at patient and provider judgment, adopt glycemic targets as close to normal as possible as long as significant hypoglycemia does not become a barrier.

Whereas many epidemiologic studies and meta-analyses (Selvin *et al.*, 2004; Stettler *et al.*, 2006) have clearly shown a direct relationship between A1C and CVD, the potential of intensive glycemic control to reduce CVD has been less clearly defined. In the DCCT, there was a trend towards lower risk of CVD events with intensive control (risk reduction 41%, 95% CI: 10–68%), but the number of events was small. However, a nine-year post-DCCT follow-up of the cohort has shown that participants previously randomized to the intensive arm had a 42% reduction ($P = 0.02$) in CVD outcomes and a 57% reduction ($P = 0.02$) in the risk of nonfatal myocardial infarction (MI), stroke, or CVD death as compared with those previously in the standard arm (Nathan *et al.*, 2005).

The UKPDS trial of type 2 diabetes observed a 16% reduction in cardiovascular complications (combined fatal or nonfatal MI and sudden death) in the intensive glycemic control arm, although this difference was not statistically significant ($P = 0.052$), and

there was no suggestion of benefit on other CVD outcomes such as stroke. In an epidemiologic analysis of the study cohort, a continuous association was observed, such that for every percentage point lower median onstudy A1C (e.g. 8 to 7%) there was a statistically significant 18% reduction in CVD events, again with no glycemic threshold. A recent report of 10 years of follow-up of the UKPDS cohort describes, for the participants originally randomized to intensive glycemic control as compared with those randomized to conventional glycemic control, long-term reductions in MI (15% with sulfonylurea or insulin as initial pharmacotherapy, 33% with metformin as initial pharmacotherapy, both statistically significant) and in all-cause mortality (13% and 27%, respectively, both statistically significant) (Holman *et al.*, 2008).

Because of ongoing uncertainty regarding whether intensive glycemic control can reduce the increased risk of CVD events in people with type 2 diabetes, several large long-term trials were launched in the past decade to compare the effects of intensive versus standard glycemic control on CVD outcomes in relatively high-risk participants with established type 2 diabetes.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study randomized 10,251 participants with either history of a CVD event (ages 40–79 years) or significant CVD risk (ages 55–79) to a strategy of intensive glycemic control (target A1C < 6.0%) or standard glycemic control (A1C target 7.0–7.9%). Investigators used multiple glycemic medications in both arms. ACCORD participants were on average 62-years old and had a mean duration of diabetes of 10 years, with 35% already treated with insulin at baseline. From a baseline median A1C of 8.1%, the intensive arm reached a median A1C of 6.4% within 12 months of randomization, while the standard group reached a median A1C of 7.5%. Other risk factors were treated aggressively and equally in both groups. The intensive glycemic control group had more use of insulin in combination with multiple oral agents, significantly more weight gain, and more episodes of severe hypoglycemia than the standard group.

In February 2008, the glycemic control study of ACCORD was halted on the recommendation of the study's data safety monitoring board due to the finding of an increased rate of mortality in the intensive arm as compared with the standard arm (1.41%/year vs. 1.14%/year; HR 1.22 [95% CI: 1.01–1.46]), with a similar increase in cardiovascular deaths. The primary outcome of ACCORD (MI, stroke, or cardiovascular death) was lower in the intensive glycemic control group due to a reduction in nonfatal MI, although this finding was not statistically significant when the study was terminated (HR 0.90 [95% CI: 0.78–1.04]; $P = 0.16$).

Exploratory analyses of the mortality findings of ACCORD (evaluating variables including weight gain, use of any specific drug or drug combination, and hypoglycemia) were reportedly unable to identify an explanation for the excess mortality in the intensive arm. Prespecified subset analyses showed that participants with no previous CVD event and those who had a baseline A1C < 8% had a statistically significant reduction in the primary CVD outcome.

The ADVANCE study randomized 11,140 participants to a strategy of intensive glycemic control (with primary therapy being the sulfonylurea gliclazide and additional medications as needed to achieve a target A1C of $\leq 6.5\%$) or to standard therapy (in which any medication but gliclazide could be used and the glycemic target was according to “local guidelines”). ADVANCE participants (who had to be at least 55-year of age with either known vascular disease or at least one other vascular risk factor) were slightly older and of similar high CVD risk as those in ACCORD. However, they had an average duration of diabetes two years shorter, a lower baseline A1C (median 7.2%), and almost no use of insulin at enrollment. The median A1C levels achieved in the intensive and standard arms were 6.3% and 7.0%, respectively, and maximal separation between the arms took several years to achieve. Use of other drugs that favorably impact CVD risk (aspirin, statins, ACE inhibitors) was lower in ADVANCE than in the ACCORD or Veterans Affairs Diabetes Trial (VADT).

The primary outcome of ADVANCE was a combination of microvascular events (nephropathy and retinopathy) and major adverse cardiovascular events (MI, stroke, and cardiovascular death). Intensive glycemic control significantly reduced the primary endpoint (HR 0.90 [95% CI: 0.82–0.98]; $P = 0.01$), although this was due to a significant reduction in the microvascular outcome (0.86 [0.77–0.97], $P = 0.01$), primarily the development of macroalbuminuria, with no significant reduction in the macrovascular outcome (0.94 [0.84–1.06]; $P = 0.32$). There was no difference in the overall or cardiovascular mortality between the intensive and the standard glycemic control arms (Patel *et al.*, 2008).

The VADT randomized 1791 participants with type 2 diabetes uncontrolled on insulin or maximal dose oral agents (median entry A1C 9.4%) to a strategy of intensive glycemic control (goal A1C < 6.0%) or standard glycemic control, with a planned A1C separation of at least 1.5%. Medication treatment algorithms were used to achieve the specified glycemic goals, with a goal of using similar medications in both groups. Median A1C levels of 6.9% and 8.4% were achieved in the intensive and standard arms, respectively, within the first year of the study. Other CVD risk factors were treated aggressively and equally in both groups.

The primary outcome of the VADT was a composite of CVD events (MI, stroke, cardiovascular death, revascularization, hospitalization for heart failure, and amputation for ischemia). During a mean 6-year follow-up period, the cumulative primary outcome was nonsignificantly lower in the intensive arm (HR 0.87 [95% CI: 0.73–1.04]; $P = 0.12$). There were more CVD deaths in the intensive arm than in the standard arm (40 vs. 33; sudden deaths 11 vs. 4), but the difference was not statistically significant. Post hoc subgroup analyses suggested that duration of diabetes interacted with randomization such that participants with duration of diabetes less than about 12 years appeared to have a CVD benefit of intensive glycemic control, while those with longer duration of disease before study entry had a neutral or even adverse effect

of intensive glycemic control. Other exploratory analyses suggested that severe hypoglycemia within the past 90 days was a strong predictor of the primary outcome and of CVD mortality (Duckworth, 2008).

The cause of the excess deaths in the intensive glycemic control arm of ACCORD as compared with the standard arm has been difficult to pinpoint. By design of the trial, randomization to the intensive arm was associated with or has led to many downstream effects, such as higher rates of severe hypoglycemia; more frequent use of insulin, TZDs, other drugs, and drug combinations; and greater weight gain. Such factors may be associated statistically with the higher mortality rate in the intensive arm but may not be causative.

It is biologically plausible that severe hypoglycemia could increase the risk of cardiovascular death in participants with high underlying CVD risk. Other plausible mechanisms for the increase in mortality in ACCORD include weight gain, unmeasured drug effects or interactions, or the overall “intensity” of the ACCORD intervention (use of multiple oral glucose-lowering drugs along with multiple doses of insulin, frequent therapy adjustments to push A1C and self-monitored blood glucose to very low targets, and an intense effort to aggressively reduce A1C by ~2% in participants with advanced diabetes and multiple comorbidities entering the trial).

Since the ADVANCE trial did not show any increase in mortality in the intensive glycemic control arm, examining the differences between ADVANCE and ACCORD supports additional hypotheses. ADVANCE participants on average appeared to have earlier or less advanced diabetes, with shorter duration by 2–3 years and a lower A1C at entry despite very little use of insulin at baseline. A1C was also lowered less and more gradually in the ADVANCE trial, and there was no significant weight gain with intensive glycemic therapy. Although severe hypoglycemia was defined somewhat differently in the three trials, it appears that this occurred in fewer than 3% of intensively treated ADVANCE participants for the entire study duration (median 5 years) as compared

with ~16% of intensively treated subjects in ACCORD and 21% in VADT.

It is likely that the increase in mortality in ACCORD was related to the overall treatment strategies for intensifying glycemic control in the population studied, not the achieved A1C *per se*. The ADVANCE study achieved a median A1C in its intensive arm similar to that in the ACCORD study, with no increased mortality hazard. Thus, the ACCORD mortality findings do not imply that patients with type 2 diabetes, who can easily achieve or maintain low A1C levels with lifestyle modifications with or without pharmacotherapy, are at risk and need to “raise” their A1C.

The three trials compared treatments to A1C levels in the “flatter” part of the observational glycemia-CVD risk curves (median A1C of 6.4–6.9% in the intensive arms as compared with 7.0–8.4% in the standard arms). Importantly, their results should not be extrapolated to imply that there would be no cardiovascular benefit of glucose lowering from very poor control (e.g. A1C > 9%) to good control (e.g. A1C < 7%).

All three trials were carried out in participants with established diabetes (mean duration 8–11 years) and either known CVD or multiple risk factors suggesting the presence of established atherosclerosis. Subset analyses of the three trials suggested a significant benefit of intensive glycemic control on CVD in participants with shorter duration of diabetes, lower A1C at entry, and/or or absence of known CVD. The DCCT-EDIC study and the long-term follow-up of the UKPDS cohort both suggest that intensive glycemic control initiated soon after diagnosis of diabetes in patients with a lower level of CVD risk may impart long-term protection from CVD events. As is the case with microvascular complications, it may be that glycemic control plays a greater role before macrovascular disease is well developed and minimal or no role when it is advanced.

The benefits of intensive glycemic control on microvascular and neuropathic complications are well established for both type 1 and type 2 diabetes. The

ADVANCE trial has added to that evidence base by demonstrating a significant reduction in the risk of new or worsening albuminuria when A1C was lowered to 6.3%, as compared with standard glycemic control, achieving an A1C of 7.0%. The lack of significant reduction in CVD events with intensive glycemic control in ACCORD, ADVANCE, and VADT should not lead clinicians to abandon the general target of an A1C < 7.0% and thereby discount the benefit of good control on what are serious and debilitating microvascular complications.

The evidence for a cardiovascular benefit of intensive glycemic control primarily rests on long-term follow-up of study cohorts treated early in the course of type 1 and type 2 diabetes and subset analyses of ACCORD, ADVANCE, and VADT. Conversely, the mortality findings in ACCORD suggest that the potential risks of very intensive glycemic control may outweigh its benefits in some patients, such as those with a very long duration of diabetes, known history of severe hypoglycemia, advanced atherosclerosis, and advanced age/frailty. Certainly, providers should be vigilant in preventing severe hypoglycemia in patients with advanced disease and should not aggressively attempt to achieve near-normal A1C levels in patients in whom such a target cannot be reasonably easily and safely achieved.

Recommended glycemic goals for nonpregnant adults are shown in Table 9. The recommendations are based on those for A1C, with listed blood glucose levels that appear to correlate with achievement of an A1C of < 7%. The issue of pre- versus postprandial SMBG targets is complex (American Diabetes Association, 2001). Elevated postchallenge (2-h OGTT) glucose values have been associated with increased cardiovascular risk independent of FPG in some epidemiological studies. In diabetic subjects, some surrogate measures of vascular pathology, such as endothelial dysfunction, are negatively affected by postprandial hyperglycemia (Ceriello *et al.*, 2002). It is clear that postprandial hyperglycemia, like preprandial hyperglycemia, contributes to elevated A1C levels, with its relative contribution being higher at A1C

Table 9 Summary of Glycemic Recommendations for Nonpregnant Adults with Diabetes

A1C	< 7.0%*
Preprandial capillary plasma glucose	70–130 mg/dl (3.9–7.2 mmol/l)
Peak postprandial capillary plasma glucose	< 180 mg/dl (< 10.0 mmol/l)

Key concepts in setting glycemic goals:

- A1C is the primary target for glycemic control.
- Goals should be individualized based on:
 - duration of diabetes
 - age/life expectancy
 - comorbid conditions
 - known CVD or advanced microvascular complications
 - hypoglycemia unawareness
 - individual patient considerations
- More or less stringent glycemic goals may be appropriate for individual patients.
- Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals.

*Referenced to a nondiabetic range of 4.0–6.0% using a DCCT-based assay. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes.

levels that are closer to 7%. However, outcome studies have clearly shown A1C to be the primary predictor of complications, and landmark glycemic control trials such as the DCCT and UKPDS relied overwhelmingly on preprandial SMBG. Additionally, a randomized controlled trial presented at the 68th Scientific Sessions of the American Diabetes Association in June 2008 found no CVD benefit of insulin regimens targeting postprandial glucose as compared with those targeting preprandial glucose. A reasonable recommendation for postprandial testing and targets is that for individuals who have premeal glucose values within target but have A1C values above target, monitoring postprandial plasma glucose (PPG) 1–2 h after the start of the meal and treatment aimed at reducing PPG values to < 180 mg/dl may help lower A1C.

As noted above, less stringent treatment goals may be appropriate for adults with limited life expectancies or advanced vascular disease. Severe or frequent hypoglycemia is an absolute indication for the modification of treatment regimens, including setting higher glycemic goals.

Regarding goals for glycemic control for women with GDM, recommendations from the Fifth International Workshop — Conference on Gestational Diabetes Mellitus (Metzger *et al.*, 2007) were to target the following maternal capillary glucose concentrations:

- preprandial: ≤ 95 mg/dl (5.3 mmol/l) and either
- 1-h postmeal: ≤ 140 mg/dl (7.8 mmol/l) or
- 2-h postmeal: ≤ 120 mg/dl (6.7 mmol/l)

For women with preexisting type 1 or type 2 diabetes who become pregnant, a recent consensus statement (Kitzmiller *et al.*, 2008) recommended the following as optimal glycemic goals, if they can be achieved without excessive hypoglycemia:

- premeal, bedtime, and overnight glucose 60–99 mg/dl
- peak postprandial glucose 100–129 mg/dl
- A1C $< 6.0\%$

1.6. Prevention and Management of Diabetes Complications

1.6.1. CVD

CVD is the major cause of morbidity and mortality for individuals with diabetes and the largest contributor to the direct and indirect costs of diabetes. The common conditions coexisting with type 2 diabetes (e.g. hypertension and dyslipidemia) are clear risk factors for CVD, and diabetes itself confers independent risk. Numerous studies have shown the efficacy of controlling individual cardiovascular risk factors in preventing

or slowing CVD in people with diabetes. Large benefits are seen when multiple risk factors are addressed globally (Gaede *et al.*, 2008). Evidence is summarized in the following sections and reviewed in detail in the ADA technical reviews on hypertension (Arauz-Pacheco, 2002); dyslipidemia (Haffner, 1998); aspirin therapy (Colwell, 1997); and smoking cessation (Haire-Joshu, 1999) and in the American Heart Association (AHA)/ADA scientific statement on prevention of CVD in people with diabetes (Buse *et al.*, 2007).

1.6.1.1. Hypertension/blood pressure control Recommendations

Screening and diagnosis

- Blood pressure should be measured at every routine diabetes visit. Patients found to have a systolic blood pressure of ≥ 130 mm Hg or a diastolic blood pressure of ≥ 80 mm Hg should have blood pressure confirmed on a separate day. Repeat systolic blood pressure of ≥ 130 mm Hg or diastolic blood pressure of ≥ 80 mm Hg confirms a diagnosis of hypertension. (C)

Goals

- Patients with diabetes should be treated to a systolic blood pressure < 130 mm Hg. (C)
- Patients with diabetes should be treated to a diastolic blood pressure < 80 mm Hg. (B)

Treatment

- Patients with a systolic blood pressure of 130–139 mm Hg or a diastolic blood pressure of 80–89 mm Hg may be given lifestyle therapy alone for a maximum of three months and then, if targets are not achieved, be treated with the addition of pharmacological agents. (E)
- Patients with more severe hypertension (systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg) at diagnosis or follow-up should receive pharmacologic therapy in addition to lifestyle therapy. (A)

- Pharmacologic therapy for patients with diabetes and hypertension should be with a regimen that includes either an ACE inhibitor or an angiotensin receptor blocker (ARB). If one class is not tolerated, the other should be substituted. If it is necessary to achieve blood pressure targets, a thiazide diuretic should be added for those with an estimated GFR (see below) ≥ 30 ml/min per 1.73 m² and a loop diuretic for those with an estimated GFR < 30 ml/min per 1.73 m². (C)
- Multiple drug therapy (two or more agents at maximal doses) is generally required to achieve blood pressure targets. (B)
- If ACE inhibitors, ARBs, or diuretics are used, kidney function and serum potassium levels should be closely monitored. (E)
- In pregnant patients with diabetes and chronic hypertension, blood pressure target goals of 110–129/65–79 mm Hg are suggested in the interest of long-term maternal health and minimizing impaired fetal growth. ACE inhibitors and ARBs are contraindicated during pregnancy. (E)

Hypertension is a common comorbidity of diabetes, affecting the majority of patients, with prevalence depending on type of diabetes, age, obesity, and ethnicity. Hypertension is a major risk factor for both CVD and microvascular complications. In type 1 diabetes, hypertension is often the result of underlying nephropathy, while in type 2, it usually coexists with other cardiometabolic risk factors.

Screening and diagnosis

Measurement of blood pressure in the office should be done by a trained individual and follow the guidelines established for nondiabetic individuals: Measurement in the seated position, with feet on the floor and arm supported at heart level, after 5 min of rest. Cuff size should be appropriate for the upper arm circumference.

Elevated values should be confirmed on a separate day. Because of the clear synergistic risks of hypertension and diabetes, the diagnostic cutoff for a

diagnosis of hypertension is lower in people with diabetes (blood pressure $\geq 130/80$) than in those without diabetes (blood pressure $\geq 140/90$ mm Hg) (Chobanian *et al.*, 2003).

Home blood pressure self-monitoring and 24-h ambulatory blood pressure monitoring may provide additional evidence of “white coat” and masked hypertension and other discrepancies between office and “true” blood pressure, and studies in nondiabetic populations show that home measurements may better correlate with CVD risk than office measurements (Bobrie *et al.*, 2004; Segal *et al.*, 2005). However, the preponderance of the clear evidence of benefits of treatment of hypertension in people with diabetes is based on office measurements.

Treatment goals

Randomized clinical trials have demonstrated the benefit (reduction of CHD events, stroke, and nephropathy) of lowering blood pressure to < 140 mm Hg systolic and < 80 mm Hg diastolic in individuals with diabetes (Chobanian *et al.*, 2003, UKPDS; 1998; Hansson *et al.*, 1998; Adler *et al.*, 2000). Epidemiologic analyses show that blood pressure $> 115/75$ mm Hg is associated with increased cardiovascular event rates and mortality in individuals with diabetes. Therefore, a target blood pressure goal of $< 130/80$ mm Hg is reasonable if it can be safely achieved. The ongoing ACCORD trial is designed to determine whether blood pressure lowering to systolic blood pressure < 120 mm Hg provides greater cardiovascular protection than a systolic blood pressure level of < 140 mm Hg in patients with type 2 diabetes (www.accord.org).

Treatment strategies

Although there are no well-controlled studies of diet and exercise in the treatment of hypertension in individuals with diabetes, studies in nondiabetic individuals have shown antihypertensive effects similar to pharmacologic monotherapy of reducing sodium intake and excess body weight; increasing consumption of fruits, vegetables, and low-fat dairy products;

avoiding excessive alcohol consumption; and increasing activity levels (Chobanian *et al.*, 2003; Sacks *et al.*, 2001). These nonpharmacological strategies may also positively affect glycemia and lipid control. Their effects on cardiovascular events have not been established. An initial trial of nonpharmacologic therapy may be reasonable in diabetic individuals with mild hypertension (systolic blood pressure 130–139 mm Hg or diastolic blood pressure 80–89 mm Hg). If the blood pressure is ≥ 140 mm Hg systolic and/or ≥ 90 mm Hg diastolic at the time of diagnosis, pharmacologic therapy should be initiated along with nonpharmacologic therapy (Chobanian *et al.*, 2003).

Lowering of blood pressure with regimens based on a variety of antihypertensive drugs, including ACE inhibitors, ARBs, β -blockers, diuretics, and calcium channel blockers, has been shown to be effective in reducing cardiovascular events. Several studies have suggested that ACE inhibitors may be superior to dihydropyridine calcium channel blockers in reducing cardiovascular events (Tatti *et al.*, 1998; Estacio *et al.*, 1998; Schrier *et al.*, 2007). However, a variety of other studies have shown no specific advantage to ACE inhibitors as an initial treatment of hypertension in the general hypertensive population, but rather an advantage on cardiovascular outcomes of an initial therapy with low-dose thiazide diuretics (Chobanian *et al.*, 2003; ALLHAT, 2002; Psaty *et al.*, 2002).

In people with diabetes, inhibitors of the renin-angiotensin system (RAS) may have unique advantages for initial or early therapy of hypertension. In a nonhypertension trial of high-risk individuals, including a large subset with diabetes, an ACE inhibitor reduced CVD outcomes (HOPE, 2000). In patients with congestive heart failure (CHF), including diabetic subgroups, ARBs have been shown to reduce major CVD outcomes (Pfeffer *et al.*, 2003; Granger *et al.*, 2003; McMurray *et al.*, 2003, Lindholm *et al.*, 2002), and in type 2 patients with significant nephropathy, ARBs were superior to calcium channel blockers for reducing heart failure (Berl *et al.*, 2003;

Laffel *et al.*, 1995; Bakris *et al.*, 2000). Though evidence for distinct advantages of RAS inhibitors on CVD outcomes in diabetes remains conflicting (UKPDS, 1998; Psaty *et al.*, 1997), the high CVD risks associated with diabetes, and the high prevalence of undiagnosed CVD, may still favor recommendations for their use as a first-line hypertension therapy in people with diabetes (Chobanian *et al.*, 2003). Recently, the blood pressure arm of the ADVANCE trial demonstrated that routine administration of a fixed combination of the ACE inhibitor perindopril and the diuretic indapamide significantly reduced combined microvascular and macrovascular outcomes, as well as CVD and total mortality. The improved outcomes could also have been due to lower achieved blood pressure in the perindopril-indapamide arm (183). The compelling benefits of RAS inhibitors in diabetic patients with albuminuria or renal insufficiency provide additional rationale for use of these agents.

An important caveat is that most patients with hypertension require multidrug therapy to reach treatment goals, especially diabetic patients whose targets are lower. Many patients will require three or more drugs to reach target goals (Chobanian *et al.*, 2003). If blood pressure is refractory to multiple agents, clinicians should consider an evaluation for secondary forms of hypertension.

During pregnancy in diabetic women with chronic hypertension, target blood pressure goals of systolic blood pressure, 110–129 mm Hg and diastolic blood pressure, 65–79 mm Hg are reasonable, as they contribute to long-term maternal health. Lower blood pressure levels may be associated with impaired fetal growth. During pregnancy, treatment with ACE inhibitors and ARBs is contraindicated, since they are likely to cause fetal damage. Antihypertensive drugs known to be effective and safe in pregnancy include methyldopa, labetalol, diltiazem, clonidine, and prazosin. Chronic diuretic use during pregnancy has been associated with restricted maternal plasma volume, which might reduce uteroplacental perfusion (Sibai, 1996).

1.6.1.2. Dyslipidemia/lipid management

Recommendations

Screening

- In most adult patients, fasting lipid profile should be measured at least annually. In adults with low-risk lipid values (LDL cholesterol < 100 mg/dl, HDL cholesterol > 50 mg/dl, and triglycerides < 150 mg/dl), lipid assessments may be repeated every two years. (E)

Treatment recommendations and goals

- Lifestyle modification focusing on the reduction of saturated fat, *trans* fat, and cholesterol intake; weight loss (if indicated); and increased physical activity should be recommended to improve the lipid profile in patients with diabetes. (A)
- Statin therapy should be added to lifestyle therapy, regardless of baseline lipid levels, for diabetic patients:
 - with overt CVD (A)
 - without CVD who are over the age of 40 and have one or more other CVD risk factors. (A)
- For lower-risk patients than the above (e.g. without overt CVD and under the age of 40), statin therapy should be considered in addition to lifestyle therapy if LDL cholesterol remains above 100 mg/dl or in those with multiple CVD risk factors. (E)
- In individuals without overt CVD, the primary goal is an LDL cholesterol < 100 mg/dl (2.6 mmol/l). (A)
- In individuals with overt CVD, a lower LDL cholesterol goal of < 70 mg/dl (1.8 mmol/l), using a high dose of a statin, is an option. (B)
- If drug-treated patients do not reach the above targets on maximal tolerated statin therapy, a reduction in LDL cholesterol of ~30–40% from baseline is an alternative therapeutic goal. (A)
- Triglycerides levels < 150 mg/dl (1.7 mmol/l) and HDL cholesterol > 40 mg/dl (1.0 mmol/l) in men and > 50 mg/dl (1.3 mmol/l) in women are desirable. However, LDL cholesterol-targeted statin therapy remains the preferred strategy. (C)
- If targets are not reached on maximally tolerated doses of statins, combination therapy using statins and other lipid lowering agents may be considered to achieve lipid targets but has not been evaluated in outcome studies for either CVD outcomes or safety. (E)
- Statin therapy is contraindicated in pregnancy. (E)

Evidence for benefits of lipid lowering therapy

Patients with type 2 diabetes have an increased prevalence of lipid abnormalities, contributing to their high risk of CVD. For the past decade or more, multiple clinical trials demonstrated significant effects of pharmacologic (primarily statin) therapy on CVD outcomes in subjects with CHD and for primary CVD prevention (Baigent, 2005). Subanalyses of diabetic subgroups of larger trials (Pyorala *et al.*, 1997; Heart Protection Study Collaborative Group, 2003; Goldberg *et al.*, 1998; Sheperd *et al.*, 2006; Sever *et al.*, 2005) and trials specifically in subjects with diabetes (Knopp *et al.*, 2006; Sing *et al.*, 2007) showed significant primary and secondary prevention of CVD events \pm CHD deaths in diabetic populations. As shown in Table 10, and similar to findings in non-diabetic subjects, reduction in “hard” CVD outcomes (CHD death and nonfatal MI) can be more clearly seen in diabetic subjects with high baseline CVD risk (known CVD and/or very high LDL cholesterol levels), but overall, the benefits of statin therapy in people with diabetes at moderate or high risk for CVD are convincing.

Low levels of HDL cholesterol, often associated with elevated triglyceride levels, are the most prevalent pattern of dyslipidemia in persons with type 2 diabetes. However, the evidence base for drugs that target these lipid fractions is significantly less robust than that for statin therapy (Singh, 2007). Nicotinic acid has been shown to reduce CVD outcomes (Canner, 1986), although the study was done in a non-diabetic cohort. Gemfibrozil has been shown to decrease rates of CVD events in subjects without diabetes (Rubins *et al.*, 1999; Frick *et al.*, 1987) and in the diabetic subgroup in one of the larger trials

Table 10 Reduction in 10-year Risk of Major CVD End Points (CHD death/non-fatal MI) in Major Statin Trials, or Substudies of Major Trials, in Diabetic Subjects ($n = 16\ 032$)

Study (ref.)	CVD Prevention	Statin Dose and Comparator	Risk Reduction (%)	Relative Risk Reduction (%)	Absolute Risk Reduction (%)	LDL Cholesterol Reduction
4S-DM (186)	2°	Simvastatin 20–40 mg vs. placebo	85.7 to 43.2	50	42.5	186 to 119 mg/dl (36%)
ASPEN 2° (191)	2°	Atorvastatin 10 mg vs. placebo	39.5 to 24.5	34	12.7	112 to 79 mg/dl (29%)
HPS-DM (187)	2°	Simvastatin 40 mg vs. placebo	43.8 to 36.3	17	7.5	123 to 84 mg/dl (31%)
CARE-DM (188)	2°	Pravastatin 40 mg vs. placebo	40.8 to 35.4	13	5.4	136 to 99 mg/dl (27%)
TNT-DM (189)	2°	Atorvastatin 80 mg vs. 10 mg	26.3 to 21.6	18	4.7	99 to 77 mg/dl (22%)
HPS-DM (187)	1°	Simvastatin 40 mg vs. placebo	17.5 to 11.5	34	6.0	124 to 86 mg/dl (31%)
CARDS (209)	1°	Atorvastatin 10 mg vs. placebo	11.5 to 7.5	35	4	118 to 71 mg/dl (40%)
ASPEN (191)	1°	Atorvastatin 10 mg vs. placebo	9.8 to 7.9	19	1.9	114 to 80 mg/dl (30%)
ASCOT-DM (190)	1°	Atorvastatin 10 mg vs. placebo	11.1 to 10.2	8	0.9	125 to 82 mg/dl (34%)

Studies were of differing lengths (3.3–5.4 years) and used somewhat different outcomes, but all reported rates of CVD death and non-fatal MI. In this tabulation, results of the statin on 10-year risk of major CVD end points (CHD death/non-fatal MI) are listed for comparison between studies. Correlation between 10-year CVD risk of the control group and the absolute risk reduction with statin therapy is highly significant ($P = 0.0007$). Analyses provided by Craig Williams, Pharm.D., Oregon Health & Science University, 2007.

(Rubins *et al.*, 1999). However, in a large trial specific to diabetic patients, fenofibrate failed to reduce overall cardiovascular outcomes (Keech *et al.*, 2005).

Dyslipidemia treatment and target lipid levels

For most patients with diabetes, the first priority of dyslipidemia therapy (unless severe hypertriglyceridemia is the immediate issue) is to lower LDL cholesterol to a target goal of < 100 mg/dl (2.60 mmol/l) (NCEP, 2001). Lifestyle intervention, including MNT, increased physical activity, weight loss, and smoking cessation, may allow some patients to reach lipid goals. 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, cholesterol, and *trans* unsaturated fat intake. Glycemic control can also beneficially modify plasma lipid levels, particularly in patients with very high triglycerides and poor glycemic control.

In those patients with clinical CVD or over age 40 with other CVD risk factors, pharmacological treatment should be added to lifestyle therapy regardless of baseline lipid levels. Statins are the drugs of choice for LDL cholesterol lowering.

In patients other than those described above, statin treatment should be considered if there is an inadequate LDL cholesterol response to lifestyle modifications and improved glucose control, or if the patient has increased cardiovascular risk (e.g. multiple cardiovascular risk factors or long duration of diabetes). Very little clinical trial evidence exists for type 2 patients under the age of 40, or for type 1 patients of any age. In the Heart Protection Study, the subgroup of 600 patients with type 1 diabetes (lower age limit 40 years) had a proportionately similar reduction in risk as patients with type 2 diabetes, although not statistically significant (Heart Protection Study Collaborative Group, 2003). Although the data are not definitive, consideration should be given to similar lipid-lowering goals in type 1 diabetic patients as those in type 2 diabetic patients, particularly if they have other cardiovascular risk factors.

Alternative LDL cholesterol goals

Virtually all trials of statins and CVD outcomes have tested specific doses of statins against placebo, other doses of statin, or other statins, rather than aiming for specific LDL cholesterol goals (Hayward *et al.*, 2006). As can be seen in Table 10, placebo-controlled trials generally achieved LDL cholesterol reductions of 30–40% from baseline.

Hence, LDL cholesterol lowering of this magnitude is an acceptable outcome for patients who cannot reach LDL cholesterol goals due to severe baseline elevations in LDL cholesterol and/or intolerance of maximal, or any, statin doses. Additionally, for those with baseline LDL cholesterol minimally above 100 mg/dl, prescribing statin therapy to lower LDL cholesterol about 30–40% from baseline is probably more effective than prescribing just enough to reduce the LDL cholesterol level to slightly below 100 mg/dl.

Recent clinical trials in high-risk patients, such as those with acute coronary syndromes or previous cardiovascular events (Cannon *et al.*, 2004; de Lemos *et al.*, 2004; Nissen *et al.*, 2004), have demonstrated that more aggressive therapy with high doses of statins to achieve an LDL cholesterol of < 70 mg/dl led to a significant reduction in further events. Therefore, a reduction in LDL cholesterol to a goal of < 70 mg/dl is an option in very-high-risk diabetic patients with overt CVD (Grundy *et al.*, 2004).

In individual patients, LDL cholesterol lowering with statins is highly variable, and this variable response is poorly understood (Chasman, 2004). Reduction of CVD events with statins correlates very closely, with LDL cholesterol lowering (Baigent *et al.*, 2005). When maximally tolerated doses of statins fail to significantly lower LDL cholesterol (< 30% reduction from patients' baseline), the primary aim of combination therapy should be to achieve additional LDL cholesterol lowering. Niacin, fenofibrate, ezetimibe, and bile acid sequestrants all offer additional LDL cholesterol lowering. The evidence that combination therapy provides a significant increment in CVD risk reduction over statin therapy alone is still elusive.

Treatment of other lipoprotein fractions or targets

Severe hypertriglyceridemia may warrant immediate therapy of this abnormality with lifestyle and usually pharmacologic therapy (fibric acid derivative or niacin) to reduce the risk of acute pancreatitis. In the absence of severe hypertriglyceridemia, therapy targeting HDL cholesterol or triglycerides has intuitive appeal but lacks the evidence base of statin therapy (Sega *et al.*, 2005). If the HDL cholesterol is < 40 mg/dl and the LDL cholesterol is between 100 and 129 mg/dl, gemfibrozil or niacin might be used, especially if a patient is intolerant to statins. Niacin is the most effective drug for raising HDL cholesterol. It can significantly increase blood glucose at high doses, but recent studies demonstrate that at modest doses (750–2000 mg/day), significant improvements in LDL cholesterol, HDL cholesterol, and triglyceride levels are accompanied by only modest changes in glucose that are generally amenable to adjustment of diabetes therapy (Elam *et al.*, 2000; Grundy *et al.*, 2002).

Combination therapy, with a statin and a fibrate or a statin and niacin, may be efficacious for treatment for all three lipid fractions, but this combination is associated with an increased risk for abnormal transaminase levels, myositis, or rhabdomyolysis. The risk of rhabdomyolysis is higher with higher doses of statins and with renal insufficiency and seems to be lower when statins are combined with fenofibrate than gemfibrozil (Jones and Davidson, 2005). Several ongoing trials may provide much-needed evidence for the effects of combination therapy on cardiovascular outcomes.

In 2008, a consensus panel convened by ADA and the American College of Cardiology recommended a greater focus on non-HDL cholesterol and apolipoprotein B (apo B) in patients who are likely to have small LDL particles, such as people with diabetes (Brunzell *et al.*, 2008). The consensus panel suggested that for statin-treated patients in whom the LDL cholesterol goal would be < 70 mg/dl (non-HDL cholesterol < 100 mg/dl), apo B should be measured and treated to achieve a goal of < 80 mg/dl. For

patients on statins with an LDL cholesterol goal of < 100 mg/dl (non-HDL cholesterol < 130 mg/dl), apo B should be measured and treated to below 90 mg/dl.

1.6.1.3. Antiplatelet agents**Recommendations**

- Aspirin therapy (75–162 mg/day) should be used as a primary prevention strategy in those with type 1 or type 2 diabetes at increased cardiovascular risk, including those who are > 40 years of age or who have additional risk factors (family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria). (C)
- Aspirin therapy (75–162 mg/day) should be used as a secondary prevention strategy in those with diabetes with a history of CVD. (A)
- For patients with CVD and documented aspirin allergy, clopidogrel (75 mg/day) should be used. (B)
- Combination therapy with ASA (75–162 mg/day) and clopidogrel (75 mg/day) is reasonable for up to a year after an acute coronary syndrome. (B)
- Aspirin therapy is not recommended for people under 30 years of age due to lack of evidence of benefit and is contraindicated in patients under the age of 21 years because of the associated risk of Reye's syndrome. (E)

The use of aspirin in diabetes is reviewed in detail in the ADA technical review (Colwell, 1997) and position statement (American Diabetic Association, 2004) on this topic. Aspirin has been recommended for primary (Hayden *et al.*, 2002; US Preventive Services Task Force, 2002) and secondary (Antithrombotic Trialists Collaboration, 2002) prevention of cardiovascular events in high-risk 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 a ~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 CVD, men and women, and patients with hypertension.

Dosages used in most clinical trials ranged from 75 to 325 mg/day. There is little evidence to support any specific dose, but using the lowest possible dosage may help reduce side effects (Campbell *et al.*, 2007). Conversely, a randomized trial of 100 mg of aspirin daily showed less of a primary prevention effect, without statistical significance, in the large diabetic subgroup in contrast to significant benefit in those without diabetes (Sacco *et al.*, 2003), raising the issue of aspirin resistance in those with diabetes.

The systematic review of evidence for the U.S. Preventive Services Task Force (USPSTF) estimated that aspirin reduced the risk for nonfatal and fatal MI (odds ratio 0.72 [95% CI: 0.60–0.87]). The review acknowledged the low numbers of diabetic subjects in most trials but concluded that subset analyses and a single trial in diabetic patients suggested that the estimates extended to those with diabetes (Hayden *et al.*, 2002). The USPSTF stated that the risk to benefit ratio favors aspirin use when a 5-year CHD risk equals or exceeds 3% and suggested aspirin therapy be considered for men > 40 years of age, postmenopausal women, and younger persons with CHD risk factors (including diabetes) (US Preventive Task Force, 2002).

There is no evidence for a specific age at which to start aspirin, but aspirin has not been studied at ages < 30 years. Clopidogrel has been demonstrated to reduce CVD events in diabetic individuals (Bhatt *et al.*, 2002). Adjunctive therapy in the first year after acute coronary syndrome in very-high-risk patients, or as alternative therapy in aspirin-intolerant patients, should be considered.

1.6.1.4. Smoking cessation

Recommendations

- Advice should be given all patients not to smoke. (A)
- Smoking cessation counselling and other forms of treatment should be included as a routine component of diabetes care. (B)

Issues of smoking in diabetes are reviewed in detail in the ADA technical review (Haire-Joshu, 1999) and position statement (American Diabetes Association, 2004) on this topic. A large body of evidence from epidemiological, case-control, and cohort studies provides convincing documentation of the causal link between cigarette smoking and health risks. Cigarette smoking contributes to one of every five deaths in the U.S. and is the most important modifiable cause of premature death. Much of the prior work documenting the impact of smoking on health did not separately discuss results on subsets of individuals with diabetes, suggesting that the identified risks are at least equivalent to those found in the general population. Other studies of individuals with diabetes consistently found a heightened risk of CVD and premature death among smokers. Smoking is also related to the premature development of microvascular complications of diabetes and may have a role in the development of type 2 diabetes.

A number of large randomized clinical trials have demonstrated the efficacy and cost-effectiveness of smoking cessation counseling in changing smoking behavior and reducing tobacco use. The routine and thorough assessment of tobacco use is important as a means of preventing smoking or encouraging cessation. Special considerations should include assessment of level of nicotine dependence, which is associated with difficulty in quitting and relapse (US Preventive Task Force, 2003; Ranney *et al.*, 2006). Free telephone quit lines are available in each state (see www.naquitline.org).

1.6.2. Retinopathy Screening and Treatment

Recommendations

General recommendations

- To reduce the risk or slow the progression of retinopathy, glycemic control should be optimized. (A)
- To reduce the risk or slow the progression of retinopathy, blood pressure control should be optimized. (A)

Screening

- Adults and children aged 10 years or older with type 1 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist within five years after the onset of diabetes. (B)
- 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. (B)
- Subsequent examinations for type 1 and type 2 diabetic patients should be repeated annually by an ophthalmologist or optometrist. Less frequent exams (every 2–3 years) may be considered following one or more normal eye exams. Examinations will be required more frequently if retinopathy is progressing. (B)
- Women with preexisting diabetes who are planning pregnancy or who have become pregnant should have a comprehensive eye examination and be counseled on the risk of development and/or progression of diabetic retinopathy. Eye examination should occur in the first trimester with close follow-up throughout the pregnancy and one year postpartum. (B)

Treatment

- 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. (A)
- Laser photocoagulation therapy is indicated to reduce the risk of vision loss in patients with high-risk PDR and clinically significant macular edema and in some cases of severe NPDR. (A)
- The presence of retinopathy is not a contraindication to aspirin therapy for cardioprotection, as this therapy does not increase the risk of retinal hemorrhage. (A)

Diabetic retinopathy is a highly specific vascular complication of both type 1 and type 2 diabetes, with

prevalence strongly related to the duration of diabetes. Diabetic retinopathy is the most frequent cause of new cases of blindness among adults aged 20–74 years. Glaucoma, cataracts, and other disorders of the eye occur earlier and more frequently in people with diabetes.

In addition to duration of diabetes, other factors that increase the risk of, or are associated with, retinopathy include chronic hyperglycemia (Klein, 1995), the presence of nephropathy (Estacio *et al.*, 1998), and hypertension (Leske *et al.*, 2005). Intensive diabetes management with the goal of achieving near normoglycemia has been shown in large prospective randomized studies to prevent and/or delay the onset and progression of diabetic retinopathy (DCCT, 1993; UKPDS, 1998a; UKPDS, 1998b). Lowering blood pressure has been shown to decrease the progression of retinopathy (UKPDS, 1998) (Table 11). Several case series and a controlled prospective study suggest that pregnancy in type 1 diabetic patients may aggravate retinopathy (Fong *et al.*, 2004; DCCT, 2000); laser photocoagulation surgery can minimize this risk (DCCT, 2000). One of the main motivations for screening for diabetic retinopathy is the established efficacy of laser photocoagulation surgery in preventing vision loss. Two large trials, the Diabetic Retinopathy Study (DRS) and the Early Treatment Diabetic Retinopathy Study (ETDRS), provide the strongest support for the therapeutic benefits of photocoagulation surgery.

The DRS (DRS, 1976) showed that panretinal photocoagulation surgery reduced the risk of severe vision loss from PDR from 15.9% in untreated eyes to 6.4% in treated eyes. The benefit was greatest among patients whose baseline evaluation revealed high-risk characteristics (chiefly disc neovascularization or vitreous hemorrhage). Given the risks of modest loss of visual acuity and contraction of the visual field from panretinal laser surgery, such therapy is primarily recommended for eyes with PDR approaching or having high-risk characteristics.

The ETDRS (ETDRS, 1985) established the benefit of focal laser photocoagulation surgery in

Table 11 Summary of Recommendations for Glycemic, Blood Pressure, and Lipid Control for Adults with Diabetes

A1C	< 7.0%*
Blood pressure	< 130/80 mm Hg
Lipids	
LDL cholesterol	< 100 mg/dl (< 2.6 mmol/l)†

*Referenced to a nondiabetic range of 4.0–6.0% using a DCCT-based assay.

†In individuals with overt CVD, a lower LDL cholesterol goal of < 70 mg/dl (1.8 mmol/l), using a high dose of a statin, is an option.

eyes with macular edema, particularly those with clinically significant macular edema, with reduction of doubling of the visual angle (e.g. 20/50 to 20/100) from 20% in untreated eyes to 8% in treated eyes. The ETDRS also verified the benefits of panretinal photocoagulation for high-risk PDR, but not for mild or moderate NPDR. In older-onset patients with severe NPDR or less-than-high-risk PDR, the risk of severe vision loss or vitrectomy was reduced ~50% by early laser photocoagulation surgery at these stages.

Laser photocoagulation surgery in both trials was beneficial in reducing the risk of further vision loss, but generally not beneficial in reversing already diminished acuity. This preventive effect and the fact that patients with PDR or macular edema may be asymptomatic provide strong support for a screening program to detect diabetic retinopathy.

As retinopathy is estimated to take at least five years to develop after the onset of hyperglycemia (Klein *et al.*, 1984), patients with type 1 diabetes should have an initial dilated and comprehensive eye examination within five years after the onset of diabetes. Patients with type 2 diabetes, who generally have had years of undiagnosed diabetes (Harris *et al.*, 1992) and who have a significant risk of prevalent diabetic retinopathy at the time of diabetes diagnosis, should have an initial dilated and comprehensive eye examination soon after diagnosis. Examinations should be performed by an ophthalmologist or optometrist who is knowledgeable and experienced in

diagnosing the presence of diabetic retinopathy and is aware of its management. Subsequent examinations for type 1 and type 2 diabetic patients are generally repeated annually. Less frequent exams (every 2–3 years) may be cost effective after one or more normal eye exams (Vijan *et al.*, 2000; Klein, 2003; Younis *et al.*, 2003), while examinations will be required more frequently if retinopathy is progressing.

Examinations can also be done with retinal photographs (with or without dilation of the pupil) read by experienced experts. In-person exams are still necessary when the photos are unacceptable and for follow-up of abnormalities detected. This technology has great potential in areas where qualified eye care professionals are not available and may enhance efficiency and reduce costs when the expertise of ophthalmologists can be utilized for more complex examinations and for therapy (Ahmed *et al.*, 2004).

Results of eye examinations should be documented and transmitted to the referring health care professional.

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