



MOLINA HEALTHCARE OF CALIFORNIA

GESTATIONAL DIABETES GUIDELINE

The following guideline was reviewed and adopted by the Molina Healthcare of California Clinical Quality Management Committee on December 12, 2001, August 14, 2002, August 6, 2003, August 4, 2004, April 6, 2005, April 5, 2006, April 4, 2007, March 12, 2008, March 10, 2010 and March 16, 2011.

Molina Care Management Guidelines

GESTATIONAL DIABETES

Molina's Gestational Diabetes Mellitus (GDM) clinical practice guidelines incorporate recommendations from the American Diabetes Association and the American College of Obstetricians and Gynecologists.

Diagnosis and appropriate management of gestational diabetes is important because studies have shown that the presence of fasting hyperglycemia (>105 mg/dl) may be associated with:

- Increase in risk of intrauterine fetal death during last 4-8 weeks of gestation
- Increase in risk of fetal macrosomia
- Increase in frequency of maternal hypertensive disorders and need for cesarean delivery

Criteria for Screening – Recommendation for screening for GDM are defined as follows:

1. **Screen for undiagnosed type 2 diabetes at the first prenatal visit in those with risk factors, using standard diagnostic criteria*:**

Testing should be considered in all adults who are overweight (BMI \geq 25 kg/m²*) and have **additional risk factors:**

- physical inactivity
- first-degree relative with diabetes
- high-risk race/ethnicity (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 mmHg 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)
- A1C \geq 5.7%, IGT, or IFG on previous testing
- other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
- history of CVD

Criteria for the diagnosis of overt diabetes (not GDM)*:

- A1C \geq 6.5%* (in the absence of unequivocal hyperglycemia, result should be confirmed by repeat testing) **or**
- FPG \geq 126 mg/dL **or**
- 2 hr plasma glucose > 200 mg/dL during a 75-g OGTT (Oral glucose tolerance test) **or**
- In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose of > 200mg/dL

2. **All women not known to have diabetes** should be screened at 24-28 weeks*

Testing for Definitive Diagnosis of GDM

- Perform a 75-g* OGTT with plasma glucose measurement fasting and at 1 and 2 hour, at 24 – 28 weeks of gestation in women not previously diagnosed with overt diabetes.
- The OGTT should be performed in the morning after an overnight fast of at least 8 hours.
- **The diagnosis of GDM** is made when any of the following plasma glucose values are exceeded:
 - Fasting \geq 92 mg/dL*
 - 1 hour \geq 180 mg/dL
 - 2 hour \geq 153 mg/dL*

*Updated - Diabetes Care, Volume 34, Supplement 1, January 2011, American Diabetes Association: Clinical Practice Recommendations 2011

Molina Care Management Guidelines GESTATIONAL DIABETES

D. Therapeutic approach for managing Gestational Diabetes:

- **Nutritional counseling:** All women who meet the definition of GDM should receive nutritional counseling from either:
 - A specialized educational program such as Sweet Success or other similar program
 - Medical Nutritional therapy from a registered dietician
- **Daily self-monitoring of blood glucose.**
 - A prescription can be written for the Accu-Check Advantage glucometer, covered by Molina, and filled at any participating Molina pharmacy.
- **Insulin Therapy** - is recommended when one of the following (as measured by the patient's self-monitored glucose) cannot be maintained at the following levels:
 - Fasting plasma glucose \leq 105 mg/dl
 - 1 hour postprandial plasma glucose \leq 155 mg/dl
 - 2 hour postprandial plasma glucose \leq 130 mg/dl
- **Maternal surveillance should include:**
 - Blood pressure and urine protein monitoring to detect hypertensive disorders
 - Increased surveillance for pregnancies at risk for fetal demise, particularly when fasting glucose levels exceed 105 mg/dl or pregnancy progresses past term
 - Assessment for asymmetric fetal growth by ultrasound
- **Referral** to one of following specialists or team of practitioners should be considered for all women with Gestational Diabetes: perinatologist; high-risk Obstetrician; endocrinologist or hospital-based high-risk obstetric group.
- **Screen** women with GDM for persistent diabetes 6-12 weeks postpartum.

Women with a history of GDM should have lifelong screening for the development of diabetes or prediabetes at least every 3 years.

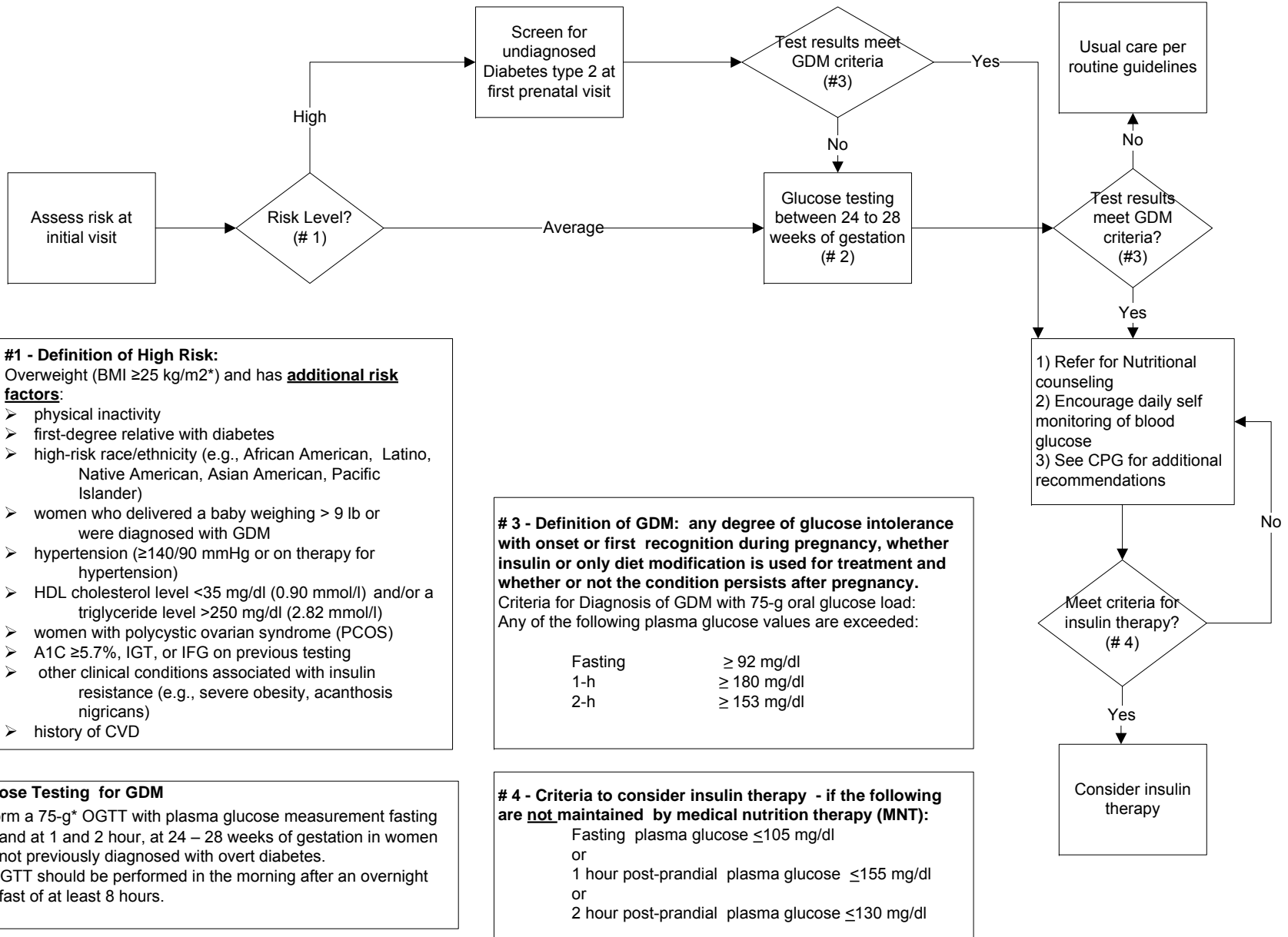
References:

Diabetes Care, Volume 34, Supplement 1, January 2011, American Diabetes Association: Clinical Practice Recommendations 2011.

Gestational Diabetes Mellitus, Diabetes Care, Volume 27, Supplement 1, January 2004, American Diabetes Association: Clinical Practice Recommendations 2004.

ACOG News Release: *Pregnant Women Should Be Screened for Gestational Diabetes: Though No One Test is Ideal*, American College of Gynecologists and Obstetricians, August 2001.

Guidelines for Screening and Treatment for Gestational Diabetes Mellitus (GDM)



#1 - Definition of High Risk:
 Overweight (BMI ≥ 25 kg/m²) and has **additional risk factors**:

- physical inactivity
- first-degree relative with diabetes
- high-risk race/ethnicity (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 ($\geq 140/90$ mmHg 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)
- A1C $\geq 5.7\%$, IGT, or IFG on previous testing
- other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
- history of CVD

2 - Glucose Testing for GDM

- Perform a 75-g* OGTT with plasma glucose measurement fasting and at 1 and 2 hour, at 24 – 28 weeks of gestation in women not previously diagnosed with overt diabetes.
- The OGTT should be performed in the morning after an overnight fast of at least 8 hours.

3 - Definition of GDM: any degree of glucose intolerance with onset or first recognition during pregnancy, whether insulin or only diet modification is used for treatment and whether or not the condition persists after pregnancy.
 Criteria for Diagnosis of GDM with 75-g oral glucose load:
 Any of the following plasma glucose values are exceeded:

Fasting	≥ 92 mg/dl
1-h	≥ 180 mg/dl
2-h	≥ 153 mg/dl

4 - Criteria to consider insulin therapy - if the following are not maintained by medical nutrition therapy (MNT):

Fasting plasma glucose	≤ 105 mg/dl
or	
1 hour post-prandial plasma glucose	≤ 155 mg/dl
or	
2 hour post-prandial plasma glucose	≤ 130 mg/dl

Standards of Medical Care in Diabetes—2011

AMERICAN DIABETES ASSOCIATION

CONTENTS

I. CLASSIFICATION AND DIAGNOSIS OF DIABETES, p. S12

- A. Classification of diabetes
- B. Diagnosis of diabetes
- C. Categories of increased risk for diabetes (prediabetes)

II. TESTING FOR DIABETES IN ASYMPTOMATIC PATIENTS, p. S13

- A. Testing for type 2 diabetes and risk of future diabetes in adults
- B. Testing for type 2 diabetes in children
- C. Screening for type 1 diabetes

III. DETECTION AND DIAGNOSIS OF GESTATIONAL DIABETES MELLITUS, p. S15

IV. PREVENTION/DELAY OF TYPE 2 DIABETES, p. S16

V. DIABETES CARE, p. S16

- A. Initial evaluation
- B. Management
- C. Glycemic control
 - 1. Assessment of glycemic control
 - a. Glucose monitoring
 - b. A1C
 - 2. Glycemic goals in adults
- D. Pharmacologic and overall approaches to treatment
 - 1. Therapy for type 1 diabetes
 - 2. Therapy for type 2 diabetes
- E. Diabetes self-management education
- F. Medical nutrition therapy
- G. Physical activity
- H. Psychosocial assessment and care
- I. When treatment goals are not met
- J. Hypoglycemia
- K. Intercurrent illness
- L. Bariatric surgery
- M. Immunization

VI. PREVENTION AND MANAGEMENT OF DIABETES COMPLICATIONS, p. S27

- A. Cardiovascular disease

- 1. Hypertension/blood pressure control
- 2. Dyslipidemia/lipid management
- 3. Antiplatelet agents
- 4. Smoking cessation
- 5. Coronary heart disease screening and treatment
- B. Nephropathy screening and treatment
- C. Retinopathy screening and treatment
- D. Neuropathy screening and treatment
- E. Foot care

VII. DIABETES CARE IN SPECIFIC POPULATIONS, p. S38

- A. Children and adolescents
 - 1. Type 1 diabetes
 - Glycemic control
 - a. Screening and management of chronic complications in children and adolescents with type 1 diabetes
 - i. Nephropathy
 - ii. Hypertension
 - iii. Dyslipidemia
 - iv. Retinopathy
 - v. Celiac disease
 - vi. Hypothyroidism
 - b. Self-management
 - c. School and day care
 - d. Transition from pediatric to adult care
 - 2. Type 2 diabetes
 - 3. Monogenic diabetes syndromes
- B. Preconception care
- C. Older adults
- D. Cystic fibrosis–related diabetes

VIII. DIABETES CARE IN SPECIFIC SETTINGS, p. S43

- A. Diabetes care in the hospital
 - 1. Glycemic targets in hospitalized patients
 - 2. Anti-hyperglycemic agents in hospitalized patients
 - 3. Preventing hypoglycemia

- 4. Diabetes care providers in the hospital
- 5. Self-management in the hospital
- 6. Diabetes self-management education in the hospital
- 7. Medical nutrition therapy in the hospital
- 8. Bedside blood glucose monitoring
- 9. Discharge planning

IX. STRATEGIES FOR IMPROVING DIABETES CARE, p. S46

Diabetes is a chronic illness that requires continuing medical care and ongoing patient self-management education and support 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, general 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 clinical judgment or more extensive evaluation and management of the patient by other specialists as needed. For more detailed information about management of diabetes, refer to references 1–3.

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 that supports each recommenda-



Originally approved 1988. Most recent review/revision October 2010.

DOI: 10.2337/dc11-S011

© 2011 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See <http://creativecommons.org/licenses/by-nc-nd/3.0/> for details.

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 Center 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</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 <p>Supportive evidence from a well-conducted case-control study</p>
C	<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 <p>Conflicting evidence with the weight of evidence supporting the recommendation</p>
E	Expert consensus or clinical experience

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

These standards of care are revised annually by the ADA's multidisciplinary Professional Practice Committee, incorporating new evidence. Members of the Professional Practice Committee and their disclosed conflicts of interest are listed on page S97. Subsequently, as with all Position Statements, the standards of care are reviewed and approved by the Executive Committee of ADA's Board of Directors.

I. CLASSIFICATION AND DIAGNOSIS OF DIABETES

A. Classification of diabetes

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 insu-

lin action, diseases of the exocrine pancreas (such as cystic fibrosis), and drug- or chemical-induced (such as in the treatment of HIV/AIDS or after organ transplantation)

- Gestational diabetes mellitus (GDM) (diabetes diagnosed during pregnancy that is not clearly overt diabetes)

Some patients cannot be clearly classified as having 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 diabetes 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.

B. Diagnosis of diabetes

For decades, the diagnosis of diabetes was based on plasma glucose criteria, either the fasting plasma glucose (FPG) or the

2-h value in the 75-g oral glucose tolerance test (OGTT) (4).

In 2009, an International Expert Committee that included representatives of the ADA, the International Diabetes Federation (IDF), and the European Association for the Study of Diabetes (EASD) recommended the use of the A1C test to diagnose diabetes, with a threshold of $\geq 6.5\%$ (5), and ADA adopted this criterion in 2010 (4). The diagnostic test should be performed using a method that is certified by the National Glycohemoglobin Standardization Program (NGSP) and standardized or traceable to the Diabetes Control and Complications Trial (DCCT) reference assay. Point-of-care A1C assays are not sufficiently accurate at this time to use for diagnostic purposes.

Epidemiologic datasets show a similar relationship between A1C and risk of retinopathy as has been shown for the corresponding FPG and 2-h plasma glucose thresholds. The A1C has several advantages to the FPG and OGTT, including greater convenience, since fasting is not required; evidence to suggest greater pre-analytical stability; and less day-to-day perturbations during periods of stress and illness. These advantages must be balanced by greater cost, the limited availability of A1C testing in certain regions of the developing world, and the incomplete correlation between A1C and average glucose in certain individuals. In addition, A1C levels can vary with patients' ethnicity (6) as well as with certain anemias and hemoglobinopathies. For patients with an abnormal hemoglobin but normal red cell turnover, such as sickle cell trait, an A1C assay without interference from abnormal hemoglobins should be used (an updated list is available at www.ngsp.org/interf.asp). For conditions with abnormal red cell turnover, such as pregnancy, recent blood loss or transfusion, or some anemias, the diagnosis of diabetes must employ glucose criteria exclusively.

The established glucose criteria for the diagnosis of diabetes (FPG and 2-h PG) remain valid as well (Table 2). Just as there is less than 100% concordance between the FPG and 2-h PG tests, there is not perfect concordance between A1C and either glucose-based test. Analyses of National Health and Nutrition Examination Survey (NHANES) data indicate that, assuming universal screening of the undiagnosed, the A1C cut point of $\geq 6.5\%$ identifies one-third fewer cases of undiagnosed diabetes than a fasting glucose cut point of ≥ 126 mg/dl (7.0 mmol/l) (7).

Table 2—Criteria for the diagnosis of diabetes

A1C $\geq 6.5\%$. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
or
FPG ≥ 126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.*
or
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.*
or
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dl (11.1 mmol/l)

*In the absence of unequivocal hyperglycemia, result should be confirmed by repeat testing.

However, in practice, a large portion of the diabetic population remains unaware of their condition. Thus, the lower sensitivity of A1C at the designated cut point may well be offset by the test's greater practicality, and wider application of a more convenient test (A1C) may actually increase the number of diagnoses made.

As with most diagnostic tests, a test result diagnostic of diabetes should be repeated to rule out laboratory error, unless the diagnosis is clear on clinical grounds, such as a patient with a hyperglycemic crisis or classic symptoms of hyperglycemia and a random plasma glucose ≥ 200 mg/dl. It is preferable that the same test be repeated for confirmation, since there will be a greater likelihood of concurrence in this case. For example, if the A1C is 7.0% and a repeat result is 6.8%, the diagnosis of diabetes is confirmed. However, if two different tests (such as A1C and FPG) are both above the diagnostic thresholds, the diagnosis of diabetes is also confirmed.

On the other hand, if two different tests are available in an individual and the results are discordant, the test whose result is above the diagnostic cut point should be repeated, and the diagnosis is made on the basis of the confirmed test. That is, if a patient meets the diabetes criterion of the A1C (two results $\geq 6.5\%$) but not the FPG (< 126 mg/dl or 7.0 mmol/l), or vice versa, that person should be considered to have diabetes.

Since there is preanalytic and analytic

variability of all the tests, it is also possible that when a test whose result was above the diagnostic threshold is repeated, the second value will be below the diagnostic cut point. This is least likely for A1C, somewhat more likely for FPG, and most likely for the 2-h PG. Barring a laboratory error, such patients are likely to have test results near the margins of the threshold for a diagnosis. The healthcare professional might opt to follow the patient closely and repeat the testing in 3–6 months.

The current diagnostic criteria for diabetes are summarized in Table 2.

C. Categories of increased risk for diabetes (prediabetes)

In 1997 and 2003, The Expert Committee on Diagnosis and Classification of Diabetes Mellitus (8,9) recognized an intermediate group of individuals whose glucose levels, although not meeting criteria for diabetes, are nevertheless too high to be considered normal. These persons were defined as having impaired fasting glucose (IFG) (FPG levels 100–125 mg/dl [5.6–6.9 mmol/l]) or impaired glucose tolerance (IGT) (2-h PG values in the OGTT of 140–199 mg/dl [7.8–11.0 mmol/l]). It should be noted that the World Health Organization (WHO) and a number of other diabetes organizations define the cutoff for IFG at 110 mg/dl (6.1 mmol/l).

Individuals with IFG and/or IGT have been referred to as having prediabetes, indicating the relatively high risk for the future development of diabetes. IFG and IGT should not be viewed as clinical entities in their own right but rather risk factors for diabetes as well as cardiovascular disease (CVD). IFG and IGT are associated with obesity (especially abdominal or visceral obesity), dyslipidemia with high triglycerides and/or low HDL cholesterol, and hypertension.

As is the case with the glucose measures, several prospective studies that used A1C to predict the progression to diabetes demonstrated a strong, continuous association between A1C and subsequent diabetes. In a systematic review of 44,203 individuals from 16 cohort studies with a follow-up interval averaging 5.6 years (range 2.8–12 years), those with an A1C between 5.5 and 6.0% had a substantially increased risk of diabetes with 5-year incidences ranging from 9–25%. An A1C range of 6.0–6.5% had a 5-year risk of developing diabetes between 25–50% and relative risk 20 times higher

Table 3—Categories of increased risk for diabetes (prediabetes)*

FPG 100–125 mg/dl (5.6–6.9 mmol/l): IFG
or
2-h plasma glucose in the 75-g OGTT 140–199 mg/dl (7.8–11.0 mmol/l): IGT
or
A1C 5.7–6.4%

*For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at higher ends of the range.

compared with an A1C of 5.0% (10). In a community-based study of black and white adults without diabetes, baseline A1C was a stronger predictor of subsequent diabetes and cardiovascular events than fasting glucose (11). Other analyses suggest that an A1C of 5.7% is associated with diabetes risk similar to that of the high-risk participants in the Diabetes Prevention Program (DPP).

Hence, it is reasonable to consider an A1C range of 5.7–6.4% as identifying individuals with high risk for future diabetes, a state that may be referred to as prediabetes (4). As is the case for individuals found to have IFG and IGT, individuals with an A1C of 5.7–6.4% should be informed of their increased risk for diabetes as well as CVD and counseled about effective strategies to lower their risks (see IV. PREVENTION/DELAY OF TYPE 2 DIABETES). As with glucose measurements, the continuum of risk is curvilinear—as A1C rises, the risk of diabetes rises disproportionately (10). Accordingly, interventions should be most intensive and follow-up particularly vigilant for those with A1Cs above 6.0%, who should be considered to be at very high risk.

Table 3 summarizes the categories of increased risk for diabetes.

II. TESTING FOR DIABETES IN ASYMPTOMATIC PATIENTS

Recommendations

- Testing to detect type 2 diabetes and assess risk for future 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 4). In those without these risk factors, testing should begin at age 45 years. (B)
- If tests are normal, repeat testing carried out at least at 3-year intervals is reasonable. (E)

Table 4—Criteria for testing for diabetes in asymptomatic adult individuals

- 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
 - high-risk race/ethnicity (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 ($\geq 140/90$ mmHg 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)
 - A1C $\geq 5.7\%$, IGT, or IFG on previous testing
 - other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
 - history of CVD
- In the absence of the above criteria, testing for diabetes should begin at age 45 years.
- 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.

- To test for diabetes or to assess risk of future diabetes, A1C, FPG, or 2-h 75-g OGTT is appropriate. (B)
- In those identified with increased risk for future diabetes, 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. 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 at increased future risk for diabetes, herein referred to as having prediabetes.

A. Testing for type 2 diabetes and risk of future diabetes in adults

Type 2 diabetes is frequently not diagnosed until complications appear, and approximately one-fourth of all people with diabetes in the U.S. may be undiagnosed. The effectiveness of early identification of prediabetes and diabetes through mass testing of asymptomatic individuals has not been proven definitively, and rigorous trials to provide such proof are unlikely to occur. However, mathematical modeling studies suggest that screening independent of risk factors beginning at age 30 or 45 years is highly cost-effective ($< \$11,000$ per quality-adjusted life-year gained) (12). Prediabetes and diabetes meet established criteria for conditions in which early detection is appropriate. Both conditions are common and 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. 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 IV. PREVENTION/DELAY OF TYPE 2 DIABETES) and to reduce risk of complications of diabetes (see VI. PREVENTION AND MANAGEMENT OF DIABETES COMPLICATIONS).

Recommendations for testing for diabetes in asymptomatic, undiagnosed adults are listed in Table 4. Testing should be considered in adults of any age with BMI ≥ 25 kg/m² and one or more of the known 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 A1C, FPG, or the 2-h OGTT is appropriate for testing. The 2-h OGTT identifies people with either IFG or IGT and thus more 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 individuals. The efficacy of interventions for primary prevention of type 2 diabetes (13–19) have primarily been demonstrated among individuals with IGT, not for individuals with IFG (who do not also have IGT) or for individuals with specific A1C levels.

The appropriate interval between tests is not known (20). The rationale for the 3-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 3 years of a negative test result. In the modeling study, repeat screening every 3 or 5 years was cost-effective (12).

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.

B. 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 (21), although the disease remains rare in the general pediatric population (22). Consistent with recommendations for adults, children and youth at increased risk for the presence or the development of type 2 diabetes should be tested within the health care setting. The recommendations of the ADA Consensus Statement on Type 2 Diabetes in Children and Youth (23), with some modifications, are summarized in Table 5.

C. 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, <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

Table 5—Testing for type 2 diabetes in asymptomatic children

Criteria
<ul style="list-style-type: none"> • 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:
<ul style="list-style-type: none"> • 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 birth weight) • 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 various methods of preventing type 1 diabetes, or reversing early type 1 diabetes, in those with evidence of autoimmunity.

III. DETECTION AND DIAGNOSIS OF GESTATIONAL DIABETES MELLITUS

Recommendations

- Screen for undiagnosed type 2 diabetes at the first prenatal visit in those with risk factors, using standard diagnostic criteria. (B)
- In pregnant women not known to have diabetes, screen for GDM at 24–28 weeks of gestation, using a 75-g 2-h OGTT and the diagnostic cut points in Table 6. (B)
- Screen women with GDM for persistent diabetes 6–12 weeks postpartum. (E)
- Women with a history of GDM should have lifelong screening for the development of diabetes or prediabetes at least every 3 years. (E)

For many years, GDM was defined as any degree of glucose intolerance with onset or first recognition during pregnancy (8), whether or not the condition persisted after pregnancy, and not excluding the possibility that unrecognized glucose intolerance may have antedated or begun concomitantly with the pregnancy. This definition facilitated a uniform strategy

for detection and classification of GDM, but its limitations were recognized for many years. As the ongoing epidemic of obesity and diabetes has led to more type 2 diabetes in women of childbearing age, the number of pregnant women with undiagnosed type 2 diabetes has increased (24). Because of this, it is reasonable to screen women with risk factors for type 2 diabetes (Table 4) for diabetes at their initial prenatal visit, using standard diagnostic criteria (Table 2). Women with diabetes found at this visit should receive a diagnosis of overt, not gestational, diabetes.

GDM carries risks for the mother and neonate. The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study (25), a large-scale (~25,000 pregnant women) multinational epidemiologic study, demonstrated that risk of adverse maternal, fetal, and neonatal outcomes continuously increased 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. After deliberations in 2008–2009, the International Association of Diabetes and Pregnancy Study Groups (IADPSG), an international consensus group with representatives from multiple obstetrical and diabetes organizations, including ADA, developed revised recommendations for diagnosing GDM. The group recommended that all women not known to have diabetes undergo a 75-g OGTT at 24–28 weeks of gestation. Additionally, the group developed diagnostic cut points for the fasting, 1-h, and 2-h plasma glucose measurements that conveyed an odds ratio for adverse outcomes of at least 1.75 compared with the mean glucose levels in the HAPO study. Current screening and diagnostic strategies, based on the IADPSG statement (26), are outlined in Table 6.

These new criteria will significantly increase the prevalence of GDM, primarily because only one abnormal value, not two, is sufficient to make the diagnosis. The ADA recognizes the anticipated significant increase in the incidence of GDM to be diagnosed by these criteria and is sensitive to concerns about the “medicalization” of pregnancies previously categorized as normal. These diagnostic criteria changes are being made in the context of worrisome worldwide increases in obesity and diabetes rates, with the intent of

Table 6—Screening for and diagnosis of GDM

Perform a 75-g OGTT, with plasma glucose measurement fasting and at 1 and 2 h, at 24–28 weeks of gestation in women not previously diagnosed with overt diabetes.
The OGTT should be performed in the morning after an overnight fast of at least 8 h.
The diagnosis of GDM is made when any of the following plasma glucose values are exceeded:
<ul style="list-style-type: none"> • Fasting ≥ 92 mg/dl (5.1 mmol/l) • 1 h ≥ 180 mg/dl (10.0 mmol/l) • 2 h ≥ 153 mg/dl (8.5 mmol/l)

optimizing gestational outcomes for women and their babies.

Admittedly, there are few data from randomized clinical trials regarding therapeutic interventions in women who will now be diagnosed with GDM based on only one blood glucose value above the specified cut points (in contrast to the older criteria that stipulated at least two abnormal values.) Expected benefits to their pregnancies and offspring is inferred from intervention trials that focused on women with more mild hyperglycemia than identified using older GDM diagnostic criteria and that found modest benefits (27,28). The frequency of their follow-up and blood glucose monitoring is not yet clear, but likely to be less intensive than women diagnosed by the older criteria. Additional well-designed clinical studies are needed to determine the optimal intensity of monitoring and treatment of women with GDM diagnosed by the new criteria (that would not have met the prior definition of GDM). It is important to note that 80–90% of women in both of the mild GDM studies (whose glucose values overlapped with the thresholds recommended herein) could be managed with lifestyle therapy alone.

Because some cases of GDM may represent preexisting undiagnosed type 2 diabetes, women with a history of GDM should be screened for diabetes 6–12 weeks postpartum, using nonpregnant OGTT criteria. Women with a history of GDM have a greatly increased subsequent risk for diabetes (29) and should be followed up with subsequent screening for the development of diabetes or prediabetes, as outlined in II. TESTING FOR DIABETES IN ASYMPTOMATIC PATIENTS.

Patient Centered Medical Home show promise in improving outcomes through coordinated primary care and offer new opportunities for team-based chronic disease care (395).

It is clear that optimal diabetes management requires an organized, systematic approach and involvement of a coordinated team of dedicated health care professionals working in an environment where patient-centered high-quality care is a priority.

References

- American Diabetes Association: *Medical Management of Type 1 Diabetes*. Alexandria, VA, American Diabetes Association, 2008
- American Diabetes Association: *Medical Management of Type 2 Diabetes*. Alexandria, VA, American Diabetes Association, 2008
- American Diabetes Association: *Intensive Diabetes Management*. Alexandria, VA, American Diabetes Association, 2009
- American Diabetes Association: *Diagnosis and Classification of Diabetes Mellitus*. *Diabetes Care* 2010;33(Suppl. 1):S62–S69
- International Expert Committee: International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. *Diabetes Care* 2009;32:1327–1334
- Ziemer DC, Kolm P, Weintraub WS, Vaccarino V, Rhee MK, Twombly JG, Narayan KM, Koch DD, Phillips LS. Glucose-independent, black-white differences in hemoglobin A1c levels: a cross-sectional analysis of 2 studies. *Ann Intern Med* 2010;152:770–777
- Cowie CC, Rust KF, Byrd-Holt DD, Gregg EW, Ford ES, Geiss LS, Bainbridge KE, Fradkin JE. Prevalence of diabetes and high risk for diabetes using A1C criteria in the U.S. population in 1988–2006. *Diabetes Care* 2010;33:562–568
- Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 1997;20:1183–1197
- Genuth S, Alberti KG, Bennett P, Buse J, DeFronzo R, Kahn R, Kitzmiller J, Knowler WC, Lebovitz H, Lernmark A, Nathan D, Palmer J, Rizza R, Saudek C, Shaw J, Steffes M, Stern M, Tuomilehto J, Zimmet P, Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care* 2003;26:3160–3167
- Zhang X, Gregg EW, Williamson DF, Barker LE, Thomas W, Bullard KM, Imperatore G, Williams DE, Albright AL. A1C level and future risk of diabetes: a systematic review. *Diabetes Care* 2010;33:1665–1673
- Selvin E, Steffes MW, Zhu H, Matsushita K, Wagenknecht L, Pankow J, Coresh J, Brancati FL. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. *N Engl J Med* 2010;362:800–811
- Kahn R, Alperin P, Eddy D, Borch-Johnsen K, Buse J, Feigelman J, Gregg E, Holman RR, Kirkman MS, Stern M, Tuomilehto J, Wareham NJ. Age at initiation and frequency of screening to detect type 2 diabetes: a cost-effectiveness analysis. *Lancet* 2010;375:1365–1374
- Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM, Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346:393–403
- Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P, Keinänen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M, Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001;344:1343–1350
- Pan XR, Li GW, Hu YH, Wang JX, Yang WY, An ZX, Hu ZX, Lin J, Xiao JZ, Cao HB, Liu PA, Jiang XG, Jiang YY, Wang JP, Zheng H, Zhang H, Bennett PH, Howard BV. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. *Diabetes Care* 1997;20:537–544
- Buchanan TA, Xiang AH, Peters RK, Kjos SL, Marroquin A, Goico J, Ochoa C, Tan S, Berkowitz K, Hodis HN, Azen SP. Preservation of pancreatic beta-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk hispanic women. *Diabetes* 2002;51:2796–2803
- Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M, STOP-NIDDM Trial Research Group. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet* 2002;359:2072–2077
- DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators, Gerstein HC, Yusuf S, Bosch J, Pogue J, Sheridan P, Dinccag N, Hanefeld M, Hoogwerf B, Laakso M, Mohan V, Shaw J, Zinman B, Holman RR. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet* 2006;368:1096–1105
- Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar AD, Vijay V, Indian Diabetes Prevention Programme (IDPP). The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). *Diabetologia* 2006;49:289–297
- Johnson SL, Tabaei BP, Herman WH. The efficacy and cost of alternative strategies for systematic screening for type 2 diabetes in the U.S. population 45–74 years of age. *Diabetes Care* 2005;28:307–311
- Dabelea D, D'Agostino RB Jr, Mayer-Davis EJ, Pettitt DJ, Imperatore G, Dolan LM, Pihoker C, Hillier TA, Marcovina SM, Linder B, Ruggiero AM, Hamman RF, SEARCH for Diabetes in Youth Study Group. Testing the accelerator hypothesis: body size, beta-cell function, and age at onset of type 1 (autoimmune) diabetes. *Diabetes Care* 2006;29:290–294
- SEARCH for Diabetes in Youth Study Group, Liese AD, D'Agostino RB Jr, Hamman RF, Kilgo PD, Lawrence JM, Liu LL, Loots B, Linder B, Marcovina S, Rodriguez B, Standiford D, Williams DE. The burden of diabetes mellitus among US youth: prevalence estimates from the SEARCH for Diabetes in Youth Study. *Pediatrics* 2006;118:1510–1518
- American Diabetes Association: Type 2 diabetes in children and adolescents (Consensus Statement). *Diabetes Care* 2000;23:381–389
- Lawrence JM, Contreras R, Chen W, Sacks DA. Trends in the prevalence of preexisting diabetes and gestational diabetes mellitus among a racially/ethnically diverse population of pregnant women, 1999–2005. *Diabetes Care* 2008;31:899–904
- HAPO Study Cooperative Research Group, Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, Coustan DR, Hadden DR, McCance DR, Hod M, McIntyre HD, Oats JJ, Persson B, Rogers MS, Sacks DA. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med* 2008;358:1991–2002
- International Association of Diabetes and Pregnancy Study Groups Consensus Panel, Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, Damm P, Dyer AR, Leiva A, Hod M, Kitzmiller JL, Lowe LP, McIntyre HD, Oats JJ, Omori Y, Schmidt MI. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care* 2010;33:676–682
- Landon MB, Spong CY, Thom E, Carpenter MW, Ramin SM, Casey B, Wapner RJ, Varner MW, Rouse DJ, Thorp JM Jr, Sciscione A, Catalano P, Harper M,

- Saade G, Lain KY, Sorokin Y, Peaceman AM, Tolosa JE, Anderson GB, Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. A multicenter, randomized trial of treatment for mild gestational diabetes. *N Engl J Med* 2009;361:1339–1348
28. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS, Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *N Engl J Med* 2005;352:2477–2486
 29. Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes: a systematic review. *Diabetes Care* 2002;25:1862–1868
 30. Li G, Zhang P, Wang J, Gregg EW, Yang W, Gong Q, Li H, Li H, Jiang Y, An Y, Shuai Y, Zhang B, Zhang J, Thompson TJ, Gerzoff RB, Roglic G, Hu Y, Bennett PH. The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. *Lancet* 2008;371:1783–1789
 31. Lindström J, Ilanne-Parikka P, Peltonen M, Aunola S, Eriksson JG, Hemiö K, Hämäläinen H, Härkönen P, Keinänen-Kiukaanniemi S, Laakso M, Louheranta A, Mannelin M, Paturi M, Sundvall J, Valle TT, Uusitupa M, Tuomilehto J, Finnish Diabetes Prevention Study Group. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. *Lancet* 2006;368:1673–1679
 32. Diabetes Prevention Program Research Group, Knowler WC, Fowler SE, Hamman RF, Christophi CA, Hoffman HJ, Brenneman AT, Brown-Friday JO, Goldberg R, Venditti E, Nathan DM. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet* 2009;374:1677–1686
 33. Herman WH, Hoerger TJ, Brandle M, Hicks K, Sorensen S, Zhang P, Hamman RF, Ackermann RT, Engelgau MM, Ratner RE, Diabetes Prevention Program Research Group. The cost-effectiveness of lifestyle modification or metformin in preventing type 2 diabetes in adults with impaired glucose tolerance. *Ann Intern Med* 2005;142:323–332
 34. Ackermann RT, Finch EA, Brizendine E, Zhou H, Marrero DG. Translating the Diabetes prevention Program into the community: the DEPLOY Pilot Study. *Am J Prev Med* 2008;35:357–363
 35. Kosaka K, Noda M, Kuzuya T. Prevention of type 2 diabetes by lifestyle intervention: a Japanese trial in IGT males. *Diabetes Res Clin Pract* 2005;67:152–162
 36. Torgerson JS, Hauptman J, Boldrin MN, Sjöström L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care* 2004;27:155–161
 37. Kawamori R, Tajima N, Iwamoto Y, Kashiwagi A, Shimamoto K, Kaku K, Voglibose Ph-3 Study Group. Voglibose for prevention of type 2 diabetes mellitus: a randomised, double-blind trial in Japanese individuals with impaired glucose tolerance. *Lancet* 2009;373:1607–1614
 38. Gerstein HC. Point: If it is important to prevent type 2 diabetes, it is important to consider all proven therapies within a comprehensive approach. *Diabetes Care* 2007;30:432–434
 39. Nathan DM, Davidson MB, DeFronzo RA, Heine RJ, Henry RR, Pratley R, Zinman B, American Diabetes Association. Impaired fasting glucose and impaired glucose tolerance: implications for care. *Diabetes Care* 2007;30:753–759
 40. Welschen LM, Bloemendal E, Nijpels G, Dekker JM, Heine RJ, Stalman WA, Bouter LM. Self-monitoring of blood glucose in patients with type 2 diabetes who are not using insulin: a systematic review. *Diabetes Care* 2005;28:1510–1517
 41. Farmer A, Wade A, Goyder E, Yudkin P, French D, Craven A, Holman R, Kinmonth AL, Neil A. Impact of self monitoring of blood glucose in the management of patients with non-insulin treated diabetes: open parallel group randomised trial. *BMJ* 2007;335:132
 42. O’Kane MJ, Bunting B, Copeland M, Coates VE, ESMON study group. Efficacy of self monitoring of blood glucose in patients with newly diagnosed type 2 diabetes (ESMON study): randomised controlled trial. *BMJ* 2008;336:1174–1177
 43. Simon J, Gray A, Clarke P, Wade A, Neil A, Farmer A, Diabetes Glycaemic Education and Monitoring Trial Group. Cost effectiveness of self monitoring of blood glucose in patients with non-insulin treated type 2 diabetes: economic evaluation of data from the DiGEM trial. *BMJ* 2008;336:1177–1180
 44. Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. *Clin Chem* 2002;48:436–472
 45. The Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Continuous glucose monitoring and intensive treatment of type 1 diabetes. *N Engl J Med* 2008;359:1464–1476
 46. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group: The effect of continuous glucose monitoring in well-controlled type 1 diabetes. *Diabetes Care* 2009;32:1378–1383
 47. DCCT: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 1993;329:977–986
 48. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000;321:405–412
 49. Cagliero E, Levina EV, Nathan DM. Immediate feedback of HbA1c levels improves glycemic control in type 1 and insulin-treated type 2 diabetic patients. *Diabetes Care* 1999;22:1785–1789
 50. Miller CD, Barnes CS, Phillips LB, Ziemer DC, Gallina DL, Cook CB, Maryman SD, El-Kebbi IM. Rapid A1c availability improves clinical decision-making in an urban primary care clinic. *Diabetes Care* 2003;26:1158–1163
 51. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ, A1c-Derived Average Glucose Study Group. Translating the A1c assay into estimated average glucose values. *Diabetes Care* 2008;31:1473–1478
 52. Rohlfing CL, Wiedmeyer HM, Little RR, England JD, Tennill A, Goldstein DE. Defining the relationship between plasma glucose and HbA(1c): analysis of glucose profiles and HbA(1c) in the Diabetes Control and Complications Trial. *Diabetes Care* 2002;25:275–278
 53. Diabetes Research in Children Network (DirecNet) Study Group, Wilson DM, Kollman. Relationship of A1C to glucose concentrations in children with type 1 diabetes: assessments by high-frequency glucose determinations by sensors. *Diabetes Care* 2008;31:381–385
 54. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, Kojima Y, Furuyoshi N, Shichiri M. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract* 1995;28:103–117
 55. UKPDS: Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:854–865
 56. UKPDS: Intensive blood-glucose control

- with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:837–853
57. DCCT-EDIC: Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. *N Engl J Med* 2000; 342:381–389
 58. Martin CL, Albers J, Herman WH, Cleary P, Waberski B, Greene DA, Stevens MJ, Feldman EL, DCCT/EDIC Research Group. Neuropathy among the diabetes control and complications trial cohort 8 years after trial completion. *Diabetes Care* 2006;29:340–344
 59. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA: 10-Year Follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008;359:1577–1589
 60. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, Zieve FJ, Marks J, Davis SN, Hayward R, Warren SR, Goldman S, McCarren M, Vitek ME, Henderson WG, Huang GD, VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009;360: 129–139
 61. Moritz T, Duckworth W, Abraira C. Veterans Affairs diabetes trial—corrections. *N Engl J Med* 2009;361:1024–1025
 62. ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompoint S, de Galan BE, Joshi R, Travert F. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;358:2560–2572
 63. Ismail-Beigi F, Craven T, Banerji MA, Basile J, Calles J, Cohen RM, Cuddihy R, Cushman WC, Genuth S, Grimm RH Jr, Hamilton BP, Hoogwerf B, Karl D, Katz L, Krikorian A, O'Connor P, Pop-Busui R, Schubart U, Simmons D, Taylor H, Thomas A, Weiss D, Hramiak I, ACCORD trial group. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. *Lancet* 2010;376:419–430
 64. ACCORD Study Group, ACCORD Eye Study Group, Chew EY, Ambrosius WT, Davis MD, Danis RP, Gangaputra S, Greven CM, Hubbard L, Esser BA, Lovato JF, Perdue LH, Goff DC Jr, Cushman WC, Ginsberg HN, Elam MB, Genuth S, Gerstein HC, Schubart U, Fine LJ. Effects of medical therapies on retinopathy progression in type 2 diabetes. *N Engl J Med* 2010;363:233–244
 65. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH Jr, Probstfield JL, Simons-Morton DG, Friedewald WT. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008;358:2545–2559
 66. Selvin E, Marinopoulos S, Berkenblit G, Rami T, Brancati FL, Powe NR, Golden SH. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med* 2004; 141:421–431
 67. Stettler C, Allemann S, Jüni P, Cull CA, Holman RR, Egger M, Krähenbühl S, Diem P. Glycemic control and macrovascular disease in types 1 and 2 diabetes mellitus: Meta-analysis of randomized trials. *Am Heart J* 2006;152:27–38
 68. Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, Raskin P, Zinman B, Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005;353: 2643–2653
 69. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group, Nathan DM, Zinman B, Cleary PA, Backlund JY, Genuth S, Miller R, Orchard TJ. Modern-day clinical course of type 1 diabetes mellitus after 30 years' duration: the diabetes control and complications trial/epidemiology of diabetes interventions and complications and Pittsburgh epidemiology of diabetes complications experience (1983–2005). *Arch Intern Med* 2009;169:1307–1316
 70. Skyler JS, Bergenstal R, Bonow RO, Buse J, Deedwania P, Gale EA, Howard BV, Kirkman MS, Kosiborod M, Reaven P, Sherwin RS, American Diabetes Association, American College of Cardiology Foundation, American Heart Association. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. *Diabetes Care* 2009;32:187–192
 71. Riddle MC, Ambrosius WT, Brillon DJ, Buse JB, Byington RP, Cohen RM, Goff DC Jr, Malozowski S, Margolis KL, Probstfield JL, Schnall A, Seaquist ER, Action to Control Cardiovascular Risk in Diabetes Investigators. Epidemiologic relationships between A1C and all-cause mortality during a median 3.4-year follow-up of glycemic treatment in the ACCORD trial. *Diabetes Care* 2010;33: 983–990
 72. Reaven PD, Moritz TE, Schwenke DC, Anderson RJ, Criqui M, Detrano R, Emanuele N, Kayshap M, Marks J, Mudaliar S, Rao RH, Shah JH, Goldman S, Reda DJ, McCarren M, Abraira C, Duckworth W: Intensive Glucose Lowering Therapy Reduces Cardiovascular Disease Events in VADT Participants with Lower Calcified Coronary Atherosclerosis. *Diabetes* published online August 3, 2009
 73. Turnbull FM, Abraira C, Anderson RJ, Byington RP, Chalmers JP, Duckworth WC, Evans GW, Gerstein HC, Holman RR, Moritz TE, Neal BC, Ninomiya T, Patel AA, Paul SK, Travert F, Woodward M: Intensive glucose control and macrovascular outcomes in type 2 diabetes. *Diabetologia* 2009;52:2288–2298
 74. American Diabetes Association: Postprandial blood glucose (Consensus Statement). *Diabetes Care* 2001;24: 775–778
 75. Ceriello A, Taboga C, Tonutti L, Quagliaro L, Piconi L, Bais B, Da Ros R, Motz E. Evidence for an independent and cumulative effect of postprandial hypertriglyceridemia and hyperglycemia on endothelial dysfunction and oxidative stress generation: effects of short- and long-term simvastatin treatment. *Circulation* 2002;106:1211–1218
 76. Raz I, Wilson PW, Strojek K, Kowalska I, Bozиков V, Gitt AK, Jermendy G, Campaigne BN, Kerr L, Milicevic Z, Jacober SJ. Effects of prandial versus fasting glycemia on cardiovascular outcomes in type 2 diabetes: the HEART2D trial. *Diabetes Care* 2009;32:381–386
 77. Metzger BE, Buchanan TA, Coustan DR, de Leiva A, Dunger DB, Hadden DR, Hod M, Kitzmiller JL, Kjos SL, Oats JN, Pettitt DJ, Sacks DA, Zouzas C. Summary and recommendations of the Fifth International Workshop-Conference on Gestational Diabetes Mellitus. *Diabetes Care* 2007;30(Suppl. 2):S251–S260
 78. Kitzmiller JL, Block JM, Brown FM, Catalano PM, Conway DL, Coustan DR, Gunderson EP, Herman WH, Hoffman LD, Inturrisi M, Jovanovic LB, Kjos SL, Knopp RH, Montoro MN, Ogata ES, Parnsomy P, Reader DM, Rosenn BM, Thomas AM, Kirkman MS. Managing preexisting diabetes for pregnancy: summary of evidence and consensus recommendations for care. *Diabetes Care* 2008;31:1060–1079
 79. DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. *JAMA* 2003;

- 289:2254–2264
80. Rosenstock J, Dailey G, Massi-Benedetti M, Fritsche A, Lin Z, Salzman A. Reduced hypoglycemia risk with insulin glargine: a meta-analysis comparing insulin glargine with human NPH insulin in type 2 diabetes. *Diabetes Care* 2005; 28:950–955
 81. Mooradian AD, Bernbaum M, Albert SG. Narrative review: a rational approach to starting insulin therapy. *Ann Intern Med* 2006;145:125–134
 82. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zinman B, American Diabetes Association, European Association for Study of Diabetes. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2009; 32:193–203
 83. Norris SL, Engelgau MM, Narayan KM. Effectiveness of self-management training in type 2 diabetes: a systematic review of randomized controlled trials. *Diabetes Care* 2001;24:561–587
 84. Norris SL, Lau J, Smith SJ, Schmid CH, Engelgau MM. Self-management education for adults with type 2 diabetes: a meta-analysis of the effect on glycemic control. *Diabetes Care* 2002;25:1159–1171
 85. Gary TL, Genkinger JM, Guallar E, Peyrot M, Brancati FL. Meta-analysis of randomized educational and behavioral interventions in type 2 diabetes. *Diabetes Educ* 2003;29:488–501
 86. Steed L, Cooke D, Newman S. A systematic review of psychosocial outcomes following education, self-management and psychological interventions in diabetes mellitus. *Patient Educ Couns* 2003;51: 5–15
 87. Ellis SE, Speroff T, Dittus RS, Brown A, Pichert JW, Elasy TA. Diabetes patient education: a meta-analysis and meta-regression. *Patient Educ Couns* 2004;52: 97–105
 88. Warsi A, Wang PS, LaValley MP, Avorn J, Solomon DH. Self-management education programs in chronic disease: a systematic review and methodological critique of the literature. *Arch Intern Med* 2004;164:1641–1649
 89. Funnell MM, Brown TL, Childs BP, Haas LB, Hoseney GM, Jensen B, Maryniuk M, Peyrot M, Piette JD, Reader D, Siminerio LM, Weinger K, Weiss MA. National standards for diabetes self-management education. *Diabetes Care* 2007;30: 1630–1637
 90. Mulcahy K, Maryniuk M, Peeples M, Peyrot M, Tomky D, Weaver T, Yarbrough P. Diabetes self-management education core outcomes measures. *Diabetes Educ* 2003;29:768–784
 91. Glasgow RE, Peeples M, Skovlund SE. Where is the patient in diabetes performance measures? The case for including patient-centered and self-management measures. *Diabetes Care* 2008;31: 1046–1050
 92. Barker JM, Goehrig SH, Barriga K, Hoffman M, Slover R, Eisenbarth GS, Norris JM, Klingensmith GJ, Rewers M, DAISY study. Clinical characteristics of children diagnosed with type 1 diabetes through intensive screening and follow-up. *Diabetes Care* 2004;27:1399–1404
 93. Cochran J, Conn VS. Meta-analysis of quality of life outcomes following diabetes self-management training. *Diabetes Educ* 2008;34:815–823
 94. Fisher EB, Thorpe CT, Devellis BM, Devellis RF. Healthy coping, negative emotions, and diabetes management: a systematic review and appraisal. *Diabetes Educ* 2007;33:1080–1103
 95. Robbins JM, Thatcher GE, Webb DA, Valdmanis VG. Nutritionist visits, diabetes classes, and hospitalization rates and charges: the Urban Diabetes Study. *Diabetes Care* 2008;31:655–660
 96. Renders CM, Valk GD, Griffin SJ, Wagner EH, Eijk Van JT, Assendelft WJ. Interventions to improve the management of diabetes in primary care, outpatient, and community settings: a systematic review. *Diabetes Care* 2001;24:1821–1833
 97. Polonsky WH, Earles J, Smith S, Pease DJ, Macmillan M, Christensen R, Taylor T, Dickert J, Jackson RA. Integrating medical management with diabetes self-management training: a randomized control trial of the Diabetes Outpatient Intensive Treatment program. *Diabetes Care* 2003;26:3048–3053
 98. Anderson RM, Funnell MM, Nwankwo R, Gillard ML, Oh M, Fitzgerald JT. Evaluating a problem-based empowerment program for African Americans with diabetes: results of a randomized controlled trial. *Ethn Dis* 2005;15:671–678
 99. Brown SA, Blozis SA, Kouzekanani K, Garcia AA, Winchell M, Hanis CL. Dosage effects of diabetes self-management education for Mexican Americans: the Starr County Border Health Initiative. *Diabetes Care* 2005;28:527–532
 100. Glazier RH, Bajcar J, Kennie NR, Willson K. A systematic review of interventions to improve diabetes care in socially disadvantaged populations. *Diabetes Care* 2006;29:1675–1688
 101. Hawthorne K, Robles Y, Cannings-John R, Edwards AG. Culturally appropriate health education for type 2 diabetes mellitus in ethnic minority groups. *Cochrane Database Syst Rev* CD006424, 2008
 102. Sarkisian CA, Brown AF, Norris KC, Wintz RL, Mangione CM. A systematic review of diabetes self-care interven-
 - tions for older, African American, or Latino adults. *Diabetes Educ* 2003;29: 467–479
 103. Chodosh J, Morton SC, Mojica W, Maglione M, Suttrop MJ, Hilton L, Rhodes S, Shekelle P. Meta-analysis: chronic disease self-management programs for older adults. *Ann Intern Med* 2005;143: 427–438
 104. Piette JD, Glasgow RE. Strategies for improving behavioral and health outcomes among people with diabetes: self management education. In *Evidence-Based Diabetes Care*. Gerstein HC, Hayes.R.B., Eds. Ontario, Canada, BC Decker, 2000
 105. Peyrot M, Rubin RR. Behavioral and psychosocial interventions in diabetes: a conceptual review. *Diabetes Care* 2007; 30:2433–2440
 106. Anderson DR, Christison-Legay J, Proctor-Gray E. Self-Management goal setting in a community health center: the impact of goal attainment on diabetes outcomes. *Diabetes Spectrum* 2010;23:97–106
 107. Rickheim PL, Weaver TW, Flader JL, Kendall DM. Assessment of group versus individual diabetes education: a randomized study. *Diabetes Care* 2002;25: 269–274
 108. Trento M, Passera P, Borgo E, Tomalino M, Bajardi M, Cavallo F, Porta M. A 5-year randomized controlled study of learning, problem solving ability, and quality of life modifications in people with type 2 diabetes managed by group care. *Diabetes Care* 2004;27:670–675
 109. Deakin T, McShane CE, Cade JE, Williams RD. Group based training for self-management strategies in people with type 2 diabetes mellitus. *Cochrane Database Syst Rev* CD003417, 2005
 110. Duke SA, Colagiuri S, Colagiuri R. Individual patient education for people with type 2 diabetes mellitus. *Cochrane Database Syst Rev* CD005268, 2009
 111. Heisler M, Vijan S, Makki F, Piette JD. Diabetes control with reciprocal peer support versus nurse care management: a randomized trial. *Ann Intern Med* 2010;153:507–515
 112. Heisler M. Different models to mobilize peer support to improve diabetes self-management and clinical outcomes: evidence, logistics, evaluation considerations and needs for future research. *Fam Pract* 2010;27(Suppl. 1):i23–i32
 113. Foster G, Taylor SJ, Eldridge SE, Ramsay J, Griffiths CJ. Self-management education programmes by lay leaders for people with chronic conditions. *Cochrane Database Syst Rev* CD005108, 2007
 114. Norris SL, Chowdhury FM, Van Le K, Horsley T, Brownstein JN, Zhang X, Jack L Jr, Satterfield DW. Effectiveness of community health workers in the care of persons with diabetes. *Diabet Med* 2006;23:544–556
 115. Duncan I, Birkmeyer C, Coughlin S, Li

- QE, Sherr D, Boren S. Assessing the value of diabetes education. *Diabetes Educ* 2009;35:752–760
116. Bantle JP, Wylie-Rosett J, Albright AL, Apovian CM, Clark NG, Franz MJ, Hoogwerf BJ, Lichtenstein AH, Mayer-Davis E, Mooradian AD, Wheeler ML. Nutrition recommendations and interventions for diabetes: a position statement of the American Diabetes Association. *Diabetes Care* 2008;31(Suppl. 1):S61–S78
 117. DAFNE Study Group. Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomised controlled trial. *BMJ* 2002;325:746
 118. Franz MJ, Monk A, Barry B, McClain K, Weaver T, Cooper N, Upham P, Bergenstal R, Mazze RS. Effectiveness of medical nutrition therapy provided by dietitians in the management of non-insulin-dependent diabetes mellitus: a randomized, controlled clinical trial. *J Am Diet Assoc* 1995;95:1009–1017
 119. Goldhaber-Fiebert JD, Goldhaber-Fiebert SN, Tristán ML, Nathan DM. Randomized controlled community-based nutrition and exercise intervention improves glycemia and cardiovascular risk factors in type 2 diabetic patients in rural Costa Rica. *Diabetes Care* 2003;26:24–29
 120. Lemon CC, Lacey K, Lohse B, Hubacher DO, Klawitter B, Palta M. Outcomes monitoring of health, behavior, and quality of life after nutrition intervention in adults with type 2 diabetes. *J Am Diet Assoc* 2004;104:1805–1815
 121. Miller CK, Edwards L, Kissling G, Sanville L. Nutrition education improves metabolic outcomes among older adults with diabetes mellitus: results from a randomized controlled trial. *Prev Med* 2002;34:252–259
 122. Wilson C, Brown T, Acton K, Gilliland S. Effects of clinical nutrition education and educator discipline on glycemic control outcomes in the Indian health service. *Diabetes Care* 2003;26:2500–2504
 123. Graber AL, Elasy TA, Quinn D, Wolff K, Brown A. Improving glycemic control in adults with diabetes mellitus: shared responsibility in primary care practices. *South Med J* 2002;95:684–690
 124. Gaetke LM, Stuart MA, Trusczyńska H. A single nutrition counseling session with a registered dietitian improves short-term clinical outcomes for rural Kentucky patients with chronic diseases. *J Am Diet Assoc* 2006;106:109–112
 125. Van Horn L, McCoin M, Kris-Etherton PM, Burke F, Carson JA, Champagne CM, Karmally W, Sikand G. The evidence for dietary prevention and treatment of cardiovascular disease. *J Am Diet Assoc* 2008;108:287–331
 126. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, Bray GA, Vogt TM, Cutler JA, Windhauser MM, Lin PH, Karanja N. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *N Engl J Med* 1997;336:1117–1124
 127. Norris SL, Zhang X, Avenell A, Gregg E, Bowman B, Schmid CH, Lau J. Long-term effectiveness of weight-loss interventions in adults with prediabetes: a review. *Am J Prev Med* 2005;28:126–139
 128. Klein S, Sheard NF, Pi-Sunyer X, Daly A, Wylie-Rosett J, Kulkarni K, Clark NG, American Diabetes Association, North American Association for the Study of Obesity, American Society for Clinical Nutrition. Weight management through lifestyle modification for the prevention and management of type 2 diabetes: rationale and strategies: a statement of the American Diabetes Association, the North American Association for the Study of Obesity, and the American Society for Clinical Nutrition. *Diabetes Care* 2004;27:2067–2073
 129. Norris SL, Zhang X, Avenell A, Gregg E, Schmid CH, Kim C, Lau J. Efficacy of pharmacotherapy for weight loss in adults with type 2 diabetes mellitus: a meta-analysis. *Arch Intern Med* 2004;164:1395–1404
 130. Wolf AM, Conaway MR, Crowther JQ, Hazen KY, L Nadler J, Oneida B, Bovbjerg VE, Improving Control with Activity and Nutrition (ICAN) Study. Translating lifestyle intervention to practice in obese patients with type 2 diabetes: Improving Control with Activity and Nutrition (ICAN) study. *Diabetes Care* 2004;27:1570–1576
 131. Manning RM, Jung RT, Leese GP, Newton RW. The comparison of four weight reduction strategies aimed at overweight patients with diabetes mellitus: four-year follow-up. *Diabet Med* 1998;15:497–502
 132. Franz MJ, VanWormer JJ, Crain AL, Boucher JL, Histon T, Caplan W, Bowman JD, Pronk NP. Weight-loss outcomes: a systematic review and meta-analysis of weight-loss clinical trials with a minimum 1-year follow-up. *J Am Diet Assoc* 2007;107:1755–1767
 133. Salas-Salvado J, Bullo M, Babio N, Martinez-Gonzalez MA, Ibarrola-Jurado N, Basora J, Estruch R, Covas MI, Corella D, Aros F, Ruiz-Gutierrez V, Ros E. Reduction in the Incidence of Type 2 Diabetes with the Mediterranean Diet: Results of the PREDIMED-Reus Nutrition Intervention Randomized Trial. *Diabetes Care* 2010;34:14–19
 134. Look AHEAD Research Group, Pi-Sunyer X, Blackburn G, Brancati FL, Bray GA, Bright R, Clark JM, Curtis JM, Espeland MA, Foreyt JP, Graves K, Haffner SM, Harrison B, Hill JO, Horton ES, Jakicic J, Jeffery RW, Johnson KC, Kahn S, Kelley DE, Kitabchi AE, Knowler WC, Lewis CE, Maschak-Carey BJ, Montgomery B, Nathan DM, Patricio J, Peters A, Redmon JB, Reeves RS, Ryan DH, Safford M, Van Dorsten B, Wadden TA, Wagenknecht L, Wesche-Thobaben J, Wing RR, Yanovski SZ. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial. *Diabetes Care* 2007;30:1374–1383
 135. Look AHEAD Research Group, Wing RR. Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: four-year results of the Look AHEAD trial. *Arch Intern Med* 2010;170:1566–1575
 136. Foster GD, Wyatt HR, Hill JO, McGuckin BG, Brill C, Mohammed BS, Szapary PO, Rader DJ, Edman JS, Klein S. A randomized trial of a low-carbohydrate diet for obesity. *N Engl J Med* 2003;348:2082–2090
 137. Stern L, Iqbal N, Seshadri P, Chicano KL, Daily DA, McGrory J, Williams M, Gracely EJ, Samaha FF. The effects of low-carbohydrate versus conventional weight loss diets in severely obese adults: one-year follow-up of a randomized trial. *Ann Intern Med* 2004;140:778–785
 138. Foster GD, Wyatt HR, Hill JO, Makris AP, Rosenbaum DL, Brill C, Stein RI, Mohammed BS, Miller B, Rader DJ, Zemel B, Wadden TA, Tenhave T, Newcomb CW, Klein S. Weight and metabolic outcomes after 2 years on a low-carbohydrate versus low-fat diet: a randomized trial. *Ann Intern Med* 2010;153:147–157
 139. Gardner CD, Kiazand A, Alhassan S, Kim S, Stafford RS, Balise RR, Kraemer HC, King AC. Comparison of the Atkins, Zone, Ornish, and LEARN diets for change in weight and related risk factors among overweight premenopausal women: the A TO Z Weight Loss Study: a randomized trial. *JAMA* 2007;297:969–977
 140. Nordmann AJ, Nordmann A, Briel M, Keller U, Yancy WS, Jr, Brehm BJ, Bucher HC. Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors: a meta-analysis of randomized controlled trials. *Arch Intern Med* 2006;166:285–293
 141. Shai I, Schwarzfuchs D, Henkin Y, Shahar DR, Witkow S, Greenberg I, Golan R, Fraser D, Bolotin A, Vardi H, Tangi-Rozental O, Zuk-Ramot R, Sarusi B, Brickner D, Schwartz Z, Sheiner E, Marko R, Katorza E, Thery J, Fiedler GM, Blüher M, Stumvoll M, Stampfer

- MJ, Dietary Intervention Randomized Controlled Trial (DIRECT) Group. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. *N Engl J Med* 2008;359:229–241
142. Institute of Medicine: *Dietary Reference Intakes: Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids*. Washington, D.C., National Academies Press, 2002
 143. Barnard ND, Cohen J, Jenkins DJ, Turner-McGrievy G, Gloede L, Jaster B, Seidl K, Green AA, Talpers S. A low-fat vegan diet improves glycemic control and cardiovascular risk factors in a randomized clinical trial in individuals with type 2 diabetes. *Diabetes Care* 2006;29:1777–1783
 144. Turner-McGrievy GM, Barnard ND, Cohen J, Jenkins DJ, Gloede L, Green AA. Changes in nutrient intake and dietary quality among participants with type 2 diabetes following a low-fat vegan diet or a conventional diabetes diet for 22 weeks. *J Am Diet Assoc* 2008;108:1636–1645
 145. Franz MJ, Bantle JP, Beebe CA, Brunzell JD, Chiasson JL, Garg A, Holzmeister LA, Hoogwerf B, Mayer-Davis E, Mooradian AD, Purnell JQ, Wheeler M. Evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications. *Diabetes Care* 2002;25:148–198
 146. Boulé NG, Haddad E, Kenny GP, Wells GA, Sigal RJ. Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials. *JAMA* 2001;286:1218–1227
 147. Boulé NG, Kenny GP, Haddad E, Wells GA, Sigal RJ. Meta-analysis of the effect of structured exercise training on cardiorespiratory fitness in Type 2 diabetes mellitus. *Diabetologia* 2003;46:1071–1081
 148. Colberg SR, Sigal RJ, Fernhall B, Regensteiner JG, Blissmer BJ, Rubin RR, Chasen-Taber L, Albright AL, Braun B. Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: joint position statement. *Diabetes Care* 2010;33:2692–2696
 149. U.S. Department of Health and Human Services: 2008 Physical Activity Guidelines for Americans. [article online], 2008. Available from <http://www.health.gov/paguidelines/guidelines/default.aspx>. Accessed December 2010.
 150. Cauza E, Hanusch-Enserer U, Strasser B, Ludvik B, Metz-Schimmerl S, Pacini G, Wagner O, Georg P, Prager R, Kostner K, Dunky A, Haber P. The relative benefits of endurance and strength training on the metabolic factors and muscle function of people with type 2 diabetes mellitus. *Arch Phys Med Rehabil* 2005;86:1527–1533
 151. Dunstan DW, Daly RM, Owen N, Jolley D, De Courten M, Shaw J, Zimmet P. High-intensity resistance training improves glycemic control in older patients with type 2 diabetes. *Diabetes Care* 2002;25:1729–1736
 152. Castaneda C, Layne JE, Munoz-Orians L, Gordon PL, Walsmith J, Foldvari M, Roubenoff R, Tucker KL, Nelson ME. A randomized controlled trial of resistance exercise training to improve glycemic control in older adults with type 2 diabetes. *Diabetes Care* 2002;25:2335–2341
 153. Sigal RJ, Kenny GP, Wasserman DH, Castaneda-Sceppa C. Physical activity/exercise and type 2 diabetes. *Diabetes Care* 2004;27:2518–2539
 154. Bax JJ, Young LH, Frye RL, Bonow RO, Steinberg HO, Barrett EJ, ADA. Screening for coronary artery disease in patients with diabetes. *Diabetes Care* 2007;30:2729–2736
 155. Berger M, Berchtold P, Cüppers HJ, Drost H, Kley HK, Müller WA, Wiegelmann W, Zimmerman-Telschow H, Gries FA, Krüskemper HL, Zimmermann H. Metabolic and hormonal effects of muscular exercise in juvenile type diabetics. *Diabetologia* 1977;13:355–365
 156. Aiello LP, Wong J, Cavallerano J, Bursell SE, Aiello LM: Retinopathy. In *Handbook of Exercise in Diabetes*. 2nd ed. Ruderman N, Devlin JT, Kriska A, Eds. Alexandria, VA, American Diabetes Association, 2002, p. 401–413
 157. Lemaster JW, Reiber GE, Smith DG, Heagerty PJ, Wallace C. Daily weight-bearing activity does not increase the risk of diabetic foot ulcers. *Med Sci Sports Exerc* 2003;35:1093–1099
 158. Vinik A, Erbas T: Neuropathy. In *Handbook of Exercise in Diabetes*. 2nd ed. Ruderman N, Devlin JT, Kriska A, Eds. Alexandria, VA, American Diabetes Association, 2002, p. 463–496
 159. Wackers FJ, Young LH, Inzucchi SE, Chyun DA, Davey JA, Barrett EJ, Taillefer R, Wittlin SD, Heller GV, Filipchuk N, Engel S, Ratner RE, Iskandrian AE. Detection of Ischemia in Asymptomatic Diabetics Investigators. Detection of silent myocardial ischemia in asymptomatic diabetic subjects: the DIAD study. *Diabetes Care* 2004;27:1954–1961
 160. Valensi P, Sachs RN, Harfouche B, Lormeau B, Paries J, Cosson E, Paycha F, Leutenegger M, Attali JR. Predictive value of cardiac autonomic neuropathy in diabetic patients with or without silent myocardial ischemia. *Diabetes Care* 2001;24:339–343
 161. Mogensen CE: Nephropathy. In *Handbook of Exercise in Diabetes*. 2nd ed. Ruderman N, Devlin JT, Kriska A, Eds. Alexandria, VA, American Diabetes Association, 2002, p. 433–449
 162. Anderson RJ, Grigsby AB, Freedland KE, de Groot M, McGill JB, Clouse RE, Lustman PJ. Anxiety and poor glycemic control: a meta-analytic review of the literature. *Int J Psychiatry Med* 2002;32:235–247
 163. Delahanty LM, Grant RW, Wittenberg E, Bosch JL, Wexler DJ, Cagliero E, Meigs JB. Association of diabetes-related emotional distress with diabetes treatment in primary care patients with Type 2 diabetes. *Diabet Med* 2007;24:48–54
 164. American Diabetes Association: Psychosocial factors affecting adherence, quality of life, and well-being: Helping Patients cope. In *Medical Management of Type 1 Diabetes*. 5 ed. Francine R. Kaufman, Ed. Alexandria, VA, American Diabetes Association, 2008, p. 173–193
 165. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. *Diabetes Care* 2001;24:1069–1078
 166. Fisher L, Skaff MM, Mullan JT, Areal P, Mohr D, Masharani U, Glasgow R, Laurencin G. Clinical depression versus distress among patients with type 2 diabetes: not just a question of semantics. *Diabetes Care* 2007;30:542–548
 167. Gary TL, Safford MM, Gerzoff RB, Ettner SL, Karter AJ, Beckles GL, Brown AF. Perception of neighborhood problems, health behaviors, and diabetes outcomes among adults with diabetes in managed care: the Translating Research Into Action for Diabetes (TRIAD) study. *Diabetes Care* 2008;31:273–278
 168. Katon W, Fan MY, Unützer J, Taylor J, Pincus H, Schoenbaum M. Depression and diabetes: a potentially lethal combination. *J Gen Intern Med* 2008;23:1571–1575
 169. Zhang X, Norris SL, Gregg EW, Cheng YJ, Beckles G, Kahn HS. Depressive symptoms and mortality among persons with and without diabetes. *Am J Epidemiol* 2005;161:652–660
 170. Rubin RR, Peyrot M. Psychological issues and treatments for people with diabetes. *J Clin Psychol* 2001;57:457–478
 171. Young-Hyman DL, Davis CL. Disordered eating behavior in individuals with diabetes: importance of context, evaluation, and classification. *Diabetes Care* 2010;33:683–689
 172. Blonde L, Merilainen M, Karwe V, Raskin P, TITRATE Study Group. Patient-directed titration for achieving glycaemic goals using a once-daily basal insulin analogue: an assessment of two different fasting plasma glucose targets - the TITRATE study. *Diabetes Obes Metab* 2009;11:623–631
 173. Cryer PE. Hypoglycaemia: the limiting factor in the glycaemic management of

- Type I and Type II diabetes. *Diabetologia* 2002;45:937–948
174. Whitmer RA, Karter AJ, Yaffe K, Quesenberry CP, Jr, Selby JV. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. *JAMA* 2009;301:1565–1572
 175. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group, Jacobson AM, Musen G, Ryan CM, Silvers N, Cleary P, Waberski B, Burwood A, Weinger K, Bayless M, Dahms W, Harth J. Long-term effect of diabetes and its treatment on cognitive function. *N Engl J Med* 2007;356:1842–1852
 176. Cryer PE. Diverse causes of hypoglycemia-associated autonomic failure in diabetes. *N Engl J Med* 2004;350:2272–2279
 177. Buchwald H, Estok R, Fahrback K, Banel D, Jensen MD, Pories WJ, Bantle JP, Sledge I. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. *Am J Med* 2009;122:248–256
 178. Dixon JB, O'Brien PE, Playfair J, Chapman L, Schachter LM, Skinner S, Proietto J, Bailey M, Anderson M. Adjustable gastric banding and conventional therapy for type 2 diabetes: a randomized controlled trial. *JAMA* 2008;299:316–323
 179. Hall TC, Pellen MG, Sedman PC, Jain PK. Preoperative factors predicting remission of type 2 diabetes mellitus after Roux-en-Y gastric bypass surgery for obesity. *Obes Surg* 2010;20:1245–1250
 180. Buchwald H, Estok R, Fahrback K, Banel D, Sledge I. Trends in mortality in bariatric surgery: a systematic review and meta-analysis. *Surgery* 2007;142:621–632
 181. Sjöström L, Narbro K, Sjöström CD, Karason K, Larsson B, Wedel H, Lystig T, Sullivan M, Bouchard C, Carlsson B, Bengtsson C, Dahlgren S, Gummesson A, Jacobson P, Karlsson J, Lindroos AK, Lönroth H, Näslund I, Olbers T, Stenlöf K, Torgerson J, Agren G, Carlsson LM, Swedish Obese Subjects Study. Effects of bariatric surgery on mortality in Swedish obese subjects. *N Engl J Med* 2007;357:741–752
 182. Hoerger TJ, Zhang P, Segel JE, Kahn HS, Barker LE, Couper S. Cost-effectiveness of bariatric surgery for severely obese adults with diabetes. *Diabetes Care* 2010;33:1933–1939
 183. Makary MA, Clarke JM, Shore AD, Magnuson TH, Richards T, Bass EB, Dominici F, Weiner JP, Wu AW, Segal JB. Medication utilization and annual health care costs in patients with type 2 diabetes mellitus before and after bariatric surgery. *Arch Surg* 2010;145:726–731
 184. Keating CL, Dixon JB, Moodie ML, Peeters A, Playfair J, O'Brien PE. Cost-efficacy of surgically induced weight loss for the management of type 2 diabetes: a randomized controlled trial. *Diabetes Care* 2009;32:580–584
 185. Smith SA, Poland GA. Use of influenza and pneumococcal vaccines in people with diabetes. *Diabetes Care* 2000;23:95–108
 186. Colquhoun AJ, Nicholson KG, Botha JL, Raymond NT. Effectiveness of influenza vaccine in reducing hospital admissions in people with diabetes. *Epidemiol Infect* 1997;119:335–341
 187. Bridges CB, Fukuda K, Uyeki TM, Cox NJ, Singleton JA. Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2002;51:1–31
 188. Buse JB, Ginsberg HN, Bakris GL, Clark NG, Costa F, Eckel R, Fonseca V, Gerstein HC, Grundy S, Nesto RW, Pignone MP, Plutzky J, Porte D, Redberg R, Stitzel KF, Stone NJ, American Heart Association, American Diabetes Association. Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. *Diabetes Care* 2007;30:162–172
 189. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* 2008;358:580–591
 190. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ, National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003;289:2560–2572
 191. Bobrie G, Genès N, Vaur L, Clerson P, Vaisse B, Mallion JM, Chatellier G. Is "isolated home" hypertension as opposed to "isolated office" hypertension a sign of greater cardiovascular risk? *Arch Intern Med* 2001;161:2205–2211
 192. Segal R, Facchetti R, Bombelli M, Cesana G, Corrao G, Grassi G, Mancia G. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. *Circulation* 2005;111:1777–1783
 193. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360:1903–1913
 194. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 1993;16:434–444
 195. UKPDS: Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *BMJ* 317:703–713, 1998
 196. Hansson L, Zanchetti A, Carruthers SG, Dahlöf B, Elmfeldt D, Julius S, Ménard J, Rahn KH, Wedel H, Westerling S. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet* 1998;351:1755–1762
 197. Adler AI, Stratton IM, Neil HA, Yudkin JS, Matthews DR, Cull CA, Wright AD, Turner RC, Holman RR. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. *BMJ* 2000;321:412–419
 198. ACCORD Study Group, Cushman WC, Evans GW, Byington RP, Goff DC Jr, Grimm RH Jr, Cutler JA, Simons-Morton DG, Basile JN, Corson MA, Probstfield JL, Katz L, Peterson KA, Friedewald WT, Buse JB, Bigger JT, Gerstein HC, Ismail-Beigi F. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010;362:1575–1585
 199. Patel A, ADVANCE Collaborative Group, MacMahon S, Chalmers J, Neal B, Woodward M, Billot L, Harrap S, Poulter N, Marre M, Cooper M, Glasziou P, Grobbee DE, Hamet P, Heller S, Liu LS, Mancia G, Mogensen CE, Pan CY, Rodgers A, Williams B. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet* 2007;370:829–840
 200. Cooper-DeHoff RM, Gong Y, Handberg EM, Bavry AA, Denardo SJ, Bakris GL, Pepine CJ. Tight blood pressure control and cardiovascular outcomes among hypertensive patients with diabetes and coronary artery disease. *JAMA* 2010;304:61–68
 201. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, Obarzanek E, Conlin PR, Miller ER 3rd, Simons-Morton DG, Karanja N, Lin PH, DASH-Sodium Collaborative Research Group.

- Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *N Engl J Med* 2001;344:3–10
202. Tatti P, Pahor M, Byington RP, Di Mauro P, Guarisco R, Strollo G, Strollo F. Outcome results of the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET) in patients with hypertension and NIDDM. *Diabetes Care* 1998;21:597–603
203. Estacio RO, Jeffers BW, Hiatt WR, Biggerstaff SL, Gifford N, Schrier RW. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. *N Engl J Med* 1998;338:645–652
204. Schrier RW, Estacio RO, Mehler PS, Hiatt WR. Appropriate blood pressure control in hypertensive and normotensive type 2 diabetes mellitus: a summary of the ABCD trial. *Nat Clin Pract Nephrol* 2007;3:428–438
205. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial: Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 288:2981–2997, 2002
206. Psaty BM, Smith NL, Siscovick DS, Koppsell TD, Weiss NS, Heckbert SR, Lemaitre RN, Wagner EH, Furberg CD. Health outcomes associated with antihypertensive therapies used as first-line agents. A systematic review and meta-analysis. *JAMA* 1997;277:739–745
207. HOPE: Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. *Lancet* 355:253–259, 2000
208. McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, Olofsson B, Yusuf S, Pfeffer MA, CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet* 2003;362:767–771
209. Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J, Yusuf S, Pocock S, CHARM Investigators and Committees. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet* 2003;362:759–766
210. Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, Ostergren J, Pfeffer MA, Swedberg K, CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet* 2003;362:772–776
211. Lindholm LH, Ibsen H, Dahlöf B, Devereux RB, Beevers G, de Faire U, Fyhrquist F, Julius S, Kjeldsen SE, Kristiansson K, Lederballe-Pedersen O, Nieminen MS, Omvik P, Oparil S, Wedel H, Aurup P, Edelman J, Snapinn S, LIFE Study Group. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002;359:1004–1010
212. Berl T, Hunsicker LG, Lewis JB, Pfeffer MA, Porush JG, Rouleau JL, Drury PL, Esmatjes E, Hricik D, Parikh CR, Raz I, Vanhille P, Wiegmann TB, Wolfe BM, Locatelli F, Goldhaber SZ, Lewis EJ, Irbesartan Diabetic Nephropathy Trial. Collaborative Study Group. Collaborative Study Group. Cardiovascular outcomes in the Irbesartan Diabetic Nephropathy Trial of patients with type 2 diabetes and overt nephropathy. *Ann Intern Med* 2003;138:542–549
213. Sibai BM. Treatment of hypertension in pregnant women. *N Engl J Med* 1996;335:257–265
214. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R, Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005;366:1267–1278
215. Pyörälä K, Pedersen TR, Kjekshus J, Faergeman O, Olsson AG, Thorgeirsson G. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease: a subgroup analysis of the Scandinavian Simvastatin Survival Study (4S). *Diabetes Care* 1997;20:614–620
216. Collins R, Armitage J, Parish S, Sleight P, Peto R, Heart Protection Study Collaborative Group: MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 361:2005–2016, 2003
217. Goldberg RB, Mellies MJ, Sacks FM, Moyé LA, Howard BV, Howard WJ, Davis BR, Cole TG, Pfeffer MA, Braunwald E. Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: subgroup analyses in the cholesterol and recurrent events (CARE) trial. The Care Investigators. *Circulation* 1998;98:2513–2519
218. Shepherd J, Barter P, Carmena R, Deedwania P, Fruchart JC, Haffner S, Hsia J, Breazna A, LaRosa J, Grundy S, Waters D. Effect of lowering LDL cholesterol substantially below currently recommended levels in patients with coronary heart disease and diabetes: the Treating to New Targets (TNT) study. *Diabetes Care* 2006;29:1220–1226
219. Sever PS, Poulter NR, Dahlöf B, Wedel H, Collins R, Beevers G, Caulfield M, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J. Reduction in cardiovascular events with atorvastatin in 2,532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial–lipid-lowering arm (ASCOT-LLA). *Diabetes Care* 2005;28:1151–1157
220. Knopp RH, d'Emden M, Smilde JG, Pocock SJ. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN). *Diabetes Care* 2006;29:1478–1485
221. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, Thomason MJ, Mackness MI, Charlton-Menys V, Fuller JH, CARDS investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004;364:685–696
222. Singh IM, Shishehbor MH, Ansell BJ. High-density lipoprotein as a therapeutic target: a systematic review. *JAMA* 2007;298:786–798
223. Canner PL, Berge KG, Wenger NK, Stamler J, Friedman L, Prineas RJ, Friedewald W. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. *J Am Coll Cardiol* 1986;8:1245–1255
224. Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, Faas FH, Linares E, Schaefer EJ, Schectman G, Wilt TJ, Wittes J. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med* 1999;341:410–418
225. Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P, Manninen V.

- Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* 1987;317:1237–1245
226. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, Forder P, Pillai A, Davis T, Glasziou P, Drury P, Kesäniemi YA, Sullivan D, Hunt D, Colman P, d'Emden M, Whiting M, Ehnholm C, Laakso M, FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 2005;366:1849–1861
227. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 2001;285:2486–2497
228. Hayward RA, Hofer TP, Vijan S. Narrative review: lack of evidence for recommended low-density lipoprotein treatment targets: a solvable problem. *Ann Intern Med* 2006; 145:520–530
229. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM, Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;350:1495–1504
230. de Lemos JA, Blazing MA, Wiviott SD, Lewis EF, Fox KA, White HD, Rouleau JL, Pedersen TR, Gardner LH, Mukherjee R, Ramsey KE, Palmisano J, Bilheimer DW, Pfeffer MA, Califf RM, Braunwald E, A to Z Investigators. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. *JAMA* 2004;292:1307–1316
231. Nissen SE, Tuzcu EM, Schoenhagen P, Brown BG, Ganz P, Vogel RA, Crowe T, Howard G, Cooper CJ, Brodie B, Grines CL, DeMaria AN, REVERSAL Investigators. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. *JAMA* 2004;291:1071–1080
232. Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, Pasternak RC, Smith SC Jr, Stone NJ, National Heart, Lung, and Blood Institute, American College of Cardiology Foundation, American Heart Association. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004;110:227–239
233. Chasman DI, Posada D, Subrahmanyam L, Cook NR, Stanton VP, Jr, Ridker PM. Pharmacogenetic study of statin therapy and cholesterol reduction. *JAMA* 2004; 291:2821–2827
234. Brunzell JD, Davidson M, Furberg CD, Goldberg RB, Howard BV, Stein JH, Witztum JL, American Diabetes Association, American College of Cardiology Foundation. Lipoprotein management in patients with cardiometabolic risk: consensus statement from the American Diabetes Association and the American College of Cardiology Foundation. *Diabetes Care* 2008;31:811–822
235. Elam MB, Hunninghake DB, Davis KB, Garg R, Johnson C, Egan D, Kostis JB, Sheps DS, Brinton EA. Effect of niacin on lipid and lipoprotein levels and glycemic control in patients with diabetes and peripheral arterial disease: the ADMIT study: A randomized trial. *Arterial Disease Multiple Intervention Trial*. *JAMA* 2000;284:1263–1270
236. Grundy SM, Vega GL, McGovern ME, Tulloch BR, Kendall DM, Fitz-Patrick D, Ganda OP, Rosenson RS, Buse JB, Robertson DD, Sheehan JP, Diabetes Multi-center Research Group. Efficacy, safety, and tolerability of once-daily niacin for the treatment of dyslipidemia associated with type 2 diabetes: results of the assessment of diabetes control and evaluation of the efficacy of niaspan trial. *Arch Intern Med* 2002;162:1568–1576
237. Jones PH, Davidson MH. Reporting rate of rhabdomyolysis with fenofibrate + statin versus gemfibrozil + any statin. *Am J Cardiol* 2005;95:120–122
238. ACCORD Study Group, Ginsberg HN, Elam MB, Lovato LC, Crouse JR 3rd, Leiter LA, Linz P, Friedewald WT, Buse JB, Gerstein HC, Probstfield J, Grimm RH, Ismail-Beigi F, Bigger JT, Goff DC Jr, Cushman WC, Simons-Morton DG, Byington RP. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med* 2010;362:1563–1574
239. Antithrombotic Trialists' (ATT) Collaboration, Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, Buring J, Hennekens C, Kearney P, Meade T, Patrono C, Roncaglioni MC, Zanchetti A. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009;373:1849–1860
240. Ogawa H, Nakayama M, Morimoto T, Uemura S, Kanauchi M, Doi N, Jinnouchi H, Sugiyama S, Saito Y, Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) Trial Investigators. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. *JAMA* 2008;300: 2134–2141
241. Belch J, MacCuish A, Campbell I, Cobbe S, Taylor R, Prescott R, Lee R, Bancroft J, MacEwan S, Shepherd J, Macfarlane P, Morris A, Jung R, Kelly C, Connacher A, Peden N, Jamieson A, Matthews D, Leese G, McKnight J, O'Brien I, Semple C, Petrie J, Gordon D, Pringle S, MacWalter R. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. *BMJ* 2008; 337:a1840
242. Pignone M, Earnshaw S, Tice JA, Pletcher MJ. Aspirin, statins, or both drugs for the primary prevention of coronary heart disease events in men: a cost-utility analysis. *Ann Intern Med* 2006;144:326–336
243. Pignone M, Alberts MJ, Colwell JA, Cushman M, Inzucchi SE, Mukherjee D, Rosenson RS, Williams CD, Wilson PW, Kirkman MS, American Diabetes Association, American Heart Association, American College of Cardiology Foundation. Aspirin for primary prevention of cardiovascular events in people with diabetes: a position statement of the American Diabetes Association, a scientific statement of the American Heart Association, and an expert consensus document of the American College of Cardiology Foundation. *Diabetes Care* 2010;33:1395–1402
244. Campbell CL, Smyth S, Montalescot G, Steinhubl SR. Aspirin dose for the prevention of cardiovascular disease: a systematic review. *JAMA* 2007;297:2018–2024
245. Davì G, Patrono C. Platelet activation and atherothrombosis. *N Engl J Med* 2007;357:2482–2494
246. Bhatt DL, Marso SP, Hirsch AT, Ringleb PA, Hacke W, Topol EJ. Amplified benefit of clopidogrel versus aspirin in patients with diabetes mellitus. *Am J Cardiol* 2002;90:625–628
247. Ranney L, Melvin C, Lux L, McClain E, Lohr KN. Systematic review: smoking cessation intervention strategies for adults and adults in special populations. *Ann Intern Med* 2006;145:845–856
248. Scognamiglio R, Negut C, Ramondo A, Tiengo A, Avogaro A. Detection of coronary artery disease in asymptomatic patients with type 2 diabetes mellitus. *J Am Coll Cardiol* 2006;47:65–71
249. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, Knudtson M, Dada M, Casperson P, Harris CL, Chaitman BR, Shaw L, Gosselin G, Nawaz S, Title LM, Gau G, Blaustein AS, Booth DC, Bates ER, Spertus JA, Berman DS, Mancini GB, Weintraub WS,

- COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007;356:1503–1516
250. BARI 2D Study Group, Frye RL, August P, Brooks MM, Hardison RM, Kelsey SF, MacGregor JM, Orchard TJ, Chaitman BR, Genuth SM, Goldberg SH, Hlatky MA, Jones TL, Molitch ME, Nesto RW, Sako EY, Sobel BE. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med* 2009;360:2503–2515
 251. Wackers FJ, Chyun DA, Young LH, Heller GV, Iskandrian AE, Davey JA, Barrett EJ, Taillefer R, Wittlin SD, Filipchuk N, Ratner RE, Inzucchi SE, Detection of Ischemia in Asymptomatic Diabetics (DIAD) Investigators. Resolution of asymptomatic myocardial ischemia in patients with type 2 diabetes in the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study. *Diabetes Care* 2007;30:2892–2898
 252. Young LH, Wackers FJ, Chyun DA, Davey JA, Barrett EJ, Taillefer R, Heller GV, Iskandrian AE, Wittlin SD, Filipchuk N, Ratner RE, Inzucchi SE, DIAD Investigators. Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with type 2 diabetes: the DIAD study: a randomized controlled trial. *JAMA* 2009;301:1547–1555
 253. Hadamitzky M, Hein F, Meyer T, Bischoff B, Martinoff S, Schömig A, Hausleiter J. Prognostic value of coronary computed tomographic angiography in diabetic patients without known coronary artery disease. *Diabetes Care* 2010;33:1358–1363
 254. Elkeles RS, Godsland IF, Feher MD, Rubens MB, Roughton M, Nugara F, Humphries SE, Richmond W, Flather MD, PREDICT Study Group. Coronary calcium measurement improves prediction of cardiovascular events in asymptomatic patients with type 2 diabetes: the PREDICT study. *Eur Heart J* 2008;29:2244–2251
 255. Choi EK, Chun EJ, Choi SI, Chang SA, Choi SH, Lim S, Rivera JJ, Nasir K, Blumenthal RS, Jang HC, Chang HJ. Assessment of subclinical coronary atherosclerosis in asymptomatic patients with type 2 diabetes mellitus with single photon emission computed tomography and coronary computed tomography angiography. *Am J Cardiol* 2009;104:890–896
 256. Braunwald E, Domanski MJ, Fowler SE, Geller NL, Gersh BJ, Hsia J, Pfeffer MA, Rice MM, Rosenberg YD, Rouleau JL, PEACE Trial Investigators. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *N Engl J Med* 2004;351:2058–2068
 257. Telmisartan Randomised Assessment Study in ACE Intolerant subjects with cardiovascular Disease (TRANSCEND) Investigators, Yusuf S, Teo K, Anderson C, Pogue J, Dyal L, Copland I, Schumacher H, Dagenais G, Sleight P. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. *Lancet* 2008;372:1174–1183
 258. Garg JP, Bakris GL. Microalbuminuria: marker of vascular dysfunction, risk factor for cardiovascular disease. *Vasc Med* 2002;7:35–43
 259. Klausen K, Borch-Johnsen K, Feldt-Rasmussen B, Jensen G, Clausen P, Scharling H, Appleyard M, Jensen JS. Very low levels of microalbuminuria are associated with increased risk of coronary heart disease and death independently of renal function, hypertension, and diabetes. *Circulation* 2004;110:32–35
 260. Gall MA, Hougaard P, Borch-Johnsen K, Parving HH. Risk factors for development of incipient and overt diabetic nephropathy in patients with non-insulin dependent diabetes mellitus: prospective, observational study. *BMJ* 1997;314:783–788
 261. Ravid M, Lang R, Rachmani R, Lishner M. Long-term renoprotective effect of angiotensin-converting enzyme inhibition in non-insulin-dependent diabetes mellitus. A 7-year follow-up study. *Arch Intern Med* 1996;156:286–289
 262. Reichard P, Nilsson BY, Rosenqvist U. The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. *N Engl J Med* 1993;329:304–309
 263. DCCT: Effect of intensive therapy on the development and progression of diabetic nephropathy in the Diabetes Control and Complications Trial. The Diabetes Control and Complications (DCCT) Research Group. *Kidney Int* 47:1703–1720, 1995
 264. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med* 1993;329:1456–1462
 265. Laffel LM, McGill JB, Gans DJ. The beneficial effect of angiotensin-converting enzyme inhibition with captopril on diabetic nephropathy in normotensive IDDM patients with microalbuminuria. North American Microalbuminuria Study Group. *Am J Med* 1995;99:497–504
 266. Bakris GL, Williams M, Dworkin L, Elliott WJ, Epstein M, Toto R, Tuttle K, Douglas J, Hsueh W, Sowers J. Preserving renal function in adults with hypertension and diabetes: a consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. *Am J Kidney Dis* 2000;36:646–661
 267. Remuzzi G, Macia M, Ruggenenti P. Prevention and treatment of diabetic renal disease in type 2 diabetes: the BENE-DICT study. *J Am Soc Nephrol* 2006;17: S90–S97
 268. Bilous R, Chaturvedi N, Sjølie AK, Fuller J, Klein R, Orchard T, Porta M, Parving HH. Effect of candesartan on microalbuminuria and albumin excretion rate in diabetes: three randomized trials. *Ann Intern Med* 2009;151:11–14
 269. Mauer M, Zinman B, Gardiner R, Suissa S, Sinaiko A, Strand T, Drummond K, Donnelly S, Goodyer P, Gubler MC, Klein R. Renal and retinal effects of enalapril and losartan in type 1 diabetes. *N Engl J Med* 2009;361:40–51
 270. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I, Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;345:851–860
 271. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S, RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;345:861–869
 272. Parving HH, Lehnert H, Bröchner-Mortensen J, Gomis R, Andersen S, Arner P, Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 2001;345:870–878
 273. Pepine CJ, Handberg EM, Cooper-DeHoff RM, Marks RG, Kowey P, Messerli FH, Mancía G, Cangiano JL, Garcia-Barreto D, Keltai M, Erdine S, Bristol HA, Kolb HR, Bakris GL, Cohen JD, Parmley WW, INVEST Investigators. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease: the International Verapamil-Trandolapril study (INVEST): a randomized controlled trial. *JAMA* 2003;290:2805–2816
 274. Bakris GL, Siomos M, Richardson D, Janssen I, Bolton WK, Hebert L, Agarwal R, Catanzaro D. ACE inhibition or angiotensin receptor blockade: impact on potassium in renal failure. VAL-K Study Group. *Kidney Int* 2000;58:2084–2092
 275. Mogensen CE, Neldam S, Tikkanen I, Oren S, Viskoper R, Watts RW, Cooper ME. Randomised controlled trial of dual blockade of renin-angiotensin system in

- patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the candesartan and lisinopril microalbuminuria (CALM) study. *BMJ* 2000;321:1440–1444
276. Schjoedt KJ, Jacobsen P, Rossing K, Boomsma F, Parving HH. Dual blockade of the renin-angiotensin-aldosterone system in diabetic nephropathy: the role of aldosterone. *Horm Metab Res* 2005; 37(Suppl. 1):4–8
277. Schjoedt KJ, Rossing K, Juhl TR, Boomsma F, Rossing P, Tarnow L, Parving HH. Beneficial impact of spironolactone in diabetic nephropathy. *Kidney Int* 2005;68:2829–2836
278. Parving HH, Persson F, Lewis JB, Lewis EJ, Hollenberg NK, AVOID Study Investigators. Aliskiren combined with losartan in type 2 diabetes and nephropathy. *N Engl J Med* 2008;358:2433–2446
279. Pijls LT, de Vries H, Donker AJ, van Eijk JT. The effect of protein restriction on albuminuria in patients with type 2 diabetes mellitus: a randomized trial. *Nephrol Dial Transplant* 1999;14: 1445–1453
280. Pedrini MT, Levey AS, Lau J, Chalmers TC, Wang PH. The effect of dietary protein restriction on the progression of diabetic and nondiabetic renal diseases: a meta-analysis. *Ann Intern Med* 1996; 124:627–632
281. Hansen HP, Tauber-Lassen E, Jensen BR, Parving HH. Effect of dietary protein restriction on prognosis in patients with diabetic nephropathy. *Kidney Int* 2002; 62:220–228
282. Kasiske BL, Lakatua JD, Ma JZ, Louis TA. A meta-analysis of the effects of dietary protein restriction on the rate of decline in renal function. *Am J Kidney Dis* 1998; 31:954–961
283. Eknoyan G, Hostetter T, Bakris GL, Hebert L, Levey AS, Parving HH, Steffes MW, Toto R. Proteinuria and other markers of chronic kidney disease: a position statement of the national kidney foundation (NKF) and the national institute of diabetes and digestive and kidney diseases (NIDDK). *Am J Kidney Dis* 2003;42:617–622
284. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, Hogg RJ, Perrone RD, Lau J, Eknoyan G, National Kidney Foundation. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med* 2003; 139:137–147
285. Kramer H, Molitch ME. Screening for kidney disease in adults with diabetes. *Diabetes Care* 2005;28:1813–1816
286. Kramer HJ, Nguyen QD, Curhan G, Hsu CY. Renal insufficiency in the absence of albuminuria and retinopathy among adults with type 2 diabetes mellitus. *JAMA* 2003;289:3273–3277
287. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999;130:461–470
288. Rigalleau V, Lasseur C, Perlemoine C, Barthe N, Raffaitin C, Liu C, Chauveau P, Baillet-Blanco L, Beauvieux MC, Combe C, Gin H. Estimation of glomerular filtration rate in diabetic subjects: Cockcroft formula or modification of Diet in Renal Disease study equation? *Diabetes Care* 2005;28:838–843
289. Levinson NG. Specialist evaluation in chronic kidney disease: too little, too late. *Ann Intern Med* 2002;137:542–543
290. Klein R. Hyperglycemia and microvascular and macrovascular disease in diabetes. *Diabetes Care* 1995;18:258–268
291. Estacio RO, McFarling E, Biggerstaff S, Jeffers BW, Johnson D, Schrier RW. Overt albuminuria predicts diabetic retinopathy in Hispanics with NIDDM. *Am J Kidney Dis* 1998;31:947–953
292. Leske MC, Wu SY, Hennis A, Hyman L, Nemesure B, Yang L, Schachat AP, Barbados Eye Study Group. Hyperglycemia, blood pressure, and the 9-year incidence of diabetic retinopathy: the Barbados Eye Studies. *Ophthalmology* 2005;112: 799–805
293. Fong DS, Aiello LP, Ferris FL 3rd, Klein R. Diabetic retinopathy. *Diabetes Care* 2004;27:2540–2553
294. Diabetes Control and Complications Trial Research Group: Effect of pregnancy on microvascular complications in the diabetes control and complications trial. The Diabetes Control and Complications Trial Research Group. *Diabetes Care* 2000;23:1084–1091
295. Preliminary report on effects of photocoagulation therapy. The Diabetic Retinopathy Study Research Group. *Am J Ophthalmol* 1976;81:383–396
296. ETDRS: Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group. *Arch Ophthalmol* 1985;103:1796–1806
297. American Diabetes Association: Retinopathy in diabetes (Position Statement). *Diabetes Care* 2004;27(Suppl. 1):S84–S87
298. Ahmed J, Ward TP, Bursell SE, Aiello LM, Cavallerano JD, Vigersky RA. The sensitivity and specificity of nonmydriatic digital stereoscopic retinal imaging in detecting diabetic retinopathy. *Diabetes Care* 2006;29:2205–2209
300. Ciulla TA, Amador AG, Zinman B. Diabetic retinopathy and diabetic macular edema: pathophysiology, screening, and novel therapies. *Diabetes Care* 2003;26: 2653–2664
301. Boulton AJ, Vinik AI, Arezzo JC, Bril V, Feldman EL, Freeman R, Malik RA, Maser RE, Sosenko JM, Ziegler D, American Diabetes Association. Diabetic neuropathies: a statement by the American Diabetes Association. *Diabetes Care* 2005; 28:956–962
302. Wile DJ, Toth C. Association of metformin, elevated homocysteine, and methylmalonic acid levels and clinically worsened diabetic peripheral neuropathy. *Diabetes Care* 2010;33:156–161
303. Freeman R. Not all neuropathy in diabetes is of diabetic etiology: differential diagnosis of diabetic neuropathy. *Curr Diab Rep* 2009;9:423–431
304. Vinik AI, Maser RE, Mitchell BD, Freeman R. Diabetic autonomic neuropathy. *Diabetes Care* 2003;26:1553–1579
305. Boulton AJ, Armstrong DG, Albert SF, Frykberg RG, Hellman R, Kirkman MS, Lavery LA, Lemaster JW, Mills JL Sr, Mueller MJ, Sheehan P, Wukich DK, American Diabetes Association, American Association of Clinical Endocrinologists. Comprehensive foot examination and risk assessment: a report of the task force of the foot care interest group of the American Diabetes Association, with endorsement by the American Association of Clinical Endocrinologists. *Diabetes Care* 2008;31:1679–1685
306. American Diabetes Association: Peripheral arterial disease in people with diabetes (Consensus Statement). *Diabetes Care* 2003;26:3333–3341
307. Silverstein J, Klingensmith G, Copeland KC, Plotnick L, Kaufman F, Laffel L, Deeb LC, Grey M, Anderson BJ, Holzman LA, Clark NG. Care of children and adolescents with type 1 diabetes mellitus: a statement of the American Diabetes Association. *Diabetes Care* 2005; 28:186–212
308. Northam EA, Anderson PJ, Werther GA, Warne GL, Adler RG, Andrewes D. Neuropsychological complications of IDDM in children 2 years after disease onset. *Diabetes Care* 1998;21:379–384
309. Rovet J, Alvarez M. Attentional functioning in children and adolescents with IDDM. *Diabetes Care* 1997;20:803–810
310. Bjørgaas M, Gimse R, Vik T, Sand T. Cognitive function in type 1 diabetic children with and without episodes of severe hypoglycaemia. *Acta Paediatr* 1997;86:148–153
311. Nimri R, Weintrob N, Benzaquen H, Ofan R, Fayman G, Phillip M. Insulin pump therapy in youth with type 1 diabetes: a retrospective paired study. *Pediatrics* 2006;117:2126–2131
312. Doyle EA, Weinzimer SA, Steffen AT, Ahern JA, Vincent M, Tamborlane WV. A randomized, prospective trial comparing the efficacy of continuous subcutaneous insulin infusion with multiple

- daily injections using insulin glargine. *Diabetes Care* 2004;27:1554–1558
313. Perantie DC, Wu J, Koller JM, Lim A, Warren SL, Black KJ, Sadler M, White NH, Hershey T. Regional brain volume differences associated with hyperglycemia and severe hypoglycemia in youth with type 1 diabetes. *Diabetes Care* 2007;30:2331–2337
 314. Mäkimattila S, Malmberg-Cèder K, Häkkinen AM, Vuori K, Salonen O, Summanen P, Yki-Järvinen H, Kaste M, Heikkinen S, Lundbom N, Roine RO. Brain metabolic alterations in patients with type 1 diabetes-hyperglycemia-induced injury. *J Cereb Blood Flow Metab* 2004;24:1393–1399
 315. Krantz JS, Mack WJ, Hodis HN, Liu CR, Liu CH, Kaufman FR. Early onset of subclinical atherosclerosis in young persons with type 1 diabetes. *J Pediatr* 2004;145:452–457
 316. Järvisalo MJ, Putto-Laurila A, Jartti L, Lehtimäki T, Solakivi T, Rönnemaa T, Raitakari OT. Carotid artery intima-media thickness in children with type 1 diabetes. *Diabetes* 2002;51:493–498
 317. Haller MJ, Samyn M, Nichols WW, Brusko T, Wasserfall C, Schwartz RF, Atkinson M, Shuster JJ, Pierce GL, Silverstein JH. Radial artery tonometry demonstrates arterial stiffness in children with type 1 diabetes. *Diabetes Care* 2004;27:2911–2917
 318. Orchard TJ, Forrest KY, Kuller LH, Becker DJ, Pittsburgh Epidemiology of Diabetes Complications Study. Lipid and blood pressure treatment goals for type 1 diabetes: 10-year incidence data from the Pittsburgh Epidemiology of Diabetes Complications Study. *Diabetes Care* 2001;24:1053–1059
 319. Kavey RE, Allada V, Daniels SR, Hayman LL, McCrindle BW, Newburger JW, Parekh RS, Steinberger J, American Heart Association Expert Panel on Population and Prevention Science, American Heart Association Council on Cardiovascular Disease in the Young, American Heart Association Council on Epidemiology and Prevention, American Heart Association Council on Nutrition, Physical Activity and Metabolism, American Heart Association Council on High Blood Pressure Research, American Heart Association Council on Cardiovascular Nursing, American Heart Association Council on the Kidney in Heart Disease, Interdisciplinary Working Group on Quality of Care and Outcomes Research. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. *Circulation* 2006;114:2710–2738
 320. McCrindle BW, Urbina EM, Dennison BA, Jacobson MS, Steinberger J, Rocchini AP, Hayman LL, Daniels SR, American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee, American Heart Association Council of Cardiovascular Disease in the Young, American Heart Association Council on Cardiovascular Nursing. Drug therapy of high-risk lipid abnormalities in children and adolescents: a scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee, Council of Cardiovascular Disease in the Young, with the Council on Cardiovascular Nursing. *Circulation* 2007;115:1948–1967
 321. Salo P, Viikari J, Hämäläinen M, Lapinleimu H, Routi T, Rönnemaa T, Seppänen R, Jokinen E, Välimäki I, Simell O. Serum cholesterol ester fatty acids in 7- and 13-month-old children in a prospective randomized trial of a low-saturated fat, low-cholesterol diet: the STRIP baby project. *Special Turku coronary Risk factor Intervention Project for children. Acta Paediatr* 1999;88:505–512
 322. Efficacy and safety of lowering dietary intake of fat and cholesterol in children with elevated low-density lipoprotein cholesterol. The Dietary Intervention Study in Children (DISC). The Writing Group for the DISC Collaborative Research Group. *JAMA* 1995;273:1429–1435
 323. McCrindle BW, Ose L, Marais AD. Efficacy and safety of atorvastatin in children and adolescents with familial hypercholesterolemia or severe hyperlipidemia: a multicenter, randomized, placebo-controlled trial. *J Pediatr* 2003;143:74–80
 324. de Jongh S, Lilien MR, op't Roodt J, Stroes ES, Bakker HD, Kastelein JJ. Early statin therapy restores endothelial function in children with familial hypercholesterolemia. *J Am Coll Cardiol* 2002;40:2117–2121
 325. Wiegman A, Hutten BA, de Groot E, Rodenburg J, Bakker HD, Büller HR, Sijbrands EJ, Kastelein JJ. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized controlled trial. *JAMA* 2004;292:331–337
 326. Holmes GK. Screening for coeliac disease in type 1 diabetes. *Arch Dis Child* 2002;87:495–498
 327. Rewers M, Liu E, Simmons J, Redondo MJ, Hoffenberg EJ. Celiac disease associated with type 1 diabetes mellitus. *Endocrinol Metab Clin North Am* 2004;33:197–214, xi
 328. Roldán MB, Alonso M, Barrio R. Thyroid autoimmunity in children and adolescents with Type 1 diabetes mellitus. *Diabetes Nutr Metab* 1999;12:27–31
 329. Kordonouri O, Deiss D, Danne T, Dorow A, Bassir C, Grüters-Kieslich A. Predictivity of thyroid autoantibodies for the development of thyroid disorders in children and adolescents with Type 1 diabetes. *Diabet Med* 2002;19:518–521
 330. Mohn A, Di Michele S, Di Luzio R, Tumini S, Chiarelli F. The effect of subclinical hypothyroidism on metabolic control in children and adolescents with Type 1 diabetes mellitus. *Diabet Med* 2002;19:70–73
 331. Chase HP, Garg SK, Cockerham RS, Wilcox WD, Walravens PA. Thyroid hormone replacement and growth of children with subclinical hypothyroidism and diabetes. *Diabet Med* 1990;7:299–303
 332. American Diabetes Association: Diabetes care in the school and day care setting (Position statement). *Diabetes Care* 2010;33(Suppl. 1):S70–S74
 333. Bryden KS, Peveler RC, Stein A, Neil A, Mayou RA, Dunger DB. Clinical and psychological course of diabetes from adolescence to young adulthood: a longitudinal cohort study. *Diabetes Care* 2001;24:1536–1540
 334. Laing SP, Jones ME, Swerdlow AJ, Burden AC, Gatling W. Psychosocial and socioeconomic risk factors for premature death in young people with type 1 diabetes. *Diabetes Care* 2005;28:1618–1623
 335. Pacaud d, Yale Jf, Stephure D, Trussell R, Davies HD. Problems in transition from pediatric care to adult care for individuals with diabetes. *Can J Diabetes* 2005;29:13–18
 336. American Academy of Pediatrics, American Academy of Family Physicians, American College of Physicians-American Society of Internal Medicine. A consensus statement on health care transitions for young adults with special health care needs. *Pediatrics* 2002;110:1304–1306
 337. Wolpert HA, Anderson BJ, Weissberg-Benchell J: *Transitions in care: Meeting the challenges of type 1 diabetes in young adults*. Alexandria VA, American Diabetes Association, 2009
 338. Eppens MC, Craig ME, Cusumano J, Hing S, Chan AK, Howard NJ, Silink M, Donaghue KC. Prevalence of diabetes complications in adolescents with type 2 compared with type 1 diabetes. *Diabetes Care* 2006;29:1300–1306
 339. Hattersley A, Bruining J, Shield J, Njolstad P, Donaghue KC. The diagnosis and

- management of monogenic diabetes in children and adolescents. *Pediatr Diabetes* 2009;12(Suppl.):33–42
340. Cooper WO, Hernandez-Diaz S, Arbogast PG, Dudley JA, Dyer S, Gideon PS, Hall K, Ray WA. Major congenital malformations after first-trimester exposure to ACE inhibitors. *N Engl J Med* 2006;354:2443–2451
341. American Diabetes Association: Preconception care of women with diabetes (Position Statement). *Diabetes Care* 2004;27(Suppl. 1):S76–S78
342. Brown AF, Mangione CM, Saliba D, Sarkisian CA, California Healthcare Foundation/American Geriatrics Society Panel on Improving Care for Elders with Diabetes. Guidelines for improving the care of the older person with diabetes mellitus. *J Am Geriatr Soc* 2003;51:S265–S280
343. Curb JD, Pressel SL, Cutler JA, Savage PJ, Applegate WB, Black H, Camel G, Davis BR, Frost PH, Gonzalez N, Guthrie G, Oberman A, Rutan GH, Stamler J. Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. Systolic Hypertension in the Elderly Program Cooperative Research Group. *JAMA* 1996;276:1886–1892
344. Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, Stoyanovsky V, Antikainen RL, Nikitin Y, Anderson C, Belhani A, Forette F, Rajkumar C, Thijs L, Banya W, Bulpitt CJ, HYVET Study Group. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med* 2008;358:1887–1898
- 344a. Moran A, Brunzell C, Cohen RC, Katz M, Marshall BC, Onady G, Robinson KA, Sabadosa KA, Stecenko A, Slovis B; the CFRD Guidelines Committee. Clinical care guidelines for cystic fibrosis–related diabetes: a position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society. *Diabetes Care* 2010;33:2697–2708
345. Clement S, Braithwaite SS, Magee MF, Ahmann A, Smith EP, Schafer RG, Hirsch IB, Hirsh IB, American Diabetes Association Diabetes in Hospitals Writing Committee. Management of diabetes and hyperglycemia in hospitals. *Diabetes Care* 2004;27:553–591
346. Moghissi ES, Korytkowski MT, DiNardo M, Einhorn D, Hellman R, Hirsch IB, Inzucchi SE, Ismail-Beigi F, Kirkman MS, Umpierrez GE, American Association of Clinical Endocrinologists, American Diabetes Association. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. *Diabetes Care* 2009;32:1119–1131
347. American Diabetes Association: Economic costs of diabetes in the U.S. in 2007. *Diabetes Care* 2008;31:596–615
348. Levetan CS, Passaro M, Jablonski K, Kass M, Ratner RE. Unrecognized diabetes among hospitalized patients. *Diabetes Care* 1998;21:246–249
349. Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrinol Metab* 2002;87:978–982
350. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in the critically ill patients. *N Engl J Med* 2001;345:1359–1367
351. Malmberg K, Norhammar A, Wedel H, Rydén L. Glycometabolic state at admission: important risk marker of mortality in conventionally treated patients with diabetes mellitus and acute myocardial infarction: long-term results from the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study. *Circulation* 1999;99:2626–2632
352. Wiener RS, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. *JAMA* 2008;300:933–944
353. Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, Moller O, Gruendling M, Oppert M, Grond S, Olthoff D, Jaschinski U, John S, Rossaint R, Welte T, Schaefer M, Kern P, Kuhnt E, Kiehntopf M, Hartog C, Natanson C, Loeffler M, Reinhart K, German Competence Network Sepsis (SepNet). Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med* 2008;358:125–139
354. NICE-SUGAR Study Investigators, Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, Bellomo R, Cook D, Dodek P, Henderson WR, Hébert PC, Heritier S, Heyland DK, McArthur C, McDonald E, Mitchell I, Myburgh JA, Norton R, Potter J, Robinson BG, Ronco JJ. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009;360:1283–1297
355. Krinsley JS, Grover A. Severe hypoglycemia in critically ill patients: risk factors and outcomes. *Crit Care Med* 2007;35:2262–2267
356. Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, Van Wijngaerden E, Bobbaers H, Bouillon R. Intensive insulin therapy in the medical ICU. *N Engl J Med* 2006;354:449–461
357. Griesdale DE, de Souza RJ, van Dam RM, Heyland DK, Cook DJ, Malhotra A, Dhaliwal R, Henderson WR, Chittock DR, Finfer S, Talmor D. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. *CMAJ* 2009;180:821–827
358. Saudek CD, Herman WH, Sacks DB, Bergenstal RM, Edelman D, Davidson MB. A new look at screening and diagnosing diabetes mellitus. *J Clin Endocrinol Metab* 2008;93:2447–2453
359. Cryer PE, Davis SN, Shamoon H. Hypoglycemia in diabetes. *Diabetes Care* 2003;26:1902–1912
360. Czosnowski QA, Swanson JM, Lobo BL, Broyles JE, Deaton PR, Finch CK. Evaluation of glycemic control following discontinuation of an intensive insulin protocol. *J Hosp Med* 2009;4:28–34
361. Shomali MI, Herr DL, Hill PC, Pehlivanova M, Sharretts JM, and Magee MF Transition to Target: A prospective randomized trial comparing three formulae for determination of subcutaneous basal insulin dosing at the time of transition from intravenous insulin therapy following cardiac surgery. *Diabetes Science and Technology* 2010. In press
362. Umpierrez GE, Smiley D, Jacobs S, Peng L, Temponi A, Newton C, Umpierrez D, Mulligan P, Olson D, McLeod J, Rizzo M. Randomized study of basal bolus insulin therapy in the inpatient management of patients with type 2 diabetes undergoing general surgery (RABBIT 2 Surgery) (Abstract). *Diabetes* 2010;59(Suppl. 1):A9
363. Pasquel FJ, Spiegelman R, McCauley M, Smiley D, Umpierrez D, Johnson R, Rhee M, Gatcliffe C, Lin E, Umpierrez E, Peng L, Umpierrez GE. Hyperglycemia during total parenteral nutrition: an important marker of poor outcome and mortality in hospitalized patients. *Diabetes Care* 2010;33:739–741
364. Schnipper JL, Liang CL, Ndumele CD, Pendergrass ML. Effects of a computerized order set on the inpatient management of hyperglycemia: a cluster-randomized controlled trial. *Endocr Pract* 2010;16:209–218
365. Wexler DJ, Shrader P, Burns SM, Cagliero E. Effectiveness of a computerized insulin order template in general medical inpatients with type 2 diabetes: a cluster randomized trial. *Diabetes Care* 2010;33:2181–2183
366. Furnary AP, Braithwaite SS. Effects of outcome on in-hospital transition from intravenous insulin infusion to subcutaneous therapy. *Am J Cardiol* 2006;98:557–564
367. Schafer RG, Bohannon B, Franz MJ, Freeman J, Holmes A, McLaughlin S, Haas LB, Kruger DF, Lorenz RA, McMahon MM. Diabetes nutrition recommendations for health care institutions. *Diabetes Care* 2004;27(Suppl. 1):S55–S57
368. Curll M, Dinardo M, Noschese M, Ko-

- rytkowski MT. Menu selection, glycaemic control and satisfaction with standard and patient-controlled consistent carbohydrate meal plans in hospitalised patients with diabetes. *Qual Saf Health Care* 2010;19:355–359
369. American Diabetes Association: Diabetes nutrition recommendations for health care institutions (Position Statement). *Diabetes Care* 2010;27(Suppl. 1):S55–S57
370. Boucher JL, Swift CS, Franz MJ, Kulkarni K, Schafer RG, Pritchett E, Clark NG. Inpatient management of diabetes and hyperglycemia: implications for nutrition practice and the food and nutrition professional. *J Am Diet Assoc* 2007;107:105–111
371. Korytkowski MT, Salata RJ, Koerbel GL, Selzer F, Karslioglu E, Idriss AM, Lee KK, Moser AJ, Toledo FG. Insulin therapy and glycemic control in hospitalized patients with diabetes during enteral nutrition therapy: a randomized controlled clinical trial. *Diabetes Care* 2009;32:594–596
372. Umpierrez GE. Basal versus sliding-scale regular insulin in hospitalized patients with hyperglycemia during enteral nutrition therapy. *Diabetes Care* 2009;32:751–753
373. Klonoff DC, Perz JF. Assisted monitoring of blood glucose: special safety needs for a new paradigm in testing glucose. *J Diabetes Sci Technol* 2010;4:1027–1031
374. D'Orazio P, Burnett RW, Fogh-Andersen N, Jacobs E, Kuwa K, Kulpmann WR, Larsson L, Lewenstam A, Maas AH, Mager G, Naskalski JW, Okorodudu AO, International Federation of Clinical Chemistry Scientific Division Working Group on Selective Electrodes and Point of Care Testing. Approved IFCC recommendation on reporting results for blood glucose (abbreviated). *Clin Chem* 2005;51:1573–1576
375. Dungan K, Chapman J, Braithwaite SS, Buse J. Glucose measurement: confounding issues in setting targets for inpatient management. *Diabetes Care* 2007;30:403–409
376. Boyd JC, Bruns DE. Quality specifications for glucose meters: assessment by simulation modeling of errors in insulin dose. *Clin Chem* 2001;47:209–214
377. Shepperd S, McClaran J, Phillips CO, Lannin NA, Clemson LM, McCluskey A, Cameron ID, Barras SL. Discharge planning from hospital to home. *Cochrane Database Syst Rev* CD000313, 2010
378. Agency for Healthcare Research and Quality [article online]. Available from <http://psnet.ahrq.gov/primer.aspx?primerID=11>. Accessed 17 August 2010
379. Hoerger TJ, Segel JE, Gregg EW, Saadine JB. Is glycemic control improving in U.S. adults? *Diabetes Care* 2008;31:81–86
380. Beaulieu N, Cutler DM, Ho K, Isham G, Lindquist T, Nelson A, O'Connor P: the business case for diabetes disease management for managed care organizations. *Forum for Health Economics and Policy* 2006;9:article 1
381. Cheung BM, Ong KL, Cherny SS, Sham PC, Tso AW, Lam KS. Diabetes prevalence and therapeutic target achievement in the United States, 1999 to 2006. *Am J Med* 2009;122:443–453
382. Coleman K, Austin BT, Brach C, Wagner EH. Evidence on the Chronic Care Model in the new millennium. *Health Aff (Millwood)* 2009;28:75–85
383. O'Connor PJ. Electronic medical records and diabetes care improvement: are we waiting for Godot? *Diabetes Care* 2003;26:942–943
384. Shojania KG, Ranji SR, McDonald KM, Grimshaw JM, Sundaram V, Rushakoff RJ, Owens DK. Effects of quality improvement strategies for type 2 diabetes on glycemic control: a meta-regression analysis. *JAMA* 2006;296:427–440
385. Davidson MB. How our current medical care system fails people with diabetes: lack of timely, appropriate clinical decisions. *Diabetes Care* 2009;32:370–372
386. McLean DL, McAlister FA, Johnson JA, King KM, Makowsky MJ, Jones CA, Tsuyuki RT, SCRIP-HTN Investigators. A randomized trial of the effect of community pharmacist and nurse care on improving blood pressure management in patients with diabetes mellitus: study of cardiovascular risk intervention by pharmacists-hypertension (SCRIP-HTN). *Arch Intern Med* 2008;168:2355–2361
387. Berikai P, Meyer PM, Kazlauskaitė R, Savoy B, Kozik K, Fogelfeld L. Gain in patients' knowledge of diabetes management targets is associated with better glycemic control. *Diabetes Care* 2007;30:1587–1589
388. Sperl-Hillen JM, O'Connor PJ. Factors driving diabetes care improvement in a large medical group: ten years of progress. *Am J Manag Care* 2005;11: S177–S185
389. Siminerio LM. Implementing diabetes self-management training programs: breaking through the barriers in primary care. *Endocr Pract* 2006;12(Suppl. 1): 124–130
390. Mahoney JJ. Reducing patient drug acquisition costs can lower diabetes health claims. *Am J Manag Care* 2005;11: S170–S176
391. Maney M, Tseng CL, Safford MM, Miller DR, Pogach LM. Impact of self-reported patient characteristics upon assessment of glycemic control in the Veterans Health Administration. *Diabetes Care* 2007;30:245–251
392. Bergenstal RM. Treatment models from the International Diabetes Center: advancing from oral agents to insulin therapy in type 2 diabetes. *Endocr Pract* 2006;12(Suppl. 1):98–104
393. Feifer C, Nemeth L, Nietert PJ, Wessell AM, Jenkins RG, Roylance L, Ornstein SM. Different paths to high-quality care: three archetypes of top-performing practice sites. *Ann Fam Med* 2007;5:233–241
394. Ornstein S, Nietert PJ, Jenkins RG, Wessell AM, Nemeth LS, Feifer C, Corley ST. Improving diabetes care through a multicomponent quality improvement model in a practice-based research network. *Am J Med Qual* 2007;22:34–41
395. Parchman ML, Zeber JE, Romero RR, Pugh JA. Risk of coronary artery disease in type 2 diabetes and the delivery of care consistent with the chronic care model in primary care settings: a STARNet study. *Med Care* 2007;45:1129–1134

Gestational Diabetes Mellitus

AMERICAN DIABETES ASSOCIATION

DEFINITION, DETECTION, AND DIAGNOSIS

Definition

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy (1). The definition applies whether insulin or only diet modification is used for treatment and whether or not the condition persists after pregnancy. It does not exclude the possibility that unrecognized glucose intolerance may have antedated or begun concomitantly with the pregnancy.

Approximately 7% of all pregnancies are complicated by GDM, resulting in more than 200,000 cases annually. The prevalence may range from 1 to 14% of all pregnancies, depending on the population studied and the diagnostic tests employed.

Detection and diagnosis

Risk assessment for GDM should be undertaken at the first prenatal visit. Women with clinical characteristics consistent with a high risk of GDM (marked obesity, personal history of GDM, glycosuria, or a strong family history of diabetes) should undergo glucose testing (see below) as soon as feasible. If they are found not to have GDM at that initial screening, they should be retested between 24 and 28 weeks of gestation. Women of average risk should have testing undertaken at 24–28 weeks of gestation. Low-risk status requires no glucose testing, but this category is limited to those women meeting all of the following characteristics:

- Age <25 years
- Weight normal before pregnancy

The recommendations in this paper are based on the evidence reviewed in the following publications: Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 21 (Suppl. 1):S5–S19, 1998; and the Proceedings of the 4th International Workshop-Conference on Gestational Diabetes Mellitus. *Diabetes Care* 21 (Suppl. 2):B1–B167, 1998.

Originally approved 1986. Most recent review/revision, 2000.

Abbreviations: GCT, glucose challenge test; GDM, gestational diabetes mellitus; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; MNT, medical nutrition therapy; OGTT, oral glucose tolerance test; SMBG, self-monitoring of blood glucose.

© 2004 by the American Diabetes Association.

- Member of an ethnic group with a low prevalence of GDM
- No known diabetes in first-degree relatives
- No history of abnormal glucose tolerance
- No history of poor obstetric outcome

A fasting plasma glucose level >126 mg/dl (7.0 mmol/l) or a casual plasma glucose >200 mg/dl (11.1 mmol/l) meets the threshold for the diagnosis of diabetes, if confirmed on a subsequent day, and precludes the need for any glucose challenge. In the absence of this degree of hyperglycemia, evaluation for GDM in women with average or high-risk characteristics should follow one of two approaches:

One-step approach: Perform a diagnostic oral glucose tolerance test (OGTT) without prior plasma or serum glucose screening. The one-step approach may be cost-effective in high-risk patients or populations (e.g., some Native-American groups).

Two-step approach: Perform an initial screening by measuring the plasma or serum glucose concentration 1 h after a 50-g oral glucose load (glucose challenge test [GCT]) and perform a diagnostic OGTT on that subset of women exceeding the glucose threshold value on the GCT. When the two-step approach is employed, a glucose threshold value >140 mg/dl (7.8 mmol/l) identifies approximately 80% of women with GDM, and the yield is further increased to 90% by using a cutoff of >130 mg/dl (7.2 mmol/l).

With either approach, the diagnosis of GDM is based on an OGTT. Diagnostic criteria for the 100-g OGTT are derived from the original work of O'Sullivan and

Mahan, modified by Carpenter and Coustan, and are shown in Table 1. Alternatively, the diagnosis can be made using a 75-g glucose load and the glucose threshold values listed for fasting, 1 h, and 2 h (Table 2); however, this test is not as well validated for detection of at-risk infants or mothers as the 100-g OGTT.

OBSTETRIC AND PERINATAL CONSIDERATIONS

The presence of fasting hyperglycemia (>105 mg/dl or >5.8 mmol/l) may be associated with an increase in the risk of intrauterine fetal death during the last 4–8 weeks of gestation. Although uncomplicated GDM with less severe fasting hyperglycemia has not been associated with increased perinatal mortality, GDM of any severity increases the risk of fetal macrosomia. Neonatal hypoglycemia, jaundice, polycythemia, and hypocalcemia may complicate GDM as well. GDM is associated with an increased frequency of maternal hypertensive disorders and the need for cesarean delivery. The latter complication may result from fetal growth disorders and/or alterations in obstetric management due to the knowledge that the mother has GDM.

Long-term considerations

Women with GDM are at increased risk for the development of diabetes, usually type 2, after pregnancy. Obesity and other factors that promote insulin resistance appear to enhance the risk of type 2 diabetes after GDM, while markers of islet cell-directed autoimmunity are associated with an increase in the risk of type 1 diabetes. Offspring of women with GDM are at increased risk of obesity, glucose intolerance, and diabetes in late adolescence and young adulthood.

THERAPEUTIC STRATEGIES DURING PREGNANCY

Monitoring

- Maternal metabolic surveillance should be directed at detecting hyperglycemia

Table 1—Diagnosis of GDM with a 100-g oral glucose load

	mg/dl	mmol/l
Fasting	95	5.3
1-h	180	10.0
2-h	155	8.6
3-h	140	7.8

Two or more of the venous plasma concentrations must be met or exceeded for a positive diagnosis. The test should be done in the morning after an overnight fast of between 8 and 14 h and after at least 3 days of unrestricted diet (≥ 150 g carbohydrate per day) and unlimited physical activity. The subject should remain seated and should not smoke throughout the test.

severe enough to increase risks to the fetus. Daily self-monitoring of blood glucose (SMBG) appears to be superior to intermittent office monitoring of plasma glucose. For women treated with insulin, limited evidence indicates that postprandial monitoring is superior to preprandial monitoring. However, the success of either approach depends on the glycemic targets that are set and achieved.

- Urine glucose monitoring is not useful in GDM. Urine ketone monitoring may be useful in detecting insufficient caloric or carbohydrate intake in women treated with calorie restriction.
- Maternal surveillance should include blood pressure and urine protein monitoring to detect hypertensive disorders.
- Increased surveillance for pregnancies at risk for fetal demise is appropriate, particularly when fasting glucose levels exceed 105 mg/dl (5.8 mmol/l) or pregnancy progresses past term. The initiation, frequency, and specific techniques used to assess fetal well-being will depend on the cumulative risk the fetus bears from GDM and any other medical/obstetric conditions present.
- Assessment for asymmetric fetal growth by ultrasonography, particularly in early third trimester, may aid in identifying fetuses that can benefit from maternal insulin therapy (see below).

Management

- All women with GDM should receive nutritional counseling, by a registered dietitian when possible, consistent with the recommendations by the American Diabetes Association. Individualization of medical nutrition therapy (MNT) de-

Table 2—Diagnosis of GDM with a 75-g oral glucose load

	mg/dl	mmol/l
Fasting	95	5.3
1-h	180	10.0
2-h	155	8.6

Two or more of the venous plasma concentrations must be met or exceeded for a positive diagnosis. The test should be done in the morning after an overnight fast of between 8 and 14 h and after at least 3 days of unrestricted diet (≥ 150 g carbohydrate per day) and unlimited physical activity. The subject should remain seated and should not smoke throughout the test.

pending on maternal weight and height is recommended. MNT should include the provision of adequate calories and nutrients to meet the needs of pregnancy and should be consistent with the maternal blood glucose goals that have been established. Noncaloric sweeteners may be used in moderation.

- For obese women (BMI > 30 kg/m²), a 30–33% calorie restriction (to ~ 25 kcal/kg actual weight per day) has been shown to reduce hyperglycemia and plasma triglycerides with no increase in ketonuria (2). Restriction of carbohydrates to 35–40% of calories has been shown to decrease maternal glucose levels and improve maternal and fetal outcomes (3).
- Insulin is the pharmacologic therapy that has most consistently been shown to reduce fetal morbidities when added to MNT. Selection of pregnancies for insulin therapy can be based on measures of maternal glycemia with or without assessment of fetal growth characteristics. When maternal glucose

levels are used, insulin therapy is recommended when MNT fails to maintain self-monitored glucose at the following levels:

Fasting plasma glucose
 ≤ 105 mg/dl (5.8 mmol/l)

or

1-h postprandial plasma glucose
 ≤ 155 mg/dl (8.6 mmol/l)

or

2-h postprandial plasma glucose
 ≤ 130 mg/dl (7.2 mmol/l)

- Measurement of the fetal abdominal circumference early in the third trimester can identify a large subset of infants with no excess risk of macrosomia in the absence of maternal insulin therapy. This approach has been tested primarily in pregnancies with maternal fasting serum glucose levels < 105 mg/dl (5.8 mmol/l).
- Human insulin should be used when insulin is prescribed, and SMBG should guide the doses and timing of the insulin regimen. The use of insulin analogs has not been adequately tested in GDM.
- Oral glucose-lowering agents have generally not been recommended during pregnancy. However, one randomized, unblinded clinical trial compared the use of insulin and glyburide in women with GDM who were not able to meet glycemic goals on MNT (4). Treatment with either agent resulted in similar perinatal outcomes. All patients were beyond the first trimester of pregnancy at the initiation of therapy. Glyburide is not FDA approved for the treatment of GDM and further studies are needed in a larger patient population to establish its safety.

Table 3—Criteria for the diagnosis of diabetes mellitus

Normoglycemia	IFG and IGT	Diabetes mellitus*
FPG < 100 mg/dl	FPG ≥ 100 mg/dl and < 126 mg/dl (IFG)	FPG ≥ 126 mg/dl
2-h PG † < 140 mg/dl	2-h PG † ≥ 140 mg/dl and < 200 mg/dl (IGT)	2-h PG † ≥ 200 mg/dl
—	—	Symptoms of DM and casual plasma glucose concentration ≥ 200 mg/dl

DM, diabetes mellitus; FPG, fasting plasma glucose; 2-h PG, 2-h postload glucose. *In the absence of unequivocal hyperglycemia, a diagnosis of diabetes must be confirmed on a subsequent day by any one of the three methods included in the chart. In clinical settings, the FPG test is greatly preferred because of ease of administration, convenience, acceptability to patients, and lower cost. Fasting is defined as no calorie intake for at least 8 h. † This test requires the use of a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

- Programs of moderate physical exercise have been shown to lower maternal glucose concentrations in women with GDM. Although the impact of exercise on neonatal complications awaits rigorous clinical trials, the beneficial glucose-lowering effects warrant a recommendation that women without medical or obstetrical contraindications be encouraged to start or continue a program of moderate exercise as a part of treatment for GDM.
- GDM is not of itself an indication for cesarean delivery or for delivery before 38 completed weeks of gestation. Prolongation of gestation past 38 weeks increases the risk of fetal macrosomia without reducing cesarean rates, so that delivery during the 38th week is recommended unless obstetric considerations dictate otherwise.
- Breast-feeding, as always, should be encouraged in women with GDM.

LONG-TERM THERAPEUTIC CONSIDERATIONS — Reclassification of maternal glycemic status should be performed at least 6 weeks after delivery and according to the guidelines of the “Report of the Expert Committee on the Diagnosis and Classification of Diabetes

Mellitus” (5). See Table 3 for diagnostic criteria. If glucose levels are normal postpartum, reassessment of glycemia should be undertaken at a minimum of 3-year intervals. Women with IFG or IGT in the postpartum period should be tested for diabetes annually; these patients should receive intensive MNT and should be placed on an individualized exercise program because of their very high risk for development of diabetes. All patients with prior GDM should be educated regarding lifestyle modifications that lessen insulin resistance, including maintenance of normal body weight through MNT and physical activity. Medications that worsen insulin resistance (e.g., glucocorticoids, nicotinic acid) should be avoided if possible. Patients should be advised to seek medical attention if they develop symptoms suggestive of hyperglycemia. Education should also include the need for family planning to ensure optimal glycemic regulation from the start of any subsequent pregnancy. Low-dose estrogen-progestogen oral contraceptives may be used in women with prior histories of GDM, as long as no medical contraindications exist.

Offspring of women with GDM should be followed closely for the devel-

opment of obesity and/or abnormalities of glucose tolerance.

References

1. Metzger BE, Coustan DR (Eds.): Proceedings of the Fourth International Workshop-Conference on Gestational Diabetes Mellitus. *Diabetes Care* 21 (Suppl. 2):B1–B167, 1998
2. Franz MJ, Bantle JP, Beebe CA, Brunzell JD, Chiasson J-L, Garg A, Holzmeister LA, Hoogwerf B, Mayer-Davis E, Mooradian AD, Purnell JQ, Wheeler M: Evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications (Technical Review). *Diabetes Care* 25:148–198, 2002
3. Major CA, Henry MJ, De Veciana M, Morgan MA: The effects of carbohydrate restriction in patients with diet-controlled gestational diabetes. *Obstet Gynecol* 91: 600–604, 1998
4. Langer L, Conway DL, Berkus MD, Xenakis EM-J, Gonzales O: A comparison of glyburide and insulin in women with gestational diabetes mellitus. *N Engl J Med* 343: 1134–1138, 2000
5. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183–1197, 1997