

**\*\* FDA Safety and Adverse Event Warning \*\***

**Carbamazepine and Patients of Asian Ancestry  
(Carbatrol®, Equetro®, Tegretol®, and generics)**

On December 12, 2007, the Food and Drug Administration (FDA) issued a Safety Information and Adverse Event Report regarding the use of Carbamazepine and the development of dangerous and even fatal skin reactions (Steven Johnson syndrome and toxic epidermal necrolysis) in patients with a particular human leukocyte antigen (HLA) allele, HLA-B\*1502. The HLA-B\*1502 allele occurs almost exclusively in patients with ancestry across Asia, including South Asian Indians.

The FDA is recommending that patients of Asian ancestry be screened for the presence of the HLA-B\*1502 allele before starting treatment with Carbamazepine. If the test is positive, then therapy with Carbamazepine should not be used unless the expected benefit clearly outweighs the increased risk of serious skin reactions.

Patients who have been taking Carbamazepine for more than a few months without developing skin reactions are at low risk for these events, even for patients of any ethnicity or genotype, including patients positive for the HLA-B\*1502 allele.

For more information, please refer to the information listed on the Food and Drug Administration's Web site.

<http://www.fda.gov/medwatch/safety/2007/safety07.htm#carbamazepine>

**\*\* FDA SAFETY AND ADVERSE EVENT WARNING \*\***

**IBUPROFEN AND ASPIRIN TAKEN TOGETHER**

On September 8, 2006, the Food and Drug Administration issued a Safety Information and Adverse Event Report regarding the concomitant use of low-dose aspirin (for cardioprotective benefits) and ibuprofen.

The report indicates that 400 mg ibuprofen taken with immediate-release low-dose aspirin (81 mg) will interfere with the antiplatelet effect of aspirin. Other over-the-counter NSAIDs should be viewed as having potential to interfere with the antiplatelet effect of aspirin.

Recommendations include taking immediate release low-dose aspirin 30 minutes prior to taking ibuprofen. If ibuprofen is taken first, aspirin should not be taken for at least 8 hours after ingestion of ibuprofen. Other analgesics that do not interfere with the antiplatelet effect of aspirin should be considered in populations at high-risk for cardiovascular events.

Enteric-coated aspirin and concomitant use of ibuprofen is unclear. One study showed that 400 mg ibuprofen interfered with the antiplatelet effect of enteric-coated low-dose aspirin at 2, 7, and 12 hours after ingestion (*Catella-Lawson, 2001*).

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>



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# Health Care Guideline

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

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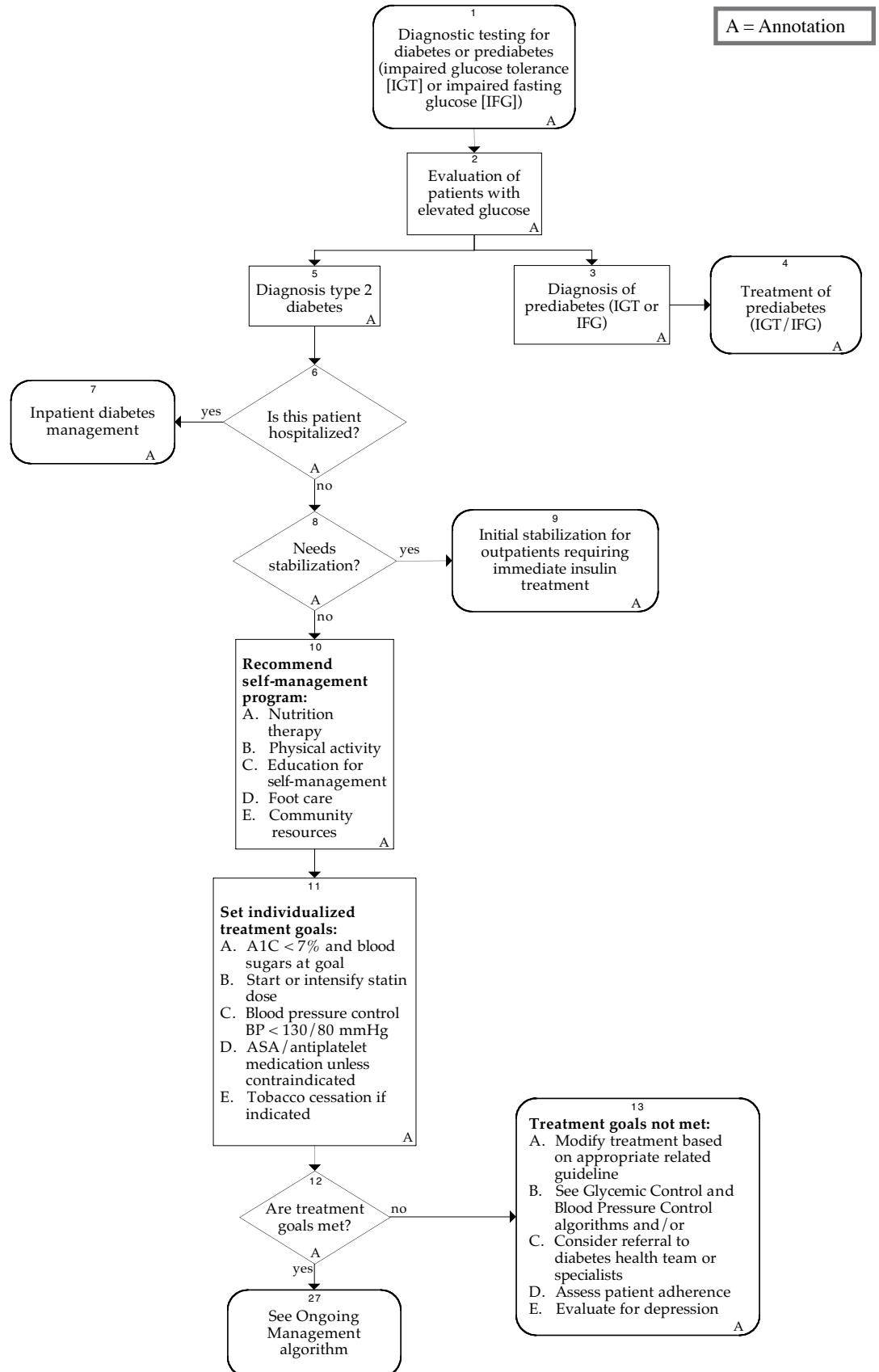
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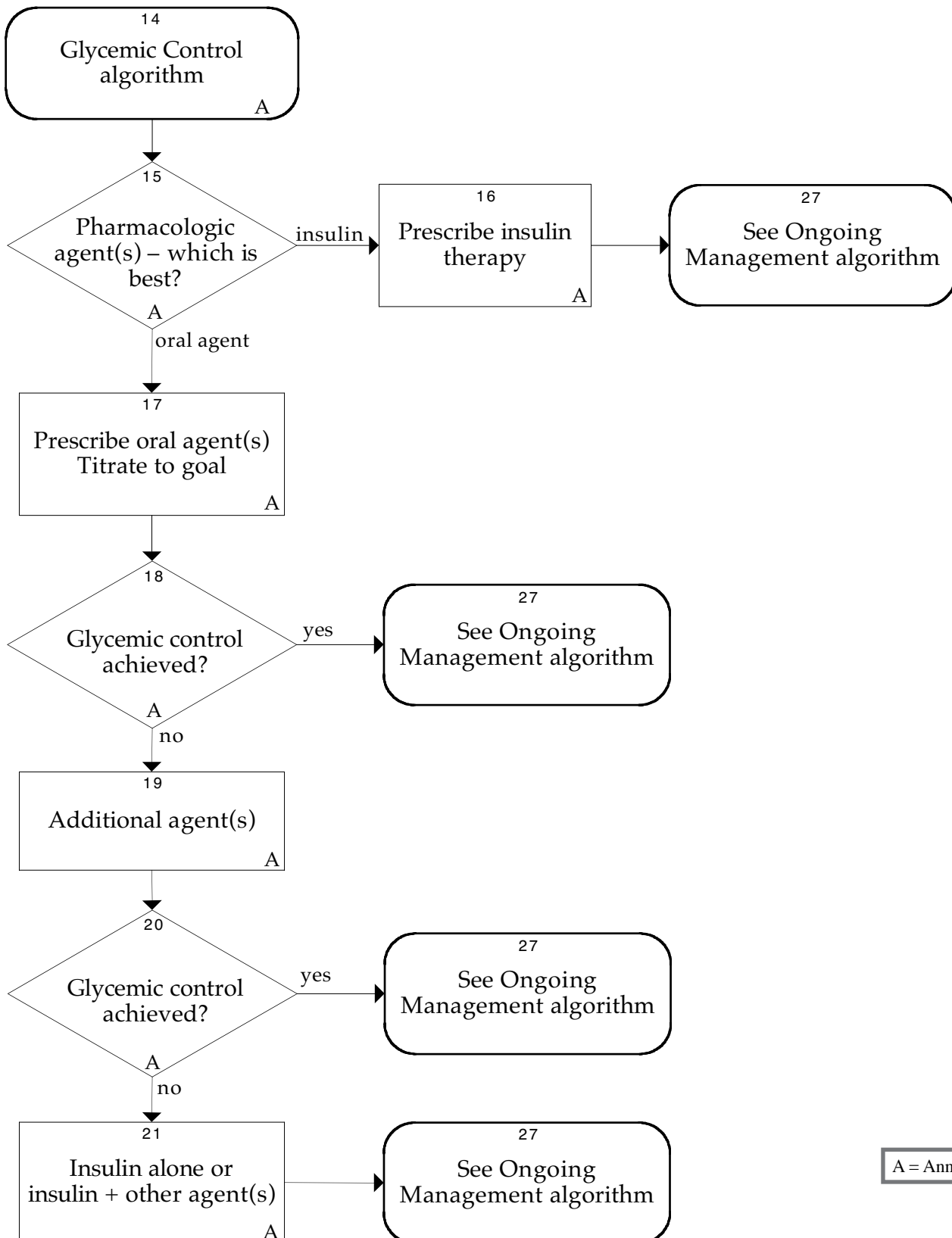
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These clinical guidelines are designed to assist clinicians by providing an analytical framework for the evaluation and treatment of patients, and are not intended either to replace a clinician's judgment or to establish a protocol for all patients with a particular condition. A guideline will rarely establish the only approach to a problem.

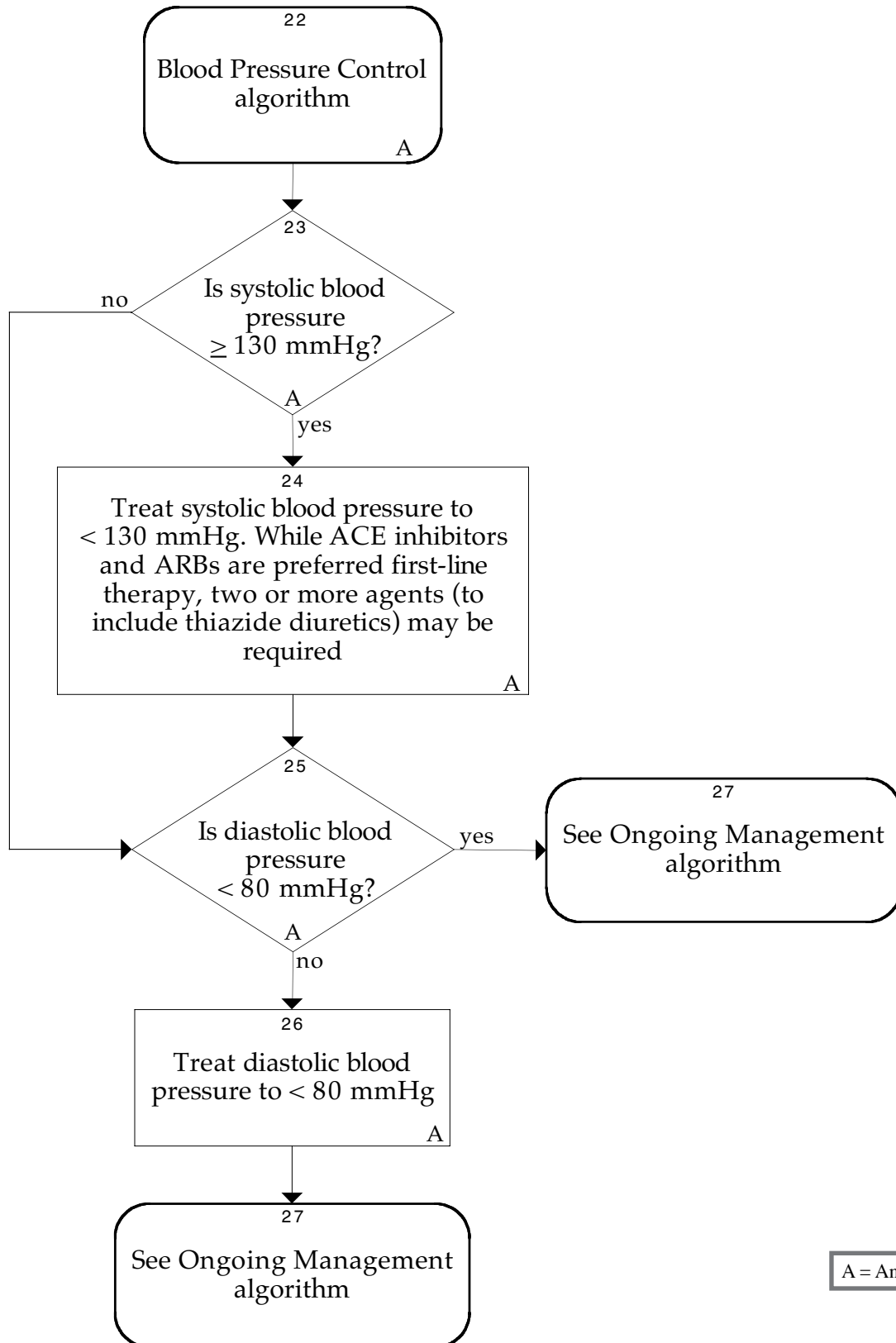


## Glycemic Control Algorithm

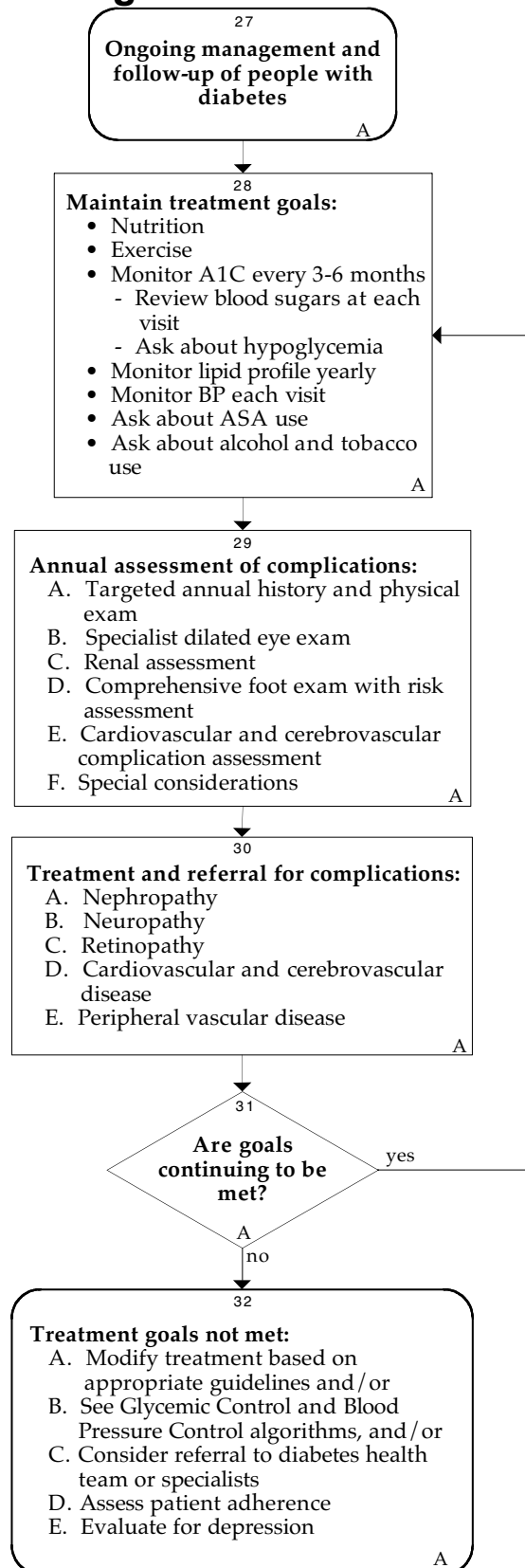


A = Annotation

## Blood Pressure Control Algorithm



## Ongoing Management Algorithm



A = Annotation

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## Foreword

### Scope and Target Population

To provide a comprehensive approach to the management of "prediabetes" (impaired fasting glucose or impaired glucose tolerance) and type 2 diabetes mellitus to include nutrition therapy, physical activity recommendations, pharmacologic therapy, self-management, as well as prevention and diagnosis of diabetes-associated complications and risk factors.

### Clinical Highlights and Recommendations

- Focus on cardiovascular risk reduction (blood pressure control, statin use, ASA, and tobacco cessation). (*Annotation #11*)
- Initial therapy with lifestyle treatment and metformin is advised unless contraindicated. (*Annotation #14*)
- Achieving an A1C of less than 7% often requires frequent drug intensification and use of combination therapy. (*Annotations #11, 17, 19, 21, 24, 25*)
- 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 #11, 20-24, 26, 30*)
- Self-management support is necessary for people with diabetes to manage their disease. (*Annotation #10*)
- Prevent microvascular complications through annual eye exams, foot risk assessments and foot care counseling, and annual screening for proteinuria. (*Annotations #13, 29*)

### 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 multifactorial interventions 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*).

1. Increase the percentage of patients with diabetes age 18-75 for whom recommended screening frequencies and ideal treatment goals are met.
2. Decrease the percentage of patients with diabetes with poorly controlled blood sugars and cardiovascular risk factors (clinical strategies that target high-risk populations may be more viable with limited resources).
3. Improve diabetes self-management skills.

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## Related ICSI Scientific Documents

### Related 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
- Stable Coronary Artery Disease
- Tobacco Use Prevention and Cessation for Adults and Mature Adolescents

### Technology Assessment Reports

- Case Management for Chronic Illness, the Frail Elderly, and Acute MI (#44, 1998)
- Diet Programs for Weight Loss in Adults (#83, 2004)
- Gastric Restrictive Surgery for Morbid Obesity (#14, 2000)
- Pancreas Transplant for Insulin-Dependent Diabetes (#4, 2003)
- Pancreatic Islet Transplantation for Patients with Type 1 Diabetes Mellitus (#60, 2002)
- Pharmacologic Approaches to Weight Loss in Adults (#71, 2003)
- Treatment of Obesity in Children and Adolescents (#90, 2005)
- Omega-3 Fatty Acids for Coronary Artery Disease (#94, 2006)
- Carotid, Vertebral and Intracranial Artery Angioplasty and Stenting (#93, 2006)

### Order Sets

- Subcutaneous Insulin Management Order Set

### Patient and Family Guidelines

- Hypertension Diagnosis and Treatment for Patients and Families
- Lipid Management in Adults for Patients and Families
- Major Depression in Adults in Primary Care for Patients and Families
- Prevention and Management of Obesity for Patients and Families
- Preventive Services for Adults for Patients and Families
- Stable Coronary Artery Disease for Patients and Families
- Tobacco Use Prevention and Cessation for Adults and Mature Adolescents for Patients and Families

## **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.

Key conclusions are assigned a conclusion grade: I, II, III, or Grade Not Assignable.

A full explanation of these designators is found in the Supporting Evidence section of the guideline.

## **Disclosure of Potential Conflict of Interest**

In the interest of full disclosure, ICSI has adopted the policy of revealing relationships work group members have with companies that sell products or services that are relevant to this guideline topic. The reader should not assume that these financial interests will have an adverse impact on the content of the guideline, but they are noted here to fully inform readers. Readers of the guideline may assume that only work group members listed below have potential conflicts of interest to disclose.

JoAnn Sperl-Hillen, MD receives grant support from KOS Pharmaceuticals for Aventis, and Pfizer.

Patrick O'Connor, MD receives grant support from Amgen, Koss and Pfizer. He is also a speaker/consultant for Merck.

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

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## Algorithm Annotations

### 1. Diagnostic Testing for Diabetes or Prediabetes (Impaired Glucose Tolerance [IGT] or Impaired Fasting Glucose [IFG])

Patients presenting with symptoms of diabetes should be tested. Possible screening tests for these conditions include a fasting plasma glucose or an oral glucose tolerance test. Testing patients with hypertension, dyslipidemia and heart disease is also recommended. Other patients at risk for diabetes are also appropriate for testing (*American Diabetes Association, 2003h*). See the ICSI Hypertension Diagnosis and Treatment guideline, the ICSI Lipid Screening guideline, the ICSI Preventive Services in Adults guideline and the Stable Coronary Artery Disease guideline.

Prediabetes is now the term recommended for patients with impaired glucose tolerance (IGT) or impaired fasting glucose (IFG).

*Supporting evidence is of class: R*

### 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.

#### A. History (*American Diabetes Association, 2003a; American Diabetes Association, 2003h*)

For all patients:

- 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, sexual function, peripheral vascular and cerebrovascular (these may be present at diagnosis)
- Current medications including over-the-counter medications and alternative therapies
- Risk factors for atherosclerosis: smoking, hypertension, dyslipidemia, family history
- Family history of diabetes, cardiovascular disease, cerebrovascular disease, dyslipidemia
- Gestational history: delivery of an infant weighing more than 9 lbs., toxemia, stillbirth or history of gestational diabetes
- Psychosocial, cultural and economic factors that might influence the management of diabetes
- Alcohol/drug use

For patients diagnosed with diabetes:

- Details of previous treatment programs, including diabetes education
- Current treatment of diabetes, including medications, nutrition, physical activity patterns and results of glucose monitoring

**Algorithm Annotations**

- Frequency, severity and cause of acute complications such as hypoglycemia, hyperglycemia, and nonketotic hyperosmolar coma

*Supporting evidence is of class: R*

**B. Physical Examination** (*American Diabetes Association, 2003a; American Diabetes Association, 2003h*)

- Weight, height, BMI, blood pressure
- Optic fundi
- Oral exam (dental and gingival health)
- Cardiovascular system: heart, peripheral circulation including pulses and bruits (abdominal, carotid, femoral)
- Skin: infections, xanthoma, insulin injection sites
- Feet: nails, web spaces, ulcers, pulses, calluses, structural deformities, protective sensation and shoes
- Neurological system: sensory state of hands and feet, muscle wasting, deep tendon reflexes
- Mental health assessment with consideration for depression/anxiety screen

*Supporting evidence is of class: R*

**C. 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 (ALT or AST)
- Urine: ketones, glucose, protein, microalbuminuria, culture (if microscopic is abnormal or symptoms of infection present)\*\*

\* Glycosylated hemoglobin assays provide an accurate indication of long-term glycemic control. A1C is formed by the continuous nonenzymatic glycosylation of hemoglobin throughout the life span 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.

A1C is not influenced by food intake, physical activity or acute metabolic stress. The test can be done at any time of day and does not require fasting.

\*\* Urine microalbumin tests can identify patients with early diabetic nephropathy when intervention may be most effective in delaying or preventing end-stage renal disease (ESRD). Single tests for urinary microalbumin and urinary creatinine can accurately detect urinary microalbumin excretion. (For more information, see Annotation #29, "Annual Assessment of Complications.") (*American Diabetes Association, 2003a; American Diabetes Association, 1994a; Nelson, 1991.*)

**Algorithm Annotations**

Increased urinary microalbumin is a predictor of increased cardiovascular mortality.

*Supporting evidence is of classes: B, R*

### **3. Diagnosis of Prediabetes (IGT or IFG)**

#### **A. Diagnosis of Impaired Fasting Glucose (IFG)** (*American Diabetes Association, 2003h*)

- Fasting plasma glucose greater than or equal to 100 mg/dL and less than 126 mg/dL

#### **B. Diagnosis of Impaired Glucose Tolerance (IGT)** (*American Diabetes Association, 2003h*)

- Oral glucose tolerance test (OGTT) two-hour plasma glucose: greater than or equal to 140 mg/dL and less than 200 mg/dL

*Supporting evidence is of class: R*

### **4. Treatment of Prediabetes (IGT/IFG)**

Intensive lifestyle behavior change programs that include monitoring of regular physical activity recommendations and nutrition counseling can reduce the risk of type 2 diabetes in this population by about 50%. The following treatments are recommended for people with prediabetes (IGT or IFG):

- 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.
- Regular follow-up and reassessment of risks including rescreening for diabetes every one-three years (*American Diabetes Association, 2003i; Chiasson, 2002; Eriksson, 1999; HOPE Study Investigators, 2002; Kelly, 2002; Miles, 2002*).
- There is some evidence of prevention of diabetes through pharmacotherapy with biguanides and alpha glucosidase inhibitors. Rosiglitazone has been shown to prevent diabetes, but the risk of congestive heart failure was increased (*DREAM Trial Investigators, 2006*). Lifestyle change remains the preferred method to prevent diabetes.

*Supporting evidence is of classes: A, R*

### **5. Diagnosis Type 2 Diabetes**

Diagnosis of type 2 diabetes (*Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003*)

- Fasting plasma glucose greater than or equal to 126 mg/dL.
- 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.

## 6. Is This Patient Hospitalized?

Diabetic inpatients 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*).

Hyperglycemia has been associated with increased infection rates and poorer short-term and long-term outcomes in critically ill patients in the ICU, post-MI, and postsurgical settings. Studies support that aggressive glucose management in medical and surgical patients can improve outcomes (*van den Berghe, 2001*).

*Supporting evidence is of class: B*

## 7. Inpatient Diabetes Management

The following are recommended in the inpatient setting:

- Intensive insulin therapy with intravenous insulin in critically ill patients.
- 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 plasma glucose levels to less than 110 mg/dL preprandial and less than 180 mg/dL postprandial
- 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:

- 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 blood glucose greater than 125 mg/dL or 6.9 mmol/L) during hospitalization should have follow-up testing for diabetes within one month of hospital discharge.

*(Clement, 2004)*

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

*Supporting evidence is of class: R*

## 8. Needs Stabilization?

Inpatient care may be appropriate in the following situations:

- Elderly patients with infection or illness, weight loss, dehydration, polyuria or polydipsia
- Life-threatening acute metabolic complications of diabetes (e.g., serum glucose greater than 400 mg/dL, 300-400 mOsm/L, lactic acidosis, small to moderate amounts of ketones, serum pH less than 7.3, bicarbonate less than 15 mEq/L, anion gap greater than 12)

## Algorithm Annotations

- Uncontrolled insulin-requiring diabetes during pregnancy.

Indications for immediate insulin treatment in type 2 diabetes mellitus\*

\* Insulin therapy may not be permanent

- Pregnancy – Oral agents do not have FDA approval for use in pregnancy. The glucose goals are different in pregnancy and require more aggressive treatment. (Treatment of this condition extends beyond the scope of this guideline.)
- Surgery, infection, steroids – If these conditions cause significant hyperglycemia, insulin may be most appropriate.
- Severe symptoms, marked weight loss, and/or ketonuria with
  - Glucose greater than 300 mg/dL fasting or
  - Random glucose over 350 mg/dL
- Hyperosmolar, nonketotic state
  - Glucose over 600 mg/dL, osmolality over 330 mosm/L

## 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, there are 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 blood glucose monitoring, hypoglycemia recognition and treatment, and how/when to contact health care support. Patients should check blood sugars 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-seven days.

Insulin therapy may not be permanent, particularly if oral agents are added or if, at presentation, the patient is in metabolic stress (e.g., infections, acute metabolic complications, recent surgery) 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 (*Clements, 1987; Peters, 1996*).

*Supporting evidence is of classes: A, D*

## 10. Recommend Self-Management Program

### A. Nutrition Therapy

Medical nutrition therapy for diabetes emphasizes improving metabolic outcomes. Major goals are to attain and maintain in the normal or as close to normal range as is safely possible blood glucose, blood pressure and lipid/lipoprotein levels. These goals help reduce the risk for chronic complications of diabetes and macro- and microvascular disease.

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; however, those with longstanding disease may not be as responsive to weight loss. 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, additional research is needed to determine the long-term efficacy. (See the ICSI Obesity guideline.)

(American Diabetes Association, 2006)

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. 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.**

1. Evaluate the patient's current eating habits and modify as needed. Recommend:
  - Setting goals and working together toward gradual, realistic lifestyle changes.
  - Healthful food choices: Foods containing carbohydrates from whole grains, fruits, vegetables and low-fat dairy products should be included in a healthy eating plan.
  - 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.
  - Reduce total caloric intake by moderating food/beverage and limiting total fat intake.
  - Because carbohydrate has the greatest impact on blood glucose, its effect can be minimized by the distribution of carbohydrate as evenly as possible throughout the day to smaller meals and snacks.
  - 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. To reduce the risk of hypoglycemia, alcohol should be consumed with food.
  - In insulin-resistant individuals, reduced energy intake and modest weight loss improve insulin-resistance and glycemia in the short term.
  - 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 has not been determined.
2. Monitoring carbohydrate – whether by carbohydrate counting, exchanges or experience-based estimation – remains a key strategy in achieving glycemic control.

Algorithm Annotations

3. 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.
  - Protein
    - a. 15-20% of the total calories
    - b. Reduction of protein intake to 0.8 -1.0 gm/kg in individuals with diabetes in the earlier stages of chronic kidney disease (CKD) and to 0.8 gm/kg in the later stages of CKD may improve measures of renal function (urine albumin excretion rate, glomerular filtration rate) and is recommended.
    - c. 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.
  - Carbohydrate
    - a. Total amount of carbohydrate is more important than the source and type of starch or sugar.
    - b. 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, appears to be safe; however, they may cause gastrointestinal side effects.
    - c. Non-nutritive sweeteners are safe when consumed within the acceptable daily intake levels established by the FDA.
    - d. A variety of fiber-containing foods, such as whole grains, fruits and vegetables has beneficial effects on hyperinsulinemia, lipids and colon health. Evidence is lacking to recommend a higher fiber intake for people with diabetes than for the population as a whole.
    - e. The use of glycemic index and load may provide a modest additional benefit over that observed when total carbohydrate is considered alone (*American Diabetes Association, 2006*).
  - Fat
    - a. Patients with normal weight and lipids: similar to National Cholesterol Education Program (NCEP) guidelines (less than or equal to 30% calories from fat, less than 10% saturated fats, limit trans-saturated fatty acids, and less than 200 mg cholesterol)
    - b. To lower LDL cholesterol, energy derived from saturated fat can be reduced if weight loss is desirable or replaced with either carbohydrate or monounsaturated fat when weight loss is not a goal.
    - c. Weight control: balance lower fat and caloric consumption with regular physical activity of 30 minutes most days.
    - d. Patients with elevated cholesterol and LDL cholesterol: implement National Cholesterol Education Program-Therapeutic Lifestyle (TLC) recommendations. TLC 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-saturated fat intake.

**Algorithm Annotations**

- e. Two or more servings of fish per week (with the exception of commercially fried fish fillets) provide n-3 polyunsaturated fatty acids and are recommended (*American Diabetes Association, 2006*).
- f. Patients with elevated triglycerides: improve blood glucose control, encourage weight loss, increase physical activity, avoid alcoholic beverages, moderate carbohydrate and add dietary saturated fat restriction.
- Sodium
  - a. Medical nutrition therapy for hypertension control focuses on weight reduction and recommended sodium intakes of 1,500-2,400 mg per day. 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. Please refer to the ICSI Hypertension guideline for additional information.

There is evidence that a 10-20 lb. weight loss may be a more reasonable expectation than recommending ideal body weights (*American Diabetes Association, 2004; Franz, 2002; Klein, 2004; Mensing, 2003; Pastors, 2002*). See the ICSI Prevention and Management of Obesity guideline.

*Supporting evidence is of class: R*

4. 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. Further research is being done in this area.
5. Provide for ongoing nutrition self-management and care (*American Diabetes Association, 2001; Franz, 1995a; Franz, 1995b; Hollander, 1998; Monk, 1995*).

*Supporting evidence is of classes: A, M, R*

**B. Physical Activity**

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.

Recent studies indicate that cumulative daily physical activity may be almost as beneficial as continuous physical exertion. 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, 2003f; DeBusk, 1990; Hardman, 1999; Helmrich, 1991; Pate, 1995; Tuomiletos, 2001*).

*Supporting evidence is of classes: A, C, R*

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.

1. 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.

**Algorithm Annotations**

- 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.
2. 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.
  - Cardiac stress testing. Coronary disease is frequently silent in patients with type 2 diabetes. Standard treadmill exercise test may have decreased reliability, particularly in women. There are no studies that answer the questions about the value and frequency of stress testing. Stress testing is recommended in patients 35 years of age and older, those patients with a history of type 2 diabetes for 10 years or longer (type 1 greater than 15 years), patients with any additional risk factor(s) for coronary artery disease, and those patients with a history of microvascular disease, peripheral vascular disease and autonomic neuropathy.
  - Assess blood glucose control.
  - Assess knowledge of physical activity in relation to blood glucose control.
  - When making a referral, make other health care providers aware of limitations for exercise.
3. Physical activity can be intermittent or cumulative.

<b>Physical Activity</b>	<b>Intermittent</b>	<b>Cumulative</b>
Frequency	4-7 days/wk	Physical activity every day (walking, taking stairs, housework, scheduled activity)
Intensity	55-69% predicted max. heart rate	Moderate activity (equivalent to brisk walk)
Time	Minimum of 8-10 minutes/ session	Accumulate 30 minutes or more each day

**C. 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. 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; the staff in such a program are multidisciplinary and include at least an RD and an RN with experiential preparation in education and diabetes management. A number of studies involving a clinical pharmacist in program with cardiac risk factors in select patient with diabetes have proven to be effective. Cultural sensitivity is an important aspect of education for self-management. Providers should be aware of culturally appropriate educational and community resources to support persons with diabetes and their families (*Cioffi, 2004*).

## Algorithm Annotations

An education plan should be identified based on the needs of the individual and referral made to either an internal or external education resource. (See the Support for Implementation Section for a list of ADA recognized education programs available.) Periodic reassessment of educational goals is recommended (Barnard, 1994; Bourn, 1994; Janand-Delenne, 1999; Lorig, 2001; Mensing, 2002).

*Supporting evidence is of classes: C, D, R*

### **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 treating chronic complications
- Self-monitoring blood glucose, ketones (when appropriate), and using results to improve control
- Incorporation of appropriate nutrition management
- Incorporation of physical activity into lifestyle
- Utilizing medications (if applicable) for therapeutic effectiveness
- Awareness of culturally appropriate community resources/support for persons with diabetes mellitus and their families and ability to access community resources
- Integrating psychosocial adjustment to daily life
- Promotion of preconception care, counseling and management during pregnancy, if applicable

### **D. 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. (See Annotation #29D, "Comprehensive Foot Exam with Risk Assessment.") (American Diabetes Association, 2003g; Mayfield, 1998)

*Supporting evidence is of class: R*

- 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, Vaseline or creams is acceptable, but do not use between the toes.
- Don't 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.
- Seek care immediately for new foot problems.

### E. 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 Individualized Treatment Goals

### Key Points:

- The following goals are recommended: A1C less than 7% and blood sugars at goal, use of statins and titrating to goal, BP less than 130/80 mmHg, ASA daily in patients greater than 40 years of age, and avoidance of tobacco use.

The physician and patient must discuss and document the treatment goals and the plan to achieve the desired goals. Less strict goals may be established for the very elderly or for the patient with severe health problems (e.g., severe coronary artery disease, metastatic cancer, dementia) (*California Healthcare Foundation/American Geriatrics Society Panel on Improving Care for Elders with Diabetes, 2003*). Control of hyperglycemia is important; however, in older persons with diabetes, a greater reduction in morbidity and mortality may result from control of cardiovascular risk factors than from tight glycemic control. The following goals are recommended:

### A. Goals for Glycemic Control – A1C Less Than 7% and Blood Sugars at Goal

For most patients with type 2 diabetes, the A1C goal is less than 7%. The goal for an individual may be higher or lower depending on the predicted life expectancy, expected clinical benefits and risks of treatment. For example, A1C goal may be set lower in patients at low risk for hypoglycemia or higher in patients who are elderly and have higher risk of drug side effects, hypoglycemia unawareness or history of severe hypoglycemia. [*Conclusion Grade II: See Conclusion Grading Worksheet A – Annotation #11A (Goal for Glycemic Control)*] (*American Diabetes Association, 2003h; Diabetes Control and Complications Trial Research Group, 1996; Ohkubo, 1995; UKPDS, 2000; UKPDS, 1998d; Nathan, 2005*).

*Supporting evidence is of classes: A, B, R*

Blood sugars should also be used to assess level of control, in addition to A1C. It is appropriate to determine need for medication changes based on blood sugars whenever this information is available.

Medical centers need to know what the standard is for A1C and glycated hemoglobin in their labs and make the appropriate conversions.

Algorithm Annotations

1. Biochemical Index

	Biochemical Index	Normal	Goal
Plasma Values	Average preprandial glucose	less than 100 mg/dL	90-130 mg/dL
	Average bedtime glucose	less than 120 mg/dL	110-150 mg/dL
<ul style="list-style-type: none"> <li>Two-hour postmeal blood sugars can be helpful for adjusting mealtime medications. The target range for postmeal sugars is controversial at this time, but a reasonable two-hour post-meal target is within 40 mg/dL higher than the premeal reading.</li> <li>More than half the blood sugar readings should fall in the desired goal range.</li> </ul>			

2. Self-Monitoring Blood Glucose (SMBG)

Set frequency and timing of glucose monitoring. Examples include:

Therapy	Frequency and Timing
Non-pharmacologic or oral agent	Twice daily, rotating times, at least two-three days per week. Postprandial may be helpful.
Simple insulin regimens (one or two shots daily)	Twice daily, rotating times, at least three-four days per week. Postprandial may be helpful.
Complex insulin regimens (three or more shots daily)	Four or more times every day. Postprandial may be helpful.

Patients can monitor blood glucose in almost any setting and at any time. This can be used to guide therapy adjustments, assess the impact of food or exercise on blood sugar, provide feedback and document whether symptoms are related to hypoglycemia.

The major hazard associated with SMBG is the risk that inaccurate data may lead the patient or physician to inappropriate therapeutic decisions. Confirmation of unexpected results by obtaining a plasma glucose or repeating the test is recommended.

Providers must review for diabetes the results of SMBG at each office visit. This reinforces the importance of SMBG, confirms the regular use of SMBG and can be used to demonstrate or review with patients the relation of exercise and diet to glucose control (*American Diabetes Association, 1994b*).

*Supporting evidence is of class: R*

B. Start or Intensify Statin Dose

The LDL goal for people with diabetes mellitus without coronary artery disease (CAD) is less than 100 mg/dL. The goal with CAD is less than 70 mg/dL.

Start a statin even if LDL is less than 100 mg/dL. Intensify statin or lipid-lowering medications to LDL goal less than 100 mg/dL without CAD or less than 70 mg/dL with CAD.

Recent evidence (*Colhoun, 2004; Heart Protection Study Group, 2002*) and ATPIII consensus guidelines (*Grundy, 2004*) suggest that statins are beneficial for high-risk patients with a 10-year risk of cardiovascular (CV) event of more than 20%, (e.g. CAD equivalency) even with baseline LDL of less than 100. [*Conclusion Grade I: See Conclusion Grading Worksheet B – Annotation*]

#11B (Statin Use)]. Use of moderate to high dose statins or other LDL lowering medications as needed to achieve an LDL value less than 70 is recommended for patients with coronary heart disease (CHD).

Three pathways to improve lipids are (1) medical nutrition therapy, (2) increased physical activity, and (3) pharmacotherapy. Beneficial effects of statins on cardiovascular risk reduction may, in part, be independent of their effects on lipids. Diabetes has been considered a coronary artery disease equivalent. Risk calculators for type 2 diabetes can be found at the following URL: <http://www.dtu.ox.ac.uk/index.html?maindoc=/riskengine/download.html>.

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.

Small density LDL cholesterol (more atherogenic) particles are increased in type 2 diabetes, and LDL cholesterol itself may differ in people with diabetes compared with people without diabetes. Patients with diabetes develop more atherosclerosis than patients without diabetes with the same quantitative lipoprotein profiles. In individuals with elevated triglycerides, a statin can reduce major vascular events

High triglycerides and low-HDL cholesterol are independent risk factors for cardiovascular disease in the patient with diabetes. Individuals with elevated triglycerides have significant cardiovascular risk reduction with the use of fibrates (Robins, 2001) or statins (Heart Protection Study Group, 2003) [Conclusion Grade I: See Conclusion Grading Worksheet B – Annotation #11B (Statin Use)]. While a number of studies support favorable changes in lipid profiles with niacin alone, randomized controlled trials considering hard cardiovascular outcomes are lacking.

A number of studies involving programs using a clinical pharmacist to reduce cardiac risk factors in select patients with diabetes have proven to be effective.

Supporting evidence is of classes: A, C, R

### **C. Goals for Blood Pressure Control: BP Less Than 130/80 mmHg, Emphasis on Systolic BP Control**

In type 2 diabetes, insulin resistance may cause hypertension by increasing sympathetic activity, renal reabsorption of sodium or vascular tone.

Uncontrolled hypertension is a major cardiovascular risk factor that also accelerates the progression of diabetic nephropathy. When hypertension is identified, it should be aggressively treated to achieve a target blood pressure of less than 130/80 mmHg. See the Blood Pressure Control algorithm.

For patients with type 2 diabetes mellitus, the systolic blood pressure (BP) goal is less than 130 and the diastolic blood pressure (BP) goal is less than 80. [Conclusion Grade II: See Conclusion Grading Worksheet C – Annotations #11C, 23, 25 (Goals for BP)]. (American Diabetes Association, 2003h; Chobanian, 2003; Hansson, 1998; UKPDS, 1998c; UKPDS, 1998e).

Supporting evidence is of classes: A, R

### **D. ASA/Antiplatelet Medication Unless Contraindicated**

Patients with type 2 diabetes are at a significantly high risk for development of heart disease. For patients with type 2 diabetes mellitus, initiate low-dose aspirin therapy (81-325 mg daily) in patients 40 and older unless there is a contraindication to aspirin therapy. [Conclusion Grade I: See Conclusion Grading Worksheet D – Annotation #11D (Aspirin Use)] (Bhatt, 2002; ETDRS, 1992; Hansson, 1998; Harpaz, 1998; Physicians Health Study Group, 1989)

Supporting evidence is of classes: A, B

If aspirin is contraindicated, consider use of clopidogrel (Plavix®) or ticlopidine (Ticlid®). For more information, please refer to the ICSI Stable Coronary Artery Disease guideline.

**E. Goals for Tobacco Use – Smoking Cessation, If Indicated**

Avoid tobacco use. See ICSI Tobacco Use Prevention and Cessation guidelines.

## 12. 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.

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.

## 13. Treatment Goals Not Met

**A. Modify Treatment Based on Appropriate Related Guideline** (e.g., Prevention and Management of Obesity, Hypertension Diagnosis and Treatment, Lipid Management in Adults, Tobacco Use Prevention and Cessation, and Depression guidelines) and/or:

**B. See Glycemic Control and Blood Pressure Control algorithms, and/or:**

**C. Consider Referral to Diabetes Care Team or Specialists**

### Diabetes Care Team

Consultation with a diabetes educator is suggested if the patient is having difficulty adhering to a nutrition and exercise 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 (CDE) or have didactic and experiential expertise in diabetes care and education.

### Eye Care Specialist

A dilated eye examination for diabetic eye disease should be performed annually for patients with type 2 diabetes mellitus (*HEDIS, 2000; American Diabetes Association, 2003b*).

DQIP and HEDIS measures allow for biennial screening of low-risk patients defined as having two out of three of the following criteria:

- Not on insulin therapy
- A1C less than 7%
- Dilated eye exam documenting no retinopathy during prior year

*Supporting evidence is of class: R*

**Endocrinologist/Nephrologist**

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 #30A, "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 CAD.

**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.

**D. 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).

1. Assess the patient's knowledge of his/her condition and his/her expectations for treatment.
2. Assess the patient's medication administration process.
3. 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*).

*Supporting evidence is of class: R*

**E. Evaluate for Depression**

There is a substantial increase in the prevalence of depression among people with diabetes as compared to the general adult population. The prevalence of depression is two times as likely in people with diabetes and without complications, and depressive symptoms may be found in up to 50% of those who have diabetes with complications. 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 (*Anderson, 2001; DeGroot, 2001; Lustman, 2001*).

Identification and management of depression is an important aspect of diabetes care. Some clinicians find that either self-administered or professionally administered instruments are useful adjuncts to the clinical interview in the identification of depression. Some examples that are recognized and validated are PHQ-9, BECK, HAM-D, QIDS-C and QID-SR. The ICSI Major Depression in Adults in Primary Care guideline provides more suggestions for the identification of depression. Intervention studies have demonstrated that when depression is treated, both quality of life and glycemic control improve. Coun-

seling 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. The ICSI Major Depression in Adults in Primary Care guideline provides more detailed suggestions for the management of depression.

*Supporting evidence is of classes: M, R*

## Glycemic Control Algorithm Annotations

### 14. 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-three months. Metformin plus lifestyle treatment is also a reasonable initial therapy at the time of diagnosis, given the low risk of hypoglycemia and benefits of metformin shown in both prediabetes and diabetes (*Nathan, 2006*).

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 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*).

*Supporting evidence is of classes: A, R*

### 15. 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.

Annotations #16 and 17 address specific medications and the treatment of hyperglycemia. 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 following clinical circumstances should be considered:

#### A. 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.

**Algorithm Annotations**

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.

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).

**B. Weight of the Patient**

Type 2 diabetes and its treatment is often associated with insulin resistance and weight gain. Metformin, acarbose, exenatide 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 UKPDS, metformin is recommended for most diabetes patients with type 2 diabetes unless contraindicated. Insulin and thiazolidinediones may be associated with weight gain.

**C. 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 need to be 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.

**D. Cardiopulmonary Comorbidities**

Metformin is contraindicated in patients with heart failure treated with medication. Metformin should be used with caution for patients with conditions that predispose them to risk of hypoxia such as COPD or obstructive sleep apnea.

Patients started on thiazolidinediones should be instructed to report signs of lower extremity swelling, rapid weight gain, and shortness of breath.

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

**E. Hepatic Disease**

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

Metformin and thiazolidinediones should not be used if 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.

## 16. Prescribe Insulin Therapy

- Insulin programs should be individualized based on the patient's life style, treatment goals and SMBG. Many patients can be taught to interpret SMBG results and adjust insulin doses (*American Diabetes Association, 2003d*).

*Supporting evidence is of class: R*

- Human insulin is now the only available insulin in the United States.
- 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 must be consistent. Synchronize insulin with food intake patterns.

Time Course of Action of Insulin Preparations:

	<b>Insulin Preparations</b>	<b>Onset of Action</b>	<b>Peak Action</b>	<b>Duration of Action*</b>	<b>Cost***</b>
Short-Acting	Regular	30 min.	2-5 hours	5-8 hours	\$
Rapid-Acting	Lispro (Humalog®)	15 min.	30-90 min.	2-4 hours	\$
	Aspart (Novolog®)	15 min.	1-3 hours	3-5 hours	\$\$\$
	Glulisine (Apidra®)	15 min.	50-100 min.	5 hours	
Intermediate-Acting	NPH	1-3 hours	6-12 hours	16-24 hours	\$\$
Long-Acting	Detemir (Levemir®)†	1 hour	**	20 hours	\$\$\$\$
	Glargine (Lantus®)	1 hour	**	24 hours	\$\$\$\$
Mixtures	Humalog® mix (75/25)	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	

† Detemir is not to be used in insulin pumps. Detemir could be given once or twice daily.

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.

\*\*\* Cost is based on AWP of 30-day supply or one vial of injectible drug. See cost indicator at end of annotation.

Source: Compiled from pdr.net

**Algorithm Annotations**

- 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 blood 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.
- Glargine (Lantus®) should not be mixed with other insulins, diluted with other solutions or given intravenously.
- Glargine (Lantus®) insulin is most often administered once a day, either at bedtime or in the morning.
- Insulin pump therapy may be helpful for patients who are interested in more intensified management of blood sugars 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.

Drug Name (Trade Name)	Indications	Onset of Action	Peak Action	Duration of Action	Cost*
Insulin human [rDNA origin] Inhalation Powder Exubera® (1, 3 mg)	Type 1 or 2	10-20 min.	30-90 min.	6 hrs.	\$\$\$\$\$
<b>Delivery Mechanism</b>					
<ul style="list-style-type: none"> <li>• Inhaled, dry-powder formulation of rapid acting human insulin. Packaged in “blisters” containing 1 or 3 mg of dry powder insulin.</li> </ul>					
<b>Efficacy</b>					
<ul style="list-style-type: none"> <li>• Approximately equivalent to 3 units or 8 units, respectively, of subcutaneously injected regular insulin.</li> <li>• In clinical trials, there was no significant difference between Exubera to conventional injected insulin in the primary endpoint of a decrease in HbA1c or in the percentage of patients achieving HbA1C less than 7%.</li> </ul>					
<b>Safety</b>					
<ul style="list-style-type: none"> <li>• Manufacturer recommends pulmonary function testing before starting inhaled insulin, at six months, and then annually, such as by office-based spirometry.</li> <li>• In clinical trials, the incidence of hypoglycemia has been about the same with Exubera with subcutaneous regular insulin.</li> <li>• Can cause mild to moderate cough, which usually occurs within studies and seems to decrease with continued use.</li> <li>• Some patients showed a decline in pulmonary function within weeks of treatment, which did not appear to progress over a two-year period.</li> <li>• Inhaled insulin should be discontinued if FEV<sub>1</sub> declines more than 20% from baseline.</li> <li>• Anti-insulin antibodies have developed in patients using inhaled insulin.</li> <li>• Smoking may increase the effect of inhaled insulin. Exubera is contraindicated in smokers or those who discontinued smoking less than six months before starting treatment.</li> <li>• Not recommended for patients with asthma, COPD or other lung diseases.</li> <li>• Pregnancy category C.</li> </ul>					

Source: Compiled from pdr.net

## 17. Prescribe Oral Agent(s)/Titrates to Goal

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

Metformin is the preferred oral agent to initiate if not contraindicated 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).

Supporting evidence is of class: R

### 1. 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*
Glipizide (Glucotrol®)	10-24 hr.	5 mg/d	2.5 mg/d	10 mg twice daily	40 mg/d	\$
Glipizide (Glucotrol XL®)	24 hr.	5 mg/d	5 mg/d	10 mg/d	20 mg/d	\$
Glyburide (Micronase®, DiaBeta®)	18-24 hr.	2.5 mg-5 mg/d	1.25 mg/d	5 mg twice daily	20 mg/d	\$
Glyburide (Glynase®, PresTab®)	18-24 hr.	1.5-3 mg/d	0.75 mg/d	6 mg twice daily	12 mg/d	\$
Glimepiride (Amaryl®)	24 hr.	1-2 mg/d	1-2 mg/d	1-4 mg/d	8 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 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.

\* Cost is based on AWP of 30-day supply or one vial of injectible drug. See cost indicators at end of annotation.

Source: Compiled from pdr.net

**Algorithm Annotations**

2. Metformin

<b>Drug Name (Trade Name)</b>	<b>Usual starting dose</b>	<b>Usual maximum clinically effective dose per day</b>	<b>Maximum dose per day</b>	<b>Cost*</b>
Metformin (Glucophage®)	500 mg daily or twice daily	1,000 mg twice daily	2,550 mg daily or 850 mg three times a day	\$\$
Metformin (Glucophage XR®)	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	\$\$
<b>EFFICACY</b>				
<ul style="list-style-type: none"> <li>• The A1C lowering commonly achieved with metformin is 1.5-2.0%.</li> <li>• Absorption and bioavailability of Glucophage XR® 2000 mg daily is similar to that of metformin 1000 mg twice daily. Costs favor the use of metformin for patients who can manage twice daily dosing.</li> <li>• The major effect may be reducing hepatic glucose production.</li> </ul> <p>Metformin is indicated for treatment of type 2 diabetes as monotherapy or in combination with sulfonylureas or insulin.</p>				
<b>SAFETY</b>				
<ul style="list-style-type: none"> <li>• Metformin is contraindicated in patients with known hypersensitivity, renal disease, congestive heart failure (treated with medications), acute or chronic metabolic acidosis (including diabetic ketoacidosis).</li> <li>• 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.</li> <li>• Do not use for patients with COPD, severe hepatic disease or alcoholism.</li> <li>• Side effects may be transient and can include metallic taste, diarrhea, nausea and anorexia.</li> <li>• The use of metformin in pregnancy or lactation is not recommended.</li> <li>• As monotherapy, metformin does not cause hypoglycemia.</li> </ul>				

\* Cost is based on AWP of 30-day supply or 1 vial of injectible drug. See cost indicator at end of annotation.

Source: Compiled from pdr.net

**Algorithm Annotations**

3. Alpha glucosidase inhibitors

Drug Name (Trade Name)	Usual starting dose	Maximum dose per day	Cost*
Acarbose (Precose®)	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 (Glyset®)	25 mg daily	100 mg three times a day	\$
<b>EFFICACY</b>			
<ul style="list-style-type: none"> <li>• The A1C lowering commonly achieved with alpha glucosidase inhibitors is 0.5-1.0%.</li> <li>• These agents are most appropriate in patients with glucose and glycosylated hemoglobin only moderately above goal.</li> <li>• These agents delay carbohydrate absorption, which reduces postprandial blood glucose, and reduces insulin levels.</li> <li>• These agents must be taken at the beginning of a meal to be effective.</li> <li>• 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).</li> </ul>			
<b>SAFETY</b>			
<ul style="list-style-type: none"> <li>• 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.</li> <li>• Absorbed metabolites of acarbose may rarely cause elevated transaminase levels. Monitor transaminase levels every three months for one year, and periodically thereafter.</li> <li>• Side effects may include abdominal cramping, flatulence and diarrhea. Tolerance develops, so start with low dose and increase gradually.</li> <li>• As monotherapy, these agents do not cause hypoglycemia.</li> </ul>			

\* Cost is based on AWP of 30-day supply or 1 vial of injectible drug. See cost indicator at end of annotation.

Source: Compiled from pdr.net

4. Thiazolidinediones (TZDs)

Drug Name (Trade Name)	Usual starting dose	Maximum dose per day	Cost*
Pioglitazone (Actos®)	15 or 30 mg once daily	45 mg daily	\$\$\$\$
Rosiglitazone (Avandia®)	4 mg daily or twice daily	4 mg twice daily or 8 mg daily	\$\$\$\$
<b>EFFICACY</b>			
<ul style="list-style-type: none"> <li>• The A1C lowering commonly achieved with thiazolidinediones is 1.0-1.5%.</li> <li>• TZDs improve insulin action in peripheral tissues, particularly muscle.</li> <li>• Both pioglitazone and rosiglitazone are indicated for combination therapy with sulfonylureas, metformin or insulin.</li> <li>• Both LDL and HDL cholesterol concentrations may increase slightly.</li> </ul>			
<b>SAFETY</b>			
<ul style="list-style-type: none"> <li>• Thiazolidinediones are contraindicated in patients with known hypersensitivity. Their use in pregnancy and lactation is not recommended.</li> <li>• 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).</li> <li>• Side effects may include moderate weight gain, edema and mild anemia, all due, at least in part, to fluid retention.</li> <li>• As monotherapy, TZDs do not cause hypoglycemia.</li> <li>• Measure ALT at baseline and periodically thereafter.</li> <li>• Administration of gemfibrozil increases plasma levels of rosiglitazone. Decreases in the dose of rosiglitazone may be needed when gemfibrozil is added.</li> </ul>			

\* Cost is based on AWP of 30-day supply or one vial of injectible drug. See cost indicator at end of annotation.

Source: Compiled from pdr.net

**Algorithm Annotations**

5. Meglitinides (short-acting secretagogues)

<b>Drug Name (Trade Name)</b>	<b>Usual starting dose</b>	<b>Maximum dose per day</b>	<b>Cost*</b>
Repaglinide (Prandin®)	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 (Starlix®)	60-120 mg three times a day before meals		\$\$
<b>EFFICACY</b>			
<ul style="list-style-type: none"> <li>• The average A1C lowering commonly achieved is 0.5%.</li> <li>• The mechanism of action of these agents is to stimulate insulin secretion (similar to sulfonylureas).</li> <li>• These agents have a short duration of action, one-four hours.</li> <li>• These agents are usually taken 15 minutes before meals (range of 0-30 minutes).</li> <li>• These agents are indicated for use in combination with metformin or TZDs.</li> </ul>			
<b>SAFETY</b>			
<ul style="list-style-type: none"> <li>• The major side effect of these agents is hypoglycemia, but the incidence may be less common than with sulfonylureas.</li> <li>• Skip the dose if the meal is not eaten.</li> <li>• Doses of nateglinide should be adjusted for hepatic impairment.</li> <li>• Administration of gemfibrozil significantly increases repaglinide blood levels, which may lead to hypoglycemia. Avoid concomitant use of gemfibrozil and repaglinide.</li> </ul>			

\* Cost is based on AWP of 30-day supply or one vial of injectible drug. See cost indicator at end of annotation.

Source: Compiled from pdr.net

Algorithm Annotations

6. Combination Products

Combination type	Trade name	Fixed dose combination (mg)	Usual start dose (mg)	Maximum dose per day	Cost*
TZD + metformin	Avandamet®	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 + metformin	Actoplus met®	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 PO twice daily or 15 mg/850 mg PO daily if on pioglitazone monotherapy	45 mg/ 2,550 mg/day	\$\$\$\$
Sulfonylurea + metformin	Glucovance®	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	\$\$
Sulfonylurea + metformin	Metaglip®	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	\$\$
TZD + sulfonylureas	Avandaryl®	Rosiglitazone/ glimepiride 4/1, 4/2, 4/4	Not recommended as initial treatment; 4/1 or 4/2 PO daily	8 mg/4 mg/day	\$\$\$\$\$

\* Cost is based on AWP of 30-day supply or one vial of injectible drug. See cost indicator at end of annotation.

Source: Compiled from pdr.net

The UKPDS study shows good evidence for prescribing metformin in obese type 2 patients as a first choice. Metformin is the only pharmacologic agent that has shown decreased overall mortality in patients with diabetes (UKPDS, 1998b).

*Supporting evidence is of class: A*

Head to head trials on rosiglitazone and pioglitazone have not been done to date and would be necessary to determine which drug is more efficacious in decreasing A1C and in cholesterol changes (*Medical Letter on Drugs and Therapeutics, 1999; Niemi, 2003*).

Cost Indicators:

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

*Supporting evidence is of classes: A, R*

## 18. Glycemic Control Achieved?

See Annotation #11, "Set Individualized Treatment Goals."

## 19. Additional Agent(s)

### Key Points:

- Because type 2 diabetes is a progressive disease, combinations of medications are often needed to achieve goals.

Combinations of medications: Because type 2 diabetes is a progressive disease, combinations of medications are often needed. Degree of poor glycemic control and expectations for response of each agent (often 0.5-2% decrease in A1C per agent) influence the timing and choice of combinations (*Turner, 1999*). Logical combinations (**not in order of effectiveness, risks or expense**) have included:

Sulfonylurea, alpha glucosidase inhibitor  
Sulfonylurea, metformin  
Sulfonylurea, thiazolidinediones\*  
Metformin, thiazolidinediones\*  
Metformin, exenatide  
Metformin, alpha glucosidase inhibitor  
Metformin, exenatide, sulfonylurea  
Thiazolidinedione, alpha glucosidase inhibitor\*  
Sulfonylurea, metformin, thiazolidinediones\*  
Sulfonylurea, exenatide  
Sulfonylurea, alpha glucosidase inhibitor, metformin, thiazolidinediones\*  
Intermediate- or long-acting insulin, alpha glucosidase inhibitor  
Intermediate- or long-acting insulin, metformin  
Intermediate- or long-acting insulin, thiazolidinediones  
Intermediate- or long-acting insulin, short-acting sulfonylurea  
(Glimepiride) or repaglinide/nateglinide with meals\*  
Multiple daily insulin injections, amylin

Insulin combinations: Because patients with type 2 diabetes often have some endogenous prandial insulin secretion with meals, increasing basal levels of insulin by the use of once- or twice-a-day intermediate insulin is often sufficient to improve glycemic control. The use of prandial short-acting insulin in combination with intermediate- and long-acting insulin may be necessary with more significant relative insulin deficiency. Fixed combination of intermediate- and short-acting insulin or insulin analogs maybe useful for individuals not capable or not motivated to mix or use separate injections.

\*Significant expense

Algorithm Annotations

**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 (Byetta®) (Detrimer®)	Type 2	0-10 min.	2.1 hrs.	6-10 hrs.	5 mcg subcutaneous twice daily	10 mcg subcutaneous twice daily after one month	\$\$\$\$
<b>Mechanism of Action</b>							
<ul style="list-style-type: none"> <li>• Stimulates glucose-dependent release of insulin and suppresses glucagons levels.               <ol style="list-style-type: none"> <li>1. Modulation of gastric emptying</li> <li>2. Prevention of the postprandial rise in plasma glucagons</li> <li>3. Satiety leading to decreased caloric intake and potential weight loss</li> </ol> </li> </ul>							
<b>EFFICACY</b>							
<ul style="list-style-type: none"> <li>• Intended for Type 2 diabetics who are on oral medication but are not achieving good blood sugar control. Offers an alternative option before starting insulin.</li> <li>• Must be administered within the 60-minutes <b>before</b> the morning and evening meals. <b>It should not be</b> administered after a meal.</li> <li>• When this agent is added to sulfonylurea therapy, a reduction in the dose of sulfonylurea may be needed to reduce the risk of hypoglycemia.</li> <li>• Advantages over insulin are yet unclear, since like insulin, it must be injected twice daily.</li> <li>• Improves HgA1C by an average of 0.9% and lowers postprandial glucose.</li> </ul>							
<b>SAFETY</b>							
<ul style="list-style-type: none"> <li>• Contraindicated in patients with known hypersensitivity to this product or any of its components.</li> <li>• Is not a substitute for insulin in insulin-requiring patients.</li> <li>• Should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.</li> <li>• Not recommended for use in patients with ESRD or severe renal impairment (CrCl less than 30 mL/min).</li> <li>• Not recommended in patients with severe gastrointestinal disease because its use is commonly associated with gastrointestinal adverse effects, including nausea, vomiting and diarrhea.</li> <li>• Caution in patients receiving oral medications that require rapid gastrointestinal absorption.</li> <li>• 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.</li> <li>• Weight loss is often associated with use of this agent, especially when used concomitantly with metformin.</li> </ul>							
* Cost is based on AWP of 30-day supply or one vial of injectible drug.							

Source: Compiled from pdr.net

Cost Indicators:

\$	=	\$0 - \$20
\$\$	=	\$21 - \$40
\$\$\$	=	\$41 - \$60
\$\$\$\$	=	\$61 - \$100
\$\$\$\$\$	=	\$101 - \$500
\$\$\$\$\$\$	=	over \$500

*Supporting evidence is of class: A*

**20. Glycemic Control Achieved?**

See treatment goals under Annotation #11, "Set Individualized Treatment Goals."

## **21. Insulin Alone or Insulin + Other Agent(s)**

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; Relimpio, 1998; Yki-Järvinen, 1999; Zimmerman, 1998*). The following are some commonly used regimens.

Insulin as an adjunct to oral therapy:

- A bedtime dose of NPH, or glargine insulin, is added to metformin or thiazolidinediones. The starting dose of basal insulin is often 0.1 U/kg, based on current body weight. If patient is also on a sulfonylurea, it may be discontinued when insulin is added.
- A bedtime dose of insulin (as above) is added to sulfonylurea. The dose of the sulfonylurea may be reduced by approximately 50% when insulin is added.

Insulin alone:

- Twice-daily insulin regimen 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.

Oral agents as an adjunct to insulin therapy:

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

Algorithm Annotations

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 (Symlin®)	Type 1 and 2 diabetes	15-30 min.	20-27 min.	3-4 hrs.	<b>Type 2</b> : 60 mcg subcutaneous <b>Type 1</b> : 15 mcg subcutaneous; titrate at 15 mcg increments to maintenance dose of 30 mcg	<b>Type 2</b> : 120 mcg subcutaneous <b>Type 1</b> : 60 mcg subcutaneous Given in divided doses three times per day	\$\$\$\$
<b>Mechanism of Action</b>							
<ul style="list-style-type: none"> <li>• Acting as an amylinomimetic agent has the following effects:               <ol style="list-style-type: none"> <li>1. Modulation of gastric emptying</li> <li>2. Prevention of the postprandial rise in plasma glucagons</li> <li>3. Satiety leading to decreased caloric intake and potential weight loss</li> </ol> </li> </ul>							
<b>EFFICACY</b>							
<ul style="list-style-type: none"> <li>• 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 is used with or without a sulfonylurea and/or metformin.</li> <li>• May decrease HbA1C by an average of 0.4% and may observe weight loss of less than 1 kg at six months.</li> <li>• Must be administered immediately prior to each major meal.</li> <li>• Reduce preprandial, rapid-acting or short-acting insulin dosages, including fixed-mix insulins by 50%.</li> <li>• The agent may be considered in highly motivated patients willing to add two-four injections and more frequent glucose monitoring to their regimen.</li> </ul>							
<b>SAFETY</b>							
<ul style="list-style-type: none"> <li>• Contraindicated in patients with a known hypersensitivity to any of its components, including metacresol.</li> <li>• 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).</li> <li>• Before initiation of therapy, HbA1C, recent blood glucose monitoring data, history of insulin-induced hypoglycemia, current insulin regimen, and body weights should be reviewed.</li> <li>• Patients meeting any of the following criteria <b>should not</b> be considered for pramlintide therapy:               <ul style="list-style-type: none"> <li>- Poor compliance with current insulin regimen</li> <li>- Poor compliance with prescribed self-blood glucose monitoring</li> <li>- Have an HbA1C greater than 9%</li> <li>- Recurrent severe hypoglycemia requiring assistance during the past six months</li> <li>- Presence of hypoglycemia unawareness</li> <li>- Confirmed diagnosis of gastroparesis</li> <li>- Require the use of drugs that stimulate gastrointestinal motility</li> <li>- Require the use of drugs that slow the intestinal absorption of nutrients</li> <li>- Pediatric patients</li> </ul> </li> <li>• Pramlintide 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.</li> <li>• Its use is commonly associated with gastrointestinal adverse effects, including nausea, anorexia and vomiting.</li> <li>• 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 pramlintide injection.</li> <li>• This product and insulin should always be administered as separate injections and never be mixed. Mixing will alter the pharmacokinetics parameters of pramlintide.</li> </ul>							

\* Cost is based on AWP of 30-day supply or one vial of injectible drug.

Source: Compiled from pdr.net

## Algorithm Annotations

### Cost Indicators:

\$	=	\$0 - \$20
\$\$	=	\$21 - \$40
\$\$\$	=	\$41 - \$60
\$\$\$\$	=	\$61 - \$100
\$\$\$\$\$	=	\$101 - \$500
\$\$\$\$\$\$	=	over \$500

*Supporting evidence is of classes: A, R*

## Blood Pressure Control Algorithm Annotations

### 22. Blood Pressure Control Algorithm

Control of BP is at least as important as glycemic control for people with diabetes.

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; SHEP Cooperative Research Group, 1991; Tuomilehto, 1999*).

*Supporting evidence is of class: A*

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

For patients with type 2 diabetes mellitus, the systolic blood pressure (BP) goal is less than 130 and the diastolic blood pressure (BP) goal is less than 80. [*Conclusion Grade II: See Conclusion Grading Worksheet C – Annotations #11C, 23, 25 (Goals for BP)*] (*Adler, 2000; Bakris, 2000; Estacio, 2000; Hansson, 1998; UKPDS, 1998c; UKPDS, 1998e*)

*Supporting evidence is of classes: A, B, R*

A report from the UKPDS study showed an inverse relationship between systolic blood pressure and the aggregate end point for any complication related to diabetes. The lowest risk occurred at a systolic BP below 120 mmHg. The ABCD trial achieved a blood pressure of 132/78 in the intensive therapy group and had a lower mortality rate (5.5% vs. 10.7%), but there were no statistically significant differences in cardiovascular events to account for the mortality difference.

The goal for patients with renal insufficiency and urinary protein excretion greater than 1-2 g/day should be less than 120/75.

### 24. 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

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 E – Annotations #24, 30A (Treatment with ACE Inhibitors or ARBs)*] (*Lewis, 1993; HOPES Investigators, 2000*).

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 F – Annotations #24, 30D (Thiazide Diuretics)*] (*ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, 2002; Wing, 2003*). In ALLHAT, chlortha-

## Algorithm Annotations

lidone, at doses of 12.5 to 25 mg daily, was superior to other treatments at reducing cardiovascular events in both diabetic and nondiabetic patients.

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

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 BP is greater than or equal to 130 mmHg. ACE inhibitors are the first choice of antihypertensive in people with diabetes if not contraindicated. The possible advantages to ACE inhibitors include renal protection, decreased insulin resistance, lack of adverse effect on lipids, and decreased CV risk reduction.

In the UKPDS population (UKPDS, 1998c), atenolol and captopril had similar effectiveness in lowering blood pressure and preventing complications. Beta-blockers have additional beneficial effects in patients with known coronary artery disease. Previous data has shown that beta-blockers worsen glucose tolerance and lipid profiles and may mask the symptoms and prolong recovery from hypoglycemia and worsen peripheral vascular disease. Diuretics transiently and modestly increase LDL cholesterol and triglycerides but do not affect HDL cholesterol. The adverse lipid effects of these medications may be accentuated in patients with a preexisting dyslipidemia. Thiazide and loop diuretics **may** worsen glucose tolerance in direct proportion to the degree of hypokalemia that they induce. Preventing or minimizing hypokalemia reduces the hyperglycemia. A low-sodium diet is therefore essential to the effective use of diuretics in patients with diabetes. Despite these potential concerns, the ALLHAT study (ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, 2002) and other long-term hypertension treatment trials demonstrate a reduction of CHD events when diuretics are used. For patients with type 2 diabetes mellitus, thiazide diuretics in the treatment of hypertension can reduce cardiovascular events, particularly heart failure (Alkharouf, 1993; American Diabetes Association, 2003h; Chobanian, 2003; HOPES Investigators, 2000; Lewis, 1993; Wing, 2003).

*Supporting evidence is of classes: A, D, R*

## 25. Is Diastolic Blood Pressure Less Than 80 mmHg?

### Key Points:

- For patients with type 2 diabetes mellitus, the systolic blood pressure (BP) goal is less than 130 mmHg and the diastolic blood pressure (BP) goal is less than 80 mmHg.

For patients with type 2 diabetes mellitus, the systolic blood pressure (BP) goal is less than 130 and the diastolic blood pressure (BP) goal is less than 80.

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 BP 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 UKPDS. UKPDS achieved an average diastolic blood pressure of 82 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).

For patients with type 2 diabetes mellitus, the systolic blood pressure (BP) goal is less than 130 and the diastolic blood pressure (BP) goal is less than 80. [Conclusion Grade II: See Conclusion Grading Worksheet C – Annotations #11C, 23, 25 (Goals for BP)]. (Hansson, 1998; UKPDS, 1998c; UKPDS, 1998e)

*Supporting evidence is of class: A*

## 26. Treat Diastolic Blood Pressure to Less Than 80 mmHg

Combinations of medications are often required to achieve goals. 30% of patients in the tight blood pressure arm of the UKPDS 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 (UKPDS, 1998a; ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, 2002).

*Supporting evidence is of classes: A, M*

## Ongoing Management Algorithm Annotations

### 27. Ongoing Management and Follow-Up of People with Diabetes

- 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 1 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 sugars 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 sugar) or has developed hypoglycemia unawareness, evaluate the treatment goals for appropriate safety.

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. Data also supports the daily use of aspirin as a method to reduce cardiovascular events in patients with diabetes. See Annotation #11B, "Start or Intensify Statin Dose" and the Blood Pressure Control algorithm (American Diabetes Association, 2003h; Hansson, 1998).

*Supporting evidence is of classes: A, R*

### 28. Maintain Treatment Goals

- Nutrition/Physical Activity. Work with individual patients regularly to set realistic goals.
- Monitor A1C every three-six months. In insulin-treated patients and non-insulin-treated patients with poor metabolic control, quarterly A1C may assist management.
- Review blood sugars at all patient encounters. Reinforce blood sugar targets with patients and educate regarding hypoglycemia.

## Algorithm Annotations

- Monitor lipid profile yearly (cholesterol triglycerides and HDL cholesterol, and LDL). Treat to achieve recommended goals (see Annotation #11B, "Start or Intensify Statin Dose"). 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. Thus, control of dyslipidemia in diabetes is important because evidence shows that correcting lipid disorders reduces the rate of coronary artery disease events.
- Monitor BP each visit and control hypertension to recommended levels. See the Blood Pressure Control algorithm.
- Ask about ASA use and recommend aspirin use in patients over 40 unless contraindicated.
- Ask about alcohol and tobacco use and assist with cessation if indicated.

## 29. Annual Assessment of Complications

### A. Targeted Annual History and Physical Exam

1. The history should assess:
  - Results of self-monitoring blood glucose – validate results at least once a year (i.e., 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, OTC medications and alternative therapies;
  - Documentation of eye care specialist exam results;
  - Alcohol/drug use patterns; and
  - Lab assessment of LFT and/or creatinine to assess ongoing acceptability of medication usage.
2. The targeted physical exam should assess:
  - Weight, BMI;
  - Blood pressure;
  - Cardiovascular – evaluation of preexisting problems; and
  - Feet (nails, web spaces, calluses, ulcers, structural deformities, protective sensation and shoes).

### B. Specialist Dilated Eye Exam

### C. Renal Assessment

See Appendix B, "Treatment of Diabetic Nephropathy."

Urinary albumin excretion should be tested annually by a microalbuminuria method. If albuminuria is above normal, serum creatinine should be measured. 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

## Algorithm Annotations

blood in the urine, prolonged heavy exercise, fever, congestive heart failure, uncontrolled diabetes, severe hypertension, UTI 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 (e.g., Micral®) can be used to detect urinary microalbumin. If qualitative is positive, a quantitative test must be performed. Another option is a timed collection of urine (24-hour or overnight), but this is not always necessary with the availability of the microalbumin creatinine ratio test. 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 yearly; a positive finding should be followed periodically to see if the interventions are effective in diminishing the albuminuria (*Bennett, 1995; Hannah, 1999; Mogensen, 1996; National Institutes of Health, 1993*).

*Supporting evidence is of class: R*

### D. 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, 2003g; Mayfield, 1998*).

*Supporting evidence is of class: 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 A, "Using a Semmes-Weinstein Monofilament to Screen the Diabetic Foot for Peripheral Sensory Neuropathy" (*Meijer, 2005*).
- 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).

### E. 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, 2003f; American Diabetes Association, 1998b; ETDRS, 1992; Garg, 1992; Morrish, 1991*).

*Supporting evidence is of classes: A, B, R*

## F. 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 (ANBP2), 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, 2000a; Wing, 2003*).
- Vitamin E has no apparent effect on cardiovascular outcomes (*HOPE Investigators, 2000b*).

*Supporting evidence is of class: A*

## 30. Treatment and Referral for Complications

- A. Nephropathy** – In an examination of diabetes complications in ethnically diverse populations with uniform medical coverage, ethnic minorities have an elevated incidence of end-stage renal disease.

In type 2 diabetes, albuminuria may be present at the time of diagnosis in about 10 percent of patients, and another 10 percent 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.

1. Glucose Control – Improved glucose control at any stage of renal function reduces renal disease progression. See the Glycemic Control algorithm.
2. ACE inhibitors and ARBs have been shown to slow the progression of microalbuminuria to clinical proteinuria and to slow the progression of overt nephropathy to end-stage renal disease. 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.

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 E – Annotations #24, 30A (Treatment with ACE Inhibitors or ARBs)*]

3. 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.

**Algorithm Annotations**

A few studies show certain calcium channel blockers reduce microalbuminuria. A goal BP of 130/80 is recommended. See the Blood Pressure Control algorithm.

4. CV 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.
5. 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 RDA 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.

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. See the Blood Pressure Control algorithm (*American Diabetes Association, 1994a; American Diabetes Association, 2003a; DeFronza, 1995; HOPE Investigators, 2000a; Karter, 2002; Lewis, 1993; Lewis, 2001; Ravid, 1993; Viberti, 1994*).

*Supporting evidence is of classes: A, B, R*

- B. 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 (*American Diabetes Association, 1999*).

*Supporting evidence is of class: R*

- C. Retinopathy** – Prevalence of retinopathy is related to the duration of diabetes mellitus. After 20 years of diabetes mellitus, more than 60% of patients with type 2 diabetes mellitus have some degree of retinopathy. 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. Generally retinopathy progresses from mild background abnormalities to proliferative 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. See the Glycemic Control and Blood Pressure Control algorithms.

Algorithm Annotations

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; American Diabetes Association, 2003b; Diabetic Retinopathy Study Research Group, The, 1981; ETDRS Research Group, 1985; ETDRS Research Group, 1991; Klein, 1984; Klein, 1987*).

*Supporting evidence is of classes: A, C, 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. See the Glycemic Control and Blood Pressure Control algorithms.

- D. Cardiovascular and Cerebrovascular Disease** – Treatment includes control of cardiovascular risk factors (HTN, hyperlipidemia and smoking cessation) and ASA use. Patients with CAD may be treated medically or surgically. Consider referring patients with known CAD to cardiology and patients with known carotid disease to surgery. CHF 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. See the Blood Pressure Control algorithm. 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 F – Annotations #24, 30D (Thiazide Diuretics)*] (*ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, The, 2002; Wing, 2003*)

*Supporting evidence is of class: A*

Advanced coronary artery disease may be treated medically or surgically. However, some studies suggest that coronary artery bypass grafting (CABG) may be less effective in older patients with diabetes than in other groups, perhaps because of microvascular disease in the coronary circulation, but most likely due to the extensive nature of diffuse disease with difficulty in bypassing the number of lesions present. One study found better survival in people with diabetes with CABG than with PTCA.

Patients with type 2 diabetes have twice the average risk of suffering a stroke. It is unsure whether good glycemic control reduces this risk. However, treatment of hypertension, smoking and hyperlipidemia reduces the risk of stroke in most persons. See Annotation #11, "Set Individualized Treatment Goals," and the Blood Pressure Control algorithm.

- E. Peripheral Vascular Disease** – Peripheral arterial disease is commonly associated with diabetes. As many as 36 percent 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 nontraumatic amputations of the lower extremity. Peripheral vascular disease may be slowed by smoking cessation and treatment of hypertension and dyslipidemia. (See Annotation #11B, "Start or Intensify Statin Dose," 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.

Treatment includes glycemic, blood pressure and lipid control, as well as smoking cessation, which may slow the progression. Proper high-risk foot management is necessary to prevent ulceration and ampu-

**Algorithm Annotations**

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tation. Consider referral of patients with claudication and/or absent pedal pulses to surgery. Vascular surgery may prevent amputation in some patients with severe peripheral vascular disease. See the Glycemic Control and Blood Pressure Control algorithms.

**31. Are Goals Continuing to Be Met?**

See Annotation #11, "Set Individualized Treatment Goals."

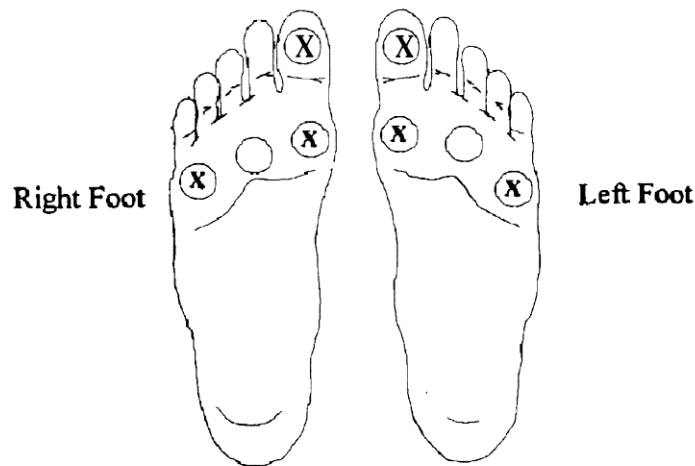
**32. Treatment Goals Not Met**

See Annotation #13, "Treatment Goals Not Met."

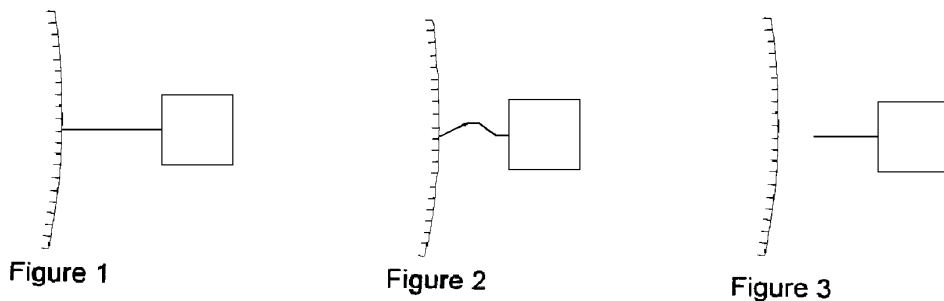
## Appendix A – Using a Semmes-Weinstein Monofilament to Screen the Diabetic Foot for Peripheral Sensory Neuropathy

Figure 1: 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.



- 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.

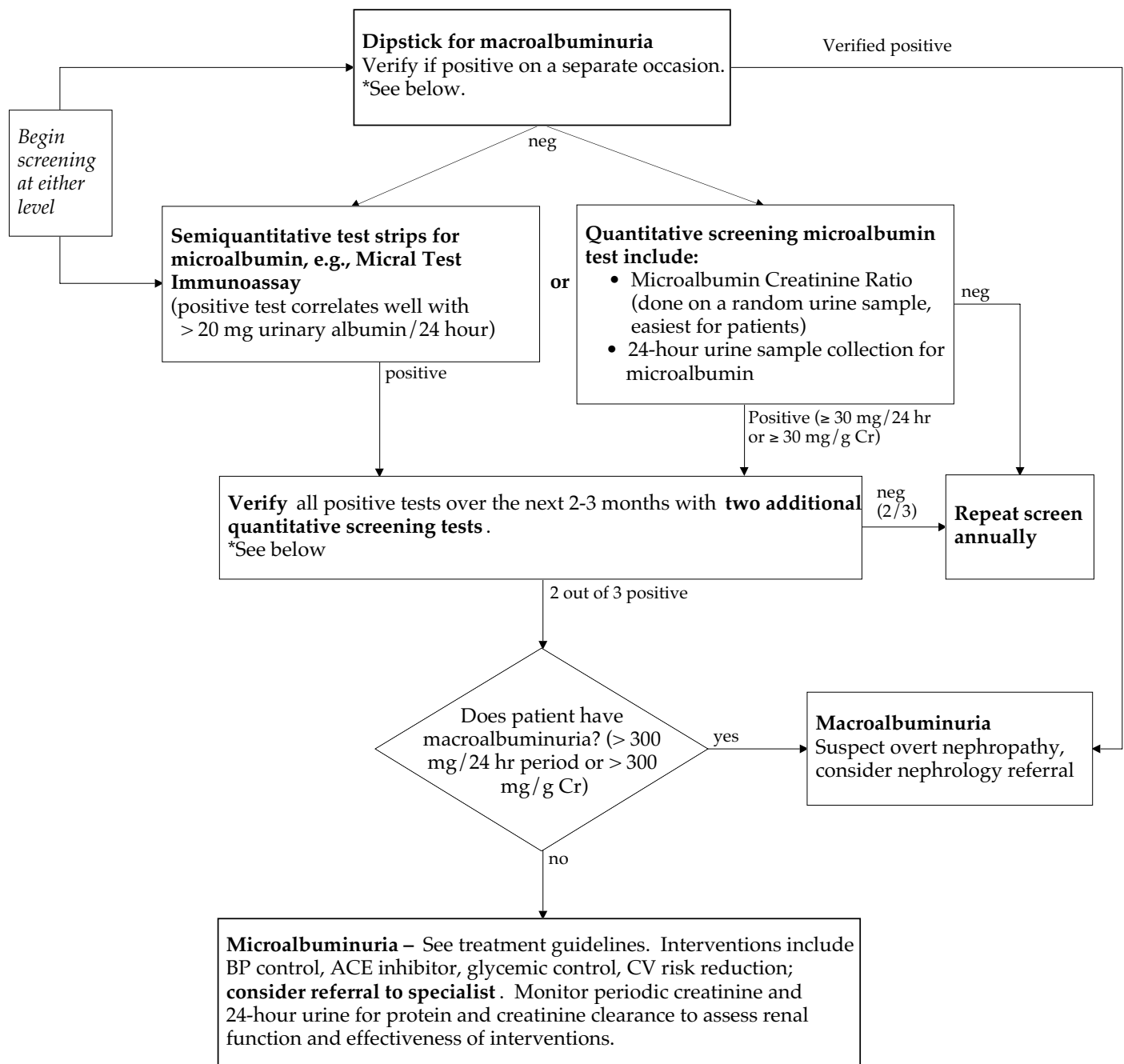


- 4) Ask the patient to respond "yes" when the filament is felt. If the patient does not respond when you touch a given site on the foot, continue on to another site in a random sequence. When you have completed testing all sites on the foot, retest any site(s) where the patient did not feel the filament.
- 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.

## Appendix B – Treatment of Diabetic Nephropathy



\* False positives may occur secondary to UTI, fever, blood in urine, congestive heart failure, extreme HTN, vaginal fluid, uncontrolled blood sugars and prolonged exercise.

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# Evidence Grading System

## I. CLASSES OF RESEARCH REPORTS

### 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

## 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 Section I, above, and are assigned a designator of +, -, or  $\emptyset$  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.

## **Evidence Grading System**

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

The symbols **+**, **-**, **∅**, 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;

**∅** 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 #11A (Goal for Glycemic Control)

**Work Group's Conclusion:** For most patients with type 2 diabetes mellitus, the A1C goal is less than 7%.

## Conclusion Grade: II

Author/Year	Design Type	Class	Quality	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/ <i>Work Group's Comments (italicized)</i>
UK Prospective Diabetes Study Group (UKPDS 33), 1998	RCT	A	+	-3867 newly diagnosed type 2 diabetes patients with mean glucose concentrations of 6.1-15.0 mmol/l after 3 months of diet treatment -all patients age 48-60 years of age -patients randomly assigned to receive treatment with a sulfonylurea (chlorpropamide, glibenclamide or glipizide), insulin, or continue with the diet -10-year follow-up	-Over 10 years, HbA1C was 11% lower in the 2 treatment groups as compared to the diet alone group (7% vs 7.9%) -treatment group had a 25% risk reduction (p=0.0099) in microvascular end points and 12% (p=0.029) reduction in any diabetes-related event as compared to the diet group -non-significant reductions for the treatment group were 10% (p=0.34) for any diabetes-related death and 6% (0.44) for all cause mortality -weight gain and hypoglycemic events were significantly higher in the treatment group (p<0.001 and p<0.0001)	-Intensive blood-glucose control by either sulphonylureas or insulin substantially decreases the risk of microvascular complications, but not macrovascular disease, in patients with type 2 diabetes.
Ohkubo et al., 1995	RCT	A	0	-110 patients with non-insulin-dependent diabetes mellitus (NIDDM) -patients randomly assigned multiple insulin injection treatment (MIT) or conventional insulin injection treatment (CIT) -patients split into primary prevention cohort (no retinopathy and urinary excretions<30mg/24hours) and secondary prevention cohort (simple retinopathy and urinary excretions<300mg/24hours) -all patients <70 years of age -6-year follow-up -ETDRS scale: worsening = increase 2+ steps in 19 stage scale for retinopathy or increase 1+ in 3-stage nephropathy scale	-near normoglycemia was obtained by month 3 in the MIT group -mean values of FBG, HbA1C, MBG, M-value, and MAGE were significantly lower in MIT group as compared to CIT group (p<0.001) -retinopathy was significantly higher in MIT groups (7.7% primary and 19.2% secondary) as compared to CIT groups (32% primary [p=0.039] and 44% secondary [0.049]) after 6 years -nephropathy was significantly higher in MIT groups (7.7% primary and 11.5% secondary) as compared to CIT groups (28% primary [p=0.032] and 32% secondary [0.044]) after 6 years -MIT group showed significant improvement in nerve conduction velocities while CIT group showed deteriorated velocities and vibration thresholds	-Intensive glycemic control by multiple insulin injection therapy can delay the onset and the progression of diabetic retinopathy, neuropathy and nephropathy in Japanese patients with NIDDM. From this study, the glycemic threshold to prevent the onset and the progression of diabetic microangiopathy is indicated by HbA1C<6.5%, FBG<110mg/dl, and 2-h postprandial blood glucose concentration<180mg/dl.

**Conclusion Grading Worksheet A –  
Annotation #11A (Goal for Glycemic Control)**

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 ( <i>italicized</i> )
UK Prospective Diabetes Study Group (UKPDS 35), 2000	Cohort study	B	0	4585 patients with HbA1C measured 3 months after diagnoses of type 2 diabetes included in analysis of incidence (3867 with fasting plasma glucose levels of 6.1-15.0 mmol/l and no symptoms of hyperglycemia included in analysis of RR) -mean age 53 years -mean 10-year follow-up	-each 1% reduction in updated mean HbA1C was associated with reductions of risk of: 21% for any end point-related to diabetes (95CI 17%-24%, p<0.0001), 21% for any end point related to diabetes (95CI 15%-27%, p<0.0001), 14% for MI (95CI 8%-21%, p<0.0001), 37% for microvascular complications (95CI 33%-41%, p<0.0001) -no threshold of risk was observed for any end point	-In patients with type 2 diabetes the risk of diabetic complications was strongly associated with previous hyperglycemia. Any reduction in HbA1C is likely to reduce the risk of complications, with the lowest risk being in those with HbA1C values in the normal range (<6.0%).
Diabetes Control and Complications Trial Research Group (DCCT), 1996	RCT	A	0	-1441 patients with insulin-dependent diabetes mellitus (IDDM) -patients randomly assigned to receive intensive treatment of 3-4 daily insulin injections or use of external insulin pump (711 patients) or conventional therapy consisting of 1-2 daily insulin injections (730 patients) -intensive treatment patients had a goal of achieving glycemic control as close to nondiabetic range as safely possible -all patients age 48-60 years of age -mean 6.5-year follow-up	-risks of retinopathy progression, developing microalbuminuria, and neuropathy were continuous but nonlinear over entire range of glycosylated hemoglobin values in both groups and in the two groups combined -no HbA1C threshold was identified, short of normal glycemia, below which there was no risk of the development or progression of complications -as HbA1C was reduced proportionately, proportional rate of decline in RR for each complication was similar for HbA1C levels 8.0% or less and greater than 8.0% -absolute risk of severe hypoglycemia in intensive group increased as HbA1C decreased but RR gradients were significantly less for HbA1C levels 8.0% or less than for levels greater than 8.0%	-DCCT data does not support the conjecture that a glycemic threshold for the development of complications exists at a HbA1C of 8.0% or that an HbA1C goal of 8% is maximally beneficial. In the DCCT, as HbA1C was reduced below 8% there were continuing relative reductions in the risk of complications, whereas there was a slower rate of increase in the risk of hypoglycemia. -The DCCT continues to recommend implementation of intensive therapy with the goal of achieving normal glycemia as early as possible in as many IDDM patients as is safely possible.

## Conclusion Grading Worksheet B – Annotation #11B (Statin Use)

**Work Group's Conclusion:** For patients with type 2 diabetes mellitus, consider the use of a statin.

**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/ <i>Work Group's Comments (italicized)</i>
Heart Protection, 2002	RCT	A	+	20536 patients 40-80 years (75% males, 35% without a prior history of CAD, 28% >70 years of age) with nonfasting LDL Chol of >3.4 mmol/L (135mgm%). 3982 patients had diabetes, 3982 without prior hx of MI or CAD.	<b>Simvastatin 40 mgm/day vs Placebo</b> 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. 4002 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.

**Conclusion Grading Worksheet B –  
Annotation #11B (Statin Use)**

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/ <i>Work Group's Comments (italicized)</i>
Colloun et al, CARDS 2004	RCT	A	+	2838 patients (age 40-75 years, 94% caucasian and 68% male), in 132 centers in the UK/Ireland	<b>Atorvastatin 10 mg vs. Placebo</b> 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	+	2531 men with coronary heart disease and low HDL-C levels (avg 32 mg/dl). 620 patients had diabetes.	<b>Gemfibrozil 1200 mgm/day vs. Placebo</b> RRR 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.

# Conclusion Grading Worksheet C – Annotations #11C, 23, 25 (Goals for BP)

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

## Conclusion Grade: II

Author/Year	Design Type	Class	Quality	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	⊖	-758 patients allocated to tight control of BP among 1148 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 age 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 equally effective in mean BP reduction (144/84 and 143/81 mm Hg, respectively) -reduction of risk of macrovascular endpoints were similar in the two groups (31% and 37% showed deterioration in retinopathy by 2 grades; 5% and 9% developed clinical grade albuminuria greater or equal to 300 mg/l) -similar percent 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	+	-1148 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 age 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) -reduction of risk in the tight BP group as compared to the less tight BP group were: 24% in diabetes-related endpoints (95CI 8% to 38%, p=0.0046), 32% in deaths related to diabetes (95CI 6% to 51%, p=0.019), 44% in strokes (95CI 11% to 65%, p=0.013), 37% in microvascular endpoints (95CI 11% to 56%, p=0.0092) -tight BP group had a 34% reduction in risk of progression 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 achieves 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	⊖	-1510 patients with diabetes (among 18,790 total patients with hypertension and diastolic BP 100-115 mm HG in trial) -all patients age 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 -3-8-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.

# Conclusion Grading Worksheet D – Annotation #11D (Aspirin Use)

**Work Group's Conclusion:** For patients with type 2 diabetes mellitus, initiate low-dose aspirin therapy (81-325 mg daily) in patients 40 and older unless there is a contraindication to aspirin therapy.

**Conclusion Grade: I**

Author/Year	Design Type	Class	Quality	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/ <i>Work Group's Comments (italicized)</i>
Early Treatment Diabetic Retinopathy Study (ETDRS) Report 14, 1992	RCT	A	⊖	-3711 patients with diabetes mellitus (31% type I, 31% type II, and 39% type I or II) randomized to receive aspirin or placebo (650 mg twice daily) -all patients age 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 II 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	⊖	-1510 patients with diabetes (among 18,790 total patients with hypertension and diastolic BP 100-115 mm Hg in trial) -all patients age 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 -3-8-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	⊖	-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.  <i>-The non-significant differences in DM group were likely due to small sample size and insufficient power.</i>

## Conclusion Grading Worksheet E – Annotations #24, 30A (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	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/ <i>Work Group's Comments (italicized)</i>
Lewis et al, NEJM, 2001	RCT	A	+	-1715 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, nonfatal 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	+	-3577 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 age 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 F – Annotations #24, 30D (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	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/ <i>Work Group's Comments (italicized)</i>
Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) Research Group, 2002  ALLHAT trial	RCT	A	+, -, 0	-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	<u>Amlodipine 2.5-10 mgm vs Chlorthalidone 12.5-25 mgm/d</u> -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)  <u>Lisinopril 10-40 mgm vs Chlorthalidone 12.5-25 mgm/d</u> -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. <i>-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.</i>
Wing et al., 2003  ANBP2 Trial	RCT	A	0	-6,083 patients (from 1594 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)	<u>Enalapril (ACE inhibitor) vs Hydrochlorothiazide (diuretic)</u> -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. <i>-There was a lower prevalence of diabetes than might have been expected [7%] mostly because the study population was overrepresented by elderly Caucasian patients.</i> <i>-Vascular outcomes and death were worse using hypertensive regimen emphasizing hydrochlorothiazide compared to ACE inhibition.</i> <i>-Also, insufficient information is provided to discern whether groups were treated equally.</i>

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
  - Definition of "Patients with Diabetes Mellitus" (Denominator Definition)
  - Measurement Specifications
- Key Implementation Recommendations
- Knowledge Products and Resources
- Other 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 multifactorial interventions, 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).

1. Increase the percentage of patients with diabetes age 18-75 for whom recommended screening frequencies and ideal treatment goals are met.

Possible measures of accomplishing this aim:

- a. Percentage of patients with diabetes with A1C test in the last 6 months.
  - b. Percentage of patients with diabetes with an A1C less than 7%.
  - c. Percentage of patients with diabetes receiving a lipid profile in the last 12 months.
  - d. Percentage of patients with diabetes with LDL less than 100 mg/dL.
  - e. Percentage of patients with diabetes with systolic BP less than 130 mmHg.
  - f. Percentage of patients with diabetes without contraindications who use aspirin (or other antiplatelet medication) regularly.
  - g. Percentage of patients with diabetes who are current documented nonsmokers.
  - h. Percentage of patients with diabetes with microalbumin test within the last 12 months.
  - i. Percentage of patients with diabetes with dilated eye exam within the last 12 months.
  - j. Percentage of patients with diabetes with a comprehensive foot exam documented in the last year.
  - k. Percentage of patients with diabetes age 18-75 who achieve comprehensive goals for measures a-g (ideal control comprehensive measure).
2. Decrease the percentage of patients with diabetes with poorly controlled blood sugars and cardiovascular risk factors (clinical strategies that target high-risk populations may be more viable with limited resources):

Possible measures of accomplishing this aim:

- a. Percentage of patients with diabetes with A1C test in the last year greater than 8%.
- b. Percentage of patients with diabetes with LDL test in the last year greater than 130 mg/dL.
- c. Percentage of patients with diabetes with BP greater than 140 mmHg.
- d. Percentage of patients with diabetes with A1C greater than 8% or LDL greater than 130 mg/dL or BP greater than 140 mmHg (high-risk comprehensive measure).

## **Priority Aims and Suggested Measures**

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3. Improve diabetes self-management skills.

Possible measures of accomplishing this aim:

- a. Percentage of patients with diabetes with documentation in the last twelve months that patient is performing self-monitoring of blood glucose.
- b. Percentage of patients with diabetes who self-report monitoring blood glucose.
- c. Percentage of patients with diabetes who report confidence in managing their diabetes.
- d. Percentage of patients with diabetes who have set self-management treatment goals for nutrition or physical activity.

## **Additional Measures**

1. Percentage of patients with diabetes with A1C less than 7% and LDL cholesterol less than 130 mg/dL.
2. Percentage of patients with diabetes assessed for risk factors for foot complications documented in the medical record.
3. Percentage of patients with diabetes with an annual comprehensive foot exam.

## Definition of "Patients with Diabetes Mellitus" (Denominator Definition)

Medical groups using the measures on the following pages should determine how the population of patients with diabetes will be operationalized. Two options are listed below; the first has been used by several medical groups participating in the ICSI Diabetes Action Group. The second definition had been established by the National Committee for Quality Assurance (NCQA) and is used for HEDIS measures.

### Definition 1

Patients 18 years or older with a primary, secondary, or tertiary diagnosis of diabetes (ICD-9 code 250.xx). Established patients with diabetes should be included. This requires both a visit in the target month AND a diabetic visit in a window of 12-24 months before the target month. Both Types 1 and 2 are included\*.

### Definition 2

Patients ages 18-75 continuously enrolled for the last 12 months AND

- a) two or more ambulatory visits or one acute inpatient or emergency room visit with a primary or secondary diagnosis of diabetes\* in the last 12 months: 250.xx, 362.0x (diabetic retinopathy), 366.41 (diabetic cataract), 357.2x (polyneuropathy in diabetes), or 648.0 (pregnancy excludes gestational diabetes), **OR**
- b) one or more prescriptions for insulin in the last 12 months (coding is available on disk from either ICSI or from the NCQA.org website): regular insulin, NPH, Lente, Lispro, Humulin, 70/30, 75/25, 50/50, Novolin, Ultralente, Glargine, Aspart, Multiple Daily Injections or Continuous Subcutaneous Infusion of Insulin, Insulin Pump, Insulin Pen, Semilente, Novolin, Penfill, Ultralente, Velosulin, Humalog, **OR**
- c) one or more prescriptions for oral agents in the last 12 months (coding is available on disk from either ICSI or from the NCQA.org website): Acarbose, Miglitol/Glycet, Amaryl, Diabeta, Diabinese, Glimepiride, Glipizide, Glipizide XL, Glucophage, Glucotrol, Glucotrol XL, Glyburide, Glynase, Metformin, Micronase, Prandin, Starlix, Glucovance, Repaglinide, Precose, Tolazamide, Tolamide, Tolbutamide, Tolinase, Rosiglitazone, Pioglitazone.

\* Note: both types 1 and 2 are included in both measures listed here, while this guideline is focused on type 2 diabetes. The inclusion of type 1 diabetes in the measures is for administrative ease, as many medical groups will not be able to determine this relatively small percentage of patients with type 1 diabetes from standard coding.

## Measurement Specifications

### Possible Success Measure #1b, 2c, 2d

Frequency of LDL cholesterol values in adult patients with diabetes by category: less than 100 mg/dL 100-130, greater than 130, incalculable, untested.

### Population Definition

Adult patients with diabetes who had an encounter in the last month.

### Data of Interest

Proportion of patients with diabetes with LDL cholesterol values for test in last 12 months by categories listed below.

### Numerator Definition

For patients with diabetes (see the denominator definition below) with the value of the most recent LDL cholesterol test performed within the last 12 months by the following categories:

- a. Less than 100
- b. 100-130
- c. Greater than 130
- d. Untested in the last 12 months\*
- e. Incalculable\*

\*Note: It is understood that some data systems do not separate these two categories. While not preferable, it may be necessary to combine these two categories.

### Denominator Definition

Two options for defining the denominator are listed in the section preceding the measurement specifications.

### Method/Source of Data Collection

It is understood that many medical groups will not have electronic access to integrated database containing both visit data and lab data. In this case, manual identification of at least 20 patients meeting the denominator definition will be necessary and the LDL cholesterol values collected from the medical record.

### Note

Several national accountability organizations have joined together to form the Diabetes Quality Improvement Project (DQIP). The charge to the DQIP was to recommend a single consistent set of diabetes specific performance measure. This group has constructed a measure assessing frequency of LDL cholesterol values in the last two years, with the following categories: less than 100, 100-129, 130-159, greater than 159, no value documented. The criteria listed above were selected by the ICSI Diabetes Action Group.

**Priority Aims and Suggested Measures**

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**Possible Success Measure #2a**

Percentage of patients with diabetes mellitus with A1C measured in the last six months.

**Population Definition**

Adult patients with diabetes who had an encounter in the last month.

**Data of Interest**

$$\frac{\# \text{ patients with diabetes mellitus who had an A1C in the last six months}}{\# \text{ patients with diabetes mellitus}}$$

**Numerator Definition**

Patients with diabetes mellitus (see denominator definition below) who have an A1C test in the most recent six months.

**Denominator Definition**

Two options for defining the denominator are listed in the section preceding the measurement specifications.

**Method/Source of Data Collection**

Measure may be collected electronically. If clinics do not have electronic databases or do not have registries, they may manually identify 20 patients with diabetes and collect data from medical records.

**Time Frame Pertaining to Data Collection and Data Reporting**

Data may be collected monthly or quarterly.

**Note**

The definition of diabetes mellitus used here will also capture older type 1 members. The guideline group felt that this expansion of the denominator was allowable because these members, too, should have their glycosylated hemoglobin routinely measured. The guideline group noted that the proportion of additional cases to the denominator would be very small. This definition may miss new diagnosis of diabetes if a person is not on insulin or oral agents.

Priority Aims and Suggested Measures

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**Possible Success Measure #2b**

Percentage of adult patients with diabetes with A1C less than 7%.

**Population Definition**

Adult patients with diabetes who had an encounter in the last month.

**Data of Interest**

$$\frac{\# \text{ patients with A1C less than 7\%}}{\# \text{ patients with diabetes mellitus}}$$

**Numerator Definition**

Patients with diabetes (see denominator definition), who have had a A1C test within six months of the target month with a value less than 7%.

**Denominator Definition**

Two options for defining the denominator are listed in the section preceding the measurement specifications.

**Method/Source of Data Collection**

It is understood that many medical groups will not have electronic access to an integrated database containing both visit data and lab data. In this case, manual identification of at least 20 patients meeting the denominator definition will be necessary and the A1C value collected from the medical record.

**Note**

Medical groups may decide to collect measure 2a, the rate of A1C testing, concurrently with this measure. Some medical groups in the ICSI Diabetes Action Group raised the concern that as they increased the rate of testing in patients, particularly those patients who may not have received regular care, that slowed the rate of improvement for this measure.

**Priority Aims and Suggested Measures**

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**Possible Success Measure #2h**

Percentage of patients with diabetes with microalbumin tested within last 12 months.

**Population Definition**

Adult patients with diabetes who had an encounter in the last month.

**Data of Interest**

# patients with diabetes mellitus who had a microalbumin test within the last 12 months

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# patients with diabetes mellitus

**Numerator Definition**

Patients with diabetes mellitus (see denominator definition option listed in the section preceding the measurement specifications) who have a documented microalbumin screening test in the most recent 12 months: CPT Codes such as 820.43 ("urine, microalbumin, quantitative"), or 841.55 ("protein; total, except refractometry").

**Denominator Definition**

Two options for defining the denominator are listed in the section preceding the measurement specifications.

**Method/Source of Data Collection**

Measure may be collected electronically. If clinics do not have electronic databases or do not have registries, they may manually identify 20 patients with diabetes and collect data from medical records.

**Time Frame Pertaining to Data Collection and Data Reporting**

Data may be collected monthly or quarterly.

Priority Aims and Suggested Measures

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**Possible Success Measure #2i**

Percentage of patients with diabetes with eye exam documented within last 12 months.

**Population Definition**

Adult patients with diabetes who had an encounter in the last month.

**Data of Interest**

$$\frac{\# \text{ patients with diabetes mellitus who had an eye exam within the last 12 months}}{\# \text{ patients with diabetes mellitus}}$$

**Numerator Definition**

Patients with diabetes mellitus (see denominator definition options listed in the section preceding the measurement specifications) who have an eye exam documented in the most recent 12 months. The nature of the exam is not specified and may be completed by any ophthalmologist or optometrist.

**Denominator Definition**

Two options for defining the denominator are listed in the section preceding the measurement specifications.

**Method/Source of Data Collection**

Measure may be collected electronically. If clinics do not have electronic databases or do not have registries, they may manually identify 20 patients with diabetes and collect data from medical records.

**Time Frame Pertaining to Data Collection and Data Reporting**

Data may be collected monthly.

**Priority Aims and Suggested Measures**

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**Possible Success Measure #2k**

Percentage of patients who have had a screen for A1C in the past six months, an annual LDL test, A1C value less than 7%, LDL less than 100, blood pressure less than 130/80, who don't use tobacco and are regularly using aspirin.

**Numerator Definition**

Patients with diabetes as defined below, who meet ALL of the following criteria: screen for A1C and LDL, A1C less than 7%, LDL less than 100, blood pressure less than 130/80, who don't use tobacco and are regularly using aspirin, clopidogrel or ticlopidine.

**Denominator Definition**

The options for defining the denominator are listed in the section preceding the measurement specifications.

**Method/Source of Data Collection**

It is understood that many medical groups will not have electronic access to integrated database containing both visit data and lab data. In this case, manual identification of at least 20 members meeting the denominator definition will be necessary and the A1C value collected from the medical record.

**Note**

For accountability purposes, other thresholds for A1C, blood pressure or lipids may be considered.

## Key Implementation Recommendations

The implementation of diabetes 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 (*O'Connor, 2001; Bodenheimer, 2002; Solberg, 2000*). These overlapping care elements can be categorized at the medical group and provider levels:

### A. Essential Elements at the Medical Group Level:

1. **Leadership.** Medical group leaders must communicate the need for change in clinical practice patterns and consistently identify improvement priorities.
2. **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.
3. **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, 2005*). 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*).
4. **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).
5. **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.

### B. Essential Elements at the Clinic Level:

1. **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.
2. **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 (*Phillips, 2001; O'Connor, 2003; O'Connor, 2005; O'Connor, 2005*). 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.
3. **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.

**Key Implementation Recommendations**

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4. **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*).

# Knowledge Products and Resources

## Criteria for Selecting Resources

The following resources were selected by the Management of Type 2 Diabetes Mellitus 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

The following materials are available to ICSI members only. Also available is a wide variety of other knowledge products, including tool kits on CQI processes and Rapid Cycling that can be helpful. To obtain copies of these or other Knowledge Products, go to <http://www.icsi.org/knowledge>.

To access these materials on the Web site, you must be logged in as an ICSI member.

### Recorded Presentations

#### Audio

- Chronic Care Model Series – Session 3: Community Outreach
- Chronic Care Model Series – Session 2: Registries
- Chronic Care Model Series – Session 1

#### Video

- Chronic Diseases
- Chronic Care Action Group – June 20, 2002
- Chronic Care Model, The

### Educational Resources

#### Process Improvement Reports (PIRs)

- Diabetes Patient Registries: Three Medical Groups' Experiences
- Diabetes Improvement at HealthPartners
- Diabetes Education Program – Patient Survey at HealthEast
- Diabetes Improvement at HealthEast
- Diabetes Improvement at CMGH

## Other Resources Available

Title/Description	Audience	Author/Organization	Web Sites/Order Information
Wide variety of information on diabetes as well as recent publications; series of journals for both consumers and health professionals; community resources.	People with diabetes and diabetes care professionals	American Diabetes Association	<a href="http://www.diabetes.org">http://www.diabetes.org</a>
Educational materials in Spanish as well as English, and low literacy, public health and community campaigns for educating about diabetes and diabetes prevention.	Health professionals, public health departments, consumers/people with DM	Centers for Disease Control and Prevention	<a href="http://www.cdc.gov/diabetes">http://www.cdc.gov/diabetes</a>
Educational materials in Spanish as well as English, and low literacy, public health and community campaigns for educating about diabetes and diabetes prevention.	Health professionals, public health departments, consumers/people with DM	National Diabetes Education Program	<a href="http://www.ndep.nih.gov">http://www.ndep.nih.gov</a>
Data, statistics, information for health professionals, educational materials in Spanish as well as English, and low literacy.	Health professionals, public health departments, consumers/people with DM	National Institutes of Diabetes and Digestive and Kidney Diseases, a division of the National Institutes of Health	<a href="http://www.niddk.nih.gov">http://www.niddk.nih.gov</a> Also, links to NDEP, NKDEP, NIDDK
Self-management interactive site, information on diabetes and managing it, chat rooms, capacity to e-mail for questions.	People with DM	Protocol Driven Healthcare	<a href="http://www.mydiabetes.com">http://www.mydiabetes.com</a>
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.	Health professionals, public health departments, consumers/people with DM	WebMD Corporation	<a href="http://www.webMD.com">http://www.webMD.com</a>
Diabetes Care Series: Type 2 Diabetes - The First Step; booklet	Patients	International Diabetes Center	<a href="http://www.idcpublishing.com">http://www.idcpublishing.com</a> IDC #2058-819
Staying Healthy with Type 2 Diabetes; booklet	Patients	International Diabetes Center	<a href="http://www.idcpublishing.com">http://www.idcpublishing.com</a> IDC #2058-824 (English) #2058-825 (Spanish)

**Other Resources Available**

<b>Title/Description</b>	<b>Audience</b>	<b>Author/Organization</b>	<b>Web Sites/Order Information</b>
Exchange Lists for Meal Planning; pamphlet	Patients	American Diabetes Assoc. & American Dietetic Assoc.	<a href="http://www.diabetes.org/nutrition-and-recipes/nutrition/exchangelist.jsp">http://www.diabetes.org/nutrition-and-recipes/nutrition/exchangelist.jsp</a> 1-800-232-6733
Exchanges for All Occasions - Pocket Edition; book	Patients	International Diabetes Center	<a href="http://www.idcpublishing.com">http://www.idcpublishing.com</a> IDC #2058-EAOP
Fast Food Facts - Pocket Edition; book	Patients	International Diabetes Center	<a href="http://www.idcpublishing.com">http://www.idcpublishing.com</a> IDC #2058-853
Carbohydrate Counting; booklet	Patients	International Diabetes Center	<a href="http://www.idcpublishing.com">http://www.idcpublishing.com</a> IDC #2058-802
My Food Plan; pamphlet	Patients	International Diabetes Center	<a href="http://www.idcpublishing.com">http://www.idcpublishing.com</a> IDC #2058-25 (English) #2058-823 (Spanish)
Healthy Eating; booklet	Patients	International Diabetes Center	IDC #2058-814 (English) #2058-821 (Spanish)
Healthy Food Choices; pamphlet	Patients	American Diabetes Association	<a href="http://www.diabetes.org/nutrition-and-recipes/nutrition/healthyfoodchoices.jsp">http://www.diabetes.org/nutrition-and-recipes/nutrition/healthyfoodchoices.jsp</a> 1-800-232-6733 #5903-03 (English) #5903-13 (Spanish)
First Step in Meal Planning; brochure	Patients	American Diabetes Association	<a href="http://www.diabetes.org/youthzone/meal-planning.jsp">http://www.diabetes.org/youthzone/meal-planning.jsp</a> 1-800-232-6733
All About Diabetes	Patients	American Diabetes Association	<a href="http://www.diabetes.org/about-diabetes.jsp">http://www.diabetes.org/about-diabetes.jsp</a> 1-800-232-6733
Blood Glucose Patterns; booklet	Patients	International Diabetes Center	<a href="http://www.idcpublishing.com">http://www.idcpublishing.com</a> IDC #2058-816A
Record Booklet; booklet	Patients	International Diabetes Center	<a href="http://www.idcpublishing.com">http://www.idcpublishing.com</a> IDC #2058-231
My Insulin Plan; pamphlet	Patients	International Diabetes Center	<a href="http://www.idcpublishing.com">http://www.idcpublishing.com</a> IDC #2058-827
Complete Guide to Diabetes; book	Patients	American Diabetes Association	<a href="http://www.diabetes.org/shop-for-books-and-gifts.jsp">http://www.diabetes.org/shop-for-books-and-gifts.jsp</a> ADA #4809-04; 1-800-232-6733
Managing Type 2 Diabetes; book	Patients	International Diabetes Center	<a href="http://www.idcpublishing.com">http://www.idcpublishing.com</a> IDC #2058-850
Type 2 Diabetes Basics - Client Book; book	Patients	International Diabetes Center	<a href="http://www.idcpublishing.com">http://www.idcpublishing.com</a> IDC-2058-BCBK

**Other Resources Available**

<b>Title/Description</b>	<b>Audience</b>	<b>Author/Organization</b>	<b>Web Sites/Order Information</b>
Diabetes and Exercise; brochure	Patients	Staywell/ Krames	1-800-333-3032
Safe and Healthy Exercise; booklet	Patients	International Diabetes Center	<a href="http://www.idcpublishing.com">http://www.idcpublishing.com</a> IDC-2058-805
Weight Management for Type 2 DM; book	Patients	Labat & Maggi	pub. by Wiley & Sons ISBN #0471347507
Basic Carbohydrate Counting; booklet	Patients	American Diabetes Association	<a href="http://www.diabetes.org/shop-for-books-and-gifts.jsp">http://www.diabetes.org/ shop-for-books-and-gifts.jsp</a> ADA #S623-01 1-800-232-6733
Complete Guide to Carbohydrate Counting; booklet	Patients	American Diabetes Association	<a href="http://www.diabetes.org/shop-for-books-and-gifts.jsp">http://www.diabetes.org/ shop-for-books-and-gifts.jsp</a> ADA #4715-02 1-800-232-6733
Translation for Patients of the ICSI Type 2 Diabetes Mellitus Guideline; guideline	Patients	ICSI	(952)814-7060 or <a href="http://www.icsi.org">http://www.icsi.org</a>