ICSI Institute for Clinical Systems Improvement

Health Care Guideline

Diagnosis and Management of Type 2 Diabetes Mellitus in Adults

How to cite this document:

Riethof M, Flavin PL, Lindvall B, Michels R, O'Connor P, Redmon B, Retzer K, Roberts J, Smith S, Sperl-Hillen J. Institute for Clinical Systems Improvement. Diagnosis and Management of Type 2 Diabetes Mellitus in Adults. http://bit.ly/Diabetes0412. Updated April 2012.

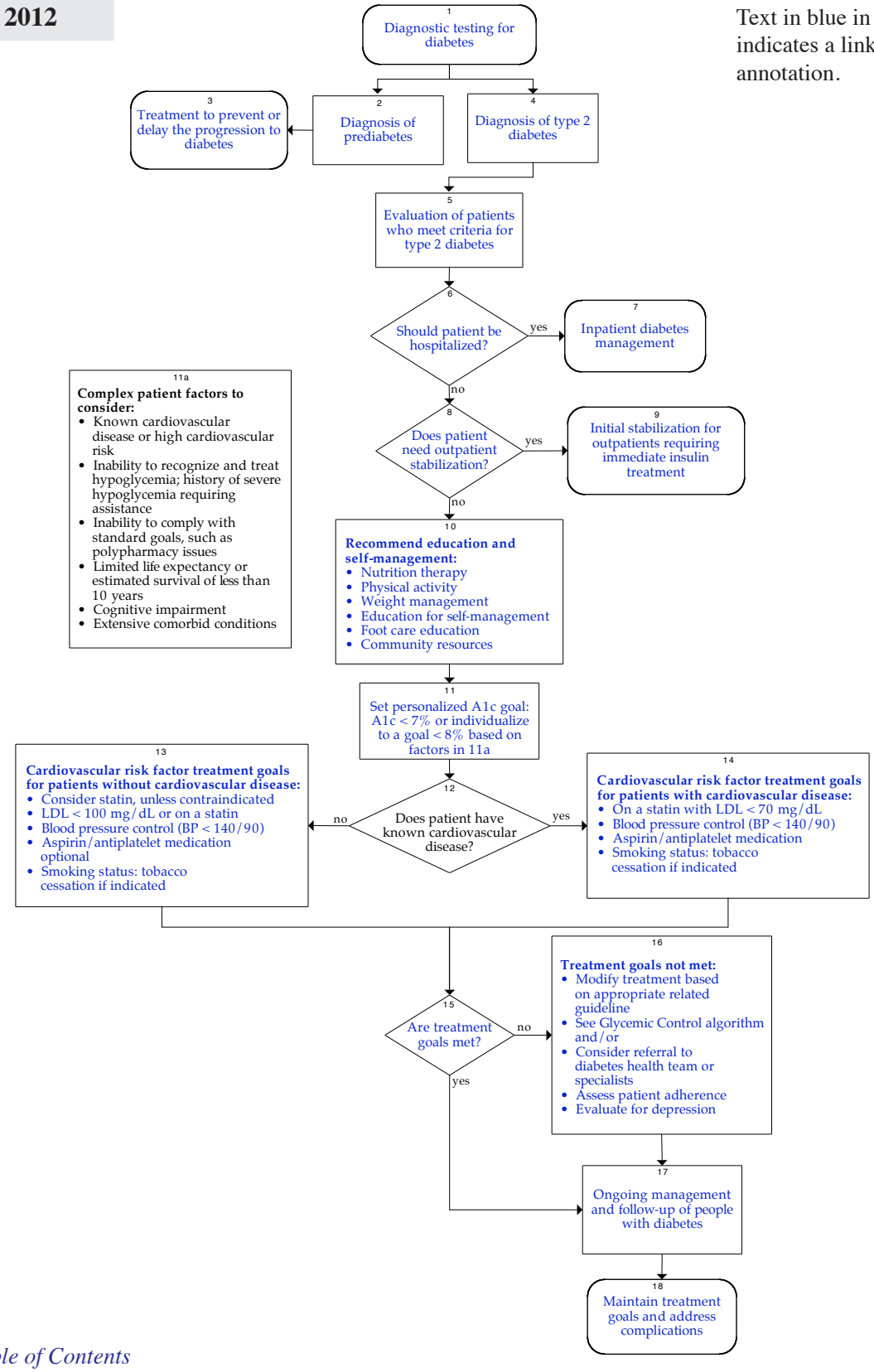
ICSI
Institute for Clinical Systems Improvement

Health Care Guideline:
Diagnosis and Management of Type 2 Diabetes Mellitus in Adults

Fifteenth Edition
April 2012

Main Algorithm

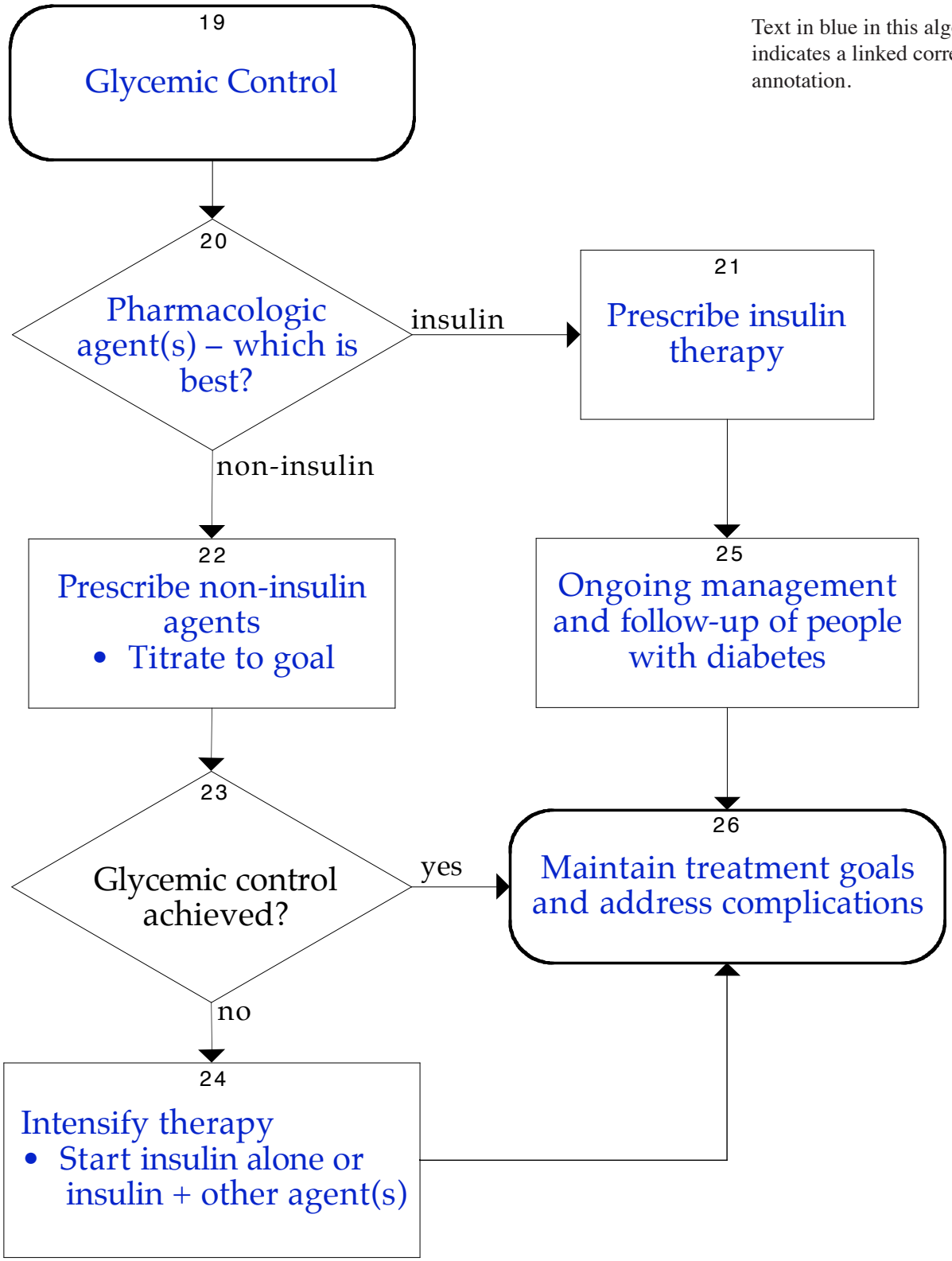
Text in blue in this algorithm indicates a linked corresponding annotation.



Return to Table of Contents

Glycemic Control Algorithm

Text in blue in this algorithm indicates a linked corresponding annotation.



Return to Table of Contents

Table of Contents

Work Group Members
Fairview Health Services
Matthew Riethof, MD
Internal Medicine

HealthPartners Medical Group and Regions Hospital
Ryan Michels, PharmD, BCPS
Pharmacy
Patrick O'Connor, MD
Family Medicine
Julie Roberts, MS, RD, CDE
Health Education
JoAnn Sperl-Hillen, MD
Internal Medicine

Mayo Clinic
Steve Smith, MD
Endocrinology

Olmsted Medical Center
Penny Louise Flavin, RN, CNP, DNP
Family Practice

University of Minnesota
Bruce Redmon, MD
Endocrinology

ICSI
Primary Facilitator
Kari Retzer, RN
Associate Facilitator
Britta Lindvall, MHA

Evidence Grading

Literature Search

A consistent and defined process is used for literature search and review for the development and revision of ICSI guidelines. The literature search was divided into two stages to identify systematic reviews, (stage I) and randomized controlled trials, meta-analysis and other literature (stage II). Literature search terms used for this revision are below and include literature from November 1, 2009, through November 1, 2011.

The databases searched included PubMed and Cochrane. The search was limited to only studies in the English language. The following searches were performed: diabetes and hospitalized patient; diabetes, hospitalization and hyperglycemia; diabetes and mortality; diabetes and renal; diabetes and blood pressure; diabetes and proteinuria; diabetes and obstructed sleep apnea (OSA); obstructed sleep apnea and glycemic control; diabetes and glycemic control; diabetes and glycemic index; diabetes and feet/foot.

GRADE Methodology

Following a review of several evidence rating and recommendation writing systems, ICSI has made a decision to transition to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.

GRADE has advantages over other systems including the current system used by ICSI. Advantages include:

- Developed by a widely representative group of international guideline developers
- Explicit and comprehensive criteria for downgrading and upgrading quality of evidence ratings
- Clear separation between quality of evidence and strength of recommendations that includes a transparent process of moving from evidence evaluation to recommendations
- Clear, pragmatic interpretations of strong versus weak recommendations for clinicians, patients and policy-makers
- Explicit acknowledgement of values and preferences and
- Explicit evaluation of the importance of outcomes of alternative management strategies.

This document is in transition to the GRADE methodology

Transition steps incorporating GRADE methodology for this document include the following:

- Priority placed upon available Systematic Reviews in literature searches.
- All existing Class A (RCTs) studies have been considered as high quality evidence unless specified differently by a work group member.
- All existing Class B, C and D studies have been considered as Low quality evidence unless specified differently by a work group member.
- All existing Class M and R studies are identified by study design versus assigning a quality of evidence. Refer to Crosswalk between ICSI Evidence Grading System and GRADE.
- All new literature considered by the work group for this revision has been assessed using GRADE methodology.

Return to Table of Contents

Crosswalk between ICSI Evidence Grading System and GRADE

ICSI GRADE System	Previous ICSI System	
High, if no limitation	**Class A:**	Randomized, controlled trial
Low	**Class B:**	[observational] Cohort study
	Class C:	[observational] Non-randomized trial with concurrent or historical controls
Low		Case-control study
Low		Population-based descriptive study
***Low**		Study of sensitivity and specificity of a diagnostic test
* Following individual study review, may be elevated to Moderate or High depending upon study design		
	Class D:	[observational]
Low		Cross-sectional study Case series Case report
Meta-analysis	**Class M:**	Meta-analysis
Systematic Review		Systematic review
Decision Analysis		Decision analysis
Cost-Effectiveness Analysis		Cost-effectiveness analysis
Low	**Class R:**	Consensus statement
Low		Consensus report
Low		Narrative review
Guideline	**Class R:**	Guideline
Low	**Class X:**	Medical opinion

Evidence Definitions:

High Quality Evidence = Further research is very unlikely to change our confidence in the estimate of effect.

Moderate Quality Evidence = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low Quality Evidence = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate or any estimate of effect is very uncertain.

In addition to evidence that is graded and used to formulate recommendations, additional pieces of literature will be used to inform the reader of other topics of interest. This literature is not given an evidence grade and is instead identified as a **Reference** throughout the document.

Return to Table of Contents

Foreword

Scope and Target Population

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

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

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

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

Return to Table of Contents

Aims

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

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

1. **Diabetes Optimal Care:** Increase the percentage of adult patients, ages 18-75 with type 2 diabetes mellitus, who in a defined period of time achieve any of the possible measures of established control. *(Annotation #13)*
2. **Diabetes Type 2 Patients Cardiovascular Risk Reduction:** Increase the percentage of type 2 diabetes mellitus patients ages 18-75 years old who have decreased cardiovascular risk in a one-year period of time. *(Annotation #14)*
3. **Diabetes Process of Care Measure:** Increase the percentage of adult patients ages 18-75 with type 2 diabetes mellitus, for whom recommended screening procedures are done. *(Annotation #18)*
4. **High-Risk Population Measures:** The purpose of this aim is to identify and focus on a higher-risk population by decreasing the percentage of adult patients, ages 18-75 with type 2 diabetes mellitus, with poorly controlled glucose and cardiovascular risk factors (clinical strategies that target high-risk populations may have more clinical input and be a better use of limited resources).

Return to Table of Contents

Clinical Highlights

- Education and self-management support is necessary for people with prediabetes and diabetes to manage their disease. *(Annotation #10)*
- Focus on cardiovascular risk reduction (blood pressure control, low-density lipoprotein cholesterol control and statin use, aspirin use and tobacco cessation). *(Annotations #11, 13, 14)*
- A1c levels should be individualized to the patient. *(Annotation #11)*
- Aggressive blood pressure control is just as important as glycemic control. Systolic blood pressure level should be the major factor for detection, evaluation and treatment of hypertension. The use of two or more blood pressure lowering agents is often required to meet blood pressure goal. *(Annotations #13, 14)*
- Prevent microvascular complications through annual or biannual eye exams, foot risk assessments and foot care counseling, and annual screening for proteinuria. *(Annotation #18)*
- Initial therapy with lifestyle treatment and metformin is advised unless contraindicated. *(Annotations #3, 10)*

Return to Table of Contents

Implementation Recommendation Highlights

The following system changes were identified by the guideline work group as key strategies for health care systems to incorporate in support of the implementation of this guideline.

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

- Essential Elements at the Medical Group Level:
  - **Leadership.** Medical group leaders must communicate the need for change in clinical practice patterns and consistently identify improvement priorities.
  - **Resources.** Resources adequate to the task at hand will be needed to assure the success of a change effort. Resources may include staff time, money and provision of tools (such as electronic medical records) to support care improvement.
  - **Select Specific Improvement Goals and Measures.** For most chronic diseases, including diabetes, the most efficient improvement strategy is to focus on a limited number of specific improvement goals. These may be based on observed gaps in care, potential clinical impact, cost considerations or other criteria *(O'Connor, 2005a [Low Quality Evidence])*. 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 [High Quality Evidence])*.
  - **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).

Return to Table of Contents

- **Prepared Practice Teams.** The medical group may need to foster the development of prepared practice teams that are designed to meet the many challenges of delivering high-quality chronic disease care.

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

Return to Table of Contents

Related ICSI Scientific Documents

Guidelines

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

Return to Table of Contents

Definition

Clinician – All health care professionals whose practice is based on interaction with and/or treatment of a patient.

Return to Table of Contents

Algorithm Annotations

Main Algorithm Annotations

1. Diagnostic Testing for Diabetes

Recommendation:

- Type 2 diabetes is frequently not diagnosed until complications appear, and approximately one-third of all people with diabetes may be undiagnosed *(American Diabetes Association, 2010 [Guideline])*. Possible tests to assess for diabetes include a fasting plasma glucose, an oral glucose tolerance test or an A1c measurement.

The decision about which test to use is at the discretion of the health care professional and may be influenced by health care coverage *(American Diabetes Association, 2010 [Guideline])*.

Patients presenting with symptoms of diabetes should be tested.

Risk factors for diabetes include:

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

Testing patients with hypertension, dyslipidemia or heart disease is also recommended.

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

Return to Algorithm *Return to Table of Contents*

2. Diagnosis of Prediabetes

Prediabetes: Prediabetes is defined as hyperglycemia not sufficient to meet the diagnostic criteria for diabetes, but that which is associated with an increased risk of progression to type 2 diabetes mellitus. Diagnosis of prediabetes is made when an individual meets one or more of the following criteria:

- **A1c 5.7-6.4% (as measured according to laboratory specifications in Annotation #4)**
- Fasting plasma glucose of 100 mg/dL to 125 mg/dL
- Oral glucose tolerance test two-hour plasma glucose: 140 mg/dL to 199 mg/dL

(American Diabetes Association, 2010 [Guideline])

Return to Algorithm *Return to Table of Contents*

3. Treatment to Prevent or Delay the Progression to Diabetes

Recommendation:

- Patients who are identified with prediabetes should be referred for education and lifestyle interventions.

Health care clinicians should follow up with patients diagnosed with prediabetes on an annual basis to monitor their progress and review treatment goals *(American Diabetes Association, 2010 [Guideline])*.

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

- Lifestyle modifications, such as nutrition, exercise and even modest weight loss, are recommended for prevention or delayed progression of patients with prediabetes.
- Pharmacotherapy, such as metformin, is effective in some patients with prediabetes.

[Conclusion Grade II: See Conclusion Grading Worksheet A – Annotation #3 (Prediabetes)]

The following initial approaches are recommended for people with prediabetes:

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

Patients who respond to lifestyle interventions:

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

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

- Intensify education and counseling on lifestyle interventions.
- There is some evidence of prevention of diabetes through pharmacotherapy with biguanides and alpha glycosidase inhibitors *(Knowler, 2002 [High Quality Evidence])*. Lifestyle change remains the preferred method to prevent diabetes *(Knowler, 2002 [High Quality Evidence])*.

Return to Algorithm *Return to Table of Contents*

4. Diagnosis of Type 2 Diabetes

Type 2 Diabetes Mellitus: Type 2 diabetes is defined as diabetes that results from a progressive insulin secretory defect on the background of insulin resistance. The diagnosis of diabetes is made when an individual meets one or more of the following criteria:

- A1c $\geq$ 6.5% on two occasions
  - The A1c test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program certified and standardized to the Diabetes Control and Complications Trial assay.

Return to Algorithm *Return to Table of Contents*

- Fasting plasma glucose of greater than or equal to 126 mg/dL (7.0 mmol/L)
  - Fasting is defined as no caloric intake for at least eight hours.
- Oral glucose tolerance test – two-hour plasma glucose of 200 mg/dL (11.1 mmol/L) on two occasions
  - The oral glucose tolerance test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water.
- Symptoms of diabetes and a casual plasma glucose of greater than or equal to 200 mg/dL (11.1 mmol/L)
  - Casual is defined as any time of day without regard to time since last meal.
  - The classic symptoms of diabetes include polyuria, polydipsia and unexplained weight loss, excessive hunger, fatigue or wounds that are slow to heal or frequent skin infections.

Notes:

- In the absence of unequivocal hyperglycemia, an abnormal A1c, fasting glucose or oral glucose tolerance test result that meets criteria for diabetes should be confirmed by repeat testing before assigning a diagnosis of type 2 diabetes.
- It is preferable that the same test be repeated for confirmation of diabetes. There may be cases in which two different tests are available (e.g., A1c and fasting glucose). If both tests meet diagnostic criteria for diabetes, then diagnosis of diabetes can be made.
- If two different tests are available and are discordant (e.g., A1c $\geq$ 6.5%, fasting glucose < 126 mg/dL), then the test whose result is above the diagnostic threshold should be repeated. If it is again above the diagnostic threshold on repeat testing, then a diagnosis of diabetes can be assigned.

(American Diabetes Association, 2010 [Guideline]; Nathan, 2009 [Reference])

Return to Algorithm *Return to Table of Contents*

5. Evaluation of Patients Who Meet Criteria for Type 2 Diabetes

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

History *(American Diabetes Association, 2010 [Guideline])*

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

Return to Algorithm *Return to Table of Contents*

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

Physical examination *(American Diabetes Association, 2010 [Guideline])*

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

Laboratory evaluation

- Fasting plasma glucose or random plasma glucose
- A1C
- Lipid profile: total cholesterol, high-density lipoprotein (HDL cholesterol), low-density lipoprotein (LDL cholesterol) and triglycerides
- Serum creatinine and liver function test alanine aminotransferase (ALT) or aspartate aminotransferase (AST)
- Urine: ketones, glucose, protein, microalbuminuria, and culture if microscopic is abnormal or symptoms of infection present
- Urine microalbumin tests can identify patients with early diabetic nephropathy when intervention may be most effective in delaying or preventing end-stage renal disease. Single tests for urinary microalbumin and urinary creatinine can accurately detect urinary microalbumin excretion.

  Increased urinary microalbumin is a predictor of increased cardiovascular mortality *(American Diabetes Association, 2010 [Guideline])*.

Return to Algorithm *Return to Table of Contents*

6. Should Patient Be Hospitalized?

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

- Elderly patients with infection or illness, weight loss, dehydration, polyuria or polydipsia
- Life-threatening acute metabolic complications of diabetes:
  - Hyperglycemic hyperosmolar state with impaired mental status, elevated plasma osmolaity that includes plasma glucose greater than 600 mg/dL

Return to Algorithm *Return to Table of Contents*

  - Diabetic ketoacidosis with a plasma glucose greater than 250 mg/dL, arterial pH less than 7.30 and serum bicarbonate level less than 15 mEq/L and the presence of moderate ketonuria and/or ketonemia
  - Hypoglycemia with neuroglycopenia that includes blood glucose less than 50 mg/dL and treatment has not resulted in prompt recovery, coma, seizures or altered behavior
- Uncontrolled insulin-requiring diabetes during pregnancy
- Surgery, infection, steroids – if these conditions cause significant hyperglycemia and rapid initiation of rigorous insulin is needed

Return to Algorithm *Return to Table of Contents*

7. Inpatient Diabetes Management

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

Hyperglycemia has been associated with increased infection rates and poorer short-term and long-term outcomes in critically ill patients in the intensive care unit, post-myocardial infarction, and post-surgical settings. Earlier studies supported that aggressive glucose management in medical and surgical patients improves outcomes *(Van den Berghe, 2001 [Moderate Quality Evidence]).* More recently, intensive management has been linked to increased hypoglycemia and increased mortality in a subset of patients including those with a long history of diabetes and cardiovascular disease *(NICE-SUGAR Study Investigators, The, 2009 [High Quality Evidence]).*

The following are recommended in the inpatient setting *(American Diabetes Association, 2012 [Guideline]; Clement, 2004 [Low Quality Evidence]):*

- Insulin therapy with intravenous insulin in critically ill patients *(Van den Berghe, 2001 [Moderate Quality Evidence])*
- Oral glycemic agents may need to be held or the dose adjusted if the patient is hospitalized. Insulin therapy is recommended for many patients during hospitalization
- Use of scheduled insulin, with basal coverage (improves glucose control compared to sliding scale coverage alone)
- For insulin-deficient patients, despite reductions or the absence of caloric intake, basal insulin must be provided to prevent diabetic ketoacidosis
- Target preprandial plasma glucose levels are 90-140 mg/dL *(American Diabetes Association, 2012 [Guideline]; NICE-SUGAR Study Investigators, The, 2009 [High Quality Evidence]; American Diabetes Association, 2004b [Guideline]; Clement, 2004 [Low Quality Evidence]; Garber, 2004 [Low Quality Evidence])*
- The random target plasma glucose is less than 180 mg/dL *(American Diabetes Association, 2012 [Guideline]; Holman, 2009 [High Quality Evidence]; NICE-SUGAR Study Investigators, The, 2009 [High Quality Evidence]; American Diabetes Association, 2004b [Guideline]; Clement, 2004 [Low Quality Evidence]; Garber, 2004 [Low Quality Evidence])*
- Hypoglycemia is < 70 mg/dL and should be treated with a protocol *(American Diabetes Association, 2012 [Guideline]; Cryer, 2009 [Low Quality Evidence])*

Return to Algorithm *Return to Table of Contents*

- Establishing a multidisciplinary team that sets and implements institutional guidelines, protocols and standardized order sets for the hospital results in reduced hypoglycemic and hyperglycemic events

Other considerations include *(Clement, 2004 [Low Quality Evidence])*:

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

See Appendix A, "Order Set: Subcutaneous Insulin Management," for more information.

Return to Algorithm *Return to Table of Contents*

8. Does Patient Need Outpatient Stabilization?

Indications for immediate insulin treatment in type 2 diabetes mellitus *(Nathan, 2006 [Reference]; Clements, 1987 [High Quality Evidence])*

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

Insulin therapy may not be permanent once patient is stabilized.

Return to Algorithm *Return to Table of Contents*

9. Initial Stabilization for Outpatients Requiring Immediate Insulin Treatment

See Annotation # 21, "Prescribe Insulin Therapy," for prescribing information.

At presentation, all patients should be instructed on glucose monitoring, hypoglycemia recognition and treatment, and how/when to contact health care support. Patients should check glucose frequently when insulin is initiated. Patients should receive daily phone or visit contact for at least three days and have 24-hour emergency phone support if needed.

Patients should be seen timely for nutrition and diabetes education, e.g., within one to seven days.

Insulin therapy may not be permanent, particularly if oral agents are added or if, at presentation, the patient is in metabolic stress such as infections, acute metabolic complications, recent surgery *(Peters, 1996 [Low Quality Evidence])*. 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.

Return to Algorithm *Return to Table of Contents*

10. Recommend Education and Self-Management

Recommendations:

Nutrition

- Patients with prediabetes or diabetes should receive individualized Medical Nutrition Therapy (MNT), preferably provided by a registered dietitian knowledgeable in the components of diabetes MNT, as needed, to achieve treatment goals.
- Weight loss is recommended for all overweight or obese patients who have or are at risk for diabetes.
- For weight loss, calorie-restricted diets – either low-carbohydrate, low-fat or Mediterranean – can be effective for up to two years.
- Utilize meal plans that incorporate a mix of carbohydrate, protein and fat, and are adjusted to meet metabolic goals, individual preferences and RDAs/DRIs.
- Monitor carbohydrate by carbohydrate counting, choices or experience-based estimation to achieve glycemic control.
- Reduction of saturated fat, trans fats and cholesterol intake, an increase in omega-3 fatty acids, soluble fiber, plant sterols/stanols is recommended to improve lipid profiles.
- Include Dietary Approaches to Stop Hypertension (DASH)-style dietary pattern in lifestyle therapy for hypertension along with weight loss (if overweight) and increased physical activity.

Physical Activity

- Perform at least 150 minutes/week of moderate-intensity aerobic physical activity (50-70% of maximum heart rate) spread over at least three days per week with no more than two consecutive days without exercise.
- In the absence of contraindications, encourage performance of resistance training at least three times per week.

Weight Management

- Lifestyle change should be the primary approach to weight loss.
- Weight loss programs should include physical activity and behavior modification.
- Bariatric surgery may be considered for adults with BMI > 35 if diabetes or comorbidities are difficult to control with lifestyle and pharmacologic therapy.

Diabetes Self-Management Education (DSME)

- People with diabetes should receive DSME according to national standards and diabetes self-management support when their diabetes is first diagnosed and as needed thereafter.
- DSME should address psychosocial issues, since emotional well-being is associated with positive diabetes outcomes.

Return to Algorithm *Return to Table of Contents*

Nutrition Therapy

Medical nutrition therapy for diabetes emphasizes improving metabolic outcomes by modifying nutrient intake and lifestyle. Major goals are to attain and maintain in the normal or as close to normal range as is safely possible glucose, blood pressure and lipid/lipoprotein levels. These prevent or slow the development of the chronic complications of diabetes *(American Diabetes Association, 2010 [Guideline])*.

The priority for nutrition therapy for type 2 diabetes is to implement lifestyle strategies that will reduce hyperglycemia and hypertension and improve dyslipidemias *(American Dietetic Association, 2010 [Guideline])*. Because many individuals are insulin resistant and overweight or obese, nutrition therapy often begins with strategies that reduce energy intake and increase energy expenditure through physical activity. Many individuals may have already tried unsuccessfully to lose weight, and it is important to note that lifestyle strategies, independent of weight loss, can improve glucose control and risk factors for cardiovascular disease.

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

Restricting total carbohydrate to less than 130 g/day is not recommended in the management of diabetes *(American Diabetes Association, 2010 [Guideline])*.

Appropriate nutrition therapy will be developed collaboratively with the person who has diabetes. Instruction may require a clinician with expertise in medical nutrition therapy, and instruction may be obtained through individual or group consultation *(Franz, 1995a [Low Quality Evidence])*. It is important that clinicians 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.

- Evaluate the patient's current eating habits and modify as needed. Recommend:
  - Working together toward gradual, realistic and culturally appropriate lifestyle change goals.
  - Maintaining the pleasure of eating by limiting only food choices indicated by scientific evidence.
  - Healthful food choices: foods containing carbohydrates from whole grains, fruits, vegetables, legumes and low-fat milk should be included in a healthy eating plan.
  - Reducing total caloric intake by moderating food/beverage and limiting total fat intake.
  - Distributing carbohydrates evenly throughout the day to smaller meals and snacks.
  - Monitoring carbohydrates remains a key strategy in achieving glycemic control, whether by carbohydrate counting, exchanges or experience-based estimation *(American Diabetes Association, 2010 [Guideline])*.
  - If one chooses to drink alcohol and has not been cautioned against it, limit intake to one drink per day for women and two drinks per day for men, according to USDA guidelines. A drink is defined as 12 oz. of regular beer, 5 oz. of wine, or 1.5 oz. of 80-proof distilled spirits. To reduce the risk of hypoglycemia, alcohol should be consumed with food.
- Individualize the nutrition prescription based on the nutrition assessment and treatment goals of each patient. For example, if the patient has been eating 45% of calories from fat, lowering fat to even 40% can be helpful.

Carbohydrate *(American Diabetes Association, 2010 [Guideline])*

- Both the quantity and the type or source of carbohydrate in food influence post-prandial glucose levels.

- For individuals with diabetes, the use of glycemic index and glycemic load may provide a modest additional benefit for glycemic control over that observed when total carbohydrate is considered alone.
- Sucrose (e.g., table sugar) and sucrose-containing foods do not need to be restricted. However, they should be substituted for other carbohydrate sources, or if added, covered with insulin or other glucose-lowering medication. They should be eaten within the context of a healthy diet and avoid excess energy intake.
- Added fructose as a sweetening agent is not recommended as it may adversely affect plasma lipids. Naturally occurring fructose in fruits, vegetables and other foods does not need to be avoided.
- The use of sugar alcohols, such as sorbitol or manitol in small amounts, appears to be safe; however, they may cause gastrointestinal side effects *(American Diabetes Association, 2010 [Guideline])*. Sugar alcohols and non-nutritive sweeteners are safe when consumed within the acceptable daily intake levels established by the Food and Drug Administration.
- Encourage consuming a wide variety of fiber-containing foods such as legumes, fiber-rich cereals, fruits, vegetables and whole grain products to achieve fiber intake goals of 14 g/1,000 calories.

Protein *(American Diabetes Association, 2010 [Guideline]; American Diabetes Association, 2007b [Guideline])*

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

Fat *(American Diabetes Association, 2010 [Guideline]; American Diabetes Association, 2007b [Guideline])*

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

Return to Algorithm *Return to Table of Contents*

Sodium *(American Diabetes Association, 2012 [Guideline])*

- Medical nutrition therapy for hypertension focuses on the use of the DASH (Dietary Approaches to Stop Hypertension) diet including reducing sodium intake (to < 1,500 mg/day) and excess body weight, increasing consumption of fruits and vegetables (8-10 servings per day) and low-fat dairy products (2-3 servings/day), and avoiding excess alcohol consumption.

Supplements *(American Diabetes Association, 2010 [Guideline])*

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

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

Physical Activity

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

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

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

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

Hypoglycemia is a risk in individuals who participate in physical activity and are taking insulin, sulfonylureas and/or meglitinides. Depending on the level of physical activity, the medication dosage or the amount of carbohydrate ingested, hypoglycemia can occur. For patients on these drug classes and pre-exercise glucose monitor results are less than 100 mg/dL, additional carbohydrate should be ingested for prevention of hypoglycemia *(American Diabetes Association, 2010 [Guideline])*.

Strategies for initiation of increased physical activity

- Start by incorporating 10 minutes of increased activity into each day
  - Use stairs instead of elevator.
  - Park car away from building entrance and walk.
  - Walk to do errands.
- Overcome barriers
  - Self-monitor activity performed using pedometer, time record and/or journal.
  - Be consistent.
  - Have alternative activities for inclement weather.

Return to Algorithm *Return to Table of Contents*

- Find enjoyable activities.
- Be active at the time of day that is best for the individual.
- Doing a physical activity with a partner and/or being accountable to someone regarding your progress greatly improves the ability to be successful *(American Diabetes Association, 2010 [Guideline])*.

Medical evaluation to assess safety of exercise program

- Assess physical condition and limitations of the patient.
- Assess for cardiovascular disease. Atypical symptoms and painless ischemia are more common in patients with diabetes *(Janard-Delenne, 1999 [Low Quality Evidence])*.
- Cardiac stress testing: there is no evidence that stress testing is routinely necessary in asymptomatic people before beginning a moderate-intensity exercise program such as walking.
- Cardiac stress testing should be considered for the previously sedentary individual at moderate to high risk for cardiovascular disease or other patients who are clinically indicated who want to undertake vigorous aerobic exercise that exceeds the demands of everyday living *(American Diabetes Association, 2010 [Guideline])*.
- Assess glucose control.
- Assess knowledge of physical activity in relation to glucose control.
- When making a referral, make other health care clinicians aware of limitations for exercise.

Physical activity can be intermittent or cumulative *(Hardman, 1999 [Narrative Review]; Pate, 1995 [Consensus Statement]; DeBusk, 1990 [Low Quality Evidence])***.**

Weight Management

Weight loss is also an important goal because it improves insulin resistance, glycemic control, blood pressure and lipid profiles. Moderate weight loss (5% of body weight) can improve fasting blood glucose in many overweight or obese persons *(Pastors, 2002 [Narrative Review])*.

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

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

Identification of the optimal mix of macronutrients for diabetes meal plans is unlikely. The best mix of carbohydrate, protein and fat appears to vary depending on individual circumstances but must be appropriate for individual metabolic status, total calories for weight management goal and/or food preferences. A variety of meal patterns is likely effective, including Mediterranean-style, plant-based (vegan or vegetarian), low-fat and lower-carbohydrate eating patterns *(American Diabetes Association, 2012 [Guideline])*.

Long-term metabolic effects of very-low-carbohydrate diets are unclear, and such diets eliminate important sources of energy, fiber, vitamins and minerals *(American Diabetes Association, 2012 [Guideline])*. For patients on low-carbohydrate diets, monitor lipid profiles, renal function and protein intake (in those with nephropathy), and adjust hypoglycemic therapy as needed *(American Diabetes Association, 2010 [Guideline])*.

Return to Algorithm *Return to Table of Contents*

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

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

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

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

Education for Self-Management

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

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

See the Implementation Tools and Resources Table for a list of American Diabetes Association-recognized education programs available.

Components of self-management include:

- Description of the diabetes disease process and treatment options
- Goal-setting to promote health, and problem-solving for daily living
- Preventing, detecting and treating acute complications
- Preventing (through risk reduction behavior), detecting and adhering to treatments for chronic complications
- Self-monitoring blood glucose, ketones (when appropriate), and using results to improve control
- Incorporation of appropriate nutrition management *(Barnard, 1994 [Low Quality Evidence])*
- Incorporation of physical activity into lifestyle *(Barnard, 1994 [Low Quality Evidence])*
- Utilizing medications (if applicable) to maximize therapeutic effectiveness
- Awareness of culturally appropriate community resources/support for persons with diabetes mellitus and their families and ability to access community resources

- Psychosocial adjustment of diabetes to daily life
- Promotion of preconception care, counseling and management during pregnancy, if applicable

Foot Care Education

Education should be tailored to patient's current knowledge, individual needs and risk factors. Patients should be aware of their risk factors and appropriate measures to avoid complications *(American Diabetes Association, 2004f [Guideline]; Mayfield, 1998 [Low Quality Evidence])*. See Annotation #18, "Maintain Treatment Goals and Address Complications," the "Comprehensive Foot Exam with Risk Assessment" section.

Education should cover:

- Self-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 clinician.
- Be careful of hot water.
- Use of lotions, creams or moisturizer is acceptable, but do not use between the toes.
- Do not walk barefoot.
- Check shoes each day for objects that may have fallen inside, excessive wear or areas that may cause irritation.
- Avoid injuries from cutting toenails; avoid self-cutting calluses or corns.
- When to seek care.

Community Resources

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

Return to Algorithm *Return to Table of Contents*

11. Set Personalized A1c Goal: A1c Less than 7% or Individualize to a Goal Less than 8% Based on Factors in 11a

Recommendation:

- Set personalized A1c goal to less than 7% or less than 8% based on the risks and benefits for each patient.

  This recommendation places high value on trying to optimize the balance of risks versus benefits of more intensive glycemic control for each individual. Potential risks of < 7% may include higher mortality rates, hypoglycemia and weight gain. Potential benefits may include lower risk of diabetes complications such as retinopathy, nephropathy and heart disease. Individual patient factors that may increase risks include known cardiovascular disease, history of severe hypoglycemia, polypharmacy-related challenges, limited life expectancy, cognitive impairment and extensive comorbid conditions.

Return to Algorithm *Return to Table of Contents*

- Blood glucose goals should be individualized according to the patient's A1c goals and treatment plan.

  This recommendation places a high value on using self-monitored blood glucose (SMBG) values to guide treatment decisions, but this benefit may not be equal for patients and is probably more helpful in patients having trouble reaching or sustaining A1c goals and in those treated with insulin. This recommendation places a relatively low value on the burden and cost of SMBG testing.

A1c target in type 2 diabetes is aimed at reducing microvascular complications while not increasing risk of morbidity or mortality. All patients with type 2 diabetes should aim to achieve an A1c less than 8%. This will reduce microvasuclar disease and not increase risk substantially. Many patients with type 2 diabetes may derive additional benefit in reduction of microvasuclar disease by reaching a target A1c less than 7% and not increase risks as long as the target is not A1c less than 6%. For patients with type 2 diabetes and the following factors, an A1c goal of less than 8% may be more appropriate than an A1c goal of less than 7% *(Action to Control Cardiovascular Risk in Diabetes Study Group, The, 2008 [High Quality Evidence]; ADVANCE Collaborative Group, The, 2008 [High Quality Evidence]; Duckworth, 2009 [Moderate Quality Evidence]). [Conclusion Grade II: See Conclusion Grading Worksheet B – Annotation #11 (A1c)]*

- Known cardiovascular disease or high cardiovascular risk. Cardiovascular risk can be determined by the Framingham or UKPDS risk equations, or alternatively as having two or more cardiovascular risks (BMI > 30, hypertension, dyslipidemia, smoking and microalbuminuria).
- Inability to recognize and treat hypoglycemia, history of severe hypoglycemia requiring assistance.
- Inability to comply with standard goals, such as polypharmacy issues.
- Limited life expectancy or estimated survival of less than 10 years.
- Cognitive impairment.
- Extensive comorbid conditions such as renal failure, liver failure and end-stage disease complications.

The clinician and patient should discuss and document specific treatment goals and develop a plan to achieve all desired goals. A multifactorial approach to diabetes care that includes emphasis on blood pressure, lipids, glucose, aspirin use, and non-use of tobacco will maximize health outcomes far more than a strategy that is limited to just one or two of these clinical domains *(American Diabetes Association, 2010 [Guideline]; Duckworth, 2009 [Moderate Quality Evidence]; Gaede, 2008 [High Quality Evidence]; Holman, 2008a [High Quality Evidence])*.

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

Return to Algorithm *Return to Table of Contents*

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

In the ACCORD Trial, excess mortality in the intensive group (A1c mean 6.4% vs. standard group A1c 7.5%) forced the safety board to discontinue the intensive treatment arm earlier than planned *(Action to Control Cardiovascular Risk in Diabetes Study Group, The, 2008 [High Quality Evidence])*. There was one excess death for every 90 patients in the intensive group over a 3.5-year period of time. In the ADVANCE trial, intensive group patients achieved A1c 6.5% (vs. 7.5% in standard group) but had no reduction in cardiovascular complications or events. In the VADT trial, intensive group patients achieved A1c of 6.9% but had no significant reduction in cardiovascular events or microvascular complications compared to standard group patients who achieved A1c 8.4%. However, the VADT Trial was underpowered for its main hypothesis tests *(Duckworth, 2009 [Moderate Quality Evidence])*. In the ADVANCE trial, intensive group patients had less progression to proteinuria (one less patient advancing to proteinuria for every 100 people in the intensive group over a five-year period of time), but no fewer eye complications in the intensive group than in the standard group. ACCORD analysis showed lower rates of early stage microvascular complications in the intensively treated group. Some patients, especially those with little comorbidity and long life expectancy, may benefit from more intensive glycemic goals as long as hypoglycemia does not become a barrier. However, the risk of lower glycemic targets may out weigh the potential benefits on microvascular complications for many patients *(ACCORD, 2010b [High Quality Evidence]; Ismail-Beigi, 2010 [High Quality Evidence])*.

A recent meta-analysis analyzed five randomized controlled trials (UKPDS, PROactive, ADVANCE, VADT and ACCORD) for the effect of intensive glucose control on cardiovascular outcomes. Overall, this meta-analysis concluded that more intensive glucose control significantly reduced non-fatal myocardial infarct events and coronary heart disease events (non-fatal myocardial infarct and all-cardiac mortality) with no evidence of either a benefit or adverse effect on all-cause mortality. Heterogeneity among studies was noted with regard to all-cause mortality, suggesting that the impact of glycemic reduction on all-cause mortality may differ among different populations *(Ray, 2009 [Meta-analysis])*. A subset analysis from ACCORD, ADVANCE and VADT suggested that intensive glucose lowering has a modest (9%) but statistically significant reduction in major CVD outcomes, primarily non-fatal MI, with no significant effect on mortality. However, a prespecified subgroup analysis suggested that major cardiovascular disease outcome reduction occurred in patients without known cardiovascular disease at baseline *(Turnbull, 2009 [Meta-analysis])*.

Glycosylated hemoglobin assays

Glycosylated hemoglobin assays provide an accurate indication of long-term glycemic control. A1c is formed by the continuous non-enzymatic glycosylation of hemoglobin throughout the lifespan of an erythrocyte. This assay yields an accurate measure of time-averaged blood glucose during the previous six to eight weeks. Clinically it can assist in determining duration and severity of hyperglycemia and can help guide treatment.

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

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

Self-monitoring blood glucose (SMBG)

Major clinical trials assessing the impact of glycemic control on diabetes complications have included self-monitoring blood glucose testing (SMBG) as part of multifactorial interventions, suggesting that self-monitoring blood glucose is a component of effective therapy *(American Diabetes Association, 2010*

Return to Algorithm *Return to Table of Contents*

[Guideline]). Several diabetes management strategies reliant on SMBG testing have demonstrated improved glucose control in patients *(Polonsky, 2011 [High Quality Evidence]; Weinger, 2011 [Moderate Quality Evidence])*. Table 1 gives ranges of self-monitored glucose readings that would be expected as goals for patients with the corresponding A1c level goals. More than half of the plasma blood glucose readings should fall in the desired goal range. Bedtime glucose goals vary dependent on the patient's treatment program, risks for hypoglycemia and time after last meal.

Self-monitoring blood glucose (SMBG) allows patients to evaluate their individual response to therapy and assess whether glucose targets are being achieved. Results of SMBG can be useful in preventing hypoglycemia and adjusting medications, medical nutrition therapy and physical activity *(American Diabetes Association, 1994 [Low Quality Evidence])*.

The frequency and timing of SMBG should be dictated by the particular needs and goals of the individual patient. Patients with type 2 diabetes on insulin typically need to perform self-monitoring blood glucose more frequently than those not using insulin, particularly if using glucose readings to guide mealtime insulin dosing. It is recommended that patients using multiple insulin injections perform SMBG three or more times daily *(American Diabetes Association, 2010 [Guideline])*. The optimal frequency and timing of SMBG for patients with type 2 diabetes on oral agent therapy are not known but should be sufficient to facilitate reaching glucose goals. SMBG should be performed more frequently when adding or modifying therapy; two-hour post-prandial glucose testing is useful in some patients. The role of SMBG in stable diet-treated patients with type 2 diabetes is not known.

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

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

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

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

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

Return to Algorithm *Return to Table of Contents*

13. Cardiovascular Risk Factor Treatment Goals for Patients without Cardiovascular Disease

Recommendation:

- The following treatment goals should be achieved: (1) Use of statins in all adult type 2 diabetes patients if tolerated; statins should be titrated to achieve low-density lipoprotein cholesterol of less than 100 mg/dL without coronary artery disease. (2) Blood pressure less than 140/90 mmHg. (3) Smoking cessation if indicated. (4) Daily aspirin use is optional for primary prevention of cardiovascular events.

  This recommendation places a high value on a multifactorial approach to lowering the cardiovascular risk of patients with diabetes. The recommendation does not place value on prioritizing these treatment interventions, and some may be more important than others for different individuals. For the lipid and blood pressure recommendations, there is low value placed on the burden of these treatment approaches, the age of the patient (the evidence is less established in patients under age 40 and over 75), and whether patients can tolerate the treatments needed to obtain the recommended goals without side effects. The aspirin recommendation places high value on assessing an individual's age and risk of bleeding related to aspirin use prior to recommending it for primary prevention.

The clinician and patient should discuss and document specific treatment goals and develop a plan to achieve all desired goals. A multifactorial approach to diabetes care that includes emphasis on blood pressure, lipids, glucose, aspirin use and non-use of tobacco will maximize health outcomes far more than a strategy that is limited to just one or two of these clinical domains *(American Diabetes Association, 2010 [Guideline]; Duckworth, 2009 [Moderate Quality Evidence]; Gaede, 2008 [High Quality Evidence]; Holman, 2008a [High Quality Evidence])*.

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

- **Consider statin, unless contraindicated**

  Seventy to seventy-five percent of adult patients with diabetes die of macrovascular disease, specifically coronary, carotid and/or peripheral vascular disease. Diabetes is considered a coronary artery disease equivalent. Dyslipidemia is a known risk factor for macrovascular disease. Patients with diabetes develop more atherosclerosis than patients without diabetes with the same quantitative lipoprotein profiles. In most patients with diabetes, use of a statin can reduce major vascular events in patients with diabetes substantially *(Pyorola, 1997 [High Quality Evidence])*. Beneficial effects of statins on cardiovascular risk reduction may go beyond their effects on lipid levels.

  For patients with type 2 diabetes mellitus, consider the use of a statin. Randomized controlled trials, including a number of large trials, and observational data consistently show a benefit of statin therapy for patients with type 2 diabetes. Some studies also report that statin therapy was well tolerated in these patients. None of these studies was able to assess long-term effects of statin treatment/use. *[Conclusion*

Return to Algorithm *Return to Table of Contents*

Grade I: See Conclusion Grading Worksheet C – Annotations #13, 14 (Statin Use)]. However, doses of simvastatin greater than 40 mg may potentially increase risk of myopathy. *(SEARCH Study Collaborative Group, 2007 [High Quality Evidence]).* Evidence *(Colhoun, 2004 [High Quality Evidence]; Heart Protection Collaborative Study Group, 2002 [High Quality Evidence])* and Adult Treatment Panel III consensus guidelines *(Grundy, 2004 [Low Quality Evidence])* suggest that statins are beneficial for high-risk patients ages 40-80 years with a 10-year risk of cardiovascular event of more than 20% based on Framingham or UKPDS risk calculators, even with baseline untreated low-density lipoprotein of less than 100 mg/dL *(Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001 [Low Quality Evidence]).*

(Malmström, 2009 [Moderate Quality Evidence]; Howard, 2008 [High Quality Evidence]; Newman, 2008 [High Quality Evidence]; Settergren, 2008 [Low Quality Evidence]; Colhoun, 2004 [High Quality Evidence]; Heart Protection Collaborative Study Group, 2002 [High Quality Evidence]; Robins, 2001 [High Quality Evidence])

For additional information on statin therapy, refer to the ICSI Lipid Management in Adults guideline.

- **LDL less than 100 mg/dL or on a statin**

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

  Three pathways to improve lipids are:

  - Medical nutrition therapy
  - Increased physical exercise
  - Pharmacotherapy

  Intensify statin to meet low-density lipoprotein (LDL) cholesterol goals *(LaRosa, 2005 [High Quality Evidence]).* If the LDL goal cannot be met with high-dose statin therapy, there is not current evidence to prove that adding LDL-lowering drug classes will improve outcomes for people with diabetes. A combination of statin and ezetimibe versus statin monotherapy has not been proven advantageous.

  High triglycerides and low high-density lipoprotein cholesterol levels are independent risk factors for cardiovascular disease in the patient with diabetes *(American Diabetes Association, 2010 [Guideline]).* Individuals with elevated triglycerides have significant cardiovascular risk reduction with the use of fibrates *(Robins, 2001 [High Quality Evidence])* or statins *(Heart Protection Collaborative Study Group, 2003 [High Quality Evidence]).*

  The current evidence does not support the use of combination therapy with statins and other lipid drugs for most patients with type 2 diabetes. The combination of statin plus ezetimibe versus statin monotherapy has not been proven advantageous (*Kastelein, 2008 [High Quality Evidence]*). The National Institutes of Health-sponsored ACCORD lipid study showed no significant reduction in myocardial infarct, stroke or cardiovascular death with a fibrate-statin combination compared to statin monotherapy. However, a subgroup analysis of the primary outcome suggested that there was a gender effect with a possible benefit for men and possible harm for women, as well as a possible benefit for men and women with both low HDL (< 34 mg/dL) and elevated triglycerides (> 204 mg/dL). AIM-HIGH was a study designed to evaluate the cardiovascular outcomes with niacin and statin combination therapy compared to statin monotherapy in patients with coronary heart disease, including a subgroup with diabetes. The study was stopped early in 2011 because of lack of benefit compared to statin therapy alone, including the diabetes subgroup *(AIM-HIGH Investigators, 2011 [Moderate Quality Evidence].*

Return to Algorithm *Return to Table of Contents*

- **Goals for blood pressure control: blood pressure less than 140/90 mmHg**

  Uncontrolled hypertension is a major cardiovascular risk factor that also accelerates the progression of diabetic nephropathy *(Morrish, 1991 [Low Quality Evidence])*. When hypertension is identified, it should be aggressively treated to achieve a target blood pressure of less than 140/90 mmHg. In many patients with diabetes, two or three or more antihypertensive agents may be needed to achieve this goal. The use of generic combination tablets (such as ACE plus calcium-channel blocker, or beta-blocker plus diuretic) can reduce the complexity of the regimen and out-of-pocket costs.

  The UKPDS, HOT, ADVANCE and ACCORD trials are all large randomized clinical trials that allow comparison of more stringent versus less stringent blood pressure levels on major cardiovascular outcomes *(ACCORD Study Group, The, 2010a [High Quality Evidence]; ADVANCE Collaborative Group, 2008 [High Quality Evidence]; Hansson, 1998 [Moderate Quality Evidence]; United Kingdom Prospective Diabetes Study Group (UKPDS), 1993e [High Quality Evidence])*. The UKPDS, HOT and ADVANCE trials all found reduced cardiovascular outcomes with lower achieved blood pressure levels. However, none of these trials achieved average systolic blood pressure levels below 130 mmHg (Table 2). The ACCORD trial found no difference in major cardiovascular outcomes between a more intensive blood pressure intervention targeting systolic blood pressure < 120 mmHg compared to a more standard intervention targeting systolic blood pressure between 130 and 139 mmHg (Table 2). The more intensive blood pressure regimen was associated with a small reduction in the rate of stroke, greater medication use and more serious adverse events *(ACCORD Study Group, The, 2010a [High Quality Evidence])*.

  The above studies support a systolic blood pressure goal < 140 mmHg for people with type 2 diabetes. We would estimate that targeting a systolic blood pressure < 140 mmHg would result in an achieved blood pressure around 135 mmHg for most people.

  Only the HOT trial specifically targeted diastolic blood pressure. In the HOT trial, targeting a lower diastolic blood pressure was associated with fewer cardiovascular events in subjects with type 2 diabetes. The average achieved diastolic blood pressure values in the three HOT intervention arms ranged from 81-85 mmHg (Table 2). Based on results from the ADVANCE and ACCORD trials, it appears likely that achieved systolic blood pressure values in the mid-130 range will be associated with diastolic blood pressure values well below 80 mmHg.

  The work group acknowledges that the evidence is not definitive for any particular general blood pressure goal for patients with diabetes. The work group feels that a blood pressure goal of < 140/90 mmHg is reasonable and defensible based on the evidence previously presented. This goal is also consistent with the current blood pressure measure for people with diabetes specified by the Physician Quality Reporting System. See https://www.cms.gov/PQRS for more information. The work group will continue to review the blood pressure goal to consider any new evidence and the recommendations of other national practice guidelines (e.g., ADA and JNC8) that are expected to announce revisions. The general recommendation of blood pressure < 140/90 mmHg does not preclude setting individual patient goals lower than that based on patient characteristics, comorbidities, risks or the preference of an informed patient.

Table 2. Comparison of Goal Versus Mean Achieved Blood Pressure Levels in Randomized Trials of Blood Pressure Control in People with Type 2 Diabetes

	UKPDS		HOT			ADVANCE		ACCORD	
	Intensive	Control	DBP			Treat	Placebo	Intensive	Standard
Goal	< 150/85	< 180/105	≤ 80	≤ 85	≤ 90	----	----	SBP ≤ 120	SBP 130-139
Achieved	144/82	154/87	140/81	141/83	144/85	134/75	144/77	119/69	133/70

Return to Algorithm *Return to Table of Contents*

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 #13, 18 (Thiazide Diuretics)] (Chobanian, 2003 [Low Quality Evidence]; Wing, 2003 [Moderate Quality Evidence]; ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, 2002 [High Quality Evidence]; Heart Outcomes Prevention Evaluation Study Investigators, The, 2000a [High Quality Evidence]; Alkaharouf, 1993 [Low Quality Evidence]; Lewis, 1993 [High Quality Evidence])*.

- **Aspirin/antiplatelet medication optional** *(Bhatt, 2002 [Moderate Quality Evidence])*

  Patients with type 2 diabetes are at a significantly increased risk for development of heart disease *(American Diabetes Association, 2010 [Guideline])*. There is insufficient evidence to recommend for or against aspirin use in the primary prevention of cardiovascular events in patients with type 2 diabetes, although there is no evidence of significant harm. *[Conclusion Grade I: See Conclusion Grading Worksheet D – Annotations #13, 14 (Aspirin Use)]*. Recent trials of aspirin use in diabetes have shown less benefit than older trials (perhaps due to better background A1c, blood pressure, and low-density lipoprotein control and lower smoking rates in recent trials) *(Belch, 2008 [High Quality Evidence]; Ogawa, 2008 [High Quality Evidence])*. Results of an aspirin meta-analysis in 2012 shows no significant benefits of aspirin for primary prevention. There are significant limitations identified in these studies, and more definitive studies would be helpful *(Seshasai, 2012 [Meta-analysis])*. Therefore, based on current evidence, low-dose aspirin is considered optional for primary prevention.

  Regular use of ibuprofen may undermine aspirin's antiplatelet effects; patients taking both medications regularly should take immediate-release aspirin at least 30 minutes prior to taking ibuprofen or wait at least eight hours after ingestion of ibuprofen.

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

  Tobacco smoking increases risk of macrovascular complications 4-400% in adults with type 2 diabetes and also increases risk of macrovascular complications. Tobacco cessation is very likely to be the single most beneficial intervention that is available, and should be emphasized by clinicians as described below.

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

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

Tobacco telephone quit lines: HHS National Quitline (1-800-QUITNOW) or 1-800-784-8669 connects you to counseling and information about quitting smoking in your state.

Return to Algorithm *Return to Table of Contents*

14. Cardiovascular Risk Factor Treatment Goals for Patients with Cardiovascular Disease

Recommendation:

- The following treatment goals should be achieved: (1) Use of statins if tolerated; to achieve low-density lipoprotein (LDL) cholesterol of less than 70 mg/dL (2) Blood pressure less than 140/90 mmHg (3) Tobacco cessation if indicated and (4) Daily aspirin use is recommended in patients with cardiovascular disease.

This recommendation places a very high value on a multifactorial approach to lowering the cardiovascular risk of patients with diabetes. The recommendation does not place value on prioritizing these treatment interventions, and some may be more important than others for different individuals. For the lipid and blood pressure recommendations, there is low value placed on the burden of these treatment approaches, the age of the patient (the evidence is less established in patients under age 40 and over 75), and whether patients can tolerate the treatments needed to obtain the recommended goals without side effects. The aspirin recommendation places high value on the benefits of aspirin for secondary prevention of cardiovascular events compared to the risks of bleeding.

- **On a statin with LDL less than 70 mg/dL**

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

  Refer to Annotation #13, "Cardiovascular Risk Factor Treatment Goals for Patients without Cardiovascular Disease." For further information, refer to the ICSI Lipid Management in Adults and the ICSI Stable Coronary Artery Disease guidelines.

- **Goals for blood pressure control: blood pressure less than 140/90 mmHg**

  The goals and treatment of blood pressure are similar for patients with and without coronary artery disease. For further information, please see Annotation #13, "Cardiovascular Risk Factor Treatment Goals for Patients without Cardiovascular Disease."

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

  There is sufficient evidence to support the use of aspirin for secondary prevention of cardiovascular events in patients with type 2 diabetes. *[Conclusion Grade I: See Conclusion Grading Worksheet D – Annotations #13, 14 (Aspirin Use)]*

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

  Regular use of ibuprofen may undermine aspirin's antiplatelet effects; patients taking both medications regularly should take immediate-release aspirin at least 30 minutes prior to taking ibuprofen or wait at least 8 hours after ingestion of ibuprofen.

Return to Algorithm *Return to Table of Contents*

- **Tobacco cessation, if indicated**

  Please see Annotation #13, "Cardiovascular Risk Factor Treatment Goals for Patients without Cardiovascular Disease," for more information on tobacco cessation.

Return to Algorithm *Return to Table of Contents*

15. Are Treatment Goals Met?

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

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

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

Return to Algorithm *Return to Table of Contents*

16. Treatment Goals Not Met

Recommendations:

- If patients are having difficulty achieving treatment goals, consider a modification of treatment goals. In addition, evaluate for potential contributing issues such as adherence, depression and obstructive sleep apnea.
- A referral to an extended care team clinician can be helpful; this could be as an endocrinologist or other specialist, diabetes educator, dietitian or pharmacist.

Modify Treatment Based on Appropriate Related Guideline

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

See the Glycemic Control algorithm.

Consider Referral to Diabetes Care Team or Specialists

- **Assess patient adherence**

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

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

Return to Algorithm *Return to Table of Contents*

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 [Low Quality Evidence])*.

- **Evaluate for depression**

  There is a substantial increase in the prevalence of depression among people with diabetes as compared to the general adult population (*Anderson, 2001 [Meta-analysis]*). 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 *(de Groot, 2001 [Meta-analysis]; Lustman, 2001 [Reference])*.

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

- **Evaluate for obstructive sleep apnea (OSA)**

  Sleep apnea is a prevalent condition in obese patients with type 2 diabetes and is associated with significant comorbidities including hypertension, cardiovascular disease and insulin resistance. Consider referral of symptomatic patients for sleep evaluation.

  Clinicians should be cognizant of potential obstructive sleep apnea, especially among obese patients *(Foster, 2009a [High Quality Evidence]; Foster, 2009b [Reference])*.

- **Diabetes care team**

  Assure the patient has an adequate care team.

- **Diabetes educator**

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

  Every primary care clinician 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 clinicians plus diabetes educators including dietitians, nurses and other health care clinicians who are Certified Diabetes Educators or have didactic and experiential expertise in diabetes care and education.

- **Endocrinologist/nephrologist**

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

  Consultation with a specialist is suggested if persistent proteinuria, worsening microalbuminuria and elevation in serum creatinine or blood urea nitrogen, or hypertension unresponsive to treatment is seen. For additional discussion, see Annotation #18, "Maintain Treatment Goals and Address Complications," the "Nephropathy" section.

Return to Algorithm *Return to Table of Contents*

- **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, or the patient has marked associated postural hypotension or symptoms of coronary artery disease.

- **Foot care specialist**

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

- **Ophthalmology/optometry**

  Retinopathy is estimated to take at least five years to develop after the onset of hyperglycemia begins. Patients with type 2 diabetes, who generally have had years of undiagnosed diabetes and who have a significant risk of prevalent diabetic retinopathy at time of diabetes diagnosis, should have an initial dilated and comprehensive eye examination soon after diagnosis. Examinations should be performed by an ophthalmologist or optometrist who is knowledgeable and experienced in diagnosing the presence of diabetic retinopathy and is aware of its management. Subsequent examinations are generally repeated annually. Less frequent exams (every two to three years) may be cost effective after one or more normal eye exams, while examinations will be required more frequently if retinopathy is progressing *(American Diabetes Association, 2010 [Guideline])*.

- **Vascular specialist/surgeon**

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

Return to Algorithm *Return to Table of Contents*

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

Recommendation:

- Regular follow-up with the health care team (via office visit, e-visit, telephone, labs, etc.) should be scheduled yearly. More frequent visits may be necessary if treatment goals are not achieved.
- Perform a targeted history and physical yearly on all patients, with particular attention to the feet, cardiovascular system and blood pressure.

Targeted Annual History and Targeted Physical Exam

- The targeted annual history should assess *(American Diabetes Association, 2010 [Guideline])*:
  - Results of self-monitoring blood glucose – validate results at least once a year (e.g., check patient's glucose meter against an office random capillary glucose)
  - Adjustments by the patient of the therapeutic regimen
  - Frequency, causes and severity of both hyperglycemia and hypoglycemia
  - Problems with adherence to therapeutic regimen
  - Symptoms suggesting development or progression of the complications of diabetes

Return to Algorithm *Return to Table of Contents*

- Current prescribed medications, over-the-counter medications, dietary supplements and alternative therapies
- Documentation of eye care specialist exam results
- Alcohol/drug use patterns

- Assessment for symptoms of depression
- The targeted physical exam should assess:
  - Weight, body mass index
  - Blood pressure – all patients with diabetic nephropathy should be on either an ACE inhibitor or ARB
  - Cardiovascular – evaluation of preexisting problems
  - Feet (nails, web spaces, calluses, ulcers, structural deformities, protective sensation and shoes)

In studies of general population groups, coronary artery disease deaths have been substantially reduced by the treatment of hypertension, dyslipidemia and smoking. Lipid treatment has also been shown to be of benefit in diabetes. Therefore, risk factor reduction is prudent for patients with diabetes *(American Diabetes Association, 2010 [Guideline]; Hansson, 1998 [Moderate Quality Evidence])*.

- 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 clinician 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 ideally not be delayed greater than one week.
- Regular follow-up (e.g., office visit, e-visit, lab work, phone consult) should be scheduled yearly. More frequent follow-up may be necessary if treatment goals are not achieved.
- Cardiovascular disease is the primary cause of morbidity and mortality in people with type 2 diabetes. The risk of coronary artery disease is approximately doubled in men and quadrupled in women with diabetes.
- At each encounter, ask if the patient has experienced symptoms of hypoglycemia or low blood glucose, review and educate the patient on appropriate recognition, prevention and management.
- If the patient has a history of severe hypoglycemia (assistance of another person was needed to treat a low glucose) or has developed hypoglycemia unawareness, evaluate the treatment goals for appropriate safety.

Return to Algorithm *Return to Table of Contents*

18. Maintain Treatment Goals and Address Complications

Recommendations:

- Annually screen for microalbuminuria.
- All patients with diabetic nephropathy should be on either an ACE inhibitor or ARB unless contraindicated.

Return to Algorithm *Return to Table of Contents*

- Consider early nephrology consultation for patients with macroalbuminuria and/or Cr above 1.5 mg/dL.
- Aggressive control of hypertension, dyslipidemia, obesity and protein restriction is recommended in all patients with nephropathy.

Specialist Dilated Eye Exam

A dilated eye examination for diabetic eye disease performed by an ophthalmologist or optometrist is recommended annually for patients with type 2 diabetes mellitus *(American Diabetes Association, 2010 [Guideline])*. Less frequent exams (every two to three years) may be considered in the setting of a normal eye exam. The role of fundus photography is still being considered but doesn't replace a comprehensive exam.

Retinopathy

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

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

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

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 clinicians who are not eye care specialists are not reliable in detecting retinopathy *(Fong, 2004 [Guideline]; American College of Physicians, 1992 [Guideline]; ETDRS Research Group, 1991 [High Quality Evidence]; Klein, 1987 [Consensus Statement]; ETDRS Research Group, 1985 [High Quality Evidence]; Klein, 1984 [Low Quality Evidence]; Diabetic Retinopathy Study Research Group, The, 1981 [Narrative Review]*).

Treatment includes glycemic and blood pressure control. Periodic screening and dilated eye exams by an eye specialist and early treatment of diabetic retinopathy can prevent visual loss *(Fong, 2004 [Guideline])*.

Renal Assessment and Nephrology

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

The recommended screening method to detect microalbuminuria is:

- Measurement of the albumin-to-creatinine ratio in a random, spot collection. Consider early nephrology consultation for patients with macroalbuminuria and/or Cr > 1.5 mg/dL. Aggressive control of hypertension, dyslipidemia, obesity and protein restriction is recommended in all patients with nephropathy.

Return to Algorithm *Return to Table of Contents*

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

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

Nephropathy

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

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

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

- Glucose Control – Improved glucose control at any stage of renal function reduces renal disease progression. See the Glycemic Control algorithm.
- ACE inhibitor or ARB should be used in all nonpregnant patients with micro or macroalbuminuria. For patients with type 2 diabetes mellitus, ACE inhibitors or ARBs can reduce progression of macrovascular complications. *[Conclusion Grade I: See Conclusion Grading Worksheet E – Annotation #18 (Treatment with ACE Inhibitors or ARBs)] (Lewis, 2001 [High Quality Evidence]; Heart Outcomes Prevention Evaluation Study Investigators, The, 2000a [High Quality Evidence])*. Within one week of initiation, check for elevations in potassium and creatinine levels.
- Measure serum creatinine at least annually and more often based on stage of chronic kidney disease (CKD).

- Hypertension Control – An ACE inhibitor or ARB should be the initial agent of choice. Current JNC 7 and NKF/DOQI recommendations call for treatment of blood pressure to < 130/80 in patients with CKD. However, no single, adequately powered intent-to-treat randomized control trial has shown a benefit of this blood pressure goal in CKD *(Appel, 2010 [High Quality Evidence]; Lewis, 2010 [Meta-analysis]; Arguedas, 2009 [Systematic Review])*. Hence, the recommendation for lower blood pressure goals in all patients with CKD is based on expert opinion and not fully supported by available prospective clinical trials. Determining whether therapy should specifically be titrated to goals lower than < 140/90 mgHg for specific subgroups of CKD patients (e.g., those with moderate proteinuria) should be considered on an individual patient basis, based on clinical judgment and patient preference.
  - Cardiovascular Risk Factor Intervention – Dyslipidemia is often present with microalbuminuria and should be treated aggressively. Dyslipidemia may be an independent risk factor for progression of renal disease. Smoking is associated with the onset and progression of microalbuminuria.
  - Restriction of dietary protein has been shown to slow progression of overt nephropathy (macroalbuminuria), and there may be some benefit in dietary protein reduction in microalbuminuric patients. In these circumstances, protein intake should be reduced to the adult recommended daily allowance of 0.8-1 g/kg body weight per day with microalbuminuria present, and 0.8 gm/kg body weight per day with macroalbuminuria present *(American Diabetes Association, 2007b [Guideline])*.

Return to Algorithm *Return to Table of Contents*

Treatment for microalbuminuria includes aggressive blood pressure control with ACE or ARB use as first-line therapy, glycemic control, 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).

Patients with a creatinine clearance of less than 30 mL/min should be referred to nephrology for discussions of future options and to enhance the ability to receive a future transplant. These patients also have significant enough renal impairment that they also benefit from more intensive nutritional interventions and proper management of anemia and bone disease *(American Diabetes Association, 2004d [Guideline]; Karter, 2002 [Low Quality Evidence]; Lewis, 2001 [High Quality Evidence]; Heart Outcomes Prevention Evaluation Study Investigators, The, 2000a [High Quality Evidence]; DeFronza, 1995 [Low Quality Evidence]; Viberti, 1994 [High Quality Evidence]; Lewis, 1993 [High Quality Evidence]; Ravid, 1993 [Moderate Quality Evidence])*.

See Appendix B, "Treatment of Diabetic Nephropathy."

Neuropathy

Peripheral neuropathy is difficult to prevent and treat. Most patients with type 2 diabetes and peripheral neuropathy have few symptoms. All patients found to have neuropathy should see a foot care specialist for preventive measures aimed at reducing the incidence of diabetic foot complications.

Good glycemic control should be the first control to symptomatic neuropathy.

For those patients with painful neuropathy treatment choices include:

- antidepressants such as the tricyclics (amitriptyline, nortriptyline or desipramine), duloxetine or venlafaxine
- anticonvulsants (gabapentin, pregablin)
- topical treatment with capsaicin

(Boulton, 2005 [Low Quality Evidence])

Comprehensive foot exam with risk assessment

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

A foot exam should include assessment for the following risk factor for complications:

- 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 C, "Using a Semmes-Weinstein Monofilament to Screen the Diabetic Foot for Peripheral Sensory Neuropathy," and Appendix D, "Using a Tuning Fork to Screen the Diabetic Foot for Peripheral Neuropathy."
- Peripheral vascular disease (absent pedal pulse, history of claudication or ischemic skin changes)
- Structural deformities (bunion, hammertoes, Charcot deformity, limited joint mobility or prior amputation)

- Skin disorders (nail deformity, callus, fissure, tinea or ulceration)
- Footwear (excessively worn, ill-fitting or inappropriate shoes)
- Medications can improve quality of life in patients with painful neuropathy

Peripheral Vascular Disease

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

Initial screening for peripheral arterial disease should include asking about claudication and assessment of pedal pulses. Consider obtaining ankle-brachial index if clinically indicated.

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

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

Proper high-risk foot management is necessary to prevent ulceration and amputation. Consider referral of patients with claudication and/or absent pedal pulses to vascular surgery.

Cardiovascular and Cerebrovascular Complication Assessment

- History of cardiovascular symptoms such as chest pain, vascular claudication, TIA
- Cardiac and carotid exams
- Screening for coronary heart disease
  - Screening is no longer recommended with cardiac stress testing
- Evaluate cardiovascular status before advising increased intensity of exercise *(American Diabetes Association, 2004e [Guideline]; Sigal, 2004 [Low Quality Evidence])*.

Cardiovascular and Cerebrovascular Disease

Treatment includes control of cardiovascular risk factors (hypertension, dyslipidemia and smoking cessation) and aspirin use. Consider referring patients with known coronary artery disease to cardiology and patients with known carotid disease to a specialist.

Heart failure is also common in patients with diabetes. Metformin may be used in stable congestive heart failure if renal function is normal.

Close monitoring of potassium and renal function is necessary especially if patients have concomitant chronic kidney disease as the common use of diuretics, ACE/ARBs and aldosterone antagonists in these patients may cause hyperkalemia and worsening renal function. Thiazolidinediones should be avoided in patients with congestive heart failure.

For patients with type 2 diabetes mellitus, thiazide diuretics in the treatment of hypertension can reduce cardiovascular events, particularly heart failure *[Conclusion Grade I: See Conclusion Grading Worksheet F – Annotations #13, 18 (Thiazide Diuretics)] (Wing, 2003 [Moderate Quality Evidence]; ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, The, 2002 [High Quality Evidence])*.

Return to Algorithm *Return to Table of Contents*

Patients with type 2 diabetes have twice the average risk of suffering a stroke *(American Diabetes Association, 1998 [Low Quality Evidence])*. It is unclear whether optimal glycemic control reduces this risk. However, treatment of hypertension, smoking and dyslipidemia reduces the risk of stroke in most persons. See Annotation #14, "Cardiovascular Risk Factor Treatment Goals for Patients with Cardiovascular Disease."

Special Considerations

- Hepatitis B vaccine should be administered to unvaccinated adults with diabetes who are < 60 years of age. It may be administered to unvaccinated adults with diabetes who are ≥ 60 years of age *(Centers for Disease Control and Prevention, 2011 [Guideline])*.
- Influenza vaccine every year
- Pneumococcal vaccine – repeat the vaccination once after age 65 if the initial vaccination was given prior to 65. Consider repeating the immunization for those at risk of losing immunity after five years including:
  - Nephrotic syndrome
  - Chronic renal disease
  - Other immunocompromised states

Return to Algorithm *Return to Table of Contents*

Glycemic Control Algorithm Annotations

19. Glycemic Control

Medical nutrition therapy should be initiated and maintained throughout the course of the disease, even as pharmacologic agents are used.

The goal of glycemic control is to both prevent acute, symptomatic hyperglycemia and to prevent the development of long-term microvascular and macrovascular complications related to chronic hyperglycemia.

Medical nutrition therapy is an essential component of glycemic control for all people with type 2 diabetes. In addition, pharmacologic therapy is appropriate and necessary for most people with type 2 diabetes in order to attain appropriate glycemic control. There are a number of pharmacologic agents and strategies for glycemic control in people with type 2 diabetes. These are discussed in Annotation #20, "Pharmacologic Agent(s) – Which Is Best?"

Return to Algorithm *Return to Table of Contents*

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

Recommendations:

- Concurrent initiation of metformin with medical nutrition therapy is recommended for most patients at diagnosis.
- At the time of diagnosis, if patients have severe symptomatic disease, insulin should be initiated.
- Metformin and alpha glucosidase inhibitors should not be used with renal dysfunction.
- Metformin should be used with caution for patients with conditions that predispose them to risk of hypoxia.

Return to Algorithm *Return to Table of Contents*

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

A recent consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes recommended concurrent initiation of metformin with medical nutrition therapy for most patients at diagnosis. Arguments for this approach include the infrequent success of medical nutrition therapy alone, and the absence of weight gain and hypoglycemia, general tolerability and relatively low cost of metformin *(Nathan, 2009 [Reference])*. Metformin, sulfonylurea medications and insulin were recommended in this consensus statement as well-validated core therapies based on their extended history of use, demonstrated effectiveness and generally favorable cost. More recent therapies such as thiazolidenediones and glucagon-like peptide 1 agonists were viewed as less-well-validated therapies. The authors of the consensus statement note that there are few well-controlled clinical trials directly comparing different diabetes treatment regimens and that their recommendations are in part based on clinical experience *(American Diabetes Association, 2010 [Guideline])*. Clinician judgment and factors such as patient comorbidities, patient desires and cost considerations should always guide design of a glycemic control regimen at the individual patient level.

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

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

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

Age of Patient

It is important to recognize that risks of medications are often increased with advancing age, but this does not justify the withholding of medications that may reduce the symptoms of polyuria and nocturia.

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

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

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

Weight of the Patient

Type 2 diabetes is often associated with insulin resistance and weight gain. Metformin, acarobose, exenatide, sitagliptin and human amylin are more often associated with weight loss or weight maintenance. Due to its weight benefits as well as general tolerability, lower cost and proven benefits in the UK Prospective

Return to Algorithm *Return to Table of Contents*

Diabetes Study Group, metformin is recommended for most diabetes patients with type 2 diabetes unless contraindicated. Insulin and thiazolidinediones may be associated with weight gain *(United Kingdom Prospective Diabetes Study Group, 1998b [High Quality Evidence])*.

Renal Dysfunction

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

Metformin and alpha glucosidase inhibitors should not be used.

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

Cardiopulmonary Comorbidities

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

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

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

Hepatic Disease

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

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

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

Return to Algorithm *Return to Table of Contents*

21. Prescribe Insulin Therapy

If the patient presents and is considered stable enough for outpatient care but meets indications noted in Annotation #8, "Does Patient Need Outpatient Stabilization?" for starting insulin, the work group offers several acceptable ways of initiating insulin:

- One example is to calculate the total daily dose of insulin at 0.3 units/kg and start bedtime glargine at 50% of the total dose, splitting the remaining 50% with short-acting insulin before meals.
- Another example is to start an oral agent(s) while simultaneously initiating long-acting insulin (glargine or detemir) at a dose of approximately 0.1 unit/kg.

Return to Algorithm *Return to Table of Contents*

- A third example is to calculate the total daily dose of insulin at 0.3 units/kg and use premixed insulin with two-thirds of the dose in the morning and one-third of the dose in the evening.
- Insulin programs should be individualized based on the patient's lifestyle, treatment goals and self-monitoring blood glucose. Many patients can be taught to interpret self-monitoring blood glucose results and adjust insulin doses *(American Diabetes Association, 2004c [Guideline])*.
- Total dose ranges from 5 units/day to several hundred units/day.
- Average insulin doses are 0.6-0.8 units/kg of body weight per day.
- Obese patients often require doses equal to or exceeding 1.2 units/kg.
- Meal times and snacks should be consistent. Synchronize insulin with food intake patterns.

A recent three-year randomized, multicenter, open label trial studied the efficacy of three different insulin regimens in over 700 patients with type 2 diabetes who had A1c values > 7% on maximum doses of metformin and a sulfonylurea. The three insulin regimens studied were (1) a long-acting basal insulin given once a day at bedtime (increased to twice a day if necessary), (2) a rapid-acting insulin given twice a day with meals and (3) a fixed ratio of intermediate insulin (70%) and rapid insulin (30%) given twice a day. The study protocol added a second type of insulin under each regimen if specified glycemic parameters were not met (A1c value > 6.5%). The primary study after years showed there were no significant differences in A1c values among the three regimens (mean A1c values 7.1%, 6.8% and 6.9% for fixed-ratio, rapid-acting and basal insulin regimens, respectively). Most subjects (70-80%) had a second type of insulin added due to failure to attain an A1c < 6.5% on the initial insulin regimen alone. Rates of hypoglycemia were low but tended to be lowest in the basal insulin group and highest in the rapid-acting insulin group. Weight gain was highest in the rapid-acting insulin group. This trial suggests the following:

- Various insulin regimens can be effective in treating type 2 diabetes.
- An insulin regimen based initially on one or two injections a day of a longer-acting insulin may be associated with less hypoglycemia and/or less weight gain compared to regimens initiated with fixed-ratio or rapid-acting insulin *(Holman, 2009 [High Quality Evidence])*.

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

Return to Algorithm *Return to Table of Contents*

- Please note the work group left the brand names for Humalog® and Novolog® in the table. The generic mix is as follows:
  - Humalog mix: lispro protamine suspension/lispro injection
  - Novolog mix: aspart protamine suspension/aspart injection
- Every facility needs to evaluate insulin safety per its specific situation.
- The utilization of regular insulin U-500 may be helpful for patients with extreme insulin resistance requiring more than 200 units of exogenous insulin per day as a total daily dose. If U-500 is to be utilized for patients, it is strongly recommended that an endocrinologist and a diabetes educator be involved in the care of the patient. Caution must be exercised with dosing calculations, patient education and instructions to pharmacy *(Ballani, 2006 [Low Quality Evidence]; Cochran, 2005 [Low Quality Evidence])*.

Time Course of Action of Insulin Preparations*

	Insulin Preparations	Onset of Action	Peak Action	Duration of Action	Cost
Short-Acting	Regular	30 min.	2-5 hours	5-8 hours	$$$
Rapid-Acting	Lispro	15 min.	30-90 min.	2-4 hours	$$$$$
	Aspart	15 min.	1-3 hours	3-5 hours	$$$$$
	Glulisine	15 min.	50-100 min.	5 hours	$$$$$
Intermediate-Acting	NPH	1-3 hours	6-12 hours	16-24 hours	$$$
Long-Acting	Detemir	1 hour	**	Up to 24 hours	$$$$$
	Glargine	1 hour	**	24 hours	$$$$$
Mixtures	Humalog® mix (75/25) or Humalog® mix (50/50)	15 min.	0.5-4 hours	16-24 hours	$$$$$
	Novolog® mix (70/30)	15 min.	1-4 hours	16-24 hours	$$$$$
	NPH and Regular (70/30; 50/50)	30 min.		16-24 hours	$$$

Source: Compiled from pdr.net

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

Cost Indicators:

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

* 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.

** Indicates no pronounced peak: small amounts of insulin are slowly released, resulting in a relatively constant concentration/time profile over 24 hours.

Return to Algorithm *Return to Table of Contents*

22. Prescribe Non-Insulin Agents

Recommendation:

- Metformin is the preferred initial oral agent for type 2 diabetes.

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

If not contraindicated, metformin is the preferred initial oral agent for type 2 diabetes due to the benefits of low cost, low risk of hypoglycemia and side effects, and lack of associated weight gain. If metformin is contraindicated, sulfonylureas are acceptable secondary choices for oral agents. Sulfonylureas have the advantage of being relatively inexpensive *(Bolen, 2007 [Reference]; Nathan, 2006 [Reference])*.

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

Cost Indicators:

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

Return to Algorithm *Return to Table of Contents*

Class	Compound	Actions(s)	Clinical Advantages	Clinical Disadvantages	Safety/Monitoring Considerations	Cost
Biguanides	Metformin	• Hepatic glucose production decreased • Intestinal glucose absorption decreased • Insulin action increased	• No weight gain • No hypoglycemia • Reduced cardiovascular events and mortality • Generally well tolerated	• Gastrointestinal side effects: diarrhea, nausea, abdominal cramping • Rare occurrence of lactic acidosis • Vitamin B12 deficiency	• Monitor serum creatinine at least annually. Contraindicated with renal dysfunction (sCr ≥ 1.5 mg/dl in men or ≥ 1.4 mg/dl in women) • Hold at least 48 hours after IV iodinated contrast media • Use cautiously with liver dysfunction, CHF, ETOH abuse, severe pulmonary disease; age > 80 years • Check B12 and folate levels if anemia present	$
Sulfonylureas (2nd generation)	Glyburide Glipizide Glimepiride	• Increased insulin secretion	• Reduced cardiovascular events and mortality • Generally well tolerated	• Hypoglycemia, particularly with deficient caloric intake • Weight gain • May blunt myocardial ischemic preconditioning • Loss of efficacy with prolonged use.	• Use cautiously with renal or hepatic impairment • Use cautiously with known hypersensitivity or severe adverse reaction to other sulfonamides • Glyburide is not recommended for use in the elderly • Glipizide/glimepiride may be safer than glyburide for patients with renal impairment and is associated with lower risks of hyoglycemia	$
Synthetic Analog of Human Amylin	Pramlintide acetate injection	• Modulation of gastric emptying • Postprandial glucagon levels decreased	• Satiety leading to decreased caloric intake and potential weight loss	• Nausea, vomiting and anorexia	• Pramlintide is used with insulin and has been associated with an increased risk of insulin-induced severe hypoglycemia. When severe hypoglycemia associated with pramlintide use occurs, it is seen within three hours following a pramlintide injection. If severe hypoglycemia occurs while operating a motor vehicle, heavy machinery, or while engaging in other high-risk activities, serious injuries may occur. Appropriate patient selection, careful patient instruction, and insulin dose adjustments are critical elements for reducing this risk.	$$$$$
Meglitinides	Repaglinide Nateglinide	• Increased insulin secretion	• Accentuated effects around meal ingestion	• Hypoglycemia (less than sulfonylureas) • Weight gain • May blunt myocardial ischemic preconditioning • Dosing frequency	• Use cautiously with renal or hepatic impairment • Gemfibrozil use is contraindicated with repaglinide	$$$$ - $$$$$
Thiazolidinediones (TZD's, glitazones)	Pioglitazone	• Peripheral Insulin sensitivity increased	• No hypoglycemia • HDL cholesterol increased • Triglycerides decreased • Once daily dosing	• Weight gain • Edema • Bone fractures • Anemia • Diabetic macular edema	• Contraindicated in patients NYHA Class III/IV heart failure. Monitor for signs/symptoms of fluid retention and heart failure. • Periodic ALT and ophthalmic exam • May increase risk of bladder cancer with prolonged use or at high dose. Avoid use with concurrent or history of bladder cancer. • Thiazolidinediones have been associated with increased risk of hospitalization for heart failure *(Eurich, 2008 (Systematic Review])*. • Health care clinicians and patients must be enrolled in the Avandia-Rosiglitazone Medicines Access Program in order to prescribe and receive rosiglitazone medicines. After *November 18, 2011*, rosiglitazone medicines will no longer be available through retail pharmacies. Patients who are enrolled in the Avandia-Rosiglitazone Medicines Access Program will receive their medicine by mail order through specially certified pharmacies participating in the program. See http://www.fda.gov/Drugs/DrugSafety/ucm255005.htm	$$$$$

Return to Algorithm *Return to Table of Contents*

Class	Compound	Actions(s)	Clinical Advantages	Clinical Disadvantages	Safety/Monitoring Considerations	Cost
Alpha Glucosidase Inhibitors	Acarbose Miglitol	• Slowed intestinal carbohydrate digestion	• Non-systemic medication • Postprandial glucose decreased	• Gastrointestinal side effects: flatulence, abdominal pain and diarrhea • Dosing frequency	• Contraindicated with serum creatinine > 2.0 mg/dl, cirrhosis, colon ulcerations, inflammatory bowel disease, conditions associated with reduced absorption/digestion, partial bowel obstruction, predisposition to bowel obstruction. • Monitor liver enzymes. • Treat hypoglycemia with oral glucose, not sucrose.	$$$$
Glucagon-like Peptide 1 (GLP-1) Agonists	Exanatide Liraglutide	• Glucose dependant insulin secretion increased • Postprandial glucagon levels decreased • Slows gastric emptying • Promotes satiety	• Weight loss • Potential for improved beta cell mass/function	• Gastrointestinal side effects: nausea, vomiting, diarrhea • Pancreatitis • Injectable	• Use is not recommended in patients with gastroparesis or severe gastrointestinal disease. • Cases of acute pancreatitis reported. • Liraglutide – thyroid C-cell tumors have developed in animal studies; relevance in humans unknown. • Liraglutide is contraindicated with personal or family history of medullary thyroid carcinoma (MTC), or multiple endocrine neoplasia syndrome type 2 (MEN 2). • Use caution with moderate to severe renal impairment. Exenatide should not be used with GFR < 30. • Long-term safety is unknown.	$$$$$
Dipeptidyl Peptidase-4 (DPP-4) Inhibitors	Sitagliptin Saxagliptin Linagliptin	• Increase active incretin (GLP-1, GIP) hormone levels • Increase insulin secretion • Decrease glucagon secretion	• No hypoglycemia • No weight gain • Once daily dosing	• Rare pancreatitis • Rare urticaria, angioedema	• Adjustments are needed for renal dysfunction (sitagliptin and saxagliptin). Monitor serum creatinine before initiation and periodically thereafter. • Saxagliptin dose adjustment required with use of strong CYP450 3A4/5 inhibitors. • Long-term safety is unknown.	$$$$$
Bile Acid Sequestrants	Colesevelam	• Unknown	• No hypoglycemia • LDL cholesterol decreased	• Gastrointestinal side effects: constipation, dyspepsia • Triglycerides increased	• Contraindicated with severe GI motility disorders, history of major GI tract surgery, history of bowel obstruction, serum triglyceride concentration > 500 mg/dL, or history of hypertriglyceridemia-induced pancreatitis. • May reduce absorption of certain medications (fat-soluble vitamins, glyburide, warfarin, levothyroxine, phenytoin, oral contraceptives).	$$$$$
Dopamine-2 Receptor Agonists	Bromocriptine	• Unclear; it may stimulate hypothalamic release of cortisol, growth hormone, and prolactin	• No hypoglycemia	• Limited clinical experience • Dizziness/syncope • Nausea, vomiting • Headache • Fatigue, weakness	• Contraindicated with past hypersensitivity to ergot-related medications, breastfeeding, history of syncopal migraine. • Should not be used in patient with psychotic disorders, or if taking dopamine agonist/antagonist medications. • Use cautiously with history of peptic ulcer disease or uncontrolled hypertension. • Monitor BP, orthostatic symptoms, liver function. • Long-term safety unknown.	$$$$

Return to Algorithm *Return to Table of Contents*

24. Intensify Therapy

Recommendation:

- 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 [Low Quality Evidence]; Yki-Järvinen, 1999 [Low Quality Evidence]; Relimpio, 1998 [Low Quality Evidence]; Zimmerman, 1998 [Low Quality Evidence])*. The following are some commonly used regimens.

Insulin as an adjunct to oral therapy:

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

Insulin alone:

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

Oral agents as an adjunct to insulin therapy:

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

Return to Algorithm *Return to Table of Contents*

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

See Annotation #17 for more information.

Return to Algorithm *Return to Table of Contents*

26. Maintain Treatment Goals and Address Complications

See Annotation #18 for more information.

Return to Algorithm *Return to Table of Contents*

The Aims and Measures section is intended to provide guideline users with a menu of measures for multiple purposes, which may include the following:

- population health improvement measures,
- quality improvement measures for delivery systems,
- measures from regulatory organizations such as Joint Commission,
- measures that are currently required for public reporting,
- measures that are part of Center for Medicare Services Physician Quality Reporting initiative,
- other measures from local and national organizations aimed at measuring population health and improvement of care delivery.

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

The subdivisions of this section are:

- Aims and Measures
- Implementation Recommendations
- Implementation Tools and Resources

Aims and Measures

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

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

1. **Diabetes Optimal Care:** Increase the percentage of patients, ages 18-75 years with type 2 diabetes mellitus, who in a defined period of time achieve any or all of the following diabetes specific measures of established control *(composite measure) (Annotation #13)*:

   Measures for accomplishing this aim:

   Percentage of patients with type 2 diabetes mellitus age 18-75 years old who achieve any or all of the following:

   a. Percentage of patients with A1c $\leq$ 8%.

   b. Percentage of patients with LDL less than 100 mg/dL or on a statin.

   c. Percentage of type 2 diabetes patients with blood pressure measurment in last 12 months and most recent BP measurement less than 140/90 mmHg.

Notes regarding diabetes specific care measures:

1a. A1c measure: Depending on patients' risk factors, the A1c goal for type 2 diabetes patients should be personalized. The optimal clinical A1c goal for some diabetes patients, depending on the risk factors, may be lower than 8% (see Annotation #11).

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

2. Diabetes type 2 patients cardiovascular risk reduction: Increase the percentage of type 2 diabetes mellitus patients ages 18-75 years old who have decreased cardiovascular risk in a one-year period of time. *(Annotation #14)*

   Measures for accomplishing this aim:

   a. Proportion of eligible adults age 18-75 with type 2 diabetes mellitus who have a decrease in their cardiovascular risk in a one-year period of time.

   b. Mean cardiovascular risk reduction in those with type 2 diabetes mellitus.

Return to Table of Contents

3. **Diabetes Process of Care Measures:** Increase the percentage of patients ages 18-75 years with type 2 diabetes mellitus who had recommended screening procedures are done. *(Annotations #14, 18)*

   Measures for accomplishing this aim:

   a. Percentage of patients with type 2 diabetes mellitus with one or more A1c tests in the last 15 months.

   b. Percentage of patients with type 2 diabetes mellitus receiving a lipid measure in the last 15 months.

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

   d. Nephropathy screening rate: percentage of patients with type 2 diabetes who are either (a) not on an ACE or ARB medication OR (b) not diagnosed with chronic kidney disease who have one or more microalbuminaria tests within the last 15 months.

   e. Retinopathy screening rate: percentage of patients with type 2 diabetes mellitus with one or more dilated eye exams within the last 36 months. The nature of the exam is not specified and may be completed by an ophthalmologist or optometrist.

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

   g. Percentage of patients with type 2 diabetes, age 18-75 years with type 2 diabetes mellitus, for whom all the recommended screening procedures (3a to 3f above) were done in the indicated time frames.

Note to diabetes process of care measure set:

The intervals for these testing procedures are related to measures, and more frequent testing may be indicated based on the patient's condition.

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

   Measures for accomplishing this aim:

   a. Percentage of patients with type 2 diabetes mellitus with Alc test in the last year greater than 9%. *(HEDIS, 2012)*

   b. Percentage of patients with type 2 diabetes mellitus with low-density lipoprotein test in the last year greater than 130 mg/dL and not on a statin.

   c. Percentage of patients with type 2 diabetes mellitus with blood pressure measurement in the last year and greater than 150/90 mmHg.

   d. Percentage of patients with poor diabetes control (4a-4c) (composite measure).

Return to Table of Contents

Measurement Specifications

Measurement #1 a, b, c: Optimal Diabetes Care

Measurement Description

Percentage of patients with type 2 diabetes mellitus age 18-75 years old who achieve any or all of the following diabetes controls:

a. Percentage of patients with A1c < 8%.
b. Percentage of patients with LDL less than 100 mg/dL or on a statin.
c. Percentage of patients with blood pressure measurement in the last 12 months and most recent BP measurement less than 140/90 mmHg.

Population Definition

Patients age 18-75 years old with type 2 diabetes mellitus.

Data of Interest

$$\frac{\text{\# of patients who achieve any or all of the following control criteria}}{\text{\# of patients age 18-75 years old with type 2 diabetes mellitus}}$$

Numerator and Denominator Definitions

Numerator: Number of patients who achieve any or all of the following control criteria at any point:

a. A1c < 8%.
b. LDL < 100 mg/dL or on a statin.
c. Blood pressure measurement in the last 12 months and most recent BP measurement less than 140/90 mmHg.

Denominator: Number of patients age 18-75 years old who have type 2 diabetes mellitus.

Method/Source of Data Collection

As the baseline, identify all patients in the clinic panel who met denominator criteria. Then of those in the denominator, identify the number of patients who met any or all of the diabetes control criteria. Thereafter, for quality improvement, every subsequent month, identify the list of patients with a clinic visit who met denominator criteria. From electronic medical record queries, identify if those patients had any or all of the diabetes control criteria met.

Notes

This is an outcome measure, and improvement is noted as an increase in the rate. This measure should be calculated as both an individual components met and a composite (all components met at the same time) measure.

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

Return to Table of Contents

Measurement #2a: Diabetes Type 2 Patients Cardiovascular Risk Reduction

Measurement Description

Proportion of eligible adults age 18-75 with type 2 diabetes mellitus who have a decrease in their cardiovascular risk in a one-year period of time.

Population Definition

Eligible adults: Those age 18-75 years at baseline with type 2 diabetes mellitus who have one or more visits to the medial group in each of two successive calendar years.

Instructions for Calculating this Measure

Baseline Cardiovascular Risk: Assign a value for lifetime CVD Risk using the UKPDS risk score proposed by Clarke, et al. (2004). The equation to be used is specific for those with type 2 diabetes. Programming language for this equations in either SAS or JAVA is available from HPRF through ICSI.

The UKPDS RISK Equation requires updated data each year on glycated hemoglobin (A1c), blood pressure (BP), total cholesterol (TC), HDL-cholesterol (HDL), and smoking status (current vs. other).

In addition, baseline year data is needed for age, gender, BMI, atrial fibrillation, history of CHD, CHF, PVD, CeVD, blindness, amputation and myocardial infarction. Duration of diabetes is requested but can be imputed at the median duration for the population, eight years, if unknown. Data definitions are provided and management of missing data is described in Figure 1.

Change in cardiovascular risk is computed for each patient by using the same UKPDS risk equation in each of two successive years. The value of the lifetime UKPDS RISK in year two minus the value of the lifetime cardiovascular risk in year one is the value that is reported for each patient, and expresses the change lifetime risk of heart attack or stroke for a given patient.

Note: This risk ordinarily increases slightly from one year to the next, but with adequate management of uncontrolled cardiovascular risk factors, may decrease from one year to the next, or increase less. When this measure is tested, an alternative measure called "reversible lifetime cardiovascular risk" will be defined and tested. It is the cardiovascular risk, net of the component of cardiovascular risk attributable to age and gender.

The measure is reported as the proportion of patients being measured who have a decrease, rather than an increase or no change, in their UKPDS lifetime cardiovascular risk. The goal is to have either a decrease in cardiovascular risk or a minimal increase in cardiovascular risk in the second year, relative to the first year used in the calculation.

Return to Table of Contents

Figure 1. Data definitions for Parameters Used to Calculate UKPDS CV Risk. A detailed description including mathematical transformations applied to some parameters is provided in Clarke, et al. (2004), Table 1, page 1749 of the article.

Parameter	Description	Source	Comment
Age	In years	EMR	
Gender	Male or female	EMR	
Race	White, Black, Other	EMR	If missing, assign as white.
Duration of diabetes since diagnosis	In years	Not usually available	Impute eight years if unknown.
Smoker	Never, former, current	EMR	If missing, assign never.
Glycated hemoglobin (A1c)	In %. Take last available test in calendar year of interest.	EMR/Labs	If missing, set at 8%.
BP	In mm Hg. Take last measure in each calendar year.	EMR/Vital Signs	If missing, assign 140/90 mmHg.
Total cholesterol	mg/dL	EMR/labs	If missing, take most recent up to four years prior. If still missing, impute 240 mg/dL for men and 250 mg/dL for women.
HDL	mg/dL	EMR/labs	If missing, take most recent up to 4 years prior. If still missing, impute 40 mg/dL for men and 50 mg/dL for women.
Atrial fibrillation	Present or absent	EMR/diagnoses, EMR problem list	ICD-9 codes
Peripheral vascular disease (PVD)	Present or absent	EMR/diagnoses, EMR problem list	ICD-9 codes
Cerebrovascular disease (CeVD)	Present or absent	EMR/diagnoses, EMR problem list	ICD-9 codes
Coronary artery disease (CHD)	Present or absent	EMR/diagnoses, EMR problem list	ICD-9 codes 410-414, 429. One or more inpatient or two or more outpatient in prior 24 months. Baseline only.
Congestive heart failure (CHF)	Present or absent	EMR/diagnoses, EMR problem list	ICD-9 codes 428 one or more inpatient, or two or more outpatient in 24 months. Baseline only.
Amputation	Present or absent	EMR/diagnoses, EMR problem list	Not needed for CV risk
Blindness	Present or absent	EMR/diagnoses, EMR problem list	Not needed for CV risk
Renal failure	Present or absent	EMR/diagnoses, EMR problem list	Not needed for CV risk

References

Clarke PM, Gray AM, Briggs A, Farmer AJ, Fenn P, Stevens RJ, Matthews DR, Stratton LM, Holman RR, on behalf of the UK Prospective Diabetes Study (UKPDS) Group. A model to estimate the lifetime health outcomes of patients with Type 2 diabetes; the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS no. 68). *Diabetologia* 2004;47:1747-59.

Return to Table of Contents

Measurement #2b: Diabetes Type 2 Patients Mean Cardiovascular Risk Reduction

The changes in cardiovascular risk for each patient are pooled to calculate a mean change in cardiovascular risk (UKPDS RISK) for the group of patients with type 2 diabetes mellitus that can be defined at the level of a health plan, medical group, clinic, or provider. The goal is to have either a decrease in cardiovascular risk or a minimal increase in cardiovascular risk in the second year, relative to the first year used in the calculation.

Return to Table of Contents

Measurement #3a

Measurement Description

Percentage of patients with type 2 diabetes mellitus with one or more A1c tests in the last 15 months.

Population Definition

Patients age 18-75 years old with type 2 diabetes mellitus.

Data of Interest

$$\frac{\text{\# of patients with one or more A1c tests in the last 15 months}}{\text{\# of patients age 18-75 years old with type 2 diabetes mellitus}}$$

Numerator and Denominator Definitions

Numerator: Number of patients who have one or more A1c tests in the last 15 months.

Denominator: Number of patients age 18-75 years old who have type 2 diabetes mellitus.

Method/Source of Data Collection

As the baseline, identify all patients in the clinic panel who met denominator criteria. Then of those in the denominator, identify the number of patients who met any or all of the diabetes control criteria. Thereafter, for quality improvement, every subsequent month, identify the list of patients with a clinic visit who met denominator criteria. From EMR queries, identify if those patients had any or all of the diabetes control criteria met.

Notes

This is a process measure, and improvement is noted as an increase in the rate. The intervals for these testing procedures are related to measures, and more frequent testing may be indicated based on the patient's condition.

Return to Table of Contents

Measurement #3b

Measurement Description

Percentage of patients with type 2 diabetes mellitus receiving a lipid measure in the last 15 months.

Population Definition

Patients age 18-75 years old with type 2 diabetes mellitus.

Data of Interest

$$\frac{\text{\# of patients with lipids measured in the last 15 months}}{\text{\# of patients age 18-75 years old with type 2 diabetes mellitus}}$$

Numerator and Denominator Definitions

Numerator: Number of patients who had lipids measured in the last 15 months.

Denominator: Number of patients age 18-75 years old who have type 2 diabetes mellitus.

Method/Source of Data Collection

As the baseline, identify all patients in the clinic panel who met denominator criteria. Then of those in the denominator, identify the number of patients who met any or all of the diabetes control criteria. Thereafter, for quality improvement, every subsequent month, identify the list of patients with a clinic visit who met denominator criteria. From EMR queries, identify if those patients had any or all of the diabetes control criteria met.

Notes

This is a process measure, and improvement is noted as an increase in the rate. The intervals for these testing procedures are related to measures, and more frequent testing may be indicated based on the patient's condition.

Return to Table of Contents

Measurement #3c

Measurement Description

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

Population Definition

Patients age 18-75 years old with type 2 diabetes mellitus.

Data of Interest

$$\frac{\text{\# of patients with one or more blood pressure measurements in the last 12 months}}{\text{\# of patients age 18-75 years old with type 2 diabetes mellitus}}$$

Numerator and Denominator Definitions

Numerator: Number of patients who had one or more blood pressure measurements in the last 12 months.

Denominator: Number of patients age 18-75 years old who have type 2 diabetes mellitus.

Method/Source of Data Collection

As the baseline, identify all patients in the clinic panel who met denominator criteria. Then of those in the denominator, identify the number of patients who met numerator criteria. Thereafter, for quality improvement, every subsequent month, identify the list of patients with a clinic visit who met denominator criteria. From EMR queries, identify if those patients numerator criteria met.

Notes

This is a process measure, and improvement is noted as an increase in the rate. The intervals for these testing procedures are related to measures, and more frequent testing may be indicated based on the patient's condition.

Return to Table of Contents

Measurement #3d

Measurement Description

Nephropathy screening rate: percentage of patients with type 2 diabetes who are either (a) not on an ACE or ARB medication OR (b) not diagnosed with chronic kidney disease who have one or more microalbuminaria tests within the last 15 months.

Population Definition

Patients age 18-75 years old with type 2 diabetes mellitus who are either (a) not on an ACE or ARB medication OR (b) not diagnosed with chronic kidney disease.

Data of Interest

$$\frac{\text{\# of patients with one or more microalbuminaria tests in the last 15 months}}{\text{\# of patients age 18-75 years old with type 2 diabetes mellitus who are either (a) not on an ACE or ARB medication OR (b) not diagnosed with chronic kidney disease}}$$

Numerator and Denominator Definitions

Numerator: Number of patients who had one or more microalbuminaria tests in the last 15 months.

Denominator: Number of patients age 18-75 years old who have type 2 diabetes mellitus who are either (a) not on an ACE or ARB medication OR (b) not diagnosed with chronic kidney disease.

Method/Source of Data Collection

As the baseline, identify all patients in the clinic panel who met denominator criteria. Then of those in the denominator, identify the number of patients who met numerator criteria. Thereafter, for quality improvement, every subsequent month, identify the list of patients with a clinic visit who met denominator criteria. From EMR queries, identify if those patients numerator criteria met.

Notes

This is a process measure, and improvement is noted as an increase in the rate. The intervals for these testing procedures are related to measures, and more frequent testing may be indicated based on the patient's condition.

Return to Table of Contents

Measurement #3e

Measurement Description

Retinopathy screening rate: percentage of patients with type 2 diabetes mellitus with one or more dilated eye exams within the last 36 months.

Population Definition

Patients age 18-75 years old with type 2 diabetes mellitus.

Data of Interest

$$\frac{\text{\# of patients with one or more dilated eye exams in the last 36 months}}{\text{\# of patients age 18-75 years old with type 2 diabetes mellitus}}$$

Numerator and Denominator Definitions

Numerator: Number of patients who had one or more dilated eyes exams in the last 36 months. The nature of the exam is not specified and may be completed by an ophthalmologist or optometrist.

Denominator: Number of patients age 18-75 years old who have type 2 diabetes mellitus.

Method/Source of Data Collection

As the baseline, identify all patients in the clinic panel who met denominator criteria. Then of those in the denominator, identify the number of patients who met numerator criteria. Thereafter, for quality improvement, every subsequent month, identify the list of patients with a clinic visit who met denominator criteria. From EMR queries, identify if those patients numerator criteria met.

Notes

This is a process measure, and improvement is noted as an increase in the rate. The intervals for these testing procedures are related to measures, and more frequent testing may be indicated based on the patient's condition.

Return to Table of Contents

Measurement #3f

Measurement Description

Foot care screening rate: percentage of patients with type 2 diabetes mellitus with a comprehensive foot exam documented in the last year.

Population Definition

Patients age 18-75 years old with type 2 diabetes mellitus.

Data of Interest

$$\frac{\text{\# of patients with a comprehensive foot exam in the last 12 months}}{\text{\# of patients age 18-75 years old with type 2 diabetes mellitus}}$$

Numerator and Denominator Definitions

Numerator: Number of patients who had a comprehensive foot exam in the last 12 months.

Denominator: Number of patients age 18-75 years old who have type 2 diabetes mellitus.

Method/Source of Data Collection

As the baseline, identify all patients in the clinic panel who met denominator criteria. Then of those in the denominator, identify the number of patients who met numerator criteria. Thereafter, for quality improvement, every subsequent month, identify the list of patients with a clinic visit who met denominator criteria. From EMR queries, identify if those patients numerator criteria met.

Notes

This is a process measure, and improvement is noted as an increase in the rate. The intervals for these testing procedures are related to measures, and more frequent testing may be indicated based on the patient's condition.

Return to Table of Contents

Measurement #3g

Measurement Description

Percentage of patients with type 2 diabetes age 18-75 years with type 2 diabetes mellitus for whom all the recommended screening procedures (3a to 3f above) were done in the indicated time frames.

Population Definition

Patients age 18-75 years old with type 2 diabetes mellitus.

Data of Interest

$$\frac{\text{\# of patients with 3a-3f done}}{\text{\# of patients age 18-75 years old with type 2 diabetes mellitus}}$$

Numerator and Denominator Definitions

Numerator: Number of patients who had 3a-3f done.

Denominator: Number of patients age 18-75 years old who have type 2 diabetes mellitus.

Method/Source of Data Collection

As the baseline, identify all patients in the clinic panel who met denominator criteria. Then of those in the denominator, identify the number of patients who met numerator criteria. Thereafter, for quality improvement, every subsequent month, identify the list of patients with a clinic visit who met denominator criteria. From EMR queries, identify if those patients numerator criteria met.

Notes

This is a process measure, and improvement is noted as an increase in the rate. The intervals for these testing procedures are related to measures, and more frequent testing may be indicated based on the patient's condition.

Return to Table of Contents

Measurement #4a

Measurement Description

Percentage of patients with type 2 diabetes mellitus with Alc test in the last year greater than 9%.

Population Definition

Patients age 18-75 years old with type 2 diabetes mellitus.

Data of Interest

$$\frac{\text{\# of patients with A1c} > 9\%}{\text{\# of patients age 18-75 years old with type 2 diabetes mellitus}}$$

Numerator and Denominator Definitions

Numerator: Number of patients who had A1c > 9%.

Denominator: Number of patients age 18-75 years old who have type 2 diabetes mellitus.

Method/Source of Data Collection

As the baseline, identify all patients in the clinic panel who met denominator criteria. Then of those in the denominator, identify the number of patients who met numerator criteria. Thereafter, for quality improvement, every subsequent month, identify the list of patients with a clinic visit who met denominator criteria. From EMR queries, identify if those patients numerator criteria met.

Notes

This is a process measure, and improvement is noted as a decrease in the rate. The purpose of this measure is to decrease the percentage of adult patients ages 18-75 with type 2 diabetes mellitus, with poorly controlled glucose and cardiovascular risk factors (clinical strategies that target high-risk populations may be more viable with limited resources).

Return to Table of Contents

Measurement #4b

Measurement Description

Percentage of patients with type 2 diabetes mellitus with low-density lipoprotein test in the last year greater than 130 mg/dL and not on a statin.

Population Definition

Patients age 18-75 years old with type 2 diabetes mellitus.

Data of Interest

$$\frac{\text{\# of patients with LDL} > 130 \text{ and not on a statin}}{\text{\# of patients age 18-75 years old with type 2 diabetes mellitus}}$$

Numerator and Denominator Definitions

Numerator: Number of patients who had LDL tests in the last year and LDL > 130 and patient was not on a statin.

Denominator: Number of patients age 18-75 years old who have type 2 diabetes mellitus.

Method/Source of Data Collection

As the baseline, identify all patients in the clinic panel who met denominator criteria. Then of those in the denominator, identify the number of patients who met numerator criteria. Thereafter, for quality improvement, every subsequent month, identify the list of patients with a clinic visit who met denominator criteria. From EMR queries, identify if those patients numerator criteria met.

Notes

This is a process measure, and improvement is noted as a decrease in the rate. The purpose of this measure is to decrease the percentage of adult patients ages 18-75 with type 2 diabetes mellitus with poorly controlled glucose and cardiovascular risk factors (clinical strategies that target high-risk populations may be more viable with limited resources).

Return to Table of Contents

Measurement #4c

Measurement Description

Percentage of patients with type 2 diabetes mellitus with blood pressure measurement in the last year and greater than 150/90 mmHg.

Population Definition

Patients age 18-75 years old with type 2 diabetes mellitus.

Data of Interest

$$\frac{\text{\# of patients with BP} > 150/90}{\text{\# of patients age 18-75 years old with type 2 diabetes mellitus}}$$

Numerator and Denominator Definitions

Numerator: Number of patients who had blood pressure measurement in the last year and BP > 150/90 mmHg.

Denominator: Number of patients age 18-75 years old who have type 2 diabetes mellitus.

Method/Source of Data Collection

As the baseline, identify all patients in the clinic panel who met denominator criteria. Then of those in the denominator, identify the number of patients who met numerator criteria. Thereafter, for quality improvement, every subsequent month, identify the list of patients with a clinic visit who met denominator criteria. From EMR queries, identify if those patients numerator criteria were met.

Notes

This is a process measure, and improvement is noted as a decrease in the rate. The purpose of this measure is to decrease the percentage of adult patients ages 18-75 with type 2 diabetes mellitus with poorly controlled glucose and cardiovascular risk factors (clinical strategies that target high-risk populations may be more viable with limited resources).

Return to Table of Contents

Measurement #4d

Measurement Description

Percentage of patients with type 2 diabetes mellitus with poor diabetes control (4a-4c) (composite measure).

Population Definition

Patients age 18-75 years old with type 2 diabetes mellitus.

Data of Interest

$$\frac{\text{\# of patients with poor diabetes control (4a-4c)}}{\text{\# of patients age 18-75 years old with type 2 diabetes mellitus}}$$

Numerator and Denominator Definitions

Numerator: Number of patients who had poor diabetes control (4a-4c).

Denominator: Number of patients age 18-75 years old who have type 2 diabetes mellitus.

Method/Source of Data Collection

As the baseline, identify all patients in the clinic panel who met denominator criteria. Then of those in the denominator, identify the number of patients who met numerator criteria. Thereafter, for quality improvement, every subsequent month, identify the list of patients with a clinic visit who met denominator criteria. From EMR queries, identify if those patients numerator criteria were met.

Notes

This is an outcome composite measure, and improvement is noted as a decrease in the rate. The purpose of this measure is to decrease the percentage of adult patients, ages 18-75 with type 2 diabetes mellitus, with poorly controlled glucose and cardiovascular risk factors (clinical strategies that target high-risk populations may be more viable with limited resources).

Return to Table of Contents

Implementation Recommendations

Prior to implementation, it is important to consider current organizational infrastructure that address the following:

- System and process design;
- Training and education; and
- Culture and the need to shift values, beliefs and behaviors of the organization.

The following system changes were identified by the guideline work group as key strategies for health care systems to incorporate in support of the implementation of this guideline:

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

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

Return to Table of Contents

- **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 clinicians and patients to intensify treatment when indicated (referred to as "clinical inertia") is a key obstacle to better diabetes care (*O'Connor, 2003 [Low Quality Evidence]; O'Connor, 2005a [Low Quality Evidence]; O'Connor, 2005b [Low Quality Evidence])*. HSR editorial. Previsit planning and best practice prompts may help to increase the efficiency of patient visits and remind clinicians of needed tests and care.

- **Develop "Active Outreach."** These are strategies to reach patients with chronic disease who have not returned for follow-up or for other selected elements of care. Outreach strategies that enhance the likeliness of a future clinician encounter that addresses one of the barriers to patient activation (discussed below) may be more effective. Simple reporting of lab test results or care suggestions through the mail may be ineffective at addressing these barriers.

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

Return to Table of Contents

Implementation Tools and Resources

Criteria for Selecting Resources

The following tools and resources specific to the topic of the guideline were selected by the work group. Each item was reviewed thoroughly by at least one work group member. It is expected that users of these tools will establish the proper copyright prior to their use. The types of criteria the work group used are:

- The content supports the clinical and the implementation recommendations.
- Where possible, the content is supported by evidence-based research.
- The author, source and revision dates for the content is included where possible.
- The content is clear about potential biases and when appropriate conflicts of interests and/or disclaimers are noted where appropriate.

Return to Table of Contents

Implementation Tools and Resources Table

Author/Organization	Title/Description	Audience	Web Sites/Order Information
American Diabetes Association	**American Diabetes Association:** The mission of the association is to prevent and cure diabetes and to improve the lives of all people affected by diabetes. Wide variety of information on diabetes as well as recent publications; series of journals for both consumers and health professionals; community resources.	Patients and Families; Health Care Professionals	http://www.diabetes.org
Centers for Disease Control and Prevention	**Centers for Disease Control and Prevention:** Educational materials in Spanish as well as English, and low literacy public health and community campaigns for educating about diabetes and diabetes prevention.	Patients and Families	http://www.cdc.gov/diabetes
The Food and Nutrition Information Center	**The Food and Nutrition Information Center:** Sponsored by the United States Department of Agriculture (USDA), this site is user friendly and filled with current information on almost any nutrition topic.	Patients and Families; Health Care Professionals	http://www.nal.usda.gov/fnic/
HealthFinder	**HealthFinder:** A-Z health information organizations and health care topics.	Patients and Families	http://www.healthfinder.gov
International Diabetes Center	**International Diabetes Center:** International Diabetes Center at Park Nicollet has provided world diabetes care, education, publications and research programs that have met the needs of people with diabetes and their families since 1967.	Patients and Families	http://www.idcpublishing.com
Labat & Maggi	Weight Management for Type II Diabetes (book)	Patients and Families	http://www.wiley.com
Mayo Clinic	**Mayo Clinic: Disease and Condition Centers** Information and tools to help you manage a chronic disease or condition.	Patients and Families	http://www.mayoclinic.com/health/type-2-diabetes/DS00585
Minnesota Community Measurement	The D5.org The D5 is a set of five treatment goals that, when achieved together, represent the gold standard for managing diabetes. Reaching all five goals greatly reduces a patient's risk for the cardiovascular problems associated with diabetes.	Patients and Families	http://www.theD5.org

Return to Table of Contents

Author/Organization	Title/Description	Audience	Web Sites/Order Information
National Institutes of Diabetes, Digestive and Kidney Diseases	**National Institute of Diabetes, Digestive and Kidney Diseases:** Data, statistics, information for health professionals, educational materials in Spanish as well as English, and low literacy. This Web site is a division of the National Institutes of Health.	Patients and Families; Health Care Professionals	http://www.niddk.nih.gov Also, links to NDEP, NKDEP, NIDDK
National Institutes of Health	**National Institutes of Health:** This user-friendly site helps you start a search for health information by directing you to some credible databases.	Health Care Professionals	http://www.nih.gov
Protocol Driven Healthcare	**Protocol Driven Healthcare:** Self-management interactive site, information on diabetes and managing it, chat rooms, capacity to e-mail for questions.	Patients and Families	http://www.mydiabetes.com
WebMD Corporation	**Web MD:** Wide variety of information on diabetes as well as recent publications; series of journals for both consumers and health professionals; clinical resource for providers, and education materials that providers can download for their patients.	Patients and Families; Health Care Professionals	http://www.webMD.com

Return to Table of Contents

The subdivisions of this section are:

- Conclusion Grading Worksheet Summary
  - Conclusion Grading Worksheets
- References
- Appendices

Conclusion Grading Worksheet Summary

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

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

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

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

Return to Table of Contents

Conclusion Grading Worksheet A – Annotation #3 (Prediabetes)

Work Group's Conclusion:

- Lifestyle modifications, such as nutrition, exercise and even modest weight loss, are recommended for prevention or delayed progression of patients with prediabetes.
- Pharmacotherapy, such as metformin, are effective in some patients with prediabetes.

Conclusion Grade: II

Author/ Year	Design Type	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Borch-Johnson, et al., 2004	Observational, cross-sectional study	Data pooled from 5 international population based studies: 1) Danish INTER99 (n=6265 adults 30-61 y) DETECT-2 Studies: 2) Paris Prospective(n=70 34 adults 44-55 y) 3) Gingdoa (China) (n=1808 adults 30-74 y) 4) NUDS (India) (n=10039 adults 22-99 y) 5) NHANES 1988-1994 (n=3517 adults 40-74 y)	Primary objective was to evaluate the consequences of 2003 American Diabetes Association expert committee revision of diagnostic criteria for impaired fasting glucose from 6.1 to 5.6 mmol/l; specifically with regard to 1) the prevalence of impaired fasting glucose in five different countries, 2) the concordance between impaired fasting glucose status and impaired glucose tolerance, and 3) The cardiovascular risk profile of these groups. The proposed changes in diagnostic criteria would increase the prevalence of impaired fasting glucose in Denmark from 11.8% to 37.6%, which would identify 60% of all subjects with impaired glucose tolerance compared to 29.2% with the old criteria. However, among individuals with the new impaired fasting glucose category, 18.5% would also have impaired glucose tolerance; furthermore, individuals with isolated impaired fasting glucose had lower insulin levels and a lower cardiovascular disease risk compared with current WHO criteria. Data from DETECT-2 also showed an increase in the prevalence of impaired fasting glucose – the number of individuals ages 40-64 years with impaired fasting glucose in urban India, urban China, and the USA would increase by 78%, 135% and 193%, respectively, with the new criteria compared to the old criteria.	The authors conclude that a revision of diagnostic criteria for impaired fasting glycemia will increase the prevalence of impaired fasting glucose two- to fourfold. Impaired fasting glucose and impaired glucose tolerance will remain two different categories of glucose intolerance. The new impaired fasting glucose group will have a more favorable cardiovascular risk profile than the group defined by WHO, and the usefulness of impaired fasting glucose as a target group for diabetes prevention may become questionable.

Updated February 2012.

Return to Table of Contents

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

Return to Table of Contents

Author/ Year	Design Type	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Schmidt, et al., 2005	Study of sensitivity and specificity of a risk prediction function	7,915 participants from the Atherosclerosis Risk in Communities study; study subjects were free of diabetes at baseline (1987-1989) and followed until 1996-1998.	-The objective of this study was to derive risk functions to predict diabetes with equal or better diagnostic properties than impaired glucose tolerance. - Logistic regression was used in a random half of the sample, then evaluate the risk functions in the other half of the sample. - Rules based on risk functions including laboratory measurements performed generally better; a risk function based on waist circumference, height, hypertension, blood pressure, family history of diabetes, ethnicity and age was performed similarly to one based on fasting glucose (area under the curve 0.71 and 0.74, respectively, p=0.2). - Rules based on the presence of elements of the metabolic syndrome produced slightly less desirable diagnostic properties (23% labeled as high risk and 50% of future cases identified) than rules based on risk function including lipids (20% labeled as high risk and 52% of future cases identified). Metabolic syndrome rules had slightly less sensitivity (2%) and specificity (4%), compared to rules using a clinical calculator or Web page.	Rules based on the metabolic syndrome criteria are reasonable alternatives to rules derived from the risk functions.
Kim, et al., 2006	Randomized, controlled trial	52 men and 47 women age 53.5±11.4 years with prediabetes or non-diabetic metabolic syndrome were enrolled and randomized to either 4mg rosiglitazone treatment group or non-treated control group and followed for 12 weeks.	At baseline and 12-week follow-up, subjects were given a 75g oral glucose tolerance test. Inflammatory markers thought to be cardiovascular risk markers, pulse-wave-velocity (a measure of arterial stiffness) and anthropometrics were also measured. Rosiglitazone treatment significantly increased circulating levels of adiponectin and decreased levels of CRP relative to the control group. The treatment group also had significantly decreased pulse-wave-velocity compared to the control group.	These data suggest that rosiglitazone therapy may have an anti-atherogenic affect in subjects with prediabetes. *[This study was not conducted in a double-blinded placebo controlled fashion. It is possible that the rosiglitazone group had more intensive lifestyle changes that could have exaggerated the beneficial effect of rosiglitazone. Also, it is difficult to impossible to tease apart the effect of pharmacotherapy and lifestyle changes in this study.]*

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

Return to Table of Contents

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

Return to Table of Contents

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

Return to Table of Contents

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

Return to Table of Contents

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

Return to Table of Contents

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

Conclusion Grading Worksheet B – Annotation #11 (A1c)

Work Group's Conclusion:

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

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

Conclusion Grade: II

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

Updated February 2012.

Return to Table of Contents

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

Return to Table of Contents

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

Return to Table of Contents

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

Return to Table of Contents

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

Return to Table of Contents

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

Return to Table of Contents

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

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

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

Conclusion Grade: I

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

Updated February 2012.

Return to Table of Contents

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

Return to Table of Contents

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

Return to Table of Contents

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

Return to Table of Contents

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

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

Return to Table of Contents

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

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

Work Group's Conclusion:

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

Conclusion Grade: I

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

Updated February 2012.

Return to Table of Contents

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

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

Return to Table of Contents

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

Return to Table of Contents

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

Return to Table of Contents

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

Return to Table of Contents

Conclusion Grading Worksheet E – Annotation #18 (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	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Lewis, et al., NEJM, 2001	RCT	-1,715 patients (30-70 years) from 210 clinical centers with hypertension, nephropathy (urinary protein excretion >899 mg/24 hour), creatinine 1.0-3.0 mg/dL (men) or 1.2-3.0 mg/dL (women), and type 2 diabetes -Patients randomly assigned 300 mg/day of irbesartan, 10 mg/day of amlodipine, or placebo -Patient, provider and data analysts were blinded -Mean follow-up 2.6 years	-Primary composite end point (PCE): doubling baseline creatinine, onset of ESRD (dialysis, transplantation or creatinine >5.9 mg/dL), or death from any cause -Cardiovascular composite end point (CCE): cardiovascular death, non-fatal MI, CHF requiring hospitalization, permanent neurological deficit from CVA, or lower limb amputation above ankle -PCE showed a 20% relative risk (RR) reduction for irbesartan vs. placebo (p=0.006) and a 23% RR reduction for irbesartan vs. amlodipine (p=0.006) -There were no significant differences in CCEs or rates of death from any cause between groups	-The angiotensin-II-receptor blocker irbesartan is effective in protecting against the progression of nephropathy due to type 2 diabetes. This protection is independent of the reduction in blood pressure it causes.
Heart Outcomes Prevention Evaluation (HOPE) Study Investigators, Lancet, 2000	RCT	-3,577 patients with diabetes included in the HOPE study (patients had previous cardiovascular event or at least one other cardiovascular risk factor, no clinical proteinuria, heart failure, or low ejection fraction, and not taking ACE inhibitors) -Patients randomly assigned ramipril (10 mg/day) or placebo, and vitamin E or placebo in 2 by 2 factorial design -All patients ages 55 years of age or older -4.5-year follow-up	-Combined primary outcome: MI, stroke and cardiovascular death -Ramipril reduced the risk of combined primary outcome by 25% (95CI 12%-36%, p=0.0004), MI by 22% (95CI 6%-36%, p=0.01), stroke by 33% (95CI 10%-50%, p=0.0074), cardiovascular death by 37% (95CI 21%-51%, p=0.0001), total mortality by 24% (95CI 8%-37%, p=0.004), revascularization by 17% (95CI 2%-30%, p=0.031), overt nephropathy by 24% (95CI 3%-40%, p=0.0004), combined primary outcome by 25% (95CI 12-36, p=0.027) -After adjustment for changes in systolic and diastolic blood pressures, ramipril still lowered the risk of the combined primary outcome by 25% (95CI 12%-36%, p=0.0004) -The study was stopped 6 months early because of a consistent benefit of ramipril compared to placebo	-Ramipril was beneficial for cardiovascular events and overt nephropathy in people with diabetes. The cardiovascular benefit was greater than that attributable to the decrease in BP. This treatment represents a vasculoprotective and renoprotective effect for people with diabetes.

Updated February 2012.

Return to Table of Contents

Conclusion Grading Worksheet F – Annotations #13, 18 (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	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) Officers and Research Group, 2002 ALLHAT trial	RCT	-12,063 patients with type 2 diabetes with hypertension as part of a large, multicenter (623 North American centers) including a total of 33,357 patients -Mean age 67 years -53% male; 47% White, 32% Black, and 15% Hispanic -Mean follow-up 4.9 years	**Amlodipine 2.5-10 mgm vs. Chlorthalidone 12.5-25 mgm/d** -All-cause mortality: relative risk (RR) 0.96 (95%CI 0.82-1.07) -Stroke: RR 0.9 (95%CI 0.75-1.08) -Combined CV disease: RR 1.06 (95%CI 0.98-1.15) -Any heart failure: RR 1.42 (95%CI 1.23-1.64) **Lisinopril 10-40 mgm vs Chlorthalidone 12.5-25 mgm/d** -All-cause mortality: RR 1.02 (95%CI 0.91-1.13) -Stroke: RR 1.07 (95%CI 0.9-1.28) -Combined CV disease: RR 1.08 (95%CI 1.0-1.17) -Any heart failure: RR 1.22 (95%CI 1.06-1.42)	-For type 2 diabetic patients, lisinopril appeared to have no special advantage (and amlodipine no special detrimental effect) for most CVD outcomes when compared with chlorthalidone. *-Because the main intent was to compare thiazide, calcium channel blocker, and ACE inhibitor treatment, the available step-up for further management of hypertension for patients on ACE inhibitors led to less than typical regimen (use of sympatholytics rather than diuretics and calcium channel blockers). Since a large proportion of diabetes patients require more than one drug to control their BP, this study suggests that a diuretic should be included in all multidrug regimens.*
Wing et al., 2003 ANBP2 Trial	RCT	-6,083 patients (from 1,594 family medical practices throughout Australia) -Only 7% with diabetes -95% Caucasian -Mean age 72 years -Patient groups were equal at randomization, followed for 4.1 years with intention-to-treat analysis (0.2% lost to f/u)	**-Enalapril (ACE inhibitor) vs. Hydrochlorothiazide (diuretic)** -All CV events or death from any cause: Hazard ratio (HR) 0.89 (95%CI 0.79-1.00) -First CV event or death from any cause: HR 0.89 (95%CI 0.79-1.01) -Death from any cause: HR 0.9 (95%CI 0.75-1.09) -58%-62% receiving treatment assigned at the end of study and equal BP response (systolic/diastolic) in both groups -in post hoc analysis, largest effect seen in male patients	-Initiation of antihypertensive treatment involving ACE inhibitors in older subjects, particularly men, appears to lead to better outcomes than treatment with diuretic agents, despite similar reductions of blood pressure. *-There was a lower prevalence of diabetes than might have been expected (7%) mostly because the study population was overrepresented by elderly Caucasian patients.* *-Vascular outcomes and death were worse using hypertensive regimen emphasizing hydrochlorothiazide compared to ACE inhibition.* *-Also, insufficient information is provided to discern whether groups were treated equally.*

Updated February 2012.

Return to Table of Contents

References

Links are provided for those new references added to this edition (author name is highlighted in blue).

Abraira C, Colwell J, Nuttall F, et al. Cardiovascular events and correlates in the veterans affairs diabetes feasibility trial: veterans affairs cooperative study on glycemic control and complications in type II diabetes. *Arch Intern Med* 1997;157:181-88. (Low Quality Evidence)

ACCORD Study Group, The. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010a;362:1575-85. (High Quality Evidence)

ACCORD Study Group, The, ACCORD Eye Study Group. Effects of medical therapies in retinopathy progression in type 2 diabetes. *N Engl J Med* 2010b;363:233-44. (High Quality Evidence)

Action to Control Cardiovascular Risk in Diabetes Study Group, The. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008;358:2545-59. (High Quality Evidence)

ADVANCE Collaborative Group, The. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;358:2560-72. (High Quality Evidence)

AIM-HIGH Investigators, Boden WE, Probstfield JL, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med* 2011;365:2255-67. (Moderate Quality Evidence)

Alkaharouf J, Nalinikumari K, Corry D Tuck M. Long term effects of the angiotensive converting enzyme inhibitor captopril on metabolic control in non-insulin dependent diabetes mellitus. *Am J Hypertension* 1993;6:337-43. (Low Quality Evidence)

ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, The. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *JAMA* 2002;288:2981-97. (High Quality Evidence)

American College of Physicians, American Diabetes Association, and American Academy of Ophthalmology. Screening guidelines for diabetic retinopathy. *Ann Intern Med* 1992;116:683-85. (Guideline)

American Diabetes Association. Consensus development conference on the diagnosis of coronary heart disease in people with diabetes. *Diabetes Care* 1998;21:1551-59. (Low Quality Evidence)

American Diabetes Association. Diabetes nutrition recommendations for health care institutions. Diabetes Care 2004;27:S55-S57. (Guideline)

American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2007a;30:S42-S47. (Guideline)

American Diabetes Association. Dyslipidemia management in adults with diabetes. *Diabetes Care* 2004a;27:S68-S71. (Guideline)

American Diabetes Association. Hospital admission guidelines for diabetes. *Diabetes Care* 2004b;27:S103. (Guideline)

American Diabetes Association. Insulin administration. *Diabetes Care* 2004c;27:S106-S109. (Guideline)

American Diabetes Association. Nephropathy in diabetes. *Diabetes Care* 2004d;27:S79-S83. (Guideline)

American Diabetes Association. Nutrition recommendations and interventions for diabetes: a position statement of the American Diabetes Association. *Diabetes Care* 2007b;30:S48-S65. (Guideline)

American Diabetes Association. Physical activity/exercise and diabetes. *Diabetes Care* 2004e;27:S58-S62. (Guideline)

Return to Table of Contents

American Diabetes Association. Prevention or delay of type 2 diabetes. *Diabetes Care* 2004g;27:S47-S54. (Guideline)

American Diabetes Association. Preventive foot care in diabetes. *Diabetes Care* 2004f;27:S63-S64. (Guideline)

American Diabetes Association. Self monitoring of blood glucose (consensus statement). *Diabetes Care* 1994;17:81-86. (Low Quality Evidence)

American Diabetes Association. Standards of medical care in diabetes – 2007. *Diabetes Care* 2007b;30:S4-S41. (Guideline)

American Diabetes Association. Standards of medical care in diabetes – 2009. *Diabetes Care* 2009;32:S13-S61. (Guideline)

American Diabetes Association. Standards of medical care in diabetes – 2010. *Diabetes Care* 2010;32:S11-S61. (Guideline)

American Diabetes Association. Standards of medical care in diabetes – 2012. *Diabetes Care* 2012;35:S11-S63. (Guideline)

Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. *Diabetes Care* 2001;24:1069-78. (Meta-analysis)

Appel LJ, Wright Jr JT, Greene T, et al. Intensive blood-pressure control in hypertensive chronic kidney disease. *N Engl J Med* 2010;363:918-29. (High Quality Evidence)

Arguedas JA, Perez MI, Wright JM. Treatment blood pressure targets for hypertension (review). *Cochrane Database Syst Rev* 2009;(3):CD004349. (Systematic Review)

Avilés-Santa L, Sinding J, Raskin P. Effects of metformin in patients with poorly controlled, insulin-treated type 2 diabetes mellitus. *Ann Intern Med* 1999;131:182-88. (Low Quality Evidence)

Ballani P, Tran MT, Navar MD, Davidson MB. Clinical experience with u-500 regular insulin in obese, markedly insulin-resistant type 2 diabetic patients. *Diabetes Care* 2006;29:2504-05. (Low Quality Evidence)

Barnard JR, Jung T, Inkeles SB. Diet and exercise in the treatment of NIDDM. *Diabetes Care* 1994;17:1469-72. (Low Quality Evidence)

Belch J, MacCuish A, Campbell I, et al. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. *BMJ* 2008. (High Quality Evidence)

Bennett PH, Haffner S, Kasiske BL, et al. Diabetic renal disease recommendations: screening and management of microalbuminuria in patients with diabetes mellitus: recommendations to the Scientific Advisory Board of the National Kidney Foundation from an ad hoc committee of the Council on Diabetes Mellitus of the National Kidney Foundation. *Am J Kidney Dis* 1995;25:107-35. (Low Quality Evidence)

Bertelsen J, Christiansen C, Thomsen C, et al. Effect of meal frequency on blood glucose, insulin and free fatty acids in NIDDM subjects. *Diabetes Care* 1993;16:4-7. (Low Quality Evidence)

Bhatt DL, Marso SP, Hirsch AT, et al. Amplified benefit of clopidogrel versus aspirin in patients with diabetes mellitus. *Am J Cardiol* 2002;90:625-28. (Moderate Quality Evidence)

Bolen S, Feldman L, Vassy J, et al. Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. *Ann Intern Med* 2007;147:386-99. (Reference)

Return to Table of Contents

Borch-Johnsen K, Colagiuri S, Balkau B, et al. Creating a pandemic of prediabetes: the proposed new diagnostic criteria for impaired fasting glycaemia. *Diabetologia* 2004;47:1396-1402. (Low Quality Evidence)

Boulton AJM, Vinik AI, Arezzo JC, et al. Diabetic neuropathies: a statement by the American Diabetes Association. *Diabetes Care* 2005;28:956-62. (Low Quality Evidence)

Bourn DM, Mann JI, McSkimming BJ, et al. Impaired glucose tolerance and NIDDM: does a lifestyle intervention program have an effect? *Diabetes Care* 1994;17:1311-19. (Low Quality Evidence)

Canadian Diabetes Association 2008 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. UKPDS – implications for the care of people with type 2 diabetes. *Canadian J Diabetes* 2008;32:Supp 1. (Guideline)

Chiasson JL, Josse RG, Gomis R, et al. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet* 2002;359:2072-77. (Moderate Quality Evidence)

Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. *JAMA* 2003;289:2560-72. (Low Quality Evidence)

Cioffi ST, Caron MF, Kalus JS, et al. Glycosylated hemoglobin, cardiovascular, and renal outcomes in a pharmacist-managed clinic. *Ann Pharmacother* 2004;38:771-75. (Low Quality Evidence)

Clement S, Braithwaite SS, Magee MF, et al. Management of diabetes and hyperglycemia in hospitals. *Diabetes Care* 2004;27:553-91. (Low Quality Evidence)

Clements RS Jr, Bell DSH, Benbarka A, et al. Rapid insulin initiation in non-insulin dependent diabetes mellitus. *Am J Med* 1987;82:415-20. (High Quality Evidence)

Cochran E, Musso C, Gorden P. The use of u-500 in patients with extreme insulin resistance. *Diabetes Care* 2005;28:1240-44. (Low Quality Evidence)

Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the collaborative atorvastatin diabetes study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004;364:685-96. (High Quality Evidence)

Cooper-DeHoff RM, Handberg EM, Mancia G, et al. INVEST revisited: a review of findings from the INternational VErepamil SR-Trandolapril STudy (INVEST). *Expert Rev Cardiovasc Ther* 2009;7:1329-40. (High Quality Evidence)

Cryer PE. Hypoglycaemia: the limiting factor in the glycaemic management of type I and type II diabetes. *Diabetologia* 2002;45:937-48. (Low Quality Evidence)

Cryer PE, Davis SN, Shamoon H. Hypoglycemia in diabetes. *Diabetes Care* 2003;26:1902-12. (Low Quality Evidence)

Davidson PC, Hebblewhite HR, Bode BW, et al. Statistically based CSII parameters: correction factor (CF) (1700 rule), carbohydrate-insulin ratio (CIR) (2.8 rule), and basal-to-total ratio. *Diabetes Technol Ther* 2003;5:237. (Reference)

Davidson JK. Endogenous insulin, proinsulin, and C-peptide. *In* Clinical Diabetes Mellitus: A Problem Oriented Approach. Thieme Inc., New York. 1986;219-22. (Reference)

DeBusk RF, Stenestrand U, Sheehan M, et al. Training effects of long versus short bouts of exercise in healthy subjects. *Am J Cardiol* 1990;65:1010-13. (Low Quality Evidence)

DeFronza RA. Diabetic nephropathy: etiologic and therapeutic considerations. *Diabetes Reviews* 1995;3:510-64. (Low Quality Evidence)

Return to Table of Contents

de Groot M, Anderson R, Freedland KE, et al. Association of depression and diabetes complications: a meta-analysis. *Psychosom Med* 2001;63:619-30. (Meta-analysis)

Dexter PR, Perkins SM, Maharry KS, et al. Inpatient computer-based standing orders vs physician reminders to increase influenza and pneumococcal vaccination rates: a randomized trial. *JAMA* 2004;292:2366-71. (High Quality Evidence)

Diabetic Retinopathy Study Research Group, The. Photocoagulation treatment of proliferative diabetic retinopathy: clinical application of diabetic retinopathy, (DRS) findings, DRS report number 8. *Ophthalmology* 1981;88:583-600. (Narrative Review)

DREAM (Diabetes Reduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators, The. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet* 2006;368:1096-1105. (High Quality Evidence)

Duckworth WC, McCarren M, Abraira C. Glucose control and cardiovascular complications: the VA diabetes trial. *Diabetes Care* 2001;24:942-45. (Moderate Quality Evidence)

Dunn C, Curran MP. Inhaled human insulin (Exubera®): a review of its use in adult patients with diabetes mellitus. *Drugs* 2006;66:1013-32. (Low Quality Evidence)

Eriksson J, Lindstrom J, Valle T, et al. Prevention of type II diabetes in subjects with impaired glucose tolerance: the diabetes prevention study (DPS) in Finland. *Diabetologia* 1999;42:793-801. (Low Quality Evidence)

ETDRS Investigators. Aspirin effects on mortality and morbidity in patients with diabetes mellitus: ETDRS report 14. *JAMA* 1992;268:1292-1300. (Moderate Quality Evidence)

ETDRS Research Group. Early photocoagulation for diabetic retinopathy: ETDRS report number 9. *Ophthalmology* 1991;98:766-85. (High Quality Evidence)

ETDRS Research Group. Photocoagulation for diabetic macular edema: ETDRS report number 1. *Arch Ophthalmol* 1985;103:1796-1806. (High Quality Evidence)

Estacio RO, Jeffers BW, Gifford N, Schrier RW. Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes. *Diabetes Care* 2000;23:B54-B64. (High Quality Evidence)

Evangelista V, De Berardis G, Totani L, et al. Persistent platelet activation in patients with type 2 diabetes treated with low doses of aspirin. *J Thromb Haemost* 2007;5:2197-2203. (Moderate Quality Evidence)

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA* 2001;285:2486-97. (Low Quality Evidence)

Farag A, Karam J, Nicasio J, McFarlane SI. Prevention of type 2 diabetes: an update. *Curr Diabetes Reports* 2007;7:200-07. (Low Quality Evidence)

Ferrer-Garceîa JC, Sanchez-Ballester E, Albalat-Galera R, et al. Efficacy of atorvastatin for achieving cholesterol targets after LDL-cholesterol based dose selection in patients with type 2 diabetes. *J Cardiovasc Pharmacol Ther* 2008;13:183-88. (Low Quality Evidence)

Fleg JL, Mete M, Howard BV, et al. Effect of statins alone versus statins plus ezetimibe on carotid atherosclerosis in type 2 diabetes: the SANDS (Stop Atherosclerosis in Native Diabetics Study) trial. *J Am Coll Cardiol* 2008;52:2198-205. (Moderate Quality Evidence)

Return to Table of Contents

Fong DS, Aiello L, Gardner TW, et al. Retinopathy in diabetes. *Diabetes Care* 2004;27:S84-S87. (Guideline)

Foster GD, Borradaile KE, Sanders MH, et al. A randomized study on the effect of weight loss on obstructive sleep apnea among obese patients with type 2 diabetes: the sleep AHEAD study. *Arch Intern Med* 2009a;169:1619-26. (High Quality Evidence)

Foster GD, Sanders MH, Millman R, et al. Obstructive sleep apnea among obese patients with type 2 diabetes. *Diabetes Care* 2009b;32:1017-19. (Low Quality Evidence)

Franz M, Bantle J. A dietitian's perspective on medical nutrition therapy for diabetes. *In* American Diabetes Association Guide to Medical Nutrition Therapy for Diabetes. Virginia: American Diabetes Association, Inc. 1999;1-17. (Reference)

Franz M. Chapter 1: medical nutrition therapy for diabetes. *In* A Core Curriculum for Diabetes Education. 5th Edition. Chicago, American Association of Diabetes Educators, 2003;1-58. (Reference)

Franz MJ, Bantle JP, Beebe CA, et al. Evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications. *Diabetes Care* 2002;25:148-98. (Low Quality Evidence)

Franz MJ, Monk A, Barry B, et al. Effectiveness of medical nutrition therapy provided by dietitians in the management of non-insulin-dependent diabetes mellitus: a randomized, controlled clinical trial. *J Am Diet Assoc* 1995a;95:1009-17. (Low Quality Evidence)

Franz MJ, Splett PL, Monk A, et al. Cost-effectiveness of medical nutrition therapy provided by dietitians for persons with non-insulin-dependent diabetes mellitus. *J Am Diet Assoc* 1995b;95:1018-24. (Low Quality Evidence)

Furnary AP, Braithwaite SS. Effects of outcome on in-hospital transition from intravenous insulin infusion to subcutaneous therapy. *Am J Cardiol* 2006;98:557-64. (Low Quality Evidence)

Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* 2008;358:580-91. (High Quality Evidence)

Gaede P, Vedel P, Larsen N, et al. Multifactoral intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003;348:383-93. (High Quality Evidence)

Garber AJ, Moghissi ES, Bransome Jr ED, et al. American college of endocrinology position statement on inpatient diabetes and metabolic control. *Endocr Pract* 2004;10:77-82. (Low Quality Evidence)

Gerich JE. Novel insulins: expanding options in diabetes management. *Am J Med* 2002;113:339-40. (Low Quality Evidence)

Greci LS, Kailasam M, Malkani S, et al. Utility of HgbA1c levels for diabetes case finding in hospitalized patients with hyperglycemia. *Diabetes Care* 2003;26:1064-68. (Low Quality Evidence)

Grundy SM, Cleeman JI, Bairey Merz CN, et al. Implications of recent clinical trials for the national cholesterol education program adult treatment panel III guidelines. *Circulation* 2004;110:227-39. (Low Quality Evidence)

Guerci B, Sauvanet JP. Subcutaneous insulin: pharmacokinetic variability and glycemic variability. *Diabetes Metab* 2005;31:4S7-4S24. (Low Quality Evidence)

Hannah R, Levin N, London R, et al, eds. Renal disease in the managed care setting: selection and monitoring of outcome criteria. *Am J Kidney Dis* 1999;33(Suppl 1):S1-S23. (Low Quality Evidence)

Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the hypertension optimal treatment (HOT) randomised trial. *Lancet* 1998;361:1755-62. (Moderate Quality Evidence)

Hardman AE. Accumulation of physical activity for health gains: what is the evidence? *Br J Sports Med* 1999;33:87-92. (Narrative Review)

Harpaz D, Gottlieb S, Graff E, et al. Effects of aspirin treatment on survival in non-insulin-dependent diabetic patients with coronary artery disease. *Am J Med* 1998;105:494-99. (High Quality Evidence)

Heart Outcomes Prevention Evaluation Study Investigators, The. Effects of an angiotensin-converting – enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2002;342:145-53. (High Quality Evidence)

Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000a;355:253-59. (High Quality Evidence)

Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Vitamin E supplementation and cardiovascular events in high-risk patients. *N Engl J Med* 2000b;342:154-60. (High Quality Evidence)

Heart Protection Study Collaborative Group. MRC/BHF heart protection study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; 360:7-22. (High Quality Evidence)

Heart Protection Study Collaborative Group. MRC/BHF heart protection study of cholesterol-lowering with simvastatin in 5,963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 2003;361:2005-16. (High Quality Evidence)

Hirsch IB. Insulin in the hospital setting. New York, Adelphi, 2002;25. (Low Quality Evidence)

Hirsch IB, Paauw DS, Brunzell J, et al. Inpatient management of adults with diabetes. *Diabetes Care* 1995;18:870. (Low Quality Evidence)

Hollander PA, Elbein SC, Hirsch IB, et al. Role of orlistat in the treatment of obese patients with type 2 diabetes. *Diabetes Care* 1998;21:1288-93. (High Quality Evidence)

Holman RR, Farmer AJ, Davies MJ, et al. Three-year efficacy of complex insulin regimens in type 2 diabetes. *N Engl J Med* 2009;361:1736-47. (High Quality Evidence)

Holman RR, Paul SK, Bethel MA, et al. Long-term follow-up after tight control of blood pressure in type 2 diabetes. *N Engl J Med* 2008a;359:1565-76. (High Quality Evidence)

Holman RR, Paul SK, Bethel MA, et al. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008b;359:1577-89. (Low Quality Evidence)

Howard BV, Roman MJ, Devereux RB, et al. Effect of lower targets for blood pressure and LDL cholesterol on atherosclerosis in diabetes: the SANDS randomized trial. *JAMA* 2008;299:1678-89. (High Quality Evidence)

Inzucchi SE. Management of hyperglycemia in the hospital setting. *N Engl J Med* 2006;355:1903-11. (Low Quality Evidence)

Inzucchi SE. Oral antihyperglycemic therapy for type 2 diabetes: scientific review. *JAMA* 2002;287:360-72. (Meta-analysis)

Ismail-Beigi F, Craven T, Banerji MA, et al. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. *Lancet* 2010;376:419-30. (High Quality Evidence)

John R, Fogelfeld L. Inpatient management of diabetes and hyperglycemia. *Disease-A-Month* 2004;50. (Low Quality Evidence)

Return to Table of Contents

Karter AJ, Ferrara A, Liu JY, et al. Ethnic disparities in diabetic complications in an insured population. *JAMA* 2002;287:2519-27. (Low Quality Evidence)

Kastelein JJP, Akdim F, Stroes ESG, et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med* 2008;358:1431-43. (High Quality Evidence)

Kelley DE, Bray GA, Pi-Sunyer FX, et al. Clinical efficacy of orlistat therapy in overweight and obese patients with insulin-treated type 2 diabetes. *Diabetes Care* 2002;25:1033-41. (High Quality Evidence)

Kermani A, Garg A. Thiazolidinedione-associated congestive heart failure and pulmonary edema. *Mayo Clinic Proc* 2003;78:1088-91. (Low Quality Evidence)

Kim SG, Ryu OH, Kim HY, et al. Effect of rosiglitazone on plasma adiponectin levels and arterial stiffness in subjects with prediabetes or non-diabetic metabolic syndrome. *Eur J Endocrinol* 2006;154:433-40. (Low Quality Evidence)

Klein R, Klein BEK, Moss SE, et al. The Wisconsin epidemiologic study of diabetic retinopathy. III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. *Arch Ophthalmol* 1984;102:527-32. (Low Quality Evidence)

Klein R, Moss SE, Klein BEK. New management concepts for timely diagnosis of diabetic retinopathy treatable by photocoagulation. *Diabetes Care* 1987;10:633-38. (Consensus Statement)

Klein S, Sheard NF, Pi-Sunyer X, et al. Weight management through lifestyle modification for the prevention and management of type 2 diabetes: rationale and strategies: a statement of the American Diabetes Association, the North American association for the study of obesity, and the American society for clinical nutrition. *Diabetes Care* 2004;27:2067-73. (Consensus Statement)

Knopp RH, d'Emden M, Smilde JG, Pocock SJ. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the atorvastatin study for prevention of coronary heart disease endpoints in non-insulin-dependent diabetes mellitus (ASPEN). *Diabetes Care* 2006;29:1478-85. (Moderate Quality Evidence)

Knowler WC, Barrett-Connor E, Fowler Se, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346:393-403. (High Quality Evidence)

Knowler WC, Hamman RF, Edelstein SL, et al. Prevention of type 2 diabetes with troglitazone in the diabetes prevention program. *Diabetes* 2005;54:1150-56. (High Quality Evidence)

LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005;352:1425-35. (High Quality Evidence)

Leiter LA, Martineau P, de Teresa E, et al. How to reach LDL targets quickly in patients with diabetes or metabolic syndrome. *J Fam Pract* 2008;57:661-68. (Moderate Quality Evidence)

Lewis EJ, Hunsicker LG, Bain RP, et al. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *N Engl J Med* 1993;329:1456-62. (High Quality Evidence)

Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;345:851-60. (High Quality Evidence)

Lewis JB. Blood pressure control in chronic kidney disease: is less really more? *J Am Soc Nephrol* 2010;21:1086-92. (Meta-analysis)

Li G, Zhang P, Wang J, et al. The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing diabetes prevention study: a 20-year follow-up study. *Lancet* 2008;371:1783-89. (Low Quality Evidence)

Return to Table of Contents

Lindström J, Ilanne-Parikka P, Peltonen M, et al. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish diabetes prevention study. *Lancet* 2006;368:1673-79. (Moderate Quality Evidence)

Lorig KR, Ritter P, Stewart AL, et al. Chronic disease self-management program: 2-year health status and health care utilization outcomes. *Med Care* 2001;39:1217-23. (Low Quality Evidence)

Lustman PJ, Gavard JA. Psychosocial aspects of diabetes in adult populations. *In* Diabetes in America, 2nd Ed. 507-18. On-line reference, accessed July, 2001 at http://diabetes-in-america.s-3.com/. (Reference)

Malmström RE, Settergren M, Böhm F, et al. No effect of lipid lowering on platelet activity in patients with coronary artery disease and type 2 diabetes or impaired glucose tolerance. *Thromb Haemost* 2009;101:157-64. (Moderate Quality Evidence)

Mayfield JA, Reiber GE, Sanders LJ, et al. Preventive foot care in people with diabetes. *Diabetes Care* 1998;21:2161-77. (Low Quality Evidence)

McFarlane SI. Diabetes prevention between RAAS inhibition and PPAR-gamma stimulation: the diabetes reduction assessment with ramipril and rosiglitazone medication (DREAM) trial. *J Cardiometab Syndr* 2007;2:149-50. (Low Quality Evidence)

Medical Letter® on Drugs and Therapeutics, The. Rosiglitazone for type 2 diabetes mellitus. 1999;41. (Low Quality Evidence)

Mensing C, Boucher J, Cypress M, et al. National standards for diabetes self-management education. *Diabetes Care* 2007;30:S96-S103. (Low Quality Evidence)

Miller CD, Phillips LS, Ziemer DC, et al. Hypoglycemia in patients with type 2 diabetes mellitus. *Arch Intern Med* 2001;161:1653-59. (Low Quality Evidence)

Misbin R, Green L, Stadel BV, et. al. Lactic acidosis in patients with diabetes treated with metformin. *N Engl J Med* 1998;338:265-66. (Reference)

Mogensen CE, Keane WF, Bennett PH, et al. Prevention of diabetic renal disease with special reference to microalbuminuria. *Lancet* 1996;346:1080-84. (Low Quality Evidence)

Morrish NJ, Stevens LK, Fuller JH, et al. Risk factors for macrovascular disease in diabetes mellitus: the London follow-up to the WHO multinational study of vascular disease in diabetes. *Diabetologia* 1991;34:590-94. (Low Quality Evidence)

Nathan DM, Buse JB, Davidson MB, et al. Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2006;29:1963-72. (Reference)

Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American diabetes association and the European association for the study of diabetes. *Diabetes Care* 2009;32:193-203. (Reference)

National Institutes of Health. Morbidity and mortality of dialysis (consensus statement, online). 1993;11:1-33. (Low Quality Evidence)

Nelson RG, Knowler WC, Pettitt DJ, et al. Assessment of risk of overt nephropathy in diabetic patients from albumin excretion in untimed urine specimens. *Arch Intern Med* 1991;151:1761-65. (Low Quality Evidence)

Return to Table of Contents

Newman CB, Szarek M, Colhoun HM, et al. The safety and tolerability of atorvastatin 10 mg in the collaborative atorvastatin diabetes study (CARDS). *Diabetes Vasc Dis Res* 2008;5:177-83. (High Quality Evidence)

NICE-SUGAR Study Investigators, The. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009;360:1283-97. (High Quality Evidence)

Nichols-English G, Poirier S. Optimizing adherence to pharmaceutical care plans. *J Am Pharm Assoc* 2000;40:475-83. (Low Quality Evidence)

Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007;356:2457-71. (Meta-analysis)

Norris SL, Zhang X, Avenell A, et al. Long-term effectiveness of weight-loss interventions in adults with pre-diabetes: a review. *Am J Prev Med* 2005;28:126-39. (Meta-analysis)

O'Connor PJ. Commentary – improving diabetes care by combating clinical inertia. *Health Serv Res* 2005a;40:1854-61. (Low Quality Evidence)

O'Connor PJ. Overcome clinical inertia to control systolic blood pressure. *Arch Intern Med* 2003;163:2677-78. (Low Quality Evidence)

O'Connor PJ, Crabtree BF, Yanoshik MK. Differences between diabetic patients who do and do not respond to a diabetes care intervention: a qualitative analysis. *Fam Med* 1997;29:424-28. (Low Quality Evidence)

O'Connor PJ, Sperl-Hillen JM, Johnson PE, et al. Advances in patient safety: clinical inertia and outpatient medical errors. *AHRQ* 2005b;2:293-308. (Low Quality Evidence)

Odegard PS, Setter SM, Iltz JL. Update in the pharmacologic treatment of diabetes mellitus: focus on pramlintide and exenatide. *Diabetes Educ* 2006;32:693-712. (Low Quality Evidence)

Ogawa S, Mori T, Nako K, et al. Reduced albuminuria with sarpogrelate is accompanied by a decrease in monocyte chemoattractant protein-1 levels in type 2 diabetes. *Clin J Soc Nephrol* 2008;3:362-68. (High Quality Evidence)

Pastors JG, Warshaw H, Daly A, et al. The evidence for the effectiveness of medical nutrition therapy in diabetes management. *Diabetes Care* 2002;25:608-13. (Narrative Review)

Pate RR, Pratt M, Blair SN, et al. Physical activity and public health: a recommendation from the Centers for Disease Control Prevention and the American College of Sports Medicine. *JAMA* 1995;273:402-07. (Consensus Statement)

Peters AL, Davidson MB. Maximal dose glyburide therapy in markedly symptomatic patients with type 2 diabetes: a new use for an old friend. *J Clin Endocrinol Metab* 1996;81:2423-27. (Low Quality Evidence)

Pettitt DJ, Opsina P, Kolaczynski JW, Jovanovic L. Comparison of an insulin analog, insulin aspart, and regular human insulin with no insulin in gestational diabetes mellitus. *Diabetes Care* 2003;26:183-86. (Moderate Quality Evidence)

Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing physicians' health study. *N Engl J Med* 1989;321:129-35. (Moderate Quality Evidence)

Polonsky WH, Fisher L, Schikman CH, et al. A structured self-monitoring of blood glucose approach in type 2 diabetes encourages more frequent, intensive, and effective physician interventions: results from the STeP study. *Diabetes Technol Ther* 2011;13:797-802. (High Quality Evidence)

Polonsky KS, Given BD, Hirsch ET, et. al. Quantitative study of insulin secretion and clearance in normal and obese subjects. *J Clin Invest* 1988a;81:435-41. (Low Quality Evidence)

Return to Table of Contents

Polonsky KS, Given BD, Van Cauter E. Twenty-four-hour profiles and pulsatile patterns of insulin secretion in normal and obese subjects. *J Clin Invest* 1988b;81:442-48. (Low Quality Evidence)

Rave K, Klein O, Frick AD, Becker RHA. Advantage of premeal-injected insulin glulisine compared with regular human insulin in subjects with type 1 diabetes. *Diabetes Care* 2006;29:1812-17. (Low Quality Evidence)

Ravid M, Savin H, Jutrin I, et al. Long-term stabilizing effect of angiotensin-converting enzyme inhibition on plasma creatinine and on proteinuria in normotensive type II diabetic patients. *Ann Intern Med* 1993;118:577-81. (Moderate Quality Evidence)

Ray KK, Seshasai SR, Wijesuriya S, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. *Lancet* 2009;373:1765-72. (Meta-analysis)

Relimpio F, Pumar A, Losada F, et al. Adding metformin versus insulin dose increase in insulin-treated but poorly controlled type 2 diabetes mellitus: an open-label randomized trial. *Diabet Med* 1998;15:997-1002. (Low Quality Evidence)

Reynolds NA, Wagstaff AJ. Insulin aspart: a review of its use in the management of type 1 or type 2 diabetes mellitus. *Drugs* 2004;64:1957-74. (Low Quality Evidence)

Robins SJ, Collins D, Wittes JT, et al. Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: a randomized controlled trial. *JAMA* 2001;285:1585-91. (High Quality Evidence)

Rodbard HW, Blonde L, Braithwaite SS, et al. American association of clinical endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus. *Endocr Pract* 2007;13:1-68. (Guideline)

Schmidt MI, Duncan BB, Bang H, et al. Identifying individuals at high risk for diabetes: the atherosclerosis risk in communities study. *Diabetes Care* 2005;28:2013-18. (Low Quality Evidence)

SEARCH Study Collaborative Group, Bowman L, Armitage J, et al. Study of the effectiveness of additional reductions in cholesterol and homocysteine (SEARCH): characteristics of a randomized trial among 12,064 myocardial infarction survivors. *Am Heart J* 2007;154:815-23. (High Quality Evidence)

Selvin E, Bolen S, Yeh HC, et al. Cardiovascular outcomes in trials of oral diabetes medications: a systematic review. *Arch Intern Med* 2008;168:2070-80. (Systematic Review)

Selvin E, Marinopoulos S, Berkenblit G, et al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med* 2004;141:421-31. (Meta-analysis)

Serebruany VL, Malinin AI, Pokov A, et al. Effects of clopidogrel and aspirin in combination versus aspirin alone on platelet activation and major receptor expression in diabetic patients: the pLavix use for treatment of diabetes (PLUTO-Diabetes) trial. *Am Heart J* 2008;155:93.e1-7. (Moderate Quality Evidence)

Seshasai SR, Wijesuriya S, Sivakumaran R, et al. Effect of aspirin on vascular and nonvascular outcomes: meta-analysis of randomized controlled trials. *Arch Intern Med* 2012;172:209-16. (Meta-analysis)

Settergren M, Böhm F, Ryden L, Pernow J. Cholesterol lowering is more important than pleiotropic effects of statins for endothelial function in patients with dyslycaemia and coronary artery disease. *Eur Heart J* 2008;29:1753-60. (Low Quality Evidence)

Sever PS, Poulter NR, Dahlöf B, et al. Reduction in cardiovascular events with atorvastatin in 2,532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial – lipid-lowering arm (ASCOT-LLA). *Diabetes Care* 2005;28:1151-57. (High Quality Evidence)

SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the systolic hypertension in the elderly program. *JAMA* 1991;265:3255-64. (High Quality Evidence)

Return to Table of Contents

Shepard J, Barter P, Carmena R, et al. Effect of lowering LDL cholesterol substantially below currently recommended levels in patients with coronary heart disease and diabetes: the treating to new targets (TNT) study. *Diabetes Care* 2006;29:1220-26. (High Quality Evidence)

Sigal RJ, Kenny GP, Wasserman DH, Castaneda-Sceppa C. Physical activity/exercise and type 2 diabetes. *Diabetes Care* 2004;27:2518-39. (Low Quality Evidence)

Sirois C, Poirier P, Moisan J, Grégoire JP. The benefit of aspirin therapy in type 2 diabetes: what is the evidence? *Int J Cardiol* 2008;129:172-79. (Meta-analysis)

Sperl-Hillen JM, O'Connor JP. Factors driving diabetes care improvement in a large medical group: ten years of progress. *Am J Manag Care* 2005;11:S177-S185. (Low Quality Evidence)

Tuomilehto J, Lindstrom J, Eriksson JH, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001;344:1343-50. (High Quality Evidence)

Tuomilehto J, Rastenyte D, Birkenhager WH, et al. Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension. *N Engl J Med* 1999;340:677-84. (High Quality Evidence)

Turnbull FM, Abraira C, Anderson RJ, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. *Diabetologia* 2009;52:2288-98. (Meta-analysis)

Turner R, Cull C, Frighi V, et al. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). *JAMA* 1999;281:2005-12. (High Quality Evidence)

Twigg SM, Kamp MC, Davis TM, et al. Prediabetes: a position statement from the Australian diabetes society and Australian diabetes educators association. *Med J Aust* 2007;186:461-65. (Low Quality Evidence)

UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837-53. (High Quality Evidence)

Umpierrez GE, Isaacs SD, Bazargan N, et al. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrinol Metab* 2002;87:978-82. (Low Quality Evidence)

Umpierrez GE, Smiley D, Zisman A, et al. Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes (RABBIT 2 trial). *Diabetes Care* 2007;30:2181-86. (High Quality Evidence)

Vague P, Selam JL, Skeie S, et al. Insulin Detemir is associated with more predictable glycemic control and reduced risk of hypoglycemia than NPH insulin in patients with type 1 diabetes on a basal-bolus regimen with premeal insulin aspart. *Diabetes Care* 2003;26:590-96. (Low Quality Evidence)

Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001;345:1359-67. (Moderate Quality Evidence)

Viberti G, Mogensen CE, Groop LC, et al. Effect of captopril on progression to clinical proteinuria in patients with insulin-dependent diabetes mellitus and microalbuminuria. *JAMA* 1994;271:275-79. (High Quality Evidence)

Walsh M, Spurling G. Aspirin in type 2 diabetes: is there any evidence base? *BMJ* 2008;337:1163-65. (Low Quality Evidence)

Wang C, Harris WS, Chung M, et al. n-3 Fatty acids from fish or fish-oil supplements, but not alpha-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: a systematic review. *Am J Clin Nutr* 2006;84:5-17. (Systematic Review)

Return to Table of Contents

Wang F, Carabino JM, Vergara CM. Insulin glargine: a systematic review of a long-acting insulin analogue. *Clin Ther* 2003;25:1541-77. (Systematic Review)

Weinger K, Beverly EA, Lee Y, et al. The effect of a structured behavioral intervention on poorly controlled diabetes: a randomized controlled trial. *Arch Intern Med* 2011;171:1990-99. (Moderate Quality Evidence)

Wing LMH, Reid CM, Ryan P, et al. A comparison of outcomes with angiotensin-converting-enzyme inhibitors and diuretics for hypertension in the elderly. *N Engl J Med* 2003;348:583-92. (Moderate Quality Evidence)

Yki-Järvinen H, Dressler A, Ziemen M, The HOE 901/3002 Study Group. Less nocturnal hypoglycemia and better post-dinner glucose control with bedtime insulin Glargine compared with bedtime NPH insulin during insulin combination therapy in type 2 diabetes. *Diabetes Care* 2000;23:1130-36. (Moderate Quality Evidence)

Yki-Järvinen H, Ryysy L, Nikkilä K, et al. Comparison of bedtime insulin regimens in patients with type 2 diabetes mellitus. *Ann Intern Med* 1999;130:389-96. (Low Quality Evidence)

Zillich AJ, Garg J, Basu S, et al. Thiazide diuretics, potassium, and the development of diabetes: a quantitative review. *Hypertension* 2006;48:219-24. (Meta-analysis)

Zimmerman BR, Hagen MD. An evaluation of new agents in the treatment of type 2 diabetes. *J Fam Pract* 1998;47(Suppl 1):S37-S43. (Low Quality Evidence)

Return to Table of Contents

Appendix A – Order Set: Subcutaneous Insulin Management

This order set will cover the orders of subcutaneous insulin management. This order will not include admission orders or other specific orders for the patient's condition outside of insulin management. The target population is hospitalized adults who require subcutaneous insulin for their clinical care and does not include orders for critical care patients.

Patient Information *(Two are required.)*

Last Name: _____

First Name: _____

Date of Birth: ___/___/_____

Patient's Age: _____

ID #: _____

Legend:
- ☐ Open boxes are orders that a clinician will need to order by checking the box.
- ☑ Pre-checked boxes are those orders with strong supporting evidence and/or regulatory requirements that require documentation if not done.

Admitting/Attending Information

Admit unit: _____

Attending physician: _____

How to contact: _____

Diagnosis

Admitting diagnosis: _____

Secondary diagnosis: _____

Nursing

Blood glucose level goals
- ☐ Preprandial = 90-140 mg/dL
- ☐ Postprandial less than 180 mg/dL
- ☐ Other: _____ mg/dL

Blood glucose monitoring frequency (Select all that apply.)
- ☐ _____ minutes before meals
- ☐ Bedtime
- ☐ 0200-0300 (all times listed in 24-hour time)
- ☐ Nothing by mouth, total parenteral nutrition (TPN), or continuous enteral feeding: monitor based on insulin dosing schedule every:
  - ☐ 4 hours
  - ☐ 6 hours

☐ Other _____

Return to Table of Contents

Dosing schedule

☐ Basal insulin (check one)

☐ Glargine insulin _____ units subcutaneous at _____ hours (24-hour time)

☐ Glargine insulin twice daily:
Units subcutaneous at hours (24-hour time) AND
Units subcutaneous at hours (24-hour time)

☐ Detemir insulin _____ units subcutaneous daily at _____ hours (24-hour time)

☐ Detemir insulin twice daily:
_____ units subcutaneous at _____ hours (24-hour time) **AND**
_____ units subcutaneous at _____ hours (24-hour time)

☐ NPH insulin _____ units subcutaneous each a.m.
_____ units subcutaneous each evening meal
_____ units subcutaneous at bedtime

☐ Other _____ units subcutaneous every _____ hours (24-hour time)

☐ Prandial insulin (***Do not give if patient is NPO or if preprandial glucose is less than 60 mg/dL.***)

☐ Lispro insulin _____ units subcutaneous at _____ hours (24-hour time)

☐ Aspart insulin _____ units subcutaneous at _____ hours (24-hour time)

☐ Glulisine insulin _____ units subcutaneous at _____ hours (24-hour time)

☐ Other _____

Breakfast	Lunch	Supper
_____ units/meal OR _____ units: CHO unit* OR _____ units per ____ grams of carbohydrates	_____ units/meal OR _____ units: CHO unit* OR _____ units per ____ grams of carbohydrates	_____ units/meal OR _____ units: CHO unit* OR _____ units per ____ grams of carbohydrates

* Note: 1 CHO (carbohydrate) unit equals 15 grams of carbohydrate.

☐ Correction (***in addition to prandial dose above***)

Glucose level	☐Low	☐Med	☐High	☐Individual
Less than 120 mg/dL	0 units	0 units	0 units	0 units
120-149 mg/dL	0 units	1 units	2 units	___ units
150-199 mg/dL	1 units	2 units	3 units	___ units
200-249 mg/dL	2 units	3 units	4 units	___ units
250-299 mg/dL	3 units	5 units	7 units	___ units
300-349 mg/dL	4 units	7 units	10 units	___ units
350 or greater	5 units	8 units	12 units	___ units

☐ Bedtime (If blood glucose is less than 200 mg/dL, do not give correction dose; if greater than 200 mg/dL, give 50% of correction dose. *Patients receiving corticosteroids may be at greater risk for nocturnal hypoglycemia, so caution is required in giving insulin correction dose at bedtime for these patients.)*

Return to Table of Contents

Corrective dose insulin for patients who have nothing by mouth, on total parenteral nutrition or on continuous enteral feeding *(to be given in addition to basal insulin)*

Check one:

☐ Regular insulin – check blood glucose every 6 hours and administer insulin dose based on correction schedule
☐ Lispro insulin – check blood glucose every 4 hours and administer insulin dose based on correction schedule
☐ Aspart insulin – check blood glucose every 4 hours and administer insulin dose based on correction schedule
☐ Glulisine insulin – check blood glucose every 4 hours and administer insulin dose based on correction schedule
☐ Other _____ – check blood glucose every ____ hours and administer insulin dose based on correction schedule
☐ Other diabetic medications: _____
_____

Transition from intravenous insulin to subcutaneous insulin:

☐ Administer initial dose of subcutaneous basal insulin two hours prior to discontinuation of intravenous insulin infusion. Record blood glucose prior to administering basal insulin dose.
☐ Initial dose of subcutaneous basal insulin
  ☐ Glargine insulin _____ units at _____hours (24-hour time)
  ☐ Detemir insulin _____ units at _____hours (24-hour time)
  ☐ NPH insulin _____ units at _____hours (24-hour time)
☐ Discontinue intravenous insulin infusion at _____hours (24-hour time). Record blood glucose at time intravenous insulin infusion is discontinued.
☐ Subsequent basal, prandial and correction insulin doses in accordance with orders above

Diet

☐ Consistent carbohydrate (CHO) meal plan
☐ Bedtime snack
☐ Other _____

Laboratory/Diagnostic Testing

☐ A1c (if A1c from past 2-3 months or unknown)
☐ Electrolytes, blood urea nitrogen (BUN), creatinine
☐ Alanine amino transaminase (ALT)
☐ Asparate transaminase (AST)
☐ Hypoglycemia protocol

Discharge/Transition Planning – Patient Education

☐ Diabetes clinical nurse specialist consult *(reason for consult):*_____
☐ Diabetes education consult inpatient survival skills *(reason for consult):* _____
☐ Diabetes education consult outpatient *(reason for consult):*_____
☐ Nutrition services consult *(reason for consult):*_____

Authorized Prescriber Signature: _____

Printed Name:_____

Date & Time of Orders: ____/____/____ _____:_____ hours

Return to Table of Contents

Glucose Goals

Suggested glucose goals are 90-140 mg/dL for preprandial values; if postprandial readings are measured, the suggested goal is less than 180 mg/dL *(Clement, 2004 [Low Quality Evidence]; Garber, 2004 [Low Quality Evidence])*. If treated with insulin, the premeal blood glucose should generally be < 140 mg/dL with random blood glucose < 180 mg/dL provided these targets can be safely achieved *(American Diabetes Association, 2010 [Guideline])*.

The work group acknowledges that at this time, there is no evidence from appropriate clinical trials to define optimal glucose goals for non-critically ill, hospitalized patients. Recommendations from professional organizations and expert opinion include fasting or preprandial glucose values less than 90-126 mg/dL and peak or postprandial values less than 180-200 mg/dL *(American Diabetes Association 2009 Standards of Care [Guideline]; Canadian Diabetes Association 2008 Clinical Practice Guidelines [Guideline]; Rodbard, 2007 [Guideline]; Clement, 2004 [Guideline]; Garber, 2004 [Low Quality Evidence])*. Based on a review of studies on this topic, organizations may wish to adopt a less stringent blood glucose goal (90-150 mg/dL), especially for the initial implementation of the order set *(Inzucchi, 2006 [Low Quality Evidence])*.

Most hospitals do not measure postprandial glucose readings. The utility of postprandial glucose readings is in helping to establish preprandial boluses. Because of several issues including overlap of insulin pharmacokinetic profiles, it is difficult to respond to a postprandial reading with subcutaneous insulin.

Glucose Monitoring

There are currently no studies testing the effect of frequency of blood glucose monitoring on rates of hyperglycemia or hypoglycemia in hospitalized patients *(Clement, 2004 [Low Quality Evidence])*. The American Diabetes Association standards of care state that frequency of blood glucose monitoring needs to be individualized in hospitalized patients *(American Diabetes Association, 2007b [Guideline])*.

Relevant reviews take the position that monitoring before meals and at bedtime is reasonable for hospitalized patients who are eating. For patients who are not eating, testing every four to six hours is generally adequate for determining insulin correction doses *(Clement, 2004 [Low Quality Evidence]; Hirsch, 1995 [Low Quality Evidence])*. Because of the risk of nocturnal hypoglycemia, some authorities feel early morning (e.g., 0300) blood glucose monitoring should be routinely considered *(Hirsch, 1995 [Low Quality Evidence])*.

With respect to the timing of glucose monitoring in relation to meals, it is recommended that glucose monitoring be performed within 15 minutes before meals in patients receiving rapid-acting insulin (e.g., lispro, aspart, glulisine) and 30-45 minutes before meals in patients receiving regular insulin *(Clement, 2004 [Low Quality Evidence])*.

Types of Insulin

Based on outpatient studies, consider insulin Glargine or Detemir as the basal insulin (there are limited inpatient studies to date). In studies comparing Glargine with NPH, the risk of nocturnal hypoglycemia was reduced *(Wang, 2003 [Systematic Review]; Yki-Jarvinen, 2000 [Moderate Quality Evidence])*. Treatment with insulin Detemir resulted in more predictable glycemic control than NPH insulin *(Vague, 2003 [Low Quality Evidence])*. While the patient's clinical situation determines the need for types of insulin and schedules during hospitalization, it would be important to keep in mind its complexity, expense and appropriateness when planning for discharge/transition of the patient. See the "Discharge/Transition Planning" section for more information.

Consider using rapid-acting insulin analogs (e.g., lispro, aspart, glulisine instead of regular insulin) unless the patient is to have nothing by mouth or is on continuous feedings. Initial studies comparing rapid-acting insulin with human regular insulin show rapid-acting insulins to be more effective at reducing the peak postprandial glucose concentration *(Reynolds, 2004 [Low Quality Evidence])*. They may also lower the

Return to Table of Contents

demand for endogenous insulin, provide superior postprandial glycemic control, and cause fewer hypoglycemic episodes requiring medical intervention *(Rave, 2006 [Low Quality Evidence]; Pettitt, 2003 [Moderate Quality Evidence]; Gerich, 2002 [Low Quality Evidence])*.

Insulin lispro, glulisine and aspart have similar pharmacokinetics; they have an earlier onset and peak of action than regular insulin. Peak action usually occurs at one hour with a duration of three to four hours, while regular insulin has a peak action of two to four hours and a duration of six to eight hours. Lispro, glulisine and aspart may then reduce the occurrence of late postprandial hypoglycemia compared to regular insulin *(Guerci, 2005 [Low Quality Evidence]; John, 2004 [Low Quality Evidence])*.

Insulin Dosing Schedule

Insulin dosing schedules must be individualized based on a variety of factors, including the severity of diabetes, oral intake, severity of illness and other concurrent diabetic medication. It is not feasible to design a single algorithm for determining an insulin regimen in every patient. The following information provides general guidance in determining initial insulin doses.

Healthy, non-diabetic people are estimated to secrete approximately 0.4-1.0 units of insulin/kg body weight per day *(Polonsky, 1988a [Low Quality Evidence]; Davidson, 1986 [Reference])*. Approximately 50% of this insulin is secreted as basal insulin and 50% as postprandial boluses following meals (Polonsky, 1988b [Low Quality Evidence]). Typical daily insulin doses for people with diabetes range from 0.5 to 0.7 units/kg per day. In the United Kingdom Prospective Diabetes Study of people with type 2 diabetes, the median daily insulin dose for people in the intensive insulin treatment arm of the study after a diabetes duration of approximately 12 years was 36 units/day *(UK Prospective Diabetes Study Group, 1998 [High Quality Evidence])*.

Fifty percent of subjects were receiving between 23 and 53 units of insulin per day. The average weight of subjects was 75 kg, so the "average" daily insulin requirement was about 0.5 units/kg *(UK Prospective Diabetes Study Group, 1998 [High Quality Evidence])*. Therefore, in initiating subcutaneous insulin in a hospitalized patient who is eating meals, a total daily insulin dose of 0.6 units/kg is probably reasonable *(Clement, 2004 [Low Quality Evidence])*. Modification can be made based on clinical judgment for factors such as severity of illness, fragility, renal function, body weight, expected nutritional intake, and medication effects (e.g., glucocorticoid medications).

Based on the normal physiology of insulin release and experience with outpatient regimens for managing diabetes with subcutaneous insulin, it has been recommended that inpatient subcutaneous insulin regimens comprise three components *(Clement, 2004 [Low Quality Evidence])*:

- A basal insulin component
- A prandial insulin component (for patients eating meals)
- A correction, sometimes referred to as "supplemental," insulin component used to treat hyperglycemia before or between meals *(Clement, 2004 [Low Quality Evidence])*

In a small, randomized trial comparing a basal/prandial insulin regimen with a traditional sliding scale insulin regimen in hospitalized patients with type 2 diabetes, the basal/prandial insulin regimen resulted in improved glycemic control during the hospitalization. Hospital length-of-stay or incidences of hypoglycemia did not differ between the basal/prandial insulin regimen or the sliding scale insulin regimen *(Umpierrez, 2007 [High Quality Evidence])*.

Basal insulin

Typical approach is to give 40-50% of the estimated total daily insulin dose as the basal insulin component. Common basal regimens include one injection per day of Glargine insulin, usually given at bedtime or

Return to Table of Contents

twice daily; Detemir insulin given once daily in the evening or given twice daily; twice-a-day injections of NPH insulin, given at breakfast and either at supper or bedtime; or once-a-day NPH insulin given at bedtime *(Vague, 2003 [Low Quality Evidence])*. Basal insulin would generally be appropriate for any patient being managed with subcutaneous insulin, whether eating meals, nothing by mouth or receiving nutrition as continuous enteral feeding or total parenteral nutrition (TPN) *(Clement, 2004 [Low Quality Evidence])*.

Prandial insulin

For patients eating meals, several approaches have been suggested to initiate a prandial insulin regimen:

- Divide 50% of the estimated daily insulin requirement into three equal insulin doses given before the three meals.
- Estimate the prandial insulin dose before each meal as 10-20% of the estimated daily insulin requirement.
- Count the carbohydrate content of the meal (one carbohydrate unit = 15 gm of meal carbohydrate) and determine the prandial insulin dose as a set number of units of insulin per meal carbohydrate unit.
- Insulin doses based on grams of carbohydrates consumed.

Typical insulin requirements using this last approach are one to two units of insulin per carbohydrate unit *(Clement, 2004 [Low Quality Evidence])*.

It is recommended that prandial insulin be given as a rapid-acting insulin analog within 0-15 minutes of the meal *(Clement, 2004 [Low Quality Evidence])*. Prandial insulin replacement has its main effect on peripheral glucose disposal into muscle. Also referred to as "bolus" or "mealtime" insulin, prandial insulin is usually administered before eating. There are occasional situations when this insulin may be injected immediately after eating, such as when it is unclear how much food will be eaten. In such situations, the quantity of carbohydrates taken can be counted and an appropriate amount of rapid-acting analog can be injected *(Clement, 2004 [Low Quality Evidence])*.

Patients who are not eating meals will not typically require a prandial insulin component, although they may need periodic correction insulin.

Correction (supplemental) insulin

Correction dose insulin is given in addition to the scheduled basal and prandial insulin in order to correct hyperglycemia. For patients eating meals, it is typically given with meals by simply increasing the rapid-acting insulin dose by an additional amount based on the correction schedule. For patients not eating meals (e.g., nothing by mouth, on continuous enteral feeding, total parenteral nutrition), it is reasonable to give periodic short-acting insulin, either as regular insulin or a rapid-acting analog, based on the correction schedule at four- to six-hour intervals *(Guerci, 2005 [Low Quality Evidence]; John, 2004 [Low Quality Evidence])*. If rapid-acting insulin is used in this situation, an every-four-hour schedule may be optimal. For regular insulin, a four- to six-hour schedule is reasonable *(Clement, 2004 [Low Quality Evidence])*.

The correction dose insulin schedule must be individualized for the patient. A typical assumption is that one unit of insulin will lower the blood glucose 50 mg/dL *(Hirsch, 2002 [Low Quality Evidence])*. An empiric "Rule of 1,700" has been proposed as one way of estimating the insulin correction requirement. This rule estimates that the decrease in glucose in response to one unit of insulin = (1,700/patient's total daily insulin dose) *(Davidson, 2003 [Reference])*. The "Low," "Medium" and "High" correction schedules included on the order set assume that one unit of insulin will lower the blood glucose by approximately 50, 25 and 15 mg/dL, respectively.

Return to Table of Contents

There does not appear to be a consensus whether correction insulin should be given at bedtime. Some experts argue against bedtime correction insulin due to a fear of nocturnal hypoglycemia with short- or rapid-acting insulin given at bedtime *(Hirsch, 1995 [Low Quality Evidence])*. If correction insulin is given at bedtime, the recommendation is that the correction dose should be reduced *(Clement, 2004 [Low Quality Evidence])*.

Hyperglycemia induced by corticosteroid therapy is often characterized by predominant postprandial hyperglycemia with lesser effects on fasting glucose levels. For patients with corticosteroid-induced hyperglycemia, caution is suggested in prescribing correction dose insulin at bedtime due to the increased risk of nocturnal hypoglycemia *(Clement, 2004 [Low Quality Evidence])*.

Example:

The following is an example of one possible initial subcutaneous insulin regimen for a hospitalized patient weighing 100 kg with hyperglycemia who is eating meals.

Estimated total daily insulin dose = 100 kg x 0.6 units insulin/kg = 60 units of insulin daily.

Basal: 50% of total daily insulin dose = 30 units given as Glargine or Detemir insulin at bedtime.

Prandial: 50% of total daily insulin dose/3 = 30 units/3 = 10 units of insulin at each meal given as Lispro, Glulisine or Aspart insulin.

Correction schedule: Assuming 1 unit of insulin will drop the blood glucose 50 mg/dL, the "Low" correction schedule on the order set could be used. Using the Rule of 1700, one would estimate that one unit of insulin = drop in blood glucose of (1,700/60) = 28 mg/dL. In this case, the "Medium" correction schedule might be chosen.

Whatever insulin regimen is initially implemented, it will likely need to be modified over the course of a patient's hospitalization. If a patient is frequently requiring use of the correction schedule, common sense would dictate that either the basal component, prandial component or both need to be modified.

Other Diabetic Medications

There are limitations to inpatient use of each of the oral antidiabetic classes. Biguanides (e.g., metformin) have been associated with lactic acidosis. Risk factors for lactic acidosis in patients treated with the biguanides include cardiac disease (including congestive heart failure) hypoperfusion, renal insufficiency, old age and chronic pulmonary disease *(Misbin, 1998 [Reference])*. The thiazolidinediones may increase intravascular volume and should be used with caution in those patients who are predisposed to congestive heart failure *(Kermani, 2003 [Low Quality Evidence])*. Sulfonylureas are generally long acting and may potentially cause hypoglycemia in patients who have diminished oral intake and/or renal insufficiency *(Miller, 2001 [Low Quality Evidence])*.

In summary, each of the classes of antidiabetic agents has limitations. They provide little flexibility or opportunity for titration. Therefore, insulin, when used properly, may have many advantages in the hospital setting *(Clement, 2004 [Low Quality Evidence])*.

Exenatide and pramlintide are injectable, typically administered before meals. Side effects include nausea and early satiety and may not be suitable for hospitalized patients with variable oral intake *(Dunn, 2006 [Low Quality Evidence]; Odegard, 2006 [Low Quality Evidence])*.

Nutrition

Medical Nutrition Therapy (MNT) is an integral component of diabetes management in the acute care setting. The term Medical Nutrition Therapy is the preferred term and should replace other terms, such as diet, diet therapy and dietary management *(Franz, 2002 [Low Quality Evidence])*. Central to the nutrition recommendations is the need to individualize therapy, to integrate nutrition into the overall diabetes management plan, and to use an interdisciplinary team approach *(American Diabetes Association, 2004 [Guideline])*.

The current recommendation for health care institutions is for the implementation of a consistent carbohydrate diabetes meal plan *(American Diabetes Association, 2004 [Guideline]; Franz, 1999 [Reference])*. Treatment with insulin or insulin secretagogues requires consistency in timing of meals and carbohydrate content. More freedom can be achieved with the implementation of a basal/bolus insulin management regimen *(American Diabetes Association, 2007a [Guideline])*. When utilizing the consistent carbohydrate meal planning method, the carbohydrate content of the meals is comparable day to day, but not necessarily equal at each meal or snack *(Franz, 2003 [Reference])*. The carbohydrate source is not an issue. The amount of carbohydrate in the meal determines the mealtime doses of rapid-acting insulin or short-acting insulin based on the insulin-to-carbohydrate ratio prescribed. There is evidence that only utilizing rapid-acting insulin and not using short-acting insulin for prandial coverage reduces the occurrence of between-meal and nocturnal hypoglycemia *(Cryer, 2003 [Low Quality Evidence])*. Individuals taking fixed doses of rapid- or short-acting insulin and intermediate- or long-acting insulin need day-to-day consistency in the amount and source of carbohydrate. By doing this, lower A1c levels have been demonstrated, and in acute care, improved metabolic control is achieved *(American Diabetes Association, 2007a [Guideline]; Franz, 2002 [Low Quality Evidence])*.

There is minimal evidence to suggest that a "bedtime" snack is necessary in diabetes medical nutrition management. A study conducted in 1993 concluded higher meal frequency acutely subdues glucose excursions and reduces insulin and free fatty acid levels during the daytime in older type 2, non-insulin dependent subjects *(Bertelsen, 1993 [Low Quality Evidence])*. Historically, bedtime snacks were to avoid nocturnal hypoglycemia.

Nocturnal hypoglycemia can be avoided with the utilization of rapid- and long-acting insulin analogues. In addition, for weight reduction, the elimination of the snack reduces excess calories. The meal plan should be individualized to meet metabolic needs and preferences *(Franz, 2002 [Low Quality Evidence])*.

There are special nutrition issues that occur. Liquid diets should not be sugar-free. Food intake postoperatively should be initiated as soon as possible *(American Diabetes Association, 2004 [Guideline])*.

Hospitals should have a system for notifying the dietitian of which patients with diabetes require an assessment. It is then the dietitian's responsibility to do the assessment, determine an appropriate nutrition prescription, and plan for self-management education *(American Diabetes Association, 2004 [Guideline])*.

Enteral feeding and total parenteral nutrition must be considered when prescribing or altering insulin regimens. In the case of continuous enteral feeding, basal and nutritional insulin requirements are combined and insulin delivery strategies should take into account the possibility that the enteral feeding may be unexpectedly discontinued. There are no clinical trials evaluating different insulin strategies for these patients. Some experts recommend that the basal/nutritional insulin be supplied as a combination of NPH and regular insulin dosed every six hours so that the components can be discontinued if enteral feeding is interrupted. Alternatively, the conventional strategy of supplying basal/nutritional insulin as Glargine can be used. Should the enteral feeding be interrupted, an amount of carbohydrate equivalent to that in the enteral feeding needs to be supplied as intravenous dextrose until the next dose of Glargine is adjusted. Some experts favor corrective dosing with regular insulin rather than rapid-acting analogues in the context of continuous enteral feeding *(Furnary, 2006 [Low Quality Evidence]; Inzucchi, 2006 [Low Quality Evidence])*.

The same considerations related to continuous carbohydrate delivery, the combining of basal and nutritional insulin, and the potential for feeding interruption occur in the case of total parenteral nutrition. Hyperglycemia with total parenteral nutrition may be difficult to manage with a subcutaneous regimen. Insulin infusion, and placing insulin in the parenteral nutrition mixture are frequently used alternatives in this situation.

Return to Table of Contents

Transition from Intravenous to Subcutaneous Insulin

When transitioning from intravenous to subcutaneous insulin, it is generally recommended that an initial subcutaneous basal insulin dose of long- or intermediate-acting insulin be given prior to discontinuation of the intravenous insulin *(Furnary, 2006 [Low Quality Evidence])*. Based on the absorption profiles of longer-acting insulins, administering the first subcutaneous insulin dose two hours prior to stopping the insulin infusion would appear to allow sufficient overlap to avoid excessive rebound hyperglycemia when the insulin infusion is discontinued *(Furnary, 2006 [Low Quality Evidence]; Clement, 2004 [Low Quality Evidence])*.

Determination of the initial basal insulin dose can be made using the guidelines above (e.g., estimating the basal insulin dose as 40-50% of the estimated total daily insulin dose). An alternative method that has been suggested is to estimate the initial basal dose based on the intravenous insulin requirements over a six- to eight-hour period leading up to the transition time. Ideally, this six- to eight-hour period would be a time when the patient was not eating and was not receiving intravenous glucose. The initial basal insulin dose could be calculated as 80% of the estimated 24-hour insulin requirement to provide a margin of safety *(Furnary, 2006 [Low Quality Evidence])*.

Example:

A patient managed on an intravenous insulin drip is to be transitioned to subcutaneous insulin. Over a recent six-hour period when the patient was not eating and was not receiving intravenous glucose, the patient received a total of 15 units of insulin via the infusion. The estimated 24-hour basal insulin requirement would be 15 x 4 = 60 units. The initial basal insulin dose could be estimated as 80% x 60 units = 48 units.

Often the clinician may want to use a bedtime long-acting insulin (e.g., Glargine insulin) as the subcutaneous basal insulin, but the transition from intravenous to subcutaneous insulin is planned to occur during the day. In these cases, one option would be to give a one-time dose of NPH insulin by subcutaneous injection to act as a bridge until the regularly scheduled long-acting insulin is given *(Clement, 2004 [Low Quality Evidence])*. A typical NPH insulin dose might be 40% of the planned long-acting insulin dose.

Example:

Using the example above, the clinician plans to give 48 units of Glargine insulin at bedtime as the basal insulin dose on the transition to subcutaneous insulin. However, the clinician would like to transition the patient to subcutaneous insulin during the day rather than waiting until later in the evening when fewer staff are present. A one-time order for NPH insulin 20 units (40% x 48 units = 19.2 units, round to 20 units) could be written to be given two hours before the insulin infusion is stopped. This intermediate-acting insulin would provide temporary basal insulin coverage until bedtime, when the 48 units of Glargine insulin could be given.

Prandial and correction insulin orders should also be written as appropriate for the patient's situation (eating, on tube feeding, etc.) on transition to subcutaneous insulin. This insulin would then be given in addition to the basal insulin in accordance with the order set.

Laboratory/Diagnostic Testing

There do not appear to be specific recommendations regarding laboratory testing in hospitalized patients with type 2 diabetes or hyperglycemia. For patients with a known history of type 2 diabetes and on outpatient therapy, a glycosylated hemoglobin value may give some indication of the adequacy of the outpatient therapy. Tests of renal and liver function may be appropriate in specific circumstances.

For hospitalized patients with hyperglycemia not previously diagnosed with diabetes, a glycosylated hemoglobin may help predict whether the hyperglycemia reflects previously undiagnosed diabetes versus stress hyperglycemia. In one small study of 35 patients with in-hospital hyperglycemia and no previous diagnosis

of diabetes, a glycosylated hemoglobin greater than 6% had a sensitivity of 57% and specificity of 100% for predicting a diagnosis of diabetes on follow-up testing. All patients with values greater than 6.8% had diabetes confirmed on follow-up testing and no patient with a value less than 5.3% was confirmed to have diabetes on follow-up *(Greci, 2003 [Low Quality Evidence])*.

Hypoglycemia

Glucose is the preferred treatment for hypoglycemia. Fifteen to twenty grams of glucose is suggested as an initial treatment for hypoglycemia with initial response in 10-20 minutes. Retesting is recommended approximately 60 minutes after treatment as the rise in glucose may be temporary *(American Diabetes Association, 2007a [Guideline])*. Glucose (intravenous) or glucagon (intramuscular or subcutaneous) can be given to hypoglycemic patients who have nothing by mouth, are unresponsive or otherwise unable to take oral glucose safely. Glucagon can cause nausea and vomiting and this possibility should be anticipated if glucagon is administered.

See Appendix E, "Sample of Hypoglycemia Protocol."

Discharge/Transition Planning

For the hospitalized patient, diabetes survival skills education is generally considered a feasible approach. Patients are taught sufficient information to enable them to go home safely. Those newly diagnosed with diabetes or who are new to insulin and/or blood glucose monitoring need to be instructed before discharge to help ensure safe care upon returning home. Those patients hospitalized because of a crisis related to diabetes management or poor care at home need education to prevent subsequent episodes of hospitalization.

Goals of inpatient diabetes self-management education include *(Clement, 2004 [Low Quality Evidence])*:

- Assessment of current knowledge and practices of diabetes self-management and how they impact patients' health status and reason for hospitalization
- Initiation of diabetes education for patients newly diagnosed with diabetes
- Providing information on basic self-management skills to help ensure safe care post discharge
- Team approach with other health professional (e.g., clinicians, nurses, dietitians, case managers and social workers) coordinating care in the hospital and post discharge
- Providing information on community resources and diabetes education programs for continuing education
- The diabetes educator serving as a resource for nursing staff and other health care clinicians
- Assessment of the complexity, appropriateness and expense of medication management (particularly insulin) when selecting medication therapy for the patient. Key questions would be:
    - Is there a need to transition back to pre-hospital medication therapy and schedules?
    - Does the patient or family have sufficient knowledge and skills for the expected management of various medication therapies?
    - Will there be sufficient support to guide the patient through this care transition?

Survival skills include:

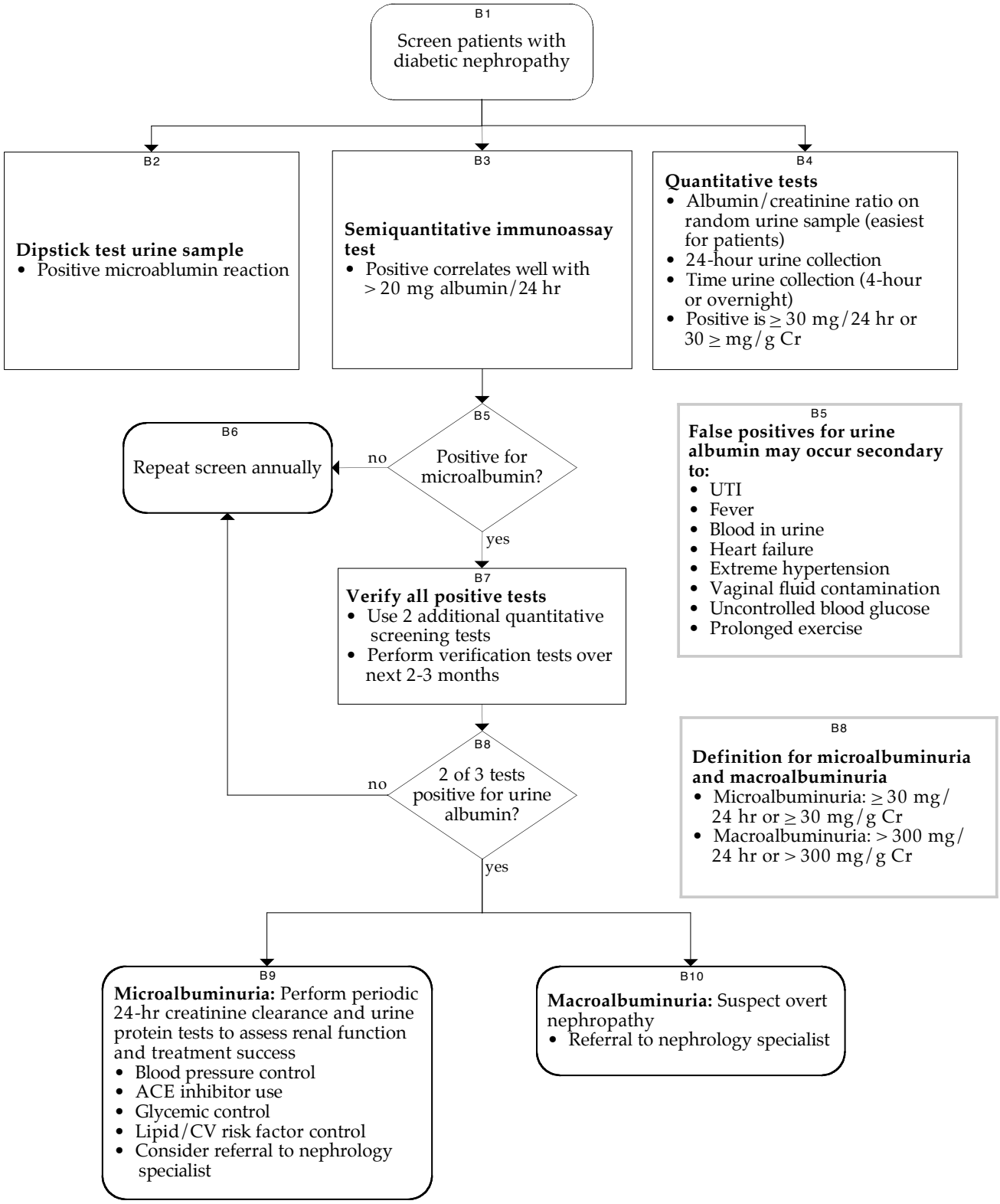
- What is diabetes? Principles of treatment and prevention of complications
- Normal values for blood glucose and target glucose levels for the individual
- Recognition, treatment and prevention of hyperglycemia and hypoglycemia

Return to Table of Contents

- Medical nutrition therapy (instructed by a registered dietician who, preferably, is a certified diabetes educator)
- Medication
- Self-monitoring of blood glucose
- Insulin administration (if going home on insulin)
- Sick-day management
- Community resources
- Universal precautions for caregivers

Return to Table of Contents

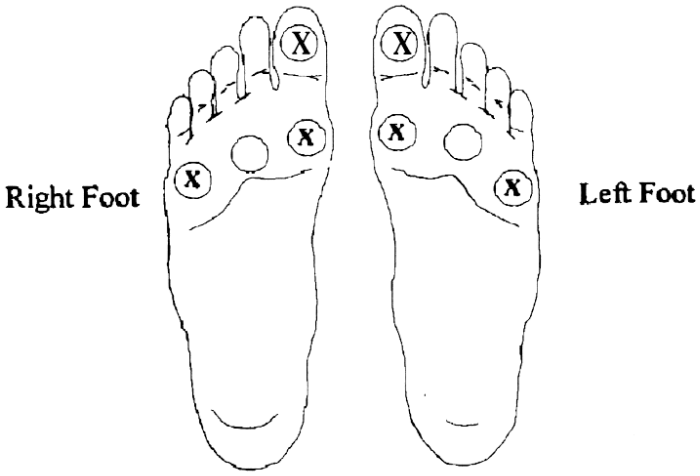
Appendix B – Treatment of Diabetic Nephropathy



Return to Table of Contents

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

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



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

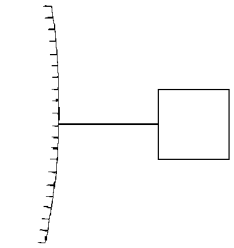


Figure 1

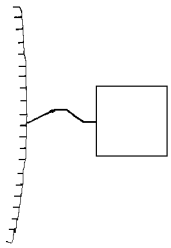


Figure 2

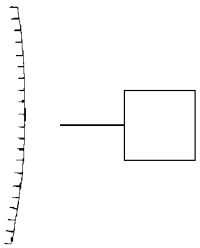


Figure 3

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

*Testing at the first and fifth metatarsal heads is sufficient. This combination of sites has been shown to detect the insensate foot with reasonable sensitivity (80%) and specificity (86%). Testing the great toes may be of added benefit.

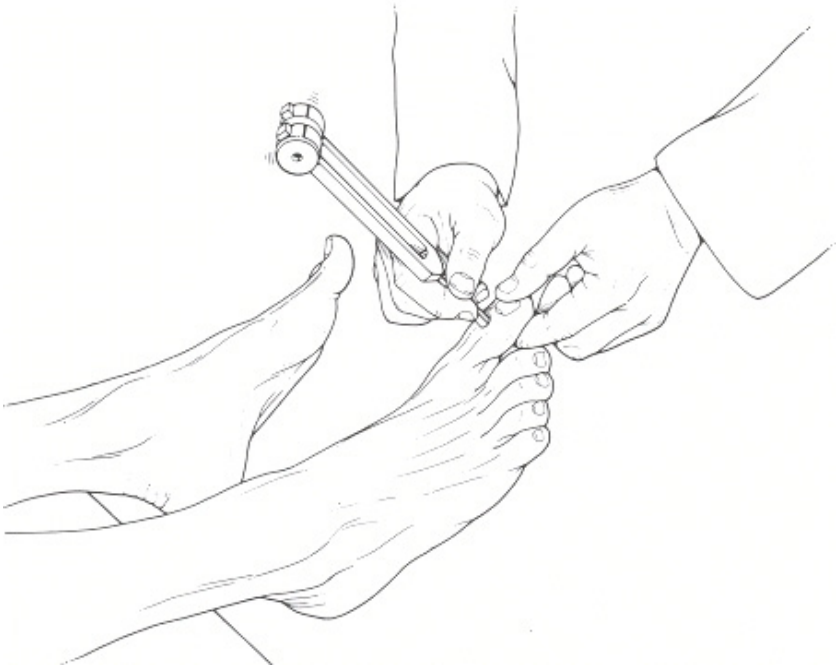
**Chart documentation is required for the American Diabetes Association – Clinician Recognition Program. An annual diabetic foot examination is also one of the eight diabetes quality improvement project (DQIP) measures adopted by the National Committee for Quality Assurance (NCQA) and the Health Care Financing Administration.

Return to Table of Contents

Appendix D – Using a Tuning Fork to Screen the Diabetic Foot for Peripheral Neuropathy

Peripheral neuropathy can be assessed by vibration perception threshold using a 128-cps tuning fork. The assessment is abnormal if the patient cannot sense the vibration of the tuning fork when it is pressed against the foot.

1. To initiate tuning fork vibration, tap the fork to the ball of your hand.
2. Apply the tuning fork on the wrist of the patient. This is a preliminary step to ensure the patient knows what sensation they should expect.
3. Next, apply the tuning fork, perpendicularly with constant pressure, on a bony part on the dorsal side of the distal phalanx of the first toe. The patient's eyes should be closed during testing.



4. Ask the patient if he/she feels the vibration. If he/she responds "yes," ask him/her to inform you when the vibration stops. An abnormal result occurs when the patient informs you that the vibration stops before you can feel the vibration end.
5. Perform the test three times.
6. The test is positive if the patient correctly answers at least two out of three applications, and negative ("at risk for ulceration") with two out of three incorrect answers.

Return to Table of Contents

Appendix E – Sample of Hypoglycemia Protocol

Sample Hypoglycemia Protocol

For glucose less than 70 mg/dL, patient is not alert/unresponsive	Give 1 amp of D50 IV If no IV access, administer 1 mg glucagon IM May repeat glucagon x1 Call covering physician
For glucose 60-70 mg/dL, but patient is NOT symptomatic	No treatment; Recheck glucose in 30 min. if more than 30 min. until next meal
For glucose 60-70 mg/dL, patient is symptomatic but alert	Give 15 gm of carbohydrates. Choose one of the following: • 4 oz. of any juice by mouth • 15 gm of glucose gel • 3 glucose tablets
For glucose 45-59 mg/dL, patient is alert	Give 20 gm of carbohydrates. Choose one of the following: • 6 oz. of any juice by mouth • 20 gm of glucose gel • 4 glucose tablets *If nothing by mouth, give 1/2 amp of D50 IV*
For glucose less than 45 mg/dL, patient is alert	Give 30 gm of carbohydrates. Choose one of the following: • 8 oz. of any juice by mouth • 30 gm of glucose gel • 6 glucose tablets *If nothing by mouth, give 1/2 amp of D50 IV*

Adapted from Hennepin County Medical Center, Minneapolis, MN

Recheck blood glucose every 15 minutes and repeat until blood glucose is greater than 60 mg/dL without symptoms, or blood glucose is greater than 70 mg/dL if symptoms persist. Once the patient is stable, recheck glucose after 60 minutes.

Return to Table of Contents

Appendix F – ICSI Shared Decision-Making Model

The technical aspects of Shared Decision-Making are widely discussed and understood.

- **Decisional conflict** occurs when a patient is presented with options where no single option satisfies all the patient's objectives, where there is an inherent difficulty in making a decision, or where external influencers act to make the choice more difficult.
- **Decision support** clarifies the decision that needs to be made, clarifies the patient's values and preferences, provides facts and probabilities, guides the deliberation and communication and monitors the progress.
- **Decision aids** are evidence-based tools that outline the benefits, harms, probabilities and scientific uncertainties of specific health care options available to the patient.

However, before decision support and decision aids can be most advantageously utilized, a Collaborative Conversation™ should be undertaken between the provider and the patient to provide a supportive framework for Shared Decision-Making.

Collaborative Conversation™

A collaborative approach toward decision-making is a fundamental tenet of Shared Decision-Making (SDM). The Collaborative Conversation™ is an inter-professional approach that nurtures relationships, enhances patients' knowledge, skills and confidence as vital participants in their health, and encourages them to manage their health care.

Within a Collaborative Conversation™ , the perspective is that both the patient and the provider play key roles in the decision-making process. The patient knows which course of action is most consistent with his/her values and preferences, and the provider contributes knowledge of medical evidence and best practices. Use of Collaborative Conversation™ elements and tools is even more necessary to support patient, care provider and team relationships when patients and families are dealing with high stakes or highly charged issues, such as diagnosis of a life-limiting illness.

The overall framework for the Collaborative Conversation™ approach is to create an environment in which the patient, family and care team work collaboratively to reach and carry out a decision that is consistent with the patient's values and preferences. A rote script or a completed form or checklist does not constitute this approach. Rather it is a set of skills employed appropriately for the specific situation. These skills need to be used artfully to address all aspects involved in making a decision: cognitive, affective, social and spiritual.

Key communication skills help build the Collaborative Conversation™ approach. These skills include many elements, but in this appendix only the questioning skills will be described. (For complete instruction, see O'Connor, Jacobsen "Decisional Conflict: Supporting People Experiencing Uncertainty about Options Affecting Their Health" [2007], and Bunn H, O'Connor AM, Jacobsen MJ "Analyzing decision support and related communication" [1998, 2003].)

1. **Listening skills:**

   Encourage patient to talk by providing prompts to continue such as "*go on, and then?, uh huh,"* or by repeating the last thing a person said, "*It's confusing*."

   Paraphrase content of messages shared by patient to promote exploration, clarify content and to communicate that the person's unique perspective has been heard. The provider should use his/her own words rather than just parroting what he/she heard.

Return to Table of Contents

Reflection of feelings usually can be done effectively once trust has been established. Until the provider feels that trust has been established, short reflections at the same level of intensity expressed by the patient without omitting any of the message's meaning are appropriate. Reflection in this manner communicates that the provider understands the patient's feelings and may work as a catalyst for further problem solving. For example, the provider identifies what the person is feeling and responds back in his/her own words like this: *"So, you're unsure which choice is the best for you."*

Summarize the person's key comments and reflect them back to the patient. The provider should condense several key comments made by the patient and provide a summary of the situation. This assists the patient in gaining a broader understanding of the situations rather than getting mired down in the details. The most effective times to do this are midway through and at the end of the conversation. An example of this is, *"You and your family have read the information together, discussed the pros and cons, but are having a hard time making a decision because of the risks."*

Perception checks ensure that the provider accurately understands a patient or family member, and may be used as a summary or reflection. They are used to verify that the provider is interpreting the message correctly. The provider can say *"So you are saying that you're not ready to make a decision at this time. Am I understanding you correctly?"*

2. **Questioning Skills**

Open and closed questions are both used, with the emphasis on open questions. Open questions ask for clarification or elaboration and cannot have a yes or no answer. An example would be *"What else would influence you to choose this?"* Closed questions are appropriate if specific information is required such as *"Does your daughter support your decision?"*

Other skills such as summarizing, paraphrasing and reflection of feeling can be used in the questioning process so that the patient doesn't feel pressured by questions.

Verbal tracking, referring back to a topic the patient mentioned earlier, is an important foundational skill (Ivey & Bradford-Ivey). An example of this is the provider saying, *"You mentioned earlier…"*

3. **Information-Giving Skills**

Providing information and **providing feedback** are two methods of information giving. The distinction between providing information and giving advice is important. Information giving allows a provider to supplement the patient's knowledge and helps to keep the conversation patient centered. Giving advice, on the other hand, takes the attention away from the patient's unique goals and values, and places it on those of the provider.

Providing information can be sharing facts or responding to questions. An example is *"If we look at the evidence, the risk is…"* Providing feedback gives the patient the provider's view of the patient's reaction. For instance, the provider can say, *"You seem to understand the facts and value your daughter's advice."*

Additional Communication Components

Other elements that can impact the effectiveness of a Collaborative Conversation™ include:

- Eye contact
- Body language consistent with message
- Respect
- Empathy
- Partnerships

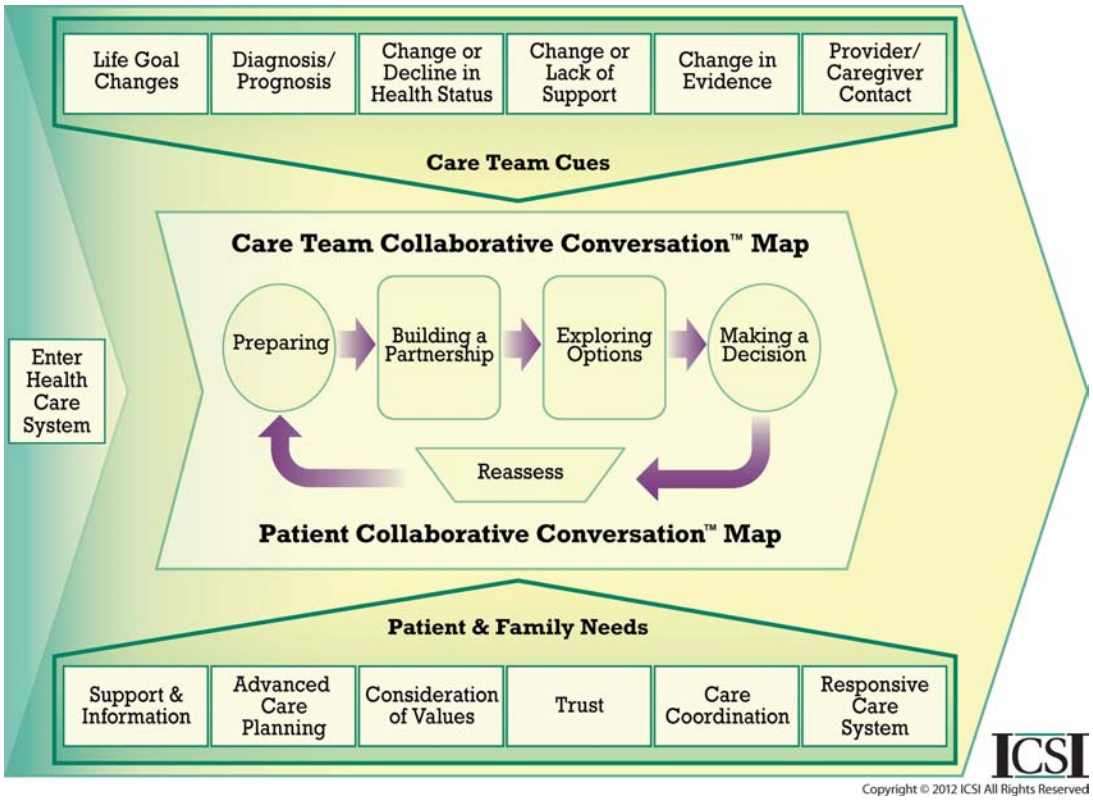
Return to Table of Contents

Self-examination by the provider involved in the Collaborative Conversation™ can be instructive. Some questions to ask oneself include:

- Do I have a clear understanding of the likely outcomes?
- Do I fully understand the patient's values?
- Have I framed the options in comprehensible ways?
- Have I helped the decision-makers recognize that preferences may change over time?
- Am I willing and able to assist the patient in reaching a decision based on his/her values, even when his/her values and ultimate decision may differ from my values and decisions in similar circumstances?

When to Initiate a Collaborative Conversation™

A Collaborative Conversation™ can support decisions that vary widely in complexity. It can range from a straightforward discussion concerning routine immunizations to the morass of navigating care for a life-limiting illness. Table 1 represents one health care event. This event can be simple like a 12 year-old coming to the clinic for routine immunizations, or something much more complex like an individual receiving a diagnosis of congestive heart failure. In either case, the event is the catalyst that starts the process represented in this table. There are cues for providers and patient needs that exert influence on this process. They are described below. The heart of the process is the Collaborative Conversation™. The time the patient spends within this health care event will vary according to the decision complexity and the patient's readiness to make a decision.



Regardless of the decision complexity there are cues applicable to all situations that indicate an opportune time for a Collaborative Conversation™. These cues can occur singularly or in conjunction with other cues.

Return to Table of Contents

Cues for the Care Team to Initiate a Collaborative Conversation™

- **Life goal changes:** Patient's priorities change related to things the patient values such as activities, relationships, possessions, goals and hopes, or things that contribute to the patient's emotional and spiritual well-being.
- **Diagnosis/prognosis changes:** Additional diagnoses, improved or worsening prognosis.
- **Change or decline in health status:** Improving or worsening symptoms, change in performance status or psychological distress.
- **Change or lack of support:** Increase or decrease in caregiver support, change in caregiver, or caregiver status, change in financial standing, difference between patient and family wishes.
- **Change in medical evidence or interpretation of medical evidence:** Providers can clarify the change and help the patient understand its impact.
- **Provider/caregiver contact:** Each contact between the provider/caregiver and the patient presents an opportunity to reaffirm with the patient that his/her care plan and the care the patient is receiving are consistent with his/her values.

Patients and families have a role to play as decision-making partners, as well. The needs and influencers brought to the process by patients and families impact the decision-making process. These are described below.

Patient and Family Needs within a Collaborative Conversation™

- **Request for support and information:** Decisional conflict is indicated by, among other things, the patient verbalizing uncertainty or concern about undesired outcomes, expressing concern about choice consistency with personal values and/or exhibiting behavior such as wavering, delay, preoccupation, distress or tension. Generational and cultural influencers may act to inhibit the patient from actively participating in care discussions, often patients need to be given "permission" to participate as partners in making decisions about his/her care.

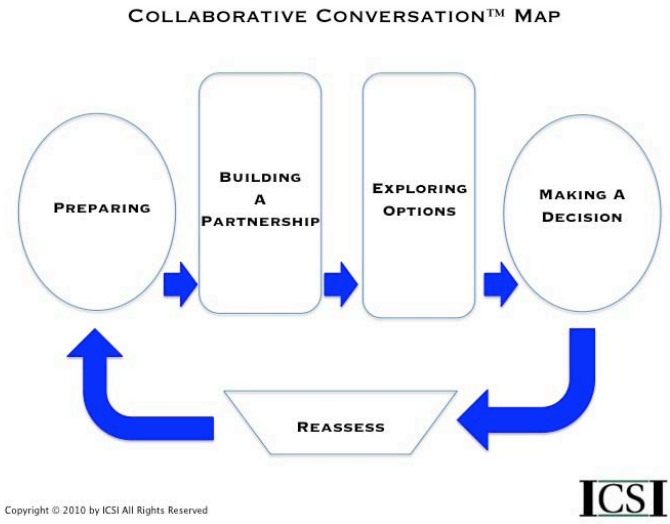
  Support resources may include health care professionals, family, friends, support groups, clergy and social workers. When the patient expresses a need for information regarding options and his/her potential outcomes, the patient should understand the key facts about options, risks and benefits, and have realistic expectations. The method and pace with which this information is provided to the patient should be appropriate for the patient's capacity at that moment.

- **Advance Care Planning:** With the diagnosis of a life-limiting illness, conversations around advance care planning open up. This is an opportune time to expand the scope of the conversation to other types of decisions that will need to be made as a consequence of the diagnosis.
- **Consideration of Values:** The personal importance a patient assigns potential outcomes must be respected. If the patient is unclear how to prioritize the preferences, value clarification can be achieved through a Collaborative Conversation™ and by the use of decision aids that detail the benefits and harms of potential outcomes in terms the patient can understand.
- **Trust:** The patient must feel confident that his/her preferences will be communicated and respected by all caregivers.
- **Care Coordination:** Should the patient require care coordination, this is an opportune time to discuss the other types of care-related decisions that need to be made. These decisions will most likely need to be revisited often. Furthermore, the care delivery system must be able to provide coordinated care throughout the continuum of care.

Return to Table of Contents

- **Responsive Care System:** The care system needs to support the components of patient- and family-centered care so the patient's values and preferences are incorporated into the care he/she receives throughout the care continuum.

The Collaborative Conversation™ Map is the heart of this process. The Collaborative Conversation™ Map can be used as a stand-alone tool that is equally applicable to providers and patients as shown in Table 2. Providers use the map as a clinical workflow. It helps get the Shared Decision-Making process initiated and provides navigation for the process. Care teams can used the Collaborative Conversation™ to document team best practices and to formalize a common lexicon. Organizations can build fields from the Collaborative Conversation™ Map in electronic medical records to encourage process normalization. Patients use the map to prepare for decision-making, to help guide them through the process and to share critical information with their loved ones.



Evaluating the Decision Quality

Adapted from O'Connor, Jacobsen "Decisional Conflict: Supporting People Experiencing Uncertainty about Options Affecting Their Health" [2007].

When the patient and family understand the key facts about the condition and his/her options, a good decision can be made. Additionally, the patient should have realistic expectations about the probable benefits and harms. A good indicator of the decision quality is whether or not the patient follows through with his/her chosen option. There may be implications of the decision on patient's emotional state such as regret or blame, and there may be utilization consequences.

Decision quality can be determined by the extent to which the patient's chosen option best matches his/her values and preferences as revealed through the Collaborative Conversation™ process.

Support for this project was provided in part by a grant from the Robert Wood Johnson Foundation.

ICSI Institute for Clinical Systems Improvement

8009 34th Ave. South, Suite 1200 • Bloomington, MN 55425 • Phone: 952-814-7060 • www.icsi.org

Return to Table of Contents

ICSI has long had a policy of transparency in declaring potential conflicting and competing interests of all individuals who participate in the development, revision and approval of ICSI guidelines and protocols.

In 2010, the ICSI Conflict of Interest Review Committee was established by the Board of Directors to review all disclosures and make recommendations to the board when steps should be taken to mitigate potential conflicts of interest, including recommendations regarding removal of work group members. This committee has adopted the Institute of Medicine Conflict of Interest standards as outlined in the report, Clinical Practice Guidelines We Can Trust (2011).

Where there are work group members with identified potential conflicts, these are disclosed and discussed at the initial work group meeting. These members are expected to recuse themselves from related discussions or authorship of related recommendations, as directed by the Conflict of Interest committee or requested by the work group.

The complete ICSI Policy regarding Conflicts of Interest is available at http://bit.ly/ICSICOI.

Funding Source

The Institute for Clinical Systems Improvement provided the funding for this guideline revision. ICSI is a not-for-profit, quality improvement organization based in Bloomington, Minnesota. ICSI's work is funded by the annual dues of the member medical groups and five sponsoring health plans in Minnesota and Wisconsin. Individuals on the work group are not paid by ICSI but are supported by their medical group for this work.

ICSI facilitates and coordinates the guideline development and revision process. ICSI, member medical groups and sponsoring health plans review and provide feedback but do not have editorial control over the work group. All recommendations are based on the work group's independent evaluation of the evidence.

Return to Table of Contents

Disclosure of Potential Conflicts of Interest

Penny Louise Flavin, RN, CNP, DNP, Work Group Member
Family Practice, Olmsted Medical Center
National, Regional, Local Committee Affiliations: None
Guideline Related Activities: None
Research Grants: None
Financial/Non-Financial Conflicts of Interest: None

Ryan Michels, PharmD, BCPS, Work Group Member
Clinical Pharmacist, HealthPartners Medical Group and Regions Hospital
National, Regional, Local Committee Affiliations: None
Guideline Related Activities: None
Research Grants: None
Financial/Non-Financial Conflicts of Interest: None

Patrick O'Connor, MD, Family Medicine/Geriatrics, Work Group Member
Senior Clinical Investigator, HealthPartners Research Foundation
National, Regional, Local Committee Affiliations: None
Guideline Related Activities: None
Research Grants: Received institutional payment for research grants from NIH (National Institute of Health), AHRQ (Agency for Healthcare Research and Quality, NIMH (National Institute of Mental Health), NHLBI (National Heart, Lung and Blood Institute) and to develop standards of diabetes care for American Diabetes Association
Financial/Non-Financial Conflicts of Interest: None

Bruce Redmon, MD, Endocrinologist, Work Group Member
Professor, University of Minnesota Medical School
National, Regional, Local Committee Affiliations: None
Guideline Related Activities: None
Research Grants: NIH (National Institute of Health) related to ongoing diabetes clinical trial
Financial/Non-Financial Conflicts of Interest: Consults for BlueCross BlueShield of Minnesota doing peer review and for Ingenix for diabetes quality measure

Matthew Riethof, MD, Internist, Work Group Member
Internist, Fairview Health Services, Oxboro Clinic
National, Regional, Local Committee Affiliations: None
Guideline Related Activities: None
Research Grants: None
Financial/Non-Financial Conflicts of Interest: None

Julie Roberts, MS, RD, CDE, Work Group Member
Registered Dietician, HealthPartners Medical Group and Regions Hospital
National, Regional, Local Committee Affiliations: None
Guideline Related Activities: None
Research Grants: None
Financial/Non-Financial Conflicts of Interest: None

Return to Table of Contents

Steve Smith, MD, Endocrinologist, Work Group Member
Consultant, Medical Director of Patient Education, Mayo Clinic
National, Regional, Local Committee Affiliations: None
Guideline Related Activities: None
Research Grants: None
Financial/Non-Financial Conflicts of Interest: None

JoAnn Sperl-Hillen, MD, Internist, Work Group Member
Investigator, HealthPartners Research Foundation
National, Regional, Local Committee Affiliations: None
Guideline Related Activities: Has served on guideline group for BMI epocrates for type 2 diabetes
Research Grants: Receives programmatic support paid to her institution for the following: Stimulated Diabetes Training for Resident Physicians (NIDDK funded), Primary investigator; Personalized Physician Learning for HTN (NHLBI), co-investigator; Priorities (NHLBI), co-investigator; Hyperlink (NHLBI), co-investigator
Financial/Non-Financial Conflicts of Interest: None

Return to Table of Contents

Acknowledgements:

The ICSI Patient Advisory Council meets regularly to respond to any scientific document review requests put forth by ICSI facilitators and work groups. Patient advisors who serve on the council consistently share their experiences and perspectives in either a comprehensive or partial review of a document, and engaging in discussion and answering questions. In alignment with the Institute of Medicine's triple aims, ICSI and its member groups are committed to improving the patient experience when developing health care recommendations.

All ICSI documents are available for review during the revision process by member medical groups and sponsors. In addition, all members commit to reviewing specific documents each year. This comprehensive review provides information to the work group for such issues as content update, improving clarity of recommendations, implementation suggestions and more. The specific reviewer comments and the work group responses are available to ICSI members at http://www.icsi.org.

Return to Table of Contents

Acknowledgements

ICSI Patient Advisory Council

The work group would like to acknowledge the work done by the ICSI Patient Advisory Council in reviewing the Diagnosis and Management of Type 2 Diabetes Mellitus in Adults and thank them for their suggestion to improve the Shared Decision-Making opportunities throughout the document.

We want to thank the following member groups for reviewing and commenting on this document.

Invited Reviewers

During this revision, the following medical groups reviewed this document. The work group would like to thank them for their comments and feedback.

CentraCare, St. Cloud, MN
HealthPartners Health Plan, Minneapolis, MN
Marshfield Clinic, Marshfield, WI
Mayo Clinic, Rochester, MN
Medica, Minneapolis, MN
Minnesota Association of Community Health Centers, Minneapolis, MN
North Clinic, Robbinsdale, MN
Winona health, Winona MN

Return to Table of Contents

ICSI
Institute for Clinical Systems Improvement

Document History and Development:

Diagnosis and Management of Type 2 Diabetes Mellitus in Adults

Document Drafted Nov 1994 – Apr 1995
First Edition Mar 1996
Second Edition Apr 1997
Third Edition May 1998
Fourth Edition Apr 1999
Fifth Edition Apr 2000
Sixth Edition Oct 2001
Seventh Edition Oct 2002
Eighth Edition Dec 2003
Ninth Edition Dec 2004
Tenth Edition Dec 2005
Eleventh Edition Dec 2006
Twelfth Edition Apr 2008
Thirteenth Edition June 2009
Fourteenth Edition Aug 2010
Fifteenth Edition Begins May 2012

Original Work Group Members

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

Richard Bergenstal, MD
Endocrinology
International Diabetes Center

Mary Bergene
BHCAG Representative
Honeywell, Inc.

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

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

Janet Davidson, RN, CDE
Nurse Clinician
Park Nicollet Clinic

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

Marion Franz, RD, CDE
Dietetics
International Diabetes Center

Patrick O'Connor, MD
Family Practice
HealthPartners

Teresa Pearson, MS, RN, CDE
Health Education
HealthPartners

Peg Sannes, RPh
Pharmacy
HealthPartners

Mary Shelerud, RN
Facilitator
Mayo Clinic

Dace Trence, MD
Endocrinology
HealthPartners

Bruce Zimmerman, MD
Endocrinology
Mayo Clinic

Released in April 2012 for Fifteenth Edition.
The next scheduled revision will occur within 24 months.

Return to Table of Contents

Contact ICSI at:
8009 34th Avenue South, Suite 1200; Bloomington, MN 55425; (952) 814-7060; (952) 858-9675 (fax)
Online at http://www.ICSI.org

ICSI Document Development and Revision Process

Overview

Since 1993, the Institute for Clinical Systems Improvement (ICSI) has developed more than 60 evidence-based health care documents that support best practices for the prevention, diagnosis, treatment or management of a given symptom, disease or condition for patients.

Audience and Intended Use

The information contained in this ICSI Health Care Guideline is intended primarily for health professionals and other expert audiences.

This ICSI Health Care Guideline should not be construed as medical advice or medical opinion related to any specific facts or circumstances. Patients and families are urged to consult a health care professional regarding their own situation and any specific medical questions they may have. In addition, they should seek assistance from a health care professional in interpreting this ICSI Health Care Guideline and applying it in their individual case.

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

Document Development and Revision Process

The development process is based on a number of long-proven approaches and is continually being revised based on changing community standards. The ICSI staff, in consultation with the work group and a medical librarian, conduct a literature search to identify systematic reviews, randomized clinical trials, meta-analysis, other guidelines, regulatory statements and other pertinent literature. This literature is evaluated based on the GRADE methodology by work group members. When needed, an outside methodologist is consulted.

The work group uses this information to develop or revise clinical flows and algorithms, write recommendations, and identify gaps in the literature. The work group gives consideration to the importance of many issues as they develop the guideline. These considerations include the systems of care in our community and how resources vary, the balance between benefits and harms of interventions, patient and community values, the autonomy of clinicians and patients and more. All decisions made by the work group are done using a consensus process.

ICSI's medical group members and sponsors review each guideline as part of the revision process. They provide comment on the scientific content, recommendations, implementation strategies and barriers to implementation. This feedback is used by and responded to by the work group as part of their revision work. Final review and approval of the guideline is done by ICSI's Committee on Evidence-Based Practice. This committee is made up of practicing clinicians and nurses, drawn from ICSI member medical groups.

Implementation Recommendations and Measures

These are provided to assist medical groups and others to implement the recommendations in the guidelines. Where possible, implementation strategies are included which have been formally evaluated and tested. Measures are included which may be used for quality improvement as well as for outcome reporting. When available, regulatory or publicly reported measures are included.

Document Revision Cycle

Scientific documents are revised every 12-24 months as indicated by changes in clinical practice and literature. Each ICSI staff monitors major peer-reviewed journals every month for the guidelines for which they are responsible. Work group members are also asked to provide any pertinent literature through check-ins with the work group mid-cycle and annually to determine if there have been changes in the evidence significant enough to warrant document revision earlier than scheduled. This process complements the exhaustive literature search that is done on the subject prior to development of the first version of a guideline.

Return to Table of Contents