ICSI

INSTITUTE FOR CLINICAL SYSTEMS IMPROVEMENT

Health Care Guideline:

Diagnosis and Management of Type 2 Diabetes Mellitus in Adults

Thirteenth Edition
May 2009

The information contained in this ICSI Health Care Guideline is intended primarily for health professionals and the following expert audiences:

- physicians, nurses, and other health care professional and provider organizations;
- health plans, health systems, health care organizations, hospitals and integrated health care delivery systems;
- health care teaching institutions;
- health care information technology departments;
- medical specialty and professional societies;
- researchers;
- federal, state and local government health care policy makers and specialists; and
- employee benefit managers.

This ICSI Health Care Guideline should not be construed as medical advice or medical opinion related to any specific facts or circumstances. If you are not one of the expert audiences listed above you are urged to consult a health care professional regarding your own situation and any specific medical questions you may have. In addition, you should seek assistance from a health care professional in interpreting this ICSI Health Care Guideline and applying it in your individual case.

This ICSI Health Care Guideline is designed to assist clinicians by providing an analytical framework for the evaluation and treatment of patients, and is not intended either to replace a clinician's judgment or to establish a protocol for all patients with a particular condition. An ICSI Health Care Guideline rarely will establish the only approach to a problem.

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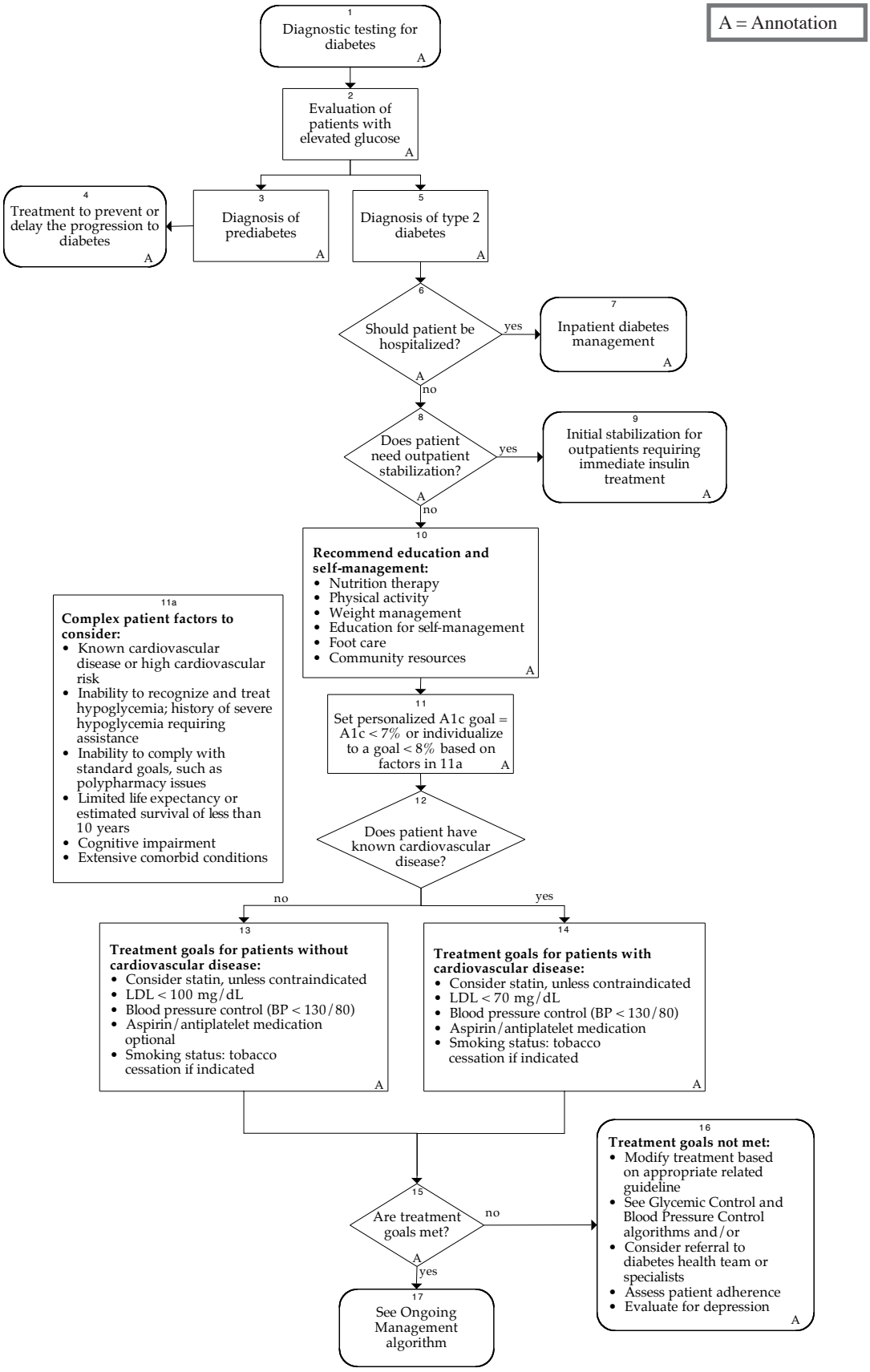

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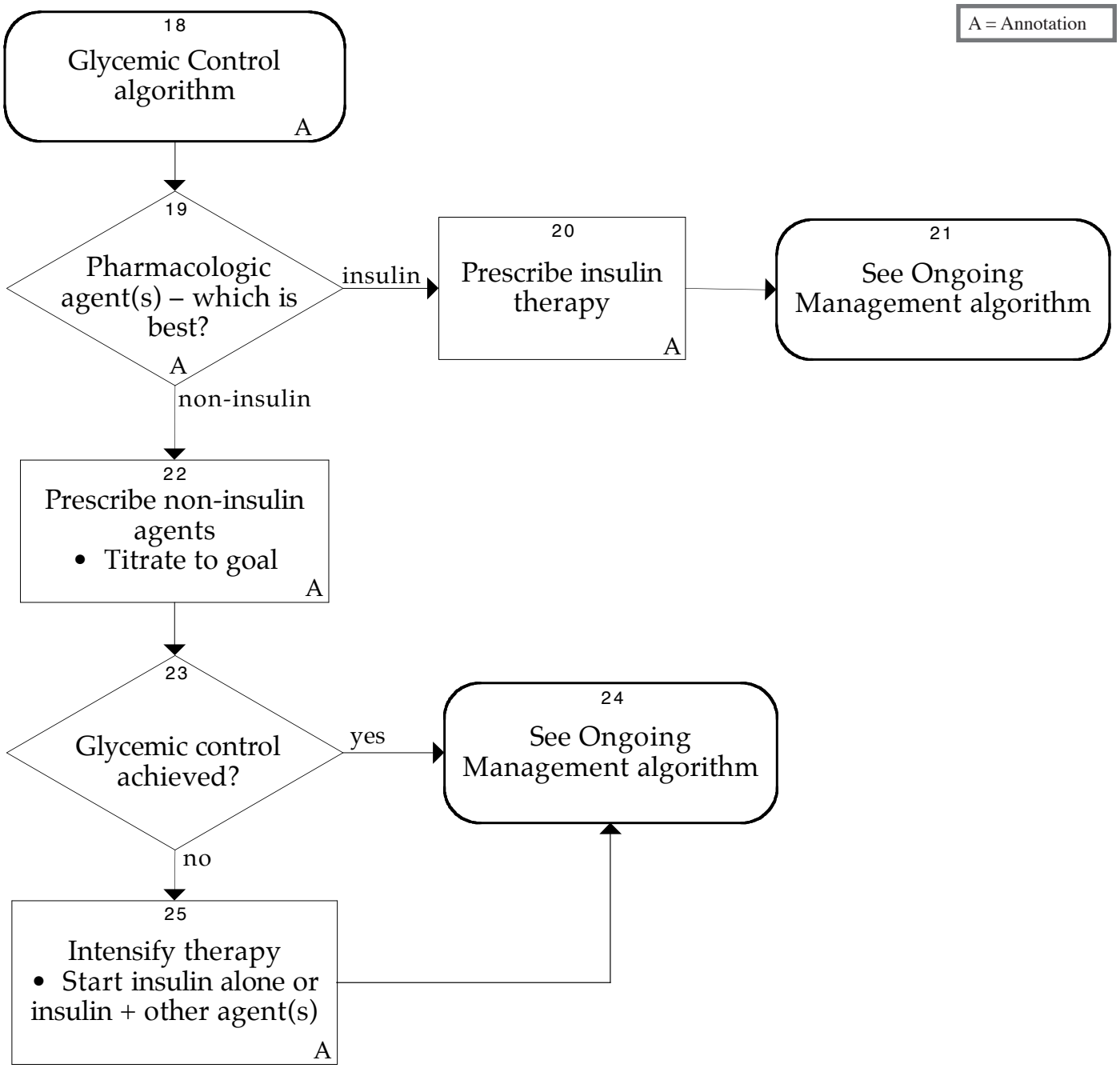

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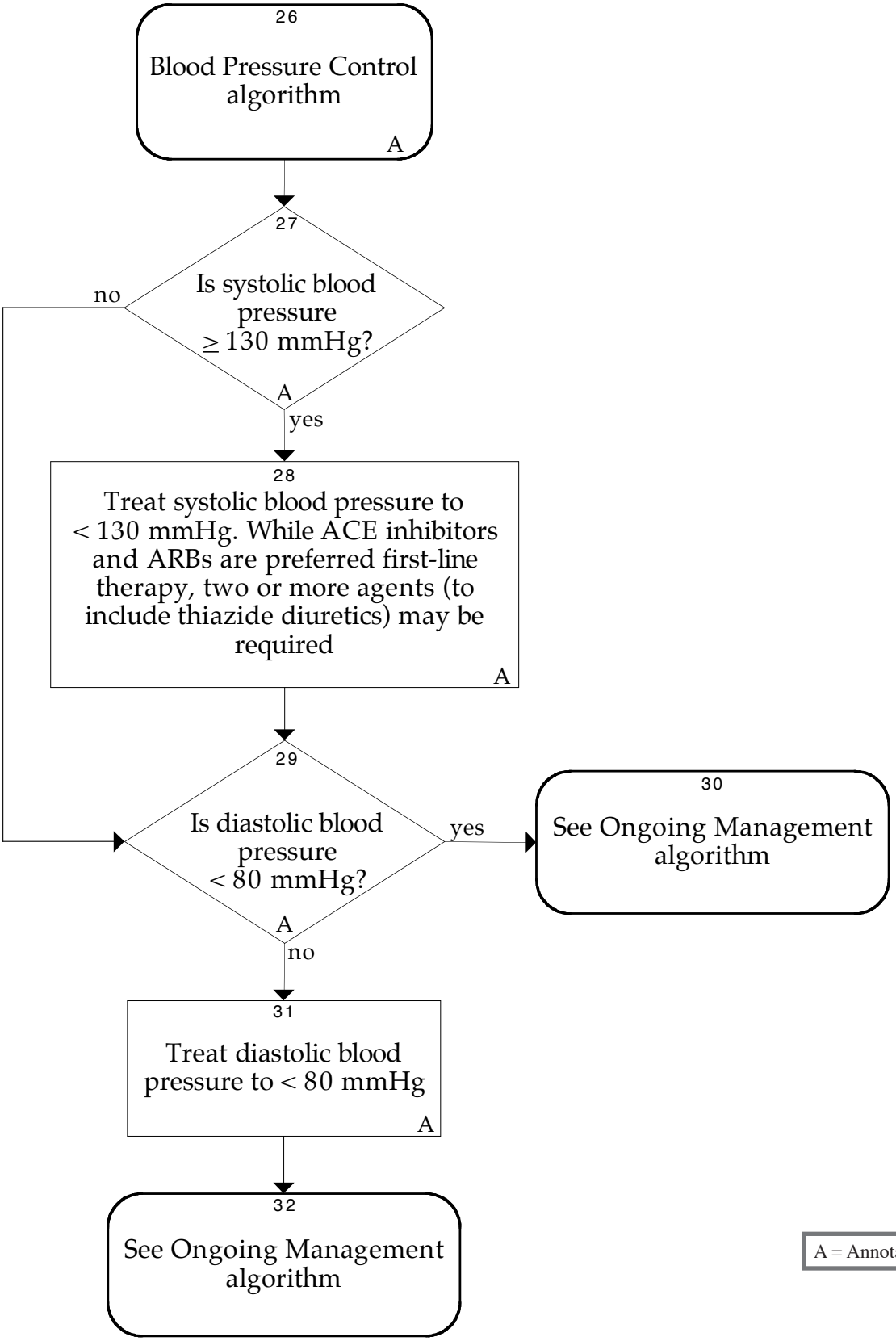
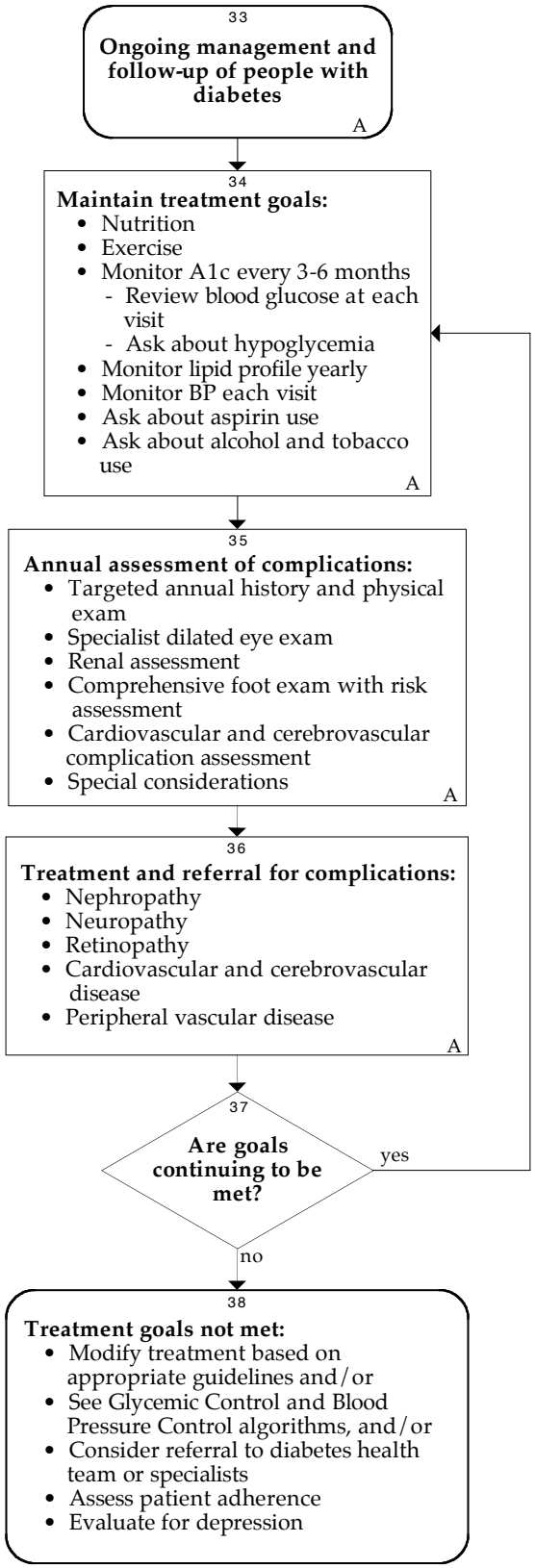


A = Annotation

Ongoing Management Algorithm



A = Annotation

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Work Group Leaders
Bruce Redmon, MD
Division of Endocrinology
University of Minnesota
JoAnn Sperl-Hillen, MD
Internal Medicine,
HealthPartners Medical Group

Work Group Members
Endocrinology
Richard Bergenstal, MD
Park Nicollet
Steve Smith, MD
Mayo Clinic

Family Medicine
Greg Frane, MD
Northwest Family Physicians
Patrick O'Connor, MD
HealthPartners Medical Group
Todd Wade, MD
Mayo Clinic

Health Education
Julie Roberts, MS, RD, CDE
HealthPartners Medical Group

Internal Medicine
Eugene Ollila, MD
Allina Medical Clinic

Nursing
Penny Louise Flavin, APRN
Olmsted Medical Center
Carol Manchester, MSN, APRN
Fairview Health Services

Pharmacy
Sarah Merbach, BS, RPh
Olmsted Medical Center
Vyvy Vo, PharmD
HealthPartners Medical Group

Facilitator
Melissa Marshall, MBA
ICSI

Foreword

Scope and Target Population

To provide a comprehensive approach to the diagnosis and management of prediabetes and type 2 diabetes mellitus in adults age 18 and older. Management will include nutrition therapy, physical activity, self-management strategies, and pharmacologic therapy recommendations, as well as the prevention and diagnosis of diabetes-associated complications and risk factors.

The diagnosis of gestational diabetes or the management of diabetes in patients who are pregnant is excluded from the scope of this guideline. Oral agents do not have Food and Drug Administration approval for use in pregnancy. The glucose goals are different in pregnancy and require more aggressive treatment.

Please refer to the ICSI Routine Prenatal guideline for information relating to gestational diabetes.

The diagnosis and management of type 1 diabetes is not included in this guideline.

Clinical Highlights and Recommendations

- Education and self-management support is necessary for people with diabetes to manage their disease. *(Annotation #10)*
- Focus on cardiovascular risk reduction (blood pressure control, low-density lipoprotein cholesterol control and statin use, aspirin use and tobacco cessation). *(Annotations #11, 13, 14)*
- A1c levels should be individualized to the patient. *(Annotation #11)*
- Aggressive blood pressure control is just as important as glycemic control. Systolic blood pressure level should be the major factor for detection, evaluation and treatment of hypertension. The use of two or more blood pressure lowering agents is often required to meet blood pressure goal. *(Annotations #13, 14)*
- Prevent microvascular complications through annual or biannual eye exams, foot risk assessments and foot care counseling, and annual screening for proteinuria. *(Annotation #35)*
- Initial therapy with lifestyle treatment and metformin is advised unless contraindicated. *(Annotations #4, 10)*

Priority Aims

A multifactorial intervention targeting hyperglycemia and cardiovascular risk factors in individuals with diabetes is most effective. Both individual measures of diabetes care as well as comprehensive measures of performance on broader sets of measures are recommended. A randomized controlled trial has shown a 50% reduction in major cardiovascular events through a multifactorial intervention targeting hyperglycemia, hypertension, dyslipidemia, microalbuminuria, aspirin and ACE inhibitor use in individuals with microalbuminuria *(Gaede, 2003 [A])*.

Goals for A1c, low-density lipoprotein, and other diabetes measures should be personalized, and lower goals for A1c and low-density lipoprotein than those included here in the priority aims and measures may be clinically justified in some adults with type 2 diabetes. However, efforts to achieve lower A1c below 7% may increase risk of mortality, weight gain, hypoglycemia and other adverse effects in many patients with type 2 diabetes. Therefore, the aims and measures listed here are selected carefully in the interests of patient safety.

1. **Diabetes Optimal Care Measures:** Maximize the percentage of adult patients, ages 18-75 with type 2 diabetes mellitus, who in a defined period of time achieve any of the possible measures of established control.
2. **Diabetes Optimal Care Comprehensive Measure Set:** Maximize the percentage of adult patients ages 18-75 with type 2 diabetes mellitus, who in a one-year period of time achieved the identified measures of care.
3. **Diabetes Process of Care Measure Set:** Maximize the percentage of adult patients ages 18-75 with type 2 diabetes mellitus for whom recommended screening procedures are done.
4. **High-Risk Population Measures:** The purpose of this aim is to identify and focus on a higher risk population by decreasing the percentage of adult patients, ages 18-75 with type 2 diabetes mellitus, with poorly controlled glucose and cardiovascular risk factors (clinical strategies that target high-risk populations may be more viable with limited resources).

Key Implementation Recommendations

The implementation of type 2 diabetes mellitus clinical guidelines at medical groups and clinics is a complex and challenging task. However, a number of key processes have been shown to accelerate effective clinical guideline implementation and care improvement *(Sperl-Hillen, 2005 [D])*. These overlapping care elements can be categorized at the medical group and provider levels:

- Essential Elements at the Medical Group Level:
  - **Leadership.** Medical group leaders must communicate the need for change in clinical practice patterns and consistently identify improvement priorities.
  - **Resources.** Resources adequate to the task at hand will be needed to assure the success of a change effort. Resources may include staff time, money and provision of tools (such as electronic medical records) to support care improvement.
  - **Select Specific Improvement Goals and Measures.** For most chronic diseases, including diabetes, the most efficient improvement strategy is to focus on a limited number of specific improvement goals. These may be based on observed gaps in care, potential clinical impact, cost considerations or other criteria *(O'Connor, 2005a [R])*. In type 2 diabetes, focusing on glycemic control, lipid control and blood pressure control is a strategy that has been shown to be effective in preventing up to 53% of heart attacks and strokes, the leading drivers of excess mortality and costs in adults with diabetes *(Gaede, 2003 [A])*.
  - **Accountability.** Accountability within the medical group is a management responsibility, but external accountability may also play an important enhancing role to motivate sustained efforts to implement guidelines and improve care. Examples of external accountability include participation in shared learning activities (such as Institute for Healthcare Improvement or ICSI and its Action Groups), or public reporting of results (such as in pay-for-performance or the Minnesota Community Measures Project).
  - **Prepared Practiced Teams.** The medical group may need to foster the development of prepared practice teams that are designed to meet the many challenges of delivering high-quality chronic disease care.
- Essential Elements at the Clinic Level:
  - **Develop "Smart" Patient Registries.** These are registries that are designed to identify, automatically monitor, and prioritize patients with diabetes based on their risk, current level of control, and possibly patient readiness-to-change.

- **Assure "Value-Added" Visits.** These are office visits or other patient encounters (by phone, e-mail, etc.) that include intensification of treatment if the patient has not yet reached his/her evidence-based clinical goals. Failure of providers and patients to intensify treatment when indicated (referred to as "clinical inertia") is a key obstacle to better diabetes care (*O'Connor, 2003 [R]; O'Connor, 2005a [R]; O'Connor, 2005b [R]).* HSR editorial. Previsit planning and best practice prompts may help to increase the efficiency of patient visits and remind providers of needed tests and care.
- **Develop "Active Outreach."** These are strategies to reach patients with chronic disease who have not returned for follow-up or for other selected elements of care. Outreach strategies that enhance the likeliness of a future provider encounter that addresses one of the barriers to patient activation (discussed below) may be more effective. Simple reporting of lab test results or care suggestions through the mail may be ineffective at addressing these barriers.
- **Emphasize "Patient Activation" Strategies.** These may include diabetes education and other actions designed to sustain engagement of patients with their diabetes care. Many patients with diabetes either (a) do not really believe they have diabetes, or (b) do not really believe that diabetes is a serious disease, or (c) lack motivation for behavioral change, or (d) do not believe that recommended treatments will make a difference to their own outcomes. For care to be effective, these issues must be addressed for many patients *(O'Connor, 1997 [D]).*

Related ICSI Scientific Documents

Guidelines

- Hypertension Diagnosis and Treatment
- Lipid Management in Adults
- Major Depression in Adults in Primary Care
- Preventive Services for Adults
- Prevention and Management of Obesity (Mature Adolescents and Adults)
- Primary Prevention of Chronic Disease Risk Factors
- Stable Coronary Artery Disease

Order Sets

- Subcutaneous Insulin Management Order Set

Disclosure of Potential Conflict of Interest

ICSI has adopted a policy of transparency, disclosing potential conflict and competing interests of all individuals who participate in the development, revision and approval of ICSI documents (guidelines, order sets and protocols). This applies to all work groups (guidelines, order sets and protocols) and committees (Committee on Evidence-Based Practice, Cardiovascular Steering Committee, Women's Health Steering Committee, Preventive & Health Maintenance Steering Committee and Respiratory Steering Committee).

Participants must disclose any potential conflict and competing interests they or their dependents (spouse, dependent children, or others claimed as dependents) may have with any organization with commercial, proprietary, or political interests relevant to the topics covered by ICSI documents. Such disclosures will be shared with all individuals who prepare, review and approve ICSI documents.

Richard Bergenstal, MD has stock in Merck through a family inheritance. Dr. Bergenstal participates in clinical research and/or serves on a scientific advisory board for Amylin, Merck, Pfizer, ResMed, Valeritas, Eli Lilly, Novo Nordisk, Sanofi-Aventis, MannKind, Intuity, Roche, LifeScan, Abbott, Bayer and Medtronic. All compensation goes directly to the non-profit Park Nicollet Institute. Dr. Bergenstal is an officer within the American Diabetes Association.

Carol Manchester, MSN, APRN received speakers' fees or honorarium from Sanofi-Aventis and Pfizer.

Patrick O'Connor, MD receives research or grant funding from HealthPartners Research Foundation; National Institute of Diabetes and Digestive and Kidney Diseases; National Institute for Health; National Heart, Lung, and Blood Institute; Robert Wood Johnson Foundation, Agency for Healthcare Research and Quality; Centers for Disease Control; Minnesota Department of Health, University of Minnesota. Dr. O'Connor received speakers' fees or honorarium from Merck.

Bruce Redmon, MD is contracted with Ingenix and receives research or grant funds from Mannkind Corp.

Steve Smith, MD is a member of the national board of directors for the American Diabetes Association.

JoAnn Sperl-Hillen, MD receives research support from National Heart, Lung, and Blood Institute; National Institute of Diabetes and Digestive and Kidney Diseases; and Merck.

No other work group members have potential conflicts of interest to disclose.

Introduction to ICSI Document Development

This document was developed and/or revised by a multidisciplinary work group utilizing a defined process for literature search and review, document development and revision as well as obtaining input from and responding to ICSI members.

For a description of ICSI's development and revision process, please see the Development and Revision Process for Guidelines, Order Sets and Protocols at http://www.icsi.org.

Evidence Grading System

A. Primary Reports of New Data Collection:

Class A: Randomized, controlled trial

Class B: Cohort study

Class C: Non-randomized trial with concurrent or historical controls
Case-control study
Study of sensitivity and specificity of a diagnostic test
Population-based descriptive study

Class D: Cross-sectional study
Case series
Case report

B. Reports that Synthesize or Reflect upon Collections of Primary Reports:

Class M: Meta-analysis
Systematic review
Decision analysis
Cost-effectiveness analysis

Class R: Consensus statement
Consensus report
Narrative review

Class X: Medical opinion

Citations are listed in the guideline utilizing the format of *(Author, YYYY [report class])*. A full explanation of ICSI's Evidence Grading System can be found at http://www.icsi.org.

Definitions

Prediabetes: Hyperglycemia not sufficient to meet the diagnostic criteria for diabetes. Formerly categorized as either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), depending on whether it is identified through a fasting plasma glucose test or oral glucose tolerance test. Diagnosis of prediabetes is based on:

- Fasting plasma glucose of 100 mg/dL to 125 mg/dL
- Oral glucose tolerance test – two-hour plasma glucose of 140 mg/dL to 199 mg/dL

Type 2 Diabetes Mellitus: Diabetes that results from a progressive insulin secretory defect on the background of insulin resistance. The diagnosis of type 2 diabetes is based on:

- Symptoms of diabetes and a casual plasma glucose of greater than or equal to 200 mg/dL
  - Casual is defined as any time of day without regard to time since last meal.
  - The classic symptoms of diabetes include polyuria, polydipsia and unexplained weight loss, excessive hunger, fatigue or wounds that are slow to heal or frequent skin infections.
- Fasting plasma glucose of greater than or equal to 126 mg/dL on two occasions
  - Fasting is defined as no caloric intake for at least eight hours.
- Oral glucose tolerance test – two-hour plasma glucose of 200 mg/dL
  - The oral glucose tolerance 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.
  - Verified by repeat test on a separate occasion.

(American Diabetes Association, 2007a [R])

Algorithm Annotations

1. Diagnostic Testing for Diabetes

Prediabetes is now the term recommended for patients with impaired glucose tolerance or impaired fasting glucose. Type 2 diabetes is frequently not diagnosed until complications appear, and approximately one-third of all people with diabetes may be undiagnosed *(American Diabetes Association, 2007c [R])*.

Possible tests to assess for diabetes include a fasting plasma glucose or an oral glucose tolerance test. A fasting blood glucose is the preferred test for screening for diabetes *(American Diabetes Association, 2007c [R])*.

Patients presenting with symptoms of diabetes should be tested.

Risk factors for diabetes include:

- Risk factors for athrosclerosis: smoking, hypertension, dyslipidemia.
- Age, race/ethnicity, family history of diabetes, prior history of diabetes, physical inactivity, cardiovascular disease, cerebral vascular disease, hyperlipidemia, overweight/obese (as defined by body mass index), low high-density lipoprotein, high triglycerides, polycystic ovarian syndrome.
- Gestation history of an infant weighing more than nine pounds, toxemia, stillbirth or previous diagnosis of gestational diabetes.

Testing patients with hypertension, blood pressure over 130/80, dyslipidemia or heart disease are also recommended.

See the ICSI Hypertension Diagnosis and Treatment guideline, the ICSI Lipid Management in Adults guideline, the ICSI Preventive Services in Adults guideline, the Prevention and Management of Obesity (Mature Adolescents and Adults) guideline, and the Stable Coronary Artery Disease guideline for more information.

2. Evaluation of Patients with Elevated Glucose

Evaluation may be completed in one or more visits over a reasonably short period of time. Clinical judgment is needed to determine the urgency of completing the evaluation.

History *(American Diabetes Association, 2007c [R])*

- Symptoms
- Eating habits, weight history
- Physical activity
- Prior or current infections, particularly skin, foot, dental and genitourinary
- Symptoms and treatment of chronic complications associated with diabetes: eye, heart, kidney, nerve, genitourinary (including sexual function), peripheral vascular and cerebrovascular (these may be present at diagnosis)
- Current medications including over-the-counter medications, dietary supplements and alternative therapies with a focus on medications known to induce diabetes-type states (e.g., steroids, atypical antipsychotics)

- Psychosocial, cultural and economic factors that might influence the management of diabetes
- Alcohol/drug use

Physical examination *(American Diabetes Association, 2007c [R])*

- Weight, height, body mass index (BMI), blood pressure
- Cardiovascular system: heart, blood pressure, peripheral vascular including pulses and bruits (abdominal, carotid, femoral)
- Feet: nails, web spaces, ulcers, pulses, calluses, structural deformities, protective sensation and shoes
- Other examinations as guided by the patient's symptoms and/or concerns:
  - Skin: infections or diseases such as acanthosis nigricans, xanthomia
  - Neurological symptoms: sensory state of hands and feet, muscle wasting, deep tendon reflexes
  - Mental health: screen for depression and/or anxiety
  - Referral to an eye specialist to assess optic health
  - Referral to a dentist to assess oral health

Laboratory evaluation

- Fasting plasma glucose or random plasma glucose
- A1c (not required for prediabetes)
- Fasting lipid profile: total cholesterol, high-density lipoprotein (HDL cholesterol), low-density lipoprotein (LDL cholesterol) and triglycerides
- Serum creatinine and liver function test alanine aminotransferase (ALT) or aspartate aminotransferase (AST)
- Urine: ketones, glucose, protein, microalbuminuria, and culture if microscopic is abnormal or symptoms of infection present

  Urine microalbumin tests can identify patients with early diabetic nephropathy when intervention may be most effective in delaying or preventing end-stage renal disease. Single tests for urinary microalbumin and urinary creatinine can accurately detect urinary microalbumin excretion.

  For more information, see Annotation #35, "Annual Assessment of Complications" *(American Diabetes Association, 2004d [R]; Nelson, 1991 [B])*.

  Increased urinary microalbumin is a predictor of increased cardiovascular mortality *(American Diabetes Association, 2007c [R])*.

3. Diagnosis of Prediabetes

- Fasting plasma glucose of 100 mg/dL to 125 mg/dL
- Oral glucose tolerance test two-hour plasma glucose: 140 mg/dL to 199 mg/dL

(American Diabetes Association, 2007c [R])

4. Treatment to Prevent or Delay the Progression to Diabetes

Patients who are identified with prediabetes should be referred for education and lifestyle interventions. Health care providers should follow up with patients diagnosed with prediabetes on an annual basis to monitor their progress and review treatment goals *(American Diabetes Association, 2007c [R])*.

Intensive lifestyle change or programs have been proven effective in delaying or preventing the onset of diabetes by about 50%. Effective lifestyle changes include setting achievable goals, obtaining weight loss when needed (ideally at least 5% total body weight), and increasing physical activity *(Tuomilehto, 2001 [A])*.

- Lifestyle modifications, such as nutrition, exercise and even modest weight loss, are recommended for prevention or delayed progression of patients with prediabetes.
- Pharmacotherapy, such as metformin, are effective in some patients with prediabetes.
- There are concerns that the recent modification of the definition of impaired fasting glucose by the American Diabetes Association has low specificity and low positive predictive value compared to the WHO definition.

[Conclusion Grade II: See Conclusion Grading Worksheet A – Annotation #4 (Prediabetes)]

The following initial approaches are recommended for people with prediabetes:

- Intensive lifestyle behavioral change including a nutrition and activity plan by a registered dietitian, health educator or other qualified health professional. Ongoing support of behavioral change is necessary.
- Cardiovascular risk reduction appropriate to the needs of the individual

Patients who respond to lifestyle interventions:

- Annual follow-up and reassessment of risks for developing diabetes *(American Diabetes Association, 2004g [R]; Chiasson, 2002 [A]; Eriksson, 1999 [R]; Heart Outcomes Prevention Evaluation Study Investigators, 2002 [A]; Kelley, 2002 [A]; Miles, 2002 [A])*

Patients who are high risk and not responding to lifestyle interventions:

- Intensify education and counseling on lifestyle interventions.
- There is some evidence of prevention of diabetes through pharmacotherapy with biguanides and alpha glycosidase inhibitors *(Diabetes Prevention Program Research Group, 2002 [A]; Gillies, 2007 [M])*. Rosiglitazone has been shown to prevent diabetes, but the risk of congestive heart failure was increased *(DREAM Trial Investigators, 2006 [A])*. Lifestyle change remains the preferred method to prevent diabetes *(Diabetes Prevention Program Research Group, 2002 [A]; Gillies, 2007 [M])*.

5. Diagnosis of Type 2 Diabetes

Diagnosis of type 2 diabetes *(American Diabetes Association, 2007a [R]):*

- Fasting plasma glucose greater than or equal to 126 mg/dL on two separate occasions.
- Casual plasma glucose greater than or equal to 200 mg/dL plus typical symptoms of diabetes.
- In the absence of unequivocal hyperglycemia associated with acute metabolic decompensation, the results should be confirmed by repeat testing on a different day.
- At the present time A1c should not be used to diagnose diabetes.

History

- Details of previous treatment programs, including diabetes education
- Current treatment of diabetes, including medications, nutrition, physical activity patterns and results of glucose monitoring
- Frequency, severity and cause of acute complications such as hypoglycemia, hyperglycemia and non-ketotic hyperosmolar coma

6. Should Patient Be Hospitalized?

Inpatient care may be appropriate in the following situations *(American Diabetes Association, 2004d [R])*:

- Elderly patients with infection or illness, weight loss, dehydration, polyuria or polydipsia
- Life-threatening acute metabolic complications of diabetes:
  - Hyperglycemic hyperosmolar state with impaired mental status, elevated plasma osmolaity that includes plasma glucose greater than 600 mg/dL
  - Diabetic ketoacidosis with a plasma glucose greater than 250 mg/dL, arterial pH less than 7.30 and serum bicarbonate level less than 15 mEq/L and the presence of moderate ketonuria and/or ketonemia
  - Hypoglycemia with neuroglycopenia that includes blood glucose less than 50 mg/dL and treatment has not resulted in prompt recovery, coma, seizures or altered behavior
- Uncontrolled insulin-requiring diabetes during pregnancy
- Surgery, infection, steroids – if these conditions cause significant hyperglycemia and rapid initiation of rigorous insulin is needed

7. Inpatient Diabetes Management

Hospitalized inpatients with diabetes suffer increased morbidity, mortality, length of stay, and other related hospital costs compared to non-hyperglycemic inpatients. These negative outcomes are observed more frequently in hospitalized patients with newly discovered hyperglycemia. Hyperglycemia is an independent marker of inpatient mortality in patients with undiagnosed diabetes (*Umpierrez, 2002 [B]*).

Hyperglycemia has been associated with increased infection rates and poorer short-term and long-term outcomes in critically ill patients in the intensive care unit, post-myocardial infarction, and post-surgical settings. Studies support that aggressive glucose management in medical and surgical patients can improve outcomes *(van den Berghe, 2001 [A])*.

The following are recommended in the inpatient setting *(Clement, 2004 [R])*:

- Intensive insulin therapy with intravenous insulin in critically ill patients *(van den Berghe, 2001 [R])*
- Use of scheduled insulin, with basal coverage (improves glucose control compared to sliding scale coverage alone)
- For insulin-deficient patients, despite reductions or the absence of caloric intake, basal insulin must be provided to prevent diabetic ketoacidosis

- Target preprandial plasma glucose levels are 90-130 mg/dL *(American Diabetes Association, 2004b [R]; Clement, 2004 [R]; Garber, 2004 [R])*
- If measured, the target postprandial plasma glucose is less than 180 mg/dL *(American Diabetes Association, 2004b [R]; Clement, 2004 [R]; Garber, 2004 [R])*
- Establishing a multidisciplinary team that sets and implements institutional guidelines, protocols and standardized order sets for the hospital results in reduced hypoglycemic and hyperglycemic events

Other considerations include *(Clement, 2004 [R])*:

- For patients who are alert and demonstrate accurate insulin self-administration and glucose monitoring, insulin self-management should be allowed as an adjunct to standard nurse-delivered diabetes management.
- Patients with no prior history of diabetes who are found to have hyperglycemia (random fasting blood glucose greater than 125 mg/dL or random glucose of 200 mg/dL or more) during hospitalization should have follow-up testing for diabetes within one month of hospital discharge *(Umpierrz, 2002 [B])*.

Please see ICSI's Subcutaneous Insulin Management order set for additional information regarding inpatient glucose management.

8. Does Patient Need Outpatient Stabilization?

Indications for immediate insulin treatment in type 2 diabetes mellitus *(Clements, 1987 [A]; Nathan, 2006 [R])*

- Severe symptoms, marked weight loss, polyuria, polydypsia
  - Fasting plasma glucose greater than 300 mg/dL fasting, or
  - Random glucose over 350 mg/dL, or
  - A1c over 10%, or
  - Presence of ketonuria

Insulin therapy may not be permanent once patient is stabilized.

9. Initial Stabilization for Outpatients Requiring Immediate Insulin Treatment

If the patient presents and is considered stable enough for outpatient care but meets indications noted above for starting insulin, the work group offers several acceptable ways of initiating insulin:

- One example is to calculate the total daily dose of insulin at 0.3 units/kg and start bedtime glargine at 50% of the total dose, splitting the remaining 50% with short-acting insulin before meals.
- Another example is to start an oral agent while simultaneously initiating glargine at a dose of approximately 0.1 units/kg.
- A third example is to calculate the total daily dose of insulin at 0.3 units/kg and use premixed insulin with 2/3 the dose in the a.m. and 1/3 in the p.m.

At presentation, all patients should be instructed on glucose monitoring, hypoglycemia recognition and treatment, and how/when to contact health care support. Patients should check glucose frequently when

insulin is initiated. Patients should receive daily phone or visit contact for at least three days and have 24-hour emergency phone support if needed.

Patients should be referred for nutrition and diabetes education and be seen in a timely way after diagnosis, e.g., within one to seven days.

Insulin therapy may not be permanent, particularly if oral agents are added or if, at presentation, the patient is in metabolic stress such as infections, acute metabolic complications, recent surgery *(Peters, 1996 [D])*. As the metabolic stress resolves, the insulin dose requirements may rapidly fall.

For the occasional unstable patient with type 2 diabetes, maximal doses of oral hypoglycemic agents may afford an approach to the patient who is psychologically resistant to or refuses insulin initiation.

10. Recommend Education and Self-Management

Nutrition Therapy

Medical nutrition therapy for diabetes emphasizes improving metabolic outcomes by modifying nutrient intake and lifestyle. Major goals are to attain and maintain in the normal or as close to normal range as is safely possible glucose, blood pressure and lipid/lipoprotein levels. These prevent or slow the development of the chronic complications of diabetes *(American Diabetes Association, 2008 [R])*.

The priority for nutrition therapy for type 2 diabetes is to implement lifestyle strategies that will reduce hyperglycemia and hypertension and improve dyslipidemias *(American Dietetic Association, 2008 [R]; American Diabetes Association, 2008 [R])*. Because many individuals are insulin resistant and overweight or obese, nutrition therapy often begins with strategies that reduce energy intake and increase energy expenditure through physical activity. Many individuals may have already tried unsuccessfully to lose weight and it is important to note that lifestyle strategies, independent of weight loss, can improve glucose control and risk factors for cardiovascular disease.

Moderate weight loss (5% of body weight) is associated with decreased insulin resistance, improved measures of glycemic and lipidemia, and reduced blood pressure. The optimal macronutrient distribution of weight loss diets has not been established *(American Diabetes Association, 2008 [R])*.

Low carbohydrate diets, restricting total carbohydrate to less than 130 g/day, are not recommended in the management of diabetes.

Appropriate nutrition therapy will be developed collaboratively with the person who has diabetes. Instruction may require a provider with expertise in medical nutrition therapy, and instruction may be obtained through individual or group consultation *(Franz, 1995a [A])*. It is important that physicians understand the general principles of medical nutrition therapy and support them for patients with diabetes. In most people, nutrition recommendations are similar to those of the general population. **Medical nutrition therapy is a Medicare Part B-covered benefit.**

- Evaluate the patient's current eating habits and modify as needed. Recommend:
  - Working together toward gradual, realistic and culturally appropriate lifestyle change goals.
  - Maintaining the pleasure of eating by limiting only food choices indicated by scientific evidence.
  - Healthful food choices: foods containing carbohydrates from whole grains, fruits, vegetables, legumes and low-fat milk should be included in a healthy eating plan.
  - Reducing total caloric intake by moderating food/beverage and limiting total fat intake.
  - Distributing carbohydrates evenly throughout the day to smaller meals and snacks.

- Monitoring carbohydrates remains a key strategy in achieving glycemic control, whether by carbohydrate counting, exchanges or experience-based estimation *(American Diabetes Association, 2008 [R])*.
- If one chooses to drink alcohol and has not been cautioned against it, limit intake to one drink per day for women and two drinks per day for men, according to USDA guidelines. A drink is defined as 12 oz. of regular beer, 5 oz. of wine, or 1.5 oz. of 80-proof distilled spirits. To reduce the risk of hypoglycemia, alcohol should be consumed with food.

• Individualize the nutrition prescription based on the nutrition assessment and treatment goals of each patient. For example, if the patient has been eating 45% of calories from fat, lowering fat to even 40% can be helpful.

Carbohydrate *(American Diabetes Association, 2009 [R])*

- Both the quantity and the type or source of carbohydrate in food influences post-prandial glucose levels.
- For individuals with diabetes, the use of glycemic index and glycemic load may provide a modest additional benefit for glycemic control over that observed when total carbohydrate is considered alone.
- Sucrose (e.g., table sugar) and sucrose-containing foods do not need to be restricted. However, they should be substituted for other carbohydrate sources, or if added, covered with insulin or other glucose-lowering medication. They should be eaten within the context of a healthy diet and avoid excess energy intake.
- Added fructose as a sweetening agent is not recommended as it may adversely affect plasma lipids. Naturally occurring fructose in fruits, vegetables and other foods does not need to be avoided.
- The use of sugar alcohols, such as sorbitol or manitol in small amounts, appears to be safe; however, they may cause gastrointestinal side effects. When calculating carbohydrate content of foods containing sugar alcohols, subtract half of sugar alcohol grams from total carbohydrate grams *(American Diabetes Association, 2008 [R])*.
- Sugar alcohols and non-nutritive sweeteners are safe when consumed within the acceptable daily intake levels established by the Food and Drug Administration.
- Encourage consuming a wide variety of fiber-containing foods such as legumes, fiber-rich cereals, fruits, vegetables and whole grain products to achieve fiber intake goals of 14 g/1,000 calories.

Protein *(American Diabetes Association, 2007b [R]; American Diabetes Association, 2008 [R])*

- 15%-20% of the total calories. Avoid protein intakes of greater than 20% of total daily energy. The long-term effects of consuming more than 20% of energy as protein on the development of nephropathy have not been determined. High-protein diets are not recommended as a method of weight loss at this time.
- Reduction of protein intake to 0.8-1 gm/kg in individuals with diabetes in the earlier stages of chronic kidney disease and to 0.8 gm/kg in the later stages of chronic kidney disease is recommended and may improve measures of renal function (urine albumin excretion rate, glomerular filtration rate).
- Protein does not increase plasma glucose concentrations but does increase serum insulin responses, and thus protein should not be used to treat acute or prevent nighttime hypoglycemia.

Fat *(American Diabetes Association, 2007b [R]; American Diabetes Association, 2008 [R])*

- Patients with normal weight and lipids: continue maintaining healthy weight and lipids that include less than or equal to 30% calories from fat, less than 7% saturated fats, limit of trans fats, and less than 200 mg cholesterol *(Klein, 2004 [R])*.
- Weight control: balance lower fat and caloric consumption with regular physical activity of 30 minutes most days.
- Patients with elevated cholesterol and low-density lipoprotein cholesterol: implement National Cholesterol Education Program-Therapeutic Lifestyle recommendations. Program-Therapeutic Lifestyle diet: reduce saturated fat to less than 7% calories and cholesterol to less than 200 mg, consider increased soluble fiber intake (10-25 g/day) and plant stanols/sterols (2 g/day), and minimize trans fat intake.
- Two or more servings of fish per week (with the exception of commercially fried fish fillets) provide omega-3 fatty acids and are recommended.
- Patients with elevated triglycerides: improve glucose control, encourage weight loss, increase physical activity, moderate carbohydrate intake and limit dietary saturated fat and trans fat. Increase consumption of omega-3 fatty acids from fish or supplements, which has been shown to reduce adverse cardiovascular outcomes *(Wang, 2006 [M])*.

Sodium *(American Diabetes Association, 2007b [R])*

- Medical nutrition therapy for hypertension control focuses on weight reduction and recommended sodium intakes of 2,300 mg/day for normotensive and hypertensive individuals and a sodium intake less than 2,000 mg/day for patients with diabetes and symptomatic heart failure. Additional recommendations include consuming five to nine servings of fruits and vegetables daily, and two to four daily servings of low-fat dairy products rich in calcium, magnesium and potassium.

Supplements *(American Diabetes Association, 2009 [R])*

- Routine supplementation with antioxidants, such as vitamins E and C and carotene, is not advised because of lack of evidence of efficacy and concern related to long-term safety.
- Benefit from chromium supplementation in people with diabetes or obesity has not been conclusively demonstrated and, therefore, cannot be recommended.

Physical activity and behavior modification are important components of weight loss programs and are most helpful in maintenance of weight loss.

Structured programs that emphasize lifestyle changes including education, reduced energy and fat intake (approximately 30% of total energy), regular physical activity and frequent participant contact are necessary to produce long-term weight loss of 5%-7% of starting weight. Lifestyle change should be the primary approach to weight loss *(American Diabetes Association, 2007b [R])*.

When usual measures to promote weight loss are unsuccessful in severely obese individuals with comorbidities, there may be a role for adjunctive pharmacotherapy or surgical procedures.

There is some evidence that pharmacotherapy for weight loss may offer short-term benefit for a subset of patients with type 2 diabetes *(Hollander, 1998 [A]; Kelley, 2002 [A]; Miles, 2002 [A])*. The studies, however, were of relatively weak design, and pharmacotherapy for weight loss cannot be recommended for most patients with type 2 diabetes.

Patients should be provided with ongoing nutrition self-management and care support *(American Diabetes Association, 2007b [R])*.

Physical Activity

People with diabetes should peform at least 150 minutes a week of moderate intensity activity (50%-70% maximum heart rate), and strengthening exercises three times a week unless contraindicated.

The positive benefits of physical activity include improved blood pressure values, improved lipid profile, improved cardiac status, increased insulin sensitivity, more effective weight management and improved glycemic control, and it helps in the management of depressive symptoms. Because the positive effects of increased physical activity diminish within days of the cessation of exercise, regular activity is recommended *(Bourn, 1994 [D])*.

Recent studies indicate that cumulative daily physical activity may be almost as beneficial as continuous physical exertion *(De Buske, 1990 [A]; Hardman, 1999 [R])*. The major emphasis is to gradually increase level of physical activity either by increasing duration or frequency.

Epidemiological studies suggest that regular aerobic physical activity is beneficial for the treatment of type 2 diabetes mellitus *(American Diabetes Association, 2004e [R]; Helmrich, 1991 [C])*.

Reinforce the ongoing need and benefits of physical activity at each visit, offering support and advice on ways to incorporate 30 minutes of physical activity into most days of the week *(Pate, 1995 [R])*.

Results of self-monitoring glucose can be useful in preventing hypoglycemia and adjusting medications, medical nutrition therapy and physical activity.

Hypoglycemia is a risk in individuals who participate in physical activity and are taking insulin, sulfonylureas and/or meglitinides. Depending on the level of physical activity, the medication dosage or the amount of carbohydrate ingested, hypoglycemia can occur. For patients on these drug classes and pre-exercise glucose monitor results are less than 100 mg/dL, additional carbohydrate should be ingested for prevention of hypoglycemia *(American Diabetes Association, 2008 [R])*.

Strategies for initiation of increased physical activity

- Start by incorporating 10 minutes of increased activity into each day
  - Use stairs instead of elevator.
  - Park car away from building entrance and walk.
  - Walk to do errands.
- Overcome barriers
  - Self-monitor activity performed using pedometer, time record and/or journal.
  - Be consistent.
  - Have alternative activities for inclement weather.
  - Find enjoyable activities.
  - Be active at the time of day that is best for the individual.
  - Doing a physical activity with a partner and/or being accountable to someone regarding your progress greatly improves the ability to be successful *(American Diabetes Association, 2008 [R])*.

Medical evaluation to assess safety of exercise program

- Assess physical condition and limitations of the patient.
- Assess for cardiovascular disease. Atypical symptoms and painless ischemia are more common in patients with diabetes *(Janard-Delenne, 1999 [D])*.
- Cardiac stress testing: there is no evidence that stress testing is routinely necessary in asymptomatic people before beginning a moderate-intensity exercise program such as walking.
- Cardiac stress testing should be considered for the previously sedentary individual at moderate to high-risk for cardiovascular disease or other patients who are clinically indicated who want to undertake vigorous aerobic exercise that exceeds the demands of everyday living *(American Diabetes Association, 2007c [R])*.
- Assess glucose control.
- Assess knowledge of physical activity in relation to glucose control.
- When making a referral, make other health care providers aware of limitations for exercise.

Physical activity can be intermittent or cumulative *(DeBuske, 1990 [A]; Hardman, 1999 [R]; Pate, 1995 [R]*.

Weight Management

When usual measures to promote weight loss are unsuccessful in severely obese individuals with comorbidities, there may be a role for adjunctive pharmacotherapy or surgical procedures.

There is some evidence that pharmacotherapy for weight loss may offer short-term benefit for a subset of patients with type 2 diabetes *(Hollander, 1998 [A]; Kelley, 2002 [A]; Miles, 2002 [A])*. The studies, however, were of relatively weak design, and pharmacotherapy for weight loss cannot be recommended for most patients with type 2 diabetes.

Bariatric surgery has recently been discussed as an option for some individuals with type 2 diabetes who have a body mass index of 35 kg/m2 or more. Bariatric surgery can result in marked improvements in glycemia; however, the long-term benefits and risks need to be studied further *(American Diabetes Association, 2007b [R])*.

Weight loss is also an important goal because it improves insulin resistance, glycemic control, blood pressure and lipid profiles. Moderate weight loss (5% of body weight) can improve fasting blood glucose in many overweight or obese persons *(Pastors, 2002 [R])*. Low-carbohydrate diets, restricting total carbohydrate to less than 130 g/day, are not recommended in the management of diabetes.

There is considerable interest in low-carbohydrate diets for weight loss; however, the long-term effects of these diets are unknown and although such diets produce short-term weight loss, maintenance of weight loss is similar to that of low-fat diets, and impact on cardiovascular disease risk profile is uncertain *(American Diabetes Association, 2007b [R])*.

Low-carbohydrate diets, restricting total carbohydrate to less than 130 g/day, are not recommended in the management of diabetes. For weight loss, either low-carbohydrate or low-fat calorie-restricted diets may be effective in the short-term (up to one year) *(Standards of Medical Care in Diabetes, 2009 [R])*.

Further research is needed to determine the long-term efficacy and safety of low-carbohydrate diets *(Klein, 2004 [R])*.

A recent meta-analysis showed at six months, low-carbohydrate diets were associated; with greater improvements in triglyceride and high-density lipoprotein cholesterol than low-fat diets, however, low-density lipoprotein cholesterol was significantly higher in low-carbohydrate diets *(Nordmann, 2006 [M])*. For patients on low-carbohydrate diets, monitor lipid profiles, renal function and protein intake (in those with nephropathy), and adjust hypoglycemic therapy as needed *(American Diabetes Association Standards of Medical Care in Diabetes, 2009 [R])*.

Please see the Prevention and Management of Obesity (Mature Adolescents and Adults) guideline for more information.

Appropriate nutrition therapy will be developed collaboratively with the person who has diabetes. Instruction may require a provider with expertise in medical nutrition therapy, and instruction may be obtained through individual or group consultation *(Franz, 1995a [A]; Franz, 1995b [M]; Franz, 2002 [R])*. It is important that physicians understand the general principles of medical nutrition therapy and support them for patients with diabetes. In most people, nutrition recommendations are similar to those of the general population. **Medical nutrition therapy is a Medicare Part B-covered benefit.**

Education for Self-Management

Adequate self-management support for patients requires integration of available self-management education and support resources into routine care. Usually appropriate education may require the expertise of the diabetes educator. This instruction can be obtained through individual or group consultation *(Franz, 1995a [A]; Franz, 1995b [M]; Franz, 2002 [R])*. Medicare reimbursement for diabetes self-management training requires this service be provided by an education program that has achieved recognition by the American Diabetes Association or American Association of Diabetes Educators; the staff in such a program are multidisciplinary and include at least a registered dietician and an registered nurse with experiential preparation in education and diabetes management *(Mensing, 2007 [R])*. A number of studies involving a clinical pharmacist in programs with cardiac risk factors in select patients with diabetes have proven to be effective *(Cioffi, 2004 [D])*. Providers should be aware of culturally appropriate educational and community resources to support persons with diabetes and their families.

An education plan should be identified based on the needs of the individual and referral made to either an internal or external education resource. Periodic reassessment of educational goals is recommended *(Lorig, 2001 [D]; Mensing, 2007 [R])*.

See the Support for Implementation Section for a list of American Diabetes Association-recognized education programs available.

Components of self-management include:

- Description of the diabetes disease process and treatment options
- Goal-setting to promote health, and problem-solving for daily living
- Preventing, detecting and treating acute complications
- Preventing (through risk reduction behavior), detecting and adhering to treatments for chronic complications
- Self-monitoring blood glucose, ketones (when appropriate), and using results to improve control
- Incorporation of appropriate nutrition management *(Barnard, 1994 [C])*
- Incorporation of physical activity into lifestyle *(Barnard, 1994 [C])*
- Utilizing medications (if applicable) to maximize therapeutic effectiveness

- Awareness of culturally appropriate community resources/support for persons with diabetes mellitus and their families and ability to access community resources
- Psychosocial adjustment of diabetes to daily life
- Promotion of preconception care, counseling and management during pregnancy, if applicable

Foot Care

Education should be tailored to patient's current knowledge, individual needs and risk factors. Patients should be aware of their risk factors and appropriate measures to avoid complications *(American Diabetes Association, 2004f [R]; Mayfield, 1998 [R])*. See Annotation #35, "Annual Assessment of Complications, Comprehensive Foot Exam with Risk Assessment."

Education should cover:

- Inspect feet daily for cuts, bruises, bleeding, redness and nail problems.
- Wash feet daily and dry thoroughly including between the toes.
- Do not soak feet unless specified by a health care provider.
- Be careful of hot water.
- Use of lotions, creams or moisturizer is acceptable, but do not use between the toes.
- Do not walk barefoot.
- Check shoes each day for objects that may have fallen inside, excessive wear or areas that may cause irritation.
- Avoid injuries from cutting toenails; avoid self-cutting calluses or corns.
- When to seek care

Community Resources

There is some evidence for the effectiveness of community-based diabetes self-management education and support. These programs may complement the care and education that are routinely part of standard medical practice, and may enhance a patient's ability to self-manage diabetes. The Task Force on Community Preventive Services, supported by the Centers for Disease Control and Prevention, recommends diabetes self-management education in community gathering places.

11. Set Personalized A1c Goal = A1c Less Than 7% or Individualized to a Goal Less Than 8% Based on Factors in 11a

Key Points:

- Individual A1c and other treatment goals should be based on the risks and benefits for each patient. Set personalized A1c goal less than 7% or individualize to goal less than 8% based on complex patient factors.

A1c target in type 2 diabetes is aimed at reducing microvascular complications while not increasing risk of morbidity or mortality.

- All patients with type 2 diabetes should aim to achieve an A1c less then 8%. This will reduce microvasuclar disease and not increase risk substantially.

- Most (many) patients with type 2 diabetes may derive additional benefit in reduction of microvasuclar disease by reaching a target A1c less than 7% (and not increase risks as long as the target is not A1c less than 6%).

[Conclusion Grade II: See Conclusion Grading Worksheet B – Annotation #11 (A1c)]

The work group defines high cardiovascular risk as the patient having two other cardiovascular risks (obesity, hypertension, dyslipidemia, smoking and proteinura). Alternative approachs to calculate cardiovascular risk include the Framingham equation, Archimedes and UKPDS.

The physician and patient should discuss and document specific treatment goals and develop a plan to achieve all desired goals. A multifactorial approach to diabetes care that includes emphasis on blood pressure, lipids, glucose, aspirin use, and non-use of tobacco will maximize health outcomes far more than a strategy that is limited to just one or two of these clinical domains *(American Diabetes Association, 2009 [R]; Duckworth, 2009 [A]; Gaede, 2008 [A]; Holman, 2008 [A])*.

For patients with type 2 diabetes and the following factors, an A1c goal of less than 8% may be more appropriate than an A1c goal of less than 7% *(Action to Control Cardiovascular Risk in Diabetes Study Group, The, 2008 [A]; ADVANCE Collaborative Group, The, 2008 [A]; Duckworth, 2009 [A])*.

- Known cardiovascular disease or high risk cardiovascular risk.
- Inability to recognize and treat hypoglycemia, history of severe hypoglycemia requiring assistance.
- Inability to comply with standard goals, such a polypharmacy issues.
- Limited life expectancy or estimated survival of less than 10 years.
- Cognitive impairment.
- Extensive comorbid conditions such as renal failure, liver failure and end-stage disease complications.

The benefits of a multifactorial approach to diabetes care are supported by the results of the Steno 2 Study of 160 patients with type 2 diabetes and microalbuminuria. Multifactorial interventions achieved a 50% reduction in mortality and significant reduction in microvascular complications five years after ending a 7.8-year multifactorial intervention that achieved A1c of 7.8%, low-density lipoprotein 83 mg/dL, blood pressure 131/73, compared to a conventional group that achieved A1c 9%, low-density lipoprotein 126 mg/dL and blood pressure 146/78 *(Gaede, 2008 [A])*. Results of this study are consistent with the need for reasonable blood sugar control with emphasis on blood pressure and lipid management.

Recently reported clinical trials have evaluated the impact of A1c less than 7% on macrovascular and microvascular complications of type 2 diabetes. These studies, the Action to Control Cardiovascular Risk in Diabetes (ACCORD), the Action in Diabetes and Vascular Disease: Preferax and Diamcron Modified Release Controlled Evaluation (ADVANCE), and VADT Trials, are the first that have ever achieved and maintained A1c less than 7% in their intensive treatment patients. A more detailed description of these trials is included in Conclusion Grading Worksheet B – Annotation #11 (A1c).

In the ACCORD Trial, excess mortality in the intensive group (A1c mean 6.4% vs. standard group A1c 7.5%) forced the safety board to discontinue the intensive treatment arm earlier than planned *(Action to Control Cardiovascular Risk in Diabetes Study Group, The, 2008 [A])*. There was one excess death for every 90 patients in the intensive group over a 3.5-year period of time. In the ADVANCE trial, intensive group patients achieved A1c 6.5% (vs. 7.5% in standard group) but had no reduction in cardiovascular complications or events. In the VADT trial, intensive group patients achieved A1c of 6.9% but had no significant reduction in cardiovascular events or microvascular complications compared to standard group patients who achieved

A1c 8.4%. However, the VADT Trial was underpowered for its main hypothesis tests *(Duckworth, 2009 [A])*. In the ADVANCE trial, intensive group patients had less progression to proteinuria (one less patient advancing to proteinuria for every 100 people in the intensive group over a five-year period of time), but no fewer eye complications in the intensive group than in the standard group. ACCORD has not yet analyzed impact of A1c control on microvascular complications.

Recent follow-up data from the United Kingdom Prospective Diabetes Study of newly diagnosed patients with type 2 diabetes confirm major macrovascular and microvascular benefits of achieving A1c in the 7.1% to 7.3% range, vs. A1c of about 8% in the comparison groups *(Holman, 2008 [A])*. The United Kingdom Prospective Diabetes Study main trial included 3,867 newly diagnosed type 2 diabetes patients and showed over a 10-year period a 25% decrease in microvascular outcomes with a policy using insulin and sulfonylureas that achieved a median A1c of 7.1%, compared to 7.9%. A subgroup of obese patients (n=1,704) treated with metformin and achieving a median A1c of 7.3% showed greater advantages over conventional treatment: a 32% reduction of diabetes-related end points (P=0.002), a 42% reduction of diabetes-related deaths (P=0.017), and a 36% reduction of all-cause mortality (P=0.011) *(UK Prospective Diabetes Study Group, 1998b [A]; United Kingdom Prospective Diabetes Study Group, 1998d [A])*.

Epidemiological studies supported the recommendation for intensive glycemic control to A1c below 7% to reduce microvascular and macrovascular disease, but the benefits have not been consistently demonstrated in randomized control trials. It is possible that some aspect of the medications used to achieve low A1c values in the ACCORD, ADVANCE and VADT trials offset the anticipated benefits. Of available glucose-lowering medications, only metformin and human insulins have been thoroughly vetted for long-term safety *(Goldfine, 2008 [R]; Inzucchi, 2002 [M]; Selvin, 2008 [M])*. Many recent reports have questioned the safety of rosiglitazone, which was widely used in ACCORD *(Nissen, 2007 [M]; Winkelmayer, 2008 [B])*. Furthermore, the microvascular benefits in recent trials (ADVANCE, VADT) have been fewer than in older trials, perhaps because of better background blood pressure and low-density lipoprotein control in recent trials.

Glycosylated hemoglobin assays provide an accurate indication of long-term glycemic control. A1c is formed by the continuous non-enzymatic glycosylation of hemoglobin throughout the lifespan of an erythrocyte. This assay yields an accurate measure of time-averaged blood glucose during the previous six to eight weeks.

There are various methodologies (e.g., HbA, A1c, glycated hemoglobin) for this assay. At present, there are no established criteria for use as a diagnostic test. Clinically it can assist in determining duration and severity of hyperglycemia and can help guide treatment.

Eating, physical activity or acute metabolic stress do not influence the A1c test. The test can be done at any time of day and does not require fasting.

Glucose should also be used to assess level of glycemic control, in addition to A1c. It is appropriate to determine need for medication changes based on blood glucose whenever this information is available.

- **Self-monitoring blood glucose**

  Major clinical trials assessing the impact of glycemic control on diabetes complications have included self-monitoring blood glucose (SMBG) as part of multifactorial interventions, suggesting that self-monitoring blood glucose is a component of effective therapy *(American Diabetes Association, 2007c [R])*. However, there have been few large published studies done specifically to assess the link between self-monitoring blood glucose and A1c levels. The following table gives ranges of self-monitored glucose readings that would be expected for patients with the corresponding A1c levels.

  Self-monitoring blood glucose allows patients to evaluate their individual response to therapy and assess whether glucose targets are being achieved. Results of self-monitoring blood glucose can be useful in

preventing hypoglycemia and adjusting medications, medical nutrition therapy and physical activity *(American Diabetes Association, 1994 [R])*.

The frequency and timing of self-monitoring blood glucose should be dictated by the particular needs and goals of the individual patient. Patients with type 2 diabetes on insulin typically need to perform self-monitoring blood glucose more frequently than those not using insulin, particularly if using glucose readings to guide mealtime insulin dosing. It is recommended that patients using multiple insulin injections perform self-monitoring blood glucose three or more times daily *(American Diabetes Association, 2007c [R])*. The optimal frequency and timing of self-monitoring blood glucose for patients with type 2 diabetes on oral agent therapy are not known but should be sufficient to facilitate reaching glucose goals. Self-monitoring blood glucose should be performed more frequently when adding or modifying therapy; two-hour postprandial glucose testing is useful in some patients. The role of self-monitoring blood glucose in stable diet-treated patients with type 2 diabetes is not known.

Because the accuracy of self-monitoring blood glucose is instrumental and user dependent, it is important for health care providers to evaluate each patient's monitoring technique. In addition, optimal use of self-monitoring blood glucose requires proper interpretation of the data. Patients should be taught how to use the data to adjust food intake, exercise or pharmacological therapy to achieve specific glycemic goals.

Examples of self-monitoring glucose goals, frequency and timing are *(American Diabetes Association, 2007c [R])*:

- Target preprandial plasma glucose values to a goal of 70-130 mg/dL for an A1c goal less than 7%. Target blood glucose readings could be higher or lower depending on individualized A1c goal.
- Average two-hour post-prandial plasma glucose values less than 140-180 mg/dL.
- Two-hour postmeal plasma blood glucoses can be helpful for adjusting mealtime medications. The target range for postmeal glucoses is controversial at this time, but a reasonable two-hour postprandial target is within 40 mg/dL higher than the preprandial reading.
- Average bedtime plasma glucose values are less than 120 mg/dL with a goal of 110-150 mg/dL.
- Bedtime glucose goals vary dependent on the patient's treatment program, risks for hypoglycemia, and time after last meal.
- More than half of the plasma blood glucose readings should fall in the desired goal range.

Table 1. Ranges of self-monitored blood glucose values for various A1c goals

A1c Target	Average Mean Fasting Blood Glucose*	Average Mean Post-Prandial Blood Glucose	Estimated Average Blood Glucose**
< 6%	< 100	< 140	126
7%	90-130	< 180	154
8%	120-160	< 210	182
9%	160-190	< 240	211

* It is not recommended to target fasting glucose values below 70 mg/dl.
** This average figures weigh both fasting and post-prandial blood glucose readings from continuous glucose monitors or from 7-point daily testing.

Table 1 was developed by the diabetes work group based on data currently available from studies of frequently monitored glucose values and will be modified if necessary as further studies become available.

13. Treatment Goals for Patients without Cardiovascular Disease

Key Points:

- A major focus of diabetes care is to achieve the following treatment goals: use of statins in all adult type 2 diabetes patients if tolerated; statins should be titrated to achieve low-density lipoprotein cholesterol of less than 100 mg/dL without coronary artery disease, blood pressure less than 130/80 mmHg. Set personalized A1c goal = A1c less than 7% or individualized to goal of less than 8% based on risk factors. Daily aspirin use is optional for primary prevention of cardiovascular events.

- **Consider statin, unless contraindicated**

  For patients with type 2 diabetes mellitus, consider the use of a statin. Randomized controlled trials, including a number of large trials, and observational data consistently show a benefit of statin therapy for patients with type 2 diabetes. Some studies also report that statin therapy was well tolerated in these patients. However, none of these studies was able to assess long-term effects of statin treatment/use. *[Conclusion Grade I: See Conclusion Grading Worksheet C – Annotations #13, 14 (Statin Use)]*. Evidence *(Colhoun, 2004 [A]; Heart Protection Collaborative Study Group, 2002 [A])* and Adult Treatment Panel III consensus guidelines *(Grundy, 2004 [R])* suggest that statins are beneficial for high-risk patients ages 40-80 years with a 10-year risk of cardiovascular event of more than 20%, even with baseline untreated low-density lipoprotein of less than 100 mg/dL. There is an online and a Palm format-downloadable cardiovascular risk calculator that is used in assessing 10-year risk of cardiovascular disease used in the Adult Treatment Panel III guideline report and this guideline on lipid management *(Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001 [R])*. The links are:

  Online calculator: http://hin.nhlbi.nih.gov/atpiii/calculator.asp?usertype=prof

  Palm format (downloadable): http://hin.nhlbi.nih.gov/atpiii/riskcalc.htm.

  [Conclusion Grade I: See Conclusion Grading Worksheet C – Annotations #13, 14 (Statin Use)] (Colhoun, 2004 [A]; Heart Protection Collaborative Study Group, 2002 [A]; Howard, 2008 [A]; Malmström, 2009 [A]; Newman, 2008 [A]; Robins, 2001 [A]; Settergren, 2008 [A])

- **LDL less than 100 mg/dL**

  The low-density lipoprotein cholesterol goal for people with diabetes mellitus without coronary artery disease is less than 100 mg/dL.

  Intensify statin or lipid-lowering medications to meet low-density lipoprotein cholesterol goals *(LaRosa, 2005 [A])*.

  Three pathways to improve lipids are:

  - Medical nutrition therapy
  - Increased physical exercise
  - Pharmacotherapy

  Beneficial effects of statins on cardiovascular risk reduction may go beyond their effects on lipid levels. Diabetes is considered a coronary artery disease equivalent.

There currently is little evidence for safety and efficacy of combination therapy with statins and other lipid drugs. National Institutes of Health-sponsored randomized controlled studies are currently underway to determine whether adding fibrates or niacin to statin therapy will lower the risk of cardiovascular events for patients with diabetes. ACCORD (fibrate plus statins in diabetes patients) results will be reported in early 2010, and AIM-HIGH (niacin plus statin) will be reported circa 2012.

Seventy to seventy-five percent of adult patients with diabetes die of macrovascular disease, specifically coronary, carotid and/or peripheral vascular disease. Dyslipidemia is a known risk factor for macrovascular disease. Patients with diabetes develop more atherosclerosis than patients without diabetes with the same quantitative lipoprotein profiles. In most diabetes patients, use of a statin can reduce major vascular events (HPS [A] 4S diabetes substantially *(Pyorola, 1997 [A])*.

High triglycerides and low high-density lipoprotein cholesterol levels are independent risk factors for cardiovascular disease in the patient with diabetes *(American Diabetes Association, 2007c [R])*. Individuals with elevated triglycerides have significant cardiovascular risk reduction with the use of fibrates *(Robins, 2001 [A])* or statins *(Heart Protection Collaborative Study Group, 2003 [A])*. While a number of studies support favorable changes in lipid profiles with niacin alone, randomized controlled trials considering hard cardiovascular outcomes are still underway (AIM-HIGH).

- **Goals for blood pressure control: blood pressure less than 130/80 mmHg, emphasis on systolic blood pressure control** *(American Diabetes Association, 2007c [R]; Chobanian, 2003 [R])*

  Uncontrolled hypertension is a major cardiovascular risk factor that also accelerates the progression of diabetic nephropathy *(Morrish, 1991 [B])*. When hypertension is identified, it should be aggressively treated to achieve a target blood pressure of less than 130/80 mmHg. In many patients with diabetes, two or three or more antihypertensive agents may be needed to achieve this goal. The use of generic combination tablets (such as ACE plus calcium-channel blocker, or else beta-blocker plus diuretic) can reduce the complexity of the regimen and out-of-pocket costs. See the Blood Pressure Control algorithm.

  For patients with type 2 diabetes mellitus, the systolic blood pressure goal is less than 130 mmHg and the diastolic blood pressure goal is less than 80 mmHg. *[Conclusion Grade II: See Conclusion Grading Worksheet D – Annotations #13, 14, 27, 29 (Goals for Blood Pressure)] (Hansson, 1998 [A]; UK Prospective Diabetes Study [A], 1998c; UK Prospective Diabetes Study, 1998e [A])*. ADVANCE trial BP results, also showed major benefits of SBP of 134 mmHg in patients with type 2 diabetes.

- **Aspirin/antiplatelet medication optional** *(Bhatt, 2002 [A])*

  Patients with type 2 diabetes are at a significantly increased risk for development of heart disease *(American Diabetes Association, 2007c [R])*. There is insufficient evidence to support aspirin use in the primary prevention of cardiovascular events in patients with type 2 diabetes, although there is no evidence of significant harm. However, there is sufficient evidence to support the use of aspirin for secondary prevention of cardiovascular events in patients with type 2 diabetes. *[Conclusion Grade I: See Conclusion Grading Worksheet E – Annotations #13, 14 (Aspirin Use)]*. Some recent trials of aspirin use in diabetes have shown less benefit than older trials (perhaps due to better background A1c, blood pressure, and low-density lipoprotein control and lower smoking rates in recent trials) *(Belch, 2008 [A]; Ogawa, 2008 [A])*. There are significant limitations identified in these studies, and more definitive studies would be helpful. *[Conclusion Grade I: See Conclusion Grading Worksheet E – Annotations #13, 14 (Aspirin Use)]*. Therefore, based on current evidence, low-dose aspirin is considered optional for primary prevention.

  On September 8, 2006, the Food and Drug Administration issued a Safety Information and Adverse Event Report regarding the concomitant use of aspirin and ibuprofen. With occasional use of ibuprofen, there is likely to be minimal risk from any attenuation of the antiplatelet effect of low-dose aspirin, because

of the long-lasting effect of aspirin on platelets. Recommendations include taking immediate-release aspirin (not enteric-coated) 30 minutes or longer prior to taking ibuprofen (400 mg). If ibuprofen is taken first, aspirin should not be taken for at least eight hours after ingestion of ibuprofen.

- **Goals for tobacco use-smoking cessation, if indicated**

  Tobacco smoking increases risk of macrovascular complications about 4%-400% in adult with type 2 diabetes and also increases risk of macrovascular complications. Although only about 14% of adult with diabetes in Minnesota are current smokers, in these patients, smoking cessation is very likely to be the single most beneficial intervention that is available, and should be emphasized by providers as described below.

  - Identify and document tobacco use status.
  - Treat every tobacco user. If the patient is unwilling, the clinician should implement motivational treatments.
  - Individual, group and telephone counseling are effective, and their effectiveness increases with treatment intensity.
  - Practical counseling (problem-solving/skills training and social support delivered as part of the treatment) are especially effective counseling strategies and should be implemented by clinicians.
  - Numerous effective medications are available.
  - The combination of counseling and medication is more effective than either alone. Therefore, clinicians should encourage all individuals making a quit attempt to use both.
  - Telephone quit line counseling is effective. Therefore, clinicians and health care delivery systems should ensure patient access to quit lines and promote their use.
  - Tobacco dependence treatments are both clinically effective and cost effective. Effective interventions require coordinated interventions. Just as the clinician must intervene with the patient, so must the health care administrator, insurer and purchaser foster and support tobacco intervention as an integral element of health care delivery.

Numerous effective pharmacotherapies for smoking cessation now exist. Except in the presence of contraindications, these may be used with all patients attempting to quit smoking. Please see the ICSI Preventive Services in Adults guideline for additional information.

Tobacco telephone quit lines: HHS National Quit line (1-800-QUITNOW) or 1-800-784-8669; other local quit lines may be available.

14. Treatment Goals for Patients with Cardiovascular Disease

Key Points:

- A major goal of diabetes care is to achieve the following treatment goals: use of statins in all adult type 2 diabetes patients if tolerated; statins should be titrated to achieve low-density lipoprotein cholesterol of less than 70 mg/dL with coronary artery disease, blood pressure less than 130/80 mmHg. Set personalized A1c goal = A1c less than 7% or individualized to goal of less than 8% based on risk factors. Daily aspirin use is recommended in patients with cardiovascular disease.

- **Consider statin, unless contraindicated**

  For patients with type 2 diabetes mellitus, consider the use of a statin. Randomized controlled trials, including a number of large trials, and observational data consistently show a benefit of statin therapy for patients with type 2 diabetes. Some studies also reported that statin therapy was well tolerated in these patients. However, none of these studies was able to assess long-term effects of statin treatment/use. *[Conclusion Grade I: See Conclusion Grading Worksheet C – Annotations #13, 14 (Statin Use)] (Colhoun, 2004 [A]; Heart Protection Collaborative Study Group, 2002 [A]; Howard, 2008 [A]; Malmström, 2009 [A]; Newman, 2008 [A]; Robins, 2001 [A]; Settergren, 2008 [A])*

- **LDL less than 70 mg/dL**

  The low-density lipoprotein cholesterol goal for people with diabetes mellitus with coronary artery disease is less than 70 mg/dL.

  Intensify statin or lipid-lowering medications to meet low-density lipoprotein cholesterol goals *(LaRosa, 2005 [A])*.

  Use of moderate- to high-dose statins or other low-density lipoprotein cholesterol-lowering medications as needed to achieve a low-density lipoprotein cholesterol value less than 70 mg/dL is recommended for patients with coronary heart disease *(Cannon, 2004 [A]; Pyorala, 1997 [A])*.

  Three pathways to improve lipids are:

  - Medical nutrition therapy
  - Increased physical exercise
  - Pharmacotherapy

  There currently is no evidence for safety and efficacy of combination therapy with statins and other lipid drugs. National Institutes of Health-sponsored randomized controlled studies are currently underway to determine whether adding fibrates or niacin to statin therapy will lower the risk of cardiovascular events for patients with diabetes.

  Seventy to seventy-five percent of adult patients with diabetes die of macrovascular disease, specifically coronary, carotid and/or peripheral vascular disease. Dyslipidemia is a known risk factor for macrovascular disease. Patients with diabetes develop more atherosclerosis than patients without diabetes with the same quantitative lipoprotein profiles. In most diabetes patients, use of a statin can reduce major vascular events (HPS [A] 4S diabetes substantially *(Pyorola, 1997 [A])*.

  High triglycerides and low high-density lipoprotein cholesterol levels are independent risk factors for cardiovascular disease in the patient with diabetes *(American Diabetes Association, 2007c [R])*. Individuals with elevated triglycerides have significant cardiovascular risk reduction with the use of fibrates *(Robins, 2001 [A])* or statins *(Heart Protection Collaborative Study Group, 2003 [A])*. While a number of studies support favorable changes in lipid profiles with niacin alone, randomized controlled trials considering hard cardiovascular outcomes are still underway (AIM-HIGH).

- **Goals for blood pressure control: blood pressure less than 130/80 mmHg, emphasis on systolic blood pressure control** *(American Diabetes Association, 2007c [R]; Chobanian, 2003 [R])*

  Uncontrolled hypertension is a major cardiovascular risk factor that also accelerates the progression of diabetic nephropathy *(Morrish, 1991 [B])*. When hypertension is identified, it should be aggressively treated to achieve a target blood pressure of less than 130/80 mmHg. In many diabetes patients, two or three or more antihypertensive agents may be needed to achieve this goal. The use of generic combination tablets (such as ACE plus calcium-channel blocker, or else beta-blocker plus diuretic) can reduce the complexity of the regimen and out-of-pocket costs. See the Blood Pressure Control algorithm.

For patients with type 2 diabetes mellitus, the systolic blood pressure goal is less than 130 mmHg and the diastolic blood pressure goal is less than 80 mmHg. *[Conclusion Grade II: See Conclusion Grading Worksheet D – Annotations #13, 14, 27, 29 (Goals for Blood Pressure)] (Hansson, 1998 [A]; UK Prospective Diabetes Study [A], 1998c; UK Prospective Diabetes Study, 1998e [A]).*

- **Aspirin/antiplatelet medication use unless contraindicated** *(Bhatt, 2002 [A])*

  There is insufficient evidence to support aspirin use in the primary prevention of cardiovascular events in patients with type 2 diabetes, although there is no evidence of significant harm. However, there is sufficient evidence to support the use of aspirin for secondary prevention of cardiovascular events in patients with type 2 diabetes. *[Conclusion Grade I: See Conclusion Grading Worksheet E – Annotations #13, 14 (Aspirin Use)]*

  If aspirin is contraindicated, consider use of clopidogrel or ticlopidine. For more information, please refer to the ICSI Stable Coronary Artery Disease guideline and the Antithrombotic Therapy Supplement.

  On September 8, 2006, the Food and Drug Administration issued a Safety Information and Adverse Event Report regarding the concomitant use of aspirin and ibuprofen. Health care professionals should counsel patients about the appropriate timing of ibuprofen dosing if they are taking aspirin for cardioprotective effects. With occasional use of ibuprofen, there is likely to be minimal risk from any attenuation of the antiplatelet effect of low-dose aspirin, because of the long-lasting effect of aspirin on platelets. Recommendations include taking immediate-release aspirin (not enteric-coated) 30 minutes or longer prior to taking ibuprofen (400 mg). If ibuprofen is taken first, aspirin should not be taken for at least eight hours after ingestion of ibuprofen.

  For more information, please refer to the information listed on the Food and Drug Administration's Web site for a complete copy of the alert and cited references.

  http://www.fda.gov/medwatch/safety/2006/safety06.htm#aspirin.

- **Goals for tobacco use-smoking cessation, if indicated**

  Tobacco smoking increases risk of macrovascular complications about 4%-400% in adult with type 2 diabetes, and also increases risk of macrovascular complications. Although only about 14% of adult with diabetes in Minnesota are current smokers, in these patients, smoking cessation is very likely to be the single most beneficial intervention that is available, and should be emphasized by providers as described below.

  - Identify and document tobacco use status.
  - Treat every tobacco user. If the patient is unwilling, the clinician should implement motivational treatments.
  - Individual, group and telephone counseling are effective, and their effectiveness increases with treatment intensity.
  - Practical counseling (problem-solving/skills training and social support delivered as part of the treatment) are especially effective counseling strategies and should be implemented by clinicians.
  - Numerous effective medications are available.
  - The combination of counseling and medication is more effective than either alone. Therefore, clinicians should encourage all individuals making a quit attempt to use both.
  - Telephone quit line counseling is effective. Therefore, clinicians and health care delivery systems should ensure patient access to quit lines and promote their use.

- Tobacco dependence treatments are both clinically effective and cost effective. Effective interventions require coordinated interventions. Just as the clinician must intervene with the patient, so must the health care administrator, insurer and purchaser foster and support tobacco intervention as an integral element of health care delivery.

15. Are Treatment Goals Met?

Major long-term goals of care in type 2 diabetes are cardiovascular disease prevention (see the Blood Pressure Control algorithm) and achieving optimal glycemic control (see Glycemic Control algorithm).

Setting initial goals that are achievable, however modest they may be, may encourage patients to take further steps along the way to the more ambitious long-term goals.

Goals and progress toward agreed-upon goals should be briefly reviewed at each office visit for diabetes. Adjustment of goals will likely be required over time, and patient involvement in this process can increase levels of patient involvement in care, give patients a greater sense of control of their diabetes, and allow flexibility in management of diabetes during periods of high stress or major life transitions.

16. Treatment Goals Not Met

Modify Treatment Based on Appropriate Related Guideline

- Prevention and Management of Obesity (Mature Adolescents and Adults)
- Hypertension Diagnosis and Treatment
- Lipid Management in Adults
- Major Depression in Adults in Primary Care

See Glycemic Control and Blood Pressure Control Algorithms

Consider Referral to Diabetes Care Team or Specialists

- **Assess patient adherence**

  Non-adherence with medications can limit the success of therapy and help to explain why a patient is not achieving treatment goals. To screen for non-adherence, clinicians can ask patients open-ended, non-threatening questions at each office visit. The assessment should include probes for factors that can contribute to non-adherence (fear of adverse reactions, misunderstanding of chronic disease treatment, depression, cognitive impairment, complex dosing regimens, or financial constraints).

  - Assess the patient's knowledge of his/her condition and his/her expectations for treatment.
  - Assess the patient's medication administration process.
  - Assess the patient's barriers to adherence.

  Interventions to enhance medication adherence should be directed at risk factors or causes of non-adherence. Interventions may include simplifying the medication regimen, using reminder systems, involving family or caregivers in care, involving multiple disciplines in team care, providing written and verbal medication instructions, setting collaborative goals with patients, and providing education about medications (including potential adverse effects) and about diabetes in general *(Nichols-English, 2000 [R])*.

- **Evaluate for depression**

  There is a substantial increase in the prevalence of depression among people with diabetes as compared to the general adult population (*Anderson, 2001 [M]).* Self-administered or professionally administered instruments (such as the PHQ-9) are useful adjuncts to the clinical interview in the identification of depression. Depression impacts the ability of a person with diabetes to achieve blood glucose control, which in turn impacts the rate of development of diabetes complications *(DeGroot, 2001 [M]; Lustman, 2001 [R]).*

  Identification and management of depression is an important aspect of diabetes care. Self-administered or professionally administered instruments, such as PHQ-9, are useful adjuncts to the clinical interview in the identification of depression. The ICSI Major Depression in Adults in Primary Care guideline provides more suggestions for the identification and mangement of depression. Intervention studies have demonstrated that when depression is treated, both quality of life and glycemic control improve. Counseling may be effective, especially among those who are having difficulty adjusting to the diagnosis of diabetes or are having difficulty living with diabetes. Pharmacotherapy for depression is also effective.

- **Diabetes care team**

  Assure the patient has an adequate care team.

  Diabetes educator

  Consultation with a diabetes educator is suggested if the patient is having difficulty adhering to a nutrition, exercise and medication regimen and the patient is having difficulty adhering to, or accurately completing, blood glucose monitoring or may need answers to some questions.

  Every primary care physician must develop a relationship with a diabetes education program to provide other options for management. The American Diabetes Association publishes a list of recognized educational programs in each state. These programs may be staffed with endocrinologists or primary care providers plus diabetes educators including dietitians, nurses and other health care providers who are Certified Diabetes Educators or have didactic and experiential expertise in diabetes care and education.

Endocrinologist/nephrologist

Most type 2 diabetes management can be managed by a primary care physician with periodic consultation as needed by an endocrinologist.

Consultation with a specialist is suggested if persistent proteinuria, worsening microalbuminuria and elevation in serum creatinine or blood urea nitrogen, or hypertension unresponsive to treatment is seen. For additional discussion, see Annotation #36, "Treatment and Referral for Complications, Nephropathy."

Endocrinologist/neurologist

Consultation with a specialist is suggested if neuropathy progresses and becomes disabling.

Endocrinologist/cardiologist/hypertension specialist

Consultation with a specialist is suggested if blood pressure is refractory to treatment, the patient has marked associated postural hypotension or symptoms of coronary artery disease.

Foot care specialist

A consultation with a specialist is suggested if the patient is unable to care properly for his/her own feet, needs prescriptive footwear and/or more serious problems such as foot deformities (e.g., Charcot deformity), infected lesions, and ulcers, deformed nails or thick calluses are present.

Vascular Specialist/Surgeon

Consider referral if patient has symptoms of peripheral vascular disease such as loss of pulses and/or claudication.

Glycemic Control Algorithm Annotations

18. Glycemic Control Algorithm

Medical nutrition therapy may be all that is required to treat diabetes, especially for the patient with early mild symptomatic disease. Medical nutrition therapy should be maintained throughout the course of the disease, even as pharmacologic agents are used. Oral agent medications are generally used if medical nutrition therapy alone does not succeed in obtaining patients' goals within a reasonable time frame, usually no longer than two to three months. Metformin plus lifestyle treatment is also a reasonable initial therapy at the time of diagnosis, given the low risk of hypoglycemia and the benefits of metformin shown in both prediabetes and diabetes *(Nathan, 2006 [R])*.

At the time of diagnosis, if patients have severe symptomatic disease, insulin should be initiated. With appropriate educational support and care, the risks of insulin may not differ from many oral agents. In some circumstances when glucose intolerance is significant and the patient is unwilling to consider insulin or it is not felt to be appropriate, the initiation of combinations of oral agents can be appropriate. Insulin is indicated when there is a failure to achieve treatment goals with oral agents.

It is important to remember that patients can move both ways on the Glycemic Control algorithm, e.g., they can move off of specific pharmacologic therapies as lifestyle changes are made that improve glycemic control. Diabetes is a progressive disease, however, and the use of pharmacologic agents will likely become necessary in the majority of patients, even if they are able to follow through with nutrition and physical activity recommendations *(Turner, 1999 [A])*.

19. Pharmacologic Agent(s) – Which Is Best?

Key Points:

- Age and weight of the patient, as well as presence of renal dysfunction, cardiopulmonary comorbidities and hepatic disease must be considered when choosing pharmacologic agents.

Only general guidelines can be given when deciding about which pharmacologic agent will be best for a specific patient. While each patient presents with unique circumstances, the work group offers the following clinical circumstances to consider.

Age of Patient

It is important to recognize that risks of medications are often increased with advancing age, but this does not justify the withholding of medications that may reduce the symptoms of polyuria, nocturia and frequent visits to the bathroom that may place the patient at risk of hip fracture or falls.

With age, decline in renal function is often not reflected in a measurable change in serum creatinine because of an accompanying decline in muscle mass. Because of this, metformin should be used with caution in elderly patients (over age 80).

Decline in ventricular function and risks for volume overload can be occult in the elderly and may become clinically apparent with the use of thiazolidinediones.

In select circumstances, because of the risks of hypoglycemia, variable diet habits and renal clearance and function, it may be safer to consider initial low-dose, short-acting sulfonylurea (e.g., glipizide or repaglinide/nateglinide when a meal is eaten).

Weight of the Patient

Type 2 diabetes is often associated with insulin resistance and weight gain. Metformin, acarobose, exenatide, sitagliptin and human amylin are more often associated with weight loss or weight maintenance. Due to its weight benefits as well as general tolerability, lower cost and proven benefits in UK Prospective Diabetes Study Group, metformin is recommended for most diabetes patients with type 2 diabetes unless contraindicated. Insulin and thiazolidinediones may be associated with weight gain *(United Kingdom Prospective Diabetes Study Group, 1998b [A])*.

Renal Dysfunction

Renal dysfunction increases the risk for hypoglycemia, in particular with the use of oral hypoglycemic agents.

Metformin and alpha glucosidase inhibitors should not be used.

Thiazolidinediones may be considered, but the potential risks of fluid retention and increased risk of cardiac events need to considered.

Short-acting oral agents glipizide, glimepiride (in which serum levels have been noted to decrease in mild renal failure), repaglinide or nateglinide may be preferred if an oral agent is felt to be necessary in the face of renal dysfunction.

Insulin may be the safest when serum creatinine is greater than 1.8 mg or creatinine clearance is less than 60 mL/min.

Cardiopulmonary Comorbidities

Metformin should be used with caution for patients with conditions that predispose them to risk of hypoxia such as congestive heart failure, chronic obstructive pulmonary disease or obstructive sleep apnea. Metformin should be promptly discontinued in situations of cardiovascular collapse from acute congestive heart failure, acute myocardial infarction or any other cause.

Patients started on thiazolidinediones should be instructed to report signs of lower extremity swelling, rapid weight gain, and shortness of breath. Risk of thiazolidinediones needs to be discussed and documented before using in patients with cardiovascular risks. Please see the thiazolidinediones warning for more information.

Short-acting sulfonylurea (e.g., glipizide), repaglinide/nateglinide, and the cautious use of long-acting sulfonylureas agents or insulin may be safest.

Hepatic Disease

Hepatic disease or insufficiency increases the risks of lactic acidosis and hypoglycemia and influences the metabolism of many oral medications.

Metformin and thiazolidinediones should not be used if alanine aminotransferase (ALT) is 2.5-3 times normal upper limits.

First-generation sulfonylureas, glipizide and glyburide have some component of hepatic metabolism and should be used with caution because of the risks of hypoglycemia. Insulin would be considered safest.

20. Prescribe Insulin Therapy

- Insulin programs should be individualized based on the patient's lifestyle, treatment goals and self-monitoring blood glucose. Many patients can be taught to interpret self-monitoring blood glucose results and adjust insulin doses *(American Diabetes Association, 2004c [R])*.
- Total dose ranges from 5 units/day to several hundred units/day.
- Average insulin doses are 0.6-0.8 units/kg of body weight per day.
- Obese patients often require doses equal to or exceeding 1.2 units/kg.
- Meal times and snacks should be consistent. Synchronize insulin with food intake patterns.

Time Course of Action of Insulin Preparations

	Insulin Preparations	Onset of Action	Peak Action	Duration of Action	Cost
Short-Acting	Regular	30 min.	2-5 hours	5-8 hours	$$
Rapid-Acting	Lispro	15 min.	30-90 min.	2-4 hours	$$$$
	Aspart	15 min.	1-3 hours	3-5 hours	$$$$
	Glulisine	15 min.	50-100 min.	5 hours	$$$$
Intermediate-Acting	NPH	1-3 hours	6-12 hours	16-24 hours	$$$
Long-Acting	Detemir	1 hour	**	Up to 24 hours	$$$$
	Glargine	1 hour	**	24 hours	$$$$
Mixtures	Humalog® mix (75/25) or Humalog® mix (50/50)	15 min.	30-240 min.	16-24 hours	$$$$
	Novolog® mix (70/30)	15 min.	60-240 min.	16-24 hours	$$$$
	NPH and Regular (70/30; 50/50)	30 min.	2-12 hours	16-24 hours	$$$

Source: Compiled from pdr.net

Cost is based on average wholesale price (AWP) of 30-day supply or one vial of injectible drug.

Cost Indicators:

$	=	$0 - $20
$$	=	$21 - $40
$$$	=	$41 - $60
$$$$	=	$61 - $100
$$$$$	=	$101 - $500
$$$$$$	=	greater than $500

Note: Lente and Ultralente are no longer being manufactured and have been removed from this table.

- This table summarizes the typical time course of action of various insulin preparations. These values are highly variable among individuals. Even in a given patient, these values vary depending on the site and depth of injection, skin temperature and exercise.
- No pronounced peak: small amounts of insulin are slowly released resulting in a relatively constant concentration/time profile over 24 hours.

- Rapid-acting insulin should not be taken more than 15 minutes before meals in contrast to regular insulin, which should ideally be taken at least 30 minutes before a meal to better match the insulin peak action with postmeal hyperglycemia.
- Patients who are testing their glucose before meals and adjusting insulin doses to match meals may find rapid-acting insulin to be more effective, although generally studies have not shown an improvement in A1c when compared to regular insulin taken according to package insert (30-45 minutes preprandial).
- Effective use of rapid-acting insulin usually requires the addition of basal intermediate or long-acting insulin.
- There are several devices available on the market for the administration of insulin (e.g., insulin pump, insulin pen).
- Insulin pump therapy may be helpful for patients who are interested in more intensified management of blood glucose and want more flexibility, or if pregnancy is desired. Candidates for pump therapy should be evaluated by an endocrinologist or diabetes specialist to assess patient understanding, self-care knowledge including medical nutrition therapy, responsibility and commitment. Insulin pump therapy is more commonly used in type 1 patients, but is also being used by some type 2 patients.
- Please note the work group left the brand names for Humalog® and Novolog® in the table. The generic mix is as follows:
  - Humalog mix: lispro protamine suspension/lispro injection
  - Novolog mix: aspart protamine suspension/aspart injection
- Every facility needs to evaluate insulin safety per their specific situation.

22. Prescribe Non-Insulin Agents

Please consult the manufacturer's product labeling insert for full prescribing information.

If not contraindicated, metformin is the preferred initial oral agent for type 2 diabetes due to low cost, low risk of hypoglycemia and side effects, and lack of associated weight gain. If metformin is contraindicated, sulfonylureas and glitazones are acceptable secondary choices for oral agents. Sulfonylureas have the advantage of being relatively inexpensive, and glitazones are contraindicated in congestive heart failure *(Nathan, 2006 [R])*.

For the following tables, cost is based on average wholesale price (AWP) of 30-day supply. Cost Indicators:

$	=	$0 - $20
$$	=	$21 - $40
$$$	=	$41 - $60
$$$$	=	$61 - $100
$$$$$	=	$101 - $500
$$$$$$	=	greater than $500

Metformin

Drug Name (Trade Name)	Usual starting dose	Usual maximum clinically effective dose per day	Maximum dose per day	Cost
Metformin (regular release)	500 mg daily or twice daily	1,000 mg twice daily	2,550 mg daily or 850 mg three times a day	$$*
Metformin (extended release)	500 mg daily with evening meal	2,000 mg daily or 1,000 mg twice daily	2,000 mg daily or 1,000 mg twice daily	$$

EFFICACY

- The A1c lowering commonly achieved with metformin is 1.5%-2.0%.
- Absorption and bioavailability of metformin (extended release) 2,000 mg daily is similar to that of metformin 1,000 mg twice daily. Costs favor the use of metformin for patients who can manage twice-daily dosing.
- The major effect may be reducing hepatic glucose production.

Metformin is indicated for treatment of type 2 diabetes as monotherapy or in combination with sulfonylureas or insulin.

SAFETY

- Metformin is contraindicated in patients with known hypersensitivity, renal disease, congestive heart failure (treated with medications), acute or chronic metabolic acidosis (including diabetic ketoacidosis).
- Do not use metformin in renal disease (creatinine greater than or equal to 1.5 mg/dL in men, creatinine greater than or equal to 1.4 mg/dL in women) because of possible lactic acidosis. In patients over age 80, check a creatinine clearance and use with caution. Even temporary reductions in renal function (e.g., pyelography or angiography) can cause lactic acidosis.
- Do not use for patients with COPD, severe hepatic disease or alcoholism.
- Side effects may be transient and can include metallic taste, diarrhea, nausea and anorexia.
- The use of metformin in pregnancy or lactation is not recommended.
- As monotherapy, metformin does not cause hypoglycemia.
- Intramuscular contrast studies with indicated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Therefore, metformin should be temporarily discontinued at the time or prior to any such study and withheld for 48 hours subsequent to the procedure. Reinstitute only after renal function has been reevaluated and found to be normal.

Source: Compiled from pdr.net

* Average wholesale price indicates a cost of $$; however, regionally this product is available for $.

Second-Generation Sulfonylureas

Drug Name (Trade Name)	Duration	Usual starting dose	Usual start dose for elderly	Usual maximum clinically effective dose	Maximum dose per day	Cost
Glimepiride	24 hr.	1-2 mg/d	1-2 mg/d	4 mg/d	8 mg/d	$
Glipizide (regular release)	10-24 hr.	5 mg/d	2.5 mg/d	10 mg twice daily	40 mg/d	$
Glipizide (extended release)	24 hr.	5 mg/d	5 mg/d	10 mg/d	20 mg/d	$
Glyburide (regular release)	18-24 hr.	2.5 mg-5 mg/d	1.25 mg/d	5 mg twice daily	20 mg/d	$
Glyburide (micronized)	18-24 hr.	1.5-3 mg/d	0.75 mg/d	6 mg twice daily	12 mg/d	$

EFFICACY

- The A1c lowering commonly achieved with sulfonylureas is 1.5%-2.0%.
- The dose should be increased every one to two weeks until satisfactory glycemic control or the maximum dose is reached.
- There are no major differences between sulfonylureas with respect to effectiveness in controlling hyperglycemia. Switching from one to another is rarely beneficial in improving hyperglycemia.

SAFETY

- These agents are contraindicated in diabetic ketoacidosis and in patients with known hypersensitivity to sulfonylureas.
- There are rare cross-sensitivities for patients with sulfa allergies.
- These agents should be used with caution for patients with hepatic or renal disease.
- Glipizide/or glimepiride may be relatively safer than glyburide patients with mild renal impairment.
- Hypoglycemia risk increases with impaired renal function. Glimepiride may cause less hypoglycemia in these circumstances.
- Glyburide has the highest rate of hypoglycemia of the sulfonylureas listed.

Source: Compiled from pdr.net

Alpha Glucosidase Inhibitors

Drug Name (Trade Name)	Usual starting dose	Maximum dose per day	Cost
Acarbose	25 mg daily	50 mg three times a day for patients weighing less than or equal to 60 kg 100 mg three times a day for patients weighing greater than 60 kg	$$$$
Miglitol	25 mg daily	100 mg three times a day	$$$$

EFFICACY

- The A1c lowering commonly achieved with alpha glucosidase inhibitors is 0.5%-1.0%.
- These agents are most appropriate in patients with glucose and glycosylated hemoglobin only moderately above goal.
- These agents delay carbohydrate absorption, which reduces postprandial blood glucose, and reduces insulin levels.
- These agents must be taken at the beginning of a meal to be effective.
- These agents are indicated for treatment of type 2 diabetes as monotherapy and as combination therapy (miglitol with sulfonylureas, acarbose with sulfonylureas, metformin or insulin).

SAFETY

- These agents are contraindicated in patients with known hypersensitivity, serum creatinine levels greater than 2 mg/dL, abnormal baseline liver function tests, and inflammatory bowel disease.
- Absorbed metabolites of acarbose may rarely cause elevated transaminase levels. Monitor transaminase levels every three months for one year, and periodically thereafter.
- Side effects may include abdominal cramping, flatulence and diarrhea. Tolerance develops, so start with low dose and increase gradually.
- As monotherapy, these agents do not cause hypoglycemia.

Source: Compiled from pdr.net

Dipeptidyl Peptidase-4 (DPP-4) Inhibitor

Drug Name (Trade name)	Usual starting dose	Usual maximum clinically effective dose	Maximum dose per day	Cost
Sitagliptin	100 mg once daily	100 mg once daily	100 mg once daily	$$$$$

EFFICACY

- Slows the inactivation of incretins, hormones that are normally released in the gut throughout the day and increased after meals. Incretins increase insulin release from pancreatic beta cells, and lower glucagon secretion from pancreatic alpha cells.
- Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
- The A1c lowering commonly achieved with sitagliptin is 0.6-0.8 mg/dL.
- Sitagliptin is indicated for monotherapy and as combination therapy (metformin, glimepiride, glimepiride plus metformin, or a TZD).
- Sitagliptin has not been studied in combination with insulin.
- Can be taken with or without food.

SAFETY

- Dosage adjustment is recommended in patients with moderate or severe renal insufficiency and in patients with ESRD. Assessment of renal function is recommended prior to initiating sitagliptin and periodically thereafter.
    - Moderate renal disease (start 50 mg once daily): CrCl ≥ 30 to < 50 mL/min; ~Serum Cr levels [mg/dL] – Men: > 1.7– ≤ 3.0; Women: > 1.5 - ≤ 2.5
    - Severe and ESRD (start 25 mg once daily): CrCl < 30 mL/min: ~Serum Cr levels [mg/dL] – Men: > 3.0; Women: > 2.5; or on dialysis
- When used with a sulfonylurea, a lower dose of sulfonylurea may be required to reduce the risk of hypoglycemia.
- Side effects reported in more than 5% of patients and more often than placebo were nasopharyngitis, upper respiratory tract infections, and headache.
- Safety and effectiveness of sitagliptin in children under 18 years have not been established.
- There are no adequate and well-controlled studies in pregnant women.
- Hypoglycemia was similar to placebo (1.2% versus 0.9%).
- Studies addressing long-term safety are not available.

Source: Compiled from pdr.net

Meglitinides (Short-Acting Secretagogues)

Drug Name (Trade Name)	Usual starting dose	Maximum dose per day	Cost
Repaglinide	0.5 mg/meal with A1c less than 8% or no previous treatment 1 or 2 mg/meal with A1c greater than 8% or on other oral agent	4 mg/meal or 16 mg/day	$$$$$
Nateglinide	60-120 mg three times a day before meals	120 mg/meal/day	$$$$$

EFFICACY

- The average A1c lowering commonly achieved is 0.5%.
- The mechanism of action of these agents is to stimulate insulin secretion (similar to sulfonylureas).
- These agents have a short duration of action, one to four hours.
- These agents are usually taken 15 minutes before meals (range of 0-30 minutes).
- These agents are indicated for use in combination with metformin or TZDs.

SAFETY

- The major side effect of these agents is hypoglycemia, but the incidence may be less common than with sulfonylureas.
- Skip the dose if the meal is not eaten.
- Doses of nateglinide should be adjusted for hepatic impairment.
- Administration of gemfibrozil significantly increases repaglinide blood levels, which may lead to hypoglycemia. Avoid concomitant use of gemfibrozil and repaglinide.

Source: Compiled from pdr.net

Glucagon-like Peptide 1 (GLP-1) Agonist:

Drug Name (Trade Name)	Indications	Onset of action	Peak action	Duration of action	Usual starting dose	Maximum dose per day	Cost
Exenatide injection	Type 2	0-10 min.	2.1 hrs.	6-10 hrs.	5 mcg subcutaneous twice daily	10 mcg subcutaneous twice daily after one month	$$$$$

Mechanism of Action

- Stimulates glucose-dependent release of insulin and suppresses glucagons levels.
  1. Modulation of gastric emptying
  2. Prevention of the postprandial rise in plasma glucagons
  3. Satiety leading to decreased caloric intake and potential weight loss

EFFICACY

- Intended for people with type 2 diabetes who are on oral medication but not achieving good blood sugar control. Offers an alternative option before starting insulin.
- Must be administered within the 60-minutes **before** the morning and evening meals. It **should not** be administered after a meal.
- When this agent is added to sulfonylurea therapy, a reduction in the dose of sulfonylurea may be needed to reduce the risk of hypoglycemia.
- Advantages over insulin are yet unclear, since like insulin, it must be injected twice daily.
- Improves A1c by an average of 0.9% and lowers postprandial glucose.

SAFETY

- Contraindicated in patients with known hypersensitivity to this product or any of its components.
- Is not a substitute for insulin in insulin-requiring patients.
- Should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.
- Not recommended for use in patients with ESRD or severe renal impairment (CrCl less than 30 mL/min).
- Not recommended in patients with severe gastrointestinal disease because its use is commonly associated with gastrointestinal adverse effects, including nausea, vomiting and diarrhea.
- Caution in patients receiving oral medications that require rapid gastrointestinal absorption.
- For oral medications that are dependent on threshold concentrations for efficacy, such as contraceptives and antibiotics, patients should be advised to take those drugs at least one hour before exenatide injection.
- Weight loss is often associated with use of this agent, especially when used concomitantly with metformin.
- Exenatide use has been associated with reports of pancreatitis, although a causal relationship has not to this point been established.

Source: Compiled from pdr.net

Synthetic Analog of Human Amylin

Drug Name (Trade Name)	Indications	Onset of action	Peak action	Duration of action	Usual starting dose	Maximum dose per day	Cost
Pramlintide acetate injection	Type 1 and 2 diabetes	15-30 min.	20-27 min.	3-4 hrs.	**Type 2** : 60 mcg subcutaneous/ meals	**Type 2** : 120 mcg subcutaneous	$$$$$

Mechanism of Action

- Acting as an amylinomimetic agent has the following effects:
  1. Modulation of gastric emptying
  2. Prevention of the postprandial rise in plasma glucagons
  3. Satiety leading to decreased caloric intake and potential weight loss

EFFICACY

- Indicated as an adjunct treatment in patients with type 1 or type 2 diabetes who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy, and it is used with or without a sulfonylurea and/or metformin.
- May decreases A1c by an average of 0.4% and may observe weight loss of less than 1 kg at six months.
- Must be administered immediately prior to each major meal.
- Reduce preprandial, rapid-acting or short-acting insulin dosages, including fixed-mix insulins by 50%.
- The agent may be considered in highly motivated patients willing to add two to four injections and more frequent glucose monitoring to their regimen.

SAFETY

- Contraindicated in patients with a known hypersensitivity to any of its components, including metacresol.
- Should only be considered in patients with insulin-using type 2 or type 1 diabetes who have failed to achieve adequate glycemic control despite individualized insulin management and are receiving ongoing care under the guidance of a health care professional skilled in the use of insulin and supported by the services of diabetes educator(s).
- Before initiation of therapy, A1c, recent glucose monitoring data, history of insulin-induced hypoglycemia, current insulin regimen, and body weights should be reviewed.
- Patients meeting any of the following criteria **should not** be considered for pramlintide therapy:
  - Poor adherence with current insulin regimen
  - Poor adherence with prescribed self-blood glucose monitoring
  - A1c greater than 9%
  - Recurrent severe hypoglycemia requiring assistance during the past six months
  - Presence of hypoglycemia unawareness
  - Confirmed diagnosis of gastroparesis
  - Require the use of drugs that stimulate gastrointestinal motility
  - Require the use of drugs that slow the intestinal absorption of nutrients
  - Pediatric patients
- Primlintide alone does not cause hypoglycemia (without the concomitant administration of insulin). However, when it is co-administered with insulin therapy, there is an increase risk of insulin-induced severe hypoglycemia. Therefore, prescribe frequent pre- and postmeal glucose monitoring combined with an initial 50% reduction in premeal doses of short-acting insulin when starting pramlintide to reduce the occurrence of hypoglycemia.
- Its use is commonly associated with gastrointestinal adverse effects, including nausea, anorexia and vomiting.
- When the rapid onset of a concomitant orally administered agent is a critical determinant of effectiveness, the agent should be administered at least one hour prior to two hours after primlintide injection.
- This product and insulin should always be administered as separate injections and never be mixed. Mixing will alter the pharmacokinetics parameters of primlintide.

Source: Compiled from pdr.net

Thiazolidinediones (TZDs)

Drug Name (Trade Name)	Usual starting dose	Maximum dose per day	Cost
Pioglitazone	15 or 30 mg once daily	45 mg daily	$$$$$
Rosiglitazone	2 mg daily or twice daily	4 mg twice daily or 8 mg daily	$$$$$

EFFICACY

- The A1c lowering commonly achieved with thiazolidinediones is 1.0%-1.5%.
- TZDs improve insulin action in peripheral tissues, particularly muscle.
- Both pioglitazone and rosiglitazone are indicated for combination therapy with sulfonylureas, metformin.
- Both LDL and HDL cholesterol concentrations may increase slightly.
- Rosiglitazone may increase cardiovascular events and is not recommended.
- When a thiazolidinedione is used, pioglitazone is preferred due to concerns about rosiglitazone cardiovascular safety in observational analysis.

SAFETY

- Thiazolidinediones are contraindicated in patients with known hypersensitivity. Their use in pregnancy and lactation is not recommended.
- TZDs alone, or in combination with other antidiabetic agents including insulin, can cause fluid retention, which may lead to heart failure. Do not use in patients with moderate to severe heart failure (NYHA Class III and IV cardiac status).
- Side effects may include moderate weight gain, edema and mild anemia, all due, at least in part, to fluid retention.
- As monotherapy, TZDs do not cause hypoglycemia.
- Measure ALT at baseline and periodically thereafter.
- Administration of gemfibrozil increases plasma levels of rosiglitazone. Decreases in the dose of rosiglitazone may be needed when gemfibrozil is added.
- Meta-analysis showed rosiglitazone may be associated with an increase in the risk of myocardial infarction and death from cardiovascular causes.
- Pioglitazone may not have the same cardiovascular concerns as rosiglitazone *(Dormandy, 2005 [R])*
- Macular edema has been reported in postmarketing experience in some diabetic patients who were taking thiazolidinedione.
- The risk of fracture should be considered in the care of patients, especially female patients, treated with thiazolidinedione.
- Physicians and patients should have an informed discussion around the risks of rosiglitazone.

Source: Compiled from pdr.net and FDA Warning 11/19/2007.

Combination Products

Combination type	Fixed dose combination (mg)	Usual start dose (mg)	Maximum dose per day	Cost
Sulfonylurea + metformin	Glipizide/metformin 2.5/250, 2.5/500, 5/500	As initial treatment: 2.5/250 daily As second-line treatment: 2.5/500 or 5/500 twice daily	As initial treatment: 10 mg/2,000 mg As second-line treatment: 20 mg/2,000 mg	$$
Sulfonylurea + metformin	Glyburide/metformin 1.25/250, 2.5/500, 5/500	As initial treatment: 1.25/250 daily or twice daily As second-line treatment: 2.5/500 or 5/500 twice daily	20 mg/2,000 mg	$$
TZD + metformin	Pioglitazone/ metformin 15/500, 15/850	Not recommended as initial treatment; one tab PO daily or twice daily if on metformin monotherapy; 15 mg/500 mg by mouth twice daily or 15 mg/850 mg by mouth daily if on pioglitazone monotherapy	45 mg/ 2,550 mg/day	$$$$
TZD + metformin	Rosiglitazone/ metformin 1/500, 2/500, 4/500, 2/1,000, 4/1,000	Not recommended as initial treatment	8 mg/2,000 mg	$$$$
TZD + sulfonylureas	Pioglitazone/glimerpiride 30/2, 30/4	Not recommended as initial treatment; 30/2 or 30/4 by mouth daily	45 mg/ 8 mg/day	$$$$$
TZD + sulfonylureas	Rosiglitzone/ glimerpiride 4/1, 4/2, 4/4	Not recommended as initial treatment; 4/1 or 4/2 by mouth daily	8 mg/4 mg/day	$$$$$
DDP-IV inhibitor + metformin	Sitaglipton/metformin 50/500, 50/1,000	As adjunct for patients in adequately controlled on metformin monotherapy: 50 mg sitaglipton plus current dose of metformin twice daily	100 mg/2,000 mg/day	$$$$$

Source: Compiled from pdr.net

25. Intensify Therapy

If treatment goals are not met on oral agents, or if oral agents are contraindicated, then it is necessary to begin insulin either alone or as an adjunct to oral therapy. There are many regimens that have been studied and are efficacious *(Aviles-Santa, 1999 [A]; Relimpio, 1998 [A]; Yki-Järvinen, 1999 [A]; Zimmerman, 1998 [R])*. The following are some commonly used regimens.

Insulin as an adjunct to oral therapy:

- A once-daily (often at bedtime) dose of NPH, detemir or glargine insulin is added to metformin or thiazolidinediones. The recommended starting dose of basal insulin is often 0.1 U/kg, based on body weight. The basal insulin should be increased by two units every three days that blood glucoses in the a.m. remain above target. While adusting the basal insulin dose, the blood glucose should be monitored twice daily to three times daily to monitor glucose values and prevent hypoglycemic episodes. If patient is also on a sulfonylurea, it may be discontinued or reduced when insulin is added.
- A once-daily (often at bedtime) dose of insulin (as above) is added to sulfonylurea. The dose of the sulfonylurea may be reduced (approximately 50%) when insulin is added. The basal insulin should be increased by two units every three days that blood glucoses in the a.m. remain above target. While adjusting the basal insulin dose, the blood glucose should be monitored twice daily to three times daily to monitor glucose values and prevent hypoglycemic episodes. It must be noted that glargine or detemir may be dosed in the a.m. or p.m. Morning dosing may prevent nighttime hypoglycemic episodes and may also provide for improved blood glucose control.

Insulin alone:

- Twice-daily insulin regimen is established with progression to increased frequency of insulin administration as necessary to achieve treatment goals or to add flexibility to a patient's meal and activity schedules. Multiple dose insulin with rapid-acting and basal insulin therapy may offer patients with active lifestyles the greatest flexibility.
- One method of starting multidose insulin is to use a total daily dose of .2-.4 units/kg and prescribe half the dose as glargine once a day (morning or bedtime) and the other half as rapid acting insulin with meals (split appropriately according to the patient's frequency and pattern of meal sizes and/or carbohydrate consumption).

Oral agents as an adjunct to insulin therapy:

- Metformin may be helpful as an adjunct for patients who require large doses of insulin (e.g., greater than 100 units/day).

Blood Pressure Control Algorithm Annotations

26. Blood Pressure Control Algorthim

Control of blood pressure is at least as important as glycemic control for people with type 2 diabetes in reducing the risk of complications *(Alder, 2000 [B]; Estacio, 2000 [A])*.

SHEP, Syst-Eur and HOT trials all showed a greater absolute benefit from antihypertensive therapy in people with diabetes than in hypertensive people without diabetes *(Hansson, 1998 [A]; SHEP Cooperative Research Group, 1991 [A]; Tuomilehto, 1999 [A])*.

27. Is Systolic Blood Pressure Greater Than or Equal to 130 mmHg?

For patients with type 2 diabetes mellitus, the systolic blood pressure goal is less than 130 mmHg and the diastolic blood pressure goal is less than 80 mmHg *[Conclusion Grade II: See Conclusion Grading Worksheet D – Annotations #13, 14, 27, 29 (Goals for Blood Pressure)] (Hansson, 1998 [A]; United Kingdom Prospective Diabetes Study [A], 1998c; UK Prospective Diabetes Study, 1998e [A])*.

A report from the UK Prospective Diabetes Study Group study showed an inverse relationship between systolic blood pressure and the aggregate end point for any complication related to diabetes *(United Kingdom Prospective Diabetes Study Group (UKPDS), 1998e [R]*. The lowest risk occurred at a systolic blood pressure below 120 mmHg.

The goal for patients with renal insufficiency and urinary protein excretion greater than 1-2 g/day should be less than 120/75 mmHg *(American Diabetes Association, 2004c [R])*.

28. Treat Systolic Blood Pressure to Less Than 130 mmHg. While ACE Inhibitors and ARBs Are Preferred First-Line Therapy, Two or More Agents (to Include Thiazide Diuretics) May Be Required

Non-pharmacologic and pharmacologic methods are recommended at blood pressures greater than or equal to 130/80 mmHg. The initial focus of treatment should be the systolic blood pressure.

For patients with type 2 diabetes mellitus, ACE inhibitors or ARBs can reduce progression of micro- and macrovascular complications. *[Conclusion Grade I: See Conclusion Grading Worksheet F – Annotations #28, 36 (Treatment with ACE Inhibitors or ARBs)] (HOPE Investigators, 2000a [A]; Lewis, 2001 [A])*.

While ACE inhibitors and ARBs are preferred first-line therapy, two or more agents (to include thiazide diuretics) may be required. For patients with type 2 diabetes mellitus, thiazide diuretics in the treatment of hypertension can reduce cardiovascular events, particularly heart failure. *[Conclusion Grade I: See Conclusion Grading Worksheet G – Annotations #28, 36 (Thiazide Diuretics)] (ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, 2002 [A]; Wing, 2003 [B])*. The possible advantages to ACE inhibitors include renal protection, decreased insulin resistance, lack of adverse effect on lipids, and decreased cardiovascular risk.

In ALLHAT, chlorthalidone, at doses of 12.5 to 25 mg daily, was superior to other treatments at reducing cardiovascular events in both diabetic and non-diabetic patients.

Treatment of isolated systolic hypertension, as well as combined systolic and diastolic hypertension, in both young and elderly people protects against major cardiovascular diseases. Drug treatment should be initiated if systolic blood pressure is greater than or equal to 130 mmHg *(Bakris, 2000 [R])*.

Thiazide diuretics used in the treatment of hypertension can reduce cardiovascular events, especially heart failure, for patients with type 2 diabetes *(Alkaharouf, 1993 [D]; American Diabetes Association, 2007c [R]; Chobanian, 2003 [R]; HOPE Investigators, 2000a [A]; Lewis, 1993 [A])*.

29. Is Diastolic Blood Pressure Less Than 80 mmHg?

For patients with type 2 diabetes mellitus, the systolic blood pressure goal is less than 130 mmHg and the diastolic blood pressure goal is less than 80 mmHg *[Conclusion Grade II: See Conclusion Grading Worksheet D – Annotations #13, 14, 27, 29 (Goals for Blood Pressure)] (Hansson, 1998 [A]; United Kingdom Prospective Diabetes Study [UKPDS] Group, 1998c [A]; United Kingdom Prospective Diabetes Study [UKPDS] Group, 1998e [A])*.

The HOT trial provides evidence that a target diastolic blood pressure less than 80 mmHg has a cardioprotective effect in people with diabetes. This study reported that in the diabetic subgroup (n=1,501) major cardiovascular events were reduced by greater than 51% (p=0.005) in those randomized to a diastolic blood pressure goal of less than 80 mmHg compared to less than 90 mmHg. The HOT study has been criticized by some because this was a post hoc analysis of a subgroup of patients in the study and the number of events is relatively small. Nevertheless, results are consistent with United Kingdom Prospective Diabetes Study. United Kingdom Prospective Diabetes Study achieved an average diastolic blood pressure of 82 mmHg in the tightly controlled

group (vs. 87 mmHg in the less tightly controlled group). The more tightly controlled group had diabetes related end points reduced by 24% (p=0.005) and death by 32% (p=.019) *(United Kingdom Prospective Diabetes Study Group, 1998b [A])*.

31. Treat Diastolic Blood Pressure to Less Than 80 mmHg

Combinations of medications are often required to achieve goals. Thirty percent of patients in the tight blood pressure arm of the United Kingdom Prospective Diabetes Study with goal less than 150/85 mmHg required three or more antihypertensive medications to achieve the mean 144/82 mmHg. Findings from the ALLHAT study suggest that thiazide diuretics be considered as part of a multidrug regimen *(United Kingdom Prospecitve Diabetes Study [UKPDS] Group, 1998a [M]; ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, 2002 [A])*.

Ongoing Management Algorithm Annotations

33. Ongoing Management and Follow-Up of People with Diabetes

In studies of general population groups, coronary artery disease deaths have been substantially reduced by the treatment of hypertension, hypercholesterolemia and smoking. Lipid treatment has also been shown to be of benefit in diabetes. Therefore, risk factor reduction is prudent for patients with diabetes *(American Diabetes Association, 2007c [R]; Hansson, 1998 [A])*.

- Frequency of visits depends on blood glucose control, changes in the treatment regimen, and presence of complications of diabetes or other medical conditions.
- Patients starting or having a major change in their treatment program (such as initiating insulin therapy) may need to be in contact with their care provider as often as daily until glucose control is achieved, the risk of hypoglycemia is low, and the patient is competent to conduct the treatment program.
- Contact with the patient after a major modification of the treatment plan (such as introducing a new medication) should not be delayed greater than one week.
- Regular visits should be scheduled for insulin-treated patients at least quarterly and for other patients at least semiannually. More frequent visits may be necessary if treatment goals are not achieved.
- Cardiovascular disease is the primary cause of morbidity and mortality in people with type 2 diabetes. The risk of coronary artery disease is approximately doubled in men and quadrupled in women with diabetes.
- At each encounter, ask if the patient has experienced symptoms of hypoglycemia or low blood glucose, and educate the patient on appropriate recognition, prevention and management.
- If the patient has a history of severe hypoglycemia (assistance of another person was needed to treat a low glucose) or has developed hypoglycemia unawareness, evaluate the treatment goals for appropriate safety.

34. Maintain Treatment Goals

- Nutrition/physical activity: work with individual patients regularly to set realistic goals.
- Monitor A1c every three to six months. In insulin-treated patients and non-insulin-treated patients with poor metabolic control, quarterly A1c may assist management.
    - Review blood glucose at all patient encounters. Reinforce blood glucose targets with patients and educate regarding hypoglycemia.

- Monitor lipid profile yearly (total cholesterol, triglycerides, high-density lipoprotein-cholesterol and low-density lipoprotein-cholesterol): treat to achieve recommended goals (see Annotation #13, "Treatment Goals for Patients Without Cardiovascular Disease"). If lipid goals are consistently met, patient is in metabolic control, has stable clinical conditions, and has not had a change in medication, an annual lipid profile is not mandatory.

  Diabetes is a major risk factor for coronary artery disease, and many patients with diabetes also have lipid disorders (*American Diabetes Association, 2004a [R])*. Thus, control of dyslipidemia in diabetes is important because evidence shows that correcting lipid disorders reduces the rate of coronary artery disease events.

- Monitor blood pressure each visit and control hypertension to recommended levels. See the Blood Pressure Control algorithm.

- Ask about aspirin use and recommend aspirin use in patients age 40 and over unless contraindicated *(American Diabetes Association, 2007c [R])*.

- Ask about alcohol and tobacco use and assist with cessation if indicated.

35. Annual Assessment of Complications

Targeted Annual History and Physical Exam

- The history should assess *(American Diabetes Association, 2007c [R])*:
  - Results of self-monitoring blood glucose – validate results at least once a year (e.g., check patient's glucose meter against an office random capillary glucose)
  - Adjustments by the patient of the therapeutic regimen
  - Frequency, causes and severity of both hyperglycemia and hypoglycemia
  - Problems with adherence to therapeutic regimen
  - Symptoms suggesting development or progression of the complications of diabetes
  - Current prescribed medications, over-the-counter medications, dietary supplements and alternative therapies
  - Documentation of eye care specialist exam results
  - Alcohol/drug use patterns
- Assess for symptoms of depression
  - Lab assessment of liver function and/or creatinine to assess ongoing acceptability of medication usage
- The targeted physical exam should assess:
  - Weight, body mass index
  - Blood pressure
  - Cardiovascular – evaluation of preexisting problems
  - Feet (nails, web spaces, calluses, ulcers, structural deformities, protective sensation and shoes)

Specialist Dilated Eye Exam

A dilated eye examination for diabetic eye disease performed by an ophthalomologist or optomostrist is recommended annually for patients with type 2 diabetes mellitus *(American Diabetes Association, 2007c [R])*. Less frequent exams (every two to three years) may be considered in the setting of a normal eye exam.

Renal Assessment

Urinary albumin excretion should be tested annually by a microalbuminuria method. There are racial/ethnic variability with regard to the prevalence of end-stage renal disease with Native Americans, Latinos (especially Mexican Americans), and African Americans having higher rates than non-Hispanic whites with type 2 diabetes *(American Diabetes Association, 2004d [R])*. If albuminuria is above normal, serum creatinine should be measured. Screening for microalbuminuria can be performed by three methods *(American Diabetes Association, 2004d [R]; Nelson, 1991 [B]; Bennett, 1995 [R])*:

- Measurement of the albumin-to-creatinine ratio in a random, spot collection. This is easiest to perform, generally accurate and therefore is the preferred screening method.
- 24-hour collection with creatinine, allowing for simultaneous measurement of creatinine clearance
- Timed (four-hour or overnight) collection

Some factors can artificially increase the levels of albumin in the urine and should be avoided at the time of the urine collection; these factors include blood in the urine, prolonged heavy exercise, fever, congestive heart failure, uncontrolled diabetes, severe hypertension, urinary tract infection and vaginal fluid contamination of specimen.

If the dipstick or urine analysis test is negative for protein, then a more sensitive early screening test is indicated. A qualitative urinary microalbumin screen can be used to detect urinary microalbumin. If the qualitative test is positive, a quantitative test must be performed.

A microalbumin screening test should be done each year on patients with type 2 diabetes. If positive (exceeds 30 mg/gm), it should be repeated twice in the next three months.

If two out of three of these screening microalbuminuria tests are positive, the individual has microalbuminuria, and interventions should be considered. A negative finding should be followed annually; a positive finding should be followed periodically to see if the interventions are effective in diminishing the albuminuria *(Bennett, 1995 [R]; Hannah, 1999 [R]; Mogensen, 1996 [R]; National Institutes of Health, 1993 [R])*.

See Appendix A, "Treatment of Diabetic Nephropathy."

Comprehensive Foot Exam with Risk Assessment

Patients with one or more risk factors for foot complications should be educated about their risk factors and appropriate measures taken to avoid complications. Measures may include self-management education, more intensive follow-up, and/or referral to appropriate specialist *(American Diabetes Association, 2007c [R]; Mayfield, 1998 [R])*.

Risk factors for foot complications include:

- Loss of protective sensation. Protective sensation can be assessed using either a 5.07 Semmes-Weinstein monofilament for light touch or by testing vibration using a 128-Hz tuning fork at the dorsum of the interphalangeal joint of the great toe, or both. Patients with reduced or absent sensation with either of these tests should be educated about their risk and the need for proper foot care to prevent foot complications. See Appendix B, "Using a Semmes-Weinstein Monofilament to Screen the Diabetic Foot for Peripheral Sensory Neuropathy."

- Peripheral vascular disease (absent pedal pulse, history of claudication or ischemic skin changes)
- Structural deformities (bunion, hammertoes, Charcot deformity, limited joint mobility or prior amputation)
- Skin disorders (nail deformity, callus, fissure, tinea or ulceration)
- Footwear (excessively worn, ill-fitting or inappropriate shoes)

Cardiovascular and Cerebrovascular Complication Assessment

- History of cardiovascular symptoms such as chest pain, vascular claudication, TIA
- Cardiac and carotid exams
- Evaluate cardiovascular status before advising increased intensity of exercise *(American Diabetes Association, 2004e [R]; Sigal, 2004 [R])*.

Special Considerations

- Influenza vaccine every year
- Pneumococcal vaccine – consider repeating the immunization for those at risk of losing immunity after five years including:
  - Nephrotic syndrome
  - Chronic renal disease
  - Other immunocompromised states
- There is evidence that ACE inhibitors and ARBs are beneficial in reducing cardiovascular morbidity and mortality in acute MI, congestive heart failure and type 2 diabetes patients at high risk for cardiovascular disease; they are also beneficial in improving renal outcomes in diabetes. Results of the HOPE (Heart Outcomes Prevention Evaluation) study strongly support the use of ACE inhibitors for patients with diabetes who are at high risk for cardiovascular disease. In the Second Australian National Blood Pressure Study (ANblood pressure2), the use of ACE inhibitors in older patients was associated with better cardiovascular outcomes, despite similar reductions in blood pressure from diuretics. Confirming studies would be helpful to strengthen this recommendation or to generalize recommendations to all patients with diabetes *(HOPE Investigators [A], 2000a; Wing, 2003 [A])*.
- Vitamin E has no apparent effect on cardiovascular outcomes *(HOPE Investigators, 2000b [A])*.
- Osteoporosis: Type 2 diabetes does not appear to be a risk factor for decreased bone mineral density; nonetheless, some studies have found an increased fracture risk for people with type 2 diabetes *(Schwartz, 2001 [B])*. Hypoglycemic episodes, decreased visual acuity secondary to retinopathy, and altered balance and postural control secondary to peripheral and autonomic neuropathy can all increase the risk of falls and fracture.

  In the absence of diabetes specific osteoporosis screening guidelines, it is reasonable to follow general osteoporosis screening recommendations for people with diabetes. See the ICSI Diagnosis and Treatment of Osteoporosis guideline for more information.

36. Treatment and Referral for Complications

Nephropathy

In type 2 diabetes, albuminuria may be present at the time of diagnosis in about 10% of patients, and another 10% later develop it. Progression to renal failure is less certain in type 2 patients than in type 1 patients and appears to be modulated by genetic and other factors.

Patients with clinical nephropathy almost always have retinopathy and coronary artery disease.

Numerous interventions are appropriate at different stages of renal function in order to prevent or slow the progression of renal disease and associated cardiovascular disease and include *(American Diabetes Association, 2004d [R]:*

- Glucose Control – Improved glucose control at any stage of renal function reduces renal disease progression. See the Glycemic Control algorithm.
- For patients with type 2 diabetes mellitus, ACE inhibitors or ARBs can reduce progression of micro- and macrovascular complications. *[Conclusion Grade I: See Conclusion Grading Worksheet F – Annotations #28, 36 (Treatment with ACE Inhibitors or ARBs)] (HOPE Investigators, 2000a [A]; Lewis, 2001 [A])*. These agents appear effective even in normotensive microalbuminuric individuals. This class of drugs must not be used in pregnancy. Within one week of initiation, check for elevations in potassium and creatinine levels and monitor for cough.
- Hypertension Control – Although ACE inhibitors and ARBs seem to have special renal protective properties beyond their antihypertensive effect, any effort to optimize blood pressure will help the kidneys. When significant microalbumin or overt nephropathy are present, there may be a tendency to retain sodium. In this case, a loop diuretic added to the antihypertensive regimen is often helpful. A goal blood pressure of less than 130/80 mmHg is recommended (*American Diabetes Association, 2007c [R])*. See the Blood Pressure Control algorithm.

  For patients with type 2 diabetes, thiazide diuretics in the treatment of hypertension can reduce cardiovascular events, particularly heart failure. *[Conclusion Grade I: See Conclusion Grading Worksheet G – Annotations #28, 36 (Thiazide Diuretics)] (ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, 2002 [A]; Wing, 2003 [B])*.

  In ALLHAT, chlorthalidone, at doses of 12.5-25 mg daily, was superior to other treatments at reducing cardiovascular events in both diabetic and non-diabetic patients.
- Cardiovascular Risk Factor Intervention – Dyslipidemia is often present with microalbuminuria and should be treated aggressively. Dyslipidemia may be an independent risk factor for progression of renal disease. Smoking is associated with the onset and progression of microalbuminuria.
- Restriction of dietary protein has been shown to slow progression of overt nephropathy (macroalbuminuria), and there may be some benefit in dietary protein reduction in microalbuminuric patients. In these circumstances, protein intake should be reduced to the adult recommended daily allowance of 0.8-1.0 g/kg body weight per day with microalbuminuria present, and 0.8 gm/kg body weight per day with macroalbuminuria present (*American Diabetes Association, 2007b [R])*.

  Treatment for microalbuminuria includes aggressive blood pressure control, glycemic control, ACE inhibitor or ARB use, and aggressive cardiovascular risk factor screening and management. Strongly consider referral to nephrology any patients with a creatinine greater than 1.5 mg, or nephrotic range proteinuria (greater than 3 gm/24 hour). Nephrology interventions often include early patient education as renal disease progresses, review and reinforcement of the medical regimen, and preservation of arm veins for future vascular access. Patients with a creatinine clearance of less than 30 mL/min should be referred to nephrology for discussions of future options and to enhance

the ability to receive a future transplant. These patients also have significant enough renal impairment that they also benefit from more intensive nutritional interventions and proper management of anemia and bone disease *(American Diabetes Association, 2004d [R]; DeFronza, 1995 [R]; HOPE Investigators, 2000a [A]; Karter, 2002 [B]; Lewis, 1993 [A]; Lewis, 2001 [A]; Ravid, 1993 [A]; Viberti, 1994 [A])*.

Neuropathy – Peripheral neuropathy is difficult to prevent and treat. Most patients with type 2 diabetes and peripheral neuropathy have few symptoms but are found on examination to have diminished reflexes and sensation. Sometimes neuropathy can be very painful, especially at night, with "pins-and-needles" numbness and tingling in a stocking-and-glove distribution. Absence of reflexes or decreased thermal, vibratory, proprioceptive or pain sensation may be noted on examination and confirm the diagnosis. Good glycemic control should be the first control to symptomatic neuropathy. Treatment with amitriptyline, nortriptyline or trazodone in doses beginning at 25 mg at night and increasing to 75 mg may help some patients. Topical treatment with capsaicin, 0.025% cream three to four times per day, has also shown benefit. Carbamazepine, duloxetine and gabapentin may also improve neuropathic pain. These medications may provide symptomatic relief, but they do not improve the neuropathy *(Boulton, 2005 [R])*.

Retinopathy – Prevalence of retinopathy is related to the duration of diabetes mellitus. After 20 years of type 2 diabetes mellitus, more than 60% of patients have some degree of retinopathy *(Fong, 2004 [R])*. Diabetic retinopathy is estimated to be the most frequent cause of new cases of blindness among adults ages 20 to 74 years.

Up to 21% of patients with type 2 diabetes mellitus are found to have retinopathy at the time of diagnosis of diabetes mellitus *(Fong, 2004 [R])*. Generally retinopathy progresses from mild background abnormalities to preproliferative retinopathy to proliferative retinopathy.

Poor glucose control is associated with progression of retinopathy. High blood pressure is a risk factor for the development of macular edema and is associated with the development of proliferative retinopathy *(Fong, 2004 [R])*.

Screening for diabetic retinopathy saves vision at a relatively low cost. In fact, screening costs may be less than the costs of disability payments for those who become blind. Laser photocoagulation surgery is effective in preventing visual loss in diabetic retinopathy.

Studies have shown that retinal examinations by physicians who are not eye care specialists are not reliable in detecting retinopathy *(American College of Physicians, American Diabetes Association, and American Academy of Ophthalmology, 1992 [R]; Diabetic Retinopathy Study Research Group, The, 1981 [R]; ETDRS Research Group, 1985 [A]; ETDRS Research Group, 1991 [A]; Fong, 2004 [R]; Klein, 1984 [C]; Klein, 1987 [R])*.

Treatment includes glycemic and blood pressure control. Periodic screening and dilated eye exams by an eye specialist and early treatment of diabetic retinopathy prevents visual loss *(Fong, 2004 [R])*. See the Glycemic Control and Blood Pressure Control algorithms.

Cardiovascular and cerebrovascular disease – Treatment includes control of cardiovascular risk factors (hypertension, hyperlipidemia and smoking cessation) and aspirin use. Consider referring patients with known coronary artery disease to cardiology and patients with known carotid disease to surgery.

Heart failure is also common in patients with diabetes. Caution should be used when prescribing spironolactone and eplerenone to people with diabetes, especially in combination with ACE inhibitors.

Close monitoring of potassium and renal function is necessary. Thiazolidinediones must also be used with caution in patients with Class I and II congestive heart failure or patients at high risk for congestive heart failure. Close monitoring for fluid retention and signs of congestive heart failure is needed. Thiazolidinediones should not be used in Class III and IV congestive heart failure.

For patients with type 2 diabetes mellitus, thiazide diuretics in the treatment of hypertension can reduce cardiovascular events, particularly heart failure. *[Conclusion Grade I: See Conclusion Grading Worksheet G – Annotations #29, 36 (Thiazide Diuretics)] (ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, The, 2002 [A]; Wing, 2003 [A])*

Patients with type 2 diabetes have twice the average risk of suffering a stroke *(American Diabetes Association, 1998 [R])*. It is unclear whether good glycemic control reduces this risk. However, treatment of hypertension, smoking and hyperlipidemia reduces the risk of stroke in most persons. See Annotation #14, "Treatment Goals for Patients With Cardiovascular Disease," and the Blood Pressure Control algorithm.

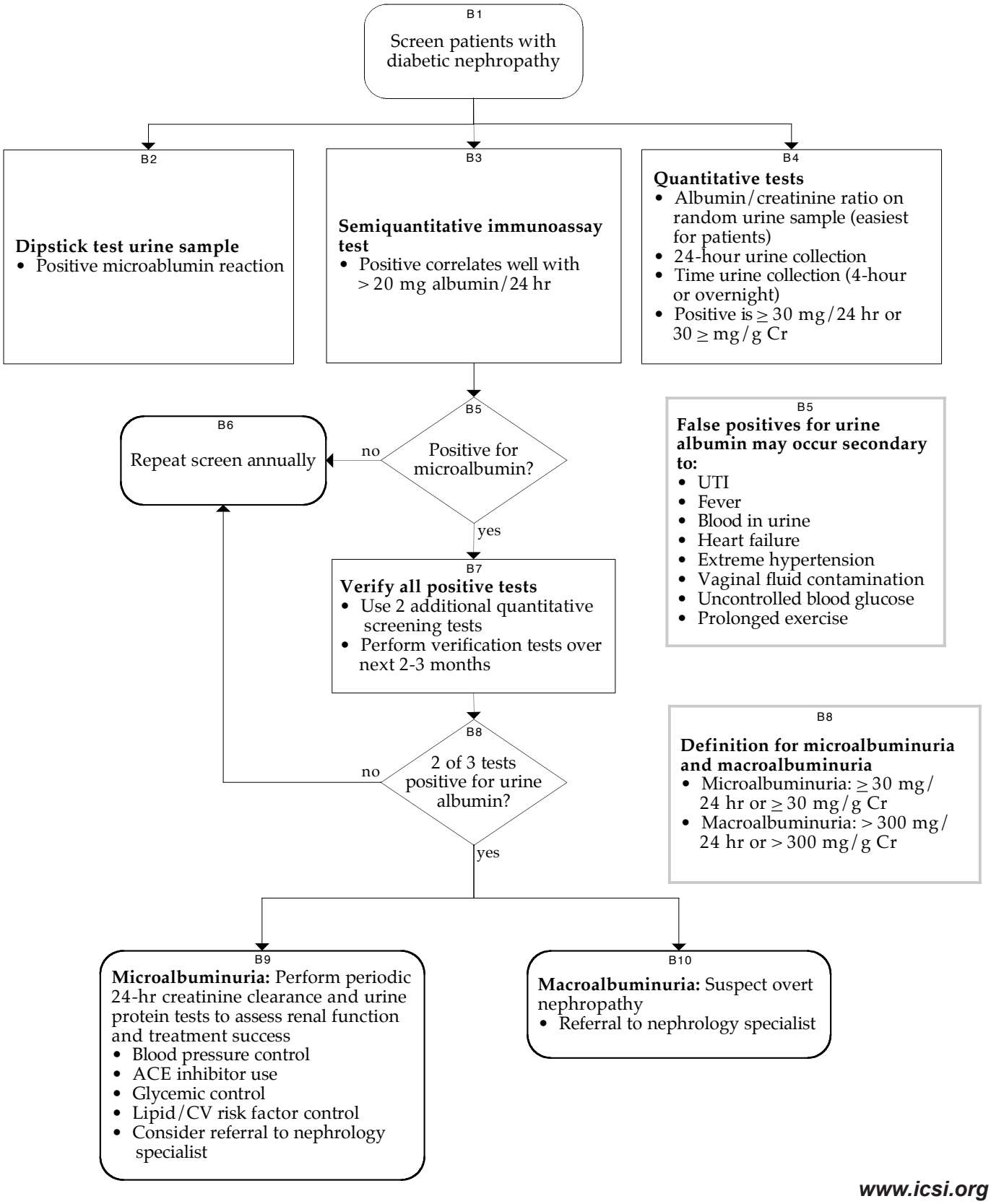
Peripheral vascular disease – Peripheral arterial disease is commonly associated with diabetes *(American Diabetes Association, 2007c [R])*. As many as 36% of patients with diabetes have lower-extremity peripheral arterial disease based on lower-extremity blood pressure readings. However, a typical history of intermittent claudication or an absent peripheral pulse is less commonly noted.

Peripheral vascular disease in combination with peripheral neuropathy places patients with diabetes at increased risk for non-traumatic amputations of the lower extremity. Peripheral vascular disease may be slowed by smoking cessation and treatment of hypertension and dyslipidemia. See Annotation #14, "Treatment Goals for Patients With Cardiovascular Disease," and the Blood Pressure Control algorithm.

Aggressive daily foot care, inspection of the feet at every office visit, early treatment of foot infections, treatment of callus, use of moisturizing lotion and proper footwear may forestall problems, including amputation. Vascular surgery may also prevent amputation in some patients with established severe peripheral vascular disease *(American Diabetes Association, 2004f [R])*.

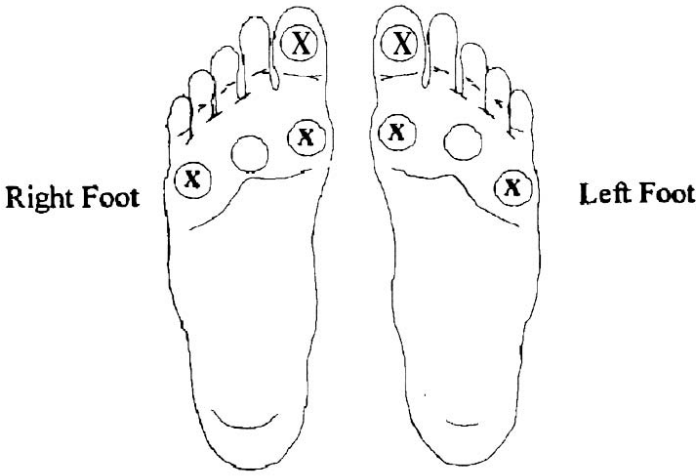
Proper high-risk foot management is necessary to prevent ulceration and amputation. Consider referral of patients with claudication and/or absent pedal pulses to surgery. See the Glycemic Control and Blood Pressure Control algorithms.

Appendix A – Treatment of Diabetic Nephropathy



Appendix B – Using a Semmes-Weinstein Monofilament to Screen the Diabetic Foot for Peripheral Sensory Neuropathy

1) Show the monofilament to the patient and touch it to his/her arm to demonstrate that it does not hurt.
2) Use the Semmes-Weinstein 5.07/10 gram monofilament to test sensation at the indicated sites on each foot*. Avoid applying the monofilament to calluses, ulcers, or scars. A foot exam is not reimbursed my Medicare without monofilament sensation testing in four locations.



3) Hold the monofilament perpendicular to the skin and touch it to the skin using a smooth motion with sufficient force to cause the filament to bend. The test should take about 1-1/2 seconds at each site.

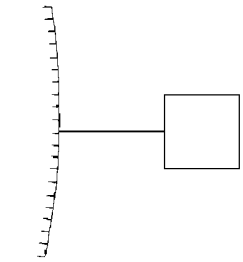


Figure 1

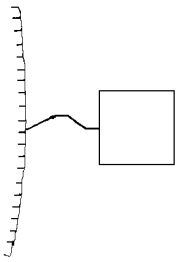


Figure 2

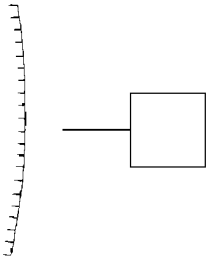


Figure 3

4) Ask the patient to respond "yes" when the filament is felt. If the patient does not respond when you touch a given site on the foot, continue on to another site in a random sequence. When you have completed testing all sites on the foot, retest any site(s) where the patient did not feel the filament.
5) The results of the monofilament testing should be documented in the medical record**. **PATIENTS WHO CANNOT FEEL THE MONOFILAMENT AT ANY SITE SHOULD BE CONSIDERED TO BE INSENSATE AND AT INCREASED RISK FOR ULCERATION AND AMPUTATION.**

*Testing at the first and fifth metatarsal heads is sufficient. This combination of sites has been shown to detect the insensate foot with reasonable sensitivity (80%) and specificity (86%). Testing the great toes may be of added benefit.
**Chart documentation is required for the American Diabetes Association – Provider Recognition Program. An annual diabetic foot examination is also one of the eight diabetes quality improvement project (DQIP) measures adopted by the National Committee for Quality Assurance (NCQA) and the Health Care Financing Administration.

Supporting Evidence:

Diagnosis and Management of Type 2 Diabetes Mellitus in Adults

Document Drafted
Nov 1994 – Apr 1995

First Edition
Mar 1996

Second Edition
Apr 1997

Third Edition
May 1998

Fourth Edition
Apr 1999

Fifth Edition
Apr 2000

Sixth Edition
Oct 2001

Seventh Edition
Oct 2002

Eighth Edition
Dec 2003

Ninth Edition
Dec 2004

Tenth Edition
Dec 2005

Eleventh Edition
Dec 2006

Twelfth Edition
Apr 2008

Thirteenth Edition
Begins June 2009

Original Work Group Members

Greg Angstman, MD
Family Practice, Work Group Leader
Mayo Clinic

Richard Bergenstal, MD
Endocrinology
International Diabetes Center

Mary Bergene
BHCAG Representative
Honeywell, Inc.

Don Bishop, PhD
Minnesota Department of Health Representatives
Minnesota Dept. of Health

Cindy Clark, MS
Minnesota Department of Health Representatives
Minnesota Dept. of Health

Janet Davidson, RN, CDE
Nurse Clinician
Park Nicollet Clinic

Jinnet Fowles, PhD
Measurement Advisor
Institute for Research and Education HealthSystem Minnesota

Marion Franz, RD, CDE
Dietetics
International Diabetes Center

Patrick O'Connor, MD
Family Practice
HealthPartners

Teresa Pearson, MS, RN, CDE
Health Education
HealthPartners

Peg Sannes, R Ph
Pharmacy
HealthPartners

Mary Shelerud, RN
Facilitator
Mayo Clinic

Dace Trence, MD
Endocrinology
HealthPartners

Bruce Zimmerman, MD
Endocrinology
Mayo Clinic

Released in May 2009 for Thirteenth Edition.
The next scheduled revision will occur within 12 months.

Contact ICSI at:
8009 34th Avenue South, Suite 1200; Bloomington, MN 55425; (952) 814-7060; (952) 858-9675 (fax)
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Brief Description of Evidence Grading

Individual research reports are assigned a letter indicating the class of report based on design type: A, B, C, D, M, R, X.

A full explanation of these designators is found in the Foreword of the guideline.

II. CONCLUSION GRADES

Key conclusions (as determined by the work group) are supported by a conclusion grading worksheet that summarizes the important studies pertaining to the conclusion. Individual studies are classed according to the system defined in the Foreword and are assigned a designator of +, -, or ø to reflect the study quality. Conclusion grades are determined by the work group based on the following definitions:

Grade I: The evidence consists of results from studies of strong design for answering the question addressed. The results are both clinically important and consistent with minor exceptions at most. The results are free of any significant doubts about generalizability, bias, and flaws in research design. Studies with negative results have sufficiently large samples to have adequate statistical power.

Grade II: The evidence consists of results from studies of strong design for answering the question addressed, but there is some uncertainty attached to the conclusion because of inconsistencies among the results from the studies or because of minor doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from weaker designs for the question addressed, but the results have been confirmed in separate studies and are consistent with minor exceptions at most.

Grade III: The evidence consists of results from studies of strong design for answering the question addressed, but there is substantial uncertainty attached to the conclusion because of inconsistencies among the results from different studies or because of serious doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from a limited number of studies of weak design for answering the question addressed.

Grade Not Assignable: There is no evidence available that directly supports or refutes the conclusion.

The symbols **+**, **–**, **ø**, and **N/A** found on the conclusion grading worksheets are used to designate the quality of the primary research reports and systematic reviews:

+ indicates that the report or review has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis;

– indicates that these issues have not been adequately addressed;

ø indicates that the report or review is neither exceptionally strong or exceptionally weak;

N/A indicates that the report is not a primary reference or a systematic review and therefore the quality has not been assessed.

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Conclusion Grading Worksheet A – Annotation #4 (Prediabetes)

Work Group's Conclusion:

- Lifestyle modifications, such as nutrition, exercise and even modest weight loss, are recommended for prevention or delayed progression of patients with prediabetes.
- Pharmacotherapy, such as metformin, are effective in some patients with prediabetes.
- There are concerns that the recent modification of the definition of impaired fasting glucose by the American Diabetes Association has low specificity and low positive predictive value compared to the WHO definition.

Conclusion Grade: II

Author/ Year	Design Type	Class	Quality +,–,0	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Borch-Johnson, et al., 2004	Observational, cross-sectional study	D	+	Data pooled from 5 international population based studies: 1) Danish INTER99 (n=6265 adults 30-61 y) DETECT-2 Studies: 2) Paris Prospective(n=7034 adults 44-55 y) 3) Gingdoa (China) (n=1808 adults 30-74 y) 4) NUDS (India) (n=10039 adults 22-99 y) 5) NHANES 1988-1994 (n=3517 adults 40-74 y)	Primary objective was to evaluate the consequences of 2003 American Diabetes Association expert committee revision of diagnostic criteria for impaired fasting glucose from 6.1 to 5.6 mmol/l; specifically with regard to 1) the prevalence of impaired fasting glucose in five different countries, 2) the concordance between impaired fasting glucose status and impaired glucose tolerance, and 3) The cardiovascular risk profile of these groups. The proposed changes in diagnostic criteria would increase the prevalence of impaired fasting glucose in Denmark from 11.8% to 37.6%, which would identify 60% of all subjects with impaired glucose tolerance compared to 29.2% with the old criteria. However, among individuals with the new impaired fasting glucose category, 18.5% would also have impaired glucose tolerance; furthermore, individuals with isolated impaired fasting glucose had lower insulin levels and a lower cardiovascular disease risk compared with current WHO criteria. Data from DETECT-2 also showed an increase in the prevalence of impaired fasting glucose – the number of individuals ages 40-64 years with impaired fasting glucose in urban India, urban China, and the USA would increase by 78%, 135% and 193%, respectively, with the new criteria compared to the old criteria.	The authors conclude that a revision of diagnostic criteria for impaired fasting glycemia will increase the prevalence of impaired fasting glucose two- to fourfold. Impaired fasting glucose and impaired glucose tolerance will remain two different categories of glucose intolerance. The new impaired fasting glucose group will have a more favorable cardiovascular risk profile than the group defined by WHO, and the usefulness of impaired fasting glucose as a target group for diabetes prevention may become questionable.

New Thirteenth Edition, May 2009.

Author/ Year	Design Type	Class	Quality +,–,0	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Twigg, et al., 2007	Position Statement based on a systematic review of literature from the Australian Diabetes Society and Australian Diabetes Educators Association	R	+	A review of peer-reviewed journals was conducted using MEDLINE 1966-2005). Search terms included prediabetes, glucose intolerance, IGT, IFG, impaired glucose tolerance, impaired fasting glucose and impaired fasting glycemia. Articles were graded according to level of evidence.	-The aim of this report was to develop recommendations for the clinical management of prediabetes for physicians and allied health care professionals. - Prediabetes is defined as the presence of impaired fasting glucose/glycemia and/or impaired glucose tolerance. - Prediabetes affects about 16.4% of Australian adults. - People with prediabetes are at increased risk of developing diabetes, ~3%-10% of people per year with prediabetes develop diabetes. In most populations studies, the rates of conversion from impaired fasting glucose or impaired glucose tolerance are similar, with impaired glucose tolerance having greater sensitivity but less specificity. - People with prediabetes have a two to threefold increased risk of cardiovascular disease compared to adults who have normal glucose tolerance. - Several randomized, prospective studies of subjects with prediabetes have documented beneficial effects of lifestyle interventions in preventing type 2 diabetes. The Diabetes Prevention Program observed a 58% risk reduction in progression to diabetes even though participants did not meet weight loss and moderate physical activity goals. - Multiple medications have been shown to reduce incidence of diabetes in people with prediabetes in randomized, double-blinded trials. In the Diabetes Prevention Program, subjects allocated to metformin therapy had a 31% reduced risk of conversion to diabetes compared with the control group. Other drugs, such as acarbose and rosiglitazone, may reduce conversion to diabetes as well as cardiovascular events, but the results need to be confirmed by other studies. - No data exist to define the utility of monitoring HbAlc in prediabetic patients.	- Assessment and management of risk factors for cardiovascular disease, such as lipid and blood pressures abnormalities, should be undertaken. Although there have been no trials in prediabetics, the lipid and blood pressure targets should be equivalent to those for type 2 diabetes. - Sustained and moderate weight loss in people with prediabetes is an important predictor of a positive outcome of lifestyle interventions. - It is recommended that a minimum of 6 months of lifestyle intervention be trialed before drug therapy is considered. - Practical health care delivery of lifestyle aspects of diabetes prevention requires further study. - Pharmacotherapy may involve metformin, which appears to be more efficacious in younger (<60 years) and more overweight people. Other drugs may be orlistat, acarbose or a thiazolidinedione. - In the absence of specific clinical indications, there is no need for routinely conducting the following tests in prediabetic patients: capillary blood glucose measurement, HbA1c, serum insulin or pancreatic C-peptide, tests for ischemic heart disease, tests for microvascular complications. - Follow-up testing in prediabetes requires a formal 75g oral glucose tolerance test. *[This position statement has not adopted American Diabetes Association recently modification to impaired fasting glucose definition of 5.6-6.9 mmol/L. The authors state that such a low threshold glucose level may cause the impaired fasting glucose categorization to lose specificity and positive predictive value as a risk factor for diabetes. The report uses the WHO definition of ≥6.1 mmol/L and < 7.0 mmol/L]*

Author/ Year	Design Type	Class	Quality +, –, 0	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Schmidt, et al., 2005	Study of sensitivity and specificity of a risk prediction function	C	+	7915 participants from the Atherosclerosis Risk in Communities study, study subjects were free of diabetes at baseline (1987-1989) and followed until 1996-1998.	-The objective of this study was to derive risk functions to predict diabetes with equal or better diagnostic properties than impaired glucose tolerance. - Logistic regression was used in a random half of the sample, then evaluate the risk functions in the other half of the sample. - Rules based on risk functions including laboratory measurements performed generally better; a risk function based on waist circumference, height, hypertension, blood pressure, family history of diabetes, ethnicity and age was performed similarly to one based on fasting glucose (area under the curve 0.71 and 0.74, respectively, p=0.2). - Rules based on the presence of elements of the metabolic syndrome produced slightly less desirable diagnostic properties (23% labeled as high risk and 50% of future cases identified) than rules based on risk function including lipids (20% labeled as high risk and 52% of future cases identified). Metabolic syndrome rules had slightly less sensitivity (2%) and specificity (4%) compared to rules using a clinical calculator or webpage.	Rules based on the metabolic syndrome criteria are reasonable alternatives to rules derived from the risk functions.
Kim, et al., 2006	Randomized, controlled trial	A	-	52 men and 47 women age 53.5±11.4 years with prediabetes or non-diabetic metabolic syndrome were enrolled and randomized to either 4mg rosiglitazone treatment group or non-treated control group and followed for 12 weeks.	At baseline and 12-week follow-up, subjects were given a 75g oral glucose tolerance test. Inflammatory markers thought to be cardiovascular risk markers, pulse-wave-velocity (a measure of arterial stiffness) and anthropometrics were also measured. Rosiglitazone treatment significantly increased circulating levels of adiponectin and decreased levels of CRP relative to the control group. The treatment group also had significantly decreased pulse-wave-velocity compared to the control group.	These data suggest that rosiglitazone therapy may have an anti-atherogenic affect in subjects with prediabetes. *[This study was not conducted in a double-blinded placebo controlled fashion. It is possible that the rosiglitazone group had more intensive lifestyle changes that could have exaggerated the beneficial effect of rosiglitazone. Also, it is difficult to impossible to tease apart the effect of pharmacotherapy and lifestyle changes in this study.]*

Author/ Year	Design Type	Class	Quality +, –, 0	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Norris, et al., 2005	Meta-analysis	M	+	Literature searches were conducted up to 2003. Randomized controlled trials in any language that examined weight loss or weight control with at least one dietary, physical activity or behavioral intervention with follow-up greater than 12 months were selected. A meta-analysis was conducted and effects were combined using a random effects model.	The objective of this meta-analysis was to assess the effectiveness of weight-loss and weight-control intervention for adults with prediabetes. A total of 5168 participants were included in pooled analyses. Follow-up ranged from 1 to 10 years. Compared to usual care, four studies with a follow-up of 1 year reduced weight by 2.8 kg (95% CI 1.0-4.7) and decreased body mass index by 1.4 kg/m^2 (0.5-2.3). Weight loss at 2 years was 2.7 kg (1.9-3.4) from two studies. Modest improvements were noted in the few studies that examined glycemic control, blood pressure, lipids. The incidence of diabetes was significantly lower in the intervention groups vs. controls in 3 or 5 studies that examined this outcome at 3 to 6 years follow-up.	Although the weight loss amounts demonstrated in this review were small, it appears that even modest weight loss may have health benefits with regard to cardiovascular disease risk factors and development of diabetes.

Author/Year	Design Type	Class	Quality +,–,0	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
McFarlane, et al., 2007	Double-blind, randomized controlled trial, the DREAM trial	A	-	The study screened 24,592 persons and randomized 5,269 in 191 sites from 21 countries with a median follow-up of 3 years. Patients enrolled were older than 30 years with prediabetes defined as impaired glucose tolerance (fasting plasma glucose <7, 2-hour plasma glucose 7.8-11 mmol/L) and/or impaired fasting glucose (fasting plasma glucose 6.1-6.9 mmol/L).	The primary aims of this study were to test 1) does ramipril prevent diabetes? and 2) does rosiglitazone prevent diabetes? Primary outcomes of the study were incident diabetes (confirmed by fasting plasma glucose >7 or 2-hour plasma glucose >11.1 or diagnosis made by a physician or death. Secondary outcomes included assessment of the rate of conversion to prediabetes to normoglycemia as well as evaluation of ramipril and rosiglitazone effects on cardiorenal events. Results: Ramipril at a dosage of 15 mg/d for 3.5 years did not prevent diabetes. However, ramipril was associated with a nonsignificant decrease (9%) in new-onset diabetes compared to placebo and was associated with a significant increase (16%) in the rate of conversion to normoglycemia from impaired glucose tolerance and impaired fasting glucose. Rosiglitazone was associated with a significant decreased (60%) in new onset diabetes compared with placebo. This effect was consistent across age, sex and racial/ethnic groups. Additionally, there was a significant increase (71%) in conversion rate to normoglycemia among those with impaired glucose tolerance and impaired fasting glucose.	The DREAM trial did not clearly demonstrate a diabetes prevention effect with ramipril and only showed a trend. However, the findings confirmed the beneficial effects of ramipril on glucose metabolism. The rosiglitazone findings confirm other findings that the drug reduces insulin resistance and preserves pancreatic B-cell function. However, due to liver toxicity, the agent that was actually tested (troglitazone) was withdrawn from the market and eventually replaced with much safer thiazolidazides that were not specifically tested in randomized controlled trials for diabetes prevention. The authors suggest that use of an ACE inhibitor, when otherwise indicated, would be a prudent choice for prediabetics because they are at increased risk of cardiovascular disease. *[This is a relatively large trial of pharmacotherapy to prevent diabetes among prediabetics. However, this article was a brief report and did not include any details of the recruitment and randomization process, nor did it include any baseline tables. In addition, there were no confidence intervals presented for the point estimates given in the text.]*

Author/ Year	Design Type	Class	Quality +,–,0	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Farag, et al., 2007	Narrative review	R	-	A non-systematic review of type 2 diabetes prevention research, including prevention among prediabetics.	There are no details of how articles were selected for inclusion in the review. However, the article covers several important areas of diabetes prevention: Prediabetic state: defines prediabetics as impaired fasting glucose of 100 to 125 mg/dL and/or impaired glucose tolerance with glucose levels of 140 to 199 mg/dL 2 hours after an oral load of glucose. Estimates that 40% of people with impaired glucose tolerance progress to diabetes. Lifestyle changes: summarizes findings that weight loss, diet and exercise have been shown separately and in combination to be effective in decreasing the incidence of type 2 diabetes in high risk patients. Pharmocologic interventions: summarizes findings for several types of drugs. Insulin sensitizing drugs (metformin, thiazolidinediones) and oral anti-diabetic agents (glucosidase inhibitors) have been shown to be effective in reducing incidence of diabetes in patients with impaired glucose tolerance or are currently being examined in ongoing trials (nateglinidines). Other drugs such as ACES, statins and fibrates have inconsistent findings for diabetes prevention. There is not sufficient evidence for a protective effect for diabetes with weight-reducing agents, but there is evidence of greater success with weight loss. Surgery: summarizes studies from Sweden and US that evaluated surgical interventions for weight loss.	The authors conclude that several interventions have been shown to be effective in preventing diabetes, including lifestyle modifications as well as anti-diabetic pharmacotherapy.

Author/Year	Design Type	Class	Quality +,–,Ø	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Tuomilehto, et al., 2001 Finnish Diabetes Prevention Study	RCT	A	+	522 middle-aged, overweight subjucts (172 men and 350 women, mean age 55 years, mean BMI 31 kg/m^2) with impaired glucose were randomized to either individualized counseling aimed at reducing weight and total fat intake and increasing physical activity and fiber intakes (intervention group) or a control group. The mean duration of follow-up was 3.2 years.	The primary aim of this study was to determine the feasibility of a lifestyle intervention to delay or prevent incidence type 2 diabetes. The mean (SD) amount of weight lost between baseline and the end of year 1 was 4.2 (5.1) kg in the intervention group and 0.8 (3.7) kg in the control group ($p<0.001$). After two years, the net weight loss was 3.5 (5.5) kg in the intervention group and 0.8 (5.5) kg in the control group ($p<0.001$). The cumulative incidence of diabetes after four years was 11% (95% CI 6 to 15%) in the intervention group and 23% (95% CI 17 to 29%) in the control group. In the trial, the risk of diabetes was reduced by 58% ($p<0.001$) in the intervention group.	The authors conclude that the reduction in incidence of diabetes was a directly associated with changes in lifestyle. *[Interestingly, achieving a relatively modest physical activity goal of 4 hr/week was associated with a significant reduction in incident diabetes in subjects who did not lose weight. It is possible that any type of physical activity is beneficial.]*
Lindström, et al., 2006 Finnish Diabetes Prevention Study (follow-up study)	RCT	A	Ø	256 intervention and 257 control articipants who were still free of diabetes after the active intervention period of 4 years (Tuomilehto, et al., 2001) were further followed up for a median of 3 years, for a total median follow-up of 7 years.	The primary outcomes of this study was incident type 2 diabetes. During the total follow-up, the incidence of diabetes was 4.3 and 7.4 per 100 person years in the intervention and control groups, respectively ($p=0.0001$), indicating a 43% reduction in relative risk. The risk reduction was related to success in achieving the intervention goals of weight loss, reduced intake of total saturated fat and increased physical activity and fiber intake. Beneficial lifestyle changes in the intervention groups were sustained after the discontinuation of the intervention, and the corresponding incidence rates during the post follow-up period were 4.6 and 7.2 ($p=0.401$), indicating a 36% reduction in relative risk.	The authors conclude that the results from the extended follow-up of the Finnish Diabetes Prevention Study show that the effect of lifestyle intervention on diabetes risk does not disappear after activity lifestyle counseling is stopped. The authors acknowledge some limitations to this study. First, the analyses related to the post-intervention period were not part of the original protocol, and post-hoc results should be interpreted with caution as the follow-up was not considered in the original sample size calculation. Second, the low drop-out rate suggests a highly health conscious population, probably more so than the general population.

Author/Year	Design Type	Class	Quality +,–,0	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Li, et al., 2008 China Da Qing Diabetes Prevention Study	RCT	A	-	577 adults with impaired glucose tolerance from 33 clinics in China were randomly assigned to either a control group or one of 3 lifestyle intervention groups (diet, exercise or diet plus exercise). The goal of the diet intervention was to increase fruit and vegetable intake and lower alcohol and sugar intake. The goal of the exercise intervention was to was to increase leisure time physical activity. The intervention was conducted for 6 years with longitudinal follow-up for 20 years.	The primary outcomes of this study were incident diabetes, CVD incidence and mortality, and all-cause mortality in the intervention groups combined and the control group. Compared to participants in the control group, those in the intervention groups combined had a 51% lower incidence of diabetes (Hazard ratio 0.49 [95% CI 0.33-0.73]) during the 6-year intervention period and 42% lower (0.57, [0.41-0.81]) over the 20-year follow-up period after controlling for age and clinic center. There was no significant difference between intervention and control groups with regard to CVD events or mortality, or all-cause mortality (but were not powered to detect such differences). Results for each intervention arm (diet alone, exercise alone, diet plus exercise) were not presented.	The authors conclude that the reduction in diabetes incidence observed during the 6-year intervention persisted for two decades. The authors cite group-based lifestyle interventions of 6 years as preventive of diabetes. Limitations of this study include the passive ascertainment of outcomes during the post-intervention period. This may explain the observed lower rate of incident diabetes. However, this bias was not systematic and likely affected both control and treatment groups similarly. *[There is no detailed description of the intervention – how it was delivered, what was included. Because the authors neither present nor discuss findings for the different treatment arms, it is impossible to ascertain which components of the lifestyle interventions were most important. Additionally, as readers, we are unable to determine what effect the group dynamic might have had on the lifestyle interventions.]*

Author/Year	Design Type	Class	Quality +,−,Ø	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
The Diabetes Prevention Program Research Group (DPP), 2005	RCT	A	Ø	Participants were randomly assigned to metformin (n=587), troglitazone (n=585), double placebo (n=582), or intensive lifestyle intervention (n=589).	The primary end point of this study was delay or prevention of type 2 diabetes with triglitazone compared to other treatments. Because of concerns of liver toxicity, the troglitazone arm was discontinued before the study's end. During the mean 0.9 years of troglitazone treatment, the diabetes incidence rate was 3 cases/100,000 person-years, compared with 12, 6.7, and 5.1 cases/100,000 person-years in the placebo, metformin and lifestyle intervention groups ($p<0.0001$ troglitazone vs. placebo, $p=0.02$ triglitazone vs. metformin, $p=0.18$ troglitazone vs. lifestyle).	The authors believe the triglitazone effect was in part due to improved insulin sensitivity with maintenance of insulin secretion. During 3 years after triglitazone withdrawal, the diabetes incidence was nearly identical to placebo group. Therefore, the authors conlude that triglitazone markedly reduced the incidence of diabetes during treatment, but this action did not persist beyond the limited period of use. There was insufficient data (only 10 cases of diabetes during 330 person-years of follow-up for troglitazone arm) to examine any effects according to age, ethnicity, BMI. However, it appears that troglitazone treatment was the most effective of all treatment arms.
Diabetes Prevention Program Research Group, 2002 DPP	RCT	A	+	3,234 nondiabetic persons with elevated fasting and post-load plasma glucose were randomized to placebo, metformin or lifestyle therapy.	The primary outcome of incident diabetes. The average follow-up time was 2.8 years. The incidence of diabetes was 11, 7.8 and 4.8 cases per 100 person-years in the placebo, metformin and lifestyle groups, respectively. Compared to placebo, the lifestyle intervention reduced the incidence of diabetes by 58% (95% CI 48 to 66%), and the metformin intervention reduced the incidence of diabetes by 31% (95% CI 17 to 43%).	In this randomized trial, both metformin and lifestyle changes reduced the incidence of diabetes compared to placebo in persons at high risk. However, the lifestyle intervention was significantly more effective than metformin. *[Interestingly, the lifestyle group lost more weight compared to the metformin and placebo groups. However, the study was not designed to test the relative contributions of dietary changes, increased physical activity and weight loss.]*

Conclusion Grading Worksheet B – Annotation #11 (A1c)

Work Group's Conclusion:
A1c target in type 2 diabetes is aimed at reducing microvascular complications while not increasing risk of morbidity or mortality.

- All patients with type 2 diabetes should aim to achieve an A1c less than 8%. This will reduce microvasuclar disease and not increase risk substantially.
- Most (many) patients with type 2 diabetes may derive additional benefit in reduction of microvasuclar disease by reaching a target A1c less than 7% and not increase risks as long as the target is not A1c less than 6%.

Conclusion Grade: II

Author/ Year	Design Type	Class	Quality (+, –, ø)	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Gaede et al., 2008	Randomized controlled trial (RCT)	A	+	-- Follow-up study after completion of interventional study (Steno-2 Study). -- 160 patients (mean age 55.1 years at baseline) with type 2 diabetes and microalbinuria randomly assigned to intensive therapy group ([IG], target HbA1c < 6.5%, fasting cholesterol < 175 mg/dl, fasting triglycerides < 150 mg/dl, blood pressure < 130/80 mm Hg, and focused behavior modification) and a conventional (CG) multifactorial treatment group. -- All patients received renin-angiotensin system blockers and low-dose aspirin. -- 3 patients withdrew, 27 died during interventional study, leaving 130 pts for start of follow-up study. -- 37 died during follow-up period, leaving 93 subjects completing follow-up study. -- Primary end point in follow-up trial was time to death (any cause), with secondary end points being death from cardiovascular (CV) causes, and composite of CV disease events. -- Total mean follow-up time 13.3 years (7.8 years in interventional study and 5.5 years for observational follow-up).	-- Used intention-to-treat principle -- Both groups similar at baseline -- Measured results were as follows: BP (mean systolic/diastolic mm Hg): IG: end of intervention: 131/73; end of follow-up: 140/74 CG: end of intervention: 146/78; end of follow-up: 146/73 HbA1c (mean %): IG: end of intervention: 7.9; end of follow-up: 7.7 CG: end of intervention: 9.0; end of follow-up: 8.0 Fasting total cholesterol (mean mg/dl): IG: end of intervention: 159; end of follow-up: 147 CG: end of intervention: 216; end of follow-up: 155 Fasting triglycerides (median mg/dl): IG: end of intervention: 115; end of follow-up: 99 CG: end of intervention: 159; end of follow-up: 148 -- During entire 13.3 years of follow-up, 24 IG pts died and 40 CG pts died (hazard ratio [HR] 0.54; p=0.02) -- 9 IG pts died of CV causes and 19 CG pts died of CV causes (HR 0.43; p=0.04) -- Total CV events: 51 in IG, 158 in CG (HR 0.41; p<0.001); no evidence of change in HR occurred between end of intervention and final observational follow-up -- Diabetic nephropathy developed in 20 IG pts and 37 CG pts (relative risk [RR] 0.44; p=0.004) -- Progression of diabetic retinopathy occurred in 41 IG pts and 54 CG pts (RR 0.57; p=0.01) -- Autonomic neuropathy progressed in 39 IG pts and in 52 CG pts (RR 0.53; p=0.004); peripheral neuropathy progression was not significantly different between the two groups -- Differences in hypoglycemic episodes were not significant between the two groups (p=0.15 trend for more episodes in IG)	-- During entire follow-up period, death rate in CG was 50%; authors state this underscores poor prognosis without intensive treatment. -- Study was not designed to show which elements of intensive treatment contributed most to the CV risk reduction. -- Significant differences in risk factors between the two groups between the intervention phase and final follow-up tended to converge (all pts were offered intensive treatment after intervention study ended), but time to first CV events continued to diverge; authors stated that this provided evidence that early intervention (intensive treatment) continues to show benefit long-term. *[Note that although original HbA1c goal for intensive treatment was < 6.5% yet avg., at end of follow-up was 7.7%, underscoring the difficulty in attaining aggressive HbA1c goals.]*

Updated Thirteenth Edition, May 2009.

Author/Year	Design Type	Class	Quality (+, –, ø)	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Selvin et al., 2004	Meta-analysis	M	ø	-- Meta-analysis of prospective observational (cohort) studies on the association between HbA1c levels and incident cardiovascular disease, including fatal and nonfatal myocardial infarction, angina and ischemic heart disease, cerebrovascular disease (fatal and nonfatal stroke), peripheral arterial disease, and a combined outcome that includes coronary disease and stroke -- Type 2 diabetes analyzed separately from type 1 -- Random effects model used to pool the results -- Total of 17 study reports included, representing 13 unique samples (10 groups of type 2 diabetics – included UKPDS studies; total n=7435 for 10 studies) -- Adjustment for possible confounding factors varied considerably – about 50% of studies used automatic stepwise methods for determining multivariate models; only 3 studies simultaneously adjusted for known cardiovascular risk factors such as age, gender, lipid levels, blood pressure and smoking	-- Pooled relative risk for total cardiovascular disease (10 independent datasets of coronary disease alone, stroke alone, and combined stroke and coronary disease in type 2 diabetics) was 1.18 (95% CI, 1.10 to 1.26) for each 1% increase in HbA1c. -- For the 5 independent studies of fatal and nonfatal coronary disease risk, the pooled relative risk was 1.15 (95% CI, 1.06 to 1.20), with the relative risk for fatal coronary disease being 1.16 (95% CI, 1.07 to 1.26) for each 1% increase in HbA1c. -- For the 3 independent studies that included stroke risk assessment, the pooled relative risk was 1.17 (95% CI, 1.09 to 1.25) for each 1% increase in HbA1c. -- For the 3 independent studies that included peripheral arterial disease risk assessment, the pooled relative risk was 1.28 (95% CI, 1.18 to 1.39). -- Small number of studies limited the ability to ascertain important sources of heterogeneity among the studies.	-- Data analysis supports moderate increase in cardiovascular risk with increasing HbA1c levels in type 1 and type 2 diabetics. -- In some studies, association of cardiovascular disease with increasing HbA1c levels was independent of other known cardiovascular risk factors. -- Linear relationship of cardiovascular risk to HbA1c levels assumed in studies, but not clear if this is actually the case. -- Future RCTs needed that specifically answer the question of the relationship of glycemic control (specifically HbA1c levels) to cardiovascular disease and disease risk.

Author/Year	Design Type	Class	Quality (+, –, **0**)	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Abraira, et al., 1997	RCT	A	–	-- Feasibility study comparing standard vs. intensive insulin therapy -- 153 men with non-insulin dependent diabetes (NIDDM) were enrolled, average age 60 years, having diabetes for an average of 7.8 years, with poor glycemic control (mean baseline HbA1c > 9%) -- Above pts randomized to a standard insulin treatment group (SG, n=78, 1 morning insulin injection per day) and an intensive treatment group (IG, n=75, stepped plan) -- Assessed cardiovascular events (new myocardial infarctions, congestive heart failure, stroke, amputations, cardiovascular mortality, angina/coronary disease, angioplasty/CABG, TIAs, peripheral vascular disease -- 38% of pts had known pre-existing CV disease -- Sample size and duration of feasibility trial not powered to demonstrate a treatment effect on CV disease, but objective was to assess frequency and types of CV end points in preparation for a longer-term trial	-- IG had mean HbA1c of 7.1%, 2.1% lower than SG pts and maintained this difference for the 27 months of follow-up ($p<0.001$). -- Mild and moderate hypoglycemic events occurred more frequently in the IG (16.5 events per patient per year vs. 1.5 events per patient per year, $p<0.001$); severe hypoglycemic events were rare and not significantly different between the groups. -- Groups were not significantly different in baseline BMI, serum TG levels, total cholesterol/LDL/HDL levels, blood pressure and cigarette smoking (but all 4 pipe smokers were randomized into the IG arm). -- 61 CV events occurred during the study; 33 occurred in 24 pts in the IG; 26 events occurred in 16 pts in the SG ($p=0.10$); 10 pts died during the study (5 in each group, with 3 in each group being CV related). -- Multivariate analysis on times to CV event showed that the only significant predictor variable was a previous history of CV disease ($p=0.04$); lower HbA1c level was a borderline correlate when substituted for the treatment assignment variable. -- When silent baseline CV abnormalities were combined with known previous CV events as the dependent variable, only the HbA1c level (lower level) rose to significance as a predictor of new CV events ($p=0.05$).	-- Authors state that intensive insulin treatment designed to lower HbA1c levels can sustain a clinically significant separation in HbA1c levels without increasing BP, dyslipidemia, severe hypoglycemia, excessive weight gain or high insulin requirement. -- Small sample size, short-duration study noted mortality rates nearly identical between groups. -- CV history had a significant effect on risk of new events. -- Borderline trend toward more CV events in patients with lower HbA1c levels, but finding needs cautious interpretation due to the short length of the study; insulin dose itself did not appear to be a significant predictor of events. -- Need further prospective study before recommendations for NIDDM treatment can be made. -- Authors state that benefit of HbA1c levels below 8% may be relatively small.

Author/ Year	Design Type	Class	Qual -ity (+, –, **0**)	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Gerstein, et al., 2008 (The ACCORD Work-group)	RCT	A	+	-10,251 patients with a median baseline A1c of 8.1% who had heart disease or evidence of atherosclerosis, albunieria, hypertension, left ventricle hypertrophy or two cardiovascular disease risk factors - Participants were randomized to receive either intensive therapy targeting reduction of A1c to below 6 or standard therapy targeting A1c between 7.0-7.9 -Inclusion/exclusion criteria clearly defined -Used intention to treat analysis	- Primary outcomes measured was a composite of non-fatal myocardial infarction, non-fatal stroke, and death from cardiovascular disease. - Over 3.5 years of follow-up, the primary outcome occurred in 352 in the intensive therapy group and 371 in the standard therapy group (RR 0.90, 95% CI 0.74-1.04, p=0.16). - There were 257 deaths in the intensive therapy group compared to 203 deaths in the standard therapy group (RR = 1.22, 95% CI 1.01-1.46, p=0.04). - In addition, hypoglycemia requiring attention and weight gain in excess of 10kg occurred more frequently in the intensive therapy group.	- Compared to standard therapy, intensive therapy led to increased mortality and did not significantly reduce cardiovascular events. - Differences in mortality emerged 1- 2 years after randomization, which may indicate that the potential benefits of intensive therapy do not emerge for several years, during which time there is increased risk of mortality. -The standard therapy group had fewer visits and used fewer drugs in fewer combinations; thus, the higher rate of mortality in the intensive therapy group may be related to the various strategies of intensive treatment.
Patel, et al., 2008 (ADV-ANCE trial)	RCT	A	+	-11,400 patients with type 2 diabetes who were diagnosed after age 30 or were over 55 and had a history microvascular or macrovascular disease or at least one cardiovascular risk factor - Randomized to standard glucose control or intensive therapy targeting <6.5% A1c	- Primary outcomes were a composite of microvascular events (new or worsening nephropathy, need for renal replacement therapy, or death to renal disease) and a composite of macrovascular events (non-fatal myocardial infarction, non-fatal stroke, and cardiovascular disease death). - Over 5 years of follow-up, A1c was lower in the intensive therapy group (6.5%) compared to the standard glucose control group (7.3%). - Intensive control reduced the incidence of combined micro- and macrovascular events (18.1% vs. 20.0% with standard control, hazard ratio 0.90 [0.82-0.98]). - A reduction in microvascular events was observed in the intensive treatment group (9.4%) compared to the standard control group (10.9%) with a hazard ration of 0.86 (0.77-0.97). - No reduction in macrovascular events was observed, (hazard ratio 0.94 [0.84-1.06]).	- The observed 10% relative reduction may be due to a reduction in worsening nephropathy. - In the ADVANCE trial, no subgroup of participants was identified to have evidence of an adverse effect of intensive glucose lowering on major vascular outcomes, including a subgroup with an initial median A1c comparable to the ACCORD study population. - Intensive therapy significantly reduced the primary composite outcome of major macrovascular or microvascular events. There was no separate significant reduction in major macrovascular events, although this benefit could not be ruled out.

Author/ Year	Design Type	Class	Quality (+, –, ø)	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Bretzel, et al., 2008	RCT	A	+	- 515 randomly assigned to insulin lispro or insulin glargine - Baseline A1c between 7.5% and 10.5%, BMI 35 or less	- Primary endpoints were changes in A1c and blood glucose at 44 weeks follow-up - Changes in A1c in the glargine group were 8.7 to 7.0 and 8.7 to 6.8 in lispro group. - 57% of patients in the glargine group and 69% in the lispro group reached A1c below 7%. - Fall in mean fasting blood glucose was 4.3 in the glargine group and -1.8 in the lispro group (p <0.0001). - Incidence of hypeglycemic events was less in the glargine group compared to lispro group. - Mean weight gains were 3.01 in the glargine group and 3.54 in the lispro group.	- The two treatments were equally effective in lowering A1c. [*Note that this study probably does not have long enough follow-up time to detect any adverse events. In addition, patients recruited for this study did not have existing cardiovascular disease or risk factors at baseline, unlike ACCORD and ADVANCE patients.*]

Author/ Year	Design Type	Class	Quality (+, –, ø)	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Holman, et al., 2008	RCT [*This is a long-term follow-up of participants post-intervention, during which time participants were not intervened on nor were they encouraged to maintain their treatment assignment.*]	A	+	- Out of a trial of 4,209 newly diagnosed diabetic patients randomly assigned to conventional therapy or intensive therapy, 3,277 were available for post-trial observation. - Differences in A1c due to treatment group were diminished by the end of the 1-year trial, at the start of post-trial follow-up the median A1c was 7.9 in the sulfonylurea treatment group, 8.5 in the comparison group and 8.4 in the metformin treatment group, 8.9 in the comparison group.	- Outcomes of interest were any diabetes related end point, diabetes-related death, death from any cause, MI, stroke, peripheral vascular disease, microvascular disease. - In the sulfonylurea arm, compared to the conventional therapy group, the RR (95% CI) of diabetes-related endpt 0.91 (0.83-0.99), diabetes-related death 0.83 (0.73-0.96), death from any cause 0.87 (0.79-0.96), MI 0.85 (0.74-0.97), stroke 0.91 (0.73-1.13), PVD 0.82 (0.56-1.19), microvascular disease 0.76 (0.64-0.89). - In the metformin arm, compared to the conventional therapy group, the RR (95% CI) of diabetes-related endpt was 0.79 (0.66-0.95), diabetes-related death 0.70 (0.53-0.92), death from any cause 0.73 (0.59-0.89), MI 0.67 (0.51-0.89), stroke 0.80 (0.50-1.27), PVD 0.63 (0.32-1.27), microvascular disease 0.84 (0.60-1.17).	- Benefits of intensive therapy to control glucose were maintained for up to 10 years after the cessation of the randomized trial. - In the sulfonylurea group, the reduction in microvascular disease risk and diabetes-related endpoint risk observed in the intensive therapy group was sustained throughout the post-trial period, despite rapid convergence of A1c values and similar use of glucose-lowering therapies. In the metformin group, made up of overweight patients, risk reductions for MI and all-cause mortality were sustained throughout the post-trial period despite similar A1c levels between treatment and control group. [*Note: This report does not indicate what the target A1c levels were for the intervention study, nor what A1cs were achieved with intensive therapy during the trial. At the beginning of post-trial follow-up, the median A1cs were around 8.*] *[Note: Participants were excluded from the study if they had MI within one year, current angina or heart failure, more than one major vascular event, malignant hypertension, uncorrected endocrine disorder, retinopathy require laser treatment, elevated serum creatinine level, ketonuria. So, these patients did not have existing vascular disease or risk factors, unlike ACCORD and ADVANCE.]*

Author/Year	Design Type	Class	Quality (+,–,0)	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Duckworth, et al., 2009	RCT	A	Ø	1,791 military veterans (mean age 60.4 years) who had a suboptimal response to therapy for type 2 diabetes were randomized to receive either intensive or standard glucose control. Forty percent of these patients had already had a cardiovascular event. The goal of the intervention was an absolute reductionin A1c of 1.5 percentage points. Patients in intensive therapy group were started on maximum doses, and patients in the standard therapy group were started on half the maximal doses of metformin plus rosiglitazone (if BMI >27 kg/m^2) or glimepiride plus rosiglitazone (if BMI < 27 kg/ m^2).	The primary end point in this study was time from randomization to the first occurrence of a major cardiovascular event, a composite of MI, stroke, death from CVD causes, congestive heart failure, surgery for vascular disease, inoperable coronary disease or amputation. After a median follow-up 5.6 years, median A1c levels were 8.4% in the standard therapy group and 6.9% in the intensive therapy group. The primary outcome occurred in 264 of standard therapy group patients and 235 of intensive therapy group patients (Hazard ratio = 0.88 95% CI 0.74-1.05). There was also no significant difference between groups with regard to the composite outcome.	The authors conclude that intensive glucose control in patients with poorly controlled type 2 diabetes had no significant effects on the rates of major cardiovascular events, death or microvascular complications. An obvious limitation of this study is that the population was predominantly men, so extrapolation of these findings to women should be done with caution. Additionally, at the beginning of the study (2000-2003), the availability of new drugs was limited, so it remains possible that newer agents may have different effects. The authors note that adverse events were more common in the intensive therapy group; however, there was no difference in CVD death between groups. *[Note: While the authors suggest that their results are consistent with the ADVANCE and ACCORD trials, it is not a valid comparison. Their finding that there was no difference in CVD death rates is likely due to lack of power to detect such differences (or lack thereof).]*

Conclusion Grading Worksheet C – Annotations #13, 14 (Statin Use)

Work Group's Conclusion: For patients with type 2 diabetes mellitus, consider the use of a statin. Randomized controlled trials, including some large trials, and observational data consistently show a benefit of statin therapy for patients with type 2 diabetes. Some studies also reported that statin therapy was well tolerated in these patients. However, none of these studies was able to assess long-term effects of statin treatment/use.

Conclusion Grade: I

Author/ Year	Design Type	Class	Quality +/–/0	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Colhoun, et al., CARDS 2004	RCT	A	+	2,838 patients (age 40-75 years, 94% Caucasion and 68% male), in 132 centers in the UK/Ireland	**Atorvastatin 10 mg vs. placebo** Acute coronary event HR 0.63 (0.48-0.83) Stroke HR 0.52 (0.31-0.89) Death from any cause HR 0.73 (0.52-0.85)	Randomization with equal groups at baseline and 1% lost to follow-up after a mean follow-up of 4 years. Analysis was with intention to treat, and during the course of study, 9% of placebo group was known to take a statin and 85% of the intervention (either atorvastatin or another statin). Overall frequency of adverse events or serious adverse events did not differ between treatments. In each group, 1.1% of patients randomized had one or more serious adverse events. Based on pre- and post-LDL values in intervention and control group, there did not appear to be a particular threshold level of LDL cholesterol to reduce cardiovascular events.
Robins, et al., 2001	RCT	A	+	2,531 men with coronary heart disease and low HDL-C levels (avg 32 mg/dL). 620 patients had diabetes.	**Gemfibrizol 1,200 mgm/day vs. placebo** RR 95% CI (4-46%)	Patients were randomized with concealed allocation; they were similar at baseline and treated relatively similarly throughout the trial; patients, study personnel, health care providers and outcomes assessors were blinded; intention-to-treat analysis was conducted; there was trivial loss to follow-up. No validity concerns.

Updated Thirteenth Edition, May 2009.

Author/ Year	Design Type	Class	Quality +,–,ø	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Heart Protection, 2002	RCT	A	+	20,536 patients 40-80 years (75% males, 35% without a prior history of CAD, 28% >70 years of age) with non-fasting LDL chol of > 3.4 mmol/L (135 mgm%). 3,982 patients had diabetes, 3,982 without prior hx of MI or CAD.	**Simvastatin 40 mgm/day vs. placebo** Major vascular event Number needed to treat 21 95% CI (14-41)	Randomization included individuals felt not to have a clear clinical indication for the use of a statin. Central telephone randomization (presumed concealed assignment) with minimization algorithm to balance treatment groups. Mean duration of follow-up was 5 years with at least 80% demonstrating compliance with use of simvastatin or placebo. 4,002 patients took a non-study statin to include the placebo arm (average of 17% for 5 years). All patients were accounted for (loss to follow-up 0.03-0.33%) with intention-to-treat analysis. Patients, providers and outcome assessors were blinded to treatment arms, and intervention and control group were similar at start of trial. Other than the intervention, it is not possible to tell if groups were treated equally.
Setter-gren, et al., 2008	RCT	A	-	43 patients with type 2 diabetes or impaired glucose tolerance and stable coronary artery disease were recruited and randomized. Patients who were on a statin or other lipid-lowering treatment in the previous 12 weeks were excluded. Patients were randomized to either simvastatin 80 mg/d or ezetimibe 10 mg/d plus simvastatin 10 mg/d for 6 weeks. 4 patients were lost to follow-up (2 from each arm) and only 39 were analyzed.	**The primary outcomes of this study were endothelial function measured by brachial artery flow-mediated vasodilations and the effects of endothelin receptor blockage, serum lipids, and inflammatory markers were evaluated at baseline and follow-up.** After 6 weeks of follow-up, LDL cholesterol levels decreased from 3.1 to 1.5 mmol/L and 3.0 to 1.3 mmol/L in the simvastatin and simvastatin plus ezetimibe groups, respectively (p=). The changes in flow mediated dilation and CRP were not different between groups; in the entire study group, flow mediated dilation increased from 4.3% to 5.5%, and CRP decreased from 3.1 to 2.3 mg/L.	The authors conclude that the two treatments did not differ with regard to their effect on endothelial function in patients with type 2 diabetes, impaired glucose tolerance and stable coronary artery disease. They further posit that in contrast to their hypothesis, the lipid-lowering effects of statins were more important for endothelial function as opposed to the pleiotropic effects of statins. *[Note: The investigators did not adhere to intention-to-treat analysis principles. There were some potentially important differences in A1c, aspirin use, as well as use of beta-blockers and calcium channel blockers between treatment groups at baseline.]*

Author/ Year	Design Type	Class	Quality +, –, Ø	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Fleg, et al., 2008 Data from the SANDS trial	Non-randomized trial	C	Ø	Secondary analysis of data from the Stop Atherosclerosis in Native Diabetics Study (SANDS) Trial. Aggressively treated patients (n=69) taking statins plus ezetimibe were compared to aggressively treated patients on statins alone (n=154) and non-aggressively treated patients (n=204).	**The primary outcomes of this study were change in LDL cholesterol and carotid intima-media thickness.** Mean LDL cholesterol was reduced by 31 mg/dL and 32 mg/dL in the aggressive group receiving statins plus ezetimibe versus statins alone compared with a change of 1mg/dL in the non-aggressive group. At 36 months follow-up, mean carotid intima-media regressed from baseline similarly in the ezetimibe (-0.025mm) and non-ezetimibe (-0.012mm) groups while it progressed in the non-aggressive treatment group (0.039).	The authors conclude that among persons with type 2 diabetes and baseline LDL cholesterol ≥ 100 mg/dL. Both aggressive treatment strategies were effective at reducing carotid intima-media thickness. *[Note: This study used data from the SANDS trial for a secondary analysis that compared groups within the aggressive treatment arm. Therefore, the study design used for this analysis is not a randomized trial; rather, the data are being analyzed as a non-randomized trial or cohort study.]*
Ferrer-Garcia, et al., 2008	Non-randomized, uncontrolled trial	C	-	202 patients with type 2 diabetes who had no statin use in the prior 24 weeks. All met criteria for pharmacologic therapy, according to the NCEP-ATP III and ADA criteria, with LDL levels in excess of 2.6 mmol/L. These patients were assigned to receive a daily dosage of atorvastatin based on their initial LDL cholesterol levels.	**The primary outcome of this study was the proportion of patients achieving the LDL cholesterol goal after 24 weeks of treatment.** 188 patients completed the study; of those, 66.5% achieved the LDL cholesterol target. At doses of 10, 20, 40 and 80 mg/day of atorvastatin, the % of patients reaching goal LDL was 75%, 67%, 58% and 59%, respectively.	The authors conclude that individualizing the starting dose of atorvastatin according to baseline and target LDL cholesterol levels allowed a high proportion of type 2 diabetes patients to achieve the target within 24 weeks. The authors noted that they observed a reduction in triglycerides, but no change in A1c. This study did not address limitations of having no control group. They also did not explain why they did not use an intention-to-treat analysis if this is a trial.

Author/ Year	Design Type	Class	Quality +,–,Ø	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Leiter, et al., 2008 The ACTFAST study	Non-randomized open label trial	C	Ø	2,717 high-risk subjects, 1,024 of whom had diabetes and 1,251 had metabolic syndrome. Patients had CHD or CHD equivalent at baseline and LDL cholesterol levels between 100 and 220 mg/dL. Patients were assigned a starting dose of artovastatin (10, 290, 40 or 80 mg/day) based on LDL cholesterol levels and statin use at baseline.	**The primary end point of this study was the proportion of patients who achieved LDL cholesterol goals.** Among patients with diabetes, 81% of subjects who were previously not on a statin (82%, 84%, 82% and 76% with 10, 20, 40 and 80 mg/day, respectively) reached the LDL cholesterol target. Among patients who were previously on a statin, 60% of subjects (61%, 68% and 47% with 20, 40 and 80 mg/day, respectively) reached LDL cholesterol target.	The authors conclude that a targeted dose of atorvastatin allows most patients with type 2 diabetes to achieve their LDL cholesterol target with the initial dose or a single titration within 12 weeks. The authors further conclude that higher starting doses of statins are beneficial and well tolerated, but lower doses work, too. Limitations of this study include that it was not blinded.
Howard, et al., 2008 The SANDS Trial	Randomized controlled trial	A	+	Participants were 499 American Indian men and women aged > 40 years with type 2 diabetes and no prior cardiovascular events. Follow-up time was for 3 years. Patients were randomized to aggressive or standard treatment groups.	**The primary objective of this study was to compare the progression of subclinical atherosclerosis in adults with type 2 diabetes treated to reach aggressive targets of low-density LDL cholesterol and blood pressure.** Mean target LDL cholesterol and systolic blood pressure levels were reached and maintained in both groups. Mean (95% confidence interval) levels for LDL cholesterol at the end of follow-up were 72 (69-75) and 104 (101-106) and SBP levels were 117 (115-118) and 129 (128-130) in the aggressive vs. standard treatment groups, respectively. From baseline to follow-up, there were greater decreases in carotid intima media thickness, left ventricular mass index, and carotid arterial cross-section in the aggressive group compared to the non-aggressive group. Serious adverse events related to blood pressure medication were higher in the aggressive group (4 vs. 1 in non-aggressive group). Cardiovascular events did not differ significantly between groups.	The authors conclude that the aggressively treated group had a regression of subclinical atherosclerosis (intima media thickness, left ventricular mass index). At the same time, the standard treatment group had a worsening in intima media thickness. There were no differences in clinical CVD outcomes between groups, and the progression of subclinical disease in the standard treatment group was lower than expected. Given the lack of difference in CVD events and the increase in adverse events in the aggressive treatment arm, there is a possibility that there may not be favorable long-term outcomes. It should be noted that this study focused on a single ethnic group. *[Note: This study did not control for confounding by oral hypoglycemic medication use, which may have biased results away from the null.]*

Author/ Year	Design Type	Class	Quality +, –, ø	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Newman, et al., 2008 The CARDS study	RCT	A	+	2,338 patients with type 2 diabetes and no history of coronary heart disease who were enrolled in the Collaborative Atorvastatin Diabetes Study (CARDS) and followed for 3.9 years. Patients were randomized to receive atorvastatin 10 mg/day or placebo in a double-blinded study.	**The primary outcome of this study was to evaluate the safety and tolerability of atorvastatin 10 mg/day with placebo.** The percentage of patients experiencing adverse events, serious adverse events, and discontinuations due to adverse events in the atorvastatin vs. placebo groups were 23.0% vs. 25.4%, 1.1% vs. 1.1%, and 2.9% vs. 3.4%, respectively. The most common adverse events were digestive system related.	The authors conclude that atorvastatin 10 mg/day was well tolerated in patients with type 2 diabetes during relatively long-term treatment (3.9 years) and that patients with diabetes benefit from statin therapy. *[Note: This study was unable to ascertain long-term outcomes of treatment.]*
Malmstrom, et al., 2009 (same study as Settergren)	RCT	A	**Ø**	32 patients with type 2 diabetes or impaired glucose tolerance and stable coronary artery disease received 6 weeks of treatment with simvastatin 80 mg/day or ezetimibe 10 mg/day plus sinvastatin 10 mg/day.	**The primary outcomes of this study were LDL cholesterol, C-reactive protein, and platelet function.** Total and low-density LDL cholesterol decreased from 3.2 (±0.6) to 1.7 (±0.7) in the ezitimibe + simvastatin group and 3.0 (±1.0) to 1.4 (±0.5) in the simvastatin-alone group. Neither treatment affected platelet activity (platelet P-selectin expression and fibrinogen binding, ADP-induced platelet aggregation).	The authors conclude that pronounced lipid-lowering did not influence indices of platelet function. These results suggest that neither the lipid-lowering nor the pleiotropic effects of statin therapy reduced the reactivity of platelet aggregation. This study is limited by a small number of patients. Also, there were some baseline differences in clopidogrel and aspirin use and gender distribution.
Sever, et al., 2005 ASCOT	RCT	A	+	2,532 patients with diabetes at randomization in the ASCOT study. Patients were hypertensive, with no history of coronary heart disease, but at least three cardiovascular risk factors. Randomized to receive 10 mg atorvastatin or placebo.	**The primary outcome of this study was a composite of total cardiovascular outcomes.** During a median follow-up of 3.3 years, concentration of total and LDL cholesterol was ~1 mmol/l lower in those randomized to atorvastatin compared with placebo. There were 166 major cardiovascular events (9.2%) in the atorvastatin group and 151 (11.9%) in the placebo group (Hazard ratio 0.77, 95% confidence interval 0.61-0.98). There were no statistically significant reductions in individual cardiovascular end points (stroke, coronary events).	The authors conclude that atorvastatin significantly reduced the risk of major cardiovascular events and procedures among diabetic patients with well-controlled hypertension and without a history of coronary heart disease. The reduction in risk was similar to that among study participants who were not diagnosed with diabetes. This study was limited by relatively short follow-up time; thus, the investigators were unable to assess long-term statin use in diabetics. This study did not assess microvascular events.

Author/ Year	Design Type	Class	Quality +,–,Ø	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Knopp, et al., 2006[9] The ASPEN study	RCT	A	Ø	2,410 subjects were randomly assigned to receive 10 mg atorvastatin or placebo in a 4-year, double-blinded study.	**The primary end point of this study was a composite compromised of cardiovascular death, non-fatal MI, non-fatal stroke, recanalization, coronary artery bypass surgery, resusicitated cardiac arrest, and worsening or unstable angina.** At the end of the 4-year study, LDL cholesterol was reduced by 30.1% in the atorvastatin group and 1.1% in the placebo group (p=0.0001). Composite end point rates were 13.7% in the atorvastatin group and 15.0% in the placebo group (Hazard ratio 0.90, 95% confidence interval 0.73-1.12).	The authors conclude that there were not significant differences between groups in composite end points. They further acknowledge that these results that are inconsistent with others reported in the literature may be due to the primary end point definition (which may have been inflated due to inclusion of hospitalization for angina) or protocol changes due to changes in treatment guidelines. Thus, because of the increased risk of coronary heart disease among diabetic patients, they should still be treated to achieve LDL cholesterol targets. Two years into the study, the study protocol was altered to include patients without prior MI or interventional procedure due to changes in treatment guidelines. Subsequent treatment guidelines necessitated all secondary prevention subjects and primary prevention subjects with a primary CVD end point to discontinue the study medication (as mandated by the DSMB).

Author/ Year	Design Type	Class	Quality +,–,ø	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Shepherd, et al., 2006 Treating to New Targets Study (TNT)	RCT	A	+	1,501 patients with diabetes and coronary heart disease, with LDL cholesterol levels <130 mg/dL were randomized to a either atorvastatin 10 or 80 mg/day. Patients were followed for a median of 4.9 years.	**The primary end point of this study was time to first cardiovascular event (defined as death from coronary heart disease, non-fatal MI, resuscitated cardiac arrest, or fatal or non-fatal stroke).** The mean LDL cholesterol levels at the end of treatment were 98.6 mg/dl with 10 mg atorvastatin and 77.0 mg/dl with 80 mg atorvastatin. A primary event occurred in 135 patients on 10 mg compared with 103 patients on 80 mg (Hazard ratio 0.75, 95% confidence interval 0.58-0.97). There were significant differences between groups in favor of atorvastatin 80 mg for time to first cerebrovascular event (0.69, 95% confidence interval 0.48-0.98) and any cardiovascular event (0.85, 95% confidence interval 0.73-1.00).	The authors conclude that among patients with coronary heart disease and diabetes, intensive statin therapy of 80 mg atorvastatin signficantly reduced the rate of major cardiovascular events by 25 compared to 10 mg atorvastatin. The were no differences in rates of adverse events between groups. This study did not assess microvascular events. This study was not powered to detect differences in mortality. This is a post-hoc analysis of a subpopulation from the larger TNT study. *[Note: Interestingly, there was no difference in cardiovascular events between patients with and without good glycemic control.]*

Conclusion Grading Worksheet D – Annotations #13, 14, 27, 29 (Goals for Blood Pressure)

Work Group's Conclusion: For patients with type 2 diabetes mellitus, the systolic blood pressure goal is less than 130 mmHg and the diastolic blood pressure goal is less than 80 mmHg.

Conclusion Grade: II

Author/ Year	Design Type	Class	Quality +,–,**0**	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
UK Prospective Diabetes Study Group (UKPDS 39), 1998	RCT	A	**0**	-758 patients allocated to tight control of BP among 1,148 hypertensive patients with type 2 diabetes -400 patients treated with captopril (25-50 mg twice daily), 358 with atenolol (50-100 mg twice daily) -All patients ages 48-60 years of age (mean age of treatment groups 56 years) -9-year follow-up -goal of BP <150/85 mm Hg	-Captopril and atenolol euallele effective in mean BP reduction (144/84 and 143/81 mm Hg, respectively) -Reduction of risk of macrovascular end points were similar in the two groups (31% and 37% showed deterioration in retinopathy by 2 grades; 5% and 9% developed clinical grade albuminuria greater than or equal to 300 mg/l) -Similar percentage of patients required 3 or more antihypertensive treatments (27% and 31%) or developed hypoglycemic attacks but mean wt gain was greater in the atenolol group (1.6 kg vs 3.4kg) -78% captopril and 65% atenolol patients taking treatment at last visit (p<0.0001)	-Blood pressure lowering with captopril or atenolol was similarly effective in reducing the incidence of diabetic complications. This study suggests that blood pressure reduction in itself may be more important than the treatment used.
UK Prospective Diabetes Study Group (UKPDS 38), 1998	RCT	A	+	-1,148 hypertensive patients with type 2 diabetes -758 patients allocated to tight control of BP with goal of <150/85 mm Hg (400 patients treated with captopril [25-50 mg twice daily], 358 with atenolol [50-100 mg twice daily]) and 390 patients allocated to less tight control of BP with goal of <180/105 mm Hg -All patients ages 48-60 years of age (mean age of treatment groups 56 years) -8.4-year follow-up	-Mean BP was significantly reduced in the tight BP group (144/82 Hg mm) as compared to the less-tight BP group (and 154/87 mm Hg, p<0.0001) -Reductions of risk in the tight BP group as compared to the less tight BP group were 24% in diabetes-related end points (95CI 8% to 38%, p=0.0046), 32% in deaths related to diabetes (95CI 11% to 51%, p=0.019), 44% in strokes (95CI 11% to 65%, p=0.013), 37% in microvascular end points (95CI 11% to 56%, p=0.0092) -Tight BP group had a 34% reduction in risk of proportion with deterioration in retinopathy by 2 grades (99CI 11% to 50%, p=0.0004), and a 47% reduced risk for deterioration in visual acuity (99CI 7% to 70%, p=0.004)	-Tight blood pressure control in patients with hypertension and type 2 diabetes achieved a clinically important reduction in the risk of deaths related to diabetes, complications related to diabetes, progression of diabetic retinopathy, and deterioration in visual acuity.
Hansson et al., 1998 Hypertension Optimal Treatment (HOT) Trial	RCT	A	**0**	-1,510 patients with diabetes (among 18,790 total patients with hypertension and diastolic BP 100-115 mm HG in trial) -All patients ages 50-80 years of age -Patients randomly assigned a target diastolic BP of less than or equal to 90 mm Hg, 85 mm Hg, or 80 mm Hg -All patients received felodipine for hypertension -ACE inhibitors or B-blockers were used to treat to given target diastolic BP -3- to 8-year follow-up	-For patients with diabetes, the blood pressure intervention led to a significant reduction (51%) in number of major cardiovascular events (45 events in 90 mm HG group, 34 in 85 mm HG group, and 22 in 80 mm HG group; p=0.005 for trend) and cardiovascular mortalities (21, 21 and 7; p=0.016) -For patients with diabetes, the blood pressure intervention reduced total mortality (30, 29, 17 events), MIs (14, 8, 7) and stroke (17, 13, 12), but none was statistically significant	-Intensive lowering of BP in diabetes patients with hypertension was associated with a significantly 51% lower rate of cardiovascular events.

Updated Thirteenth Edition, May 2009.

Conclusion Grading Worksheet E – Annotations #13, 14 (Aspirin Use)

Work Group's Conclusion:

There is insufficient evidence to support aspirin use in the primary prevention of cardiovascular events in patients with type 2 diabetes, although there is no evidence of significant harm. However, there is sufficient evidence to support the use of aspirin for secondary prevention of cardiovascular events in patients with type 2 diabetes.

Conclusion Grade: I

Author/Year	Design Type	Class	Quality +, –, 0	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Early Treatment Diabetic Retinopathy Study (ETDRS) Report 14, 1992	RCT	A	0	-3,711 patients with diabetes mellitus (31% type 1, 31% type 2, and 39% type 1 or 2) randomized to receive aspirin or placebo (650 mg twice daily) -All patients ages 18-70 years of age -5-year follow-up	-RR for total mortality was 0.91 (99CI 0.75-1.11, p=NS) overall and 0.92 in type 2 patients (99CI 0.69-1.23, p=NS) treated vs. placebo patients -Myocardial infarction rates were 9.1% with aspirin and 12.3% with placebo (RR 0.83, p=0.04) overall -The NNT to prevent one MI in 5 years with aspirin was 31 patients	-Aspirin use may reduce the risk of myocardial infarction in adults with diabetes but did not reduce total mortality or CV mortality rates. -There was no evidence of harmful effects of aspirin. -The ETDRS results support use of aspirin in persons with diabetes at increased risk of cardiovascular disease.
Hansson et al., 1998 Hypertension Optimal Treatment (HOT) Trial	RCT	A	0	-1,510 patients with diabetes (among 18,790 total patients with hypertension and diastolic BP 100-115 mm HG in trial) -All patients ages 50-80 years of age -Patients randomly assigned a target diastolic BP of less than or equal to 90 mm Hg, 85 mm Hg, or 80 mm Hg -All study subjects were randomized to receive aspirin 75 mg/day or placebo -3 to 8-year follow-up	-For all patients, aspirin use significantly reduced cardiovascular events 15% (p=0.03) and reduced MI rates 36% (p=0.002) but did not reduce mortality -The relative benefit of aspirin to those with diabetes was "about the same" as in the whole trial population	-Use of aspirin in diabetes and in non-diabetes patients significantly reduced MIs (36%) and cardiovascular events (15%) but did not significantly reduce mortality. -Aspirin use (75 mg/day) appears to benefit diabetes patients with hypertension, even those in whom blood pressure is very well controlled.
Harpaz, et al., 1998	Cohort	B	+	-2,368 NIDDM adults with CHD and 8,586 non-NIDDM adults with CHD -Mean follow-up 5.1 years -52% of NIDDM patients reported no ASA use	-All-cause mortality was 18.4% in NIDDM ASA users and 26.2% in NIDDM ASA non-users ($p < 0.001$) -Cardiac mortality was 10.9% in NIDDM ASA users and 15.9% in NIDDM ASA non-users ($p < 0.001$) -Both significant differences persisted after adjustment for possible confounders	-Treatment with ASA was associated with a significant reduction in cardiac and total mortality among NIDDM adults with CHD. -The absolute benefit of aspirin was greater in diabetes versus non-diabetes adults.
Physician's Health Study Research Group, 1989	RCT	A	0	-Primary prevention of MI in subgroup of 533 physicians with diabetes (among 22,071 total participants) -Patients randomized to either 325 mg ASA/day or placebo -Mean follow-up 5 years	-Overall, 44% reduction in MI ($p<0.00001$) in those who took ASA -In diabetes subgroup, 4.0% had MI in ASA group (11/275) and 10.1% had MI in non-ASA group (p=0.22, NS) -Relative risk of MI in ASA group was 0.60 in entire cohort, and 0.39 in diabetes	-Aspirin reduced MI rate in overall study. -Benefits in DM group appear to be at least as great as in non-DM group. *-The non-significant differences in DM group were likely due to small sample size and insufficient power.*

Updated Thirteenth Edition, May 2009.

Author/ Year	Design Type	Class	Quality +,-,0	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Ogawa, et al., 2008	RCT	A	+	2,539 patients with type 2 diabetes free of atherosclerotic disease recruited from 163 institutions throughout Japan. Patients were randomized to 81 or 100 mg aspirin per day or non-aspirin group (JPAD study). Trial was conducted from 2002-2006. Median follow-up time was 4.37 years.	The primary outcome was atherosclerotic events, including fatal and non-fatal ischemic heart disease, fatal and non-fatal stroke, and peripheral arterial disease. Hazard ratios: (95% confidence intervals) All atherosclerotic events: 0.80 (0.58-1.10) Coronary and cerebrovascular mortality: 0.10 (0.01-0.79) CHD events (fatal and non-fatal): 0.81 (0.49-1.33) Non-fatal MI: 1.34 (0.57-3.19) Unstable angina: 0.40 (0.13-1.29) Stable angina: 1.10 (0.49-2.50) Cerebrovascular disease (fatal and non-fatal): 0.84 (0.53-1.32) Fatal stroke: 0.20 (0.24-1.74) Non-fatal stroke ischemic: 0.93 (0.52-1.66) Non-fatal stroke hemorrhagic: 1.68 (0.40-7.04) Transient ischemic attack: 0.63 (0.21-1.93) PAD: 0.64 (0.25-1.65)	The authors conclude that low-dose aspirin use does not reduce cardiovascular events in patients with type 2 diabetes. This study faced two important limitations: 1) the study design was not blinded because law in Japan does not allow doctors to dispense placebo; and 2) the atherosclerotic event rate was lower than anticipated and as a result, the JPAD trial was not powered to demonstrate that aspirin had a significant effect on reducing total atherosclerotic events. However, the authors adequately acknowledge these limitations. Additionally, they indicate that the results should be taken into the context of low atherosclerotic disease rates in Japan.

Author/ Year	Design Type	Class	Quality +,–, ø	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Belch, et al., 2008	RCT	A	+	1,276 adults aged 40 or more years with type 1 or type 2 diabetes and ankle brachial pressure index of 0.99 or less but no symptomatic CVD. Patients were randomized to 100 mg aspirin per day plus antioxidant capsule (n=320), placebo tablet plus antioxidants capsule (n=320), or placebo tablet plus placebo capsule (n=318). The median length of follow-up was 6.7 years and for those with a final follow-up in 2006, follow-up ranged from 4.5 to 8.6 years, resulting in a total 8.127 person-years of observation.	There were two primary outcome measures: 1) a composite of death from CHD or stroke, non-fatal MI or stroke, or amputation above the ankle for critical limb ischemia; or 2) death from CHD or stroke. Secondary endpoints included death from any cause; death from stroke, non-fatal MI or stroke, or amputation above the ankle for critical limb ischemia; development of angina; CABG; angioplasty; PAD bypass surgery; PAD angioplasty. Hazard ratios (95% confidence intervals) for aspirin vs. non-aspirin Composite end point: 0.98 (0.76-1.26) Death from CHD or stroke: 1.23 (0.79-1.93) Death any cause: 0.93 (0.71-1.24) CHD death: 0.93 (0.81-2.25) Stroke death: 0.89 (0.34-2.30) Non-fatal MI: 0.98 (0.68-1.43) Non-fatal stroke: 0.71 (0.44-1.14) Above-ankle amputation: 1.23 (0.51-2.97) Transient ischemic attack: 0.70 (0.36-1.39)	The authors found no evidence to support the use of aspirin in the primary prevention of cardiovascular events or mortality in people with diabetes. The authors note that aspirin should be used for secondary prevention of cardiovascular events. This study was originally designed to recruit 1,600 patients with follow-up of four years, with one effective treatment that would have provided power of 90% to detect a 25% relative risk reduction in a four-year event rate of 28% (8% per annum at the 0.05 level) – equating to 392 events. With both treatments equally effective, that would have provided 80% power to detect for each treatment rate the same relative reduction in event rate as significant, resulting in 343 events. However, due to slower than anticipated recruitment and lower event rates, only 1,276 patients were recruited, with 256 events resulting power being reduced to 73% to detect a 25% relative reduction in event rate and 89% power to detect a 30% reduction in event rate if only one treatment was effective.
Walsh and Spurling, 2008	Narrative review	R	-	Narrative review of evidence to support prophylactic use of aspirin in type 2 diabetes.	Summarized findings from a systematic review that only examined diabetes as a subset of the study; also, they reviewed 3 randomized controlled trials. The systematic review and 2 of the RCTs did not support the use of aspirin in people with diabetes for prevention of MI or mortality. Only one (small) RCT supported the use of aspirin.	The authors conclude that most available evidence do not support guidelines from the American Diabetes Association and the Australian National Health and Medical Research Council.

Author/ Year	Design Type	Class	Quality +,–,Ø	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Gaede, et al., 2008 The Steno-2 Study	RCT	A	-	160 patients with type 2 diabetes and persistent microalbunaria were randomized to receive either intensive therapy or conventional therapy. The mean treatment period was 7.8 years.	The primary end point was death from any cause. 24 patients died in the intensive therapy group compared with 40 in the conventional therapy group, (Hazard ratio 0.54, [95% confidence interval 0.32-0.89]). Intensive therapy was associated with a lower risk of death from cardiovascular causes, (Hazard ratio 0.43 (95% CI 0.19-0.94) and lower risk of cardiovascular events (Hazard ratio 0.41 [95% CI 0.25-0.67]). Aspirin use for the intensive vs. conventional group, respectively, were 14% and 13% at baseline, 87% and 56% at end of intervention, and 85% and 76% at end of follow-up. At the end of follow-up, there was not a statistical difference in aspirin use between groups.	The authors conclude that in at-risk patients with type 2 diabetes, intensive intervention with multiple drug combinations and behavior modification had sustained beneficial effects with respect to vascular complications and on rates of death from any cause and from cardiovascular causes. This study was not designed to identify which elements of intensive diabetes therapy contributed most to reduction in cardiovascular risk. *[With regard to aspirin, there is no evidence in this paper that directly supports the use of aspirin for primary prevention in patients with diabetes. Based on the findings presented, it is impossible to determine what, if any, of the benefit is attributable to aspirin. It is further complicated by fact that at the end of the follow-up period, there was no difference in aspirin use between groups.]*
Sirois, et al., 2008	Systematic review	M	Ø	Medline and Embase databases were searched for studies evaluating the effect of aspirin on cardiovascular outcomes in patients with type 2 diabetes.	Four studies met the inclusion criteria – three RCTs and one observational study. The three RCTs did not provide evidence to support aspirin therapy in type 2 diabetes. Reduction in cardiac mortality was found in the observational study.	These findings suggest that the clinical guidelines may be based on expected benefit correlated to what has been observed in other high-risk populations. Given the lack of hard evidence and the difference in platelet physiology in diabetes patients, aspirin use as a standard treatment should be revisited.

Author/ Year	Design Type	Class	Quality +,–,Ø	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Evangelista, et al., 2007	Case control study	C	Ø	Cases were 82 patients who were taking aspirin 100 mg/day for at least one month with and without prior CVD events. Controls patients were identified among those attending cardiology outpatient unit for a routine visit. Control patients did not have diabetes. Consecutive patients were enrolled with a match of 2:1 (cases:controls).	The objective of this study was to explore the hypothesis that aspirin is less likely to adequately suppress biochemical markers of inflammation and platelet activation in patients with diabetes compared to those without diabetes. The results showed that TxA2 (pharmacological target of aspirin) synthesis and circulation levels of markers of platelet activation sCD40L and sP-selection) in patients with and without diabetes who were treated with low-dose aspirin. The odds of having 11-dehydro-TxB2 within the upper quartile was 3.9 (95% CI 1.1-14.3) in patients with diabetes compared to controls. The odds of having sCD40L and sP-selection within the upper quartile was 12.6 (95% CI 2.4-65.5) higher in cases than controls. There were not substantial differences in low-grade inflammatory reaction between cases and controls.	The authors suggest reconsideration of the clinical pharmacology of aspirin in diabetes. They further explain that the similarity of inflammatory markers in cases and controls indicates a similar atherosclerotic and inflammatory background and suggests that up-regulation of the platelet response is not mainly related to differences in vascular-inflammatory environment. Rather, an up-regulation of platelet response appears to be due to intrinsic platelet alteration associated with insufficient metabolic control.

Author/ Year	Design Type	Class	Quality +,–,Ø	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Serebruany, et al., 2008 PLUTO-Diabetes Trial	RCT	A	Ø	70 patients with documented diabetes already treated with antecedent aspirin were randomly assigned to receive clopidogrel and 81 mg aspirin or 81 mg aspirin alone.	The primary objective of this study was to compare changes in multiple platelet activation biomarkers with 2 antiplatelet strategies over a treatment period of 3 days. There were no significant changes from baseline to 30 days in the aspirin-alone group. In the clopidogrel-plus-aspirin group, there was significant inhibition of platelet activity assessed by adenosine diphosphate aggregation (p=0.0001), closure time prolongation (p=0.0003) and reduction of platelet activation units (p=0.0001) and expression of platelet/endothelial cell adhesion molecule (p=0.02), glycoprotein antigen (p=0.0002).	The authors conclude that treatment with clopidogrel and aspirin for 1 month provides significantly greater inhibition of platelet activity than aspirin alone in patients with type 2 diabetes. This is in contrast to identically designed studies in coronary artery disease, post-stroke or heart failure patients who exhibit lower residual platelet activation compared to diabetes patients. The implications of this study for clinical practice are not evident. It cannot be determined from this short study whether more potent anti-platelet potency with combination therapy will result in better outcomes. *[This study is designed as a pilot, so it is not powered adequately to detect small differences.]*

Conclusion Grading Worksheet F – Annotations #28, 36 (Treatment with ACE Inhibitors or ARBs)

Work Group's Conclusion: For patients with type 2 diabetes mellitus, ACE inhibitors or ARBs can reduce progression of micro- and macrovascular complications.

Conclusion Grade: I

Author/ Year	Design Type	Class	Quality +,–,0	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Lewis, et al., NEJM, 2001	RCT	A	+	-1,715 patients (30-70 years) from 210 clinical centers with hypertension, nephropathy (urinary protein excretion >899 mg/24 hour), creatinine 1.0-3.0 mg/dL (men) or 1.2-3.0 mg/dL (women), and type 2 diabetes -Patients randomly assigned 300 mg/day of irbesartan, 10 mg/day of amlodipine, or placebo -Patient, provider and data analysts were blinded -Mean follow-up 2.6 years	-Primary composite end point (PCE): doubling baseline creatinine, onset of ESRD (dialysis, transplantation or creatinine >5.9 mg/dL), or death from any cause -Cardiovascular composite end point (CCE): cardiovascular death, non-fatal MI, CHF requiring hospitalization, permanent neurological deficit from CVA, or lower limb amputation above ankle -PCE showed a 20% relative risk (RR) reduction for irbesartan vs. placebo (p=0.006) and a 23% RR reduction for irbesartan vs. amlodipine (p=0.006) -There were no significant differences in CCEs or rates of death from any cause between groups	-The angiotensin-II-receptor blocker irbesartan is effective in protecting against the progression of nephropathy due to type 2 diabetes. This protection is independent of the reduction in blood pressure it causes.
Heart Outcomes Prevention Evaluation (HOPE) Study Investigators, Lancet, 2000	RCT	A	+	-3,577 patients with diabetes included in the HOPE study (patients had previous cardiovascular event or at least one other cardiovascular risk factor, no clinical proteinuria, heart failure, or low ejection fraction, and not taking ACE inhibitors) -Patients randomly assigned ramipril (10 mg/day) or placebo, and vitamin E or placebo in 2 by 2 factorial design -All patients ages 55 years of age or older -4.5-year follow-up	-Combined primary outcome: MI, stroke and cardiovascular death -Ramipril reduced the risk of combined primary outcome by 25% (95CI 12%-36%, p=0.0004), MI by 22% (95CI 6%-36%, p=0.01), stroke by 33% (95CI 10%-50%, p=0.0074), cardiovascular death by 37% (95CI 21%-51%, p=0.0001), total mortality by 24% (95CI 8%-37%, p=0.004), revascularization by 17% (95CI 2%-30%, p=0.031), overt nephropathy by 24% (95CI 3%-40%, p=0.0004), combined primary outcome by 25% (95CI 12-36, p=0.027) -After adjustment for changes in systolic and diastolic blood pressures, ramipril still lowered the risk of the combined primary outcome by 25% (95CI 12%-36%, p=0.0004) -The study was stopped 6 months early because of a consistent benefit of ramipril compared to placebo	-Ramipril was beneficial for cardiovascular events and overt nephropathy in people with diabetes. The cardiovascular benefit was greater than that attributable to the decrease in BP. This treatment represents a vasculoprotective and renoprotective effect for people with diabetes.

Conclusion Grading Worksheet G – Annotations # 28, 36 (Thiazide Diuretics)

Work Group's Conclusion: For patients with type 2 diabetes mellitus, thiazide diuretics in the treatment of hypertension can reduce cardiovascular events, particularly heart failure.

Conclusion Grade: I

Author/ Year	Design Type	Class	Quality +,–,ø	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) Officers and Research Group, 2002 ALLHAT trial	RCT	A	+	-12,063 patients with type 2 diabetes with hypertension as part of a large, multicenter (623 North American centers) including a total of 33,357 patients -Mean age 67 years -53% male; 47% White, 32% Black, and 15% Hispanic -Mean follow-up 4.9 years	**Amlodipine 2.5-10 mgm vs. Chlorthalidone 12.5-25 mgm/d** -All-cause mortality: relative risk (RR) 0.96 (95%CI 0.82-1.07) -Stroke: RR 0.9 (95%CI 0.75-1.08) -Combined CV disease: RR 1.06 (95%CI 0.98-1.15) -Any heart failure: RR 1.42 (95%CI 1.23-1.64) **Lisinopril 10-40 mgm vs Chlorthalidone 12.5-25 mgm/d** -All-cause mortality: RR 1.02 (95%CI 0.91-1.13) -Stroke: RR 1.07 (95%CI 0.9-1.28) -Combined CV disease: RR 1.08 (95%CI 1.0-1.17) -Any heart failure: RR 1.22 (95%CI 1.06-1.42)	-For type 2 diabetic patients, lisinopril appeared to have no special advantage (and amlodipine no special detrimental effect) for most CVD outcomes when compared with chlorthalidone. *-Because the main intent was to compare thiazide, calcium channel blocker, and ACE inhibitor treatment, the available step-up for further management of hypertension for patients on ACE inhibitors led to less than typical regimen (use of sympatholytics rather than diuretics and calcium channel blockers). Since a large proportion of diabetes patients require more than one drug to control their BP, this study suggests that a diuretic should be included in all multidrug regimens.*
Wing et al., 2003 ANBP2 Trial	RCT	A	ø	-6,083 patients (from 1,594 family medical practices throughout Australia) -Only 7% with diabetes -95% Caucasian -Mean age 72 years -Patient groups were equal at randomization, followed for 4.1 years with intention-to-treat analysis (0.2% lost to f/u)	-**Enalapril (ACE inhibitor) vs. Hydrochlorothiazide (diuretic)** -All CV events or death from any cause: Hazard ratio (HR) 0.89 (95%CI 0.79-1.00) -First CV event or death from any cause: HR 0.89 (95%CI 0.79-1.01) -Death from any cause: HR 0.9 (95%CI 0.75-1.09) -58%-62% receiving treatment assigned at the end of study and equal BP response (systolic/diastolic) in both groups -in post hoc analysis, largest effect seen in male patients	-Initiation of antihypertensive treatment involving ACE inhibitors in older subjects, particularly men, appears to lead to better outcomes than treatment with diuretic agents, despite similar reductions of blood pressure. *-There was a lower prevalence of diabetes than might have been expected (7%) mostly because the study population was overrepresented by elderly Caucasian patients.* *-Vascular outcomes and death were worse using hypertensive regimen emphasizing hydrochlorothiazide compared to ACE inhibition.* *-Also, insufficient information is provided to discern whether groups were treated equally.*

This section provides resources, strategies and measurement specifications for use in closing the gap between current clinical practice and the recommendations set forth in the guideline.

The subdivisions of this section are:

- Priority Aims and Suggested Measures
- Key Implementation Recommendations
- Knowledge Resources
- Resources Available

Priority Aims and Suggested Measures

A multifactorial intervention targeting hyperglycemia and cardiovascular risk factors in individuals with diabetes is most effective. Both individual measures of diabetes care, as well as comprehensive measures of performance on broader sets of measures, are recommended. A randomized controlled trial has shown a 50% reduction in major cardiovascular events through a multifactorial intervention targeting hyperglycemia, hypertension, dyslipidemia, microalbuminuria, aspirin and ACE inhibitor use in individuals with microalbuminuria *(Gaede, 2003 [A])*.

Goals for A1c, low-density lipoprotein and other diabetes measures should be personalized, and lower goals for A1c and low-density lipoprotein than those included here in the priority aims and measures may be clinically justified in some adults with type 2 diabetes. However, efforts to achieve lower A1c below 7% may increase risk of mortality, weight gain, hypoglycemia and other adverse effects in many patients with type 2 diabetes. Therefore, the aims and measures listed here are selected carefully in the interests of patient safety.

1. **Diabetes Optimal Care Measures:** Maximize the percentage of adult patients, ages 18-75 with type 2 diabetes mellitus, who in a defined period of time achieve any of the following measures of established control:

   Possible measures for accomplishing this aim:

   a. Percentage A1c less than 8%

   b. Percentage on a statin

   c. Percentage with LDL less than 100 mg/dL

   d. Percentage of type 2 diabetes patients with blood pressure measured in last year and most recent BP less than 130/80 mmHg

   e. Percentage of type 2 diabetes patients who are current documented non-smokers

   f. Percentage of type 2 diabetes patients ages 41-75 with type 2 diabetes mellitus and with coronary artery disease (CHD, defined as one or more ICD-9 codes for CHD listed at ncqa.org) who take daily aspirin or another antiplatelet medication

Notes to diabetes optimal care measures:

1a. A1c measure: The A1c goal for type 2 diabetes patients should be personalized. The optimal clinical A1c goal for many diabetes patients is lower than 8% (see Annotation # 11).

1c. Low-density lipoprotein measure: The optimal clinical low-density protein goal for some patients with diabetes, such as those with coronary artery disease, may be lower than 100 mg/dL. Patients who are or may become pregnant should not use most lipid-lowering agents including statins. The benefit of low-density protein reduction is less in younger than in middle-aged or older patients with type 2 diabetes.

1f. Aspirin measure: This recommendation is subject to modification on the basis of clinical trials that are expected to report their findings in the next year.

2. **Diabetes Optimal Care Comprehensive Measure Set:** Maximize the percentage of adult patients ages 18-75 with type 2 diabetes mellitus, who in a one-year period of time achieve each of the following measures of care.

   Possible measures for accomplishing this aim:

   a. Percentage with A1c less than 8%

   b. Percentage with LDL less than 100 mg/dL

   c. Percentage with blood pressure measured in last year and most recent blood pressure less than or equal to 130/80 mmHg

   d. Percentage who are current documented non-smokers.

Notes to diabetes optimal care comprehensive measures:

All-or-none approach of process quality yields a picture quite different from either the item-by-item approach or the composite approach *(Nolan, 2006 [])*. All or none more closely reflects the interests and likely desires of the patient.

2a. A1c measure: The A1c goal for type 2 diabetes patients should be personalized. The optimal clinical A1c goal for many diabetes patients is lower than 8% (see Annotation #11).

2b. Low-density protein measure: The optimal clinical low-density protein goal for some patients with diabetes, such as those with coronary artery disease, may be lower than 100 mg/dL. Patients who are or may become pregnant should not use most lipid-lowering agents including statins. The benefit of low-density protein reduction is less in younger than in middle-aged or older patients with type 2 diabetes.

3. **Diabetes Process of Care Measure Set:** Maximize the percentage of adult patients ages 18-75 with type 2 diabetes mellitus for whom recommended screening procedures are done.

   Possible measures for accomplishing this aim:

   a. Percentage of patients with type 2 diabetes mellitus with A1c test in the last 12 months.

   b. Percentage of patients with type 2 diabetes mellitus receiving a lipid profile in the last 12 months.

   c. Percentage of patients with type 2 diabetes mellitus receiving one or more blood pressure measurements in the last 12 months.

   d. Nephropathy screening rate: DENOMINATOR: Include those patients with type 2 diabetes mellitus who are either (a) not on an ACE or ARB medication OR (b) not diagnosed with chronic kidney disease. NUMERATOR: Those who are included in the denominator who have one or more microalbuminuria tests within the last 12 months. (Suitable tests include CPT Codes such as 820.43 ["urine, microalbumin, quantitative"], or 841.55 ["protein; total, except refractometry"]).

   e. Retinopathy screening rate: percentage of patients with type 2 diabetes mellitus with dilated eye exam within the last 24 months. The nature of the exam is not specified and may be completed by an ophthalmologist or optometrist.

   f. Foot care screening rate: percentage of patients with type 2 diabetes mellitus with a comprehensive foot exam documented in the last year *(HEDIS, 2009)*.

   g. **Diabetes process of care comprehensive measure:** percentage of patients with type 2 diabetes, age 18-75 with type 2 diabetes mellitus, for whom all the recommended screening procedures (3a to 3f above) were done in the indicated time frames.

Notes to diabetes process of care measure set:

3e. Retinopathy screening intervals should be personalized to the patient. Some patients, especially those with elevated A1c or blood pressure, or with a previously abnormal retinal exam, may benefit from shorter screening intervals.

3g. Unlike the Diabetes Optimal Measures, there is no upper limit recommended on appropriate levels of performance on the Diabetes Process of Care Measure Set.

4. **High-Risk Population Measures:** The purpose of this aim is to identify and focus on a higher risk population by decreasing the percentage of adult patients, ages 18-75 with type 2 diabetes mellitus, with poorly controlled glucose and cardiovascular risk factors (clinical strategies that target high-risk populations may be more viable with limited resources).

   Possible measures for accomplishing this aim:

   a. Percentage of patients with type 2 diabetes mellitus with Alc test in the last year greater than 9%. *(HEDIS, 2009)*

   b. Percentage of patients with type 2 diabetes mellitus with low-density lipoprotein test in the last year greater than 130 mm/dL.

   c. Percentage of patients with type 2 diabetes mellitus with blood pressure greater than 140/90 mmHg.

   d. Percentage of patients with type 2 diabetes mellitus with A1c greater than 9% or low-density lipoprotein greater than 130 Mg/dL or blood pressure greater than 140/90 mmHg (high-risk comprehensive measures).

   e. Percentage of patients with type 2 diabetes mellitus who are active smokers.

At this point in development for this guideline, there are no specifications written for possible measures listed above. ICSI will seek input from the medical groups on what measures are of most use as they implement the guideline. In a future revision of the guideline, measurement specifications may be included.

Key Implementation Recommendations

The implementation of type 2 diabetes mellitus clinical guidelines at medical groups and clinics is a complex and challenging task. However, a number of key processes have been shown to accelerate effective clinical guideline implementation and care improvement *(Sperl-Hillen, 2005 [D])*. These overlapping care elements can be categorized at the medical group and provider levels:

- Essential Elements at the Medical Group Level:
  - **Leadership.** Medical group leaders must communicate the need for change in clinical practice patterns and consistently identify improvement priorities.
  - **Resources.** Resources adequate to the task at hand will be needed to assure the success of a change effort. Resources may include staff time, money and provision of tools (such as electronic medical records) to support care improvement.
  - **Select Specific Improvement Goals and Measures.** For most chronic diseases, including diabetes, the most efficient improvement strategy is to focus on a limited number of specific improvement goals. These may be based on observed gaps in care, potential clinical impact, cost considerations or other criteria *(O'Connor, 2005a [D])*. In type 2 diabetes, focusing on glycemic control, lipid control and blood pressure control is a strategy that has been shown to be effective in preventing up to 53% of heart attacks and strokes, the leading drivers of excess mortality and costs in adults with diabetes *(Gaede, 2003 [A])*.
  - **Accountability.** Accountability within the medical group is a management responsibility, but external accountability may also play an important enhancing role to motivate sustained efforts to implement guidelines and improve care. Examples of external accountability include participation in shared learning activities (such as Institute for Healthcare Improvement or ICSI and its action groups), or public reporting of results (such as in pay-for-performance or the Minnesota Community Measures Project).
  - **Prepared Practiced Teams.** The medical group may need to foster the development of prepared practice teams that are designed to meet the many challenges of delivering high-quality chronic disease care.
- Essential Elements at the Clinic Level:
  - **Develop "Smart" Patient Registries.** These are registries that are designed to identify, automatically monitor, and prioritize patients with diabetes based on their risk, current level of control, and possibly patient readiness-to-change.
  - **Assure "Value-Added" Visits.** These are office visits or other patient encounters (by phone, e-mail, etc.) that include intensification of treatment if the patient has not yet reached his/her evidence-based clinical goals. Failure of providers and patients to intensify treatment when indicated (referred to as "clinical inertia") is a key obstacle to better diabetes care (*O'Connor, 2003 [R]; O'Connor, 2005a [R]; O'Connor, 2005b [R]*). HSR editorial. Previsit planning and best practice prompts may help to increase the efficiency of patient visits and remind providers of needed tests and care.
  - **Develop "Active Outreach."** These are strategies to reach patients with chronic disease who have not returned for follow-up or for other selected elements of care. Outreach strategies that enhance the likeliness of a future provider encounter that addresses one of the barriers to patient activation (discussed below) may be more effective. Simple reporting of lab test results or care suggestions through the mail may be ineffective at addressing these barriers.

- **Emphasize "Patient Activation" Strategies.** These may include diabetes education and other actions designed to sustain engagement of patients with their diabetes care. Many patients with diabetes either (a) do not really believe they have diabetes, or (b) do not really believe that diabetes is a serious disease, or (c) lack motivation for behavioral change, or (d) do not believe that recommended treatments will make a difference to their own outcomes. For care to be effective, these issues must be addressed for many patients *(O'Connor, 1997 [D])*.

Knowledge Resources

Criteria for Selecting Resources

The following resources were selected by the Diagnosis and Management of Type 2 Diabetes Mellitus in Adults guideline work group as additional resources for providers and/or patients. The following criteria were considered in selecting these resources.

- The site contains information specific to the topic of the guideline.
- The content is supported by evidence-based research.
- The content includes the source/author and contact information.
- The content clearly states revision dates or the date the information was published.
- The content is clear about potential biases, noting conflict of interest and/or disclaimers as appropriate.

Resources Available to ICSI Members Only

ICSI has a wide variety of knowledge resources that are ***only*** available to ICSI members (these are indicated with an asterisk in far left-hand column of the Resources Available table). In addition to the resources listed in the table, ICSI members have access to a broad range of materials including tool kits on CQI processes and Rapid Cycling that can be helpful. To obtain copies of these or other Knowledge Resources, go to http://www.icsi.org/improvement_resources. To access these materials on the Web site, you must be logged in as an ICSI member.

The resources in the table on the next page that are not reserved for ICSI members are available to the public free-of-charge.

Resources Available

*	Author/Organization	Title/Description	Audience	Web Sites/Order Information
	American Diabetes Association	**American Diabetes Association:** The mission of the association is to prevent and cure diabetes and to improve the lives of all people affected by diabetes. All About Diabetes	Patients and Families	http://www.diabetes.org/about-diabetes.jsp 1-800-232-6733
	American Diabetes Association	**American Diabetes Association:** The mission of the association is to prevent and cure diabetes and to improve the lives of all people affected by diabetes. Basic Carbohydrate Counting (booklet)	Patients and Families	http://www.diabetes.org/shop-for-books-and-gifts.jsp American Drug Administration #S623-01 1-800-232-6733
	American Diabetes Association	**American Diabetes Association:** The mission of the association is to prevent and cure diabetes and to improve the lives of all people affected by diabetes. Complete Guide to Diabetes (book)	Patients and Families	http://www.diabetes.org/shop-for-books-and-gifts.jsp American Drug Administration #4809-04; 1-800-232-6733
	American Diabetes Association	**American Diabetes Association:** The mission of the association is to prevent and cure diabetes and to improve the lives of all people affected by diabetes. Complete Guide to Carbohydrate Counting (booklet)	Patients and Families	http://www.diabetes.org/shop-for-books-and-gifts.jsp American Drug Administration #4715-02 1-800-232-6733
	American Diabetes Association	**American Diabetes Association:** The mission of the association is to prevent and cure diabetes and to improve the lives of all people affected by diabetes. Complete Guide to Diabetes (book)	Patients and Families	http://www.diabetes.org/shop-for-books-and-gifts.jsp American Drug Administration #4809-04; 1-800-232-6733
	American Diabetes Association	**American Diabetes Association and American Dietetic Association:** The mission of the associations are to prevent and cure diabetes and to improve the lives of all people affected by diabetes. Exchange Lists for Meal Planning (pamphlet)	Patients and Families	http://www.diabetes.org/nutrition-and-recipes/nutrition/exchangelist.jsp 1-800-232-6733

* Available to ICSI members only.

*	Author/Organization	Title/Description	Audience	Web Sites/Order Information
	American Diabetes Association	**American Diabetes Association:** The mission of the association is to prevent and cure diabetes and to improve the lives of all people affected by diabetes. Healthy Food Choices (pamphlet)	Patients and Families	http://www.diabetes.org/nutrition-and-recipes/nutrition/healthyfoodchoices.jsp 1-800-232-6733 #5903-03 (English) #5903-13 (Spanish)
	American Diabetes Association	**American Diabetes Association:** The mission of the association is to prevent and cure diabetes and to improve the lives of all people affected by diabetes. Wide variety of information on diabetes as well as recent publications; series of journals for both consumers and health professionals; community resources.	Patients and Families; Health Care Professionals	http://www.diabetes.org
	Centers for Disease Control and Prevention	**Centers for Disease Control and Prevention:** Educational materials in Spanish as well as English, and low literacy public health and community campaigns for educating about diabetes and diabetes prevention.	Patients and Families	http://www.cdc.gov/diabetes
	HealthFinder	**HealthFinder:** A-Z health information organizations and health care topics.	Patients and Families	http://www.healthfinder.gov
*	ICSI	**Chronic Care Action Group Summary 2002:** ICSI Action Group/ Redesign Collaborative Summary Reports are designed to describe key activities conducted in a collaborative while highlighting results achieved by participating member organizations.	Health Care Professionals	http://www.icsi.org
*	ICSI	**Chronic Care Action Group Summary 2003:** ICSI Action Group/ Redesign Collaborative Summary Reports are designed to describe key activities conducted in a collaborative while highlighting results achieved by participating member organizations.	Health Care Professionals	http://www.icsi.org
*	ICSI	**Continual Improvement Collaborative within the Disease Management Strategy Program at Mayo Clinic, Rochester:** Describes Mayo Clinic's approach to utilizing teams to implement health care guidelines & improve care to patients. (12/99)	Health Care Professionals	http://www.icsi.org

* Available to ICSI members only.

*	Author/Organization	Title/Description	Audience	Web Sites/Order Information
*	ICSI	**Diabetes Action Group 1997-2005 Summary:** ICSI Action Group/Redesign Collaborative Summary Reports are designed to describe key activities conducted in a collaborative while highlighting results achieved by participating member organizations.	Health Care Professionals	http://www.icsi.org
*	ICSI	**Diabetes Education Program – Patient Survey at HealthEast:** HealthEast implemented a Diabetes Education Program to increase patient self-management of diabetes. Feedback was solicited from patients to identify the types of education & follow-up they needed to manage their diabetes. (12/99)	Health Care Professionals	http://www.icsi.org
*	ICSI	**Diabetes Patient Registries:** Three Medical Groups' Experience: HealthEast Clinics, HealthPartners Medical Group and Mayo Clinic have developed a patient registry to improve management of diabetes care. This report explores how these three groups are using the registry to best use and design criteria for the registry. (3/01)	Health Care Professionals	http://www.icsi.org
	ICSI	Translation for Patients of the ICSI Type 2 Diabetes Mellitus guideline (guideline)	Patients and Families	(952) 814-7060 or http://www.icsi.org
	International Diabetes Center	**International Diabetes Center:** International Diabetes Center at Park Nicollet has provided world-class diabetes care, education, publications and research programs that have met the needs of people with diabetes and their families since 1967. Blood Glucose Patterns (booklet)	Patients and Families	http://www.idcpublishing.com IDC #2058-816A
	International Diabetes Center	**International Diabetes Center:** International Diabetes Center at Park Nicollet has provided world-class diabetes care, education, publications and research programs that have met the needs of people with diabetes and their families since 1967. Carbohydrate Counting Booklet	Patients and Families	http://www.idcpublishing.com IDC #2058-802

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	International Diabetes Center	**International Diabetes Center:** International Diabetes Center at Park Nicollet has provided world-class diabetes care, education, publications and research programs that have met the needs of people with diabetes and their families since 1967. Exchanges for All Occasions - Pocket Edition (book)	Patients and Families	http://www.idcpublishing.com IDC #2058-EAOP
	International Diabetes Center	**International Diabetes Center:** International Diabetes Center at Park Nicollet has provided world-class diabetes care, education, publications and research programs that have met the needs of people with diabetes and their families since 1967. Fast Food Facts - Pocket Edition (book)	Patients and Families	http://www.idcpublishing.com IDC #2058-853
	International Diabetes Center	**International Diabetes Center:** International Diabetes Center at Park Nicollet has provided world-class diabetes care, education, publications and research programs that have met the needs of people with diabetes and their families since 1967. Healthy Eating (booklet)	Patients and Families	IDC #2058-814 (English) #2058-821 (Spanish)
	International Diabetes Center	**International Diabetes Center:** International Diabetes Center at Park Nicollet has provided world-class diabetes care, education, publications and research programs that have met the needs of people with diabetes and their families since 1967. Managing Type 2 Diabetes (book)	Patients and Families	http://www.idcpublishing.com IDC #2058-850
	International Diabetes Center	**International Diabetes Center:** International Diabetes Center at Park Nicollet has provided world-class diabetes care, education, publications and research programs that have met the needs of people with diabetes and their families since 1967. My Food Plan (pamphlet)	Patients and Families	http://www.idcpublishing.com IDC #2058-25 (English) #2058-823 (Spanish)

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	International Diabetes Center	**International Diabetes Center:** International Diabetes Center at Park Nicollet has provided world-class diabetes care, education, publications and research programs that have met the needs of people with diabetes and their families since 1967. My Insulin Plan (pamphlet)	Patients and Families	http://www.idcpublishing.com IDC #2058-827
	International Diabetes Center	**International Diabetes Center:** International Diabetes Center at Park Nicollet has provided world-class diabetes care, education, publications and research programs that have met the needs of people with diabetes and their families since 1967. Record booklet	Patients and Families	http://www.idcpublishing.com IDC #2058-231
	International Diabetes Center	**International Diabetes Center:** International Diabetes Center at Park Nicollet has provided world-class diabetes care, education, publications and research programs that have met the needs of people with diabetes and their families since 1967. Safe and Healthy Exercise (booklet)	Patients and Families	http://www.idcpublishing.com IDC-2058-805
	International Diabetes Center	**International Diabetes Center:** International Diabetes Center at Park Nicollet has provided world-class diabetes care, education, publications and research programs that have met the needs of people with diabetes and their families since 1967. Staying Healthy with Type 2 Diabetes (booklet)	Patients and Families	http://www.idcpublishing.com IDC #2058-824 (English) #2058-825 (Spanish)
	International Diabetes Center	**International Diabetes Center:** International Diabetes Center at Park Nicollet has provided world-class diabetes care, education, publications and research programs that have met the needs of people with diabetes and their families since 1967. Type 2 Diabetes Basics (client book)	Patients and Families	http://www.idcpublishing.com IDC-2058-BCBK

* Available to ICSI members only.

Resources Available

*	Author/Organization	Title/Description	Audience	Web Sites/Order Information
	Labat & Maggi	Weight Management for Type II Diabetes (book)	Patients and Families	pub. by Wiley & Sons ISBN #0471347507
	Mayo Clinic	**Mayo Clinic: Disease and Condition Centers** Information and tools to help you manage a chronic disease or condition.	Patients and Families	http://www.mayoclinic.com
	Minnesota Community Measurement	The D5.org The D5 is a set of five treatment goals that, when achieved together, represent the gold standard for managing diabetes. Reaching all five goals greatly reduces a patient's risk for the cardiovascular problems associated with diabetes.	Patients and Families	http://www.theD5.org
	National Institutes of Diabetes, Digestive and Kidney Diseases	**National Institute of Diabetes, Digestive and Kidney Diseases:** Data, statistics, information for health professionals, educational materials in Spanish as well as English, and low literacy. This Web site is a division of the National Institutes of Health.	Patients and Families; Health Care Professionals	http://www.niddk.nih.gov Also, links to NDEP, NKDEP, NIDDK
	National Institutes of Health	**National Institutes of Health:** This user-friendly site helps you start a search for health information by directing you to some credible databases.	Health Care Professionals	http://www.nih.gov
*	Park Nicollet Health Services	**Diabetes, What You Need To Know:** Provided by Park Nicollet Health Services (brochure)	Patients and Families	http://www.icsi.org
	Protocol Driven Healthcare	**Protocol Driven Healthcare:** Self-management interactive site, information on diabetes and managing it, chat rooms, capacity to e-mail for questions.	Patients and Families	http://www.mydiabetes.com
	Staywell/Krames	Diabetes and Exercise (brochure)	Patients and Families	1-800-333-3032

* Available to ICSI members only.

*	Author/Organization	Title/Description	Audience	Web Sites/Order Information
	The Food and Nutrition Information Center	**The Food and Nutrition Information Center:** Sponsored by the United States Department of Agriculture (USDA), this site is user friendly and filled with current information on almost any nutrition topic.	Patients and Families; Health Care Professionals	http://www.nal.usda.gov/fnic/
	WebMD Corporation	**Web MD:** Wide variety of information on diabetes as well as recent publications; series of journals for both consumers and health professionals; clinical resource for providers, and education materials that providers can download for their patients.	Patients and Families; Health Care Professionals	http://www.webMD.com

* Available to ICSI members only.